

*Third ACTION Scientific Workshop  
Transformative Strategies-Development of Pain Therapies*

---

*June 24, 2014*

---

*A Matter of Record  
(301) 890-4188*

Page 1

1	THIRD ACTION SCIENTIFIC WORKSHOP
2	
3	
4	TRANSFORMATIVE STRATEGIES FOR THE
5	DEVELOPMENT OF PAIN THERAPIES
6	
7	
8	
9	
10	
11	Tuesday, June 24, 2014
12	8:35 a.m. to 4:44 p.m.
13	
14	
15	
16	
17	
18	FDA White Oak Campus
19	White Oak Conference Center
20	Building 31, The Great Room
21	silver Spring, Maryland
22	

Page 2

1	C O N T E N T S	
2	AGENDA ITEM	PAGE
3	Keynote Address: Human Pluripotent Stem Cells	
4	Clive Svendsen	5
5	Stem Cells and Pain	
6	Allan Basbaum	75
7	Gene Therapy Potential in Pain	
8	Joseph Glorioso	112
9	Toxins for Pain	
10	Baldomero (Toto) Olivera	137
11	Q&A and Panel Discussion	169
12	Preclinical and Clinical Studies of	
13	Angiotensin II Receptor Blockers	
14	Andrew Rice	195
15	Preclinical and Clinical Studies of	
16	Anti-NGF Antibodies	
17	Nathaniel Katz	227
18	Preclinical Studies of Anti-CGRP Agents	
19	Lars Edvinsson	272
20		
21		
22		

Page 3

1	C O N T E N T S (continued)	
2	AGENDA ITEM	PAGE
3	Clinical Studies of Anti-CGRP Agents	
4	Marcelo Bigal	295
5	Q&A and Panel Discussion	332
6	Adjournment	353
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		

Page 4

1 PROCEEDINGS

2 (8:35 a.m.)

3 DR. PORRECA: All right. Well, good

4 morning, everybody, and welcome to the second day

5 of our meeting. And it's my great pleasure to

6 introduce our first speaker this morning. Our

7 keynote address is going to be presented by

8 Dr. Clive Svendsen on the topic of human

9 pluripotent stem cells.

10 Just to tell you a little bit about Clive,

11 he is the director of the Regenerative Medicine

12 Institute at Cedars-Sinai. He's been working in

13 the area of stems cells and regenerative medicine

14 now for many years. He was at the University of

15 Wisconsin for some time and founded and ran the

16 stem cell biology program there.

17 He's subsequently moved to Cedars-Sinai,

18 where he's set up and directed Regenerative

19 Medicine Institute, which now consists of 120

20 people and 16 faculty, and working on stem-cell

21 based therapies for all different types of

22 diseases, as he's explained to me, from liver to

Page 5

1 brain.  
2 So today, he is going to be presenting on  
3 the topic that I know very little about, but really  
4 offers perhaps tremendous promise for the  
5 development of pain therapies. And he's going to  
6 be talking about stem cells, GDNF, and pain. And  
7 so Clive, thank you very much for coming.  
8 Presentation – Clive Svendsen  
9 DR. SVENDSEN: Thanks very much, Frank, and  
10 to everybody for the invite. Despite United's best  
11 efforts, I made it here. Just a bit of advice.  
12 Never go through Chicago on United at 4:00 in the  
13 afternoon.  
14 I actually changed the title a little bit.  
15 Yes, I work on stem cells, but I've also got a long  
16 history in GDNF and somewhat neural transplantation  
17 as well, which I thought would fit a little bit  
18 with the next speaker, Allan, who's going to talk  
19 about some of the work he's doing presumably on  
20 putting neurons in the spinal cord to control pain.  
21 So I was asked to give a broad overview, so  
22 I'm going to do that first. And then I'm going to

Page 6

1 try and keep mentioning pain as I go through to get  
2 it back to pain and how the stuff we do may impact  
3 pain.  
4 So this is the building I work in at  
5 Cedars-Sinai. Cedars-Sinai is a 1,000-bed hospital  
6 in Los Angeles that is now becoming a major medical  
7 center. We have over 600 faculty working in the  
8 sciences and a huge science program, really  
9 matching all the pinnacle efforts that we have.  
10 The big picture, first, I'll talk about stem  
11 cells at the moment to update you. Then I'll talk  
12 about modeling diseases. And I think many of the  
13 impacts of stem cells may not be a therapy. It may  
14 actually be modeling, so modeling pain in the dish.  
15 Then I'll talk about a new trial to treat  
16 ALS, Lou Gehrig's disease, using GDNF-secreting  
17 stem cells, which again I think has impact for  
18 pain, given the work Steven's done. Sorry I missed  
19 yesterday. But the impact of GDNF on pain may be  
20 significant, and we may be able to revisit that in  
21 the discussion, and then talk about iPS cells at  
22 the end and how we might be converting to those for

Page 7

1 different types of therapy.  
2 So the big picture, if I'm going to lead you  
3 with anything, this will be the thing to remember.  
4 Up until recently, stem cells were mainly thought  
5 of as ethical issues. The embryonic stem cell era  
6 that just ended about four years ago was fraught  
7 with problems.  
8 When I arrived in Wisconsin in 2000, the  
9 paper from Jamie Thompson had just been published,  
10 where he destroyed embryos in order to make  
11 embryonic stem cells. And this whole fervor in the  
12 field, there's been more ethics about this topic,  
13 that science has really been the driving force of  
14 media attention to the field.  
15 This all changed when Shinya Yamanaka, who  
16 got the Nobel Prize a few years ago, discovered  
17 that we don't actually need embryonic stem cells  
18 anymore. And I'm going to really play the view  
19 here that embryonic stem cells, while important,  
20 today are probably not going to be relevant anymore  
21 for the field.  
22 The reason is that you can take a diseased

Page 8

1 patient, or any patient, up to 100 years old,  
2 isolate cells from either the blood, the skin, or  
3 even the liver, any adult cell, put them in the  
4 petri dish, and grow them for a day or two, and  
5 then expose them. And I'm not going to go through  
6 all the technology.  
7 The main factor is Oct-4. It's a  
8 transcription factor that if you just put the  
9 protein in an adult cell, any cell, it reprograms  
10 the cell. It spins it back in time through  
11 demethylation events back to a pluripotent state.  
12 So once you do that, you end up with a dish with a  
13 cell that's almost identical to an embryonic stem  
14 cell.  
15 Now, this reprogramming of any somatic cell  
16 really took the field by surprise. Unlike STAP  
17 technology that's just been discredited  
18 recently -- those of you in the field know a new  
19 technology from Japan -- iPS technology is real,  
20 and many groups have reproduced it. In fact, there  
21 are over a thousand papers now using these induced  
22 pluripotent stem cells. And you can generate them

Page 9

1 from humans. So any human patient or human, you  
2 can generate these pluripotent stem cells from. So  
3 now, essentially, you can all have your own  
4 personalized embryonic stem cell line.  
5 We use these cells for a number of different  
6 tasks. We can also engineer them. They're easy to  
7 engineer because they're pluripotent. So we can  
8 edit genes, put genes in, take genes out. In the  
9 institute, we actually grow them into skin, brain,  
10 nerve, blood, heart, kidney, muscle, lungs,  
11 stomach, liver, and pancreas.  
12 In fact, in testing, we can actually make  
13 whole organoids from these iPS cells, so we've  
14 taken them from Crohn's patients, made them into  
15 iPS cells, skin cells from Crohn's patients, and  
16 then developed them back into whole gut organoids  
17 in the dish. So we can get a Crohn's gut in the  
18 dish and look at things like absorption across  
19 that, the tissues in that gut.  
20 So this has really opened up the whole area  
21 of autologous stem-cell transplantation, allowing  
22 now to have matched cell types from patients'

Page 10

1 transplants.  
2 At Cedars, we're really entering into this  
3 personalized medicine area where disease  
4 stratification will be important. And that means  
5 also we can generate cells from the same patients  
6 for transplants, maybe correct the mutation if  
7 there is a mutation, and generate these patients'  
8 specific lines.  
9 So transplantation is important, but also,  
10 I'll talk about making tissues and organs in the  
11 dish means we can learn about disease mechanisms.  
12 We can actually recreate a lot of diseases now in  
13 the dish with human cells.  
14 Finally, we can make beating cardiomyocytes  
15 from these iPS cells. So if you think about  
16 toxicity screens for drugs in big PhRMA, a lot of  
17 the problems in the drugs occur because they have  
18 problems with arrhythmia and cause arrhythmia in  
19 patients.  
20 Here, we have shown now, and other groups  
21 have shown, you can put drugs on beating  
22 cardiomyocytes from a single patient and show

Page 11

1 whether that patient cardiomyocyte beating will be  
2 affected by that specific drug. So this is  
3 personalized medicine and drug screening that means  
4 you can now screen drugs with side effects on  
5 patients using their cells in a dish.  
6 All of that is coming, so I think you have  
7 to be ready for this kind of revolution that's  
8 happening in that we can now grow tissues and  
9 organs in the dish.  
10 This is my simple slide. The problem is, if  
11 you make these iPS cells incorrectly, you end up  
12 getting false data out of the other end, so rubbish  
13 in, rubbish out. I think the key is to make  
14 quality cells and quality lines, which is why we  
15 have an iPS core facility that qualifies the iPS  
16 production and runs it through a stringent test  
17 before releasing it out to the faculty we have.  
18 But really, the idea of this disease in a  
19 dish, for me, it's a little bit like Avatar. You  
20 can now have your patient in a dish, essentially.  
21 Now, as we get more sophisticated -- we started in  
22 this field back in 2009, and I think it's one of

Page 12

1 the first papers showing we can actually do this.  
2 And this is a disease called spinal muscular  
3 atrophy, a serious disease in children. At six  
4 months, they become floppy, lose all muscle  
5 innovation, so essentially, this is a multineuron  
6 disorder.  
7 We took these patients, made iPS cells from  
8 them, as I just described, from the skin. And then  
9 we pushed them from an iPS state to being neurons.  
10 And in fact, we can make them into specifically the  
11 multineurons that die in these children.  
12 What we showed in this paper was that, up  
13 until about 4 to 6 weeks of differentiation, the  
14 multineurons are okay. But between 6 and 10 weeks,  
15 the neurons from the children started to die,  
16 whereas the neurons from the healthy parent lived.  
17 So this was the first model of a neurological  
18 disease in the dish, and we can play this over and  
19 over again.  
20 Once you get iPS cells, they essentially  
21 mortally reactivate telomerase. You can grow them  
22 forever. And now you have a limitless source of

Page 13

1 pluripotent cells that you can do these  
2 disease-modeling tricks with. And in fact, this  
3 now we have taken on -- I won't show you the  
4 data -- into drug screening, looking for molecules,  
5 which prevent this cell death in the dish, which  
6 mimics the human condition, a very exciting  
7 technology.  
8 We have also done this for Lou Gehrig's  
9 disease, and I'll talk about, in a moment, a more  
10 specific type, a genetic form of Lou Gehrig's. And  
11 we managed to get a disease model here where there  
12 wasn't overt cell death, but we saw physiological  
13 changes and toxicity changes that we could reverse  
14 with anti-sense oligonucleotides in the dish.  
15 So this is almost a patient in the dish  
16 that's now ISIS Pharmaceuticals -- very unfortunate  
17 name, ISIS -- anyway, that ISIS Pharmaceuticals  
18 have taken now, and are taking now, through to  
19 clinical trials based really on a dish model  
20 without even having a transgenic mouse line.  
21 So we are getting to the point where we can  
22 do this in the dish. And finally, we also did one

Page 14

1 of the first molecules of Huntington's disease.  
2 It's a huge consortium, NIH-funded effort, which I  
3 had the dubious task of pulling together. We  
4 didn't want to give any authorship to anyone, so we  
5 called it -- the HD iPS Consortium was the author.  
6 But it had over 70 authors on it and seven  
7 different labs.  
8 But we really showed nice, specific changes  
9 in Huntington's disease neurons that we could model  
10 in the dish. And now, again, NIH in partnership  
11 with a number of companies are using this model to  
12 screen drugs for Huntington's disease, which has  
13 been very difficult to model in mice. In fact,  
14 there were very few models in the mouse of  
15 neurodegenerative disease in humans that are really  
16 efficient. So this was another new model.  
17 We're getting more sophisticated now with  
18 these models. We can put these cells into  
19 different chambers. And, for instance, we put  
20 cells in this one like muscle, and we can put cells  
21 in this one like DRGs and connect them together,  
22 and the spinal cord in this one with microfluidics.

Page 15

1 I think this opens up the opportunity for  
2 modeling human conditions such as pain. We can  
3 isolate DRGs. We can, perhaps, then combine them  
4 with spinal cord cultures and look for models of  
5 neuropathy or other interesting models.  
6 Now, we have access to the cells, we can do  
7 it. And if there are genetic forms of neuropathy,  
8 we could actually have the patients' own cells in  
9 the dish and their DRGs connecting with the spinal  
10 cord.  
11 We have recently taken this to the next  
12 level by collaborating now very strongly with the  
13 Wyss Institute set up by Don Ingber at Harvard with  
14 a \$250 million gift from Wyss, who is a Swiss  
15 entrepreneur. What they are doing is actually  
16 making what they call an organ on a chip. And  
17 DARPA and I think FDA are funding a chunk of this  
18 work.  
19 Again, really, the long-term goal is to  
20 create much more sophisticated organs. And as an  
21 example, this is kind of the size of a memory  
22 stick. They have a microfluidic system where they

Page 16

1 put endothelial cells on one side, in this case,  
2 lung cells on the other side of this membrane.  
3 This microchip essentially is a mini-human  
4 lung. If you go in and blow this up, they're very,  
5 very clever engineering. This is the endothelial  
6 layer. This is the lung layer. They blow air in  
7 along the top and they put blood in along the  
8 bottom. And then these two things pull and stretch  
9 the tissues to simulate breathing.  
10 In fact, the movement in tissue culture is  
11 very important. We haven't really appreciated  
12 this, but when you move the cells, they start  
13 behaving more like real lung endothelium. If you  
14 do this with gut tissue, they start creating  
15 microvilli and producing more like gut tissues, so  
16 movement and mechanical forces are important.  
17 I think, with DARPA funding, they've now put  
18 five of these different organ systems together in  
19 one incubator, so we're trying to reconnect and  
20 mimic the human body through these kind of  
21 technologies. Now, this is very cutting edge.  
22 We're providing now stem cells to move into this

Page 17

1 model. And in partnership with these, we hope to  
2 create some interesting models on a chip of  
3 different organ systems.  
4 I would really love to move this into pain  
5 as soon as we can and work with anybody here who  
6 would like to collaborate. For actually trying to  
7 make some sort of pain-on-a-chip models that we  
8 could think about how systems interact to create  
9 normal models of pain, I know the field needs some  
10 boosting, I think, in certain areas. And this may  
11 be an area where we can really work hard to get  
12 newer models of pain that will be more relevant to  
13 human disease. So that's my in vitro part.  
14 The last part of the talk will be focusing  
15 more on the in vivo side and the experiences we've  
16 had with FDA moving stem cells to the clinic and  
17 trying to think about how these stem cells will be  
18 used.  
19 I think, before I go any further, I'm just  
20 going to acknowledge Steven for the work he used to  
21 do in GDNF and still does perhaps. But these kind  
22 of papers on GDNF and pain were very important a

Page 18

1 few years ago in thinking about how we could use  
2 GDNF to treat pain.  
3 I've been interested in GDNF for many years,  
4 and I'll show you why in a moment, because GDNF is  
5 part of a larger family of molecules, all of which  
6 interact essentially with the RET receptor. They  
7 float along in this little graph. They bind with  
8 the RET receptor. And this family of molecules has  
9 various effects in models of pain and, indeed, in  
10 many neurogenetic diseases.  
11 Once the GFR alpha-2 receptor, neurturin, or  
12 GFR alpha-1 and GDNF are bound. This activates a  
13 whole set of intracellular signaling pathways,  
14 which essentially, I'm interested in cell survival  
15 and neurite outgrowth, but also, through this  
16 mechanism, interact with pain pathways in a  
17 significant way.  
18 A gene is great, but it can't penetrate the  
19 blood-brain barrier very easily. And so it needs  
20 to be infused, many studies infused into the CSF.  
21 That does lead to Limette syndrome and other  
22 issues, non-specific issues that are related to

Page 19

1 GDNF. So actually getting it into the spinal cord  
2 has been very difficult.  
3 Into the brain, as we showed some time ago,  
4 we can get that GDNF into the brain. And we, in  
5 this study, with my long-term friend, Steven Gill,  
6 put together a project with Amgen supplying the  
7 GDNF a few years ago, where we infused GDNF  
8 directly into the brain of patients with  
9 Parkinson's.  
10 One of the first uses for GDNF, because it  
11 protects dopamine neurons, was going to be to treat  
12 Parkinson's disease. They struggled. They put it  
13 in the ventricles. They did not have a paper, but  
14 it caused all sorts of side effects and no real  
15 effect.  
16 That's because to penetrate deep into the  
17 brain tissue, the GDNF really needs to be in the  
18 brain -- and I'll get back to this -- or the spinal  
19 cord because the human spinal cord is so big and  
20 the aqueduct is more or less not there. Getting  
21 GDNF to the motor neurons, I'll mention in a  
22 minute, is different. So we decided to be a little

Page 20

1 gung ho in England and did a small trial of five  
2 patients.  
3 We did see a nice change in the Parkinson's  
4 scale in this paper. And we also saw some PET  
5 changes in the patients that we infused GDNF, where  
6 the dopamine levels seemed to go up where we were  
7 infusing the GDNF, so very encouraging. I could  
8 show you videos of miracle patients, but it was an  
9 open-label trial.  
10 Parkinson's is notorious for false  
11 positives. It's actually a disease that dopamine  
12 neurons are a reward mechanism. So if a patient  
13 thinks they're getting something, they will jump  
14 out of bed in the morning and respond if they  
15 thought they were getting the drug.  
16 So we were very cautious in our  
17 interpretation. This needs to be double blind.  
18 Amgen were less cautious and very excited and ended  
19 up doing a very large double blind trial in 40  
20 patients, which failed. I'm not going to go into  
21 the details. Maybe in the discussion, this could  
22 be a discussion of maybe how not to take

Page 21

1 preliminary trials into the clinic further.  
2 But they use a different catheter. The  
3 catheter they use was an open catheter. We used  
4 convection-enhanced delivery, and it's just a  
5 simple host pipe analogy. If you're trying to get  
6 a drug into the brain and you put it through a very  
7 wide-bore catheter, it's going to reflex back up.  
8 If you put it through a very tight catheter under  
9 pressure, it sprays out. You get convection-  
10 enhanced delivery, which is what we did in our  
11 initial trial.  
12 So that trial failed. We still don't know  
13 if it could work. Steve Gill has just currently  
14 started a new trial in Bristol, in England, using  
15 the same catheter with a new set of patients and  
16 blinded. And so we'll wait and see what happens  
17 because we still don't know if GDNF works with  
18 Parkinson's.  
19 There's always the cumbersome aspect of  
20 having to make the recombinant protein. It's very  
21 expensive. So I was always kind of keen on other  
22 delivery mechanisms. This is where my worlds met,

Page 22

1 the GDNF world and the stem cell world came fused  
2 together. And I thought, if you can make stem  
3 cells secrete growth factors such as GDNF, you get  
4 over the delivery problem. I think maybe the stem  
5 cells will do something useful on their own.  
6 That really got me into the era of stem cell  
7 biology. I started with Parkinson's back in  
8 Cambridge with Anders Bjorklund and others, trying  
9 to get dopamine neurons for Parkinson's, but then  
10 rapidly developed into a different area.  
11 Of course, I've mentioned pluripotent cells.  
12 We could use these for delivering cells into the  
13 brain. And maybe you'll hear in a little bit from  
14 Allan about tunnel suffix cells being used for  
15 this, for interacting with neural circuits.  
16 But the idea usually is, you take these  
17 pluripotent cells, you make them into progenitors,  
18 and then you get your three types of the brain, the  
19 neuron, the oligodendrocyte, or the astrocyte, and  
20 use these for repairing damaged brain tissues.  
21 Now, neurons are fine. The problem is, you  
22 need to really have integration into circuits. And

Page 23

1 again, you might hear more about this from Allan in  
2 a moment.  
3 For ALS, which I'm going to talk about, you  
4 not only need an integration to a circuit, you need  
5 to get that axon of that motor neuron to grow about  
6 three feet out to the muscle. Now, this has been a  
7 huge problem for the field, for motor neuron  
8 replacement.  
9 Again, this is just to reference Allan's  
10 work he'll probably talk about in a moment. There  
11 is some beautiful data on neurons being able to  
12 interact with pathways in the dorsal spinal cord to  
13 modulate pain.  
14 So neurons are important. Oligodendrocytes  
15 is the other cell type we can make. Here, they're  
16 being used now in a trial in New York, Steve  
17 Goldman, for remyelination of multiple sclerosis,  
18 which is because myelination goes and the  
19 oligodendrocytes may remyelinate. And also for  
20 spinal cord injury, remyelination is being used by  
21 Geron, a company in California, that just  
22 reactivated a trial for these cells in spinal cord

Page 24

1 injury.  
2 Here, they're actually trying to remyelinate  
3 areas of the cord, which are demyelinated in the  
4 injury, in hope to get a little bit of function  
5 back in these patients. They're not trying to  
6 restore the whole circuit, the motor neuron circuit  
7 in these spinal cord injury patients. They're just  
8 trying to get a bit of remyelination, which is a  
9 very interesting approach. It would be nice to get  
10 more patients into that trial.  
11 Finally, the astrocyte. Now, this guy is  
12 the poor guy of the brain, but there are three more  
13 astrocytes for every neuron in the brain. When  
14 they looked at Einstein's brain, they chased it all  
15 around the world and finally analyzed it. Guess  
16 what? He had more astrocytes than any other human  
17 known to man, a whole load of astrocytes. Nobody  
18 knows why.  
19 I can tell you, the astrocytes are probably  
20 the most important cell in the brain. They  
21 modulate neurotransmission and may well modulate  
22 pain. They have a whole role of functions. They

Page 25

1 interact with the blood-brain barrier. So I  
2 converted to astrocytes about 10 years ago.  
3 I always tell my students, publish in Glia  
4 Journal now, not Neuron, because in 10 years, Glia  
5 will have a bigger impact factor than Neuron and  
6 it's easier to get it. But nobody takes any notice  
7 on me. We'll just have to wait and see if history  
8 shows that's true.  
9 So the astrocytes are very important. And  
10 they may be sick in certain diseases. We always  
11 focus on the neuron, but in ALS, there's good  
12 evidence that the astrocytes are sick, and I'll get  
13 to that in a second.  
14 They can also be used to deliver drugs.  
15 They are a very nice cell. They migrate in the CNS  
16 and the spinal cord. So if we engineer them to  
17 make drugs, maybe they can help increase  
18 plasticity, increase protection of neurons in the  
19 brain, and of course reduce pain if they are  
20 releasing GDNF. I don't have any data to show this  
21 can happen, but I do have a lot of pre-clinical and  
22 clinical data to suggest it's now possible.

Page 26

1 We haven't really moved so fast with these  
2 pluripotent cells because I think, as Spiderman  
3 once said, "With great power comes great  
4 responsibility." So, yes, these are very powerful  
5 cells, and that means we have to be incredibly  
6 careful about moving to clinical trials because one  
7 tumor in one patient would set the alarm bells off  
8 with the FDA correctly.  
9 So we have to be very cautious. And people  
10 are moving these cells into the clinic, but it's a  
11 lot slower than another source, which is fetal  
12 brain tissue, which has been around for 20, 30  
13 years. People have been growing stem cells and  
14 neural stem cells. And that's really the main  
15 amount of clinical data at the moment, is from  
16 human fetal tissue that's been driven down this  
17 route. Human fetal tissue is not as plastic, but  
18 it is much safer to go into patients.  
19 This is ALS. For those of you that don't  
20 know this disorder, the worst diagnosis you can  
21 get, neurologists can give you, probably is ALS,  
22 Lou Gehrig's disease. Of course, the baseball

Page 27

1 player had it and his batting average actually went  
2 down five years or two years before he actually had  
3 onset of symptoms, so there are things going on in  
4 your body and you're losing motor neurons. You  
5 compensate. And then finally, you go off the edge  
6 and get this horrific disease.  
7 It's actually a complex disease. The motor  
8 neuron system starts up here. When I want to move  
9 my hand, I have to activate upper motor neurons.  
10 These upper motor neurons go all the way down to  
11 the cord. In a human, they actually go all the way  
12 down, about four foot, all the way down to the  
13 spinal cord, where they activate the second motor  
14 neuron, which is called the lower motor neuron.  
15 That's the one that goes out to the muscle, and  
16 that's what enables you to move, so really two  
17 circuits from your brain to your muscle.  
18 In ALS, both of these neurons die. We don't  
19 really understand so much about the upper. I have  
20 a whole story on that, but I don't have time to  
21 tell you. But we do understand quite a bit about  
22 the lower. And in this lower motor neuron in ALS

Page 28

1 patients, you lose about 90 percent of these lower  
2 motor neurons. And probably when you get to  
3 70 percent loss, you start getting paralysis.  
4 So from onset to death, total paralysis, you  
5 don't actually die from ALS. You die because you  
6 decide not to go on a respirator. The total time  
7 is usually three years. That's the average. You  
8 start with muscle fasciculations. It moves from  
9 one arm to the next arm. And then about a month or  
10 two later, it starts in your legs maybe.  
11 Everything becomes paralyzed until, finally,  
12 your lungs paralyze and you have to choose or your  
13 family chooses whether to go on a respirator.  
14 Usually, at that stage, people decide not to in the  
15 U.S.A., about 70 percent of people. Interestingly,  
16 in Japan, 70 percent choose to go on the  
17 respirator. Whether that's to do with healthcare,  
18 family, we don't understand the ethics behind that.  
19 We don't know what causes ALS. It is  
20 completely unknown. There are no drugs. There's  
21 one drug called riluzole, which does very little.  
22 There's no drugs for ALS, death normally within



Page 29

1 three years. It'll happen between 30 and 70 years  
2 old. A majority of cases are sporadic, but like  
3 every other disease, neurological disease, there's  
4 a genetic form like Parkinson's, like Alzheimer's,  
5 all these diseases.  
6 About 10 percent are familial and about  
7 90 percent are sporadic. But the familial types,  
8 this SOD1 gene, if you've over-expressed a mutation  
9 in SOD1, you get a beautiful ALS model in the wrap.  
10 And this has been the real workhorse, where motor  
11 neurons die. And I'll show you that in a second.  
12 There's been varied new genes and one called  
13 C9ORF, which are coming up in ALS, which may now  
14 account for about 50 percent of familial forms now  
15 that turn out to be associated with a C9ORF  
16 mutation, which is also responsible for  
17 frontal-temple dementia. So there's an interesting  
18 link here between Alzheimer's and ALS that's being  
19 actively investigated right now.  
20 We haven't even got a name for this gene  
21 yet, it's so new. I mentioned earlier, we've  
22 modeled now ALS with iPS cells and have shown we

Page 30

1 can reverse some of the pathology caused by that  
2 gene, so that's a lot of excitement. The SOD1 gene  
3 is still the workhorse.  
4 The pain pathways in ALS were of interest to  
5 me as well with regard to GDNF, having come from  
6 out of the Parkinson's field. And you've heard a  
7 lot of this yesterday; maybe yesterday, you've  
8 heard some of this.  
9 But GDNF acts on many different levels in  
10 the spinal cord. Of course, the most interesting  
11 one here is the GFR alpha-1 sensory neuron pathway  
12 that can be modulated to change pain thresholds and  
13 sensitivity, a number of papers by Steve and  
14 colleagues, who have shown the effects of GDNF in  
15 pain modulation.  
16 This is, again, the intact spinal cord with  
17 the motor neuron coming out to the muscle. This is  
18 from an old review we did. And really, in ALS, we  
19 don't know the mechanism, but, clearly, you can  
20 have the mutation, this SOD1 mutation. The  
21 astrocytes change. They become actually toxic and  
22 aggressive.

Page 31

1 The motor neurons retract from the muscle  
2 and the astrocytes also retract from the blood-  
3 brain barrier. So the idea here is to replace the  
4 astrocytes, where they can actually then restore  
5 function, because we're assuming that some of the  
6 cause of ALS is the death or damage to the  
7 astrocytes.  
8 So again, we're putting the cells into the  
9 patients to try and modulate motor neuron function,  
10 and protect the neurons that are still there in the  
11 patients, because we can't replace the whole  
12 circuit. But also, we're going to arm them with  
13 GDNF, so the idea is, GDNF was shown by Chris  
14 Henderson many years ago now to be more active on  
15 motor neurons and survival pathways than dopamine  
16 neurons. So it's a well-known survival pathway for  
17 motor neurons undergoing degeneration. So this is  
18 the concept, genetically modify cells to release  
19 GDNF.  
20 Which cells do we use? I won't go into a  
21 lot of detail, but we've been using cortical cells  
22 from fetal tissue now since the early '90s,

Page 32

1 actually, in Cambridge. And these cells can be  
2 expanded in EGF and FGF. We call them  
3 neurospheres.  
4 We developed this novel chopping method.  
5 Martin Raff once told me that any cell, a single  
6 cell and culture, from a multicellular organism is  
7 abnormal. You should never clone a cell because  
8 cells in multicellular organisms are together.  
9 So I took this to heart 20 years ago after  
10 dinner with Martin. Martin will convince you to do  
11 anything, those of you that know him. And we  
12 developed a new way. I thought, well, how can we  
13 grow cells without passaging them in single cells?  
14 And in fact, it's quite simple.  
15 What you do with these aggregates that grow  
16 spheres is, you take a knife and you chop the  
17 sphere into quarters. If you do that, the cells  
18 within that chunk -- and this is about half a  
19 million cells, 500,000 cells in this  
20 aggregate -- the cells in these little trunks don't  
21 know they've been dissociated. In fact, they  
22 haven't been dissociated because you've chopped it.

Page 33

1 So this chopping method, we've pushed  
2 through now, and I'll show you, all the way to a  
3 GMP facility at City of Hope. And it allows you to  
4 grow these cells very consistently without  
5 dissociation over long periods of time.  
6 We found, using this model, interesting  
7 things with these fetal-derived cells, is that  
8 they're not really stem cells. They're  
9 progenitors. And what we do when we expand them  
10 over a period of weeks and month -- and in fact, up  
11 to 70 doublings -- is that they grow, but they are  
12 changing over time.  
13 First, they make neurons. If you take them,  
14 and expand them, and then you have to differentiate  
15 them on a laminate substrate to make them into  
16 neurons. If you grow them for around 2 to 4  
17 population doublings, they make beautiful large  
18 projection neurons. If you then grow them for  
19 another 4 to 20, they make interneurons when you  
20 differentiate them.  
21 If you push them past 20 passages, they make  
22 nearly exclusively astrocytes, particularly when

Page 34

1 you plant them into the brain. You can still make  
2 them into neurons in the dish, but at this later  
3 phase, they naturally change their ability to make  
4 different types of cells. And it's this that we  
5 capitalized on when we took these cells forward.  
6 There are many companies that use similar  
7 cells, but they're not the same. Neural stem is  
8 actually in the clinical trial, I'll mention in a  
9 moment, Stem Cells, Inc., and Q Therapeutics. And  
10 they just use different variations on a theme, but  
11 none of them use a chopping method. And in the  
12 clinical trials they're doing now, none of them use  
13 engineered cells.  
14 So these late passage cells are important.  
15 And now we've managed to actually grow these cells  
16 in a GMP facility and under GMP conditions. And we  
17 have a paper in JoVE that just came out if you want  
18 to see how you do this  
19 With Patrick Aebischer many years ago, we  
20 started engineering these cells to secrete growth  
21 factors. And what we simply do is add lentivirus,  
22 which permanently engineers the cells, so this is

Page 35

1 integrating to release GDNF. And we've now shown a  
2 number, probably over 20 papers that we can grow  
3 these cells, make them produce GDNF. And they  
4 release GDNF under the PGK promoter consistently  
5 over long periods of time following  
6 transplantation.  
7 So what do we want to do? In ALS, we are  
8 currently attacking here the lower motor neuron.  
9 We have a lot of data on the cervical. We can put  
10 these cells in the cervical part of the central  
11 nervous system, of the central nervous system  
12 spinal cord. We also are looking in the muscle to  
13 try and protect the muscle. And we're also looking  
14 at the upper motor neuron circuit.  
15 So we have a very comprehensive lab focusing  
16 on all of these areas. And I only have time to  
17 show you some examples from the work that we do  
18 now. And I'll focus down here, really, in the  
19 lumbar spinal cord. A lot of this started with a  
20 graduate student in my lab many years ago, Sandy  
21 Klein. And we really worked until today, and still  
22 today, the rat model of ALS. It's a bigger model.

Page 36

1 We can do spinal cord transplants effectively in  
2 that model. And the neurosurgeons like it.  
3 In this model, we get up to 100 days.  
4 Nothing happens. And then around 120 days, these  
5 animals start getting paralysis. The motor neurons  
6 die. Here are the motor neurons alive and they die  
7 over time.  
8 So by 150 days, the rats are completely  
9 paralyzed and they over-express as a mutant form of  
10 SOD1. So this is a fantastic model of a  
11 neurological disease. I think it's one of the best  
12 models of a neurological disease that we have in  
13 the motor neurons die.  
14 The bad thing of this disease is it only  
15 reflects about 3 percent of all ALS patients  
16 because the other 97 percent don't have a mutation  
17 in SOD1. So this is our dilemma with the FDA and  
18 with others. And I'll get to the data in a moment.  
19 Yes. It's an interesting model, but, no, it's not  
20 sporadic ALS. So we don't have a model of sporadic  
21 ALS, which has been a problem for us.  
22 So what we do is -- this is how the rat

Page 37

1 looks at the end. I won't show you the video.  
2 They have come totally paralyzed. And we  
3 [indiscernible] requests, and we like to sacrifice  
4 them when they can't write themselves after  
5 30 seconds. So that's our defined endpoint for  
6 this animal model.  
7       Microsurgery, we put a microsyringe into the  
8 lumbar spinal cord. And actually, Guido Nikkhah  
9 developed this technique in Lund, when I was there  
10 with Anders Bjorklund, very elegant technique with  
11 a micro-syringe because we don't want to damage the  
12 cord. We squirt the cells in a little bit under  
13 pressure as well and they spread out nicely, and  
14 they integrate. And so I'll just show you we can  
15 follow them, actually, with MRI if we SPIO-label  
16 them.  
17       These are five sites in the spinal cord just  
18 three days after grafting. You can see one, two,  
19 three, four, five sites here, one missed here. We  
20 only had four sites with the MRI scan. So we can  
21 MRI-track the transplants.  
22       The labeling is pretty good. In fact, Pablo

Page 38

1 Avalos is a neurosurgeon that we collaborate with.  
2 He's training in my lab. He's fantastic, micron  
3 eyeball for getting these cells in the right place.  
4 It's not trivial, spinal cord surgery. So we do  
5 reasonably good. We do miss the target in the rat  
6 occasionally, but he's got pretty good at  
7 targeting.  
8       This is an old-ish paper now, but it really  
9 shows you the concept. When we put one deposit of  
10 cells in the spinal cord, they can migrate up to  
11 5 millimeters. These are cortical-derived  
12 neuroprogenitors in a human. They migrate. They  
13 like to migrate in the gray matter and the white  
14 matter, but they stop eventually. Here, they stop  
15 and about down here. But they get enough migration  
16 so they can fill an area up.  
17       Every red dot here is a human cell. These  
18 are rats with human cells, so we can use human-  
19 specific markers. We have to use suppression and  
20 we actually use cyclosporine. But the key thing to  
21 see here is in this animal -- and they are  
22 releasing GDNF. So this is human nucleus staining

Page 39

1 for the human cells. And you can see they stay on  
2 one side of the cord. This is GDNF staining. You  
3 can see there, where the cells are, they're  
4 releasing GDNF, only where the cells are.  
5       Here is the survival effect. This is the  
6 same animal. One side doesn't have a transplant.  
7 I think you can see all the motor neurons are  
8 pretty much gone. And here's the transplant side,  
9 and you can see the motor neurons are still alive.  
10       So we have reproduced the survival effect of  
11 GDNF release, the astrocytes are made, and we get  
12 increased survival.  
13       I moved to L.A. I was very worried it  
14 wouldn't work when we repeated this in Los Angeles  
15 versus Wisconsin, and it works in L.A. Here's the  
16 same effect, a good significant increase on the  
17 ipsilateral side, where the GDNF cells are on the  
18 number of motor neurons, shown up here.  
19       Really beautiful transplants. They kind of  
20 crawl in around. They love the degenerating  
21 environment. The stem cells differentiate into  
22 nested positive and some GFAP-positive cell and

Page 40

1 wrap themselves around the dying motor neurons.  
2 These red colors here are the human cells in and  
3 around the dying rat motor neurons, and again,  
4 releasing GDNF along the way.  
5       So this was all great. We were headed for  
6 Nature Medicine, and we got beautiful cell  
7 survival. The problem was, in these animals, we  
8 couldn't get functional recovery. So even though  
9 the cells were surviving, long story short, the  
10 axons were still withdrawing from the muscle. So  
11 we got increased survival, but when we did  
12 behavioral assays, the rat still became paralyzed  
13 at about the same time as a non-transplanted  
14 animal.  
15       So it was very difficult to get a  
16 high profile paper because you want the whole  
17 story, but that was what it was. And we actually  
18 showed that number of innovations were less in the  
19 ALS model, and the GDNF level of the spinal cord  
20 couldn't correct that.  
21       In other studies I don't have time to tell  
22 you and publish now, we've actually put GDNF in the

Page 41

1 muscle at the same time, and we can restore  
2 function with GDNF in the muscle at the same time.  
3 However, we don't know why we can't get full  
4 recovery with astrocytes just in the spinal cord.  
5 But as I mentioned, this is not a model of ALS,  
6 sporadic ALS, and that's our patient target  
7 population.  
8 Also, the timing is difficult in xenografts.  
9 The human cells take a long time to mature, and the  
10 rat goes down with ALS. We have about 15 days from  
11 onset to death. So we have a mismatch here. This  
12 is a real problem.  
13 Should we go forward? I think yes. The  
14 cell protection is very reliable, very robust.  
15 Yes, they don't connect to the muscle still, but  
16 again, in ALS, in patients that don't have the  
17 mutation, we have no idea of the pathology of the  
18 mechanism. And so it could well be that, in ALS,  
19 this technique would also restore function and keep  
20 the cells innervated to the muscle. We'll only  
21 know if we try it in patients.  
22 So this led us to our CIRM. And this is the

Page 42

1 California agency, no accident that I moved to  
2 California. My wife is originally from Los  
3 Angeles. We've been in the frozen tundra of  
4 Wisconsin for 10 years, so that was certainly one  
5 reason. The other was Cedars-Sinai and how  
6 fantastic it is, but the third one is CIRM. They  
7 have \$3 billion for stem cell research, and it has  
8 to go more or less to translational projects. And  
9 there is nowhere else in the world that we could  
10 get a \$17.8 million grant to move from concept  
11 through to patients unless we had a CIRM grant. We  
12 have actually expanded these studies, even since  
13 writing this grant, that we got two years ago.  
14 So we want to expand cells and then replace  
15 astrocytes. The work plan is now -- and I'll  
16 update you a little bit. We've been making these  
17 cells now that I've showed you at City of Hope,  
18 clinical grade. We use the National Gene Bacteria  
19 Labs to make virus, and we are now in the process.  
20 It was two years. It's now one year away from  
21 filing with the FDA, an IND with the FDA, to do  
22 this trial in human patients.

Page 43

1 I'll mention the trial design, but it's  
2 essentially phase 1/2A. I'll show you how we got  
3 around the blinding issue, by doing unilateral  
4 transplants. We're collaborating with NGH for the  
5 data monitoring. And there will be three sites  
6 initially, Cedars-Sinai, Emory, and California  
7 Pacific Medical Center, which are big ALS centers.  
8 For those of you who are in clinical trials  
9 and design, this is the normal procedure. First,  
10 we have to make the cells, clinical-grade cells.  
11 Then we need to do the dose ranging in animals by  
12 distribution and toxicology studies, which are  
13 currently underway. We need to do pig as large  
14 animal, shows safety as well for this product, and  
15 then follow the IND.  
16 Master-cell bank is now in the final phases  
17 of production. We did a research lot at Cedars and  
18 we did some of our pre-clinical dose-ranging  
19 studies with those cells releasing GDNF. And now  
20 we've done a process-comparable lot, and we're in  
21 the middle of the final run of a GMP grade of cells  
22 secreting GDNF, human, that will be compliant with

Page 44

1 FDA regulations for going into humans.  
2 We are willing to share the drug master  
3 files with other groups, so if we were  
4 collaborating with a pain group, we'd be very happy  
5 to share. We're not commercial. I kept away from  
6 patents on this technology, so in order that we can  
7 actually share and collaborate with other groups;  
8 although some aspects of GDNF and stem cells are  
9 under different patents. But my feeling is that  
10 let's get something to work academically, and then  
11 license the technology out to whoever feels they  
12 have the best patents in the areas we're working  
13 in.  
14 So we continue to move ahead academically.  
15 As I'll mention, we're not even scared to change  
16 the cell source from fetal to iPS, if that was the  
17 best way forward, again, avoiding the patent issues  
18 for now.  
19 I'll just mention, this is how we do the  
20 cell production. We end up with about 1,000 vials  
21 of product, which is simply thaw on the day, rinse,  
22 and inject into the patient. We've shown in all

Page 45

1 pre-clinical studies, we can get that product of  
2 GDNF-secreting cells that survive for and inject  
3 into patients.  
4 This is, again, the series of things that we  
5 have been doing. And I won't run through them all,  
6 but we can maybe, in the discussion, see sort of  
7 the process of going from an idea into the clinic.  
8 Just to give you some updates, we do get a nice  
9 dose response in a number of cells. We've done  
10 different doses ranging from 20,000 to  
11 2 million cells in a spinal cord. That's our  
12 maximum feasible dose, nice correlation with cell  
13 survival.  
14 We also get a nice correlation with GDNF  
15 release. Remember, we are putting more cells in,  
16 so we're getting more GDNF. We do ELISAs on the  
17 spinal cord. And we see that the amount of GDNF  
18 correlates with a cell number quite nicely. The  
19 maximum feasible dose here, we get up to high  
20 levels of GDNF production in the spinal cord and  
21 the vehicle. Basically, these cells make no GDNF  
22 on their own. They have to be engineered, and then

Page 46

1 they start secreting it. So they don't produce  
2 endogenous GDNF.  
3 Again, just from the different doses, nice  
4 and consistent graphs, getting obviously to the  
5 endpoint. When we put in the quarter-million cells  
6 per microliter, it's almost a solid transplant at  
7 the core, and the cells don't migrate as much.  
8 Lower doses, we actually get more migration. So  
9 we're actually coming down to a dose between 10,000  
10 and 50,000 cells as being the optimal dose.  
11 We see the same with the dose response,  
12 rather flat curve. We were surprised. Even a low  
13 dose has a threefold increase in the number of  
14 motor neurons surviving in the spinal cord. So  
15 even a little bit of GDNF secreted from these cells  
16 is effective. If you put the cells alone, you get  
17 no effect. We have done this many times. So they  
18 have to be secreting GDNF in order to have this  
19 effect, and we think it's synergistic with the  
20 cells themselves.  
21 In behavioral aspects of the work -- and I  
22 wanted to get to the pain aspect -- we don't see

Page 47

1 any major changes of these doses in the GDNF, but  
2 we did do the pain thresholds and sensitivity.  
3 Given the effects of GDNF on pain, we wanted to  
4 check that it's not having adverse effects on pain.  
5 We did the usual. You guys are very  
6 familiar with this, much more than I am, von Frey,  
7 the Randall-Selitto test, the flinch-jump, just to  
8 see if the GDNF-secreting cells increase pain in  
9 these animals. And we're in the process of  
10 analyzing all this data, but I will show you that  
11 we didn't see any overt changes. They're actually  
12 at time zero. We didn't train these animals in the  
13 von Frey for weeks before. We only did three  
14 tests. We found there was a continual training  
15 effect, where they wanted to withdraw their paw  
16 over time, but then it stabilized.  
17 The bottom line is, with the von Frey, there  
18 was no significant differences between any of the  
19 groups. So we didn't suddenly see a spike in pain  
20 in the maximum feasible dose, which was releasing a  
21 whole lot of GDNF.  
22 We didn't look at the opposite, either. We

Page 48

1 could have been having a pain modulation of  
2 reducing pain, but we haven't used these cells in  
3 any models of pain. We would love to if anybody is  
4 interested in collaborating, to see if we'd get a  
5 reduction. And we're targeting the ventral horn,  
6 not the dorsal, with this study, although some  
7 cells do spread out because you can see into the  
8 dorsal area, which is why we wanted to assess pain.  
9 With the paw pinch, the same, no physical  
10 differences between the groups. There's a lot of  
11 data in here again. Just the bottom line is, we  
12 didn't get a significant difference or increase in  
13 pain using this assay; and finally, the finished  
14 jump, again, no difference in pain.  
15 So we don't think that these cells are  
16 overtly increasing pain. We haven't tested yet  
17 whether they may decrease pain if we used a pain  
18 model. So there are my pain slides. I got them  
19 in. I'm almost done.  
20 So basically, the other issue that we've had  
21 is how to get the cells into the spinal cord. I  
22 think this has been holding the field back a lot.

Page 49

1 Now, Nick Boulis and I developed a frame many years  
2 ago, which is a bit like a Meccano set, but we use  
3 this frame for pigs to show that we can target the  
4 spinal cord nicely here at GDNF-secreted cells, the  
5 pig spinal cord injected using the stereotaxic  
6 device, which you basically bolt onto the pig or  
7 the patient.  
8 It's actually a bit like a Meccano set, so  
9 if you're a neurosurgeon, you love this kind of  
10 stuff. But we wanted to make a simpler device for  
11 surgeries and the cord for either spinal cord  
12 injury, pain-related rhizotomies, et cetera.  
13 We are in the process of developing a  
14 minimally invasive system that has an X-Y arm.  
15 We've done now about 20 pig surgeries using this  
16 device, and it looks to be very successful. And we  
17 will probably be using this device in the clinical  
18 trial next year, but we're still in the process of  
19 finishing up the ISA forms and the requirements of  
20 using this device in a clinical trial, so it's an  
21 interesting device.  
22 Finally, the trial itself -- and this is the

Page 50

1 last point to make -- is an 18-patient trial, but  
2 it's unique in that the nice thing with stem cells  
3 releasing a growth factor is, rather than a pill,  
4 which you have to give to the whole patient, we can  
5 localize the delivery. And this is really unique,  
6 and it's allowing us to do a very interesting trial  
7 design, and that is that we're going to do a  
8 unilateral transplant. So the neurosurgeon will  
9 put the cells either into the right or the left  
10 side of the lumbar spinal cord.  
11 Obviously, in ALS, it's interesting. Even  
12 though the rates are very variable between  
13 patients, if you get ALS in one leg -- and what I  
14 mean by that is in some patients, it may take two  
15 years, and in others, it may take 10 years to  
16 become paralyzed in a leg.  
17 The neurologist will tell you, though, if  
18 you're a fast progressor and it goes fast in one  
19 leg, it will go fast in the other leg. And if  
20 you're a slow progressor, it will go slow in both  
21 legs as well. So in a way, either leg is a  
22 control.

Page 51

1 So the idea of this design, if the IRB  
2 approves it, is we do a unilateral injection, which  
3 would only affect one leg. The neurosurgeon will  
4 decide, based on blood vessels, which side to go  
5 in. The neurologist will be blinded. The patient  
6 will be blinded. So in effect, the patient and the  
7 neurologist won't know which leg had the  
8 transplant. And the beauty is, with paired  
9 statistics, we can get a lot of power because we'll  
10 be analyzing the amount of the rapid decline in  
11 paralysis over time in one leg versus the other.  
12 Using paired statistics, we can actually get  
13 a lot of power in the analysis. In fact, in  
14 18 patients, we can actually get significant  
15 differences in onset. And if we can get a  
16 significance in this small trial, it'll give us a  
17 lot of momentum to move forward to doing cervical  
18 injections and being more ambitious. So that's our  
19 goal.  
20 There are other trials going on in this  
21 area, but really only two main ones. One is  
22 Mazzini in Italy. She's been putting mesenchymal

Page 52

1 cells into the spinal cord of patients. And we're  
2 not quite sure of the mechanism here. They're not  
3 engineered to release GDNF. They may release some  
4 growth factors. In our hands, these cells don't  
5 survive. If you put mesenchymal cells in the  
6 spinal cord, they die within about two weeks. We  
7 have no idea. There's really not a lot of pre-  
8 clinical data to justify this, but they have moved  
9 ahead in Italy.  
10 There's a neural stem company that's based  
11 on a lot of work we did early on with Nick Boulis.  
12 They've done about 30 patients with ALS now.  
13 They're in a phase 2 currently in Michigan. So  
14 they have shown that you can safely put cells in  
15 the spinal cord, which is very good for everybody.  
16 We have our trial at Cedars, which hopefully we  
17 will get off the ground next year. And then  
18 there's Q Therapeutics and Angelo Vescovi in Italy  
19 has done a few patients.  
20 So we are able to, remarkably in humans,  
21 transplant cells into the spinal cord and not make  
22 things worse. These patients, none of them, got

Page 53

1 worse. There are some claims that some of them are  
2 getting better. We're still waiting to see the  
3 clinical outcomes of these trials. But I was so  
4 impressed that you can actually do this. I was  
5 always worried initially, if you put these cells  
6 in, they're going to interrupt spinal cord  
7 function. You're going to get pain. You're going  
8 to get all sorts of symptoms; nothing in any of the  
9 patients. So it's quite remarkable, I think, these  
10 studies.

11 They are also moving onto cervical. They  
12 were so happy with the results, FDA gave them  
13 permission to move to cervical. They have now done  
14 a number of patients in the cervical areas to help  
15 with breathing. And they'll probably be moving  
16 bulbar at some point.

17 We're out here. We just got our funding  
18 from the DoD to inject GDNF into the muscle.  
19 That's kind of interesting as well and a whole  
20 other story. We're using AAV here, gene therapy  
21 approach, not stem cells, to try and restore this  
22 connection that I mentioned was missing. And

Page 54

1 finally, we were working up here. You could  
2 restore the whole function here. If the upper  
3 motor neuron dies, you're still paralyzed. So we  
4 have some ideas up here that I can discuss at the  
5 break.

6 This platform product, I just want to  
7 emphasize, we're also looking at for Huntington's  
8 disease, we're looking at for retinitis pigmentosa,  
9 and macular degeneration. These cells work very  
10 well in that context, and we have a grant from NIH  
11 now to put them in the back of the eye. They seem  
12 to slow down degeneration in that disease.

13 In stroke with Gary Steinberg, and I've got  
14 a joint appointment up there at Stanford, we've  
15 shown these cells can integrate after stroke, and  
16 increase plasticity, and survive. And the  
17 astrocytes are doing something good, not secreting  
18 GDNF in his case, just normal wild-type cortical  
19 derived progenitors.

20 Where I started was in Parkinson's, really  
21 was keen to use these cells to deliver GDNF in  
22 Parkinson's. Why didn't we move ahead? My feeling

Page 55

1 is that the one thing with this technology is, we  
2 can't regulate the GDNF release. If you put the  
3 cells in, they're going to make GDNF for the rest  
4 of that patient's life. And they survive and they  
5 release.

6 So I didn't want to have a situation in four  
7 years with Parkinson's, where the patients are  
8 getting side effects and we couldn't switch off the  
9 GDNF. And that was rather similar to the fetal  
10 transplants, so you know that field. It worked  
11 very well for Parkinson's. Twenty-five percent of  
12 patients got dyskinesia, is they couldn't switch  
13 off, and they had to do pallidotomies.

14 To get over this is possible and for pain as  
15 well. And the way to do it -- and we've been  
16 trying five years to get it to work. We think  
17 we're close now. It's using inducible system. And  
18 the old doxycycline systems weren't that good, and  
19 we tried them. They work in vitro but not in vivo.  
20 We're now coming up with newer ones with Josh  
21 Breunig, a graduate student. We now can regulate  
22 GDNF release very nicely, no doxycycline and

Page 56

1 doxycycline.

2 So if you get doxycycline, you switch on the  
3 secretion of GDNF from the cells. And that, I'd be  
4 happy with in Parkinson's. And then a Parkinson's  
5 patient takes a pill to turn on the GDNF release,  
6 and then turn it off again if they don't want the  
7 GDNF anymore, if you find that it's only useful for  
8 a while or need it for a while.

9 We've got a cool study. We've actually done  
10 this in vivo now, transplanted cells. And the  
11 animals that received dox are lit up here with  
12 luciferase. We attached a luciferin gene, and the  
13 animals that didn't get docs off. So we can  
14 actually, in vivo now, switch on and off the GDNF  
15 secretion.

16 So this is kind of cool. We need to move it  
17 into primate studies and are currently looking at  
18 doing that with this construct. And we'll probably  
19 use this construct for ALS eventually as well.  
20 ALS, I'm not so concerned about because you're  
21 faced with dying after three years. I'd rather  
22 have a side effect in GDNF than not be around

Page 57

1 anymore. But ultimately, we'd love to regulate it  
2 in ALS as well, so I think we want to take this  
3 forward.  
4 I think for pain, it would be kind of  
5 interesting that we can actually now modulate pain;  
6 if we can put these cells in, that we can actually  
7 adjust the GDNF levels. We can put them in, and  
8 turn them on and off at will, and see how that  
9 affects pain and pain thresholds in animals. And I  
10 think that would follow on nicely from Steve's work  
11 and others with GDNF in the future.  
12 So this is all fetal tissue, just to say  
13 that we have this new technique now, where we can,  
14 from iPS cells, get these. We call them  
15 EZ spheres, and in England, that doesn't mean  
16 anything, just E-Zed [ph] spheres. Anyway, good  
17 old USA, that's EZ spheres. It's a bit like  
18 soccer. There are always problems. America seems  
19 to be doing quite well for soccer at the moment,  
20 Britain not so well.  
21 So we make EZ spheres, and those spheres can  
22 then be used for all the things I talked about.

Page 58

1 And the interesting thing is, first of all, we can  
2 make this a GMP process. Again, we use chopping to  
3 make these EZ spheres. We lift them off the iPS,  
4 and EGF, and FGF. But more importantly, we have  
5 generated now, just published a way of going from  
6 an EZ sphere from an iPS culture to something  
7 that's very, very similar to a neural progenitor  
8 cell that I've talked about from fetal tissue.  
9 We worked very hard to find the conditions  
10 where we can generate the progenitor that's almost  
11 identical to fetal cells, but now it comes from  
12 iPS.  
13 So now, we don't need fetal tissue anymore  
14 theoretically. We'd like to try the trial with  
15 fetal tissue, but then behind that, we have a wave  
16 coming where we'd like to try a trial with  
17 iPS-derived cells because that's ethically easier,  
18 and we have more control over the manufacturing of  
19 cells from iPS. So it's a very exciting time in  
20 the field.  
21 These cells, by the way, do -- again,  
22 another little paper we just published. The

Page 59

1 iPS-derived fetal progenitors look identical to the  
2 fetal progenitors, so the iPS cells made into fetal  
3 progenitors look very similar. These are fetal-  
4 derived progenitors that I showed you the pictures  
5 of. And these are now progenitors derived from iPS  
6 cells, induced pluripotent stem cells, and they  
7 look almost identical, the way we've manufactured  
8 them, to the fetal-derived cells. So we're getting  
9 away from the need for fetal tissue as well.  
10 This actually allows for autologous  
11 transplants. And I'm off to a meeting in a couple  
12 of weeks to talk about whether we need that for the  
13 brain. But for the PNS transplants, you could use  
14 the same patient cells. I think you wouldn't have  
15 to use suppression, we hope. There's a whole story  
16 on that as well, but that would maybe help. We  
17 don't need to use fetal tissue or destroy embryos.  
18 The downside is, in the brain, neural  
19 progenitors may not need rejection, may not reject.  
20 There's a blood-brain barrier protection from  
21 rejection. So do we even need to go to the effort  
22 of autologous for CNS transplants? That's a big

Page 60

1 topic of discussion.  
2 If you develop them from an ALS patient,  
3 autologously, maybe the after-science already,  
4 they're going to have the disease. It doesn't look  
5 like it. It looks like, when we reprogram, we wipe  
6 the slate clean, and the disease may come back in  
7 40 years. But if you get another 40 years of a new  
8 astrocyte, that's probably enough.  
9 The regulatory pathway for autologous is  
10 very complex, but if it works, we'll work out the  
11 pathway. If we get something to work, we don't  
12 need suppression. Remember the cost of suppression  
13 in these trials is huge. You have to weigh that  
14 against the cost of manufacturing an autologous  
15 way.  
16 I'm not worried about autologous manufacture  
17 of the cells if they work better than non-  
18 autologous cells. But we will have to do  
19 individual GDNF infections, which will be a pain.  
20 Sorry for the pun. It would be difficult, but we  
21 could do it. It would be expensive, but again, if  
22 it works, we'd do it.



Page 61

1 So I think the first part of it would be  
2 allogeneic iPS-derived cells. So use iPS, but make  
3 an allogeneic line that can be used for many, many  
4 different uses. And that's what we'll probably be  
5 able to have and distribute.

6 The last couple of slide -- I know I'm  
7 running a little long. But I just thought I'd  
8 finish with kind of where we are with this iPS  
9 technology and try to tie those two, clinical side  
10 together with the research side.

11 This is the old Waddington slide of  
12 totipotent cells. Up here, for embryonic stem  
13 cells and now induced pluripotent stem cells that  
14 we can make, they go down into these pathways,  
15 which essentially used to be differentiated  
16 tissues. This may be skin. This may be blood. It  
17 may be bone. So you have this sort of  
18 differentiation. And it used to be thought this  
19 was the end and you couldn't go anywhere, but now  
20 we find you can go back.

21 I thought this was a bit boring, so we  
22 updated this a few years ago. And this is my

Page 62

1 pinball wizard. Who remembers the Who? I'm sure  
2 Steven does. And Shinya Yamanaka is kind of our  
3 pinball wizard for iPS cells.

4 Anyway, my contribution here, Dhruv Sareen  
5 and I did this. It was really the sperm and the  
6 egg, sort of British humor. Anyway, this is the  
7 fertilization part. And now, the pinball goes up.  
8 Up here, you're pluripotent. But when you start  
9 going down and falling down -- and essentially,  
10 embryonic stem cells and iPS cells have an energy.  
11 You've got to keep them pluripotent, which is  
12 similar to the pinball machines. They've got a lot  
13 of energy, inertia up there.

14 Then it differentiates, and differentiation  
15 is going to take off the energy. And they start to  
16 spontaneously differentiate. But you direct them  
17 with growth factors, and with transcription  
18 factors, and here, small flippers, down into the  
19 different lineages, endoderm, mesoderm, ectoderm.  
20 And eventually, they get more and more  
21 differentiated until you flipped them with the  
22 Oct-4 flipper, and they become pluripotent again.

Page 63

1 So that's kind of the idea. And it's  
2 actually not a bad analogy. Sox-2 is another  
3 pluripotent factor. Even within tissues, like the  
4 pancreas, you can have flippers that are smaller  
5 transcription factors that drive from a secretory  
6 cell to a non-secretory cell. And in fact, what  
7 people have found now is, you can take a skin cell,  
8 for instance, and convert it directly into a neuron  
9 by using two sets of transcription factors. You  
10 don't have to go back to a pluripotent state up  
11 here.

12 So it's a very exciting time. And I think  
13 it really tells you about DNA. Most of our DNA is  
14 the same. I'll take out blood cells from  
15 that -- or cancers. Obviously, terminal things  
16 happen to the DNA. But healthy cells, most of the  
17 DNA is probably the same in every cell in your  
18 body. So if you can manipulate it with iPS  
19 technology, you can go back to a pluripotent state.

20 So to conclude, I hope I've given you a lot  
21 of information, but modeling with iPS may be the  
22 biggest thing. If we can model pain in the dish

Page 64

1 with human cells, it's going to be very, very  
2 powerful to test drugs because stem cells can  
3 secrete factors that help motor neurons. If you  
4 combine that technology of stem cells with growth  
5 factors, those are combined stem cell gene therapy.  
6 It's like putting the troops in, but giving them  
7 the weapon, which is GDNF, so they can actually  
8 help modify the area that they go into.

9 Localized delivery of cells is important for  
10 pain, I think, as well. With stem cells, you can  
11 target areas very specifically. You can do that  
12 with genes as well, you'll probably hear in a  
13 moment.

14 The nice thing with stem cells is you don't  
15 have to modify the host cells as you do with gene  
16 therapy. You put in a new cell, which has its own  
17 complications. But at least the host cells remain  
18 the same, and you just engineer the cells that you  
19 put in. And there's pros and cons with both of  
20 those we can discuss at the panel.

21 So the localization, I like. Autologous is  
22 possible now with iPS cells. I still think that

Page 65

1 slow and steady win the day. Rushing into trials  
2 is not the right way to go, and I really appreciate  
3 the interactions we've had with FDA. In fact, I  
4 was in this room, I think, last year with a bunch  
5 of ALS patients trying to lobby the FDA and to  
6 going easy on us, to get trials going.  
7 I think the consensus is FDA is doing a  
8 pretty good job of regulating this field because,  
9 when you mention stem cells, it's like snake oil.  
10 And a lot of companies want to jump in and charge  
11 you \$40,000 for their stem cells, and that's not  
12 good because a lot of those therapies are not  
13 proven.  
14 So I think we're on quite a good balance.  
15 Obviously, we'd like a little more flexibility in  
16 ALS, in a disease where there is nothing with the  
17 FDA to try and help us move trials forward. And I  
18 hope that some outcomes from the discussions we've  
19 had with them will allow this to happen.  
20 So most importantly, this is the team that  
21 worked with me. I get the fun job of giving these  
22 talks. But really, we've had a lot of

Page 66

1 collaborators over the years. I'd particularly  
2 like to thank Jamie Thomson for the original,  
3 getting into iPS cells when I was in Wisconsin.  
4 The cells that we make are really true -- Sareen.  
5 And this huge group now is working on the ALS  
6 project led by Gen Gowing and Brandon Shelly, who  
7 actually just got married, which is rather nice.  
8 The lab, sometimes it works and sometimes doesn't.  
9 So they kind of run the lab together.  
10 So I'll stop there, and I'll thank also our  
11 funders, of course, which is CIRM, the NIH, and  
12 Cedars, and the ALS association. Thanks very much.  
13 (Applause.)  
14 DR. PORRECA: Thank you for the fantastic  
15 job. Questions?  
16 DR. MCMAHON: The ALS studies in the  
17 SOD1 mice, is delivery of GNF from the muscle  
18 sufficient to protect motor neurons as well as  
19 maintain terminals?  
20 DR. SVENDSEN: Yes.  
21 DR. MCMAHON: But if not, why not? Is it  
22 something that you have to overcome additionally in

Page 67

1 the cord?  
2 DR. SVENDSEN: So in the model that we use,  
3 we get -- in all these models, eventually, the rats  
4 succumb to the disease. But GDNF can delay that by  
5 about 20 days if you deliver it to the muscle with  
6 a virus or with actually a cell delivery to the  
7 muscle. So you can delay it about 20 days, but  
8 then they finally succumb, even though they get a  
9 lot of GDNF in the muscle. But early on, yes, the  
10 GDNF is retrogradely taken back to the spinal cord,  
11 and you do get increased protection in the spinal  
12 cord itself.  
13 We're currently doing Jewell transplants,  
14 which is cells secreting GDNF in the spinal cord  
15 along with cells and GDNF in the muscle. And we're  
16 in the middle of those studies, and we're really  
17 hoping that that will extend it maybe 100 days.  
18 We'd love to get to the point where we keep the  
19 animals alive, but I think those combined  
20 therapies, muscle and spinal cord, is going to be  
21 the eventual way of getting a bigger effect.  
22 But let's just go back. In ALS, again, this

Page 68

1 SOD1 model is not sporadic ALS, so we're not sure  
2 of the mechanism in sporadic ALS. Yes.  
3 DR. MCMAHON: [Inaudible – off mic] -- the  
4 increasing toxicity of the astrocytes in the  
5 animal?  
6 DR. SVENDSEN: I think it's a very, very  
7 aggressive model. To get the rats to actually show  
8 the degeneration, they had to put 12 copies of the  
9 CD1 mutant gene in. And the brain is full of  
10 mutant SOD1. So I think the model is so  
11 aggressive --  
12 DR. MCMAHON: Everything's dying.  
13 DR. SVENDSEN: Everything is dying. So you  
14 can get protection, but it's very limited. But I  
15 think, if we do Jewell transplants, if we could get  
16 it to 50 days, that would be a first for the field  
17 because most people manage to get these models out  
18 maybe 20 days.  
19 DR. MCMAHON: But it will be very  
20 attractive to have a therapy that just involved an  
21 intramuscular injection.  
22 DR. SVENDSEN: Much better, much easier.

Page 69

1 And in fact, that trial may get into the clinic  
2 before the spinal cord one if we run into any  
3 difficulties with the spinal cord trial. Yes.  
4 DR. BASBAUM: Thank you. I thoroughly  
5 enjoyed it. One simple question, and then one a  
6 little more complex. Insulin growth factor, there  
7 was obviously that large trial, and it was  
8 controversial. But I was kind of surprised that  
9 you -- have you ever tried this with insulin growth  
10 factor, was the first question, which I thought was  
11 the one that was going to save the motor neurons.  
12 The other question is, you're putting GDNF  
13 in the cord. Is it producing or have you looked to  
14 see if it's producing any sprouting from, say,  
15 afferents or something else that might be RET  
16 positive?  
17 DR. SVENDSEN: So the first question, IGF1,  
18 of course, we followed Feldman's data in the IGF  
19 trial, which failed, unfortunately, in the skin.  
20 IGF-secreting cells, we have made them. They don't  
21 have an effect in this model, in the way that GDNF  
22 does. In fact, we've got a paper coming out, back-

Page 70

1 to-back comparisons of VEGF, IGF1, and GDNF. And  
2 the GDNF wins out on cell survival.  
3 The only one we're interested in is CNTF.  
4 In the old days, CNTF was another molecule that  
5 Aebischer and others promoted. And that seems to  
6 have an effect at the terminal and the -- from the  
7 mouse data, from the motor neuron, and at the  
8 terminal.  
9 So CNTF may sprout, and we're in the middle  
10 of a CNTF-secreting line put into the spinal cord.  
11 But there's nothing dramatic happening even with  
12 CNTF as far as we can see. So I think the answer  
13 is, put in the growth factor in the muscle as well.  
14 DR. MCMAHON: [Inaudible – off mic] -- well,  
15 because of the cachexia.  
16 DR. SVENDSEN: Well, the toxicity of  
17 CNTF -- see, all of these drugs were originally put  
18 into the CSF. And in ALS, many years ago, they  
19 tried them all. And they had side effects of  
20 toxicity, but they never actually did anything in  
21 ALS. But now, we're actually putting the drugs  
22 around the motor neurons, where it's needed. We'll

Page 71

1 see the actual effects, I think, without the side  
2 effects, because we don't get secretion outside of  
3 the area where you want it, which is where the  
4 cells are.  
5 So I think the side effects, to a large  
6 extent, may disappear, unless they're relevant, of  
7 course, to the motor neuron and causing sprouting.  
8 Now, we didn't see aberrant sprouting. We looked  
9 very carefully in the dorsal horn to look for any  
10 GRP-positive fibers. We didn't see anything  
11 massive, and I think it's because that's an intact  
12 system.  
13 So maybe, in an intact system, if you put  
14 GDNF in, you won't see anything. But if we did a  
15 crush or we did something out peripherally, then I  
16 think the GDNF would interact, and maybe Steve can  
17 talk to that as well later in the discussion about  
18 that it's doing there. But we didn't see any overt  
19 sprouting. Most of the GDNF was in the ventral  
20 horn, though, not so much in the dorsal. Yes.  
21 DR. GLORIOSO: That was a lovely talk. What  
22 is the viability of the cells that you implant, and

Page 72

1 what's their immunogenicity?  
2 DR. SVENDSEN: So the viability is around 20  
3 to 30 percent of cells that we put in. So if we  
4 put 50,000 cells in, after 10 days, we'll see  
5 around 10,000 to 20,000 cells absolute. Then they  
6 actually divide. Over the first six weeks, we get  
7 maybe one or two divisions. And then, if you look  
8 at 12 weeks and after 50, the division completely  
9 stops.  
10 So they go in as a progenitor, and they  
11 actually divide a couple of times. So the total  
12 number of cells is almost the same as you put in.  
13 But there's immediate shock and death. And then  
14 they divide a couple of times, and then they  
15 stabilize.  
16 Are they immune? Well, they're immunogenic.  
17 This is xenografted. If you put them in with no  
18 suppression, they will completely reject. The  
19 cyclosporine works, and it actually works very  
20 efficiently in the rat model. We've had huge  
21 problems in pig suppression, which is a whole other  
22 talk. We have had to use very, very severe

Page 73

1 suppression regimes in the pig, try suppression to  
2 get the cells to survive, and now, we've got it.  
3 But the rats seemed fine with not oral  
4 cyclosporine, but IP cyclosporine daily, 50 mgs per  
5 kg. That will keep the cells alive.  
6 That's a whole other topic discussion. We  
7 are planning to do pretty severe immunotherapies,  
8 just like we do for organ transplants, for the  
9 first set of patients, assuming they're going to  
10 have a rejection issue.  
11 But again, the field is very -- there's a  
12 whole meeting at SOMA, actually, in a couple of  
13 weeks, discussing what the best approach for immune  
14 suppression is. Patients don't like the very  
15 strong suppression, the ALS patients, but that's  
16 the way we're going to try first of all, I think,  
17 because we don't know in an allograft what would  
18 happen. There's no model of allogeneic human  
19 transplants, and we can't use mouse.  
20 Yes?  
21 DR. FETELL: This is an exciting talk. I  
22 was wondering, it seemed like, in your early

Page 74

1 experiments, the animals weren't recovering  
2 behaviorally.  
3 DR. SVENDSEN: Correct.  
4 DR. FETELL: So has that changed?  
5 DR. SVENDSEN: Yes, and no with the cells  
6 secreting GDNF. We always get cell survival  
7 effect, but they always retract back from the  
8 muscle a little bit, and we just don't know why.  
9 DR. FETELL: That's why you want to do the  
10 dual transplants, yes.  
11 DR. SVENDSEN: Exactly. That's why I think,  
12 ultimately, if ALS faithfully recapitulates the  
13 SOD1 rat model, which I don't think it will,  
14 because we're using sporadic patients, then we will  
15 need to do GDNF to the muscle. If, as I predict,  
16 ALS is a different mechanism, it's not an SOD1  
17 disease, we don't know.  
18 I mean, it could leave the GDNF alone and  
19 the spinal cord could maintain the functional  
20 connection or it might not. And so we'll only tell  
21 from that first patient trial.  
22 DR. PORRECA: Thanks, Clive. We're running

Page 75

1 a little bit late, and we're going to have more  
2 time for discussion afterwards, so let's move on to  
3 the next lecture.  
4 So it's a pleasure to introduce Allan  
5 Basbaum from UCSF, and Allan is going to continue  
6 in the theme of stem cells, and, in this case, more  
7 focused on pain, a very exciting topic.  
8 Presentation – Allan Basbaum  
9 DR. BASBAUM: Thank you. Thank you very  
10 much. I am learning a lot, which is great. It's  
11 the best thing I can say about any meeting,  
12 especially if you try to put it together with  
13 Frank. We have had a good time.  
14 So I like to begin with this slide. I was  
15 editor-in-chief of Pain for 10 years, and the only  
16 good thing about being editor-in-chief is I got to  
17 pick the covers. So I thought, this is my legacy,  
18 and it's kind of fun. I'll mention a couple of  
19 these as we go through because they are somewhat  
20 relevant.  
21 What I'm going to talk about is the use of  
22 transplants, and you heard this. And it was a

Page 76

1 great segue, so it's a good opportunity. And I'll  
2 talk not only about pain, but also a little bit at  
3 the end about itch. I have nothing to report -- I  
4 wish I did -- that is relevant to this at all.  
5 So this is the kind of problem that we're  
6 dealing with. We're not trying to treat acute  
7 pain. I'm going to speak specifically about  
8 neuropathic pain, which is a pain produced  
9 associated with nerve injury, usually peripheral  
10 nerve injury.  
11 This is a patient with complex regional pain  
12 syndrome. The individual probably has a minor  
13 nerve injury of the limb. And you can see that  
14 there's swelling, there's redness, there's ongoing  
15 pain, and incredible hypersensitivity. There's  
16 also a dystonic posture, which is something that's  
17 characteristic of this particular condition, very  
18 difficult to treat, doesn't respond to the  
19 traditional therapies such as opioids or NSAIDs.  
20 Clearly, something needs to be done.  
21 This is, in a sense, one of my favorite  
22 covers from the journal. It's actually a patient

Page 77

1 who is a sculptor, who generated this sculpture of  
2 his foot, trying to illustrate what his problem is.  
3 And I think it's emotive, pretty dramatic, but it  
4 illustrates what the clinical problem is. And that  
5 is what the clinicians -- I am not a clinician, but  
6 I have seen patients, and it's a clear major unmet  
7 need.  
8 So what are the contributors to neuropathic  
9 pain? And I could give a two-hour lecture on that  
10 quite easily. And there's a whole list. And  
11 everybody has their favorite mechanism. And I just  
12 put a few in here. And I'm not going to go through  
13 them at all because I'm going to focus specifically  
14 on the first, but there are issues of -- Frank  
15 likes to talk about descending facilitation  
16 mechanisms, microglial activation. Yves De Koninck  
17 has published some of the most elegant work on  
18 chloride changes, chloride gradient changes.  
19 Sprouting is another issue, sympathetics.  
20 Let's just talk about GABAergic loss of  
21 inhibition, which I think is one of the major  
22 contributors, particularly the level of the spinal

Page 78

1 cord. And so I'm going to use this diagram in an  
2 illustrative way.  
3 It's a half of a spinal cord. Here is an  
4 afferent fiber. They're all glutamatergic,  
5 provides input to the spinal cord, cell body, and  
6 dorsal root ganglion. Here's the output cells,  
7 that if this were an acute painful stimulus, the  
8 information would go to the brain and the patient  
9 would experience pain or the animal. I threw in a  
10 few inhibitory interneurons. The great majority,  
11 if not all of them, the superficial dorsal horn,  
12 are GABAergic. Some also contain glycine.  
13 They're of course excitatory interneurons,  
14 but that's not the point of the topic today. And  
15 what we know is that when there's a peripheral  
16 nerve injury, usually a partial nerve injury, there  
17 is a loss of inhibition. In this case, I've  
18 illustrated as if there's a loss of, actually, the  
19 interneurons. That's controversial.  
20 There is a paper from Clifford Woolf's group  
21 suggesting that you can lose about 20 percent of  
22 the cells. That's controversial, but what everyone

Page 79

1 agrees is that there is certainly decreased  
2 inhibition. And that could be reflected in  
3 measuring inhibitory potentials in the output  
4 cells, measure levels of the enzyme that  
5 synthesizes GABA. It's decreased.  
6 So there's no question, in many ways, it's a  
7 seizure-like condition, where you have in a  
8 cortex -- in epilepsy, you have a loss of  
9 inhibition. And how you treat that, of course, is  
10 with anticonvulsants.  
11 In this case, the loss of inhibition is  
12 associated with increased ongoing pain because of  
13 spontaneous pain that's not regulated, and  
14 hypersensitivity because the information coming in  
15 intact afferents is now on a hyperexcited spinal  
16 cord.  
17 So how do you treat this? Just as in  
18 epilepsy, the standard treatment would be to use  
19 anticonvulsants. You're trying to increase  
20 inhibition, not necessarily GABA, but you're  
21 basically trying to increase inhibition. And any  
22 time a new anticonvulsant comes on the market, it's

Page 80

1 immediately put into patients with neuropathic pain  
2 because that's the source of the ones that have  
3 been effective so far. And the idea is, hopefully,  
4 that will reduce the pain.  
5 This is a pharmacological approach that  
6 works in some patients. There are clearly many  
7 patients who do not respond, and the amount of  
8 relief they get is less than ideal. I would think  
9 people would agree.  
10 So our approach is really to try to consider  
11 this more of a disease, and where the disease is a  
12 loss of cells or inhibition, and can we actually  
13 fix the problem, fix the neurological problem. And  
14 the approach that we're taking is to use cells,  
15 progenitor cells, from the cortex. Our initial  
16 studies from the embryonic mouse cortex to -- these  
17 are progenitors of GABAergic neurons, transplant  
18 them into spinal cord and see if you will repair  
19 the spinal cord.  
20 The story begins with the work of John  
21 Rubenstein at UCSF. And John is a psychiatrist who  
22 studies the development of cortex. In this case,

Page 81

1 it's a mouse. You're looking at a mouse embryo.  
2 And what John is interested in is what is the  
3 origin of all different cell types in the cerebral  
4 cortex?  
5 The relevant studies for our work was his  
6 demonstration that all of the GABAergic  
7 interneurons, inhibitory interneurons of the  
8 cortex, derive from a region of forebrain. The  
9 medial ganglionic eminence; that's MGE. And the  
10 MGE is the source of all cells in the cerebral  
11 cortex. The cells are born there, and then they  
12 will migrate, and they will turn into GABAergic  
13 interneurons.  
14 It was this paper that turned us on to the  
15 approach. This is a paper in PNAS by Scott  
16 Baraban, along with other colleagues at UCSF. And  
17 what they did is they took mouse, 13.5 embryo. It  
18 was a GAD-GFP mouse, where the enzyme that  
19 synthesizes GABA was linked to GFP so that you  
20 could see green GABA progenitors.  
21 They took those cells. They transplanted  
22 them in that time into a neonatal rat/mouse cortex.

Page 82

1 And then they followed them over time. And what  
2 they found is that the cells would take on  
3 properties, neurochemical properties characteristic  
4 of GABAergic interneurons. And they would look  
5 like interneurons, and they would distribute  
6 through the cortex. In fact, you can put them in  
7 occipital cortex, and they would populate the  
8 entire brain, just as the normal embryonic cells  
9 do.  
10 When I saw this paper, it was interesting,  
11 but what was even more interesting with this paper  
12 is, they also transplanted the cells into a mouse  
13 with a potassium-channel defect. And this mouse  
14 with the potassium-channel defect had high  
15 propensity for seizures, spontaneous seizures.  
16 So they transplanted into the neonatal  
17 mouse, and what they found is that the animal had  
18 significantly reduced seizures. That's what caught  
19 my attention, of course, because, as I said, I see  
20 to some extent that problem of neuropathic pain, at  
21 least at the level of spinal cord, has a loss of  
22 inhibition and a sense of seizure-like condition.

Page 83

1 So I went to John. I like telling this  
2 story because it's true. I asked John, "Do you  
3 think we could try it in spinal cord?" And he  
4 said, "Sure. You can try anything." But he says  
5 he didn't think it would work for a variety of  
6 reasons. Number one, we wanted to transplant it  
7 into adult and, at that time, we were only  
8 transplanting into neonatal. He thought that the  
9 adult might not accept the cells.  
10 Also, these are destined to become cortical  
11 cells, not spinal cord cells, so he says they might  
12 not survive, wrong environment. And then, in the  
13 best case, even if they survived, they will  
14 probably migrate. And like E.T. come home, they'll  
15 actually go back to the cortex, because in the  
16 cortex, they will really move a long way.  
17 So as I say, with that encouragement, we  
18 went ahead and tried it. And Joao Braz, a terrific  
19 fellow, is actually a virologist originally and now  
20 a terrific neurobiologist, tried it, transplanted  
21 into spinal cord. And the reason why I'm here is  
22 that it works.

Page 84

1 So the first question is can these  
2 cells -- now, we're taking from 13.5 embryo.  
3 They're progenitors. They are postmitotic. They  
4 are not yet neurons. And the question is, will  
5 they survive?  
6 So here's the model. Here's our half a  
7 spinal cord again. We have an afferent. And I put  
8 in a few of the output yellow cells and then lots  
9 of inhibitory interneurons. What I told you is  
10 that when there's peripheral nerve injury, either  
11 lose the cells -- and I actually personally think  
12 that the major problem is loss of inhibition, not  
13 so much the cells.  
14 Then we transplant. We started at about  
15 50,000 cells. That's what we start with. We end  
16 up with maybe 10 percent of those cells. And to be  
17 honest, we don't know where they went. They might  
18 end up in CSF. They might get lost. They might  
19 die. We have looked at later for tunnel staining  
20 for apoptosis. We don't see it. It's possible  
21 they die very early on. We're not sure. And so we  
22 transplant them. And the question is, do they

Page 85

1 survive.

2 So this is what a transplant looks like at

3 one day. You get a plug of cells. Here is the

4 spinal cord. Here's the dorsal horn. The ventral

5 horn would be here, the dorsal column, white

6 matter.

7 So here's the plug of cells at one day and

8 this is what it looks like at four weeks. The

9 cells start to migrate, but they don't migrate very

10 far, fortunately. They stay relatively close to

11 the segment. They never go to the opposite side.

12 They certainly don't go up the cervical cord.

13 This is an illustration. It's a sagittal

14 section of spinal cord, caudal. This is the tail

15 and here's the head of the animal. In this case,

16 you can see there were four injections, and what I

17 want to point out is, if you look, you can actually

18 see what looks like axons. And I'll try to

19 convince you that that's in fact what we're seeing.

20 So these things will send out long processes, but

21 the cells pretty much stay near to where you inject

22 it.

Page 86

1 This is what a single cell can look like.

2 They are very happy. They survive. They put out

3 processes. And I will try to convince you that

4 they really are integrated into a circuit.

5 Do they actually synthesize GABA and with an

6 antibody against GABA? Here are some cells. These

7 are the green cells, the progenitors. These are

8 all terminals from the transplanted cells with an

9 antibody against GABA. You can see that there

10 clearly are GABA expressing.

11 Just for the record, we have recently

12 transplanted cells from a VGAT mutant mouse that

13 can't -- it can make GABA, but it can't store it in

14 vesicles. And those cells survive, but they don't

15 work, as you'll see later, but here are examples.

16 I'm just going through this part quickly.

17 This part is published. Do they integrate? And I

18 think this is really perhaps our biggest

19 contribution because one of the major questions

20 that was mentioned earlier is, are you generating a

21 pump or is it actually integrating into the host

22 circuit?

Page 87

1 So what we did in this case was just looking

2 at primary afferents, but we've done it with other

3 host cells. Over the years, we have generated a

4 variety of tracer mice, where we can turn tracers

5 on in the host and ask whether the tracer ends up

6 in the transplanted cell or does the host talk to

7 the trace, to the cells that contain the tracer.

8 The idea is that the question we're asking

9 is does this cell, for example, talk to this cell,

10 and do the transplanted cells talk to the host

11 cells, interneurons and primary afferents, actually

12 make synapses with the transplanted cells, which

13 would suggest that they're really integrated.

14 So, as I said, we can turn a tracer on in

15 the afferent, and it'll jump synapses. It's wheat

16 germ agglutinin. And when we do that, we can

17 look -- and just give you one example. Here's a

18 cell where the tracer was turned on way out here in

19 the dorsal ganglion, and it went into the cord -- a

20 transplant that ends up in a cell in the cord.

21 Here is the transplant. So we turn the

22 cells on, turn the tracer on, in a four-week-old

Page 88

1 transplant. Here are some cells. And if we go to

2 high power, what you can see is here's the cell

3 that receives the tracer from the afferent, jump

4 the synapse, ended up in a post-synaptic cell in

5 the dorsal horn. And you can see terminals from

6 the transplant surrounding the cell.

7 Now, many people will look at this and say,

8 "Wow. There are synapses there," but I was trained

9 as an anatomist, and if you want to see synapses,

10 you take it to the electron-microscopic level,

11 which my colleague, Ida Llewellyn Smith, has now

12 done. She comes to the lab twice a year.

13 Here's an example now, taking these

14 transplanted cells to the EM level. Here is a

15 synapse from the host, talking to a labeled cell

16 body. This is a transplanted cell, so there's

17 clear synapses. Here's a dendrite. People who

18 know this would see this as almost certainly a

19 primary afferent characteristic, scallop-shaped

20 afferent terminal with vesicles. It's pre-synaptic

21 to a host dendrite, pre-synaptic to the

22 transplanted dendrite.

Page 89

1 This is an example of a terminal from the  
2 transplant that is now talking to the host. And  
3 most recently, we've actually done this. This is  
4 kind of tough. I honestly can't see it from here.  
5 There are black dots here, which is gold that marks  
6 GABA, just to illustrate that a labeled  
7 profile -- I hope you can see it, it's very fuzzy  
8 to me -- actually is GABA -- indeed, the terminal  
9 is GABA positive.

10 Here's an example, which was a bit  
11 surprising, that here's a dendrite from the  
12 transplant. And it is actually post-synaptic to a  
13 GABA terminal, which suggests that, in fact,  
14 inhibitory interneurons, host inhibitory  
15 interneurons, are really talking to the transplant.

16 Here's a better example. This is a terminal  
17 that has the gold particles, a gold marking, a  
18 GABAergic host terminal that is pre-synaptic to a  
19 dendrite that is expressing, so that the cell can  
20 even itself come under inhibitory control, so that  
21 it is integrating into the circuit. It receives  
22 afferent input, and it is controllable, if you

Page 90

1 will, by the host. So this transplant is really  
2 well integrated.

3 Is it actually functional? Well, very  
4 recently, with terrific post doc Alex Etlin, we've  
5 been doing sliced physiology in transplanted cells.  
6 Here's an example of a slice of spinal cord from an  
7 eight-week-old mouse. You can see the green cells.  
8 And then he's patching on to the cells. If you  
9 just depolarize them, the cells will fire.

10 Then more recently, using a variety of other  
11 electrical stimulation of attached dorsal route or  
12 more recently using channelrhodopsin that's been  
13 put into afferent fibers, into TRPV1 afferents, you  
14 can stimulate this and show that you can actually  
15 drive the transplant from stimulation of the  
16 afferent.

17 So the host is definitely talking to the  
18 circuit and, most interestingly, recently, we've  
19 made transplants from channelrhodopsin expressing  
20 mice. And then you can just stimulate the entire  
21 slice, stimulate all the cells with light, and you  
22 can show that the host cells are inhibited.

Page 91

1 So these are very functional. Another  
2 functional way of demonstrating this is to take, in  
3 this case, a four-week-old transplanted mouse.  
4 These are the cells. And then stimulate the paw of  
5 the animal and induce Fos expression, just a  
6 genetic marker of activity of populations of  
7 interneurons using antibody against the Fos  
8 protein. And every one of these red dots  
9 represents a nucleus that contains the Fos protein.  
10 And the question is, are they double-labeled? And  
11 the answer is, some of them are.

12 So these cells clearly were driven by  
13 activity in the periphery -- this is in a  
14 four-week-old animal -- and induced Fos in response  
15 to a stimulation of the afferent. So the  
16 transplanted cells are engaged, are integrated, and  
17 can be driven by peripheral activity.

18 The question, of course, is, so what? Can  
19 they actually influence the hypersensitivity that's  
20 characteristic of not only the patient, but more in  
21 the animal models that we use? And we discussed  
22 this yesterday, the complexity of the animal

Page 92

1 models. But we use a model of CRPS, or it's a  
2 model of mechanical hypersensitivity is a better  
3 description. And it's in this case the SNI,  
4 sciatic nerve injury model.

5 In the rodent, the sciatic nerve trifurcates  
6 to three branches. We cut two of the three  
7 branches and then isolate the tibial in this case.  
8 Other people do it by isolating the sural. And  
9 what you find out is, within 24 hours of this  
10 surgical procedure, the animals are extremely  
11 hypersensitive through the intact afferent. And  
12 you look at that and the question is, can the  
13 transplant mitigate the hypersensitivity produced  
14 by this.

15 This is the result that was published. So  
16 what we're plotting here is a normalized threshold  
17 on the Y axis. Both the control animals that  
18 receive either dead cells or medium start off at  
19 100 percent. You injure. Threshold plummets. And  
20 then you transplant. This is all done blind.

21 The person transplanting does not test the  
22 animals. The person testing the animals doesn't



Page 93

1 know which cells have been put in or whether this  
2 is a control. And the code is only broken well  
3 after the experiment is done. The animals are  
4 killed. The cells or the distribution is  
5 monitored.  
6 What you see is that this is the control  
7 animals where the animals are hypersensitive. And  
8 this will last for long periods of time. They  
9 don't recover. And the transplanted animals, over  
10 time, will normalize.  
11 What's interesting is we never see them go  
12 above normal. We have done this many times now.  
13 This is the first example. We have repeated this  
14 in a Taxol model of hypersensitivity using four  
15 repeated injections of Taxol. The animals become  
16 very hypersensitive over all four limbs, but the  
17 transplant will only treat one of the limbs,  
18 wherever you transplant. And it'll treat both  
19 mechanical and heat hypersensitivity, which is  
20 characteristic of that model. So it's not unique  
21 just to this model.  
22 We never see the animals go above. In other

Page 94

1 words, if we take a normal animal and transplant,  
2 the animals don't become analgesic. And this is an  
3 interesting issue, and we can talk about it in  
4 discussion. Our feeling is that the transplant is  
5 reestablishing a level of inhibition. In fact,  
6 we've monitored GAD levels. They normalize. They  
7 never go above normal. And I think this adjustment  
8 is what is critical to the function of the  
9 transplant.  
10 So I will conclude at this point to say  
11 that, because of the nature of the integration, the  
12 extent of integration, this isn't just a transplant  
13 that's providing GABA as in a pump-like fashion. I  
14 do believe that the integration into the circuit  
15 is, in that sense, disease modifying to the extent  
16 that you can call this type of neuropathic pain  
17 condition a disease. Now, the neurological world,  
18 I know, doesn't like that term, but I think it's a  
19 reasonable description of the nature of this  
20 condition.  
21 So where do we go from here? Now, some of  
22 you have seen this, but I just love it. It's very

Page 95

1 San Francisco.  
2 (Laughter.)  
3 DR. BASBAUM: This was a sign that was  
4 outside my daughter's home. There's a psychic that  
5 literally lives there and comes in next door in  
6 this restaurant. But due to unforeseen  
7 circumstances, I'm not sure this is the best  
8 psychic to go to. I love it.  
9 (Laughter.)  
10 DR. BASBAUM: Anyway, as I said, one of the  
11 things we've done is we're using other models, and  
12 it is very effective in the Taxol model. We're  
13 trying some others. The other thing we're  
14 interested in doing from a clinical  
15 perspective -- because we would like to think that  
16 this could be taken forward -- is transplanting  
17 into dorsal ganglion and trigeminal ganglion.  
18 In particular, I'm most interested in  
19 trigeminal ganglion. I'm part of this advisory  
20 board looking at facial pains and particularly  
21 trigeminal neuralgia, which is a miserable  
22 condition. Many of you may be familiar with it.

Page 96

1 This is a characteristic picture of an  
2 individual with trigeminal neuralgia. The actual  
3 etiology is not clear. Some patients respond to  
4 carbamazepine. Some don't. Some will undergo a  
5 pretty drastic surgery, decompression surgery, to  
6 remove a blood vessel that may be affecting the  
7 trigeminal nerve, but in other cases, nothing  
8 works.  
9 It seems plausible that this could be  
10 treated in the same fashion. We are transplanting  
11 it to nucleus caudalis, the dorsal horn of the  
12 medulla, in animal facial pain models. There is no  
13 good model of trigeminal neuralgia, unfortunately,  
14 that I know of in rodents or any animal for that  
15 matter.  
16 But the question is, could you just  
17 transplant into the ganglion? And the answer is  
18 yes. Someone said, why would you? There's no  
19 synapses there. Well, that's true, but there are  
20 receptors. These cells make the receptors that are  
21 targets of GABA. And it's perfectly plausible to  
22 think that you could use this as a clinical target,

Page 97

1 readily accessible from a neurosurgical  
2 perspective.  
3 This is an example of a transplant into the  
4 ganglion. These are green cells. And if you stain  
5 for GFAP, which will mark the satellite cells,  
6 there's no overlap. These are neurons. They  
7 express. They're NeuN positive, which is the same  
8 that we find in the spinal cord. I did mention  
9 that we find about 80 to 85 percent of transplanted  
10 cells are NeuN positive. We don't see oligo or  
11 astrocyte markers in these cells.  
12 This is just to illustrate that we're doing  
13 these studies now with Xiaobing Yu, who is an  
14 anesthesiologist pain fellow in the lab. And it's  
15 been a bear and a mouse, but this is just a mouse  
16 that's been injected, in this case, with dye just  
17 to illustrate here, the trigeminal ganglion. It's  
18 done stereotaxically. This is just to illustrate  
19 it can be done. We're now recording before  
20 transplanting.  
21 These are some green cells that are in the  
22 trigeminal ganglion. It was an early example.

Page 98

1 Xiaobing is getting a lot better at it. So we are  
2 trying to see whether this can be effective in a  
3 variety of animal models of pain.  
4 A little segue, chronic itch. This paper  
5 caught our attention from Sarah Ross, who is at  
6 University of Pittsburgh. When she was working  
7 with Mike Greenberg at Harvard, they found that a  
8 BHLHB5 mutant mouse -- this is a transcription  
9 factor that expresses and is necessary for the  
10 survival of a population of GABAergic interneurons  
11 in the dorsal horn of the spinal cord.  
12 You lose many of them in this mouse. And  
13 what they found is, after about two months, six to  
14 eight weeks, actually, the animals start to develop  
15 this spontaneous syndrome of intense scratching,  
16 terrible scratching.  
17 Their hypothesis is as follows, that under  
18 normal conditions, just like in the pain, it looks  
19 like a gate control theory model, there is an  
20 afferent input that drives the itch circuit like a  
21 pain circuit, but there's also a feet-forward  
22 inhibition that regulates the output of the cell to

Page 99

1 keep it under control. And in this mouse, where  
2 you lose these cells, the animals have heightened  
3 itch.  
4 So I wrote to Sarah and I said, "Do you  
5 think we could try this?" The animals are not  
6 healthy animals, so it was tough, but she sent us  
7 the mice, and we've now -- Joao has now  
8 transplanted, and we have a paper in JCI that's  
9 just been accepted.  
10 This is the spontaneous scratching that  
11 occurs, so the animals are just scratching. And so  
12 somebody is now monitoring. They don't know which  
13 side. The animals will scratch on both sides and  
14 usually have symmetrical scratching. The  
15 individual who is monitoring this doesn't know  
16 where the transplant was. Within two weeks, we  
17 actually start to see a significant decrease. You  
18 can't go much longer because the control animals  
19 have to be euthanized.  
20 This is an example, and it really is  
21 characteristic of an animal in following it out.  
22 This is what it looked like at about six weeks of

Page 100

1 age. The animals were transplanted and follow the  
2 animal out. And then by this time, literally, the  
3 hair is starting to grow back.  
4 When we saw this initially, I called Sarah,  
5 and I said, "Have you ever seen spontaneous  
6 recovery in these animals?" And she's done a lot,  
7 and she's never, absolutely never. They always  
8 have to euthanize them. And we've done this many  
9 times at back of the neck, depending on where the  
10 scratching occurs. It's not predictable. And we  
11 transplant where the scratching -- the part of the  
12 appropriate dermatome spinal segment, and you can  
13 treat these animals.  
14 Finally, this is where we'd like to go. We  
15 actually did try fetal transplants. We went to  
16 16-week and 13-week fetus, tried to get  
17 MGE-equivalent cells from human fetus, and we  
18 transplanted. And the cells survive in the mouse.  
19 These are in SCID mice, but we never got neurons.  
20 All we got was oligos, beautiful oligos, lots of  
21 them. And I'd like to learn more about that  
22 because I'm not a stem cell person, but we're

Page 101

1 getting these cells from our stem cell folks at  
2 UCSF.  
3 But most recently, we have been using human  
4 embryonic stem cells that are modified to become  
5 GABAergic neurons. And the answer is that they  
6 work. They will survive. This is now transplanted  
7 to SCID mice. This is now six months  
8 post-transplant. These are markers. I noticed the  
9 similar markers. It's a stem cell marker to  
10 identify the cells. This just illustrates  
11 doublecortin and Ki-67 will mark cells that are  
12 dividing, and we don't see that. By six months, we  
13 no longer see that these are dividing.  
14 We don't see tumors. This is, as you said,  
15 one of the big concerns. We have not seen tumors  
16 in the mice. So the cells, they become, they take,  
17 they grow, they move a lot more than the medial  
18 ganglionic eminent cells; don't go to the other  
19 side. They'll go to white matter. We don't see  
20 them going to cervical cord, but they are  
21 definitely moving more. And by six months, they  
22 take on -- this is staining for GABA, bunches of

Page 102

1 cells. We've got NPY-positive cells, different  
2 co-markers. So the cells do take on the properties  
3 of the inhibitory interneurons, a smaller  
4 percentage than the MGE cells for sure.  
5 I'm not going to show the data, but I'll  
6 just tell you, can it do anything in that same  
7 model of nerve injury. And the answer is yes.  
8 After six months, it takes a long time. We can get  
9 about 50 percent recovery of threshold. We never  
10 get anything like the MGE cells, where we can  
11 return it back to normal.  
12 We get about 50 percent recovery, but it  
13 takes a very long time. And the real reason,  
14 unfortunately -- well, not unfortunately; it's the  
15 nature of the cells, my understanding. And it's a  
16 fact; we tried it. If you transplant the cells  
17 after they've been differentiated, if you will, or  
18 driven into a GABAergic phenotype in vitro, and  
19 then transplant them, they don't take.  
20 So you need to feed them, and then  
21 transplant them, and then keep your fingers, and it  
22 takes a long time. So this is one of the

Page 103

1 limitations when you're working with mice.  
2 I assume the stem cell people are going to  
3 work out ways to get these things to grow a little  
4 bit better. We are also doing the same approach  
5 you described of using Lenti and doing this mostly  
6 in the MGE cells to turn different elements,  
7 different things on in the transplanted cells.  
8 For example, enkephalin, to release  
9 enkephalin in a circuit fashion rather than pouring  
10 it on the spinal cord, we think that we can enhance  
11 the utility of the GABAergic component by having  
12 the cells generate something else. So we're  
13 excited, and this is where we are continuing. We  
14 would love to be able to see this taken all the  
15 way. There's a lot of hurdles before. But that's  
16 where we are now.  
17 In conclusion, there are a lot of things  
18 that cause neuropathic pain, but I think thinking  
19 of it as a neurological disease that can be  
20 repaired is something to consider. And with that,  
21 I'll introduce you. It's not as cute as your  
22 slide, but I have a lot of cute people in the lab.

Page 104

1 For the record, what this says here is,  
2 "Pain is in the brain," and that's because Frank is  
3 sitting in the front row. And I know that pain is  
4 in the brain. And this is Joao Braz, who did most  
5 of the transplant work. Alex did the slice  
6 physiology. Xidao did a lot of the behavior, the  
7 blind behavior work. And Reza Sharif-Naeini, who  
8 is now on the faculty at McGill, did some of the  
9 early work with Joao. Ida did the electron  
10 microscopy. And most recently, I've been working  
11 with the stem cell folks to try to get the  
12 embryonic stem cells to work.  
13 We do want to move to iPS cells. We're not  
14 there yet. Thanks very much.  
15 (Applause.)  
16 DR. PORRECA: Thanks, Allan. Very exciting.  
17 Any questions? Andrew?  
18 DR. RICE: Thank you. As I was listening, I  
19 was just wondering what kind of clinical trials we  
20 would think about in the ethos of this meeting.  
21 And you've partially already mentioned this in your  
22 reference to other polyneuropathies, but I was

Page 105

1 wondering, we're increasingly recognizing the  
2 heterogeneity of neuropathic pain presentations in  
3 the clinic and even now in animal models. And you  
4 referred to some of the other animal models. But  
5 many of the polyneuropathies, diabetes, HIV, drug-  
6 induced, are characterized largely by sensory loss,  
7 the diabetic neuropathies in the clinic. And the  
8 central core of this is the loss of GABAergic cells  
9 in the DRG associated, I presume.

10 DR. BASBAUM: In the cord.

11 DR. RICE: It's in the cord, with traumatic  
12 nerve injury. And I just wondered to what extent  
13 that is shared with the other models you've  
14 mentioned like the trigeminal ganglion? And  
15 obviously, it's not the cord, but also the Taxol  
16 neuropathies. Do you see a similar loss of  
17 GABAergic cells?

18 DR. BASBAUM: No. No. In the case of the  
19 Taxol, we don't, but what you do see is a decreased  
20 GAD function. We have never seen loss of cells. I  
21 should point that out. The literature has reported  
22 loss of cells. But you do see decreased GAD in

Page 106

1 these models. It's true that most of the models we  
2 use are traumatic.

3 Now, one of the key questions is, if we're  
4 right in our hypothesis that what the transplants  
5 are doing is readjusting, normalizing the level of  
6 inhibition, then I think it would be effective  
7 regardless. You don't have to lose cells. For  
8 whatever reason, you get decreased inhibitory  
9 regulation, and the idea is to re-establish that.

10 There's a variety of other interesting  
11 aspects. These cells retain their cortical  
12 phenotype. So cortical GABAergic cells have a  
13 different neurochemistry from those in the cord.  
14 And most characteristic is -- somatostatin is  
15 characteristic of many of the cells, and the cord,  
16 somatostatin, doesn't co-occur. In fact, it's in a  
17 different population. It's not in GABA cells.  
18 These stay -- many of them are still somatostatin  
19 positive.

20 So the environment is not driving them into  
21 a spinal cord phenotype. They're just sitting  
22 there. And by the way, the electron microscopy

Page 107

1 changes over time. Ida has looked at four weeks  
2 and looked a six months. The number of axial  
3 somatic synapses at four weeks is much greater than  
4 at six months.

5 So the integration is occurring over time.  
6 The system is unbelievably plastic. And my  
7 take-home lesson is the system is remarkably  
8 plastic. And I really do believe it's adjusting to  
9 a level of inhibition and that it can be useful  
10 under any circumstances.

11 In the same case, why does gabapentin work,  
12 at least to some extent, in so many of these  
13 heterogeneous polyneuropathies and conditions, even  
14 though they have a different etiology, adjusting  
15 the level of inhibition, can help.

16 DR. MCMAHON: That's very interesting from  
17 lots of points of view. One question is whether  
18 the effects are specific on pain or whether you  
19 have effects on locomotion, where the animals are  
20 kind of --

21 DR. BASBAUM: We've popped them on a  
22 rotarod, and it doesn't make any difference. Now,

Page 108

1 we haven't targeted ventral horn. And once in a  
2 while, you do miss, but Joao is getting pretty good  
3 at making those injections to dorsal horn. So if  
4 we target specifically a ventral horn, would it  
5 make a difference? I don't know.

6 DR. MCMAHON: My main interest is what the  
7 mechanism is. And so you raised the question of  
8 whether it's just passage secretion or whether it's  
9 a neuronal integration. Some of your early  
10 behavioral data, so in both the itch and in the  
11 spared nerve injury, you're seeing effects from a  
12 few days or a couple of weeks.

13 I assume, at that stage, there wouldn't have  
14 been a lot of integration then. So early on, they  
15 may be pump-like --

16 DR. BASBAUM: Good point.

17 DR. MCMAHON: -- as you said, with time, it  
18 looks as if they become more stabilized. But that  
19 is critical because maybe you could just use some  
20 astrocytes and make them make GABA. And we'd have  
21 one quality-controlled line and save everyone  
22 making the weak cells.

Page 109

1 DR. BASBAUM: Absolutely, yes.  
2 DR. MCMAHON: So you haven't tried, either,  
3 to do that, to deliver GABA from a non-excitabile  
4 cell or maybe I was wondering whether there was an  
5 easy way of making neurons non-excitabile so that  
6 you could turn them into pump-only for a direct  
7 comparison.  
8 DR. BASBAUM: If I wanted to do that  
9 experiment. I really don't want to do that  
10 experiment because my philosophy is that the  
11 pump-only would be equivalent to administering the  
12 drug intrathecally, which is associated with side  
13 effects.  
14 DR. MCMAHON: Yes.  
15 DR. BASBAUM: And I think the reason why the  
16 therapeutic window might be better with this is  
17 that it is being delivered in a circuit fashion.  
18 Remember when I said, if we transplant from the  
19 VGAT mutants, the cells take beautifully, but they  
20 don't do anything. So you need GABA for sure to  
21 come out of these cells.  
22 I don't know. I could be wrong. A pump

Page 110

1 might work just fine, but somehow it seems to me  
2 that the integration is key.  
3 DR. MCMAHON: In the last talk, though, we  
4 heard that the location might be as important as  
5 integration. Just having the neurons in the  
6 neutrophil delivering loci, that may overcome.  
7 DR. BASBAUM: Fair enough.  
8 DR. MCMAHON: It's obviously just an  
9 interesting question to know what the contribution  
10 is from these distinct mechanisms.  
11 DR. BASBAUM: No. I completely agree with  
12 you, but I don't have CERN money.  
13 (Laughter.)  
14 DR. BASBAUM: No. We actually applied for  
15 it and didn't get it because we were too late. We  
16 got into this too late, and now, all they care  
17 about is they want a therapy. No. They were  
18 very -- they said this is really cool, but as long  
19 as you're using mice, we're not interested,  
20 seriously.  
21 DR. PORRECA: Allan, just a follow-up  
22 question, you were talking about different types of

Page 111

1 cells, some of which have this GABA phenotype, as  
2 you are presented, but how do you know the effect  
3 is from GABA? The cells may be releasing other  
4 factors --  
5 DR. BASBAUM: No. Sure. No, completely  
6 true. Did you review our grant?  
7 (Laughter.)  
8 DR. BASBAUM: That was one of the questions.  
9 The other one, you've got to do physiology. You've  
10 got to do ultrastructures, so that's why we're  
11 doing it all.  
12 No. It's a very important question. That's  
13 why we did the VGAT mutant mice, where they are  
14 identical cells, except they can't store GABA. So  
15 they have no GABA. These animals will not survive  
16 because they are just born and they'd seize all the  
17 time. But we're taking embryonic cells, so we can  
18 take from the 13.5 embryo, and they don't work,  
19 basically. The cells integrate beautifully. They  
20 don't do anything.  
21 So I think that it looks pretty good that  
22 GABA is at least necessary. It may not be

Page 112

1 sufficient. We don't know that.  
2 Now it's my pleasure to introduce Joe  
3 Glorioso, who is not only a terrific scientist, but  
4 a colleague and friend. Joe trained, I think,  
5 originally in Louisiana State, and then went to  
6 Michigan, and is now -- well, he was professor and  
7 chair of -- not microbiology --  
8 DR. GLORIOSO: Molecular genetics.  
9 DR. BASBAUM: -- molecular genetics.  
10 DR. GLORIOSO: Twenty years is enough.  
11 DR. BASBAUM: Twenty years is enough. I'm  
12 chair of the department. I've been 15. I saw it,  
13 and I got worried when I saw he was 20 years -- at  
14 University of Pittsburgh.  
15 Joe is really one of the leaders, if not  
16 "the" leader, in the development of gene therapy  
17 approaches, particularly using viral vectors both  
18 in animal models and definitely an interest in  
19 taking this to humans. And the work is terrific,  
20 and I look forward to hearing his story. Welcome.  
21 Presentation -- Joseph Glorioso  
22 DR. GLORIOSO: Thank you for that kind

Page 113

1 introduction.

2 Well, I have to say, it's been a great  
3 meeting. I really have learned some interesting  
4 things. So I'm pleased to have the opportunity to  
5 tell you about some of the new work that we're  
6 doing.

7 I have two disclosures to make. One of  
8 those is I'm a founding partner of Switch Bio,  
9 which is a company we just began, and also  
10 NuvoVec srl, which is an Italian company.

11 So this is the important biology of herpes  
12 simplex, and this is why we got into this, to treat  
13 pain. The virus naturally is neurotropic, meaning  
14 that it only establishes latency in sensory  
15 neurons. It can also establish latency in the  
16 brain, but it can't reactivate it. It usually  
17 doesn't reactivate.

18 The virus is transmitted by direct contact  
19 with the lesion, and it goes through the  
20 replication cycle. New particles are made, which,  
21 as you can see, they are transported retrogradely  
22 down axons. And they can go very long distance,

Page 114

1 and it's a very efficient process. The virus  
2 establishes latency in the nerve cell body.

3 The lytic genes are inactivated and, rather,  
4 you have an activation of this latency-associated  
5 transcript, which is a large messenger RNA that's  
6 non-coding. There is an interesting intron that's  
7 spliced from this, that's highly stable. It's  
8 associated with the nucleolus. You can rarely  
9 detect it by in situ hybridization.

10 This is the hallmark of latency. The  
11 natural virus can reactivate usually as a result of  
12 nerve cell damage. In rare cases, it can go back  
13 and cause encephalitis. For doing gene transfer to  
14 sensory nerves, we want to use a virus that's  
15 highly defective.

16 It can establish a latent light condition  
17 and serve as a platform for expression of trans  
18 genes. The virus cannot reactivate or cause lytic  
19 infection. Again, you can detect gene products in  
20 the nerve cell body.

21 So what I'm going to focus on today is  
22 treatment of post-herpetic neuralgia as a good

Page 115

1 target, we think, for this kind of therapy. The  
2 post-herpetic neuralgia is caused by varicella  
3 zoster virus. It's the virus that causes  
4 chickenpox, usually occurs at an early age.

5 It establishes latency in sensory nerves  
6 just like HSV-1 and HSV-2, usually as people age.  
7 There's a recurrence of about 20 percent where the  
8 virus reactivates and causes herpes zoster,  
9 referred to as shingles. And this is an important  
10 problem because it causes pain.

11 Ninety percent of these patients are given  
12 pain meds. About 30 percent have a long-lasting or  
13 chronic pain lasting beyond 90 days, and this is  
14 referred to as PHN. There is an estimated about  
15 200,000 new cases in the U.S. every year, and the  
16 principal complaint is allodynia.

17 So one of the tricky things about doing pain  
18 modeling research is to find a good model. This is  
19 the one that's available. It was a model  
20 established by Fleetwood Walker in 1999. What he  
21 did was injected VZV-infected cells. This is the  
22 vaccine strain P-Oka. The cell lines is MeWo.

Page 116

1 They injected it in the footpad of rats.

2 The reason we used infected cells as opposed  
3 to virus is because these viruses are very hard to  
4 purify from infected cells, and everybody in the  
5 field that works with VZV uses infected cells. And  
6 we looked for mechanical allodynia and pain  
7 responses due to heat.

8 So this is the general approach, that we  
9 injected infected cells about 2 times 10 to the 5th  
10 into the footpad and into the right-hind paw, and  
11 then we measured pain responses over a period of  
12 about nine weeks.

13 So these animals both develop mechanical  
14 allodynias. You can see here as well as in a paw  
15 withdrawal latency model, latency response. They  
16 also developed thermal hyperalgesia.

17 So in addition, we can see that the virus  
18 enters by leaving these infected cells, going up by  
19 axonal transport to the nerve cell bodies. You can  
20 detect viral antigens. And for example, this is an  
21 antibody specific for one of the metered early  
22 proteins, 62, and you don't see this with

Page 117

1 uninfected cells.  
2       So one of the first set of experiments we  
3 did was to use preproenkephalin as an analgesic.  
4 We have a lot of experience with that in the first  
5 of these experiments back in the mid '90s.  
6 Preproenkephalin, as you know, is processed into  
7 these opiate peptides, and they combine to both  
8 delta and mu receptors.  
9       So this is the general approach, that we  
10 inject virus into the skin. And the virus can  
11 enter these nerve terminals, both the C fiber and  
12 A delta fibers, be transported back to the nerve  
13 cell body. And here, the virus can produce in the  
14 dorsal horn and the spinal cord enkephalin, as  
15 shown here. Enkephalin then can bind back to its  
16 receptors both in the primary afferent as well as  
17 the second-order neurons.  
18       Enkephalin is also made by descending  
19 neurons as well as GABA, and this also can be  
20 analgesic. However, you can't control when these  
21 products are going to be made in natural  
22 occurrences. So the idea is to produce this

Page 118

1 product locally and treat pain at its source.  
2       So this is the general approach, to treat  
3 PHN with enkephalin vectors. And what happens here  
4 is we inject the infected cells. Several weeks  
5 later, the animals begin to develop pain responses.  
6 And we inject the vector about two weeks after the  
7 primary infection. And the virus either expresses  
8 enkephalin or just a reporter gene.  
9       So this is an example of the kind of data  
10 you get with mechanical allodynia, that the animals  
11 initially, if they are injected just with cells  
12 without virus infection or plus the control virus,  
13 you don't get any allodynic response. However, if  
14 you inject animals with the pOka-infected cells  
15 with PBS or control virus, you get this very strong  
16 allodynic response, which you can reverse by  
17 infection and expression of enkephalin.  
18       Now, we also ask the question whether you  
19 can preempt this response, thinking that maybe even  
20 in a prodromal situation, you could treat patients.  
21 And so we injected the vector, making enkephalin  
22 our control. And a week later, we injected the

Page 119

1 cells that were going to cause pain in these  
2 animals.  
3       You can indeed block pain responses. So for  
4 example, in animals that got enkephalin-producing  
5 virus plus the pOka-infected cells, we didn't see  
6 any evidence of the development of allodynia.  
7       So while this looks pretty good, there are  
8 some limitations, we feel, in this approach. And  
9 that is, enkephalin therapy is transient. And if  
10 you want to keep it on longer, you have to do  
11 repeat dosing, which I think over months is not  
12 going to be feasible in patients.  
13       You can achieve long-term expression of  
14 enkephalin by using the latency promoter system,  
15 but this might cause tolerance or some other  
16 unwanted side effects. And how do you turn off  
17 this therapy if you no longer need it? So our view  
18 was that we needed a solution, which involved some  
19 kind of regulated gene therapy, and that's what I'm  
20 going to talk about.  
21       So a few years ago, we had the idea that if  
22 you used a chloride channel -- in this case, it's

Page 120

1 the glycine receptor, which is not found in sensory  
2 nerves, it's only found in the central nervous  
3 system -- we might be able to induce silencing in  
4 these cells by delivery of glycine. And it turns  
5 out you can only use the alpha subunit because this  
6 has turned out to be pretty fortuitous because this  
7 product is spread up and down the axon. Rather  
8 than hyper-polarization, we think probably it's  
9 silencing the neurons by depolarizing the cells,  
10 and up and down the axon, blocking the development  
11 of an action potential.  
12       We published some experiments fairly  
13 recently in which we used the glycine receptor, the  
14 alpha subunit, and injected glycine into these  
15 animals, and we could in fact silence these neurons  
16 and block pain in a lot of different kinds of  
17 models.  
18       We tried this also in a bladder model, which  
19 worked very well, and we gave the glycine  
20 systemically. However, the treatment window was  
21 very narrow. In other words, as you increase the  
22 amount of glycine being given -- we inject their

Page 121

1 IP, for example -- you begin to see effects in the  
2 central nervous system, so we needed some solution  
3 to that problem.  
4 So about that same time, Joe Lynch's lab in  
5 Australia published this nice study where he made  
6 mutations in the glycine receptor that made it  
7 resistant to glycine activation, but rather was  
8 strongly activated by the drug ivermectin, which is  
9 an antihelminthic drug that's been approved for  
10 patient use as well as in animals for a number of  
11 years.  
12 So we tested this system, and what we did is  
13 we injected either the normal receptor that's  
14 responsive to glycine or the mutant receptor that  
15 was responsive to ivermectin, and we tested this in  
16 a standard pain model.  
17 What you see here is in a paw withdrawal  
18 latency test, this is what the average responses  
19 are like, that if you inject the virus that's  
20 making this a normal receptor, it's highly  
21 responsive to glycine and you change for paw  
22 withdrawal latency. But it's not responsive to

Page 122

1 ivermectin, and we did these experiments in two and  
2 three weeks.  
3 The opposite was true if you inject a vector  
4 that's making the mutant receptor, that it's highly  
5 responsive to ivermectin and not responsive to  
6 glycine. We saw this. We got this data about 10  
7 months ago, and we were very excited because this,  
8 for the first time, would allow us to target a  
9 specific receptor, and we could give this drug  
10 systemically.  
11 So we tested this in a rat PHN model. And  
12 what we did, again, was, we injected cells. And  
13 after two weeks, we injected the vector either  
14 making the normal glycine receptor or the mutant  
15 glycine receptor. And I'm just going to show you  
16 the data with the mutant.  
17 So in this experiment, this is mechanical  
18 allodynia here and thermal hyperalgesia here. And  
19 what we did is we injected either a control vector  
20 that made just GFP, or a vector that made the  
21 wild-type glycine receptor, or the mutant glycine  
22 receptor. And here we got a strong response,

Page 123

1 reversing mechanical allodynia by injecting the  
2 ivermectin.  
3 We did a dosing experiment, so when we got  
4 down, even as far down as 10 nanomolar, we were  
5 able to show an effect. And it turns out that if  
6 you use the glycine receptor, you can see effects  
7 out to 25 millimolars. So this is a very sensitive  
8 way to activate this receptor.  
9 The experiment was done by injecting the  
10 drug into the footpad, where we injected the virus.  
11 And we're going to test very soon systemic delivery  
12 and see how well that works. We've got similar  
13 results with the thermal responses.  
14 So we want to further develop this regulated  
15 nerve silencing because the use of this mutant  
16 glycine receptor is attractive. However, what  
17 about off-target effects? And since we're  
18 silencing every neuron where this product is being  
19 expressed, if it's expressed in neurons where we  
20 don't want silencing, such as neurons involving  
21 touch or proprioception, then we want to avoid  
22 those neurons. And so we started working with

Page 124

1 targeting viruses to the peripheral nervous system.  
2 Now, there are a couple of ways that we are  
3 using this targeting strategy, and these are the  
4 two classes or subpopulations of neurons that we're  
5 after. Unmyelinated C fibers are most commonly  
6 thought of as being involved in chronic pain  
7 responses. And these can either be peptidergic or  
8 non-peptidergic.  
9 So we used promoters that would give us  
10 transcriptional silencing, either for example N of  
11 200, or the NPY promoter, or TRPV1, CGRP, and so  
12 on, and see if we can get expression of the  
13 receptor in the appropriate cell population.  
14 Now, we have also done a lot of work with  
15 targeting the virus, which I won't have time to  
16 discuss. It's a pretty involved story. But if you  
17 knock out the virus's ability to recognize its  
18 cognate receptors by mutagenesis of a protein  
19 called glycoprotein D and fuse it with a pre-pro  
20 NGF or GDNF, you can target it to these two  
21 different receptors efficiently. So we haven't  
22 tested the combination of transcriptional and



Page 125

1 transductional targeting, but I think we're going  
2 to try that in the near term.  
3       So this is the experiment where we  
4 introduced these recombinant promoters into the  
5 virus genome. In between these two insulator are  
6 two boundary elements that the virus naturally has.  
7 And we remove the latency promoter and replaced it  
8 with a tissue-specific promoter driving a  
9 transgene, mCherry. And this is just the series of  
10 promoters that I just told you about.  
11       So I'm going to show you just examples of  
12 two of these. This is the GCRP promoter driving  
13 mCherry. This was done in a bladder model. And  
14 this particular ganglion, we stained with an  
15 antibody to GCRP, and we got about 65 positive  
16 cells.  
17       Viruses that infected these cells that were  
18 expressing mCherry, using the GCRP promoter, found  
19 out that was pretty good overlap between those  
20 positive cells and those cells which were  
21 activating mCherry by this tissue-specific  
22 promoter. To use another promoter, which is

Page 126

1 non-specific, such as CMV, you get good expression,  
2 but very little overlap between the two types of  
3 cells.  
4       This is an example with the TRPV1 promoter  
5 driving mCherry. This is in the rat footpad model.  
6 These are the numbers of TRPV1-positive cells that  
7 we saw. About 40 of these were M-cherry specific.  
8 They were driven by the TRPV1 promoter. And again,  
9 there was pretty good overlap in this particular  
10 experiment, 83 percent between the two. And for  
11 TRPV1 and mCherry expressed from the CMV promoter,  
12 again, there was not very good overlap.  
13       So one strategy to use the mutant glycine  
14 receptor, then, is to silence TRPV1-positive cells  
15 because these are normally thought to be involved  
16 in chronic pain where TRPV1 itself is involved in,  
17 say, allodynia. It's not clear. But we might be  
18 able to enhance the specificity in certainly  
19 efficacy.  
20       A second strategy would be targeting TRPV1  
21 receptor by the expression of an antagonist. So we  
22 set out to find antagonists of TRPV1. TRPV1 is a

Page 127

1 tetramer that is activated by phosphorylation using  
2 PKC and other phosphorylating events, also in the  
3 inflammatory soup can activate this particular  
4 receptor, sensitize it, as well as asset. It can  
5 be down-regulated or desensitized by calcium-  
6 dependent phosphatases like calmodulin.  
7       So what we were looking for is an antagonist  
8 which would block the activation of TRPV1. So what  
9 we did was to use the virus system, and we  
10 expressed two copies of TRPV1 in this virus. We  
11 had to use two because we found that mutations  
12 would occur that would give us false-positives,  
13 which didn't occur if we used two copies of the  
14 gene.  
15       In the joint region of the virus -- this is  
16 a region that flanks the unique long and unique  
17 short portion of the genome -- we replace this with  
18 a library of expressed genes from PC12 cells after  
19 activation with NGF. And we analyzed this library  
20 by DNA microarray and found that we had about  
21 15,000 unique genes. So this represents a large  
22 number of genes coming from these cell types.

Page 128

1       So this is the general strategy that when  
2 you infect with the virus that makes TRPV1 and  
3 activate it with capsaicin, calcium floods into the  
4 cell. You get osmotic destabilization. The cells  
5 die, and you don't get any virus plaques as a  
6 result.  
7       However, if you infect with a TRPV1 virus  
8 that also expresses the gene that inactivates or  
9 blocks the activation of TRPV1, then many of these  
10 cells survive. You can get plaque formation. You  
11 can isolate these plaques, clone them in that way,  
12 sequence the insert, remark the virus, and retest  
13 it, and look for ones that are specific for  
14 blocking the activation of TRPV1.  
15       For these experiments, we also used as a  
16 positive control a dominant negative form of TRPV1,  
17 which is called poreless, which had the  
18 transmembrane region deleted, so when it makes  
19 heterodimers, inactivates TRPV1.  
20       So in this experiment, if you infect cells  
21 and don't treat with capsaicin, with the vector,  
22 and it doesn't contain any antagonists, you get

Page 129

1 absolutely no virus being made. However, if that  
2 cell expresses one of the genes that we found,  
3 common phosphatase, PP1-alpha, compared with  
4 poreless, we've got very good rescue of virus  
5 growth.  
6 So by looking at about 500,000 plaques,  
7 we've picked up about 50 genes which could  
8 antagonize TRPV1, and this was the most potent one  
9 we've found.  
10 We could also show that, in rat fetal  
11 neurons on infection, using Fura-2 assays for  
12 calcium uptake, that both PP1-alpha and poreless,  
13 compared to the control vector, would block the  
14 uptake of calcium.  
15 We tested this vector in a number of model  
16 systems. This is showing you one with a heat ramp,  
17 where we changed the temperature from 30 degrees up  
18 to about 44 degrees over a period of 15 minutes and  
19 looked at the response, the heat-related responses,  
20 pain-related responses in these animals, which for  
21 example they would curl up their foot and lift it  
22 or bite and lick at it. When you get to about 43

Page 130

1 degrees, then you start to see this TRPV1 receptor  
2 being turned on.  
3 However, you can really exaggerate this  
4 response by treating with capsaicin. And you can  
5 see, with the control virus, you've got very little  
6 effect on the development of this pain response.  
7 However, PP1-alpha, as well as poreless, gave you a  
8 dramatic difference. And we were shocked to see  
9 how impervious these animals were to pain up to 45  
10 degrees.  
11 So we have also used this in the PHN model,  
12 and I'll show you the data from a couple of these  
13 experiments. What we did is we injected the  
14 VZV-infected cells two weeks later. We infected  
15 these animals with a PP1-alpha or a control vector.  
16 And we measured pain responses over a period of  
17 weeks.  
18 What we saw was that in the case of the  
19 GFP-expressing vector, these animals rapidly  
20 developed mechanical allodynia. However, the  
21 vector that expressed PP1-alpha, it reversed this  
22 process, and it looked like a normal animal.

Page 131

1 The same is true with our paw withdrawal  
2 latency model, that the GFP didn't have any effect,  
3 whereas the vector that's making PP1-alpha had a  
4 dramatic effect on heat sensitivity.  
5 I'm not going to show you all the data, but  
6 we've tested these in cold models. We have tested  
7 these in the formal and footpad test, where  
8 different receptors are known to be involved, and  
9 this product has no effect.  
10 So to summarize, then, we think that gene  
11 therapy for PHN is feasible, and it should be  
12 effective, but we really need human trials to  
13 validate efficacy. Regulated gene silencing is, I  
14 think, a good strategy because it ignores  
15 essentially what the cause of pain is, but rather  
16 just silences those neurons, which are involved in  
17 pain.  
18 I have to say that, at least if you inject  
19 ivermectin locally, the animals begin to lose the  
20 pain response within seconds, and it lasts for  
21 about three or four hours. So this particular drug  
22 has a good half-life in humans. It's about

Page 132

1 16 hours. And so it's a very benign drug. It  
2 doesn't go into the central nervous system. So it  
3 may be a good first step at trying to use the nerve  
4 silencing technology for blocking pain.  
5 But we think that targeting subpopulations  
6 is going to be important, and it may be even  
7 possible that we can use antagonists, like the  
8 PP1-alpha story that I just told you about, as an  
9 additional therapeutic strategy.  
10 I didn't say anything about the mechanism,  
11 but PP1-alpha has a lot of effects in cells, as you  
12 know, but it does dephosphorylate TRPV1. And it  
13 dephosphorylates R2, and probably has an effect on  
14 HDACs as an HDAC inhibitor.  
15 So there are a number of people involved in  
16 this work. A couple of people I want to mention in  
17 particular, Bill Goins and Kip Kinchington, and  
18 Jean-Marc Guedon are the people that developed the  
19 PHN model and did all the PHN work that I'm showing  
20 you; Mark Doyal, who is an MSTP student that's  
21 worked on the transcriptional targeting methods.  
22 Bonnie Reinhart was the person that's done the

Page 133

1 targeting by modifying the virus infectivity. And  
2 Yoshitaka Miyagawa is our critical person in  
3 engineering the viruses. We have a whole new  
4 stable of engineered viruses that I didn't have  
5 time to show you. Thank you.  
6 (Applause.)  
7 DR. PORRECA: Some questions for Joe?  
8 DR. BASBAUM: Joe, thank you. The thing I  
9 must say is, I was very surprised. I didn't know  
10 that promoters for these genes had actually been  
11 identified. Where did you get them?  
12 DR. GLORIOSO: Yes. I don't have that on  
13 the tip of my tongue, but I can tell you what they  
14 are. There's been some publications for these  
15 different promoters, and we're using a fairly large  
16 piece of DNA for expression, so we have added  
17 additional sequences.  
18 One of the advantages of HSV is, this new  
19 class of vectors, which I really haven't told you  
20 anything about, we can put up to 40 kilobases of  
21 foreign sequences into. And so we can put very  
22 complicated or large genes or complex promoter

Page 134

1 constructs, and I think that's going to be an  
2 advantage here.  
3 DR. BASBAUM: If you inject the ivermectin  
4 in the opposite pod, does it do anything?  
5 DR. GLORIOSO: No.  
6 DR. BASBAUM: So it's not a systemic effect.  
7 DR. GLORIOSO: It's not a systemic effect,  
8 but we're hoping that -- we haven't tried it  
9 systemically yet. So we're hoping that we can use  
10 it systemically. And ivermectin is used as a cream  
11 and it's used in a lot of different ways, so we  
12 will try to do that.  
13 DR. BASBAUM: I apologize. I forgot I was  
14 chairing this session. That's why Brian gave me  
15 the microphone.  
16 Any other questions? Andrew?  
17 DR. RICE: Just a comment about the  
18 model -- and it may be a little -- well, it is  
19 pedantic, but it is important for thinking about  
20 how we translate this to the clinic.  
21 First of all, I'd certainly echo your view  
22 that it's absolutely vital to have expert

Page 135

1 virologists working with you on this model, and Kip  
2 Kinchington is obviously well known in that field.  
3 But I think to call it a model of  
4 post-herpetic neuralgia is pushing it too far, and  
5 we've probably made the same mistake, too. It's a  
6 model of acute zoster infection and the pain that  
7 occurs with that. And while it may share features  
8 of post-herpetic neuralgia, I think it's important  
9 to bear that in mind because, when we start to try  
10 and think about translating it into clinical  
11 trials, that may actually be important.  
12 DR. GLORIOSO: Yes. This is an acute model,  
13 and we don't have a virus reactivation model to  
14 look at that. That's a good point.  
15 DR. BASBAUM: Do you have evidence that the  
16 released enkephalin is actually acting on the  
17 primary afferent or is that just a hypothesis?  
18 DR. GLORIOSO: It's a hypothesis because  
19 enkephalin is actually released into the skin as  
20 well. And it's released into the spinal cord. So  
21 I don't think it goes very far. I mean, some  
22 people -- we were thinking earlier, well, it may be

Page 136

1 a bystander effect, but I doubt that's really true.  
2 So I'm thinking that it's released locally and  
3 presumably can bind to its normal receptors.  
4 DR. BASBAUM: It looks encouraging.  
5 We should take a break. Then Toto will give  
6 us a talk, and then we'll have time for lots of  
7 questions. Thanks very much, Joe.  
8 (Applause.)  
9 (Whereupon, a brief recess was taken.)  
10 DR. BASBAUM: If everyone can please grab a  
11 seat, so we can get started. So it's been a  
12 morning of somewhat esoteric approaches. And the  
13 next talk is not quite esoteric, but definitely  
14 unique, and we're in for a treat. I'd like to  
15 introduce Toto Olivera. Now, Toto grew up in the  
16 Philippines, where he I think got introduced as a  
17 kid to cone snails. And we're going to hear a lot  
18 about cone snails.  
19 I think he did his undergraduate work in the  
20 Philippines and then went to Cal Tech, where he got  
21 his PhD. And after work at Stanford, he went to  
22 Salt Lake, where he's been for a long time as a

Page 137

1 professor -- not forever -- a professor of biology  
2 and has demonstrated the incredible utility of the  
3 products of these cone snails. And we will hear  
4 about this in a variety of conditions, but  
5 particularly in potentially the management of pain.  
6 So it's really a pleasure. Toto, welcome.  
7 Presentation – Baldomero (Toto) Olivera  
8 DR. OLIVERA: So I'd like to thank Allan and  
9 Frank for inviting me here. And I'd like to start  
10 out by just reviewing both the biology of cone  
11 snails and some of the older work that we did. But  
12 let me start out by saying that I have no  
13 disclosures, and I wasn't able to e-mail my  
14 presentation because there are lots of movies. So  
15 we ended up with no title slide and no disclosure  
16 slide.  
17 But let me tell you about the cone snails.  
18 There are about 700 species of cone snails and all  
19 of them are venomous. And they are useful in that  
20 each species is quite specialized. So this species  
21 will only eat fish. This species will only eat  
22 certain types of marine worms. And this species

Page 138

1 will only eat certain types of snails.  
2 As you will see, our cone snails are pretty  
3 good neuropharmacologists. And so what I'd like to  
4 do is not just tell you about the individual toxins  
5 that have applications to pain, but also what we've  
6 learned about the philosophy of how this  
7 neuropharmacological system has evolved because we  
8 believe that there are some applications of the  
9 general principles that the cone snails have  
10 evolved in practicing neuropharmacology.  
11 So some of these snails are lethal to  
12 people. This one causes a fatality rate of  
13 70 percent in the absence of medical intervention.  
14 And so we started long ago to ask the question, why  
15 is this snail able to kill people? And the answer  
16 is that there are two components in the venom that  
17 are paralytic. One of them blocks the nicotinic  
18 acetylcholine receptor, the post-synaptic terminus  
19 of the neuromuscular junction, just like cobra  
20 toxin or alpha bungarotoxin, while the other  
21 essentially wipes out action potentials in muscle  
22 by blocking the same site that tetrodotoxin blocks

Page 139

1 in this voltage-gated sodium channel.  
2 So the sting of this snail is deadly because  
3 it's equivalent to being bitten by a cobra and  
4 eating a lethal dose of pufferfish at the same  
5 time. And that accounts for the 70 percent  
6 fatality rate.  
7 Now, the unusual thing about the venom  
8 components is that they're all small peptides, most  
9 of them, highly cross-linked by disulfide bonds.  
10 And they have post-translationally modified amino  
11 acids very often.  
12 So since we answered the question we first  
13 wanted to a long time ago, why am I still working  
14 on cone snails, the reason is really, an  
15 undergraduate at the University of Utah made a key  
16 discovery. So if you take the venom of that conus  
17 geographus and separate the venom components  
18 according to size, you can separate out peptides  
19 that are about 10 amino acids from those that are  
20 about 20 amino acids. And if you take this  
21 fraction and separate the peptides in that  
22 fraction, you can see there are lots of peptides.

Page 140

1 Only a few of them were paralytic using the  
2 assay that we had developed, which was IP injection  
3 into mice. Then this kid came along -- his name  
4 was Craig Clark -- and as is typical of 18-year-old  
5 kids, said, "Well, you're doing your assay all  
6 wrong. You shouldn't be injecting IP. You should  
7 be injecting ICV or intracranially." And I wasn't  
8 persuaded, but I think the nice thing about being  
9 at the university is that the students do what they  
10 want, not what we tell them.  
11 (Laughter.)  
12 DR. OLIVERA: So luckily for us, Craig did  
13 his experiment anyway. And so what I am going to  
14 show you is what he found by injecting this  
15 particular fraction of the venom into the brain of  
16 a mouse.  
17 What he found was the paralytic toxins of  
18 course we knew about, but this peptide makes mice  
19 jump and twist as they are jumping. This peptide  
20 made mice uncoordinated. This major peak put mice  
21 to sleep. They'd be asleep for 12 to 24 hours, and  
22 then they'd wake up and be perfectly fine. But

Page 141

1 that was only true if the mice were under three  
2 weeks of age. If they were over three weeks of  
3 age, instead of going to sleep, they'd climb their  
4 cages constantly.  
5 This made them drag their back legs. This  
6 peptide made them run around in circles. This made  
7 them swing their heads back and forth. This made  
8 them kick on their back and scratch. This made  
9 them depressed. This one caused convulsions. This  
10 one caused scratching, and there are a few that  
11 didn't do anything.  
12 But as you can see, the remarkable result  
13 was that there was a behavioral phenotype that was  
14 induced when each component was injected directly  
15 into the central nervous system.  
16 So this experiment of Craig told us that the  
17 venom of these snails was not a mixture of a few  
18 paralytic toxins, but was rather this very complex  
19 pharmacological brew of small peptides.  
20 So all of these are just the peptides.  
21 There are about 20 amino acids. And then there are  
22 three other major fractions. And so you can see

Page 142

1 that the diversity in the venom is probably about  
2 80 or 100 peptides that all seem to be biologically  
3 active.  
4 So at the time, we had a whole troop of  
5 undergraduates coming in. They could choose any  
6 snail they wanted, and using Craig's assay, they  
7 could follow the activity of any peptide that they  
8 wanted. And their job was to purify the peptide  
9 that caused the behavioral phenotype until we knew  
10 the sequence of the peptide. Then we could  
11 synthesize it, and that way, we could continue to  
12 follow it up.  
13 So this guy, again, an 18-year-old kid at  
14 the time, he chose conus magus, and he decided to  
15 purify an activity that he called the shaker  
16 peptide because it induced tremors when injected  
17 intracranially into mice.  
18 The reason I am telling you this is because  
19 this peptide that Michael purified and  
20 characterized is today an approved drug for  
21 intractable pain. It's called Prialt. We called  
22 it Omega Conotoxin MVIIA. And so this was approved

Page 143

1 in 2004. And what I'd like to do is  
2 retrospectively tell you what we've learned about  
3 the development of Prialt.  
4 So why did the snail evolve this peptide in  
5 the first place? Well, it's a fish-hunting cone  
6 snail. And in fact, of course, what's targeted is  
7 the neuromuscular circuitry. And in order for a  
8 fish to be able to swim, then of course an action  
9 potential has to cross a neuromuscular junction.  
10 If we zero in into a signal vutron [ph],  
11 then we can see that the key event is when the  
12 electrical signal reaches the end of the  
13 neuromuscular junction, voltage-gated calcium  
14 channels needed to open. And when they open, of  
15 course, that causes neurotransmitter release. And  
16 that's necessary to get the signal across the  
17 synapse.  
18 So of course, once acetylcholine is  
19 released, then it binds to the acetylcholine  
20 receptor, and that opens this ion channel that then  
21 causes a depolarization on the post-synaptic side  
22 and causes the action potential to be initiated on

Page 144

1 the muscle membrane. So that's of course the  
2 normal physiology.  
3 The reason that the snail evolved this  
4 peptide is it's part of its paralytic strategy.  
5 And so what the peptide will target are these  
6 voltage-gated calcium channels. It's a channel  
7 blocker and very efficiently therefore knocks out  
8 functionally these voltage-gated calcium channels.  
9 And as a result, no neurotransmitter is released,  
10 and, therefore, the neuromuscular system is  
11 blocked, and the fish becomes paralyzed.  
12 So if you inject this peptide into a fish,  
13 what you get is a paralyzed fish. So how do you  
14 make a drug out of that?  
15 Well, it turns out that if in fact you look  
16 at what happens in the mammals instead of in fish,  
17 then of course neuromuscular transmission is pretty  
18 much the same. You have action potentials, and the  
19 same events occur. But there is one critical  
20 difference. And the difference is that, in  
21 mammals, the calcium channels are not the green  
22 calcium channels, but they're red and

Page 145

1 Prialt-resistance. And for those who are into  
2 calcium channels, the green calcium channels are  
3 Cav2.2 and, in mammals, the neuromuscular junction  
4 has Cav2.1 channels. And so in fact, this peptide  
5 is not paralytic when it's injected into any  
6 mammal.  
7       However, we do have Cav2.2 channels, and it  
8 happens that they're in the pain circuitry. And  
9 so, of course, that is the basis for this becoming  
10 a drug because, now, as C fibers fire from the  
11 periphery in the synapse with this spinal cord  
12 neuron, if you block the release of glutamate at  
13 the synapse by adding this peptide, then what  
14 happens is that, even though you have a very  
15 powerful pain signal entering, because that signal  
16 does not cross the synapse, you therefore end up  
17 not perceiving the pain.  
18       So what I think this tells us is, first of  
19 all, that the components of the nervous system are  
20 extraordinarily conserved. Whether the Cav2.2  
21 channel is in fish or in mammals, this peptide  
22 recognizes it with very high affinity. It also can

Page 146

1 differentiate between this calcium channel and all  
2 other calcium channels that are present in any  
3 vertebrate system.  
4       However, the reason this peptide is a drug  
5 is because, although the structure of these ion  
6 channels is conserved, their pattern of expression  
7 is not. And the fact that we have a lot of  
8 different expression patterns and different  
9 animals, gives us an opportunity, therefore, to  
10 take advantage of natural products that haven't  
11 been evolved over millions of years. And even  
12 though it's not targeted for the purposes that we  
13 would like, it turns out that because of this  
14 variable expression, very often you will find  
15 something that's very useful for the purposes that  
16 the biomedical community is interested in.  
17       So what I'd like to do is to go back to the  
18 biology of the snails. And these snails, when they  
19 sniff a fish, extend their highly extensible  
20 proboscis. And this particular snail goes for the  
21 lateral line of the fish. And the moment it  
22 touches the skin of a fish, what happens is that,

Page 147

1 from that, it extrudes a disposable harpoon-like  
2 tooth, which also serves as a hypodermic needle.  
3       So the venom flows through the proboscis,  
4 through the tooth that's extended, and it comes out  
5 at the other end. And as you can see, this is  
6 highly barbed, so this is both a harpoon and  
7 hypodermic needle. And so these snails got their  
8 opportunity 55 million years ago when, essentially,  
9 they evolved a drug delivery device that's the  
10 equivalent of disposable hypodermic needles.  
11       (Laughter.)  
12       DR. OLIVERA: So each snail has its own  
13 particular design. And what you see is how it's  
14 used. And so you can see the fish is tethered and  
15 venom is being injected. And in a very short time,  
16 the fish is immobilized. And now, the snail will  
17 completely engulf the fish. And in about an hour  
18 and a half, it will predigest the fish in this  
19 false mouth, called a rostrum, and it will  
20 regurgitate the scales and bones of the fish and  
21 the one harpoon that it used to inject its venom.  
22       So that's how these particular snails make a

Page 148

1 living. So you can see that this is an efficient  
2 way for a snail to be able to catch a fish.  
3       Now, if we want to understand the  
4 biochemistry and pharmacology of how they do this,  
5 we have to find out what the components are of the  
6 venom that are necessary for capturing a fish.  
7 Now, here is another snail, a related snail in the  
8 same clay.  
9       What you're going to see is how fast this  
10 is. So they use a chemosensory mechanism to figure  
11 out where the fish is. And this is real time. And  
12 what you're going to see is just how quickly these  
13 snails are able to capture a fish.  
14       So in this particular case, the snail  
15 doesn't even have to go above the substrate. And  
16 so this is a very, very efficient process.  
17       So that's the fish-hunting cone snails. And  
18 fish-hunting cone snails have been the source of  
19 most of the work that we have done on cone snails  
20 so far. However, since the shells of these snails  
21 are pretty, there's a lot of interest from the  
22 collector community in classifying them. And so

Page 149

1 the molecular phylogeny of these snails is known.  
2 And in fact, it turns out that there are four  
3 different clades of fish-hunting species. And what  
4 I've shown you are species that belong to the  
5 F2 clade.  
6 So let's look at one of the other branches  
7 of fish-hunting cone snails. And what you're going  
8 to see is that, in fact, there's a different  
9 strategy for catching fish. So if you drop a fish  
10 with one of these snails, instead of sticking out  
11 its proboscis, it opens its mouth. And, as you can  
12 see, it has a really huge mouth. You might say  
13 cavernous mouth.  
14 Here's another species in that clade. And  
15 these guys always engulf the fish first before they  
16 sting it. Then they sting once it's in their  
17 mouth. And so it's a behavioral strategy that's  
18 completely different for how to catch a fish.  
19 So what happens is that these snails crawl  
20 out of the reef at night. And what they do is,  
21 they approach a school of small fish that are  
22 hiding in reef crevices. And if they are lucky,

Page 150

1 they can bite the whole school and then pick them  
2 off one by one.  
3 In order to have success at this, they have  
4 to be able to capture as much of the school as they  
5 can. And so they release a little bit of their  
6 venom. And as a result -- even before they inject  
7 the individual fish, they release a little bit of  
8 their venom. And the effect of the venom released  
9 is to make the fish act as if they are all spaced  
10 out, as if they are in an opium den.  
11 (Laughter.)  
12 DR. OLIVERA: Now, we called our groups of  
13 peptides that act together -- so if you look at all  
14 of the peptides that act together for a particular  
15 physiological purpose, we call that a cabal because  
16 cabals are secret societies out to overthrow  
17 existing authority. And so for this snail to  
18 capture a whole school, there are two cabals.  
19 First is the cabal necessary to quiet down the  
20 neuronal circuitry of the prey before it's  
21 engulfed. And then, after that, the venom is  
22 injected. The fish get all relaxed. And

Page 151

1 therefore, they can be eaten.  
2 Those two cabals, we call the one that  
3 causes sensory deadening the nirvana cabal because  
4 that essentially causes the fish to become  
5 hyperactive. And then when they inject the rest of  
6 their venom directly into the fish, that causes a  
7 complete paralysis and a relaxed fish. So it's  
8 this combination of nirvana cabal and motor cabal  
9 that these particular snails use.  
10 So if in fact the nirvana cabal makes them  
11 hyperactive and puts the fish in a sedated,  
12 quiescent state, one might ask the question, does  
13 this have biomedical applications to quiet down  
14 overactive neuronal circuitry. And we have  
15 identified members of what we call the nirvana  
16 cabal, and here are a few of those peptides that  
17 are released by these particular snails.  
18 It turns out that one can indeed use this  
19 for a variety of biomedical applications, and two  
20 of these have reached the human clinical trials.  
21 One of them, the sleeper peptide that Craig Clark  
22 originally characterized, it turns out, that's a

Page 152

1 subtype selective NMDA receptor antagonist, and  
2 that reached human clinical trials for epilepsy.  
3 But the one more interesting to this  
4 audience is a peptide that we call contulakin-G,  
5 which really is a neurotensin homologue, except the  
6 snails have changed the N-terminus of the peptide  
7 and have glycosylated this threonine residue. But  
8 you can see that the C terminus is very similar to  
9 neurotensin.  
10 This turns out to really be very, very  
11 effective and a very attractive compound in various  
12 animal models of pain. So this is potentially a  
13 new target for pain, the neurotensin receptor. And  
14 Allan Basbaum has actually looked at this peptide  
15 and found that it does have a lot of problems.  
16 However, because it is a peptide, to get  
17 it -- it's also been injected into spinal cord  
18 injury patients in a clinical study, and efficacy  
19 was shown in that particular study. So I think it  
20 would be nice to be able to develop this one  
21 further.  
22 So in addition to the approved peptide, a

Page 153

1 number of these conus peptides have now reached  
2 human clinical trials. And as you can see, they  
3 are not opioid like in their mechanism at all. But  
4 we are able to identify some new targets. And I'd  
5 like to tell you about the peptides of this class  
6 that target a certain type of nicotinic receptor.  
7       So as targets, nicotinic receptors are  
8 complex because, of course, they are pentamers, and  
9 you can assemble these subunits in various ways.  
10 And we were really still not sure which of the  
11 different forms exist and which ones don't. So the  
12 molecular identity of the function of different  
13 nicotinic receptors is not completely known.  
14       This is, I think, a general problem in  
15 neuroscience. To figure out the subunit  
16 composition of heteromeric ion-channel assembly  
17 just is quite hard. But it turns out that the  
18 snails know what's being assembled. And it turns  
19 out that conus venoms are a great source for  
20 peptides that are very highly specific for each of  
21 these nicotinic receptor subtypes. And the same  
22 Michael McIntosh who discovered Prialt is now a

Page 154

1 professor of psychiatry at the University of Utah.  
2 And he has defined a lot of the peptides that are  
3 very highly specific for each of these molecular  
4 isoforms.  
5       So what is found is that there are peptides  
6 that target what's called the alpha 9, alpha 10  
7 receptor and peptides that target the alpha 7  
8 receptor. And these are the most closely receptors  
9 that you find, that are all alpha subunits, that  
10 are found in the human nervous system.  
11       Curiously, these peptides do not come from a  
12 fish-hunting cone snail. Instead, they come from a  
13 clade of cone snails that eat worms. So it's a  
14 worm-hunting clade. And so these snails, what they  
15 really love to eat are fireworms. And so if you go  
16 scuba diving, you are told never to touch these  
17 things because they have really painful spicules,  
18 but that's the favorite prey of these particular  
19 cone snails.  
20       That's the source of where we are able to  
21 find these alpha 9/alpha 10 nicotinic receptors,  
22 the all-alpha subtype. And the reason seems to be

Page 155

1 that, although we have this type of nicotinic  
2 receptor at a neuromuscular junction,  
3 invertebrates, nematodes, polychaetes, drosophila,  
4 they have a lot of subunits that are related to  
5 alpha 7, alpha 9, alpha 10.  
6       I think C. elegans has 30 subunits of this  
7 type. And therefore, if you want to paralyze a  
8 marine worm, instead of targeting this type of  
9 receptor, they have involved a lot of peptides that  
10 target these types of receptors.  
11       So again, this is the case where the human  
12 homologues of these receptors that are in the  
13 neuromuscular junctions of these invertebrates have  
14 very restricted distribution, but invertebrate  
15 systems are distributed all over the place. And so  
16 it really pays to screen venoms even though they're  
17 for a completely different purpose for things that  
18 might be specific for the type of ion-channel  
19 receptor that you want.  
20       So what Michael has done is he's looked at  
21 what alpha 7 receptors do in various circuits and  
22 what alpha 9, alpha 10 receptors do. And it turns

Page 156

1 out that, if you inhibit alpha 9/alpha 10  
2 receptors, this peptide is anti-nociceptive in  
3 nerve injury models of pain. And so what seems to  
4 happen is that if you have a nerve injury model of  
5 pain -- so we use the chronic constriction injury  
6 model. If you inject this peptide, then you  
7 reverse the pain that results from the nerve  
8 injury.  
9       The basis of this is interesting because  
10 what the peptide seems to prevent is inflammation.  
11 And so when a nerve is injured, it's therefore  
12 attacked by macrophages, lymphocytes. And what you  
13 can see is that if you block this particular  
14 nicotinic receptor, then you count how many immune  
15 cells accumulated at the site of nerve injury. You  
16 can see that that's much decreased. And so you get  
17 less inflammation as a result of nerve injury by  
18 blocking the alpha 9/alpha 10 receptor.  
19       Now, this just shows you how the  
20 pharmacology has to be really well-tolerated,  
21 because if you block the other closely related  
22 nicotinic receptor, the alpha 7 nicotinic receptor,



Page 157

1 what happens is it makes things worse. You get an  
2 increased attack of the immune system on the site  
3 of nerve injury. And the emerging story seems to  
4 be that if you activate the alpha 7 receptor,  
5 that's anti-inflammatory; but if you activate the  
6 alpha 9/alpha 10 receptor, that's pro-inflammatory.  
7 So when you inhibit that particular receptor, then  
8 you inhibit the nerve injury.

9 So what you can see is that by having very  
10 specific ligands, we can therefore have  
11 applications that are completely unexpected.

12 So what I'd like to do is take the last few  
13 minutes just to say that I think the future of  
14 venom peptides is that because these critters have  
15 evolved ways to recognize heteromeric combinations,  
16 that this is a class of targets that's very  
17 difficult to accurately target with small  
18 molecules, because differentiating between closely  
19 related heteromeric combinations is really a  
20 challenge.

21 So the worst ion channel family in that  
22 regard is potassium channels because there are

Page 158

1 70 genes, and the number of combinations that you  
2 can make for potassium channels is vast. And we  
3 really don't know which combinations actually exist  
4 and where those heteromeric combinations are.

5 So I'd like to take the last few minutes  
6 just to tell you about how we are approaching that.

7 So what we do is, we take a region of the nervous  
8 system, in this case DRG neurons, where they are  
9 thought to be 25 to 30 different subclasses of  
10 neurons. And what we do is we culture them  
11 overnight, load them with Fura-2, and we can  
12 therefore measure intracellular calcium.

13 We can put about 200 cells in a well. And  
14 so here are a few cells. Now, if you add menthol,  
15 you can see that a few of the cells light up. If  
16 you have potassium chloride, then almost all of the  
17 cells light up. And so what we are doing is, we  
18 are using pharmacology to differentiate between the  
19 different cell types.

20 So here is an experiment where we're adding  
21 acetylcholine, ATP, histamine, menthol, and AITC.  
22 And what you can see is that these different cells

Page 159

1 respond differently. And so, clearly, these  
2 represent six different types of neurons. So if  
3 you monitor the cell population at this point, then  
4 you have low calcium in all of the cells. If you  
5 monitor calcium at this point, where you're adding  
6 menthol, you can see a few of the cells light up.

7 If you monitor calcium at this point, where  
8 you're adding potassium chloride, you can see  
9 almost all of the cells light up. So in this way,  
10 we are able to differentiate the different cell  
11 types of the DRG functionally.

12 Now, the other protocol we use is to add  
13 potassium chloride and to add a pharmacological  
14 agent before a pulse of potassium chloride. So if  
15 you add the tetrodotoxin, for example, of course,  
16 you decrease the influx of calcium. If you add a  
17 block of potassium channels, you increase the  
18 influx of calcium. And that's because, for calcium  
19 to enter when you have potassium chloride, you have  
20 to activate sodium channels, which then activate  
21 calcium channels. And then you terminate the  
22 excitation by potassium channels opening.

Page 160

1 So this is a very high-content assay because  
2 we are looking at all the sodium channels, all the  
3 calcium channels, and all of the potassium channels  
4 that are present in any of the DRG neurons and were  
5 simultaneously assaying all of those. And so we  
6 were using this as a way of discovering new  
7 compounds that are targeted to certain channels.

8 So we also make use of all of our other  
9 peptides that we know are specific for subtypes.

10 And so we previously showed that some conus  
11 peptides are specific for KV1.2 and some for KV1.6.  
12 And so this just shows your field. We have  
13 genetically labeled some of the DRG cells. These  
14 are mice that David Ginty labeled. And now, we  
15 apply two of these peptides.

16 What you can see is that the majority of  
17 neurons are not affected by either peptide, so  
18 about 85 percent of the DRG neurons look like this.  
19 However, here's a class of neurons that are  
20 affected by the KV1.6-specific peptide, but not by  
21 the KV1.2 specific peptide. Here is a class of  
22 neurons that are affected by the KV1.2, not by the

Page 161

1 KV1.6.  
2 The labeled neurons, it turns out, are not  
3 affected by the KV1.6-specific neurons, but are  
4 affected by the KV1.2-specific peptide, but the  
5 effects are very subtle, and we wouldn't have  
6 believed it if it weren't the fact that all of  
7 these neurons have a slight broadening when you add  
8 that particular peptide.  
9 So you can see that, although this peptide  
10 was supposed to be specific for KV1.2, it actually  
11 had different effects on different neurons. And  
12 what I'd like to do is just to show you why that's  
13 the case.  
14 So I don't have time to go into details, but  
15 we've looked in some detail at cold-sensitive  
16 neurons that are responsive to menthol, and they  
17 fall into two classes. The thermal sensors that  
18 are activated with mild cold temperatures and  
19 nociceptors, where you have to go to noxious cold  
20 temperatures.  
21 Basically, what we find is that they have  
22 entirely different ion channels except for the

Page 162

1 menthol receptor. And now, if you apply these  
2 peptides, what you see is that the thermal sensors  
3 are not affected by these peptides at all, but the  
4 nociceptors are affected when you give them a  
5 menthol pulse. They respond much more to two  
6 peptides, one specific for KV1.2, one specific for  
7 KV1.1.  
8 So originally, we interpreted this by saying  
9 nociceptors have KV1.1 and KV1.2. But our  
10 collaborator, Heinz Terlau, has shown that, in  
11 fact, the true target of the peptide that we  
12 thought was specific for KV1.2 is in fact this  
13 heteromeric combination because that peptide has a  
14 thousand-fold greater affinity for this heteromer  
15 than for the KV1.2 homomer.  
16 So now, this is the forum of potassium  
17 channel that we believe is present in cold  
18 nociceptors. And so it is a problem, of course, of  
19 pain during chemotherapy, where what happens is  
20 during chemotherapy, you get a cold sensitivity.  
21 And I think we can explain that.  
22 So the menthol receptor is present in both

Page 163

1 thermosensors and nociceptors, but the difference  
2 is that, in thermosensors, you have the menthol  
3 receptor, which then recruits calcium channels and  
4 activates the cell. But in nociceptors, you have  
5 the menthol receptor. And when it opens, the first  
6 thing that's recruited is this potassium channel,  
7 which is three KV1.2 and one KV 1.1 subunit. And  
8 of course, that repolarizes the cell.  
9 So it's not until you go to very cold  
10 temperatures that you can overcome this potassium  
11 channel and begin to recruit calcium channels. And  
12 so this potassium channel therefore plays a role in  
13 how the temperature at which a cell is activated.  
14 And therefore, under chemotherapy conditions, it's  
15 the balance between the menthol receptor and this  
16 potassium channel that is dysregulated.  
17 Therefore, if you want to cure that  
18 particular condition, this is the potassium channel  
19 that should be targeted. So I'm just making that  
20 point to show that, unfortunately, because of the  
21 nature of potassium channels, we don't really know  
22 the molecular composition of what we want to

Page 164

1 target. In this case, it turns out the potassium  
2 channel we want to target has three KV1.2 subunits  
3 and one KV 1.1 subunit, and we didn't know that  
4 before.  
5 So I'd like to end by just saying that this  
6 has been a huge collaboration, both with colleagues  
7 in Utah and colleagues in the Philippines, Germany,  
8 California, and France. And here are the people  
9 who did the work at the University of Utah. Thank  
10 you very much for your attention.  
11 (Applause.)  
12 DR. BASBAUM: I have a practical question.  
13 I know that, in the case of Prialt, it can't be  
14 used orally, either because it won't get into the  
15 central nervous system or because of postural  
16 hypertension, peripheral actions. Is it possible,  
17 following along the lines of Joe's talk, where he's  
18 using virus to deliver a peptide that one assumes  
19 is going to be released by the neuron to act back  
20 on itself, have you ever tried or anyone ever tried  
21 to have these virally synthesized and then to get  
22 into neurons?

Page 165

1 DR. OLIVERA: As far as I know, no one's  
2 actually tried it. I think it's been talked about,  
3 and people would like to do that. What people have  
4 done is they have expressed tethered forms of these  
5 toxins. And they have tried to introduce those  
6 into particular neurons by having the right viral  
7 vectors. And that's been tried, and it works, at  
8 least in some cases.  
9 DR. BASBAUM: Is this in vitro or in vivo?  
10 DR. OLIVERA: This is in vivo.  
11 DR. MCMAHON: So one very naive question.  
12 Are the snails themselves resistant to their own  
13 toxins?  
14 DR. OLIVERA: No. They are not. So if you  
15 put too many fish into an aquarium of fish-hunting  
16 cone snails, what happens is, you saturate their  
17 chemo receptors. And so, if they're hungry,  
18 they'll all come out, and they'll all have their  
19 proboscis out, and they'll sting anything that  
20 moves. And very often, they will sting each other.  
21 And individuals that get stung will die, not as  
22 quickly as a fish does, but clearly, they are not

Page 166

1 resistant to their own venoms.  
2 So as long as it's in their venom apparatus  
3 in their gut, they're okay, but if the venom is  
4 injected into the body cavity, they're sensitive.  
5 So unlike snakes, where they have evolved  
6 nicotinic receptors that are intrinsically  
7 resistant to their own venoms, the snails are not  
8 resistant.  
9 DR. BASBAUM: Roy?  
10 DR. FREEMAN: So I've got a quick question.  
11 The primary receptor in the autonomic ganglia is  
12 also the nicotinic acetyl choline receptor. And I  
13 was wondering -- and this is a somewhat naive  
14 question -- whether those subunits, the alpha 7,  
15 alpha 9, alpha 10, were also present in that  
16 receptor.  
17 DR. OLIVERA: I'm sorry. Which ganglion are  
18 you --  
19 DR. FREEMAN: The autonomic ganglia.  
20 DR. OLIVERA: So in sympathetic ganglia, you  
21 have alpha 3, beta 2 receptors and alpha 7  
22 primarily. So as far as I know, there's no alpha

Page 167

1 9, alpha 10, but there is alpha 7 and alpha 3,  
2 beta 2  
3 DR. SVENDSEN: So do snails feel pain?  
4 DR. OLIVERA: That's a good question. I  
5 suspect they do.  
6 DR. SVENDSEN: How would you prove it?  
7 Because they have a different receptor system, and  
8 it might be -- somewhere along the line, that  
9 switch has been -- I mean, there's a lot of debate  
10 on whether fish and snails experience pain in the  
11 same way. But what you seem to have shown is a  
12 very different usage of the same --.  
13 DR. OLIVERA: I think, among mollusks,  
14 probably people have done work in cephalopods. And  
15 I think that there is some work that shows that  
16 there's certainly somatosensation because they  
17 react by changing their chromatophores. But I am not  
18 familiar with that work as far as I know.  
19 DR. BASBAUM: No. The British government  
20 thinks that invertebrates don't feel pain. You  
21 need a license to do almost anything in Britain to  
22 an animal, but you don't need anything to do it to

Page 168

1 an invertebrate. I think when that gene was  
2 cloned, the so-called painless gene in drosophila  
3 was a little bit annoying, just the notion that  
4 drosophila has a painless gene. So they have  
5 nociceptors. I mean, they will respond to injury,  
6 but to say they have pain, I think you do need a  
7 brain.  
8 (Laughter.)  
9 DR. BASBAUM: Another question I had -- I'm  
10 pretty sure you're familiar with Diane Lipscombe's  
11 work. So for the audience, the interesting  
12 observation that she made -- and I don't know where  
13 it's gone -- is that there is a splice variant of  
14 2.2 in C fibers, selectively in the nociceptors,  
15 which raise the possibility that one could develop  
16 either a conotoxin or an antagonist that would take  
17 a 2.2 from the nociceptor and not get the side  
18 effect profile that would arise when the molecule  
19 gets to the brain, which can be pretty problematic.  
20 Has that story gone anywhere? I really  
21 haven't seen much more.  
22 DR. OLIVERA: At least not

Page 169

1 pharmacologically. I haven't seen anybody try to  
2 develop a specific pharmacological agent that  
3 distinguishes between spliced variants. But it's a  
4 good idea.  
5 DR. BASBAUM: I think we've had a long  
6 morning. Why don't we have lunch? And then we'll  
7 get together after lunch. Thank you all for an  
8 entertaining morning.  
9 We're doing that now? What? Are we  
10 cancelling lunch? I'm sorry. I was concerned  
11 about the time. Tell you what. We'll try. We'll  
12 have an overall discussion for a half-hour and  
13 then -- I'm just jet-lagged. I didn't sleep well  
14 last night.  
15 (Pause.)  
16 Q&A and Panel Discussion  
17 DR. PORRECA: So I think it's open questions  
18 for the panel, and Mac has the first question.  
19 DR. MCMAHON: I was told to ask questions.  
20 So I thought I would ask the same question that I  
21 asked Yves yesterday. And that is, you all  
22 presented different technologies, different

Page 170

1 approaches, that seemed to be a fantastic promise  
2 for the future, but what do you know about them  
3 that makes it difficult? Or what's the downside of  
4 each of these approaches?  
5 DR. GLORIOSO: I can start with that one.  
6 The hardest problem about doing gene therapy for  
7 pain is delivery to the right cells. And we have  
8 debated this a lot. And the reason I picked on  
9 post-herpetic neuralgia is because at least we can  
10 identify a dermatome where pain is arising and  
11 might have a good shot. But there are many other  
12 types of pain where it's maybe a lot more  
13 problematic to deliver the vector.  
14 DR. SVENDSEN: I guess, just to go on, with  
15 the stem cell delivery, we haven't done it in pain  
16 models yet, so we don't know what the problems will  
17 be, but I imagine that you have different growth  
18 factors one could choose and different peptides.  
19 And it's going to be a case of choosing the right  
20 one. And GDNF, based on your work and many other  
21 papers, is the best bet.  
22 It's not a very clean pharmacological agent.

Page 171

1 But my experience is, the dirtier the drug, the  
2 more likelier it is to work. And I think when you  
3 don't know the origins of something, it's kind of a  
4 shot in the dark, but at least try it. But I think  
5 the delivery seems pretty straightforward for us in  
6 that the cells release where they are.  
7 So I think we can get it delivered. Just  
8 will it work? That's the main problem.  
9 DR. FREEMAN: So picking up on Steve's  
10 comment -- or question -- and Joe's comment about  
11 delivery to the right cells, early on, in fact, I  
12 think there's still some ongoing studies in  
13 neurodegenerative disease, intrathecal therapy, and  
14 there was very early on intra-arterial injection  
15 therapy, where using stem cells was proposed.  
16 I wanted to hear some comments. Obviously,  
17 the ease of delivery is much greater, and there  
18 will certainly be much more uptake if the  
19 microinjections were not involved. So I want to  
20 hear both from Allan and Clive what your view is on  
21 those modes of delivery.  
22 DR. BASBAUM: Many years ago, Jackie

Page 172

1 Sagen -- actually, she even had a company. I don't  
2 remember the name of it. It didn't last too long.  
3 But the approach there was intrathecal delivery.  
4 And there were some patients, and what they were  
5 using was originally bovine adrenal cells because  
6 they released enkephalin. Adrenal cells make  
7 buckets of enkephalins and norepi [ph], the two of  
8 which independently, at the level of the spinal  
9 cord, can be anti-nociceptive analgesic through an  
10 alpha 2 site and through an opiate receptor.  
11 They implanted these cells intrathecally  
12 initially in animals and then in humans. There  
13 were a few humans that were trialed. It was in  
14 France. It was Yves Lasorte, the neurosurgeon  
15 there who did it.  
16 The problem there is that that's a pump.  
17 There's no question. That's all it is, is a pump.  
18 And then, do the cells sit down? They don't  
19 penetrate. What happens to the molecules? And it  
20 just didn't go anywhere.  
21 So I'm not sure that that's any different  
22 from just putting a pump in and having a catheter

Page 173

1 that will put out the compound for you. I do think  
2 there's a big difference between putting it in  
3 intraparenchymally.  
4 DR. RICE: Just to comment, if my memory  
5 serves me correct, the other reason that died was  
6 because it was bovine tissue. It was exactly the  
7 same time as the bovine spongiform encephalopathy  
8 crisis. And I think it was a safety concern that  
9 essentially killed it rather than an efficacy  
10 issue, although efficacy may have been a problem.  
11 But it was bad timing.  
12 DR. BASBAUM: Okay.  
13 DR. PORRECA: Andrew, could you continue?  
14 So in what circumstances would an ethics committee  
15 approve this kind of a therapy, and what types of  
16 patients might be considered?  
17 DR. RICE: Tough question. I mean,  
18 Jacquelyn Sagen's idea was killed for a very  
19 specific reason at the time, that may or may not  
20 have been a problem. It's something we discussed  
21 in the coffee break. Because of the potential  
22 downside of this, I think an ethics committee would

Page 174

1 have difficulties -- very much my personal view;  
2 you asked me the question -- with a non-fatal  
3 symptomatic condition, although of course they have  
4 given approval for retinitis pigmentosa, for  
5 example.  
6 But that's why I suspect that conditions  
7 like ALS, which I have very personal experience of,  
8 would be much more likely. And it's also  
9 associated with a rapid death. But that's a very  
10 personal view, and there's people who know more  
11 about ethics in the room than me. But I think it's  
12 going to be difficult to justify paying for such  
13 approaches.  
14 DR. SVENDSEN: I kind of agree. It's a  
15 cost/risk benefit. But I don't know. I'm not  
16 familiar with the pain syndromes enough, but I  
17 imagine there are certain pain syndromes where  
18 there's nothing. And you know, the chronic pain,  
19 the risk of putting some cells in the spinal  
20 cord -- the good thing with ALS trial, as we've  
21 shown now and Boulis has shown, we can put cells in  
22 the cord without doing too much damage -- as we get

Page 175

1 better with the surgery and less invasive put them  
2 in.  
3 Just going back to the last question, if we  
4 put the cells in the CSF, if we put them in the  
5 blood, they don't penetrate into the core. In our  
6 experience, mesenchymal cells don't get into the  
7 brain. Neural cells don't get in. And I think  
8 UCSF would agree, you have to do them  
9 intraparenchymally. We'd love in stroke to be able  
10 to get in through the blood. And we've tried, and  
11 tried, and tried, but we have to go  
12 intraparenchymally to get the cells in and  
13 integrate it.  
14 So what pain syndromes would you  
15 think -- maybe the FDA's in the back -- would be  
16 severe enough?  
17 DR. BASBAUM: I really disagree with Andrew.  
18 DR. RICE: You asked the question.  
19 DR. BASBAUM: No. You suggested you would  
20 only want a terminal condition, and this is a true  
21 story. On the first grant that we submitted on  
22 this proposal, it didn't get funded. It did

Page 176

1 eventually get funded, but one of the reviewers  
2 wrote, "Why would you ever want a transplant  
3 therapy for a non-life-threatening condition like  
4 chronic pain?"  
5 To me, that's an unbelievable  
6 misunderstanding. And you no better than most,  
7 there are some patients who will actually commit  
8 suicide when you can't treat them. If the mantra  
9 in the field is that the best there is in some of  
10 the neuropathic pain conditions is 30 percent  
11 efficacy and 30 percent of patients, then what do  
12 you tell the rest of the patients?  
13 So the real issue is risk/benefit. And  
14 that's the question, but that's no different from  
15 any drug. If you have a spinal cord injury case,  
16 where 70 percent of those individuals have  
17 intractable pains -- that is one of the things that  
18 makes their life so miserable -- is that  
19 potentially a therapy where there's already damage  
20 to the spinal cord?  
21 I think the real question is how much damage  
22 is produced by the intraparenchymal therapy. And I

Page 177

1 don't know the answer to that, but surgeons have  
2 been clearly going in, and putting probes in, and  
3 putting stimulators, intrathecal pumps, injecting  
4 alcohol into trigeminal ganglion.  
5 So I think one can manipulate the nervous  
6 system quite considerably. And it's a matter of  
7 time. We'll find out when it's tried.  
8 DR. PORRECA: Just to clarify, I mean, the  
9 30 percent efficacy number that you mentioned, I  
10 think you have to compare it with intrathecal  
11 delivery by pump of drugs that we have available.  
12 And I think that that number is considerably  
13 higher.  
14 DR. BASBAUM: I agree.  
15 DR. MCMAHON: [Inaudible – off  
16 mic] -- provocative. Surgeons do lots of things  
17 that are not necessarily good.  
18 (Laughter.)  
19 DR. MCMAHON: There's a big argument about  
20 surgical fusion for low back pain. I mean, is that  
21 a good thing or a bad thing? I mean, someone does  
22 it because the people are desperate doesn't mean

Page 178

1 it's a good idea.  
2 Now, when the stem cell therapy started, one  
3 of the questions asked was -- so maybe I can ask  
4 you -- how sick would you have to be to have this  
5 very invasive procedure? I mean, I would not have  
6 it for a bit of sciatica. I just wouldn't.  
7 DR. RICE: I can see your point of view  
8 exactly, and I don't -- I was putting in an extreme  
9 point, but I can see the corollary, for example,  
10 with heart transplantation.  
11 In the beginning, before we knew it worked,  
12 we only took the very, very sickest patients. Now,  
13 it's not a routine procedure, but it's done on  
14 people who are really quite healthy because they're  
15 better potential recipients for a transplant.  
16 So I guess the point I was making is that we  
17 probably need to look for the dangers and the  
18 issues in the fatal conditions before we go on to  
19 symptomatic conditions. That's the point I was  
20 making.  
21 DR. BASBAUM: Be provocative, Frank.  
22 DR. PORRECA: I could be. I could ask you

Page 179

1 about intrathecal baclofen and its efficacy in  
2 pain.  
3 DR. BASBAUM: That actually is one of the  
4 more disappointing things, I have to admit. So  
5 Frank is asking the question. GABA-B  
6 agonists -- there are GABA-B receptors on primary  
7 afferents, on post-synaptic neurons. Baclofen,  
8 which is a GABA-B agonist, particularly effective  
9 in animal models, in a variety of animal pain  
10 models that have been intrathecally.  
11 It is not effective for pain in humans.  
12 It's effective for spasticity and maybe the pain  
13 secondary to the spasticity, so it's used in MS  
14 patients, for example.  
15 That's a puzzle that I don't understand.  
16 That's one of the examples of poor translation.  
17 Now, is it also possible that when you give a GABA  
18 agonist, that it's targeting both GABA-A and B and,  
19 together, the two might be effective?  
20 Again, it's empirical. We know that GABA-A  
21 agonists can help, and some of the benzos probably  
22 enhance the effect of some of the existing

Page 180

1 compounds. You have a side-effect therapeutic  
2 window if it starts to get to motor neurons.  
3 I think the GABA-B story is one of the  
4 puzzles. As far as I know, the only pain condition  
5 in which it ever really has worked is trigeminal  
6 neuralgia. The neurologists can concur it's not  
7 used anymore because there's better drugs.  
8 But I would then argue, because I know where  
9 you're going, Frank, if I were to transplant, then,  
10 trigeminal neuralgia, it may be actually a terrific  
11 first place to go.  
12 Am I right about the baclofen?  
13 DR. PORRECA: Yes. Misha?  
14 DR. BACKONJA: Just to kind of inject a  
15 little bit of clinical perspective as one of the  
16 clinicians here, to argue for some conditions, that  
17 they're really painful -- and as Allan pointed,  
18 some patients really got to the point of suicide,  
19 where pain is so intractable. Again, we don't have  
20 statistics, but if you talk to any clinicians who  
21 have a large practice, that's one of the things  
22 that does happen, unfortunately.

Page 181

1 So as already stated, probably spinal cord  
2 injury or post-central pain syndromes, they're very  
3 level [indiscernible] one would consider. And  
4 especially, if there's any evidence that would be  
5 of benefit to some neural recovery, their sensory  
6 motor, or any, would be a benefit.

7 So maybe it's one of those things, as we  
8 talked about yesterday. We should widen our  
9 scopes, what we're measuring, if you're indeed  
10 looking for motor recovery. Also Clive and his  
11 team is literally working on pain as well. He's  
12 looking for adverse effects, but also potential  
13 recovery. So it's an appropriate strategy and  
14 something to be considered.

15 But regarding the efficacy of intrathecal  
16 therapies, our feeling in managing so many pumps,  
17 they were nearly not as effective. I mean, there's  
18 really no good trials to compare, any comparator  
19 studies. But one of the big issues in intrathecal  
20 delivery of drugs is, there are a limited number of  
21 things that are proved, but in clinical practice, a  
22 number of things are utilized. And unfortunately,

Page 182

1 we end up doing in intrathecal therapy what they do  
2 in systemic therapy, which is frequently  
3 combination therapy.

4 Again, something that's evolved as a  
5 clinical practice, we're thinking that maybe one  
6 system is addressed, but there are other systems  
7 that are not. By combining therapies, you will  
8 look at some efficacy.

9 The sad story in all of this is, there's  
10 really no good prospective data. So one hope is  
11 that with the registries that are now being  
12 implemented, led by the Stanford effort and  
13 Huro [ph] is a part of PROMISE effort, that we will  
14 learn from real-life experience if it works or  
15 doesn't. But there's really so few data points  
16 regarding the comparison.

17 DR. PORRECA: Yes. But I think that our  
18 understanding is emerging with the intrathecal  
19 therapies. And I know that there is a lot of  
20 observation at the moment, and different clinicians  
21 use different drugs and/or cocktails of drugs to  
22 produce or try to titrate the effects for

Page 183

1 individual patients. I think that understanding  
2 will increase over time.

3 Also, kind of an interesting emerging story,  
4 even in patients that are not responding to  
5 systemic delivery of opioids, that weaning them off  
6 the opioids and then beginning an intrathecal pump  
7 seems to potentially be effective.

8 So a lot of questions that I think we don't  
9 understand, but there may be still more to learn  
10 with a mechanism that potentially could be  
11 effective in some patients.

12 DR. BACKONJA: Another unfortunate  
13 observation against intrathecal therapy is that,  
14 frequently, there is development of tolerance,  
15 which is really a big problem.

16 DR. PORRECA: Well, sometimes.

17 DR. BACKONJA: A lot of times.

18 DR. PORRECA: I don't know.

19 DR. BACKONJA: Clinical experience.

20 DR. PORRECA: Yes.

21 DR. BASBAUM: I wonder if I could ask Toto a  
22 question. So Prialt has been around for quite a

Page 184

1 while now. And you showed that some of the other  
2 toxins are in trials. I'm actually kind of  
3 curious, because there are so many -- I mean, I was  
4 familiar with the contulakin, as you mentioned.

5 But what is slowing down the development? Prialt  
6 had an interesting history, as you know. I mean,  
7 it can be incredibly effective. It had a weird  
8 side effect profile, and I think it scared a lot of  
9 people, but it can be remarkably effective.

10 As you said, there's so many potential  
11 targets. Is there some explanation for the  
12 relatively slow clinical development?

13 DR. OLIVERA: So I think it's the delivery  
14 problem again, intrathecal delivery. There's no  
15 financing at the moment to push a drug for a market  
16 of only intrathecal patients that have to. So  
17 there are a number of strategies.

18 DR. BASBAUM: Chas still here?

19 DR. OLIVERA: Yes. There are a number of  
20 strategies to try to make these more systemically  
21 delivered.

22 DR. BASBAUM: Can you talk about that?

Page 185

1 DR. OLIVERA: Well, one of them is to  
2 circularize the peptide. And in a number of cases,  
3 if you have no ends, that's much more resistant to  
4 proteases, and so you can put massive amounts into  
5 the circulation. And you can also modify the  
6 peptide to get more of it across the blood-brain  
7 barrier. And so people are trying that.  
8 DR. PORRECA: I don't think that Prialt is  
9 universally effective. I think there are some  
10 patients that respond, but there are plenty that  
11 don't, which is kind of interesting from a  
12 mechanistic point of view as well.  
13 Yes?  
14 DR. GLORIOSO: I wanted to ask Clive a  
15 question, which is that I'm a big fan of iPS cells  
16 as well, and they're great as model systems for  
17 understanding disease. So I was wondering, in the  
18 case of deriving iPS from ALS patients and  
19 transdifferentiating back into neurons, what are  
20 the differences between those neurons, if any, and  
21 the neurons that are normal?  
22 DR. SVENDSEN: That's another whole talk.

Page 186

1 But I think that the lessons we learned from spinal  
2 muscular atrophy, like I showed, when you reprogram  
3 skin cells from a patient there, where the motor  
4 neurons die, and then you push them forward again  
5 to be motor neurons, after six weeks they just  
6 start dying, just like they did in the kid.  
7 When we did that with ALS patients, which is  
8 an adult onset disorder, we reprogrammed them. We  
9 then pushed them to be motor neurons. The motor  
10 neurons looked pretty happy. And in fact, they  
11 lasted six weeks. They lasted 10 weeks. They  
12 didn't undergo that death -- with the patient.  
13 Now, maybe we have to wait 40 years or  
14 60 years, and the graduate students weren't that  
15 keen. So maybe we have to accelerate, perhaps, the  
16 differentiation or aid the cells somehow,  
17 artificially, to bring out a phenotype. But we did  
18 see some more interesting phenotypes, which were  
19 electrophysiological changes in the cells, more  
20 firing. So there were, actually, interestingly,  
21 some phenotypic changes in the cells.  
22 DR. GLORIOSO: So if you do the obvious,

Page 187

1 like look at transcripts, and profiles, and things  
2 like that, what do you see with that?  
3 DR. SVENDSEN: Beautiful transcript. I have  
4 another whole talk on big data. And I think one of  
5 the things that's coming out is they do have a very  
6 unique transcription profile. We did RNA seq, and  
7 you can tell the difference between HD, SMA,  
8 Parkinson's, and ALS just on the transcript done.  
9 And it segregates beautifully into those with  
10 non-bias -- so you can do it on the transcript.  
11 DR. GLORIOSO: So you're desperate for  
12 models, so have you tried making transgenic animals  
13 with the cells? In other words, use them as stem  
14 cell for generating animals.  
15 DR. SVENDSEN: That's a little bit further  
16 on than our IRB would probably go. I'm not sure  
17 what you mean.  
18 DR. GLORIOSO: Other people have taken iPS  
19 cells and put them into developing embryos, and  
20 gotten mosaic-type animals.  
21 DR. SVENDSEN: We're constricted by our SCRO  
22 committees as to what we can do with the human iPS.

Page 188

1 You're not allowed to put them back into developing  
2 monkey embryos, for instance, or even rat embryos  
3 by the SCROs.  
4 DR. GLORIOSO: I see. That's right. You  
5 have human cells, so you can't do it. I'm sorry.  
6 DR. SVENDSEN: Yes. So they get very  
7 nervous that you're going to --  
8 DR. GLORIOSO: Yes, of course.  
9 DR. SVENDSEN: -- make a mini-human. But  
10 what we are doing is making organoids. And we can  
11 almost make now a spinal cord organoid where the  
12 cells self-aggregate and start making something  
13 that looks a bit like a spinal cord, so we're  
14 getting closer to that technology.  
15 But I just wanted to go back to the last  
16 discussion briefly and the consensus. And  
17 something that would be very useful to me, and I'm  
18 sure to Allan and Joe is -- because we're all on  
19 the edge, it seems like, of clinical -- all four of  
20 us, clinical trials.  
21 Me, as an outsider to this field, I was  
22 talking earlier on with Steve. If we had a list of



Page 189

1 the appropriate diseases, we could then pick the  
2 appropriate animal models that would gel with the  
3 diseases, the types of pain that the clinicians say  
4 this is what we need, and have some kind of  
5 consortium effort -- maybe that the FDA would be  
6 interested in funding or the NIH -- to, in a small  
7 way, just get the experts together and put a  
8 translational team in.

9 We talk about this at meetings, but then you  
10 go away and you start to get busy. But it would be  
11 nice to have a consensus because all of these  
12 therapies sound very exciting, but I know the  
13 problem. We had \$20 million from CERN, but it's  
14 still a struggle. I had to reshape my whole lab to  
15 become a mini-company, essentially. It doesn't  
16 happen easily. And if we're all trying to get our  
17 neuron papers, it's almost impossible.

18 So why not have FDA and Pain and try to get  
19 a consortium? And we're trying that with some  
20 other diseases. It seems to be working. And you  
21 need the clinicians to guide us, because we could  
22 get the best animal model that's completely

Page 190

1 irrelevant for pain in humans. I think I've heard  
2 that today.

3 So is that something that could come out of  
4 a meeting like this? I don't know.

5 DR. BASBAUM: Yes.

6 (Laughter.)

7 DR. PORRECA: Other questions or comments?

8 DR. BASBAUM: I think people are hungry.

9 Why don't we take a break, have some lunch, and  
10 we'll continue after? Thanks, everybody.

11 (Whereupon, at 12:19 p.m., a luncheon recess  
12 was taken.)

13  
14  
15  
16  
17  
18  
19  
20  
21  
22

Page 191

1 AFTERNOON SESSION  
2 (1:23 p.m.)

3 DR. TURK: For those that don't know me, my  
4 name is Dennis Turk, and I'm one of -- the small  
5 font. Those of you who were here yesterday, you  
6 saw there was a big font who organized the meeting,  
7 and then the small font. I'm one of the small-font  
8 people, with Bob Dworkin.

9 I just wanted to add my thanks to all of the  
10 speakers for their presentations. I think this has  
11 been one of the most stimulating conversations,  
12 discussions. And what's really been gratifying is  
13 that, number one, hearing that from some of the  
14 other people in the audience, but number two, just  
15 looking in and watching the interactions that are  
16 going on among the people who are here.

17 I think the most gratifying thing is really  
18 seeing how much stimulation, how much excitement,  
19 and enthusiasm. And even for those of us that some  
20 of these topics may not be exactly what we normally  
21 work in, it's an opportunity just so we get some  
22 overview, and perspective, and some understanding.

Page 192

1 So thanks to all of the speakers. I think we've  
2 had a tremendous day and a half, and I want to  
3 thank you.

4 Some people may not have been here, and I  
5 want to remind them that we want to emphasize that  
6 these sessions have been videotaped, and there will  
7 be a transcript put on the ACTION website. And I  
8 know some people have said I'd like to have  
9 students see this or I'd like to have colleagues  
10 see this. And I think it's probably three or four  
11 weeks, it'll be up. It takes us about that long to  
12 get there.

13 So it will be available to you. And we  
14 hope, Bob, I, Allan, and Frank, that in fact this  
15 will go beyond just the two days of the meeting,  
16 but we'll actually be stimulating you.

17 So thank you all very much for being here.  
18 Thank you for staying. And thank you for your  
19 enthusiasm that we've heard so far.

20 In one of the previous scientific programs  
21 that ACTION had conducted, there was a lot of  
22 discussion about the failures and the difficulties

Page 193

1 of doing some of the trials, and the inability to  
2 bring new drugs forward, and that the  
3 pharmaceutical industry was actually losing  
4 enthusiasm, losing interest, backing away from the  
5 neuroscience area, the pain area. We heard Chas  
6 Bountra yesterday tell us a little bit, reinforce  
7 that particular concept.

8 One of the things that we did as we  
9 organized this meeting, we were thinking, is there  
10 a way to try to get away from some of that gloom  
11 and doom? Are there some successes that would be  
12 useful for people to hear about, what the  
13 procedures, what the studies are, and what are some  
14 development areas. So it's not just that there are  
15 areas where we've had failures, but there are in  
16 fact some successes.

17 So what we were hoping to do this afternoon,  
18 at least the first session, is to cover some areas  
19 that have been relatively successful attempts from  
20 both the pre-clinical and moving into the clinical  
21 area, to start looking at some areas that may be  
22 promising, not that we guarantee or anybody can

Page 194

1 guarantee anything is going to be the perfect  
2 solution to the dilemma, but at least to see that  
3 there are in fact some promising directions and  
4 things that are happening.

5 So I'm going to be co-chairing this with Bob  
6 Dworkin. The first speaker is going to be Andrew  
7 Rice. I want to thank Andrew especially, one of  
8 the people who came all the way from U.K., a long  
9 distance, and we appreciate that. However, I have  
10 a hunch, coming from Seattle, where I live, it may  
11 have taken me about as long as it took you to get  
12 here.

13 Andrew is going to be speaking about some  
14 pre-clinical and clinical studies that he's been  
15 involved with on angiotensin 2 type 2 receptor  
16 blockers to give us a perspective of how that  
17 process evolved, not just the outcome, I guess I'm  
18 hoping, but how it developed and how it moved  
19 along, so that maybe it will give us some guidance  
20 as we think about studies going forward.

21 So Andrew from Imperial College London,  
22 you're on.

Page 195

1 Presentation – Andrew Rice

2 DR. RICE: Thank you, Dennis, and thank you  
3 for the invitation to talk about the angiotensin 2  
4 type 2 receptor blocker program that I've been  
5 involved with Spinifex in, and really just to point  
6 out that perhaps I'm just a spokesman for this.  
7 There are several people in this room who are also  
8 involved in that program. And their names will  
9 become apparent as I run through the presentation.

10 First of all, my conflicts. I've been  
11 involved with Spinifex since 2005 as a paid  
12 consultant and advisory board member, and I've been  
13 engaged in both pre-clinical and the clinical trial  
14 development activities. I received research funds  
15 from Spinifex for my lab at Imperial for two sets  
16 of pre-clinical studies in 2005 and 2007. And I  
17 own share options in the company.

18 So just a little briefing in terms of the  
19 renin-angiotensin system, because this is really  
20 the first thing that would spring to mind when  
21 you're thinking of potential neuropathic pain  
22 targets.

Page 196

1 For those of you who know me, you might know  
2 that I enjoy history. And there's a lovely piece  
3 of history in that the discoverer of the system was  
4 a hypertension researcher, Stan Peart, who was my  
5 first teacher at medical school some 40 years ago,  
6 so it's a nice return to history for me.

7 Angiotensin 2 is the active substance in the  
8 system. It is formed from two precursors. And  
9 until relatively recently, it was known that the  
10 major pharmacological site of action of  
11 angiotensin 2 was the AT1 receptor, which is  
12 involved in blood pressure regulation and various  
13 other cardiovascular functions.

14 Interestingly, some of the genes associated  
15 with this have fairly recently been elucidated by  
16 colleagues at UCL as being involved in high-  
17 altitude syndrome and potentially survival in  
18 intensive care units and endurance athletics.

19 As I am sure you're aware, there have been  
20 two broad strategies in terms of cardiovascular  
21 disease involving the system, angiotensin-  
22 converting-enzyme inhibitors and angiotensin 1

Page 197

1 receptor antagonists for hypertension.  
2 82 has been investigated in several spheres.  
3 Much less is known about the 82 receptor,  
4 particularly its intracellular signaling  
5 mechanisms, and really haven't been thought of as a  
6 drug target. And I think our trial is the first  
7 82-receptor antagonist to successfully have gone  
8 through a phase 2 clinical trial.  
9 The first important point to make out is  
10 that 82 is not involved in the control of blood  
11 pressure, although of course we did look carefully  
12 for cardiovascular adverse effects.  
13 I'm going to talk about a number of  
14 compounds, which were used in the pre-clinical  
15 development. The most important one is EMA401,  
16 which is the sodium salt. And that was the one  
17 which we used in the clinical trial, and it has  
18 selectivity for 82 over 81 receptors. Some of  
19 these early ones are also referred to by old Parke-  
20 Davis numbers.  
21 So bearing in mind the nature of this  
22 meeting, I did look at some of our G microarray

Page 198

1 data, where we looked at various animal models, and  
2 we can see that the gene for angiotensin 82  
3 receptors is decreased in the rat dorsal root  
4 ganglion in rats that have been subject to spinal  
5 nerve transection. But it remains at levels in a  
6 model of HIV neuropathy. But we also know that it  
7 networks with other pain genes.  
8 There are other angiotensin signals,  
9 sometimes conflicting, hinting at involvement in  
10 pain. For example, we know that consumption of ACE  
11 inhibitors is a risk factor for complex regional  
12 pain syndrome, type 1.  
13 There's a paper in Cell at the moment which  
14 shows that a Baruli ulcer, which is a  
15 microbacterial infection associated with painless  
16 ulcers, isn't like another microbacteria, leprosy.  
17 The painlessness in that is not due to destruction  
18 of sensory nerve fibers. It's shown to be an  
19 angiotensin signaling mechanism. And there are  
20 various other hints that it may be involved in pain  
21 and nociception in some way.  
22 Studies in Smith's lab have shown that

Page 199

1 estrogen-evoked neurite sprouting in small medium  
2 cultured dorsal root ganglion cells is eliminated  
3 by AC2 receptor blockades, so it appears to be  
4 active at the DRG level. And the 82 receptor, but  
5 importantly not the AT1 receptors, is localized to  
6 small- and medium-sized neurons in both  
7 human -- and in Praveen Anand's lab, it's been  
8 shown in the human cells and also in rat DRG, and  
9 trigeminal ganglia.  
10 I think quite an important point is that the  
11 expression of angiotensin to receptor doesn't  
12 appear to change in the DRGs of rat nerve injury  
13 models, but expression of the ligand angiotensin 2  
14 does increase.  
15 So Praveen Anand is involved in this  
16 Spinifex development program and has done a lot of  
17 work with cultured rat and, more importantly, human  
18 DRG cells, including those taken from patients with  
19 brachial plexus avulsion. And it's shown that the  
20 EMA401 82 receptor antagonist that we used in the  
21 clinical trials -- we used the sodium salt in the  
22 clinical trials -- inhibits capsaicin-induced

Page 200

1 calcium influx, and, conversely, angiotensin 2  
2 itself enhances that effect. And 81 receptor and  
3 blocker, losartan, had no such effect. Rather like  
4 as has been shown in Smith's lab, angiotensin 2  
5 enhances neurite outgrowth and EMA401 is a type  
6 that inhibits it.  
7 We also know that CFA induces proliferation  
8 of dermal and epidermal sensory nerve fibers in  
9 skin and 82 receptor antagonists prevent that. So  
10 there appears to be some involvement of neurite  
11 sprouting under nociceptive conditions or pain  
12 conditions.  
13 I'll come on to Maree Smith's role at the  
14 end, but probably one of the most important studies  
15 was the inventor of this technology, Maree Smith at  
16 the University of Queensland in Brisbane. And this  
17 is one of her early studies, although we desisted  
18 in publishing quite a lot of this pre-clinical work  
19 until we had the confidence of a clinical trial.  
20 But she showed that a number of  
21 angiotensin 2 receptor antagonists do act as  
22 analgesics in the CCI model of peripheral nerve

Page 201

1 injury and has shown this for three of the  
2 development compounds that we've used, with the  
3 last one being similar to the one that is used in  
4 the clinical trial I'm going to talk about.  
5 There's a lot of talk about replication of  
6 pre-clinical data. And we took a decision sometime  
7 ago. These were experiments performed, at least in  
8 my lab, in around 2007. But we needed to replicate  
9 the work in my lab and Maree Smith's lab with  
10 regard to the activity of these compounds in  
11 neuropathic pain models, and we just also took a  
12 decision to publish these together.  
13 Now, certainly, my view and, I think, most  
14 of you who would work in this area would agree that  
15 exact replication of a protocol between two  
16 distinct laboratories is really, really difficult,  
17 if not impossible. There are so many confounds,  
18 the supplier of the animals, the exact strain of  
19 the animals.  
20 So what we did, which was different, was to  
21 ask both labs to replicate the question. In other  
22 words, are 82 receptor antagonists or the same 82

Page 202

1 receptor antagonists effective in animal models of  
2 antiretroviral toxic polyneuropathy? And there  
3 were variations between the study, but the  
4 important thing is, they came to the same result.  
5 On this slide, you can see the results from  
6 Maree Smith's, and there's a slight difference in  
7 the dosing, the effective dosing, but they're in  
8 the same ballpark. And we were both able to show  
9 that the highest dose is examined. The efficacy in  
10 this model of toxic neuropathy was roughly  
11 equivalent to that of gabapentin. And we were able  
12 to show dose-response function.  
13 But I think the important point is that it  
14 was replicated in two independent labs, about as  
15 far away geographically as you can get, London and  
16 Brisbane.  
17 I am very keen that we declare various  
18 factors concerned with how we did our studies. And  
19 these are pre- the ARRIVE guidelines. They were  
20 done again in 2007, but we were able to report  
21 inclusion and exclusion criteria, randomization,  
22 blinding, et cetera. We didn't do a sample size

Page 203

1 calculation. That would be different today. And  
2 concealed allocation, again, we didn't do, but that  
3 would be different if I was to do the study today.  
4 We also commissioned some studies in  
5 Aberdeen from Cameron and Cotter in the  
6 streptozotocin-induced model of diabetic  
7 neuropathy. And these were fascinating to me.  
8 Firstly, they were able to show that, similar to  
9 gabapentin, an 82 receptor antagonist here had  
10 similar efficacy in terms of mechanical and thermal  
11 hypersensitivity in this model, and this was  
12 sustained over a period of time.  
13 More interestingly -- and it's something we  
14 haven't actually pursued in the clinical program  
15 yet; we're still discussing it -- the nerve  
16 conduction velocity of both motor and sensory  
17 nerves was restored with the 82 receptor  
18 antagonists, but not with gabapentin, which may  
19 have some reflections in terms of the mechanisms  
20 that I was talking about. And they used the sodium  
21 salt of EMA401, which is the same compound we used  
22 in the clinical trials.

Page 204

1 Maree Smith, in a recent publication, has  
2 also showed that in 82 receptor knock-out mice, the  
3 effect is largely abolished and has suggested the  
4 inhibition of MAP kinase is maybe one of the  
5 intracellular signaling routes involved in that, in  
6 dorsal root ganglion cells.  
7 I won't run through the pre-clinical  
8 toxicology. We obviously looked quite hard for  
9 cardiovascular signals, except to say that there  
10 really wasn't anything that has unduly alarmed us.  
11 One quite interesting feature that we discussed a  
12 lot at the time was in the phase 1 human studies.  
13 We saw episodes of non-sustained ventricular  
14 tachycardia both in the placebo-treated people and  
15 in the drug-treated people.  
16 I think there's an increasing awareness,  
17 with that kind of monitoring, long-term ECG  
18 monitoring, you are likely to see these adverse  
19 events that, in our case, don't appear actually to  
20 be related to the drug, although we did go and look  
21 if there was a potential mechanism for it, and  
22 there appears to be no association with the drug

Page 205

1 effect. It was a coincidental finding.  
2 So that was a brief summary of the  
3 pre-clinical program. There were some differences  
4 to other pre-clinical programs, but nothing  
5 actually stands out as really obvious to any other  
6 pre-clinical program that I have been involved in.  
7 So we went on to a phase 2 clinical trial in  
8 post-herpetic neuralgia. It's a rather typical  
9 design. We had a four-week treatment period of  
10 EMA401, and it shows post-herpetic neuralgia as the  
11 clinical trial model, I think, for two reasons. It  
12 was something we discussed an awful lot.  
13 The first is that, as Bob Dworkin and his  
14 colleagues have shown, you're most likely to see an  
15 effect, which is of course what you want to do in a  
16 phase 2 trial, with post-herpetic neuralgia  
17 compared to other neuropathic pain models that are  
18 used in clinical trials.  
19 Secondly, to me, if you're looking at  
20 excitatory or blocking excitation in  
21 hyper-excitabile DRG cells or sensory neurons, then  
22 having a clinical trial model where there is both

Page 206

1 patients with sensory gain and sensory loss  
2 phenomena makes sense, whereas largely in, say, a  
3 diabetic neuropathy model, you may just see sensory  
4 loss phenomena.  
5 So inclusion criteria were pain for PHN of  
6 more than six months' duration. One thing that we  
7 did do that I've not seen done before is that the  
8 patients, the investigator, and the sites were all  
9 masked for the inclusion criteria. And we used an  
10 algorithm that is still confidential, that excludes  
11 patients on the basis of the numerical rating scale  
12 for pain variability and excessively high scores,  
13 and excessively low scores, and whether they  
14 completed their diaries.  
15 Now, we haven't published that trial because  
16 it would lose its masking effect for future trials,  
17 but we are prepared to share it with people who are  
18 proposing to use it in other trials, if you contact  
19 us. In terms of con-meds, we allowed a maximum of  
20 one drug at stable dose.  
21 The study protocol is now freely available,  
22 full study protocol, at the Spinifex website. And

Page 207

1 it was registered with the Australian and  
2 New Zealand clinical trials registry. Spinifex is  
3 originally an Australian company.  
4 We recruited between August 2011 and  
5 May 2012 at an estimated sample size of 77 per  
6 group in 6 countries and 29 centers. The centers  
7 were in eastern Europe and South Africa. We  
8 randomized 183 patients, assigned 92 to EMA401 and  
9 91 to placebo. And of those, very few patients  
10 dropped out. 86 completed the EMA401 arm and 83  
11 patients completed the placebo arm.  
12 I'll come on to the adverse events profile,  
13 but just to say at this stage, there were very few  
14 patients who dropped out because of adverse events,  
15 but we didn't get a serious-adverse-events signal.  
16 The demographics are very characteristic for  
17 a PHN trial. The average age of the population was  
18 around 62, 63. There was a slight female  
19 preponderance, as you'd expect in a population of  
20 that age. And they have had PHN for a duration of,  
21 on average, about two years with a baseline pain  
22 intensity of around 6, 6 and a half.

Page 208

1 Because of the countries that we recruited  
2 in, the number of con-meds were not similar to what  
3 you'd expect in trials that were perhaps done in  
4 Europe or North America. But a small number of  
5 patients were taking either pregabalin or  
6 gabapentin. They were the most common con-meds, or  
7 some certain anticonvulsant drugs. Capsaicin,  
8 8 percent, isn't available in those countries yet.  
9 The primary efficacy pain endpoint is pain  
10 intensity comparison between baseline and the final  
11 dose, end week. And we did both BOCF and LOCF  
12 imputations. There was actually no difference in  
13 the outcome, but the primary was on LOCF.  
14 We saw a gradual increase in efficacy across  
15 the trial in comparison to placebo. So by weeks 3  
16 and 4, there's a clear separation of EMA401 from  
17 placebo.  
18 I should emphasize that there was no dose-  
19 titration phase, and we have had some discussions  
20 as to why the efficacy takes a little bit of time  
21 to appear. And this is clearly something we'd want  
22 to investigate in future clinical trials.

Page 209

1 We did a number of secondary and comparative  
2 efficacy studies and looked at both the percentage  
3 of patients to achieve 30 percent pain relief and  
4 50 percent pain relief. And they come out with, if  
5 you like NNTs, at about 4 and a half for 30 percent  
6 and about 6.7 for 50 percent.

7 Now, there's a strange thing that happens  
8 when you're flying across the Atlantic, in that we  
9 seem to favor the 50 percent in Europe and  
10 30 percent in U.S.A. They've both been justified.  
11 But we also took an idea that John Farrar published  
12 a few years ago. Actually taking these pretty  
13 arbitrary 30 percent and 50 percent fixed measures  
14 of responder rate are somewhat illogical, and we  
15 produced this cumulative estimation of responder  
16 rate, which I think gives a much better, certainly  
17 visual depiction of the efficacy against placebo.  
18 And certainly, I think that's a useful way of  
19 showing that information.

20 Just before we published the trial, Andrew  
21 Moore, fairly typically, published a fairly  
22 innovative and thought-provoking way of looking at

Page 210

1 success for neuropathic pain -- neuropathic pain  
2 efficacy in the BMJ. I won't go into it in detail  
3 because it takes time to explain, but basically,  
4 it's a computation of success and failure rates of  
5 drugs based on the difference between the maximum  
6 effect that you can achieve against the active drug  
7 and the difference between active drug and placebo.

8 But basically, what this computation tells  
9 us is that the efficacy of the drug that we're  
10 looking at, the EMA401, is very similar to that  
11 seen by pregabalin, and topical capsaicin, and  
12 gabapentin, although quite an important point to  
13 make is that we were looking at it in the context  
14 of a four-week treatment period, whereas the  
15 duration of the data for the other drugs is in  
16 12 week, because they're much further ahead in  
17 development.

18 We had a number of other pain efficacy  
19 measures, and we're very encouraged to see that,  
20 generally, they all move in the same direction. So  
21 on the new version of the short form McGill, all  
22 the parameters separated between placebo and EMA401

Page 211

1 with the exception of intermittent pain, which is  
2 probably what you'd expect for post-herpetic  
3 neuralgia, and the scores on the brief pain  
4 inventory measures did, as did the patient  
5 impression of change. We used the Insomnia  
6 Severity Index, and that just failed to reach  
7 statistical difference between placebo and EMA401.

8 So in general, all the secondary outcome  
9 measures for efficacy measures for pain moved in  
10 the same direction as the primary.

11 We didn't see this for depression, anxiety,  
12 and positive outlook or pain catastrophizing, but I  
13 think you really wouldn't expect to see that in a  
14 four-week study. And also, certainly my personal  
15 view is that these are probably more useful as  
16 stratification measures than outcome measures.

17 I'm not sure how often they actually change,  
18 even in longer pain trials. And I think that would  
19 be quite an interesting discussion to have around  
20 the group, as to where we ought to be placing these  
21 measures in clinical trial design.

22 There was really nothing to separate EMA401

Page 212

1 from placebo in terms of the adverse events with  
2 the exception of a slightly increased number of  
3 people that treated with the randomized EMA401 that  
4 had headache. And there were a couple of L3  
5 episodes of allergic dermatitis in the EMA401 group  
6 and one in the placebo group.

7 I think I may have missed the slide that  
8 showed the number of centers. We did a per-country  
9 analysis that was preplanned and saw no difference  
10 in the efficacy between countries. Because two  
11 centers recruited a large number of patients, there  
12 is a center effect, but we've looked very closely  
13 into that, and we don't think it compromised the  
14 results at all.

15 So we've now secured venture capital funding  
16 for the rest of the phase 2 and getting into  
17 phase 3 plans. And we are currently discussing  
18 this. These are not yet set in stone, but we've  
19 put them in a press release to date. We are  
20 planning to do a phase 2B multidose  
21 placebo-controlled trial in PHN with a 12-week  
22 treatment period.

Page 213

1 We don't think we have hit the full efficacy  
2 dose yet because we really weren't seeing adverse  
3 effects in this trial, so we think we can push the  
4 dose somewhat higher. And we're also discussing  
5 other clinical proof-of-concept studies at phase 2  
6 level in other neuropathic pain conditions. And  
7 I'm sure we'd love some feedback from the meeting  
8 as to the relative importance or usefulness of  
9 different trial models, but we are certainly  
10 looking at diabetic neuropathy, and we're also  
11 considering non-neuropathic pain conditions such as  
12 osteoarthritis, although the pre-clinical rationale  
13 is not that strong.

14 One study I have left out is that Maree  
15 Smith has also recently published efficacy and pre-  
16 clinical models of cancer-induced bone pain.

17 So that's really a brief summary of the  
18 EMA401 story to date. We're at phase 2. We've got  
19 a long way to go. You will have seen from the  
20 authors the people who have been involved, but I  
21 would like to highlight two particular people who  
22 deserve special mention in regards to this program.

Page 214

1 First is Maree Smith, who is basically at  
2 the University of Queensland. She is essentially  
3 the inventor, came up with the original hypothesis,  
4 and made contributions to some of the pre-clinical  
5 data. And Tom McCarthy, who is here, has been the  
6 CEO of Spinifex. We worked it out. It was eight  
7 years now, Tom. It seems shorter. And Tom has  
8 done a sterling job in leading what is a very small  
9 company so far, not only through the scientific  
10 aspects, but dealing with the venture capital  
11 funding for the company.

12 So thank you for your attention, and I'm  
13 happy to answer any questions.

14 (Applause.)

15 DR. TURK: Questions for Andrew?

16 DR. MCMAHON: So thanks. I think Chas is  
17 back again. Now, after his pessimism the whole of  
18 yesterday, it's good to see some positive news in  
19 the pain field.

20 But a few things, really. One, do the  
21 patients know whether they're on placebo or  
22 compound? I mean, is there any unblinding from

Page 215

1 their perspective, if they guess?

2 DR. RICE: We didn't specifically look for  
3 that, but from the adverse effects profiles, you  
4 wouldn't expect that to be the case. I'm quite a  
5 big fan of asking patients at the end whether they  
6 know which group they were allocated to, but we  
7 didn't do that in the phase 2 study.

8 DR. MCMAHON: The second question is a bit  
9 more scientific. And that's, do you know whether  
10 the compound is CNS penetrant, may have other  
11 actions that you haven't explored?

12 DR. RICE: In rat, anyway, it doesn't  
13 penetrate into the CNS. It's peripherally  
14 restricted.

15 DR. CLARK: I noticed one of the outcomes  
16 that you looked at was spontaneous pain in the  
17 clinical study and I think the result was positive.

18 DR. RICE: Yes.

19 DR. CLARK: In the pre-clinical models, did  
20 you happen to look at spontaneous pain, and do you  
21 think it would correlate?

22 DR. RICE: Yes. Whether we can measure

Page 216

1 spontaneous pain at all in animal models is another  
2 issue. And Frank has already stood up. You want  
3 to talk?

4 DR. PORRECA: No, not for that. I had a  
5 different question.

6 DR. RICE: So my take on that is we look for  
7 changes in ethologically relevant behaviors. And  
8 we looked in a paradigm that is thigmotaxis in the  
9 open field. It's essentially predator avoidance  
10 behavior, and the hypothesis, animals that are in  
11 pain, would engage in increased predator avoidance  
12 behavior.

13 We did that in two of the pre-clinical  
14 studies and the signals were quite interesting.

15 The first one, we did see a signal at the  
16 intermediate doses, but at the higher doses, we  
17 didn't, and I'll explain that.

18 With EMA401, we didn't see a signal in that  
19 regard. And we think the reason is that we made  
20 observations with both drugs that the injections  
21 were highly -- we used intraperitoneal dosing, and  
22 the injections themselves were aversive. We think

Page 217

1 it was a pH effect from the solution. And I don't  
2 want to use the word anxiety, but the anxiety  
3 related to that injection immediately prior to that  
4 may have confounded it, so it's picking up a signal  
5 in other regards. But in the EMA300 studies, we  
6 did see something of a signal in that regard. But  
7 they're not conclusive. That's why I didn't put  
8 them up.

9 So we did look for what might be a surrogate  
10 measure of spontaneous pain in animal models, but  
11 as we all know, we've got a long way to go in that  
12 regard.

13 DR. PORRECA: That was a very, very  
14 interesting story and very exciting. I am not  
15 really sure I understand the mechanism, I have to  
16 say, so that's one thing that I think seems  
17 mysterious. You were going kind of fast with he  
18 slides, so I didn't see the selectivity of the  
19 molecules for 82 versus 81. I know it was probably  
20 up there, but maybe I didn't catch it.

21 Then the other question related to this is,  
22 what is the interaction of these molecules with

Page 218

1 other targets? So ultimately, I guess what I'm  
2 asking is how do you know that the effect that  
3 you're producing, that you're seeing, is due to  
4 this 82 mechanism? How can that be? Is that  
5 established or what?

6 DR. RICE: Here is the selectivity data.  
7 But we hadn't put it in for other targets. As far  
8 as we know, it isn't interacting with other  
9 targets, but I don't think we can be fully  
10 confident in that.

11 DR. PORRECA: Yes. So how can you  
12 demonstrate that it is this mechanism, I guess?

13 DR. RICE: Yes. So there was the 82  
14 knock-out.

15 DR. PORRECA: But that was affecting the  
16 actions of angiotensin, right?

17 DR. RICE: No, no. The effect of the drug  
18 is abolished in 82 knock-out animals in CCI. So  
19 they put that one up. But in terms of the  
20 screening we've done so far, we don't think it's  
21 active in other sites, but it's not really my area  
22 of expertise.

Page 219

1 DR. KATZ: Andrew, nice presentation. I'm  
2 curious whether you guys made any effort to subtype  
3 the patients with PHN, because if you believe in  
4 typology of PHN, you could imagine that a  
5 peripherally restricted compound might not work on  
6 the deafferentation subtype, which is present  
7 supposedly in a minority of patients.

8 DR. RICE: We didn't and we discussed it  
9 extensively before initiating that trial.

10 Remember, it's a phase 2 study, so it's a small  
11 trial. And at that time, we were engaged with the  
12 German Neuropathic Pain Network, QST profiling,  
13 which we do in our group. It takes probably one  
14 and a half hours per patient. It would be very  
15 costly to supply all the centers with the  
16 equipment, and to train them, and ensure data  
17 validity.

18 That was before Roy has published his  
19 experiences with the Pfizer, sort of, if you like,  
20 bedside QST profiling. And at the moment, we are  
21 currently discussing whether we should include that  
22 in the next study. My personal view is that we

Page 220

1 should.

2 There is also a paper that has come out of  
3 the IMI Euro Pain Network, that I think is going to  
4 be a landmark paper. It comes from Charles Jenson  
5 and Nana Finrap. It's still under review, so I  
6 don't want to say too much about it. But they have  
7 fairly conclusively shown that, in a mixed group of  
8 patients with peripheral nerve injury, PHN, and  
9 diabetic neuropathy, using the full German QST  
10 profiling, patients who you would allocate to  
11 sensory gain phenomena respond to oxcarbazepine,  
12 and those that don't have a sensory loss profile do  
13 not. To me, that is a very important paper. It's  
14 a paper we've been asking for in our field.

15 So the short answer is, we didn't include it  
16 for this study. We did think about it. But the  
17 barriers to getting robust sentry phenotyping data  
18 were not conducive to a phase 2 study. We're  
19 actively talking about it for the next study. It's  
20 one of the things we're thinking about.

21 DR. KATZ: Thanks.

22 DR. BASBAUM: Last question. I am trying to



Page 221

1 get a sense of the patients. Some of them were  
2 still on meds. Some weren't. Were they not on  
3 because they didn't work? And in the results, if  
4 you look at the results, rather than an average  
5 effect, those that were still on gabapentin, for  
6 example, did they have a better effect?  
7 What I'm really getting at in a more general  
8 question is, does a patient that responds to  
9 gabapentin also respond to duloxetine, also respond  
10 to this antagonist, or are they completely  
11 unpredictable?  
12 DR. RICE: We saw no such effect, whether  
13 they were on treatment or off treatment. But this  
14 trial wasn't designed to look at that. It's  
15 probably too small to look at that. And the  
16 numbers of patients on any one drug or any one  
17 class of drug wouldn't really be enough to conclude  
18 much from that.  
19 DR. BASBAUM: But many of the patients, the  
20 great majority, were on nothing --  
21 DR. RICE: Yes.  
22 DR. BASBAUM: -- which seems surprising.

Page 222

1 DR. RICE: Not when you consider that they  
2 were recruited in eastern Europe. Many of the  
3 drugs that are currently available are not  
4 available there.  
5 DR. BASBAUM: Good point.  
6 DR. RICE: Even for South Africa, a lot of  
7 the drugs are not available.  
8 DR. TURK: Roy, you want to get the last  
9 word in this session? There will be an opportunity  
10 for a panel, so don't feel, anybody who wants to  
11 come up, that we didn't let you. Roy?  
12 DR. FREEMAN: So maybe three quick  
13 questions, 1A, B, and C. So 1A, Allan asked me a  
14 question yesterday about criteria for moving from  
15 pre-clinical to clinical. And here, you are  
16 presenting, I guess -- and I've put Tom in this  
17 position once before -- the poster child of the  
18 move from bench to bedside. What clues do we get  
19 from the decisions that were made at the  
20 pre-clinical stage as to when to move to the  
21 bedside, 1A?  
22 1B, and I'll just ask two. There is a, I

Page 223

1 don't know, growing conventional wisdom that  
2 neuropathic pain trials should be done in western  
3 Europe or the U.S.A. This really confronts that  
4 conventional wisdom square in the face. And it  
5 confronts it in a way that is somewhat surprising.  
6 It actually shows that the placebo response was  
7 attenuate.  
8 Your effect size -- I think those of us who  
9 look at these trials pretty frequently -- was  
10 driven by the attenuated placebo response that  
11 occurred in the second half of the trial.  
12 So comment on those two questions.  
13 DR. RICE: So before giving this  
14 presentation, I was talking with Tom and various  
15 other people about what differentiates this  
16 pre-clinical program from many others. And  
17 actually, there are some bells and whistles that  
18 prevented the human DRG studies, for example, that  
19 gave us confidence.  
20 We replicated some of the pre-clinical model  
21 findings in independent labs, but that's actually  
22 not fundamentally different from many other drug

Page 224

1 development programs that have not had success in  
2 phase 2. And the other thing to emphasize is,  
3 we're still only in phase 2. We've got phase 3 to  
4 go.  
5 So I think the problem with pre-clinical  
6 development programs is they are great at  
7 identifying the drugs that do work, but they're not  
8 good at identifying the drugs that don't work. So  
9 to a degree, I don't want to use the word "luck,"  
10 but we're using a drug that now is shown to have  
11 efficacy in phase 2. We didn't know that when we  
12 were doing the pre-clinical studies. But there's  
13 nothing that really differentiates the pre-clinical  
14 studies, that I can see, that is fundamentally  
15 different from any other drug development  
16 strategies.  
17 Eastern Europe. I don't share your  
18 conventional wisdom, actually. I think one of the  
19 problems with doing studies in the U.S. and Europe  
20 is you tend to recruit from secondary care or even  
21 professional patients and professional research  
22 centers. And you often then attract the

Page 225

1 treatment-resistant patients who haven't responded  
2 to anybody else. And that's why in the U.K., we  
3 are piloting -- recruiting patients direct from  
4 primary care using the electronic healthcare  
5 records that, for example, cover the whole of  
6 London or Scotland.

7 So one of the reasons we went to eastern  
8 Europe is, of course, cost, but also we are more  
9 likely to recruit a population that might, in a way  
10 reflect a truer PHN population, if you like, than  
11 those that have been through a lot of treatments  
12 that are available in the U.K. and Europe that are  
13 probably treatment resistant. So that was one of  
14 the rationales.

15 I think that would be an interesting point  
16 for the discussion about the geographical location  
17 of studies. I think Bob has talked a couple of  
18 times about some of the problems related to  
19 becoming professional patients in trials.

20 Can I just make one other point? It's  
21 actually not in this study, but it is something I  
22 would like to do in another trial. We've got a

Page 226

1 paper in press on the Pain website, which is a  
2 negative trial of pregabalin in HIV neuropathy.

3 An important thing in that study, although  
4 it didn't make any difference to the negative  
5 outcome, was that we randomly sampled the patients  
6 because it's the culture in HIV for drug sharing,  
7 for plasma levels of pregabalin. And we found that  
8 an appreciable number of patients allocated to  
9 pregabalin, despite all the normal controls for  
10 adherence, had no detectible pregabalin in their  
11 blood. Con-meds were found more often than we  
12 expected, and some patients allocated to placebo  
13 had detectible pregabalin in their blood.

14 I think that's something that isn't reported  
15 in clinical trials more often and probably  
16 something we should be taking more notice of.

17 (Applause.)

18 DR. TURK: Thank you for that great  
19 presentation. And again, to stimulate us to be  
20 thinking of the trials we're doing, and advancing  
21 trials, and moving things forward, the next  
22 presentation is going to be along the same vein,

Page 227

1 although we're talking about something that's a  
2 little bit different, of course, with a different  
3 molecule.

4 We'll be talking about anti-NGF antibodies,  
5 and Nat Katz is going to be presenting to us. Many  
6 of you know Nat. He's been involved with analgesia  
7 solutions for a long time. He's also affiliated  
8 with Tufts University and has been for many years.  
9 And I'll just thank him for all the assistance he's  
10 given us over the years to ACTION IMPACT. So  
11 thank you very much, Nat.

12 Nat is going to start giving you another  
13 story about how a molecule moved forward, with the  
14 idea being, again, we're trying to be on this,  
15 where are we seeing some positive findings to maybe  
16 balance some of the concerns or some of the  
17 negative that we've been hearing or have been  
18 hearing for a number of years.

19 So Nat, they're all yours.

20 Presentation – Nathaniel Katz

21 DR. KATZ: Thanks very much, Dennis, and  
22 thanks to the conference organizers. It turns out

Page 228

1 that my talk follows up perfectly from Andrew's  
2 and, more particularly, perfectly from Roy's  
3 question 1A to Andrew. And I think, if I had more  
4 time, I would have retitled my talk, "An Answer to  
5 Roy's Question 1A."

6 (Laughter.)

7 DR. KATZ: The only reason I agreed to give  
8 this presentation is because I know that probably  
9 half the people in the room have been involved in  
10 the anti-NGF story much more intimately than I have  
11 and probably know it better.

12 But I thought it would be a good opportunity  
13 for me to go back and look at what I think is  
14 probably the most definitive success story that we  
15 have in translation of efficacy. With the anti-NGF  
16 antibodies, we now have more than 30 trials, more  
17 than 10,000 patients that have been studied.

18 So the clinical efficacy signal is  
19 incontrovertible. There's really nothing to talk  
20 about there, except if you want to talk about how  
21 massive it is. And of course, there is a strong  
22 pre-clinical signal as well.

Page 229

1 So the reason I agreed to give this talk is  
2 to try to figure out, at least in my own mind, what  
3 might be an answer to Roy's question 1A. What does  
4 differentiate a true success story like this, from  
5 an efficacy translation perspective, from all of  
6 the other compounds that I and others have been  
7 giving to people for decades, that seem, at least  
8 on the surface, to look similar from a pre-clinical  
9 perspective, but of course have not worked out yet  
10 in patients.

11 In terms of disclosures, I have consulted  
12 extensively for, first, Rinat, and then Pfizer, and  
13 also J&J on their anti-NGF programs. I also worked  
14 for virtually every other company in the analgesic  
15 space at one time or another. However, I do not  
16 have any long-term stake in these compounds or any  
17 other compounds, actually, in terms of patents,  
18 royalties, equity, et cetera.

19 So it's been stated many times that rational  
20 analgesic drug development, in terms of trying to  
21 find new compounds for new targets, has not worked.  
22 And the anti-NGF antibodies is clearly the most

Page 230

1 definitive exception with due deference to the  
2 story that Andrew told a minute ago and the one  
3 that we'll hear momentarily.

4 So again, my purpose is to try to figure out  
5 if there really is anything different about the  
6 pre-clinical efficacy profile that was seen at the  
7 time that the decisions were made with this class  
8 to carry them forward into clinical trials that  
9 gave extra confidence.

10 Now, I will focus just on one of this class,  
11 which is tanezumab, which used to be called RN624,  
12 purely for my own personal convenience. I didn't  
13 have the time to look into the origins and data of  
14 all the products in this class. And for the  
15 purpose of today's presentation, I'm just going to  
16 make the assumption that this product represents  
17 the class. If that turns out to be wrong, then  
18 I'll be wrong, and I'll have to give a revised  
19 version of this presentation sometime in the  
20 future.

21 Anything that I have to say that is  
22 intelligent, you can attribute to this guy over

Page 231

1 here. You can see him walking around the room.  
2 His name is Dave Shelton. He's sitting in the  
3 back. And Dave has been intimately involved in  
4 this whole story, and has witnessed, and has  
5 continued to witness, the living history of the  
6 development of this class of compounds from the  
7 very beginning.

8 So he has been very generous in spending a  
9 lot of time with me, helping me get these stories  
10 straight myself in making sure I understand the  
11 concepts, especially on the pre-clinical side,  
12 which I never present pre-clinical data because  
13 it's not my thing. So only because of Dave's  
14 collaboration do I have the confidence to present  
15 you a little bit.

16 Another person who has very generously spent  
17 some time allowing me to interview her is Pat  
18 Walicke. Pat Walicke gave me a call in 2004 and  
19 said, "We have this interesting class of compounds.  
20 We think it might work for pain," the same question  
21 I get asked every day, "What kind of clinical trial  
22 do you think we should do?"

Page 232

1 So Pat ran the program, the early clinical  
2 program on tanezumab and spent some time with me  
3 over the last few days telling me what was going  
4 through her mind as she was making decisions for  
5 this program.

6 Finally, Leslie Tive, who many of you  
7 probably know, who is currently at Pfizer and  
8 currently has a key position in this program, also  
9 provided me a lot of insight and information.

10 So I'm going to tell this story in seven  
11 chapters. First chapter, at least the way that  
12 I've chosen to divide it up, is that nerve growth  
13 factor itself was very well known. There was a  
14 very well-established science going back to the  
15 1950s as the first in the neurotrophin family. And  
16 its main role had been perceived as being growth  
17 and survival of neurons, neural structures in the  
18 context of development.

19 Then data emerged in the 1980s that not only  
20 did NGF have a role during development, but it also  
21 appeared to have a role in inflammation, where it  
22 was dramatically upregulated. That paper came out

Page 233

1 in 1987 and that observation actually just sat  
2 there, that NGF seems to have a role in  
3 inflammation as well.  
4 This is actually the paper that I'm  
5 referring to, Weskamp and Otten, 1987. And as you  
6 can see, it was interesting to me -- I've not  
7 really been intimately involved in this field at  
8 all -- that looking back at this paper as being one  
9 of the progenitors of the whole notion that NGF  
10 might have some involvement in pain, you can't even  
11 find that in the title of the paper.  
12 ELISA for nerve growth factor, they were  
13 basically developing a tool for studying it. But  
14 if you look at the paper itself, you can see data  
15 showing that NGF is dramatically upregulated. This  
16 is a blister-based preparation here. This is  
17 intraplural injection of carrageenan here, where  
18 there was this very major finding of regulation of  
19 NGF and inflammation.  
20 So that observation was sitting there. And  
21 then, at the same time -- I will call this  
22 chapter 2, and I've titled this chapter, "NGF

Page 234

1 Hurts." And so in the early 1990s, two  
2 observations happened at more or less the same  
3 time. The first is that NGF was being developed by  
4 Genentech at this time. And I know there's some  
5 folks from Genentech in the room, and maybe they  
6 can pipe in after, too, and fill in anything that I  
7 leave out.  
8 NGF itself, because of its role in promoting  
9 and supporting neural growth, was being developed  
10 as a therapeutic treatment for diabetic neuropathy.  
11 There were some laboratory findings that suggested  
12 that it could be beneficial, and then there were  
13 first some phase 1 and then some phase 2 studies.  
14 And the observation was that, when you injected NGF  
15 into people, it hurt. And I'll tell you more about  
16 that in a minute.  
17 The second set of observations occurring at  
18 around the same time is that the same thing was  
19 happening in animals. If you injected NGF into a  
20 rat, it hurt. And I know that there are people in  
21 the room that were involved in that, and I'll look  
22 forward to any further insights you have about that

Page 235

1 as it evolved.  
2 This is just a quote from one of the papers  
3 of one of the two phase 1 studies that was done on  
4 NGF itself. And I think it's worth listening to  
5 this because it gives you a flavor from a clinical  
6 perspective how unusual and how intense and  
7 provocative this observation was.  
8 "Subjects who received recombinant human NGF  
9 developed diffuse myalgias beginning about 60 to  
10 90 minutes after administration, worsening over the  
11 next 4 to 6 hours, and then slowly resolving over 2  
12 to 8 days.  
13 "The subjects reported mild to moderate pain  
14 with swallowing, pain in the masseter muscles,  
15 increased by chewing, sore throat, and pain with  
16 eye movements. You never see anything like this in  
17 a clinical trial.  
18 "Sometimes, abdominal and limb muscles were  
19 involved. These myalgias were described as though  
20 one had run a marathon without preconditioning, or  
21 as though one had done a thousand sit-ups or push-  
22 ups."

Page 236

1 That was a quote from one of the patients.  
2 I've got more quotes, too, but I cut them out for  
3 the interest of time. This is a very stunning  
4 observation, I would say, from someone who does  
5 clinical trials.  
6 So that's just a piece to give you a flavor  
7 of what was going on in the clinical side. The  
8 same observations were made in the other phase 1,  
9 the phase 2, and then finally the phase 3 study of  
10 NGF before, finally, that program was stopped  
11 because of failure of the phase 3 study.  
12 Then on the pre-clinical side, you've got  
13 another paper showing that the same thing applies  
14 to the rat. And here is his paper from Lewin and  
15 Mendell in 1993. And this is just one of the many  
16 tables and figures in that paper that gives you a  
17 sense for, if you give NGF to rats, you get this  
18 major mechanical hyperalgesia, also a thermal  
19 hyperalgesia compared to the control rats.  
20 There are many other similar convergent  
21 findings, and the interpretation of the authors was  
22 that administration of NGF can lead to a profound

Page 237

1 behavioral hyperalgesia, similar to what we were  
2 seeing in the patients.  
3 The next chapter in this story is that,  
4 well, if NGF provokes pain, why don't we give some  
5 kind of anti-NGF and see if that blocks pain? That  
6 would be the next logical step in the story. So  
7 there were three main research groups that were  
8 working in this area, and there are folks in the  
9 room who were involved in those studies. And  
10 essentially, the findings were that, if you do a  
11 model of inflammation in rats and you give anti-NGF  
12 either before, or even during, or after the  
13 induction of the inflammation, you prevent the  
14 hyperalgesia.  
15 However, interestingly, you don't modify the  
16 science of inflammation. And this was one of the  
17 interesting findings early on, that although this  
18 is being given in the context of inflammatory  
19 model, you're modifying the pain behavior without  
20 modifying the manifestations of inflammation.  
21 I think it's also worth noting that this  
22 finding was convergent across three different labs,

Page 238

1 different continents, different investigators,  
2 different countries, different approaches to  
3 neutralizing NGF; and I would imagine, if we went  
4 into it in more detail, different strains,  
5 different feed, different bedding, different this,  
6 different that.  
7 So part of what we'll get to later when we  
8 talk about what seemed to be the hallmarks of  
9 robust clinical data -- and this follows directly  
10 on Andrew's comment -- this sort of convergence of  
11 findings that are robust across multiple conditions  
12 may be one of those clues.  
13 This just happens to be the paper that  
14 Clifford and his group published of the three. I  
15 just pulled it out because Clifford wasn't here to  
16 disagree with how I would present it. And here is  
17 just the sensitivity score from one of these models  
18 comparing the CFA injection to the CFA plus the  
19 NGF, showing a substantial reduction in the  
20 sensitivity.  
21 So scientific research doesn't happen in a  
22 vacuum. It always happens in a social context, and

Page 239

1 in a cultural context, and in a funding context.  
2 And so I think it's interesting to talk about what  
3 was going on that facilitated what seemed to be  
4 very rapid progress for across a few chapters of  
5 this story in a relatively short amount of time.  
6 Again, a lot of this thinking comes from  
7 Dave Shelton. First, this wasn't brand new,  
8 although actually, interestingly, Andrew's science  
9 is kind of brand new. But one of the things that  
10 gave comfort at this time is that there was  
11 widespread experience with a concept of what NGF  
12 did.  
13 For that reason, a lot of labs had materials  
14 lying around that they had relatively ready access  
15 to relatively rapidly initiate different kinds of  
16 experiments. Because of that, there was also  
17 dispersion of skills and materials in multiple  
18 different labs. And from what Dave indicated to me  
19 at the time in Genentech, there was very little  
20 experience in Genentech. There was no experience,  
21 actually, in developing an analgesic.  
22 So the folks at Genentech saw value in

Page 240

1 collaboration with external labs, some of whom are  
2 in this room. And what facilitated those  
3 collaborations at the labs is that those labs were  
4 there with knowledge, experience, and materials  
5 ready to go.  
6 Then finally, I think that it seems that the  
7 convergence between what was being seen pre-  
8 clinically and the pain provocation that was being  
9 seen in the human model clinically, that synergism  
10 of findings between the rat and the human also gave  
11 people more confidence to proceed.  
12 Chapter 4, I called "Back in the Real  
13 World." And again, things happen in the context of  
14 funding. So what was going on in the real world  
15 while all of this elegant science was progressing?  
16 So Genentech was transitioning its focus to  
17 oncology and not pain, although rumor has it that  
18 there is a renewed focus on pain at Genentech, and  
19 that would be nice to hear more about now.  
20 But back then, pain was being transitioned  
21 out until, finally, the entire Genentech  
22 neuroscience group was shut down, and there were

Page 241

1 folks that believed in the program, but the company  
2 had decided not to pursue it.  
3 So Rinat Neuroscience was spun out in 2001  
4 based on VC funding, and the main drivers of this  
5 new entity were the folks that you see here, Arnon  
6 Rosenthal, Patrick Lynn, and Alun Davies, although  
7 of course there are multiple others involved as  
8 well.  
9 As Dave indicated to me, they looked at  
10 their new building just down the road from  
11 Genentech on September 11th, 2001, so a memorable  
12 day for a variety of different reasons, announced  
13 their funding two months later, and then they were  
14 in business, trying to figure out, "Now, what  
15 should we do with this? What should we spend our  
16 investors' money on?"  
17 This is what determines what progresses.  
18 And so there were a variety of different factors  
19 that facilitated the decision to accelerate into a  
20 pain program, but there were a few obstacles as  
21 well. And I think it's interesting to think about  
22 these practicalities.

Page 242

1 They were a new VC-backed company. They  
2 wanted a clinical-stage molecule. That's what the  
3 investors wanted. They were very comfortable with  
4 antibodies. That was their sweet spot. The  
5 pre-clinical efficacy data was deemed at the time  
6 to be robust. And so we've just had a discussion  
7 of, "What does that mean? Is one pre-clinical  
8 package any more robust than another?"  
9 On the next slide that I'll show you in a  
10 minute, I have done my best to define what  
11 robustness is in terms of what the perspective was  
12 at that time about the data. And I think that's  
13 one of my take-home messages from this  
14 presentation, is what does robustness mean? So  
15 you'll see that in a second.  
16 There was a recognize at Rinat at the time  
17 that we can fool around all we want with  
18 pre-clinical models, but the only way to actually  
19 characterize the efficacy and safety of the  
20 compound is in the clinic. And finally, there was  
21 directionality for the pre-clinical program. There  
22 was somewhat better efficacy in one type of pain

Page 243

1 than other types of pain, and I'll tell you more  
2 about that later. But the conclusion of the group  
3 was that what they called deep somatic pain,  
4 arthritis models, that seemed to be where the  
5 strength in the pre-clinical program was.  
6 It was very interesting to me to hear what  
7 the obstacles were, and this may astonish some of  
8 you as much as it astonished me. First of all,  
9 apparently, there was a lot of debate at the  
10 company at the time about whether -- the quote was,  
11 "How can we compete with aspirin?" was the quote.  
12 "Do we really need a new pain therapeutic?"  
13 What I heard in my mind, what I said to  
14 myself in my mind, when I heard that was actually a  
15 question is, "Wow. How disconnected these  
16 companies are from the real world." How can you  
17 ask a question like that? You just have to walk  
18 into a pain clinic and spend 15 minutes there, and  
19 you know that aspirin is really not doing the job  
20 out there in the real world. Forget about the GI  
21 bleeds.  
22 But that was actually a topic of discussion.

Page 244

1 And boy, if this is actually still a question in  
2 boardrooms of investors, then we really have a  
3 communication problem on our hands that we need to  
4 fix. I don't know if it is or it isn't, but if it  
5 is, we need to work on that.  
6 Another interesting dimension of this  
7 decision-making process was a concern that, well,  
8 pain is a primary care problem. Everybody's got  
9 it. Is a biologic ever going to be a primary care  
10 drug? With the implication being that, "Unless we  
11 can really get it out there in primary care, where  
12 pain lives, it's not going to be successful in the  
13 marketplace."  
14 On the other hand, there was exactly the  
15 opposite argument, which is that, well, what if we  
16 get some weird safety issue? Aren't we going to be  
17 glad if we start studying cancer pain or some more  
18 niche part of the population, where we can make a  
19 more compelling risk/benefit argument if there does  
20 happen to be some weird risk that we run across?  
21 I think I'll leave that in your mind for  
22 later because it remains an interesting issue,

Page 245

1 given some of the safety questions that have been  
2 raised around this class of a product. And I will  
3 say a word about that later, although my focus will  
4 not be on safety during today's presentation.  
5 So having said all that, the facilitators  
6 outweigh the obstacles. They decide that there was  
7 room for a new pain therapy, and the program  
8 proceeded.  
9 Now, here is what I mean by robustness. So  
10 this is sort of a summary of the large amount of  
11 pre-clinical data that was available at that time.  
12 You saw efficacy. Regardless -- despite the fact  
13 that it was studied in different pain models,  
14 different endpoints within those models were all  
15 positive. It wasn't just the von Frey or just the  
16 radiant heat.  
17 Virtually, whatever endpoint you looked at  
18 in those models was positive, different time points  
19 within, though. It wasn't just positive at hour 4,  
20 but it was positive across a spectrum of time  
21 points. There were different types of rats used in  
22 the different experiments. There were different

Page 246

1 types of experimental conditions that were used,  
2 different feed, different bedding, different  
3 researchers, et cetera.  
4 Even the antibodies that were used in the  
5 different studies were different, providing again  
6 convergent validation of the mechanism, different  
7 molecules that are not anti-NGF antibodies. For  
8 example, molecules that blocked binding to track A  
9 also produced similar findings, providing more  
10 convergence, and again, labs, investigators,  
11 continence, and finally and importantly, although I  
12 put it at the end, is that there was consistent  
13 superiority against active comparators.  
14 That was important to the team for, really,  
15 two different reasons that may sound the same, but  
16 they are different. One reason is that, if  
17 something really is better than morphine,  
18 gabapentin, et cetera, maybe you will be more  
19 likely to see technical success in your clinical  
20 trials if the drug's that good.  
21 Then secondly, there's the commercial flip  
22 side of that coin, which is that not only might we

Page 247

1 eventually see p less than .05, but maybe out in  
2 the marketplace, we'll see the commercial  
3 differentiation that really is the requirement  
4 these days for successful commercialization,  
5 especially of expensive drugs.  
6 So this, to me, is actually a conclusion  
7 slide, although it's buried in the middle of my  
8 presentation.  
9 So what did the team do next? This is  
10 chapter 5. It seemed like there was a lot of data,  
11 although most of it was out there in the  
12 literature, rather than having being done at  
13 Genentech or by some very closely held  
14 collaborator. And a lot of the models that were  
15 done, one can ask what the relevance is to human  
16 clinical pain.  
17 So the next step that was taken was to  
18 confirm the pre-clinical efficacy profile with  
19 studies that were sparked by Genentech, but then  
20 conducted with the insight, and knowledge, and  
21 experience, and laboratory expertise of a number of  
22 different collaborators.

Page 248

1 So the key papers are the one from Tim  
2 Brennan's group of the hind paw incision model; a  
3 paper authored by Dave Shelton and collaborators  
4 with a more aggressive model of CFA, where it's  
5 injected into the tail base and produces a profound  
6 destruction of the joint; and then also a cancer  
7 bone pain model from Pat Mantyh's group that we've  
8 heard mentioned previously.  
9 This is a picture of a cute little rat foot  
10 with an incision from the hind paw incision model  
11 and just a graph from the paper from Tim Brennan's  
12 group showing that the anti-NGF antibody brought  
13 your pain sensitivity just about to what it was  
14 after the sham procedure.  
15 This is a picture from the bone pain study  
16 from Pat Mantyh and his group, and  
17 shows -- actually, there is a lot on this slide,  
18 and in the interest of time, I'm going to gloss  
19 over it.  
20 First of all, when you put sarcoma cells in  
21 bone, in this model, you get this perfusion of an  
22 aroma in neurite formation. And that, as well as

Page 249

1 the pain associated with it, are blocked by the  
2 administration of NGF.  
3 So that gave a very powerful convergence  
4 with the other pre-clinical findings. And all  
5 those three studies that I mentioned were positive,  
6 so done under much more careful conditions, and  
7 with more visibility to the sponsor at Genentech,  
8 and all convergently positive.  
9 Chapter 6, in the meantime while all this is  
10 going on, nothing that I've showed you  
11 today -- I've not mentioned the word tanezumab yet  
12 because nothing that I've showed you has anything  
13 to do with tanezumab. It was not used in any of  
14 those studies. And so meanwhile, Genentech is  
15 trying to figure out what antibodies should we  
16 actually bring forward into the clinic.  
17 I'm not going to go through this in any  
18 detail. Suffice it to say that there were a number  
19 of criteria that the company had for what would be  
20 an appropriate antibody among the many options that  
21 they had. And they finally ended up in April 2002  
22 with the product that they had ultimately decided

Page 250

1 to bring forward. And if you have any questions  
2 about that, then we can ask Dave at the break.  
3 The next chapter and the last chapter is  
4 where I personally got involved in this program,  
5 which is now, what clinical syndrome -- given this  
6 pre-clinical data, what do we do clinically. And  
7 there were a number of drivers of that decision.  
8 And, again, that program is led by Pat Walicke.  
9 First is that I'm not actually showing you  
10 any details of the breadth of pre-clinical data,  
11 but it was studied in both somatic, and  
12 neuropathic, and visceral pain models. And while  
13 there were positive signals of efficacy across all  
14 three types of pain, the feeling the team was that  
15 the efficacy was most profound in the bone pain  
16 model.  
17 So the pre-clinical was driving them towards  
18 bone pain. Because of funding, and the pressures,  
19 and the need for success, there was a drive to try  
20 to get early signals of efficacy from the phase 1  
21 studies. And this is a question that I get asked  
22 all the time. We need to do phase 1. Is there any

Page 251

1 way we can get early signals of efficacy, of human  
2 efficacy, out of the phase 1 study, and what are  
3 the options?  
4 The options are studying patients in phase 1  
5 using human experimental pain models in your  
6 healthy volunteers, which, as much as they might  
7 show you interesting data, they raise all sorts of  
8 other questions about whether that itself is going  
9 to translate into patients when you get there. And  
10 that's pretty much it.  
11 So the drive was to try to do phase 1 in  
12 patients. And that was not really an issue at a  
13 biologics company because, given all their  
14 experience in oncology, they were used to doing  
15 their phase 1 studies in patients anyway, so that  
16 felt very natural to them, although it might feel  
17 awkward in a small molecule environment.  
18 So if we're going to study patients, what  
19 kind of patients? If we're interested in bone  
20 pain, then the feeling was that osteoarthritis is  
21 probably the most practical, and convenient, and  
22 representative model of bone pain. You can find

Page 252

1 the patients. There's lots of them out there.  
2 Their pain syndromes tend to be relatively stable.  
3 It's not like back pain, which is complicated for  
4 reasons that were discussed in detail yesterday  
5 during another talk.  
6 So the decision was made to -- there had  
7 been lots of positive studies in various kinds of  
8 agents in osteoarthritis, relatively well-  
9 established how to do those studies, validated  
10 endpoints, et cetera, et cetera.  
11 So the other interesting facet of their  
12 phase 1 studies, and what gave them an opportunity  
13 to capture early signals of efficacy, is that  
14 because of the prolonged half-life of these  
15 antibodies, you need weeks between dose escalation  
16 cohorts. And observing patients for weeks gives  
17 you more opportunity to capture efficacy data than  
18 if you're just observing a patient for a few hours  
19 with a chronic pain syndrome; although that can be  
20 done, too, which is another story. But at that  
21 time, that was viewed as a positive reason to do  
22 phase 1 in OA and try to get early signals of



Page 253

1 efficacy.  
2 Now, to Pat Walicke's credit, she's a very  
3 smart woman and has a lot of experience in clinical  
4 research. She read a lot, and she caught on to  
5 this whole assay sensitivity concept. And back in  
6 2004, it was still early days. Our first impact  
7 meeting was, what, 2002 or something like that?  
8 And so I was very gratified to hear from her on the  
9 phone the other day when I spoke to her, that she  
10 read all the IMPACT papers at that time, was very  
11 familiar with all the contributors. And it made me  
12 feel good that we had accomplished something  
13 without necessarily knowing it at that time.  
14 So the phase 1 studies are not published, so  
15 I don't have that data to show you, but suffice it  
16 to say they were positive, as you probably could  
17 guess. And that led to proof of concept, a rather  
18 large landmark proof-of-concept study of tanezumab  
19 in patients with osteoarthritis of the knee. This  
20 was published in the New England Journal of  
21 Medicine in 2010 and showed essentially a degree of  
22 efficacy that had, to my mind, never been seen

Page 254

1 before in a clinical trial of an analgesic for any  
2 kind of chronic pain indication.  
3 Just to give you a flavor, this is the  
4 placebo in this grayish color. And they had a  
5 15-ish-millimeter reduction from baseline in their  
6 average pain intensity. And here, in the highest  
7 dose of the tanezumab group, you've got a  
8 45 millimeter reduction in pain intensity, a  
9 30 millimeter difference between active and  
10 placebo. And I can tell you, from the world of  
11 clinical trials, you just don't see that. You just  
12 don't see that.  
13 So the rest kind of is a history. I'm not  
14 going to dwell in detail on what's happened since  
15 then, since this is a meeting about translation.  
16 And I think the focus is about, well, what was it  
17 about the pre-clinical data that might have been  
18 different?  
19 I will give you a quick overview of where we  
20 are now with this particular compound. This is an  
21 overview of all the randomized control trials that  
22 have been done up until the point where this

Page 255

1 product was put on clinical hold by the FDA in 2012  
2 because of a joint safety issue. So there has been  
3 very little done since 2012.  
4 In fact, I think the only other studies that  
5 I've read out since then is the cancer study  
6 because that's the only study that was allowed to  
7 proceed at that time.  
8 So here is what tanezumab does. So first of  
9 all, just in terms of the breadth of the program,  
10 you've got 30 clinical trials that have been  
11 completed, 28 plus 2 phase 1 studies that are not  
12 on this slide.  
13 You've got 17 studies in osteoarthritis,  
14 2 studies in chronic low back pain, the cancer  
15 study that I mentioned, a bunionectomy study, which  
16 was negative. And I've organized these studies by  
17 pain category. So the bone pain or the somatic  
18 pain are up here. There have been two small  
19 neuropathic pain studies and four small visceral  
20 pain studies.  
21 The results, what these pluses and minuses  
22 mean are the following. Two pluses means that the

Page 256

1 p value of the study was less than .05. One plus  
2 means that the p value of the study was not less  
3 than .05, but there was a numerical trend favoring  
4 the active group. And the minus sign means that  
5 the study was flat. There was no sign of efficacy  
6 whatsoever.  
7 So just to give you the quick overview,  
8 there's strong evidence of efficacy and  
9 osteoarthritis, 2 positive studies in chronic low  
10 back pain with 1500 patients in them. The bone  
11 cancer study was not statistically significant, but  
12 there was a trend in favor of the active group that  
13 manuscript is soon to be submitted into the  
14 literature.  
15 The bunionectomy study, which is an acute  
16 pain study, that failed totally. There was no sign  
17 of efficacy of tanezumab. But for reasons that I  
18 don't understand, they had no positive control in  
19 that study, which is a mistake. You'd never do a  
20 bunionectomy study without a positive control. I'm  
21 not sure why. There must have been a reason, but I  
22 don't know what it is; and now, more than a decade

Page 257

1 or so later. But so far as we know, this drug was  
2 not effective in this acute pain model.  
3 Interestingly, you've got statistically  
4 significant results in painful diabetic neuropathy  
5 and a very small 30-ish per-arm clinical trial. In  
6 another 30-ish per-arm post-herpetic neuralgia  
7 study, the p value was -- I forget -- .09 or  
8 something like that, with about a .6 or .7  
9 difference. So I think, actually, this medication  
10 probably works in neuropathic pain as well.  
11 Visceral pain is kind of an interesting  
12 story. So there was a very small interstitial  
13 cystitis study. And a lot of people view  
14 interstitial cystitis as a graveyard. Good luck  
15 getting a positive study of anything in that  
16 syndrome, but in fact, the study was positive,  
17 prostatitis, a trend, but negative p value.  
18 They started a study in pancreatitis, but  
19 stopped it because of the clinical hold after two  
20 patients, and there was a negative endometriosis  
21 study. So I think, again, an encouraging signal in  
22 visceral pain as well.

Page 258

1 So that's where we are right now with  
2 tanezumab. In the interests of time, the only  
3 point that I'll make with this slide, which is a  
4 pooled analysis of all the OA studies, is that  
5 there is superiority over an active comparator,  
6 which in this case was naproxen. And in the world  
7 of pain research, we don't see superiority over  
8 active comparators.  
9 Also, superiority of oxycodone in a clinical  
10 trial, another osteoarthritis clinical trial;  
11 again, that's good, although I do feel obligated to  
12 point out that oxycodone was not superior to  
13 placebo in this study. So there may have been  
14 technical issues with how it was dosed, but still,  
15 I sense that it's superior to an opioid comparator  
16 as well.  
17 Again, my talk is not on safety, but I feel  
18 compelled to mention that these programs were put  
19 on clinical hold since 2012. And the two main  
20 concerns have been joint safety. That was how it  
21 all started, and also sympathetic nervous system  
22 safety has been another concern.

Page 259

1 So I have two conclusion slides. And these  
2 are the lessons that I think I've learned as a  
3 non-scientist, as a clinician and a clinical  
4 trialist, from looking back at this particular  
5 program and trying to ask myself the question,  
6 "What was different here, if anything?"  
7 These are my thoughts about it, and, again,  
8 there are people out here that know much more about  
9 this program than I do, and I'll be curious to how  
10 people react to this.  
11 First is, I can envision in my own mind a  
12 robustness checklist. And what I mean by  
13 robustness checklist is that slide that I showed  
14 before. When your efficacy is robust across all  
15 those different sorts of conditions, it's more  
16 persuasive than if it's not robust across those  
17 conditions. That's the first lesson that I have  
18 learned.  
19 I have looked at a lot of pre-clinical data  
20 from the perspective of the clinic over the last  
21 25 years of giving drugs to patients in clinical  
22 trials, and I don't think I've seen a package with

Page 260

1 this degree of robustness. I haven't looked back  
2 in the bowels of my computer to confirm that that's  
3 really true. I'll be curious what other people  
4 think. But this feels very different to me.  
5 The second checklist that I could imagine  
6 using is what I would call a methodology checklist.  
7 And what I'm thinking there is the checklist that  
8 Andrew Rice and colleagues have contributed to the  
9 literature, where if studies are not done and with  
10 all the features that Andrew has shown on his  
11 slide -- randomization, blinding, et cetera,  
12 et cetera, et cetera -- they are hypothesis  
13 generating only.  
14 Thirdly, benefit over standards, that's  
15 something worth looking out for in the pre-clinical  
16 data set. And of course, I have seen a lot of data  
17 that shows supposedly superiority over standards,  
18 but I would bet money that, looking back at all the  
19 data that I've seen, you would not see that  
20 superiority over standards replicated across that  
21 robustness checklist that I gave you.  
22 Next, just a word of caution -- and this is

Page 261

1 really more Dave's thought -- that beware of  
2 interpreting results about superiority when you're  
3 studying a drug that was -- when you're using a  
4 model that was developed for another drug. So for  
5 example, if you were testing ibuprofen versus  
6 morphine in a CFA model, you might be tempted to  
7 say, "Well, look at this great new drug, ibuprofen.  
8 It's better than morphine." But, of course, that  
9 model preferentially shows the efficacy of NSAIDs  
10 over opioids.

11 So be careful about drawing superiority  
12 conclusions with certain models since the models  
13 themselves may bias you in favor of one class over  
14 another.

15 This is a point that I got from Steve  
16 McMahon -- I'll give you the American pronunciation  
17 of his last name for the purposes of today -- which  
18 maybe he'll want to discuss in more detail during  
19 the break, which is that -- and I didn't really  
20 appreciate this -- a number of our efficacy models;  
21 if the drug that we're testing produces sedation,  
22 or dizziness, or nausea, or Lord knows what, the

Page 262

1 readout might be an analgesic readout. You might  
2 interpret that sedation as analgesia.

3 I actually hadn't ever thought about that  
4 before, but that makes me very skeptical now about  
5 models where a side effect might actually confound  
6 the primary efficacy endpoint. And I'm going to  
7 have to think a little bit more about which models  
8 ought to be viewed more skeptically because of that  
9 problem or, alternatively, what models should be  
10 viewed favorably because the side effects do not  
11 confound the readout of the primary efficacy  
12 endpoint.

13 So this is what I think I'm going to be  
14 looking for in the future when someone presents me  
15 a pre-clinical data set and says, "Do you think we  
16 should bring this into patients?"

17 From a clinical perspective, I think there  
18 are also some interesting lessons to be derived  
19 from this story. But one lesson is that, now that  
20 we have methods for improved assay sensitivity,  
21 which we could present a long list of what those  
22 are, maybe we should be doing more phase 1 studies

Page 263

1 in patients and utilizing those methods to try to  
2 get more early signals of efficacy. And I see that  
3 happening in pain research from my vantage point.

4 I think that if the phase 1 studies had been  
5 done on volunteers and there was some readout on  
6 experimental pain, that would not have been  
7 persuasive as what they had, which was a readout in  
8 real patients. So I'm a fan of studying patients  
9 and getting clinical endpoints when you can as  
10 opposed to experimental endpoints, although  
11 hopefully we'll learn more about those over time.

12 The methods to augment assay sensitivity are  
13 really critical, especially in the early small  
14 studies. It seemed like, in this case, there was  
15 some pre-clinical suggestion about where the most  
16 robust findings were. And that does seem, at least  
17 from what we can tell right now, to map onto what  
18 we're seeing clinically.

19 Finally, you don't know what your clinical  
20 efficacy profile is until you study your drug in  
21 patients with different clinical syndromes.  
22 There's just no shortcut. And I think it's

Page 264

1 fabulous that Pfizer, J&J, and other people that  
2 are working on these compounds have the courage and  
3 vision to test diverse clinical syndromes, even  
4 where we actually don't know a lot about how to do  
5 clinical trials.

6 Who knows how to do a chronic prostatitis  
7 study? If you raise your hand, you're a liar.  
8 Nobody knows how to do those studies. And so I  
9 give the sponsor credit for at least beginning the  
10 process of exploring how to do studies in clinical  
11 syndrome, where there is a high unmet need, but not  
12 a lot of track record about how to do the studies.

13 That minor point there is that we and the  
14 clinical research methods development community  
15 need to develop better visceral pain models to  
16 foster research in that area. Thank you very much  
17 for your attention.

18 (Applause.)

19 DR. TURK: [Inaudible -- off  
20 mic] -- stimulating to get us again thinking about,  
21 what are the things we want to be thinking about as  
22 different molecules potentially move forward. We

Page 265

1 are running a little behind schedule, so we'll just  
2 take a couple questions. Then we'll save other  
3 ones for the discussion.  
4 Sharon?  
5 DR. HERTZ: Sharon Hertz. So you presented  
6 a lot, and you really focused on the efficacy. But  
7 we can't escape thinking about the safety. And  
8 this is a really good example of situations that  
9 arise.  
10 So two points that I'd like to make is  
11 there's been a lot of discussion about how dirty  
12 molecules work better, but they also hurt more.  
13 And we still have some pretty notable safety issues  
14 that need to be addressed with this. And what's  
15 interesting from a translation perspective is how  
16 the efficacy here seems to have been very  
17 predictive, with the safety not so much. And  
18 that's something that would be interesting to see  
19 if there's any way to think about that and  
20 anticipate it more in the future.  
21 There was one other point I wanted to make,  
22 but I think I lost it already. But anyway, I don't

Page 266

1 know what else could have been done. We have  
2 looked back at the non-clinical work, trying to see  
3 if there's any way that we could have anticipated  
4 the arthropathy signal. I'm not sure that there's  
5 anything there that would have anticipated that.  
6 But to the extent that we don't have them  
7 yet, I am still a fan of more specific targeting,  
8 even if it's not an expected target, in terms of  
9 reducing the amount of noise in the safety side of  
10 things.  
11 DR. KATZ: What do you mean by more specific  
12 targeting, Sharon?  
13 DR. HERTZ: So even though this is called  
14 nerve growth factor and we're targeting anybody  
15 who's against it, it's not specific for nerves or  
16 nerve growth in any way. And that's where we're  
17 starting to see the other -- some of this toxicity  
18 profile is nerve related, but it's also not nerve  
19 related. And apparently, if you start really  
20 exploring the targets or the areas where nerve  
21 growth factor are active, it's pretty diverse,  
22 which then gives you the opportunity for many

Page 267

1 potential safety signals, including ones that  
2 aren't anticipated.  
3 DR. KATZ: It's a very interesting point,  
4 and I also took note of the fact that NGF  
5 inhibition produces a cascade of all sorts of  
6 different effects. And the question is, well, is  
7 that positive because it's necessary? Maybe that's  
8 a way to produce better efficacy from new compounds  
9 rather than narrow targeting. But maybe that  
10 creates safety risks.  
11 Chas?  
12 DR. BOUNTRA: Nat, I thought that was  
13 brilliant. Thank you. Just a couple of comments.  
14 It's interesting -- I mean, all the data that Steve  
15 and Clifford generated in the mid-90s. I mean,  
16 everybody was aware of that. But it was  
17 interesting that big PhRMA weren't leaders in this  
18 target. Secondly, both the two stories we've heard  
19 today, this afternoon, have been peripheral  
20 mechanisms.  
21 Thirdly, you seem to be implying that, if  
22 you have a target or an asset that works in loads

Page 268

1 of animal models, treating pain almost as one big  
2 thing, it's going to work in all pains in the  
3 clinic. I'm not sure I agree with that. I also am  
4 not sure I agree that the data package for this is  
5 more robust than everything else we've taken into  
6 the clinic.  
7 DR. KATZ: I think that's a question. It's  
8 a latter point that you made, Chas, is this  
9 pre-clinical efficacy profile really more robust in  
10 the ways that I suggested than other compounds that  
11 have been brought into the clinic and have been  
12 shown in clinical trials to fail?  
13 I personally think that, if anything were to  
14 come out of this meeting, that would be something  
15 very important to look at, because if there is a  
16 way of predicting in advance what products are  
17 going to work in the clinic and what aren't, by  
18 looking at the pre-clinical efficacy profile, if my  
19 intuition is right, that's worth knowing. And if  
20 it's wrong, it's also worth knowing.  
21 DR. TURK: We're going to have the last  
22 question this session from Allan.

Page 269

1 DR. BASBAUM: I'm just curious. I'm very  
2 familiar with the program. The discussion is, you  
3 seem to be convinced, in retrospect, it's correct,  
4 of course, that OA was a good indication to go  
5 after. And I don't know -- and Dave Shelton would  
6 know the answer to this. I don't know if it was  
7 ever tested in the MIA model, the monoiodoacetate  
8 model that's ostensibly an arthritis model.  
9 Then, of course, the real issue is, is OA,  
10 even though it responds to an NSAID, an  
11 inflammatory condition. And one wonders whether  
12 that choice in retrospect was great, but really, if  
13 one had to sit around a table, would one say,  
14 "Given that pre-clinical package, let's go after  
15 OA."  
16 Deep somatic pain in OA, I don't find those  
17 necessarily the same.  
18 DR. KATZ: So obviously, I don't know the  
19 answer to your question, but I'll throw out an  
20 idea. I think, because none of these pre-clinical  
21 models are models of OA, the more convergence you  
22 have from different poorly representative models,

Page 270

1 the more robust the overall conclusion is that will  
2 ultimately work in some human.  
3 DR. BASBAUM: What would you say about  
4 post-op?  
5 DR. KATZ: What would I say about post-op in  
6 terms of what?  
7 DR. BASBAUM: [Inaudible – off mic.]  
8 DR. KATZ: Why didn't it work in the  
9 bunionectomy study, do you mean?  
10 DR. BASBAUM: [Inaudible – off mic.]  
11 DR. KATZ: I don't know. And Dave and I  
12 actually have spoke at length about that. And I  
13 don't know why. But I think -- Dave, maybe you  
14 remember. I think that the drug was dosed pretty  
15 close to the actual time of the surgery.  
16 If there needs to be some time for these  
17 anti-NGF antibodies to do whatever they do, then  
18 perhaps dosing further in advance of surgery would  
19 be a strategy where it could have worked. Or it  
20 could be that the other idea that we discussed was  
21 that maybe whatever's going on early after a  
22 somatic insult of one kind of another is not

Page 271

1 dependent upon these NGF-related mechanisms, and  
2 it's only what's going on after some period of  
3 time, 12 hours, 24 hours, whatever, that becomes  
4 dependent upon NGF mechanisms.  
5 So I don't know the answer, but there may be  
6 an answer.  
7 DR. BASBAUM: That's a good question.  
8 DR. SHELTON: Just to add one thing, that  
9 was probably more properly called a broken study.  
10 We went to sort of great pains to use one surgeon  
11 and be very careful that the surgeries were all  
12 very similar. And what we ended up with is  
13 patients with essentially pain scores of zero  
14 within 24 hours. So to be clear, we saw nothing  
15 that looked like efficacy, but we didn't have a lot  
16 to work with.  
17 DR. TURK: Thank you, Nat. And there will  
18 be time again for more questions after, when we  
19 have the panel discussion. So if you've had  
20 questions for any of the speakers, we'll be  
21 bringing that back up. So we're continuing in the  
22 same pattern, which is to be looking at stories to

Page 272

1 tell us about how things have evolved. And,  
2 hopefully, at the end, you'll be able to start  
3 pulling some things together. And maybe you can  
4 give us some guidance and some advice on future  
5 molecules and future development of those.  
6 Our next speaker is going to be Dr. Lars  
7 Edvinsson -- I'm probably saying your name  
8 wrong -- who is a professor and chairman of the  
9 department of medicine at Lund University in Lund,  
10 Sweden. It's my pleasure to have him come and join  
11 us. He's another one of these people who's  
12 traveled a great distance for coming here.  
13 So now, we're going to be hearing about CGRP  
14 and blocking agents with potential for antimigraine  
15 therapy.  
16 Presentation – Lars Edvinsson  
17 DR. EDVINSSON: Thank you very much for the  
18 invitation to come here and speak to you. It's  
19 been a fabulous two days for me. A migraine is a  
20 very common disease. Perhaps up to 1 out of 6  
21 people here in this room have migraine. And what  
22 does it characterize? Well, it's pain, moderate to

Page 273

1 severe pain, lasting between 4 and 72 hours,  
2 associated with a lot symptoms that you are  
3 familiar with.  
4       The socioeconomic costs of migraine is  
5 astronomical. It's actually in the same level as a  
6 stroke. I didn't know that, so it's a very  
7 important issue to care for. I put on this girl  
8 here because we didn't qualify for the world  
9 championship, but in soccer for women, we are very  
10 good. And actually, she has a migraine.  
11       There is a good match between blood flow in  
12 the brain and neurology symptoms. And as we can  
13 see here, this is blood flow in the brain. This  
14 patient has a visual aura. The blood flow in the  
15 visual cortex is low, coupling between the neuronal  
16 symptoms and flow of metabolism.  
17       This patient has a visual aura that  
18 continues to be a sensory motor aura with the  
19 numbness and weakness of the arm. So it's a nice  
20 coupling. And another issue is just, you can say,  
21 some kind of a background because I would like to  
22 tell you that migraine is a disease of the central

Page 274

1 nervous system.  
2       In a German study, they looked on patients  
3 with acute migraine attacks, and they had to come  
4 to the clinic in the middle of the night and they  
5 put on the PET camera.  
6       What happened was that in these 9 patients,  
7 they had activation in the brain stem, in a region  
8 which is around, shall we say, the rough and the  
9 PAG. And also a very other notable finding, which  
10 has been not discussed so much, is this one. It's  
11 actually in the cerebellum.  
12       Today's findings, we have seen that the  
13 purkinje cells of the cerebellum are heavy with  
14 CGRP, and the dendrites and axons are full of their  
15 CGRP receptors. So that's one issue we are looking  
16 into.  
17       Another interesting aspect here is that,  
18 after treating these patients with sumatriptan, the  
19 pain disappeared, but these changes remained. So  
20 the attack was still there. And some of Peter  
21 Goadsby's work adds further to this that brain stem  
22 and other areas, like the hypothalamus, are

Page 275

1 involved in these attacks. So I'm just giving you  
2 this aspect. It's a CNS disorder.  
3       So what am I doing here? Well, I am going  
4 to speak to you about my part of this kind of  
5 puzzle. And my original work was centered around  
6 understanding cerebral blood flow, its regulation  
7 in health and disease. And as we can see here, we  
8 have one brain vessel. We have the sympathetic  
9 nerves with, like, three signal substances. We  
10 have the parasympathetics with a lot of other  
11 signals like nitric oxide, acetylcholine, PACA, and  
12 VIP, and finally the trigeminal system, again, with  
13 many substances, including CGRP.  
14       So why I tell you this is because we were  
15 doing all this kind of work as the first in the  
16 world, and we looked upon how these signals can  
17 regulate blood flow and their role. But the story  
18 about the CGRP came when the CALCA gene was mapped,  
19 the calcitonin gene, in 1983. Immediately when  
20 that was published, we made antibodies, set up  
21 Regimmune assays, and we had a whole lot of methods  
22 to examine this in the cerebral circulation.

Page 276

1       For example, like we have seen here with  
2 immunogold methods, antibodies towards, in this  
3 case, neuro peptide Y in sympathetics and here in  
4 the sensory, the large vesicles containing CGRP and  
5 the electron-lucent ones, presumably substance P at  
6 that time.  
7       So that was a neat method. We also saw  
8 these kind of thin fibers in the blood vessels of  
9 the brain and also in other cranial vessels. We  
10 did tracing, anterograde and retrograde, and found  
11 that it comes from the trigeminal ganglion. And  
12 again, co-localization with substance P, which was  
13 the agent that was very hot for pain in those days.  
14       The question we had at that time was to find  
15 out what are these sensory fibers doing for the  
16 cerebral circulation? At that time, we were not  
17 interested in migraine. We were just interested in  
18 how do these fibers regulate blood flow? And we  
19 did a lot of experiments, I can tell you, and  
20 different kinds.  
21       This is, you can say, a cortical vision on  
22 top of a CAT, and you can measure the diameter of

Page 277

1 the PL vessels. We can apply a different kind of  
2 stimuli. And we tried a lot of vasodilators. We  
3 tried vasoconstrictors, only vasoconstrictors  
4 caused click contraction, like in this case,  
5 noradrenaline, and then returned very quickly to  
6 control. And that is to be expected, of course.  
7 But in animals, where we had taken away the  
8 trigeminal nerve, innervated the sensory system.  
9 We got the same amount of constriction, but it took  
10 a long way to get back. So this was a trigeminal  
11 vascular pathway that we had found.  
12 What is a bit funny for the migraine field  
13 was that people give vasodilators, and that causes  
14 a migraine or a headache-like symptom today. And I  
15 don't think that is activating this. What can  
16 activate it? We went actually into stroke models  
17 to look on that. And in patients with subarachnoid  
18 hemorrhage, this mechanism is activated to defend  
19 the brain towards vasoconstriction.  
20 I also went to the pathology and pulled out  
21 the vessels from patients that have died from a  
22 subarachnoid hemorrhage, and it seemed that they

Page 278

1 were completely devoid of CGRP, but not of any  
2 other signal substance. So the theory worked.  
3 So that's kind of where I think this  
4 mechanism comes into play, shall we say, in this  
5 defense role. It could, of course -- you talk  
6 about spreading depression in the migraine field.  
7 That is a kind of vasoconstrictor that you can  
8 elicit. And the aura is thought to be such a  
9 vasoconstrictor. And it has been shown that CGRP  
10 is part of this early hyperemic phase in spreading  
11 depression.  
12 Now, if we now move into the CGRP receptor,  
13 this first part is something Frank asked me to do  
14 to give us a little bit of the history. Now, the  
15 more modern thing is that the CGRP receptor, as you  
16 see here, consists of this part, the 70 calcitonin  
17 receptor-like receptor, CLR, and ramp 1. When CGRP  
18 comes here, it docks here and this moves together,  
19 activating receptor, and recombinant protein, and  
20 then the G protein to produce its effect.  
21 When we looked, where could the receptors  
22 be, because that's where the questions are today

Page 279

1 for the treatment of migraine -- at some time, it  
2 was a very large discussion. How about the  
3 endothelium? Is there any kind of CGRP receptors  
4 in the endothelium? And as you can see here, this  
5 is just a marker of the endothelium. And if you  
6 look on CLR or ramp, there is none.  
7 So in other experiments, we showed it has  
8 nothing to do with the endothelium. The receptors  
9 are on the smooth muscle cells. And you can see,  
10 actually, they're all ramp 1, 2, and 3. But the  
11 experiments have shown that, if ramp is present, it  
12 predominates, so ramp 1 and CLR joins to form this  
13 receptor complex.  
14 You have seen other kinds of antibodies.  
15 You can see, again, co-localization on the smooth  
16 muscle cells. They are recent, specific, ramp 1  
17 and CLR antibodies.  
18 If we compare human middle meningeal artery,  
19 that's a dura mater artery which lacks the  
20 blood-brain barrier and then middle cerebral  
21 artery, we can easily go down here and say that  
22 CGRP is 10 times more potent on the cerebral

Page 280

1 artery. The reason I think is due to number of  
2 CGRP receptors available in these vessels.  
3 The dura mater has been used in a lot of  
4 migraine models as a surrogate. And since you are  
5 paying the researchers, you are well aware of  
6 C fibers, A delta, and the other kind of A fibers.  
7 We find that in the dura, we have thin,  
8 unmyelinated C fibers and they contain CGRP. We  
9 have the A fibers, and they contain ramp 1 and CLR.  
10 So there's a clear separation between their  
11 localization.  
12 Another issue is the mast cells, which have  
13 been discussed a lot. We can just move up to this  
14 one. There are lots of mast cells on the  
15 dura mater; virtually none in the brain. And in  
16 rodents, they contain the CGRP receptor complex,  
17 CLR and ramp 1. You can get them stimulated, and  
18 they release histamine, which is one of the  
19 signals.  
20 However, we have done it in humans as well.  
21 And then we don't find a receptor. And we have  
22 done experiments. We can't get CGRP to release

Page 281

1 histamine from the human muscles. So again, as  
2 people have been saying here, man is our key model.  
3 Strange, isn't it?  
4 Here is a picture that Peter Goadsby gave  
5 me. So you can figure out that I did a lot of this  
6 kind of work since three decades. And at this  
7 meeting -- actually, it was '86. Peter came to  
8 Lund, to a meeting we had. And we met there for  
9 the first time. He was a young researcher working  
10 in Sydney. So we agreed upon collaboration and  
11 that's perhaps what started his career. I can  
12 always be nice to friends.  
13 Very early, we did a kind of study where we  
14 stimulated a trigeminal ganglion in patients with  
15 trigeminal neuralgia. And what happened was that  
16 each patient secreted CGRP and substance P. That  
17 was to be expected. Both peptides are in the  
18 trigeminal ganglion, so no strange thing.  
19 The key issue, what we did in all these  
20 experiments, was that we compared -- initially, if  
21 we take the samples from the external jugular vein  
22 or from the cubital fossa, it turned out very

Page 282

1 quickly that we never got any signal when we took  
2 the peptide measurements in the cubital fossa. And  
3 of course, it's because it's released from the hip.  
4 In the migraine patients, it was also a very  
5 strange finding. CGRP was released in all the  
6 migraine patients, and it correlated with the pain  
7 of the patients. After triptan treatment, it  
8 normalized, and the pain disappeared.  
9 At the same time, we did substance P and  
10 we'd never saw any substance P release. And  
11 actually, subsequently, I've taken samples and done  
12 studies of 10 more of the neural transmitters  
13 related to the cranial circulation, and it seems to  
14 be very unique that's it's CGRP that is released.  
15 For example, you can see again substance P.  
16 VIP has a special story, and VIP is  
17 co-released in cluster headache, what is now  
18 cluster headache. Well, if you have a colleague  
19 that has migraine, and they have an attack, they  
20 have, of course, a severe headache, they are pale  
21 in the face bilaterally, so to say. A cluster  
22 headache, they have unilateral reddening. They

Page 283

1 have rhinorrhea, nasal congestion, other symptoms  
2 from the parasympathetics.  
3 So we see this is from a migraine, but in  
4 those cluster patients, there is a co-release of  
5 VIP, as you can see, and also in another kind of  
6 chronic paroxysmal headache. The interesting issue  
7 with a cluster headache is that triptans work also  
8 on these. So there is a kind of brain stem  
9 interaction between the two systems.  
10 Now, we move into something perhaps a little  
11 more interesting for you as general pain  
12 researchers. We have these small molecules. They  
13 are called gepants, and they have been tried in  
14 acute migraine trials. Patients having an acute  
15 migraine attack, they get a tablet, or sometimes  
16 injection with olcegepant, which was the first one.  
17 That caused the pain to be less, significantly  
18 less, so they work.  
19 But that is not always the issue. If you  
20 like, you can just look at my review in the Lancet  
21 about all these results. But the burning issue is,  
22 where can they act? And of course, do they need

Page 284

1 the blood-brain barrier? And then we have the  
2 issues of antibodies and these Spiegelmers, which  
3 are another group of agents which can block CGRP.  
4 I'll try to dissect the kind of parts that  
5 we need to discuss to understand where they could  
6 act because we know if they act. If we just take  
7 telcagepant, which is the one that is mostly  
8 studied, you can see that this is CGRP dilatation.  
9 And this is a human brain vessel gotten from  
10 neurosurgery. So that's your English part of the  
11 cortex when that is removed -- sorry.  
12 Now, they have the tumor or an epileptic  
13 focus, which they are operated for. And sometimes,  
14 there is a small vessel which we can use. So we  
15 can see, here's a nice parallel shift with  
16 telcagepant, and here is a middle meningeal artery.  
17 Same thing. We can calculate to dissociation  
18 constant. And of course, it's the same receptor,  
19 so the PA2 values are the same.  
20 What you can see also, if you are interested  
21 in pharmacology, is that the first part is a  
22 parallel shift without dropping Emax, but later on,



Page 285

1 that's dropping Emax. So there's competition and  
2 then some non-competition in the higher doses. It  
3 doesn't matter so much for the patient.  
4 Are there other parts where these blockers  
5 connect? Where are the receptors? And this is not  
6 for you do any kind of major thing, but this is  
7 just a list to show inside the brain, that there  
8 are lots of different sites where we have CGRP  
9 receptors available, and some of them are listed  
10 here. Of course, in PAG, there are colliculus, for  
11 example, and some other regions here and also in  
12 the cerebellum; so not many binding sites that it  
13 could act there [indiscernible]. Do they pass the  
14 blood-brain barrier?  
15 Then this has been discussed ever since the  
16 triptans were introduced into the market. People  
17 have said yes or no. They have been saying  
18 patients get stiff when they get their sumatriptan  
19 or some kind of neurasthenia.  
20 Nork [ph] did this study. They gave a PET  
21 tracer, which was marked for CGRP receptors. And  
22 as you can see, perhaps not so good, but here is

Page 286

1 the brain, and some small radiance in the brain  
2 stem, but the cerebellum lights up like a beacon.  
3 Then they gave systemically tercagepant in a dose  
4 which is used in the clinic. Nothing happened.  
5 It's the same amount of PET tracing, PET signal.  
6 Only when they gave about 10 times higher dose of  
7 tercagepant did they, as I say, get the initial PET  
8 tracer to disappear from the binding sides.  
9 So it suggests, if anything, that if there  
10 is a little tercagepant passing into the brain, it  
11 does not have much to do with the efficacy of the  
12 drug. So this is my current view, that even this  
13 small molecule doesn't pass in, shall we say, a  
14 dose that is producing the clinical efficacy.  
15 What other issues do we have, and where else  
16 could the CGRP blockers and antibodies work? Could  
17 it be on the dural extracranial vessels or, which I  
18 would be advocating for today, the trigeminal  
19 ganglion.  
20 For the gepants, we now have five of them.  
21 They have no effect on the general circulation when  
22 you give them. Why? Probably, CGRP doesn't have

Page 287

1 any tone effect on the circulation. So it's a good  
2 disease that nothing happens until you have the  
3 specific pathway activated. So that's when it can  
4 do something.  
5 How about the antibodies? We have now three  
6 antibodies towards CGRP. We have one antibody  
7 towards the CGRP receptor available. Are they  
8 effective? Well, I think, a month or ago or so, it  
9 was presented data for two of the CGRP antibodies,  
10 that they were effective in chronic migraine.  
11 How specific are they? Well, they are very  
12 specific for CGRP. And they don't cross a reactor  
13 towards other members of the same family, like  
14 amylin, calcitonin, or adrenomedullin. The  
15 antibodies are directed towards the C terminal.  
16 It's also interesting, just like tercagepant, they  
17 have the better focus and, here, better binding to  
18 primates than to rodents, and they are active in  
19 picomole concentrations. It's been studied in  
20 Cal Sure [ph], and of course, CGRP induces cyclic  
21 AMP generation, and this can be blocked.  
22 There's also been a study looking on the

Page 288

1 skin vasodilatation and on an increase in middle  
2 meningeal artery diameter. And it was compared  
3 with one of the gepants and virtually showed that  
4 the antibody that they studied was effective, but  
5 it was slow or in onset, and it lasted much longer.  
6 We have another group of agents, which are  
7 called CGRP-binding Spiegelmers, oligonucleotides.  
8 And it's been difficult for me, really. I followed  
9 it a little to understand what they do, but it  
10 appears from people working there that you have  
11 this CGRP molecule in the circulation and these,  
12 should I say, oligonucleotides often are the size  
13 of 10 marrow or something like that. They can bind  
14 on to CGRP in making a complex, which is hindered  
15 or blocked from having an effect on the receptor  
16 sides.  
17 The first one that I got my hands on was  
18 NOX/C89. And we had some effects, and I'll show  
19 you them. So there is also others coming out from  
20 the same company. They haven't tried them in  
21 migraines as I know yet, but speaking with the  
22 Kirk [ph], it's -- you can say -- it's like a

Page 289

1 chemical entity, almost like an antibody, but in a  
2 different way, but doing the same job.  
3 Topical application of this NOX/C89 could  
4 inhibit CGRP-induced dilatation. And when you came  
5 to other methods, like electrical stimulation, it  
6 took some time in the method. And as I wrote here,  
7 "It was significant, not until there had been 7 or  
8 9 stimulations." So it seems that it takes a long  
9 time for it to act in vivo, at least. And more  
10 recently, there is even more specific NOX molecule  
11 appearing.  
12 So just having a look on the trigeminal  
13 ganglion, you can say we have small- to medium-size  
14 ganglion cells, and they contain CGRP. But the  
15 large ganglion cells, they contain the CGRP  
16 receptor. Can they communicate as I indicated?  
17 These red balls, I put out. I think so because we  
18 have, also, this -- it's actually nerve fibers that  
19 you can find within the ganglion.  
20 Another very important aspect is these  
21 cells, the satellite glial cells. And they are  
22 like glia in other places. They've formed around

Page 290

1 the neurons, and they also contain the CGRP  
2 receptor elements.  
3 Another aspect, which you probably are very  
4 familiar with is that if you give Evans blue, which  
5 is an old dye, the whole rat is blue, but the brain  
6 is -- of course, if you haven't manipulated it,  
7 it's pale. If you take out the pineal, it's bluish  
8 because it has a very poor blood-brain barrier. If  
9 you take out the trigeminal ganglion, it's blue, so  
10 it lacks the blood-brain barrier.  
11 You can, of course, see that lots of dye  
12 mingle in the trigeminal ganglion. That would mean  
13 that this is an excellent site where your agents  
14 easily can go to. I think we have forgotten this  
15 kind of obvious place.  
16 Another aspect is, you can see here, there  
17 are blood vessels. They're also full of Evans blue  
18 staining, so here is a good case that we have a lot  
19 of agents that can pass into that.  
20 We have done some experiments using the MCA.  
21 Am I out of time or are you getting tired of  
22 me?

Page 291

1 Just some obvious points. If we perfuse  
2 MCA, it maintains its blood-brain barrier. If we  
3 put in CGRP in this vessel, it doesn't dilate if we  
4 give it luminally. Again, it doesn't affect the  
5 endothelium, but if we give it abluminally, it  
6 dilates.  
7 So I jumped on this. And if we don't take  
8 this same vessel -- here is the CGRP response. We  
9 put on CGRP abluminally, on the outside, where the  
10 nerves are. So this is sensory nerves going to the  
11 perivascular space. And if we put on a CGRP  
12 blocker -- this is the old one, CGRP 8 to 37. And  
13 if we put it abluminal on the same side, you can  
14 block the response. If you put it luminally, it  
15 has no effect.  
16 Here is the case for the antibody. So if  
17 you put the antibody on the outside, you can block  
18 it. If you put it on the inside, nothing happens.  
19 And this is one of the gepants, same thing. And  
20 here is the NOX blocker. So it did, in my hands,  
21 very little even when it was put on the outside.  
22 So that was for the trigeminal ganglion. I

Page 292

1 will just come to nearly the end here. The third  
2 place where we can imagine is the brain stem, the  
3 trigeminal nucleocomplex. And one thing which has  
4 been discussed is where do these trigeminal fibers  
5 go in the brain stem? Of course, to luminal 1 and  
6 2, but they are separate.  
7 So in the outer part, we see the fibers from  
8 the containing receptors, the A fibers, and on the  
9 slightly more inner part, that's where we have  
10 CGRP. And they are on separate fibers, so they  
11 could interact here in some way or, of course, to  
12 go to other parts.  
13 I'm not boring you with any more of this, I  
14 think. The main issue, I would think, is that we  
15 should look more into the trigeminal ganglion as a  
16 possible site where we could have the therapeutic  
17 effect of the CGRP antagonistic agents. Thank you  
18 very much.  
19 (Applause.)  
20 DR. TURK: We're running a little late, and  
21 we want to maybe even end a little bit early. So  
22 what we're going to do is, I'll take two questions.

Page 293

1 We'll have a 15-minute coffee break. We'll come  
2 back for a last presentation and then a short  
3 panel. So two questions if there are. I know  
4 we're keeping you from coffee.  
5 Allan?  
6 DR. BASBAUM: Why not? What I've always  
7 been puzzled is -- not puzzled -- is there  
8 something unique about the trigeminal vasculature  
9 or even the ganglion? Because one tends to  
10 analogize to other parts of the body. And is it  
11 absolutely clear that the anti-CGRP has no effects  
12 in other parts of the body and in other conditions,  
13 even particularly, say, ischemic conditions where  
14 there might be a vascular component?  
15 DR. EDVINSSON: One aspect with CGRP in the  
16 trigeminal ganglion, which is a bit unique, is that  
17 50 percent of the neurons contain CGRP. So it's  
18 very high. And the other half contain the  
19 receptor, so it seems to be very concentrated on  
20 that. I haven't really gone through in detail the  
21 dorsal root ganglia yet, but it's a tempting  
22 scenario. Other signals, we have looked on in the

Page 294

1 trigeminal ganglion -- I mean, I have gone through  
2 a lot of them -- there is nothing standing out so  
3 beautifully as the CGRP system. So it could be  
4 that whatever, epigenetics or something, makes this  
5 kind of prime CGRP site.  
6 When it comes to the ischemia question,  
7 there was one study on the heart. They had the  
8 dogs. They were exercised, and then nothing  
9 happened. But then if you make the coronary artery  
10 very much thinner, you can exercise them again, and  
11 they are on the verge of developing ischemia, but  
12 nothing happens. You give a CGRP blocker, same  
13 thing, but if you give it triptan, they develop an  
14 infarct.  
15 DR. TURK: Any last question before we have  
16 a coffee break? And there will be a chance for  
17 questions a little bit later. So let's come back  
18 at 20 to -- what, Bob? Make it a short coffee  
19 break. Come back at 25 to 4:00.  
20 (Whereupon, a brief recess was taken.)  
21 DR. DWORKIN: So we're going to start again.  
22 Thank you all for your endurance. So we have one

Page 295

1 more presentation left and then we'll have a panel  
2 discussion, like we have had before, for about  
3 45 minutes at most. And the plan is to call the  
4 meeting to an end at 4:45. So if you're planning  
5 to have a taxi or a shuttle bus outside at 5:00,  
6 you don't really have to rush and leave the meeting  
7 early because we'll end at 4:45.  
8 So it's a great pleasure to introduce our  
9 last speaker, Dr. Marcelo Bigal, who was at Albert  
10 Einstein College of Medicine for a great many  
11 years. And then he moved a few years ago to Merck  
12 and, more recently, moved to Labrys, a small  
13 start-up in San Mateo, California. And so it's  
14 delightful to have him here with us to talk about  
15 clinical studies of anti-CGRP agents.  
16 Presentation -- Marcelo Bigal  
17 DR. BIGAL: Good afternoon, everybody. I  
18 know it has been an incredibly busy two days for  
19 everybody. I'm going to try to be concise and make  
20 the clinical points here. As a disclosure, I am  
21 the chief medical officer of Labrys Biologics.  
22 Labrys is developing one antibody, anti-CGRP, and

Page 296

1 Labrys is in the process of being acquired by Teva  
2 Pharmaceuticals.  
3 Before Labrys, I was at Merck, developing  
4 the CGRP antagonist platform. And I have been on  
5 the other side as well since 2001, heading two  
6 headache research centers in the United States, in  
7 Connecticut and in New York City.  
8 What I would like to discuss with you is, I  
9 am not going to repeat what Dr. Edvinsson has  
10 presented already. He's the main source. He is  
11 the man that discovered and described the story.  
12 I'm going to, however, present my perspective on  
13 some specific aspects of the relevance of CGRP in  
14 migraine, then the challenges we face when we try  
15 to develop a small molecule for, again, CGRP, where  
16 we are in antibodies. And I'm going to talk a  
17 little bit about the one I am developing because  
18 it's one that I have more data about.  
19 So CGRP migraine, migraine is a disease that  
20 actually is a disease of stages. The disease is  
21 artificially divided in chronic and episodic in  
22 absolute lack of data. Why? There is a stage of

Page 297

1 migraine that's called chronic and is defined when  
2 people have more than 15 days of headache per month  
3 and another one that is episodic, and they have  
4 less than 15. It's very scientific. It's like  
5 this, 15, less than 15, symmetric, symmetrical,  
6 let's divide the disease in two stages.  
7       There is migraine. Migraine is a disease  
8 that may be very benign, and people have very  
9 infrequent headache attacks. And they treat with  
10 over-the-counters or symptomatic medication.  
11 Migraine may be a disease that effects individuals  
12 on a daily basis, and there is everything in  
13 between.  
14       So it's a disease. And to complicate  
15 matters, meaning migraine patients evolve into a  
16 more chronic stage and remit to a more benign state  
17 through their lives until they find a stage where  
18 they belong and they stay there.  
19       So I prefer to divide migraine as I am  
20 saying here, as single disease, with stages, each  
21 of them with different medical needs. So in the  
22 very low frequent stages, patients are well-

Page 298

1 attended with OTCs. Patients with more frequent  
2 headaches, we require the triptans, specific  
3 migraine medications that block the serotonin  
4 pathways.  
5       These are easy to manage most of the time,  
6 easy-to-manage patients with low risk of  
7 complications, but as patients start evolving, some  
8 of them start developing more frequent forms of  
9 migraine. They require prophylaxis now, not only  
10 symptomatic medication. They require prophylaxis.  
11 And some of them, 1 percent in the population, will  
12 evolve to a stage where they have migraines on more  
13 days than not, full-blown migraines, headache,  
14 photophobia, phonophobia, nausea, the whole  
15 picture. And this can be incredibly debilitating,  
16 meaning incompatible with normal functioning.  
17       The biology of the disease is the same,  
18 however, largely the same. There are added  
19 factors, risk factors, biological vulnerability,  
20 that stages may have that others don't, but the  
21 disease is largely once.  
22       You learned this story about CGRP. Right?

Page 299

1 CGRP stands for calcitonin gene-related peptide.  
2 It's the most potent vasodilator that we are aware  
3 of. It causes brutal vasodilation when on the top  
4 of blood vessels. But more important, it was  
5 initially discovered when we were developing the  
6 triptans for the acute therapy of migraine.  
7       We found that, actually, when blocking  
8 triptans, the therapeutic discovery, actually,  
9 Dr. Edvinsson discovered all these steps that  
10 actually preceded the triptans. But the  
11 therapeutic importance of CGRP became evidence when  
12 we realized that, when we give a triptan like  
13 sumatriptan for the acute therapy of migraine and  
14 we address the serotonin pathways, we would block  
15 the degranulation of the trigeminal nerve. And  
16 among the substances that were not being released  
17 any longer, we had CGRP.  
18       At the time, we thought that migraine was a  
19 vascular disease, not as nowadays, that we know  
20 that migraine is a neurological disease. So  
21 basically, we were thinking about this vascular  
22 condition that I can give vasoconstrictive

Page 300

1 medications and block the attack. And by the way,  
2 I just discovered this important and potent  
3 vasodilatory molecule. Bingo. Let's block this to  
4 avoid the vasodilation because the vasodilation is  
5 the cause of the migraine pain.  
6       It is not. Right? Although CGRP caused  
7 vasodilation, and although vasodilation caused  
8 edema in the blood vessels -- which blood vessels?  
9 The dura mater blood vessels and the blood vessels  
10 innervated by the trigeminal nerve. But actually,  
11 CGRP is indeed released when the trigeminal nucleus  
12 caudalis is activated.  
13       So the vasodilation that happens in migraine  
14 is very late in the process of the migraine attack.  
15 And indeed, CGRP seems to be involved, but not only  
16 on vasodilation, but on an inflammatory cascade  
17 that happens outside of the blood-brain barrier at  
18 the level of the trigeminal endings.  
19       But this is also not primary migraine.  
20 What's primary migraine is actually what you saw  
21 Dr. Edvinsson showing, some activations that happen  
22 at the brain stem. That's where migraine begins.

Page 301

1 Migraine begins when individuals that suffer from  
2 the disease, for reasons that we do not fully  
3 understand, have activation in the brain  
4 stem -- have activations in certain areas of the  
5 brain stem.  
6       When they have these activations, the gate  
7 opens. The gate to what? To everything. Now,  
8 minor insults are perceived as severe pain. Normal  
9 light is perceived as photophobia. Normal sound is  
10 perceived as phonophobia. Right? Your brain  
11 became hypersensitive to the internal and external  
12 environment. Right?  
13       So the gate opens and the gate is inside the  
14 brain, but the gate means nothing. It's like a  
15 road where the gate opens. The gate means nothing  
16 if a car doesn't go through. And what is  
17 happening, the CGRP, therefore, in my way of  
18 seeing, has a dual importance.  
19       First, CGRP is represented here and is  
20 involved in the activations that actually are  
21 initiated in the beginning of the migraine attack  
22 and are involved in opening the gate. But CGRP is

Page 302

1 going to release it outside of the blood-brain  
2 barrier.  
3       So inside, outside of the blood-brain  
4 barrier, creating a low degree of inflammation  
5 that's now perceived as a lot of pain just because  
6 the gate is open inside the brain. And this CGRP  
7 is going to cause this mass at the trigeminal  
8 endings. We also come and sensitize the trigeminal  
9 endings, causing primary sensitization, secondary  
10 sensitization, and eventually thalamic  
11 sensitization.  
12       So it's released, and it comes back to bite  
13 the brain. It releases and comes back again. And  
14 patients will start having pain and photophobia,  
15 and phonophobia, and central sensitization. And  
16 therefore, they become more predisposed to pain and  
17 everything else. And they evolve from very low-  
18 frequency forms of migraine into very high  
19 frequency forms of migraine.  
20       So you can block the CGRP pathway inside the  
21 brain. You can block the CGRP pathway outside of  
22 the brain. And, basically, as Dr. Edvinsson

Page 303

1 clearly demonstrated -- and the work was pivotal  
2 because it settled 15 years of discussion or  
3 more -- you can clearly have efficacy blocking CGRP  
4 with compounds that do not penetrate the brain.  
5       So when we are giving these compounds, we  
6 are basically targeting the trigeminal ganglion and  
7 what else is distal to the trigeminal ganglia.  
8       Very interesting, although CGRP is the most  
9 potent vasodilatory molecule that we know, blocking  
10 CGRP does not cause vasoconstriction. It restored  
11 the normal tone, as it does not cause  
12 vasoconstriction. I'm going to talk a little bit  
13 about clinical data on that.  
14       Levels of CGRP are elevated. Peripheral  
15 levels and jugular levels of CGRP are elevated in  
16 the course of migraine attacks, as his pivotal work  
17 showed, and the levels are restored by  
18 administration of sumatriptan, as I mentioned.  
19       The levels are further elevated in chronic  
20 migraine versus episodic. The more headaches they  
21 have, the higher is the level of CGRP, even in  
22 between attacks. I'm not talking during the pain;

Page 304

1 in between attacks. So CGRP is not only involved  
2 in the paraphysiology of migraine, it's involved in  
3 the paraphysiology of transformation from episodic  
4 into chronic.  
5       So I told you a little bit about this story.  
6 We can block this molecule. We don't cause  
7 vasoconstriction. Let's go for it. It's much more  
8 selective. Remember, the acute therapy of migraine  
9 is started with ergotamine compounds, the specific  
10 therapy, that would block every single receptor  
11 that we know of.  
12       Then we developed the triptans that are  
13 second generation or gotamines, where we block only  
14 certain serotonin receptors, and we stop the  
15 release of CGRP and other molecules. Let's be more  
16 selective. Let's try to block CGRP alone -- again  
17 only. I'm sorry, only.  
18       Five small molecules have been advanced  
19 into -- this is just illustrative. Don't try to  
20 read this. But five molecules were advanced into  
21 phase 2, phase 3. They're small molecules. They  
22 never failed on efficacy. There has never been a

Page 305

1 small molecule that we brought into phase 2 and  
2 phase 3 that failed on efficacy. Nonetheless, we  
3 still don't have anything approved because of  
4 something that I'm going to discuss with you, that  
5 was a challenge, that forced us to change the  
6 paradigm.

7 The initial molecules were being developed  
8 for the acute therapy of migraine, not prophylaxis.  
9 Right? They were being developed to be used as a  
10 symptomatic. Patients would use when they have  
11 pain, only when they have pain.

12 The initial medication that was advanced  
13 into phase 2, Dr. Edvinsson mentioned, was  
14 olcegepant. Olcegepant was developed by Boehringer  
15 Ingelheim. It was an IV molecule when these  
16 studies were done. First proof of concept,  
17 beautiful. Right? I mean, classical pharmacology  
18 textbook, dose response, efficacy in the primary,  
19 efficacy in the secondary.

20 The efficacy was coming at a very  
21 interesting level. So for those of you that  
22 actually do not follow the regulatory path for

Page 306

1 migraine, the primary endpoint in acute therapies,  
2 for acute therapies, is a proportion of patients  
3 that become pain-free, zero pain at two hours. Two  
4 hours after administration, they become pain free.  
5 The secondary endpoint is called pain relief. They  
6 can have pain, but the pain has to be mild.

7 So for pain relief, two-thirds of the  
8 patients had pain relief; 42 percent had sustained  
9 pain free. This is a very strict endpoint. They  
10 become pain free at 2 hours and the pain does not  
11 come back in 24 hours.

12 All the medications that we have available  
13 in the market, the triptans have lower rates than  
14 that, no serious adverse events, no cardiovascular  
15 events. Remember, this is a vasodilatory. We  
16 started developing these. Our main and solo  
17 concern was hemodynamics. So nothing came here.

18 The medication was discontinued. And the  
19 reason given was that, actually, they could not  
20 formulate into just oral tablet.

21 The second medication was the one that I was  
22 involved in, and Dr. Edvinsson showed the data on

Page 307

1 the PET scan and stuff. It was telcagepant.  
2 Telcagepant was an oral medication. And here you  
3 have the two pivotals, Protocol 11 and Protocol 16  
4 were the two phase 3 studies, clearly showing that,  
5 actually, the efficacy was aligned with a very good  
6 triptan, better than placebo for primary endpoints  
7 and secondary endpoints, but not only this, for  
8 photophobia, for phonophobia, and for nausea. It  
9 was an approved med based on efficacy parameters.

10 But something happened -- and save this,  
11 because there's something that happened with  
12 telcagepant that happened to most of the  
13 medications, as a small molecule. But the  
14 medication was coming clean, and beautiful, and  
15 most important -- and I really ask you to save this  
16 parameter -- placebo-like adverse events, every  
17 single CGRP that was ever developed has a  
18 tolerability that's similar to placebo, not  
19 telcagepant. All.

20 You do not find a pattern of adverse events.  
21 They are very well-tolerated. You don't find a  
22 syndrome that actually could -- so very tolerable.

Page 308

1 Patients receiving zolmitriptan, which is one  
2 triptan, 40 percent of them have drug-related  
3 adverse events versus 20 percent, 22 percent in the  
4 telcagepant.

5 As we were developing telcagepant, we were  
6 developing a back-up compound that was 10 times  
7 more potent than telcagepant. It was called  
8 MK3207. We didn't give a name because we had  
9 killed it before. We also advanced it into  
10 phase 2. It was an adaptive design, so it was an  
11 exploratory of the doses. So that's why you don't  
12 see a clear signal as you saw with the others, but  
13 that from an efficacy perspective, significantly  
14 more promising than telcagepant, which is the one  
15 that I just showed you, meaning this was coming  
16 really great, but something happened.

17 There were, so far, three CGRP antagonists  
18 and three affected stories. Boehringer, after  
19 olcegepant, developed a 4-CGRP receptor antagonist.  
20 And what they did here is, actually, they compared  
21 with an incredibly effective triptan called  
22 eletriptan. And what you have here is, actually,

Page 309

1 the efficacy of the molecule in early time points  
2 going all the way to 48 hours, and in very dark,  
3 you have eletriptan.  
4 So another attribute -- I already told you  
5 about the brutal tolerability of CGRP antagonists.  
6 The other attribute of the compounds in general,  
7 the class, they are not the fastest medications in  
8 town -- triptans can be faster -- but they last  
9 long.  
10 So if you start seeing -- I mean, they go in  
11 parallel to eletriptan. At two hours, eletriptan  
12 was better, at least numerically, than the doses of  
13 CGRP antagonists. At 24 hours, there is a reversal  
14 of the trend, at 48 hours a little bit, and it  
15 lasts. The efficacy of CGRP receptor antagonists  
16 lasts.  
17 Everything that I am telling you here is for  
18 the acute therapy of migraine. And finally, later,  
19 Bristol-Myers -- and there is the co-author of this  
20 study over there in the back. Bristol-Myers  
21 developed a fifth CGRP receptor antagonist. The  
22 active comparator was sumatriptan. And once more,

Page 310

1 several of the doses came effective, and, once  
2 more, brutal tolerability. I happened to be  
3 invited to write an editorial to this paper that  
4 was published in Cephalalgia a few months ago.  
5 So the question is, actually, if they are  
6 always effective and they become tolerable, why  
7 don't they get into approval?  
8 I cannot tell about the others, but I can  
9 tell you about what I did, the ones that I did.  
10 You have liver tox. So what happened with this  
11 CGRP receptor? You don't have liver tox when you  
12 give it sporadically. But because migrainers, many  
13 migrainers who have very frequent migraines, many  
14 migrainers will not use this medication  
15 sporadically. They may use it daily.  
16 So the agency properly asks us to stress the  
17 molecule and create studies where we test the  
18 molecules in frequent paradigms of usage. And when  
19 we did this with telcagepant in a study that they  
20 were using daily -- as some people could eventually  
21 do in real life. But remember, 12 percent of the  
22 population has migraines. So a lot of things may

Page 311

1 happen and you have to stress the molecule.  
2 What we've found is that, actually, the more  
3 frequent was the use, the more likely they were to  
4 develop hepatotoxicity. Nobody got really sick,  
5 but the increase was severe, as I'm going to show  
6 you. We did not know at the time that the  
7 accumulation of telcagepant was low  
8 creatinine [ph], so when we gave these very  
9 frequent exposure paradigms, we increased the area  
10 under the curve by eightfold, so we largely gave a  
11 lot, more than we should.  
12 But we saw this pattern in other studies  
13 with other molecules, where we were giving less.  
14 And the reason was never related to the CGRP,  
15 meaning knock-out animals have no liver problems.  
16 With the antibodies that you are going to see,  
17 there is no liver problems. The problem was with  
18 the molecule and the fact that we rescaffolded the  
19 same molecule into its likely different copies,  
20 trying to improve the qualities of the molecule.  
21 And we were scaffolding the liver tox group in the  
22 molecule.

Page 312

1 The liver tox could be like this, meaning  
2 look what happened with the ALTs in some patients.  
3 Very scary. So we discontinued telcagepant. The  
4 rate of liver tox with telcagepant was lower than  
5 what we have with a proven medication such as  
6 Maxoud, significantly lower than what we have with  
7 Tylenol, only happen at frequent exposures, but it  
8 eventually caused a voluntary discontinuation of  
9 the program. The FDA didn't even wait on this.  
10 So then, after five trials and five  
11 failures, what's next for us? There is something  
12 here. The medication works. The tolerability is  
13 excellent. So when you have medication, so for  
14 migraine, every time you have something that's very  
15 tolerable, it becomes a great candidate for  
16 prophylaxis.  
17 Efficacy drives the Q2s [ph]. If you are  
18 miserable because of pain, you are going to take  
19 whatever they give you, and you are going to accept  
20 the side effects. But if I'm asking you to use  
21 something for months in a row or for years in a  
22 row, it better be tolerable.

Page 313

1 So what we tried to do here is actually  
2 switch the paradigm and use the fact -- take  
3 advantage of the fact that monoclonal antibodies  
4 are not created in the liver, are very unlikely  
5 related to liver toxicity. And however, they have  
6 incredibly long half-lives.  
7 So what can I do if a medication that has a  
8 very long half-life, is very tolerable for my  
9 prophylaxis? I can give very infrequent use of  
10 something for patients that are currently  
11 absolutely miserable with what they have, mainly  
12 patients with chronic migraine.  
13 I'm not going to discuss this with you, the  
14 entire course, for there are many talks about this,  
15 many. But we took advantage of the exquisite  
16 specificity that antibodies have. They go to CGRP  
17 and only through CGRP, nothing else.  
18 They do not go to any of the cousin  
19 molecules like amylin, adrenomedullin, calcitonin.  
20 The half-life that they carry is, if they prove to  
21 be safe, an incredible advantage, meaning you can  
22 get these patients -- so for example, the

Page 314

1 medication that I'm developing has a 45-day  
2 half-life. So you can basically, if it works and  
3 if it proves to be safe, actually take these  
4 patients that actually now have daily headaches,  
5 daily migraine headaches, and use two or three  
6 classes of medication twice of them each, and  
7 eventually treat with one injection every six weeks  
8 or an injection every month.  
9 You know how monoclonal antibodies are  
10 developed. I am not going to spend your time here.  
11 You're all bored. You're all tired. But actually,  
12 it was a paradigm shift. It's the first time that  
13 we are developing a biological for the treatment of  
14 migraine and headaches. Biologicals are known for  
15 a neurology. Biologicals are known for pain, but  
16 never for migraine.  
17 So all the processes that other areas  
18 acquired very early in the development, such as  
19 master-cell banks and all the quality control, is  
20 new to the migraine field, and I think we are doing  
21 well.  
22 The monoclonal antibodies that are being

Page 315

1 developed are either fully humanized or human. And  
2 I'm going to talk a little bit about this, meaning  
3 there are several -- meaning, of course, developing  
4 a monoclonal antibody is very different than  
5 developing a small molecule, and the studies are  
6 different, and the paradigm is different. And  
7 there are four companies navigating this ocean, and  
8 I'm going to share a little bit of this with you.  
9 I'm running a little bit on these topics  
10 that I assume you guys are very comfortable with,  
11 but I'll be happy to discuss in the Q&A any details  
12 that you have.  
13 Right now, there are four antibodies being  
14 developed against CGRP. The one that I am  
15 developing is this one. And I'm going to talk  
16 about what I know about the other three, what's in  
17 the public domain, and focus a little bit on us.  
18 So one important difference is, actually,  
19 one of these antibodies, the antibody being  
20 developed by Amgen, targets the receptor to CGRP.  
21 The other three target the ligand CGRP receptor.  
22 Three of them are going for episodic migraine,

Page 316

1 which is actually high-frequency episodic, patients  
2 with less than 15 days of migraine that require  
3 prophylaxis. And we are going for both. I find it  
4 of absolutely no sense to treat people with 5 to 14  
5 and not 15 to 30. So we have an individual  
6 development, one trial for episodic, one trial for  
7 chronic.  
8 We are all in phase 2. All of us are in  
9 phase 2. Most of us are subcutaneous. One is IV.  
10 They are developing a subcutaneous. And the  
11 paradigms of that administration vary according to  
12 the half-life of the molecule.  
13 So let's talk a little bit about the  
14 clinical. You asked me to come here and talk about  
15 what's available clinically. I did from my small  
16 molecule perspective. There is still very little  
17 on clinical efficacy for the antibodies, short of  
18 the company's release of data in the form of  
19 abstracts. So everything that I am aware is in  
20 this slide.  
21 The first one is this medication calls  
22 ALD-334. This medication, different than all the



Page 317

1 others, is not manufactured using a mammal cell  
2 platform. This is yeast, and there are pros and  
3 cons. However, they validated the target.  
4 Basically, it's very interesting. They gave a very  
5 simple phase 2 study, one IV dose, very high dose,  
6 IV, once. Why? Because they did not yet have the  
7 toxicology package required by the FDA.  
8 But although they only gave once, they  
9 followed them for six months after a single  
10 administration, not monthly administration. And as  
11 you can see, with a single administration,  
12 67 percent of the patients had very meaningful  
13 improvement over the first three months of the  
14 study, a single administration.  
15 This was superior to placebo, although this  
16 is the highest placebo rate I've seen in a migraine  
17 trial in ages. And we can discuss a little bit  
18 about this in a migraine trial.  
19 So the therapeutic gain is not that  
20 impressive, but if you consider that they only gave  
21 once -- and this is a competitor, so I have no  
22 interest in coming here and -- but we have to give

Page 318

1 credit where it belongs. If you only consider that  
2 they gave only once and they were able to find  
3 superiority statistically, that's something to pay  
4 attention to. They do not penetrate the brain,  
5 which validates what Dr. Edvinsson said. We are  
6 going to the trigeminal ganglia and to whatever  
7 comes downstream to that.  
8 The second antibody that released data is  
9 being manufactured and developed by Lilly. They  
10 had the toxicology package in place before they  
11 started phase 2, so instead of doing what the first  
12 one did, they gave subcutaneous administrations  
13 every two weeks for three months. It resembled  
14 what phase 3 would look like for them, double-blind  
15 placebo-controlled, and very similar results,  
16 63 percent efficacy, very high placebo rate as  
17 well.  
18 Both of them included patients with less  
19 than 15 days of headache per month. So this is the  
20 efficacy for the antibodies available so far.  
21 There have been five small molecules. The five  
22 were effective, so there are four antibodies. Two

Page 319

1 have efficacy data so far in early stages. Two are  
2 more advanced in Amgen, but still do not have  
3 efficacy data where it should be. And so far, the  
4 two antibodies succeeded.  
5 This is us. LBR-101 is fully humanized at  
6 IgG2. We engineered two mutations to avoid  
7 effector functions. We on purpose want to stay  
8 away from the receptor. And the reason being is  
9 that we don't know who is right. There is one  
10 company that has an incredible know-how engine that  
11 is going to the receptor, and there are others that  
12 are not.  
13 My justification is, I don't want to knock  
14 out the signaling. I don't want you to bring the  
15 signaling down to zero. This is not acute therapy.  
16 I want to have a pool of circulating CGRP able to  
17 be recruited to homeostatic functions. You don't  
18 have a molecule that's so distributed doing  
19 nothing.  
20 So we want to preserve some  
21 tone [indiscernible]. That's why we are not going  
22 to the receptor. Actually, we voluntarily induce

Page 320

1 the 2-point mutations to stay away from the  
2 receptor. We don't bind to anything else. We only  
3 bind to CGRP.  
4 We concluded six phase 1 studies already,  
5 five with IV, going as high as 2,000 mgs. The  
6 highest dose we were testing in phase 2 is 900, in  
7 phase 2. But in phase 1, we came all the way to  
8 2,000 mgs. And in the toxicology package, which I  
9 didn't present since I was asked to focus on  
10 clinical -- but in the toxicology package, we went  
11 to 300 per kilo per week, almost as much as the  
12 weight of the animals.  
13 We did six phase 1 studies to bridge the IV  
14 formulation to subcutaneous formulation. The  
15 half-life of the molecule varies a little bit  
16 according to the dose we are giving, but it's  
17 around 45 days. And we are in the midst of two  
18 phase 2B studies, one for chronic migraine and one  
19 for high-frequency episodic migraine.  
20 In each of these three studies, we tested  
21 two doses versus placebo. And the doses are  
22 different and staggered. So in between the two

Page 321

1 studies, we are testing four dosing paradigms.  
2 There is no reason to believe that something that  
3 works in chronic does not work in episodic and  
4 something that works in episodic does not work in  
5 chronic. It's irrational.  
6 So we are taking is advantage of these and  
7 testing for those new paradigms. They are both  
8 underway. Both of them have -- altogether, we  
9 already have around 280 patients in phase 2.  
10 Several of them already finished. They are going  
11 to receive medication monthly for three months. So  
12 the duration of this study is four months. These  
13 studies are parallel. There are three doses, three  
14 dosing, and four dosing paradigms.  
15 I'm blinded. I don't know if this is going  
16 to work or it's not going to work. But I tell you  
17 that, actually, we only lost two patients after  
18 randomization, so only two drop-outs, none for  
19 adverse events. It's an attribute of the class.  
20 Everyone else is going to come like that.  
21 It's an attribute of the class. It's even  
22 difficult for us when I was writing the

Page 322

1 investigator brochure that, as you know, you have  
2 to release what are the expected adverse events. I  
3 had trouble coming with the adverse events because  
4 we see very little.  
5 If phase 2 becomes positive, we are  
6 eventually going to start a dual phase 3 program,  
7 one for chronic migraine, one for high-frequency  
8 episodic migraines. This is just details of the  
9 IV-completed studies. Many doses that we tested in  
10 IV were super therapeutic. I don't know about  
11 super therapeutic, but actually significantly  
12 superior to the doses that we are testing in  
13 phase 2.  
14 This is phase 1. Treatment-related adverse  
15 events happen in 17.8 percent of participants  
16 receiving placebo, 20, 22 percent of patients  
17 receiving LBR-101. The rate did not increase with  
18 the dose. So 2,000 mgs had the same rate of  
19 1,000 mgs, which had the same rate of 250 mgs.  
20 There was not a dose dependent, and we see this  
21 again, and again, and again.  
22 I have one final slide, and I want to

Page 323

1 preserve time for the discussion, but I just want  
2 to pause a little bit here and say the main  
3 concern -- and I've been doing this now for almost  
4 a decade. The main concern of inhibiting CGRP was  
5 what happens to your body when you inhibit such a  
6 potent vasodilator.  
7 So in the very beginning, we were insane  
8 about that. Two knock-out models of mice were  
9 created without any CGRP. They do not have  
10 increased blood pressure. They are not more likely  
11 to die from cardiovascular events. Actually, they  
12 live longer. Go figure.  
13 When we were developing telcagepant, we got  
14 to the extremes of the study that Dr. Edvinsson  
15 mentioned. So we did pre-clinical studies in pigs,  
16 in dogs, in human coronaries, for clinical animal  
17 studies. Then we got to a point where we did one  
18 study for telcagepant in humans with stable angina.  
19 So we basically got patients with stable  
20 angina, ran them, of course, in an intensive care  
21 unit and, of course, upon the request of the  
22 agency.

Page 324

1 We randomized the patients to a treadmill  
2 test until pain. So they were randomized to  
3 receive placebo or four times the highest dose of  
4 telcagepant, four times the highest dose that we  
5 were testing in clinic. They walk it until pain,  
6 and there was no difference.  
7 So now, we build so much confidence that,  
8 actually, this is less of an issue, that we are  
9 moving to other issues. What about infusion  
10 reaction? What about potential for immunogenicity  
11 or for things like that? But obviously, in  
12 phase 1, we were -- I am sure the others were as  
13 well. I have hours.  
14 We were almost insanely looking for  
15 cardiovascular signals. So everybody in our  
16 phase 1 study stayed confined for seven days. The  
17 Tmax and the IV was three hours. For example, just  
18 inn day 1, where the Tmax happened, they would be  
19 on continuous monitorization plus 12 EKGs. Then we  
20 did triplicate EKGs daily for seven days. Then we  
21 followed these people that receive medication only  
22 once for 90 days. And we just published these

Page 325

1 results and nothing happened.  
2 Did it surprise us? No, it didn't, because  
3 actually, now, at this point, I think we are  
4 getting to a point that we totally understand that  
5 there is so much redundancy in the homeostatic  
6 control of cardiovascular functions. My  
7 understanding now is CGRP over evolution -- CGRP is  
8 so preserved. And it started in evolutionary terms  
9 as a cardiovascular molecule and evolve into a  
10 neuropeptide that is key in pain transmission and  
11 pain modulation.  
12 So in summary, CGRP is a relevant molecule  
13 for a migraine. CGRP receptors, antagonists have  
14 never failed on efficacy. CGRP antagonists have  
15 been difficult to develop due to issues of liver  
16 toxicity.  
17 Monoclonal antibodies may target CGRP, as we  
18 are doing, or its receptor, as Amgen is doing.  
19 They are not degraded by the liver. And several  
20 antibodies, anti-CGRP, are currently in  
21 development. Thanks for your attention.  
22 (Applause.)

Page 326

1 DR. DWORKIN: I'd like to invite Drs. Rice,  
2 Katz, Edvinsson, and also Dr. Rappaport, who is  
3 director of the Division of Anesthesia, Analgesia,  
4 and Addiction Products at the FDA to the panel.  
5 And what we'll do is -- and you can all have a seat  
6 up here. And I will keep my promise of ending in  
7 exactly 30 minutes. And so let's start with any  
8 questions for Dr. Bigal since I preempted a  
9 discussion section for his talk. Steve?  
10 DR. MCMAHON: So one question on the CGRPs.  
11 It may sound slightly esoteric. About five or six  
12 years ago, there was a reasonably high-profile  
13 paper from Jeff Mogil, who is a geneticist, and  
14 Peter Reeh, who is a pain electrophysiologist.  
15 The thrust of this paper is that it started  
16 with Jeff Mogil's interest as to why different  
17 mouse strains have different pain sensitivities.  
18 He did the genetics and Peter did the recordings  
19 and the functional studies. And the conclusion of  
20 the paper was, the mice strains have different pain  
21 sensitivities because they release more or less  
22 CGRP from peripheral nerve terminals

Page 327

1 constitutively. And that was supposed to act back  
2 on auto receptors.  
3 I don't know if that paper was true, but you  
4 have a great opportunity to test some of those  
5 ideas in humans. So a direct prediction of that  
6 paper would be that CGRP blockage would lead to an  
7 increase in heat pain threshold. People will  
8 become less sensitive.  
9 It's a very simple measure to do that's done  
10 every day in all kinds of testing. And I wondered  
11 whether you've ever looked at that or seriously  
12 considered the possibility that the mechanism they  
13 propose might be a side effect in your treatments.  
14 And if it's true, it could actually be of relevance  
15 to an understanding of the pathophysiology of  
16 migraine.  
17 DR. BIGAL: Thank you. I appreciate your  
18 comment. It's unfortunate that Dr. Brick [ph] is  
19 not here anymore. He is doing a study using our  
20 antibody, where he is basically inducing allodynia  
21 into rats. And he is using two models. One model  
22 is, he induces allodynia with sumatriptan. The

Page 328

1 other model, he induces allodynia with opioids.  
2 Some of the animals are pretreated with placebo.  
3 Some of the animals are pretreated with our  
4 antibody.  
5 These are not migraine models. These are  
6 pain models. And he demonstrated what you said,  
7 when you knock out CGRP in the animals, in both  
8 allodynia models, the threshold -- it's not a  
9 hyperalgesia model. It's an allodynia model, but  
10 it goes to the same direction that you predicted.  
11 DR. MCMAHON: That begs the question  
12 [inaudible -- off mic.]  
13 DR. BIGAL: I think it's relevant to  
14 migraine progression. So basically, when people  
15 evolve from episodic migraine into chronic  
16 migraine, the biological features of migraine are  
17 retained, but migraine acquires components of  
18 chronic pain now. So episodic migraine is pure  
19 migraine. It has very little resemblance with  
20 chronic pain syndromes.  
21 Chronic migraine is migraine plus chronic  
22 pain. They acquire everything else. They acquire

Page 329

1 the allodynia. They require the extracephalic  
2 allodynia. And they acquired all the co-  
3 morbidities of chronic pain. So I think that's why  
4 I'm so keen to study these on chronic migraine  
5 because I think that, actually, this molecule,  
6 based on what we did at Merck, has the attributes  
7 to revert the biology of migraine and the secondary  
8 chronic pain features that develop over the years.  
9 DR. MCMAHON: I don't want to keep going on  
10 about it, but they have an interesting mechanism.  
11 They claimed that the animals that release lots of  
12 CGRP acted on autoreceptors to further reinforce  
13 CGRP production. So actually, a migraine is, you  
14 could imagine, a slow cumulative wind-up of the  
15 whole system that would take you from normal, to  
16 occasional, to a kind of chronic migraine stage if  
17 it was true. Yes.  
18 DR. BACKONJA: Actually, just a follow-up on  
19 the same question regarding the sensitivity -- I'm  
20 aware that some of the investigators have done  
21 quite the sensory testing in patients with  
22 migraines and it clearly demonstrated the presence

Page 330

1 of allodynia and hyperalgesia as a manifestation of  
2 migraine.  
3 Are you aware of or do you have any results  
4 of the effects of any intervention of either small  
5 molecule or antibody on that sensitivity, that a  
6 change improved, got worse?  
7 DR. BIGAL: I am. So allodynia, meaning  
8 over the past years, trigeminal allodynia, is the  
9 most potent marker of migrant refractoriness in  
10 clinical trials. So basically, when we were  
11 developing this, the reason I ask -- we worked with  
12 Brick on the allodynia models is because we  
13 strongly believe that, if you do not revert to  
14 allodynia, you may symptomatically treat migraine,  
15 but you don't bring them back from chronic to  
16 episodic. Allodynia is key here as a marker of  
17 trigeminal sensitization.  
18 So we developed and validated a  
19 questionnaire called the ASC12, the Allodynia  
20 Symptom Checklist 12, versus QST for using migraine  
21 and migraine research. So we are talking about  
22 trigeminal allodynia only. And our phase 2

Page 331

1 clinical trial applies there. Everybody is having  
2 their allodynia captured by the questionnaire.  
3 So one of the a priori described analyses  
4 that we are going to do is actually the efficacy as  
5 a function of allodynia or not.  
6 DR. BACKONJA: But nobody did any of the  
7 quantitative sensory testing like Rami Burstein or  
8 a few other investigators. I mean, I am not aware.  
9 DR. BIJAL: We did not. So Rami Burstein  
10 allodynia studies for us with animals. So we  
11 developed one CGRP antagonist called AA25. And he  
12 used his animals of inflammatory soup to induce  
13 allodynia in animals and show that, actually,  
14 triptans could not revert several of these  
15 neuronal activations in the presence of allodynia,  
16 but CGRP receptor antagonists did.  
17 What we did not do and we are doing now with  
18 our trial -- but what we did not do is in humans  
19 with QST.  
20 DR. DWORKIN: Other questions for Dr. Bigal?  
21 (No response.)  
22 DR. DWORKIN: I don't want any of you to

Page 332

1 leave this afternoon without having had your  
2 questions answered for this panel. So any  
3 questions from the audience for any of the other  
4 speakers from this afternoon's session?  
5 (No response.)  
6 Q&A and Panel Discussion  
7 DR. DWORKIN: Then I will ask the members of  
8 the panel. So the focus of this afternoon's  
9 session was translational success stories. What  
10 Allan, and Dennis, and Frank, and I hoped to put  
11 together here were three examples of the success of  
12 translation from pre-clinical to at least one, and  
13 often many more, demonstrations of efficacy in  
14 clinical studies. And so we've seen three examples  
15 of that.  
16 I'd just like to ask the panel to comment,  
17 are there any kind of take-home messages from these  
18 three translational success stories? Can we  
19 conclude something about the characteristics of  
20 successful translation from pre-clinical to  
21 clinical? Andrew?  
22 DR. RICE: Can I start with what I hope will

Page 333

1 be a slightly provocative comment, but could be  
2 something that the group actually could take  
3 forward?  
4 I was in conversation with my colleague the  
5 other day, and he made a quip that I thought was  
6 very true. To translate, you need to speak two  
7 languages, at least. And one of the things that we  
8 tend to do is work in our silos of pre-clinical and  
9 clinical. And the clinical people have a lot to  
10 learn from the pre-clinical people and vice versa.  
11 The past few weeks, I've been thinking about  
12 how we could facilitate that. One way might be to  
13 encourage internships of trainees in research, so  
14 that basic scientists might come, and spend some  
15 time doing clinical trials, and seeing what the  
16 issues were, and vice versa because I do think we  
17 tend to sit -- we assume that we know what the pre-  
18 clinical people do.  
19 We take their word for it and vice versa,  
20 and they seem to believe that we know what we're  
21 doing in clinical trials. And a little bit more  
22 learning of each other's languages, I think

Page 334

1 wouldn't be a bad thing. And that's exactly  
2 something that a group like ACTION could probably  
3 facilitate, or at least we could talk about how we  
4 would facilitate it. It is actually what we're  
5 doing here already.  
6 DR. DWORKIN: But you're saying something a  
7 little bit more intensive, that there would  
8 actually be a period of time that the individual  
9 would spend in a lab of someone doing something  
10 different than what they do. Potentially, ACTION  
11 could support something like that?  
12 DR. RICE: I don't know whether anybody's  
13 got any comments on that, or is it naive?  
14 DR. BIGAL: I think there are two  
15 translations that need to be done, and one  
16 translation is this translation that we discuss  
17 here today. So for example, if we take the example  
18 of the CGRP drug development, it represents the  
19 accumulation of knowledge of many largely driven by  
20 Lars.  
21 If he once was not doing the trigeminal  
22 vascular test, and describing the trigeminal

Page 335

1 vascular loop, and showing that CGRP, and not  
2 substance P, and not VIP, or the ones released, and  
3 map this into the biology of migraine, we could  
4 never develop.  
5 I think that, actually, the age of  
6 serendipity is over, and we do not know how to  
7 develop drugs differently anymore. We need this  
8 translation.  
9 The second translation that I think is  
10 important is, when you go to this science,  
11 translational science, as this requires, we very  
12 often miss a second translation that's needed,  
13 which is basically, science apart, what patients  
14 really need.  
15 Now, we know the science. I know that I  
16 want to go to the trigeminal ganglia. I develop a  
17 molecule that goes there. But when it comes to  
18 develop the clinical trial, who are these patients?  
19 In real life, a patient with chronic migraine who  
20 would use something as I am developing, would they  
21 stop the medications that they currently are on  
22 before starting or phase out before starting? Or

Page 336

1 would they add this medication on whatever they  
2 have? If they improve, they phase out, meaning,  
3 who are these patients? Are these patients,  
4 patients that are going to use generic first? And  
5 once they fail, they would go to a high-end therapy  
6 like that?  
7 This translation, I think, is where we are  
8 missing, trying to identify now that we know the  
9 signs and that we are developing the clinical  
10 trial, who is the true beneficiary of something  
11 like that, and develop a clinical trial that  
12 reflects the population?  
13 DR. DWORKIN: So let me follow up. Are you  
14 suggesting that the reason for the success of the  
15 CGRP antagonist studies -- and you said all of  
16 those trials were positive, and it looks like the  
17 data we have from the antibody studies also, so  
18 far, are positive -- are you suggesting that the  
19 reason that those trials were all positive has to  
20 do with really thoughtful selection of the patients  
21 that were enrolled in the trials?  
22 DR. BIGAL: No. The reason I think they are

Page 337

1 coming so nice is because the translation from  
2 basic to clinical has been well done. I think  
3 that's the reason. I think the second step, the  
4 future step, is now how to bring this a step  
5 forward. And I don't mean cherry-pick the  
6 population, but basically really try to tailor the  
7 clinical development and make the clinical studies  
8 and the clinical trials reflect the population that  
9 actually is going to end-use it, because right now,  
10 my point is, 12 percent of the population has  
11 migraine.  
12 About 12 percent of them will need an  
13 antibody. Who are they? How do they look like?  
14 What are the co-morbidities that they have? And  
15 instead of excluding these guys, as we typically  
16 do, go for them.  
17 DR. DWORKIN: Maybe we should.  
18 DR. BACKONJA: I would just go back to a  
19 more general comment that Andrew made. And I will  
20 definitely say that we are in terrible need of  
21 really better communication, again, because we  
22 definitely do speak two different languages, basic

Page 338

1 science language and a clinical language.  
2 For this to be a translational endeavor, we  
3 really have to speak the same language and probably  
4 a little more disciplined the way we use our  
5 language because, in pre-clinical settings, we do  
6 not study pain. You study nociception and  
7 neuropathic pain processes. But when do they  
8 become pain is -- human subjects say they have a  
9 pain. Otherwise, before that, it's all  
10 nociception.  
11 But it goes back to -- in some of the words  
12 used during this meeting, I have to give credit to  
13 Allan, who is gone. He made it, in his  
14 presentation, clear that he was studying mechanical  
15 hyperalgesia or thermal allodynia. And that's what  
16 he studied, rather than generalizing it to pain in  
17 general.  
18 I think that these are the kind of steps  
19 that we need to do. But do we really need to go  
20 back to where and how do we do this? There's  
21 really no good model and maybe an occasion like  
22 this is a good model just to really start to set

Page 339

1 the criteria for good translational pain research.  
2 DR. DWORKIN: Dr. Edvinsson?  
3 DR. EDVINSSON: I think you touch a very  
4 important issue. I think, for my part, I am a  
5 clinician also, and I have a good laboratory. And  
6 that makes it more easy to see the patients' needs  
7 and the way to translate it. But I think it would  
8 have been difficult for someone just training as an  
9 M.D. to see how the lab works.  
10 I did a long period in my young days to do  
11 my PhD in a neuroscience laboratory, so then I can  
12 understand the methodology. And I think you need  
13 to have this kind of MD, PhD training to understand  
14 the methodology that the great guys in the novel  
15 technologies have. So you must share, get it  
16 together.  
17 DR. RICE: I just wanted to completely  
18 concur with you and Misha and ask you, Misha, one  
19 of the phrases I heard today was -- or maybe it was  
20 yesterday -- measuring symptoms in rodents. And to  
21 a clinician, that's anathema. You can't measure  
22 symptoms. It's something that can't communicate

Page 340

1 with you.  
2 But I think, in neuropathic pain, I've said  
3 it many times, we suffer from a rather bizarre  
4 disconnect. But by and large, we tend to do our  
5 pre-clinical work in models of traumatic nerve  
6 injury, and our outcome measures are, at best,  
7 something we use to profile patients in clinical  
8 trials. That's certainly not an outcome measure,  
9 in other words, sensory thresholds.  
10 Yet, in the clinical trials, we'll often do  
11 a product predominantly in polyneuropathy or PHN  
12 and measure pain as an outcome. There's just a  
13 really obvious disconnect there that, sometimes, we  
14 don't talk too much about. And I don't want to  
15 repeat last year's meeting, but there's also the  
16 whole issue of design standards by its reduction  
17 methodologies in pre-clinical research, which is a  
18 whole other meeting, but they merit just  
19 mentioning.  
20 DR. DWORKIN: So Andrew, I have to ask this  
21 question. As I understood your comments, they  
22 assume that there's a kind of history of failed

Page 341

1 translation, of compounds that were efficacious in  
2 pre-clinical models that didn't show efficacy in  
3 the clinical situation. And there is such a large  
4 history of failed compounds. I mean, we all talk  
5 about NK1 antagonists. But I just don't know of  
6 that many clear examples of a compound that showed  
7 maybe not even a robust pre-clinical pattern, that  
8 when done in careful clinical studies, failed to  
9 show efficacy.

10 So there's a premise I'm not sure we have  
11 solid data for, that there are a lot of failures of  
12 the pre-clinical models.

13 DR. RICE: We are doing some work on that.  
14 But I think publication bias, both at the clinical  
15 trials that failed -- which is probably less than  
16 we think it is. We recently have not published it  
17 yet, but you were at the meeting where we had an  
18 assessment of publication bias for clinical trials.  
19 It seemed to be surprisingly low compared to the  
20 pre-clinical studies, where it's much higher.

21 So it's actually gaining access to the  
22 evidence. And one thing that surprised me recently

Page 342

1 is, we are currently conducting a meta-analysis of  
2 all pre-clinical neuropathic pain studies that  
3 involved behavior and outcomes with a  
4 pharmacological intervention in animals. The first  
5 sweep of that revealed 65,000 publications. When  
6 we've got those down, we're now somewhere around  
7 6,000 publications that are admissible to a  
8 meta-analysis.

9 You compare that to roughly 220 randomized  
10 control trials that will be in the latest  
11 meta-analysis of neuropathic pain. We're dealing  
12 with a totally different scale. But the problem is  
13 we don't have a meta-analysis yet -- we are  
14 conducting it -- of the pre-clinical data.

15 Once we have that, probably later this year,  
16 I think we'll be in a very different position to be  
17 able to address that issue.

18 DR. DWORKIN: Steve?

19 DR. MCMAHON: So we heard on your  
20 part -- we heard from Chas yesterday that his  
21 numerical assessment was, what, 90 percent of  
22 compounds failed in phase 2 trials? And that's for

Page 343

1 lack of efficacy. And actually, implicit in your  
2 last comment was that was all due to the pre--  
3 clinical sides. But don't you get that it was also  
4 due to poor clinical design. Even with the NK1, we  
5 said, for antagonists, astonishingly, when the  
6 knock-outs were evaluated, which they were being  
7 done whilst the clinical trials were going on for  
8 the small molecules, the knock-outs had very little  
9 phenotype other than in a visceral pain context.

10 And as far as I know, that's never been tested  
11 clinically.

12 So you could even argue that good old NK1  
13 hasn't even been disproven as a target. But my  
14 main point was that maybe at the end of two days,  
15 we should be smug and slap ourselves on the back,  
16 three examples sitting there of positive efficacy  
17 in phase 2 in the last few years. Another one  
18 supposedly announced last week, at least in the  
19 form of a press release from Convergence, who  
20 claimed that they have positive data in trigeminal  
21 neuralgia with their sodium channel program, and  
22 another one last year and being followed up on P2X3

Page 344

1 receptor antagonism. So that's not 90 percent  
2 failure.

3 Maybe we're doing something wrong in the  
4 sense that we have got -- definitely, there's been  
5 a lot of navel-gazing and hard thought about the  
6 animal models, the measures we have. There's a  
7 wider range of animal models being applied. I  
8 think the tests are being applied more rigorously.

9 We have heard a lot about how clinical trial design  
10 may have been improved.

11 So maybe this is the beginning of a golden  
12 era where I am starting to see a lot of successes.

13 DR. DWORKIN: So Steve, I completely agree  
14 with you. And I want to highlight something that  
15 Andrew said earlier about an as-yet-unpublished  
16 study of oxcarbazepine in patients with, I guess, a  
17 variety of peripheral neuropathic pain conditions.

18 So in fact, there are, in the literature,  
19 three negative trials, phase 3 negative trials of  
20 oxcarbazepine and diabetic peripheral neuropathy,  
21 and I think one positive trial. And so that drug  
22 never made it to the clinic because of the three

Page 345

1 negative trials and one positive trial.  
2 But now, we hear that in a trial conducted  
3 carefully in Europe with heterogeneous patients,  
4 not just diabetic neuropathy or PHN, and  
5 sophisticated quantitative sensory testing, that  
6 they were able to support their prediction that the  
7 drug was efficacious in patients who had, what,  
8 pinpricked hyperalgesia. Right? Something like  
9 that?  
10 DR. RICE: It's not my study, and I can't  
11 give too much away because it's under review.  
12 Basically, it was the German Neuropathic Pain  
13 Network full protocol, and the Germans have  
14 developed and published a system for assigning  
15 sensory loss or gain as a phenotype.  
16 DR. DWORKIN: To me, that raises the  
17 question of whether the three large, very large,  
18 negative trials of oxcarbazepine, a sodium channel  
19 blocker, of course, in patients with diabetic  
20 neuropathy were falsely negative; and that when  
21 it's done exquisitely carefully by a group of  
22 European academic investigators, this

Page 346

1 anti-epileptic shows efficacy in the patients we  
2 would have predicted it would show efficacy in.  
3 Nat, you have to say something.  
4 DR. KATZ: I am going to say something, but  
5 probably not what you think I'm going to say.  
6 (Laughter.)  
7 DR. DWORKIN: I actually have no idea what  
8 you're going to say.  
9 DR. KATZ: I'm yet again going to wander  
10 into dangerous territory, which is to talk about  
11 the pre-clinical data. And I want to pick up on a  
12 point that you just made.  
13 I've got this idea in my head that the  
14 pre-clinical models fail to predict human efficacy.  
15 And the reason I have that in my head is because I  
16 have done dozens of studies over the last 15 or  
17 20 years of new molecular entities that were  
18 presented to me as years of pre-clinical data,  
19 we're taking this into humans. Can you help us  
20 design a study or carry out a study? And we do it  
21 and it fails.  
22 So that's happened to me numerous times, and

Page 347

1 most of the clinical studies never get published  
2 for all the reasons that we're all familiar with.  
3 But now, as I think about it, I never really  
4 had a sense of responsibility to look at the pre-  
5 clinical data myself and to ask myself the  
6 question, "Do I really feel like these data are  
7 robust enough to take into humans?" because I  
8 didn't feel I had the qualifications to make a  
9 decision like that.  
10 But now, as I think back upon it, it seems  
11 to me that, rarely was it the case that the  
12 pre-clinical data met any of their criteria that I  
13 put on my slides earlier. Rarely was their  
14 replication in multiple laboratories. Rarely could  
15 you find out whether the pre-clinical animals were  
16 randomized, whether it was blinded, et cetera,  
17 et cetera.  
18 I really have no idea whether the  
19 pre-clinical data that I saw was robust data or not  
20 robust data. This whole connection between, oh,  
21 the pre-clinical studies showed this and the  
22 clinical studies showed that, I don't know what

Page 348

1 those pre-clinical studies showed.  
2 So lately, in the last year or so, as I  
3 become more aware and sensitized to the flimsy  
4 nature of a lot of the pre-clinical data that comes  
5 to me, I've gotten into the habit of asking people  
6 who come to me now, and when I see the usual  
7 slides, "Just out of curiosity, was that study  
8 randomized?"  
9 I never can get an answer to that question.  
10 "Well, just out of curiosity, was that study  
11 blinded?" "I don't know. I guess I'll have to go  
12 back to the people that did it." "How about any  
13 other labs? Did any other labs replicate that  
14 study?" "I don't know. Maybe I ought to go back."  
15 And these are people who are controlling millions  
16 and millions of dollars of investor money.  
17 So I think, in a way, we have to go back and  
18 ask ourselves, what did those pre-clinical studies  
19 really show? And maybe your meta-analysis will get  
20 us there, but I think, based on what's published in  
21 the literature, with the enormous publication bias  
22 that we all acknowledge to exist, I'm not sure how



Page 349

1 to figure that out.  
2 DR. RICE: I mean, I think there's one  
3 probable truism, that most of the strategies and  
4 models we have are good at predicting the drugs we  
5 know work. They're not good at predicting the  
6 drugs that would fail. And I think that's an  
7 important message.  
8 But you wouldn't be surprised to hear I  
9 totally concur with you about the reporting of  
10 methodological quality. And we can take a lot from  
11 my collaborators in the stroke field, Malcolm  
12 MacLeod and his group, in Edinburgh, who have done  
13 a lot of work on this.  
14 We certainly know that classic things like  
15 randomization and/or studies that fail to  
16 report -- that's all we can say. We can't say  
17 whether studies did it or not. But studies that  
18 fail to report blinding and randomization tend to  
19 overestimate efficacy, as you'd expect.  
20 But about 30 percent of reports in  
21 neuropathic pain models report blinding, so we can  
22 take some encouragement from that.

Page 350

1 I think there are other facets of that, that  
2 are virtually never reported, and that is sample  
3 size calculations and, even more importantly, the  
4 predetermined criteria for excluding animals from  
5 the analysis and if animals were excluded from the  
6 analysis.  
7 From the inquiries we made, that is actually  
8 quite a widespread practice to take out animals,  
9 and we had an ACTION meeting on this topic last  
10 year. Animals are often excluded from the analysis  
11 without being declared in the write-up, and that's  
12 a cultural issue. And that seems to be a major  
13 bias that has not been addressed.  
14 This area has moved forward fantastically in  
15 the last two years. We now have something called  
16 the ARRIVE guidelines, which is standard reporting  
17 guidelines, rather like CONSORT, which have been  
18 adopted by over 350 journals now, by certainly  
19 major U.K. funding agencies. The NIH have looked  
20 at it and proposed similar type-reporting  
21 standards.  
22 So I think we are going to move into an area

Page 351

1 where we will have better reporting standards. And  
2 we remember what difference CONSORT made to  
3 clinical trial methodology. And I'm sure that will  
4 have some impact.  
5 So again, I share Nat's optimism that  
6 there's no point in looking too much into the past.  
7 There's a lot that is changing, and they are  
8 examples of success. But again, I think it speaks  
9 to learning to speak each other's languages. Some  
10 of what we do is obvious to us in designing  
11 clinical trials and not necessarily obvious to a  
12 clinical trialist in animals.  
13 DR. DWORKIN: So we're coming to the end,  
14 and I just want to give Dr. Rappaport a moment, if  
15 he'd like it, to comment on the presentations we've  
16 had this afternoon, the successful translation from  
17 pre-clinical studies into phase 2 and, ideally,  
18 phase 3.  
19 DR. RAPPAPORT: I think I'll use the  
20 opportunity to comment more broadly on the meeting  
21 both days. I hope that we are in the beginning of  
22 a golden age. That would be wonderful. It needs

Page 352

1 to move forward more quickly. And I am obviously a  
2 big proponent of public/private partnerships, so I  
3 was really quite impressed with what Chas Bountra  
4 has been able to do in that paradigm.  
5 I think we need to move further in that  
6 direction in the pain area because what we can  
7 accomplish working together in the private and  
8 public sectors, in the pre-competitive area, to  
9 share with the general community, that can then be  
10 picked up when we have evidence of efficacy or  
11 preliminary safety data, whatever it is that we  
12 need to do, and then share it, and then at that  
13 point, have industry pick-up and develop a product,  
14 I think we could move things so much more quickly.  
15 I think, with the advent of better  
16 methodology and reporting in the pre-clinical area,  
17 I think that will really speed things up, too. So  
18 I think there are all kinds of things coming  
19 together right now, and the best way to take  
20 advantage of this is to -- I mean, I have obviously  
21 somewhat of a personal stake in ACTION, at least  
22 for a while, and I think that this is the right

1 place to center what we're doing in pain because we  
2 have representatives from all of the important  
3 sectors, including the advocacy groups who are  
4 represented here today. So I just want to put in a  
5 word for pushing that direction.

6 If you see a way to share what we're doing,  
7 I think that's what we should be doing.

8 Adjourment

9 DR. DWORKIN: Thank you very much. I think  
10 that's the perfect way to end these two days.

11 Thank you all very much for your participation, for  
12 your endurance. And if you want to get in touch  
13 with us, e-mail us, go to the ACTION website for  
14 updates. And if you'd like to be on the  
15 distribution list for ACTION newsletters, just let  
16 me know.

17 Thank you all very much and safe travels.

18 (Whereupon, at 4:44 p.m., the workshop was  
19 adjourned.)

20

21

22

	157:6;166:15;167:1; 186:11;279:22;282:12; 286:6;288:13;308:6	232:19	<b>2007 (3)</b> 195:16;201:8;202:20	208:16;209:5;235:11; 240:12;245:19;273:1
<b>\$</b>		<b>1983 (1)</b> 275:19	<b>2009 (1)</b> 11:22	<b>4:00 (2)</b> 5:12;294:19
<b>\$17.8 (1)</b> 42:10	<b>10,000 (3)</b> 46:9;72:5;228:17	<b>1987 (2)</b> 233:1,5	<b>2010 (1)</b> 253:21	<b>4:44 (1)</b> 353:18
<b>\$20 (1)</b> 189:13	<b>100 (5)</b> 8:1;36:3;67:17;92:19; 142:2	<b>1990s (1)</b> 234:1	<b>2011 (1)</b> 207:4	<b>4:45 (2)</b> 295:4,7
<b>\$250 (1)</b> 15:14	<b>11 (1)</b> 307:3	<b>1993 (1)</b> 236:15	<b>2012 (4)</b> 207:5;255:1,3;258:19	<b>40 (8)</b> 20:19;60:7,7;126:7; 133:20;186:13;196:5; 308:2
<b>\$3 (1)</b> 42:7	<b>11th (1)</b> 241:11	<b>1999 (1)</b> 115:20	<b>22 (2)</b> 308:3;322:16	<b>42 (1)</b> 306:8
<b>\$40,000 (1)</b> 65:11	<b>12 (10)</b> 68:8;72:8;140:21; 210:16;271:3;310:21; 324:19;330:20;337:10, 12	<b>1A (6)</b> 222:13,13,21;228:3,5; 229:3	<b>24 (6)</b> 92:9;140:21;271:3,14; 306:11;309:13	<b>43 (1)</b> 129:22
<b>[</b>		<b>1B (1)</b> 222:22	<b>25 (4)</b> 123:7;158:9;259:21; 294:19	<b>44 (1)</b> 129:18
<b>[Inaudible (7)</b> 68:3;70:14;177:15; 264:19;270:7,10;328:12	<b>12:19 (1)</b> 190:11	<b>2</b>	<b>250 (1)</b> 322:19	<b>45 (4)</b> 130:9;254:8;295:3; 320:17
<b>[indiscernible] (4)</b> 37:3;181:3;285:13; 319:21	<b>120 (2)</b> 4:19;36:4	<b>2 (56)</b> 33:16;45:11;52:13; 116:9;166:21;167:2; 172:10;194:15,15;195:3, 4;196:7,11;197:8; 199:13;200:1,4,21; 205:7,16;212:16;213:5, 18;215:7;219:10; 220:18;224:2,3,11; 233:22;234:13;235:11; 236:9;255:11,14;256:9; 279:10;292:6;304:21; 305:1,13;306:10; 308:10;316:8,9;317:5; 318:11;320:6,7;321:9; 322:5,13;330:22; 342:22;343:17;351:17	<b>28 (1)</b> 255:11	<b>45-day (1)</b> 314:1
<b>[ph] (10)</b> 57:16;143:10;172:7; 182:13;285:20;287:20; 288:22;311:8;312:17; 327:18	<b>12-week (1)</b> 212:21		<b>280 (1)</b> 321:9	<b>48 (2)</b> 309:2,14
	<b>13.5 (3)</b> 81:17;84:2;111:18		<b>29 (1)</b> 207:6	<b>4-CGRP (1)</b> 308:19
	<b>13-week (1)</b> 100:16		<b>2B (2)</b> 212:20;320:18	
	<b>14 (1)</b> 316:4		<b>2-point (1)</b> 320:1	<b>5</b>
<b>0</b>	<b>15 (13)</b> 41:10;112:12;129:18; 243:18;297:2,4,5,5; 303:2;316:2,5;318:19; 346:16		<b>3</b>	<b>5 (3)</b> 38:11;247:10;316:4
<b>05 (3)</b> 247:1;256:1,3	<b>15,000 (1)</b> 127:21		<b>3 (16)</b> 36:15;166:21;167:1; 208:15;212:17;224:3; 236:9,11;279:10; 304:21;305:2;307:4; 318:14;322:6;344:19; 351:18	<b>5:00 (1)</b> 295:5
<b>09 (1)</b> 257:7	<b>150 (1)</b> 36:8	<b>2,000 (3)</b> 320:5,8;322:18		<b>50 (12)</b> 29:14;68:16;72:8; 73:4;102:9,12;129:7; 209:4,6,9,13;293:17
<b>1</b>	<b>1500 (1)</b> 256:10	<b>2.2 (2)</b> 168:14,17		<b>50,000 (3)</b> 46:10;72:4;84:15
<b>1 (34)</b> 196:22;198:12; 204:12;234:13;235:3; 236:8;250:20,22;251:2, 4,11,15;252:12,22; 253:14;255:11;262:22; 263:4;272:20;278:17; 279:10,12,16;280:9,17; 292:5;298:11;320:4,7, 13;322:14;324:12,16,18	<b>15-ish-millimeter (1)</b> 254:5	<b>20 (19)</b> 26:12;32:9;33:19,21; 35:2;49:15;67:5,7; 68:18;72:2;78:21; 112:13;115:7;139:20; 141:21;294:18;308:3; 322:16;346:17		<b>500,000 (2)</b> 32:19;129:6
<b>1,000 (2)</b> 44:20;322:19	<b>15-minute (1)</b> 293:1	<b>20,000 (2)</b> 45:10;72:5	<b>30 (22)</b> 26:12;29:1;37:5; 52:12;72:3;115:12; 129:17;155:6;158:9; 176:10,11;177:9;209:3, 5,10,13;228:16;254:9; 255:10;316:5;326:7; 349:20	<b>55 (1)</b> 147:8
<b>1,000-bed (1)</b> 6:5	<b>16 (3)</b> 4:20;132:1;307:3	<b>200 (2)</b> 124:11;158:13		<b>5th (1)</b> 116:9
<b>1.1 (2)</b> 163:7;164:3	<b>16-week (1)</b> 100:16	<b>200,000 (1)</b> 115:15		<b>6</b>
<b>1/2A (1)</b> 43:2	<b>17 (1)</b> 255:13	<b>2000 (1)</b> 7:8	<b>300 (1)</b> 320:11	<b>6 (9)</b> 12:13,14;207:6,22,22; 235:11;249:9;257:8; 272:20
<b>1:23 (1)</b> 191:2	<b>17.8 (1)</b> 322:15	<b>2001 (3)</b> 241:3,11;296:5	<b>30-ish (2)</b> 257:5,6	<b>6,000 (1)</b> 342:7
<b>10 (28)</b> 12:14;25:2,4;29:6; 42:4;50:15;72:4;75:15; 84:16;116:9;122:6; 123:4;139:19;154:6,21; 155:5,22;156:1,18;	<b>18 (1)</b> 51:14	<b>2002 (2)</b> 249:21;253:7	<b>350 (1)</b> 350:18	<b>6.7 (1)</b> 209:6
	<b>183 (1)</b> 207:8	<b>2004 (3)</b> 143:1;231:18;253:6	<b>37 (1)</b> 291:12	<b>60 (2)</b> 186:14;235:9
	<b>18-patient (1)</b> 50:1	<b>2005 (2)</b> 195:11,16	<b>4</b>	<b>600 (1)</b> 6:7
	<b>18-year-old (2)</b> 140:4;142:13		<b>4 (9)</b> 12:13;33:16,19;	<b>62 (2)</b> 116:22;207:18
	<b>1950s (1)</b> 232:15			
	<b>1980s (1)</b>			

<p><b>63 (2)</b> 207:18;318:16</p> <p><b>65 (1)</b> 125:15</p> <p><b>65,000 (1)</b> 342:5</p> <p><b>67 (1)</b> 317:12</p> <hr/> <p style="text-align: center;"><b>7</b></p> <hr/> <p><b>7 (10)</b> 154:7;155:5,21; 156:22;157:4;166:14, 21;167:1;257:8;289:7</p> <p><b>70 (11)</b> 14:6;28:3,15,16;29:1; 33:11;138:13;139:5; 158:1;176:16;278:16</p> <p><b>700 (1)</b> 137:18</p> <p><b>72 (1)</b> 273:1</p> <p><b>77 (1)</b> 207:5</p> <hr/> <p style="text-align: center;"><b>8</b></p> <hr/> <p><b>8 (3)</b> 208:8;235:12;291:12</p> <p><b>8:35 (1)</b> 4:2</p> <p><b>80 (2)</b> 97:9;142:2</p> <p><b>81 (3)</b> 197:18;200:2;217:19</p> <p><b>82 (17)</b> 197:2,3,10,18;198:2; 199:4,20;200:9;201:22, 22;203:9,17;204:2; 217:19;218:4,13,18</p> <p><b>82-receptor (1)</b> 197:7</p> <p><b>83 (2)</b> 126:10;207:10</p> <p><b>85 (2)</b> 97:9;160:18</p> <p><b>86 (2)</b> 207:10;281:7</p> <hr/> <p style="text-align: center;"><b>9</b></p> <hr/> <p><b>9 (7)</b> 154:6;155:5,22; 166:15;167:1;274:6; 289:8</p> <p><b>9/alpha (4)</b> 154:21;156:1,18; 157:6</p> <p><b>90 (7)</b> 28:1;29:7;115:13; 235:10;324:22;342:21; 344:1</p>	<p><b>900 (1)</b> 320:6</p> <p><b>90s (2)</b> 31:22;117:5</p> <p><b>91 (1)</b> 207:9</p> <p><b>92 (1)</b> 207:8</p> <p><b>97 (1)</b> 36:16</p> <hr/> <p style="text-align: center;"><b>A</b></p> <hr/> <p><b>AA25 (1)</b> 331:11</p> <p><b>AAV (1)</b> 53:20</p> <p><b>abdominal (1)</b> 235:18</p> <p><b>Aberdeen (1)</b> 203:5</p> <p><b>aberrant (1)</b> 71:8</p> <p><b>ability (2)</b> 34:3;124:17</p> <p><b>able (29)</b> 6:20;23:11;52:20; 61:5;103:14;120:3; 123:5;126:18;137:13; 138:15;143:8;148:2,13; 150:4;152:20;153:4; 154:20;159:10;175:9; 202:8,11,20;203:8; 272:2;318:2;319:16; 342:17;345:6;352:4</p> <p><b>abluminal (1)</b> 291:13</p> <p><b>abluminally (2)</b> 291:5,9</p> <p><b>abnormal (1)</b> 32:7</p> <p><b>abolished (2)</b> 204:3;218:18</p> <p><b>above (4)</b> 93:12,22;94:7;148:15</p> <p><b>absence (1)</b> 138:13</p> <p><b>absolute (2)</b> 72:5;296:22</p> <p><b>absolutely (7)</b> 100:7;109:1;129:1; 134:22;293:11;313:11; 316:4</p> <p><b>absorption (1)</b> 9:18</p> <p><b>abstracts (1)</b> 316:19</p> <p><b>AC2 (1)</b> 199:3</p> <p><b>academic (1)</b> 345:22</p> <p><b>academically (2)</b> 44:10,14</p>	<p><b>accelerate (2)</b> 186:15;241:19</p> <p><b>accept (2)</b> 83:9;312:19</p> <p><b>accepted (1)</b> 99:9</p> <p><b>access (3)</b> 15:6;239:14;341:21</p> <p><b>accessible (1)</b> 97:1</p> <p><b>accident (1)</b> 42:1</p> <p><b>accomplish (1)</b> 352:7</p> <p><b>accomplished (1)</b> 253:12</p> <p><b>according (3)</b> 139:18;316:11;320:16</p> <p><b>account (1)</b> 29:14</p> <p><b>accounts (1)</b> 139:5</p> <p><b>accumulated (1)</b> 156:15</p> <p><b>accumulation (2)</b> 311:7;334:19</p> <p><b>accurately (1)</b> 157:17</p> <p><b>ACE (1)</b> 198:10</p> <p><b>acetyl (1)</b> 166:12</p> <p><b>acetylcholine (5)</b> 138:18;143:18,19; 158:21;275:11</p> <p><b>achieve (3)</b> 119:13;209:3;210:6</p> <p><b>acids (4)</b> 139:11,19,20;141:21</p> <p><b>acknowledge (2)</b> 17:20;348:22</p> <p><b>acquire (2)</b> 328:22,22</p> <p><b>acquired (3)</b> 296:1;314:18;329:2</p> <p><b>acquires (1)</b> 328:17</p> <p><b>across (14)</b> 9:18;143:16;185:6; 208:14;209:8;237:22; 238:11;239:4;244:20; 245:20;250:13;259:14, 16;260:20</p> <p><b>act (11)</b> 150:9,13,14;164:19; 200:21;283:22;284:6,6; 285:13;289:9;327:1</p> <p><b>acted (1)</b> 329:12</p> <p><b>acting (1)</b> 135:16</p> <p><b>action (6)</b> 120:11;138:21;143:8, 22;144:18;196:10</p> <p><b>actions (3)</b> 164:16;215:11;218:16</p> <p><b>activate (10)</b> 27:9,13;123:8;127:3; 128:3;157:4,5;159:20, 20;277:16</p> <p><b>activated (7)</b> 121:8;127:1;161:18; 163:13;277:18;287:3; 300:12</p> <p><b>activates (2)</b> 18:12;163:4</p> <p><b>activating (3)</b> 125:21;277:15;278:19</p> <p><b>activation (9)</b> 77:16;114:4;121:7; 127:8,19;128:9,14; 274:7;301:3</p> <p><b>activations (5)</b> 300:21;301:4,6,20; 331:15</p> <p><b>active (16)</b> 31:14;142:3;196:7; 199:4;210:6,7;218:21; 246:13;254:9;256:4,12; 258:5,8;266:21;287:18; 309:22</p> <p><b>actively (2)</b> 29:19;220:19</p> <p><b>activities (1)</b> 195:14</p> <p><b>activity (6)</b> 91:6,13,17;142:7,15; 201:10</p> <p><b>acts (1)</b> 30:9</p> <p><b>ACTION (9)</b> 192:7,21;227:10; 334:2,10;350:9;352:21; 353:13,15</p> <p><b>actual (3)</b> 71:1;96:2;270:15</p> <p><b>actually (168)</b> 5:14;6:14;7:17;9:9,12; 10:12;12:1;15:8,15; 17:6;19:1;20:11;24:2; 27:1,2,7,11;28:5;30:21; 31:4;32:1;34:8,15;37:8, 15;38:20;40:17,22; 42:12;44:7;46:8,9; 47:11;49:8;51:12,14; 53:4;56:9,14;57:5,6; 59:10;63:2;64:7;66:7; 67:6;68:7;70:20,21; 72:6,11,19;73:12;76:22; 78:18;80:12;83:15,19; 84:11;85:17;86:5,21; 87:11;89:3,8,12;90:3,14; 91:19;98:14;99:17; 100:15;110:14;133:10; 135:11,16,19;152:14; 158:3;161:10;165:2;</p>	<p>172:1;176:7;179:3; 180:10;184:2;186:20; 192:16;193:3;203:14; 204:19;205:5;208:12; 209:12;211:17;223:6,17, 21;224:18;225:21; 229:17;233:1,4;239:8, 21;242:18;243:14,22; 244:1;247:6;248:17; 249:16;250:9;257:9; 262:3,5;264:4;270:12; 273:5,10;274:11; 277:16;279:10;281:7; 282:11;289:18;296:20; 299:7,8,10;300:10,20; 301:20;305:22;306:19; 307:5,22;308:20,22; 310:5;311:2;313:1; 314:3,4,11;315:18; 316:1;319:22;321:17; 322:11;323:11;324:8; 325:3;327:14;329:5,13, 18;331:4,13;333:2; 334:4,8;335:5;337:9; 341:21;343:1;346:7; 350:7</p> <p><b>acute (17)</b> 76:6;78:7;135:6,12; 256:15;257:2;274:3; 283:14,14;299:6,13; 304:8;305:8;306:1,2; 309:18;319:15</p> <p><b>adaptive (1)</b> 308:10</p> <p><b>add (10)</b> 34:21;158:14;159:12, 13,15,16;161:7;191:9; 271:8;336:1</p> <p><b>added (2)</b> 133:16;298:18</p> <p><b>Addiction (1)</b> 326:4</p> <p><b>adding (4)</b> 145:13;158:20;159:5, 8</p> <p><b>addition (2)</b> 116:17;152:22</p> <p><b>additional (2)</b> 132:9;133:17</p> <p><b>additionally (1)</b> 66:22</p> <p><b>address (3)</b> 4:7;299:14;342:17</p> <p><b>addressed (3)</b> 182:6;265:14;350:13</p> <p><b>adds (1)</b> 274:21</p> <p><b>adherence (1)</b> 226:10</p> <p><b>adjourned (1)</b> 353:19</p> <p><b>Adjournment (1)</b> 353:8</p>
---	--	---	--

<b>adjust (1)</b> 57:7	<b>affecting (2)</b> 96:6;218:15	276:13	<b>all-alpha (1)</b> 154:22	172:10
<b>adjusting (2)</b> 107:8,14	<b>affects (1)</b> 57:9	<b>agents (8)</b> 252:8;272:14;284:3; 288:6;290:13,19; 292:17;295:15	<b>Allan (19)</b> 5:18;22:14;23:1;75:4; 5,8;104:16;110:21; 137:8;152:14;171:20; 180:17;188:18;192:14; 222:13;268:22;293:5; 332:10;338:13	<b>alpha-1 (2)</b> 18:12;30:11
<b>adjustment (1)</b> 94:7	<b>afferent (14)</b> 78:4;84:7;87:15;88:3; 19,20;89:22;90:13,16; 91:15;92:11;98:20; 117:16;135:17	<b>ages (1)</b> 317:17	<b>Allan's (1)</b> 23:9	<b>alpha-2 (1)</b> 18:11
<b>administering (1)</b> 109:11	<b>afferents (6)</b> 69:15;79:15;87:2,11; 90:13;179:7	<b>agglutinin (1)</b> 87:16	<b>allergic (1)</b> 212:5	<b>ALS (54)</b> 6:16;23:3;25:11; 26:19,21;27:18,22;28:5; 19,22;29:9,13,18,22; 30:4,18,31:6;35:7,22; 36:15,20,21;40:19;41:5; 6,10,16,18;43:7;50:11, 13;52:12;56:19,20;57:2; 60:2;65:5,16;66:5,12,16; 67:22;68:1,2;70:18,21; 73:15;74:12,16;174:7, 20;185:18;186:7;187:8
<b>administration (10)</b> 235:10;236:22;249:2; 303:18;306:4;316:11; 317:10,10,11,14	<b>affiliated (1)</b> 227:7	<b>aggregate (1)</b> 32:20	<b>allocate (1)</b> 220:10	<b>alternatively (1)</b> 262:9
<b>administrations (1)</b> 318:12	<b>affinity (2)</b> 145:22;162:14	<b>aggregates (1)</b> 32:15	<b>allocated (3)</b> 215:6;226:8,12	<b>although (31)</b> 44:8;48:6;146:5; 155:1;161:9;173:10; 174:3;197:11;200:17; 204:20;210:12;213:12; 226:3;227:1;237:17; 239:8;240:17;241:6; 245:3;246:11;247:7,11; 251:16;252:19;258:11; 263:10;300:6,7;303:8; 317:8,15
<b>admissible (1)</b> 342:7	<b>Africa (2)</b> 207:7;222:6	<b>aggressive (4)</b> 30:22;68:7,11;248:4	<b>allocation (1)</b> 203:2	<b>altitude (1)</b> 196:17
<b>admit (1)</b> 179:4	<b>afternoon (6)</b> 5:13;193:17;267:19; 295:17;332:1;351:16	<b>ago (28)</b> 7:6,16;18:1;19:3,7; 25:2;31:14;32:9;34:19; 35:20;42:13;49:2;61:22; 70:18;119:21;122:7; 138:14;139:13;147:8; 171:22;196:5;201:7; 209:12;230:2;287:8; 295:11;310:4;326:12	<b>allodynia (29)</b> 115:16;116:6;118:10; 119:6;122:18;123:1; 126:17;130:20;327:20, 22;328:1,8,9;329:1,2; 330:1,7,8,12,14,16,19, 22;331:2,5,10,13,15; 338:15	<b>altogether (1)</b> 321:8
<b>adopted (1)</b> 350:18	<b>afternoon's (2)</b> 332:4,8	<b>agonist (2)</b> 179:8,18	<b>allodynias (1)</b> 116:14	<b>ALTs (1)</b> 312:2
<b>adrenal (2)</b> 172:5,6	<b>after-science (1)</b> 60:3	<b>agonists (2)</b> 179:6,21	<b>allodynic (2)</b> 118:13,16	<b>Alun (1)</b> 241:6
<b>adrenalmedullin (1)</b> 313:19	<b>afterwards (1)</b> 75:2	<b>agree (9)</b> 80:9;110:11;174:14; 175:8;177:14;201:14; 268:3,4;344:13	<b>allogenic (3)</b> 61:2,3;73:18	<b>always (15)</b> 21:19,21;25:3,10; 53:5;57:18;74:6,7; 100:7;149:15;238:22; 281:12;283:19;293:6; 310:6
<b>adrenomedullin (1)</b> 287:14	<b>again (69)</b> 6:17;12:19;14:10; 15:19;23:1,9;30:16; 31:8;40:3;41:16;44:17; 45:4;46:3;48:11,14; 56:6;58:2,21;60:21; 62:22;67:22;73:11;84:7; 114:19;122:12;126:8, 12;142:13;155:11; 179:20;180:19;182:4; 184:14;186:4;202:20; 203:2;214:17;226:19; 227:14;230:4;239:6; 240:13;246:5,10;250:8; 257:21;258:11,17; 259:7;264:20;271:18; 275:12;276:12;279:15; 281:1;282:15;291:4; 294:10,21;296:15; 302:13;304:16;322:21, 21,21;337:21;346:9; 351:5,8	<b>aid (1)</b> 186:16	<b>allograph (1)</b> 73:17	<b>Alzheimer's (2)</b> 29:4,18
<b>adult (5)</b> 8:3,9;83:7,9;186:8	<b>against (10)</b> 60:14;86:6,9;91:7; 183:13;209:17;210:6; 246:13;266:15;315:14	<b>ahead (5)</b> 44:14;52:9;54:22; 83:18;210:16	<b>allow (2)</b> 65:19;122:8	<b>ambitious (1)</b> 51:18
<b>advance (2)</b> 268:16;270:18	<b>age (9)</b> 100:1;115:4,6;141:2, 3;207:17,20;335:5; 351:22	<b>aid (1)</b> 186:16	<b>allowed (3)</b> 188:1;206:19;255:6	<b>America (2)</b> 57:18;208:4
<b>advanced (5)</b> 304:18,20;305:12; 308:9;319:2	<b>agency (3)</b> 42:1;310:16;323:22	<b>agrees (1)</b> 79:1	<b>allowing (3)</b> 9:21;50:6;231:17	<b>American (1)</b> 261:16
<b>advancing (1)</b> 226:20	<b>agent (4)</b> 159:14;169:2;170:22;	<b>agreed (3)</b> 228:7;229:1;281:10	<b>allows (2)</b> 33:3;59:10	<b>Amgen (5)</b> 19:6;20:18;315:20; 319:2;325:18
<b>advantage (7)</b> 134:2;146:10;313:3, 15,21;321:6;352:20		<b>agrees (1)</b> 79:1	<b>almost (18)</b> 8:13;13:15;46:6; 48:19;58:10;59:7;72:12; 88:18;158:16;159:9; 167:21;188:11;189:17; 268:1;289:1;320:11; 323:3;324:14	<b>among (4)</b> 167:13;191:16; 249:20;299:16
<b>advantages (1)</b> 133:18		<b>aid (1)</b> 186:16	<b>alone (3)</b> 46:16;74:18;304:16	<b>amount (10)</b> 26:15;45:17;51:10; 80:7;120:22;239:5;
<b>advantaging (1)</b> 226:20		<b>air (1)</b> 16:6	<b>along (11)</b> 16:7,7;18:7;40:4; 67:15;81:16;140:3; 164:17;167:8;194:19; 226:22	
<b>advantage (7)</b> 134:2;146:10;313:3, 15,21;321:6;352:20		<b>AITC (1)</b> 158:21	<b>alpha (29)</b> 120:5,14;138:20; 154:6,6,7,9,21;155:5,5,5, 21,22,22;156:1,18,22; 157:4,6;166:14,15,15, 21,21,22;167:1,1,1;	
<b>advantages (1)</b> 133:18		<b>alarm (1)</b> 26:7		
<b>advent (1)</b> 352:15		<b>alarmed (1)</b> 204:10		
<b>adverse (17)</b> 47:4;181:12;197:12; 204:18;207:12,14; 212:1;213:2;215:3; 306:14;307:16,20; 308:3;321:19;322:2,3,14		<b>Albert (1)</b> 295:9		
<b>advice (2)</b> 5:11;272:4		<b>alcohol (1)</b> 177:4		
<b>advisory (2)</b> 95:19;195:12		<b>ALD-334 (1)</b> 316:22		
<b>advocacy (1)</b> 353:3		<b>Alex (2)</b> 90:4;104:5		
<b>advocating (1)</b> 286:18		<b>algorithm (1)</b> 206:10		
<b>Aebischer (2)</b> 34:19;70:5		<b>aligned (1)</b> 307:5		
<b>affect (2)</b> 51:3;291:4		<b>alive (4)</b> 36:6;39:9;67:19;73:5		
<b>affected (9)</b> 11:2;160:17,20,22; 161:3,4;162:3,4;308:18				

245:10;266:9;277:9; 286:5 <b>amounts (1)</b> 185:4 <b>AMP (1)</b> 287:21 <b>amylin (2)</b> 287:14;313:19 <b>analgesia (3)</b> 227:6;262:2;326:3 <b>analgesic (9)</b> 94:2;117:3,20;172:9; 229:14,20;239:21; 254:1;262:1 <b>analgesics (1)</b> 200:22 <b>analogize (1)</b> 293:10 <b>analogy (2)</b> 21:5;63:2 <b>analyses (1)</b> 331:3 <b>analysis (6)</b> 51:13;212:9;258:4; 350:5,6,10 <b>analyzed (2)</b> 24:15;127:19 <b>analyzing (2)</b> 47:10;51:10 <b>Anand (1)</b> 199:15 <b>Anand's (1)</b> 199:7 <b>anathema (1)</b> 339:21 <b>anatomist (1)</b> 88:9 <b>and/or (2)</b> 182:21;349:15 <b>Anders (2)</b> 22:8;37:10 <b>Andrew (20)</b> 104:17;134:16; 173:13;175:17;194:6,7, 13,21;195:1;209:20; 214:15;219:1;228:3; 230:2;260:8,10;332:21; 337:19;340:20;344:15 <b>Andrew's (3)</b> 228:1;238:10;239:8 <b>Anesthesia (1)</b> 326:3 <b>anesthesiologist (1)</b> 97:14 <b>Angeles (3)</b> 6:6;39:14;42:3 <b>Angelo (1)</b> 52:18 <b>angina (2)</b> 323:18,20 <b>angiotensin (14)</b> 194:15;195:3;196:7, 11,22;198:2,8,19;	199:11,13;200:1,4,21; 218:16 <b>angiotensin- (1)</b> 196:21 <b>animal (37)</b> 37:6;38:21;39:6; 40:14;43:14;68:5;78:9; 82:17;85:15;91:5,14,21, 22;94:1;96:12,14;98:3; 99:21;100:2;105:3,4; 112:18;130:22;152:12; 167:22;179:9,9;189:2, 22;198:1;202:1;216:1; 217:10;268:1;323:16; 344:6,7 <b>animals (73)</b> 36:5;40:7;43:11;47:9, 12;56:11,13;57:9;67:19; 74:1;92:10,17,22,22; 93:3,7,7,9,15,22;94:2; 98:14;99:2,5,6,11,13,18; 100:1,6,13;107:19; 111:15;116:13;118:5,10, 14;119:2,4;120:15; 121:10;129:20;130:9,15, 19;131:19;146:9; 172:12;187:12,14,20; 201:18,19;216:10; 218:18;234:19;277:7; 311:15;320:12;328:2,3, 7;329:11;331:10,12,13; 342:4;347:15;350:4,5,8, 10;351:12 <b>announced (2)</b> 241:12;343:18 <b>annoying (1)</b> 168:3 <b>answered (2)</b> 139:12;332:2 <b>antagonism (1)</b> 344:1 <b>antagonist (13)</b> 126:21;127:7;152:1; 168:16;197:7;199:20; 203:9;221:10;296:4; 308:19;309:21;331:11; 336:15 <b>antagonistic (1)</b> 292:17 <b>antagonists (18)</b> 126:22;128:22;132:7; 197:1;200:9,21;201:22; 202:1;203:18;308:17; 309:5,13,15;325:13,14; 331:16;341:5;343:5 <b>antagonize (1)</b> 129:8 <b>anterograde (1)</b> 276:10 <b>antibodies (33)</b> 227:4;228:16;229:22; 242:4;246:4,7;249:15; 252:15;270:17;275:20;	276:2;279:14,17;284:2; 286:16;287:5,6,9,15; 296:16;311:16;313:3, 16;314:9,22;315:13,19; 316:17;318:20,22; 319:4;325:17,20 <b>antibody (21)</b> 86:6,9;91:7;116:21; 125:15;248:12;249:20; 287:6;288:4;289:1; 291:16,17;295:22;315:4, 19;318:8;327:20;328:4; 330:5;336:17;337:13 <b>anti-CGRP (4)</b> 293:11;295:15,22; 325:20 <b>anticipate (1)</b> 265:20 <b>anticipated (3)</b> 266:3,5;267:2 <b>anticonvulsant (2)</b> 79:22;208:7 <b>anticonvulsants (2)</b> 79:10,19 <b>anti-epileptic (1)</b> 346:1 <b>antigens (1)</b> 116:20 <b>antihelminthic (1)</b> 121:9 <b>anti-inflammatory (1)</b> 157:5 <b>antimigraine (1)</b> 272:14 <b>anti-NGF (10)</b> 227:4;228:10,15; 229:13,22;237:5,11; 246:7;248:12;270:17 <b>anti-nociceptive (2)</b> 156:2;172:9 <b>antiretroviral (1)</b> 202:2 <b>anti-sense (1)</b> 13:14 <b>anxiety (3)</b> 211:11;217:2,2 <b>anymore (8)</b> 7:18,20;56:7;57:1; 58:13;180:7;327:19; 335:7 <b>apart (1)</b> 335:13 <b>apologize (1)</b> 134:13 <b>apoptosis (1)</b> 84:20 <b>apparatus (1)</b> 166:2 <b>apparent (1)</b> 195:9 <b>apparently (2)</b> 243:9;266:19 <b>appear (3)</b>	199:12;204:19;208:21 <b>appeared (1)</b> 232:21 <b>appearing (1)</b> 289:11 <b>appears (4)</b> 199:3;200:10;204:22; 288:10 <b>Applause (10)</b> 66:13;104:15;133:6; 136:8;164:11;214:14; 226:17;264:18;292:19; 325:22 <b>application (1)</b> 289:3 <b>applications (5)</b> 138:5,8;151:13,19; 157:11 <b>applied (3)</b> 110:14;344:7,8 <b>applies (2)</b> 236:13;331:1 <b>apply (3)</b> 160:15;162:1;277:1 <b>appointment (1)</b> 54:14 <b>appreciable (1)</b> 226:8 <b>appreciate (4)</b> 65:2;194:9;261:20; 327:17 <b>appreciated (1)</b> 16:11 <b>approach (14)</b> 24:9;53:21;73:13; 80:5,10,14;81:15;103:4; 116:8;117:9;118:2; 119:8;149:21;172:3 <b>approaches (6)</b> 112:17;136:12;170:1, 4;174:13;238:2 <b>approaching (1)</b> 158:6 <b>appropriate (6)</b> 100:12;124:13; 181:13;189:1,2;249:20 <b>approval (2)</b> 174:4;310:7 <b>approve (1)</b> 173:15 <b>approved (6)</b> 121:9;142:20,22; 152:22;305:3;307:9 <b>approves (1)</b> 51:2 <b>April (1)</b> 249:21 <b>aquarium (1)</b> 165:15 <b>aqueduct (1)</b> 19:20 <b>arbitrary (1)</b> 209:13	<b>area (23)</b> 4:13;9:20;10:3;17:11; 22:10;38:16;48:8;51:21; 64:8;71:3;193:5,5,21; 201:14;218:21;237:8; 264:16;311:9;350:14, 22;352:6,8,16 <b>areas (14)</b> 17:10;24:3;35:16; 44:12;53:14;64:11; 193:14,15,18,21;266:20; 274:22;301:4;314:17 <b>argue (3)</b> 180:8,16;343:12 <b>argument (3)</b> 177:19;244:15,19 <b>arise (2)</b> 168:18;265:9 <b>arising (1)</b> 170:10 <b>arm (7)</b> 28:9,9;31:12;49:14; 207:10,11;273:19 <b>Arnon (1)</b> 241:5 <b>aroma (1)</b> 248:22 <b>around (30)</b> 24:15;26:12;33:16; 36:4;39:20;40:1,3;43:3; 56:22;70:22;72:2,5; 141:6;183:22;201:8; 207:18,22;211:19; 231:1;234:18;239:14; 242:17;245:2;269:13; 274:8;275:5;289:22; 320:17;321:9;342:6 <b>arrhythmia (2)</b> 10:18,18 <b>ARRIVE (2)</b> 202:19;350:16 <b>arrived (1)</b> 7:8 <b>artery (6)</b> 279:18,19,21;280:1; 284:16;294:9 <b>arthritis (2)</b> 243:4;269:8 <b>arthropathy (1)</b> 266:4 <b>artificially (2)</b> 186:17;296:21 <b>ASC12 (1)</b> 330:19 <b>asleep (1)</b> 140:21 <b>aspect (8)</b> 21:19;46:22;274:17; 275:2;289:20;290:3,16; 293:15 <b>aspects (5)</b> 44:8;46:21;106:11; 214:10;296:13
--	--	--	---	---

<b>aspirin (2)</b> 243:11,19	196:11;199:5	<b>authorship (1)</b> 14:4	<b>B</b>	<b>barriers (1)</b> 220:17
<b>assay (8)</b> 48:13;140:2,5;142:6; 160:1;253:5;262:20; 263:12	<b>athletics (1)</b> 196:18	<b>auto (1)</b> 327:2		<b>back (71)</b> 6:2;8:10,11;9:16; 11:22;19:18;21:7;22:7; 24:5;48:22;54:11;60:6; 61:20;63:10,19;67:10, 22;74:7;83:15;100:3,9; 102:11;114:12;117:5,12, 15;141:5,7,8;146:17; 164:19;175:3,15; 177:20;185:19;188:1, 15;214:17;228:13; 231:3;232:14;233:8; 240:12,20;252:3;253:5; 255:14;256:10;259:4; 260:1,18;266:2;271:21; 277:10;293:2;294:17, 19;302:12,13;306:11; 309:20;327:1;330:15; 337:18;338:11,20; 343:15;347:10;348:12, 14,17
<b>assaying (1)</b> 160:5	<b>ATP (1)</b> 158:21	<b>autologous (8)</b> 9:21;59:10,22;60:9, 14,16,18;64:21	<b>BASBAUM (56)</b> 69:4;75:5,8,9;95:3,10; 105:10,18;107:21; 108:16;109:1,8,15; 110:7,11,14;111:5,8; 112:9,11;133:8;134:3,6, 13;135:15;136:4,10; 152:14;164:12;165:9; 166:9;167:19;168:9; 169:5;171:22;173:12; 175:17,19;177:14; 178:21;179:3;183:21; 184:18,22;190:5,8; 220:22;221:19,22; 222:5;269:1;270:3,7,10; 271:7;293:6	
<b>assays (3)</b> 40:12;129:11;275:21	<b>atrophy (2)</b> 12:3;186:2	<b>autologously (1)</b> 60:3		
<b>assemble (1)</b> 153:9	<b>attached (2)</b> 56:12;90:11	<b>autonomic (2)</b> 166:11,19		
<b>assembled (1)</b> 153:18	<b>attack (7)</b> 157:2;274:20;282:19; 283:15;300:1,14;301:21	<b>autoreceptors (1)</b> 329:12		
<b>assembly (1)</b> 153:16	<b>attacked (1)</b> 156:12	<b>available (16)</b> 115:19;177:11; 192:13;206:21;208:8; 222:3,4,7;225:12; 245:11;280:2;285:9; 287:7;306:12;316:15; 318:20		
<b>assess (1)</b> 48:8	<b>attacking (1)</b> 35:8	<b>Avalos (1)</b> 38:1		
<b>assessment (2)</b> 341:18;342:21	<b>attacks (6)</b> 274:3;275:1;297:9; 303:16,22;304:1	<b>Avatar (1)</b> 11:19		
<b>asset (2)</b> 127:4;267:22	<b>attempts (1)</b> 193:19	<b>average (7)</b> 27:1;28:7;121:18; 207:17,21;221:4;254:6		
<b>assigned (1)</b> 207:8	<b>attended (1)</b> 298:1	<b>aversive (1)</b> 216:22		
<b>assigning (1)</b> 345:14	<b>attention (8)</b> 7:14;82:19;98:5; 164:10;214:12;264:17; 318:4;325:21	<b>avoid (3)</b> 123:21;300:4;319:6		
<b>assistance (1)</b> 227:9	<b>attenuate (1)</b> 223:7	<b>avoidance (2)</b> 216:9,11		
<b>associated (11)</b> 29:15;76:9;79:12; 105:9;109:12;114:8; 174:9;196:14;198:15; 249:1;273:2	<b>attenuated (1)</b> 223:10	<b>avoiding (1)</b> 44:17		
<b>association (2)</b> 66:12;204:22	<b>attract (1)</b> 224:22	<b>avulsion (1)</b> 199:19		
<b>assume (5)</b> 103:2;108:13;315:10; 333:17;340:22	<b>attractive (3)</b> 68:20;123:16;152:11	<b>aware (9)</b> 196:19;267:16;280:5; 299:2;316:19;329:20; 330:3;331:8;348:3		
<b>assumes (1)</b> 164:18	<b>attribute (5)</b> 230:22;309:4,6; 321:19,21	<b>awareness (1)</b> 204:16		
<b>assuming (2)</b> 31:5;73:9	<b>attributes (1)</b> 329:6	<b>away (11)</b> 42:20;44:5;59:9; 189:10;193:4,10; 202:15;277:7;319:8; 320:1;345:11		
<b>assumption (1)</b> 230:16	<b>audience (4)</b> 152:4;168:11;191:14; 332:3	<b>awful (1)</b> 205:12		
<b>astonish (1)</b> 243:7	<b>augment (1)</b> 263:12	<b>awkward (1)</b> 251:17		
<b>astonished (1)</b> 243:8	<b>August (1)</b> 207:4	<b>axial (1)</b> 107:2		
<b>astonishingly (1)</b> 343:5	<b>aura (4)</b> 273:14,17,18;278:8	<b>axis (1)</b> 92:17		
<b>astrocyte (4)</b> 22:19;24:11;60:8; 97:11	<b>Australia (1)</b> 121:5	<b>axon (3)</b> 23:5;120:7,10		
<b>astrocytes (18)</b> 24:13,16,17,19;25:2,9, 12;30:21;31:2,4,7; 33:22;39:11;41:4;42:15; 54:17;68:4;108:20	<b>Australian (2)</b> 207:1,3	<b>axonal (1)</b> 116:19		
<b>astronomical (1)</b> 273:5	<b>author (1)</b> 14:5	<b>axons (4)</b> 40:10;85:18;113:22; 274:14		
<b>as-yet-unpublished (1)</b> 344:15	<b>authored (1)</b> 248:3			
<b>AT1 (2)</b>	<b>authority (1)</b> 150:17			
	<b>authors (3)</b> 14:6;213:20;236:21			

<b>became (3)</b> 40:12;299:11;301:11	<b>benign (3)</b> 132:1;297:8,16	143:19	233:16	16:20;27:4;63:18; 78:5;88:16;114:2,20; 117:13;166:4;293:10, 12;323:5
<b>become (21)</b> 12:4;30:21;50:16; 62:22;83:10;93:15;94:2; 101:4,16;108:18;151:4; 189:15;195:9;302:16; 306:3,4,10;310:6;327:8; 338:8;348:3	<b>benzos (1)</b> 179:21	<b>Bingo (1)</b> 300:3	<b>block (21)</b> 119:3;120:16;127:8; 129:13;145:12;156:13, 21;159:17;284:3; 291:14,17;298:3; 299:14;300:1,3;302:20, 21;304:6,10,13,16	<b>Boehringer (2)</b> 305:14;308:18
<b>becomes (5)</b> 28:11;144:11;271:3; 312:15;322:5	<b>best (14)</b> 5:10;36:11;44:12,17; 73:13;75:11;83:13;95:7; 170:21;176:9;189:22; 242:10;340:6;352:19	<b>Bio (1)</b> 113:8	<b>biochemistry (1)</b> 148:4	<b>bolt (1)</b> 49:6
<b>becoming (3)</b> 6:6;145:9;225:19	<b>bet (2)</b> 170:21;260:18	<b>biologic (1)</b> 244:9	<b>biological (3)</b> 298:19;314:13;328:16	<b>bonds (1)</b> 139:9
<b>bed (1)</b> 20:14	<b>beta (2)</b> 166:21;167:2	<b>biologically (1)</b> 142:2	<b>blockage (1)</b> 327:6	<b>bone (11)</b> 61:17;213:16;248:7, 15,21;250:15,18;251:19, 22;255:17;256:10
<b>bedding (2)</b> 238:5;246:2	<b>better (29)</b> 53:2;60:17;68:22; 89:16;92:2;98:1;103:4; 109:16;175:1;176:6; 178:15;180:7;209:16; 221:6;228:11;242:22; 246:17;261:8;264:15; 265:12;267:8;287:17, 17;307:6;309:12; 312:22;337:21;351:1; 352:15	<b>Biologicals (2)</b> 314:14,15	<b>blocked (5)</b> 144:11;246:8;249:1; 287:21;288:15	<b>bones (1)</b> 147:20
<b>bedside (3)</b> 219:20;222:18,21	<b>beware (1)</b> 261:1	<b>biologies (2)</b> 251:13;295:21	<b>blocker (7)</b> 144:7;195:4;200:3; 291:12,20;294:12; 345:19	<b>Bonnie (1)</b> 132:22
<b>began (1)</b> 113:9	<b>beyond (2)</b> 115:13;192:15	<b>biology (9)</b> 4:16;22:7;113:11; 137:1,10;146:18; 298:17;329:7;335:3	<b>blockers (3)</b> 194:16;285:4;286:16	<b>boosting (1)</b> 17:10
<b>begin (5)</b> 75:14;118:5;121:1; 131:19;163:11	<b>BHLHB5 (1)</b> 98:8	<b>biomedical (3)</b> 146:16;151:13,19	<b>blocking (10)</b> 120:10;128:14;132:4; 138:22;156:18;205:20; 272:14;299:7;303:3,9	<b>bored (1)</b> 314:11
<b>beginning (9)</b> 178:11;183:6;231:7; 235:9;264:9;301:21; 323:7;344:11;351:21	<b>bias (5)</b> 261:13;341:14,18; 348:21;350:13	<b>bit (53)</b> 4:10;5:11,14,17; 11:19;22:13;24:4,8; 27:21;37:12;42:16; 46:15;49:2,8;57:17; 61:21;74:8;75:1;76:2; 89:10;103:4;150:5,7; 168:3;178:6;180:15; 187:15;188:13;193:6; 208:20;215:8;227:2; 231:15;262:7;277:12; 278:14;292:21;293:16; 294:17;296:17;303:12; 304:5;309:14;315:2,8,9, 17;316:13;317:17; 320:15;323:2;333:21; 334:7	<b>blocks (4)</b> 128:9;138:17,22; 237:5	<b>born (2)</b> 81:11;111:16
<b>begins (3)</b> 80:20;300:22;301:1	<b>big (18)</b> 6:10;7:2;10:16;19:19; 43:7;59:22;101:15; 173:2;177:19;181:19; 183:15;185:15;187:4; 191:6;215:5;267:17; 268:1;352:2	<b>bite (3)</b> 129:22;150:1;302:12	<b>blood (27)</b> 8:2;9:10;16:7;51:4; 61:16;63:14;96:6;175:5, 10;196:12;197:10; 226:11,13;273:11,13,14; 275:6,17;276:8,18; 290:17;299:4;300:8,8,9, 9;323:10	<b>both (41)</b> 27:18;50:20;64:19; 92:17;93:18;99:13; 108:10;112:17;116:13; 117:7,11,16;129:12; 137:10;147:6;162:22; 164:6;171:20;179:18; 193:20;195:13;199:6; 201:21;202:8;203:16; 204:14;205:22;208:11; 209:2,10;216:20; 250:11;267:18;281:17; 316:3;318:18;321:7,8; 328:7;341:14;351:21
<b>begs (1)</b> 328:11	<b>Bigal (10)</b> 295:9,16,17;326:8; 327:17;328:13;330:7; 331:20;334:14;336:22	<b>bitten (1)</b> 139:3	<b>blood- (1)</b> 31:2	<b>bottom (3)</b> 16:8;47:17;48:11
<b>behaving (1)</b> 16:13	<b>bigger (3)</b> 25:5;35:22;67:21	<b>bizarre (1)</b> 340:3	<b>blood-brain (13)</b> 18:19;25:1;59:20; 185:6;279:20;284:1; 285:14;290:8,10;291:2; 300:17;302:1,3	<b>Boulis (3)</b> 49:1;52:11;174:21
<b>behavior (6)</b> 104:6,7;216:10,12; 237:19;342:3	<b>biggest (2)</b> 63:22;86:18	<b>Bjorklund (2)</b> 22:8;37:10	<b>blow (2)</b> 16:4,6	<b>bound (1)</b> 18:12
<b>behavioral (7)</b> 40:12;46:21;108:10; 141:13;142:9;149:17; 237:1	<b>BIJAL (1)</b> 331:9	<b>black (1)</b> 89:5	<b>blue (4)</b> 290:4,5,9,17	<b>boundary (1)</b> 125:6
<b>behaviorally (1)</b> 74:2	<b>bilaterally (1)</b> 282:21	<b>black (1)</b> 89:5	<b>bluish (1)</b> 290:7	<b>Bountra (3)</b> 193:6;267:12;352:3
<b>behaviors (1)</b> 216:7	<b>Bill (1)</b> 132:17	<b>bladder (2)</b> 120:18;125:13	<b>BMJ (1)</b> 210:2	<b>bovine (3)</b> 172:5;173:6,7
<b>behind (3)</b> 28:18;58:15;265:1	<b>billion (1)</b> 42:7	<b>bleeds (1)</b> 243:21	<b>board (2)</b> 95:20;195:12	<b>bowels (1)</b> 260:2
<b>bells (2)</b> 26:7;223:17	<b>bind (6)</b> 18:7;117:15;136:3; 288:13;320:2,3	<b>blind (4)</b> 20:17,19;92:20;104:7	<b>boardrooms (1)</b> 244:2	<b>boy (1)</b> 244:1
<b>belong (2)</b> 149:4;297:18	<b>binding (4)</b> 246:8;285:12;286:8; 287:17	<b>blinded (6)</b> 21:16;51:5,6;321:15; 347:16;348:11	<b>Bob (6)</b> 191:8;192:14;194:5; 205:13;225:17;294:18	<b>brachial (1)</b> 199:19
<b>belongs (1)</b> 318:1	<b>binds (1)</b>	<b>blinding (5)</b> 43:3;202:22;260:11; 349:18,21	<b>BOCF (1)</b> 208:11	<b>brain (60)</b> 5:1;9:9;19:3,4,8,17, 18;21:6;22:13,18,20; 24:12,13,14,20;25:19; 26:12;27:17;31:3;34:1;
<b>bench (1)</b> 222:18		<b>blister-based (1)</b>	<b>bodies (1)</b> 116:19	
<b>beneficial (1)</b> 234:12			<b>body (12)</b>	
<b>beneficiary (1)</b> 336:10				
<b>benefit (4)</b> 174:15;181:5,6; 260:14				



59:13,18;68:9;78:8; 82:8;104:2,4;113:16; 140:15;168:7,19;175:7; 273:12,13;274:7,21; 275:8;276:9;277:19; 280:15;283:8;284:9; 285:7;286:1,1,10;290:5; 292:2,5;300:22;301:3,5, 10,14;302:6,13,21,22; 303:4;318:4	<b>broad (2)</b> 5:21;196:20	<b>CALCA (1)</b> 275:18	38:10,16,18;39:1,3,7,9; 41:1;44:6;45:1,6;48:7; 49:3;50:4;51:9,12,14,15; 52:14;53:4;54:4,15; 55:21;56:13;57:5,6,6,7, 13,21;58:1,10;61:3,14, 20;63:4,7,18,19,22;64:2, 7,10,11,20;67:4,7;68:14; 70:12;71:16;75:11; 76:13;78:21;80:12;82:6; 83:4;84:1;85:16,17; 86:1,9,13;87:4,14,16; 88:2,5;89:7,19;90:7,14, 14,20,22;91:17,18; 92:12;94:3,16;97:19; 98:2;100:12;102:6,8,10; 103:10,19;107:9,15; 111:17;113:15,21,22; 114:8,11,12,16,19; 116:14,17,19;117:10,13, 15,19;118:16,19;119:3, 13;120:5;123:6;124:7, 12,20;127:3,4;128:10, 11;130:3,4;132:7; 133:13,20,21;134:9; 136:3,10,11;139:18,22; 141:12,22;143:11; 145:22;147:5,14;148:1; 149:11;150:1,5;151:1, 18;152:8;153:2,9; 156:13,16;157:9,10; 158:2,11,13,15,22; 159:6,8;160:16;161:9; 162:21;163:10;168:19; 170:5,9;171:7;172:9; 174:21;177:5;178:3,7,9; 179:21;180:6;184:7,9, 22;185:4,5;187:7,10,22; 188:10;193:22;198:2; 202:5,15;210:6;213:3; 215:22;218:4,9,11; 224:14;225:20;230:22; 231:1;233:6,14;234:6; 236:22;242:17;243:11, 16;244:11,18;247:15; 250:2;251:1,22;252:19; 254:10;259:11;263:9, 17;272:3;273:12,20; 275:7,16;276:19,21,22; 277:1,15;278:7;279:4,9, 15,21;280:13,17;281:5, 11;282:15;283:5,20,22; 284:3,8,14,15,17,20; 285:22;287:3,21;288:13, 22;289:13,16,19;290:11, 14,16,19;291:13,17; 292:2;294:10;298:15; 299:22;302:20,21; 303:3;304:6;306:6; 309:8;310:8;313:7,9,21; 314:2;317:11,17;326:5; 332:18,22;339:11; 346:19;348:9;349:10,16,	21;352:6,9
92:6,7;149:6	<b>broadening (1)</b> 161:7	<b>calcitonin (5)</b> 275:19;278:16; 287:14;299:1;313:19	<b>cancelling (1)</b> 169:10	
<b>brand (2)</b> 239:7,9	<b>broadly (1)</b> 351:20	<b>calcium (24)</b> 128:3;129:12,14; 143:13;144:6,8,21,22; 145:2,2;146:1,2;158:12; 159:4,5,7,16,18,18,21; 160:3;163:3,11;200:1	<b>cancer (5)</b> 244:17;248:6;255:5, 14;256:11	
<b>Brandon (1)</b> 66:6	<b>brochure (1)</b> 322:1	<b>calcium- (1)</b> 127:5	<b>cancer-induced (1)</b> 213:16	
<b>Braz (2)</b> 83:18;104:4	<b>broken (2)</b> 93:2;271:9	<b>calculate (1)</b> 284:17	<b>cancers (1)</b> 63:15	
<b>breadth (2)</b> 250:10;255:9	<b>brought (3)</b> 248:12;268:11;305:1	<b>calculation (1)</b> 203:1	<b>candidate (1)</b> 312:15	
<b>break (9)</b> 54:5;136:5;173:21; 190:9;250:2;261:19; 293:1;294:16,19	<b>brutal (3)</b> 299:3;309:5;310:2	<b>calculations (1)</b> 350:3	<b>capital (2)</b> 212:15;214:10	
<b>breathing (2)</b> 16:9;53:15	<b>buckets (1)</b> 172:7	<b>California (6)</b> 23:21;42:1,2;43:6; 164:8;295:13	<b>capitalized (1)</b> 34:5	
<b>Brennan's (2)</b> 248:2,11	<b>build (1)</b> 324:7	<b>call (13)</b> 15:16;32:2;57:14; 94:16;135:3;150:15; 151:2,15;152:4;231:18; 233:21;260:6;295:3	<b>capsaicin (5)</b> 128:3,21;130:4;208:7; 210:11	
<b>Breunig (1)</b> 55:21	<b>building (2)</b> 6:4;241:10	<b>called (28)</b> 12:2;14:5;27:14; 28:21;29:12;100:4; 124:19;128:17;142:15, 21,21;147:19;150:12; 154:6;230:11;240:12; 243:3;266:13;271:9; 283:13;288:7;297:1; 306:5;308:7,21;330:19; 331:11;350:15	<b>capsaicin-induced (1)</b> 199:22	
<b>brew (1)</b> 141:19	<b>bulbar (1)</b> 53:16	<b>calls (1)</b> 316:21	<b>capture (5)</b> 148:13;150:4,18; 252:13,17	
<b>Brian (1)</b> 134:14	<b>bunch (1)</b> 65:4	<b>calmodulin (1)</b> 127:6	<b>captured (1)</b> 331:2	
<b>Brick (2)</b> 327:18;330:12	<b>bunches (1)</b> 101:22	<b>Cambridge (2)</b> 22:8;32:1	<b>capturing (1)</b> 148:6	
<b>bridge (1)</b> 320:13	<b>bungarotoxin (1)</b> 138:20	<b>came (13)</b> 22:1;34:17;140:3; 194:8;202:4;214:3; 232:22;275:18;281:7; 289:4;306:17;310:1; 320:7	<b>car (1)</b> 301:16	
<b>brief (5)</b> 136:9;205:2;211:3; 213:17;294:20	<b>unionectomy (4)</b> 255:15;256:15,20; 270:9	<b>camera (1)</b> 274:5	<b>carbamazepine (1)</b> 96:4	
<b>briefing (1)</b> 195:18	<b>buried (1)</b> 247:7	<b>Cameron (1)</b> 203:5	<b>cardiomyocyte (1)</b> 11:1	
<b>briefly (1)</b> 188:16	<b>burning (1)</b> 283:21	<b>can (335)</b> 7:22;8:22;9:2,3,6,7,12, 17;10:5,11,12,14,21; 11:4,8,20;12:1,10,18,21; 13:1,21;14:18,20;15:2,3, 6;17:5,11;19:4;22:2; 23:15;24:19;25:14,17, 21;26:20,21;30:1,12,19; 31:4;32:1,12;34:1;35:2, 9;36:1;37:14,18,20;	<b>cardiomyocytes (2)</b> 10:14,22	
<b>brilliant (1)</b> 267:13	<b>Burstein (2)</b> 331:7,9	<b>calls (1)</b> 316:21	<b>cardiovascular (9)</b> 196:13,20;197:12; 204:9;306:14;323:11; 324:15;325:6,9	
<b>bring (8)</b> 186:17;193:2;249:16; 250:1;262:16;319:14; 330:15;337:4	<b>bus (1)</b> 295:5	<b>calmodulin (1)</b> 127:6	<b>care (9)</b> 110:16;196:18; 224:20;225:4;244:8,9, 11;273:7;323:20	
<b>bringing (1)</b> 271:21	<b>business (1)</b> 241:14	<b>Cambridge (2)</b> 22:8;32:1	<b>career (1)</b> 281:11	
<b>Brisbane (2)</b> 200:16;202:16	<b>busy (2)</b> 189:10;295:18	<b>came (13)</b> 22:1;34:17;140:3; 194:8;202:4;214:3; 232:22;275:18;281:7; 289:4;306:17;310:1; 320:7	<b>careful (5)</b> 26:6;249:6;261:11; 271:11;341:8	
<b>Bristol (1)</b> 21:14	<b>bystander (1)</b> 136:1	<b>calls (1)</b> 316:21	<b>carefully (4)</b> 71:9;197:11;345:3,21	
<b>Bristol-Myers (2)</b> 309:19,20	<b>C</b>	<b>calmodulin (1)</b> 127:6	<b>carrageenan (1)</b> 233:17	
<b>Britain (2)</b> 57:20;167:21	<b>C9ORF (2)</b> 29:13,15	<b>Cambridge (2)</b> 22:8;32:1	<b>carry (3)</b> 230:8;313:20;346:20	
<b>British (2)</b> 62:6;167:19	<b>cabaals (1)</b> 151:2	<b>came (13)</b> 22:1;34:17;140:3; 194:8;202:4;214:3; 232:22;275:18;281:7; 289:4;306:17;310:1; 320:7	<b>cascade (2)</b> 267:5;300:16	
	<b>cabal (7)</b> 150:15,19;151:3,8,8, 10,16	<b>camera (1)</b> 274:5	<b>case (35)</b> 16:1;54:18;75:6; 78:17;79:11;80:22; 83:13;85:15;87:1;91:3; 92:3,7;97:16;105:18; 107:11;119:22;130:18;	
	<b>cabals (2)</b> 150:16,18	<b>Cameron (1)</b> 203:5		
	<b>cachexia (1)</b> 70:15	<b>can (335)</b> 7:22;8:22;9:2,3,6,7,12, 17;10:5,11,12,14,21; 11:4,8,20;12:1,10,18,21; 13:1,21;14:18,20;15:2,3, 6;17:5,11;19:4;22:2; 23:15;24:19;25:14,17, 21;26:20,21;30:1,12,19; 31:4;32:1,12;34:1;35:2, 9;36:1;37:14,18,20;		
	<b>cages (1)</b> 141:4	<b>calls (1)</b> 316:21		
	<b>Cal (2)</b> 136:20;287:20	<b>calmodulin (1)</b> 127:6		

148:14;155:11;158:8; 161:13;164:1,13; 170:19;176:15;185:18; 204:19;215:4;258:6; 263:14;276:3;277:4; 290:18;291:16;347:11	43:6 <b>cell (83)</b> 4:16;7:5;8:3,9,10,13, 14,15;9:4,22;13:5,12; 18:14;22:1,6;23:15; 24:20;25:15;32:5,6,7; 38:17;39:22;40:6;41:14; 42:7;44:16,20;45:12,18; 58:8;63:6,6,7,17;64:5; 16;67:6;70:2;74:6;78:5; 81:3;86:1;87:6,9,9,18, 20;88:2,4,6,15,16;89:19; 98:22;100:22;101:1,9; 103:2;104:11;109:4; 114:2,12,20;115:22; 116:19;117:13;124:13; 127:22;128:4;129:2; 158:19;159:3,10;163:4, 8,13;170:15;178:2; 187:14;198:13;317:1	108:22;109:19,21;111:1, 3,14,17,19;115:21; 116:2,4,5,9,18;117:1; 118:4,11,14;119:1,5; 120:4,9;122:12;125:16; 17,20,20;126:3,6,14; 127:18;128:4,10,20; 130:14;132:11;156:15; 158:13,14,15,17,22; 159:4,6,9;160:13;170:7; 171:6,11,15;172:5,6,11, 18;174:19,21;175:4,6,7, 12;185:15;186:3,16,19, 21;187:13,19;188:5,12; 199:2,8,18;204:6; 205:21;248:20;274:13; 279:9,16;280:12,14; 289:14,15,21,21	200:7;238:18,18; 248:4;261:6 <b>CGRP (108)</b> 124:11;272:13; 274:14,15;275:13,18; 276:4;278:1,9,12,15,17; 279:3,22;280:2,8,16,22; 281:16;282:5,14;284:3, 8;285:8,21;286:16,22; 287:6,7,9,12,20;288:11, 14;289:14,15;290:1; 291:3,8,9,11,12;292:10, 17;293:15,17;294:3,5, 12;296:4,13,15,19; 298:22;299:1,11,17; 300:6,11,15;301:17,19, 22;302:6,20,21;303:3,8, 10,14,15,21;304:1,15, 16;307:17;308:17; 309:5,13,15,21;310:11; 311:14;313:16,17; 315:14,20,21;319:16; 320:3;323:4,9;325:7,7, 12,13,14,17;326:22; 327:6;328:7;329:12,13; 331:11,16;334:18; 335:1;336:15	119:22;139:1;143:20; 144:6;145:21;146:1; 157:21;162:17;163:6,11, 12,16,18;164:2;343:21; 345:18 <b>channelrhodopsin (2)</b> 90:12,19 <b>channels (25)</b> 143:14;144:6,8,21,22; 145:2,2,4,7;146:2,6; 157:22;158:2;159:17,20, 21,22;160:2,3,3,7; 161:22;163:3,11,21 <b>chapter (9)</b> 232:11;233:22,22; 237:3;240:12;247:10; 249:9;250:3,3 <b>chapters (2)</b> 232:11;239:4 <b>characteristic (10)</b> 76:17;82:3;88:19; 91:20;93:20;96:1;99:21; 106:14,15;207:16 <b>characteristics (1)</b> 332:19 <b>characterize (2)</b> 242:19;272:22 <b>characterized (3)</b> 105:6;142:20;151:22 <b>charge (1)</b> 65:10 <b>Charles (1)</b> 220:4 <b>Chas (7)</b> 184:18;193:5;214:16; 267:11;268:8;342:20; 352:3 <b>chased (1)</b> 24:14 <b>check (1)</b> 47:4 <b>checklist (7)</b> 259:12,13;260:5,6,7, 21;330:20 <b>chemical (1)</b> 289:1 <b>chemo (1)</b> 165:17 <b>chemosensory (1)</b> 148:10 <b>chemotherapy (3)</b> 162:19,20;163:14 <b>cherry-pick (1)</b> 337:5 <b>chewing (1)</b> 235:15 <b>Chicago (1)</b> 5:12 <b>chickenpox (1)</b> 115:4 <b>chief (1)</b> 295:21 <b>child (1)</b>
<b>cases (6)</b> 29:2;96:7;114:12; 115:15;165:8;185:2	<b>cells (349)</b> 4:9,13;5:6,15;6:11,13, 17,21;7:4,11,17,19;8:2, 22;9:2,5,13,15,15;10:5, 13,15;11:5,11,14;12:7, 20;13:1;14:18,20,20; 15:6,8;16:1,2,12,22; 17:16,17;22:3,5,11,12, 14,17;23:22;26:2,5,10, 13,14;29:22;31:8,18,20, 21;32:1,8,13,13,17,19, 19,20;33:4,7,8;34:4,5,7, 9,13,14,15,20,22;35:3, 10;37:12;38:3,10,18; 39:1,3,4,17,21;40:2,9; 41:9,20;42:14,17;43:10, 10,19,21;44:8;45:2,9,11, 15,21;46:5,7,10,15,16, 20;47:8;48:2,7,15,21; 49:4;50:2,9;52:1,4,5,14, 21;53:5,21;54:9,15,21; 55:3;56:3,10;57:6,14; 58:11,17,19,21;59:2,6,6, 8,14;60:17,18;61:2,12, 13,13;62:3,10,10;63:14, 16;64:1,2,4,9,10,14,15, 17,18,22;65:9,11;66:3,4; 67:14,15;69:20;71:4,22; 72:3,4,5,12;73:2,5;74:5; 75:6;78:6,22;79:4; 80:12,14,15;81:10,11, 21;82:2,8,12;83:9,11,11; 84:2,8,11,13,15,16;85:3, 7,9,21;86:6,7,8,12,14; 87:3,7,10,11,12,22;88:1, 14;90:5,7,8,9,21,22; 91:4,12,16;92:18;93:1,4; 96:20;97:4,5,10,11,21; 99:2;100:17,18;101:1,4, 10,11,16,18;102:1,1,2,4, 10,15,16;103:6,7,12; 104:12,13;105:8,17,20, 22;106:7,11,12,15,17;	<b>center (4)</b> 6:7;43:7;212:12;353:1 <b>centered (1)</b> 275:5 <b>centers (8)</b> 43:7;207:6,6;212:8, 11;219:15;224:22;296:6 <b>central (10)</b> 35:10,11;105:8;120:2; 121:2;132:2;141:15; 164:15;273:22;302:15 <b>CEO (1)</b> 214:6 <b>Cephalalgia (1)</b> 310:4 <b>cephalopods (1)</b> 167:14 <b>cerebellum (4)</b> 274:11,13;285:12; 286:2 <b>cerebral (7)</b> 81:3,10;275:6,22; 276:16;279:20,22 <b>CERN (2)</b> 110:12;189:13 <b>certain (11)</b> 17:10;25:10;137:22; 138:1;153:6;160:7; 174:17;208:7;261:12; 301:4;304:14 <b>certainly (16)</b> 42:4;79:1;85:12; 88:18;126:18;134:21; 167:16;171:18;201:13; 209:16,18;211:14; 213:9;340:8;349:14; 350:18 <b>cervical (8)</b> 35:9,10;51:17;53:11, 13,14;85:12;101:20 <b>cetera (12)</b> 49:12;202:22;229:18; 246:3,18;252:10,10; 260:11,12,12;347:16,17 <b>CFA (5)</b>	<b>CGRP-binding (1)</b> 288:7 <b>CGRP-induced (1)</b> 289:4 <b>CGRPs (1)</b> 326:10 <b>chair (2)</b> 112:7,12 <b>chairing (1)</b> 134:14 <b>chairman (1)</b> 272:8 <b>challenge (2)</b> 157:20;305:5 <b>challenges (1)</b> 296:14 <b>chambers (1)</b> 14:19 <b>championship (1)</b> 273:9 <b>chance (1)</b> 294:16 <b>change (11)</b> 20:3;30:12,21;34:3; 44:15;121:21;199:12; 211:5,17;305:5;330:6 <b>changed (5)</b> 5:14;7:15;74:4; 129:17;152:6 <b>changes (13)</b> 13:13,13;14:8;20:5; 47:1,11;77:18,18;107:1; 186:19,21;216:7;274:19 <b>changing (3)</b> 33:12;167:17;351:7 <b>channel (16)</b>	

222:17 <b>children (3)</b> 12:3,11,15 <b>chip (2)</b> 15:16;17:2 <b>chloride (8)</b> 77:18,18;119:22; 158:16;159:8,13,14,19 <b>choice (1)</b> 269:12 <b>choline (1)</b> 166:12 <b>choose (4)</b> 28:12,16;142:5; 170:18 <b>chooses (1)</b> 28:13 <b>choosing (1)</b> 170:19 <b>chop (1)</b> 32:16 <b>chopped (1)</b> 32:22 <b>chopping (4)</b> 32:4;33:1;34:11;58:2 <b>chose (1)</b> 142:14 <b>chosen (1)</b> 232:12 <b>Chris (1)</b> 31:13 <b>chromophores (1)</b> 167:17 <b>chronic (36)</b> 98:4;115:13;124:6; 126:16;156:5;174:18; 176:4;252:19;254:2; 255:14;256:9;264:6; 283:6;287:10;296:21; 297:1,16;303:19;304:4; 313:12;316:7;320:18; 321:3,5;322:7;328:15, 18,20,21,21;329:3,4,8, 16;330:15;335:19 <b>chunk (2)</b> 15:17;32:18 <b>circles (1)</b> 141:6 <b>circuit (14)</b> 23:4;24:6,6;31:12; 35:14;86:4,22;89:21; 90:18;94:14;98:20,21; 103:9;109:17 <b>circuitry (4)</b> 143:7;145:8;150:20; 151:14 <b>circuits (4)</b> 22:15,22;27:17; 155:21 <b>circularize (1)</b> 185:2 <b>circulating (1)</b> 319:16	<b>circulation (7)</b> 185:5;275:22;276:16; 282:13;286:21;287:1; 288:11 <b>circumstances (3)</b> 95:7;107:10;173:14 <b>CIRM (4)</b> 41:22;42:6,11;66:11 <b>City (3)</b> 33:3;42:17;296:7 <b>claimed (2)</b> 329:11;343:20 <b>claims (1)</b> 53:1 <b>clarify (1)</b> 177:8 <b>Clark (4)</b> 140:4;151:21;215:15, 19 <b>class (17)</b> 133:19;153:5;157:16; 160:19,21;221:17;230:7, 10,14,17;231:6,19; 245:2;261:13;309:7; 321:19,21 <b>classes (3)</b> 124:4;161:17;314:6 <b>classic (1)</b> 349:14 <b>classical (1)</b> 305:17 <b>classifying (1)</b> 148:22 <b>clave (4)</b> 149:5,14;154:13,14 <b>claves (1)</b> 149:3 <b>clay (1)</b> 148:8 <b>clean (3)</b> 60:6;170:22;307:14 <b>clear (11)</b> 77:6;88:17;96:3; 126:17;208:16;271:14; 280:10;293:11;308:12; 338:14;341:6 <b>clearly (14)</b> 30:19;76:20;80:6; 86:10;91:12;159:1; 165:22;177:2;208:21; 229:22;303:1,3;307:4; 329:22 <b>clever (1)</b> 16:5 <b>click (1)</b> 277:4 <b>Clifford (4)</b> 78:20;238:14,15; 267:15 <b>climb (1)</b> 141:3 <b>clinic (20)</b> 17:16;21:1;26:10;	45:7;69:1;105:3,7; 134:20;242:20;243:18; 249:16;259:20;268:3,6, 11,17;274:4;286:4; 324:5;344:22 <b>clinical (126)</b> 13:19;25:22;26:6,15; 34:8,12;42:18;43:8; 49:17,20;52:8;53:3; 61:9;77:4;95:14;96:22; 104:19;135:10;151:20; 152:2,18;153:2;180:15; 181:21;182:5;183:19; 184:12;188:19,20; 193:20;194:14;195:13; 197:8,17;199:21,22; 200:19;201:4;203:14, 22;205:7,11,18,22; 207:2;208:22;211:21; 213:5,16;215:17; 222:15;226:15;228:18; 230:8;231:21;232:1; 235:5,17;236:5,7;238:9; 246:19;247:16;250:5; 253:3;254:1,11;255:1, 10;257:5,19;258:9,10, 19;259:3,21;262:17; 263:9,19,21;264:3,5,10, 14;268:12;286:14; 295:15,20;303:13; 316:14,17;320:10; 323:16;330:10;331:1; 332:14,21;333:9,9,15, 18,21;335:18;336:9,11; 337:2,7,7,8;338:1;340:7, 10;341:3,8,14,18;343:3, 4,7;344:9;347:1,5,22; 351:3,11,12 <b>clinical-grade (1)</b> 43:10 <b>clinically (6)</b> 240:8,9;250:6;263:18; 316:15;343:11 <b>clinical-stage (1)</b> 242:2 <b>clinician (4)</b> 77:5;259:3;339:5,21 <b>clinicians (6)</b> 77:5;180:16,20; 182:20;189:3,21 <b>Clive (8)</b> 4:8,10;5:7,8;74:22; 171:20;181:10;185:14 <b>clone (2)</b> 32:7;128:11 <b>cloned (1)</b> 168:2 <b>close (3)</b> 55:17;85:10;270:15 <b>closely (5)</b> 154:8;156:21;157:18; 212:12;247:13 <b>closer (1)</b>	188:14 <b>CLR (6)</b> 278:17;279:6,12,17; 280:9,17 <b>clues (2)</b> 222:18;238:12 <b>cluster (5)</b> 282:17,18,21;283:4,7 <b>CMV (2)</b> 126:1,11 <b>CNS (5)</b> 25:15;59:22;215:10, 13;275:2 <b>CNTF (5)</b> 70:3,4,9,12,17 <b>CNTF-secreting (1)</b> 70:10 <b>co- (1)</b> 329:2 <b>co-author (1)</b> 309:19 <b>cobra (2)</b> 138:19;139:3 <b>co-chairing (1)</b> 194:5 <b>cocktails (1)</b> 182:21 <b>code (1)</b> 93:2 <b>coffee (5)</b> 173:21;293:1,4; 294:16,18 <b>cognate (1)</b> 124:18 <b>cohorts (1)</b> 252:16 <b>coin (1)</b> 246:22 <b>coincidental (1)</b> 205:1 <b>cold (6)</b> 131:6;161:18,19; 162:17,20;163:9 <b>cold-sensitive (1)</b> 161:15 <b>collaborate (3)</b> 17:6;38:1;44:7 <b>collaborating (4)</b> 15:12;43:4;44:4;48:4 <b>collaboration (4)</b> 164:6;231:14;240:1; 281:10 <b>collaborations (1)</b> 240:3 <b>collaborator (2)</b> 162:10;247:14 <b>collaborators (4)</b> 66:1;247:22;248:3; 349:11 <b>colleague (4)</b> 88:11;112:4;282:18; 333:4 <b>colleagues (8)</b>	30:14;81:16;164:6,7; 192:9;196:16;205:14; 260:8 <b>collector (1)</b> 148:22 <b>College (2)</b> 194:21;295:10 <b>colliculus (1)</b> 285:10 <b>co-localization (2)</b> 276:12;279:15 <b>color (1)</b> 254:4 <b>colors (1)</b> 40:2 <b>column (1)</b> 85:5 <b>co-markers (1)</b> 102:2 <b>combination (4)</b> 124:22;151:8;162:13; 182:3 <b>combinations (5)</b> 157:15,19;158:1,3,4 <b>combine (3)</b> 15:3;64:4;117:7 <b>combined (2)</b> 64:5;67:19 <b>combining (1)</b> 182:7 <b>comfort (1)</b> 239:10 <b>comfortable (2)</b> 242:3;315:10 <b>coming (23)</b> 5:7;11:6;29:13;30:17; 46:9;55:20;58:16;69:22; 79:14;127:22;142:5; 187:5;194:10;272:12; 288:19;305:20;307:14; 308:15;317:22;322:3; 337:1;351:13;352:18 <b>comment (13)</b> 134:17;171:10,10; 173:4;223:12;238:10; 327:18;332:16;333:1; 337:19;343:2;351:15,20 <b>comments (5)</b> 171:16;190:7;267:13; 334:13;340:21 <b>commercial (3)</b> 44:5;246:21;247:2 <b>commercialization (1)</b> 247:4 <b>commissioned (1)</b> 203:4 <b>commit (1)</b> 176:7 <b>committee (2)</b> 173:14,22 <b>committees (1)</b> 187:22 <b>common (3)</b>
--	---	---	--	--

129:3;208:6;272:20 <b>commonly (1)</b> 124:5 <b>communicate (2)</b> 289:16;339:22 <b>communication (2)</b> 244:3;337:21 <b>community (4)</b> 146:16;148:22; 264:14;352:9 <b>co-morbidities (1)</b> 337:14 <b>companies (5)</b> 14:11;34:6;65:10; 243:16;315:7 <b>company (17)</b> 23:21;52:10;113:9,10; 172:1;195:17;207:3; 214:9,11;229:14;241:1; 242:1;243:10;249:19; 251:13;288:20;319:10 <b>company's (1)</b> 316:18 <b>comparative (1)</b> 209:1 <b>comparator (4)</b> 181:18;258:5,15; 309:22 <b>comparators (2)</b> 246:13;258:8 <b>compare (4)</b> 177:10;181:18; 279:18;342:9 <b>compared (8)</b> 129:3,13;205:17; 236:19;281:20;288:2; 308:20;341:19 <b>comparing (1)</b> 238:18 <b>comparison (4)</b> 109:7;182:16;208:10, 15 <b>comparisons (1)</b> 70:1 <b>compelled (1)</b> 258:18 <b>compelling (1)</b> 244:19 <b>compensate (1)</b> 27:5 <b>compete (1)</b> 243:11 <b>competition (1)</b> 285:1 <b>competitor (1)</b> 317:21 <b>complaint (1)</b> 115:16 <b>complete (1)</b> 151:7 <b>completed (4)</b> 206:14;207:10,11; 255:11	<b>completely (16)</b> 28:20;36:8;72:8,18; 110:11;111:5;147:17; 149:18;153:13;155:17; 157:11;189:22;221:10; 278:1;339:17;344:13 <b>complex (11)</b> 27:7;60:10;69:6; 76:11;133:22;141:18; 153:8;198:11;279:13; 280:16;288:14 <b>complexity (1)</b> 91:22 <b>compliant (1)</b> 43:22 <b>complicate (1)</b> 297:14 <b>complicated (2)</b> 133:22;252:3 <b>complications (2)</b> 64:17;298:7 <b>compound (3)</b> 103:11;141:14;293:14 <b>components (6)</b> 138:16;139:8,17; 145:19;148:5;328:17 <b>composition (2)</b> 153:16;163:22 <b>compound (10)</b> 152:11;173:1;203:21; 214:22;215:10;219:5; 242:20;254:20;308:6; 341:6 <b>compounds (21)</b> 160:7;180:1;197:14; 201:2,10;229:6,16,17, 21;231:6,19;264:2; 267:8;268:10;303:4,5; 304:9;309:6;341:1,4; 342:22 <b>comprehensive (1)</b> 35:15 <b>compromised (1)</b> 212:13 <b>computation (2)</b> 210:4,8 <b>computer (1)</b> 260:2 <b>concealed (1)</b> 203:2 <b>concentrated (1)</b> 293:19 <b>concentrations (1)</b> 287:19 <b>concept (8)</b> 31:18;38:9;42:10; 193:7;239:11;253:5,17; 305:16 <b>concepts (1)</b> 231:11 <b>concern (6)</b> 173:8;244:7;258:22; 306:17;323:3,4	<b>concerned (3)</b> 56:20;169:10;202:18 <b>concerns (3)</b> 101:15;227:16;258:20 <b>concise (1)</b> 295:19 <b>conclude (4)</b> 63:20;94:10;221:17; 332:19 <b>concluded (1)</b> 320:4 <b>conclusion (6)</b> 103:17;243:2;247:6; 259:1;270:1;326:19 <b>conclusions (1)</b> 261:12 <b>conclusive (1)</b> 217:7 <b>conclusively (1)</b> 220:7 <b>concur (3)</b> 180:6;339:18;349:9 <b>condition (15)</b> 13:6;76:17;79:7; 82:22;94:17,20;95:22; 114:16;163:18;174:3; 175:20;176:3;180:4; 269:11;299:22 <b>conditions (24)</b> 15:2;34:16;58:9; 98:18;107:13;137:4; 163:14;174:6;176:10; 178:18,19;180:16; 200:11,12;213:6,11; 238:11;246:1;249:6; 259:15,17;293:12,13; 344:17 <b>conducive (1)</b> 220:18 <b>conducted (3)</b> 192:21;247:20;345:2 <b>conducting (2)</b> 342:1,14 <b>conduction (1)</b> 203:16 <b>cone (18)</b> 136:17,18;137:3,10, 17,18;138:2,9;139:14; 143:5;148:17,18,19; 149:7;154:12,13,19; 165:16 <b>conference (1)</b> 227:22 <b>confidence (6)</b> 200:19;223:19;230:9; 231:14;240:11;324:7 <b>confident (1)</b> 218:10 <b>confidential (1)</b> 206:10 <b>confined (1)</b> 324:16 <b>confirm (2)</b>	247:18;260:2 <b>conflicting (1)</b> 198:9 <b>conflicts (1)</b> 195:10 <b>confound (2)</b> 262:5,11 <b>confounded (1)</b> 217:4 <b>confounds (1)</b> 201:17 <b>confronts (2)</b> 223:3,5 <b>congestion (1)</b> 283:1 <b>con-meds (4)</b> 206:19;208:2,6; 226:11 <b>connect (3)</b> 14:21;41:15;285:5 <b>Connecticut (1)</b> 296:7 <b>connecting (1)</b> 15:9 <b>connection (3)</b> 53:22;74:20;347:20 <b>Conotoxin (2)</b> 142:22;168:16 <b>cons (2)</b> 64:19;317:3 <b>consensus (3)</b> 65:7;188:16;189:11 <b>conserved (2)</b> 145:20;146:6 <b>consider (6)</b> 80:10;103:20;181:3; 222:1;317:20;318:1 <b>considerably (2)</b> 177:6,12 <b>considered (3)</b> 173:16;181:14;327:12 <b>considering (1)</b> 213:11 <b>consistent (2)</b> 46:4;246:12 <b>consistently (2)</b> 33:4;35:4 <b>consists (2)</b> 4:19;278:16 <b>CONSORT (2)</b> 350:17;351:2 <b>consortium (4)</b> 14:2,5;189:5,19 <b>constant (1)</b> 284:18 <b>constantly (1)</b> 141:4 <b>constitutively (1)</b> 327:1 <b>constricted (1)</b> 187:21 <b>constriction (2)</b> 156:5;277:9	<b>construct (2)</b> 56:18,19 <b>constructs (1)</b> 134:1 <b>consultant (1)</b> 195:12 <b>consulted (1)</b> 229:11 <b>consumption (1)</b> 198:10 <b>contact (2)</b> 113:18;206:18 <b>contain (11)</b> 78:12;87:7;128:22; 280:8,9,16;289:14,15; 290:1;293:17,18 <b>containing (2)</b> 276:4;292:8 <b>contains (1)</b> 91:9 <b>context (9)</b> 54:10;210:13;232:18; 237:18;238:22;239:1,1; 240:13;343:9 <b>continence (1)</b> 246:11 <b>continents (1)</b> 238:1 <b>continual (1)</b> 47:14 <b>continue (5)</b> 44:14;75:5;142:11; 173:13;190:10 <b>continued (1)</b> 231:5 <b>continues (1)</b> 273:18 <b>continuing (2)</b> 103:13;271:21 <b>continuous (1)</b> 324:19 <b>contraction (1)</b> 277:4 <b>contributed (1)</b> 260:8 <b>contribution (3)</b> 62:4;86:19;110:9 <b>contributions (1)</b> 214:4 <b>contributors (3)</b> 77:8,22;253:11 <b>control (28)</b> 5:20;50:22;58:18; 89:20;92:17;93:2,6; 98:19;99:1,18;117:20; 118:12,15,22;122:19; 128:16;129:13;130:5, 15;197:10;236:19; 254:21;256:18,20; 277:6;314:19;325:6; 342:10 <b>controllable (1)</b> 89:22
--	--	--	---	--

<b>controlling (1)</b> 348:15	30:10,16;35:12,19;36:1; 37:8,12,17;38:4,10;39:2;	<b>couple (14)</b> 59:11;61:6;72:11,14; 73:12;75:18;108:12; 124:2;130:12;132:16; 212:4;225:17;265:2; 267:13	347:12;350:4	<b>cyclic (1)</b> 287:20
<b>controls (1)</b> 226:9	40:19;41:4;45:11,17,20; 46:14;48:21;49:4,5,11, 11;50:10;52:1,6,15,21; 53:6;67:1,10,12,14,20; 69:2,3,13;70:10;74:19; 78:1,3,5;79:16;80:18,19; 82:21;83:3,11,21;84:7; 85:4,12,14;87:19,20; 90:6;97:8;98:11;101:20; 103:10;105:10,11,15; 106:13,15,21;117:14; 135:20;145:11;152:17; 172:9;174:20,22;176:15, 20;181:1;188:11,13	<b>courage (1)</b> 264:2	<b>critical (5)</b> 94:8;108:19;133:2; 144:19;263:13	<b>cyclosporine (4)</b> 38:20;72:19;73:4,4
<b>controversial (3)</b> 69:8;78:19,22		<b>course (54)</b> 22:11;25:19;26:22; 30:10;66:11;69:18;71:7; 78:13;79:9;82:19;91:18; 140:18;143:6,8,15,18; 144:1,17;145:9;153:8; 159:15;162:18;163:8; 174:3;188:8;197:11; 205:15;225:8;227:2; 228:21;229:9;241:7; 260:16;261:8;269:4,9; 277:6;278:5;282:3,20; 283:22;284:18;285:10; 287:20;290:6,11;292:5, 11;303:16;313:14; 315:3;323:20,21;345:19	<b>critters (1)</b> 157:14	<b>cystitis (2)</b> 257:13,14
<b>contulakin (1)</b> 184:4	<b>core (4)</b> 11:15;46:7;105:8; 175:5	<b>coupling (2)</b> 273:15,20	<b>Crohn's (3)</b> 9:14,15,17	<b>D</b>
<b>contulakin-G (1)</b> 152:4	<b>co-release (1)</b> 283:4	<b>courage (1)</b> 264:2	<b>cross (3)</b> 143:9;145:16;287:12	<b>daily (7)</b> 73:4;297:12;310:15, 20;314:4,5;324:20
<b>conus (5)</b> 139:16;142:14;153:1, 19;160:10	<b>co-released (1)</b> 282:17	<b>course (54)</b> 22:11;25:19;26:22; 30:10;66:11;69:18;71:7; 78:13;79:9;82:19;91:18; 140:18;143:6,8,15,18; 144:1,17;145:9;153:8; 159:15;162:18;163:8; 174:3;188:8;197:11; 205:15;225:8;227:2; 228:21;229:9;241:7; 260:16;261:8;269:4,9; 277:6;278:5;282:3,20; 283:22;284:18;285:10; 287:20;290:6,11;292:5, 11;303:16;313:14; 315:3;323:20,21;345:19	<b>cross-linked (1)</b> 139:9	<b>damage (6)</b> 31:6;37:11;114:12; 174:22;176:19,21
<b>convection- (1)</b> 21:9	<b>corollary (1)</b> 178:9	<b>cover (2)</b> 193:18;225:5	<b>CRPS (1)</b> 92:1	<b>damaged (1)</b> 22:20
<b>convection-enhanced (1)</b> 21:4	<b>coronaries (1)</b> 323:16	<b>covers (2)</b> 75:17;76:22	<b>crush (1)</b> 71:15	<b>dangerous (1)</b> 346:10
<b>convenience (1)</b> 230:12	<b>coronary (1)</b> 294:9	<b>Craig (4)</b> 140:4,12;141:16; 151:21	<b>CSF (4)</b> 18:20;70:18;84:18; 175:4	<b>dangers (1)</b> 178:17
<b>convenient (1)</b> 251:21	<b>correctly (1)</b> 26:8	<b>Craig's (1)</b> 142:6	<b>cubital (2)</b> 281:22;282:2	<b>dark (2)</b> 171:4;309:2
<b>conventional (3)</b> 223:1,4;224:18	<b>correlate (1)</b> 215:21	<b>cranial (2)</b> 276:9;282:13	<b>cultural (2)</b> 239:1;350:12	<b>DARPA (2)</b> 15:17;16:17
<b>Convergance (1)</b> 343:19	<b>correlated (1)</b> 282:6	<b>crawl (2)</b> 39:20;149:19	<b>culture (5)</b> 16:10;32:6;58:6; 158:10;226:6	<b>data (76)</b> 11:12;13:4;23:11; 25:20,22;26:15;35:9; 36:18;43:5;47:10;48:11; 52:8;69:18;70:7;102:5; 108:10;118:9;122:6,16; 130:12;131:5;182:10, 15;187:4;198:1;201:6; 210:15;214:5;218:6; 219:16;220:17;230:13; 231:12;232:19;233:14; 238:9;242:5,12;245:11; 247:10;250:6,10;251:7; 252:17;253:15;254:17; 259:19;260:16,16,19; 262:15;267:14;268:4; 287:9;296:18,22; 303:13;306:22;316:18; 318:8;319:1,3;336:17; 341:11;342:14;343:20; 346:11,18;347:5,6,12, 19,19,20;348:4;352:11
<b>convergence (5)</b> 238:10;240:7;246:10; 249:3;269:21	<b>correlates (1)</b> 45:18	<b>creates (1)</b> 267:10	<b>cultured (2)</b> 199:2,17	<b>date (2)</b> 212:19;213:18
<b>convergent (3)</b> 236:20;237:22;246:6	<b>correlation (2)</b> 45:12,14	<b>creating (2)</b> 16:14;302:4	<b>cultures (1)</b> 15:4	<b>daughter's (1)</b> 95:4
<b>convergently (1)</b> 249:8	<b>cortex (14)</b> 79:8;80:15,16,22; 81:4,8,11,22;82:6,7; 83:15,16;273:15;284:11	<b>creatinine (1)</b> 311:8	<b>cumbersome (1)</b> 21:19	<b>Dave (10)</b> 231:2,3;239:7,18; 241:9;248:3;250:2; 269:5;270:11,13
<b>conversation (1)</b> 333:4	<b>cortical (6)</b> 31:21;54:18;83:10; 106:11,12;276:21	<b>credit (4)</b> 253:2;264:9;318:1; 338:12	<b>cumulative (2)</b> 209:15;329:14	<b>Dave's (2)</b> 231:13;261:1
<b>conversations (1)</b> 191:11	<b>cortical-derived (1)</b> 38:11	<b>crevices (1)</b> 149:22	<b>cure (1)</b> 163:17	<b>David (1)</b> 160:14
<b>conversely (1)</b> 200:1	<b>cost (3)</b> 60:12,14;225:8	<b>crisis (1)</b> 173:8	<b>curios (1)</b> 348:7,10	<b>Davis (1)</b> 241:6
<b>convert (1)</b> 63:8	<b>cost/risk (1)</b> 174:15	<b>criteria (8)</b> 202:21;206:5,9; 222:14;249:19;339:1;	<b>curiosity (2)</b> 348:7,10	<b>Davis (1)</b> 197:20
<b>converted (1)</b> 25:2	<b>costly (1)</b> 219:15		<b>curious (5)</b> 184:3;219:2;259:9; 260:3;269:1	
<b>converting (1)</b> 6:22	<b>costs (1)</b> 273:4		<b>Curiously (1)</b> 154:11	
<b>converting-enzyme (1)</b> 196:22	<b>Cotter (1)</b> 203:5		<b>curl (1)</b> 129:21	
<b>convince (3)</b> 32:10;85:19;86:3	<b>count (1)</b> 156:14		<b>current (1)</b> 286:12	
<b>convinced (1)</b> 269:3	<b>countries (5)</b> 207:6;208:1,8;212:10; 238:2		<b>currently (15)</b> 21:13;35:8;43:13; 52:13;56:17;67:13; 212:17;219:21;222:3; 232:7,8;313:10;325:20; 335:21;342:1	
<b>convulsions (1)</b> 141:9			<b>curve (2)</b> 46:12;311:10	
<b>co-occur (1)</b> 106:16			<b>cut (2)</b> 92:6;236:2	
<b>cool (3)</b> 56:9,16;110:18			<b>cute (3)</b> 103:21,22;248:9	
<b>copies (4)</b> 68:8;127:10,13; 311:19			<b>cutting (1)</b> 16:21	
<b>cord (92)</b> 5:20;14:22;15:4,10; 19:1,19,19;23:12,20,22; 24:3,7;25:16;27:11,13;			<b>cycle (1)</b> 113:20	

<b>day (13)</b> 4:4;8:4;44:21;65:1; 85:3,7;192:2;231:21; 241:12;253:9;324:18; 327:10;333:5	48:17;99:17;159:16 <b>decreased (7)</b> 79:1,5;105:19,22; 106:8;156:16;198:3 <b>deemed (1)</b> 242:5 <b>deep (3)</b> 19:16;243:3;269:16 <b>defect (2)</b> 82:13,14 <b>defective (1)</b> 114:15 <b>defend (1)</b> 277:18 <b>defense (1)</b> 278:5 <b>deference (1)</b> 230:1 <b>define (1)</b> 242:10 <b>defined (3)</b> 37:5;154:2;297:1 <b>definitely (7)</b> 90:17;101:21;112:18; 136:13;337:20,22;344:4 <b>definitive (2)</b> 228:14;230:1 <b>degenerating (1)</b> 39:20 <b>degeneration (4)</b> 31:17;54:9,12;68:8 <b>degraded (1)</b> 325:19 <b>degranulation (1)</b> 299:15 <b>degree (4)</b> 224:9;253:21;260:1; 302:4 <b>degrees (4)</b> 129:17,18;130:1,10 <b>delay (2)</b> 67:4,7 <b>deleted (1)</b> 128:18 <b>delightful (1)</b> 295:14 <b>deliver (6)</b> 25:14;54:21;67:5; 109:3;164:18;170:13 <b>delivered (3)</b> 109:17;171:7;184:21 <b>delivering (2)</b> 22:12;110:6 <b>delivery (23)</b> 21:4,10,22;22:4;50:5; 64:9;66:17;67:6;120:4; 123:11;147:9;170:7,15; 171:5,11,17,21;172:3; 177:11;181:20;183:5; 184:13,14 <b>delta (3)</b> 117:8,12;280:6 <b>dementia (1)</b>	29:17 <b>demethylation (1)</b> 8:11 <b>demographics (1)</b> 207:16 <b>demonstrate (1)</b> 218:12 <b>demonstrated (4)</b> 137:2;303:1;328:6; 329:22 <b>demonstrating (1)</b> 91:2 <b>demonstration (1)</b> 81:6 <b>demonstrations (1)</b> 332:13 <b>demyelinated (1)</b> 24:3 <b>den (1)</b> 150:10 <b>dendrite (5)</b> 88:17,21,22;89:11,19 <b>dendrites (1)</b> 274:14 <b>Dennis (4)</b> 191:4;195:2;227:21; 332:10 <b>department (2)</b> 112:12;272:9 <b>dependent (4)</b> 127:6;271:1,4;322:20 <b>depending (1)</b> 100:9 <b>dephosphorylate (1)</b> 132:12 <b>dephosphorylates (1)</b> 132:13 <b>depiction (1)</b> 209:17 <b>depolarization (1)</b> 143:21 <b>depolarize (1)</b> 90:9 <b>depolarizing (1)</b> 120:9 <b>deposit (1)</b> 38:9 <b>depressed (1)</b> 141:9 <b>depression (3)</b> 211:11;278:6,11 <b>derive (1)</b> 81:8 <b>derived (4)</b> 54:19;59:4,5;262:18 <b>deriving (1)</b> 185:18 <b>dermal (1)</b> 200:8 <b>dermatitis (1)</b> 212:5 <b>dermatome (2)</b> 100:12;170:10	<b>des (1)</b> 303:10 <b>descending (2)</b> 77:15;117:18 <b>described (5)</b> 12:8;103:5;235:19; 296:11;331:3 <b>describing (1)</b> 334:22 <b>description (2)</b> 92:3;94:19 <b>desensitized (1)</b> 127:5 <b>deserve (1)</b> 213:22 <b>design (12)</b> 43:1,9;50:7;51:1; 147:13;205:9;211:21; 308:10;340:16;343:4; 344:9;346:20 <b>designed (1)</b> 221:14 <b>designing (1)</b> 351:10 <b>desisted (1)</b> 200:17 <b>desperate (2)</b> 177:22;187:11 <b>Despite (3)</b> 5:10;226:9;245:12 <b>destabilization (1)</b> 128:4 <b>destined (1)</b> 83:10 <b>destroy (1)</b> 59:17 <b>destroyed (1)</b> 7:10 <b>destruction (2)</b> 198:17;248:6 <b>detail (9)</b> 31:21;161:15;210:2; 238:4;249:18;252:4; 254:14;261:18;293:20 <b>details (5)</b> 20:21;161:14;250:10; 315:11;322:8 <b>detect (3)</b> 114:9,19;116:20 <b>detectible (2)</b> 226:10,13 <b>determines (1)</b> 241:17 <b>develop (20)</b> 60:2;98:14;116:13; 118:5;123:14;152:20; 168:15;169:2;264:15; 294:13;296:15;311:4; 325:15;329:8;335:4,7, 16,18;336:11;352:13 <b>developed (30)</b> 9:16;22:10;32:4,12; 37:9;49:1;116:16;	130:20;132:18;140:2; 194:18;234:3,9;235:9; 261:4;304:12;305:7,9, 14;307:17;308:19; 309:21;314:10;315:1,14, 20;318:9;330:18; 331:11;345:14 <b>developing (24)</b> 49:13;187:19;188:1; 233:13;239:21;294:11; 295:22;296:3,17;298:8; 299:5;306:16;308:5,6; 314:1,13;315:3,5,15; 316:10;323:13;330:11; 335:20;336:9 <b>development (30)</b> 5:5;80:22;112:16; 119:6;120:10;130:6; 143:3;183:14;184:5,12; 193:14;195:14;197:15; 199:16;201:2;210:17; 224:1,6,15;229:20; 231:6;232:18,20; 264:14;272:5;314:18; 316:6;325:21;334:18; 337:7 <b>device (7)</b> 49:6,10,16,17,20,21; 147:9 <b>devoid (1)</b> 278:1 <b>Dhruv (1)</b> 62:4 <b>diabetes (1)</b> 105:5 <b>diabetic (10)</b> 105:7;203:6;206:3; 213:10;220:9;234:10; 257:4;344:20;345:4,19 <b>diagnosis (1)</b> 26:20 <b>diagram (1)</b> 78:1 <b>diameter (2)</b> 276:22;288:2 <b>Diane (1)</b> 168:10 <b>diaries (1)</b> 206:14 <b>die (16)</b> 12:11,15;27:18;28:5, 5;29:11;36:6,13;52:6; 84:19,21;128:5;165:21; 186:4;323:11 <b>died (2)</b> 173:5;277:21 <b>dies (1)</b> 54:3 <b>difference (22)</b> 48:12,14;107:22; 108:5;130:8;144:20,20; 163:1;173:2;187:7; 202:6;208:12;210:5,7;
--	--	--	---	--

211:7;212:9;226:4; 254:9;257:9;315:18; 324:6;351:2 <b>differences (5)</b> 47:18;48:10;51:15; 185:20;205:3 <b>different (123)</b> 4:21;7:1;9:5;14:7,19; 16:18;17:3;19:22;21:2; 22:10;30:9;34:4,10; 44:9;45:10;46:3;61:4; 62:19;74:16;81:3;102:1; 103:6,7;106:13,17; 107:14;110:22;120:16; 124:21;131:8;133:15; 134:11;146:8,8;149:3,8, 18;153:11,12;155:17; 158:9,19,22;159:2,10; 161:11,11,22;167:7,12; 169:22,22;170:17,18; 172:21;176:14;182:20, 21;201:20;203:1,3; 213:9;216:5;223:22; 224:15;227:2,2;230:5; 237:22;238:1,1,2,2,4,5,5, 5,6;239:15,18;241:12, 18;245:13,14,18,21,22, 22;246:2,2,2,5,5,6,15,16; 247:22;254:18;259:6, 15;260:4;263:21; 264:22;267:6;269:22; 276:20;277:1;285:8; 289:2;297:21;311:19; 315:4,6,6;316:22; 320:22;326:16,17,20; 334:10;337:22;342:12, 16 <b>differentiate (8)</b> 33:14,20;39:21;62:16; 146:1;158:18;159:10; 229:4 <b>differentiated (3)</b> 61:15;62:21;102:17 <b>differentiates (3)</b> 62:14;223:15;224:13 <b>differentiating (1)</b> 157:18 <b>differentiation (5)</b> 12:13;61:18;62:14; 186:16;247:3 <b>differently (2)</b> 159:1;335:7 <b>difficult (14)</b> 14:13;19:2;40:15; 41:8;60:20;76:18; 157:17;170:3;174:12; 201:16;288:8;321:22; 325:15;339:8 <b>difficulties (3)</b> 69:3;174:1;192:22 <b>diffuse (1)</b> 235:9 <b>dilatation (2)</b>	284:8;289:4 <b>dilate (1)</b> 291:3 <b>dilates (1)</b> 291:6 <b>dilemma (2)</b> 36:17;194:2 <b>dimension (1)</b> 244:6 <b>dinner (1)</b> 32:10 <b>direct (5)</b> 62:16;109:6;113:18; 225:3;327:5 <b>directed (2)</b> 4:18;287:15 <b>direction (5)</b> 210:20;211:10; 328:10;352:6;353:5 <b>directionality (1)</b> 242:21 <b>directions (1)</b> 194:3 <b>directly (5)</b> 19:8;63:8;141:14; 151:6;238:9 <b>director (2)</b> 4:11;326:3 <b>dirtier (1)</b> 171:1 <b>dirty (1)</b> 265:11 <b>disagree (2)</b> 175:17;238:16 <b>disappear (2)</b> 71:6;286:8 <b>disappeared (2)</b> 274:19;282:8 <b>disappointing (1)</b> 179:4 <b>disciplined (1)</b> 338:4 <b>disclosure (2)</b> 137:15;295:20 <b>disclosures (3)</b> 113:7;137:13;229:11 <b>disconnect (2)</b> 340:4,13 <b>disconnected (1)</b> 243:15 <b>discontinuation (1)</b> 312:8 <b>discontinued (2)</b> 306:18;312:3 <b>discovered (6)</b> 7:16;153:22;296:11; 299:5,9;300:2 <b>discoverer (1)</b> 196:3 <b>discovering (1)</b> 160:6 <b>discovery (2)</b> 139:16;299:8	<b>discredited (1)</b> 8:17 <b>discuss (11)</b> 54:4;64:20;124:16; 261:18;284:5;296:8; 305:4;313:13;315:11; 317:17;334:16 <b>discussed (11)</b> 91:21;173:20;204:11; 205:12;219:8;252:4; 270:20;274:10;280:13; 285:15;292:4 <b>discussing (5)</b> 73:13;203:15;212:17; 213:4;219:21 <b>discussion (27)</b> 6:21;20:21,22;45:6; 60:1;71:17;73:6;75:2; 94:4;169:12,16;188:16; 192:22;211:19;225:16; 242:6;243:22;265:3,11; 269:2;271:19;279:2; 295:2;303:2;323:1; 326:9;332:6 <b>discussions (3)</b> 65:18;191:12;208:19 <b>disease (56)</b> 6:16;10:3,11;11:18; 12:2,3,18;13:9,11;14:1, 9,12,15;17:13;19:12; 20:11;26:22;27:6,7; 29:3,3;36:11,12,14;54:8, 12;60:4,6;65:16;67:4; 74:17;80:11,11;94:15, 17;103:19;171:13; 185:17;196:21;272:20; 273:22;275:7;287:2; 296:19,20,20;297:6,7, 11,14,20;298:17,21; 299:19,20;301:2 <b>diseased (1)</b> 7:22 <b>disease-modeling (1)</b> 13:2 <b>diseases (9)</b> 4:22;6:12;10:12; 18:10;25:10;29:5;189:1, 3,20 <b>dish (21)</b> 6:14;8:4,12;9:17,18; 10:11,13;11:5,9,19,20; 12:18;13:5,14,15,19,22; 14:10;15:9;34:2;63:22 <b>disorder (4)</b> 12:6;26:20;186:8; 275:2 <b>dispersion (1)</b> 239:17 <b>disposable (2)</b> 147:1,10 <b>disproven (1)</b> 343:13 <b>dissect (1)</b>	284:4 <b>dissociated (2)</b> 32:21,22 <b>dissociation (2)</b> 33:5;284:17 <b>distal (1)</b> 303:7 <b>distance (3)</b> 113:22;194:9;272:12 <b>distinct (2)</b> 110:10;201:16 <b>distinguishes (1)</b> 169:3 <b>distribute (2)</b> 61:5;82:5 <b>distributed (2)</b> 155:15;319:18 <b>distribution (4)</b> 43:12;93:4;155:14; 353:15 <b>disulfide (1)</b> 139:9 <b>diverse (2)</b> 264:3;266:21 <b>diversity (1)</b> 142:1 <b>divide (6)</b> 72:6,11,14;232:12; 297:6,19 <b>divided (1)</b> 296:21 <b>dividing (2)</b> 101:12,13 <b>diving (1)</b> 154:16 <b>division (2)</b> 72:8;326:3 <b>divisions (1)</b> 72:7 <b>dizziness (1)</b> 261:22 <b>DNA (6)</b> 63:13,13,16,17; 127:20;133:16 <b>doc (1)</b> 90:4 <b>docks (1)</b> 278:18 <b>docs (1)</b> 56:13 <b>DoD (1)</b> 53:18 <b>dogs (2)</b> 294:8;323:16 <b>dollars (1)</b> 348:16 <b>domain (1)</b> 315:17 <b>dominant (1)</b> 128:16 <b>Don (1)</b> 15:13 <b>done (67)</b>	6:18;13:8;43:20;45:9; 46:17;48:19;49:15; 52:12,19;53:13;56:9; 76:20;87:2;88:12;89:3; 92:20;93:3,12;95:11; 97:18,19;100:6,8;123:9; 124:14;125:13;132:22; 148:19;155:20;165:4; 167:14;170:15;178:13; 187:8;199:16;202:20; 206:7;208:3;214:8; 218:20;223:2;235:3,21; 242:10;247:12,15; 249:6;252:20;254:22; 255:3;260:9;263:5; 266:1;280:20,22; 282:11;290:20;305:16; 327:9;329:20;334:15; 337:2;341:8;343:7; 345:21;346:16;349:12 <b>doom (1)</b> 193:11 <b>door (1)</b> 95:5 <b>dopamine (5)</b> 19:11;20:6,11;22:9; 31:15 <b>dorsal (21)</b> 23:12;48:6,8;71:9,20; 78:6,11;85:4,5;87:19; 88:5;90:11;95:17;96:11; 98:11;108:3;117:14; 198:3;199:2;204:6; 293:21 <b>dose (29)</b> 43:11;45:9,12,19; 46:9,10,11,13;47:20; 139:4;202:9;206:20; 208:11;213:2,4;252:15; 254:7;286:3,6,14; 305:18;317:5,5;320:6, 16;322:18,20;324:3,4 <b>dose- (1)</b> 208:18 <b>dosed (2)</b> 258:14;270:14 <b>dose-ranging (1)</b> 43:18 <b>dose-response (1)</b> 202:12 <b>doses (15)</b> 45:10;46:3,8;47:1; 216:16,16;285:2; 308:11;309:12;310:1; 320:21,21;321:13;322:9, 12 <b>dosing (9)</b> 119:11;123:3;202:7,7; 216:21;270:18;321:1,14, 14 <b>dot (1)</b> 38:17 <b>dots (2)</b>
---	--	--	--	---

89:5;91:8 <b>double (2)</b> 20:17,19 <b>double-blind (1)</b> 318:14 <b>doublecortin (1)</b> 101:11 <b>double-labeled (1)</b> 91:10 <b>doublings (2)</b> 33:11,17 <b>doubt (1)</b> 136:1 <b>down (28)</b> 26:16;27:2,10,12,12; 35:18;38:15;41:10;46:9; 54:12;61:14;62:9,9,18; 113:22;120:7,10;123:4, 4;150:19;151:13; 172:18;184:5;240:22; 241:10;279:21;319:15; 342:6 <b>down-regulated (1)</b> 127:5 <b>downside (3)</b> 59:18;170:3;173:22 <b>downstream (1)</b> 318:7 <b>dox (1)</b> 56:11 <b>doxycycline (4)</b> 55:18,22;56:1,2 <b>Doyal (1)</b> 132:20 <b>dozens (1)</b> 346:16 <b>DR (264)</b> 4:3,8;5:9;66:14,16,20, 21;67:2;68:3,6,12,13,19, 22;69:4,17;70:14,16; 71:21;72:2;73:21;74:3, 4,5,9,11,22;75:9;95:3, 10;104:16,18;105:10,11, 18;107:16,21;108:6,16, 17;109:1,2,8,14,15; 110:3,7,8,11,14,21; 111:5,8;112:8,9,10,11, 22;133:7,8,12;134:3,5,6, 7,13,17;135:12,15,18; 136:4,10;137:8;140:12; 147:12;150:12;164:12; 165:1,9,10,11,14;166:9, 10,17,19,20;167:3,4,6, 13,19;168:9,22;169:5, 17,19;170:5,14;171:9, 22;173:4,12,13,17; 174:14;175:17,18,19; 177:8,14,15,19;178:7, 21,22;179:3;180:13,14; 182:17;183:12,16,17,18, 19,20,21;184:13,18,19, 22;185:1,8,14,22; 186:22;187:3,11,15,18,	21;188:4,6,8,9;190:5,7, 8;191:3;195:2;214:15, 16;215:2,8,12,15,18,19, 22;216:4,6;217:13; 218:6,11,13,15,17; 219:1,8;220:21,22; 221:12,19,21,22;222:1, 5,6,8,12;223:13;226:18; 227:21;228:7;264:19; 265:5;266:11,13;267:3, 12;268:7,21;269:1,18; 270:3,5,7,8,10,11;271:7, 8,17;272:6,17;292:20; 293:6,15;294:15,21; 295:9,17;296:9;299:9; 300:21;302:22;305:13; 306:22;318:5;323:14; 326:1,2,8,10;327:17,18; 328:11,13;329:9,18; 330:7;331:6,9,20,20,22; 332:7,22;334:6,12,14; 336:13,22;337:17,18; 339:2,2,3,17;340:20; 341:13;342:18,19; 344:13;345:10,16;346:4, 7,9;349:2;351:13,14,19; 353:9 <b>drag (1)</b> 141:5 <b>dramatic (4)</b> 70:11;77:3;130:8; 131:4 <b>dramatically (2)</b> 232:22;233:15 <b>drastic (1)</b> 96:5 <b>drawing (1)</b> 261:11 <b>DRG (11)</b> 105:9;158:8;159:11; 160:4,13,18;199:4,8,18; 205:21;223:18 <b>DRGs (4)</b> 14:21;15:3,9;199:12 <b>drive (4)</b> 63:5;90:15;250:19; 251:11 <b>driven (7)</b> 26:16;91:12,17; 102:18;126:8;223:10; 334:19 <b>drivers (2)</b> 241:4;250:7 <b>drives (2)</b> 98:20;312:17 <b>driving (6)</b> 7:13;106:20;125:8,12; 126:5;250:17 <b>drop (1)</b> 149:9 <b>drop-outs (1)</b> 321:18 <b>dropped (2)</b>	207:10,14 <b>dropping (2)</b> 284:22;285:1 <b>drosophila (3)</b> 155:3;168:2,4 <b>Drs (1)</b> 326:1 <b>drug (49)</b> 11:2,3;13:4;20:15; 21:6;28:21;44:2;109:12; 121:8,9;122:9;123:10; 131:21;132:1;142:20; 144:14;145:10;146:4; 147:9;171:1;176:15; 184:15;197:6;204:20, 22;206:20;210:6,7,9; 218:17;221:16,17; 223:22;224:10,15; 226:6;229:20;244:10; 257:1;261:3,4,7,21; 263:20;270:14;286:12; 334:18;344:21;345:7 <b>drug- (1)</b> 105:5 <b>drug-related (1)</b> 308:2 <b>drugs (31)</b> 10:16,17,21;11:4; 14:12;25:14,17;28:20, 22;64:2;70:17,21; 177:11;180:7;181:20; 182:21,21;193:2;208:7; 210:5,15;216:20;222:3, 7;224:7,8;247:5;259:21; 335:7;349:4,6 <b>drug's (1)</b> 246:20 <b>drug-treated (1)</b> 204:15 <b>dual (3)</b> 74:10;301:18;322:6 <b>dubious (1)</b> 14:3 <b>due (9)</b> 95:6;116:7;198:17; 218:3;230:1;280:1; 325:15;343:2,4 <b>duloxetine (1)</b> 221:9 <b>dura (5)</b> 279:19;280:3,7,15; 300:9 <b>dural (1)</b> 286:17 <b>duration (4)</b> 206:6;207:20;210:15; 321:12 <b>during (9)</b> 162:19,20;232:20; 237:12;245:4;252:5; 261:18;303:22;338:12 <b>dwell (1)</b> 254:14	<b>Dworkin (19)</b> 191:8;194:6;205:13; 294:21;326:1;331:20, 22;332:7;334:6;336:13; 337:17;339:2;340:20; 342:18;344:13;345:16; 346:7;351:13;353:9 <b>dye (3)</b> 97:16;290:5,11 <b>dying (6)</b> 40:1,3;56:21;68:12, 13;186:6 <b>dyskinesia (1)</b> 55:12 <b>dysregulated (1)</b> 163:16 <b>dystonic (1)</b> 76:16 <b>E</b> <b>earlier (6)</b> 29:21;86:20;135:22; 188:22;344:15;347:13 <b>early (33)</b> 31:22;52:11;67:9; 73:22;84:21;97:22; 104:9;108:9,14;115:4; 116:21;171:11,14; 197:19;200:17;232:1; 234:1;237:17;250:20; 251:1;252:13,22;253:6; 263:2,13;270:21; 278:10;281:13;292:21; 295:7;309:1;314:18; 319:1 <b>ease (1)</b> 171:17 <b>easier (3)</b> 25:6;58:17;68:22 <b>easily (5)</b> 18:19;77:10;189:16; 279:21;290:14 <b>eastern (4)</b> 207:7;222:2;224:17; 225:7 <b>easy (5)</b> 9:6;65:6;109:5;298:5; 339:6 <b>easy-to-manage (1)</b> 298:6 <b>eat (5)</b> 137:21,21;138:1; 154:13,15 <b>eaten (1)</b> 151:1 <b>eating (1)</b> 139:4 <b>ECG (1)</b> 204:17 <b>echo (1)</b> 134:21 <b>ectoderm (1)</b>	62:19 <b>edema (1)</b> 300:8 <b>edge (3)</b> 16:21;27:5;188:19 <b>Edinburgh (1)</b> 349:12 <b>edit (1)</b> 9:8 <b>editorial (1)</b> 310:3 <b>editor-in-chief (2)</b> 75:15,16 <b>Edvinsson (15)</b> 272:7,16,17;293:15; 296:9;299:9;300:21; 302:22;305:13;306:22; 318:5;323:14;326:2; 339:2,3 <b>effect (50)</b> 19:15;39:5,10,16; 46:17,19;47:15;51:6; 56:22;67:21;69:21;70:6; 74:7;111:2;123:5;130:6; 131:2,4,9;132:13;134:6, 7;136:1;150:8;168:18; 179:22;184:8;200:2,3; 204:3;205:1,15;206:16; 210:6;212:12;217:1; 218:2,17;221:5,6,12; 223:8;262:5;278:20; 286:21;287:1;288:15; 291:15;292:17;327:13 <b>effective (27)</b> 46:16;80:3;95:12; 98:2;106:6;131:12; 152:11;179:8,11,12,19; 181:17;183:7,11;184:7, 9;185:9;202:1,7;257:2; 287:8,10;288:4;308:21; 310:1,6;318:22 <b>effectively (1)</b> 36:1 <b>effector (1)</b> 319:7 <b>effects (34)</b> 11:4;18:9;19:14; 30:14;47:3,4;55:8; 70:19;71:1,2,5;107:18, 19;108:11;109:13; 119:16;121:1;123:6,17; 132:11;161:5,11; 181:12;182:22;197:12; 213:3;215:3;262:10; 267:6;288:18;293:11; 297:11;312:20;330:4 <b>efficacious (2)</b> 341:1;345:7 <b>efficacy (90)</b> 126:19;131:13; 152:18;173:9,10; 176:11;177:9;179:1; 181:15;182:8;202:9;
--	---	---	---	---



203:10;208:9,14,20; 209:2,17;210:2,9,18; 211:9;212:10;213:1,15; 224:11;228:15,18; 229:5;230:6;242:5,19, 22;245:12;247:18; 250:13,15,20;251:1,2; 252:13,17;253:1,22; 256:5,8,17;259:14; 261:9,20;262:6,11; 263:2,20;265:6,16; 267:8;268:9,18;271:15; 286:11,14;303:3; 304:22;305:2,18,19,20; 307:5,9;308:13;309:1, 15;312:17;316:17; 318:16,20;319:1,3; 325:14;331:4;332:13; 341:2,9;343:1,16;346:1, 2,14;349:19;352:10	186:19 <b>electrophysiologist (1)</b> 326:14 <b>elegans (1)</b> 155:6 <b>elegant (3)</b> 37:10;77:17;240:15 <b>elements (3)</b> 103:6;125:6;290:2 <b>eletriptan (4)</b> 308:22;309:3,11,11 <b>elevated (3)</b> 303:14,15,19 <b>elicit (1)</b> 278:8 <b>eliminated (1)</b> 199:2 <b>ELISA (1)</b> 233:12 <b>ELISAs (1)</b> 45:16 <b>else (13)</b> 42:9;69:15;103:12; 225:2;266:1;268:5; 286:15;302:17;303:7; 313:17;320:2;321:20; 328:22 <b>elucidated (1)</b> 196:15 <b>EM (1)</b> 88:14 <b>EMA300 (1)</b> 217:5 <b>EMA401 (16)</b> 197:15;199:20;200:5; 203:21;205:10;207:8, 10;208:16;210:10,22; 211:7,22;212:3,5; 213:18;216:18 <b>e-mail (2)</b> 137:13;353:13 <b>Emax (2)</b> 284:22;285:1 <b>embryo (4)</b> 81:1,17;84:2;111:18 <b>embryonic (13)</b> 7:5,11,17,19;8:13;9:4; 61:12;62:10;80:16;82:8; 101:4;104:12;111:17 <b>embryos (5)</b> 7:10;59:17;187:19; 188:2,2 <b>emerged (1)</b> 232:19 <b>emerging (3)</b> 157:3;182:18;183:3 <b>eminence (1)</b> 81:9 <b>eminent (1)</b> 101:18 <b>Emory (1)</b> 43:6 <b>emotive (1)</b>	77:3 <b>emphasize (4)</b> 54:7;192:5;208:18; 224:2 <b>empirical (1)</b> 179:20 <b>enables (1)</b> 27:16 <b>encephalitis (1)</b> 114:13 <b>encephalopathy (1)</b> 173:7 <b>encourage (1)</b> 333:13 <b>encouraged (1)</b> 210:19 <b>encouragement (2)</b> 83:17;349:22 <b>encouraging (3)</b> 20:7;136:4;257:21 <b>end (27)</b> 6:22;8:12;11:11,12; 37:1;44:20;61:19;76:3; 84:15,18;143:12; 145:16;147:5;164:5; 182:1;200:14;208:11; 215:5;246:12;272:2; 292:1,21;295:4,7; 343:14;351:13;353:10 <b>endeavor (1)</b> 338:2 <b>ended (6)</b> 7:6;20:18;88:4; 137:15;249:21;271:12 <b>ending (1)</b> 326:6 <b>endings (3)</b> 300:18;302:8,9 <b>endoderm (1)</b> 62:19 <b>endogenous (1)</b> 46:2 <b>endometriosis (1)</b> 257:20 <b>endothelial (2)</b> 16:1,5 <b>endothelium (6)</b> 16:13;279:3,4,5,8; 291:5 <b>endpoint (9)</b> 37:5;46:5;208:9; 245:17;262:6,12;306:1, 5,9 <b>endpoints (6)</b> 245:14;252:10;263:9, 10;307:6,7 <b>ends (3)</b> 87:5,20;185:3 <b>endurance (3)</b> 196:18;294:22;353:12 <b>end-use (1)</b> 337:9 <b>energy (3)</b>	62:10,13,15 <b>engage (1)</b> 216:11 <b>engaged (3)</b> 91:16;195:13;219:11 <b>engine (1)</b> 319:10 <b>engineer (4)</b> 9:6,7;25:16;64:18 <b>engineered (5)</b> 34:13;45:22;52:3; 133:4;319:6 <b>engineering (3)</b> 16:5;34:20;133:3 <b>engineers (1)</b> 34:22 <b>England (4)</b> 20:1;21:14;57:15; 253:20 <b>English (1)</b> 284:10 <b>engulf (2)</b> 147:17;149:15 <b>engulfed (1)</b> 150:21 <b>enhance (3)</b> 103:10;126:18;179:22 <b>enhanced (1)</b> 21:10 <b>enhances (2)</b> 200:2,5 <b>enjoy (1)</b> 196:2 <b>enjoyed (1)</b> 69:5 <b>enkephalin (14)</b> 103:8,9;117:14,15,18; 118:3,8,17,21;119:9,14; 135:16,19;172:6 <b>enkephalin-producing (1)</b> 119:4 <b>enkephalins (1)</b> 172:7 <b>enormous (1)</b> 348:21 <b>enough (9)</b> 38:15;60:8;110:7; 112:10,11;174:16; 175:16;221:17;347:7 <b>enrolled (1)</b> 336:21 <b>ensure (1)</b> 219:16 <b>enter (2)</b> 117:11;159:19 <b>entering (2)</b> 10:2;145:15 <b>enters (1)</b> 116:18 <b>entertaining (1)</b> 169:8 <b>enthusiasm (3)</b> 191:19;192:19;193:4	<b>entire (4)</b> 82:8;90:20;240:21; 313:14 <b>entirely (1)</b> 161:22 <b>entities (1)</b> 346:17 <b>entity (2)</b> 241:5;289:1 <b>entrepreneur (1)</b> 15:15 <b>environment (5)</b> 39:21;83:12;106:20; 251:17;301:12 <b>envision (1)</b> 259:11 <b>enzyme (2)</b> 79:4;81:18 <b>epidermal (1)</b> 200:8 <b>epigenetics (1)</b> 294:4 <b>epilepsy (3)</b> 79:8,18;152:2 <b>epileptic (1)</b> 284:12 <b>episodes (2)</b> 204:13;212:5 <b>episodic (14)</b> 296:21;297:3;303:20; 304:3;315:22;316:1,6; 320:19;321:3,4;322:8; 328:15,18;330:16 <b>equipment (1)</b> 219:16 <b>equity (1)</b> 229:18 <b>equivalent (4)</b> 109:11;139:3;147:10; 202:11 <b>era (3)</b> 7:5;22:6;344:12 <b>ergotamine (1)</b> 304:9 <b>escalation (1)</b> 252:15 <b>escape (1)</b> 265:7 <b>esoteric (3)</b> 136:12,13;326:11 <b>especially (6)</b> 75:12;181:4;194:7; 231:11;247:5;263:13 <b>essentially (21)</b> 9:3;11:20;12:5,20; 16:3;18:6,14;43:2; 61:15;62:9;131:15; 138:21;147:8;151:4; 173:9;189:15;214:2; 216:9;237:10;253:21; 271:13 <b>establish (2)</b> 113:15;114:16
---	---	---	--	---

<b>established (3)</b> 115:20;218:5;252:9	<b>event (1)</b> 143:11	178:9;179:14;198:10; 221:6;223:18;225:5; 246:8;261:5;265:8; 276:1;282:15;285:11; 313:22;324:17;334:17, 17	171:1;174:7;175:6; 182:14;183:19;239:11, 20,20;240:4;247:21; 251:14;253:3	<b>extend (2)</b> 67:17;146:19
<b>establishes (3)</b> 113:14;114:2;115:5	<b>events (17)</b> 8:11;127:2;144:19; 204:19;207:12,14; 212:1;306:14,15;307:16, 20;308:3;321:19;322:2, 3,15;323:11	<b>examples (9)</b> 35:17;86:15;125:11; 179:16;332:11,14; 341:6;343:16;351:8	<b>experiences (2)</b> 17:15;219:19	<b>extended (1)</b> 147:4
<b>estimated (2)</b> 115:14;207:5	<b>eventual (1)</b> 67:21	<b>excellent (2)</b> 290:13;312:13	<b>experiment (12)</b> 93:3;109:9,10;122:17; 123:3,9;125:3;126:10; 128:20;140:13;141:16; 158:20	<b>extensible (1)</b> 146:19
<b>estimation (1)</b> 209:15	<b>eventually (11)</b> 38:14;56:19;62:20; 67:3;176:1;247:1; 302:10;310:20;312:8; 314:7;322:6	<b>except (5)</b> 111:14;152:5;161:22; 204:9;228:20	<b>experimental (4)</b> 246:1;251:5;263:6,10	<b>extensively (2)</b> 219:9;229:12
<b>estrogen-evoked (1)</b> 199:1	<b>everybody (11)</b> 4:4;5:10;52:15;77:11; 116:4;190:10;267:16; 295:17,19;324:15;331:1	<b>exception (3)</b> 211:1;212:2;230:1	<b>experiments (16)</b> 74:1;117:2,5;120:12; 122:1;128:15;130:13; 201:7;239:16;245:22; 276:19;279:7,11; 280:22;281:20;290:20	<b>extent (7)</b> 71:6;82:20;94:12,15; 105:12;107:12;266:6
<b>et (13)</b> 49:12;83:14;202:22; 229:18;246:3,18;252:10, 10;260:11,12,12;347:16, 17	<b>Everybody's (1)</b> 244:8	<b>excitation (2)</b> 159:22;205:20	<b>expert (1)</b> 134:22	<b>external (3)</b> 240:1;281:21;301:11
<b>ethical (1)</b> 7:5	<b>everyone (4)</b> 78:22;108:21;136:10; 321:20	<b>excitatory (2)</b> 78:13;205:20	<b>expertise (2)</b> 218:22;247:21	<b>extra (1)</b> 230:9
<b>ethically (1)</b> 58:17	<b>Everything's (1)</b> 68:12	<b>excited (3)</b> 20:18;103:13;122:7	<b>experts (1)</b> 189:7	<b>extracephalic (1)</b> 329:1
<b>ethics (5)</b> 7:12;28:18;173:14,22; 174:11	<b>evidence (8)</b> 25:12;119:6;135:15; 181:4;256:8;299:11; 341:22;352:10	<b>excitement (2)</b> 30:2;191:18	<b>explain (3)</b> 162:21;210:3;216:17	<b>extracranial (1)</b> 286:17
<b>ethologically (1)</b> 216:7	<b>evolution (1)</b> 325:7	<b>exciting (8)</b> 13:6;58:19;63:12; 73:21;75:7;104:16; 189:12;217:14	<b>explained (1)</b> 4:22	<b>extraordinarily (1)</b> 145:20
<b>ethos (1)</b> 104:20	<b>evolutionary (1)</b> 325:8	<b>excluded (2)</b> 350:5,10	<b>explanation (1)</b> 184:11	<b>extreme (1)</b> 178:8
<b>etiology (2)</b> 96:3;107:14	<b>evolve (6)</b> 143:4;297:15;298:12; 302:17;325:9;328:15	<b>excludes (1)</b> 206:10	<b>explore (1)</b> 215:11	<b>extremely (1)</b> 92:10
<b>Etlin (1)</b> 90:4	<b>evolved (11)</b> 138:7,10;144:3; 146:11;147:9;157:15; 166:5;182:4;194:17; 235:1;272:1	<b>excluding (2)</b> 337:15;350:4	<b>explaining (1)</b> 184:11	<b>extremes (1)</b> 323:14
<b>Euro (1)</b> 220:3	<b>evolving (1)</b> 298:7	<b>exclusion (1)</b> 202:21	<b>explains (3)</b> 162:21;210:3;216:17	<b>extrudes (1)</b> 147:1
<b>Europe (10)</b> 207:7;208:4;209:9; 222:2;223:3;224:17,19; 225:8,12;345:3	<b>exact (2)</b> 201:15,18	<b>exclusively (1)</b> 33:22	<b>explained (1)</b> 4:22	<b>eye (2)</b> 54:11;235:16
<b>European (1)</b> 345:22	<b>Exactly (7)</b> 74:11;173:6;178:8; 191:20;244:14;326:7; 334:1	<b>exercise (1)</b> 294:10	<b>explains (1)</b> 184:11	<b>eyeball (1)</b> 38:3
<b>ethanize (1)</b> 100:8	<b>exaggerate (1)</b> 130:3	<b>exercised (1)</b> 294:8	<b>explains (1)</b> 184:11	<b>EZ (5)</b> 57:15,17,21;58:3,6
<b>ethanized (1)</b> 99:19	<b>examine (1)</b> 275:22	<b>exist (3)</b> 153:11;158:3;348:22	<b>explains (1)</b> 184:11	<b>E-Zed (1)</b> 57:16
<b>evaluated (1)</b> 343:6	<b>examined (1)</b> 202:9	<b>existing (2)</b> 150:17;179:22	<b>explains (1)</b> 184:11	
<b>Evans (2)</b> 290:4,17	<b>example (38)</b> 15:21;87:9,17;88:13; 89:1,10,16;90:6;93:13; 97:3,22;99:20;103:8; 116:20;118:9;119:4; 121:1;124:10;126:4; 129:21;159:15;174:5;	<b>expand (3)</b> 33:9,14;42:14	<b>explains (1)</b> 184:11	
<b>even (54)</b> 8:3;13:20;29:20;40:8; 42:12;44:15;46:12,15; 50:11;59:21;63:3;67:8; 70:11;82:11;83:13; 89:20;105:3;107:13; 118:19;123:4;132:6; 145:14;146:11;148:15; 150:6;155:16;172:1; 183:4;188:2;191:19; 211:18;222:6;224:20; 233:10;237:12;246:4; 264:3;266:8,13;269:10; 286:12;289:10;291:21; 292:21;293:9,13; 303:21;312:9;321:21; 341:7;343:4,12,13;350:3		<b>expanded (2)</b> 32:2;42:12	<b>explains (1)</b> 184:11	
		<b>expect (6)</b> 207:19;208:3;211:2, 13;215:4;349:19	<b>explains (1)</b> 184:11	
		<b>expensive (3)</b> 21:21;60:21;247:5	<b>explains (1)</b> 184:11	
		<b>experience (15)</b> 78:9;117:4;167:10;	<b>explains (1)</b> 184:11	

**F**

<b>F2 (1)</b> 149:5
<b>fabulous (2)</b> 264:1;272:19
<b>face (3)</b> 223:4;282:21;296:14
<b>faced (1)</b> 56:21
<b>facet (1)</b> 252:11
<b>facets (1)</b> 350:1
<b>facial (2)</b> 95:20;96:12
<b>facilitate (3)</b> 333:12;334:3,4
<b>facilitated (3)</b> 239:3;240:2;241:19
<b>facilitation (1)</b> 77:15
<b>facilitators (1)</b> 245:5
<b>facility (3)</b>

<p>11:15;33:3;34:16  <b>fact (45)</b>                  8:20;9:12;12:10;13:2;                  14:13;16:10;32:14,21;                  33:10;37:22;51:13;63:6;                  65:3;69:1,22;82:6;                  85:19;89:13;94:5;                  102:16;106:16;120:15;                  143:6;144:15;145:4;                  146:7;149:2,8;151:10;                  161:6;162:11,12;                  171:11;186:10;192:14;                  193:16;194:3;245:12;                  255:4;257:16;267:4;                  311:18;313:2,3;344:18  <b>factor (14)</b>                  8:7,8;25:5;50:3;63:3;                  69:6,10;70:13;98:9;                  198:11;232:13;233:12;                  266:14,21  <b>factors (15)</b>                  22:3;34:21;52:4;                  62:17,18;63:5,9;64:3,5;                  111:4;170:18;202:18;                  241:18;298:19,19  <b>faculty (4)</b>                  4:20;6:7;11:17;104:8  <b>fail (6)</b>                  268:12;336:5;346:14;                  349:6,15,18  <b>failed (13)</b>                  20:20;21:12;69:19;                  211:6;256:16;304:22;                  305:2;325:14;340:22;                  341:4,8,15;342:22  <b>fails (1)</b>                  346:21  <b>failure (3)</b>                  210:4;236:11;344:2  <b>failures (4)</b>                  192:22;193:15;                  312:11;341:11  <b>Fair (1)</b>                  110:7  <b>fairly (6)</b>                  120:12;133:15;                  196:15;209:21,21;220:7  <b>faithfully (1)</b>                  74:12  <b>fall (1)</b>                  161:17  <b>falling (1)</b>                  62:9  <b>false (3)</b>                  11:12;20:10;147:19  <b>falsely (1)</b>                  345:20  <b>false-positives (1)</b>                  127:12  <b>familial (3)</b>                  29:6,7,14  <b>familiar (11)</b>                  47:6;95:22;167:18;</p>	<p>168:10;174:16;184:4;                  253:11;269:2;273:3;                  290:4;347:2  <b>family (7)</b>                  18:5,8;28:13,18;                  157:21;232:15;287:13  <b>fan (4)</b>                  185:15;215:5;263:8;                  266:7  <b>fantastic (5)</b>                  36:10;38:2;42:6;                  66:14;170:1  <b>fantastically (1)</b>                  350:14  <b>far (23)</b>                  70:12;80:3;85:10;                  123:4;135:4,21;148:20;                  165:1;166:22;167:18;                  180:4;192:19;202:15;                  214:9;218:7,20;257:1;                  308:17;318:20;319:1,3;                  336:18;343:10  <b>Farrar (1)</b>                  209:11  <b>fasciculations (1)</b>                  28:8  <b>fascinating (1)</b>                  203:7  <b>fashion (4)</b>                  94:13;96:10;103:9;                  109:17  <b>fast (6)</b>                  26:1;50:18,18,19;                  148:9;217:17  <b>faster (1)</b>                  309:8  <b>fastest (1)</b>                  309:7  <b>fatal (1)</b>                  178:18  <b>fatality (2)</b>                  138:12;139:6  <b>favor (3)</b>                  209:9;256:12;261:13  <b>favorably (1)</b>                  262:10  <b>favoring (1)</b>                  256:3  <b>favorite (3)</b>                  76:21;77:11;154:18  <b>FDA (18)</b>                  15:17;17:16;26:8;                  36:17;42:21,21;44:1;                  53:12;65:3,5,7,17;189:5;                  18;255:1;312:9;317:7;                  326:4  <b>FDA's (1)</b>                  175:15  <b>feasible (5)</b>                  45:12,19;47:20;                  119:12;131:11  <b>feature (1)</b>                  204:11</p>	<p><b>features (4)</b>                  135:7;260:10;328:16;                  329:8  <b>feed (3)</b>                  102:20;238:5;246:2  <b>feedback (1)</b>                  213:7  <b>feel (10)</b>                  119:8;167:3,20;                  222:10;251:16;253:12;                  258:11,17;347:6,8  <b>feeling (6)</b>                  44:9;54:22;94:4;                  181:16;250:14;251:20  <b>feels (2)</b>                  44:11;260:4  <b>feet (1)</b>                  23:6  <b>feet-forward (1)</b>                  98:21  <b>Feldman's (1)</b>                  69:18  <b>fellow (2)</b>                  83:19;97:14  <b>felt (1)</b>                  251:16  <b>female (1)</b>                  207:18  <b>fertilization (1)</b>                  62:7  <b>fervor (1)</b>                  7:11  <b>fetal (18)</b>                  26:11,16,17;31:22;                  44:16;55:9;57:12;58:8,                  11,13,15;59:1,2,2,9,17;                  100:15;129:10  <b>fetal- (1)</b>                  59:3  <b>fetal-derived (2)</b>                  33:7;59:8  <b>FETELL (3)</b>                  73:21;74:4,9  <b>fetus (2)</b>                  100:16,17  <b>few (35)</b>                  7:16;14:14;18:1;19:7;                  52:19;61:22;77:12;                  78:10;84:8;108:12;                  119:21;140:1;141:10,                  17;151:16;157:12;                  158:5,14,15;159:6;                  172:13;182:15;207:9,                  13;209:12;214:20;                  232:3;239:4;241:20;                  252:18;295:11;310:4;                  331:8;333:11;343:17  <b>FGF (2)</b>                  32:2;58:4  <b>fiber (2)</b>                  78:4;117:11  <b>fibers (20)</b>                  71:10;90:13;117:12;</p>	<p>124:5;145:10;168:14;                  198:18;200:8;276:8,15,                  18;280:6,6,8,9;289:18;                  292:4,7,8,10  <b>field (28)</b>                  7:12,14,21;8:16,18;                  11:22;17:9;23:7;30:6;                  48:22;55:10;58:20;65:8;                  68:16;73:11;116:5;                  135:2;160:12;176:9;                  188:21;214:19;216:9;                  220:14;233:7;277:12;                  278:6;314:20;349:11  <b>fifth (1)</b>                  309:21  <b>figure (9)</b>                  148:10;153:15;229:2;                  230:4;241:14;249:15;                  281:5;323:12;349:1  <b>figures (1)</b>                  236:16  <b>files (1)</b>                  44:3  <b>filing (1)</b>                  42:21  <b>fill (2)</b>                  38:16;234:6  <b>final (4)</b>                  43:16,21;208:10;                  322:22  <b>Finally (22)</b>                  10:14;13:22;24:11,15;                  27:5;28:11;48:13;49:22;                  54:1;67:8;100:14;232:6;                  236:9,10;240:6,21;                  242:20;246:11;249:21;                  263:19;275:12;309:18  <b>financing (1)</b>                  184:15  <b>find (28)</b>                  56:7;58:9;61:20;92:9;                  97:8,9;115:18;126:22;                  146:14;148:5;154:9,21;                  161:21;177:7;229:21;                  233:11;251:22;269:16;                  276:14;280:7,21;                  289:19;297:17;307:20,                  21;316:3;318:2;347:15  <b>finding (5)</b>                  205:1;233:18;237:22;                  274:9;282:5  <b>findings (12)</b>                  223:21;227:15;                  234:11;236:21;237:10,                  17;238:11;240:10;                  246:9;249:4;263:16;                  274:12  <b>fine (4)</b>                  22:21;73:3;110:1;                  140:22  <b>fingers (1)</b>                  102:21  <b>finish (1)</b></p>	<p>61:8  <b>finished (2)</b>                  48:13;321:10  <b>finishing (1)</b>                  49:19  <b>Finrap (1)</b>                  220:5  <b>fire (2)</b>                  90:9;145:10  <b>fireworms (1)</b>                  154:15  <b>firing (1)</b>                  186:20  <b>first (72)</b>                  4:6;5:22;6:10;12:1,17;                  14:1;19:10;33:13;43:9;                  58:1;61:1;68:16;69:10,                  17;72:6;73:9,16;74:21;                  77:14;84:1;93:13;117:2,                  4;122:8;132:3;134:21;                  139:12;143:5;145:18;                  149:15;150:19;163:5;                  169:18;175:21;180:11;                  193:18;194:6;195:10,                  20;196:5;197:6,9;                  205:13;214:1;216:15;                  229:12;232:11,15;234:3,                  13;239:7;243:8;248:20;                  250:9;253:6;255:8;                  259:11,17;275:15;                  278:13;281:9;283:16;                  284:21;288:17;301:19;                  305:16;314:12;316:21;                  317:13;318:11;336:4;                  342:4  <b>Firstly (1)</b>                  203:8  <b>fish (34)</b>                  137:21;143:8;144:11,                  12,13,16;145:21;146:19,                  21,22;147:14,16,17,18,                  20;148:2,6,11,13;149:9,                  9,15,18,21;150:7,9,22;                  151:4,6,7,11;165:15,22;                  167:10  <b>fish-hunting (7)</b>                  143:5;148:17,18;                  149:3,7;154:12;165:15  <b>fit (1)</b>                  5:17  <b>five (15)</b>                  16:18;20:1;27:2;                  37:17,19;55:16;286:20;                  304:18,20;312:10,10;                  318:21,21;320:5;326:11  <b>fix (3)</b>                  80:13,13;244:4  <b>fixed (1)</b>                  209:13  <b>flanks (1)</b>                  127:16  <b>flat (2)</b>                  46:12;256:5</p>
--	---	---	---	---

<b>flavor (3)</b> 235:5;236:6;254:3	27:12;77:2;129:21; 248:9	<b>found (25)</b> 33:6;47:14;63:7;82:2, 17;98:7,13;120:1,2; 125:18;127:11,20;129:2, 9;140:14,17;152:15; 154:5,10;226:7,11; 276:10;277:11;299:7; 311:2	29:17	<b>G</b>
<b>Fleetwood (1)</b> 115:20	<b>footpad (5)</b> 116:1,10;123:10;	<b>founder (1)</b> 4:15	<b>frozen (1)</b> 42:3	
<b>flexibility (1)</b> 65:15	126:5;131:7	<b>foundings (1)</b> 113:8	<b>full (8)</b> 41:3;68:9;206:22; 213:1;220:9;274:14; 290:17;345:13	
<b>flimsy (1)</b> 348:3	<b>force (1)</b> 7:13	<b>four (24)</b> 7:6;27:12;37:19,20; 55:6;85:8,16;93:14,16; 107:1,3;131:21;149:2; 188:19;192:10;255:19; 315:7,13;318:22;321:1, 12,14;324:3,4	<b>full-blown (1)</b> 298:13	
<b>flinch-jump (1)</b> 47:7	<b>forced (1)</b> 305:5	<b>four-week (3)</b> 205:9;210:14;211:14	<b>fully (4)</b> 218:9;301:2;315:1; 319:5	
<b>flip (1)</b> 246:21	<b>forces (1)</b> 16:16	<b>four-week-old (3)</b> 87:22;91:3,14	<b>fun (2)</b> 65:21;75:18	
<b>flipped (1)</b> 62:21	<b>forebrain (1)</b> 81:8	<b>fraction (3)</b> 139:21,22;140:15	<b>function (12)</b> 24:4;31:5,9;41:2,19; 53:7;54:2;94:8;105:20; 153:12;202:12;331:5	
<b>flipper (1)</b> 62:22	<b>foreign (1)</b> 133:21	<b>fractions (1)</b> 141:22	<b>functional (6)</b> 40:8;74:19;90:3;91:1, 2;326:19	
<b>flippers (2)</b> 62:18;63:4	<b>forever (2)</b> 12:22;137:1	<b>frame (2)</b> 49:1,3	<b>functionally (2)</b> 144:8;159:11	
<b>float (1)</b> 18:7	<b>Forget (2)</b> 243:20;257:7	<b>France (2)</b> 164:8;172:14	<b>functioning (1)</b> 298:16	
<b>floods (1)</b> 128:3	<b>forgot (1)</b> 134:13	<b>Francisco (1)</b> 95:1	<b>functions (5)</b> 24:22;196:13;319:7, 17;325:6	
<b>floppy (1)</b> 12:4	<b>forgotten (1)</b> 290:14	<b>Frank (12)</b> 5:9;75:13;77:14; 104:2;137:9;178:21; 179:5;180:9;192:14; 216:2;278:13;332:10	<b>fundamentally (2)</b> 223:22;224:14	
<b>flow (7)</b> 273:11,13,14,16; 275:6,17;276:18	<b>form (8)</b> 13:10;29:4;36:9; 128:16;210:21;279:12; 316:18;343:19	<b>fraught (1)</b> 7:6	<b>funded (2)</b> 175:22;176:1	
<b>flows (1)</b> 147:3	<b>formal (1)</b> 131:7	<b>free (3)</b> 306:4,9,10	<b>funders (1)</b> 66:11	
<b>flying (1)</b> 209:8	<b>formation (2)</b> 128:10;248:22	<b>freely (1)</b> 206:21	<b>funding (12)</b> 15:17;16:17;53:17; 189:6;212:15;214:11; 239:1;240:14;241:4,13; 250:18;350:19	
<b>focus (14)</b> 25:11;35:18;77:13; 114:21;230:10;240:16, 18;245:3;254:16; 284:13;287:17;315:17; 320:9;332:8	<b>formed (2)</b> 196:8;289:22	<b>FREEMAN (4)</b> 166:10,19;171:9; 222:12	<b>funny (1)</b> 277:12	
<b>focused (2)</b> 75:7;265:6	<b>forms (8)</b> 15:7;29:14;49:19; 153:11;165:4;298:8; 302:18,19	<b>frequency (2)</b> 302:18,19	<b>Fura-2 (2)</b> 129:11;158:11	
<b>focusing (2)</b> 17:14;35:15	<b>formulate (1)</b> 306:20	<b>frequent (8)</b> 297:22;298:1,8; 310:13,18;311:3,9;312:7	<b>further (12)</b> 17:19;21:1;123:14; 152:21;187:15;210:16; 234:22;270:18;274:21; 303:19;329:12;352:5	
<b>folks (7)</b> 101:1;104:11;234:5; 237:8;239:22;241:1,5	<b>formulation (2)</b> 320:14,14	<b>Freight (1)</b> 7:6	<b>fuse (1)</b> 124:19	
<b>follow (8)</b> 37:15;43:15;57:10; 100:1;142:7,12;305:22; 336:13	<b>forth (1)</b> 141:7	<b>free (3)</b> 306:4,9,10	<b>fused (1)</b> 22:1	
<b>followed (6)</b> 69:18;82:1;288:8; 317:9;324:21;343:22	<b>fortuitous (1)</b> 120:6	<b>freeman (4)</b> 166:10,19;171:9; 222:12	<b>fusion (1)</b> 177:20	
<b>following (4)</b> 35:5;99:21;164:17; 255:22	<b>fortunately (1)</b> 85:10	<b>frequency (2)</b> 302:18,19	<b>future (11)</b> 57:11;157:13;170:2; 206:16;208:22;230:20; 262:14;265:20;272:4,5; 337:4	
<b>follows (3)</b> 98:17;228:1;238:9	<b>forum (1)</b> 162:16	<b>free (3)</b> 306:4,9,10	<b>fuzzy (1)</b> 89:7	
<b>follow-up (2)</b> 110:21;329:18	<b>forward (22)</b> 34:5;41:13;44:17; 51:17;57:3;65:17;95:16; 112:20;186:4;193:2; 194:20;226:21;227:13; 230:8;234:22;249:16; 250:1;264:22;333:3; 337:5;350:14;352:1	<b>freely (1)</b> 206:21		
<b>font (3)</b> 191:5,6,7	<b>Fos (4)</b> 91:5,7,9,14	<b>freeman (4)</b> 166:10,19;171:9; 222:12		
<b>fool (1)</b> 242:17	<b>fossa (2)</b> 281:22;282:2	<b>frequency (2)</b> 302:18,19		
<b>foot (4)</b>	<b>foster (1)</b> 264:16	<b>frequent (8)</b> 297:22;298:1,8; 310:13,18;311:3,9;312:7		

<b>GDNF (88)</b> 5:6,16;6:19;17:21,22; 18:2,3,4,12;19:1,4,7,7, 10,17,21;20:5,7;21:17; 22:1,3;25:20;30:5,9,14; 31:13,13,19;35:1,3,4; 38:22;39:2,4,11,17;40:4, 19,22;41:2;43:19,22; 44:8;45:14,16,17,20,21; 46:2,15,18;47:1,3,21; 52:3;53:18;54:18,21; 55:2,3,9,22;56:3,5,7,14, 22;57:7,11;60:19;64:7; 67:4,9,10,14,15;69:12, 21;70:1,2;71:14,16,19; 74:6,15,18;124:20; 170:20	231:8 <b>generously (1)</b> 231:16 <b>genes (17)</b> 9:8,8,8;29:12;64:12; 114:3,18;127:18,21,22; 129:2,7;133:10,22; 158:1;196:14;198:7 <b>genetic (4)</b> 13:10;15:7;29:4;91:6 <b>genetically (2)</b> 31:18;160:13 <b>geneticist (1)</b> 326:13 <b>genetics (3)</b> 112:8,9;326:18 <b>genome (2)</b> 125:5;127:17 <b>geographical (1)</b> 225:16 <b>geographically (1)</b> 202:15 <b>geographus (1)</b> 139:17 <b>gepants (4)</b> 283:13;286:20;288:3; 291:19 <b>germ (1)</b> 87:16 <b>German (4)</b> 219:12;220:9;274:2; 345:12 <b>Germans (1)</b> 345:13 <b>Germany (1)</b> 164:7 <b>Geron (1)</b> 23:21 <b>gets (1)</b> 168:19 <b>GFAP (1)</b> 97:5 <b>GFAP-positive (1)</b> 39:22 <b>GFP (3)</b> 81:19;122:20;131:2 <b>GFP-expressing (1)</b> 130:19 <b>GFR (3)</b> 18:11,12;30:11 <b>GI (1)</b> 243:20 <b>gift (1)</b> 15:14 <b>Gill (2)</b> 19:5;21:13 <b>Ginty (1)</b> 160:14 <b>girl (1)</b> 273:7 <b>given (13)</b> 6:18;47:3;63:20; 115:11;120:22;174:4;	227:10;237:18;245:1; 250:5;251:13;269:14; 306:19 <b>gives (6)</b> 146:9;209:16;235:5; 236:16;252:16;266:22 <b>giving (10)</b> 64:6;65:21;223:13; 227:12;229:7;259:21; 275:1;303:5;311:13; 320:16 <b>glad (1)</b> 244:17 <b>Glia (3)</b> 25:3,4;289:22 <b>glial (1)</b> 289:21 <b>gloom (1)</b> 193:10 <b>GLORIOSO (18)</b> 71:21;112:3,8,10,21, 22;133:12;134:5,7; 135:12,18;170:5; 185:14;186:22;187:11, 18;188:4,8 <b>gloss (1)</b> 248:18 <b>glutamate (1)</b> 145:12 <b>glutamatergic (1)</b> 78:4 <b>glycine (19)</b> 78:12;120:1,4,13,14, 19,22;121:6,7,14,21; 122:6,14,15,21,21; 123:6,16;126:13 <b>glycoprotein (1)</b> 124:19 <b>glycosylated (1)</b> 152:7 <b>GMP (5)</b> 33:3;34:16,16;43:21; 58:2 <b>GNF (1)</b> 66:17 <b>Goadsby (1)</b> 281:4 <b>Goadsby's (1)</b> 274:21 <b>goal (2)</b> 15:19;51:19 <b>goes (11)</b> 23:18;27:15;41:10; 50:18;62:7;113:19; 135:21;146:20;328:10; 335:17;338:11 <b>Goins (1)</b> 132:17 <b>gold (3)</b> 89:5,17,17 <b>golden (2)</b> 344:11;351:22 <b>Goldman (1)</b>	23:17 <b>good (67)</b> 4:3;25:11;37:22;38:5, 6;39:16;52:15;54:17; 55:18;57:16;65:8,12,14; 75:13,16;76:1;96:13; 108:2,16;111:21; 114:22;115:18;119:7; 125:19;126:1,9,12; 129:4;131:14,22;132:3; 135:14;138:3;167:4; 169:4;170:11;174:20; 177:17,21;178:1; 181:18;182:10;214:18; 222:5;224:8;228:12; 246:20;253:12;257:14; 258:11;265:8;269:4; 271:7;273:10,11; 285:22;287:1;290:18; 295:17;307:5;338:21, 22;339:1,5;343:12; 349:4,5 <b>gotamines (1)</b> 304:13 <b>government (1)</b> 167:19 <b>Gowing (1)</b> 66:6 <b>grab (1)</b> 136:10 <b>grade (2)</b> 42:18;43:21 <b>gradient (1)</b> 77:18 <b>gradual (1)</b> 208:14 <b>graduate (3)</b> 35:20;55:21;186:14 <b>grafting (1)</b> 37:18 <b>grant (6)</b> 42:10,11,13;54:10; 111:6;175:21 <b>graph (2)</b> 18:7;248:11 <b>graphs (1)</b> 46:4 <b>gratified (1)</b> 253:8 <b>gratifying (2)</b> 191:12,17 <b>graveyard (1)</b> 257:14 <b>gray (1)</b> 38:13 <b>grayish (1)</b> 254:4 <b>great (24)</b> 4:5;18:18;26:3,3;40:5; 75:10;76:1;78:10;113:2; 153:19;185:16;221:20; 224:6;226:18;261:7; 269:12;271:10;272:12;	295:8,10;308:16; 312:15;327:4;339:14 <b>greater (3)</b> 107:3;162:14;171:17 <b>green (7)</b> 81:20;86:7;90:7;97:4, 21;144:21;145:2 <b>Greenberg (1)</b> 98:7 <b>grew (1)</b> 136:15 <b>ground (1)</b> 52:17 <b>group (27)</b> 44:4;66:5;78:20; 207:6;211:20;212:5,6; 215:6;219:13;220:7; 238:14;240:22;243:2; 248:2,7,12,16;254:7; 256:4,12;284:3;288:6; 311:21;333:2;334:2; 345:21;349:12 <b>groups (9)</b> 8:20;10:20;44:3,7; 47:19;48:10;150:12; 237:7;353:3 <b>grow (16)</b> 8:4;9:9;11:8;12:21; 23:5;32:13,15;33:4,11, 16,18;34:15;35:2;100:3; 101:17;103:3 <b>growing (2)</b> 26:13;223:1 <b>growth (18)</b> 22:3;34:20;50:3;52:4; 62:17;64:4;69:6,9; 70:13;129:5;170:17; 232:12,16;233:12; 234:9;266:14,16,21 <b>GRP-positive (1)</b> 71:10 <b>guarantee (2)</b> 193:22;194:1 <b>Guedon (1)</b> 132:18 <b>Guess (11)</b> 24:15;170:14;178:16; 194:17;215:1;218:1,12; 222:16;253:17;344:16; 348:11 <b>guidance (2)</b> 194:19;272:4 <b>guide (1)</b> 189:21 <b>guidelines (3)</b> 202:19;350:16,17 <b>Guido (1)</b> 37:8 <b>gung (1)</b> 20:1 <b>gut (6)</b> 9:16,17,19;16:14,15; 166:3
--	--	--	---	---

<b>guy (4)</b> 24:11,12;142:13; 230:22	153:17;204:8;344:5	274:13	<b>highlight (2)</b> 213:21;344:14	48:5;71:9,20;78:11; 85:4,5;88:5;96:11; 98:11;108:1,3,4;117:14
<b>guys (6)</b> 47:5;149:15;219:2; 315:10;337:15;339:14	<b>hardest (1)</b> 170:6	<b>heightened (1)</b> 99:2	<b>highly (10)</b> 114:7,15;121:20; 122:4;139:9;146:19; 147:6;153:20;154:3; 216:21	<b>horrific (1)</b> 27:6
<b>H</b>	<b>harpoon (2)</b> 147:6,21	<b>Heinz (1)</b> 162:10	<b>held (1)</b> 247:13	<b>hospital (1)</b> 6:5
	<b>harpoon-like (1)</b> 147:1	<b>help (9)</b> 25:17;53:14;59:16; 64:3,8;65:17;107:15; 179:21;346:19	<b>high-profile (1)</b> 326:12	<b>host (16)</b> 21:5;64:15,17;86:21; 87:3,5,6,10;88:15,21; 89:2,14,18;90:1,17,22
<b>habit (1)</b> 348:5	<b>Harvard (2)</b> 15:13;98:7	<b>helping (1)</b> 231:9	<b>hind (2)</b> 248:2,10	<b>hot (1)</b> 276:13
<b>hair (1)</b> 100:3	<b>HD (2)</b> 14:5;187:7	<b>hemodynamics (1)</b> 306:17	<b>hindered (1)</b> 288:14	<b>hour (2)</b> 147:17;245:19
<b>half (11)</b> 32:18;78:3;84:6; 147:18;192:2;207:22; 209:5;219:14;223:11; 228:9;293:18	<b>HDAC (1)</b> 132:14	<b>hemorrhage (2)</b> 277:18,22	<b>hinting (1)</b> 198:9	<b>hours (21)</b> 92:9;131:21;132:1; 140:21;219:14;235:11; 252:18;271:3,3,14; 273:1;306:3,4,10,11; 309:2,11,13,14;324:13, 17
<b>half-hour (1)</b> 169:12	<b>HDACs (1)</b> 132:14	<b>Henderson (1)</b> 31:14	<b>hints (1)</b> 198:20	<b>HSV (1)</b> 133:18
<b>half-life (7)</b> 131:22;252:14;313:8, 20;314:2;316:12;320:15	<b>head (3)</b> 85:15;346:13,15	<b>hepatotoxicity (1)</b> 311:4	<b>hip (1)</b> 282:3	<b>HSV-1 (1)</b> 115:6
<b>half-lives (1)</b> 313:6	<b>headache (12)</b> 212:4;282:17,18,20, 22;283:6,7;296:6;297:2, 9;298:13;318:19	<b>here's (19)</b> 39:8,15;78:6;84:6,6; 85:4,7,15;87:17;88:2,13, 17;89:10,11,16;90:6; 149:14;160:19;284:15	<b>histamine (3)</b> 158:21;280:18;281:1	<b>HSV-2 (1)</b> 115:6
<b>hallmark (1)</b> 114:10	<b>headache-like (1)</b> 277:14	<b>herpes (2)</b> 113:11;115:8	<b>history (11)</b> 5:16;25:7;184:6; 196:2,3,6;231:5;254:13; 278:14;340:22;341:4	<b>huge (8)</b> 6:8;14:2;23:7;60:13; 66:5;72:20;149:12; 164:6
<b>hallmarks (1)</b> 238:8	<b>headed (1)</b> 40:5	<b>HERTZ (3)</b> 265:5,5;266:13	<b>hit (1)</b> 213:1	<b>human (53)</b> 4:8;9:1,1;10:13;13:6; 15:2;16:20;17:13;19:19; 24:16;26:16,17;27:11; 38:12,17,18,22;39:1; 40:2;41:9;42:22;43:22; 64:1;73:18;100:17; 101:3;131:12;151:20; 152:2;153:2;154:10; 155:11;187:22;188:5; 199:7,8,17;204:12; 223:18;235:8;240:9,10; 247:15;251:1,5;270:2; 279:18;281:1;284:9; 315:1;323:16;338:8; 346:14
<b>hand (3)</b> 27:9;244:14;264:7	<b>heading (1)</b> 296:5	<b>heterodimers (1)</b> 128:19	<b>HIV (4)</b> 105:5;198:6;226:2,6	<b>human- (1)</b> 38:18
<b>hands (4)</b> 52:4;244:3;288:17; 291:20	<b>heads (1)</b> 141:7	<b>heterogeneity (1)</b> 105:2	<b>ho (1)</b> 20:1	<b>humanized (2)</b> 315:1;319:5
<b>happen (16)</b> 25:21;29:1;63:16; 65:19;73:18;156:4; 180:22;189:16;215:20; 238:21;240:13;244:20; 300:21;311:1;312:7; 322:15	<b>health (1)</b> 275:7	<b>heterogeneous (2)</b> 107:13;345:3	<b>hold (3)</b> 255:1;257:19;258:19	<b>humans (16)</b> 9:1;14:15;44:1;52:20; 112:19;131:22;172:12, 13;179:11;190:1; 280:20;323:18;327:5; 331:18;346:19;347:7
<b>happened (16)</b> 234:2;254:14;274:6; 281:15;286:4;294:9; 307:10,11,12;308:16; 310:2,10;312:2;324:18; 325:1;346:22	<b>healthcare (2)</b> 28:17;225:4	<b>heteromer (1)</b> 162:14	<b>holding (1)</b> 48:22	<b>humor (1)</b> 62:6
<b>happening (6)</b> 11:8;70:11;194:4; 234:19;263:3;301:17	<b>healthy (5)</b> 12:16;63:16;99:6; 178:14;251:6	<b>heteromeric (5)</b> 153:16;157:15,19; 158:4;162:13	<b>home (2)</b> 83:14;95:4	<b>hunch (1)</b> 194:10
<b>happens (21)</b> 21:16;36:4;118:3; 144:16;145:8,14; 146:22;149:19;157:1; 162:19;165:16;172:19; 209:7;238:13,22;287:2; 291:18;294:12;300:13, 17;323:5	<b>hear (14)</b> 22:13;23:1;64:12; 136:17;137:3;171:16, 20;193:12;230:3; 240:19;243:6;253:8; 345:2;349:8	<b>high (12)</b> 40:16;45:19;82:14; 88:2;145:22;206:12; 264:11;293:18;302:18; 317:5;318:16;320:5	<b>homeostatic (2)</b> 319:17;325:5	<b>hungry (2)</b>
<b>happy (7)</b> 44:4;53:12;56:4;86:2; 186:10;214:13;315:11	<b>hearing (5)</b> 112:20;191:13; 227:17,18;272:13	<b>high- (1)</b> 196:16	<b>homologue (1)</b> 152:5	
<b>hard (6)</b> 17:11;58:9;116:3;	<b>heart (4)</b> 9:10;32:9;178:10; 294:7	<b>high-content (1)</b> 160:1	<b>homologues (1)</b> 155:12	
	<b>heat (6)</b> 93:19;116:7;129:16; 131:4;245:16;327:7	<b>high-end (1)</b> 336:5	<b>homomer (1)</b> 162:15	
	<b>heat-related (1)</b> 129:19	<b>higher (7)</b> 177:13;213:4;216:16; 285:2;286:6;303:21; 341:20	<b>hoped (1)</b> 332:10	
	<b>heavy (1)</b>	<b>highest (6)</b> 202:9;254:6;317:16; 320:6;324:3,4	<b>hopefully (4)</b> 52:16;80:3;263:11; 272:2	
		<b>high-frequency (3)</b> 316:1;320:19;322:7	<b>hoping (5)</b> 67:17;134:8,9;193:17;	
			<b>horn (13)</b>	

165:17;190:8	<b>ideas (2)</b>	6:13	<b>included (1)</b>	8:21;59:6;61:13;
<b>Huntington's (4)</b>	54:4;327:5	<b>Imperial (2)</b>	318:18	91:14;105:6;141:14;
14:1,9,12;54:7	<b>identical (5)</b>	194:21;195:15	<b>including (4)</b>	142:16
<b>hurdles (1)</b>	8:13;58:11;59:1,7;	<b>impervious (1)</b>	199:18;267:1;275:13;	<b>induces (4)</b>
103:15	111:14	130:9	353:3	200:7;287:20;327:22;
<b>Huro (1)</b>	<b>identified (2)</b>	<b>implant (1)</b>	<b>inclusion (3)</b>	328:1
182:13	133:11;151:15	71:22	202:21;206:5,9	<b>inducible (1)</b>
<b>hurt (3)</b>	<b>identify (4)</b>	<b>implanted (1)</b>	<b>incompatible (1)</b>	55:17
234:15,20;265:12	101:10;153:4;170:10;	172:11	298:16	<b>inducing (1)</b>
<b>Hurts (1)</b>	336:8	<b>implemented (1)</b>	<b>incontrovertible (1)</b>	327:20
234:1	<b>identifying (2)</b>	182:12	228:19	<b>induction (1)</b>
<b>hybridization (1)</b>	224:7,8	<b>implication (1)</b>	<b>incorrectly (1)</b>	237:13
114:9	<b>identity (1)</b>	244:10	11:11	<b>industry (2)</b>
<b>hyperactive (2)</b>	153:12	<b>implicit (1)</b>	<b>increase (18)</b>	193:3;352:13
151:5,11	<b>IGF (1)</b>	343:1	25:17,18;39:16;46:13;	<b>inertia (1)</b>
<b>hyperalgesia (10)</b>	69:18	<b>implying (1)</b>	47:8;48:12;54:16;79:19,	62:13
116:16;122:18;	<b>IGF1 (2)</b>	267:21	21:120;21:159;17;	<b>infarct (1)</b>
236:18,19;237:1,14;	69:17;70:1	<b>importance (3)</b>	183:2;199:14;208:14;	294:14
328:9;330:1;338:15;	<b>IGF-secreting (1)</b>	213:8;299:11;301:18	288:1;311:5;322:17;	<b>infect (3)</b>
345:8	69:20	<b>important (40)</b>	327:7	128:2,7,20
<b>hyperemic (1)</b>	<b>IgG2 (1)</b>	7:19;10:4,9;16:11,16;	<b>increased (10)</b>	<b>infected (8)</b>
278:10	319:6	17:22;23:14;24:20;25:9;	39:12;40:11;67:11;	116:2,4,5,9,18;118:4;
<b>hyper-excitabile (1)</b>	<b>ignores (1)</b>	34:14;64:9;110:4;	79:12;157:2;212:2;	125:17;130:14
205:21	131:14	111:12;113:11;115:9;	216:11;235:15;311:9;	<b>infection (7)</b>
<b>hyperexcited (1)</b>	<b>illogical (1)</b>	132:6;134:19;135:8,11;	323:10	114:19;118:7,12,17;
79:15	209:14	197:9,15;199:10;	<b>increasing (3)</b>	129:11;135:6;198:15
<b>hyper-polarization (1)</b>	<b>illustrate (5)</b>	200:14;202:4,13;	48:16;68:4;204:16	<b>infections (1)</b>
120:8	77:2;89:6;97:12,17,18	210:12;220:13;226:3;	<b>increasingly (1)</b>	60:19
<b>hypersensitive (4)</b>	<b>illustrated (1)</b>	246:14;268:15;273:7;	105:1	<b>infectivity (1)</b>
92:11;93:7,16;301:11	78:18	289:20;299:4;300:2;	<b>incredible (4)</b>	133:1
<b>hypersensitivity (8)</b>	<b>illustrates (2)</b>	307:15;315:18;335:10;	76:15;137:2;313:21;	<b>inflammation (10)</b>
76:15;79:14;91:19;	77:4;101:10	339:4;349:7,353:2	319:10	156:10,17;232:21;
92:2,13;93:14,19;203:11	<b>illustration (1)</b>	<b>importantly (6)</b>	<b>incredibly (6)</b>	233:3,19;237:11,13,16,
<b>hypertension (3)</b>	85:13	58:4;65:20;199:5,17;	26:5;184:7;295:18;	20;302:4
164:16;196:4;197:1	<b>illustrative (2)</b>	246:11;350:3	298:15;308:21;313:6	<b>inflammatory (5)</b>
<b>hypodermic (3)</b>	78:2;304:19	<b>impossible (2)</b>	<b>incubator (1)</b>	127:3;237:18;269:11;
147:2,7,10	<b>imagine (7)</b>	189:17;201:17	16:19	300:16;331:12
<b>hypothalamus (1)</b>	170:17;174:17;219:4;	<b>impressed (2)</b>	<b>IND (2)</b>	<b>influence (1)</b>
274:22	238:3;260:5;292:2;	53:4;352:3	42:21;43:15	91:19
<b>hypothesis (7)</b>	329:14	<b>impression (1)</b>	<b>indeed (7)</b>	<b>influx (3)</b>
98:17;106:4;135:17,	<b>IMI (1)</b>	211:5	18:9;89:8;119:3;	159:16,18;200:1
18;214:3;216:10;260:12	220:3	<b>impressive (1)</b>	151:18;181:9;300:11,15	<b>information (5)</b>
	<b>immediate (1)</b>	317:20	<b>independent (2)</b>	63:21;78:8;79:14;
<b>I</b>	72:13	<b>improve (2)</b>	202:14;223:21	209:19;232:9
	<b>immediately (3)</b>	311:20;336:2	<b>independently (1)</b>	<b>infrequent (2)</b>
<b>ibuprofen (2)</b>	80:1;217:3;275:19	<b>improved (3)</b>	172:8	297:9;313:9
261:5,7	<b>immobilized (1)</b>	262:20;330:6;344:10	<b>Index (1)</b>	<b>infused (4)</b>
<b>ICV (1)</b>	147:16	<b>improvement (1)</b>	211:6	18:20,20;19:7;20:5
140:7	<b>immune (4)</b>	317:13	<b>indicated (3)</b>	<b>infusing (1)</b>
<b>Ida (3)</b>	72:16;73:13;156:14;	<b>imputations (1)</b>	239:18;241:9;289:16	20:7
88:11;104:9;107:1	157:2	208:12	<b>indication (2)</b>	<b>infusion (1)</b>
<b>idea (24)</b>	<b>immunogenic (1)</b>	<b>inability (1)</b>	254:2;269:4	324:9
11:18;22:16;31:3,13;	72:16	193:1	<b>individual (9)</b>	<b>Ingber (1)</b>
41:17;45:7;51:1;52:7;	<b>immunogenicity (2)</b>	<b>inactivated (1)</b>	60:19;76:12;96:2;	15:13
63:1;80:3;87:8;106:9;	72:1;324:10	114:3	99:15;138:4;150:7;	<b>Ingelheim (1)</b>
117:22;119:21;169:4;	<b>immunogold (1)</b>	<b>inactivates (2)</b>	183:1;316:5;334:8	305:15
173:18;178:1;209:11;	276:2	128:8,19	<b>individuals (4)</b>	<b>inhibit (5)</b>
227:14;269:20;270:20;	<b>immunotherapies (1)</b>	<b>Inc (1)</b>	165:21;176:16;	156:1;157:7,8;289:4;
346:7,13;347:18	73:7	34:9	297:11;301:1	323:5
<b>ideal (1)</b>	<b>impact (8)</b>	<b>incision (3)</b>	<b>induce (4)</b>	<b>inhibited (1)</b>
80:8	6:2,17,19;25:5;	248:2,10,10	91:5;120:3;319:22;	90:22
<b>ideally (1)</b>	227:10;253:6,10;351:4	<b>include (2)</b>	331:12	<b>inhibiting (1)</b>
351:17	<b>impacts (1)</b>	219:21;220:15	<b>induced (7)</b>	323:4

<b>inhibition (17)</b> 77:21;78:17;79:2,9, 11,20,21;80:12;82:22; 84:12;94:5;98:22;106:6; 107:9,15;204:4;267:5	199:12;201:1;220:8; 340:6	<b>intelligent (1)</b> 230:22	333:13	171:14
<b>inn (1)</b> 324:18	<b>inn (1)</b> 324:18	<b>intense (2)</b> 98:15;235:6	<b>interpret (1)</b> 262:2	<b>intracellular (4)</b> 18:13;158:12;197:4; 204:5
<b>inner (1)</b> 292:9	<b>inner (1)</b> 292:9	<b>intensity (4)</b> 207:22;208:10;254:6, 8	<b>interpretation (2)</b> 20:17;236:21	<b>intracranially (2)</b> 140:7;142:17
<b>inhibitor (1)</b> 132:14	<b>innervated (3)</b> 41:20;277:8;300:10	<b>intensive (3)</b> 196:18;323:20;334:7	<b>interpreted (1)</b> 162:8	<b>intractable (3)</b> 142:21;176:17;180:19
<b>inhibitors (2)</b> 196:22;198:11	<b>innovation (1)</b> 12:5	<b>interact (7)</b> 17:8;18:6,16;23:12; 25:1;71:16;292:11	<b>interpreting (1)</b> 261:2	<b>intramuscular (1)</b> 68:21
<b>inhibitory (9)</b> 78:10;79:3;81:7;84:9; 89:14,14,20;102:3;106:8	<b>innovations (1)</b> 40:18	<b>interacting (2)</b> 22:15;218:8	<b>interrupt (1)</b> 53:6	<b>intraparenchymal (1)</b> 176:22
<b>inhibits (2)</b> 199:22;200:6	<b>innovative (1)</b> 209:22	<b>interaction (2)</b> 217:22;283:9	<b>interstitial (2)</b> 257:12,14	<b>intraparenchymally (3)</b> 173:3;175:9,12
<b>initial (5)</b> 21:11;80:15;286:7; 305:7,12	<b>input (3)</b> 78:5;89:22;98:20	<b>interactions (2)</b> 65:3;191:15	<b>intervention (3)</b> 138:13;330:4;342:4	<b>intraperitoneal (1)</b> 216:21
<b>initially (7)</b> 43:6;53:5;100:4; 118:11;172:12;281:20; 299:5	<b>inquiries (1)</b> 350:7	<b>interest (9)</b> 30:4;108:6;112:18; 148:21;193:4;236:3; 248:18;317:22;326:16	<b>interview (1)</b> 231:17	<b>intraplural (1)</b> 233:17
<b>initiate (1)</b> 239:15	<b>insane (1)</b> 323:7	<b>interested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>intimately (3)</b> 228:10;231:3;233:7	<b>intrathecal (13)</b> 171:13;172:3;177:3, 10;179:1;181:15,19; 182:1,18;183:6,13; 184:14,16
<b>initiated (2)</b> 143:22;301:21	<b>insanely (1)</b> 324:14	<b>interesting (59)</b> 15:5;17:2;24:9;29:17; 30:10;33:6;36:19;49:21; 50:6,11;53:19;57:5; 58:1;82:10,11;93:11; 94:3;106:10;107:16; 110:9;113:3;114:6; 152:3;156:9;168:11; 183:3;184:6;185:11; 186:18;204:11;211:19; 216:14;217:14;225:15; 231:19;233:6;237:17; 239:2;241:21;243:6; 244:6,22;251:7;252:11; 257:11;262:18;265:15; 18;267:3,14,17;274:17; 283:6,11;287:16;303:8; 305:21;317:4;329:10	<b>into (168)</b> 9:9,14,16;10:2;12:10; 13:4;14:18;16:22;17:4; 18:20;19:1,3,4,8,16; 20:20;21:1,6;22:6,10,12, 17,22;24:10;26:10,18; 31:8,20;32:17;33:15; 34:1,2;37:7;39:21;44:1, 22;45:3,7;48:7,21;50:9; 52:1,21;53:18;56:17; 59:2;61:14;62:18;63:8; 64:8;65:1;66:3;69:1,2; 70:10,18;80:1,18;81:12, 22;82:12,16;83:7,8,21; 86:4,21;87:19;89:21; 90:13,13;94:14;95:17; 96:17;97:3;102:18; 106:20;109:6;110:16; 113:12;116:10,10;117:6, 10;120:14;123:10; 125:4;128:3;132:2; 133:21;135:10,19,20; 140:3,15;141:15; 142:17;143:10;144:12; 145:1,5;151:6;152:17; 161:14,17;164:14,22; 165:6,15;166:4;175:5,6; 177:4;185:4,19;187:9, 19;188:1;193:20;210:2; 212:13,16;215:13;230:8, 13;234:15,19;238:4; 241:19;243:18;248:5; 249:16;251:9;256:13; 262:16;268:5,11; 274:16;277:16;278:4, 12;283:10;285:16; 286:10;290:19;292:15; 297:15;302:18;304:4,19, 20;305:1,13;306:20; 308:9;310:7;311:19; 325:9;327:21;328:15; 335:3;346:10,19;347:7; 348:5;350:22;351:6,17	<b>intrathecally (3)</b> 109:12;172:11;179:10
<b>initiating (1)</b> 219:9	<b>insert (1)</b> 128:12	<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>intrinsically (1)</b> 166:6
<b>inject (19)</b> 44:22;45:2;53:18; 85:21;117:10;118:4,6, 14;120:22;121:19; 122:3;131:18;134:3; 144:12;147:21;150:6; 151:5;156:6;180:14	<b>insight (2)</b> 232:9;247:20	<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
<b>injected (25)</b> 49:5;97:16;115:21; 116:1,9;118:11,21,22; 120:14;121:13;122:12, 13,19;123:10;130:13; 141:14;142:16;145:5; 147:15;150:22;152:17; 166:4;234:14,19;248:5	<b>insights (1)</b> 234:22	<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
<b>injecting (6)</b> 123:1,9;140:6,7,14; 177:3	<b>Insomnia (1)</b> 211:5	<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
<b>injection (10)</b> 51:2;68:21;140:2; 171:14;217:3;233:17; 238:18;283:16;314:7,8	<b>instance (3)</b> 14:19;63:8;188:2	<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
<b>injections (6)</b> 51:18;85:16;93:15; 108:3;216:20,22	<b>instead (7)</b> 141:3;144:16;149:10; 154:12;155:8;318:11; 337:15	<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
<b>injure (1)</b> 92:19	<b>Institute (4)</b> 4:12,19;9:9;15:13	<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
<b>injured (1)</b> 156:11	<b>insulator (1)</b> 125:5	<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
<b>injury (31)</b> 23:20;24:1,4,7;49:12; 76:9,10,13;78:16,16; 84:10;92:4;102:7; 105:12;108:11;152:18; 156:3,4,5,8,15,17;157:3, 8;168:5;176:15;181:2;	<b>Insulin (2)</b> 69:6,9	<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
	<b>insult (1)</b> 270:22	<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
	<b>insults (1)</b> 301:8	<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
	<b>intact (5)</b> 30:16;71:11,13;79:15; 92:11	<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
	<b>integrate (5)</b> 37:14;54:15;86:17; 111:19;175:13	<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
	<b>integrated (4)</b> 86:4;87:13;90:2;91:16	<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
	<b>integrating (3)</b> 35:1;86:21;89:21	<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
	<b>integration (10)</b> 22:22;23:4;94:11,12, 14;107:5;108:9,14; 110:2,5	<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,18;110:19; 146:16;189:6;251:19; 276:17,17;284:20	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8	<b>introduce (7)</b> 4:6;75:4;103:21; 112:2;136:15;165:5; 295:8
		<b>intested (14)</b> 18:3,14;48:4;70:3; 81:2;95:14,		



241:16 <b>invitation (2)</b> 195:3;272:18 <b>invite (2)</b> 5:10;326:1 <b>invited (1)</b> 310:3 <b>inviting (1)</b> 137:9 <b>involved (40)</b> 68:20;119:18;124:6; 16:126:15,16;131:8,16; 132:15;155:9;171:19; 194:15;195:5,8,11; 196:12,16;197:10; 198:20;199:15;204:5; 205:6;213:20;227:6; 228:9;231:3;233:7; 234:21;235:19;237:9; 241:7;250:4;275:1; 300:15;301:20,22;304:1, 2;306:22;342:3 <b>involvement (3)</b> 198:9;200:10;233:10 <b>involving (2)</b> 123:20;196:21 <b>ion (4)</b> 143:20;146:5;157:21; 161:22 <b>ion-channel (2)</b> 153:16;155:18 <b>IP (4)</b> 73:4;121:1;140:2,6 <b>iPS (34)</b> 6:21;8:19;9:13,15; 10:15;11:11,15,15;12:7, 9,20;14:5;29:22;44:16; 57:14;58:3,6,12,19;59:2, 5;61:2,8;62:3,10;63:18, 21;64:22;66:3;104:13; 185:15,18;187:18,22 <b>iPS-derived (3)</b> 58:17;59:1;61:2 <b>ipsilateral (1)</b> 39:17 <b>IRB (2)</b> 51:1;187:16 <b>irrational (1)</b> 321:5 <b>irrelevant (1)</b> 190:1 <b>ISA (1)</b> 49:19 <b>ischemia (2)</b> 294:6,11 <b>ischemic (1)</b> 293:13 <b>ISIS (3)</b> 13:16,17,17 <b>isoforms (1)</b> 154:4 <b>isolate (4)</b> 8:2;15:3;92:7;128:11	<b>isolating (1)</b> 92:8 <b>issue (27)</b> 43:3;48:20;73:10; 77:19;94:3;173:10; 176:13;216:2;244:16, 22;251:12;255:2;269:9; 273:7,20;274:15; 280:12;281:19;283:6,19, 21;292:14;324:8;339:4; 340:16;342:17;350:12 <b>issues (14)</b> 7:5;18:22,22;44:17; 77:14;178:18;181:19; 258:14;265:13;284:2; 286:15;324:9;325:15; 333:16 <b>Italian (1)</b> 113:10 <b>Italy (3)</b> 51:22;52:9,18 <b>itch (5)</b> 76:3;98:4,20;99:3; 108:10 <b>IV (8)</b> 305:15;316:9;317:5,6; 320:5,13;322:10;324:17 <b>IV-completed (1)</b> 322:9 <b>ivermectin (8)</b> 121:8,15;122:1,5; 123:2;131:19;134:3,10	<b>Joe (8)</b> 112:2,4,15;121:4; 133:7,8;136:7;188:18 <b>Joe's (2)</b> 164:17;171:10 <b>John (6)</b> 80:20,21;81:2;83:1,2; 209:11 <b>join (1)</b> 272:10 <b>joins (1)</b> 279:12 <b>joint (5)</b> 54:14;127:15;248:6; 255:2;258:20 <b>Joseph (1)</b> 112:21 <b>Josh (1)</b> 55:20 <b>Journal (3)</b> 25:4;76:22;253:20 <b>journals (1)</b> 350:18 <b>JoVE (1)</b> 34:17 <b>jugular (2)</b> 281:21;303:15 <b>jump (6)</b> 20:13;48:14;65:10; 87:15;88:3;140:19 <b>jumped (1)</b> 291:7 <b>jumping (1)</b> 140:19 <b>junction (5)</b> 138:19;143:9,13; 145:3;155:2 <b>junctions (1)</b> 155:13 <b>justification (1)</b> 319:13 <b>justified (1)</b> 209:10 <b>justify (2)</b> 52:8;174:12	<b>kept (1)</b> 44:5 <b>key (12)</b> 11:13;38:20;106:3; 110:2;139:15;143:11; 232:8;248:1;281:2,19; 325:10;330:16 <b>keynote (1)</b> 4:7 <b>kg (1)</b> 73:5 <b>Ki-67 (1)</b> 101:11 <b>kick (1)</b> 141:8 <b>kid (4)</b> 136:17;140:3;142:13; 186:6 <b>kidney (1)</b> 9:10 <b>kids (1)</b> 140:5 <b>kill (1)</b> 138:15 <b>killed (4)</b> 93:4;173:9,18;308:9 <b>kilo (1)</b> 320:11 <b>kilobases (1)</b> 133:20 <b>kinase (1)</b> 204:4 <b>Kinchington (2)</b> 132:17;135:2 <b>kind (65)</b> 11:7;15:21;16:20; 17:21;21:21;39:19;49:9; 53:19;56:16;57:4;61:8; 62:2;63:1;66:9;69:8; 75:18;76:5;89:4;104:19; 107:20;112:22;115:1; 118:9;119:19;171:3; 173:15;174:14;180:14; 183:3;184:2;185:11; 189:4;204:17;217:17; 231:21;237:5;239:9; 251:19;254:2,13; 257:11;270:22;273:21; 275:4,15;276:8;277:1; 278:3,7;279:3;280:6; 281:6,13;283:5,8;284:4; 285:6,19;290:15;294:5; 329:16;332:17;338:18; 339:13;340:22 <b>kinds (7)</b> 120:16;239:15;252:7; 276:20;279:14;327:10; 352:18 <b>Kip (2)</b> 132:17;135:1 <b>Kirk (1)</b> 288:22 <b>Klein (1)</b>	35:21 <b>knee (1)</b> 253:19 <b>knew (3)</b> 140:18;142:9;178:11 <b>knife (1)</b> 32:16 <b>knock (3)</b> 124:17;319:13;328:7 <b>knock-out (5)</b> 204:2;218:14,18; 311:15;323:8 <b>knock-outs (2)</b> 343:6,8 <b>knocks (1)</b> 144:7 <b>know-how (1)</b> 319:10 <b>knowing (3)</b> 253:13;268:19,20 <b>knowledge (3)</b> 240:4;247:20;334:19 <b>known (10)</b> 24:17;131:8;135:2; 149:1;153:13;196:9; 197:3;232:13;314:14,15 <b>knows (4)</b> 24:18;261:22;264:6,8 <b>Koninck (1)</b> 77:16 <b>KV (2)</b> 163:7;164:3 <b>KV1.1 (2)</b> 162:7,9 <b>KV1.2 (10)</b> 160:11,21,22;161:10; 162:6,9,12,15;163:7; 164:2 <b>KV1.2-specific (1)</b> 161:4 <b>KV1.6 (2)</b> 160:11;161:1 <b>KV1.6-specific (2)</b> 160:20;161:3	
	<b>J</b>				
	<b>J&amp;J (2)</b> 229:13;264:1 <b>Jackie (1)</b> 171:22 <b>Jacquelyn (1)</b> 173:18 <b>Jamie (2)</b> 7:9;66:2 <b>Japan (2)</b> 8:19;28:16 <b>JCI (1)</b> 99:8 <b>Jean-Marc (1)</b> 132:18 <b>Jeff (2)</b> 326:13,16 <b>Jenson (1)</b> 220:4 <b>jet-lagged (1)</b> 169:13 <b>Jewell (2)</b> 67:13;68:15 <b>Joao (5)</b> 83:18;99:7;104:4,9; 108:2 <b>job (7)</b> 65:8,21;66:15;142:8; 214:8;243:19;289:2	<b>K</b>			
		<b>KATZ (16)</b> 219:1;220:21;227:5, 20,21;228:7;266:11; 267:3;268:7;269:18; 270:5,8,11;326:2;346:4, 9 <b>keen (5)</b> 21:21;54:21;186:15; 202:17;329:4 <b>keep (10)</b> 6:1;41:19;62:11; 67:18;73:5;99:1;102:21; 119:10;326:6;329:9 <b>keeping (1)</b> 293:4			
			<b>L</b>		
			<b>L3 (1)</b> 212:4 <b>LA (2)</b> 39:13,15 <b>lab (19)</b> 35:15,20;38:2;66:8,9; 88:12;97:14;103:22; 121:4;189:14;195:15; 198:22;199:7;200:4; 201:8,9,9;334:9;339:9 <b>labeled (5)</b> 88:15;89:6;160:13,14; 161:2 <b>labeling (1)</b> 37:22 <b>laboratories (2)</b>		

201:16;347:14 <b>laboratory (4)</b> 234:11;247:21;339:5, 11 <b>Labrys (5)</b> 295:12,21,22;296:1,3 <b>labs (14)</b> 14:7;42:19;201:21; 202:14;223:21;237:22; 239:13,18;240:1,3,3; 246:10;348:13,13 <b>lack (2)</b> 296:22;343:1 <b>lacks (2)</b> 279:19;290:10 <b>Lake (1)</b> 136:22 <b>laminate (1)</b> 33:15 <b>Lancet (1)</b> 283:20 <b>landmark (2)</b> 220:4;253:18 <b>language (4)</b> 338:1,1,3,5 <b>languages (4)</b> 333:7,22;337:22; 351:9 <b>large (20)</b> 20:19;33:17;43:13; 69:7;71:5;114:5;127:21; 133:15,22;180:21; 212:11;245:10;253:18; 276:4;279:2;289:15; 340:4;341:3;345:17,17 <b>largely (7)</b> 105:6;204:3;206:2; 298:18,21;311:10; 334:19 <b>larger (1)</b> 18:5 <b>Lars (3)</b> 272:6,16;334:20 <b>Lasorte (1)</b> 172:14 <b>last (33)</b> 17:14;50:1;61:6;65:4; 93:8;110:3;157:12; 158:5;169:14;172:2; 175:3;188:15;201:3; 220:22;222:8;232:3; 250:3;259:20;261:17; 268:21;293:2;294:15; 295:9;309:8;340:15; 343:2,17,18,22;346:16; 348:2;350:9,15 <b>lasted (3)</b> 186:11,11;288:5 <b>lasting (2)</b> 115:13;273:1 <b>lasts (3)</b> 131:20;309:15,16 <b>late (6)</b>	34:14;75:1;110:15,16; 292:20;300:14 <b>lately (1)</b> 348:2 <b>latency (12)</b> 113:14,15;114:2,10; 115:5;116:15,15; 119:14;121:18,22; 125:7;131:2 <b>latency-associated (1)</b> 114:4 <b>latent (1)</b> 114:16 <b>later (18)</b> 28:10;34:2;71:17; 84:19;86:15;118:5,22; 130:14;238:7;241:13; 243:2;244:22;245:3; 257:1;284:22;294:17; 309:18;342:15 <b>lateral (1)</b> 146:21 <b>latest (1)</b> 342:10 <b>latter (1)</b> 268:8 <b>Laughter (12)</b> 95:2,9;110:13;111:7; 140:11;147:11;150:11; 168:8;177:18;190:6; 228:6;346:6 <b>layer (2)</b> 16:6,6 <b>LBR-101 (2)</b> 319:5;322:17 <b>lead (4)</b> 7:2;18:21;236:22; 327:6 <b>leader (1)</b> 112:16 <b>leaders (2)</b> 112:15;267:17 <b>leading (1)</b> 214:8 <b>learn (6)</b> 10:11;100:21;182:14; 183:9;263:11;333:10 <b>learned (7)</b> 113:3;138:6;143:2; 186:1;259:2,18;298:22 <b>learning (3)</b> 75:10;333:22;351:9 <b>least (24)</b> 64:17;82:21;107:12; 111:22;131:18;165:8; 168:22;170:9;171:4; 193:18;194:2;201:7; 229:2,7;232:11;263:16; 264:9;289:9;309:12; 332:12;333:7;334:3; 343:18;352:21 <b>leave (5)</b> 74:18;234:7;244:21;	295:6;332:1 <b>leaving (1)</b> 116:18 <b>lecture (2)</b> 75:3;77:9 <b>led (5)</b> 41:22;66:6;182:12; 250:8;253:17 <b>left (3)</b> 50:9;213:14;295:1 <b>leg (8)</b> 50:13,16,19,19,21; 51:3,7,11 <b>legacy (1)</b> 75:17 <b>legs (3)</b> 28:10;50:21;141:5 <b>length (1)</b> 270:12 <b>Lenti (1)</b> 103:5 <b>lentivirus (1)</b> 34:21 <b>leprosy (1)</b> 198:16 <b>lesion (1)</b> 113:19 <b>Leslie (1)</b> 232:6 <b>less (23)</b> 19:20;20:18;40:18; 42:8;80:8;156:17;175:1; 197:3;234:2;247:1; 256:1,2;283:17,18; 297:4,5;311:13;316:2; 318:18;324:8;326:21; 327:8;341:15 <b>lesson (3)</b> 107:7;259:17;262:19 <b>lessons (3)</b> 186:1;259:2;262:18 <b>lethal (2)</b> 138:11;139:4 <b>level (18)</b> 15:12;40:19;77:22; 82:21;88:10,14;94:5; 106:5;107:9,15;172:8; 181:3;199:4;213:6; 273:5;300:18;303:21; 305:21 <b>levels (13)</b> 20:6;30:9;45:20;57:7; 79:4;94:6;198:5;226:7; 303:14,15,15,17,19 <b>Lewin (1)</b> 236:14 <b>liar (1)</b> 264:7 <b>library (2)</b> 127:18,19 <b>license (2)</b> 44:11;167:21 <b>lick (1)</b>	129:22 <b>life (4)</b> 55:4;176:18;310:21; 335:19 <b>lift (2)</b> 58:3;129:21 <b>ligand (2)</b> 199:13;315:21 <b>ligands (1)</b> 157:10 <b>light (7)</b> 90:21;114:16;158:15, 17;159:6,9;301:9 <b>lights (1)</b> 286:2 <b>likelier (1)</b> 171:2 <b>likely (8)</b> 174:8;204:18;205:14; 225:9;246:19;311:3,19; 323:10 <b>likes (1)</b> 77:15 <b>Lilly (1)</b> 318:9 <b>limb (2)</b> 76:13;235:18 <b>limbs (2)</b> 93:16,17 <b>Limette (1)</b> 18:21 <b>limitations (2)</b> 103:1;119:8 <b>limited (2)</b> 68:14;181:20 <b>limitless (1)</b> 12:22 <b>line (9)</b> 9:4;13:20;47:17; 48:11;61:3;70:10; 108:21;146:21;167:8 <b>lineages (1)</b> 62:19 <b>lines (4)</b> 10:8;11:14;115:22; 164:17 <b>link (1)</b> 29:18 <b>linked (1)</b> 81:19 <b>Lipscombe's (1)</b> 168:10 <b>list (5)</b> 77:10;188:22;262:21; 285:7;353:15 <b>listed (1)</b> 285:9 <b>listening (2)</b> 104:18;235:4 <b>lit (1)</b> 56:11 <b>literally (3)</b> 95:5;100:2;181:11	<b>literature (6)</b> 105:21;247:12; 256:14;260:9;344:18; 348:21 <b>little (68)</b> 4:10;5:3,14,17;11:19; 18:7;19:22;22:13;24:4; 28:21;32:20;37:12; 42:16;46:15;58:22;61:7; 65:15;69:6;74:8;75:1; 76:2;98:4;103:3;126:2; 130:5;134:18;150:5,7; 168:3;180:15;187:15; 193:6;195:18;208:20; 227:2;231:15;239:19; 248:9;255:3;262:7; 265:1;278:14;283:10; 286:10;288:9;291:21; 292:20,21;294:17; 296:17;303:12;304:5; 309:14;315:2,8,9,17; 316:13,16;317:17; 320:15;322:4;323:2; 328:19;333:21;334:7; 338:4;343:8 <b>live (2)</b> 194:10;323:12 <b>lived (1)</b> 12:16 <b>liver (14)</b> 4:22;8:3;9:11;310:10, 11;311:15,17,21;312:1, 4;313:4,5;325:15,19 <b>lives (3)</b> 95:5;244:12;297:17 <b>living (2)</b> 148:1;231:5 <b>Llewellyn (1)</b> 88:11 <b>load (2)</b> 24:17;158:11 <b>loads (1)</b> 267:22 <b>lobby (1)</b> 65:5 <b>localization (2)</b> 64:21;280:11 <b>localize (1)</b> 50:5 <b>Localized (2)</b> 64:9;199:5 <b>locally (3)</b> 118:1;131:19;136:2 <b>location (2)</b> 110:4;225:16 <b>LOCF (2)</b> 208:11,13 <b>loci (1)</b> 110:6 <b>locomotion (1)</b> 107:19 <b>logical (1)</b> 237:6
--	---	--	---	--

<b>London (3)</b> 194:21;202:15;225:6	8,18;98:18;108:18; 111:21;119:7;136:4; 188:13;336:16	<b>love (12)</b> 17:4;39:20;48:3;49:9; 57:1;67:18;94:22;95:8; 103:14;154:15;175:9; 213:7	<b>macrophages (1)</b> 156:12	176:8
<b>long (34)</b> 5:15;33:5;35:5;40:9; 41:9;61:7;83:16;85:20; 93:8;102:8,13,22; 110:18;113:22;127:16; 136:22;138:14;139:13; 166:2;169:5;172:2; 192:11;194:8,11; 213:19;217:11;227:7; 262:21;277:10;289:8; 309:9;313:6,8;339:10	<b>loop (1)</b> 335:1	<b>lovely (2)</b> 71:21;196:2	<b>macular (1)</b> 54:9	<b>Mantyh (1)</b> 248:16
<b>longer (8)</b> 99:18;101:13;119:10, 17,211:18;288:5; 299:17;323:12	<b>Lord (1)</b> 261:22	<b>low (12)</b> 46:12;159:4;177:20; 206:13;255:14;256:9; 273:15;297:22;298:6; 302:4;311:7;341:19	<b>magus (1)</b> 142:14	<b>Mantyh's (1)</b> 248:7
<b>long-lasting (1)</b> 115:12	<b>Los (3)</b> 6:6;39:14;42:2	<b>low- (1)</b> 302:17	<b>main (15)</b> 8:7;26:14;51:21; 108:6;171:8;232:16; 237:7;241:4;258:19; 292:14;296:10;306:16; 323:2,4;343:14	<b>manufacture (1)</b> 60:16
<b>long-term (5)</b> 15:19;19:5;119:13; 204:17;229:16	<b>losartan (1)</b> 200:3	<b>lower (9)</b> 27:14,22,22;28:1; 35:8;46:8;306:13;312:4, 6	<b>mainly (2)</b> 7:4;313:11	<b>manufactured (3)</b> 59:7;317:1;318:9
<b>look (52)</b> 9:18;15:4;47:22;59:1, 3,7;60:4;71:9;72:7;82:4; 85:17;86:1;87:17;88:7; 92:12;112:20;128:13; 135:14;144:15;149:6; 150:13;160:18;178:17; 182:8;187:1;197:11,22; 204:20;215:2,20;216:6; 217:9;221:4,14,15; 223:9;228:13;229:8; 230:13;233:14;234:21; 261:7;268:15;277:17; 279:6;283:20;289:12; 292:15;312:2;318:14; 337:13;347:4	<b>loss (18)</b> 28:3;77:20;78:17,18; 79:8,11;80:12;82:21; 84:12;105:6,8,16,20,22; 206:1,4;220:12;345:15	<b>lucidiferase (1)</b> 56:12	<b>maintain (2)</b> 66:19;74:19	<b>manufacturing (2)</b> 58:18;60:14
<b>looked (32)</b> 24:14;69:13;71:8; 84:19;99:22;107:1,2; 116:6;129:19;130:22; 152:14;155:20;161:15; 186:10;198:1;204:8; 209:2;212:12;215:16; 216:8;241:9;245:17; 259:19;260:1;266:2; 271:15;274:2;275:16; 278:21;293:22;327:11; 350:19	<b>lost (3)</b> 84:18;265:22;321:17	<b>luck (2)</b> 224:9;257:14	<b>maintains (1)</b> 291:2	<b>manuscript (1)</b> 256:13
<b>looking (32)</b> 13:4;35:12,13;54:7,8; 56:17;81:1;87:1;95:20; 127:7;129:6;160:2; 181:10,12;191:15; 193:21;205:19;209:22; 210:10,13;213:10; 233:8;259:4;260:15,18; 262:14;268:18;271:22; 274:15;287:22;324:14; 351:6	<b>lot (101)</b> 10:12,16;25:21;26:11; 30:2,7;31:21;35:9,19; 43:17,20;47:21;48:10, 22;51:9,13,17;52:7,11; 62:12;63:20;65:10,12, 22;67:9;75:10;98:1; 100:6;101:17;103:15,17, 22;104:6;108:14;117:4; 120:16;124:14;132:11; 134:11;136:17;146:7; 148:21;152:15;154:2; 155:4,9;167:9;170:8,12; 182:19;183:8,17;184:8; 192:21;199:16;200:18; 201:5;204:12;205:12; 222:6;225:11;231:9; 232:9;239:6,13;243:9; 247:10,14;248:17;253:3, 4;257:13;259:19; 260:16;264:4,12;265:6, 11;271:15;273:2; 275:10,21;276:19; 277:2;280:3,13;281:5; 290:18;294:2;302:5; 310:22;311:11;333:9; 341:11;344:5,9,12; 348:4;349:10,13;351:7	<b>luckily (1)</b> 140:12	<b>major (14)</b> 6:6;47:1;77:6,21; 84:12;86:19;140:20; 141:22;196:10;233:18; 236:18;285:6;350:12,19	<b>many (61)</b> 4:14;6:12;8:20;18:3, 10,20;30:9;31:14;34:6, 19;35:20;46:17;49:1; 61:3,3;70:18;79:6;80:6; 88:7;93:12;95:22;98:12; 100:8;105:5;106:15,18; 107:12;128:9;156:14; 165:15;170:11,20; 171:22;181:16;184:3, 10;201:17;221:19; 222:2;223:16,22;227:5, 8;229:19;232:6;236:15, 20;249:20;266:22; 275:13;285:12;295:10; 310:12,13;313:14,15; 322:9;332:13;334:19; 340:3;341:6
<b>looks (13)</b> 37:1;49:16;60:5;85:2,	<b>lots (13)</b> 84:8;100:20;107:17; 136:6;137:14;139:22; 177:16;252:1,7;280:14; 285:8;290:11;329:11	<b>lucky (1)</b> 149:22	<b>majority (4)</b> 29:2;78:10;160:16; 221:20	<b>MAP (3)</b> 204:4;263:17;335:3
	<b>lottery (1)</b> 288:2	<b>lumber (3)</b> 35:19;37:8;50:10	<b>makes (11)</b> 128:2,18;140:18; 151:10;157:1;170:3; 176:18;206:2;262:4; 294:4;339:6	<b>mapped (1)</b> 275:18
	<b>Lou (4)</b> 6:16;13:8,10;26:22	<b>luminal (1)</b> 292:5	<b>making (20)</b> 10:10;15:16;42:16; 108:3,22;109:5;118:21; 121:20;122:4,14;131:3; 163:19;178:16,20; 187:12;188:10,12; 231:10;232:4;288:14	<b>marathon (1)</b> 235:20
	<b>Louisiana (1)</b> 112:5	<b>luminally (2)</b> 291:4,14	<b>Malcolm (1)</b> 349:11	<b>Marcelo (2)</b> 295:9,16
		<b>lunch (4)</b> 169:6,7,10;190:9	<b>mammal (2)</b> 145:6;317:1	<b>Maree (7)</b> 200:13,15;201:9; 202:6;204:1;213:14; 214:1
		<b>luncheon (1)</b> 190:11	<b>mammals (4)</b> 144:16,21;145:3,21	<b>marine (2)</b> 137:22;155:8
		<b>Lund (4)</b> 37:9;272:9,9;281:8	<b>man (3)</b> 24:17;281:2;296:11	<b>mark (3)</b> 97:5;101:11;132:20
		<b>lung (4)</b> 16:2,4,6,13	<b>manage (2)</b> 68:17;298:5	<b>marked (1)</b> 285:21
		<b>lungs (2)</b> 9:10;28:12	<b>managed (2)</b> 13:11;34:15	<b>marker (5)</b> 91:6;101:9;279:5; 330:9,16
		<b>lying (1)</b> 239:14	<b>management (1)</b> 137:5	<b>markers (4)</b> 38:19;97:11;101:8,9
		<b>lymphocytes (1)</b> 156:12	<b>managing (1)</b> 181:16	<b>market (4)</b> 79:22;184:15;285:16; 306:13
		<b>Lynch's (1)</b> 121:4	<b>manifestation (1)</b> 330:1	<b>marketplace (2)</b> 244:13;247:2
		<b>Lynn (1)</b> 241:6	<b>manifestations (1)</b> 237:20	<b>marking (1)</b> 89:17
		<b>lytic (2)</b> 114:3,18	<b>manipulate (2)</b> 63:18;177:5	<b>marks (1)</b> 89:5
			<b>manipulated (1)</b> 290:6	
			<b>mantra (1)</b>	
		<b>M</b>		
		<b>Mac (1)</b> 169:18		
		<b>machines (1)</b> 62:12		
		<b>MacLeod (1)</b> 349:12		

<b>married (1)</b> 66:7	246:15;258:13;261:13; 271:5;297:8,11;298:20; 310:15,22;325:17; 326:11;330:14;344:10	<b>meaningful (1)</b> 317:12	<b>Medicine (9)</b> 4:11,13,19;10:3;11:3; 40:6;253:21;272:9; 295:10	62:19
<b>marrow (1)</b> 288:13		<b>means (9)</b> 10:4,11;11:3;26:5; 255:22;256:2,4;301:14, 15	<b>medium (2)</b> 92:18;199:1	<b>message (1)</b> 349:7
<b>Martin (3)</b> 32:5,10,10	<b>maybe (54)</b> 10:6;20:21,22;22:4, 13;25:17;28:10;30:7; 45:6;59:16;60:3;67:17; 68:18;71:13,16;72:7; 84:16;108:19;109:4; 118:19;170:12;175:15; 178:3;179:12;181:7; 182:5;186:13,15;189:5; 194:19;204:4;217:20; 222:12;227:15;234:5; 246:18;247:1;261:18; 262:22;267:7,9;270:13, 21;272:3;292:21; 337:17;338:21;339:19; 341:7;343:14;344:3,11; 348:14,19	<b>meantime (1)</b> 249:9	<b>medium-size (1)</b> 289:13	<b>messages (2)</b> 242:13;332:17
<b>masking (1)</b> 206:16		<b>meanwhile (1)</b> 249:14	<b>medium-sized (1)</b> 199:6	<b>messenger (1)</b> 114:5
<b>masks (1)</b> 206:9		<b>measure (9)</b> 79:4;158:12;215:22; 217:10;276:22;327:9; 339:21;340:8,12	<b>meds (2)</b> 115:12;221:2	<b>met (3)</b> 21:22;281:8;347:12
<b>mass (1)</b> 302:7		<b>measured (2)</b> 116:11;130:16	<b>medulla (1)</b> 96:12	<b>meta-analysis (5)</b> 342:1,8,11,13;348:19
<b>masseter (1)</b> 235:14		<b>measurements (1)</b> 282:2	<b>meeting (25)</b> 4:5;59:11;73:12; 75:11;104:20;113:3; 190:4;191:6;192:15; 193:9;197:22;213:7; 253:7;254:15;268:14; 281:7,8;295:4,6;338:12; 340:15,18;341:17; 350:9;351:20	<b>metabolism (1)</b> 273:16
<b>massive (3)</b> 71:11;185:4;228:21		<b>measures (10)</b> 209:13;210:19;211:4, 9,9,16,16,21;340:6; 344:6	<b>meetings (1)</b> 189:9	<b>metered (1)</b> 116:21
<b>mast (2)</b> 280:12,14		<b>measuring (3)</b> 79:3;181:9;339:20	<b>member (1)</b> 195:12	<b>method (5)</b> 32:4;33:1;34:11; 276:7;289:6
<b>master (1)</b> 44:2		<b>Meccano (2)</b> 49:2,8	<b>members (3)</b> 151:15;287:13;332:7	<b>methodological (1)</b> 349:10
<b>Master-cell (2)</b> 43:16;314:19	<b>Mazzini (1)</b> 51:22	<b>mechanical (12)</b> 16:16;92:2;93:19; 116:6,13;118:10; 122:17;123:1;130:20; 203:10;236:18;338:14	<b>membrane (2)</b> 16:2;144:1	<b>methodologies (1)</b> 340:17
<b>match (1)</b> 273:11	<b>MCA (2)</b> 290:20;291:2	<b>mechanism (23)</b> 18:16;20:12;30:19; 41:18;52:2;68:2;74:16; 77:11;108:7;132:10; 148:10;153:3;183:10; 198:19;204:21;217:15; 218:4,12;246:6;277:18; 278:4;327:12;329:10	<b>memorable (1)</b> 241:11	<b>methodology (5)</b> 260:6;339:12,14; 351:3;352:16
<b>matched (1)</b> 9:22	<b>McCarthy (1)</b> 214:5	<b>mechanisms (9)</b> 10:11;21:22;77:16; 110:10;197:5;203:19; 267:20;271:1,4	<b>memory (2)</b> 15:21;173:4	<b>methods (8)</b> 132:21;262:20;263:1, 12;264:14;275:21; 276:2;289:5
<b>matching (1)</b> 6:9	<b>McGill (2)</b> 104:8;210:21	<b>mechanistic (1)</b> 185:12	<b>Mendell (1)</b> 236:15	<b>MeWo (1)</b> 115:22
<b>Mateo (1)</b> 295:13	<b>mCherry (6)</b> 125:9,13,18,21;126:5, 11	<b>med (1)</b> 307:9	<b>meningeal (3)</b> 279:18;284:16;288:2	<b>mgs (6)</b> 73:4;320:5,8;322:18, 19,19
<b>mater (3)</b> 279:19;280:3;300:9	<b>M-cherry (1)</b> 126:7	<b>media (1)</b> 7:14	<b>menthol (10)</b> 158:14,21;159:6; 161:16;162:1,5,22; 163:2,5,15	<b>MIA (1)</b> 269:7
<b>mater' (1)</b> 280:15	<b>McIntosh (1)</b> 153:22	<b>medial (2)</b> 81:9;101:17	<b>mention (11)</b> 19:21;34:8;43:1; 44:15,19;65:9;75:18; 97:8;132:16;213:22; 258:18	<b>mic] (7)</b> 68:3;70:14;177:16; 264:20;270:7,10;328:12
<b>materials (3)</b> 239:13,17;240:4	<b>MCMAHON (24)</b> 66:16,21;68:3,12,19; 70:14;107:16;108:6,17; 109:2,14;110:3,8; 165:11;169:19;177:15, 19;214:16;215:8; 261:16;326:10;328:11; 329:9;342:19	<b>medication (20)</b> 257:9;297:10;298:10; 305:12;306:18,21;307:2, 14;310:14;312:5,12,13; 313:7;314:1,6;316:21, 22;321:11;324:21;336:1	<b>mentioned (16)</b> 22:11;29:21;41:5; 53:22;86:20;104:21; 105:14;177:9;184:4; 248:8;249:5,11;255:15; 303:18;305:13;323:15	<b>mice (21)</b> 14:13;66:17;87:4; 90:20;99:7;100:19; 101:7,16;103:1;110:19; 111:13;140:3,18,20,20; 141:1;142:17;160:14; 204:2;323:8;326:20
<b>matter (7)</b> 38:13,14;85:6;96:15; 101:19;177:6;285:3		<b>medications (6)</b> 298:3;300:1;306:12; 307:13;309:7;335:21	<b>merit (1)</b> 340:18	<b>microbiology (1)</b> 112:7
<b>matters (1)</b> 297:15	<b>MD (2)</b> 339:9,13		<b>mesenchymal (3)</b> 51:22;52:5;175:6	
<b>mature (1)</b> 41:9	<b>mean (35)</b> 50:14;57:15;74:18; 135:21;167:9;168:5; 173:17;177:8,20,21,22; 178:5;181:17;184:3,6; 187:17;214:22;242:7, 14;245:9;255:22; 259:12;266:11;267:14, 15;270:9;290:12;294:1; 305:17;309:10;331:8; 337:5;341:4;349:2; 352:20		<b>mesoderm (1)</b>	
<b>maximum (5)</b> 45:12,19;47:20; 206:19;210:5	<b>meaning (11)</b> 113:13;297:15; 298:16;308:15;311:15; 312:1;313:21;315:2,3; 330:7;336:2			
<b>Maxoud (1)</b> 312:6				
<b>may (67)</b> 6:2,13,13,19,20;17:10; 23:19;24:21;25:10; 29:13;48:17;50:14,15; 52:3;59:19,19;60:6; 61:16,16,17;63:21;69:1; 70:9;71:6;95:22;96:6; 108:15;110:6;111:3,22; 132:3,6;134:18;135:7, 11,22;173:10,19,19; 180:10;183:9;191:20; 192:4;193:21;194:10; 198:20;203:18;206:3; 207:5;212:7;215:10; 217:4;238:12;243:7;				

<b>microchip (1)</b> 16:3	317:16,18;320:18,19; 322:7;325:13;327:16;	326:7	95:11;96:12;98:3;105:3, 4,13;106:1,1;112:18; 120:17;131:6;152:12;	<b>mollusks (1)</b> 167:13
<b>microfluidic (1)</b> 15:22	328:5,14,15,16,16,17,18, 19,21,21;329:4,7,13,16;	<b>miracle (1)</b> 20:8	156:3;170:16;179:9,10; 187:12;189:2;198:1; 199:13;201:11;202:1; 205:17;213:9,16; 215:19;216:1;217:10; 238:17;242:18;243:4; 245:13,14,18;247:14; 250:12;251:5;261:12,12, 20;262:5,7,9;264:15; 268:1;269:21,21,22; 277:16;280:4;323:8; 327:21;328:5,6,8; 330:12;340:5;341:2,12; 344:6,7;346:14;349:4,21	<b>moment (16)</b> 6:11;13:9;18:4;23:2, 10;26:15;34:9;36:18; 57:19;64:13;146:21; 182:20;184:15;198:13; 219:20;351:14
<b>microfluidics (1)</b> 14:22	330:2,14,20,21;335:3, 19;337:11	<b>miserable (4)</b> 95:21;176:18;312:18; 313:11	205:17;213:9,16; 215:19;216:1;217:10; 238:17;242:18;243:4; 245:13,14,18;247:14; 250:12;251:5;261:12,12, 20;262:5,7,9;264:15; 268:1;269:21,21,22; 277:16;280:4;323:8; 327:21;328:5,6,8; 330:12;340:5;341:2,12; 344:6,7;346:14;349:4,21	<b>momentarily (1)</b> 230:3
<b>microglial (1)</b> 77:16	<b>migrainers (3)</b> 310:12,13,14	<b>Misha (3)</b> 180:13;339:18,18	<b>moderate (2)</b> 235:13;272:22	<b>momentum (1)</b> 51:17
<b>microinjections (1)</b> 171:19	<b>migraines (7)</b> 288:21;298:12,13; 310:13,22;322:8;329:22	<b>mismatch (1)</b> 41:11	<b>modern (1)</b> 278:15	<b>money (4)</b> 110:12;241:16; 260:18;348:16
<b>microliter (1)</b> 46:6	<b>migrant (1)</b> 330:9	<b>miss (3)</b> 38:5;108:2;335:12	<b>modes (1)</b> 171:21	<b>monitor (3)</b> 159:3,5,7
<b>micron (1)</b> 38:2	<b>migrate (9)</b> 25:15;38:10,12,13; 46:7;81:12;83:14;85:9,9	<b>missed (3)</b> 6:18;37:19;212:7	<b>modified (2)</b> 101:4;139:10	<b>monitored (2)</b> 93:5;94:6
<b>microphone (1)</b> 134:15	<b>migration (2)</b> 38:15;46:8	<b>missing (2)</b> 53:22;336:8	<b>modify (5)</b> 31:18;64:8,15;185:5; 237:15	<b>monitoring (5)</b> 43:5;99:12,15;204:17, 18
<b>microscopy (2)</b> 104:10;106:22	<b>Mike (1)</b> 98:7	<b>mistake (2)</b> 135:5;256:19	<b>modifying (4)</b> 94:15;133:1;237:19, 20	<b>monitorization (1)</b> 324:19
<b>Microsurgery (1)</b> 37:7	<b>mild (3)</b> 161:18;235:13;306:6	<b>misunderstanding (1)</b> 176:6	<b>modulate (5)</b> 23:13;24:21,21;31:9; 57:5	<b>monkey (1)</b> 188:2
<b>microsyringe (1)</b> 37:7	<b>millimeter (2)</b> 254:8,9	<b>mitigate (1)</b> 92:13	<b>modulated (1)</b> 30:12	<b>monoclonal (5)</b> 313:3;314:9,22;315:4; 325:17
<b>micro-syringe (1)</b> 37:11	<b>millimeters (1)</b> 38:11	<b>mixed (1)</b> 220:7	<b>modulation (3)</b> 30:15;48:1;325:11	<b>monoiodoacetate (1)</b> 269:7
<b>microvilli (1)</b> 16:15	<b>millimolars (1)</b> 123:7	<b>mixture (1)</b> 141:17	<b>Mogil (1)</b> 326:13	<b>month (6)</b> 28:9;33:10;287:8; 297:2;314:8;318:19
<b>mid (1)</b> 117:5	<b>million (6)</b> 15:14;32:19;42:10; 45:11;147:8;189:13	<b>Miyagawa (1)</b> 133:2	<b>Mogil's (1)</b> 326:16	<b>monthly (2)</b> 317:10;321:11
<b>mid-90s (1)</b> 267:15	<b>millions (3)</b> 146:11;348:15,16	<b>MK3207 (1)</b> 308:8	<b>Molecular (7)</b> 112:8,9;149:1;153:12; 154:3;163:22;346:17	<b>months (18)</b> 12:4;98:13;101:7,12, 21;102:8;107:2,4; 119:11;122:7;241:13; 310:4;312:21;317:9,13; 318:13;321:11,12
<b>middle (9)</b> 43:21;67:16;70:9; 247:7;274:4;279:18,20; 284:16;288:1	<b>mimic (1)</b> 16:20	<b>model (96)</b> 12:17;13:11,19;14:9, 11,13,16;17:1;29:9; 33:6;35:22,22;36:2,3,10, 19,20;37:6;40:19;41:5; 48:18;63:22;67:2;68:1, 7,10;69:21;72:20;73:18; 74:13;84:6;92:1,2,4; 93:14,20,21;95:12; 96:13;98:19;102:7; 115:18,19;116:15; 120:18;121:16;122:11; 125:13;126:5;129:15; 130:11;131:2;132:19; 134:18;135:1,3,6,12,13; 156:4,6;185:16;189:22; 198:6;200:22;202:10; 203:6,11;205:11,22; 206:3;223:20;237:11, 19;240:9;248:2,4,7,10, 21;250:16;251:22; 257:2;261:4,6,9;269:7,8, 8;281:2;327:21;328:1,9, 9;338:21,22	<b>modulated (1)</b> 30:12	<b>months' (1)</b> 206:6
<b>midst (1)</b> 320:17	<b>mimics (1)</b> 13:6	<b>Miyagawa (1)</b> 133:2	<b>modulation (3)</b> 30:15;48:1;325:11	<b>Moore (1)</b> 209:21
<b>might (41)</b> 6:22;23:1;69:15; 74:20;83:9,11;84:17,18, 18;109:16;110:1,4; 119:15;120:3;126:17; 149:12;151:12;155:18; 167:8;170:11;173:16; 179:19;196:1;217:9; 219:5;225:9;229:3; 231:20;233:10;246:22; 251:6,16;254:17;261:6; 262:1,1,5;293:14; 327:13;333:12,14	<b>mind (10)</b> 135:9;195:20;197:21; 229:2;232:4;243:13,14; 244:21;253:22;259:11	<b>MK3207 (1)</b> 308:8	<b>Mogil (1)</b> 326:13	<b>morbidity (1)</b> 329:3
<b>midst (1)</b> 320:17	<b>mingle (1)</b> 290:12	<b>model (96)</b> 12:17;13:11,19;14:9, 11,13,16;17:1;29:9; 33:6;35:22,22;36:2,3,10, 19,20;37:6;40:19;41:5; 48:18;63:22;67:2;68:1, 7,10;69:21;72:20;73:18; 74:13;84:6;92:1,2,4; 93:14,20,21;95:12; 96:13;98:19;102:7; 115:18,19;116:15; 120:18;121:16;122:11; 125:13;126:5;129:15; 130:11;131:2;132:19; 134:18;135:1,3,6,12,13; 156:4,6;185:16;189:22; 198:6;200:22;202:10; 203:6,11;205:11,22; 206:3;223:20;237:11, 19;240:9;248:2,4,7,10, 21;250:16;251:22; 257:2;261:4,6,9;269:7,8, 8;281:2;327:21;328:1,9, 9;338:21,22	<b>Mogil's (1)</b> 326:16	<b>more (150)</b> 7:12;11:21;13:9; 14:17;15:20;16:13,15; 17:12,15;19:20;23:1; 24:10,12,16;31:14;42:8; 45:15,16;46:8;47:6; 51:18;58:4,18;62:20,20; 65:15;69:6;75:1,6; 80:11;82:11;90:10,12; 91:20;100:21;101:17, 21;108:18;152:3;162:5; 168:21;170:12;171:2, 18;174:8,10;179:4; 183:9;184:20;185:3,6; 186:18,19;199:17;
<b>might (41)</b> 6:22;23:1;69:15; 74:20;83:9,11;84:17,18, 18;109:16;110:1,4; 119:15;120:3;126:17; 149:12;151:12;155:18; 167:8;170:11;173:16; 179:19;196:1;217:9; 219:5;225:9;229:3; 231:20;233:10;246:22; 251:6,16;254:17;261:6; 262:1,1,5;293:14; 327:13;333:12,14	<b>mini-company (1)</b> 189:15	<b>modeled (1)</b> 29:22	<b>molecule (33)</b> 70:4;168:18;227:3,13; 242:2;251:17;286:13; 288:11;289:10;296:15; 300:3;303:9;304:6; 305:1,15;307:13;309:1; 310:17;311:1,18,19,20, 22;315:5;316:12,16; 319:18;320:15;325:9, 12;329:5;330:5;335:17	<b>morbidity (1)</b> 329:3
<b>might (41)</b> 6:22;23:1;69:15; 74:20;83:9,11;84:17,18, 18;109:16;110:1,4; 119:15;120:3;126:17; 149:12;151:12;155:18; 167:8;170:11;173:16; 179:19;196:1;217:9; 219:5;225:9;229:3; 231:20;233:10;246:22; 251:6,16;254:17;261:6; 262:1,1,5;293:14; 327:13;333:12,14	<b>mini-human (2)</b> 16:3;188:9	<b>modeling (6)</b> 6:12,14,14;15:2; 63:21;115:18	<b>molecules (24)</b> 13:4;14:1;18:5,8; 157:18;172:19;217:19, 22;246:7,8;264:22; 265:12;272:5;283:12; 304:15,18,20,21;305:7; 310:18;311:13;313:19; 318:21;343:8	<b>more (150)</b> 7:12;11:21;13:9; 14:17;15:20;16:13,15; 17:12,15;19:20;23:1; 24:10,12,16;31:14;42:8; 45:15,16;46:8;47:6; 51:18;58:4,18;62:20,20; 65:15;69:6;75:1,6; 80:11;82:11;90:10,12; 91:20;100:21;101:17, 21;108:18;152:3;162:5; 168:21;170:12;171:2, 18;174:8,10;179:4; 183:9;184:20;185:3,6; 186:18,19;199:17;
<b>might (41)</b> 6:22;23:1;69:15; 74:20;83:9,11;84:17,18, 18;109:16;110:1,4; 119:15;120:3;126:17; 149:12;151:12;155:18; 167:8;170:11;173:16; 179:19;196:1;217:9; 219:5;225:9;229:3; 231:20;233:10;246:22; 251:6,16;254:17;261:6; 262:1,1,5;293:14; 327:13;333:12,14	<b>minimally (1)</b> 49:14	<b>models (79)</b> 14:14,18;15:4,5;17:2, 7,9,12;18:9;36:12;48:3; 67:3;68:17;91:21;92:1;	<b>molecule (33)</b> 70:4;168:18;227:3,13; 242:2;251:17;286:13; 288:11;289:10;296:15; 300:3;303:9;304:6; 305:1,15;307:13;309:1; 310:17;311:1,18,19,20, 22;315:5;316:12,16; 319:18;320:15;325:9, 12;329:5;330:5;335:17	<b>more (150)</b> 7:12;11:21;13:9; 14:17;15:20;16:13,15; 17:12,15;19:20;23:1; 24:10,12,16;31:14;42:8; 45:15,16;46:8;47:6; 51:18;58:4,18;62:20,20; 65:15;69:6;75:1,6; 80:11;82:11;90:10,12; 91:20;100:21;101:17, 21;108:18;152:3;162:5; 168:21;170:12;171:2, 18;174:8,10;179:4; 183:9;184:20;185:3,6; 186:18,19;199:17;
<b>might (41)</b> 6:22;23:1;69:15; 74:20;83:9,11;84:17,18, 18;109:16;110:1,4; 119:15;120:3;126:17; 149:12;151:12;155:18; 167:8;170:11;173:16; 179:19;196:1;217:9; 219:5;225:9;229:3; 231:20;233:10;246:22; 251:6,16;254:17;261:6; 262:1,1,5;293:14; 327:13;333:12,14	<b>minor (3)</b> 76:12;264:13;301:8	<b>modeling (6)</b> 6:12,14,14;15:2; 63:21;115:18	<b>molecule (33)</b> 70:4;168:18;227:3,13; 242:2;251:17;286:13; 288:11;289:10;296:15; 300:3;303:9;304:6; 305:1,15;307:13;309:1; 310:17;311:1,18,19,20, 22;315:5;316:12,16; 319:18;320:15;325:9, 12;329:5;330:5;335:17	<b>more (150)</b> 7:12;11:21;13:9; 14:17;15:20;16:13,15; 17:12,15;19:20;23:1; 24:10,12,16;31:14;42:8; 45:15,16;46:8;47:6; 51:18;58:4,18;62:20,20; 65:15;69:6;75:1,6; 80:11;82:11;90:10,12; 91:20;100:21;101:17, 21;108:18;152:3;162:5; 168:21;170:12;171:2, 18;174:8,10;179:4; 183:9;184:20;185:3,6; 186:18,19;199:17;
<b>might (41)</b> 6:22;23:1;69:15; 74:20;83:9,11;84:17,18, 18;109:16;110:1,4; 119:15;120:3;126:17; 149:12;151:12;155:18; 167:8;170:11;173:16; 179:19;196:1;217:9; 219:5;225:9;229:3; 231:20;233:10;246:22; 251:6,16;254:17;261:6; 262:1,1,5;293:14; 327:13;333:12,14	<b>minority (1)</b> 219:7	<b>models (79)</b> 14:14,18;15:4,5;17:2, 7,9,12;18:9;36:12;48:3; 67:3;68:17;91:21;92:1;	<b>molecule (33)</b> 70:4;168:18;227:3,13; 242:2;251:17;286:13; 288:11;289:10;296:15; 300:3;303:9;304:6; 305:1,15;307:13;309:1; 310:17;311:1,18,19,20, 22;315:5;316:12,16; 319:18;320:15;325:9, 12;329:5;330:5;335:17	<b>more (150)</b> 7:12;11:21;13:9; 14:17;15:20;16:13,15; 17:12,15;19:20;23:1; 24:10,12,16;31:14;42:8; 45:15,16;46:8;47:6; 51:18;58:4,18;62:20,20; 65:15;69:6;75:1,6; 80:11;82:11;90:10,12; 91:20;100:21;101:17, 21;108:18;152:3;162:5; 168:21;170:12;171:2, 18;174:8,10;179:4; 183:9;184:20;185:3,6; 186:18,19;199:17;
<b>might (41)</b> 6:22;23:1;69:15; 74:20;83:9,11;84:17,18, 18;109:16;110:1,4; 119:15;120:3;126:17; 149:12;151:12;155:18; 167:8;170:11;173:16; 179:19;196:1;217:9; 219:5;225:9;229:3; 231:20;233:10;246:22; 251:6,16;254:17;261:6; 262:1,1,5;293:14; 327:13;333:12,14	<b>minus (1)</b> 256:4	<b>modeled (1)</b> 29:22	<b>molecule (33)</b> 70:4;168:18;227:3,13; 242:2;251:17;286:13; 288:11;289:10;296:15; 300:3;303:9;304:6; 305:1,15;307:13;309:1; 310:17;311:1,18,19,20, 22;315:5;316:12,16; 319:18;320:15;325:9, 12;329:5;330:5;335:17	<b>more (150)</b> 7:12;11:21;13:9; 14:17;15:20;16:13,15; 17:12,15;19:20;23:1; 24:10,12,16;31:14;42:8; 45:15,16;46:8;47:6; 51:18;58:4,18;62:20,20; 65:15;69:6;75:1,6; 80:11;82:11;90:10,12; 91:20;100:21;101:17, 21;108:18;152:3;162:5; 168:21;170:12;171:2, 18;174:8,10;179:4; 183:9;184:20;185:3,6; 186:18,19;199:17;
<b>might (41)</b> 6:22;23:1;69:15; 74:20;83:9,11;84:17,18, 18;109:16;110:1,4; 119:15;120:3;126:17; 149:12;151:12;155:18; 167:8;170:11;173:16; 179:19;196:1;217:9; 219:5;225:9;229:3; 231:20;233:10;246:22; 251:6,16;254:17;261:6; 262:1,1,5;293:14; 327:13;333:12,14	<b>minuses (1)</b> 255:21	<b>modeling (6)</b> 6:12,14,14;15:2; 63:21;115:18	<b>molecule (33)</b> 70:4;168:18;227:3,13; 242:2;251:17;286:13; 288:11;289:10;296:15; 300:3;303:9;304:6; 305:1,15;307:13;309:1; 310:17;311:1,18,19,20, 22;315:5;316:12,16; 319:18;320:15;325:9, 12;329:5;330:5;335:17	<b>more (150)</b> 7:12;11:21;13:9; 14:17;15:20;16:13,15; 17:12,15;19:20;23:1; 24:10,12,16;31:14;42:8; 45:15,16;46:8;47:6; 51:18;58:4,18;62:20,20; 65:15;69:6;75:1,6; 80:11;82:11;90:10,12; 91:20;100:21;101:17, 21;108:18;152:3;162:5; 168:21;170:12;171:2, 18;174:8,10;179:4; 183:9;184:20;185:3,6; 186:18,19;199:17;
<b>might (41)</b> 6:22;23:1;69:15; 74:20;83:9,11;84:17,18, 18;109:16;110:1,4; 119:15;120:3;126:17; 149:12;151:12;155:18; 167:8;170:11;173:16; 179:19;196:1;217:9; 219:5;225:9;229:3; 231:20;233:10;246:22; 251:6,16;254:17;261:6; 262:1,1,5;293:14; 327:13;333:12,14	<b>minute (4)</b> 19:22;230:2;234:16; 242:10	<b>models (79)</b> 14:14,18;15:4,5;17:2, 7,9,12;18:9;36:12;48:3; 67:3;68:17;91:21;92:1;	<b>molecule (33)</b> 70:4;168:18;227:3,13; 242:2;251:17;286:13; 288:11;289:10;296:15; 300:3;303:9;304:6; 305:1,15;307:13;309:1; 310:17;311:1,18,19,20, 22;315:5;316:12,16; 319:18;320:15;325:9, 12;329:5;330:5;335:17	<b>more (150)</b> 7:12;11:21;13:9; 14:17;15:20;16:13,15; 17:12,15;19:20;23:1; 24:10,12,16;31:14;42:8; 45:15,16;46:8;47:6; 51:18;58:4,18;62:20,20; 65:15;69:6;75:1,6; 80:11;82:11;90:10,12; 91:20;100:21;101:17, 21;108:18;152:3;162:5; 168:21;170:12;171:2, 18;174:8,10;179:4; 183:9;184:20;185:3,6; 186:18,19;199:17;
<b>might (41)</b> 6:22;23:1;69:15; 74:20;83:9,11;84:17,18, 18;109:16;110:1,4; 119:15;120:3;126:17; 149:12;151:12;155:18; 167:8;170:11;173:16; 179:19;196:1;217:9; 219:5;225:9;229:3; 231:20;233:10;246:22; 251				

203:13;206:6;211:15; 215:9;221:7;225:8; 226:11,15,16;228:2,3, 10,16,16;234:2,15; 236:2;238:4;240:11,19; 242:8;243:1;244:17,19; 246:9,18;248:4;249:6,7; 252:17;256:22;259:8, 15;261:1,18;262:7,8,22; 263:2,11;265:12,20; 266:7,11;268:5,9; 269:21;270:1;271:9,18; 278:15;279:22;282:12; 283:11;289:9,10;292:9, 13,15;295:1,12;296:18; 297:2,16,16;298:1,8,12; 299:4;302:16;303:3,20; 304:7,15;308:7,14; 309:22;310:2;311:2,3, 11;319:2;323:10; 326:21;332:13;333:21; 334:7;337:19;338:4; 339:6;344:8;348:3; 350:3;351:20;352:1,14	73:19;80:16;81:1,1,17, 18;82:12,13,17;86:12; 90:7;91:3;97:15,15; 98:8,12;99:1;100:18; 140:16;326:17 <b>mouth (5)</b> 147:19;149:11,12,13, 17 <b>move (27)</b> 16:12,22;17:4;27:8, 16;42:10;44:14;51:17; 53:13;54:22;56:16; 65:17;75:2;83:16; 101:17;104:13;210:20; 222:18,20;264:22; 278:12;280:13;283:10; 350:22;352:1,5,14 <b>moved (11)</b> 4:17;26:1;39:13;42:1; 52:8;194:18;211:9; 227:13;295:11,12; 350:14 <b>movement (2)</b> 16:10,16 <b>movements (1)</b> 235:16 <b>moves (3)</b> 28:8;165:20;278:18 <b>movies (1)</b> 137:14 <b>moving (10)</b> 17:16;26:6,10;53:11, 15;101:21;193:20; 222:14;226:21;324:9 <b>MRI (2)</b> 37:15,20 <b>MRI-track (1)</b> 37:21 <b>MSTP (1)</b> 132:20 <b>mu (1)</b> 117:8 <b>much (69)</b> 5:7,9;15:20;26:18; 27:19;39:8;46:7;47:6; 66:12;68:22,22;71:20; 75:10;84:13;85:21; 99:18;104:14;107:3; 136:7;144:18;150:4; 156:16;162:5;164:10; 168:21;171:17,18;174:1, 8,22;176:21;185:3; 191:18,18;192:17; 197:3;209:16;210:16; 220:6;221:18;227:11, 21;228:10;243:8;249:6; 251:6,10;259:8;264:16; 265:17;272:17;274:10; 285:3;286:11;288:5; 292:18;294:10;304:7; 320:11;324:7;325:5; 340:14;341:20;345:11; 351:6;352:14;353:9,11,	17 <b>multicellular (2)</b> 32:6,8 <b>multidose (1)</b> 212:20 <b>multineuron (1)</b> 12:5 <b>multineurons (2)</b> 12:11,14 <b>multiple (5)</b> 23:17;238:11;239:17; 241:7;347:14 <b>muscle (30)</b> 9:10;12:4;14:20;23:6; 27:15,17;28:8;30:17; 31:1;35:12,13;40:10; 41:1,2,15,20;53:18; 66:17;67:5,7,9,15,20; 70:13;74:8,15;138:21; 144:1;279:9,16 <b>muscles (3)</b> 235:14,18;281:1 <b>muscular (2)</b> 12:2;186:2 <b>must (3)</b> 133:9;256:21;339:15 <b>mutagenesis (1)</b> 124:18 <b>mutant (13)</b> 36:9;68:9,10;86:12; 98:8;111:13;121:14; 122:4,14,16,21;123:15; 126:13 <b>mutants (1)</b> 109:19 <b>mutation (8)</b> 10:6,7;29:8,16;30:20, 20;36:16;41:17 <b>mutations (4)</b> 121:6;127:11;319:6; 320:1 <b>MVIA (1)</b> 142:22 <b>myalgias (2)</b> 235:9,19 <b>myelination (1)</b> 23:18 <b>myself (5)</b> 231:10;243:14;259:5; 347:5,5 <b>mysterious (1)</b> 217:17	<b>Nana (1)</b> 220:5 <b>nanomolar (1)</b> 123:4 <b>naproxen (1)</b> 258:6 <b>narrow (2)</b> 120:21;267:9 <b>nasal (1)</b> 283:1 <b>Nat (8)</b> 227:5,6,11,12,19; 267:12;271:17;346:3 <b>Nathaniel (1)</b> 227:20 <b>National (1)</b> 42:18 <b>Nat's (1)</b> 351:5 <b>natural (4)</b> 114:11;117:21; 146:10;251:16 <b>naturally (3)</b> 34:3;113:13;125:6 <b>Nature (7)</b> 40:6;94:11,19;102:15; 163:21;197:21;348:4 <b>nausea (3)</b> 261:22;298:14;307:8 <b>navel-gazing (1)</b> 344:5 <b>navigating (1)</b> 315:7 <b>near (2)</b> 85:21;125:2 <b>nearly (3)</b> 33:22;181:17;292:1 <b>neat (1)</b> 276:7 <b>necessarily (5)</b> 79:20;177:17;253:13; 269:17;351:11 <b>necessary (6)</b> 98:9;111:22;143:16; 148:6;150:19;267:7 <b>neck (1)</b> 100:9 <b>need (49)</b> 7:17;22:22;23:4,4; 43:11,13;56:8,16;58:13; 59:9,12,17,19,21;60:12; 74:15;77:7;102:20; 109:20;119:17;131:12; 167:21,22;168:6; 178:17;189:4,21; 243:12;244:3,5;250:19, 22;252:15;264:11,15; 265:14;283:22;284:5; 333:6;334:15;335:7,14; 337:12,20;338:19,19; 339:12;352:5,12 <b>needed (6)</b> 70:22;119:18;121:2;	143:14;201:8;335:12 <b>needle (2)</b> 147:2,7 <b>needles (1)</b> 147:10 <b>needs (9)</b> 17:9;18:19;19:17; 20:17;76:20;270:16; 297:21;339:6;351:22 <b>negative (12)</b> 128:16;226:2,4; 227:17;255:16;257:17, 20;344:19,19;345:1,18, 20 <b>nematodes (1)</b> 155:3 <b>neonatal (3)</b> 81:22;82:16;83:8 <b>nerve (49)</b> 9:10;76:9,10,13; 78:16,16;84:10;92:4,5; 96:7;102:7;105:12; 108:11;114:2,12,20; 116:19;117:11,12; 123:15;132:3;156:3,4,7, 11,15,17;157:3,8;198:5, 18;199:12;200:8,22; 203:15;220:8;232:12; 233:12;266:14,16,18,18, 20;277:8;289:18; 299:15;300:10;326:22; 340:5 <b>nerves (8)</b> 114:14;115:5;120:2; 203:17;266:15;275:9; 291:10,10 <b>nervous (15)</b> 35:11,11;120:2;121:2; 124:1;132:2;141:15; 145:19;154:10;158:7; 164:15;177:5;188:7; 258:21;274:1 <b>nested (1)</b> 39:22 <b>Network (3)</b> 219:12;220:3;345:13 <b>networks (1)</b> 198:7 <b>NeuN (2)</b> 97:7,10 <b>neural (12)</b> 5:16;22:15;26:14; 34:7;52:10;58:7,59;18; 175:7;181:5;232:17; 234:9;282:12 <b>neuralgia (17)</b> 95:21;96:2,13;114:22; 115:2;135:4,8;170:9; 180:6,10;205:8,10,16; 211:3;257:6;281:15; 343:21 <b>neurasthenia (1)</b> 285:19
		<b>N</b>		
		<b>naive (3)</b> 165:11;166:13;334:13 <b>name (9)</b> 13:17;29:20;140:3; 172:2;191:4;231:2; 261:17;272:7;308:8 <b>names (1)</b> 195:8		

<b>neurite (5)</b> 18:15;199:1;200:5,10; 248:22	176:10;195:21;201:11; 205:17;210:1,1;213:6; 219:12;223:2;250:12;	245:7;253:20;261:7; 267:8;296:7;314:20; 321:7;346:17	341:5;343:4,12	<b>normal (22)</b> 17:9;43:9;54:18;82:8; 93:12;94:1,7;98:18; 102:11;121:13,20; 122:14;130:22;136:3; 144:2;185:21;226:9; 298:16;301:8,9;303:11; 329:15
<b>neuro (1)</b> 276:3	255:19;257:10;338:7; 340:2;342:2,11;344:17;	<b>newer (2)</b> 17:12;55:20	<b>NMDA (1)</b> 152:1	<b>normalize (2)</b> 93:10;94:6
<b>neurobiologist (1)</b> 83:20	345:12;349:21	<b>news (1)</b> 214:18	<b>NNTs (1)</b> 209:5	<b>normalizing (1)</b> 106:5
<b>neurochemical (1)</b> 82:3	<b>neuropathies (2)</b> 105:7,16	<b>newsletters (1)</b> 353:15	<b>Nobel (1)</b> 7:16	<b>normally (3)</b> 28:22;126:15;191:20
<b>neurochemistry (1)</b> 106:13	<b>neuropathy (14)</b> 15:5,7;198:6;202:10; 203:7;206:3;213:10; 220:9;226:2;234:10; 257:4;344:20;345:4,20	<b>next (21)</b> 5:18;15:11;28:9; 49:18;52:17;75:3;95:5; 136:13;219:22;220:19; 226:21;235:11;237:3,6; 242:9;247:9,17;250:3; 260:22;272:6;312:11	<b>Nobody (5)</b> 24:17;25:6;264:8; 311:4;331:6	<b>North (1)</b> 208:4
<b>neurodegenerative (2)</b> 14:15;171:13	<b>neuropeptide (1)</b> 325:10	<b>NGF (24)</b> 124:20;127:19; 232:20;233:2,9,15,19, 22;234:3,8,14,19;235:4, 8;236:10,17,22;237:4; 238:3,19;239:11;249:2; 267:4;271:4	<b>nociception (3)</b> 198:21;338:6,10	<b>notable (2)</b> 265:13;274:9
<b>neurogenetic (1)</b> 18:10	<b>neuropharmacological (1)</b> 138:7	<b>NGF-related (1)</b> 271:1	<b>nociceptive (1)</b> 200:11	<b>note (1)</b> 267:4
<b>neurological (8)</b> 12:17;29:3;36:11,12; 80:13;94:17;103:19; 299:20	<b>neuropharmacologists (1)</b> 138:3	<b>NGH (1)</b> 43:4	<b>nociceptor (1)</b> 168:17	<b>notice (2)</b> 25:6;226:16
<b>neurologist (3)</b> 50:17;51:5,7	<b>neuropharmacology (1)</b> 138:10	<b>nice (22)</b> 14:8;20:3;24:9;25:15; 45:8,12,14;46:3;50:2; 64:14;66:7;121:5;140:8; 152:20;189:11;196:6; 219:1;240:19;273:19; 281:12;284:15;337:1	<b>nociceptors (8)</b> 161:19;162:4,9,18; 163:1,4;168:5,14	<b>noticed (2)</b> 101:8;215:15
<b>neurologists (2)</b> 26:21;180:6	<b>neuroprogenitors (1)</b> 38:12	<b>nicely (5)</b> 37:13;45:18;49:4; 55:22;57:10	<b>noise (1)</b> 266:9	<b>noting (1)</b> 237:21
<b>neurology (2)</b> 273:12;314:15	<b>neuroscience (5)</b> 153:15;193:5;240:22; 241:3;339:11	<b>niche (1)</b> 244:18	<b>non- (1)</b> 60:17	<b>notion (2)</b> 168:3;233:9
<b>neuromuscular (9)</b> 138:19;143:7,9,13; 144:10,17;145:3;155:2, 13	<b>neurospheres (1)</b> 32:3	<b>Nick (2)</b> 49:1;52:11	<b>non-bias (1)</b> 187:10	<b>notorious (1)</b> 20:10
<b>neuronal (5)</b> 108:9;150:20;151:14; 273:15;331:15	<b>neurosurgeon (5)</b> 38:1;49:9;50:8;51:3; 172:14	<b>nicotinic (12)</b> 138:17;153:6,7,13,21; 154:21;155:1;156:14,22, 22;166:6,12	<b>non-clinical (1)</b> 266:2	<b>novel (2)</b> 32:4;339:14
<b>neurons (88)</b> 5:20;12:9,15,16;14:9; 19:11,21;20:12;22:9,21; 23:11,14;25:18;27:4,9, 10,18;28:2;29:11;31:1, 10,15,16,17;33:13,16, 18;34:2;36:5,6,13;39:7, 9,18;40:1,3;46:14;64:3; 66:18;69:11;70:22; 80:17;84:4;97:6;100:19; 101:5;109:5;110:5; 113:15;117:17,19;120:9, 15;123:19,20,22;124:4; 129:11;131:16;158:8, 10;159:2;160:4,17,18, 19,22;161:2,3,7,11,16; 164:22;165:6;179:7; 180:2;185:19,20,21; 186:4,5,9,10;199:6; 205:21;232:17;290:1; 293:17	<b>neurosurgeons (1)</b> 36:2	<b>night (3)</b> 149:20;169:14;274:4	<b>non-coding (1)</b> 114:6	<b>nowadays (1)</b> 299:19
<b>neuropathic (26)</b> 76:8;77:8;80:1;82:20; 94:16;103:18;105:2;	<b>neurotensin (3)</b> 152:5,9,13	<b>NIH (5)</b> 14:10;54:10;66:11; 189:6;350:19	<b>non-competition (1)</b> 285:2	<b>nowhere (1)</b> 42:9
	<b>neurotransmission (1)</b> 24:21	<b>NIH-funded (1)</b> 14:2	<b>non-competing (1)</b> 34:11,12;52:22; 269:20;279:6;280:15; 321:18	<b>NOX (2)</b> 289:10;291:20
	<b>neurotransmitter (2)</b> 143:15;144:9	<b>Nikkhah (1)</b> 37:8	<b>non-coding (1)</b> 114:6	<b>NOX/C89 (2)</b> 288:18;289:3
	<b>neurotrophin (1)</b> 232:15	<b>nine (1)</b> 116:12	<b>non-coding (1)</b> 114:6	<b>noxious (1)</b> 161:19
	<b>neurotropic (1)</b> 113:13	<b>Ninety (1)</b> 115:11	<b>non-clinical (1)</b> 266:2	<b>NPY (1)</b> 124:11
	<b>neurturin (1)</b> 18:11	<b>nirvana (4)</b> 151:3,8,10,15	<b>non-coding (1)</b> 114:6	<b>NPY-positive (1)</b> 102:1
	<b>neutralizing (1)</b> 238:3	<b>nitric (1)</b> 275:11	<b>non-coding (1)</b> 114:6	<b>NSAID (1)</b> 269:10
	<b>neutrophil (1)</b> 110:6	<b>NK1 (3)</b>	<b>non-coding (1)</b> 114:6	<b>NSAIDs (2)</b> 76:19;261:9
	<b>new (40)</b> 6:15;8:18;14:16; 21:14,15;23:16;29:12, 21;32:12;57:13;60:7; 64:16;79:22;113:5,20; 115:15;133:3,18; 152:13;153:4;160:6; 193:2;207:2;210:21; 229:21,21;239:7,9; 241:5,10;242:1;243:12;		<b>non-coding (1)</b> 114:6	<b>N-terminus (1)</b> 152:6
			<b>non-coding (1)</b> 114:6	<b>nucleocomplex (1)</b> 292:3
			<b>non-coding (1)</b> 114:6	<b>nucleolus (1)</b> 114:8
			<b>non-coding (1)</b> 114:6	<b>nucleus (4)</b> 38:22;91:9;96:11; 300:11
			<b>non-coding (1)</b> 114:6	<b>number (44)</b> 9:5;14:11;30:13;35:2;

39:18;40:18;45:9,18; 46:13;53:14;72:12;83:6; 107:2;121:10;127:22; 129:15;132:15;153:1; 158:1;177:9,12;181:20, 22;184:17,19;185:2; 191:13,14;197:13; 200:20;208:2,4;209:1; 210:18;212:2,8,11; 226:8;227:18;247:21; 249:18;250:7;261:20; 280:1	<b>occurred (1)</b> 223:11 <b>occurrences (1)</b> 117:22 <b>occurring (2)</b> 107:5;234:17 <b>occurs (4)</b> 99:11;100:10;115:4; 135:7 <b>ocean (1)</b> 315:7 <b>Oct-4 (2)</b> 8:7;62:22 <b>off (24)</b> 26:7;27:5;52:17;55:8, 13;56:6,13,14;57:8; 58:3;59:11;62:15;68:3; 70:14;92:18;119:16; 150:2;177:15;183:5; 221:13;264:19;270:7, 10;328:12 <b>offers (1)</b> 5:4 <b>officer (1)</b> 295:21 <b>off-target (1)</b> 123:17 <b>often (12)</b> 139:11;146:14; 165:20;211:17;224:22; 226:11,15;288:12; 332:13;335:12;340:10; 350:10 <b>oil (1)</b> 65:9 <b>olcegepant (4)</b> 283:16;305:14,14; 308:19 <b>old (11)</b> 8:1;29:2;30:18;55:18; 57:17;61:11;70:4; 197:19;290:5;291:12; 343:12 <b>older (1)</b> 137:11 <b>old-ish (1)</b> 38:8 <b>oligo (1)</b> 97:10 <b>oligodendrocyte (1)</b> 22:19 <b>Oligodendrocytes (2)</b> 23:14,19 <b>oligonucleotides (3)</b> 13:14;288:7,12 <b>oligos (2)</b> 100:20,20 <b>Olivera (17)</b> 136:15;137:7,8; 140:12;147:12;150:12; 165:1,10,14;166:17,20; 167:4,13;168:22;184:13, 19;185:1	<b>Omega (1)</b> 142:22 <b>once (20)</b> 8:12;12:20;18:11; 26:3;32:5;108:1;143:18; 149:16;222:17;298:21; 309:22;310:1;317:6,8, 21;318:2;324:22; 334:21;336:5;342:15 <b>oncology (2)</b> 240:17;251:14 <b>one (227)</b> 11:22;13:22;14:20,21, 22;16:1,19;19:10;26:6, 7;27:15;28:9,21;29:12; 30:11;36:11;37:18,19; 38:9;39:2,6;42:4,6,20; 50:13,18;51:3,11,21; 55:1;69:2,5,5,11;70:3; 72:7;76:21;77:21;83:6; 85:3,7;86:19;87:17; 91:8;93:17;95:10; 101:15;102:22;106:3; 107:17;108:21;111:8,9; 112:15;113:7;115:17, 19;116:21;117:2; 126:13;129:2,8,16; 133:18;138:12,17;141:9, 10;144:19;147:21; 149:6,10;150:2,2;151:2, 12,18,21;152:3,20; 162:6,6;163:7;164:3,18; 165:11;168:15;170:5,18, 20;176:1,17;177:5; 178:2;179:3,16;180:3, 15,21;181:3,7,19;182:5, 10;185:1;187:4;191:4,7, 11,13;192:20;193:8; 194:7;197:15,16;200:14, 17;201:3,3;204:4,11; 206:6,20;212:6;213:14; 214:20;215:15;216:15; 217:16;218:19;219:13; 220:20;221:16,16; 224:18;225:7,13,20; 229:15;230:2,10;233:8; 235:2,3,20,21;236:1,15; 237:16;238:12,17; 239:9;242:7,13,22; 246:16;247:15;248:1; 256:1;261:13;262:19; 265:21;268:1;269:11,13, 13;270:22;271:8,10; 272:11;274:10,15; 275:8;280:14,18; 283:16;284:7;287:6; 288:3,17;291:12,19; 292:3;293:9,15;294:7, 22;295:22;296:17,18; 297:3;306:21;308:1,14; 314:7;315:14,15,18,19; 316:6,6,9,21;317:5; 318:12;319:9;320:18,	18;322:7,7,22;323:17; 326:10;327:21;331:3, 11;332:12;333:7,12; 334:15;339:18;341:22; 343:17,22;344:21; 345:1;349:2 <b>ones (11)</b> 51:21;55:20;80:2; 128:13;153:11;197:19; 265:3;267:1;276:5; 310:9;335:2 <b>one's (1)</b> 165:1 <b>ongoing (3)</b> 76:14;79:12;171:12 <b>only (64)</b> 23:4;35:16;36:14; 37:20;39:4;41:20;47:13; 51:3,21;56:7;70:3; 74:20;75:15;76:2;83:7; 91:20;93:2,17;112:3; 113:14;120:2,5;137:21, 21;138:1;140:1;141:1; 175:20;178:12;180:4; 184:16;214:9;224:3; 228:7;231:13;232:19; 242:18;246:22;255:4,6; 258:2;260:13;271:2; 277:3;286:6;298:9; 300:15;304:1,13,17,17; 305:11;307:7;312:7; 313:17;317:8,20;318:1, 2;320:2;321:17,18; 324:21;330:22 <b>onset (6)</b> 27:3;28:4;41:11; 51:15;186:8;288:5 <b>onto (3)</b> 49:6;53:11;263:17 <b>open (6)</b> 21:3;143:14,14; 169:17;216:9;302:6 <b>opened (1)</b> 9:20 <b>opening (2)</b> 159:22;301:22 <b>open-label (1)</b> 20:9 <b>opens (7)</b> 15:1;143:20;149:11; 163:5;301:7,13,15 <b>operated (1)</b> 284:13 <b>opiate (2)</b> 117:7;172:10 <b>opioid (2)</b> 153:3;258:15 <b>opioids (5)</b> 76:19;183:5,6;261:10; 328:1 <b>opium (1)</b> 150:10 <b>opportunity (13)</b>	15:1;76:1;113:4; 146:9;147:8;191:21; 222:9;228:12;252:12, 17;266:22;327:4;351:20 <b>opposed (2)</b> 116:2;263:10 <b>opposite (5)</b> 47:22;85:11;122:3; 134:4;244:15 <b>optimal (1)</b> 46:10 <b>optimism (1)</b> 351:5 <b>options (4)</b> 195:17;249:20;251:3, 4 <b>oral (3)</b> 73:3;306:20;307:2 <b>orally (1)</b> 164:14 <b>order (5)</b> 7:10;44:6;46:18; 143:7;150:3 <b>organ (4)</b> 15:16;16:18;17:3;73:8 <b>organism (1)</b> 32:6 <b>organisms (1)</b> 32:8 <b>organized (3)</b> 191:6;193:9;255:16 <b>organizers (1)</b> 227:22 <b>organoid (1)</b> 188:11 <b>organoids (3)</b> 9:13,16;188:10 <b>organs (3)</b> 10:10;11:9;15:20 <b>origin (1)</b> 81:3 <b>original (3)</b> 66:2;214:3;275:5 <b>originally (8)</b> 42:2;70:17;83:19; 112:5;151:22;162:8; 172:5;207:3 <b>origins (2)</b> 171:3;230:13 <b>osmotic (1)</b> 128:4 <b>ostensibly (1)</b> 269:8 <b>osteoarthritis (7)</b> 213:12;251:20;252:8; 253:19;255:13;256:9; 258:10 <b>OTCs (1)</b> 298:1 <b>others (16)</b> 22:8;36:18;50:15; 57:11;70:5;95:13; 223:16;229:6;241:7;
---	--	--	--	--



288:19;298:20;308:12; 310:8;317:1;319:11; 324:12 <b>other's (2)</b> 333:22;351:9 <b>Otherwise (1)</b> 338:9 <b>Otten (1)</b> 233:5 <b>ought (3)</b> 211:20;262:8;348:14 <b>ourselves (2)</b> 343:15;348:18 <b>out (126)</b> 9:8;11:12,13,17; 20:14;21:9;23:6;27:15; 29:15;30:6,17;34:17; 37:13;44:11;48:7;53:17; 60:10;63:14;68:17; 69:22;70:2;71:15;85:17; 20:86:2;87:18;92:9; 99:21;100:2;103:3; 105:21;109:21;120:5,6; 123:5,7;124:17;125:19; 126:22;137:10,12; 138:21;139:18;144:7,14, 15;146:13;147:4;148:5, 11;149:2,10,20;150:10, 16;151:18,22;152:10; 153:15,17,19;156:1; 161:2;164:1;165:18,19; 173:1;177:7;186:17; 187:5;190:3;195:6; 197:9;205:5;207:10,14; 209:4;213:14;214:6; 220:2;227:22;229:2,9; 230:4,17;232:22;234:7; 236:2;238:15;240:21; 241:3,14;243:20; 244:11;247:1,11; 249:15;251:2;252:1; 255:5;258:12;259:8; 260:15;268:14;269:19; 272:20;276:15;277:20; 281:5,22;288:19; 289:17;290:7,9,21; 294:2;319:14;328:7; 335:22;336:2;346:20; 347:15;348:7,10;349:1; 350:8 <b>outcome (8)</b> 194:17;208:13;211:8, 16;226:5;340:6,8,12 <b>outcomes (4)</b> 53:3;65:18;215:15; 342:3 <b>outer (1)</b> 292:7 <b>outgrowth (2)</b> 18:15;200:5 <b>outlook (1)</b> 211:12 <b>output (4)</b>	78:6;79:3;84:8;98:22 <b>outside (10)</b> 71:2;95:4;291:9,17, 21;295:5;300:17;302:1, 3,21 <b>outsider (1)</b> 188:21 <b>outweigh (1)</b> 245:6 <b>over (57)</b> 6:7;8:21;12:18,19; 14:6;22:4;33:5,10,12; 35:2,5;36:7;47:16; 51:11;55:14;58:18;66:1; 72:6;82:1;87:3;93:9,16; 107:1,5;116:11;119:11; 129:18;130:16;141:2; 146:11;155:15;183:2; 197:18;203:12;227:10; 230:22;232:3;235:10, 11;248:19;258:5,7; 259:20;260:14,17,20; 261:10,13;263:11; 309:20;317:13;325:7; 329:8;330:8;335:6; 346:16;350:18 <b>overactive (1)</b> 151:14 <b>overall (2)</b> 169:12;270:1 <b>overcome (3)</b> 66:22;110:6;163:10 <b>overestimate (1)</b> 349:19 <b>over-express (1)</b> 36:9 <b>over-expressed (1)</b> 29:8 <b>overlap (5)</b> 97:6;125:19;126:2,9, 12 <b>overnight (1)</b> 158:11 <b>overt (3)</b> 13:12;47:11;71:18 <b>over-the-counters (1)</b> 297:10 <b>overthrow (1)</b> 150:16 <b>overtly (1)</b> 48:16 <b>overview (5)</b> 5:21;191:22;254:19, 21;256:7 <b>own (13)</b> 9:3;15:8;22:5;45:22; 64:16;147:12;165:12; 166:1,7;195:17;229:2; 230:12;259:11 <b>oxcarbazepine (4)</b> 220:11;344:16,20; 345:18 <b>oxide (1)</b>	275:11 <b>oxycodone (2)</b> 258:9,12  <b>P</b>  <b>P2X3 (1)</b> 343:22 <b>PA2 (1)</b> 284:19 <b>Pablo (1)</b> 37:22 <b>PACA (1)</b> 275:11 <b>Pacific (1)</b> 43:7 <b>package (8)</b> 242:8;259:22;268:4; 269:14;317:7;318:10; 320:8,10 <b>PAG (2)</b> 274:9;285:10 <b>paid (1)</b> 195:11 <b>pain (291)</b> 5:5,6,20;6:1,2,3,14,18, 19;15:2;17:4,9,12,22; 18:2,9,16;23:13;24:22; 25:19;30:4,12,15;44:4; 46:22;47:2,3,4,8,19; 48:1,2,3,8,13,14,16,17, 17,18;53:7;55:14;57:4,5, 9,9;60:19;63:22;64:10; 75:7,15;76:2,7,8,8,11, 15;77:9;78:9;79:12,13; 80:1,4;82:20;94:16; 96:12;97:14;98:3,18,21; 103:18;104:2,3;105:2; 107:18;113:13;115:10, 12,13,17;116:6,11; 118:1,5;119:1,3;120:16; 121:16;124:6;126:16; 130:6,9,16;131:15,17, 20;132:4;135:6;137:5; 138:5;142:21;145:8,15, 17;152:12,13;156:3,5,7; 162:19;167:3,10,20; 168:6;170:7,10,12,15; 174:16,17,18;175:14; 176:4,10;177:20;179:2, 9,11,12;180:4,19;181:2, 11;189:3,18;190:1; 193:5;195:21;198:7,10, 12,20;200:11;201:11; 205:17;206:5,12; 207:21;208:9,9;209:3,4; 210:1,1,18;211:1,3,9,12, 18;213:6,11,16;214:19; 215:16,20;216:1,11; 217:10;219:12;220:3; 223:2;226:1;231:20; 233:10;235:13,14,15; 237:4,5,19;240:8,17,18,	20;241:20;242:22; 243:1,3,12,18;244:8,12, 17;245:7,13;247:16; 248:7,13,15;249:1; 250:12,14,15,18;251:5, 20,22;252:2,3,19;254:2, 6,8;255:14,17,17,18,19, 20;256:10,16;257:2,10, 11,22;258:7;263:3,6; 264:15;268:1;269:16; 271:13;272:22;273:1; 274:19;276:13;282:6,8; 283:11,17;300:5;301:8; 302:5,14,16;303:22; 305:11,11;306:3,4,5,6,6, 7,8,9,10,10;312:18; 314:15;324:2,5;325:10, 11;326:14,17,20;327:7; 328:6,18,20,22;329:3,8; 338:6,7,8,9,16;339:1; 340:2,12;342:2,11; 343:9;344:17;345:12; 349:21;352:6;353:1 <b>pain-free (1)</b> 306:3 <b>painful (4)</b> 78:7;154:17;180:17; 257:4 <b>painless (3)</b> 168:2,4;198:15 <b>painlessness (1)</b> 198:17 <b>pain-on-a-chip (1)</b> 17:7 <b>pain-related (2)</b> 49:12;129:20 <b>pains (4)</b> 95:20;176:17;268:2; 271:10 <b>paired (2)</b> 51:8,12 <b>pale (2)</b> 282:20;290:7 <b>pallidotomies (1)</b> 55:13 <b>pancreas (2)</b> 9:11;63:4 <b>pancreatitis (1)</b> 257:18 <b>panel (12)</b> 64:20;169:16,18; 222:10;271:19;293:3; 295:1;326:4;332:2,6,8, 16 <b>paper (39)</b> 7:9;12:12;19:13;20:4; 34:17;38:8;40:16;58:22; 69:22;78:20;81:14,15; 82:10,11;98:4;99:8; 198:13;220:2,4,13,14; 226:1;232:22;233:4,8, 11,14;236:13,14,16; 238:13;248:3,11;310:3;	326:13,15,20;327:3,6 <b>papers (10)</b> 8:21;12:1;17:22; 30:13;35:2;170:21; 189:17;235:2;248:1; 253:10 <b>paradigm (6)</b> 216:8;305:6;313:2; 314:12;315:6;352:4 <b>paradigms (6)</b> 310:18;311:9;316:11; 321:1,7,14 <b>parallel (4)</b> 284:15,22;309:11; 321:13 <b>paralysis (5)</b> 28:3,4;36:5;51:11; 151:7 <b>paralytic (6)</b> 138:17;140:1,17; 141:18;144:4;145:5 <b>paralyse (2)</b> 28:12;155:7 <b>paralyzed (8)</b> 28:11;36:9;37:2; 40:12;50:16;54:3; 144:11,13 <b>parameter (1)</b> 307:16 <b>parameters (2)</b> 210:22;307:9 <b>paraphysiology (2)</b> 304:2,3 <b>parasympathetics (2)</b> 275:10;283:2 <b>parent (1)</b> 12:16 <b>Parke- (1)</b> 197:19 <b>Parkinson's (16)</b> 19:9,12;20:3,10; 21:18;22:7,9;29:4;30:6; 54:20,22;55:7,11;56:4,4; 187:8 <b>paroxysmal (1)</b> 283:6 <b>part (24)</b> 17:13,14;18:5;35:10; 61:1;62:7;86:16,17; 95:19;100:11;144:4; 182:13;238:7;244:18; 275:4;278:10,13,16; 284:10,21;292:7,9; 339:4;342:20 <b>partial (1)</b> 78:16 <b>partially (1)</b> 104:21 <b>participants (1)</b> 322:15 <b>participation (1)</b> 353:11 <b>particles (2)</b>
---	--	--	---	--

89:17;113:20 <b>particular (26)</b> 76:17;95:18;125:14; 126:9;127:3;131:21; 132:17;140:15;146:20; 147:13,22;148:14; 150:14;151:9,17; 152:19;154:18;156:13; 157:7;161:8;163:18; 165:6;193:7;213:21; 254:20;259:4 <b>particularly (10)</b> 33:22;66:1;77:22; 95:20;112:17;137:5; 179:8;197:4;228:2; 293:13 <b>partner (1)</b> 113:8 <b>partnership (2)</b> 14:10;17:1 <b>partnerships (1)</b> 352:2 <b>parts (5)</b> 284:4;285:4;292:12; 293:10,12 <b>pass (3)</b> 285:13;286:13;290:19 <b>passage (2)</b> 34:14;108:8 <b>passages (1)</b> 33:21 <b>passaging (1)</b> 32:13 <b>passing (1)</b> 286:10 <b>past (4)</b> 33:21;330:8;333:11; 351:6 <b>Pat (7)</b> 231:17,18;232:1; 248:7,16;250:8;253:2 <b>patching (1)</b> 90:8 <b>patent (1)</b> 44:17 <b>patents (4)</b> 44:6,9,12;229:17 <b>path (1)</b> 305:22 <b>pathology (3)</b> 30:1;41:17;277:20 <b>pathophysiology (1)</b> 327:15 <b>pathway (8)</b> 30:11;31:16;60:9,11; 277:11;287:3;302:20,21 <b>pathways (8)</b> 18:13,16;23:12;30:4; 31:15;61:14;298:4; 299:14 <b>patient (35)</b> 8:1,1;9:1;10:22;11:1, 20;13:15;20:12;26:7;	41:6;44:22;49:7;50:4; 51:5,6;56:5;59:14;60:2; 74:21;76:11,22;78:8; 91:20;121:10;186:3,12; 211:4;219:14;221:8; 252:18;273:14,17; 281:16;285:3;335:19 <b>patients (162)</b> 9:14,15;10:5,19;11:5; 12:7;19:8;20:2,5,8,20; 21:15;24:5,7,10;26:18; 28:1;31:9,11;36:15; 41:16,21;42:11,22;45:3; 50:13,14;51:14;52:1,12, 19,22;53:9,14;55:7,12; 65:5;73:9,14,15;74:14; 77:6;80:1,6,7;96:3; 115:11;118:20;119:12; 152:18;172:4;173:16; 176:7,11,12;178:12; 179:14;180:18;183:1,4, 11;184:16;185:10,18; 186:7;199:18;206:1,8, 11;207:8,9,11,14;208:5; 209:3;212:11;214:21; 215:5;219:3,7;220:8,10; 221:1,16,19;224:21; 225:1,3,19;226:5,8,12; 228:17;229:10;236:1; 237:2;251:4,9,12,15,18, 19;252:1,16;253:19; 256:10;257:20;259:21; 262:16;263:1,8,8,21; 271:13;274:2,6,18; 277:17,21;281:14;282:4, 6,7;283:4,14;285:18; 297:15,22;298:1,6,7; 302:14;305:10;306:2,8; 308:1;312:2;313:10,12, 22;314:4;316:1;317:12; 318:18;321:9,17; 322:16;323:19;324:1; 329:21;335:13,18;336:3, 3,4,20;340:7;344:16; 345:3,7,19;346:1 <b>patient's (1)</b> 55:4 <b>patients' (4)</b> 9:22;10:7;15:8;339:6 <b>Patrick (2)</b> 34:19;241:6 <b>pattern (5)</b> 146:6;271:22;307:20; 311:12;341:7 <b>patterns (1)</b> 146:8 <b>Pause (2)</b> 169:15;323:2 <b>paw (10)</b> 47:15;48:9;91:4; 116:10,14;121:17,21; 131:1;248:2,10 <b>pay (1)</b>	318:3 <b>paying (2)</b> 174:12;280:5 <b>pays (1)</b> 155:16 <b>PBS (1)</b> 118:15 <b>PC12 (1)</b> 127:18 <b>peak (1)</b> 140:20 <b>Peart (1)</b> 196:4 <b>pedantic (1)</b> 134:19 <b>penetrant (1)</b> 215:10 <b>penetrate (7)</b> 18:18;19:16;172:19; 175:5;215:13;303:4; 318:4 <b>pentamers (1)</b> 153:8 <b>people (75)</b> 4:20;26:9,13;28:14, 15;63:7;68:17;80:9; 88:7,17;92:8;103:2,22; 115:6;132:15,16,18; 135:22;138:12,15; 164:8;165:3,3;167:14; 174:10;177:22;178:14; 184:9;185:7;187:18; 190:8;191:8,14,16; 192:4,8;193:12;194:8; 195:7;204:14,15; 206:17;212:3;213:20, 21;223:15;228:9;229:7; 234:15,20;240:11; 257:13;259:8,10;260:3; 264:1;272:11,21; 277:13;281:2;285:16; 288:10;297:2,8;310:20; 316:4;324:21;327:7; 328:14;333:9,10,18; 348:5,12,15 <b>peptide (39)</b> 140:18,19;141:6; 142:7,8,10,16,19;143:4; 144:4,5,12;145:4,13,21; 146:4;151:21;152:4,6, 14,16,22;156:2,6,10; 160:17,20,21;161:4,8,9; 162:11,13;164:18;185:2, 6;276:3;282:2;299:1 <b>peptidergic (1)</b> 124:7 <b>peptides (28)</b> 117:7;139:8,18,21,22; 141:19,20;142:2;150:13, 14;151:16;153:1,5,20; 154:2,5,7,11;155:9; 157:14;160:9,11,15; 162:2,3,6;170:18;281:17	<b>per (8)</b> 46:6;73:4;207:5; 219:14;297:2;318:19; 320:11,11 <b>per-arm (2)</b> 257:5,6 <b>perceived (5)</b> 232:16;301:8,9,10; 302:5 <b>perceiving (1)</b> 145:17 <b>percent (53)</b> 28:1,3,15,16;29:6,7, 14;36:15,16;55:11;72:3; 78:21;84:16;92:19;97:9; 102:9,12;115:7,11,12; 126:10;138:13;139:5; 160:18;176:10,11,16; 177:9;208:8;209:3,4,5,6, 9,10,13,13;293:17; 298:11;306:8;308:2,3,3; 310:21;317:12;318:16; 322:15,16;337:10,12; 342:21;344:1;349:20 <b>percentage (2)</b> 102:4;209:2 <b>per-country (1)</b> 212:8 <b>perfect (2)</b> 194:1;353:10 <b>perfectly (4)</b> 96:21;140:22;228:1,2 <b>performed (1)</b> 201:7 <b>perfuse (1)</b> 291:1 <b>perfusion (1)</b> 248:21 <b>perhaps (12)</b> 5:4;15:3;17:21;86:18; 186:15;195:6;208:3; 270:18;272:20;281:11; 283:10;285:22 <b>period (11)</b> 33:10;116:11;129:18; 130:16;203:12;205:9; 210:14;212:22;271:2; 334:8;339:10 <b>periods (3)</b> 33:5;35:5;93:8 <b>peripheral (13)</b> 76:9;78:15;84:10; 91:17;124:1;164:16; 200:22;220:8;267:19; 303:14;326:22;344:17, 20 <b>peripherally (3)</b> 71:15;215:13;219:5 <b>periphery (2)</b> 91:13;145:11 <b>perivascular (1)</b> 291:11 <b>permanently (1)</b>	34:22 <b>permission (1)</b> 53:13 <b>person (6)</b> 92:21,22;100:22; 132:22;133:2;231:16 <b>personal (7)</b> 174:1,7,10;211:14; 219:22;230:12;352:21 <b>personalized (3)</b> 9:4;10:3;11:3 <b>personally (3)</b> 84:11;250:4;268:13 <b>perspective (16)</b> 95:15;97:2;180:15; 191:22;194:16;215:1; 229:5,9;235:6;242:11; 259:20;262:17;265:15; 296:12;308:13;316:16 <b>persuaded (1)</b> 140:8 <b>persuasive (2)</b> 259:16;263:7 <b>pessimism (1)</b> 214:17 <b>PET (7)</b> 20:4;274:5;285:20; 286:5,5,7;307:1 <b>Peter (5)</b> 274:20;281:4,7; 326:14,18 <b>petri (1)</b> 8:4 <b>Pfizer (4)</b> 219:19;229:12;232:7; 264:1 <b>PGK (1)</b> 35:4 <b>pH (1)</b> 217:1 <b>pharmaceutical (1)</b> 193:3 <b>Pharmaceuticals (3)</b> 13:16,17;296:2 <b>pharmacological (7)</b> 80:5;141:19;159:13; 169:2;170:22;196:10; 342:4 <b>pharmacologically (1)</b> 169:1 <b>pharmacology (5)</b> 148:4;156:20;158:18; 284:21;305:17 <b>phase (73)</b> 34:3;43:2;52:13; 197:8;204:12;205:7,16; 208:19;212:16,17,20; 213:5,18;215:7;219:10; 220:18;224:2,3,3,11; 234:13,13;235:3;236:8, 9,9,11;250:20,22;251:2, 4,11,15;252:12,22; 253:14;255:11;262:22;
--	--	---	--	--

263:4;278:10;304:21; 21:305:1,2,13;307:4; 308:10;316:8,9;317:5; 318:11,14;320:4,6,7,7, 13,18;321:9;322:5,6,13, 14;324:12,16;330:22; 335:22;336:2;342:22; 343:17;344:19;351:17, 18	144:2 <b>pick (4)</b> 75:17;150:1;189:1; 346:11 <b>picked (3)</b> 129:7;170:8;352:10 <b>picking (2)</b> 171:9;217:4 <b>pick-up (1)</b> 352:13 <b>picomole (1)</b> 287:19 <b>picture (7)</b> 6:10;7:2;96:1;248:9, 15;281:4;298:15 <b>pictures (1)</b> 59:4 <b>piece (3)</b> 133:16;196:2;236:6 <b>pig (6)</b> 43:13;49:5,6,15; 72:21;73:1 <b>pigmentosa (2)</b> 54:8;174:4 <b>pigs (2)</b> 49:3;323:15 <b>pill (2)</b> 50:3;56:5 <b>piloting (1)</b> 225:3 <b>pinball (4)</b> 62:1,3,7,12 <b>pinch (1)</b> 48:9 <b>pineal (1)</b> 290:7 <b>pinnacle (1)</b> 6:9 <b>pinpricked (1)</b> 345:8 <b>pipe (2)</b> 21:5;234:6 <b>Pittsburgh (2)</b> 98:6;112:14 <b>pivotal (2)</b> 303:1,16 <b>pivotals (1)</b> 307:3 <b>PKC (1)</b> 127:2 <b>PL (1)</b> 277:1 <b>place (8)</b> 38:3;143:5;155:15; 180:11;290:15;292:2; 318:10;353:1 <b>placebo (26)</b> 207:9,11;208:15,17; 209:17;210:7,22;211:7; 212:1,6;214:21;223:6, 10;226:12;254:4,10; 258:13;307:6,18;317:15, 16;318:16;320:21;	322:16;324:3;328:2 <b>placebo-controlled (2)</b> 212:21;318:15 <b>placebo-like (1)</b> 307:16 <b>placebo-treated (1)</b> 204:14 <b>places (1)</b> 289:22 <b>placing (1)</b> 211:20 <b>plan (2)</b> 42:15;295:3 <b>planning (3)</b> 73:7;212:20;295:4 <b>plans (1)</b> 212:17 <b>plant (1)</b> 34:1 <b>plaque (1)</b> 128:10 <b>plaques (3)</b> 128:5,11;129:6 <b>plasma (1)</b> 226:7 <b>plastic (3)</b> 26:17;107:6,8 <b>plasticity (2)</b> 25:18;54:16 <b>platform (4)</b> 54:6;114:17;296:4; 317:2 <b>plausible (2)</b> 96:9,21 <b>play (3)</b> 7:18;12:18;278:4 <b>player (1)</b> 27:1 <b>plays (1)</b> 163:12 <b>please (1)</b> 136:10 <b>pleased (1)</b> 113:4 <b>pleasure (6)</b> 4:5;75:4;112:2;137:6; 272:10;295:8 <b>plenty (1)</b> 185:10 <b>plexus (1)</b> 199:19 <b>plotting (1)</b> 92:16 <b>plug (2)</b> 85:3,7 <b>plummets (1)</b> 92:19 <b>pluripotent (17)</b> 4:9;8:11,22;9:2,7; 13:1;22:11,17;26:2; 59:6;61:13;62:8,11,22; 63:3,10,19 <b>plus (7)</b>	118:12;119:5;238:18; 255:11;256:1;324:19; 328:21 <b>pluses (2)</b> 255:21,22 <b>pm (3)</b> 190:11;191:2;353:18 <b>PNAS (1)</b> 81:15 <b>PNS (1)</b> 59:13 <b>pod (1)</b> 134:4 <b>point (45)</b> 13:21;50:1;53:16; 67:18;78:14;85:17; 94:10;105:21;108:16; 135:14;159:3,5,7; 163:20;178:7,9,16,19; 180:18;185:12;195:5; 197:9;199:10;202:13; 210:12;222:5;225:15, 20;254:22;258:3,12; 261:15;263:3;264:13; 265:21;267:3;268:8; 323:17;325:3,4;337:10; 343:14;346:12;351:6; 352:13 <b>pointed (1)</b> 180:17 <b>points (8)</b> 107:17;182:15; 245:18,21;265:10; 291:1;295:20;309:1 <b>P-Oka (1)</b> 115:22 <b>pOka-infected (2)</b> 118:14;119:5 <b>polychaetes (1)</b> 155:3 <b>polyneuropathies (3)</b> 104:22;105:5;107:13 <b>polyneuropathy (2)</b> 202:2;340:11 <b>pool (1)</b> 319:16 <b>pooled (1)</b> 258:4 <b>poor (4)</b> 24:12;179:16;290:8; 343:4 <b>poorly (1)</b> 269:22 <b>popped (1)</b> 107:21 <b>populate (1)</b> 82:7 <b>population (17)</b> 33:17;41:7;98:10; 106:17;124:13;159:3; 207:17,19;225:9,10; 244:18;298:11;310:22; 336:12;337:6,8,10	<b>populations (1)</b> 91:6 <b>poreless (4)</b> 128:17;129:4,12; 130:7 <b>PORRECA (21)</b> 4:3;66:14;74:22; 104:16;110:21;133:7; 169:17;173:13;177:8; 178:22;180:13;182:17; 183:16,18,20;185:8; 190:7;216:4;217:13; 218:11,15 <b>portion (1)</b> 127:17 <b>position (3)</b> 222:17;232:8;342:16 <b>positive (37)</b> 39:22;69:16;89:9; 97:7,10;106:19;125:15, 20;128:16;211:12; 214:18;215:17;227:15; 245:15,18,19,20;249:5, 8;250:13;252:7,21; 253:16;256:9,18,20; 257:15,16;267:7;322:5; 336:16,18,19;343:16,20; 344:21;345:1 <b>positives (1)</b> 20:11 <b>possibility (2)</b> 168:15;327:12 <b>possible (8)</b> 25:22;55:14;64:22; 84:20;132:7;164:16; 179:17;292:16 <b>post (1)</b> 90:4 <b>post-central (1)</b> 181:2 <b>poster (1)</b> 222:17 <b>post-herpetic (10)</b> 114:22;115:2;135:4,8; 170:9;205:8,10,16; 211:2;257:6 <b>postmitotic (1)</b> 84:3 <b>post-op (2)</b> 270:4,5 <b>post-synaptic (5)</b> 88:4;89:12;138:18; 143:21;179:7 <b>post-translationally (1)</b> 139:10 <b>post-transplant (1)</b> 101:8 <b>postural (1)</b> 164:15 <b>posture (1)</b> 76:16 <b>potassium (18)</b> 157:22;158:2,16;
---	---	---	---	--

159:8,13,14,17,19,22; 160:3;162:16;163:6,10, 12,16,18,21;164:1	10;338:5;340:5,17; 341:2,7,12,20;342:2,14; 346:11,14,18;347:12,15, 19,21;348:1,4,18; 351:17;352:16	329:22;331:15	<b>prey (2)</b> 150:20;154:18	20;183:15;184:14; 189:13;224:5;244:3,8; 262:9;311:17;342:12
<b>potassium-channel (2)</b> 82:13,14	<b>pre-competitive (1)</b> 352:8	<b>present (13)</b> 146:2;160:4;162:17, 22;166:15;219:6; 231:12,14;238:16; 262:21;279:11;296:12; 320:9	<b>Prialt (7)</b> 142:21;143:3;153:22; 164:13;183:22;184:5; 185:8	<b>problematic (2)</b> 168:19;170:13
<b>potent (8)</b> 129:8;279:22;299:2; 300:2;303:9;308:7; 323:6;330:9	<b>preconditioning (1)</b> 235:20	<b>Presentation (23)</b> 5:8;75:8;112:21; 137:7,14;195:1,9;219:1; 223:14;226:19,22; 227:20;228:8;230:15, 19;242:14;245:4;247:8; 272:16;293:2;295:1,16; 338:14	<b>Prialt-resistance (1)</b> 145:1	<b>problems (11)</b> 7:7;10:17,18;57:18; 72:21;152:15;170:16; 224:19;225:18;311:15, 17
<b>potential (12)</b> 120:11;143:9,22; 173:21;178:15;181:12; 184:10;195:21;204:21; 267:1;272:14;324:10	<b>precursors (1)</b> 196:8	<b>presented (7)</b> 105:2;191:10;351:15	<b>primarily (1)</b> 166:22	<b>proboscis (4)</b> 146:20;147:3;149:11; 165:19
<b>potentially (8)</b> 137:5;152:12;176:19; 183:7,10;196:17; 264:22;334:10	<b>predator (2)</b> 216:9,11	<b>presentations (3)</b> 4:7;111:2;169:22; 265:5;287:9;296:10; 346:18	<b>primary (23)</b> 87:2,11;88:19;117:16; 118:7;135:17;166:11; 179:6;208:9,13;211:10; 225:4;244:8,9,11;262:6, 11;300:19,20;302:9; 305:18;306:1;307:6	<b>procedure (5)</b> 43:9;92:10;178:5,13; 248:14
<b>potentials (3)</b> 79:3;138:21;144:18	<b>predict (2)</b> 74:15;346:14	<b>preserved (1)</b> 325:8	<b>primate (1)</b> 56:17	<b>procedures (1)</b> 193:13
<b>pouring (1)</b> 103:9	<b>predictable (1)</b> 100:10	<b>press (3)</b> 212:19;226:1;343:19	<b>primates (1)</b> 287:18	<b>proceed (2)</b> 240:11;255:7
<b>power (4)</b> 26:3;51:9,13;88:2	<b>predicted (2)</b> 328:10;346:2	<b>pressing (3)</b> 5:2;222:16;227:5	<b>prime (1)</b> 294:5	<b>proceeded (1)</b> 245:8
<b>powerful (4)</b> 26:4;64:2;145:15; 249:3	<b>predicting (3)</b> 268:16;349:4,5	<b>presents (1)</b> 262:14	<b>principal (1)</b> 115:16	<b>process (14)</b> 42:19;45:7;47:9; 49:13,18;58:2;114:1; 130:22;148:16;194:17; 244:7;264:10;296:1; 300:14
<b>PP1-alpha (8)</b> 129:3,12;130:7,15,21; 131:3;132:8,11	<b>prediction (2)</b> 327:5;345:6	<b>preserve (2)</b> 319:20;323:1	<b>principles (1)</b> 138:9	<b>process-comparable (1)</b> 43:20
<b>practical (2)</b> 164:12;251:21	<b>predictive (1)</b> 265:17	<b>presumably (3)</b> 5:19;136:3;276:5	<b>prior (1)</b> 217:3	<b>processed (1)</b> 117:6
<b>practicalities (1)</b> 241:22	<b>predigest (1)</b> 147:18	<b>pressures (1)</b> 250:18	<b>priori (1)</b> 331:3	<b>processes (4)</b> 85:20;86:3;314:17; 338:7
<b>practice (4)</b> 180:21;181:21;182:5; 350:8	<b>predisposed (1)</b> 302:16	<b>presume (1)</b> 105:9	<b>private (1)</b> 352:7	<b>prodromal (1)</b> 118:20
<b>practicing (1)</b> 138:10	<b>predominantly (1)</b> 340:11	<b>pre-synaptic (3)</b> 88:20,21;89:18	<b>Prize (1)</b> 7:16	<b>produce (7)</b> 35:3;46:1;117:13,22; 182:22;267:8;278:20
<b>Praveen (2)</b> 199:7,15	<b>predominates (1)</b> 279:12	<b>pretreated (2)</b> 328:2,3	<b>probable (1)</b> 349:3	<b>produced (5)</b> 76:8;92:13;176:22; 209:15;246:9
<b>pre- (7)</b> 52:7;202:19;213:15; 240:7;333:17;343:2; 347:4	<b>preempt (1)</b> 118:19	<b>pretty (28)</b> 37:22;38:6;39:8;65:8; 73:7;77:3;85:21;96:5; 108:2;111:21;119:7; 120:6;124:16;125:19; 126:9;138:2;144:17; 148:21;168:10,19; 171:5;186:10;209:12; 223:9;251:10;265:13; 266:21;270:14	<b>probably (49)</b> 7:20;23:10;24:19; 26:21;28:2;35:2;49:17; 53:15;56:18;60:8;61:4; 63:17;64:12;76:12; 83:14;120:8;132:13; 135:5;142:1;167:14; 178:17;179:21;181:1; 187:16;192:10;200:14; 211:2,15;217:19; 219:13;221:15;225:13; 226:15;228:8,11,14; 232:7;251:21;253:16; 257:10;271:9;272:7; 286:22;290:3;334:2; 338:3;341:15;342:15; 346:5	<b>produces (3)</b> 248:5;261:21;267:5
<b>preceded (1)</b> 299:10	<b>preempted (1)</b> 326:8	<b>presumably (3)</b> 5:19;136:3;276:5	<b>problem (32)</b> 11:10;22:4,21;23:7; 36:21;40:7;41:12;76:5; 77:2,4;80:13,13;82:20; 84:12;115:10;121:3; 153:14;162:18;170:6; 171:8;172:16;173:10,	<b>producing (5)</b> 16:15;69:13,14;218:3; 286:14
<b>pre-clinical (77)</b> 25:21;43:18;45:1; 193:20;194:14;195:13, 16;197:14;200:18; 201:6;204:7;205:3,4,6; 213:12;214:4;215:19; 216:13;222:15,20; 223:16,20;224:5,12,13; 228:22;229:8;230:6; 231:11,12;236:12;242:5, 7,18,21;243:5;245:11; 247:18;249:4;250:6,10, 17;254:17;259:19; 260:15;262:15;263:15; 268:9,18;269:14,20; 323:15;332:12,20;333:8,	<b>prefer (1)</b> 297:19	<b>pre- (7)</b> 52:7;202:19;213:15; 240:7;333:17;343:2; 347:4	<b>probes (1)</b> 177:2	<b>production (5)</b> 11:16;43:17;44:20; 45:20;329:13
<b>pre- (7)</b> 52:7;202:19;213:15; 240:7;333:17;343:2; 347:4	<b>preferentially (1)</b> 261:9	<b>preempted (1)</b> 326:8	<b>problem (32)</b> 11:10;22:4,21;23:7; 36:21;40:7;41:12;76:5; 77:2,4;80:13,13;82:20; 84:12;115:10;121:3; 153:14;162:18;170:6; 171:8;172:16;173:10,	<b>products (7)</b> 114:19;117:21;137:3; 146:10;230:14;268:16; 326:4
<b>preceded (1)</b> 299:10	<b>pregabalin (7)</b> 208:5;210:11;226:2,7, 9,10,13	<b>preempted (1)</b> 326:8	<b>previously (2)</b> 160:10;248:8	<b>professional (3)</b> 224:21,21;225:19
<b>pre-clinical (77)</b> 25:21;43:18;45:1; 193:20;194:14;195:13, 16;197:14;200:18; 201:6;204:7;205:3,4,6; 213:12;214:4;215:19; 216:13;222:15,20; 223:16,20;224:5,12,13; 228:22;229:8;230:6; 231:11,12;236:12;242:5, 7,18,21;243:5;245:11; 247:18;249:4;250:6,10, 17;254:17;259:19; 260:15;262:15;263:15; 268:9,18;269:14,20; 323:15;332:12,20;333:8,	<b>preliminary (2)</b> 21:1;352:11	<b>preempted (1)</b> 326:8		
<b>pre-clinical (77)</b> 25:21;43:18;45:1; 193:20;194:14;195:13, 16;197:14;200:18; 201:6;204:7;205:3,4,6; 213:12;214:4;215:19; 216:13;222:15,20; 223:16,20;224:5,12,13; 228:22;229:8;230:6; 231:11,12;236:12;242:5, 7,18,21;243:5;245:11; 247:18;249:4;250:6,10, 17;254:17;259:19; 260:15;262:15;263:15; 268:9,18;269:14,20; 323:15;332:12,20;333:8,	<b>premise (1)</b> 341:10	<b>preempted (1)</b> 326:8		
<b>pre-clinical (77)</b> 25:21;43:18;45:1; 193:20;194:14;195:13, 16;197:14;200:18; 201:6;204:7;205:3,4,6; 213:12;214:4;215:19; 216:13;222:15,20; 223:16,20;224:5,12,13; 228:22;229:8;230:6; 231:11,12;236:12;242:5, 7,18,21;243:5;245:11; 247:18;249:4;250:6,10, 17;254:17;259:19; 260:15;262:15;263:15; 268:9,18;269:14,20; 323:15;332:12,20;333:8,	<b>preparation (1)</b> 233:16	<b>preempted (1)</b> 326:8		
<b>pre-clinical (77)</b> 25:21;43:18;45:1; 193:20;194:14;195:13, 16;197:14;200:18; 201:6;204:7;205:3,4,6; 213:12;214:4;215:19; 216:13;222:15,20; 223:16,20;224:5,12,13; 228:22;229:8;230:6; 231:11,12;236:12;242:5, 7,18,21;243:5;245:11; 247:18;249:4;250:6,10, 17;254:17;259:19; 260:15;262:15;263:15; 268:9,18;269:14,20; 323:15;332:12,20;333:8,	<b>prepared (1)</b> 206:17	<b>preempted (1)</b> 326:8		
<b>pre-clinical (77)</b> 25:21;43:18;45:1; 193:20;194:14;195:13, 16;197:14;200:18; 201:6;204:7;205:3,4,6; 213:12;214:4;215:19; 216:13;222:15,20; 223:16,20;224:5,12,13; 228:22;229:8;230:6; 231:11,12;236:12;242:5, 7,18,21;243:5;245:11; 247:18;249:4;250:6,10, 17;254:17;259:19; 260:15;262:15;263:15; 268:9,18;269:14,20; 323:15;332:12,20;333:8,	<b>preplanned (1)</b> 212:9	<b>preempted (1)</b> 326:8		
<b>pre-clinical (77)</b> 25:21;43:18;45:1; 193:20;194:14;195:13, 16;197:14;200:18; 201:6;204:7;205:3,4,6; 213:12;214:4;215:19; 216:13;222:15,20; 223:16,20;224:5,12,13; 228:22;229:8;230:6; 231:11,12;236:12;242:5, 7,18,21;243:5;245:11; 247:18;249:4;250:6,10, 17;254:17;259:19; 260:15;262:15;263:15; 268:9,18;269:14,20; 323:15;332:12,20;333:8,	<b>preponderance (1)</b> 207:19	<b>preempted (1)</b> 326:8		
<b>pre-clinical (77)</b> 25:21;43:18;45:1; 193:20;194:14;195:13, 16;197:14;200:18; 201:6;204:7;205:3,4,6; 213:12;214:4;215:19; 216:13;222:15,20; 223:16,20;224:5,12,13; 228:22;229:8;230:6; 231:11,12;236:12;242:5, 7,18,21;243:5;245:11; 247:18;249:4;250:6,10, 17;254:17;259:19; 260:15;262:15;263:15; 268:9,18;269:14,20; 323:15;332:12,20;333:8,	<b>pre-pro (1)</b> 124:19	<b>preempted (1)</b> 326:8		
<b>pre-clinical (77)</b> 25:21;43:18;45:1; 193:20;194:14;195:13, 16;197:14;200:18; 201:6;204:7;205:3,4,6; 213:12;214:4;215:19; 216:13;222:15,20; 223:16,20;224:5,12,13; 228:22;229:8;230:6; 231:11,12;236:12;242:5, 7,18,21;243:5;245:11; 247:18;249:4;250:6,10, 17;254:17;259:19; 260:15;262:15;263:15; 268:9,18;269:14,20; 323:15;332:12,20;333:8,	<b>preproenkephalin (2)</b> 117:3,6	<b>preempted (1)</b> 326:8		
<b>pre-clinical (77)</b> 25:21;43:18;45:1; 193:20;194:14;195:13, 16;197:14;200:18; 201:6;204:7;205:3,4,6; 213:12;214:4;215:19; 216:13;222:15,20; 223:16,20;224:5,12,13; 228:22;229:8;230:6; 231:11,12;236:12;242:5, 7,18,21;243:5;245:11; 247:18;249:4;250:6,10, 17;254:17;259:19; 260:15;262:15;263:15; 268:9,18;269:14,20; 323:15;332:12,20;333:8,	<b>presence (2)</b>	<b>preempted (1)</b> 326:8		

<b>professor (5)</b> 112:6;137:1,1;154:1; 272:8	35:4;119:14;124:11; 125:7,8,12,18,22,22; 126:4,8,11;133:22	<b>proved (1)</b> 181:21	109:6,11	<b>puzzled (2)</b> 293:7,7
<b>profile (14)</b> 40:16;89:7;168:18; 184:8;187:6;207:12; 220:12;230:6;247:18; 263:20;266:18;268:9, 18;340:7	<b>promoters (5)</b> 124:9;125:4,10; 133:10,15	<b>proven (2)</b> 65:13;312:5	<b>pumps (2)</b> 177:3;181:16	<b>puzzles (1)</b> 180:4
<b>profiles (2)</b> 187:1;215:3	<b>promoting (1)</b> 234:8	<b>proves (1)</b> 314:3	<b>pun (1)</b> 60:20	
<b>profiling (3)</b> 219:12,20;220:10	<b>pronunciation (1)</b> 261:16	<b>provided (1)</b> 232:9	<b>pure (1)</b> 328:18	<b>Q</b>
<b>profound (3)</b> 236:22;248:5;250:15	<b>proof (2)</b> 253:17;305:16	<b>provides (1)</b> 78:5	<b>purely (1)</b> 230:12	<b>Q&amp;A (3)</b> 169:16;315:11;332:6
<b>progenitor (4)</b> 58:7,10;72:10;80:15	<b>proof-of-concept (2)</b> 213:5;253:18	<b>providing (4)</b> 16:22;94:13;246:5,9	<b>purified (1)</b> 142:19	<b>Q2s (1)</b> 312:17
<b>progenitors (14)</b> 22:17;33:9;54:19; 59:1,2,3,4,5,19;80:17; 81:20;84:3;86:7;233:9	<b>propensity (1)</b> 82:15	<b>provocation (1)</b> 240:8	<b>purify (3)</b> 116:4;142:8,15	<b>QST (5)</b> 219:12,20;220:9; 330:20;331:19
<b>program (29)</b> 4:16;6:8;195:4,8; 199:16;203:14;205:3,6; 213:22;223:16;232:1,2, 5,8;236:10;241:1,20; 242:21;243:5;245:7; 250:4,8;255:9;259:5,9; 269:2;312:9;322:6; 343:21	<b>properly (2)</b> 271:9;310:16	<b>provocative (4)</b> 177:16;178:21;235:7; 333:1	<b>purpose (5)</b> 150:15;155:17;230:4, 15;319:7	<b>qualifications (1)</b> 347:8
<b>programs (6)</b> 192:20;205:4;224:1,6; 229:13;258:18	<b>properties (3)</b> 82:3,3;102:2	<b>provokes (1)</b> 237:4	<b>purposes (3)</b> 146:12,15;261:17	<b>qualifies (1)</b> 11:15
<b>progress (1)</b> 239:4	<b>prophylaxis (6)</b> 298:9,10;305:8; 312:16;313:9;316:3	<b>psychiatrist (1)</b> 80:21	<b>pursue (1)</b> 241:2	<b>qualify (1)</b> 273:8
<b>progresses (1)</b> 241:17	<b>proponent (1)</b> 352:2	<b>psychiatry (1)</b> 154:1	<b>pursued (1)</b> 203:14	<b>qualities (1)</b> 311:20
<b>progressing (1)</b> 240:15	<b>proportion (1)</b> 306:2	<b>psychic (2)</b> 95:4,8	<b>push (4)</b> 33:21;184:15;186:4; 213:3	<b>quality (4)</b> 11:14,14;314:19; 349:10
<b>progression (1)</b> 328:14	<b>proposal (1)</b> 175:22	<b>public (2)</b> 315:17;352:8	<b>push- (1)</b> 235:21	<b>quality-controlled (1)</b> 108:21
<b>progressor (2)</b> 50:18,20	<b>propose (1)</b> 327:13	<b>public/private (1)</b> 352:2	<b>pushed (3)</b> 12:9;33:1;186:9	<b>quantitative (2)</b> 331:7;345:5
<b>pro-inflammatory (1)</b> 157:6	<b>proposed (2)</b> 171:15;350:20	<b>publication (4)</b> 204:1;341:14,18; 348:21	<b>pushing (2)</b> 135:4;353:5	<b>quarter-million (1)</b> 46:5
<b>project (2)</b> 19:6;66:6	<b>proposing (1)</b> 206:18	<b>publications (3)</b> 133:14;342:5,7	<b>put (85)</b> 8:3,8;9:8;10:21;14:18, 19,20;16:1,7,17;19:6,12; 21:6,8;35:9;37:7;38:9; 40:22;46:5,16;50:9; 52:5,14;53:5;54:11; 55:2;57:6,7;64:16,19; 68:8;70:10,13,17;71:13; 72:3,4,12,17;75:12; 77:12;80:1;82:6;84:7; 86:2;90:13;93:1;133:20, 21;140:20;158:13; 165:15;173:1;174:21; 175:1,4,4;185:4;187:19; 188:1;189:7;192:7; 212:19;217:7;218:7,19; 222:16;246:12;248:20; 255:1;258:18;273:7; 274:5;289:17;291:3,9, 11,13,14,17,18,21; 332:10;347:13;353:4	<b>quarters (1)</b> 32:17
<b>projection (1)</b> 33:18	<b>proprioception (1)</b> 123:21	<b>publish (3)</b> 25:3;40:22;201:12	<b>putting (13)</b> 5:20;31:8;45:15; 51:22;64:6;69:12;70:21; 172:22;173:2;174:19; 177:2,3;178:8	<b>Queensland (2)</b> 200:16;214:2
<b>projects (1)</b> 42:8	<b>pros (2)</b> 64:19;317:2	<b>published (24)</b> 7:9;58:5,22;77:17; 86:17;92:15;120:12; 121:5;206:15;209:11,20, 21;213:15;219:18; 238:14;253:14,20; 275:20;310:4;324:22; 341:16;345:14;347:1; 348:20	<b>quiet (2)</b> 150:19;151:13	<b>questionnaire (2)</b> 330:19;331:2
<b>proliferation (1)</b> 200:7	<b>prospective (1)</b> 182:10	<b>publishing (1)</b> 200:18	<b>quip (1)</b> 333:5	<b>quick (4)</b> 166:10;222:12; 254:19;256:7
<b>prolonged (1)</b> 252:14	<b>prostatitis (2)</b> 257:17;264:6	<b>pufferfish (1)</b> 139:4	<b>quiescent (1)</b> 151:12	<b>quickly (7)</b> 86:16;148:12;165:22; 277:5;282:1;352:1,14
<b>promise (4)</b> 5:4;170:1;182:13; 326:6	<b>proteases (1)</b> 185:4	<b>pull (1)</b> 16:8	<b>quiet (2)</b> 150:19;151:13	<b>quites (25)</b> 27:21;32:14;45:18; 52:2;53:9;57:19;65:14; 77:10;136:13;137:20; 153:17;177:6;178:14; 183:22;199:10;200:18; 204:8,11;210:12; 211:19;215:4;216:14; 329:21;350:8;352:3
<b>promising (3)</b> 193:22;194:3;308:14	<b>protect (3)</b> 31:10;35:13;66:18	<b>pulled (2)</b> 238:15;277:20	<b>quote (4)</b> 235:2;236:1;243:10, 11	<b>quotes (1)</b> 236:2
<b>promoted (1)</b> 70:5	<b>protection (5)</b> 25:18;41:14;59:20; 67:11;68:14	<b>pulling (2)</b> 14:3;272:3		
<b>promoter (13)</b>	<b>protects (1)</b> 19:11	<b>pulse (2)</b> 159:14;162:5		
	<b>protein (7)</b> 8:9;21:20;91:8,9; 124:18;278:19,20	<b>pump (7)</b> 86:21;109:22;172:16, 17,22;177:11;183:6		
	<b>proteins (1)</b> 116:22	<b>pump-like (2)</b> 94:13;108:15		
	<b>protocol (7)</b> 159:12;201:15; 206:21,22;307:3,3; 345:13	<b>pump-only (2)</b>		
	<b>prove (2)</b> 167:6;313:20			

<b>R</b>	<p><b>rates (3)</b> 50:12;210:4;306:13</p> <p><b>rather (21)</b> 46:12;50:3;55:9; 56:21;66:7;103:9;114:3; 120:7;121:7;131:15; 141:18;173:9;200:3; 205:8;221:4;247:12; 253:17;267:9;338:16; 340:3;350:17</p> <p><b>rating (1)</b> 206:11</p> <p><b>rational (1)</b> 229:19</p> <p><b>rational (1)</b> 213:12</p> <p><b>rational (1)</b> 225:14</p> <p><b>rats (12)</b> 36:8;38:18;67:3;68:7; 73:3;116:1;198:4; 236:17,19;237:11; 245:21;327:21</p> <p><b>reach (1)</b> 211:6</p> <p><b>reached (3)</b> 151:20;152:2;153:1</p> <p><b>reaches (1)</b> 143:12</p> <p><b>react (2)</b> 167:17;259:10</p> <p><b>reaction (1)</b> 324:10</p> <p><b>reactivate (5)</b> 12:21;113:16,17; 114:11,18</p> <p><b>reactivated (1)</b> 23:22</p> <p><b>reactivates (1)</b> 115:8</p> <p><b>reactivation (1)</b> 135:13</p> <p><b>reactor (1)</b> 287:12</p> <p><b>read (4)</b> 253:4,10;255:5; 304:20</p> <p><b>readily (1)</b> 97:1</p> <p><b>readjusting (1)</b> 106:5</p> <p><b>readout (5)</b> 262:1,1,11;263:5,7</p> <p><b>ready (3)</b> 11:7;239:14;240:5</p> <p><b>real (17)</b> 8:19;16:13;19:14; 29:10;41:12;102:13; 148:11;176:13,21; 240:12,14;243:16,20; 263:8;269:9;310:21; 335:19</p> <p><b>realized (1)</b> 299:12</p> <p><b>real-life (1)</b> 182:14</p> <p><b>really (139)</b> 5:3;6:8;7:13,18;8:16; 9:20;10:2;11:18;13:19; 14:8,15;15:19;16:11; 17:4,11;19:17;22:6,22; 26:1,14;27:16,19;30:18; 33:8;35:18,21;38:8; 39:19;50:5;51:21;52:7; 54:20;62:5;63:13;65:2, 22;66:4;67:16;80:10; 83:16;86:4,18;87:13; 89:15;90:1;99:20;107:8; 109:9;110:18;112:15; 113:3;130:3;131:12; 133:19;136:1;137:6; 139:14;149:12;152:5, 10;153:10;154:15,17; 155:16;156:20;157:19; 158:3;163:21;168:20; 175:17;178:14;180:5,17, 18;181:18;182:10,15; 183:15;191:12,17;195:5, 19;197:5;201:16,16; 204:10;205:5;211:13, 22;213:2,17;214:20; 217:15;218:21;221:7, 17;223:3;224:13; 228:19;230:5;233:7; 243:12,19;244:2,11; 246:14,17;247:3; 251:12;260:3;261:1,19; 263:13;265:6,8;266:19; 268:9;269:12;288:8; 293:20;295:6;307:15; 308:16;311:4;335:14; 336:20;337:6,21;338:3, 19,21,22;340:13;347:3, 6,18;348:19;352:3,17</p> <p><b>reason (33)</b> 7:22;42:5;83:21; 102:13;106:8;109:15; 116:2;139:14;142:18; 144:3;146:4;154:22; 170:8;173:5,19;216:19; 228:7;229:1;239:13; 246:16;252:21;256:21; 280:1;306:19;311:14; 319:8;321:2;330:11; 336:14,19,22;337:3; 346:15</p> <p><b>reasonable (1)</b> 94:19</p> <p><b>reasonably (2)</b> 38:5;326:12</p> <p><b>reasons (9)</b> 83:6;205:11;225:7; 241:12;246:15;252:4; 256:17;301:2;347:2</p> <p><b>recapitulates (1)</b> 74:12</p> <p><b>receive (4)</b> 92:18;321:11;324:3, 21</p> <p><b>received (3)</b> 56:11;195:14;235:8</p> <p><b>receives (2)</b> 88:3;89:21</p> <p><b>receiving (3)</b> 308:1;322:16,17</p> <p><b>recent (2)</b> 204:1;279:16</p> <p><b>recently (19)</b> 7:4;8:18;15:11;86:11; 89:3;90:4,10,12,18; 101:3;104:10;120:13; 196:9,15;213:15; 289:10;295:12;341:16, 22</p> <p><b>receptor (95)</b> 18:6,8,11;120:1,13; 121:6,13,14,20;122:4,9, 14,15,21,22;123:6,8,16; 124:13;126:14,21; 127:4;130:1;138:18; 143:20;152:1,13;153:6, 21;154:7,8;155:2,9,19; 156:14,18,22,22;157:4, 6,7;162:1,22;163:3,5,15; 166:11,12,16;167:7; 172:10;194:15;195:4; 196:11;197:1,3;199:3,4, 11,20;200:2,9,21; 201:22;202:1;203:9,17; 204:2;278:12,15,17,19; 279:13;280:16,21; 284:18;287:7;288:15; 289:16;290:2;293:19; 304:10;308:19;309:15, 21;310:11;315:20,21; 319:8,11,22;320:2; 325:18;331:16;344:1</p> <p><b>receptor-like (1)</b> 278:17</p> <p><b>receptors (36)</b> 96:20,20;117:8,16; 124:18,21;131:8;136:3; 153:7,13;154:8,21; 155:10,12,21,22;156:2; 165:17;166:6,21;179:6; 197:18;198:3;199:5; 274:15;278:21;279:3,8; 280:2;285:5,9,21;292:8; 304:14;325:13;327:2</p> <p><b>recess (3)</b> 136:9;190:11;294:20</p> <p><b>recipients (1)</b> 178:15</p> <p><b>recognize (3)</b> 124:17;157:15;242:16</p> <p><b>recognizes (1)</b> 145:22</p> <p><b>recognizing (1)</b> 105:1</p> <p><b>recombinant (4)</b> 21:20;125:4;235:8; 278:19</p> <p><b>reconnect (1)</b> 16:19</p> <p><b>record (3)</b> 86:11;104:1;264:12</p> <p><b>recording (1)</b> 97:19</p> <p><b>recordings (1)</b> 326:18</p> <p><b>records (1)</b> 225:5</p> <p><b>recover (1)</b> 93:9</p> <p><b>recovering (1)</b> 74:1</p> <p><b>recovery (8)</b> 40:8;41:4;100:6; 102:9,12;181:5,10,13</p> <p><b>recreate (1)</b> 10:12</p> <p><b>recruit (3)</b> 163:11;224:20;225:9</p> <p><b>recruited (6)</b> 163:6;207:4;208:1; 212:11;222:2;319:17</p> <p><b>recruiting (1)</b> 225:3</p> <p><b>recruits (1)</b> 163:3</p> <p><b>recurrence (1)</b> 115:7</p> <p><b>red (5)</b> 38:17;40:2;91:8; 144:22;289:17</p> <p><b>reddening (1)</b> 282:22</p> <p><b>redness (1)</b> 76:14</p> <p><b>reduce (2)</b> 25:19;80:4</p> <p><b>reduced (1)</b> 82:18</p> <p><b>reducing (2)</b> 48:2;266:9</p> <p><b>reduction (5)</b> 48:5;238:19;254:5,8; 340:16</p> <p><b>redundancy (1)</b> 325:5</p> <p><b>reef (2)</b> 149:20,22</p> <p><b>Reeh (1)</b> 326:14</p> <p><b>re-establish (1)</b> 106:9</p> <p><b>reestablishing (1)</b> 94:5</p> <p><b>reference (2)</b> 23:9;104:22</p> <p><b>referred (4)</b> 105:4;115:9,14;</p>
----------	--

197:19 <b>referring (1)</b> 233:5 <b>reflect (2)</b> 225:10;337:8 <b>reflected (1)</b> 79:2 <b>reflections (1)</b> 203:19 <b>reflects (2)</b> 36:15;336:12 <b>reflex (1)</b> 21:7 <b>refractoriness (1)</b> 330:9 <b>regard (6)</b> 30:5;157:22;201:10; 216:19;217:6,12 <b>regarding (3)</b> 181:15;182:16;329:19 <b>regardless (2)</b> 106:7;245:12 <b>regards (2)</b> 213:22;217:5 <b>Regenerative (3)</b> 4:11,13,18 <b>regimes (1)</b> 73:1 <b>Regimmune (1)</b> 275:21 <b>region (6)</b> 81:8;127:15,16; 128:18;158:7;274:7 <b>regional (2)</b> 76:11;198:11 <b>regions (1)</b> 285:11 <b>registered (1)</b> 207:1 <b>registries (1)</b> 182:11 <b>registry (1)</b> 207:2 <b>regulate (5)</b> 55:2,21;57:1;275:17; 276:18 <b>regulated (4)</b> 79:13;119:19;123:14; 131:13 <b>regulates (1)</b> 98:22 <b>regulating (1)</b> 65:8 <b>regulation (4)</b> 106:9;196:12;233:18; 275:6 <b>regulations (1)</b> 44:1 <b>regulatory (2)</b> 60:9;305:22 <b>regurgitate (1)</b> 147:20 <b>reinforce (2)</b>	193:6;329:12 <b>Reinhart (1)</b> 132:22 <b>reject (2)</b> 59:19;72:18 <b>rejection (3)</b> 59:19,21;73:10 <b>related (14)</b> 18:22;148:7;155:4; 156:21;157:19;204:20; 217:3,21;225:18;266:18, 19;282:13;311:14;313:5 <b>relative (1)</b> 213:8 <b>relatively (9)</b> 85:10;184:12;193:19; 196:9;239:5,14,15; 252:2,8 <b>relaxed (2)</b> 150:22;151:7 <b>release (28)</b> 31:18;35:1,4;39:11; 45:15;52:3,3;55:2,5,22; 56:5;103:8;143:15; 145:12;150:5,7;171:6; 212:19;280:18,22; 282:10;302:1;304:15; 316:18;322:2;326:21; 329:11;343:19 <b>released (18)</b> 135:16,19,20;136:2; 143:19;144:9;150:8; 151:17;164:19;172:6; 282:3,5,14;299:16; 300:11;302:12;318:8; 335:2 <b>releases (1)</b> 302:13 <b>releasing (9)</b> 11:17;25:20;38:22; 39:4;40:4;43:19;47:20; 50:3;111:3 <b>relevance (3)</b> 247:15;296:13;327:14 <b>relevant (9)</b> 7:20;17:12;71:6; 75:20;76:4;81:5;216:7; 325:12;328:13 <b>reliable (1)</b> 41:14 <b>relief (6)</b> 80:8;209:3,4;306:5,7, 8 <b>remain (1)</b> 64:17 <b>remained (1)</b> 274:19 <b>remains (2)</b> 198:5;244:22 <b>remark (1)</b> 128:12 <b>remarkable (2)</b> 53:9;141:12	<b>remarkably (3)</b> 52:20;107:7;184:9 <b>remember (11)</b> 7:3;45:15;60:12; 109:18;172:2;219:10; 270:14;304:8;306:15; 310:21;351:2 <b>remembers (1)</b> 62:1 <b>remind (1)</b> 192:5 <b>remit (1)</b> 297:16 <b>remove (2)</b> 96:6;125:7 <b>removed (1)</b> 284:11 <b>remyelinate (2)</b> 23:19;24:2 <b>remyelination (3)</b> 23:17,20;24:8 <b>renewed (1)</b> 240:18 <b>renin-angiotensin (1)</b> 195:19 <b>repair (1)</b> 80:18 <b>repaired (1)</b> 103:20 <b>repairing (1)</b> 22:20 <b>repeat (3)</b> 119:11;296:9;340:15 <b>repeated (3)</b> 39:14;93:13,15 <b>replace (4)</b> 31:3,11;42:14;127:17 <b>replaced (1)</b> 125:7 <b>replacement (1)</b> 23:8 <b>replicate (3)</b> 201:8,21;348:13 <b>replicated (3)</b> 202:14;223:20;260:20 <b>replication (4)</b> 113:20;201:5,15; 347:14 <b>repolarizes (1)</b> 163:8 <b>report (5)</b> 76:3;202:20;349:16, 18,21 <b>reported (4)</b> 105:21;226:14; 235:13;350:2 <b>reporter (1)</b> 118:8 <b>reporting (4)</b> 349:9;350:16;351:1; 352:16 <b>reports (1)</b> 349:20	<b>represent (1)</b> 159:2 <b>representative (2)</b> 251:22;269:22 <b>representatives (1)</b> 353:2 <b>represented (2)</b> 301:19;353:4 <b>represents (4)</b> 91:9;127:21;230:16; 334:18 <b>reproduced (2)</b> 8:20;39:10 <b>reprogram (2)</b> 60:5;186:2 <b>reprogrammed (1)</b> 186:8 <b>reprogramming (1)</b> 8:15 <b>reprograms (1)</b> 8:9 <b>request (1)</b> 323:21 <b>requests (1)</b> 37:3 <b>require (5)</b> 298:2,9,10;316:2; 329:1 <b>required (1)</b> 317:7 <b>requirement (1)</b> 247:3 <b>requirements (1)</b> 49:19 <b>requires (1)</b> 335:11 <b>rescaffolded (1)</b> 311:18 <b>rescue (1)</b> 129:4 <b>research (18)</b> 42:7;43:17;61:10; 115:18;195:14;224:21; 237:7;238:21;253:4; 258:7;263:3;264:14,16; 296:6;330:21;333:13; 339:1;340:17 <b>researcher (2)</b> 196:4;281:9 <b>researchers (3)</b> 246:3;280:5;283:12 <b>resemblance (1)</b> 328:19 <b>resembled (1)</b> 318:13 <b>reshape (1)</b> 189:14 <b>residue (1)</b> 152:7 <b>resistant (7)</b> 121:7;165:12;166:1,7, 8;185:3;225:13 <b>resolving (1)</b>	235:11 <b>respirator (3)</b> 28:6,13,17 <b>respond (11)</b> 20:14;76:18;80:7; 96:3;159:1;162:5;168:5; 185:10;220:11;221:9,9 <b>responded (1)</b> 225:1 <b>responder (2)</b> 209:14,15 <b>responding (1)</b> 183:4 <b>responds (2)</b> 221:8;269:10 <b>response (19)</b> 45:9;46:11;91:14; 116:15;118:13,16,19; 122:22;129:19;130:4,6; 131:20;223:6,10;291:8, 14;305:18;331:21;332:5 <b>responses (10)</b> 116:7,11;118:5;119:3; 121:18;123:13;124:7; 129:19,20;130:16 <b>responsibility (2)</b> 26:4;347:4 <b>responsible (1)</b> 29:16 <b>responsive (7)</b> 121:14,15,21,22; 122:5,5;161:16 <b>rest (5)</b> 55:3;151:5;176:12; 212:16;254:13 <b>restaurant (1)</b> 95:6 <b>restore (6)</b> 24:6;31:4;41:1,19; 53:21;54:2 <b>restored (3)</b> 203:17;303:10,17 <b>restricted (3)</b> 155:14;215:14;219:5 <b>result (9)</b> 92:15;114:11;128:6; 141:12;144:9;150:6; 156:17;202:4;215:17 <b>results (14)</b> 53:12;123:13;156:7; 202:5;212:14;221:3,4; 255:21;257:4;261:2; 283:21;318:15;325:1; 330:3 <b>RET (3)</b> 18:6,8;69:15 <b>retain (1)</b> 106:11 <b>retained (1)</b> 328:17 <b>retest (1)</b> 128:12 <b>retinitis (2)</b>
---	---	---	--	--

54:8;174:4 <b>retitled (1)</b> 228:4 <b>retract (3)</b> 31:1,2;74:7 <b>retrograde (1)</b> 276:10 <b>retrogradely (2)</b> 67:10;113:21 <b>retrospect (2)</b> 269:3,12 <b>retrospectively (1)</b> 143:2 <b>return (2)</b> 102:11;196:6 <b>returned (1)</b> 277:5 <b>revealed (1)</b> 342:5 <b>reversal (1)</b> 309:13 <b>reverse (4)</b> 13:13;30:1;118:16; 156:7 <b>reversed (1)</b> 130:21 <b>reversing (1)</b> 123:1 <b>revert (3)</b> 329:7;330:13;331:14 <b>review (5)</b> 30:18;111:6;220:5; 283:20;345:11 <b>reviewers (1)</b> 176:1 <b>reviewing (1)</b> 137:10 <b>revised (1)</b> 230:18 <b>revisit (1)</b> 6:20 <b>revolution (1)</b> 11:7 <b>reward (1)</b> 20:12 <b>Reza (1)</b> 104:7 <b>rhinorrhea (1)</b> 283:1 <b>rhizotomies (1)</b> 49:12 <b>RICE (32)</b> 104:18;105:11; 134:17;173:4,17; 175:18;178:7;194:7; 195:1,2;215:2,12,18,22; 216:6;218:6,13,17; 219:8;221:12,21;222:1, 6;223:13;260:8;326:1; 332:22;334:12;339:17; 341:13;345:10;349:2 <b>right (28)</b> 4:3;29:19;38:3;50:9;	65:2;106:4;165:6;170:7, 19;171:11;180:12; 188:4;218:16;258:1; 263:17;268:19;298:22; 300:6;301:10,12;305:9, 17;315:13;319:9;337:9; 345:8;352:19,22 <b>right-hind (1)</b> 116:10 <b>rigorously (1)</b> 344:8 <b>riluzole (1)</b> 28:21 <b>Rinat (3)</b> 229:12;241:3;242:16 <b>rinse (1)</b> 44:21 <b>risk (5)</b> 174:19;198:11; 244:20;298:6,19 <b>risk/benefit (2)</b> 176:13;244:19 <b>risks (1)</b> 267:10 <b>RN624 (1)</b> 230:11 <b>RNA (2)</b> 114:5;187:6 <b>road (2)</b> 241:10;301:15 <b>robust (16)</b> 41:14;220:17;238:9, 11;242:6,8;259:14,16; 263:16;268:5,9;270:1; 341:7;347:7,19,20 <b>robustness (7)</b> 242:11,14;245:9; 259:12,13;260:1,21 <b>rodent (1)</b> 92:5 <b>rodents (4)</b> 96:14;280:16;287:18; 339:20 <b>role (10)</b> 24:22;163:12;200:13; 232:16,20,21;233:2; 234:8;275:17;278:5 <b>room (11)</b> 65:4;174:11;195:7; 228:9;231:1;234:5,21; 237:9;240:2;245:7; 272:21 <b>root (5)</b> 78:6;198:3;199:2; 204:6;293:21 <b>Rosenthal (1)</b> 241:6 <b>Ross (1)</b> 98:5 <b>rostrum (1)</b> 147:19 <b>rotarod (1)</b> 107:22	<b>rough (1)</b> 274:8 <b>roughly (2)</b> 202:10;342:9 <b>route (2)</b> 26:17;90:11 <b>routes (1)</b> 204:5 <b>routine (1)</b> 178:13 <b>row (3)</b> 104:3;312:21,22 <b>Roy (4)</b> 166:9;219:18;222:8, 11 <b>royalties (1)</b> 229:18 <b>Roy's (3)</b> 228:2,5;229:3 <b>rubbish (2)</b> 11:12,13 <b>Rubenstein (1)</b> 80:21 <b>rumor (1)</b> 240:17 <b>run (9)</b> 43:21;45:5;66:9;69:2; 141:6;195:9;204:7; 235:20;244:20 <b>running (5)</b> 61:7;74:22;265:1; 292:20;315:9 <b>runs (1)</b> 11:16 <b>rush (1)</b> 295:6 <b>Rushing (1)</b> 65:1	<b>Salt (4)</b> 136:22;197:16; 199:21;203:21 <b>same (72)</b> 10:5;21:15;34:7;39:6, 16;40:13;41:1,2;46:11; 48:9;59:14;63:14,17; 64:18;72:12;96:10;97:7; 102:6;103:4;107:11; 121:4;131:1;135:5; 138:22;139:4;144:18, 19;148:8;153:21; 167:11,12;169:20; 173:7;201:22;202:4,8; 203:21;210:20;211:10; 226:22;231:20;233:21; 234:2,18,18;236:8,13; 246:15;269:17;271:22; 273:5;277:9;282:9; 284:17,18,19;286:5; 287:13;288:20;289:2; 291:8,13,19;294:12; 298:17,18;311:19; 322:18,19;328:10; 329:19;338:3 <b>sample (3)</b> 202:22;207:5;350:2 <b>sampled (1)</b> 226:5 <b>samples (2)</b> 281:21;282:11 <b>San (2)</b> 95:1;295:13 <b>Sandy (1)</b> 35:20 <b>Sarah (3)</b> 98:5;99:4;100:4 <b>sarcoma (1)</b> 248:20 <b>Sareen (2)</b> 62:4;66:4 <b>sat (1)</b> 233:1 <b>satellite (2)</b> 97:5;289:21 <b>saturate (1)</b> 165:16 <b>save (5)</b> 69:11;108:21;265:2; 307:10,15 <b>saw (23)</b> 13:12;20:4;82:10; 100:4;112:12,13;122:6; 126:7;130:18;191:6; 204:13;208:14;212:9; 221:12;239:22;245:12; 271:14;276:7;282:10; 300:20;308:12;311:12; 347:19 <b>saying (8)</b> 137:12;162:8;164:5; 272:7;281:2;285:17; 297:20;334:6	<b>scaffolding (1)</b> 311:21 <b>scale (3)</b> 20:4;206:11;342:12 <b>scales (1)</b> 147:20 <b>scallop-shaped (1)</b> 88:19 <b>scan (2)</b> 37:20;307:1 <b>scared (2)</b> 44:15;184:8 <b>scary (1)</b> 312:3 <b>scenario (1)</b> 293:22 <b>schedule (1)</b> 265:1 <b>school (5)</b> 149:21;150:1,4,18; 196:5 <b>sciatic (2)</b> 92:4,5 <b>sciatica (1)</b> 178:6 <b>SCID (2)</b> 100:19;101:7 <b>science (11)</b> 6:8;7:13;232:14; 237:16;239:8;240:15; 335:10,11,13,15;338:1 <b>sciences (1)</b> 6:8 <b>scientific (5)</b> 192:20;214:9;215:9; 238:21;297:4 <b>scientist (1)</b> 112:3 <b>scientists (1)</b> 333:14 <b>sclerosis (1)</b> 23:17 <b>scopes (1)</b> 181:9 <b>score (1)</b> 238:17 <b>scores (4)</b> 206:12,13;211:3; 271:13 <b>Scotland (1)</b> 225:6 <b>Scott (1)</b> 81:15 <b>scratch (2)</b> 99:13;141:8 <b>scratching (8)</b> 98:15,16;99:10,11,14; 100:10,11;141:10 <b>screen (3)</b> 11:4;14:12;155:16 <b>screening (3)</b> 11:3;13:4;218:20 <b>screens (1)</b>
		<b>S</b>		
		<b>sacrifice (1)</b> 37:3 <b>sad (1)</b> 182:9 <b>safe (3)</b> 313:21;314:3;353:17 <b>safely (1)</b> 52:14 <b>safer (1)</b> 26:18 <b>safety (17)</b> 43:14;173:8;242:19; 244:16;245:1,4;255:2; 258:17,20,22;265:7,13, 17;266:9;267:1,10; 352:11 <b>Sagen (1)</b> 172:1 <b>Sagen's (1)</b> 173:18 <b>sagittal (1)</b> 85:13		



10:16 <b>SCRO (1)</b> 187:21 <b>SCROs (1)</b> 188:3 <b>scuba (1)</b> 154:16 <b>sculptor (1)</b> 77:1 <b>sculpture (1)</b> 77:1 <b>seat (2)</b> 136:11;326:5 <b>Seattle (1)</b> 194:10 <b>second (16)</b> 4:4;25:13;27:13; 29:11;126:20;215:8; 223:11;234:17;242:15; 260:5;304:13;306:21; 318:8;335:9,12;337:3 <b>secondary (9)</b> 179:13;209:1;211:8; 224:20;302:9;305:19; 306:5;307:7;329:7 <b>Secondly (3)</b> 205:19;246:21;267:18 <b>second-order (1)</b> 117:17 <b>seconds (2)</b> 37:5;131:20 <b>secret (1)</b> 150:16 <b>secrete (3)</b> 22:3;34:20;64:3 <b>secreted (2)</b> 46:15;281:16 <b>secreting (6)</b> 43:22;46:1,18;54:17; 67:14;74:6 <b>secretion (4)</b> 56:3,15;71:2;108:8 <b>secretory (1)</b> 63:5 <b>section (2)</b> 85:14;326:9 <b>sectors (2)</b> 352:8;353:3 <b>secured (1)</b> 212:15 <b>sedated (1)</b> 151:11 <b>sedation (2)</b> 261:21;262:2 <b>seeing (11)</b> 85:19;108:11;191:18; 213:2;218:3;227:15; 237:2;263:18;301:18; 309:10;333:15 <b>seem (9)</b> 54:11;142:2;167:11; 209:9;229:7;263:16; 267:21;269:3;333:20	<b>seemed (11)</b> 20:6;73:3,22;170:1; 238:8;239:3;243:4; 247:10;263:14;277:22; 341:19 <b>seems (24)</b> 57:18;70:5;96:9; 110:1;154:22;156:3,10; 157:3;171:5;183:7; 188:19;189:20;214:7; 217:16;221:22;233:2; 240:6;265:16;282:13; 289:8;293:19;300:15; 347:10;350:12 <b>segment (2)</b> 85:11;100:12 <b>segregates (1)</b> 187:9 <b>segue (2)</b> 76:1;98:4 <b>seize (1)</b> 111:16 <b>seizure-like (2)</b> 79:7;82:22 <b>seizures (3)</b> 82:15,15,18 <b>selection (1)</b> 336:20 <b>selective (3)</b> 152:1;304:8,16 <b>selectively (1)</b> 168:14 <b>selectivity (3)</b> 197:18;217:18;218:6 <b>self-aggregate (1)</b> 188:12 <b>send (1)</b> 85:20 <b>sense (10)</b> 76:21;82:22;94:15; 206:2;221:1;236:17; 258:15;316:4;344:4; 347:4 <b>sensitive (3)</b> 123:7;166:4;327:8 <b>sensitivities (2)</b> 326:17,21 <b>sensitivity (12)</b> 30:13;47:2;131:4; 162:20;238:17,20; 248:13;253:5;262:20; 263:12;329:19;330:5 <b>sensitization (5)</b> 302:9,10,11,15;330:17 <b>sensitize (2)</b> 127:4;302:8 <b>sensitized (1)</b> 348:3 <b>sensors (2)</b> 161:17;162:2 <b>sensory (27)</b> 30:11;105:6;113:14; 114:14;115:5;120:1;	151:3;181:5;198:18; 200:8;203:16;205:21; 206:1,1,3;220:11,12; 273:18;276:4,15;277:8; 291:10;329:21;331:7; 340:9;345:5,15 <b>sent (1)</b> 99:6 <b>sentry (1)</b> 220:17 <b>separate (6)</b> 139:17,18,21;211:22; 292:6,10 <b>separated (1)</b> 210:22 <b>separation (2)</b> 208:16;280:10 <b>September (1)</b> 241:11 <b>seq (1)</b> 187:6 <b>sequence (2)</b> 128:12;142:10 <b>sequences (2)</b> 133:17,21 <b>serendipity (1)</b> 335:6 <b>series (2)</b> 45:4;125:9 <b>serious (2)</b> 12:3;306:14 <b>serious-adverse-events (1)</b> 207:15 <b>seriously (2)</b> 110:20;327:11 <b>serotonin (3)</b> 298:3;299:14;304:14 <b>serve (1)</b> 114:17 <b>serves (2)</b> 147:2;173:5 <b>session (6)</b> 134:14;193:18;222:9; 268:22;332:4,9 <b>sessions (1)</b> 192:6 <b>set (16)</b> 4:18;15:13;18:13; 21:15;26:7;49:2,8;73:9; 117:2;126:22;212:18; 234:17;260:16;262:15; 275:20;338:22 <b>sets (2)</b> 63:9;195:15 <b>settings (1)</b> 338:5 <b>settled (1)</b> 303:2 <b>seven (4)</b> 14:6;232:10;324:16, 20 <b>Sever (8)</b> 118:4;195:7;197:2;	310:1;315:3;321:10; 325:19;331:14 <b>severe (7)</b> 72:22;73:7;175:16; 273:1;282:20;301:8; 311:5 <b>Severity (1)</b> 211:6 <b>shaker (1)</b> 142:15 <b>shall (3)</b> 274:8;278:4;286:13 <b>sham (1)</b> 248:14 <b>share (13)</b> 44:2,5,7;135:7; 195:17;206:17;224:17; 315:8;339:15;351:5; 352:9,12;353:6 <b>shared (1)</b> 105:13 <b>Sharif-Naeini (1)</b> 104:7 <b>sharing (1)</b> 226:6 <b>Sharon (3)</b> 265:4,5;266:12 <b>shells (1)</b> 148:20 <b>Shelly (1)</b> 66:6 <b>Shelton (5)</b> 231:2;239:7;248:3; 269:5;271:8 <b>shift (3)</b> 284:15,22;314:12 <b>shingles (1)</b> 115:9 <b>Shinya (2)</b> 7:15;62:2 <b>shock (1)</b> 72:13 <b>shocked (1)</b> 130:8 <b>short (9)</b> 40:9;127:17;147:15; 210:21;220:15;239:5; 293:2;294:18;316:17 <b>shortcut (1)</b> 263:22 <b>shorter (1)</b> 214:7 <b>shot (2)</b> 170:11;171:4 <b>show (41)</b> 10:22;13:3;18:4;20:8; 25:20;29:11;33:2;35:17; 37:1,14;43:2;47:10; 49:3;68:7;90:14,22; 102:5;122:15;123:5; 125:11;129:10;130:12; 131:5;133:5;140:14; 161:12;163:20;202:8,	12;203:8;242:9;251:7; 253:15;285:7;288:18; 311:5;331:13;341:2,9; 346:2;348:19 <b>showed (25)</b> 12:12;14:8;19:3; 40:18;42:17;59:4; 160:10;184:1;186:2; 200:20;204:2;212:8; 249:10,12;253:21; 259:13;279:7;288:3; 303:17;306:22;308:15; 341:6;347:21,22;348:1 <b>showing (12)</b> 12:1;129:16;132:19; 209:19;233:15;236:13; 238:19;248:12;250:9; 300:21;307:4;335:1 <b>shown (30)</b> 10:20,21;29:22;30:14; 31:13;35:1;39:18;44:22; 52:14;54:15;117:15; 149:4;152:19;162:10; 167:11;174:21,21; 198:18,22;199:8,19; 200:4;201:1;205:14; 220:7;224:10;260:10; 268:12;278:9;279:11 <b>shows (13)</b> 25:8;38:9;43:14; 156:19;160:12;167:15; 198:14;205:10;223:6; 248:17;260:17;261:9; 346:1 <b>shut (1)</b> 240:22 <b>shuttle (1)</b> 295:5 <b>sick (4)</b> 25:10,12;178:4;311:4 <b>sickest (1)</b> 178:12 <b>side (37)</b> 11:4;16:1,2;17:15; 19:14;39:2,6,8,17;50:10; 51:4;55:8;56:22;61:9; 10;70:19;71:1,5;85:11; 99:13;101:19;109:12; 119:16;143:21;168:17; 184:8;231:11;236:7,12; 246:22;262:5,10;266:9; 291:13;296:5;312:20; 327:13 <b>side-effect (1)</b> 180:1 <b>sides (4)</b> 99:13;286:8;288:16; 343:3 <b>sign (4)</b> 95:3;256:4,5,16 <b>signal (19)</b> 143:10,12,16;145:15, 15;207:15;216:15,18;
--	---	---	--	---

217:4,6;228:18,22; 257:21;266:4;275:9; 278:2;282:1;286:5; 308:12 <b>signaling (6)</b> 18:13;197:4;198:19; 204:5;319:14,15 <b>signals (15)</b> 198:8;204:9;216:14; 250:13,20;251:1;252:13, 22;263:2;267:1;275:11, 16;280:19;293:22; 324:15 <b>significance (1)</b> 51:16 <b>significant (10)</b> 6:20;18:17;39:16; 47:18;48:12;51:14; 99:17;256:11;257:4; 289:7 <b>significantly (5)</b> 82:18;283:17;308:13; 312:6;322:11 <b>signs (1)</b> 336:9 <b>silence (2)</b> 120:15;126:14 <b>silences (1)</b> 131:16 <b>silencing (8)</b> 120:3,9;123:15,18,20; 124:10;131:13;132:4 <b>silos (1)</b> 333:8 <b>similar (22)</b> 34:6;55:9;58:7;59:3; 62:12;101:9;105:16; 123:12;152:8;201:3; 203:8,10;208:2;210:10; 229:8;236:20;237:1; 246:9;271:12;307:18; 318:15;350:20 <b>simple (6)</b> 11:10;21:5;32:14; 69:5;317:5;327:9 <b>simpler (1)</b> 49:10 <b>simplex (1)</b> 113:12 <b>simply (2)</b> 34:21;44:21 <b>simulate (1)</b> 16:9 <b>simultaneously (1)</b> 160:5 <b>single (10)</b> 10:22;32:5,13;86:1; 297:20;304:10;307:17; 317:9,11,14 <b>sit (3)</b> 172:18;269:13;333:17 <b>site (8)</b> 138:22;156:15;157:2;	172:10;196:10;290:13; 292:16;294:5 <b>sites (8)</b> 37:17,19,20;43:5; 206:8;218:21;285:8,12 <b>sitting (5)</b> 104:3;106:21;231:2; 233:20;343:16 <b>situ (1)</b> 114:9 <b>situation (3)</b> 55:6;118:20;341:3 <b>situations (1)</b> 265:8 <b>sit-ups (1)</b> 235:21 <b>six (19)</b> 12:3;72:6;98:13; 99:22;101:7,12,21; 102:8;107:2,4;159:2; 186:5,11;206:6;314:7; 317:9;320:4,13;326:11 <b>size (7)</b> 15:21;139:18;202:22; 207:5;223:8;288:12; 350:3 <b>skeptical (1)</b> 262:4 <b>skeptically (1)</b> 262:8 <b>skills (1)</b> 239:17 <b>skin (13)</b> 8:2;9:9,15;12:8;61:16; 63:7;69:19;117:10; 135:19;146:22;186:3; 200:9;288:1 <b>slap (1)</b> 343:15 <b>slate (1)</b> 60:6 <b>sleep (3)</b> 140:21;141:3;169:13 <b>sleeper (1)</b> 151:21 <b>slice (3)</b> 90:6,21;104:5 <b>sliced (1)</b> 90:5 <b>slide (18)</b> 11:10;61:6,11;75:14; 103:22;137:15,16; 202:5;212:7;242:9; 247:7;248:17;255:12; 258:3;259:13;260:11; 316:20;322:22 <b>slides (5)</b> 48:18;217:18;259:1; 347:13;348:7 <b>slight (3)</b> 161:7;202:6;207:18 <b>slightly (4)</b> 212:2;292:9;326:11;	333:1 <b>slow (7)</b> 50:20,20;54:12;65:1; 184:12;288:5;329:14 <b>slower (1)</b> 26:11 <b>slowing (1)</b> 184:5 <b>slowly (1)</b> 235:11 <b>SMA (1)</b> 187:7 <b>small (36)</b> 20:1;51:16;62:18; 139:8;141:19;149:21; 157:17;189:6;191:4,7; 199:1;208:4;214:8; 219:10;221:15;251:17; 255:18,19;257:5,12; 263:13;283:12;284:14; 286:1,13;295:12; 296:15;304:18,21; 305:1;307:13;315:5; 316:15;318:21;330:4; 343:8 <b>small- (2)</b> 199:6;289:13 <b>smaller (2)</b> 63:4;102:3 <b>small-font (1)</b> 191:7 <b>smart (1)</b> 253:3 <b>Smith (5)</b> 88:11;200:15;204:1; 213:15;214:1 <b>Smith's (5)</b> 198:22;200:4,13; 201:9;202:6 <b>smooth (2)</b> 279:9,15 <b>smug (1)</b> 343:15 <b>snail (15)</b> 138:15;139:2;142:6; 143:4,6;144:3;146:20; 147:12,16;148:2,7,7,14; 150:17;154:12 <b>snails (37)</b> 136:17,18;137:3,11, 17,18;138:1,2,9,11; 139:14;141:17;146:18, 18;147:7,22;148:13,17, 18,19,20;149:1,7,10,19; 151:9,17;152:6;153:18; 154:13,14,19;165:12,16; 166:7;167:3,10 <b>snake (1)</b> 65:9 <b>snakes (1)</b> 166:5 <b>SNI (1)</b> 92:3	<b>sniff (1)</b> 146:19 <b>so-called (1)</b> 168:2 <b>soccer (3)</b> 57:18,19;273:9 <b>social (1)</b> 238:22 <b>societies (1)</b> 150:16 <b>socioeconomic (1)</b> 273:4 <b>SOD1 (11)</b> 29:8,9;30:2,20;36:10, 17;66:17;68:1,10;74:13, 16 <b>sodium (8)</b> 139:1;159:20;160:2; 197:16;199:21;203:20; 343:21;345:18 <b>solid (2)</b> 46:6;341:11 <b>solo (1)</b> 306:16 <b>solution (4)</b> 119:18;121:2;194:2; 217:1 <b>solutions (1)</b> 227:7 <b>SOMA (1)</b> 73:12 <b>somatic (7)</b> 8:15;107:3;243:3; 250:11;255:17;269:16; 270:22 <b>somatosensation (1)</b> 167:16 <b>somatostatin (3)</b> 106:14,16,18 <b>somebody (1)</b> 99:12 <b>somehow (2)</b> 110:1;186:16 <b>Someone (6)</b> 96:18;177:21;236:4; 262:14;334:9;339:8 <b>sometime (2)</b> 201:6;230:19 <b>sometimes (8)</b> 66:8,8;183:16;198:9; 235:18;283:15;284:13; 340:13 <b>somewhat (9)</b> 5:16;75:19;136:12; 166:13;209:14;213:4; 223:5;242:22;352:21 <b>somewhere (2)</b> 167:8;342:6 <b>soon (3)</b> 17:5;123:11;256:13 <b>sophisticated (4)</b> 11:21;14:17;15:20; 345:5	<b>sore (1)</b> 235:15 <b>Sorry (7)</b> 6:18;60:20;166:17; 169:10;188:5;284:11; 304:17 <b>sort (8)</b> 17:7;45:6;61:17;62:6; 219:19;238:10;245:10; 271:10 <b>sorts (5)</b> 19:14;53:8;251:7; 259:15;267:5 <b>sound (4)</b> 189:12;246:15;301:9; 326:11 <b>soup (2)</b> 127:3;331:12 <b>source (10)</b> 12:22;26:11;44:16; 80:2;81:10;118:1; 148:18;153:19;154:20; 296:10 <b>South (2)</b> 207:7;222:6 <b>Sox-2 (1)</b> 63:2 <b>space (2)</b> 229:15;291:11 <b>spaced (1)</b> 150:9 <b>spared (1)</b> 108:11 <b>sparked (1)</b> 247:19 <b>spasticity (2)</b> 179:12,13 <b>speak (7)</b> 76:7;272:18;275:4; 333:6;337:22;338:3; 351:9 <b>speaker (5)</b> 4:6;5:18;194:6;272:6; 295:9 <b>speakers (4)</b> 191:10;192:1;271:20; 332:4 <b>speaking (2)</b> 194:13;288:21 <b>speaks (1)</b> 351:8 <b>special (2)</b> 213:22;282:16 <b>specialized (1)</b> 137:20 <b>species (8)</b> 137:18,20,20,21,22; 149:3,4,14 <b>specific (34)</b> 10:8;11:2;13:10;14:8; 38:19;107:18;116:21; 122:9;126:7;128:13; 153:20;154:3;155:18;
--	--	---	---	---

157:10;160:9,11,21; 161:10;162:6,6,12; 169:2;173:19;266:7,11, 15;279:16;287:3,11,12; 289:10;296:13;298:2; 304:9	<b>splice (1)</b> 168:13 <b>spliced (2)</b> 114:7;169:3 <b>spoke (2)</b> 253:9;270:12 <b>spokesman (1)</b> 195:6 <b>spongiform (1)</b> 173:7 <b>sponsor (2)</b> 249:7;264:9 <b>spectrum (1)</b> 245:20 <b>speed (1)</b> 352:17 <b>spend (5)</b> 241:15;243:18; 314:10;333:14;334:9 <b>spending (1)</b> 231:8 <b>spent (2)</b> 231:16;232:2 <b>sperm (1)</b> 62:5 <b>sphere (2)</b> 32:17;58:6 <b>spheres (8)</b> 32:16;57:15,16,17,21, 21;58:3;197:2 <b>spicules (1)</b> 154:17 <b>Spiderman (1)</b> 26:2 <b>Spiegelmers (2)</b> 284:2;288:7 <b>spike (1)</b> 47:19 <b>spinal (79)</b> 5:20;12:2;14:22;15:4, 9;19:1,18,19;23:12,20, 22;24:7;25:16;27:13; 30:10,16;35:12,19;36:1; 37:8,17;38:4,10;40:19; 41:4;45:11,17,20;46:14; 48:21;49:4,5,11;50:10; 52:1,6,15,21;53:6;67:10, 11,14,20;69:2,3;70:10; 74:19;77:22;78:3,5; 79:15;80:18,19;82:21; 83:3,11,21;84:7;85:4,14; 90:6;97:8;98:11;100:12; 103:10;106:21;117:14; 135:20;145:11;152:17; 172:8;174:19;176:15, 20;181:1;186:1;188:11, 13;198:4 <b>Spinifex (7)</b> 195:5,11,15;199:16; 206:22;207:2;214:6 <b>spins (1)</b> 8:10 <b>SPIO-label (1)</b> 37:15	<b>splice (1)</b> 168:13 <b>spliced (2)</b> 114:7;169:3 <b>spoke (2)</b> 253:9;270:12 <b>spokesman (1)</b> 195:6 <b>spongiform (1)</b> 173:7 <b>sponsor (2)</b> 249:7;264:9 <b>spectrum (1)</b> 245:20 <b>speed (1)</b> 352:17 <b>spend (5)</b> 241:15;243:18; 314:10;333:14;334:9 <b>spending (1)</b> 231:8 <b>spent (2)</b> 231:16;232:2 <b>sperm (1)</b> 62:5 <b>sphere (2)</b> 32:17;58:6 <b>spheres (8)</b> 32:16;57:15,16,17,21, 21;58:3;197:2 <b>spicules (1)</b> 154:17 <b>Spiderman (1)</b> 26:2 <b>Spiegelmers (2)</b> 284:2;288:7 <b>spike (1)</b> 47:19 <b>spinal (79)</b> 5:20;12:2;14:22;15:4, 9;19:1,18,19;23:12,20, 22;24:7;25:16;27:13; 30:10,16;35:12,19;36:1; 37:8,17;38:4,10;40:19; 41:4;45:11,17,20;46:14; 48:21;49:4,5,11;50:10; 52:1,6,15,21;53:6;67:10, 11,14,20;69:2,3;70:10; 74:19;77:22;78:3,5; 79:15;80:18,19;82:21; 83:3,11,21;84:7;85:4,14; 90:6;97:8;98:11;100:12; 103:10;106:21;117:14; 135:20;145:11;152:17; 172:8;174:19;176:15, 20;181:1;186:1;188:11, 13;198:4 <b>Spinifex (7)</b> 195:5,11,15;199:16; 206:22;207:2;214:6 <b>spins (1)</b> 8:10 <b>SPIO-label (1)</b> 37:15	320:22 <b>stain (1)</b> 97:4 <b>stained (1)</b> 125:14 <b>staining (5)</b> 38:22;39:2;84:19; 101:22;290:18 <b>stake (2)</b> 229:16;352:21 <b>Stan (1)</b> 196:4 <b>standard (3)</b> 79:18;121:16;350:16 <b>standards (6)</b> 260:14,17,20;340:16; 350:21;351:1 <b>standing (1)</b> 294:2 <b>stands (2)</b> 205:5;299:1 <b>Stanford (3)</b> 54:14;136:21;182:12 <b>STAP (1)</b> 8:16 <b>start (35)</b> 16:12,14;28:3,8;36:5; 46:1;62:8,15;84:15; 85:9;92:18;98:14;99:17; 130:1;135:9;137:9,12; 170:5;186:6;188:12; 189:10;193:21;227:12; 244:17;266:19;272:2; 294:21;298:7,8;302:14; 309:10;322:6;326:7; 332:22;338:22 <b>started (20)</b> 11:21;12:15;21:14; 22:7;34:20;35:19;54:20; 84:14;123:22;136:11; 138:14;178:2;257:18; 258:21;281:11;304:9; 306:16;318:11;325:8; 326:15 <b>starting (5)</b> 100:3;266:17;335:22, 22;344:12 <b>starts (3)</b> 27:8;28:10;180:2 <b>start-up (1)</b> 295:13 <b>state (7)</b> 8:11;12:9;63:10,19; 112:5;151:12;297:16 <b>stated (2)</b> 181:1;229:19 <b>States (1)</b> 296:6 <b>statistical (1)</b> 211:7 <b>statistically (3)</b> 256:11;257:3;318:3 <b>statistics (3)</b>	51:9,12;180:20 <b>stay (7)</b> 39:1;85:10,21;106:18; 297:18;319:7;320:1 <b>stayed (1)</b> 324:16 <b>staying (1)</b> 192:18 <b>steady (1)</b> 65:1 <b>Steinberg (1)</b> 54:13 <b>stem (66)</b> 4:9,16;5:6,15;6:10,13, 17;7:4,5,11,17,19;8:13, 22;9:2,4;16:22;17:16, 17;22:1,2,4,6;26:13,14; 33:8;34:7,9;39:21;42:7; 44:8;50:2;52:10;53:21; 59:6;61:12,13;62:10; 64:2,4,5,10,14;65:9,11; 75:6;100:22;101:1,4,9; 103:2;104:11,12; 170:15;171:15;178:2; 187:13;274:7,21;283:8; 286:2;292:2,5;300:22; 301:4,5 <b>stem-cell (2)</b> 4:20;9:21 <b>stems (1)</b> 4:13 <b>step (6)</b> 132:3;237:6;247:17; 337:3,4,4 <b>steps (2)</b> 299:9;338:18 <b>stereotaxic (1)</b> 49:5 <b>stereotaxically (1)</b> 97:18 <b>sterling (1)</b> 214:8 <b>Steve (10)</b> 21:13;23:16;30:13; 71:16;188:22;261:15; 267:14;326:9;342:18; 344:13 <b>Steven (3)</b> 17:20;19:5;62:2 <b>Steven's (1)</b> 6:18 <b>Steve's (2)</b> 57:10;171:9 <b>stick (1)</b> 15:22 <b>sticking (1)</b> 149:10 <b>stiff (1)</b> 285:18 <b>still (37)</b> 17:21;21:12,17;30:3; 31:10;34:1;35:21;39:9; 40:10,12;41:15;49:18;	53:2;54:3;64:22;106:18; 139:13;153:10;171:12; 183:9;184:18;189:14; 203:15;206:10;220:5; 221:2,5;224:3;244:1; 253:6;258:14;265:13; 266:7;274:20;305:3; 316:16;319:2 <b>stimulate (5)</b> 90:14,20,21;91:4; 226:19 <b>stimulated (2)</b> 280:17;281:14 <b>stimulating (3)</b> 191:11;192:16;264:20 <b>stimulation (5)</b> 90:11,15;91:15; 191:18;289:5 <b>stimulations (1)</b> 289:8 <b>stimulators (1)</b> 177:3 <b>stimuli (1)</b> 277:2 <b>stimulus (1)</b> 78:7 <b>sting (5)</b> 139:2;149:16,16; 165:19,20 <b>stomach (1)</b> 9:11 <b>stone (1)</b> 212:18 <b>stood (1)</b> 216:2 <b>stop (5)</b> 38:14,14;66:10; 304:14;335:21 <b>stopped (2)</b> 236:10;257:19 <b>stops (1)</b> 72:9 <b>store (2)</b> 86:13;111:14 <b>stories (6)</b> 231:9;267:18;271:22; 308:18;332:9,18 <b>story (36)</b> 27:20;40:9,17;53:20; 59:15;80:20;83:2; 112:20;124:16;132:8; 157:3;168:20;175:21; 180:3;182:9;183:3; 213:18;217:14;227:13; 228:10,14;229:4;230:2; 231:4;232:10;237:3,6; 239:5;252:20;257:12; 262:19;275:17;282:16; 296:11;298:22;304:5 <b>straight (1)</b> 231:10 <b>straightforward (1)</b> 171:5
--	--	--	---	--	---

<b>strain (2)</b> 115:22;201:18	217:5;223:18;224:12,14, 19;225:17;234:13;	4:17;282:11	274:18;285:18;	<b>surprised (5)</b> 46:12;69:8;133:9;
<b>strains (3)</b> 238:4;326:17,20	235:3;237:9;246:5;	<b>substance (9)</b> 196:7;276:5,12;278:2;	299:13;303:18;309:22;	341:22;349:8
<b>strange (4)</b> 209:7;281:3,18;282:5	247:19;249:5,14;	281:16;282:9,10,15;	327:22	<b>surprising (3)</b> 89:11;221:22;223:5
<b>strategies (5)</b> 184:17,20;196:20;	250:21;251:15;252:7,9, 12;253:14;255:4,11,13,	335:2	<b>summarize (1)</b> 131:10	<b>surprisingly (1)</b> 341:19
224:16;349:3	14,16,19,20;256:9;	<b>substances (3)</b> 275:9,13;299:16	<b>summary (4)</b> 205:2;213:17;245:10;	<b>surrogate (2)</b> 217:9;280:4
<b>strategy (11)</b> 124:3;126:13,20;	258:4;260:9;262:22;	<b>substantial (1)</b> 238:19	325:12	<b>surrounding (1)</b> 88:6
128:1;131:14;132:9;	263:4,14;264:8,10,12;	<b>substrate (2)</b> 33:15;148:15	<b>super (2)</b> 322:10,11	<b>survival (14)</b> 18:14;31:15,16;39:5,
144:4;149:9,17;181:13;	282:12;295:15;305:16;	<b>subtle (1)</b> 161:5	<b>superficial (1)</b> 78:11	10,12;40:7,11;45:13;
270:19	307:4;310:17;311:12;	<b>subtype (4)</b> 152:1;154:22;219:2,6	<b>superior (4)</b> 258:12,15;317:15;	70:2;74:6;98:10;196:17;
<b>stratification (2)</b> 10:4;211:16	315:5;320:4,13,18,20;	<b>subtypes (2)</b> 153:21;160:9	322:12	232:17
<b>strength (1)</b> 243:5	321:1,13;322:9;323:15,	<b>subunit (5)</b> 120:5,14;153:15;	<b>superiority (9)</b> 246:13;258:5,7,9;	<b>survive (14)</b> 45:2;52:5;54:16;55:4;
<b>streptozotocin-induced (1)</b> 203:6	17;326:19;331:10;	163:7;164:3	260:17,20;261:2,11;	73:2;83:12;84:5;85:1;
<b>stress (2)</b> 310:16;311:1	332:14;336:15,17;	<b>subunits (6)</b> 153:9;154:9;155:4,6;	318:3	86:2,14;100:18;101:6;
<b>stretch (1)</b> 16:8	337:7;341:8,20;342:2;	164:2;166:14	<b>supplier (1)</b> 201:18	111:15;128:10
<b>strict (1)</b> 306:9	346:16;347:1,21,22;	<b>succeeded (1)</b> 319:4	<b>supply (1)</b> 219:15	<b>survived (1)</b> 83:13
<b>stringent (1)</b> 11:16	348:1,18;349:15,17,17;	<b>success (13)</b> 150:3;210:1,4;224:1;	<b>supplying (1)</b> 19:6	<b>surviving (2)</b> 40:9;46:14
<b>stroke (6)</b> 54:13,15;175:9;273:6;	351:17	228:14;229:4;246:19;	<b>support (2)</b> 334:11;345:6	<b>suspect (2)</b> 167:5;174:6
277:16;349:11	<b>study (74)</b> 19:5;48:6;56:9;121:5;	250:19;332:9,11,18;	<b>supporting (1)</b> 234:9	<b>sustained (2)</b> 203:12;306:8
<b>strong (6)</b> 73:15;118:15;122:22;	152:18,19;202:3;203:3;	336:14;351:8	<b>supposed (2)</b> 161:10;327:1	<b>Svensden (24)</b> 4:8;5:8,9;66:20;67:2;
213:13;228:21;256:8	206:21,22;211:14;	<b>successes (3)</b> 193:11,16;344:12	<b>supposedly (3)</b> 219:7;260:17;343:18	68:6,13,22;69:17;70:16;
<b>strongly (3)</b> 15:12;121:8;330:13	213:14;215:7,17;219:10,	<b>successful (6)</b> 49:16;193:19;244:12;	<b>suppression (10)</b> 38:19;59:15;60:12,12;	72:2;74:3,5,11;167:3,6;
<b>structure (1)</b> 146:5	22;220:16,18,19;225:21;	247:4;332:20;351:16	72:18,21;73:1,1,14,15	170:14;174:14;185:22;
<b>structures (1)</b> 232:17	226:3;236:9,11;248:15;	<b>successfully (1)</b> 197:7	<b>sural (1)</b> 92:8	187:3,15,21;188:6,9
<b>struggle (1)</b> 189:14	251:2,18;253:18;255:5,	<b>succumb (2)</b> 67:4,8	<b>sure (28)</b> 52:2;62:1;68:1;83:4;	<b>swallowing (1)</b> 235:14
<b>struggled (1)</b> 19:12	6,15,15;256:1,2,5,11,15,	<b>suddenly (1)</b> 47:19	84:21;95:7;102:4;	<b>Sweden (1)</b> 272:10
<b>student (3)</b> 35:20;55:21;132:20	16,19,20;257:7,13,15,16,	<b>suffer (2)</b> 301:1;340:3	109:20;111:5;153:10;	<b>sweep (1)</b> 342:5
<b>students (4)</b> 25:3;140:9;186:14;	18,21;258:13;263:20;	<b>Suffice (2)</b> 249:18;253:15	168:10;172:21;187:16;	<b>sweet (1)</b> 242:4
192:9	264:7;270:9;271:9;	<b>sufficient (2)</b> 66:18;112:1	188:18;196:19;211:17;	<b>swelling (1)</b> 76:14
<b>studied (6)</b> 228:17;245:13;	274:2;281:13;285:20;	<b>suffix (1)</b> 22:14	213:7;217:15;231:10;	<b>swim (1)</b> 143:8
250:11;284:8;287:19;	287:22;294:7;309:20;	<b>suggest (2)</b> 25:22;87:13	256:21;266:4;268:3,4;	<b>swing (1)</b> 141:7
288:4	310:19;317:5,14;	<b>suggested (4)</b> 175:19;204:3;234:11;	287:20;324:12;341:10;	<b>Swiss (1)</b> 15:14
<b>studies (99)</b> 18:20;40:21;42:12;	321:12;323:14,18;	268:10	348:22;351:3	<b>switch (7)</b> 55:8,12;56:2,14;
43:12,19;45:1;53:10;	324:16;327:19;329:4;	<b>suggesting (3)</b> 78:21;336:14,18	<b>surface (1)</b> 229:8	113:8;167:9;313:2
56:17;66:16;67:16;	338:6,6;344:16;345:10;	<b>suggestion (1)</b> 263:15	<b>surgeon (1)</b> 271:10	<b>Sydney (1)</b> 281:10
80:16,22;81:5;97:13;	346:20,20;348:7,10,14	<b>suggests (2)</b> 89:13;286:9	<b>surgeries (3)</b> 49:11,15;271:11	<b>symmetric (1)</b> 297:5
171:12;181:19;193:13;	<b>studying (6)</b> 233:13;244:17;251:4;	<b>suicide (2)</b> 176:8;180:18	<b>surgery (6)</b> 38:4;96:5,5;175:1;	<b>symmetrical (2)</b> 99:14;297:5
194:14,20;195:16;	261:3;263:8;338:14	<b>sumatriptan (6)</b>	270:15,18	<b>sympathetic (3)</b> 166:20;258:21;275:8
198:22;200:14,17;	<b>stuff (3)</b> 6:2;49:10;307:1		<b>surgical (2)</b> 92:10;177:20	<b>sympathetics (2)</b>
202:18;203:4;204:12;	<b>stung (1)</b> 165:21		<b>surprise (2)</b> 8:16;325:2	
209:2;213:5;216:14;	<b>stunning (1)</b> 236:3			
	<b>subarachnoid (2)</b> 277:17,22			
	<b>subclasses (1)</b> 158:9			
	<b>subcutaneous (4)</b> 316:9,10;318:12;			
	320:14			
	<b>subject (1)</b> 198:4			
	<b>Subjects (3)</b> 235:8,13;338:8			
	<b>submitted (2)</b> 175:21;256:13			
	<b>subpopulations (2)</b> 124:4;132:5			
	<b>subsequently (2)</b>			

77:19;276:3 <b>symptom (2)</b> 277:14;330:20 <b>symptomatic (5)</b> 174:3;178:19;297:10; 298:10;305:10 <b>symptomatically (1)</b> 330:14 <b>symptoms (8)</b> 27:3;53:8;273:2,12, 16;283:1;339:20,22 <b>synapse (6)</b> 88:4,15;143:17; 145:11,13,16 <b>synapses (7)</b> 87:12,15;88:8,9,17; 96:19;107:3 <b>syndrome (10)</b> 18:21;76:12;98:15; 196:17;198:12;250:5; 252:19;257:16;264:11; 307:22 <b>syndromes (8)</b> 174:16,17;175:14; 181:2;252:2;263:21; 264:3;328:20 <b>synergism (1)</b> 240:9 <b>synergistic (1)</b> 46:19 <b>synthesize (2)</b> 86:5;142:11 <b>synthesized (1)</b> 164:21 <b>synthesizes (2)</b> 79:5;81:19 <b>system (40)</b> 15:22;27:8;35:11,11; 49:14;55:17;71:12,13; 107:6,7;119:14;120:3; 121:2,12;124:1;127:9; 132:2;138:7;141:15; 144:10;145:19;146:3; 154:10;157:2;158:8; 164:15;167:7;177:6; 182:6;195:19;196:3,8, 21;258:21;274:1; 275:12;277:8;294:3; 329:15;345:14 <b>systemic (5)</b> 123:11;134:6,7;182:2; 183:5 <b>systemically (6)</b> 120:20;122:10;134:9, 10;184:20;286:3 <b>systems (9)</b> 16:18;17:3,8;55:18; 129:16;155:15;182:6; 185:16;283:9	269:13 <b>tables (1)</b> 236:16 <b>tablet (2)</b> 283:15;306:20 <b>tachycardia (1)</b> 204:14 <b>tail (2)</b> 85:14;248:5 <b>tailor (1)</b> 337:6 <b>take-home (3)</b> 107:7;242:13;332:17 <b>talk (60)</b> 5:18;6:10,11,15,21; 10:10;13:9;17:14;23:3, 10;59:12;71:17,21; 72:22;73:21;75:21;76:2; 77:15,20;87:6,9,10;94:3; 110:3;119:20;136:6,13; 164:17;180:20;184:22; 185:22;187:4;189:9; 195:3;197:13;201:4,5; 216:3;228:1,4,19,20; 229:1;238:8;239:2; 252:5;258:17;278:5; 295:14;296:16;303:12; 315:2,15;316:13,14; 326:9;334:3;340:14; 341:4;346:10 <b>talked (5)</b> 57:22;58:8;165:2; 181:8;225:17 <b>talking (14)</b> 5:6;88:15;89:2,15; 90:17;110:22;188:22; 203:20;220:19;223:14; 227:1,4;303:22;330:21 <b>talks (2)</b> 65:22;313:14 <b>tanezumab (9)</b> 230:11;232:2;249:11, 13;253:18;254:7;255:8; 256:17;258:2 <b>target (27)</b> 38:5;41:6;49:3;64:11; 96:22;108:4;115:1; 122:8;124:20;144:5; 152:13;153:6;154:6,7; 155:10;157:17;162:11; 164:1,2;197:6;266:8; 267:18,22;315:21; 317:3;325:17;343:13 <b>targeted (5)</b> 108:1;143:6;146:12; 160:7;163:19 <b>targeting (17)</b> 38:7;48:5;124:1,3,15; 125:1;126:20;132:5,21; 133:1;155:8;179:18; 266:7,12,14;267:9;303:6 <b>targets (12)</b> 96:21;153:4,7;157:16;	184:11;195:22;218:1,7, 9;229:21;266:20;315:20 <b>task (1)</b> 14:3 <b>tasks (1)</b> 9:6 <b>taxi (1)</b> 295:5 <b>Taxol (5)</b> 93:14,15;95:12; 105:15,19 <b>teacher (1)</b> 196:5 <b>team (6)</b> 65:20;181:11;189:8; 246:14;247:9;250:14 <b>Tech (1)</b> 136:20 <b>technical (2)</b> 246:19;258:14 <b>technique (4)</b> 37:9,10;41:19;57:13 <b>technologies (3)</b> 16:21;169:22;339:15 <b>technology (14)</b> 8:6,17,19,19;13:7; 44:6,11,55:1;61:9; 63:19;64:4;132:4; 188:14;200:15 <b>telcagepant (17)</b> 284:7,16;307:1,2,12, 19;308:4,5,7,14;310:19; 311:7;312:3,4;323:13, 18;324:4 <b>telling (4)</b> 83:1;142:18;232:3; 309:17 <b>tells (3)</b> 63:13;145:18;210:8 <b>telomerase (1)</b> 12:21 <b>temperature (2)</b> 129:17;163:13 <b>temperatures (3)</b> 161:18,20;163:10 <b>tempted (1)</b> 261:6 <b>tempting (1)</b> 293:21 <b>tend (6)</b> 224:20;252:2;333:8, 17;340:4;349:18 <b>tends (1)</b> 293:9 <b>tercagepant (4)</b> 286:3,7,10;287:16 <b>Terlau (1)</b> 162:10 <b>term (2)</b> 94:18;125:2 <b>terminal (11)</b> 63:15;70:6,8;88:20; 89:1,8,13,16,18;175:20;	287:15 <b>terminals (5)</b> 66:19;86:8;88:5; 117:11;326:22 <b>terminate (1)</b> 159:21 <b>terminus (2)</b> 138:18;152:8 <b>terms (15)</b> 195:18;196:20; 203:10,19;206:19; 212:1;218:19;229:11,17, 20;242:11;255:9;266:8; 270:6;325:8 <b>terrible (2)</b> 98:16;337:20 <b>terrific (6)</b> 83:18,20;90:4;112:3, 19;180:10 <b>territory (1)</b> 346:10 <b>test (12)</b> 11:16;47:7;64:2; 92:21;121:18;123:11; 131:7;264:3;310:17; 324:2;327:4;334:22 <b>tested (12)</b> 48:16;121:12,15; 122:11;124:22;129:15; 131:6,6;269:7;320:20; 322:9;343:10 <b>testing (13)</b> 9:12;92:22;261:5,21; 320:6;321:1,7;322:12; 324:5;327:10;329:21; 331:7;345:5 <b>tests (2)</b> 47:14;344:8 <b>tethered (2)</b> 147:14;165:4 <b>tetramer (1)</b> 127:1 <b>tetrodotoxin (2)</b> 138:22;159:15 <b>Teva (1)</b> 296:1 <b>textbook (1)</b> 305:18 <b>thalamic (1)</b> 302:10 <b>Thanks (14)</b> 5:9;66:12;74:22; 104:14,16;136:7; 190:10;191:9;192:1; 214:16;220:21;227:21, 22;325:21 <b>thaw (1)</b> 44:21 <b>theme (2)</b> 34:10;75:6 <b>theoretically (1)</b> 58:14 <b>theory (2)</b>	98:19;278:2 <b>therapeutic (11)</b> 109:16;132:9;180:1; 234:10;243:12;292:16; 299:8,11;317:19;322:10, 11 <b>Therapeutics (2)</b> 34:9;52:18 <b>therapies (11)</b> 4:21;5:5;65:12;67:20; 76:19;181:16;182:7,19; 189:12;306:1,2 <b>therapy (35)</b> 6:13;7:1;53:20;64:5, 16;68:20;110:17; 112:16;115:1;119:9,17, 19;131:11;170:6; 171:13,15;173:15;176:3, 19,22;178:2;182:1,2,3; 183:13;245:7;272:15; 299:6,13;304:8,10; 305:8;309:18;319:15; 336:5 <b>therefore (14)</b> 144:7,10;145:16; 146:9;151:1;155:7; 156:11;157:10;158:12; 163:12,14,17;301:17; 302:16 <b>thermal (8)</b> 116:16;122:18; 123:13;161:17;162:2; 203:10;236:18;338:15 <b>thermosensors (2)</b> 163:1,2 <b>thigmotaxis (1)</b> 216:8 <b>thin (2)</b> 276:8;280:7 <b>thinking (18)</b> 18:1;103:18;118:19; 134:19;135:22;136:2; 182:5;193:9;195:21; 220:20;226:20;239:6; 260:7;264:20,21;265:7; 299:21;333:11 <b>thinner (1)</b> 294:10 <b>third (2)</b> 42:6;292:1 <b>Thirdly (2)</b> 260:14;267:21 <b>Thompson (1)</b> 7:9 <b>Thomson (1)</b> 66:2 <b>thoroughly (1)</b> 69:4 <b>though (15)</b> 40:8;50:12,17;67:8; 71:20;107:14;110:3; 145:14;146:12;155:16; 235:19,21;245:19;
<b>T</b>				
<b>table (1)</b>				

266:13;269:10 <b>thought (25)</b> 5:17;7:4;20:15;22:2; 32:12;61:7,18,21;69:10; 75:17;83:8;124:6; 126:15;158:9;162:12; 169:20;197:5;228:12; 261:1;262:3;267:12; 278:8;299:18;333:5; 344:5 <b>thoughtful (1)</b> 336:20 <b>thought-provoking (1)</b> 209:22 <b>thoughts (1)</b> 259:7 <b>thousand (2)</b> 8:21;235:21 <b>thousand-fold (1)</b> 162:14 <b>three (50)</b> 22:18;23:6;24:12; 28:7;29:1;37:18,19; 43:5;47:13;56:21;92:6, 6;122:2;131:21;141:1,2, 22;163:7;164:2;192:10; 201:1;222:12;237:7,22; 238:14;249:5;250:14; 275:9;281:6;287:5; 308:17,18;314:5;315:16, 21,22;317:13;318:13; 320:20;321:11,13,13; 324:17;332:11,14,18; 343:16;344:19,22; 345:17 <b>threefold (1)</b> 46:13 <b>threonine (1)</b> 152:7 <b>threshold (5)</b> 92:16,19;102:9;327:7; 328:8 <b>thresholds (4)</b> 30:12;47:2;57:9;340:9 <b>threw (1)</b> 78:9 <b>throat (1)</b> 235:15 <b>throw (1)</b> 269:19 <b>thrust (1)</b> 326:15 <b>tibial (1)</b> 92:7 <b>tie (1)</b> 61:9 <b>tight (1)</b> 21:8 <b>Tim (2)</b> 248:1,11 <b>times (16)</b> 46:17;72:11,14;93:12; 100:9;116:9;183:17;	225:18;229:19;279:22; 286:6;308:6;324:3,4; 340:3;346:22 <b>timing (2)</b> 41:8;173:11 <b>tip (1)</b> 133:13 <b>tired (2)</b> 290:21;314:11 <b>tissue (14)</b> 16:10,14;19:17;26:12, 16,17;31:22;57:12;58:8, 13,15;59:9,17;173:6 <b>tissues (8)</b> 9:19;10:10;11:8;16:9, 15;22:20;61:16;63:3 <b>tissue-specific (2)</b> 125:8,21 <b>title (3)</b> 5:14;137:15;233:11 <b>titled (1)</b> 233:22 <b>titrate (1)</b> 182:22 <b>titration (1)</b> 208:19 <b>Tive (1)</b> 232:6 <b>Tmax (2)</b> 324:17,18 <b>to-back (1)</b> 70:1 <b>today (19)</b> 5:2;7:20;35:21,22; 78:14;114:21;142:20; 190:2;203:1,3;249:11; 261:17;267:19;277:14; 278:22;286:18;334:17; 339:19;353:4 <b>today's (3)</b> 230:15;245:4;274:12 <b>together (21)</b> 14:3,21;16:18;19:6; 22:2;32:8;61:10;66:9; 75:12;150:13,14;169:7; 179:19;189:7;201:12; 272:3;278:18;332:11; 339:16;352:7,19 <b>told (11)</b> 32:5;84:9;125:10; 132:8;133:19;141:16; 154:16;169:19;230:2; 304:5;309:4 <b>tolerability (4)</b> 307:18;309:5;310:2; 312:12 <b>tolerable (5)</b> 307:22;310:6;312:15, 22;313:8 <b>tolerance (2)</b> 119:15;183:14 <b>Tom (5)</b> 214:5,7,7;222:16;	223:14 <b>tone (3)</b> 287:1;303:11;319:21 <b>tongue (1)</b> 133:13 <b>took (16)</b> 8:16;12:7;32:9;34:5; 81:17,21;178:12; 194:11;201:6,11; 209:11;267:4;277:9; 282:1;289:6;313:15 <b>tool (1)</b> 233:13 <b>tooth (2)</b> 147:2,4 <b>top (3)</b> 16:7;276:22;299:3 <b>topic (9)</b> 4:8;5:3;7:12;60:1; 73:6;75:7;78:14;243:22; 350:9 <b>topical (2)</b> 210:11;289:3 <b>topics (2)</b> 191:20;315:9 <b>total (3)</b> 28:4,6;72:11 <b>totally (5)</b> 37:2;256:16;325:4; 342:12;349:9 <b>totipotent (1)</b> 61:12 <b>Toto (6)</b> 136:5,15,15;137:6,7; 183:21 <b>touch (4)</b> 123:21;154:16;339:3; 353:12 <b>touches (1)</b> 146:22 <b>tough (3)</b> 89:4;99:6;173:17 <b>towards (7)</b> 250:17;276:2;277:19; 287:6,7,13,15 <b>town (1)</b> 309:8 <b>tox (5)</b> 310:10,11;311:21; 312:1,4 <b>toxic (3)</b> 30:21;202:2,10 <b>toxicity (8)</b> 10:16;13:13;68:4; 70:16,20;266:17;313:5; 325:16 <b>toxicology (6)</b> 43:12;204:8;317:7; 318:10;320:8,10 <b>toxin (1)</b> 138:20 <b>toxins (6)</b> 138:4;140:17;141:18;	165:5,13;184:2 <b>trace (1)</b> 87:7 <b>tracer (9)</b> 87:4,5,7,14,18,22; 88:3;285:21;286:8 <b>tracers (1)</b> 87:4 <b>tracing (2)</b> 276:10;286:5 <b>track (2)</b> 246:8;264:12 <b>traditional (1)</b> 76:19 <b>train (2)</b> 47:12;219:16 <b>trained (2)</b> 88:8;112:4 <b>trainees (1)</b> 333:13 <b>training (4)</b> 38:2;47:14;339:8,13 <b>trans (1)</b> 114:17 <b>transcript (5)</b> 114:5;187:3,8,10; 192:7 <b>transcription (6)</b> 8:8;62:17;63:5,9;98:8; 187:6 <b>transcriptional (3)</b> 124:10,22;132:21 <b>transcripts (1)</b> 187:1 <b>transdifferentiating (1)</b> 185:19 <b>transductional (1)</b> 125:1 <b>transection (1)</b> 198:5 <b>transfer (1)</b> 114:13 <b>transformation (1)</b> 304:3 <b>transgene (1)</b> 125:9 <b>transgenic (2)</b> 13:20;187:12 <b>transient (1)</b> 119:9 <b>transitioned (1)</b> 240:20 <b>transitioning (1)</b> 240:16 <b>translate (4)</b> 134:20;251:9;333:6; 339:7 <b>translating (1)</b> 135:10 <b>translation (16)</b> 179:16;228:15;229:5; 254:15;265:15;332:12, 20;334:16,16;335:8,9,	12;336:7;337:1;341:1; 351:16 <b>translational (7)</b> 42:8;189:8;332:9,18; 335:11;338:2;339:1 <b>translations (1)</b> 334:15 <b>transmembrering (1)</b> 128:18 <b>transmission (2)</b> 144:17;325:10 <b>transmitted (1)</b> 113:18 <b>transmitters (1)</b> 282:12 <b>transplant (40)</b> 39:6,8;46:6;50:8;51:8; 52:21;80:17;83:6;84:14, 22;85:2;87:20,21;88:1, 6;89:2,12,15;90:1,15; 92:13,20;93:17,18;94:1, 4,9,12;96:17;97:3; 99:16;100:11;102:16,19, 21;104:5;109:18;176:2; 178:15;180:9 <b>transplantation (5)</b> 5:16;9:21;10:9;35:6; 178:10 <b>transplanted (23)</b> 56:10;81:21;82:12,16; 83:20;86:8,12;87:6,10, 12;88:14,16,22;90:5; 91:3,16;93:9;97:9;99:8; 100:1,18;101:6;103:7 <b>transplanting (5)</b> 83:8;92:21;95:16; 96:10;97:20 <b>transplants (19)</b> 10:1,6;36:1;37:21; 39:19;43:4;55:10;59:11, 13,22;67:13;68:15;73:8, 19;74:10;75:22;90:19; 100:15;106:4 <b>transport (1)</b> 116:19 <b>transported (2)</b> 113:21;117:12 <b>traumatic (3)</b> 105:11;106:2;340:5 <b>traveled (1)</b> 272:12 <b>travels (1)</b> 353:17 <b>treadmill (1)</b> 324:1 <b>treat (21)</b> 6:15;18:2;19:11;76:6, 18;79:9,17;93:17,18; 100:13;113:12;118:1,2, 20;128:21;136:14; 176:8;297:9;314:7; 316:4;330:14 <b>treated (2)</b>
--	--	---	---	---

96:10;212:3 <b>treating (3)</b> 130:4;268:1;274:18 <b>treatment (13)</b> 79:18;114:22;120:20; 205:9;210:14;212:22; 221:13,13;225:13; 234:10;279:1;282:7; 314:13 <b>Treatment-related (1)</b> 322:14 <b>treatment-resistant (1)</b> 225:1 <b>treatments (2)</b> 225:11;327:13 <b>tremendous (2)</b> 5:4;192:2 <b>tremors (1)</b> 142:16 <b>trend (4)</b> 256:3,12;257:17; 309:14 <b>trial (72)</b> 6:15;20:1,9,19;21:11, 12,14;23:16,22;24:10; 34:8;42:22;43:1;49:18, 20,22;50:1,6;51:16; 52:16;58:14,16;69:1,3,7, 19;74:21;174:20; 195:13;197:6,8,17; 200:19;201:4;205:7,11, 16,22;206:15;207:17; 208:15;209:20;211:21; 212:21;213:3,9;219:9, 11;221:14;223:11; 225:22;226:2;231:21; 235:17;254:1;257:5; 258:10,10;316:6,6; 317:17,18;331:1,18; 335:18;336:10,11;344:9, 21;345:1,2;351:3 <b>trialed (1)</b> 172:13 <b>trialist (2)</b> 259:4;351:12 <b>trials (68)</b> 13:19;21:1;26:6; 34:12;43:8;51:20;53:3; 60:13;65:1,6,17;104:19; 131:12;135:11;151:20; 152:2;153:2;181:18; 184:2;188:20;193:1; 199:21,22;203:22; 205:18;206:16,18; 207:2;208:3,22;211:18; 223:2,9;225:19;226:15, 20,21;228:16;230:8; 236:5;246:20;254:11, 21;255:10;259:22; 264:5;268:12;283:14; 312:10;330:10;333:15, 21;336:16,19,21;337:8; 340:8,10;341:15,18;	342:10,22;343:7;344:19, 19;345:1,18;351:11 <b>tricks (1)</b> 13:2 <b>tricky (1)</b> 115:17 <b>tried (25)</b> 55:19;69:9;70:19; 83:18,20;100:16; 102:16;109:2;120:18; 134:8;164:20,20;165:2, 5,7;175:10,11,11;177:7; 187:12;277:2,3;283:13; 288:20;313:1 <b>trifurcates (1)</b> 92:5 <b>trigeminal (47)</b> 95:17,19,21;96:2,7,13; 97:17,22;105:14;177:4; 180:5,10;199:9;275:12; 276:11;277:8,10;281:14, 15,18;286:18;289:12; 290:9,12;291:22;292:3, 4,15;293:8,16;294:1; 299:15;300:10,11,18; 302:7,8;303:6,7;318:6; 330:8,17,22;334:21,22; 335:16;343:20 <b>triplicate (1)</b> 324:20 <b>triptan (6)</b> 282:7;294:13;299:12; 307:6;308:2,21 <b>triptans (10)</b> 283:7;285:16;298:2; 299:6,8,10;304:12; 306:13;309:8;331:14 <b>trivial (1)</b> 38:4 <b>troop (1)</b> 142:4 <b>troops (1)</b> 64:6 <b>trouble (1)</b> 322:3 <b>TRPV1 (20)</b> 90:13;124:11;126:4,8, 11,16,20,22,22;127:8, 10;128:2,7,9,14,16,19; 129:8;130:1;132:12 <b>TRPV1-positive (2)</b> 126:6,14 <b>true (19)</b> 25:8;66:4;83:2;96:19; 106:1;111:6;122:3; 131:1;136:1;141:1; 162:11;175:20;229:4; 260:3;327:3,14;329:17; 333:6;336:10 <b>truer (1)</b> 225:10 <b>truism (1)</b> 349:3	<b>trunks (1)</b> 32:20 <b>try (42)</b> 6:1;31:9;35:13;41:21; 53:21;58:14,16;61:9; 65:17;73:1,16;75:12; 80:10;83:3,4;85:18; 86:3;99:5;100:15; 104:11;125:2;134:12; 135:9;169:1,11;171:4; 182:22;184:20;189:18; 193:10;229:2;230:4; 250:19;251:11;252:22; 263:1;284:4;295:19; 296:14;304:16,19;337:6 <b>trying (29)</b> 16:19;17:6,17;21:5; 22:8;24:2,5,8;55:16; 65:5;76:6;77:2;79:19, 21;95:13;98:2;132:3; 185:7;189:16,19; 220:22;227:14;229:20; 241:14;249:15;259:5; 266:2;311:20;336:8 <b>Tufts (1)</b> 227:8 <b>tumor (2)</b> 26:7;284:12 <b>tumors (2)</b> 101:14,15 <b>tundra (1)</b> 42:3 <b>tunnel (2)</b> 22:14;84:19 <b>TURK (10)</b> 191:3,4;214:15;222:8; 226:18;264:19;268:21; 271:17;292:20;294:15 <b>turn (12)</b> 29:15;56:5,6;57:8; 81:12;87:4,14,21,22; 103:6;109:6;119:16 <b>turned (5)</b> 81:14;87:18;120:6; 130:2;281:22 <b>turns (15)</b> 120:4;123:5;144:15; 146:13;149:2;151:18, 22;152:10;153:17,18; 155:22;161:2;164:1; 227:22;230:17 <b>Twenty (2)</b> 112:10,11 <b>Twenty-five (1)</b> 55:11 <b>twice (2)</b> 88:12;314:6 <b>twist (1)</b> 140:19 <b>two (98)</b> 8:4;16:8;27:2,16; 28:10;37:18;42:13,20; 50:14;51:21;52:6;61:9;	63:9;72:7;92:6;98:13; 99:16;113:7;118:6; 122:1,13;124:4,20; 125:5,6,12;126:2,10; 127:10,11,13;130:14; 138:16;150:18;151:2, 19;160:15;161:17; 162:5;172:7;179:19; 191:14;192:15;195:15; 196:8,20;201:15; 202:14;205:11;207:21; 212:10;213:21;216:13; 222:22;223:12;234:1; 235:3;241:13;246:15; 255:18,22;257:19; 258:19;259:1;265:10; 267:18;272:19;283:9; 287:9;292:22;293:3; 295:18;296:5;297:6; 306:3,3;307:3,4;309:11; 314:5;318:13,22;319:1, 4,6;320:17,21,22; 321:17,18;323:8; 327:21;333:6;334:14; 337:22;343:14;350:15; 353:10 <b>two-hour (1)</b> 77:9 <b>two-thirds (1)</b> 306:7 <b>Tylenol (1)</b> 312:7 <b>type (13)</b> 13:10;23:15;94:16; 153:6;155:1,7,8,18; 194:15;195:4;198:12; 200:5;242:22 <b>type-reporting (1)</b> 350:20 <b>types (23)</b> 4:21;7:1,9;22;22:18; 29:7;34:4;81:3;110:22; 126:2;127:22;137:22; 138:1;155:10;158:19; 159:2,11;170:12; 173:15;189:3;243:1; 245:21;246:1;250:14 <b>typical (2)</b> 140:4;205:8 <b>typically (2)</b> 209:21;337:15 <b>typology (1)</b> 219:4	350:19 <b>ulcer (1)</b> 198:14 <b>ulcers (1)</b> 198:16 <b>ultimately (5)</b> 57:1;74:12;218:1; 249:22;270:2 <b>ultrastructures (1)</b> 111:10 <b>unbelievable (1)</b> 176:5 <b>unbelievably (1)</b> 107:6 <b>unblinding (1)</b> 214:22 <b>uncoordinated (1)</b> 140:20 <b>under (16)</b> 21:8;34:16;35:4; 37:12;44:9;89:20;98:17; 99:1;107:10;141:1; 163:14;200:11;220:5; 249:6;311:10;345:11 <b>undergo (2)</b> 96:4;186:12 <b>undergoing (1)</b> 31:17 <b>undergraduate (2)</b> 136:19;139:15 <b>undergraduates (1)</b> 142:5 <b>understood (1)</b> 340:21 <b>underway (2)</b> 43:13;321:8 <b>unduly (1)</b> 204:10 <b>unexpected (1)</b> 157:11 <b>unforeseen (1)</b> 95:6 <b>unfortunate (3)</b> 13:16;183:12;327:18 <b>unfortunately (7)</b> 69:19;96:13;102:14, 14;163:20;180:22; 181:22 <b>unilateral (4)</b> 43:3;50:8;51:2;282:22 <b>uninfected (1)</b> 117:1 <b>unique (11)</b> 50:2,5;93:20;127:16, 16,21;136:14;187:6; 282:14;293:8,16 <b>unit (1)</b> 323:21 <b>United (2)</b> 5:12;296:6 <b>United's (1)</b> 5:10 <b>units (1)</b>
---	---	---	---	---

196:18 <b>universally (1)</b> 185:9 <b>University (11)</b> 4:14;98:6;112:14; 139:15;140:9;154:1; 164:9;200:16;214:2; 227:8;272:9 <b>unknown (1)</b> 28:20 <b>unless (3)</b> 42:11;71:6;244:10 <b>Unlike (2)</b> 8:16;166:5 <b>unlikely (1)</b> 313:4 <b>unmet (2)</b> 77:6;264:11 <b>Unmyelinated (2)</b> 124:5;280:8 <b>unpredictable (1)</b> 221:11 <b>unusual (2)</b> 139:7;235:6 <b>unwanted (1)</b> 119:16 <b>up (83)</b> 4:18;7:4;8:1,12;9:20; 11:11;12:12;15:1,13; 16:4;20:6,19;21:7;27:8; 29:13;33:10;36:3;38:10; 16;39:18;44:20;45:19; 49:19;54:1,4,14;55:20; 56:11;61:12;62:7,8,13; 63:10;84:16,18;85:12; 87:5,20;88:4;116:18; 120:7,10;129:7,17,21; 130:9;133:20;136:15; 137:15;140:22;142:12; 145:16;158:15,17;159:6, 9;171:9;182:1;192:11; 214:3;216:2;217:4,8,20; 218:19;222:11;228:1; 232:12;249:21;254:22; 255:18;271:12,21; 272:20;275:20;280:13; 286:2;326:6;336:13; 343:22;346:11;352:10, 17 <b>update (2)</b> 6:11;42:16 <b>updated (1)</b> 61:22 <b>updates (2)</b> 45:8;353:14 <b>upon (6)</b> 271:1,4;275:16; 281:10;323:21;347:10 <b>upper (5)</b> 27:9,10,19;35:14;54:2 <b>upregulated (2)</b> 232:22;233:15 <b>ups (1)</b>	235:22 <b>uptake (3)</b> 129:12,14;171:18 <b>USA (4)</b> 28:15;57:17;209:10; 223:3 <b>usage (2)</b> 167:12;310:18 <b>use (74)</b> 9:5;18:1;21:2,3;22:12, 20;31:20;34:6,10,11,12; 38:18,19,20;42:18;49:2; 54:21;56:19;58:2;59:13, 15,17;61:2;67:2;72:22; 73:19;75:21;78:1;79:18; 80:14;91:21;92:1;96:22; 106:2;108:19;114:14; 117:3;120:5;121:10; 123:6,15;125:22; 126:13;127:9,11;132:3, 7;134:9;148:10;151:9, 18;156:5;159:12;160:8; 182:21;187:13;206:18; 217:2;224:9;271:10; 284:14;305:10;310:14, 15;311:3;312:20;313:2, 9;314:5;335:20;336:4; 338:4;340:7;351:19 <b>used (50)</b> 17:18,20;21:3;22:14; 23:16,20;25:14;48:2,17; 57:22;61:3,15,18;116:2; 119:22;120:13;124:9; 127:13;128:15;130:11; 134:10,11;147:14,21; 164:14;179:13;180:7; 197:14,17;199:20,21; 201:2,3;203:20,21; 205:18;206:9;211:5; 216:21;230:11;245:21; 246:1,4;249:13;251:14; 280:3;286:4;305:9; 331:12;338:12 <b>useful (9)</b> 22:5;56:7;107:9; 137:19;146:15;188:17; 193:12;209:18;211:15 <b>usefulness (1)</b> 213:8 <b>uses (3)</b> 19:10;61:4;116:5 <b>using (51)</b> 6:16;8:21;11:5;14:11; 21:14;31:21;33:6;48:13; 49:5,15,17,20;51:12; 53:20;55:17;63:9;74:14; 90:10,12;91:7;93:14; 95:11;101:3;103:5; 110:19;112:17;119:14; 124:3;125:18;127:1; 129:11;133:15;140:1; 142:6;158:18;160:6; 164:18;171:15;172:5;	220:9;224:10;225:4; 251:5;260:6;261:3; 290:20;310:20;317:1; 327:19,21;330:20 <b>usual (2)</b> 47:5;348:6 <b>usually (10)</b> 22:16;28:7,14;76:9; 78:16;99:14;113:16; 114:11;115:4,6 <b>Utah (4)</b> 139:15;154:1;164:7,9 <b>utility (2)</b> 103:11;137:2 <b>utilized (1)</b> 181:22 <b>utilizing (1)</b> 263:1	18:9;152:11;153:9; 155:21;196:12;198:1, 20;202:17;223:14;252:7 <b>vary (1)</b> 316:11 <b>vascular (6)</b> 277:11;293:14; 299:19,21;334:22;335:1 <b>vasculature (1)</b> 293:8 <b>vasoconstriction (4)</b> 277:19;303:10,12; 304:7 <b>vasoconstrictive (1)</b> 299:22 <b>vasoconstrictor (2)</b> 278:7,9 <b>vasoconstrictors (2)</b> 277:3,3 <b>vasodilatation (1)</b> 288:1 <b>vasodilation (7)</b> 299:3;300:4,4,7,7,13, 16 <b>vasodilator (2)</b> 299:2;323:6 <b>vasodilators (2)</b> 277:2,13 <b>vasodilatory (3)</b> 300:3;303:9;306:15 <b>vast (1)</b> 158:2 <b>VC (1)</b> 241:4 <b>VC-backed (1)</b> 242:1 <b>vector (14)</b> 118:6,21;122:3,13,19, 20;128:21;129:13,15; 130:15,19,21;131:3; 170:13 <b>vectors (4)</b> 112:17;118:3;133:19; 165:7 <b>VEGF (1)</b> 70:1 <b>vehicle (1)</b> 45:21 <b>vein (2)</b> 226:22;281:21 <b>velocity (1)</b> 203:16 <b>venom (19)</b> 138:16;139:7,16,17; 140:15;141:17;142:1; 147:3,15,21;148:6; 150:6,8,8,21;151:6; 157:14;166:2,3 <b>venomous (1)</b> 137:19 <b>venoms (4)</b> 153:19;155:16;166:1, 7	<b>ventral (5)</b> 48:5;71:19;85:4; 108:1,4 <b>ventricles (1)</b> 19:13 <b>ventricular (1)</b> 204:13 <b>venture (2)</b> 212:15;214:10 <b>verge (1)</b> 294:11 <b>versa (3)</b> 333:10,16,19 <b>version (2)</b> 210:21;230:19 <b>versus (8)</b> 39:15;51:11;217:19; 261:5;303:20;308:3; 320:21;330:20 <b>vertebrate (1)</b> 146:3 <b>Vescovi (1)</b> 52:18 <b>vesicles (3)</b> 86:14;88:20;276:4 <b>vessel (6)</b> 96:6;275:8;284:9,14; 291:3,8 <b>vessels (13)</b> 51:4;276:8,9;277:1, 21;280:2;286:17; 290:17;299:4;300:8,8,9, 9 <b>VGAT (3)</b> 86:12;109:19;111:13 <b>viability (2)</b> 71:22;72:2 <b>vials (1)</b> 44:20 <b>vice (3)</b> 333:10,16,19 <b>video (1)</b> 37:1 <b>videos (1)</b> 20:8 <b>videotaped (1)</b> 192:6 <b>view (14)</b> 7:18;107:17;119:17; 134:21;171:20;174:1, 10;178:7;185:12; 201:13;211:15;219:22; 257:13;286:12 <b>viewed (3)</b> 252:21;262:8,10 <b>VIP (5)</b> 275:12;282:16,16; 283:5;335:2 <b>viral (3)</b> 112:17;116:20;165:6 <b>virally (1)</b> 164:21 <b>virologist (1)</b>
<b>V</b>				
<b>vaccine (1)</b> 115:22 <b>vacuum (1)</b> 238:22 <b>validate (1)</b> 131:13 <b>validated (3)</b> 252:9;317:3;330:18 <b>validates (1)</b> 318:5 <b>validation (1)</b> 246:6 <b>validity (1)</b> 219:17 <b>value (5)</b> 239:22;256:1,2;257:7, 17 <b>values (1)</b> 284:19 <b>vantage (1)</b> 263:3 <b>variability (1)</b> 206:12 <b>variable (2)</b> 50:12;146:14 <b>variant (1)</b> 168:13 <b>variants (1)</b> 169:3 <b>variations (2)</b> 34:10;202:3 <b>varicella (1)</b> 115:2 <b>varied (1)</b> 29:12 <b>varies (1)</b> 320:15 <b>variety (11)</b> 83:5;87:4;90:10;98:3; 106:10;137:4;151:19; 179:9;241:12,18;344:17 <b>various (10)</b>				



83:19 <b>virologists (1)</b> 135:1 <b>virtually (5)</b> 229:14;245:17; 280:15;288:3;350:2 <b>virus (39)</b> 42:19;67:6;113:13,18; 114:1,11,14,18;115:3,3, 8;116:3,17;117:10,10, 13;118:7,12,12,15; 119:5;121:19;123:10; 124:15;125:5,6;127:9, 10,15;128:2,5,7,12; 129:1,4;130:5;133:1; 135:13;164:18 <b>viruses (5)</b> 116:3;124:1;125:17; 133:3,4 <b>virus's (1)</b> 124:17 <b>visceral (6)</b> 250:12;255:19; 257:11,22;264:15;343:9 <b>visibility (1)</b> 249:7 <b>vision (2)</b> 264:3;276:21 <b>visual (4)</b> 209:17;273:14,15,17 <b>vital (1)</b> 134:22 <b>vitro (4)</b> 17:13;55:19;102:18; 165:9 <b>vivo (7)</b> 17:15;55:19;56:10,14; 165:9,10;289:9 <b>voltage-gated (4)</b> 139:1;143:13;144:6,8 <b>voluntarily (1)</b> 319:22 <b>voluntary (1)</b> 312:8 <b>volunteers (2)</b> 251:6;263:5 <b>von (4)</b> 47:6,13,17;245:15 <b>vulnerability (1)</b> 298:19 <b>vutron (1)</b> 143:10 <b>VZV (1)</b> 116:5 <b>VZV-infected (2)</b> 115:21;130:14	312:9 <b>waiting (1)</b> 53:2 <b>wake (1)</b> 140:22 <b>Walicke (3)</b> 231:18,18;250:8 <b>Walicke's (1)</b> 253:2 <b>walk (2)</b> 243:17;324:5 <b>Walker (1)</b> 115:20 <b>walking (1)</b> 231:1 <b>wander (1)</b> 346:9 <b>wants (1)</b> 222:10 <b>watching (1)</b> 191:15 <b>wave (1)</b> 58:15 <b>way (64)</b> 18:17;27:10,11,12; 32:12;33:2;40:4;44:17; 50:21;55:15;58:5,21; 59:7;60:15;65:2;67:21; 69:21;73:16;78:2;83:16; 87:18;91:2;103:15; 106:22;109:5;123:8; 128:11;142:11;148:2; 159:9;160:6;167:11; 189:7;193:10;194:8; 198:21;209:18,22; 213:19;217:11;223:5; 225:9;232:11;242:18; 251:1;265:19;266:3,16; 267:8;268:16;277:10; 289:2;292:11;300:1; 301:17;309:2;320:7; 333:12;338:4;339:7; 348:17;352:19;353:6,10 <b>ways (7)</b> 79:6;103:3;124:2; 134:11;153:9;157:15; 268:10 <b>weak (1)</b> 108:22 <b>weakness (1)</b> 273:19 <b>weaning (1)</b> 183:5 <b>weapon (1)</b> 64:7 <b>website (4)</b> 192:7;206:22;226:1; 353:13 <b>week (5)</b> 118:22;208:11; 210:16;320:11;343:18 <b>weeks (35)</b> 12:13,14;33:10;47:13;	52:6;59:12;72:6,8; 73:13;85:8;98:14;99:16, 22;107:1,3;108:12; 116:12;118:4,6;122:2, 13;130:14,17;141:2,2; 186:5,11,11;192:11; 208:15;252:15,16; 314:7;318:13;333:11 <b>weigh (1)</b> 60:13 <b>weight (1)</b> 320:12 <b>weird (3)</b> 184:7;244:16,20 <b>welcome (3)</b> 4:4;112:20;137:6 <b>well- (2)</b> 252:8;297:22 <b>well-established (1)</b> 232:14 <b>well-known (1)</b> 31:16 <b>well-tolerated (2)</b> 156:20;307:21 <b>weren't (7)</b> 55:18;74:1;161:6; 186:14;213:2;221:2; 267:17 <b>Weskamp (1)</b> 233:5 <b>western (1)</b> 223:2 <b>whatever's (1)</b> 270:21 <b>what's (15)</b> 72:1;93:11;143:6; 153:18;154:6;170:3; 191:12;254:14;265:14; 271:2;300:20;312:11; 315:16;316:15;348:20 <b>whatsoever (1)</b> 256:6 <b>wheat (1)</b> 87:15 <b>whereas (4)</b> 12:16;131:3;206:2; 210:14 <b>Whereupon (4)</b> 136:9;190:11;294:20; 353:18 <b>wherever (1)</b> 93:18 <b>whilst (1)</b> 343:7 <b>whistles (1)</b> 223:17 <b>white (3)</b> 38:13;85:5;101:19 <b>whole (39)</b> 7:11;9:13,16,20; 18:13;24:6,17,22;27:20; 31:11;40:16;47:21;50:4; 53:19;54:2;59:15;72:21;	73:6,12;77:10;133:3; 142:4;150:1,18;185:22; 187:4;189:14;214:17; 225:5;231:4;233:9; 253:5;275:21;290:5; 298:14;329:15;340:16, 18;347:20 <b>who's (3)</b> 5:18;266:15;272:11 <b>wide-bore (1)</b> 21:7 <b>widen (1)</b> 181:8 <b>wider (1)</b> 344:7 <b>widespread (2)</b> 239:11;350:8 <b>wife (1)</b> 42:2 <b>wild-type (2)</b> 54:18;122:21 <b>willing (1)</b> 44:2 <b>win (1)</b> 65:1 <b>window (3)</b> 109:16;120:20;180:2 <b>wind-up (1)</b> 329:14 <b>wins (1)</b> 70:2 <b>wipe (1)</b> 60:5 <b>wipes (1)</b> 138:21 <b>Wisconsin (5)</b> 4:15;7:8;39:15;42:4; 66:3 <b>wisdom (3)</b> 223:1,4;224:18 <b>wish (1)</b> 76:4 <b>withdraw (1)</b> 47:15 <b>withdrawal (4)</b> 116:15;121:17,22; 131:1 <b>withdrawing (1)</b> 40:10 <b>within (11)</b> 28:22;32:18;52:6; 63:3;92:9;99:16;131:20; 245:14,19;271:14; 289:19 <b>without (14)</b> 13:20;32:13;33:4; 71:1;118:12;174:22; 235:20;237:19;253:13; 256:20;284:22;323:9; 332:1;350:11 <b>witness (1)</b> 231:5 <b>witnessed (1)</b>	231:4 <b>wizard (2)</b> 62:1,3 <b>woman (1)</b> 253:3 <b>women (1)</b> 273:9 <b>wonder (1)</b> 183:21 <b>wondered (2)</b> 105:12;327:10 <b>wonderful (1)</b> 351:22 <b>wondering (6)</b> 73:22;104:19;105:1; 109:4;166:13;185:17 <b>wonders (1)</b> 269:11 <b>Woolf's (1)</b> 78:20 <b>word (8)</b> 217:2;222:9;224:9; 245:3;249:11;260:22; 333:19;353:5 <b>words (6)</b> 94:1;120:21;187:13; 201:22;338:11;340:9 <b>work (90)</b> 5:15,19;6:4,18;15:18; 17:5,11,20;21:13;23:10; 35:17;39:14;42:15; 44:10;46:21;52:11;54:9; 55:16,19;57:10;60:10, 11,17;77:17;80:20;81:5; 83:5;86:15;101:6;103:3; 104:5,7,9,12;107:11; 110:1;111:18;112:19; 113:5;124:14;132:16, 19;136:19,21;137:11; 148:19;164:9;167:14,15, 18;168:11;170:20; 171:2,8;191:21;199:17; 200:18;201:9,14;219:5; 221:3;224:7,8;231:20; 244:5;265:12;266:2; 268:2,17;270:2,8; 271:16;274:21;275:5, 15;281:6;283:7,18; 286:16;303:1,16;321:3, 4,16,16;333:8;340:5; 341:13;349:5,13 <b>worked (15)</b> 35:21;55:10;58:9; 65:21;120:19;132:21; 178:11;180:5;214:6; 229:9,13,21;270:19; 278:2;330:11 <b>workhorse (2)</b> 29:10;30:3 <b>working (19)</b> 4:12,20;6:7;44:12; 54:1;66:5;98:6;103:1; 104:10;123:22;135:1;
<b>W</b>				
<b>Waddington (1)</b> 61:11 <b>wait (4)</b> 21:16;25:7;186:13;				

<p>139:13;181:11;189:20;                  237:8;264:2;281:9;                  288:10;352:7  <b>works (21)</b>                  21:17;39:15;60:10,22;                  66:8;72:19,19;80:6;                  83:22;96:8;116:5;                  123:12;165:7;182:14;                  257:10;267:22;312:12;                  314:2;321:3,4;339:9  <b>workshop (1)</b>                  353:18  <b>world (13)</b>                  22:1,1;24:15;42:9;                  94:17;240:13,14;243:16,                  20;254:10;258:6;273:8;                  275:16  <b>worlds (1)</b>                  21:22  <b>worm (1)</b>                  155:8  <b>worm-hunting (1)</b>                  154:14  <b>worms (2)</b>                  137:22;154:13  <b>worried (4)</b>                  39:13;53:5;60:16;                  112:13  <b>worse (4)</b>                  52:22;53:1;157:1;                  330:6  <b>worsening (1)</b>                  235:10  <b>worst (2)</b>                  26:20;157:21  <b>worth (5)</b>                  235:4;237:21;260:15;                  268:19,20  <b>Wow (2)</b>                  88:8;243:15  <b>wrap (2)</b>                  29:9;40:1  <b>write (2)</b>                  37:4;310:3  <b>write-up (1)</b>                  350:11  <b>writing (2)</b>                  42:13;321:22  <b>wrong (8)</b>                  83:12;109:22;140:6;                  230:17,18;268:20;                  272:8;344:3  <b>wrote (3)</b>                  99:4;176:2;289:6  <b>Wyss (2)</b>                  15:13,14</p>	<p><b>Xiaobing (2)</b>                  97:13;98:1  <b>Xidao (1)</b>                  104:6  <b>X-Y (1)</b>                  49:14</p> <p style="text-align: center;"><b>Y</b></p> <p><b>Yamanaka (2)</b>                  7:15;62:2  <b>year (10)</b>                  42:20;49:18;52:17;                  65:4;88:12;115:15;                  342:15;343:22;348:2;                  350:10  <b>years (64)</b>                  4:14;7:6,16;8:1;18:1,                  3;19:7;25:2,4;26:13;                  27:2,2;28:7;29:1,1;                  31:14;32:9;34:19;35:20;                  42:4,13,20;49:1;50:15,                  15;55:7,16;56:21;60:7,                  7;61:22;66:1;70:18;                  75:15;87:3;112:10,11,                  13;119:21;121:11;                  146:11;147:8;171:22;                  186:13,14;196:5;                  207:21;209:12;214:7;                  227:8,10,18;259:21;                  295:11,11;303:2;                  312:21;326:12;329:8;                  330:8;343:17;346:17,                  18;350:15  <b>year's (1)</b>                  340:15  <b>yeast (1)</b>                  317:2  <b>yellow (1)</b>                  84:8  <b>yesterday (13)</b>                  6:19;30:7,7;91:22;                  169:21;181:8;191:5;                  193:6;214:18;222:14;                  252:4;339:20;342:20  <b>York (2)</b>                  23:16;296:7  <b>Yoshitaka (1)</b>                  133:2  <b>young (2)</b>                  281:9;339:10  <b>Yu (1)</b>                  97:13  <b>Yves (3)</b>                  77:16;169:21;172:14</p>	<p><b>zolmitriptan (1)</b>                  308:1  <b>zoster (3)</b>                  115:3,8;135:6</p>		
<b>X</b>	<b>Z</b>			
<p><b>xenografted (1)</b>                  72:17  <b>xenografts (1)</b>                  41:8</p>	<p><b>Zealand (1)</b>                  207:2  <b>zero (5)</b>                  47:12;143:10;271:13;                  306:3;319:15</p>			