Failed Analgesic Programs – Wrong Targets or Wrong Drugs

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Which pain targets have we genuinely invalidated in man?

A small selection of analgesic targets tested with published outcomes

Compound/mechanism	**Model**	Clinical Activity
NK1	CFA, carrageenan, CCI	OA, dental, NP[1]
A1	CCI, acute inflamm models	Dental, NP[2]
Lamictal	CCI	NP[3]
Valproate	CCI, SNL	NP[4]
4030W92	CCI, SNL, CFA	NP[6]
FAAH	MIA, CFA,	OA[7]
TRPV1 antagonists	CFA, Carra	OA[?]
D3 agonist	MIA, Brennan, capsaicin	OA[8]

1. Sindrup SH et al, Eur J Pain. 2006 10(6):567-71, 2. Sneyd JR et al, Br J Anaesth. 2007 98(5):672-6, 3. Rao RD et al, Cancer. 2008 112(12):2802-8, 4. Otto M et al, Neurology. 2004 62(2):285-8, 5. Davies et al, Eur Spine J. 2008., 6. Wallace MS et al, J Pain 2002 3(3): 227-233, 7. Huggins JP et al, Pain 2012 (153): 1837-1846, 8. Morgan P et al, DDT 2012 (17): 419-424

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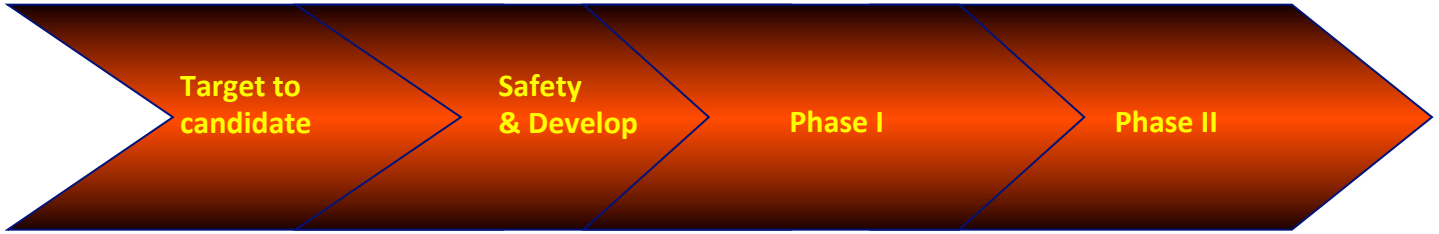
Pressures and outcomes

- Increased regulatory pressure- new drugs have to be “better and safer”
- Diminishing target tractability
- *Failure to demonstrate efficacy in early development phases*

Approximate industry-wide success rates for small molecule pain drugs



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- What are the reasons for failure to demonstrate efficacy?
  - Pharmacological engagement of target in man; limited by off-target effects: Selectivity
    - 70% of the disclosed failures cite target engagement or dose limited by safety/tolerability as reason for failure
  - Did not penetrate correct compartment in man: Biodistribution
  - Inappropriate patient population for mechanism: Study design/population
  - Invalid target (<5%)

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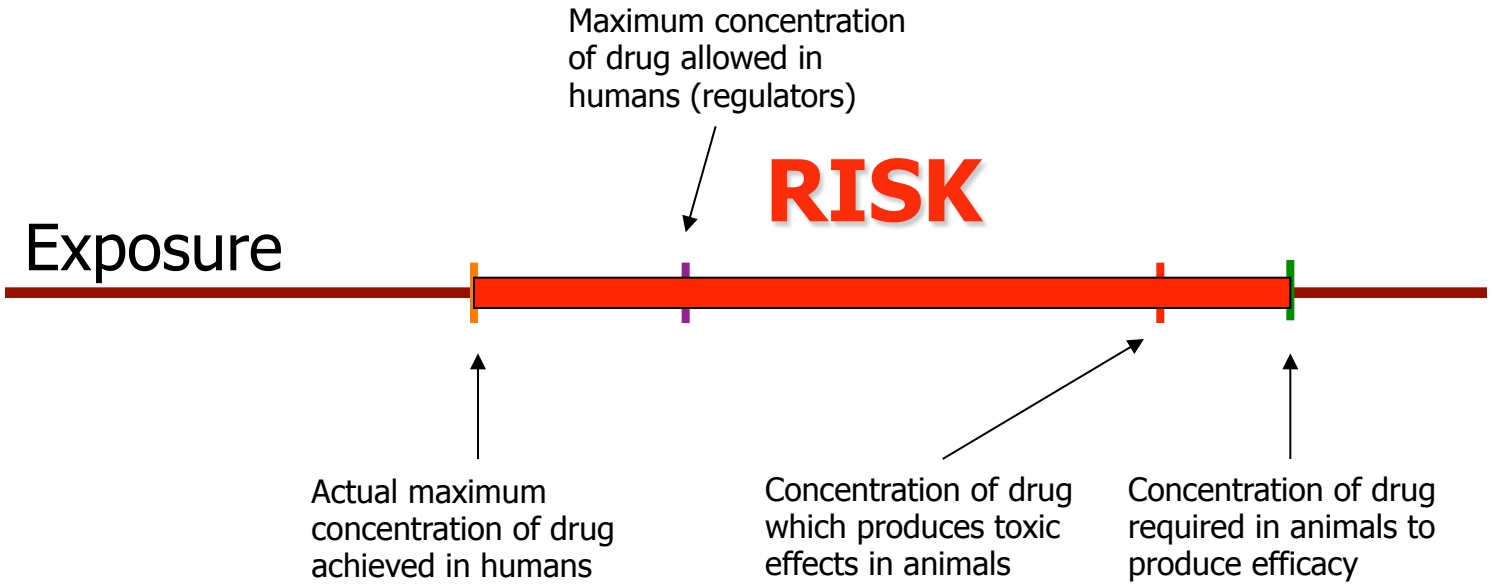
Target engagement in humans

The exposure gap- defining risk



Significant reason for failure of drugs in Phase II is inability to reach concentration in humans to engage the target/reach the right compartment and test the mechanism

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What limits target engagement in humans?

- Safety and tolerability set the limits for exposure
  - Upper limits defined by GLP toxicology or unexpected observations in PhI
  - Tolerability findings often not predicted by toxicology studies; need to test in humans
- Is it target related pharmacology?
  - Usually not
    - Typical detailed cross screens focus on 3-6 “related” targets
    - “Receptograms” cover ~25% of human genome druggable receptors and targets; discovery of liabilities outside of the screened targets remain empirical
    - Metabolism, metabolites, HERG etc are nothing to do with the target
  - But not always
    - TRPV1- heat pain thresholds thresholds, CB1- known psychogenic effects, COX-1/2 – role of products in clotting pathways
- Balance of evidence suggests that attrition would be significantly reduced by step change increases in selectivity of investigational drugs

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Safety/tolerability limits chosen target engagement

A small selection of analgesic targets tested with published outcomes

Compound/ mechanism	**Model**	Clinical Activity	Reason for failure
NK1	CFA, carrageenan, CCI	OA, dental, NP[1]	Target?
A1	CCI, acute inflamm models	Dental, NP[2]	CNS penetration
Lamictal	CCI	NP[3]	Dose/safety/ tolerability
Valproate	CCI, SNL	NP[4]	Dose/safety/ tolerablity
4030W92	CCI, SNL, CFA	NP[6]	Dose/safety/ tolerability
FAAH	MIA, CFA,	OA[7]	Target?
TRPV1 antagonists	CFA, Carra	OA[?]	Target related pharmacol
D3 agonists	MIA, Brenna, Caps	OA	Dose/safety/ tolerability

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Other reasons for failure – which don't test the target

- Access to the right compartment
  - Preclinical predictions of CNS penetration may not translate to humans (e.g. A1 agonist- different facilitated transporter in man vs rodents)
  - Advances in PET biodistribution/occupancy increasingly helping to address this issue
- Wrong disease/subpopulation/endpoint
  - Traditional pressure to test new drugs in commercially appealing segments, sometimes counter to scientific evidence (e.g. Gabapentinoids in OA)
  - Massive heterogeneity of patient populations; stratification paradigms required in early clinical investigation
- Duration of treatment
  - Can be required simply to manage placebo response or for titration
  - Mechanism related
  - Or both (e.g. gabapentin)

Are animal models useful?

- Yes:
  - Can be used to determine at what concentration (exposure) a drug is pharmacologically active
  - Can give guidance on disease segment
  - There are no substitutes at present
- No:
  - Most measures are reflexive, not measures of spontaneous pain
  - Models are not disease models… they are PD models only
  - Mechanisms, redundancy and ADME may be different in animals vs man
- But:
  - The overall validity of models is hard to judge when the sample size of targets which are positive in models but genuinely negative in the clinic is so small

Animal model face validity is good…

Compound	**Model**	Clinical Activity
Pregabalin	CCI	NP
Duloxetine	CCI	NP
Gabapentin	CCI	NP
COX2i	CFA, joint pain	OA Dental
TNFa	Joint pain	RA
NSAID	CFA, joint pain, carra	Broad Spect
Opioid	Nociception	Broad Spect

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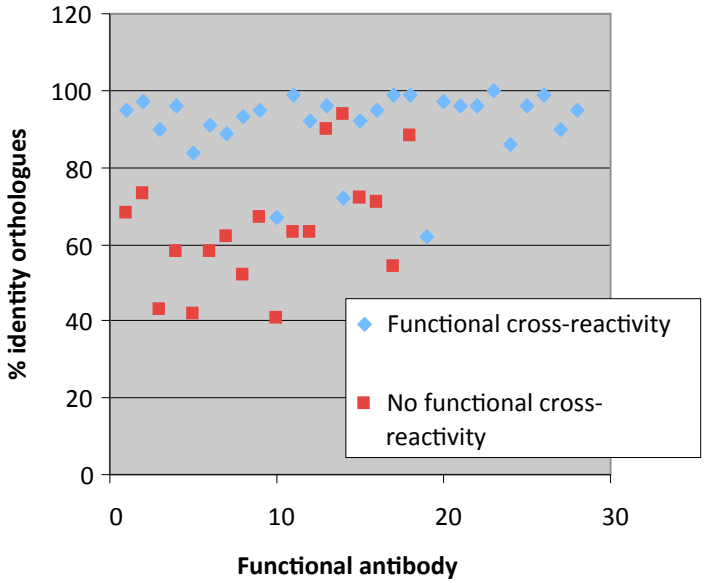
Where do we go from here?

- Ruthless termination
  - If tox or PhI data isn't completely convincing that animal exposures or target engagement required for efficacy equivalent to SoC can be reached in man, stop
  - In the early running, match the science to the patient segment; science first, commercial second – do the right experiment for signal searching
  - If CNS penetration is required in man, consider PET etc to demonstrate it
- Use man as the target ID species
  - Higher reliance on genetic linkage to pursue targets (eg NaV1.7, TrpA1, NGF etc)
  - Serendipitous observation of efficacy with drugs aimed at other diseases need to be investigated with RCTs
- Better selectivity
  - Should lead to lower attrition and reduced numbers of compounds in series to test a target
  - Consider the use of mAbs to validate the target with no off-target activites

Monoclonal antibodies (mAbs) offer the selectivity advantage?

- **The key advantage of a mAb approach is selectivity**
  - Emergent toxicity profiles are target related- no unexpected off-target issues
  - Allows a single shot on goal to test a target in man
- mAbs may offer a better ability to genuinely test a target for efficacy in humans; directing future efforts for small molecule discovery?

- Exquisite selectivity is a bonus and a curse:
  - > 50% of the time, mAbs raised against a human target do not cross-react with a rodent orthologue
  - A single amino acid difference in an epitope coding region can abolish binding
  - Savings in time and resource can be negated by the need to generate a rodent cross-reactive surrogate



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Summary

- Wrong targets or wrong drugs – in most cases the wrong drugs
  - Of many dozens of novel targets tested, only a handful have been invalidated, suggesting that we are not taking the right drug or approach to genuinely test the target in the clinic
  - Balance of evidence suggests that in the majority of cases we have been unable to reach concentrations in humans to fully engage the target; safety, tolerability, off-target effects and failure to reach the target are all contributing factors
  - Heterogeneity or match of mechanism to target population should also be considered a reason for failure to test a target
- The challenge of selectivity can be mitigated using biologics
  - If the target is accessible, this may represent a path forward to test a target and it's pharmacology to add confidence in investing in small molecule discovery and development
  - Large molecules also represent stand alone drugs!

Questions and answers

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