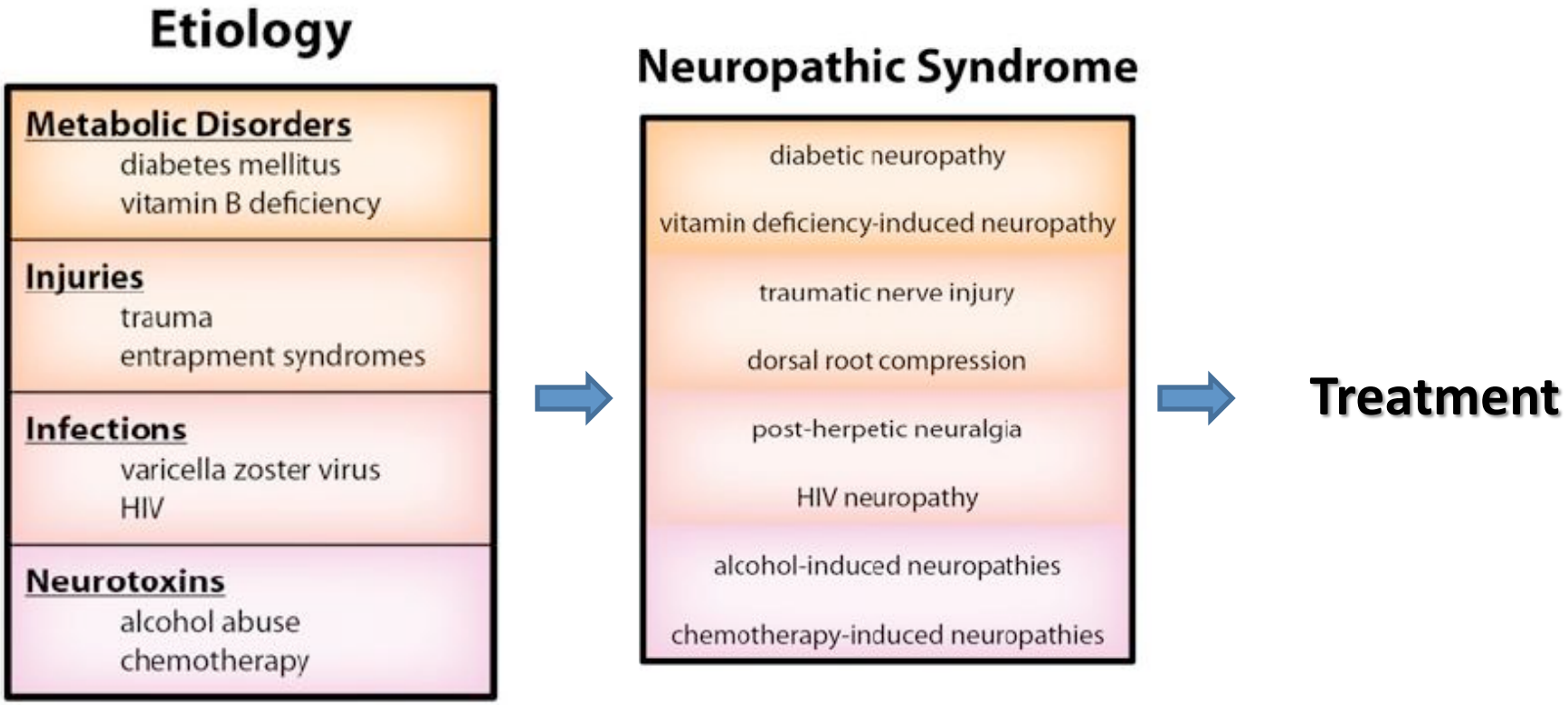
Disease phenotype as the target for novel analgesics

Clifford Woolf

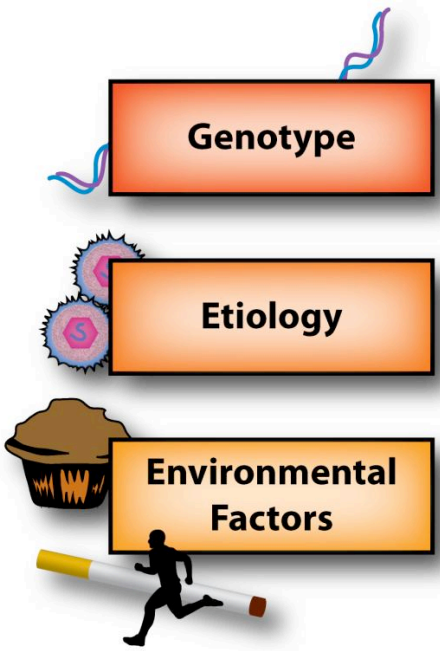
Boston Children's Hospital
Harvard Medical School

The standard pain treatment path



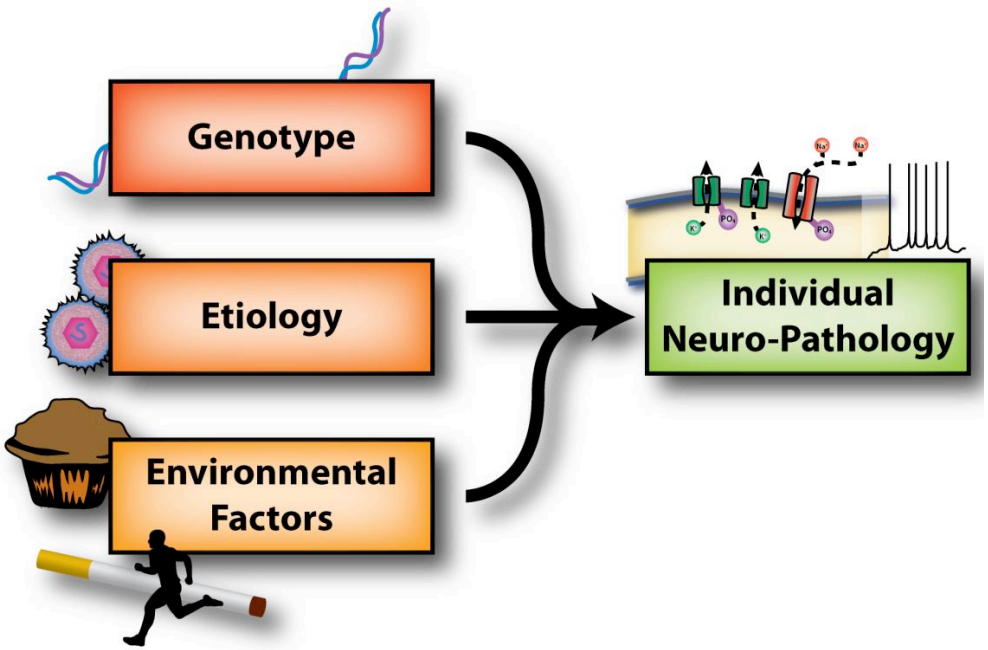
Von Hehn, Baron and Woolf Neuron 2012

An alternative pain treatment path….



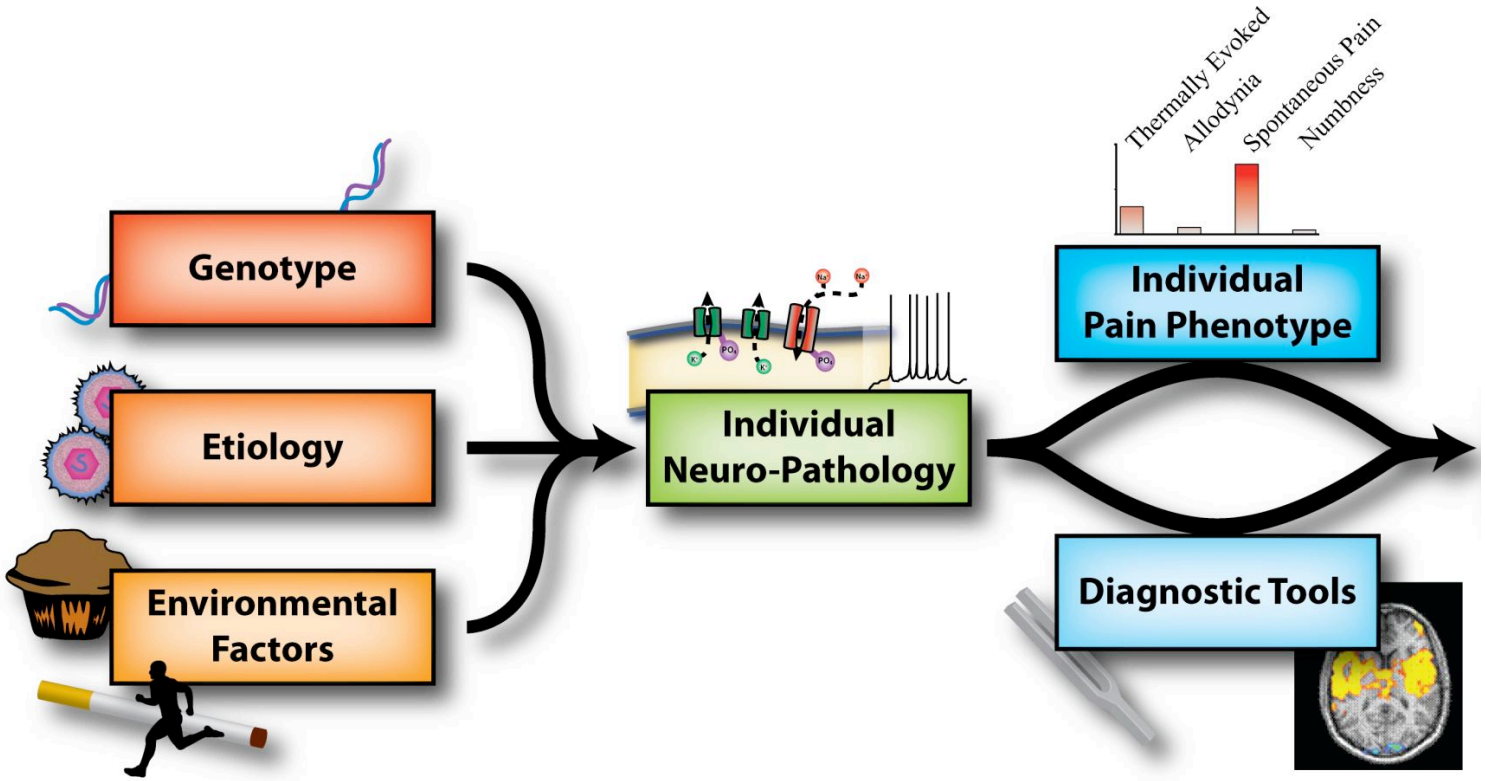
Von Hehn, Baron and Woolf Neuron 2012

An alternative pain treatment path….



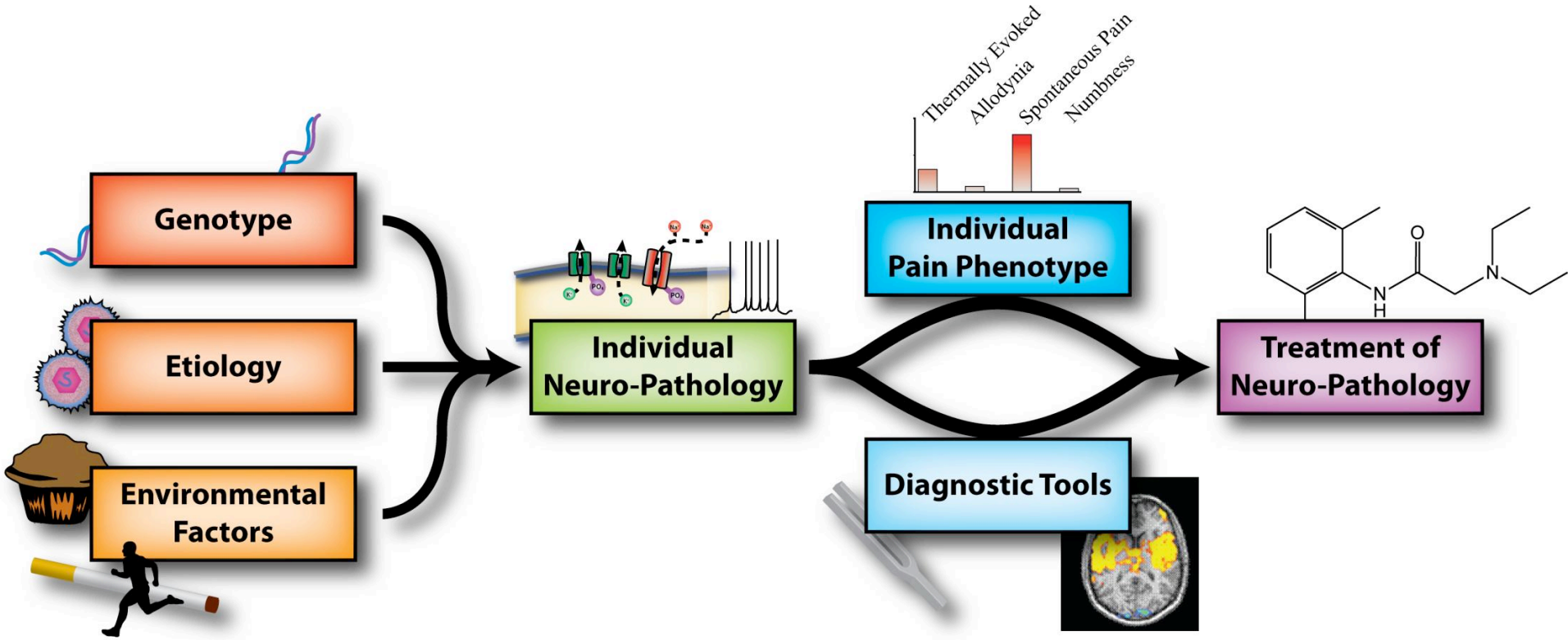
Von Hehn, Baron and Woolf Neuron 2012

An alternative pain treatment path….



Von Hehn, Baron and Woolf Neuron 2012

An alternative pain treatment path….



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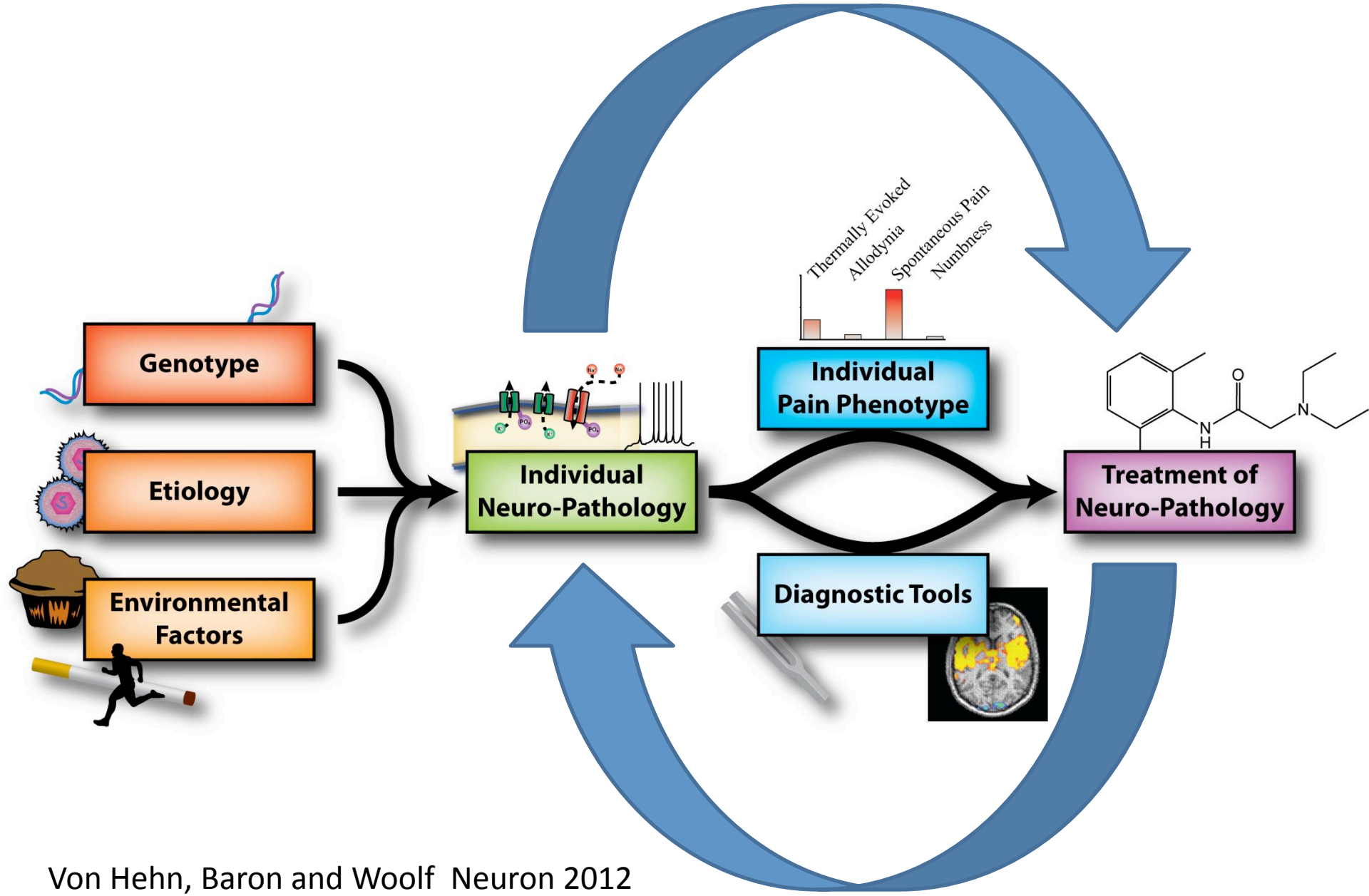
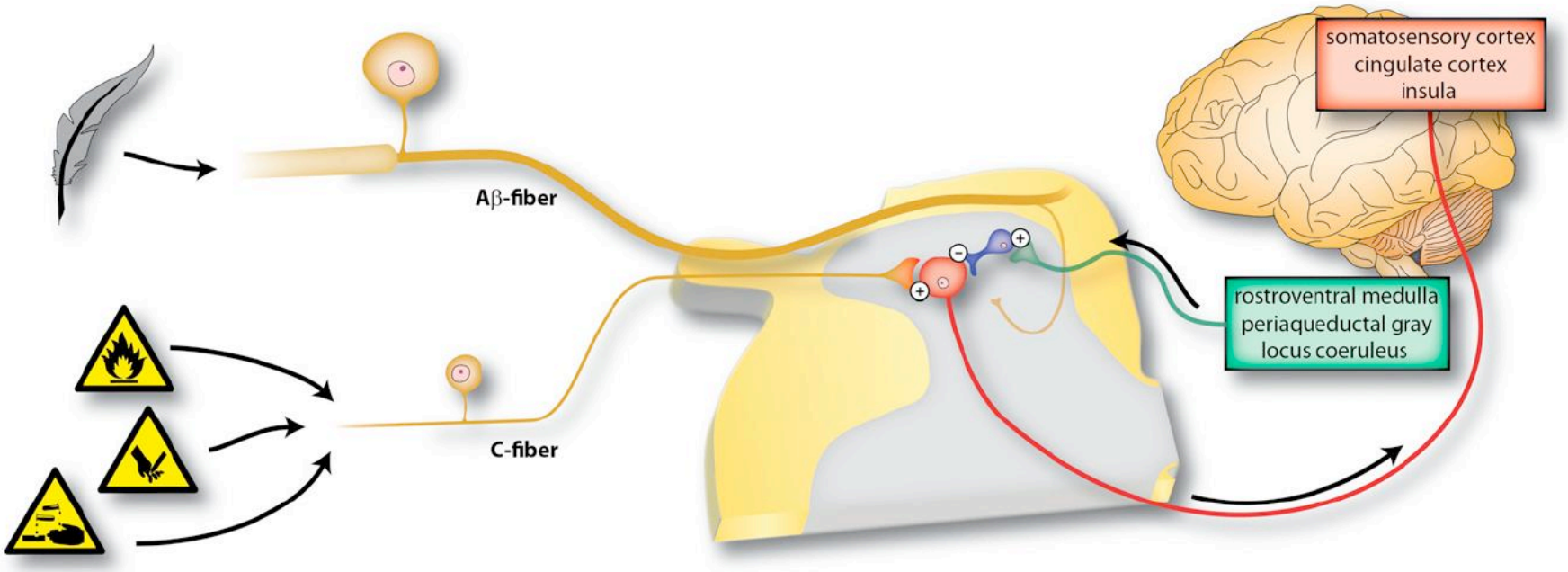


Von Hehn, Baron and Woolf Neuron 2012

Can we identify pain mechanisms
Can we use this to <u>develop/select</u> appropriate treatments?



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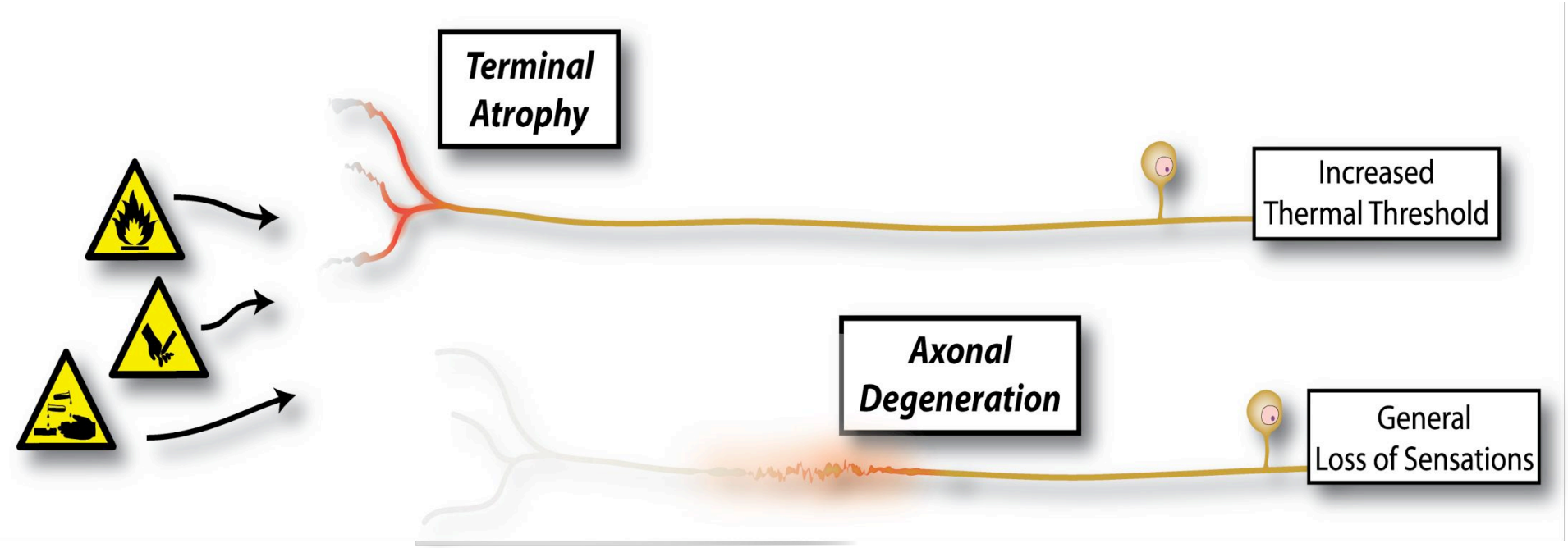
Use pain phenotype as a guide…

Negative Symptoms



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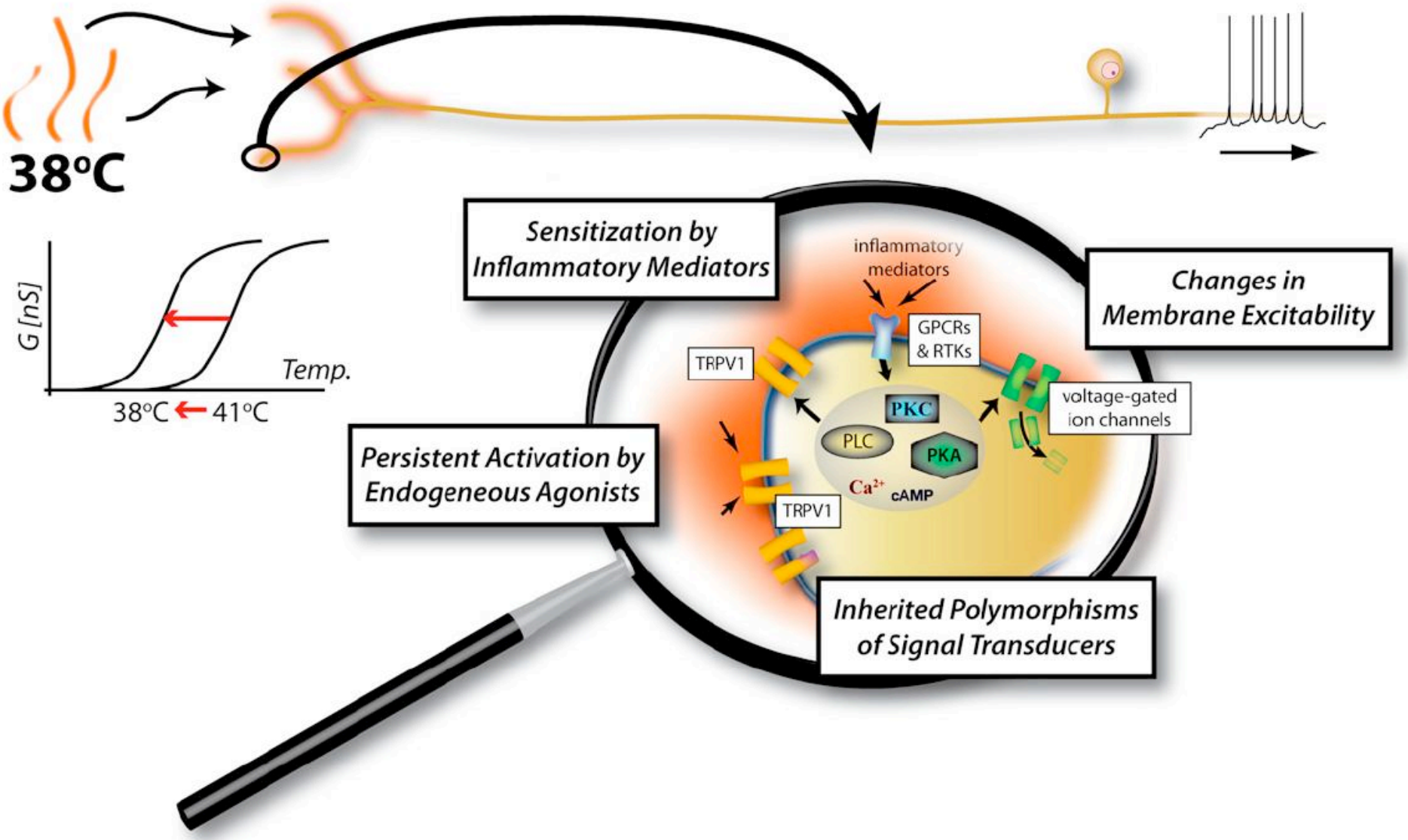
Positive Symptoms



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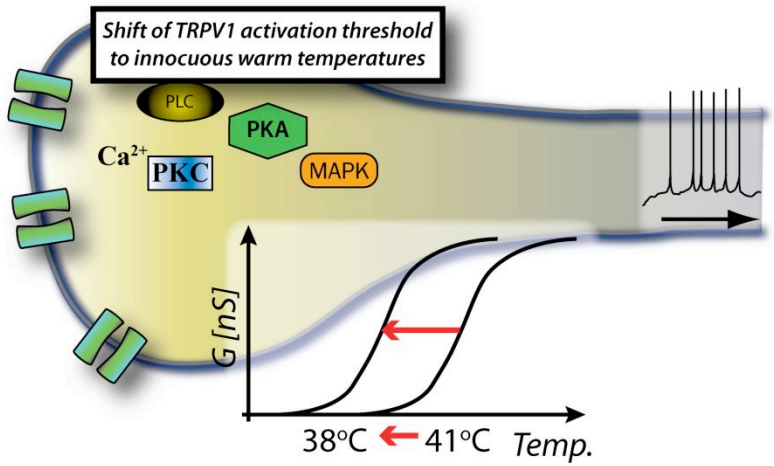
Individual Neuro-Pathology

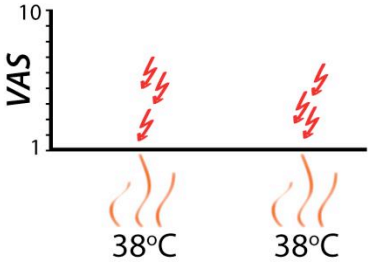
Individual Pain Phenotype

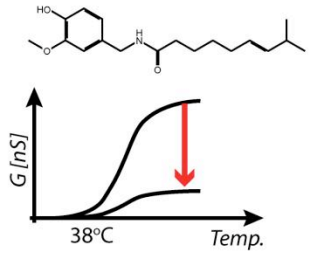
Treatment of Neuro-Pathology

TRPV1



heat allodynia





TRPV1 antagonists
TRPV1 desensitization

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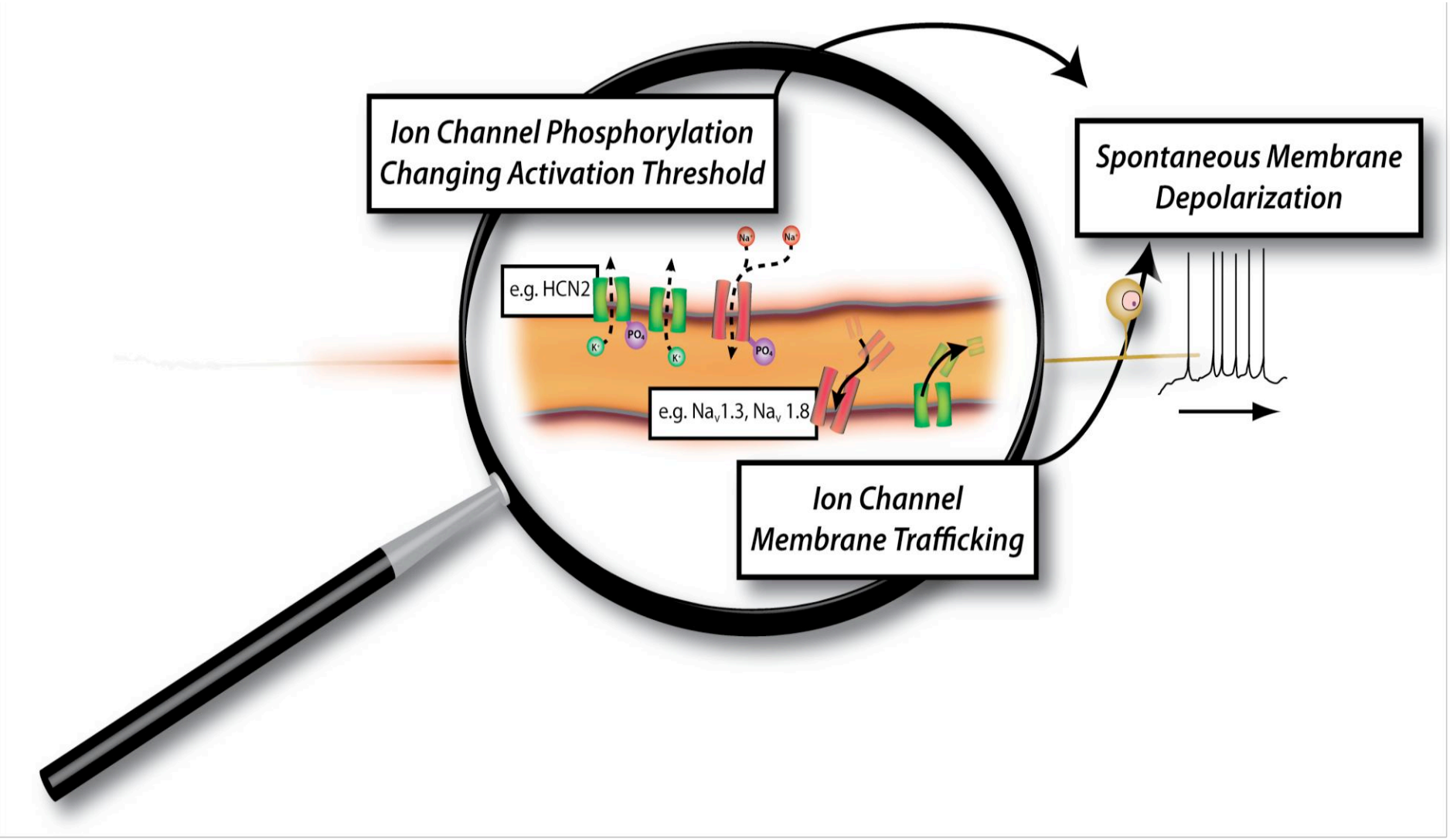
Ectopic activity



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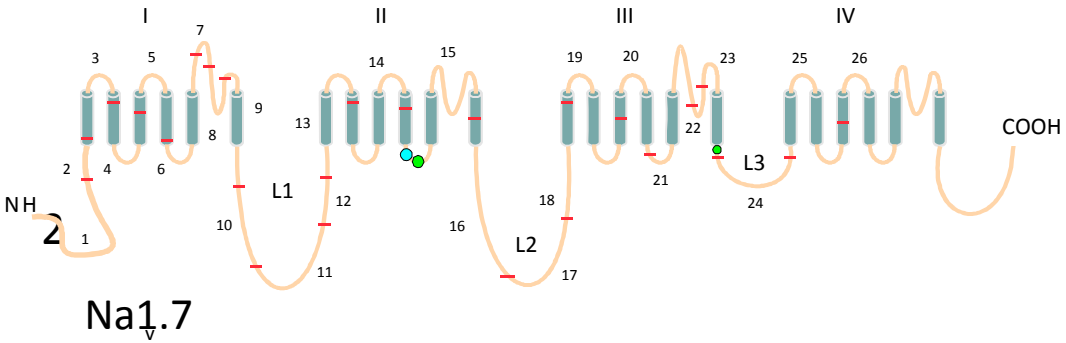
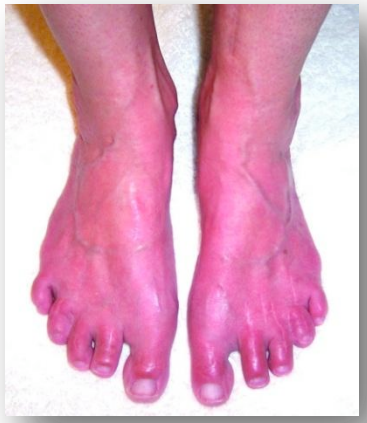
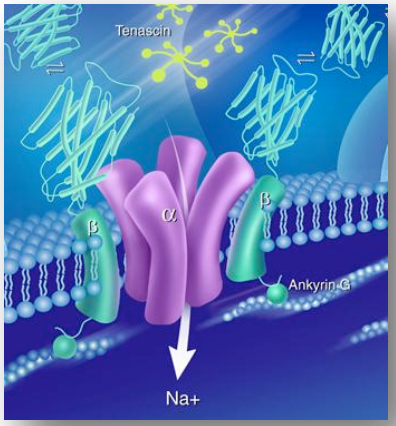




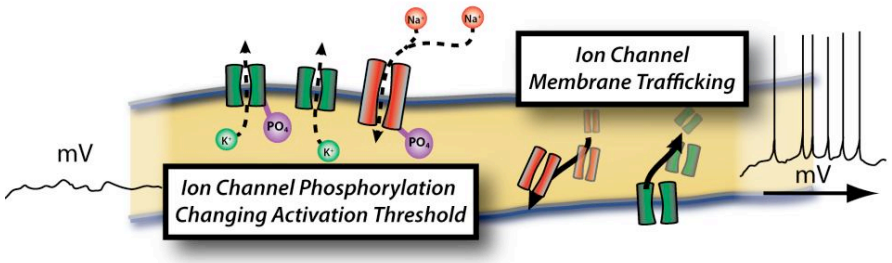


Nav1.7

Gain-of-function mutations

Inherited erythromelalgia

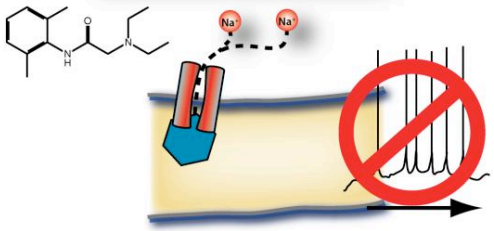
Individual Neuro-Pathology



Individual Pain Phenotype

ectopic activity / spontaneous bouts of pain

Treatment of Neuro-Pathology



Sodium channel blockers

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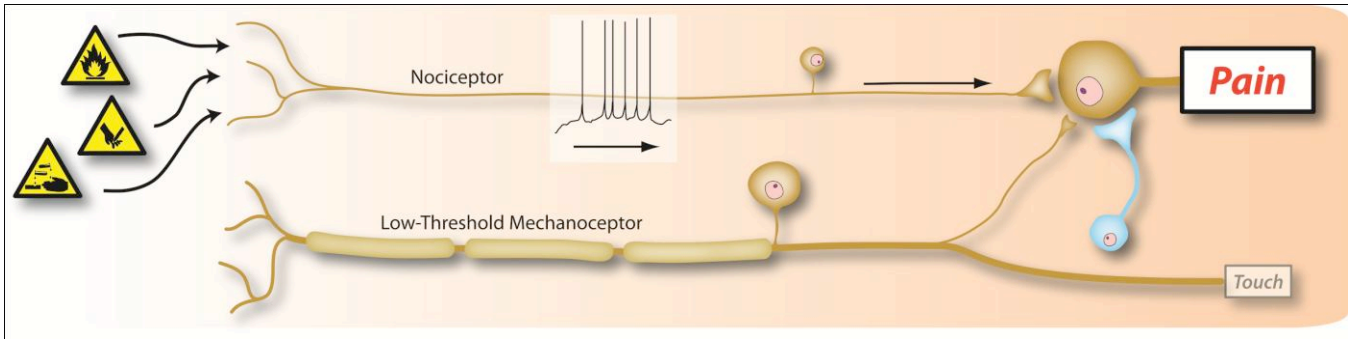
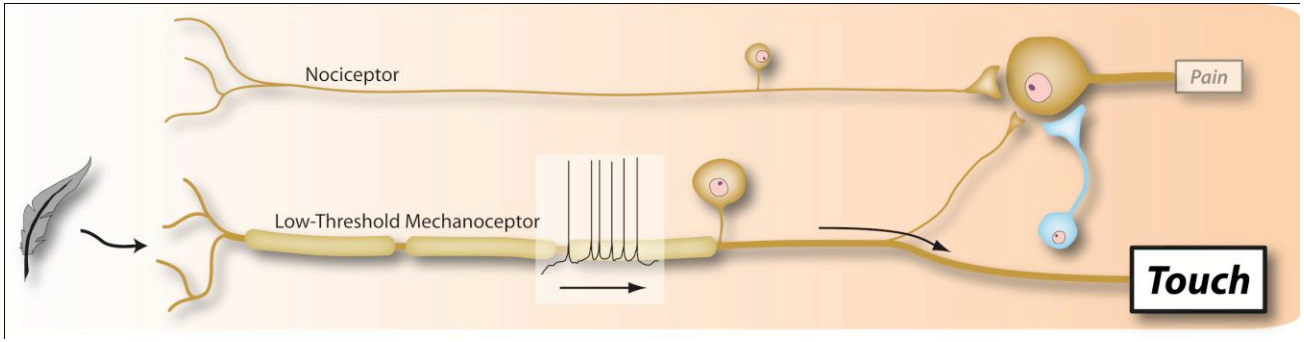
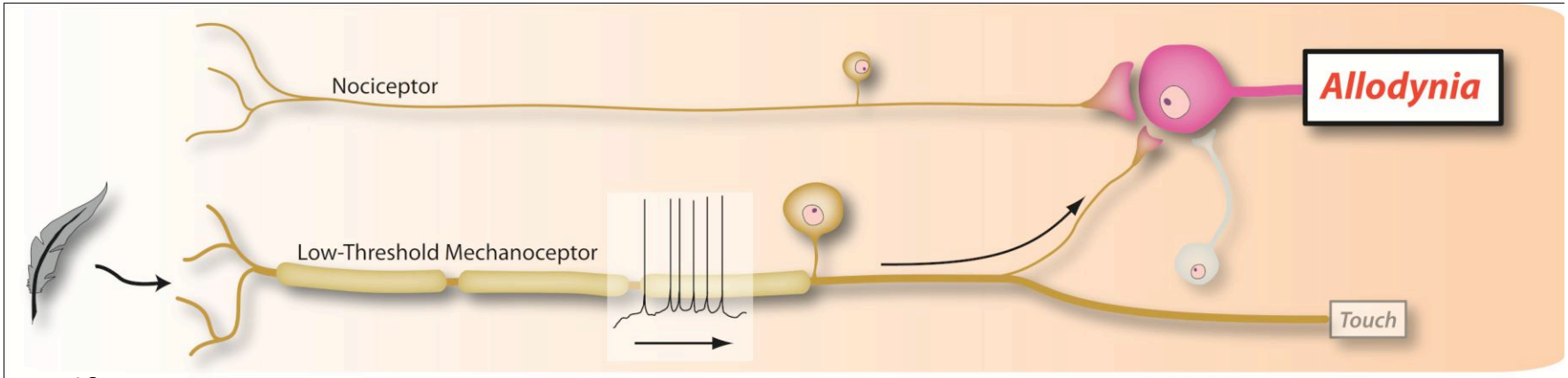
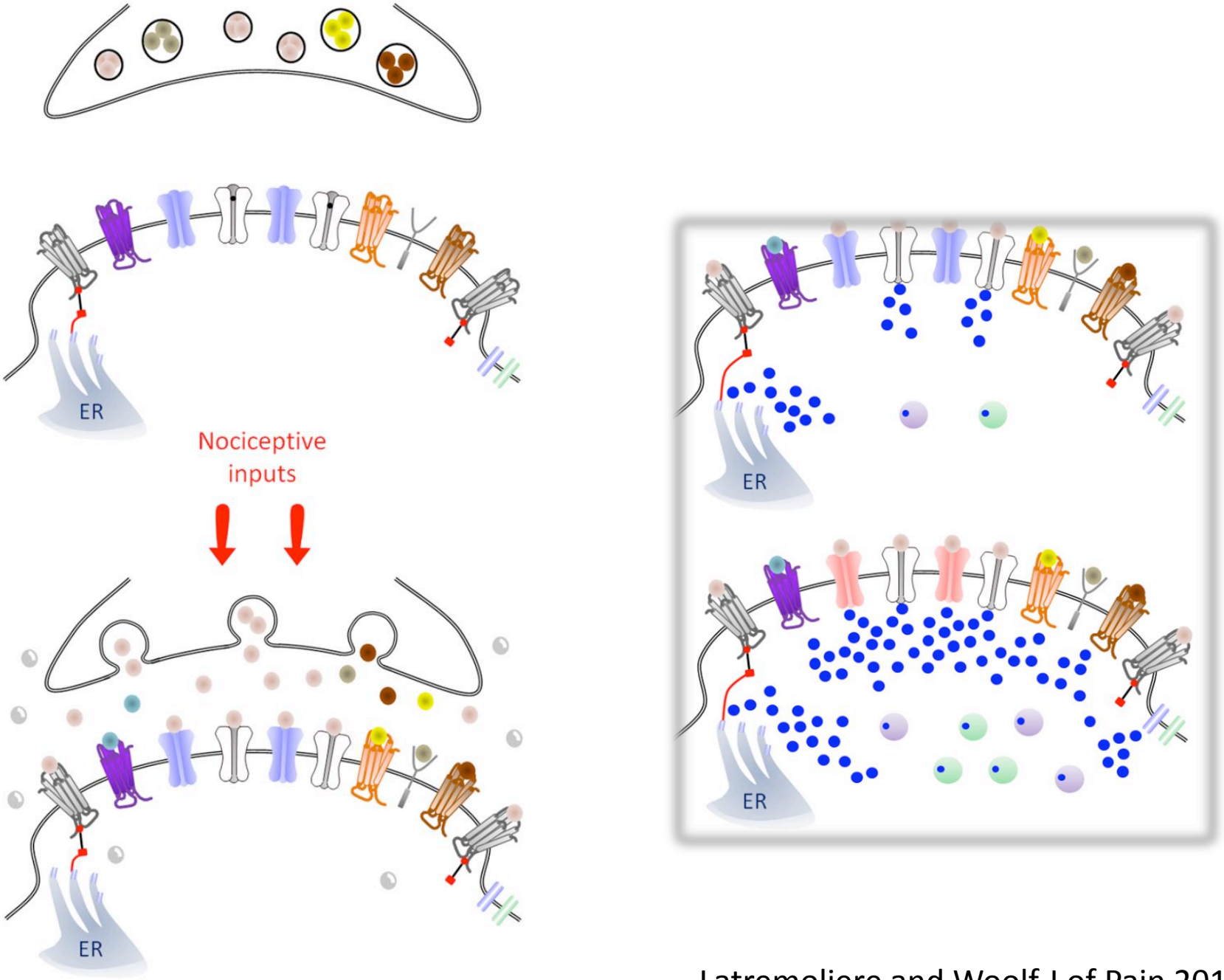




Central Sensitization

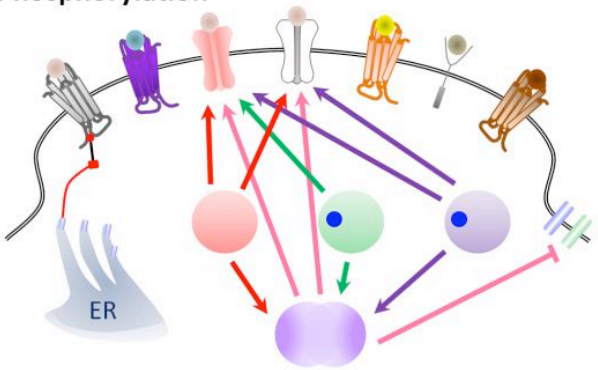


Woolf Pain 2011

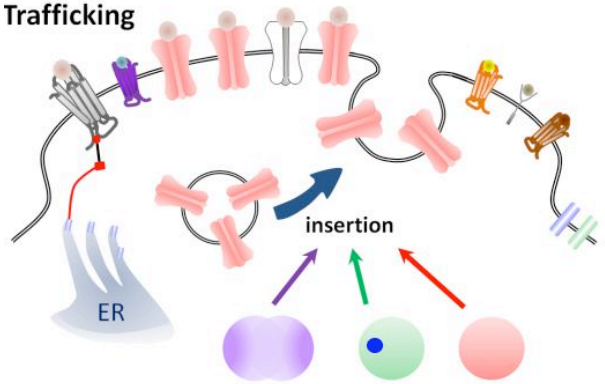


Latremoliere and Woolf J of Pain 2010

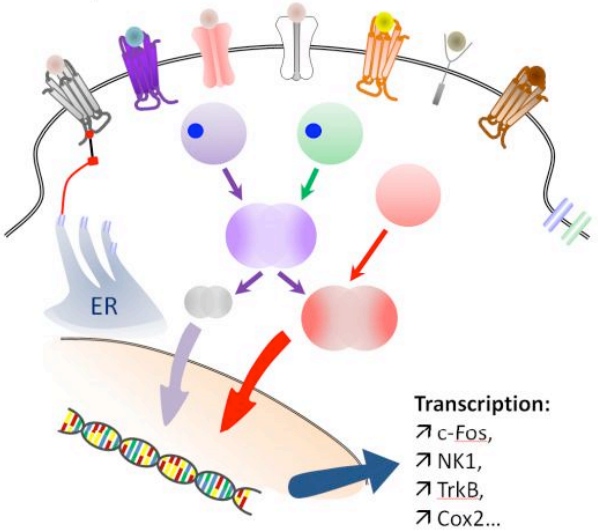
Phosphorylation



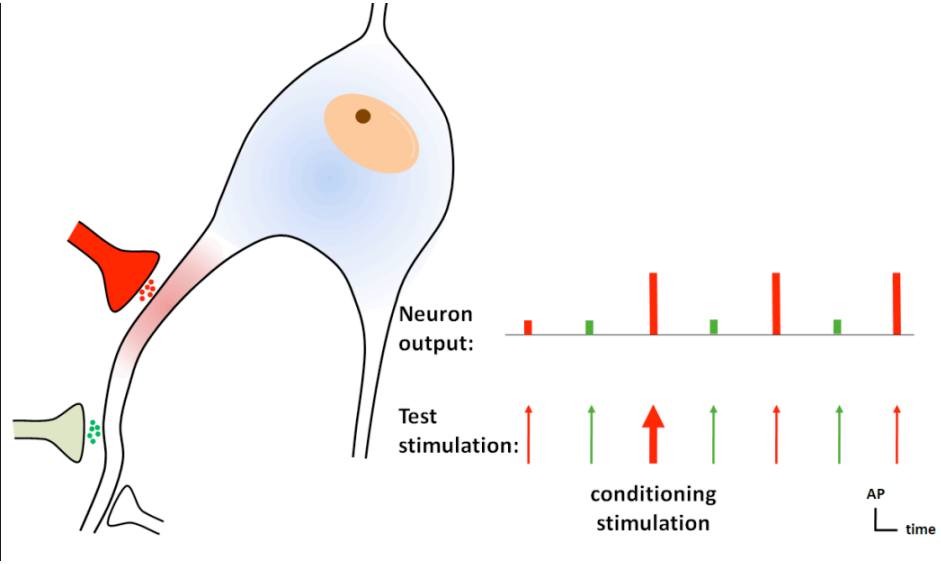
Trafficking

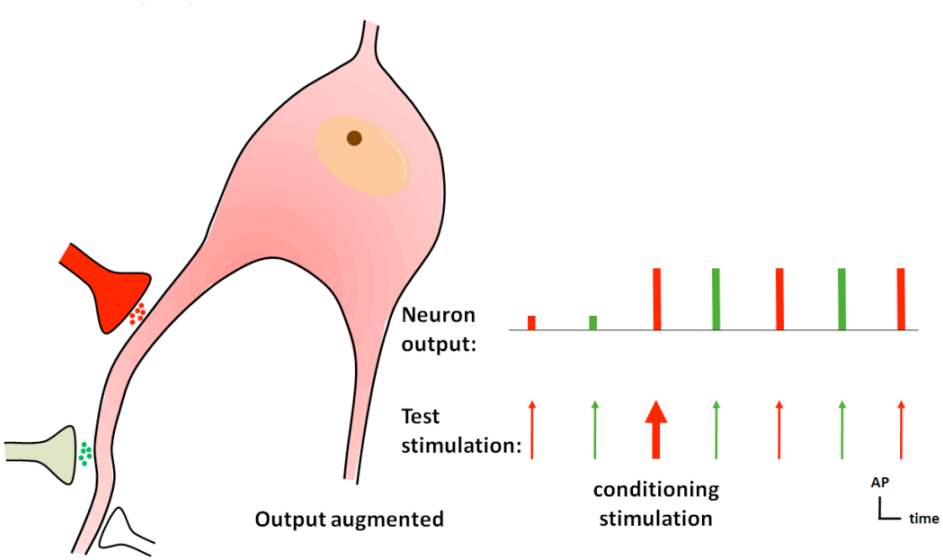


transcription

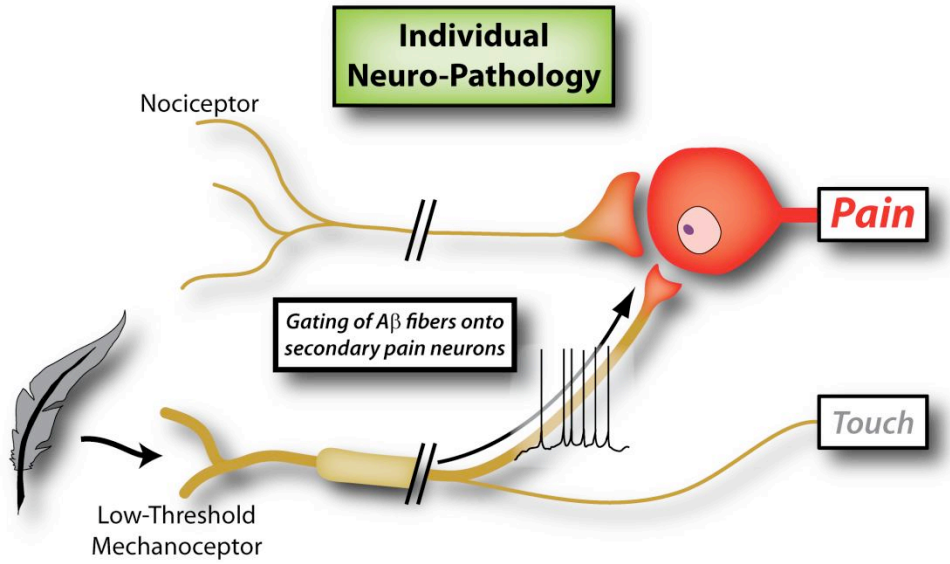


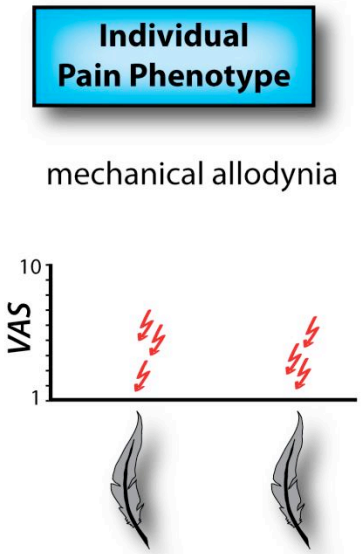
Latremoliere and Woolf J of Pain 2010

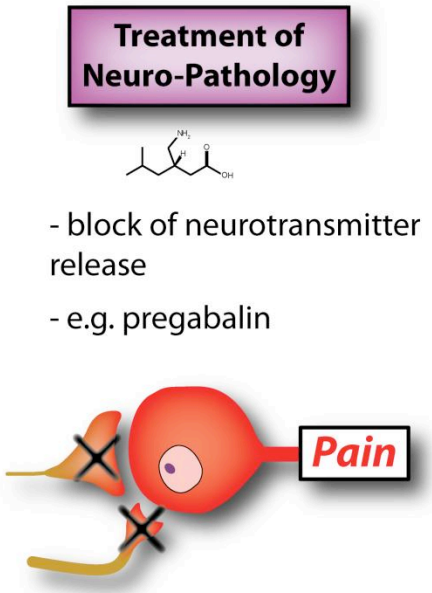




Latremoliere and Woolf J of Pain 2010

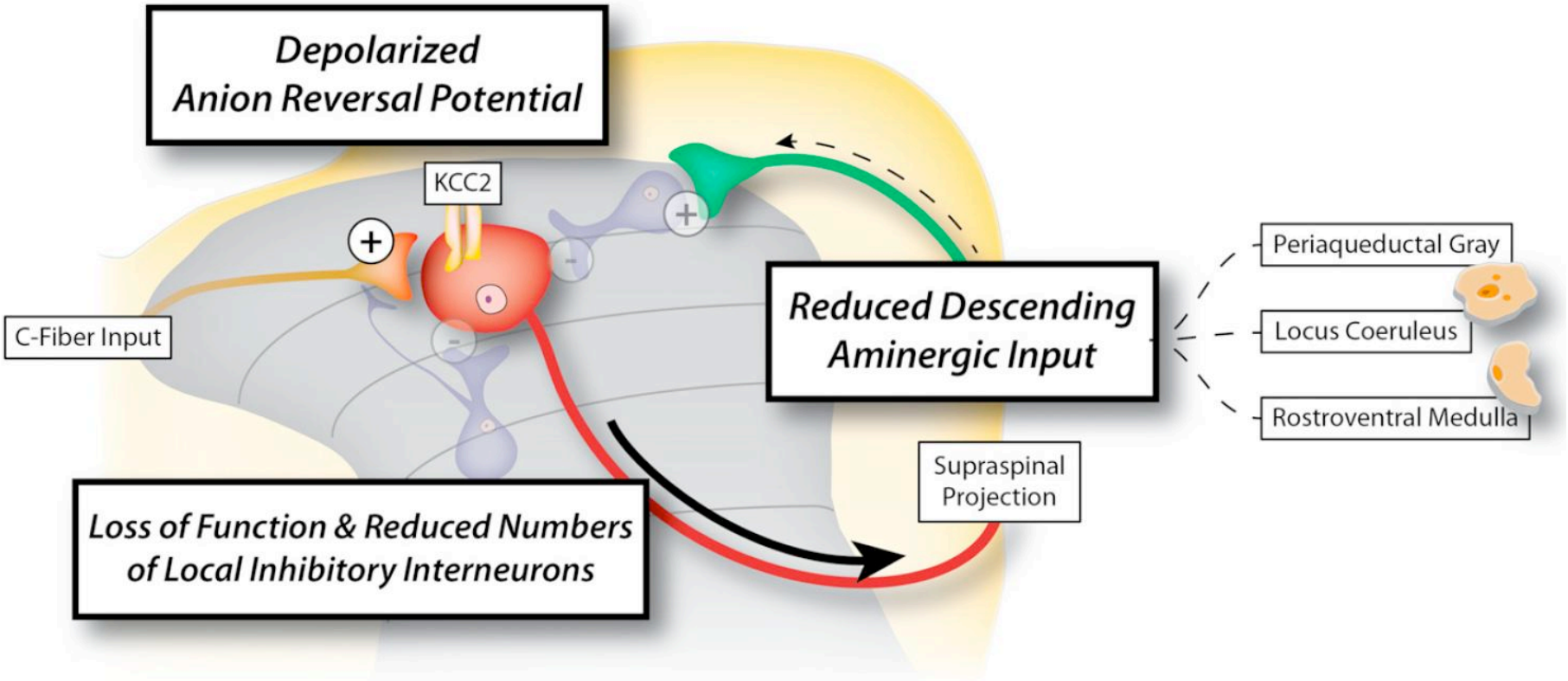






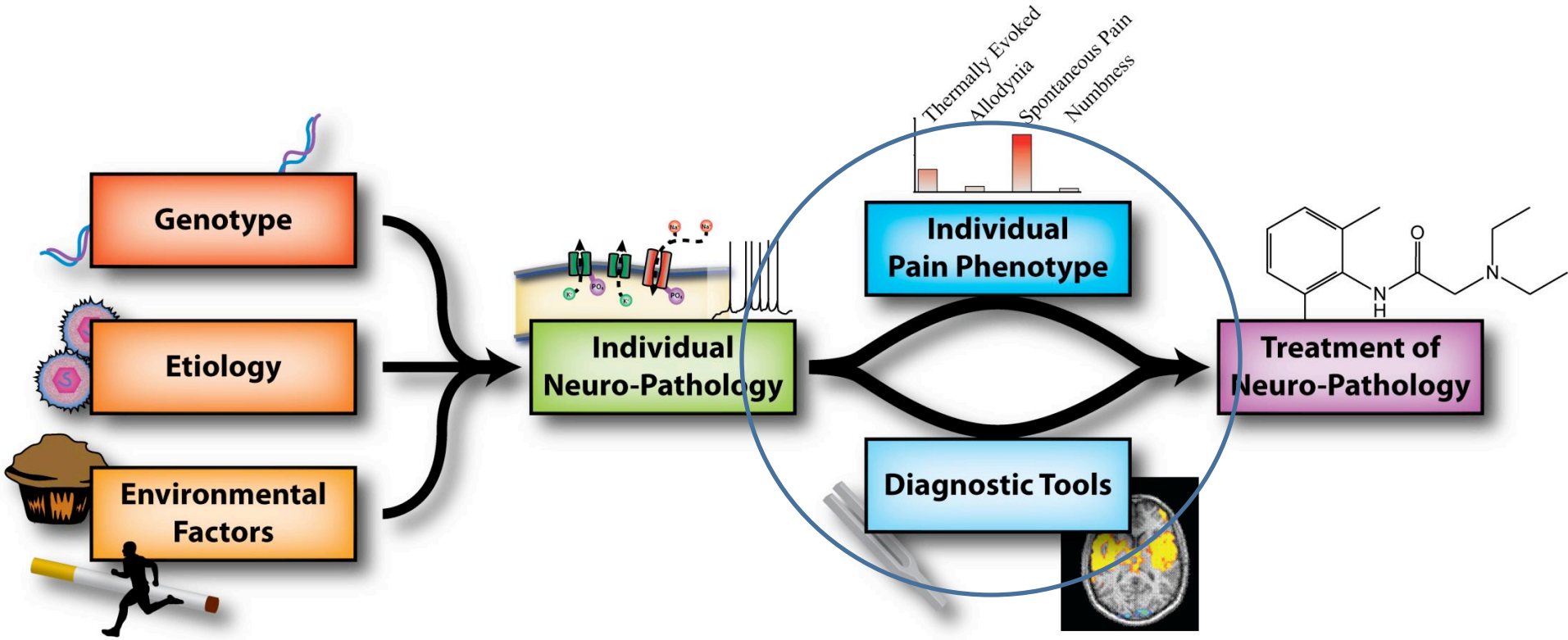
Von Hehn, Baron and Woolf Neuron 2012

Disinhibition

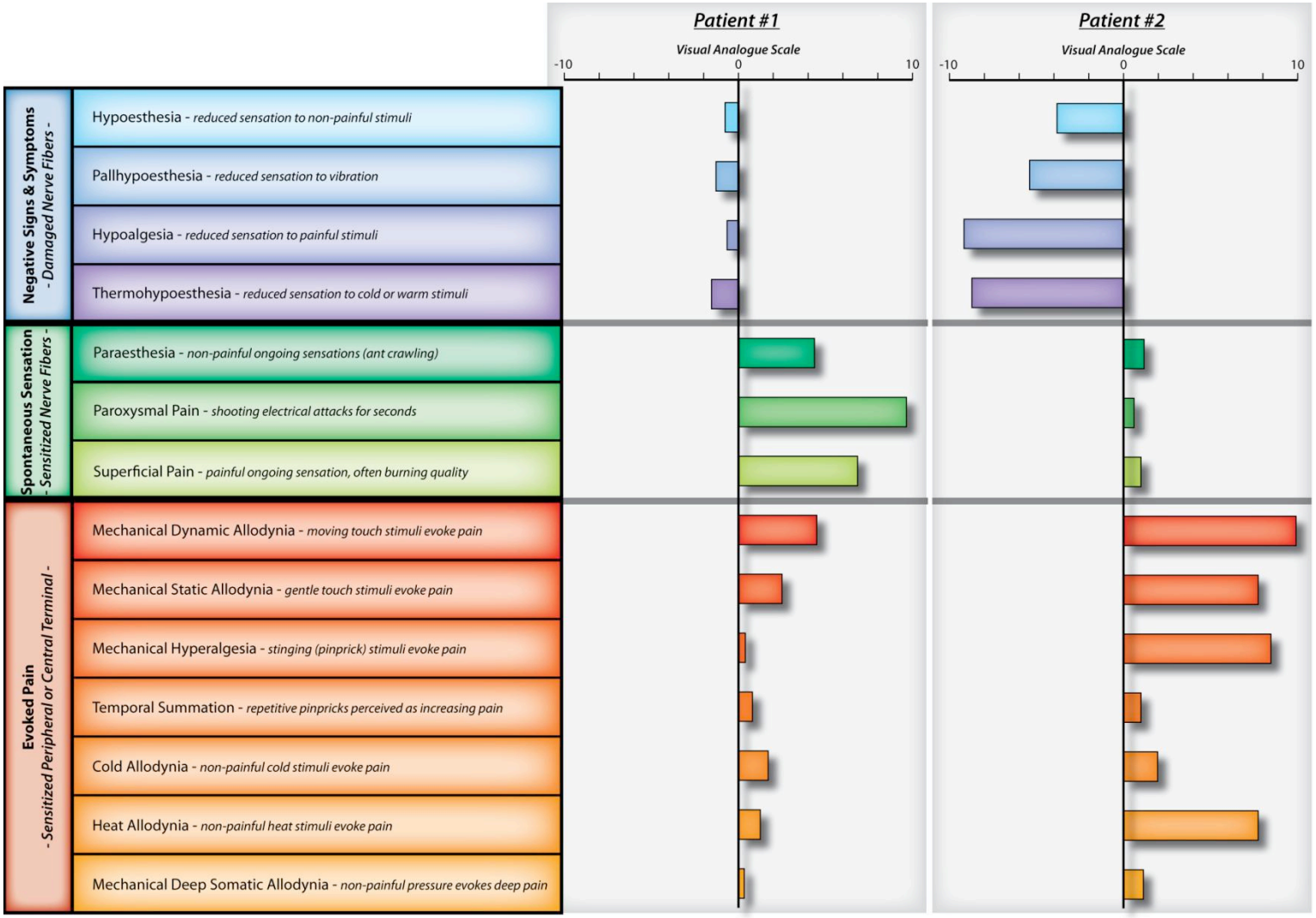


Amine uptake inhibitors; GABA agonists; KCC2 modulators

Von Hehn, Baron and Woolf Neuron 2012



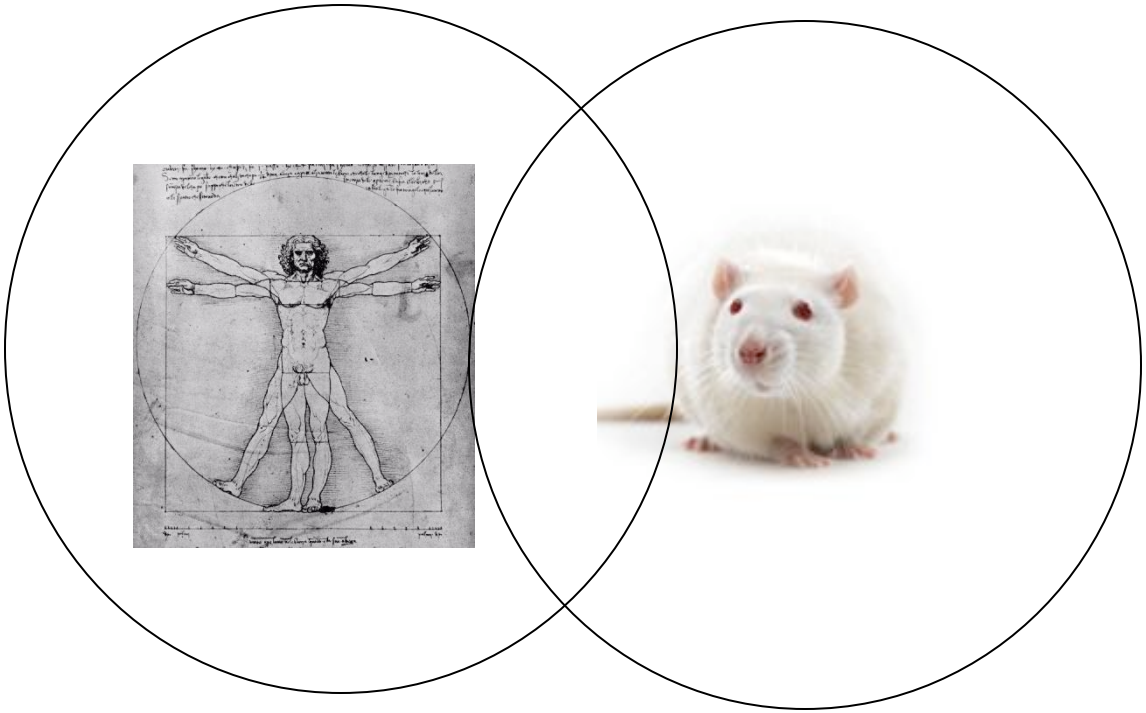
Von Hehn, Baron and Woolf Neuron 2012



Personalized Response Histogram
Predictor of Treatment Response?

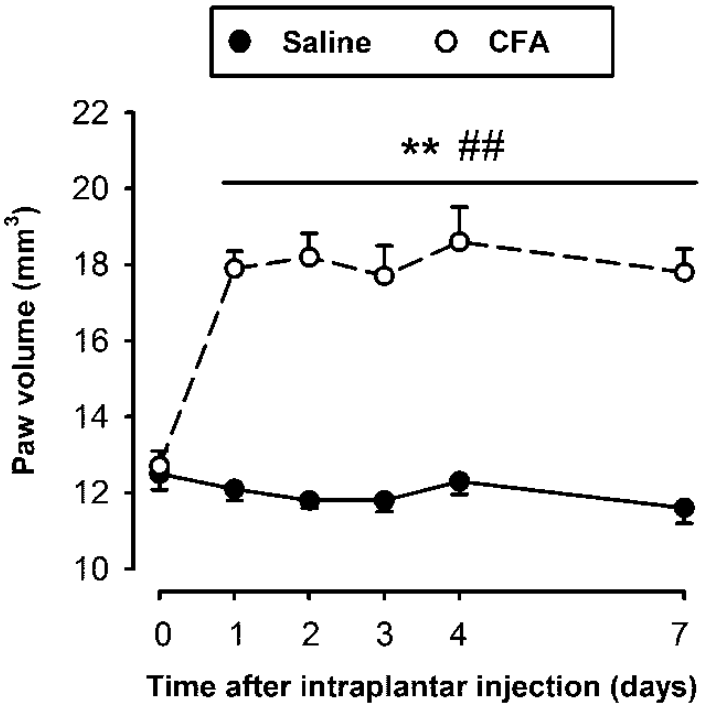
Von Hehn, Baron and Woolf Neuron 2012

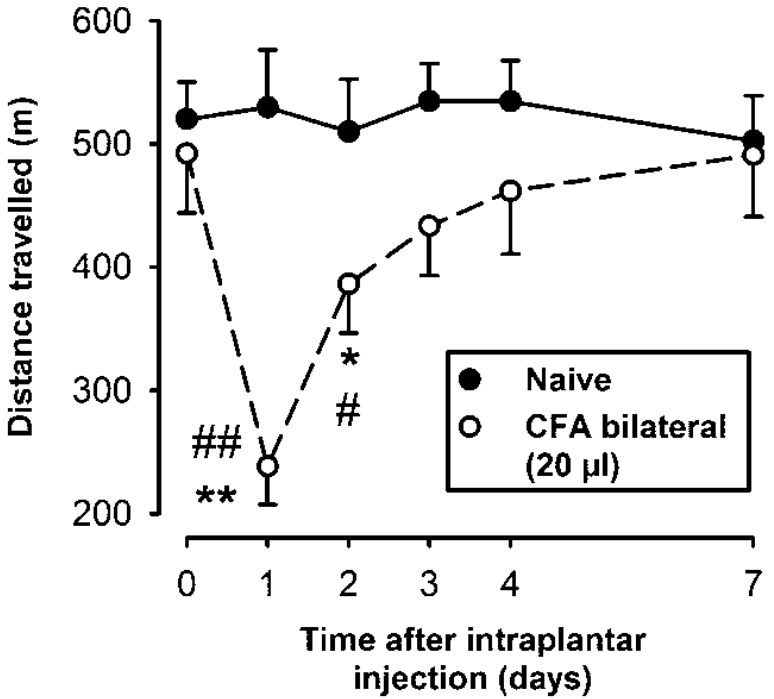
Mechanism versus Disease Phenotype



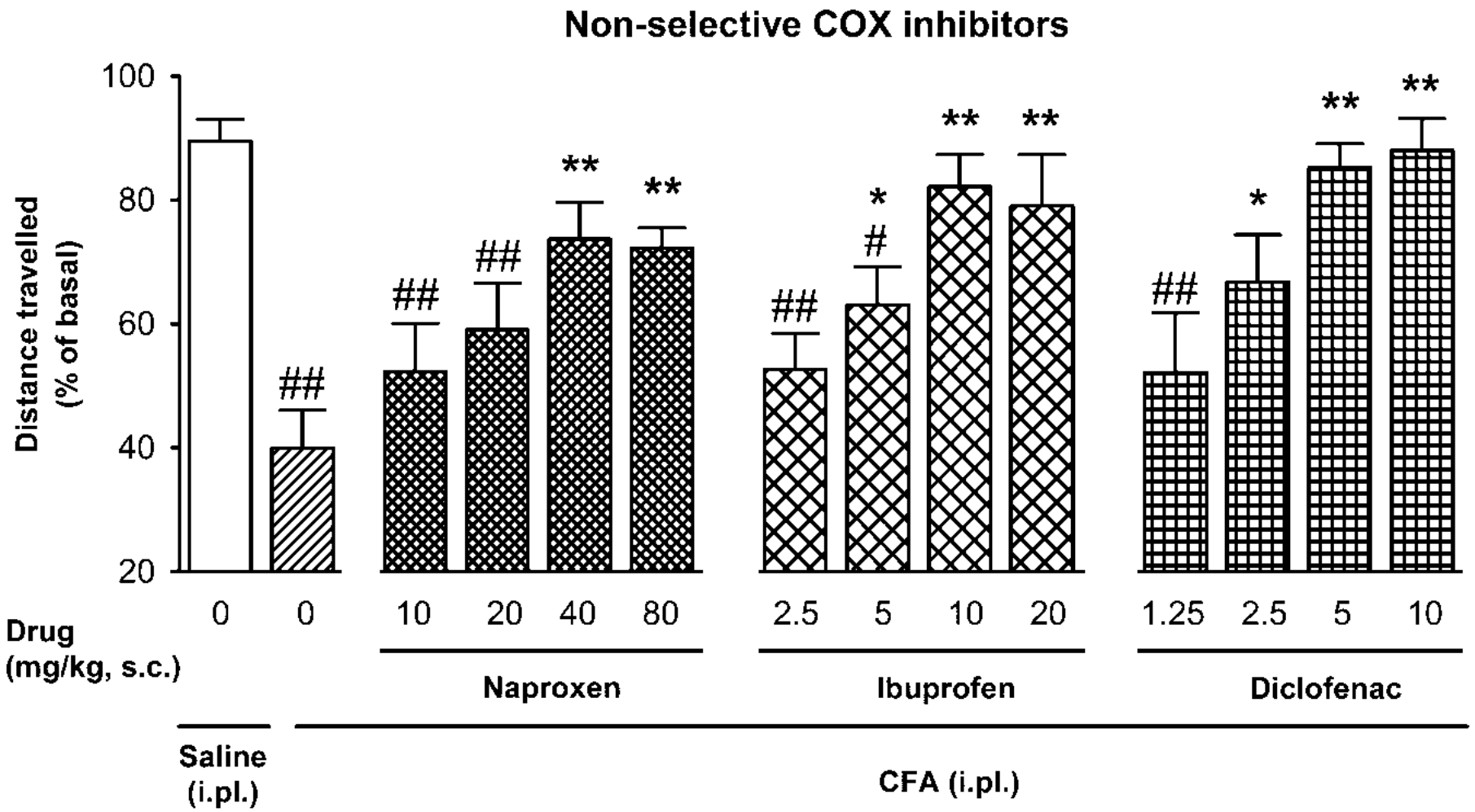
What outcome measure?


Cl
Cl
NH
OH
O
OH
O
O

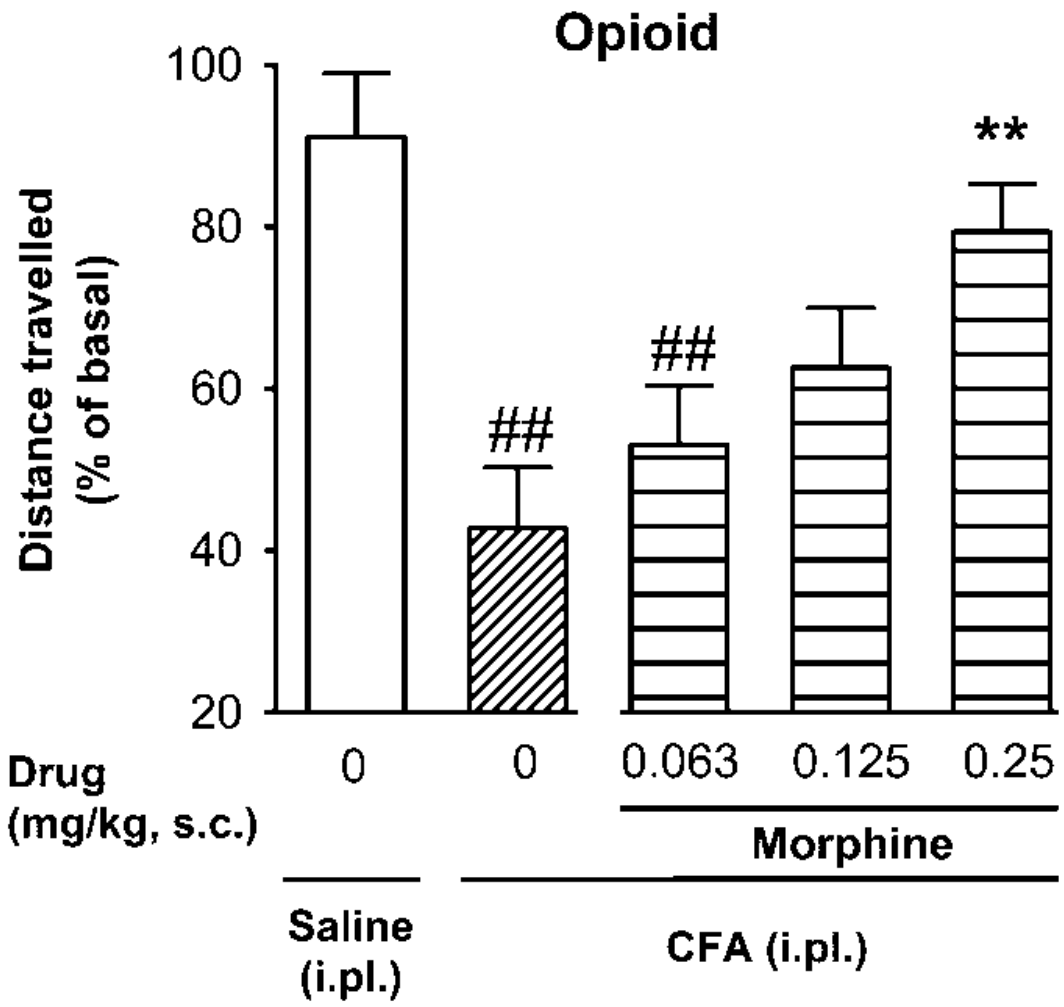




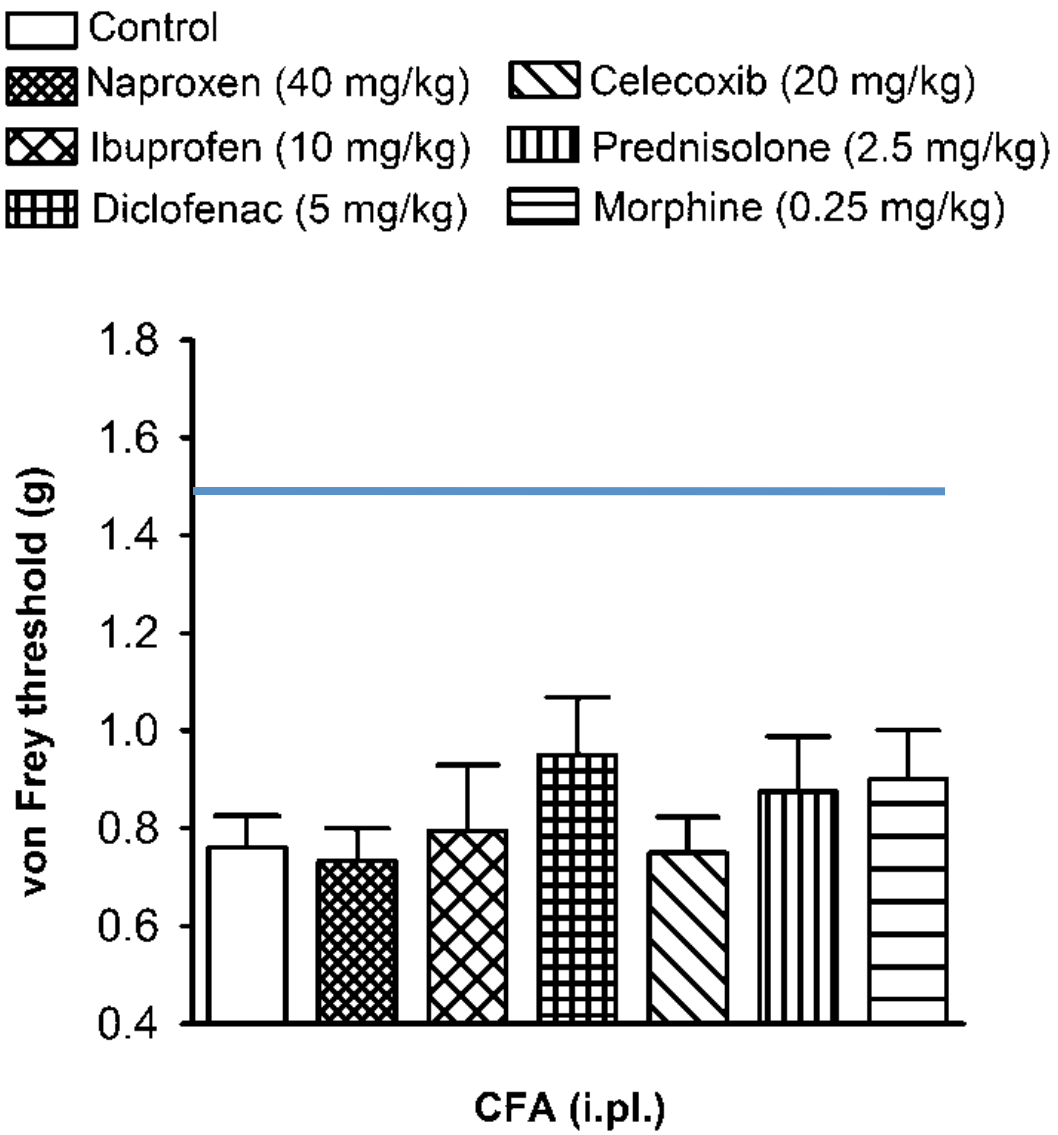
Cobos et al 2012



Cobos et al Pain 2012



Cobos et al Pain 2012



Cobos et al Pain 2012

- Individual neuropathological changes are pain targets
- Pain phenotype is a window on pain mechanisms
- Need to measure phenotype quantitatively
- Need to match phenotype with mechanisms and sensory experience

Latremoliere A, Woolf CJ Synaptic plasticity and central sensitization: author reply.
J Pain. 2010 Aug;11(8):801-3.

von Hehn CA, Baron R, Woolf CJ.
Deconstructing the neuropathic pain phenotype to reveal neural mechanisms.
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Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain.
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Woolf CJ. Overcoming obstacles to developing new analgesics.
Nat Med. 2010 Nov;16(11):1241-7