Multiple Mechanisms for Pain - How Can We Improve the Chances of Success?

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What are the different types of pain?

**Neuropathic**
- Diabetic neuropathy, PHN, sciatica
- Caused by damage to neurones
- Involves central and peripheral sensitization

**Inflammatory**
- Arthritis, trauma, back pain
- Caused by tissue damage and release of inflammatory mediators
- Involves central and peripheral sensitization

**Nociceptive**
- Caused by potentially tissue damaging stimuli
- Defensive role
- Involves transmission along pain pathway

**Functional/Visceral**
- Fibromyalgia, IBS, migraine
- May be caused by visceral stimulation; cause often unknown
- Mixed pathophysiology
What drugs are used to treat pain in the clinic?

**Inflammatory Pain**
- Paracetamol
- NSAIDs – ibuprofen, diclofenac, naproxen
- Opioids – morphine, oxycodone, codeine
- Combinations

**Neuropathic Pain**
- Gabapentinoids – gabapentin, pregabalin
- Monoamine reuptake inhibitors – amitriptyline, duloxetine
- Opioids
- Local anaesthetics – lidocaine patch

- Generally old drugs
- Efficacy?
  - Opioids less effective vs neuropathic pain
  - NSAIDs low ceiling
  - Neuropathic pain drugs only effective in 30-50% of patients
- Side effects
  - Opioids: respiratory depression, dependence, constipation
  - NSAIDs: GI and CV effects
  - Gabapentinoids: sedation
Huge effort to find new drugs!

3006 Ph II/III trials found in clinicaltrials.gov searching on ‘pain and drug’ in July 2017

**Successes**
- COX2 inhibitors
- New gabapentinoids, pregabalin
- Ziconotide for intractable pain
- Noradrenaline uptake inhibitors for fibromyalgia and neuropathic pain
- Triptans for migraine

**Failures**
- Fatty Acid Amide Hydrolase (FAAH) inhibitors
- Trpv1 antagonists
- Purinergic P2X7 antagonists
- Cannabinoid CB2 agonists
- Glial cell modulators
- Neurokinin NK1 antagonists
- Adenosine A1 agonists
- C-C chemokine receptor type 2 (CCR2) antagonists
- α4β2 nicotinic receptor agonists
- NMDA glycine site inhibitors
What can we learn from successes and failures to increase our chances of success?
**Use clinically validated mechanisms?**

**Successes**
- COX2 inhibitors
- New gabapentinoids, pregabalin
- Ziconotide for intractable pain
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**Failures (lack of efficacy)**
- Fatty Acid Amide Hydrolase (FAAH) inhibitors
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Inhibitors of voltage-gated calcium channels

Gabapentin

- Originally launched for epilepsy
- Trialled in neuropathic pain because of precedented use of anticonvulsants like carbamazepine
- Mechanism subsequently identified as inhibition of \( \alpha_{2\delta} \) calcium channel subunits
- And inhibition of neurotransmitter release eg glutamate

Pregabalin

Ziconotide
Ziconotide – N-type calcium channel inhibitor

- Synthetic form of ω-conotoxin peptide, derived from cone snail
- N-type calcium channel inhibitor; binds to pore and occludes channel
- Effective in severe, intractable pain
- Has to be given intrathecally (CV effects)
- Poor T.I. – CNS effects

Rauck et al, J Pain Symptom Manage. 2006;31(5):393-406
Use-dependent Inhibitors of N-type calcium channels e.g. CNV2197944 (Calchan/Biogen)

- **State-dependent** channel blocker
- Well tolerated in ph I
- Inactive in 2 Ph II studies; on company website says ‘company is considering alternative dosing regimes’
- Other state-dependent blocker, Z160 (Zalicus) also inactive in the clinic

**WHY?**
- Wrong target
- Wrong clinical population? (lumbosacral radiculopathy, diabetic neuropathy, post herpetic neuralgia)
- Insufficient target engagement?

Inhibitors of voltage-gated sodium channels

Local anaesthetics
(eg lidocaine patch for post-herpetic neuropathy)

Anticonvulsants
(eg carbamazepine for trigeminal neuralgia)

- Use dependent blockers
- Effective but poor side-effect profile after systemic/oral administration
- Non-selective
## Voltage-gated sodium channels

<table>
<thead>
<tr>
<th>Channel (Nav)</th>
<th>Location</th>
<th>Pathophysiology</th>
<th>Desired activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>CNS, heart</td>
<td>Epilepsy</td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td>CNS, peripheral neurones</td>
<td>Epilepsy</td>
<td></td>
</tr>
<tr>
<td>1.3</td>
<td>CNS, peripheral neurones, heart</td>
<td>Epilepsy, pain</td>
<td>?</td>
</tr>
<tr>
<td>1.4</td>
<td>Skeletal muscle</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>1.5</td>
<td>Heart, GI tract</td>
<td>Cardiac function</td>
<td>X</td>
</tr>
<tr>
<td>1.6</td>
<td>CNS, DRG, heart, glia</td>
<td>Epilepsy</td>
<td></td>
</tr>
<tr>
<td>1.7</td>
<td>Sensory afferents</td>
<td>Pain</td>
<td>✓</td>
</tr>
<tr>
<td>1.8</td>
<td>Sensory afferents</td>
<td>Pain</td>
<td>✓</td>
</tr>
<tr>
<td>1.9</td>
<td>Sensory afferents</td>
<td>Pain</td>
<td>✓</td>
</tr>
</tbody>
</table>
What can we learn from successes and failures to increase our chances of success?

Use mechanisms validated by human genetics?
Nav1.7 gene mutations and pain

**Gain of function mutations**
- Erythromelalgia
- Burning pain of feet, lower legs and hands
- Increased channel activity
- Other mutations cause paroxysmal extreme pain disorder, due to impaired channel inactivation

**Loss of function mutations**
- Congenital insensitivity to pain
- Patients have injuries to mouth, cuts/bruises and unnoticed fractures
- Impaired firing of action potentials in DRG
## Clinical effects of Nav1.7 blockers

<table>
<thead>
<tr>
<th>Compound</th>
<th>Selectivity</th>
<th>State dependence</th>
<th>CNS penetration</th>
<th>Clinical activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vixotrigine/ CNV1014802 Biogen</td>
<td>50X vs Nav1.5 Lower selectivity vs other Navs (1)</td>
<td>State dependent</td>
<td>Yes</td>
<td>• Positive efficacy in trigeminal neuralgia and sciatica; well tolerated (2)</td>
</tr>
<tr>
<td>Funapide (XEN402/TV-45070), Teva</td>
<td>Nav1.7 &amp;Nav1.8</td>
<td>State dependent</td>
<td>??</td>
<td>• +ve effect in 4 erythromelalgia patients after oral admin (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• No effect on primary endpoint in PHN after topical admin; but did show increased responders vs placebo (2)</td>
</tr>
<tr>
<td>PF-050589771</td>
<td>Nav1.7 selective</td>
<td>State dependent</td>
<td>??</td>
<td>• No effect in erythromelalgia or dental pain; well tolerated</td>
</tr>
</tbody>
</table>

1 - Zakrzewska et al, Trials. 2013; 14: 402  
2 - GlobalData database, July 2017  
Where to go with sodium channel blockers?

Activity against channels other than Nav1.7 may be useful eg 1.8, 1.9, even central channels like 1.2 and 1.3

Nav 1.8 mutations → painful neuropathy (Faber et al, 2012)
Nav 1.9 mutations → pain syndromes (Zhang et al, 2013; Huang et al, 2014)
Hereditary sensory and autonomic neuropathy (HSAN)

- Genetic disorder characterised by loss of pain sensation
- Caused by mutations in either nerve growth factor (NGF) or its receptor, Trk-A

NGF sensitises nociceptors in a variety of ways
NGF antibodies are analgesic in the clinic

Tanezumab (Pfizer)
Fasinumab (Regeneron)
Fulranumab (Amgen/JNJ)

Osteoarthrits
Chronic low back pain
Diabetic neuropathy
Cystitis
Cancer pain

FDA clinical hold in 2010 due to osteonecrosis & increased hip replacements; lifted 2012

Tanezumab, Ph III
Fasinumab, Ph III
Fulranumab, ??
NEW YORK & INDIANAPOLIS - Pfizer Inc. (NYSE:PFE) and Eli Lilly and Company (NYSE:LLY) today announced that the U.S. Food and Drug Administration (FDA) has granted Fast Track designation for tanezumab for the treatment of chronic pain in patients with osteoarthritis (OA) and chronic low back pain (CLBP). Tanezumab is an investigational humanized monoclonal antibody that selectively targets, binds to and inhibits nerve growth factor (NGF). It is the first NGF inhibitor to receive Fast Track designation, a process designed to facilitate the development and expedite the review of new therapies to treat serious conditions and fill unmet medical needs.
Effect of NGF antibody tanezumab in PhIII trial in osteoarthritis pain (WOMAC pain subscale)

What can we learn from failures?

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**Was target engagement demonstrated in man at site of action?**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Target Engagement</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAAH inhibitors</td>
<td>√</td>
<td>Enzyme inhibition</td>
</tr>
<tr>
<td>Trpv1 antagonists</td>
<td>√</td>
<td>Increased heat pain threshold</td>
</tr>
<tr>
<td>P2X7 antagonists</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CB2 agonists</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Glial cell modulators</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>NK1 antagonists</td>
<td>√</td>
<td>PET</td>
</tr>
<tr>
<td>A1 agonists</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CCR2 antagonists</td>
<td>√</td>
<td>Inhibition of ligand CCL2</td>
</tr>
<tr>
<td>α4β2 agonists</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>NMDA-glycine inhibs</td>
<td>X</td>
<td></td>
</tr>
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</table>

Without demonstration of target engagement, don’t know if molecule or mechanism has failed.
Single target/mechanism selectivity?

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Need to target key control pathways

Or final common pathway
Issues with animal models

- Choose a specialist (CRO or academic lab) that routinely does pain testing
- Have the studies replicated in an independent lab
- Check blinding and randomisation procedures
- Is an appropriate positive control being used, at an appropriate dose?
- Add a negative control?
- Animals should only be excluded to pre-stated criteria
- Use a range of models if possible and a range of endpoints across all sensory modalities
- Try to incorporate endpoints that reflect ongoing pain (eg weight-bearing) and emotional aspects (eg conditioned place preference)
- Need to test compounds therapeutically rather than prophylactically ie after development of pain
Issues with pain clinical trials.....

- Subjective endpoints
- Heterogeneous patient populations (diagnosis and pathophysiology)
- Placebo response rates

CGRP antagonist olcegepant in acute migraine

NGF antibody in OA
Conclusions

• If possible pick a mechanism with some clinical validation
• Key approach is better selectivity eg COX2, but if single target needs to be on key control or convergent point in pathway
• Knowledge from genetic mutations has been helpful
• Target engagement at the site of action, in man, should be demonstrated
• In the clinic, choice of an appropriate clinical model or population may increase probability of success