

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

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October 2017

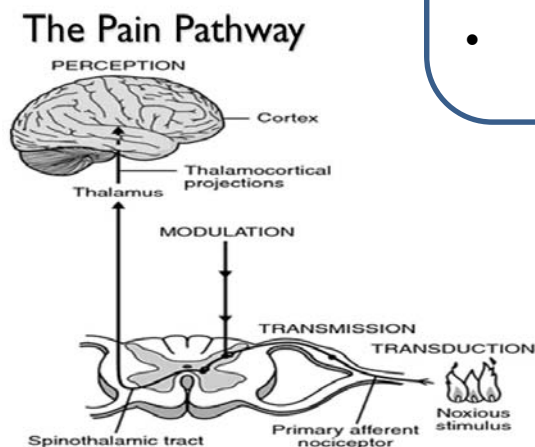
What are the different types of pain?

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
- $\alpha 4\beta 2$ 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
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Failures (lack of efficacy)

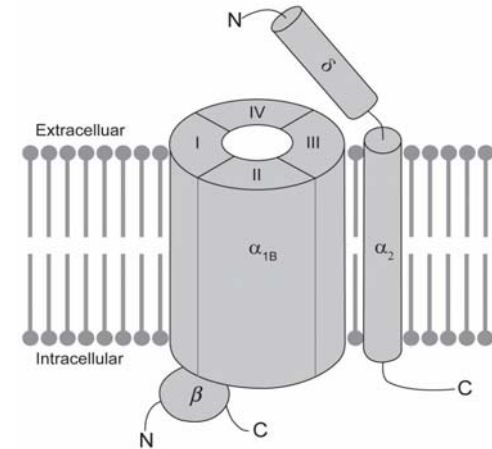


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Inhibitors of voltage-gated calcium channels

Gabapentin

- Originally launched for epilepsy
- Trialled in neuropathic pain because of preceded use of anticonvulsants like carbamazepine
- Mechanism subsequently identified as inhibition of $\alpha_2\delta$ calcium channel subunits
- And inhibition of neurotransmitter release eg glutamate



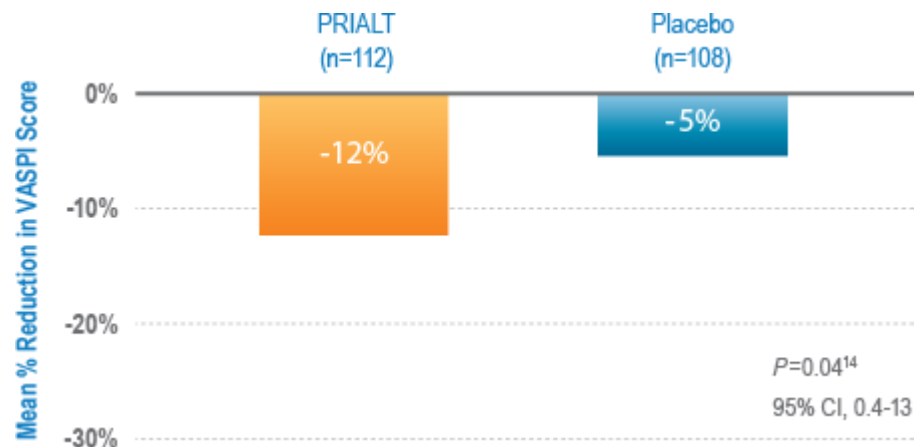
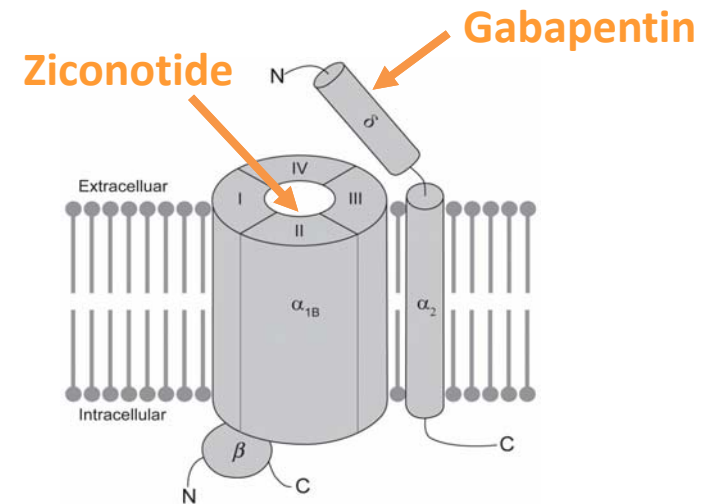
Pregabalin



Ziconotide

Ziconotide – N-type calcium channel inhibitor

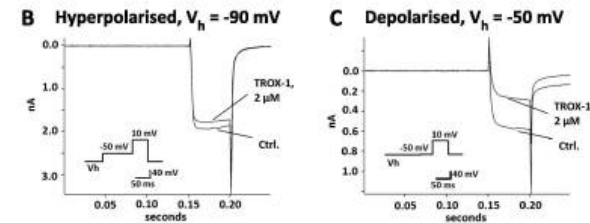
- Synthetic form of ω -conotoxin peptide, derived from cone snail
- N-type calcium channel inhibitor; binds to pore and occludes channel



- Effective in severe, intractable pain
- Has to be given intrathecally (CV effects)
- Poor T.I. – CNS effects

Use-dependent Inhibitors of N-type calcium channels e.g. CNV2197944 (Calchan/Biogen)

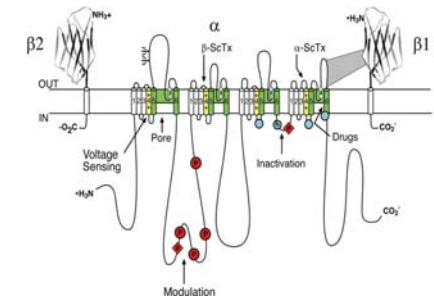
- State-dependent channel blocker
- Well tolerated in ph I
- Inactive in 2 Ph II studies; on company website says 'company is considering alternative dosing regimes'
- Other state-dependent blocker, Z160 (Zalicus) also inactive in the clinic



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)



"Mrs. Danford, I asked you THREE TIMES if the Novocaine had taken effect yet!"

- Use dependent blockers
- Effective but poor side-effect profile after systemic/oral administration
- **Non-selective**

Voltage-gated sodium channels

Channel (Nav)	Location	Pathophysiology	Desired activity
1.1	CNS, heart	Epilepsy	
1.2	CNS, peripheral neurones	Epilepsy	
1.3	CNS, peripheral neurones, heart	Epilepsy, pain	?
1.4	Skeletal muscle		X
1.5	Heart, GI tract	Cardiac function	X
1.6	CNS, DRG, heart, glia	Epilepsy	
1.7	Sensory afferents	Pain	✓
1.8	Sensory afferents	Pain	✓
1.9	Sensory afferents	Pain	✓



**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

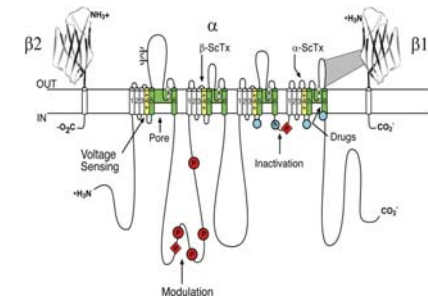
Compound	Selectivity	State dependence	CNS penetration	Clinical activity
Vixotrigine/ CNV1014802 Biogen	50X vs Nav1.5 Lower selectivity vs other Navs (1)	State dependent	Yes	<ul style="list-style-type: none"> Positive efficacy in trigeminal neuralgia and sciatica; well tolerated (2)
Funapide (XEN402/TV-45070), Teva	Nav1.7 & Nav1.8	State dependent	??	<ul style="list-style-type: none"> +ve effect in 4 erythromelalgia patients after oral admin (3) No effect on primary endpoint in PHN after topical admin; but did show increased responders vs placebo (2)
PF-050589771	Nav1.7 selective	State dependent	??	<ul style="list-style-type: none"> No effect in erythromelalgia or dental pain; well tolerated

1 - Zakrzewska et al, *Trials*. 2013; 14: 402

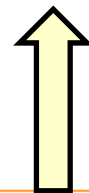
2 - GlobalData database, July 2017

3 - Goldberg et al, *Pain*. 2012, 153:80-5

Where to go with sodium channel blockers?



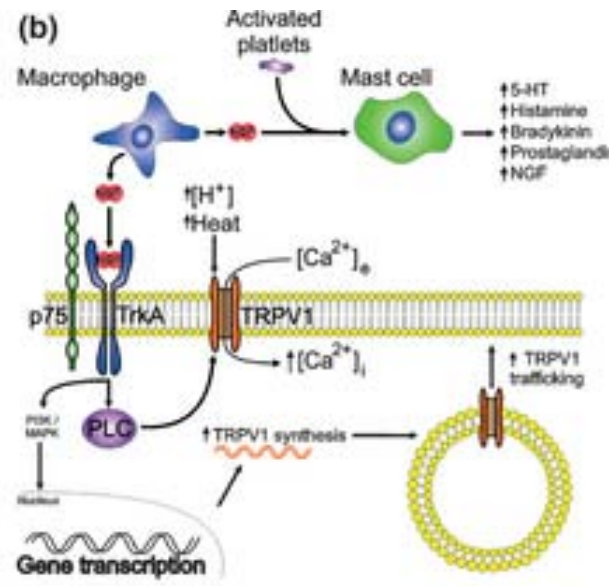
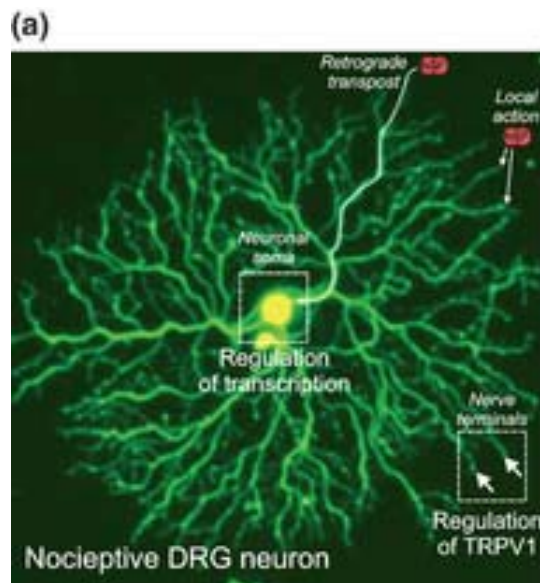
Activity against channels other than Nav1.7 may be useful
eg 1.8, 1.9, even central channels like 1.2 and 1.3



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

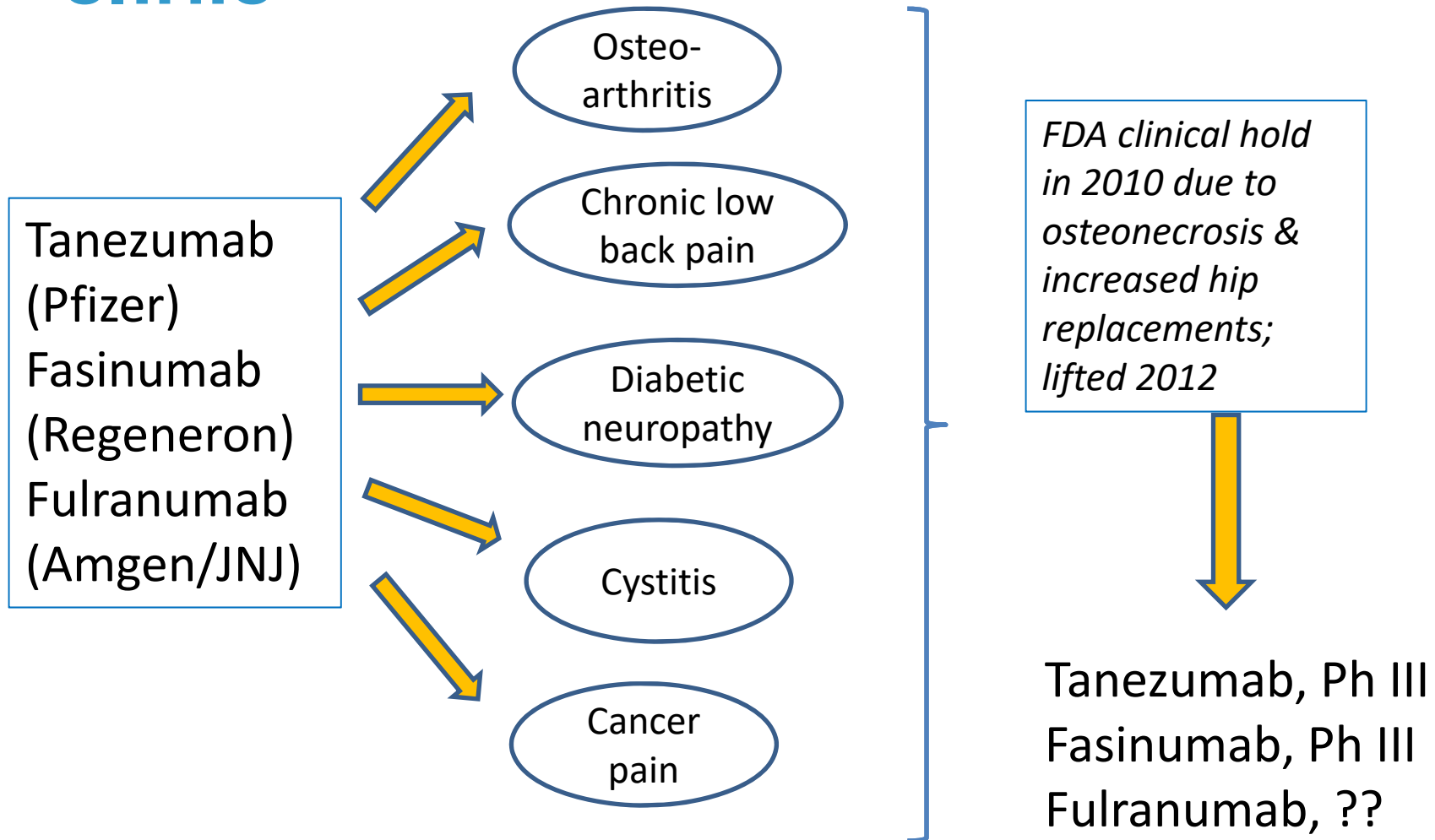
Hereditary sensory and autonomic neuropathy (HSAN)

- 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

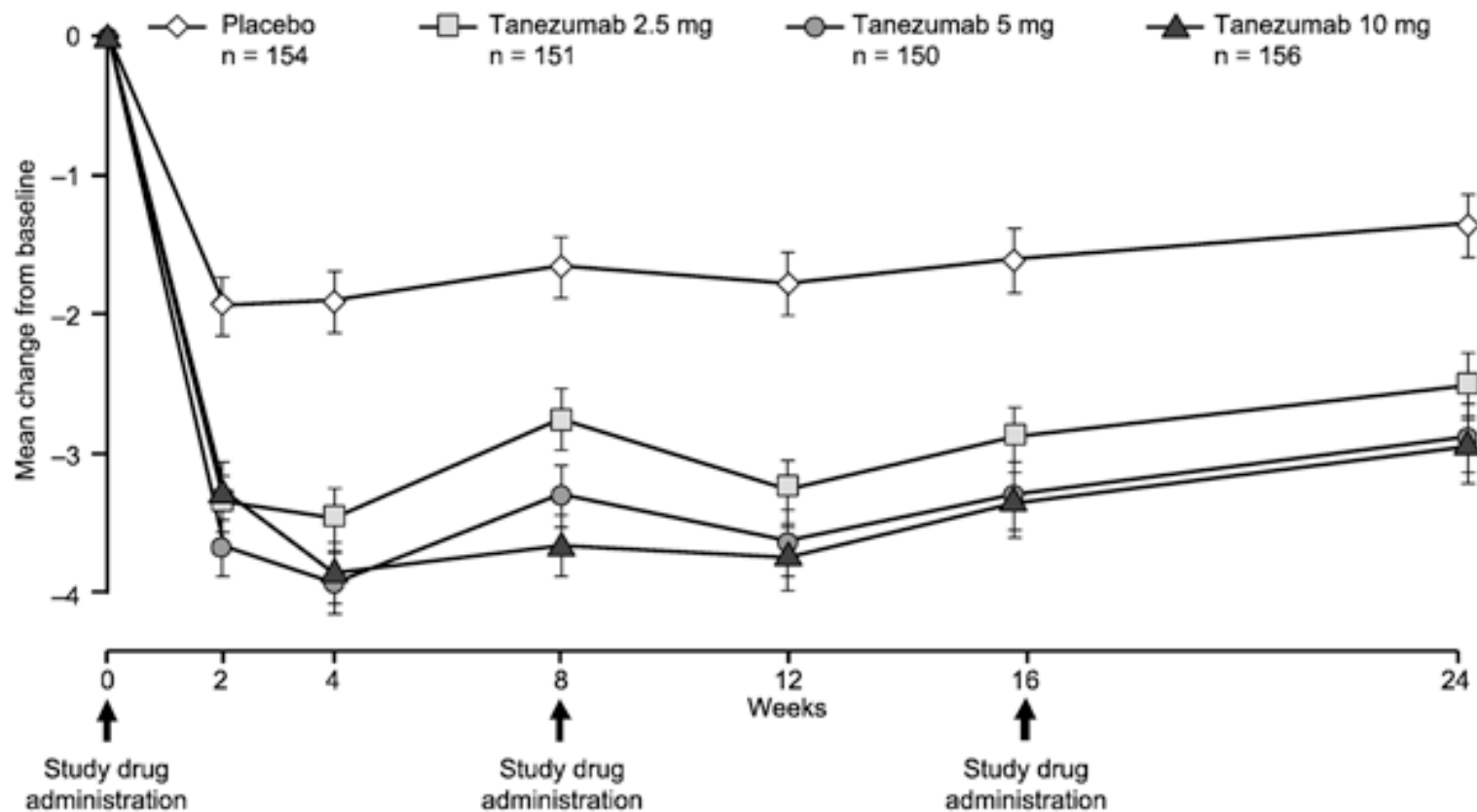




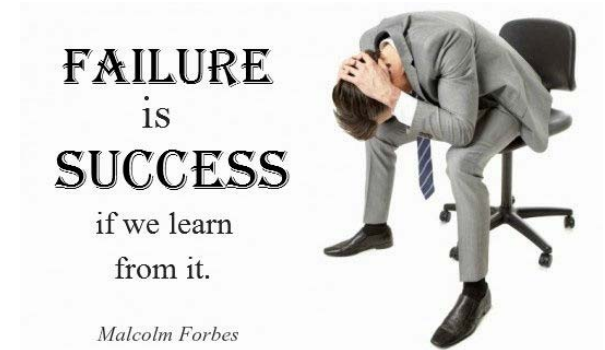
June 13, 2017 08:00 AM Eastern Daylight Time

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 Ph III trial in osteoarthritis pain (WOMAC pain subscale)



What can we learn from failures?



Fatty Acid Amide Hydrolase (FAAH)
inhibitors

Trpv1 antagonists

Purinergic P2X7 antagonists

Cannabinoid CB2 agonists

Glial cell modulators

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NMDA glycine site inhibitors

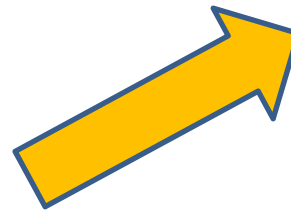
Was target engagement demonstrated in man at site of action?

Compound	Target Engagement	Method
FAAH inhibitors	✓	Enzyme inhibition
Trpv1 antagonists	✓	Increased heat pain threshold
P2X7 antagonists	✗	
CB2 agonists	✗	
Glial cell modulators	✗	
NK1 antagonists	✓	PET
A1 agonists	✗	
CCR2 antagonists	✓	Inhibition of ligand CCL2
α4β2 agonists	✗	
NMDA-glycine inhbs	✗	

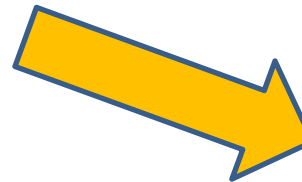
Without demonstration of target engagement, don't know if molecule or mechanism has failed

Single target/mechanism selectivity?

Fatty Acid Amide Hydrolase (FAAH)
inhibitors
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Need to target
key control
pathways



Or final common
pathway

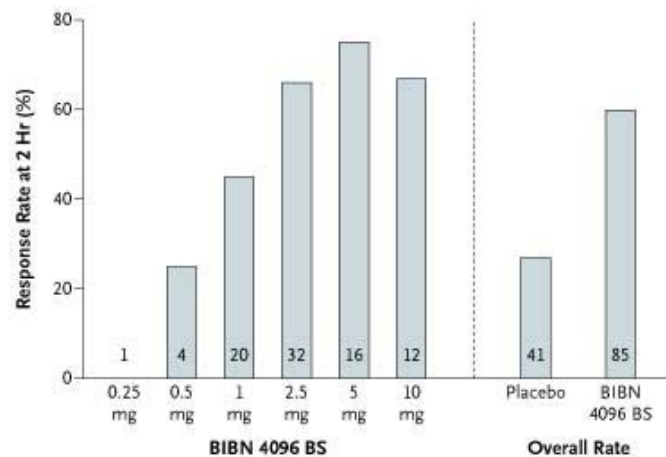
Issues with animal models

- 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

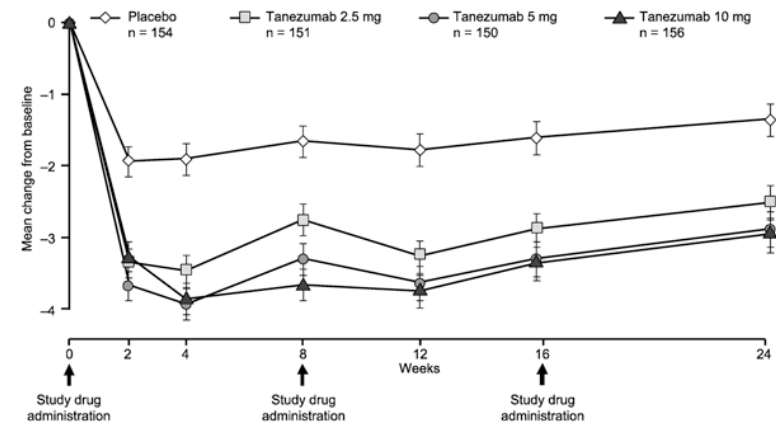


Issues with pain clinical trials.....

- 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