New Inroads in Pain Management

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Insight Series Webinar
April 24, 2012
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In Pain, The Balance Between Commercial and Scientific Risk Has Shifted

- To date, the pain market has been dominated by marginally-differentiated products based on some very old mechanisms.
- As we are seeing across therapeutic categories and disease indications, the good old days of low risk me-too’s are also ending for pain.

PoR (Proof of Relevance) is the pragmatic pursuit of meaningfully differentiated medicines representing the optimal balance of scientific and commercial risk.
And That Shift is Sending Some Pharma Running?

- The remaining unmet need and size of the potential market opportunity in pain is undisputed. Yet, the shift to scientific risk has resulted in several major pharmaceutical companies (who had begun to dip their toes back in) spinning out pain programs or leaving the pain space completely.
The Exit From Pain Seems Justified by Failure in the Clinic

- Over the last several years, we have seen a rash of novel pain targets and mechanisms move in and out of the spotlight.
- But virtually every new chemical entity for pain developed over the past 20 years has failed in the clinic, often despite great early promise.

**Moving Out?**
- Delta-opioids, kappa-opioids
- N-type calcium channels
- Cannabinoids / Endocannabinoids
  - FAAH inhibitors
- TRPV-1

**Moving In?**
- Voltage-gated sodium channels (Nav1.7)
- Purinergic receptors (P2X3 and P2X7 antagonists)
- Cytokines (TNF alpha, IL-6, resolvins)

**Not sure yet**
- Nerve Growth Factor
But Do We Really Understand the Reason for Failure?

- We are unable to answer the question of whether a drug has failed in a clinical trial or whether the trial has failed to rise to the complexity of pain.

**Moving Out?**
- Delta-opioids, kappa-opioids
- N-type calcium channels
- Cannabinoids / Endocannabinoids
  - FAAH inhibitors
- TRPV-1

Woolf, C.J. 2010 Nature Medicine Vol. 16 No. 11
And Will the New “In Vogue” Targets Suffer the Same Fate?

• Do we have the ability to adequately predict which, if any, of the new targets/mechanisms will ultimately be proven to be effective in the treatment of pain and for which individual patients?

Moving In?

• Voltage-gated sodium channels (Nav1.7)
• Purinergic receptors (P2X3 and P2X7 antagonists)
• Cytokines (TNF alpha, IL-6, resolvins)

Woolf, C.J. 2010 Nature Medicine Vol. 16 No. 11
Opportunities to Balance the Risk in Pain

• Can we better balance scientific and commercial risk, based on differentiation that is relevant to multiple stakeholders (including the increasingly tough regulators and payers)?

• We believe that Pharma and biotech can utilize multiple strategies to produce meaningfully differentiated medicines, balancing scientific and commercial risk.

- Targeting non-responders
- Sub-segmenting via biomarkers and companion diagnostics
- Orphan diseases
- Working in “well validated” spaces
It’s Worth It … Pain is Epidemic

• Chronic Pain is the leading cause of disability in the developed world, with more than 270 million sufferers worldwide.

• Chronic pain is more widespread than heart disease, cancer and diabetes combined.

• During the past two decades, the under treatment of acute pain has been widely recognized as an important issue in health care. Researchers have estimated that only one in four surgical patients in the US received adequate relief of acute pain.

And Pain is Still a Huge and Growing Market

- The market for pain drugs is huge, with no sign of slowing growth. Narcotics and non-narcotic analgesics sold over $10 B worldwide in 2010—and this doesn’t include drugs for neuropathic pain!
This Revenue Was Generated With Some Very Old Mechanisms

• Poppies and chili peppers ...

• Neuropathic Pain
  • Anti-depressants
  • Anti-epileptics
  • Topical Capsaicin
  • Topical Lidocaine
  • Local Anesthetics

• Nociceptive Pain
  • Acetaminophen
  • NSAIDs
  • Opiates
  • Local Anesthetics
  • Muscle Relaxants
Current Therapies Are Associated With Plenty of Unmet Need

Treatment is Largely Guided By Side Effects & Tolerability

Constipation, sedation, confusion, respiratory depression, mental clouding, renal colic, tolerance to prolonged use and risk of abuse, misuse, addiction.

Gastrointestinal ulcers, stomach bleeding, tinnitus.

Liver toxicity.

Gastric erosion, peptic ulcer, inflammation of the duodenum & of the colon, renal toxicity with prolonged use; cardiovascular issues with COX II’s.

WHO Analgesic Ladder
Neuropathic Pain Drugs Have Their Own Side Effect & Safety Issues

Lyrica (pregabalin), Pfizer’s GABA receptor agonist is associated with dizziness, somnolence, dry mouth and peripheral edema, as well as more serious risks such as angioedema, hypersensitivity reactions, seizures and suicidality.

Lilly’s Cymbalta (duloxetine), a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) carries warnings of nausea, somnolence, insomnia and dizziness, as well as a possible risk of hepatotoxicity, orthostatic hypotension, abnormal bleeding, mania, seizures and suicidal ideation.
The Biggest Unmet Need is Patients Who are Still in Pain

Pain’s limited tool box ... 
leaves us with “one size fits some”

> 50% of Patients Report Suboptimal Relief of Pain
Efficacy for Some Has Been Good Enough ... Until Now

• Today, clinical success is defined as some patients respond to some treatments some of the time - and some don’t.
  - At best, non-opioid analgesics only make pain more manageable in those who respond (reducing global pain scores by ~30%).
  - Typically, even in successful phase 3 regulatory analgesic trials, the majority of subjects are still eligible at the end to enter that same trial.
  - The number of patients who need to be treated (NNT) to achieve a 50% reduction in neuropathic pain in one patient is more than four, a high cost for the three unsuccessfully treated patients, who have to try another treatment empirically.

All Pain is Not the Same

Woolf, C.J. 2010 Nature Medicine Vol. 16 No. 11
Pain is a Pain

Pain has a notoriously high development risk and history of clinical failure. Reasons are numerous and include:

- Complex neurobiology
- Inadequate animal models
- Difficulty in reaching optimal therapeutic dose; limited by safety/tolerability
- Inability to cross the blood brain barrier and reach CNS target
- Lack of specificity and off-target effects
- Paucity of reliable biomarkers
- High placebo response rate
- Subjective clinical endpoints

Pain is Highly Subjective

Verbal, self-reporting of pain is entirely subjective, and can vary in one individual from day to day even though there is no difference in the input coming from their central nervous system.”

Iain Chessell, Head, Neuroscience Centre of Excellence at MedImmune

“Please be gentle. I have a very low threshold for pain.”

(Note tattoos and piercings)

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Opportunities to Balance the Risk in Pain

• Can we better balance scientific and commercial risk, based on differentiation that is relevant to *multiple* stakeholders (including the increasingly tough regulators and payers)?

• We believe that Pharma and biotech can utilize multiple strategies to produce *meaningfully* differentiated medicines, *balancing* scientific and commercial risk.

  1. Targeting non-responders
  2. Sub-segmenting via biomarkers and companion diagnostics
  3. Orphan diseases
  4. Working in “well validated” spaces
Target the Patients Who Have Little/No Other Options

- Should novel mechanisms, with unknown safety and side effect profiles, target pain types notorious for not responding well to currently available therapies (e.g., metastatic cancer pain, visceral pain)?
- This approach makes the most sense when there is actually a reason to believe these patients are likely to respond.
Targeting Non-Responders with Purinergic Receptor Antagonists

Afferent Pharmaceuticals was launched in December 2009 as a spin-out of Roche with a $23M Series A by Pappas Ventures, Third Rock Ventures, Domain Associates, New Leaf Ventures and Roche. Afferent is led by Anthony P. Ford, Ph.D., chief scientific officer and a recognized expert in the P2X3 field.

• ATP-gated purinergic receptors are known to be involved in pain signal transmission, and are among the systems altered by cannabinoid analgesia.

• The P2X3 receptor subtypes are expressed specifically on C-fiber afferent neurons in multiple tissues and organ systems, including joints and hollow visceral organs, suggesting a high degree of specificity to the nociceptive system.

• As a result, there is a lower likelihood of adverse effects in the brain or cardiovascular tissues, even with oral dosing.

NeuroPerspective June 2011; Afferent company website
Targeting Non-Responders with Purinergic Receptor Antagonists

• Sensory fibers in visceral organs, especially the urinary bladder, express high levels of P2X3 receptors that are elevated in pathological conditions.

• P2X3 antagonists suppress afferent excitation and raise filling volume thresholds, especially in rodent models of cystitis.

• The distressing and largely unmet painful and irritative symptoms of bladder pain syndrome/interstitial cystitis and chronic prostatitis as well as lower urinary tract symptoms (urgency, frequency, and nocturia) associated with overactive bladder and benign prostatic hyperplasia, represent important visceral indications for novel P2X3 antagonists.
Targeting Non-Responders with Purinergic Receptor Antagonists

- Afferent is now conducting Phase II studies with its lead P2X3 antagonist, AF-219, in patients with chronic bladder pain syndrome, a prevalent and painful condition with currently limited therapeutic options.
- AF-219 is also in Phase II for moderate-to-severe pain due to osteoarthritis of the knee and idiopathic chronic cough.

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Targeting Non-Responders - What Not To Do

- Pfizer conducted virtually simultaneous Phase IIa exploratory studies across multiple pain types with its anti-NGF (nerve growth factor) monoclonal antibody, tanezumab.
- At a March 2012 Arthritis Advisory Committee Meeting, Pfizer detailed results for tanezumab that included 30 studies that enrolled more than 11,000 patients. More than 6,400 were treated with tanezumab monotherapy and 3,400 with a tanezumab /NSAID combination.

**Inflammatory Pain**
- OA (knee and hip)
- Chronic Low Back Pain

**Visceral Pain**
- Interstitial Cystitis
- Endometriosis Pain

**Neuropathic Pain**
- Post-herpetic Neuralgia

**Cancer Pain**
- Metastatic Bone Pain


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Pain Insight Briefing
Anti-NGF Approaches On Clinical Hold

The first potential biological for the treatment of chronic pain suffered a major setback in December 2010 when the US FDA placed a hold on most clinical trials for experimental therapies targeting nerve growth factor (NGF).

• Tanezumab's steady progress faltered when some individuals in Phase III osteoarthritis trials developed cases of joint damage, several of which needed surgery to replace joints when they developed progressively worsening osteoarthritis with evidence of bone necrosis. An additional case of joint failure then suggested problems with the entire class of drugs.

• Sanofi/Regeneron, J&J and AstraZeneca/MedImmune also halted their NGF inhibitor programs.

• The FDA has allowed trials of anti-NGF antibodies to continue for cancer pain (both Pfizer and J&J have programs).

Should Anti-NGF Studies Have Started in Metastatic Bone Pain?

A strong biological rationale for the mechanism in bone cancer pain, as well as the high unmet need (and greater tolerance for side effects), suggest it may have been better to start with cancer pain and then expand to multiple other pain types – rather than the other way around.

- Bone has a unique and restricted pattern of sensory innervation compared to skin.
  - The periosteum tissue that surrounds bone contains the majority of bone-associated nerve fibers, with the bone marrow and mineralized bone receiving a significant, but much less dense, innervation and normal cartilage, none at all.

- The phenotype of nerve fibers in bone is also much different from skin.
  - There are fewer types, with no rapidly conducting Aβ fibers or nonpeptidergic C fibers in bone. Most (80%) of the sensory afferents are peptidergic C fibers that express the NGF receptor TrkA, compared to 30% of fibers that are TrkA positive in skin.

- NGF appears to be integrally involved in the upregulation, sensitization, and disinhibition of multiple neurotransmitters, ion channels, and receptors in the primary afferent nerve and DRG fibers that synergistically increase nociceptive signals originating from the tumor-bearing bone.
If Allowed, Pfizer Will Target Non-Responders

Pfizer Statement: Anti NGF FDA Arthritis Advisory Committee Meeting Vote
March 12, 2012

The panel voted unanimously, 21 to 0, that there is a role for the ongoing development of the NGF inhibitors in conditions such as osteoarthritis. The panel also voted 20 to 1 that there is a role for the ongoing development of NGF inhibitors to manage the pain associated with conditions other than osteoarthritis for which there are no agents with demonstrated analgesic effect.

“Physicians and patients are in need of options for difficult-to-treat pain conditions and the panel’s vote today is an important step towards helping us more fully understand the benefit/risk profile of this important new class of medicines,” said Steve Romano, M.D., senior vice president, Medicines Development Group head, Primary Care Business Unit. “We look forward to continuing our discussions with the FDA as the agency reviews the panel’s recommendation.”

In 2010, with the exception of cancer pain studies, the FDA placed trials of all NGF inhibitors on hold following investigator-reported cases of osteonecrosis or the worsening of osteoarthritis leading to joint replacement. Pfizer also presented a risk-mitigation strategy, including recommendations that future trials of NGF inhibitors study only those patients who do not benefit from existing therapies and exclude chronic concomitant NSAID use with NGF inhibitors.

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After Fighting It for Years, Pharma Has Warmed Up to the De-Risking Benefits of Sub-Segmenting

Sub-segmenting via biomarkers and companion diagnostics

Orphan diseases
Biomarkers in Pain

• To offset the cost of development (including failure), there is an ongoing effort to generate more discriminatory biomarkers of efficacy and toxicity for potential pain therapies, which may eliminate suboptimal compounds earlier in development.
• Traditional preclinical animal studies often do not predict human-specific metabolic and toxic effects. Currently, the most commonly used toxicity biomarkers generate safety signals only when substantial organ damage has occurred.

The Translational Sciences group at MedImmune (now AstraZeneca’s CNS iMED) pursues a two-pronged biomarker strategy, says VP of Translational Science Laura Richman: developing **biomarkers first for patient selection and, second, for assessing the neutralization of the target.** “If there is a correlation of target neutralization with that biomarker changing in some way, that’s very powerful,” she said.

MedImmune also uses biomarkers for optimizing dose selection and predicting toxicity. Richman cites accessibility of the target organ as the biggest challenge in translational research in pain.

Companion Diagnostics in Pain

Genentech will work with Xenon Pharma to discover and develop compounds and companion diagnostics for the treatment of pain, a therapeutic area that is relatively new to Genentech.

'The Pink Sheet' DAILY
January 11, 2012

Under its pain therapeutics discovery alliance with Xenon, Genentech has an exclusive license to compounds and a non-exclusive license to diagnostics for development and commercialization. In exchange, Xenon will receive an undisclosed upfront payment and research funding, and is eligible to receive additional research, development and commercialization milestones totaling up to $646 million for multiple products and indications.
Orphan Diseases … and Beyond

• In a December 2006 *Nature* paper, researchers, including scientists from Pfizer, identified a mutation in the gene encoding the alpha-subunit of the voltage-gated sodium channel, Nav1.7, which is strongly expressed in nociceptive neurons, as the source for the inability to feel pain in an extremely rare congenital condition.

• Pfizer is making substantial investments in the voltage-gated sodium channel, Nav1.7.

An *SCN9A* channelopathy causes congenital inability to experience pain

The complete inability to sense pain in an otherwise healthy individual is a very rare phenotype. In three consanguineous families from northern Pakistan, we mapped the condition as an autosomal-recessive trait to chromosome 2q24.3. This region contains the gene *SCN9A*, encoding the α-subunit of the voltage-gated sodium channel, Na\(_v\)1.7, which is strongly expressed in nociceptive neurons. Sequence analysis of *SCN9A* in affected individuals revealed three distinct homozygous nonsense mutations (S459X, I767X and W897X). We show that these mutations cause loss of function of Na\(_v\)1.7 by co-expression of wild-type or mutant human Na\(_v\)1.7 with sodium channel β\(_1\) and β\(_2\) subunits in HEK293 cells. In cells expressing mutant Na\(_v\)1.7, the currents were no greater than background. Our data suggest that *SCN9A* is an essential and non-redundant requirement for nociception in humans. These findings should stimulate the search for novel analgesics that selectively target this sodium channel subunit.
Orphan Diseases ... and Beyond

Yale School of Medicine entered into a collaboration with Icagen and Pfizer to explore the potential efficacy of investigational compounds as novel treatments for pain. These compounds may be useful in treating pain in people with a rare genetic disorder called inherited erythromelalgia (IEM), or the “man on fire syndrome.” Individuals afflicted with the syndrome experience a debilitating, life-long burning pain.

P. Kay Wagoner, Ph.D., CEO of Icagen added, “The studies we are jointly undertaking should help us better understand how modulating Nav1.7 channels in IEM patients may reduce the extreme pain they experience. This information may additionally assist our broader efforts to find novel sodium channel treatments for patients with various pain conditions.”
Pfizer Hones its Expertise in Ion Channels

- Icagen is now part of Neusentis, a Pfizer research-and-development unit focused on treatments for pain and sensory disorders.
- Nav1.7, a focus on Neusentis’ research, appears to be largely restricted to the peripheral nervous system. Molecules that inhibit Nav1.7 function are thus seen as having the potential to produce potent and potentially safer analgesics.
- In December 2010, Pfizer began the first clinical trial of a Nav1.7 channel blocker, a Phase I ascending-dose study.
- Several other companies, including Convergence (spin out from GSK) and Xenon Pharmaceuticals Inc. also have Nav1.7 discovery programs underway.

Neusentis:
1. Evaluate druggability of ion channel targets
2. Identify small molecule binding sites
3. Seek opportunities for biologics molecules
Is There Still Opportunity to Work in Comfortable, “Well Validated” Spaces?

- The pharmaceutical industry’s greatest R&D successes have come from working in comfortable, “well validated” spaces.
- The key challenge for a “Therapeutic Class Evolution v2” strategy is to make the product commercially relevant in today’s world.
Janssen Pharmaceuticals’ Nucynta (tapentadol) is a novel MOA combination mu-opioid agonist and norepinephrine reuptake inhibitor. Nucynta IR and ER showed equivalent efficacy in head-to-head studies versus oxycodone (both IR and ER) with meaningfully reduced side effects (nausea and vomiting, constipation, somnolence).
Relevant Differentiation in Well Validated Spaces

• NKTR-181 is a novel mu-opioid analgesic investigational drug candidate engineered to enter the central nervous system (CNS) at a substantially lower rate compared to existing opioid therapies.

• By slowing the entry of the drug into the CNS, NKTR-181 has the potential to eliminate the euphoria that underlies opioid abuse liability and dependence, but also the serious CNS-related side effects of respiratory depression and sedation.

• The molecular design of the polymer conjugate also prevents conversion of NKTR-181 into a free opioid or an abusable form of an opioid.

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Nektar Therapeutics Product Fact Sheet 2012

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Pain Insight Briefing
Relevant Differentiation in Well Validated Spaces

Preclinical Development
In preclinical trials, NKTR-181 has demonstrated:
• Significantly slower rate of entry into the CNS
• Equal analgesia to oxycodone
• Lower abuse liability
• Reduced CNS side effects, including respiratory distress and sedation

Clinical Development
• Phase 1 studies are currently underway to assess the pharmacokinetics, pharmacology, safety and efficacy of NKTR-181.
Relevant Differentiation in Well Validated Spaces

- Fatty-acid amide hydrolase (FAAH) catalyzes the intracellular hydrolysis of the endocannabinoid, anandamide.
- Inhibitors of FAAH are well validated as potential analgesics, but they can cause unacceptable CNS-related psychiatric side effects and/or abuse potential.
- The May 2012 issue of Pharmacology Research (Piomelli, et al.) reports an inhibitor of endocannabinoid breakdown that has analgesic activity generated in the periphery.
Relevant Differentiation in Well Validated Spaces

- The antinociceptive effects of oral URB937 were investigated in mouse models of acute inflammation (carrageenan), peripheral nerve injury (chronic sciatic nerve ligation) and arthritis (complete Freund’s adjuvant).
- In all models, URB937 was as effective or more effective than standard analgesic and anti-inflammatory drugs (indomethacin, gabapentin, dexamethasone) and reversed pain-related responses (mechanical hyperalgesia, thermal hyperalgesia, and mechanical allodynia) in a dose-dependent manner.
- URB937 was significantly more effective than two global FAAH inhibitors, URB597 and PF-04457845, in the complete Freund’s adjuvant model.

Antihyperalgesic effects of URB937 in the sciatic nerve constriction model of peripheral neuropathy

Relevant Differentiation in Well Validated Spaces

• A combination of URB937 with the non-steroidal anti-inflammatory agent, indomethacin, showed that the two compounds interacted synergistically to attenuate pain related behaviors.

• In addition to no association with CNS side effects and/or abuse potential, URB937 appears to reduce the number and severity of gastric lesions produced by indomethacin.

Pharmacol Res. 2012 May;65
Relevant Differentiation in Well Validated Spaces

• EXPAREL is a liposomal injection of bupivacaine, an amide local anesthetic, indicated for single-dose infiltration into the surgical site to produce postsurgical analgesia.
  
  — There are an estimated 70 M annual surgical procedures in the US; 5 M uses of bupivacaine.

• Provides postsurgical analgesia for up to 72 hours (versus 7-10 hours with conventional IR bupivacaine) with a single-dose local administration (clinical studies in patients undergoing soft tissue surgery and orthopedic surgery).

• US launch commenced in April 2012; to be promoted with a ~70-rep hospital sales force.

http://www.pacira.com/index.php; Piper Jaffray analyst report
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Relevant Differentiation in Well Validated Spaces

• Medical and cost benefits include:
  
  – Opioid-sparing, locally-acting analgesic.
    
    Reduce opioid-related GI side effects (e.g., constipation, postoperative ileus) and CNS safety/side effect issues (nausea, sedation, respiratory depression).
  
  – Potential to reduce hospital stay.
  
  – Potential to replace use of elastomeric infusion pumps, which are relatively expensive, catheter-based systems that deliver bupivacaine over a long period (i.e., 0.5 days to 5 days post-operation) directly to the surgical site.
  
  – May reduce the dependence on opioid use in the postsurgical setting.

http://www.pacira.com/index.php; Piper Jaffray analyst report
Conclusions

• Big Pharma presence overall in pain has been minimal, and specialty pharma (e.g., Purdue, Endo) have dominated the category -- typically with marginally-differentiated products based on some very old mechanisms.

• But the good old days of low risk me-too’s are ending.

• While established mechanisms can still yield meaningful clinical differentiation, the opportunities are few (and usually early in development).

• Several of the Big Pharma players were starting to dip their toes back into pain, but as the risk shifts from commercial to scientific, they are getting back out.

• Traditional specialty players in pain, who will likely be later-stage development and commercialization partners, will eventually need to accept increased scientific risk of novel programs to stay in the game.

• The good news is that biotech (and the few dedicated Pharma) are taking on the challenge and advancing the science with meaningfully differentiated medicines that better balance scientific and commercial risk.
Swearing as a Response to Pain—Effect of Daily Swearing Frequency
Richard Stephens, School of Psychology, Keele University, Staffordshire, United Kingdom
November 2011
Abstract
Previously we showed that swearing produces a pain lessening (hypoalgesic) effect for many people. This paper assesses whether habituation to swearing occurs such that people who swear more frequently in daily life show a lesser pain tolerance effect of swearing, compared with people who swear less frequently. Pain outcomes were assessed in participants asked to repeat a swear word versus a nonswear word. Additionally, sex differences and the roles of pain catastrophizing, fear of pain, and daily swearing frequency were explored. Swearing increased pain tolerance and heart rate compared with not swearing. Moreover, the higher the daily swearing frequency, the less was the benefit for pain tolerance when swearing, compared with when not swearing. This paper shows apparent habituation related to daily swearing frequency, consistent with our theory that the underlying mechanism by which swearing increases pain tolerance is the provocation of an emotional response.
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24th ANNUAL CANCER PROGRESS CONFERENCE

March 2013, New York
Dates to be advised soon!

www.cancerprogressbyDH.com

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