New Inroads in Pain Management

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The contents of this presentation are not meant to be comprehensive, but to encourage a spirited dialogue. Feedback, comments and corrections are welcome.
Today’s Pain Therapies: A Lot Like Your Grandmother’s

- Poppies and chili peppers ...

- Nociceptive Pain
  - Acetaminophen
  - NSAIDs
  - Opiates
  - Local Anesthetics
  - Muscle Relaxants

- Neuropathic Pain
  - Anti-depressants
  - Anti-epileptics
  - Topical Capsaicin
  - Topical Lidocaine
  - Local Anesthetics
Step 1: Mild Pain (1-3/10)
- Aspirin (ASA)
- Acetaminophen (APAP)
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- +/- Adjuvants

Step 2: Moderate Pain (4-6/10)
- APAP or ASA +
  - Codeine
  - Hydrocodone
  - Oxycodone
  - Dihydrocodeine
  - Tramadol (not available with APAP or ASA)
  - +/- Adjuvants

Step 3: Severe Pain (7-10/10)
- Morphine
- Hydromorphone
- Methadone
- Levorphanol
- Fentanyl
- Oxycodone
- +/- Nonopiod analgesics
- +/- Adjuvants

Adjuvant Therapy:
- Anticonvulsants
- Antidepressants
- Corticosteroids
- Dermal analgesics
- Muscle relaxants
- Stimulants

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.

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

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Pain Insight Briefing
Neuropathic Pain Drugs Have their Own Side Effect and 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.
Pain’s Limited Tool Box

Leaves us with “One Size Fits Some”

> 50% of Patients Report Suboptimal Relief of Pain
But Pain is Still a Huge and Growing Market
The Newest Market Entrants Improve on What We Already Have

- **Onsolis**: Fentanyl buccal soluble film
- **EXALGO**: Hydromorphone HCl
  - Extended-Release Tablets Once Daily
- **Gralise**: Gabapentin tablets
  - Once-daily
  - For the full day
- **Vimovo**: Naproxen/esomeprazole magnesium
  - 375/20-500/20 mg delayed-release tablets
- **EMBEDA**: Morphine sulfate and naltrexone hydrochloride Extended Release Capsules
Nucynta Breaks Out From the Pack

- Janssen Pharmaceuticals’ Nucynta (tapentadol) is a novel MOA combination mu-opioid agonist and norepinephrine reuptake inhibitor.
- In clinical studies 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).
- Nucynta is considered by pain specialists as a good option for more moderate pain.

**GI TOLERABILITY PROFILE**
In a clinical study in chronic low back pain
Composite incidence of nausea and/or vomiting²
While the Pipeline is Focused on Chronic Pain, There is Still Unmet Need in Acute Pain

Particularly in the hospital and ambulatory surgery center settings.

Ambulatory Surgery Center Association
Opportunities in Acute Pain: Postsurgical Pain

• EXPAREL is a liposome 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 expected early 2012; to be promoted with a ~70-rep hospital sales force.

http://www.pacira.com/index.php; Piper Jaffray analyst report
Opportunities in Acute Pain: Postsurgical Pain

• 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
Undermanaged Acute Postoperative Pain Can Transition to a Chronic State

THE LANCET

• It is estimated that only one in four surgical patients in the US receive adequate relief of pain.
• In addition to the safety and side effect issues associated with standard of care analgesics, the development of a chronic pain state after surgery, termed persistent postsurgical pain (PPP), is being increasingly recognized as a not uncommon sequel of surgery.
• Although incidence can vary depending on the nature of the surgery, many common operations (e.g., mastectomy, thoracotomy, hernia repair, coronary artery bypass surgery, amputation) are associated with an incidence of PPP of up to 30–50%.
• Ongoing inflammation or injury to peripheral nerves during the surgery have been postulated as primary causal factors leading to persistent pain.
• Data suggest that use of specific analgesic agents or techniques, particularly regional analgesia (e.g., epidural or peripheral nerve analgesia) and local anesthetic-based regimens, can affect major postoperative morbidity.
Chronic Pain is the Leading Cause of Disability in the Developed World

- An estimated one in three individuals experience pain lasting more than 3 months at some point in their lives.
- Chronic pain is the most common symptom for which patients seek medical help.
- More than 270 million people worldwide suffer from chronic pain.
- However, current treatments are poorly effective, with only approximately 50% of patients obtaining effective relief of their pain.

Over the last several years, we have seen a rash of novel pain targets and mechanisms move in and out of the spotlight.

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

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

**Not sure yet**
- Nerve Growth Factor
Transient receptor potential cation channel, subfamily V, member 1 (TRPV1)

- The transient receptor potential cation channel, subfamily V, member 1 also known as TRPV1 is a ligand-gated nonselective cation channel that may be activated by a wide variety of exogenous and endogenous physical and chemical stimuli, including heat, low pH (acidic conditions), the endocannabinoid anandamide, N-arachidonoyl-dopamine, and capsaicin.

- TRPV1 receptors are found in the central nervous system and the peripheral nervous system and are involved in the transmission and modulation of pain, as well as the integration of diverse painful stimuli.

- TRPV1 blockade in vivo elicits hyperthermia in multiple species, from rodents to humans, suggesting that TRPV1 is involved in body temperature maintenance.

Homology model of the TRPV1 ion channel tetramer (where the monomers are individually colored cyan, green, blue, and magenta respective) imbedded in a cartoon representation of a lipid bilayer. PIP2 signaling ligands are represented by space-filling models (carbon = white, oxygen = red, phosphorous = orange).
TRPV1: Potential to Address Multiple Types of Pain

Antagonists to the TRPV1 ligand-gated nonselective cation channel promise to address multiple types of pain, as well as GI indications and chronic cough.

TRPV1 Antagonists: Hot ... Too Hot

AMG 517 caused marked hyperthermia in subjects who underwent molar extraction.

- TRPV1 antagonists causing hyperthermia in rodents, dogs, monkeys, and humans indicates an evolutionarily conserved role of TRPV1 in thermoregulation.

Gawwa et al., 2008 Pain 136:202-210

Hypothesized that the thermoregulation is CNS-modulated, but peripheral restriction of action still caused heat.
What’s Next for Endocannabinoids?

The endocannabinoid approach has hit some road bumps as pain therapies (although not dead yet), but may show promise in addressing obesity.

Endocannabinoid signal in the gut controls dietary fat intake.

DiPatrizio NV, Astarita G, Schwartz G, Li X, Piomelli D.

Oral sensory signals drive dietary fat intake, but the neural mechanisms underlying this process are largely unknown. The endocannabinoid system has gained recent attention for its central and peripheral roles in regulating food intake, energy balance, and reward. Here, we used a sham-feeding paradigm, which isolates orosensory from postingestive influences of foods, to examine whether endocannabinoid signaling participates in the positive feedback control of fat intake. Sham feeding a lipid-based meal stimulated endocannabinoid mobilization in the rat proximal small intestine by altering enzymatic activities that control endocannabinoid metabolism. This effect was abolished by surgical transection of the vagus nerve and was not observed in other peripheral organs or in brain regions that control feeding. Sham feeding of a nutritionally complete liquid meal produced a similar response to that of fat, whereas protein or carbohydrate alone had no such effect. Local infusion of the CB(1)-cannabinoid receptor antagonist, rimonabant, into the duodenum markedly reduced fat sham feeding. Similarly to rimonabant, systemic administration of the peripherally restricted CB(1)-receptor antagonist, URB 447, attenuated sham feeding of lipid. Collectively, the results suggest that the endocannabinoid system in the gut exerts a powerful regulatory control over fat intake and might be a target for antiobesity drugs.
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
- Subjective clinical endpoints
- High placebo response rate
- Paucity of reliable biomarkers

There Are No Biomarkers for Pain

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

(Note tattoos and piercings)
But Progress is Being Made

The Imaging Consortium for Drug Development (ICD) is a collaborative research effort between academia and pharmaceutical companies who are developing novel drugs to treat central nervous system (CNS) disorders. The ICD uses functional MRI (fMRI) to elucidate the effects of pain modulating drugs on neural activity within the brain in humans and in animal models of CNS disease. This landmark effort builds on more than a decade of fMRI research into the study of pain, and realizes the benefits of standardization and cost-sharing among consortium members, for pre-competitive Neuroscience research.

The Translational Sciences group at MedImmune 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.

The AZ - MedImmune “Co-Opetition”*

*Term coined by Michael Goodman, “The Pink Sheet”

AZ is focused on small molecules and MedImmune on large molecules in an open and collaborative framework that the two organizations share across R&D, encompassing infrastructure, capabilities and business models.

AZ’s small molecule pain pipeline includes Phase II including an mGluR5 antagonist and a chemokine antagonist against chronic neuropathic pain.

Pain R&D at MedImmune sits within AstraZeneca’s CNS Pain iMED, one of nine Innovative Medicines Units. The focus is on biologicals.

AstraZeneca’s Target the Patient’s #1 Complaint

- AstraZeneca has rights to two Nektar molecules: NKTR-118, a peripherally-acting derivative of the opioid antagonist naloxone, currently enrolling a Phase III trial for opioid-induced constipation, and NKTR-119, a co-formulation of NKTR-118 with an opioid, which is in preclinical testing targeting moderate to severe chronic pain.

- A comprehensive Phase 3 Program for NKTR-118 is underway with a regulatory filing expected in 2013.

- For NKTR-118, Nektar is eligible for:
  - up to $235 million in filing and launch milestones
  - $375 million in sales milestones at certain commercial levels
  - Significant, escalating double-digit royalties

MedImmune Bets on Biologicals

- MedImmune believes that the high selectivity biologics may be able to circumvent many of the issues associated with small molecule approaches to pain (e.g., the inability to engage the target without having off-target toxicity profiles).
- The most advanced biological approaches are the anti-NGF (nerve growth factor) antibodies and inhibitors to the cytokines TNF (tumor necrosis factor) and IL-6.
- Ion channels and GPCRs both have numerous members that are involved in pain pathways. While elusive, research is making advances toward developing antibodies against these targets.
- Of course, there are challenges with antibodies including:
  - Not all targets are amenable to the approach
  - Potential immunogenicity (and neutralizing antibodies) with long term therapy
  - Administration via injection, but long half life allows relatively infrequent dosing (once every 6-8 weeks)

MedImmune is in Stealth Mode

• MedImmune is keeping quiet about their pain projects with only two programs listed in the public pipeline databases:
  
  — **IL-6 antibody**: Preclinical stage in the UK and the US.
  
  — **NGF inhibitor**: MED1578 (voluntarily suspended).
  
• In March 2010 MedImmune obtained exclusive licenses to four peptides from Xenome’s xdiscover venom peptide library against an undisclosed target involved in a key pain pathway.

Inflammation produces several inflammatory factors, most notably nerve growth factor (NGF), which sensitize nerve cells by acting on their cognate receptors and activating signal transduction. These activated pathways phosphorylate transient receptor potential (TRP) channels, which alter their trafficking and reduce the membrane's threshold, resulting in an increased excitability of pain neurons. Image courtesy of *Nat. Rev. Drug. Disc.* (8, 55–56, 2009).
Anti-NGF Approaches Are On Clinical Hold

• The first potential biological for the treatment of chronic pain suffered a severe 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, 16 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.

• These biologics were poised to be the first important new class of drugs for general pain since the prototype NSAID, aspirin, came into general use at the end of the nineteenth century. “We've had over a hundred years without having really a major new pain drug,” says Thomas Schnitzer, a professor of medicine at Northwestern University in Chicago.
Anti-NGF Trials Continue for Cancer Pain

• The FDA has allowed trials of anti-NGF antibodies to continue for cancer pain (both Pfizer and J&J have programs).
• In hindsight, the strong biological rationale for the mechanism in bone cancer pain (NGF associated with nociceptive signaling originating from the tumor-bearing bone) 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.

Pfizer conducted virtually simultaneous Phase IIa exploratory studies with its anti-NGF tanezumab across multiple pain types.

- **Neuropathic Pain**
  - Post-herpetic Neuralgia
- **Cancer Pain**
  - Metastatic Bone Pain
- **Inflammatory Pain**
  - OA (knee and hip)
  - Chronic Low Back Pain
- **Visceral Pain**
  - Interstitial Cystitis
  - Endometriosis Pain

We Will Soon Learn the Fate of Anti-NGF

March 12, 2012: Arthritis Advisory Committee Meeting Announcement

Agenda
On March 12, 2012, the committee will discuss the anti-nerve growth factor (Anti-NGF) drug class that is currently under development and the safety issues possibly related to these drugs. These drugs are being developed for the treatment of a variety of chronic painful conditions including osteoarthritis, chronic lower back pain, diabetic peripheral neuropathy, post-herpetic neuralgia, chronic pancreatitis, endometriosis, interstitial cystitis, vertebral fracture, thermal injury, and cancer pain. The committee will be asked to determine whether reports of joint destruction represent a safety signal related to the Anti-NGF class of drugs, and whether the risk benefit balance for these drugs favors continued development of the drugs as analgesics.

http://www.fda.gov/AdvisoryCommittees/Calendar/ucm286556.htm
Pfizer Still Making Big Bets in Pain

• While most VCs and several Big Pharma players have exited the field, Pfizer seems to agree that there's still plenty of opportunity in pain despite the risk – the focus is on innovation.

In October 2010, Pfizer's Pain Portfolio Vice President and Development Head, Kenneth Verburg, PhD, at an investors' update session:

"It's our view at Pfizer, that really the only way to move on this market and grow this market is to take a step aside and go after innovative drug targets that produce innovative medicines that deliver substantially on the efficacy and safety over the existing therapeutic classes."
Pfizer Hones its Expertise in Ion Channels

Pfizer’s new Neusentis Unit consolidates Pfizer's Pain & Sensory Disorders and Regenerative Medicine units into a new biotech-like unit in Cambridge, UK.

Fueled by the late 2011 acquisition of Icagen, Pfizer continues to build leading expertise in the field of ion channels, and Neusentis scientists focus this expertise on delivering new medicines across all forms of pain influenced by this mechanism.

Neusentis:

1. Evaluate druggability of ion channel targets
   Prioritize the targets to invest from the viewpoints of druggability

2. Identify small molecule binding sites
   Through combination of 3D protein modeling and site-directed mutagenesis

3. Seek opportunities for biologics molecules
   Estimate likely interaction modes of toxins and peptides with ion channels using cutting-edge software packages
In Pursuit of the Sodium Channel Nav1.7

- One ion channel target in which Pfizer has made substantial investment is the voltage-gated sodium channel, Nav1.7.
- 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.

**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 β1 and β2 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.
Sodium Channel Nav1.7: Selectivity is Key

• Nav1.7 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.

• The key to modulating pain through sodium channels will be selectivity, according to Icagen's Richard Katz, MD, EVP, finance and corporate development, and CFO. "It's hard not to have effects at other sodium channels in the CNS and cardiac conduction systems. We think their programs are not selective."
While Some Pharma’s Spin In, Others Spin Out
Convergence Pharmaceuticals

Convergence Pharmaceuticals Fast Facts
- Convergence is developing novel analgesics for the treatment of chronic pain
- Formed in October 2010
- Spin out from GSK
- $35.4 million raised to date in a Series A
- Investors include Apposite Capital, New Leaf Ventures and SV Life Sciences
- GSK has an 18% equity interest
Convergence is Also Pursuing the Nav1.7 Target

Convergence Pharmaceuticals’ CNV 1014802 is a small molecule sodium channel antagonist, that specifically targets the Nav1.7 sodium channel, in development for the treatment of neuropathic pain.

- The safety, tolerability and pharmacokinetics of CNV 1014802 was originally evaluated by GSK in Phase I studies in normal volunteers, as well as subjects with bipolar disorder and depression. Additional Phase I studies conducted by Convergence in over 150 healthy volunteers showed a good pharmacokinetic and safety profile.

- While displaying a highly state-dependent block of sodium channels conveying painful sensations, CNV1014802 has a superior and differentiated profile of activity at the Nav1.7 channel. This profile translates into significant block of Nav1.7 channels in experimental models that mimic the higher frequency and spontaneous neuronal firing observed in entrapment neuropathies such as lumbosacral radiculopathy (LSR). CNV1014802 began a Phase II clinical trial for the treatment of LSR in July 2011.
  - LSR is a common neuropathic pain condition caused by compression of the nerve roots in the lumbar region of the spine. Common symptoms include pain radiating from the lower back down the legs, together with sensory and motor impairment in the lower limbs.

- A study for the treatment of pain associated with trigeminal neuralgia also has been initiated.

Convergence company website

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Pain Insight Briefing
Roche Spins Out Its Purinergic Receptor Program

Afferent Pharmaceuticals was launched in December 2009 with a $23M Series A by Roche, Pappas Ventures, Third Rock Ventures, Domain Associates and New Leaf Ventures.

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

- The P2X3 subtypes are expressed specifically on C-fiber afferent neurons in multiple tissues and organ systems, including joints and hollow 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
Afferent is Targeting Multiple Pain Types – & Cough

• Afferent’s lead compound, AF-219, has completed two Phase I clinical studies, and is being prepared for entry into Phase 2 clinical testing in patients with osteoarthritis, interstitial cystitis/bladder pain syndrome and chronic cough.

• Preclinical *in vivo* results demonstrating that an investigational P2X3 receptor antagonist significantly prevented and reversed bone cancer pain behavior in comparison to vehicle controls. These data expand on earlier findings and reveal that a marked reduction in apparent bone cancer pain occurs following oral administration of the proprietary P2X3 antagonist.

![Afferent's Development Pipeline](image-url)
Affectis’ Purinergic Antagonists Penetrate the CNS

- Afferent Pharmaceuticals, a spin-off from the Max Planck Institute of Psychiatry, is a pioneer in the field of the P2X7 receptor subtypes for the treatment of neurodegenerative and neuroinflammatory conditions.

- The company’s lead molecule, AFC-5128, is a potent CNS-penetrant oral P2X7 antagonist being developed for the treatment of neuropathic pain and multiple sclerosis.

- A key competitive advantage of AFC-5128 is its ability to cross the blood-brain barrier and target P2X7 expressing cells such as glia cells which have been linked to neurodegenerative processes.

- AFC-5128 is currently in preclinical development with IND filing and initiation of Phase I studies planned for 2012.
Genentech’s Collaboration with Xenon is Taking a Personal Approach

While Roche spun out its early-stage pain program in purinergic receptors with Afferent in 2009, Genentech brought them back into pain through a recent deal with Xenon – a clinical genetics-based drug development company. Genentech, like MedImmune, is keeping mum about the details.

'The Pink Sheet' DAILY
January 11, 2012
Genentech will work with Xenon to discover and develop compounds and companion diagnostics for the treatment of pain, a therapeutic area that is relatively new to Genentech.

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.
But, If It’s Any Hint, Xenon’s Own Efforts Are Focused on Nav1.7

- Xenon’s lead – and as yet unpartnered – program is XEN402, a voltage-gated sodium channel Nav1.7 inhibitor in clinical development for acute inflammatory pain and inherited erythromelalgia, a disorder of spontaneous or easily provoked severe pain caused by mutations that activate the Nav1.7 channel.

- Xenon has completed a Phase II study with a topical formulation of XEN402 in patients with post herpetic neuralgia. The proportion of patients reporting clinically meaningful reductions in pain was significantly greater for topical XEN402 than for placebo (p=0.049 for >30% and p=0.0078 for >50%). In this trial, the product also showed favorable trends in other co-morbidities commonly associated with PHN, including improvements in sleep.

By treating pain locally at its source through blockage of Na\textsubscript{v}1.7, topical XEN402 could be an effective and safe treatment option both as a mono-therapy and an adjuvant to oral therapies.

'The Pink Sheet' DAILY - January 11, 2012; Xenon company website
To Cross, or Not to Cross (the BBB)

Reasons for failure (2): CNS penetration

- 25% of PhII trial failures conclude insufficient CNS penetration as the most likely reason for failure (n=20 PhII studies)
- Case study: A1 agonist GR79236

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**Complete reversal in carrageenan induced hypersensitivity**

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<th>Dose (mgkg⁻¹ s.c.)</th>
<th>% inhibition of the decrease in weight bearing on the inflamed paw</th>
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$ED_{50} = 0.02\text{mgkg}^{-1} \text{ s.c.}$

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**Complete reversal in established FCA induced hypersensitivity**

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$ED_{50} = 0.19\text{mgkg}^{-1} \text{ s.c.}$


NeuroDiscovery/NeuroSolutions presentations, Arrowhead Pain Conference 2008
Pain is Not All in Your Head

For Diabetic Neuropathy, It’s in Your Feet

Arcion Therapeutics is developing a pipeline of product candidates to treat neuropathic pain.

- The benefits of a topical approach to managing neuropathic pain include:
  - Optimal drug concentrations at the site of origin of the pain
  - Lower systemic drug levels and therefore, fewer systemic side-effects
  - Fewer drug interactions
  - Potential to address pain symptoms with a combination therapy approach
  - Conformal application to the skin enables uniform coverage of the painful area

Arcion company website; BioCentury Aug. 2, 2010
Targeting Pain at Its Source

- Arcion’s lead product candidate, ARC-4558, is a 0.1% topical gel formulation of clonidine hydrochloride in development for the treatment of painful diabetic neuropathy (PDN) (fast track designation).

- Arcion believes it can amplify the efficacy signal by focusing on a subset of patients. According to James Campbell, M.D., President and CEO of Arcion, “What has begun to emerge in the neuropathic pain field is the concept that the disease involves two phenotypes.”

  - “One involves patients who experience pain originating in the nociceptors or pain fibers that are expressed in the skin, in which case a topical therapy makes sense.”

  - “The other extreme involves pain signaling that has shifted upstream to more proximal levels of the peripheral nervous system, such as the spinal cord, or in some cases even the central nervous system, in which case a systemic therapy is likely to be more effective.”

Arcion company website; BioCentury Aug. 2, 2010
And Predicting Responders

• To identify these patients, the company devised a test that involves putting a metered amount of OTC capsaicin cream on a distal part of the leg, covering it for 30 minutes, and then asking a patient to rate the pain on a 0-10 scale.

• In subjects with at least minimal nociceptor function, Phase IIb results showed that ARC-4558 was significantly more effective in reducing pain than placebo (p<0.05).

• “Through this study, we identified a simple, predictive clinical test to identify non-responders to ARC-4558, which should enable us to optimize subject enrollment in future studies.”

Arcion plans to include “all comers” in the Phase III study of ARC-4558, including patients on baseline oral therapy for their pain.

Positioning as either a stand alone or adjunct therapy will be important, particularly as the newer branded oral agents (e.g., Cymbalta, Lyrica) become increasingly entrenched as SOC (a trend only likely to grow as these products become generically available).
Key Considerations

• The old complaints about CNS R&D, including pain, are getting old (e.g., can’t get to the target; off-target side effects, subjective clinical endpoints, etc.).

• We are starting to address these issues in pain with some early (yet-be-validated) programs that promise to transform the way we treat pain.

• To avoid the dreaded partnering booth mantra “Come back when you have Phase IIb data”, you must establish that your program is relevant in the current and future clinical and payer environment.
Key Considerations

• **Answer the right questions:**
  - Have I reached the intended target?
    - Being addressed through advances in functional imaging, biomarkers, technologies to cross the BBB
  - Have I minimized off target effects?
    - Promise to address with more specific approaches such as monoclonal antibodies; localized targets, such as P2X3 receptors, Nav1.7 Na+ channels
    - Avoid CNS effects through delivery methods
    - Minimize side effects of SOC – e.g., opioid-sparing approaches
  - Have I addressed the right patient population / segment?
    - Tough-to-treat pain with no good therapeutic options, such as bone metastatic pain or interstitial cystitis
    - Patients on oral SOC, but still in significant pain
    - Specific type of pain-related symptom, such as allodynia, entrapment neuropathy
    - Predict responders with relevant biomarkers
  - Do I fit into the current SOC / payer environment?
    - Consider position as add-on therapy
    - Provide evidence to payers that the patient is still in pain – e.g., via biomarkers.
Swearing as a Response to Pain—Effect of Daily Swearing Frequency
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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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