Hitting pain where it hurts

By Michael J. Haas, Senior Writer

The molecular mechanisms of neuropathic pain are not well understood, and existing treatments typically provide only temporary relief—often with significant side effects—by blocking pain signaling instead of stopping pain at the source. Now, Boston-area researchers have shed new light on the mechanisms of acute and chronic neuropathic pain, offering

potential new targets for both indications.

In a *Nature Medicine* article published online Feb. 10, researchers from Brigham and Women's Hospital, Harvard Medical School, Children's Hospital Boston and Massachusetts General Hospital reported that two matrix metalloproteinases (MMPs) play distinct roles in different types of glial cells in the development of neuropathic pain in mice.

The team found that nerve trauma induced rapid and short-lived neuropathic pain by upregulating MMP9 in dorsal root ganglia (DRG), which then activated a feedback loop between p38 mitogen-activated protein kinase (p38 MAPK) and interleukin-1 β (IL-1 β) in microglial cells.

They also found that nerve trauma induced delayed, longer-lasting neuropathic pain by upregulating MMP2 in both DRG and astrocytes. In DRG, MMP2 upregulated IL-1 β expression. In astrocytes, MMP2 activated a feedback loop between IL-1 β and MAP kinases ERK-1 and ERK-2. (See Figure 1, "MMP-mediated mechanisms for early- and late-phase neuropathic pain.")

Figure 1. MMP-mediated mechanisms for early- and late-phase neuropathic pain. Different matrix metalloproteinases (MMPs) were found to be associated with different phases of neuropathic pain—the early phase, which is characterized by rapid but short-lived pain (1–3 days), and the late phase, which involves delayed but longer-lasting pain (7–21 days).

[1a] MMP9 activation is seen in the early phase of neuropathic pain in the dorsal root ganglia and results in activation of microglial cells in the spinal cord.

[1b] Additionally, upregulated MMP9 activates a feedback loop between p38 mitogen-activated protein kinase (p38 MAPK) and IL-1 β in spinal cord microglial cells, as IL-1 β induces p38 activation and p38 further induces IL-1 β release.

IL-1 β is known to cause pain by various mechanisms after binding to inflammatory mediator receptors.

[2a] In the late phase of neuropathic pain, MMP2 is activated in the dorsal root ganglia, resulting in increased pro-IL-1 β cleavage.

[2b] In spinal cord astrocytes, MMP2 activation is tied to increased cleavage of pro-IL-1 β and activation of MAP kinases ERK-1 and ERK-2. Moreover, ERK activation has been tied to MMP2 upregulation and pro-IL-1 β cleavage, whereas IL-1 β has been found to activate ERK and MMP2.

As a result, the researchers suggest that MMP9 and MMP2 are potential therapeutic targets for acute and chronic neuropathic pain, respectively.¹

“Current treatments for neuropathic pain, such as opioids and neurotransmitter inhibitors, are mostly ineffective and can have severe side effects,” said Ru-Rong Ji, assistant professor of anesthesiology at Brigham and Women’s Hospital and leader of the research team that published the *Nature Medicine* paper. “For instance, drugs like Lyrica only mask the pain temporarily without addressing the underlying pathology.”

He noted that annual sales of Lyrica pregabalin, which came in at \$1.8 billion in 2007, underscore patients’ need for pain relief, temporary or otherwise. **Pfizer Inc.** markets Lyrica for neurological pain, epilepsy and fibromyalgia syndrome. The drug is an analog of γ -aminobutyric acid, which is an inhibitory neurotransmitter that blocks transmission of pain signals to the brain.

Companies contacted by *SciBX* agreed that the pathways described in the *Nature Medicine* paper hold potential for improving neuropathic pain treatments, but they said that MMP9 and MMP2 might not be the best targets in those pathways.

Eliot Forster, CEO of **Solace Pharmaceuticals Inc.**, said the results were consistent with the company’s working hypotheses about the central role glial cells play in neuropathic pain. Solace’s SLC022 modulator of glial cell activity is in a Phase II trial for neuropathic pain, with results expected in late 2009. The company in-licensed the compound from an undisclosed pharma company and has not disclosed its mechanism of action.

“We’re really happy to see independent confirmation,” Forster said. “Targeting glial modulation offers an opportunity for more effective treatments for neuropathic pain than current drugs.”

In addition, Forster noted that many marketed pain drugs carry “reasonably significant liabilities. For example, Cymbalta carries black-box warnings for increased incidence of nausea, somnolence, dizziness and fatigue. Similarly, Neurontin can increase dizziness, somnolence and peripheral edema—and not all patients benefit from it.”

Eli Lilly and Co. markets Cymbalta duloxetine, a serotonin and norepinephrine reuptake inhibitor, for diabetic peripheral neuropathic pain, as well as for depression and generalized anxiety disorder. Pfizer markets Neurontin gabapentin for postherpetic neuralgia, as well as for epilepsy. Neurontin’s mechanism of action is unknown.

However, despite the promise of the newly identified pain pathway, Forster was not sure whether MMP inhibitors (MMPIs) were the optimal therapeutic approach. “The paper results are compelling,” he said. “It’s definitely worth looking at MMPIs for neuropathic pain. But I would first want to know what else MMP9 and MMP2 do biologically.”

Forster also noted that companies developing MMPIs have had difficulty hitting upon the right combination of efficacy and tolerability.

Indeed, in the last nine years at least four companies had MMPIs fail in the clinic, mostly in cancer indications, where they were being pursued based on the role MMPs play in tissue repair and remodeling and in the degradation of extracellular matrix proteins. MMPIs were therefore anticipated to inhibit tumor invasion, metastasis and possibly angiogenesis.^{2,3}

Marimastat, a broad-spectrum MMPI from British Biotech plc (now part of **Vernalis plc**), failed in multiple Phase III cancer trials between 1999 and 2001. Marimastat was also associated with increased incidence of musculoskeletal pain.

In 1999, **Bayer AG** discontinued development of BAY 12-9566, a selective MMPI, after it performed worse than placebo in a Phase II/III trial for small-cell lung cancer.⁴

In 2000, Pfizer halted two Phase III cancer trials of prinomastat, also a selective MMPI.³

Also in 2000, **Roche** halted the development of two MMPIs after interim clinical trial data showed the compounds were unlikely to prevent structural joint damage in both rheumatoid arthritis (RA) and osteoarthritis (OA).

An exception in the MMPI space has been Periostat doxycycline, which **CollaGenex Pharmaceuticals Inc.** began marketing for periodontitis in 1999.⁵ The compound is now a generic.

Brad Zerler, VP of research at CollaGenex, agreed that care should be taken when directly targeting MMPs.

“MMPs play an important temporal role in wound healing and tissue remodeling,” he said. “Consequently, there are times when inhibition may be appropriate; but there are times when the enzymes are required and, for those reasons, inhibition would be inappropriate. Therefore, inhibition of MMPs post-trauma may be quite tricky in regard to timing and needed tissue repair and remodeling.”

Zerler said doxycycline is less potent than other MMPIs, which he said could account for the lower incidence of side effects.

“Most in the field think of MMP inhibition in terms of treating chronic conditions, and perhaps that is why their development has been somewhat disappointing,” he said. He proposed

that treatment of acute, rather than chronic, pain “may just be the niche for this class of compounds.”

But, Zerler added, the *Nature Medicine* paper “suggests that inhibition of downstream mediators such as IL-1 β or perhaps p38 may be more appropriate targets for neuropathic pain.”

Although CollaGenex no longer actively markets Periostat, the company does sell Oracea, a controlled-release subantimicrobial formulation of the antibiotic doxycycline, for facial rosacea. The company also has Oracea in a Phase III trial for blepharitis (inflammation of the eyelid).

Kirk Johnson, VP of R&D at **Avigen Inc.**, said the research done by Ji’s team “both affirms and further extends the concept that glial activation is an important component in both the establishment and maintenance of neuropathic pain.”

Avigen’s ibudilast (AV411), a glial attenuator suppressing IL-1 β , completed a Phase IIa trial in diabetic peripheral neuropathic (DPN) pain in 2007. The company plans to take the compound into Phase IIb testing in DPN pain and a Phase IIa trial in opioid withdrawal this year. Avigen also has a next-generation glial modulator in preclinical development.

Johnson said the pathway uncovered by Ji’s team has commercial potential because it offers new targets for pain—MMP2 and MMP9—while validating existing targets, such as IL-1 β and p38 MAPK.

Nevertheless, he said more work will be necessary before the findings are ready for commercial development.

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Solace Pharmaceuticals

"There is no information provided about safety, selectivity, pharmacokinetics, formulation and so on," Johnson said. "I would like to see validation of MMP9 or MMP2 as relevant neuropathic pain targets in other animal models of neuropathic pain, as well as in human pain indications."

Johnson also noted that it is unclear whether the ultimate drugs or approach would be systemic or limited to intrathecal application.

Ji agreed that p38 MAPKs, MAP kinase ERKs and IL-1 β could be targets for neuropathic pain, along with MMP9 and MMP2.

He also acknowledged that long-term treatment of neuropathic pain with MMPis could interfere with other important MMP functions. "Spinal delivery of MMP9 and MMP2 inhibitors for a relatively short duration may be more practical," he said.

"Direct spinal infusion, via an epidural or intrathecal route, is a common practice for chronic pain patients or the terminally ill," whether for a few days, months or even years, Ji said. "Many patients in the operating room have epidural catheters implanted for analgesic injection. For these patients, injection of MMP inhibitors perioperatively is convenient, and may reduce the incidence of chronic pain caused by major surgeries such as thoracotomy."

Ji's team is now examining the mechanisms of inflammatory pain in an undisclosed type of arthritis. "The results indicate that MMPs also play an important role there," he said.

Although MMPis have failed to halt progression of other arthritis symptoms—as Roche found in its clinical trials in OA and RA—Ji suggested such inhibition still might be effective in reducing arthritis pain.

The results of the team's arthritis pain study will be described in a forthcoming paper, he said.

The team has longer-term plans to determine whether other MMPs are involved in neuropathic pain.

Forster hopes Ji is looking at OA. "There is an academic debate as to whether osteoarthritis has a neuropathic component or not," he said.

More broadly, Foster said it was "intriguing" that Ji's ongoing work might establish a link between arthritic inflammatory pain and neuropathic pain via MMPs. "If they were to demonstrate that these both operate through MMP2 or MMP9, we would have two types of pain with a common platform," he said. "The therapeutic and commercial benefits of that commonality would expand the market substantially."

GlaxoSmithKline plc began a Phase II trial of SB681323, a p38 MAPK inhibitor, for neuropathic pain in 2006.

In February, **Array BioPharma Inc.** completed enrollment in a Phase II trial of ARRY-797, also a p38 MAPK inhibitor, to treat postsurgical dental pain.

The most important aspect of Ji's paper is the characterization of the differences between the acute phase and the chronic phase of neuropathic pain, said Kevin Koch, president and CSO of Array. He said these differences could have important implications for compound development and clinical trial design.

"The data would seem to support evaluation of p38 inhibitors in acute or surgical indications of pain, or where substantial nerve trauma has occurred," said Koch. "Conversely, the data would support the potential of modulators of the RAS/RAF/Mek/ERK pathway for chronic neuropathic pain."

Brigham and Women's Hospital and Harvard Medical School hold a provisional patent on the findings reported in *Nature Medicine*.

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COMPANIES AND RESEARCH INSTITUTIONS MENTIONED

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