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Innovations

Metaphore Pharmaceuticals:
Mimicking Nature's Enzyme

When the Monsanto Corporation, through its G.D. Searle division, made a strategic decision in the late 1990s to focus on its COX-2 pain and antiinflammatory drug program, the effect was not only the creation of its blockbuster drug, Celebrex, but also the launch of a spin-off company focusing on other pain and inflammation treatment strategies. That company, Metaphore Pharmaceuticals, now based in St. Louis, MO, grew from the research team at Searle who were targeting the natural enzyme superoxide dismutase (SOD), an essential component in limiting damage caused by superoxide, a naturally toxic free radical harmful to cells and tissues.

"The focus of the company is based on what the chemists did at Searle initially, then was fine-tuned and developed here at Metaphore," says Alan Dunton, MD, Metaphore CEO. "They created drug-like small molecules mimicking the activity of superoxide dismutase in the human body."

Superoxide: Toxic Free Radical

Free radical oxygen, such as superoxide, is formed every time the body uses oxygen in respiration. "And, superoxide anions are also some of the primary mediators of inflammation, causing toxic damage if not removed by the body's own supply of superoxide dismutase," explains Dunton, who joined the privately held, 32-member company early this year.

Following a proinflammatory stimulus, the body responds by upregulating cytokine production, increasing neutrophil infiltration and adhesion, and superoxide anion production. "We have also known for a number of years that during inflammatory disease progression there is a downregulation of the endogenous SOD enzyme," explains Daniela Salvemini, PhD, Senior Vice President of Research at Metaphore and a member of the original Monsanto SOD research team. "In inflammation, the [endogenous SOD] enzyme can no longer remove superoxide sufficiently. When that happens, you have superoxide-mediated cell and tissue damage. Our technology is aimed at removing this radical oxygen species and downregulating inflammation."

The initial research team at Monsanto postulated that if it could create a mimetic of the SOD enzyme to augment the body's own SOD levels, they could help any disease where inflammation played a key role. "That's the platform for the company," says Dunton. "The thinking behind the company's name is that these small drug molecules are mimetics that stand for something greater, which is the SOD enzyme itself," explains Dunton. "So, our drugs are metaphors, if you will, of the greater enzyme."

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The SOD Scavenger

In all animals, including humans, superoxide dismutase circulates in the body to remove superoxide once formed. The human SOD enzyme is a metalloprotein of about 32K molecular weight, but the molecules Metaphore creates are about 300–400 molecular weight on average. "And, they have the same or greater activity as the native human enzyme," says Dunton.

Two forms of SOD are found in the body: a copper/zinc form and a manganese form located in the mitochondria. All of Metaphore's compounds are based on the manganese form of the SOD enzyme. "The manganese form is the least toxic of the metals used by the enzyme and it is the most crucial one," explains Salvemini.

SOD-based drug therapy is not new. In the 1980s, a bovine-derived, copper/zinc injectable form of the SOD enzyme, Orgotein, was tested in humans with some exciting data, particularly in arthritis and in radiation-induced damage, providing proof of concept that removing superoxide has a beneficial outcome. However, problems arose due to the large size of the molecule and immunogenic responses due to its bovine source. Orgotein is now classified by the FDA as an orphan drug for the treatment of familial amyotrophic lateral sclerosis and is used in veterinary formulations for treatment of soft tissue inflammation. "But our SOD mimetics are smaller and very selective for superoxide," explains Salvemini. "You do not want to remove all of the reactive oxygen species in the body."

Supplementing Pain and Inflammation Relief

"We have identified superoxide as a novel mediator of pain and SOD mimetics as novel nonnarcotic analgesics for the management of pain of multiple origin," says Salvemini. "Therefore, the foundation of our pain relief technology is to use SOD mimetics to selectively remove superoxide and therefore address the pain associated with conditions like acute inflammation, neuropathic pain, cancer pain, and pain associated with chronic use of morphine, an event also known as opiate tolerance," says Salvemini. The idea is to supplement the body's own sup-

ply of SOD that cannot keep up with all the free radical oxygen formed in an inflammatory state. "These also include chronic diseases like rheumatoid arthritis, inflammatory bowel disease, and even some cardiovascular ischemic conditions," adds Dunton.

At the recent Society for Neuroscience 2003 conference, Dr. Salvemini presented a novel role for superoxide in acute inflammatory pain. "One pathway involves modification of the inflammatory response in development of hyperalgesia, or increased sensitivity to pain at the site of the painful stimuli," she says, "and the other is a novel central pathway identified at the level of the spinal cord."

Metaphore researchers have shown that one of their lead mimetics, M40403, reduces inflammation and hyperalgesia in in vivo models both peripherally and centrally. At the site of inflammation, antihyperalgesic actions were associated with inhibition of cytokines and peroxynitrite formation and attenuation of poly-ADP-ribose-polymerase activation. Additionally, M40403 inhibited a central hyperalgesic response by preventing nitration and subsequent deactivation of endogenous spinal SOM. "This key finding supports the concept that nitration and subsequent inactivation of endogenous spinal SOM is a critical event in the hyperalgesic response, possibly by allowing the levels of superoxide to remain elevated," according to Salvemini.

"In addition, our results have demonstrated that during pain, nitration of key proteins involved in the regulation of glutamate occurs by superoxide," explains Salvemini. Glutamate is a key excitatory amino acid implicated in central sensitization associated with pain of multiple origin. "Our results show that glutamine synthase (the glial enzyme involved in metabolizing glutamate into nontoxic glutamine), the glutamate transporter (responsible for taking up glutamate from the synaptic cleft), and the N-methyl-D-aspartate (NMDA) receptor subunits are key targets for superoxide-mediated nitration and subsequent inactivation," says Salvemini. Overall, inactivation provides a sustained source of glutamate in the synaptic cleft and glutamate-mediated activation of the NMDA receptor. Removal of superoxide by SOD mimetic inhibits nitration of this pathway, inhibiting central sensitization and pain.

"In summary, our studies so far have unraveled a critical role for superoxide in the nociceptive signaling cascade both peripherally and centrally," says Salvemini. "The discovery of superoxide in pain opens a new therapeutic strategy for the development of novel, nonnarcotic antihyperalgesic agents that then reduce pain, acute and chronic, without efficacy limits or significant side effects."

The company hinges its long-term goals on the comparatively smaller molecular weights of its compounds, hopefully allowing them to develop orally active agents as well as parenteral therapies. "Though our lead agents are parenteral therapies, we are now really focusing on the development of oral compounds," says Salvemini.

Injectable Lead Agents

Metaphore currently has two identified lead agents in human clinical testing. "Our human proof of concept in pain was achieved this year with our M40403 mimetic," says Dunton. Phase II tests were recently completed with this IV therapy. The first indication Metaphore is aiming for is treatment of pain in combination with opiates or morphine-like drugs. Over time, cancer patients often require higher doses of morphine-like, narcotic agents for pain relief. "We have seen that our agents can prevent the tolerance from occurring or can actually reverse it once developed," explains Dunton. "This would be a tremendous advance because of the side effects caused by morphine including sedation, constipation, respiratory depression, and altered sensoria."

M40419, also an IV agent, is in phase I safety trials. "And animal studies have shown we now also have found orally active molecules," explains Dunton. "That is critical since it will allow us to expand into treatment of chronic disease indications where you could not go with an injectable agent." He explains that the best way to estimate the commercial opportunity for nonnarcotic pain medications is to look at molecules like Remicade or Enbrel. "Those are huge blockbuster products and they are both injectable therapies," says Dunton. "We are developing novel oral agents more active than those products and cheaper to produce." Metaphore will be initiating human testing with an oral agent in 2004.

Other Competitors

"Other companies are developing metal-based drugs with the intent of removing SOD," acknowledges Salvemini. And others have pursued much larger SOD molecules in the past, "but we are the first company to successfully synthesize small molecule SOD mimetics," claims Dunton. "And smaller, easier to produce mimetics are fundamental to our success where others have failed with larger SOD derivatives or even native enzyme therapies." Metaphore will be forming alliances in the future with larger pharma companies that have the wherewithal to do the large-scale 5,000–6,000 person clinical trials and subsequent large-scale marketing required for a primary care indication like rheumatoid arthritis or inflammatory bowel disease. This explains why the company has recently opened a Fort Lee, NJ office where they will center their clinical and business development capabilities. "It makes sense to reason we will be interested in partnering with companies that know the pain/inflammation markets intimately," says Dunton.

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