"WE ALL CAME FROM THE SEA…"

Ironwood's Mark Currie talks about treatments for painful intestinal disorders and more

BY LLOYD DUNLAP

ACCORDING TO Mark Currie, chief scientific officer and president of research and development at Ironwood Pharmaceutical Inc., "There is something indescribably special about creating a new drug that goes on to make a difference in people's lives. Earlier in my career, I had been part of development teams that had created drugs for cardiovascular and central nervous system diseases, and I knew drug discovery was something I wanted to keep doing."

So, we invited him to talk to us a bit about Ironwood and what treatments he's helping to shepherd along there.

***DDNews:* What was your motivation for joining Ironwood?**

Mark Currie: When I met the team at Ironwood, I could immediately tell they shared that passion. I came on board in 2002, just a few years after the company was formed out of MIT. It was extraordinary to have the opportunity to build and shape this nascent discovery team. From the beginning there was huge emphasis on drug hunting. We called ourselves "disciples of pharmacology," and we started a "Great Drugmaking" lecture series where we brought in folks like Roy Vagelos from Merck and Nick Lydon, who had developed Gleevec, to tell us about their journeys. We immersed ourselves in the culture of drug discovery, and it wasn't long before our team created the molecule that would one day be Ironwood's first medicine, linaclotide.

***DDNews:* Can you tell us more about the first medicine you and your team developed at Ironwood?**

Currie: Linaclotide is the first drug approved by the FDA in a class of molecules called guanylate cyclase-C agonists, or GC-C agonists. GC-C is an enzyme found mainly on the surface of the intestine. It triggers the release of cyclic guanosine monophosphate, or cGMP, and is involved in regulating water and sodium levels within the gut.

I led the discoveries of guanylin and uroguanylin, two natural hormones that bind to and activate GC-C. After I joined Ironwood, we began to explore whether we could develop molecules that bound to and activated GC-C and would be potentially useful as therapeutic agents. The Ironwood team began creating GC-C agonists, small peptides that could bind to and activate GC-C. The lead molecule that resulted from our efforts was linaclotide.

Linaclotide is a 14-amino acid peptide that is orally administered within a capsule. Most peptide drugs approved by the FDA to date are administered by injection—this is necessary because the stomach is designed to digest peptides and does so quite efficiently, breaking up orally administered peptide drugs before they can exert their effect. But linaclotide was created with three disulfide bridges that essentially cause the molecule to fold itself into a knot, protecting it from degradation in the stomach.

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Mark Currie
CSO and president of R&D for Ironwood Pharmaceutical

We knew that GC-C was involved in regulating water and sodium levels within the gut, and we hoped to see this confirmed in nonclinical studies. And in fact, nonclinical studies indicated that linaclotide activation of GC-C resulted in elevation of intracellular cGMP, stimulating secretion of fluids into the intestine and accelerating intestinal transit. However, our nonclinical studies also showed that linaclotide had an important effect on reducing abdominal pain. According to our nonclinical studies, activation of GC-C also resulted in elevation of extracellular cGMP, which was shown to decrease the activity of pain-sensing nerves. This was really the first time published studies had shown the inhibitory role of the GC-C/cGMP pathway on pain-sensing nerves, following activation of GC-C, so it was a very exciting preclinical breakthrough in understanding not only linaclotide's mechanism of action, but this whole pathway involved in pain signaling within the intestine.

Based on our preclinical observations, and through conversations we had with doctors and patients, we prioritized linaclotide for further development as a potential treatment for irritable bowel syndrome with constipation and chronic idiopathic constipation. There are millions who suffer from these two conditions, and there were a limited number of prescription treatment options. Linaclotide went on to become the first GC-C agonist approved by the U.S. FDA, establishing GC-C agonists as a new class of medicines.

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***DDNews:* I understand Ironwood is also doing research on treatment for painful disorders of the small intestine and has an early-stage product called IW-9179. The drug passed a Phase 2a study in 2013 and showed effects in treating functional dyspepsia (indigestion or heartburn). What is the future for IW-9179?**

Currie: Ironwood and our partner Actavis are exploring the utility of linaclotide in additional dosages, indications and patient populations. We are also studying linaclotide in novel formulations to assess its potential in treating various gastrointestinal conditions. The clinical data we generate may allow us to pursue additional regulatory approvals.

As you noted, Ironwood continues to make progress with IW-9179, also a GC-C agonist, and recently initiated a Phase 2a clinical study evaluating the ability of IW-9179 to provide symptomatic relief to patients with diabetic gastroparesis. Although GC-C is found throughout the gastrointestinal tract, IW-9179 is designed to act primarily in the upper gastrointestinal tract. Data from this trial are expected in the first half of 2016.

***DDNews:* You have contributed to the development of several very successful drugs—Linzess, Celebrex, Lunesta and others. How does this earlier work interface with your discoveries related to guanylin and uroguanylin that activate GC-C?**

Currie: Much of my research has been rooted in my interest in understanding the homeostasis of water and sodium within the body. Former President John F. Kennedy spoke about this in his 1962 America's Cup speech, and he said, "…we all came from the sea. And it is an interesting biological fact that all of us have in our veins the exact same percentage of salt in our blood that exists in the ocean, and, therefore, we have salt in our blood, in our sweat, in our tears. We are tied to the ocean."

I've always been fascinated with the fact that when humans evolved from the sea, we took a bit of the sea with us, in our blood. That fascination and ultimately my research into this balance led me to play a leading role in the discovery of three different hormones that impact water and sodium homeostasis: atrial natriuretic peptide, guanylin and uroguanylin.

Atrial natriuretic peptide, a hormone made in the heart, acts through guanylate cyclase-A to regulate water and sodium in the blood and to regulate blood pressure. Guanylin and uroguanylin act through guanylate cyclase-C to regulate water and sodium within the gut, and thereby play a role in the control of salt in the blood. And over the past several years, the Ironwood R&D team has been researching soluble guanylate cyclase, which also impacts fluid regulation and is found in many cells throughout the human body.

So I'd say that a lot of the research I've been fortunate to be a part of has been grounded in striving to better understand the fundamental way the body regulates vascular tone and water and sodium. By gaining a better understanding of these processes throughout the body, and insight into the hormones that regulate them, I believe we can continue to develop medicines to address a variety of diseases and help patients who are suffering. ■

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Dr. Mark Currie is Ironwood Pharmaceutical Inc.'s senior vice president of research and development and chief scientific officer, and has led the company's R&D efforts since joining in 2002. Currie has more than 30 issued U.S. patents and is the primary inventor of linaclotide, which activates guanylate cyclase-c. Linaclotide is marketed in the United States as Linzess and in Europe as Constella. The drug, which reduces abdominal pain, has had four highly successful Phase 3 trials in chronic constipation and irritable bowel syndrome. Prior to joining Ironwood, Currie directed cardiovascular and central nervous system disease research as vice president of discovery research at Sepracor Inc. (now known as Sunovion Pharmaceuticals Inc.), where he led discovery and supported development of Xopenex and Lunesta.

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