Université de Sherbrooke Partnership Aims to Develop Iron Overload Disorder Treatment

For patients with iron overload disorders (IOD), such as beta-thalassemia or hereditary hemochromatosis, current treatments may seem like something from medieval times. To remove excess iron, blood-letting (phlebotomy) along with treatment with iron chelators, provide the best current therapy options. Patients with IOD suffer from fatigue and pain and can develop serious complications due to iron deposition within internal organs. This requires lifelong treatment.

Richard Leduc, Ph.D., Chairman of the Department of Pharmacology-Physiology at Université de Sherbrooke in Quebec, Canada, has an idea that could potentially lead to a completely new treatment approach to IOD. By partnering with GlaxoSmithKline (GSK), via the Discovery Fast Track Challenge, Leduc is now rapidly moving this idea forwards toward the development of a new medicine.

Richard Leduc, Ph.D.
Université de Sherbrooke

An Enzyme That Plays A Key Role In Iron Homeostasis

In 2008, Leduc came across a set of recently published scientific papers that suggested a key role for the liver trans-membrane protease, matriptase-2 (TMPRSS6), in controlling the production of the peptide hepcidin. Hepcidin, released from the liver into the bloodstream, is known to be the central regulator of iron homeostasis.

In IOD patients, hepcidin levels are abnormally low, which is a key molecular event in iron accumulation. Hepcidin is up-regulated by a signaling pathway that is in turn inhibited by matriptase-2. Therefore, Leduc postulated that an inhibitor of matriptase-2 could increase hepcidin to a normal range and thus reduce iron overload.

Having found the connection between matriptase-2 and hepcidin production, Leduc would spend the next two years trying to answer a single driving question: "How could we develop a molecule that potently and selectively inhibits this enzyme's activity?" Leduc and his collaborators became pioneers in trying to identify inhibitors of matriptase-2 and demonstrate their potential effectiveness as treatments for IOD.

"It was a jigsaw puzzle to see the larger picture," said Leduc. "We had to learn more about iron metabolism: Who are the molecular players? We had to reeducate ourselves in this field."

It would take working with physicians and specialists to fully understand how to develop a potential treatment. And in the process, Leduc underwent a transformation himself.

"Young scientists need to get into this frame of thinking as quickly as possible. I got into it late. I changed my mentality. How can I apply my knowledge to translational research? How can I impact human lives?"

Transformations Lead To Translation

Leduc instills in his students the need to work with others. As he thought more about what it would take to translate his work into something that would really help patients, he knew he would need help…and he worried. Partnering with a pharmaceutical or biotech company could mean losing control—not only of his idea, but ownership of intellectual property, and the opportunity to publish his findings.

In 2013, Leduc was the first academic to enter GSK's first Discovery Fast Track Challenge. At a face-to-face meeting with a panel of senior drug discovery experts, he made a compelling and exciting case for the discovery and development of matriptase-2 inhibitors as an innovative treatment approach to IOD. GSK selected his project, along with six others, as winners of the inaugural Discovery Fast Track Challenge. GSK quickly formed a multi-disciplinary team with Leduc and colleagues to perform screening using both high throughput screening (HTS) and encoded library technologies (ELT) against matriptase-2.

The partnership with scientists in GSK proved to be a very positive experience. "My team never felt trapped in this relationship," said Leduc. "We always felt that the GSK scientists listened to us, problems were quickly solved, and a course of action was established."

Leduc's team focused on ways to express highly active matriptase-2, whilst GSK scaled up production of the enzyme and optimized Leduc's assay protocols to allow rapid screening against their libraries of millions of compounds (billions in the case of ELT) — chemical diversity an academic could only normally dream of accessing.

"There was a very clear objective and goals. We all knew the stakes and we worked together to find solutions and alternatives when challenges presented themselves."

Before long, Leduc and colleagues were amazed to learn that the screens had yielded a number of novel inhibitors of matriptase-2, some of which were highly potent.

"In less than a year, we went from working on expression of the enzyme to screening for hits to discovering hits. That is pretty phenomenal. It is a true partnership."

What Partnerships May Bring

Leduc's initial worries about working with big pharma were quickly dispelled, replaced by success through true scientific teamwork. GSK and Leduc, together with the Université de Sherbrooke, have partnered to develop the starting points from the Discovery Fast Track screens towards a new medicine that could potentially revolutionize the treatment of patients with IOD. This is a very exciting prospect for both teams of scientists.

Advancing the work of promising academics is the goal of GSK's Discovery Fast Track Challenge. For Leduc, he has a message for his students: "Always ask yourself if what you are studying can somehow help people with diseases."

To learn more about GSK's Discovery Fast Track Challenge, please visit gsk.com/discoveryfasttrack