Chemistry & Biology, Vol. 11, 147–148, February, 2004, ©2004 Elsevier Science Ltd. All rights reserved. DOI 10.1016/j.chembiol.2004.02.008

Innovations

Thios Pharmaceuticals

Targeting Sulfation Pathways

Appropriately named by using the Greek word for the element sulfur, Thios Pharmaceuticals is a 3-year-old, 24-person company based in Emeryville, California, focused on one of the body's major regulatory mechanisms: sulfation.

This process involves the addition (or removal) of sulfate groups to important glycoproteins, a modification that can modulate interactions at the cell surface and in the extracellular space. If one or more of the key components of sulfation pathways becomes dysregulated, several biological processes like cell adhesion, cell migration, immune responses, and cell proliferation may be inappropriately regulated, leading to specific diseases such as inflammation and cancer.

Productive Pathways for Drug Discovery

"Our mission is to discover, develop, and commercialize innovative therapies targeting biological sulfation to treat serious unmet medical needs," says Bruce A. Hironaka, President and CEO of Thios. "Simply, we want to be the leader in the development of this new class of therapies and to improve the lives of many through the development of safer, more effective therapies."

To achieve this, Thios is focusing on two types of programs. "Our major emphasis is in small-molecule drug discovery, and we also have a therapeutic antibody program," according to Carolyn Bertozzi, PhD, Professor, Chemistry and Molecular and Cell Biology, University of California, Berkeley, and a Thios cofounder. The company currently focuses on three classes of sulfation targets: sulfated molecules, sulfotransferases, and sulfatases. Thios is targeting sulfated molecules as either therapeutics in their own right or as targets for an antibody drug it has under development. In January 2004, Thios in-licensed a sulfated glycoprotein called TS1 from Wyeth for acute sickle cell crisis and delayed graft function after kidney transplant. "These represent serious unmet medical needs for which there are currently no effective therapies," says Mr. Hironaka. In addition, Thios has a therapeutic antibody program targeting sulfoadhesin, a sulfated polysaccharide contributing to chronic inflammation.

Thios' small molecule drug development programs revolve around sulfation enzymes. "Our goal over the long term is to develop small molecule modulators of the sulfotransferase and sulfatase enzymes that are involved in sulfation biology which have the greatest therapeutic value," says Stephen Harrison, PhD, Vice President of Research at Thios.

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Analogies to Kinases

"The big picture here is that sulfation is a regulatory modification of biopolymers and even small molecules," says Dr. Bertozzi. She draws an analogy between sulfation of biomolecules with protein phosphorylation. "Proteins are phosphorylated by kinases and dephosphorylated by phosphatases. So the kinases and phosphatases serve a regulatory function in signaling cascades." Likewise, sulfotransferases and sulfatases regulate the sulfation of biomolecules controlling their activities.

Kinases have generated a lot of interest because of their involvement in a variety of regulatory events, many related to cancer and proliferative disease. There are more than 500 kinases, but far fewer sulfotransferases are found in the human genome, about 50. Says Dr.Bertozzi, "Among the kinases, there are some clean kinases upregulated only in cancers, and there are messier kinases with functions in normal physiology. If you hit those latter kinases, toxic side effects become a problem. The same will be true of some of the sulfotransferases and the sulfatases, so we are being very strategic about our target selection."

Thios is honing in on druggable "clean" sulfotransferase and sulfatase targets that are upregulated only in disease tissue. "Fifty targets are enough so that there are plenty to work on from the point of view of drug discovery, but not so overwhelming a number that selectivity problems arise," says Dr. Bertozzi. The company is hoping sulfation inhibition will echo the commercial success of kinase inhibitors, such as the cancer therapy, Gleevec. Gleevec was FDA approved in 2001 for treatment of chronic myeloid leukemia and in 2003 generated sales of over $1.1 billion.

Sulfation Science Is Fairly New

"The field of biological sulfation has developed only recently," says Dr. Bertozzi. "The pharmaceutical relevance was brought to light only in the late 1990s due to a handful of discoveries linking sulfation with inflammatory disease and, more recently, correlations between sulfotransferase or sulfatase expression and cancer."

Most of the founders of Thios Pharmaceuticals spent time at one point in the lab of Steven Rosen, PhD, at the University of California, San Francisco. Dr. Rosen has been studying leukocyte-endothelial cell adhesion, one of the first steps in the inflammatory cascade, since the late 1980s. In late 2000, Dr. Bertozzi (a former post-doc in the Rosen lab) joined forces with Rosen, another former Rosen post-doc, Stefan Hemmerich, then working at Roche Bio-

sciences, and Ted Yednock at Elan Pharmaceuticals to form Thios. "We realized sulfation wasn't just important in inflammation, but there were papers in the literature linking dysregulated sulfation to viral infection and cancer," explains Dr. Bertozzi. "It became clear there was a whole niche of biology that could be mined for drug development."

Inflammation

Inflammation is a primary indication for Thios. The TS1 biotherapeutic molecule in-licensed from Wyeth has been through two phase II trials involving more than 500 patients but in a separate indication than those Thios is pursuing. TS1, formerly rPSGL-Ig, is a sulfated recombinant fusion protein based on P-selectin glycoprotein ligand 1 (PSGL-1). PSGL-1 extends from the surface of leukocytes, helping cells bind to the blood vessel wall both in normal tissue repair and after ischemia/reperfusion injury and vaso-occlusion. Attachment of leukocytes to damaged blood vessels intensifies local inflammation, causing further tissue damage. TS1 protects the site of tissue damage by preventing leukocytes and platelets from adhering and causing inappropriate inflammation and/or thrombosis. It may also have potential for other conditions like deep vein thrombosis and arterial vascular diseases, including stroke. According to Mr. Hironaka, "The in-licensing of TS1 was part of our strategy to mature our product candidate pipeline in the short term and to position us to be an early stage development company early on in our history." Thios plans to reenter the clinic with TS1 by yearend 2004.

The sulfoadhesin antibody anti-inflammatory program is presently in preclinical development. Sulfoadhesin is found on the surface of endothelial cells in the blood vessel wall at sites of chronic inflammation. Thios is working on developing a therapeutic antibody that binds to sulfoadhesin and prevents its association with L-selectin, a receptor on circulating white blood cells. "By blocking that ligand, we should be able to block leukocyte recruitment at the sites of inflammation and therefore block the inflammation even before the leukocytes have become activated," explains Dr. Harrison. This is a mechanism that is not yet being approached by available anti-inflammatories. "In combination with other anti-inflammatory agents, we have the theoretic potential then to get synergistic activity," he says, though Thios is currently focusing on single-agent therapy.

Another of Thios' anti-inflammatory programs targets sulfoadhesin via a different mechanism. Thios is pursuing small molecule inhibitors of the sulfotransferase that adds sulfate to sulfoadhesin during its biosynthesis inside the cell. L-selectin binding requires sulfation of the ligand, thus inhibition of the sulfotransferase would prevent leukocyte adhesion and the resulting pathology of inflammation. Thios believes the small molecule inhibitors of the sulfotransferase have the potential to treat asthma, rheumatoid arthritis, psoriasis, and inflammatory bowel disease.

"The classes of sulfotransferases we are targeting in general reside within the Golgi," explains Harrison. "But there are a number of sulfotransferases we find in the cytosol that are often involved in detoxification and the metabolism of toxins within the body. Clearly, it would not be a good idea to inhibit those." As such, an essential element of Thios' screening funnel eliminates compounds that offer broad-based sulfotransferase inhibition.

Bertozzi explains that the antibody project is moving more quickly than the small molecule project. "We think we'll be able to get IND filing and our first clinical candidates in the antibody program in a reasonable time frame," she says. And if that pans out, it will validate the sulfotransferase inhibitor program. "The small molecule compound could be the orally bioavailable pill, while the antibody would be an injectable."

Cancer

"We're looking at some particularly interesting sulfatases with potential in the area of oncology," says Dr. Harrison. Thios has identified two extracellular sulfatases as potential targets for the development of small molecule therapeutics that inhibit tumor growth. Its Sulf-1 sulfatase is highly active in prostate and central nervous system cancers, whereas its activity in normal tissues is much lower. Sulf-2 is present at very high levels in breast cancer tissue.

"We expect big pharma companies to have a growing interest in sulfation targets if they don't already," suspects Dr. Bertozzi. Aside from the Wyeth deal, other companies have approached Thios with an interest in sulfation biotherapies. "We are inevitably coming up with additional targets that, given the resources we have, we're not able to move forward, which makes us an ideal partner in this area," adds Dr. Harrison. Thios is interested in partnering with other companies, both large pharma and biotech, interested in accessing some of the Thios' targets or around programs with potential complementary activities.

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