Ancora Pharmaceuticals: Counting Carbs Synthetically

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With many biotech companies reaching for commercial success, it helps when the founding science comes from an unquestioned leader in the field. Such is the case with Ancora Pharmaceuticals (http://www.ancorapharma.com), founded in 2003 to develop a synthetic carbohydrate platform based on work licensed from MIT. In 2002, the company's scientific cofounder, Dr. Peter Seeberger, a world-class carbohydrate chemist then based at MIT, helped establish the company after winning an MIT-based entrepreneurial competition, setting in motion the foundation for the now 20 person company based in Medford, Massachusetts.

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Why Carbohydrates?

When seeking to target an infectious agent, the first place to look is usually the invading organism's cell surface, which is made up of proteins, lipids, and carbohydrates. For decades, medicine has been perfecting protein-based approaches both in drugs and vaccines. Yet carbohydrates extend well into the cell's neighborhood and are often involved in initial interactions with other cells and in cell signaling. This makes them attractive antigens, explaining why they are of interest for vaccine development.

In the vaccine field, perhaps the leading application for carbohydrate-based therapies to date, many opportunities go unpursued or are pursued until they reach a technical hurdle that cannot be overcome. "This is mainly due to poor access to large amounts of homogenous carbohydrate material to work with," explains Stewart Campbell, Ph.D., Ancora's vice president of R&D. However, isolating or purifying attractive carbohydrate targets from a bacterium, fungus, or other organism in the quantities needed can be challenging.

"There are a number of reasons why carbohydrate synthesis is more attractive than isolation from the pathogen," explains Geert-Jan Boons, Ph.D., Franklin Professor of Chemistry, Complex Carbohydrate Research Center, University of Georgia. Dr. Boons's lab is focused on the development of synthetic cancer and bacterial vaccines. He explains that oligosaccharides require conjugation to a protein for immunization. "With synthesis, the conjugation chemistry is much better because it provides you with an opportunity to attach a linker with unique reactivity so that it can be done in a controlled fashion," he says. "Further, with synthesis, you can do really detailed structure activity relationship studies and thereby define the most attractive structure for achieving optimal immunity."

Automated carbohydrate synthesis is one of the remaining frontiers in automated synthesis technology. This is due to the carbohydrates' inherent complexity. Historically, it has been very difficult to produce homogenous glycoproteins using an in vitro technique. "If you have bacterial cells, or even mammalian cells, making them, if there is even a slight change in genetics, they could start making different glycoforms of the glycoproteins," explains J. David Warren, Ph.D., Director, Organic Synthesis Core Facility, Weill Cornell Medical College. This can lead to antigenicity and an unintended and undesired immune response that may not initially be noticeable because of its subtlety.

"People have shown that differing glycoforms can have completely different biological effects," adds Warren. "One of the goals of synthetic glycoproteins would be to have a single glycoform where you have absolute control over the form made, thereby eliminating the need for antigenicity concerns.

Adds Campbell, "Our carbohydrate synthesis approach takes away the uncertainty or inability to attain certain structures that might be of high biological interest, but, practically, people have not been able to access or produce."

Synthesis Platform

"We've licensed technology in from MIT and created a lot of know-how to make the most encompassing carbohydrate synthesis platform in the world," says John Pena, Ph.D., Ancora's president. "The intellectual property which we licensed was a unique set of reaction chemistries and protecting group strategies and linker chemistries that would allow synthetic chemists to make carbohydrate molecules more time and cost effectively than had been possible to date within industry."

The initial technology was focused on a limited set of classes of carbohydrate molecules. Ancora's first order was to prove it had a commercially relevant set of technologies and develop a more commercially relevant platform. "We had to prove we could make different classes of carbohydrate structures and that we could get access to larger amounts/quantities of these structures, so the technology needs to be scalable," says Pena.

Ancora's technology overcomes the labor-intensive nature of traditional carbohydrate synthesis. To make polysaccharides in the laboratory, reactions are made on a single building block. That product is purified. You would then do another glycosylation and go through the process again. "This process can take days, weeks, months to build up a polysaccharide," explains Warren. "With the technology Ancora has, they can do this in some cases in a matter of hours or a day. It really opens the possibilities of doing this on a large scale." Seeberger explains that the founding technology offered an automated oligosaccharide synthesis platform capable of producing synthetic carbohydrates about 500 times faster than previously.

Building Blocks

From a core platform of building blocks and modification chemistries, Ancora can make a wide array of structures. Says Pena, "We can make 30, 40, 100 mg of a desired carbohydrate synthetically and have the chemistries to develop hundreds of grams or kilograms as required."

Ancora realizes that making the core carbohydrate structures—while essential—is not the end game. "We can make core carbohydrate structures and then derivitize them very rapidly," says Pena. The structures can be manipulated onto proteins, onto glycochips, or onto a device using linker chemistry or by modifying the conjugation chemistry as needed. "We are able in that way to do medicinal chemistry or optimization on a carbohydrate structure which has never really been done," he says.

Further, Ancora applies their technology to tease out activity for a polysaccharide with promising activity for vaccine development. In some cases, researchers cannot pinpoint the exact subcomponent of a sequence or the carbohydrate epitope that is responsible for activity. "We make defined fragments synthetically using our building blocks and assembly approaches with very defined sites for conjugation," explains Campbell. "We then have a series of tools we can use to evaluate which structures are the most interesting. We can use glycochips, where we can put a library of carbohydrates on a slide and evaluate which ones bind antibodies to the known polysaccharide." While binding does not inherently mean it is going to be functional, it provides some validation that the carbohydrate structure is at least partially responsible for the immune response.

Malaria and *Staphylococcus*

Ancora's business model is to develop synthetic carbohydrate-based vaccines. They seek to own a piece of the $13 billion global vaccine market that already includes a few carbohydrate-based vaccines, including Prevnar, Comvax, Menactra, and Pneumovax. "The carbohydrate vaccine is very well commercially validated," says Pena. Prevnar, launched in 2002, became the first billion dollar product in the vaccine field in 2004. "But these are made from purified sources, not synthetically," he adds.

Ancora has two in-house preclinical vaccine programs and is working with other companies on others. "We come in from a synthetic approach," says Campbell. "They are not mixtures, which is often a problem with purified materials. They do not have copurifying toxic contaminants, such as endotoxin-related molecules, that you would often need to be rid of when doing purifications." Boons adds that a chemically synthetic approach is much more effective and safe, perhaps essential, if the oligosaccharide of interest derives from a dangerous pathogen, such as anthrax.

The advantages to Ancora's synthetic carbohydrate approach are two-fold: (1) access to previously unattainable structures expands the opportunity for new vaccine strategies and (2) the quality of the material produced allows researchers to pursue vaccine programs with a reproducible, robust source of materials. "We take away the purification variable during the early discovery phase when you are trying to determine exactly what material to move forward with," says Campbell. Cell-based carbohydrate antigen expression can change with the scale and parameters of the fermentation. What might be defined as the antigen of interest at the early discovery, 1-liter fermentation stage can change when scaled up to a 100-liter fermentor. Surface to volume ratios change, aeration changes, and the fermenting organism may respond and modify the carbohydrate.

Ancora's malaria vaccine targets the glycoslyphosphatidylinositol (GPI) class of carbohydrate. The company also hopes to develop a carbohydrate-based preventive vaccine against *Staphylococcus*, including MRSA, by targeting another carbohydrate class.

Beyond Vaccines

"We look past the vaccine horizon as well," says Pena, who cites Sanofi Aventis' Lovenox synthetic antithrombotic as an example of a carbohydrate-based drug. Synthetic carbohydrates may also be important for signaling pathways in cancer applications or they may play a role in adhesion events (binding) for inflammation.

"We believe that what we can do with carbohydrates helps the rest of the industry think seriously about carbohydrate-based targets and products in a way they have not been able to before," says Pena. "They have a lot of different products they would like to pursue, but up until now the technology has not existed to allow it. We fill that void, and that means more medicines will be available to help people."

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