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# Macrocycles: Going Where No Drugs Have Gone Before

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Big pharma and biotech start-ups have embarked on a federated mission to explore the expansive chemical space between small molecules and biologics to seek out new therapies that will boldly go where no drugs have gone before.

In this voyage of discovery, one focus is on synthetic macrocycles. "Nature has been using macrocycles for its purposes for many, many years," Mark Peterson, vice president of intellectual property and operations at Tranzyme Pharma Inc., told *BioWorld Today*. Macrocycles, especially in the form of antibiotics, seem to be nature's way of responding to some difficult problems.

While macrocycles are naturally found in the universe, today's explorers are seeking ways to design synthetic, fixed-ringed compounds that will mimic the benefits of both small molecules and larger biologics.

Such a compound would have the dense functionality of a biologic but the oral bioavailability and cell permeability of a small molecule. Although they are challenging, synthetic macrocycles could be manufactured the same way as small molecules, making them less expensive than biologics, said Helmut Thomas, senior vice president of research and preclinical development at Tranzyme.

Another benefit, especially for small biotechs, is that they would have the same strong intellectual property (IP) protection as a small molecule without a lot of competition. "It's really a green field from an IP perspective," Ensemble Therapeutics Inc.'s President and CEO Mike Taylor told *BioWorld Today*.

Companies making synthetic macrocycles wouldn't have to compete much for patents, he said, adding that "they trip over each other in the antibody space."

The key to a macrocycle is the fixed ring, which allows a larger molecule to behave like a small one, Thomas said. It is that ring that enables the molecule to cross membranes. And that ring can be loaded with various functionalities that can get at the root of a disease.

Macrocycles aren't a new discovery. The effectiveness of natural macrocyclic antibiotics has led to some synthetic modifications, either in the compound or the production process. Optimer Pharmaceuticals Inc.'s Dificid (fidaxomicin) is a case in point.

But in the past few years, the possibility of a synthetic macrocycle has grabbed scientific attention. While the potential of a synthetic ringed compound is intriguing, "a bizarre 14- or 15-member ring is not going to be anybody's first choice for a drug target," Derek Lowe, a veteran pharmaceutical chemist and a scientific blogger, told *BioWorld Today*.

Since macrocycles are "not a walk in the park" to make, he said a drug company is only going to be willing to put that effort into a high-value target, such as protein-protein interactions.

Inspired by nature and challenged by chemistry, the quest for synthetic macrocycles is taking on new life today, launching partnerships, vast libraries and the development of treatments for unmet needs.

That interest may be fanned now that Tranzyme has two synthetic macrocycles in clinical development. "It's still a technology that's proving itself," Peterson said. If the Tranzyme trials provide the proof, Peterson said he expects other companies will begin exploring the space.

Tranzyme, of Research Triangle Park, N.C., has been working on macrocyclic compounds for 12 years. Using its MATCH (macrocyclic template chemistry) technology, it is developing macrocycles for gastrointestinal (GI) motility disorders. Its ghrelin agonist ulimorelin, an intravenous drug, is in Phase III trials for patients in acute settings. (See *BioWorld Today*, April 5, 2011, and Nov. 9, 2011.)

Tranzyme's TZP-102, an oral drug granted fast-track status, is in a Phase IIb trial in patients suffering from diabetic gastroparesis, a chronic GI condition affecting both Type I and Type II diabetics. TZP-102 is designed to target the ghrelin receptor, which plays a direct role in the stimulation of GI motility. Tranzyme expects top-line data from the trial by the end of next year.

The ghrelin receptor is one of those high-value targets biopharma has had difficulty hitting, Lowe said, as it's been tricky to come up with small molecules that could go after the large signaling protein.

While Tranzyme may be the first to bring a synthetic macrocycle to clinic, it's not the only pioneer in the space. Ensemble, of Cambridge, Mass., hopes to get its first macrocycle into the clinic in two to three years.

## Logging the Discoveries

Ensemble, like Tranzyme, is developing immense libraries of macrocyclic compounds. Ensemble's libraries, which include synthetic compounds and natural products with synthetic feasibilities, have grown from about 80,000 macrocycles in 2008 to more than 4 million today, and it's doubling every six months, Taylor said.

Using its libraries, Ensemble can screen all of the compounds against a single target in a matter of weeks. And with its current staffing, the biotech can make 30 new compounds a week, Nick Territt, Ensemble's chief scientific officer, said.

That kind of innovation is vital, Lowe said. It is the kind of exploration small companies are good at, because it's their focus, he added. The next step is for big pharma to turn to them with targets.

That's happening at Tranzyme and Ensemble. Ensemble signed a strategic alliance with Pfizer Inc. last year, and both biotechs signed multimillion-dollar agreements with New York-based Bristol-Myers Squibb Co. (BMS) in 2009. (See *BioWorld Today*, April 15, 2009.)

In addition to its work with Ensemble and Tranzyme, BMS is developing its own macrocycles and collaborating with a third, unnamed, biotech. Its interest in macrocycles is part of its millamolecular strategy, which is focused on compounds with a molecular weight between 500 daltons, considered a small molecule, and 10,000 daltons, or a macro molecule. Historically, biopharma, following the Lipinski drug "rules," has steered away from this range.

"That's a big mistake, in my opinion," Carl Decicco, senior vice president for molecular sciences and candidate optimization at BMS, told *BioWorld Today*. "We want to have the ability at BMS to go after any target."

The targets the company is using in its macrocycle development are ones small molecules and biologics missed. "It's a very high bar," and the targets cross all areas of interest at BMS, Decicco said.

The biopharma firm is in the early days of macrocycle development. It has had some preclinical successes that have helped it find the tools to understand the biology and crack specific targets. Building on that success and its access to the ever-expanding libraries, BMS hopes to see its first macrocycle enter the clinic in a year or two, Decicco said. ■