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Macrocycle Diary's New Entry: Ensemble Deal with Boehringer

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By entering a potential $186 million research pact with Ensemble Therapeutics Inc. for synthetic macrocycles, Boehringer Ingelheim GmbH became the latest to place its bet on a newish, challenging approach that could combine the all-in-a-pill possibility of small molecules with the biological bull's-eye talent of large ones.

"Virtually all of the pharmas that we're aware of – and we're talking to most of them – have dedicated strategies or have articulated intent to access this molecular space between small molecules and biologics, and macrocycles is generating a lot of traction," said Cambridge, Mass.-based Ensemble's CEO Mike Taylor.

Natural macrocycles can be turned into drugs such as antibiotics. An example is Dificid (fidaxomicin) for the treatment of *Clostridium difficile* infection, for which San Diego-based Optimer Pharmaceuticals Inc. won FDA approval in 2011. (See *BioWorld Today*, June 1, 2011.)

But until Ensemble, no company had assembled a library like the firm's collection known as Ensemblin, which contains about 5 million of the midsized, fixed-ringed, synthetic molecules known as macrocycles that will be deployed in an effort to nail drug targets assigned by Boehringer, of Ingelheim, Germany.

"Without a doubt, we're the leader," Taylor said, based on the size of Ensemble's macrocycle library. "Just this week, we made another quarter of a million. We expect to be well over 10 million by the end of the year, and we'll probably go 12 to 15 million early next year," he added.

Orally active Ensemblins – "large small molecules" – bind nicely to targets such as those involving protein-to-protein interaction, including targets with hard-to-reach extended binding domains, which typically call for injected biologics, and intra-cellular targets that previously seemed impossible to hit, Taylor said.

"They're more stable, they penetrate cells better, and the conformational constraints of the macrocycle ring tend to improve the affinity of the molecules for certain kinds of targets," he told *BioWorld Today*. "The program we delivered to [Bristol Myers Squibb Co.] last year involved an intracellular target and it was quite effective in hitting that protein."

Ensemble, of Cambridge, Mass., gets research funding from Boehringer and an up-front payment, the amount of which was not disclosed. The overseas firm keeps exclusive rights to develop and commercialize drugs arising from the effort.

"In terms of structure, I would say it's pretty similar overall to the three other deals we've done" with BMS and Pfizer Inc., both of New York, and, in May, with South San Francisco-based Genentech (now a unit of Roche AG), Taylor said.

"In terms of amounts, it's a little bit complicated because we don't disclose the number of targets," he said, "but in more recent deals, we've tried to focus on a smaller number of targets, in order not to encumber the target space too much," since each deal works exclusively on particular targets for the partner.

Ensemble's platform, DNA-Programmed Chemistry, is based on research by David Liu at Harvard University, who is Ensemble's scientific founder. "DNA-tagged libraries are incredibly useful for finding the initial hit molecules," Taylor said, "but we very quickly transition to milligram-scale synthesis of individual, discrete macrocycles with no DNA involved at all."

Should synthetic macrocycles work for pharma customers long term, it could mean getting around the costs of screening loads of small molecules against targets, and of manufacturing drugs. (See *BioWorld Today*, Nov. 28, 2011.)

Genentech and Boehringer remain in active discovery mode, while BMS has "transitioned more to pursuing things we have delivered to them," Taylor said. "We've done these two deals in the last six months, and we're talking to other companies about doing a third deal, which is about all we can comfortably handle."

Ensemble has its own internal knitting to see after.

"Right now, we're spending a ton of time and a very considerable allocation of our resources on our anti-IL-17 program," Taylor said. "It's the only small-molecule antagonist program of IL-17, and we have quite a robust oral efficacy package that's developing. This is going to be a real kick-ass kind of program as we start to roll it out." A poster on the research will be offered at the American College of Rheumatology meeting in about two weeks in Washington, he said.

"We're actively out partnering that program," Taylor said. Many pharma firms are sniffing around, intrigued by the possibility of an oral anti-IL-17 drug, given the success of biologics in indications such as psoriasis, he said. The oral therapy could be "both a great complement to the biologicals, and potentially quite disruptive to them," Taylor added. ■