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Delivery Of First Macrocyle To BMS Enables Ensemble Therapeutics To Look Ahead

Ensemble Therapeutics, which is developing synthetic macrocyclic compounds against difficult-to-drug targets in partnerships with **Bristol-Myers Squibb** and **Pfizer**, reached a key inflection point April 12, delivering a preclinical compound to Bristol for further development and collecting an undisclosed milestone payment under their 2009 deal.

Using its proprietary *DNA-Programmed Chemistry* platform, the privately held Cambridge, Mass., biotech produces thousands of what it calls *Ensemblins* - oral, small molecule macrocyclic compounds that interact with substrates through difficult extended binding motifs to reach targets not adequately reached by small molecules or biologics.

The theoretical benefit of macrocycles is that they enable protein/protein interactions, sometimes occurring inside cells (where biologics cannot get), by offering advantages that include stability and improved membrane permeability compared to acyclic molecules of similar size, Ensemble CEO Michael Taylor explained in an interview.

Ensemble received $5 million upfront and $7.5 million in R&D funding two years ago from Bristol to develop Ensemblin candidates against eight undisclosed targets. The biotech can earn up to $29.5 million in clinical development and commercialization milestones plus global sales royalties for each of the eight programs ('Ensemble to discover macrocyclic drug candidates for BMS,' Elsevier's Strategic Transactions Database, April 2009).

"What we're trying to do with Bristol-Myers, and with our Pfizer collaboration also, is to open the door to both a very challenging set of drug targets so [our partners] don't have to deal with biological types of products to access these targets," Taylor said. "These are also targets that they've largely failed on with the resources and the techniques that they have internally. It's still early-stage, but we took this program well down the preclinical path - we had to meet a really robust set of criteria that BMS set out for us."

Those criteria include potency, selectivity and pharmacokinetics. Ensemble was able to deliver its first candidate with a high-throughput screening technology that enables it to grow libraries of Ensemblins at an exponential pace. Ensemble went into its work with Bristol with about 80,000 candidates in its library, but now has about 1.6 million diverse macrocycles and expects that number to increase to about 3.4 million during the second quarter.

The company reports it is making progress towards identifying other candidates under the Bristol tie-up as well as under a 2010 deal with Pfizer, which covers a smaller number of targets.

Taylor said the tie-up with Bristol has been greatly collaborative, although the pharma determined all of the targets for the discovery work.

"We drive all of the chemistry, do all of the screening and identify the initial lead compounds," he said. "Our basic platform is to use DNA-tagged molecules with an affinity selection-based screening method so

then as we identify the hit molecules, we then make them using traditional methods off the DNA platform and validate them in biochemical and biophysical screening. We do all of the chemistry, some of the biology and we leverage Bristol's biological expertise and resources wherever it makes sense."

Although Ensemble cannot divulge the targets of its discovery work for Bristol or Pfizer, the biotech also has its own internal programs and has produced candidates against BCL-XL, tumor necrosis factor, proteases and phosphatases.

Standing Alone And Branching Out

Going forward, Ensemble hopes to find one more collaboration partner - it thinks the announcement of the first Ensemblin delivery to Bristol will spur ongoing partnership conversations with other pharmas and biotechs - and continue developing expertise and generating cash that will enable it to advance its internal pipeline.

"There are hundreds of targets that cannot be adequately addressed by biologics or small molecules," said Ted Hibben, Ensemble's senior VP of corporate development. "A dozen or so of them have been locked up in these collaborations with BMS and Pfizer. We think if we do another collaboration, maybe another half-dozen targets could be a part of that collaboration, but that leaves the rest of the world for us to exploit as a standalone company."

What Ensemble does not plan - beyond its next collaboration - is to become a platform technology play, Taylor added. "We don't see ourselves in any way as a discovery services corporation," he said. "We don't see ourselves as selling the library or licensing the library technology - we feel that the Ensemblin platform is potentially extremely valuable on the order of many of the other therapeutic platforms that have been developed over the years around antibodies."

That's why the delivery of the Ensemblin program to Bristol is a key milestone for Ensemble - beyond the check in the mail, Taylor said.

"We've been running these collaborations for a period of time and this demonstrates that we've been able to deliver a high-quality set of chemical leads against a really tough protein/protein interaction target for one of our partners," he said. "It's an unambiguous declaration that we've been able to deliver and people don't have to just take our word for it anymore - it's in black and white."

– Joseph Haas (j.haas@elsevier.com)