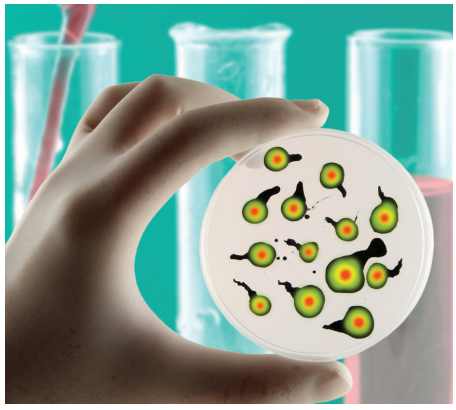
Genentech, Ensemble partner for macrocycle drug discovery



Ensemble Therapeutics has entered into its third major collaborative deal, with Genentech, a subsidiary of Roche, to support a proprietary drug discovery platform. The two plan to work together on discovering macrocyclic drug candidates against undisclosed protein targets specified by Genentech, in therapeutic areas that for now remain confidential.

Ensemble, a venture-backed, Cambridge, Massachusetts-based company founded in 2004, uses its DNA-programmed chemistry (DPC) drug discovery platform to produce a new class of drugs – synthetic macrocycles, which it calls 'Ensemblins', designating them 'small molecules with the power of biologics.' Like small molecules, ensemblins can be orally deliverable and can reach intracellular locations which are generally not addressable by biologics.

For Genentech, one of the attractions of the platform is that the macrocycles are a familiar drug class, to which Ensemble has added a new dimension. Dr Angele Maki, senior manager of business development at Genentech, told *Scrip* that "there are already drugs on the market that fall into this class of macrocycles, so there is evidence that this area of drug discovery can be fruitful".

Natural macrocyclic antibiotics such as erythromycin and rifampicin have clearly proven themselves, and newer modified macrocyclic compounds such as fidaxomicin (Optimer's anti-*Clostridium difficile* antibiotics Dificid) continue to demonstrate the merit of the class.

Ensemble chief executive Dr Michael Taylor told *Scrip* that macrocycles have historically been poorly explored within drug discovery because there was no fast, inexpensive, industrial way to synthesise libraries of new varieties. But that is changing. Already, Ensemble's Ensemblin library consists of over five million new macrocycles and is expected to be 10 million by the end of 2012).

"We make macrocycles in such quantities that we can run hundreds of screens against them," Dr Taylor said. The firm can screen the entire library of five million against new hard-to-reach biological targets in just a matter of a few weeks, and then validate those hits and within three to four months have a good starting off point for a medicinal chemistry programme. "Speed is really the emphasis," he added.

The new collaboration will deploy the platform and the collection of Ensemblins to discover novel candidates screened against Genentech's targets. While Genentech's Dr Maki would not identify the targets involved, she did indicate that the focus would be on protein-protein interactions: "We can say that this type of technology is amenable for targeting either protein-protein interactions, or other proteins that are difficult to target with other approaches…so there is a sort of sweet spot for macrocyles in general."

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Dr Maki said that Ensemble's work fits in nicely with what Genentech is already doing, and Ensemble's large library helps drive the collaboration and could open up new ways of discovering drugs.

Genentech will have the right to develop and commercialise lead molecules in return for paying Ensemble an undisclosed upfront fee, development milestones and royalties on future sales of any products from the deal. Detailed financial terms were not disclosed.

Ensemble is not the only firm developing a library: Tranzyme Pharma, which has a couple of synthetic macrocycles in clinical development for GI disorders, has one, too, albeit not as extensive as Ensemble's. "Their technology is more traditional combinatorial methods that have been adapted for macrocycles, and our best estimate is that they might have 50,000 to 60,000 macrocycles", Dr Taylor said.

BMS, Pfizer collaborations

Ensemble has two continuing discovery and development partnerships: one with Bristol-Myers Squibb which began in 2009 and another with Pfizer which began in 2010.

BMS is deploying Ensemble's drug discovery platforms and Ensemblin compound libraries to discover and advance drug candidates against up to eight undisclosed pharma targets for which a strong therapeutic rationale exists but which have not previously been successfully addressed with small molecules. BMS agreed to pay $5 million upfront, $7.5 million to fund R&D, and development milestones up to $29.5 million per compound plus royalties. In April 2011, Ensemble announced the achievement of the development of Ensemblins against one of the designated targets in the collaboration, resulting in the transition of that programme to BMS for further research and optimisation and a milestone payment to Ensemble.

Details on the Pfizer agreement were sparse.

Ensemble's pipeline

The firm is utilising its technology and Ensemblins library to secure partnerships as well as for an in-house pipeline. The focus is primarily on autoimmune biological targets, in addition to a few cancer targets, Dr Taylor said.

The most advanced internal programme surrounds a preclinical-stage, small-molecule antagonist of interleukin-17, a cytokine implicated in inflammatory and autoimmune diseases (and thus far only addressed with protein therapeutics). Dr Taylor emphasises that this is a classic protein-protein interaction, and many in the industry would consider it undruggable by a small molecule. The progress Ensemble has made "has turned a lot of heads," he said. "We are on track to have an orally active development candidate by the end of the year. We may partner it later this year." The firm plans to present some preclinical data on the IL-17 target in June 2012, the first disclosure of its work on macrocycles.

Dr Taylor has said that, to his knowledge, no other small-molecule antagonists of IL-17 exist in spite of the active efforts of a number of major pharmaceutical companies to find such compounds.

Ensemble's investors include Flagship Ventures, ARCH Venture Partners, CMEA Ventures, Harris & Harris Group, Kisco Ltd and Boston University. The firm has raised $40 million in equity financing to date, and this has been augmented by non-dilutive funding from partnerships, Dr Taylor said. The firm has funding until next year, he added.

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