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Tools & Techniques

Assembling around Ensemblins

By Michael Flanagan
Senior Writer

Ensemble Therapeutics Corp. thinks its DNA-Programmed Chemistry discovery technology is more efficient than competing platforms in the macrocycle space. The biotech now has its third major partnership, a d eal with **Genentech Inc.** to try to raise drugs against challenging targets in the **Roche** unit's preclinical pipeline.

Ensemble will receive an undisclosed upfront payment and is eligible for milestones and royalties. Genentech is not disclosing the precise targets, but did say it wants to generate macrocyclic agents that address protein-protein interactions.

Macrocycles are a class of organic compound featuring a ring structure found in many natural products. They typically range in size from 500-2,000 Da., making them larger than most small molecules but smaller than biologics.

Ensemble's DNA-Programmed Chemistry (DPC) discovery platform synthesizes molecules, dubbed Ensemblins, with cyclic backbones that typically range in size from 600 to 1,000 Da. *(see SciBX:Science-Business eXchange, Jan. 26).*

That size range is a sweet spot between small molecules and biologics, making Ensemblins small enough to be orally available and cell permeable, but big enough to interact with targets against which small molecules have been ineffectual, according to Ensemble President and CEO Michael Taylor.

> ***"We believe Ensemblins can take the best characteristics from small molecules and protein therapeutics and will apply them to challenging targets in our pipeline, like protein-protein interactions, where we're already familiar with the biology."***
>
> **James Sabry, Genentech**

Ensemblins are also easier to manufacture and have a lower cost of goods than biologics, he said.

The DPC technology relies on DNA as a template to generate macrocycles using synthetic building blocks, according to CSO Nick Terrett. "Each template contains four to five codons so that after four to five chemical steps we will have constructed a unique sequence of building blocks attached to the DNA template," he said.

For screening, Ensemble incubates the templates in an assay containing the intended target immobilized on a solid support. Components that have not bound are then washed off, and the template DNA of bound components is cleaved, amplified by PCR and sequenced to identify which macrocycles were active.

Other companies "synthesize the DNA by adding base sequences after the addition of each new synthetic building block," resulting in slower and less efficient synthesis and purification processes, said Terrett.

According to Taylor, ideal targets for Ensemblins include phosphatases, proteases and protein-protein interactions.

"We believe Ensemblins can take the best characteristics from small molecules and protein therapeutics and will apply them to challenging targets in our pipeline, like protein-protein interactions, where we're already familiar with the biology," said James Sabry, VP of partnering at Genentech.

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Genentech's R&D group focuses on oncology, immunology, neuroscience and infectious diseases.

Sabry said Genentech picked Ensemble from among other companies working on molecules in the same size range because of Ensemble's "ability to synthetically engineer large numbers of macrocyclic compounds for use in drug discovery."

Ensemble has a library of more than 4.2 million macrocycles, which it says is the largest in the industry. In addition, Taylor said the company's chemistry approach, which works by combining small stretches of tagged DNA via controlled reactions, is more modular and scalable than competing technologies.

Other companies working in the space include **Bicycle Therapeutics Ltd.**, **PeptiDream Inc.**, **Ra Pharmaceuticals Inc.** and **Tranzyme Inc.**

Bicycle applies phage selection to chemically constrained cyclic peptides to identify and optimize molecules with target specificity and binding affinity.

PeptiDream uses transfer RNA tethered to amino acids to create peptide macrocycle libraries for target selection and screening.

Ra Pharma is using *in vitro* display technologies to produce libraries of cyclic peptidomimetics.

Tranzyme's macrocycle discovery technology is based on a synthetic chemical fragment with three recognition moieties locked in place that can be modified or replaced to optimize binding stability, permeability and potency.

Ensemble's prior deals include discovery collaborations with **Bristol-Myers Squibb Co.** in 2009 and with **Pfizer Inc.** in 2010.

The biotech's most advanced in-house program consists of macrocyclic IL-17 inhibitors in preclinical testing for autoimmune conditions. The company hopes to identify a lead candidate this year and begin Phase I testing in 2014.

There are a number of anti-IL-17 mAbs in development, including **Eli Lilly and Co.**'s ixekizumab and secukinumab from **Novartis AG**. Both are in Phase III testing for autoimmune conditions.

COMPANIES AND OTHER INSTITUTIONS MENTIONED

Bicycle Therapeutics Ltd., Cambridge, U.K.
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Ensemble Therapeutics Corp., Cambridge, Mass.
Genentech Inc., South San Francisco, Calif.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
PeptiDream Inc., Tokyo, Japan
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Ra Pharmaceuticals Inc., Boston, Mass.
Roche (SIX:ROG; OTCGX:RHHBY), Basel, Switzerland
Tranzyme Inc. (NASDAQ:TZYM), Durham, N.C.