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BIOTECHNOLOGY

Ensemble Therapeutics Corp.

Making mid-sized macrocyclic molecules, en masse

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Business: Drug discovery technology
Founded: January 2004
Founders: Douglas Cole, MD; Noubar Afeyan, PhD; David Liu, PhD
Employees: 35
Financing to Date: $38.5 million
Investors: Flagship Ventures; ARCH Venture Partners; CMEA Capital; Boston University; Kisco Ltd.; Harris & Harris Group
Board of Directors: Noubar Afeyan (Flagship Ventures); Douglas Cole (Flagship Ventures); Robert Nelsen (ARCH Venture Partners); Anna Protopapas (Millennium Pharmaceuticals); Michael D. Taylor
Scientific Advisory Board: David Liu (Harvard University); David Armistead, PhD (Oxford Bioscience Partners); Francis Barany, PhD (Weil Cornell Medical College); Simon Campbell (former SVP, Pfizer); Pat Confalone, PhD (DuPont Crop Protection); Gerard Evan, PhD (University of California San Francisco); Gerald Joyce, MD, PhD (Scripps Research Institute); Mark Murcko, PhD (Vertex Pharmaceuticals); Craig A. Smith, PhD (VLST Corp.); Michael E. Weinblatt, MD (Brigham and Women's Hospital and Harvard University)\

Major pharmaceutical manufacturers have been plied with many, many kinds of drug discovery technologies over the past 15 years: randomly mutated mice and zebra fish, assorted antibody production methods, combinatorial chemistries, bioinformatics, high-throughput screening, massive arrays of DNA, crystallized protein structures and exotic natural compounds are but some of the temptations offered by wave after wave of fresh young biotech companies. Some of the methods have proved to be useful tools, others disappointments, and a few have emerged as powerfully enabling platforms.

Ensemble Therapeutics Corp. believes it is one of the rare outfits whose discovery methodology will come to be recognized as highly productive. The firm was founded in 2004 as Ensemble Discovery, but was re-christened in mid-2010 to emphasize the promise that its large-scale libraries of chemicals with macrocyclic structures will yield worthy drug candidates and ultimately marketable therapeutics. Macrocycles are chemicals that contain a closed ring of 12 or more atoms. This distinctive structure occurs sometimes in nature and is a trait of numerous marketed drugs; potent oral medicines such as cyclosporine, erythromycin and rifampicin are all macrocycles.

Although medicinal chemists have long appreciated the appeal of the ring structure, most have found macrocycles difficult to synthesize and thus not ideal candidates for commercial research that must eventually be scaled up. In some labs, macrocycles were avoided because they do not meet all of the drug candidate selection criteria widely observed in the drug industry and known as the "Rule of 5." The relatively large size of macrocycles is the attribute most out of keeping with convention: typically, a molecular weight of 500 daltons is considered the maximum acceptable for a chemical meant to be administered orally. By contrast, macrocycles tend to weigh in at 500 to 2,000 daltons.

The hefty size of macrocyclic compounds is the key characteristic that Ensemble and other companies are betting will make certain of them valuable drugs. Whereas small molecules generally interact with their targets by binding to them, a matter of both fit and electric charge, the thinking goes that macrocycles will be big enough to spread across the surface of disease-relevant proteins and so physically disrupt interactions that smaller molecules are too puny and weak to influence. If so, macrocycles could hit targets that only protein therapeutics can address now, and potentially do so orally. Because the ring structure of macrocycles can help the chemicals move across cell membranes, compounds of this class may also be able to address intracellular targets that proteins such as antibodies can never reach.

Ensemble's method for making macrocyclic compounds entails tethering chemical domains to unique sequences of DNA that not only function like bar codes to identify the individual components, but also influence the synthesis of progressively complex molecules. As tagged reagents hybridize to a template DNA strand, their close proximity forges new covalent bonds; repeating the process several times allows novel molecules to grow piece by piece. The final step of the synthesis is closing the macrocyclic ring, by adding compounds that induce classic chemical reactions such as the Wittig reaction. This synthesis method, called *DNA-Programmed Chemistry* was devised by **Harvard University** chemist David Liu. Liu was just 30 years old when he became a co-founder of Ensemble along with two VCs taken with his idea to harness molecular machinery to drive the synthesis of organic molecules.

The company's focus on building macrocycles and developing them as therapeutics has evolved over time. When Michael Taylor, formerly an SVP in **Pfizer Inc.**'s global R&D division replaced Richard Begley as CEO in 2007, the company was still publicly emphasizing the method's ability to create numerous classes of compounds and its relevance for diagnostics. A research alliance with **Roche** in July 2007 was geared to detecting protein complexes that might serve as companion diagnostics to drugs already on the market.

These days, Mike Taylor is emphasizing recent improvements in the company's

ability to make macrocyclic compounds in quantities far beyond the capacity of other companies, like **Tranzyme Pharma Inc.**, that are also offering libraries of molecules in this class. Whereas Ensemble's first significant library reportedly contained about 20,000 compounds, in 2010 the company says it made a million. Taylor declares: "2011 will be a tipping point for us. We have made improvements in yield and cost, so we can make more libraries on diverse macrocyclic scaffolds." Roughly doubling the size of its collections every six months, Ensemble now has 1.6 million compounds aliquotted out and ready for selections.

Describing Ensemble as a tool company would be far too narrow, Taylor asserts: "We are an enabling platform company. We consider ourselves like an antibody company, because our technology can be applied against numerous targets." Ensemble will *not* be following the model previously favored by companies offering large-scale compound libraries, Taylor states. "We do not intend to enter a large number of alliances, where we are merely paid for our library." Ensemble entered a discovery-oriented alliance with **Bristol-Myers Squibb Co.** (BMS) early in 2009 and with Pfizer as 2010 began, and would like to do at least one more.

Ensemble's deal with BMS called for it to develop candidates against up to eight targets for which therapeutic rationale exists, but which have previously been considered "undruggable." Deal terms were announced as including an upfront payment of $5 million and up to $7.5 million to fund R&D, with development milestones of up to $29.5 million per compound plus royalties on sales. No terms were disclosed for the Pfizer arrangement. Although Taylor concedes "there is not a lot of transparency into the status of the collaborations," he says Ensemble has made "exceptional progress on a number of BMS targets."

Ensemble has permission from its partners to reveal that it has "identified the first small-molecule inhibitors of an important cytokine/receptor interaction," Taylor announces. His company has also, he says, "identified compounds that inhibit an intracellular target by hitting two related binding sites." This news about disrupting protein-protein interactions with something other than a protein is noteworthy, Taylor asserts, "because both Big Pharma and biotech companies have tried to do this and failed." In fact, he recalls that when he joined Ensemble in mid-2007, "BMS was one of the few companies that recognized the value of going after protein targets with small molecules. Other companies had kind of written it off."

The information that Ensemble gets about structure and activity when its compounds bind targets is "much more intense and rich than the old yes/no data you could get in the past," Taylor claims. "We can do a single experiment, and often get hundreds of millions of sequences back. We immediately see families of active compounds and can rank them." The macrocyclic compounds that can be seen to be interacting with protein targets do not necessarily become candidates that go straight on for optimization, but they can provide "a rich starting point for medicinal chemists to look at and see patterns and new variants," Taylor says. X-ray crystallographic data from the literature or a partner's proprietary information can further enhance Ensemble's discovery efforts, he notes. "We have had a couple of successes where we have designed libraries with structural information in mind."

Taylor says Ensemble has been assembling some internal tools and capabilities over the past couple years that are allowing it to leapfrog other discovery methods. "There were lots of platforms in the past that could identify hits based on affinity binding, but then it could take months to produce compounds for further testing. We have been able to do that often in a matter of weeks," he says. The company has built some pharmacogenomic capacities, to understand targets that exist within certain cells, Taylor notes. Although there are thousands of protein-protein interactions known to be medically relevant, many considered undruggable, Taylor says Ensemble has been focusing primarily on proteins pertinent to oncology and inflammation, such as interleukin (IL)-6 and IL-15, TNF, and Notch DLL4.

Taylor says he is optimistic that Ensemble is and will increasingly be perceived as creating value in a number of areas: "We have now shown our ability to generate macrocyclic compounds against partners' targets, and produced some pharmacokinetic data to show that these are or can be orally active. We feel that even over the last year, we have developed a more demonstrable and proven value proposition."

Ted Hibben, who joined Ensemble as SVP, corporate development in September 2010, says he, too, is optimistic that the company's recent achievements will attract a third discovery partnership to bring additional early-stage, near term funding. "We have the capacity to handle that with our current staff," he says, adding, "Our ideal new collaborator would have biological sophistication, be trying to find compounds against nettlesome targets, and think macrocycles are good bets." Hibben most recently served as chief business officer of Cequent Pharmaceuticals, a company focused on RNAi therapeutics, and has guided business development and managed alliances at a number of biotech firms.

Intent as Taylor is on finding a new partner and pleasing existing ones, it is never too early to consider the company investors' exit strategy. Ensemble's could come about, Taylor muses, by "a company wanting to enter this space and offering us to be incorporated." Or, like the heads of just about every other platform-based company operating these days, Taylor would not be averse to a deal such as the one that **Celgene Corp.** signed with **Agios Pharmaceuticals Inc.** in April 2010: Celgene paid $130 million up front in exchange for the option to license compounds after Phase I, and agreed to fully fund development of any projects it takes over and to pay Agios for each up to $120 million in milestones and royalties. All while permitting Agios to co-promote some products in the US. Nice work if you can get it. Until a deal like that comes along, Ensemble will continue applying what it learns in partnerships to build value in its own pipeline.

To date, Ensemble has received financing of $38.5 million from investors including Flagship Ventures, ARCH Venture Partners, DMEA Capital, Boston University, Kisco Ltd., and Harris & Harris Group.

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— Deborah Erickson