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Autoimmune RORγt Program May Portend Change Of Direction For Vitae

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Vitae Pharmaceuticals Inc. tells a different story than many other clinical-stage companies, but then how many biotechs without a commercial product have not needed to raise funds in nearly nine years? Focused on structure-based drug design, the Ft. Washington, Pa., firm is nearing an inflection point as it decides which among several suitors to partner with on a ROR gamma t inhibitor program that could offer utility in multiple autoimmune indications.

Using a discovery platform derived from computational chemistry research initiated at **Harvard University**, Vitae has generated roughly $130 million from a pair of partnerships signed with Germany's **Boehringer Ingelheim GMBH** for diabetes and Alzheimer's disease. With that cash alone, it is able to keep pushing on multiple fronts, notably on drug discovery against multiple targets, even as it takes its time selecting a partner for its lead optimization program in the burgeoning and already deal-heavy RORγt inhibitor space.

RORγt theoretically works by blocking production of interleukin-17, an inflammatory cytokine implicated in the pathogenesis of immune-mediated disease. RORγt inhibitors offer the potential to selectively suppress T-helper 17 cells that produce IL-17, while not disturbing other targets and receptors in the patient's immune system, Vitae says.

While Vitae could keep the RORγt program for itself, its breadth and versatility mean the company will need a partner to maximize the value. Several potential partners for the program are in the later stages of due diligence, says CEO Jeffrey Hatfield. Vitae hopes to announce a partnership, if it elects to sign one, in September or October.

"With RORγt, cash is not a top priority," Hatfield said. "But the driver here is that it is a very specialized field. Autoimmune disorders have a variety of different animal models and none of them are perfect predictors of what will happen in the human condition, so a great deal of expertise is needed in immunology to help make the transition to selecting the final candidate, driving that into the clinic and then finding the best potential indications."

Structure-Based Design Platform

The key to Vitae's initial success is the proprietary Contour structure-based drug-discovery engine, which made its first splash by quickly producing only the second renin-inhibition compound to achieve proof-of-concept in animal models.

The first and only such drug to reach the market so far is **Novartis AG**'s *aliskiren* (Tekturna/Rasilez), indicated for hypertension. Intended as a successor to *Diovan* (valsartan), Novartis' blockbuster which lost patent exclusivity last year, Tekturna to date has been a disappointment. For 2012, Novartis did not list Tekturna/Rasilez as one of its top 20 sellers, while Diovan, although down 22% from 2011, was its second-best seller at $4.42 billion.

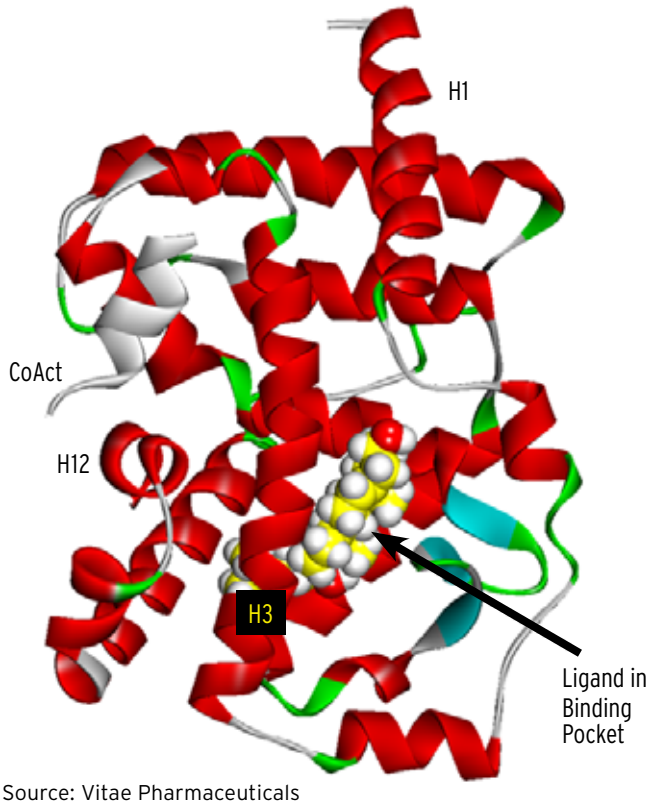
Inhibition of renin, which acts upstream of angiotensin receptors in the hypertension cascade, has proved to be a challenging target to drug ("Vitae Pharmaceuticals Inc." – START-UP, March 2005). Renin is an aspartyl protease and inhibitors of this class historically have demonstrated poor drug-like properties.

Other than aliskiren, R&D teams industry-wide failed to produce a small-molecule renin inhibitor for about 30 years, Hatfield noted. But the Contour system yielded novel, patentable structures within seven months and a compound that achieved animal-model POC in 14 months. Vitae's compounds were non-peptidic mimetics, a different chemical class from other companies' experimental renin inhibitors with better drug-like properties.

GlaxoSmithKline PLC expressed interest and licensed exclusive, worldwide rights to the preclinical program in 2005 for an undisclosed upfront payment and equity investment. Overall, including research funding and potential clinical and regulatory milestones, the companies said the transaction could have brought Vitae up to $175 million.

Structure-based drug design

RORγt: Ligand Binding Domain



Source: Vitae Pharmaceuticals

However, GSK exited the collaboration in late 2008, returning the program to Vitae, which since has advanced lead compound VTP-27999 to a ready-for-Phase IIb status. At present, Vitae is in discussions with potential partners for this compound, while it also considers a go-it-alone approach, Hatfield said.

In the aftermath of GSK's decision, Vitae signed a $13 million loan with Silicon Valley Bank and Oxford Finance, intended to provide cash runway into 2010 ("Vitae's Debt Financing: Crucial Lifeline in a Tightening Financial Market " – START-UP, November 2008). But runway ceased being an issue for the firm as its 2007 and 2009 partnerships with BI advanced steadily and produced a consistent stream of income that Hatfield says has amounted to about $130 million to date, with another $50 million expected in near-term milestone payouts.

In addition to VTP-27999, Vitae has the 11 beta hydroxysteroid dehydrogenase (HSD)-1 program for type 2 diabetes and the beta secretase (BACE 1) inhibitor program for Alzheimer's, both partnered with Boehringer, and the RORγt inhibitor program. In addition, it has Liver X Receptor (LXR) modulating candidates in preclinical development for acute coronary syndrome, psoriasis and atopic dermatitis. Finally, for any John LeCarre fans out there, Vitae also has a secret collaboration around a proprietary diabetes target with an undisclosed partner.

The 11 beta-HSD1 program yielded novel structures in two months and animal model POC in 16 months, Vitae notes, while the firm needed six months to produce novel compounds and 14 months for animal POC in the BACE 1 program. In LXR, discovery yielded novel candidates in six months and animal POC in 12 months, while the RORγt work produced Vitae's fastest results yet – novel, patentable structures in two months, animal POC in nine months.

Chief Scientific Officer Richard Gregg said Vitae's discovery process can yield results in two to four weeks that generally might take a big pharma eight to 10 weeks to produce.

People And Technology Combined

Yale University chemistry professor Bill Jorgensen, a member of Vitae's scientific advisory board, said the company succeeds in quick-paced drug discovery against challenging, known targets because of a combination of technology and expertise. The Contour system produces a 3-D representation of a molecule that Vitae chemists and biologists build out together for optimal pharmacokinetic and pharmacodynamic properties.

"Many larger pharmaceutical companies also do structure-based drug design but probably not as their only activity," he explained. "But Vitae focuses on biomolecular targets, proteins in its case, for which it has or can obtain an X-ray crystal structure, and then that information is very helpful in its efforts to design compounds that should be active in regulating the proteins."

Vitae's ability to advance multiple programs for nine years without seeking additional VC investment means its capital structure remains non-dilutive to its early investors.

Atlas could not have foreseen that the biotech would not come back for additional financing any time soon when it co-led Vitae's $34 million Series B round with Wellcome Trust in 2004. "When we invested in that timeframe, the picture we saw was they had a program offering the ability to be partnered in renin with several pharmaceutical companies," Peter Barrett, a managing partner at Atlas and Vitae board member, said. "But did we believe that we wouldn't have to bring in any more equity capital? No, you never go into a deal thinking that way, because that's when you get burned."

Although Vitae says its last venture round was the Series B, GSK led a special $15 million Series C in 2005 in tandem with the license for the renin inhibitor program. BI also funded a Series D in tandem with its first deal with Vitae in 2007 – both deals with BI involved an equity stake going to the family-owned German pharma, but Vitae has not disclosed the Series D amount or what BI's total holding amounts to.

Harvard To Concurrent To Vitae

Hatfield, who joined the firm two years after its founding in 2002, was charged by the board with converting a scientific idea into a money-generating business. In short order, he

Vitae Pipeline

Indication/Compound	Target	Development Stage	Time from lead generation to animal-model POC
Chronic kidney disease, VTP-27999	Renin inhibition	Phase IIb-ready	14 months
Type 2 diabetes	11 beta-HSD-1	Phase I, partnered with Boehringer Ingelheim	16 months
Alzheimer's disease	BACE-1 inhibition	Not disclosed, partnered with BI	14 months
Acute coronary syndrome, Psoriasis, Atopic dermatitis	Liver X Receptor	Preclinical	12 months
Diabetes	Proprietary undisclosed target	Undisclosed, with unnamed partner	Undisclosed
Autoimmune disorders, psoriasis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, asthma	ROR gamma t inhibition, suppresses T-helper 17-mediated chronic inflation	Lead optimization	9 months

Source: Vitae Pharmaceuticals

changed the company name from its original **Concurrent Pharmaceuticals** to Vitae to reflect a focus on drug development and brought in former **Bristol-Myers Squibb Co.** colleagues Gregg as CSO and Tina Fiumenero as CFO. The firm's first CEO, John Baldwin, also had served as CSO and when he retired, Hatfield knew he needed to hire someone with broad expertise and capabilities.

"What we needed was the translational medicine to know where we were going with our drug-discovery efforts to be able to optimize the drugs and transition to meaningful value," the CEO said. "Gregg led clinical discovery at Bristol for all therapeutic areas. We are therapeutically agnostic, so we might look at kidney disease one program and then autoimmune disease the next."

"Gregg not only has direct experience there but even more importantly he knows a broad network of opinion leaders that he became friends with at Bristol," Hatfield continued. "So, we not only have the benefit of his experience but a vast opinion leader network to call in and help with any program that we are working on."

Vitae is semi-virtual, with a headcount of about 50. Among the tasks it contracts out are animal studies, a majority of its synthetic chemistry, and Phase I and II clinical trials.

"There are different shades of virtual," Hatfield said. "You could even argue that big pharma is somewhat virtual, [those companies] don't discover that many of their pipeline drugs anymore. Everybody is moving into very specific areas of expertise. Ours is drug discovery."

Hatfield says Vitae is not chasing anyone else's business model. This is what could make the partnering of its RORγt program such a crucial decision, although marketing for primary care indications would require a larger scale than Vitae is likely to achieve any time soon.

"There are some similarities with Vertex in that it was an innovator in the field of structure-based drug discovery, so that's a natural comparison," he noted. "What was different was that Vertex took in an enormous amount of capital over the years to be able to find a product that it advanced. It's still undefined for Vitae whether we hold a compound and try to become a fully integrated company or continue to build a pipeline by being maybe one of the best in the world at small-molecule drug discovery on known targets."

It's unclear whether Vitae's investors have an appetite to fund the large and expensive pivotal trials needed to obtain approval in indications such as atherosclerosis. Vitae seems unlikely to become a vertically integrated company on its own. Clinical trials for medications targeting large patient population diseases can run tabs nearing $1 billion.

The X-factor here is the amount of equity BI already holds, leading to the question of whether the German company might have an eye on someday acquiring or absorbing its U.S. partner.

One thing is certain. Vitae's investors say they are not eagerly seeking an exit and are not pushing for additional cash generation through vehicles such as platform technology licensing deals. Fiumenero indicated that Vitae has turned away potential investors – the company watches the financial markets but has not felt the pull of an initial public offering – and the pressure public investors bring to bear – so far.

Atlas' Barrett feels confident that platform license deals are not a necessary avenue for the firm. "The value of one of those deals [is minimal] because it's more of a service-based

deal," he explained. "The real value in these companies is in producing chemical equity that obviously is patent-protected. That's what the industry ascribes the most value to, so doing non-exclusive platform-service deals almost devalues the work and capability that they've created."

Deal-Making Strategy

Different imperatives informed each of Vitae's first two deals with Boehringer Ingelheim and that will be the case again when/if the company partners its RORγt program, Hatfield said. Vitae got $36.5 million upfront from BI in the 2007 license of 11 beta-HSD1 compounds for diabetes and other metabolic diseases. The upfront consisted of cash, an equity stake and R&D funding.

Vitae also was eligible to earn up to $300 million in development, regulatory and sales milestones related to the transaction – it got $8 million for a performance milestone in 2009 and a $14 million payment for the beginning of Phase I work in 2010. Vitae says it has earned an additional $37 million over four milestone payments during the course of the first partnership so far.

In 2009, Vitae licensed its BACE 1 inhibitor program to BI for $42 million upfront, comprising cash and equity . The biotech can earn up to $200 million in development and regulatory milestones under the agreement – Hatfield said it has garnered $15 million total in three such payments to date ("Second Collaboration With Boehringer Provides Extended Cash Runway For Vitae" – "The Pink Sheet" DAILY, Jun. 15, 2009).

"My experience with deals is that doing a deal is not a finish line for a program. It's the end of one chapter, but the beginning of many chapters thereafter that lead to whether we get a breakthrough drug, because that ought to be our long-term goal," Hatfield said. "The dollars that we take in are important but more important is what's the [other] company's commitment to the program, what are its resources, and what is the culture? If it's a good fit, we will work with them."

BI was a good fit twice, out of about 10 suitors for the 11 beta-HSD1 program and as many as 30 for the BACE 1 program, even though Vitae's deal-making goals were different each time. In the initial deal, Hatfield said, the company's priority was to raise cash, while in the second, it wanted a partner it could rely upon to take its BACE 1 intellectual property to its full potential.

In both instances, Vitae liked BI's stability and long-term outlook as a privately held, family-owned company.

"[In 2009], we already had the track record with BI where we knew we could work really well with their team," Hatfield said. "We had confidence, all the way up to their chairman, that the asset would be taken care of properly and that we would be able to create synergistic value together."