BioWorld
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Actionable Intelligence • Incisive Analysis

Clarivate Analytics

October 17, 2017
Volume 28, No. 201
Special Reprint

Newco News

Eyes on Exicure: Reverse merger puts SNA technology before broader audience

By Marie Powers, News Editor

Considering that Chicago isn't exactly a breeding ground for biopharma, Exicure Inc. already had defied expectations by raising more than $42 million since its inception in 2011 as Aurasense Therapeutics LLC and attracting the attention of tech and business notables such as Microsoft Corp. co-founder and philanthropist Bill Gates, along with Craig Mundie, former Microsoft chief research and strategy officer, Eric Lefkofsky, chairman and co-founder of Groupon, David Walt, co-founder of Illumina Inc., and Patrick G. Ryan, founder and retired CEO of Aon. Exicure also had attracted more conventional backers, including Abbvie Ventures and the Rathmann Family Foundation.

Despite that support, the Skokie, Ill.-based company decided to cast a wider net.

Exicure's technology and data from a phase I test of its topical anti-TNF compound, AST-005, in 15 patients with mild to moderate psoriasis received a warm reception at the J.P. Morgan (JPM) Healthcare Conference in January, according to David Giljohann, the company's CEO. Exicure is developing a class of immunomodulatory and gene silencing drugs based on three-dimensional, spherical nucleic acid, or SNA, architecture that can address a range of diseases, from inflammatory disorders to oncology.

The densely packed, synthetic nucleic acid sequences are radially arranged on the surface of a nanoparticle but are "sequence agonistic," providing options for the platform to incorporate antisense, siRNA, miRNA, aptamer and Toll-like receptor (TLR) targeting.

"We're doing nucleic acids but in a completely different way than folks have done in the past, mainly in that we're using localized applications of DNA and RNA in our spherical nucleic acid format rather than thinking about nucleic acids as systemic drugs," Giljohann told *BioWorld*.

Exicure's SNAs achieve extensive cellular entry without lipid or polymer encapsulation and with limited chemical modification, offering improved safety and efficacy along with rapid and low-cost development.

Toxicity and delivery have been the primary challenge for biopharmas seeking to incorporate nucleic acids into drug development, Giljohann said. SNA construction solves those issues, and Exicure is working on mechanisms – topical creams, eye drops, nebulizers and orals – that allow local delivery in a variety of tissues.

CEO David Giljohann

The phase I psoriasis findings confirmed that the SNA technology could knock down genes locally. Treatment with the highest dosing strength of the AST-005 gel resulted in a statistically significant decrease in TNF mRNA expression in psoriatic skin.

Feedback at JPM consistently supported the notion that Exicure should position its story in front of a broader audience. Because its "unusual" investor base didn't lend itself easily to a traditional IPO, "we were trying to find a bridge between a private company and a public company," Giljohann explained. "We came up with an alternative public offering strategy that involved a reverse merger. Rather than take on a fallen angel or a public company that had failed clinical programs in the past, we went after a clean shell."

Late last month, the company completed the reverse merger with Max-1 Acquisition Corp., which then changed its name to Exicure Inc. and assumed the company's historical business. Simultaneously, Exicure closed a $20 million private placement that included its existing investors alongside new investors Mark Tompkins and Katalyst Securities LLC.

'Looking for a balanced approach'

Exicure was founded by prolific researcher Chad Mirkin, director of the International Institute for Nanotechnology at Northwestern University, where he also serves as professor in the departments of chemistry, chemical and biological engineering, biomedical engineering, materials science and engineering, and medicine, and Shad Thaxton, associate professor in the department of urology at Northwestern's Feinberg School of Medicine and a former member of Mirkin's lab during his PhD studies. Giljohann, the company's founding scientist, also completed his PhD work in Mirkin's lab, where he developed oligonucleotide-modified nanoparticles, including the SNA constructs. He previously served as principal scientist and chief operating officer before being named CEO of Exicure (then Aurasense) in 2013.

Behind AST-005, the company has some half-dozen assets, according to Cortellis Competitive Intelligence. In the third quarter, Exicure filed a clinical trial application in Canada for a phase I study of its IL-17RA modulator to treat mild to moderate psoriasis, with phase I data expected in the first quarter of 2018.

AST-008, a TLR9 agonist, is moving toward the clinic in a combination approach with checkpoint inhibitors to treat solid tumors. Preclinically, AST-008 produced potent TLR9 activation in cell-based assays and localized to the endosome where TLR9 is expressed. The agent also elicited systemic pro-inflammatory cytokine responses, resulting in suppression of regulatory T cells and myeloid-derived suppressor cells and an increase in effector T cells. To date, Exicure has evaluated AST-008 in breast, colon, bladder, melanoma and lymphoma cancer models, showing efficacy both in prevention and established tumor models – administered subcutaneously, intratumorally or intravenously – and demonstrating synergy with checkpoint inhibitors.

Exicure also has a preclinical IL-4RA modulator targeting mild to moderate atopic dermatitis and an IL-1 beta expression inhibitor aimed at epidermolysis bullosa, according to Cortellis.

With approximately 20 employees, the company has executed its semi-virtual model efficiently, moving AST-005 from nomination through phase I in less than 18 months at a cost of about $3.7 million.

Even before the reverse merger, Exicure's progress did not go entirely unnoticed. In December 2016, the company inked a strategic research collaboration, option and license agreement with Purdue Pharma LP for global development and commercial rights to AST-005 plus an option to three additional collaboration targets, so far undisclosed. The up-front payment, equity investment and potential milestone payments could total $790 million. Exicure also stands to receive royalties on product sales.

The company's commercial potential isn't limited by the Purdue deal. Exicure is sitting on an IP portfolio that includes some 75 pending applications and more than three dozen issued or allowed patents across multiple nucleic acid modalities.

"We're not calling ourselves an sRNA company or an antisense company or a microRNA company," Giljohann said. "We can do all of all of those on the SNA. Our claims are built around the densities of the nucleic acid structures."

Because Exicure is the only company that can make, modify and use SNAs for therapeutic applications, the company can pursue narrow indications on its own as well as broader disease states where partners can add value.

"We're looking for a balanced approach," Giljohann said. "We have the ability to expand this technology, given that it's easy to design these molecules."

Ophthalmology and respiratory diseases represent two additional areas where the company might seek alliances, and Exicure is open to creative partnering structures.

Purdue, for example, "was not a classic handover," Giljohann maintained. Although the Stamford, Conn.-based pharma gained an option on AST-005, "we're jointly working on that molecule, which allows us to contribute our expertise and history with it."

Options on the additional targets allow Purdue to "take a bet on the technology and watch it mature a little more," he added.

Exicure – the name is a mashup of Latin words meaning to cure outside the liver – now awaits several inflection points over the next months to a year, including ongoing dermatology studies and the first oncology data. The private round was sized to move the company through those milestones while "broadening the number of people who are paying attention" to it.

"We're still a small biotech company based in Chicago so we're off the beaten Boston and San Fran paths," Giljohann acknowledged.

But Exicure also holds a strong position in a field that's starting to gain genuine forward momentum.

"In general, this is an important moment in DNA and RNA therapies," Giljohann said, citing the recent phase III success by Alnylam Pharmaceuticals Inc. with its RNAi therapy patisiran in hereditary transthyretin-mediated amyloidosis and progress in the clinic addressing liver disease, spinal muscular atrophy and other challenging targets. (See *BioWorld Today*, Dec. 28, 2016, and Sept. 21, 2017.)

"A lot of work has gone into the antibody space, into understanding the biology," Giljohann pointed out. "On the other side, nucleic acids now have 20 or 30 years of history. Some people have figured out how they work and how to manufacture them, but they haven't been able to solve the delivery challenge. We think we're at a unique point in history where we have great biology pointing to the right targets for disease modification and great tools from the nucleic acid space. At Exicure, we have a technology that we think can bridge the two."