BioWorld™
The news source of record covering the development of innovative human therapies for 30 years

Clarivate™

June 18, 2024
Volume 35, No. 117
Special Reprint

Deals bring $3B+ for Ascidian, Belharra, Mabcare

By Karen Carey, Managing Editor

Following a day of deals that collectively bring a potential $3.75 billion into three biopharma companies – namely Ascidian Therapeutics Inc., Belharra Therapeutics Inc. and Mabcare Therapeutics – researchers will be busy discovering new therapies for neurological and immunological diseases, and advancing globally a candidate for solid tumors.

Privately held Ascidian joined with Roche Holding AG to discover and develop RNA exon editing neurology therapeutics for up to $1.84 billion, while Belharra, also privately held, partnered in an immunology small-molecule deal worth $700 million with Sanofi SA. Another large deal was completed by Mabcare, which out-licensed rights to cancer drug MTX-13 to Day One Biopharmaceuticals Inc. for up to $1.2 billion.

Ascidian's RNA exon editing

Daniel Rosan,chief financial and business officer, Ascidian

Michael Ehlers, president and CEO, Ascidian

Boston-based Ascidian is focused on rewriting RNA, editing RNA exons at the kilobase scale, to treat diseases not addressed by current gene editing technologies. The platform targets large genes with high mutational variance, but maintains native gene expression patterns and levels. The technology aims to provide the durability of gene therapy, while reducing risks that come from direct DNA editing and replacing genes.

Ascidian's worldwide deal with Roche, of Basel, Switzerland, to discover and develop RNA exon editing therapeutics for neurological diseases, includes $42 million in an up-front payment, as well as up to $1.8 billion in research, clinical and commercial milestone payments, plus royalties. Roche gains exclusive, target-specific rights to Ascidian's technology for undisclosed neurological targets. Ascidian retains rights to develop programs against other neurological targets, either internally or with another partner.

The deal is Ascidian's first major partnership.

"Ascidian's RNA exon editing approach edits thousands of RNA bases in vivo with a single therapeutic that fits in a single AAV [adeno-associated virus]; it defines a new class of RNA therapeutics," Daniel Rosan, Ascidian's chief financial and business officer, told *BioWorld*. "We know that Roche has invested in next-gen AAV capsids, and we think this has the potential to be a great fit for the RNA exon editing cargo that only we can provide. Together, Roche and Ascidian have the potential to expand the reach of RNA exon editing and develop first-in-class RNA exon editing medicines for multiple neurological diseases. In our view, Roche and Ascidian are ideal partners."

At the start, Ascidian will conduct discovery and certain preclinical activities, while Roche will be responsible for other preclinical activities, as well as further clinical development, manufacturing and commercialization.

"The deal includes multiple targets," Rosan said. "We are not discussing the specific number of targets or diseases at this point, but would note that our platform is designed to make kilobase-scale, RNA-level corrections to genes that we know are fundamental to disease."

Ascidian has a pipeline of discovery programs in retinal, neurological, neuromuscular and genetically defined diseases. Earlier this year, Ascidian received U.S. FDA IND clearance for ACDN-01, its lead RNA exon editing candidate, to enter the phase I/II Stellar clinical trial. ACDN-01 targets Stargardt disease and other *ABCA4* retinopathies. More than 900 mutations across the gene have been found to cause Stargardt, resulting in different protein expression and disease severity. Diseases caused by *ABCA4* loss of function are genetic disorders that can't be addressed by replacing the gene because of its large size, or by base editing because of the high mutational variance of the gene.

Ascidian launched in October 2022 with a $50 million series A financing from founder Apple Tree Partners. It raised another $40 million through a series A extension financing from Apple Tree in November 2023.

Michael Ehlers, Ascidian's president and CEO, who is also chief scientific officer and venture partner at Apple Tree, noted that current gene therapy and gene editing approaches to neurological conditions are challenged in that "many disease

Continues on next page

Continued from previous page

genes expressed in the central nervous system are under tight regulation where too much expression can have deleterious effects," adding that large disease genes cannot be packaged for in vivo delivery and most editing approaches require foreign enzymes.

"With Ascidian's technology, a single exon editing molecule can be used to replace multiple mutated exons simultaneously without any foreign enzyme through pre-mRNA trans-splicing," Ehlers said. "The resulting edited mRNA is expressed using the native gene expression circuitry of the cell, and can be packaged into a single AAV for in vivo delivery."

Belharra's chemoproteomics platform

San Diego-based Belharra, which also has a presence in San Mateo, Calif., joined with Paris-based Sanofi to advance discovery of novel small-molecule therapeutics for immunological diseases in a $700 million deal that includes $40 million in up-front and near-term milestone payments, with the rest related to research, development and commercial milestone payments. Belharra also is eligible for tiered royalties on net sales.

This is Belharra's second major deal this year.

In January, at the same time the company emerged from stealth and secured a $50 million series A from founding investor Versant Ventures, Belharra signed with Genentech, a unit of Roche, on a small-molecule drug discovery pact focused on oncology, immuno-oncology, autoimmune diseases and neurodegenerative diseases. The deal included an $80 million up-front payment and up to $2 billion in potential milestones.

Jeff Jonker, CEO, Belharra

"Belharra's business model is to have an equal mix of internal and partnered pipeline projects," Belharra CEO Jeff Jonker told *BioWorld*, adding that the company's "platform is only limited by disease biology that has yet to be treated effectively," making room for the company to develop internal products while partners work on other programs in an effort "to maximize and scale the broad potential of our platform."

Belharra focuses on next-generation chemoproteomics and seeks to transform small-molecule discovery by illuminating binding pockets on drug targets across the proteome.

The deal with Sanofi will leverage Belharra's non-covalent chemoproteomics platform to screen and validate hits against undisclosed immunology targets.

"We're not disclosing specifics on the targets, but we're very excited about the immunological disease-driving targets that Sanofi has selected. They are grounded in well-validated biology and the discovery of novel therapeutics against these targets could address significant unmet needs," Jonker said. "Genentech, Sanofi and Belharra are all working on separate targets that are strategic fits for their respective disease strategies."

John Bertin, Sanofi's global head of immunology and inflammation research, said the immunology targets have all been considered undruggable. Of about 5,000 proteins involved in human disease, small molecules have successfully targeted only about 600 of them, according to Belharra.

Belharra's platform consists of a computationally designed library of non-covalent drug-like molecules that use photoaffinity chemistry to find the proteins that bind the molecules, as well as their binding location. This leads to the discovery of novel drug targets and of new drugs for elusive protein targets.

"With the ability to illuminate any pocket, on any protein, in any cell type, our non-covalent drug discovery platform enables perhaps the broadest and most unbiased chemoproteomic screening capabilities in the industry," Jonker said. "We expect to increasingly be a partner of choice" for innovative companies trying to access challenging targets.

In its early stage pipeline, Belharra has several small-molecule drug candidates for targets in oncology and immunology. Its ligand library has successfully targeted different protein classes, including transcription factors, channels, transporters, receptors, chaperones and others.

Day One takes on Mabcare's MTX-13

Brisbane, Calif.-based Day One gained an exclusive license to develop and commercialize MTX-13 for solid tumors through an agreement with Shanghai-based Mabcare, a little-known company that first appeared in publications about a year ago. Through the deal, Mabcare gets $55 million up front and is eligible for $1.152 billion in development, regulatory and commercial milestones, plus low-to-mid single-digit royalties.

The product, which will be called DAY-301 going forward, received IND clearance by the U.S. FDA in April. It is an antibody-drug conjugate that targets protein-tyrosine kinase 7 (PTK7), a highly-conserved, catalytically inactive transmembrane protein that is highly expressed in multiple adult cancers, such as esophageal, ovarian, lung and endometrial cancer, as well as pediatric cancers, such as neuroblastoma, rhabdomyosarcoma and osteosarcoma. PTK7 also has limited expression in normal tissues or organs.

According to Samuel Blackman, co-founder and head of R&D at Day One, DAY-301 is a good addition that fits with the company's mission. "We believe the linker-payload technology embodied in DAY-301 will overcome the limitations of earlier PTK7-targeted ADCs, giving us a potential first-in-class drug against a clinically validated target."

Continues on next page

Continued from previous page

The company expects to dose the first patient in a phase I trial in either the fourth quarter of 2024 or the first quarter of 2025. Day One gains exclusive rights to develop, manufacture and commercialize DAY-301 worldwide, except for greater China, where Mabcare retains rights.

In April, Day One received U.S. FDA approval of its first product, Ojemda (tovorafenib), as the first type II RAF inhibitor for relapsed or refractory BRAF-altered pediatric low-grade glioma (pLGG), earning the company a rare pediatric disease priority review voucher. Also in the pipeline is MEK inhibitor pimasertib for MAPK-altered solid tumors to be used in combination with Ojemda. It is part of the phase I Firelight-1 trial. Ojemda is also in phase III development (Firefly-2) for RAF-altered pLGG.

Day One's stock (NASDAQ:DAWN) closed at $13.39, up 11%, on June 18.