BIOCENTURY

EMERGING COMPANY PROFILE | REPRINT FROM OCT. 12, 2022

Ascidian: correcting mutations via trans-splicing to edit RNA exons

BY PAUL BONANOS, ASSOCIATE EDITOR

BIOCENTURY & GETTY IMAGES

Launched by ATP with $50 million, Ascidian believes its RNA trans-splicing technique will provide the capability to correct genetic mutations by mimicking a naturally occurring process, offering a safety advantage and greater therapeutic reach than other gene therapy and gene editing approaches.

Ascidian Therapeutics Inc. is developing RNA exon-editing molecules that can replace mutations with wild-type genetic material at the pre-mRNA stage. The approach is designed to produce durable results akin to most gene therapies, but the company believes it can address a wider variety of genes and mutations without using exogenous enzymes that can pose risks.

President and CEO Romesh Subramanian told BioCentury that the technique represents a differentiated category of therapeutics, providing a way to edit multiple exons at once without disrupting the genome, and without using foreign enzymes to avoid unwanted immunological effects that can occur with some gene editing approaches.

The molecules can also be delivered via viral or non-viral vehicles, including lipid nanoparticles, which may permit Ascidian to correct large genes that couldn't be carried in smaller vectors.

The company's RNA exon editors are synthetic molecules that include a functional coding sequence meant to replace the patient's mutated exons, plus linking and binding domains. Upon delivery to pre-mRNA, the functional exons are swapped into the transcript and joined with the patient's normal exons in a process known as trans-splicing. Once introns are removed, the mature, corrected mRNA is translated into protein.

Until about two decades ago, trans-splicing had been observed only in small organisms. A 2001 paper in Genes & Development described the process as it occurred in a chordate, Ciona intestinalis, also known as a sea squirt or an ascidian.

Apple Tree Partners (ATP) CSO and venture partner Michael Ehlers told BioCentury that although researchers had sought for decades to use trans-splicing to edit genetic material for therapeutic benefit, the tools weren't available to do it successfully. He pointed to advances across several fields — high-throughput molecular biology, DNA barcoding, next-

generation sequencing, computational design and RNA biology — that have enabled Ascidian to attain better results.

He said the firm, the sole investor in Ascidian's series A round, was able to build much of the start-up's platform in-house, though it in-licensed some IP from the University of Pennsylvania.

Ascidian will first attempt to show clinical proof of concept via its lead program addressing the ABCA4 gene to treat retinopathies, including Stargardt disease. Ascidian has already presented non-human primate data showing that sub-retinal administration of the therapy led to full-length ABCA4 expression. It intends to complete IND-enabling work and begin a first-in-human trial. Subramanian declined to give a timeline, but said the start-up is working with regulators to start clinical work as soon as possible.

Ehlers said the ocular setting represented a "perfect use case" for Ascidian's technology, offering advantages via the eye's small and localized tissue. The ABCA4-related retinopathies are associated with a gene too large for standard adeno-associated viral vectors, with high mutational variance and an unmet need.

Subramanian said Ascidian's pipeline will also include programs for CNS and neuromuscular indications, and the platform's broad applicability will open the door to multiple indications.

Subramanian was most recently CEO and CSO at Dyne Therapeutics Inc., which he co-founded as an entrepreneur-in-residence at Atlas Venture. He has also been an employee at Alexion Pharmaceuticals Inc., Pfizer Inc. (NYSE:PFE) and RaNA Therapeutics Inc., which changed its name to Translate Bio Inc. before Sanofi (Euronext:SAN; NASDAQ:SNY) acquired it in September 2021.

Ehlers was EVP of R&D at Biogen Inc. (NASDAQ:BIIB). He was Ascidian's founding CEO and became chairman upon Subramanian's arrival. He is also CEO of ATP portfolio company Intergalactic Therapeutics Inc., which is developing non-viral gene therapies that use covalently closed and circular DNA (C3DNA).

Although Subramanian declined to discuss Ascidian's current business development activities in detail, he said the company's financial strategy will include "a combination of equity and partnerships."

COMPANY PROFILE
ASCIDIAN THERAPEUTICS INC.
Boston, Mass.

Technology: RNA exon editing
Origin of technology: In-house, University of Pennsylvania
Disease focus: Ophthalmology, neurology, musculoskeletal
Clinical status: Preclinical
Founded: 2020 by Apple Tree Partners
Academic collaborators: None
Corporate partners: None
Number of employees: 30
Funds raised: $50 million
Investors: ATP
CEO: Romesh Subramanian
Patents: Undisclosed

BIOCENTURY

BIOCENTURY INC.

BioCentury's mission is to provide value-added business intelligence & analysis for life science companies, investors, academia and government on the strategic issues essential to the formation, development and sustainability of life science ventures.

NEWSROOM
news@biocentury.com

SAN CARLOS, CA
+1 650-595-5333; Fax: +1 650-595-5589

CHICAGO
+1 312-755-0798; Fax: +1 650-595-5589

WASHINGTON, DC
+1 202-462-9582; Fax: +1 202-667-2922

UNITED KINGDOM
+44 (0)1865-512184; Fax: +1 650-595-5589