Category

Best Startup

Product/Solution Name

Rewriting RNA by RNA Exon Editing

Date of Approval

N/A

Indications

We are a pre-clinical biotech start-up, with no currently approved indications. We have active discovery and preclinical programs in retinal, neurological, neuromuscular, and genetically defined diseases

Therapeutic Categories

Genetically Defined Diseases

Attached Files:

- Ascidian Prix Gallien Award Submission FINAL 53023.docx
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Background information and need for solution/product

Ascidian Therapeutics engineers RNA Exon Editors that replace whole exons in vivo, thereby rewriting RNA in patients with genetically defined diseases while overcoming limitations of current gene therapy and gene editor technologies. Ascidian's first-of-its-kind platform removes and replaces multiple whole exons simultaneously in a single reaction, without any DNA edits and without the use of any foreign enzymes.

Our differentiated RNA editing approach provides the durability and benefits of gene therapy because it is delivered as a one-time therapy in vivo. By replacing whole exons, Ascidian's RNA Exon Editors can address hundreds of different mutations within a particular target with a single therapeutic agent, so we can address the therapeutic needs of more patients, across more diseases, with less risk than competing approaches.

Compared to gene or base editing, RNA Exon Editor advantages include:
1. Edits RNA, not DNA: Reduces risks associated with genomic modifications.
2. Edits multiple whole exons, not just single bases: Precisely corrects multiple whole exons, which can address more mutations for more patients than current gene editing or base editing approaches.
3. No exogenous/foreign enzymes: Does not require foreign enzymes (e.g., bacterial enzymes), which can pose immunological risks or require delivery with dual AAV vectors.
4. Maintains native gene expression: Ensures target gene expression is precisely controlled by the cell.
5. Agnostic to delivery vehicle: Overcomes packaging capacity limitations of delivery vectors such as AAV, and can be used with multiple, clinically validated delivery vehicles – viral and non-viral – tailored appropriately for each program; delivered as a single construct.

Ascidian was founded by renowned neuroscientist Michael Ehlers, M.D., Ph.D. Serial entrepreneur and RNA researcher Romesh Subramanian, Ph.D., joined as President and CEO when Ascidian publicly launched in 2022. Over the past two years, Ascidian scientists have propelled RNA exon editing technology forward, with the lead program demonstrating in vivo exon editing in non-human primates and multiple other programs across diverse genes and cell types demonstrating efficient RNA exon editing.

History of the development of the solution/product

In Ascidian's labs, RNA biology meets today's cutting-edge genomics, computational biology, and deep-sequencing technologies to create a new class of medicines that address the underlying causes of disease.
Ascidians – also known as sea squirts – are ocean creatures and primordial ancestors of vertebrates. To grow from larvae to adults, ascidians re-engineer their transcriptome through RNA trans-splicing and alternative splicing. Inspired by its namesake, Ascidian Therapeutics has engineered RNA Exon Editors that harness the cell's endogenous machinery to edit and replace human exons without the need for foreign enzymes.
Our lead program targets ABCA4-related retinopathies, including Stargardt disease, and is currently in IND-enabling studies. ABCA4 loss of function causes loss of central vision – robbing patients of the ability to drive, read or focus on the faces of loved ones. More patients go blind from ABCA4 retinopathy than any other genetic cause. Stargardt cannot be addressed by standard gene replacement given the large size of the gene, or by base editing due to the high mutational variance of the affected gene. By rewriting ABCA4 RNA, Ascidian's approach has the potential to treat a majority of patients with ABCA4-related retinopathies with one dose of an RNA exon editing therapeutic delivered with a single AAV vector.

To date, we've demonstrated ABCA4 RNA exon editing in multiple model systems, including a cell line carrying ABCA4 mutations, human retinal explants, and non-human primates at time points extending to six months. The latest six-month data from non-human primates demonstrate the production of full-length ABCA4 protein, effectively replacing 30% of the endogenous ABCA4 protein, as measured by a first-of-its-kind quantitative assay developed by Ascidian Therapeutics. This is the first report quantifying therapeutically relevant levels of ABCA4 protein resulting from trans-splicing, and the most efficient and durable RNA exon editing via trans-splicing ever demonstrated in large animals. The therapeutic threshold in Stargardt is approximately 10%, as determined by multiple labs using ABCA4 knockout mice. We have exceeded this threshold in a large animal at six months and replicated the data in human retinal explants – robust translational predictions for what we expect to achieve in patients.

Why this solution/product is innovative, the broad implications for future research, and/or how it will improve the human condition

Treating the underlying cause of disease by replacing entire mutant exons via rewriting RNA is now in reach. Ascidian scientists have achieved the goal of developing RNA exon editing therapeutics with evidence-based potential to redefine the treatment of human disease by addressing the underlying cause of disease.
As we move our lead program toward the clinic, we are also progressing a diversified pipeline of programs using our proprietary platform for rewriting RNA by exon editing in other retinal diseases, as well as in neurological, neuromuscular, and other genetically defined diseases.

Ascidian is currently focused on using its platform to replace mutant exons with wild-type exons, enabling cells to tune their own precise protein expression in order to treat disease in patients with few or no treatment options. But the potential of the Ascidian approach goes much further.
Editing large stretches of RNA offers the potential to regulate the transcriptome even more dramatically. For example, hypermorph sequences could be edited into RNA to protect patients at risk for serious diseases and feedback loops could be engineered to short circuit inflammatory pathways.
According to Mariano Garcia-Blanco, M.D., Ph.D., who performed the earliest foundational work in RNA trans-splicing, “When we first began to elucidate RNA trans-splicing in the 1990s, my hope was such research would be taken forward to help patients with intractable genetic diseases. Ascidian is bringing that vision to fruition – and with efficiencies even more than I dared to imagine. I’m optimistic about Ascidian's potential to translate decades of effort in the lab into meaningful treatments in the clinic. Doing so could bring the RNA therapeutics revolution to the treatment of many more human diseases."
The potential and breadth of RNA exon editing is vast – and it holds promise to impact some of today’s most complex and devastating diseases. We are extremely excited about the platform and its potential to deliver a safer, more powerful and versatile approach that could transform the health and well-being of people around the world.

Please provide appropriate references (ie Pubmed links)

Scientific posters and presentations are attached for your reference.

Attached Files:

- Ascidian ASGCT 2023.pdf
- ARVO23 Poster Final.pdf
- Doi 2022 ESGCT.pdf
- Gray 2022 GRC.pdf
- Burkhart 2022 ASGCT.pdf
- Bell 2022 ASGCT.pdf
- Krumbach 2022 ASGCT.pdf