4th RNA Editing Summit 2023

Speaker Interview

July 11-13, 2023 | Boston, MA

At the **4th RNA Editing Summit**, we are delighted to partner with **Wave Life Sciences** as we tackle the challenge of developing RNA editing that is both safe and effective. Wave is providing us with exclusive insights on their position in the RNA editing field, and offering valuable input into the hurdles and opportunities that will be explored during the summit to optimize RNA editing technology and progress the field.

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Why is RNA editing such an area of current interest?

Leveraging ADAR enzymes for RNA editing was first published on in the 1990s, however, it's optimization as a modality took a backseat as DNA editing approaches gained momentum. Flash forward, as DNA editing approaches have started to enter the clinic, they have revealed challenges, such as delivery and concerns on the impact of permanent, off-target genome editing. Meanwhile, innovation in RNA medicines has made it possible to safely deliver oligonucleotides to numerous cell types and have durable effects with extended dosing intervals, without permanent modification of DNA. We also have demonstrated that Wave's RNA editing oligonucleotides ("AIMers") are highly specific and that we see no bystander editing. So RNA editing offers benefits to patients in scalability, delivery, safety and titratability without sacrificing potency and durability.

RNA editing also provides the opportunity to address diseases in novel ways and which are not accessible to other modalities. For example, Wave is pioneering novel downstream applications of RNA editing, including upregulation of mRNA to restore or enhancing protein function. The majority of human disease targets relate to conditions where a protein is in suboptimal supply, which requires restoration of function versus a knockdown approach. So this application has potential to significantly expand the number of conditions and the number of patients that may be treated with RNA editing.

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What are the potential clinical and therapeutic implications of RNA editing?

RNA editing has potential to slow, stop, or reverse disease progression. Take our WVE-006 program for example – this is the industry's first RNA editing development candidate and is being developed by Wave to treat alpha-1 antitrypsin deficiency. At the RNA Editing Summit, we'll share data demonstrating that mice treated with WVE-006 showed improvement in several markers of liver disease and that restored, wild-type AAT was able to reach the lungs to protect from proteases. Beyond WVE-006, we are expanding our pipeline of AIMer candidates and see potential for this modality in diseases of the liver, central nervous system, kidneys and beyond.

We are also excited about upregulation with AIMers, which one should think of as our approach to endogenous mRNA delivery. Rather than giving exogenous mRNA therapies, we can increase the expression of mRNA inside the cell using our AIMers. This means that rather than correcting each of the mutations associated with a genetic disease one-by-one, we see opportunities to significantly increase the total addressable market by restoring healthy levels of proteins independent of mutations. The potential of this approach is extraordinary. Additionally, upregulation with AIMers could be used in diseases with large patient populations, like metabolic disorders.

What are the biggest scientific bottlenecks holding back the development of RNA editing?

We don't see scientific bottlenecks holding back the development of RNA editing – in fact, at Wave we have been able to rapidly advance our AATD program from discovery research in vitro to delivering the first-ever RNA editing clinical candidate. We benefitted from being

able to apply Wave's best-in-class, proprietary chemistry, including chiral control and PN modifications, as well as clinical and preclinical learnings from our other oligonucleotide modalities, to rapidly advance our RNA editing capability. We also are using GalNAc conjugation – a validated ligand for delivery to the liver – for WVE-006 and in our ongoing discovery work as we build additional hepatic programs.


For RNA editing therapeutics, we can also leverage established regulatory and commercial pathways for oligonucleotides. So as we look toward bringing WVE-006 and other future programs into the clinic, we expect they will follow well-trodden paths for development, approval and commercialization.

In your opinion, what have been the most exciting breakthroughs so far in the RNA editing space?


Several come to mind. First, in 1995, Tod Woolf and his colleagues at Ribozyme Pharmaceuticals became the first to publish on using antisense oligonucleotides to recruit ADAR enzymes and elicit RNA editing in vitro, and Dr. Woolf continues to be credited with first demonstrating the principle of therapeutic RNA editing. In 2012 and 2013, several researchers including Drs. Joshua Rosenthal and Thortsen Stafforst published on different mechanisms of connecting guide RNAs to ADAR. Another significant step forward came in 2022, when Wave became the first to publish on the achievement of RNA editing with endogenous ADAR in non-human primates (NHPs). This was a key milestone that demonstrated translation from cells and mice to NHPs, as well as the ability of Wave's AIMers to achieve robust, durable editing.

As we look to the year ahead, another breakthrough for the field will be when we initiate clinical development of WVE-006, which is expected in the second half of 2023. This would make WVE-006 the first RNA editing therapeutic to ever be evaluated in humans, and demonstration of proof-of-concept in the clinic would validate this new modality for the field and hopefully accelerate research overall.

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Can you elaborate on Wave Life Science's approach to RNA editing?


Wave's AIMers are designed to change single bases on an RNA transcript, which avoids permanent changes to the genome that occur with DNA-targeting approaches. Rather than using an exogenous editing enzyme like CRISPR-Cas9, AIMers recruit ADAR enzymes, which are already present in our cells and naturally edit certain adenine (A) bases to inosine (I). Because I is read as G (guanine) by the cellular translational machinery, sequence-directed editing with ADAR has the potential to revert transcripts with single G-to-A point mutations that cause genetic diseases. This is the approach we are using with our WVE-006 program. Changing single A-to-I bases can also be used for our downstream applications – like upregulation and modulation of protein-protein interactions – to increase endogenous protein levels.

This approach redirects a natural system for therapeutic purposes, enables simplified delivery without viral particles or liposomes, and avoids the risk of irreversible off-target effects of DNA-targeting approaches. AIMers are short in length, fully chemically modified, and use our best-in-class chemistry and platform learnings, which makes them distinct from other ADAR-mediated editing approaches.

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In 2023, Wave Life Sciences is poised to deliver the first RNA editing candidate to the clinic. You will be speaking on that at the 4th RNA Editing Summit, but can you give us a glimpse of the current status of the program?


WVE-006 is on track to become the first investigational RNA editing therapeutic to enter clinical development. WVE-006 is uniquely designed to address both lung and liver manifestations of AATD, with the opportunity for reversibility and a favorable safety profile. There is a major unmet need in AATD, as current therapies are largely confined to treating either pulmonary, or, in the future, hepatic manifestations of disease. We have successfully completed the in-life portion of GLP toxicology studies as planned for WVE-006 and, we are rapidly advancing towards CTA submissions this year. This milestone will be an exciting moment not just for Wave, but for the entire nucleic acids field.


Another exciting milestone for WVE-006 was the announcement of our collaboration with GSK in December 2022. As part of the collaboration, GSK received the global license for WVE-006 and the program will transition to GSK after we complete the proof-of-concept study in AATD patients. GSK is a leader in respiratory outcomes studies and global clinical development, which will be important for delivering this potentially transformative medicine to patients.

Why are you partnering with the RNA Editing Summit?

We've attended the RNA Editing Summit since 2020 and have been inspired by the opportunity to come together with colleagues at other companies and discuss how we can work together to move RNA editing forward. Hanson Wade has been ahead of the curve in offering the RNA Editing Summit, as it remains the only RNA editing-specific conference that is open to all who wish to join. The agenda this year reflects how this space continues to evolve, with established RNA editing companies and a number of new companies attending. We're thrilled to partner with the RNA Editing Summit and are looking forward to attending again in 2023.

What are you most excited to learn about and takeaway from the 4th RNA Editing Summit?

We're looking forward to seeing the progress that our colleagues have made in the year since we last came together at the 3rd RNA Editing Summit. We are also interested in and are advancing the integration of machine learning to enable target discovery. Identifying new targets or novel insights about targets is of interest to Wave and was one of the driving factors for our GSK collaboration, which also includes a discovery research component where we are combining our platform capabilities – including RNA editing – with GSK's insights on genetics and genomics. We're tracking closely on this area so that we can continue pushing into new areas of biology with RNA editing and tackling diseases with limited therapeutic options.

We are looking forward to your participation at the 4th RNA Editing Summit. Can you give us a sneak peak of the 3 key learnings that attendees will walk away with that will support their pipelines?

Our presentations and panels will cover a variety of topics that underscore the enormous opportunity for RNA editing to change the lives of patients. Prashant will share an overview of our WVE-006 program and how we've designed a therapeutic approach that addresses all goals of treatment in AATD. Ian will speak about our rapidly advancing capabilities for increasing or enhancing the function of proteins, which allows us to think about applications in diseases with both large and small populations. I'll be joining a panel focused on clinical, regulatory, and commercial considerations as RNA editing therapeutics move out of the lab and start to reach patients. We're hopeful that our insights will be helpful to others in their discovery and development efforts. We look forward to seeing you all there!

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