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5th Annual RNA Editing Summit

Pioneering RNA Editing Drugs towards Clinical Realities

Exclusive Speaker Interview

At the **5th RNA Editing Summit**, we are delighted to be partnering with **Wave Life Sciences**. During an exclusive interview, we were able to hear insights into their latest work and why they are excited to be joining the meeting again in 2024.

Ginnie Yang, PhD
Senior Vice President, Translational Medicine
Wave Life Sciences

Cynthia Caracta, MD
Executive Medical Director
Wave Life Sciences

Kenneth Longo, PhD
Vice President, Data Science
Wave Life Sciences

There are currently a lot of new companies entering the RNA editing field as well as new interest within this field. Where specifically does your interest for this space come from?

Ginnie: RNA editing was a natural extension of our PRISM discovery and drug development platform, and we are at an advantage relative to others as Wave has been leading the science of next-generation oligonucleotide design for more than a decade. Our platform combines multiple RNA-targeting modalities and chemistry innovation to efficiently engage biological machinery that already exists in our cells and can be harnessed for therapeutic purposes – such as ADAR enzymes for editing. Using our proprietary chemistry, we were able to effectively recruit endogenous ADAR enzymes and achieve potent and durable editing in preclinical studies. We rapidly translated this into potent, durable editing in a variety of tissues and cells, including with GalNAc in the liver and through free uptake outside the liver. Importantly, we have been able to achieve high levels of editing across cells without lipid nanoparticles (LNPs) or other complex delivery vehicles. Bringing RNA editing into our toolkit of RNA-targeting modalities opened up new areas of disease biology for Wave to pursue.

Cynthia: Our multimodal platform enables us to select the optimal tool for each therapeutic indication and AATD is an excellent example. This is a disease with two impacted organs – the liver and the lung – yet the majority of approved or investigational programs would only address one. With RNA editing, we can correct the underlying "Z" mRNA mutation to replace the mutant "Z-AAT" with healthy "M" AAT protein, thereby reducing Z-AAT protein aggregation in the liver. This healthy M-AAT would then travel to the lungs through the bloodstream and serve to protect from proteases. The corrected, endogenous M-AAT protein retains physiological regulation, which is not possible with protein replacement or gene replacement strategies. Importantly, RNA editing is highly specific with no evidence of bystander edits, which have been seen with DNA base editing approaches.

Ginnie: RNA editing in AATD is an example of mRNA "correction," but we also are pioneering mRNA "upregulation." This approach is designed to stabilize mRNA transcripts that otherwise would have been degraded, thereby increasing endogenous protein levels. As we look at the universe of genetic mutations driving disease, the majority of these mutations lead to loss of protein function, meaning they can't be addressed with silencing tools such as RNA interference or antisense. A novel mRNA upregulation approach has huge opportunity, including in diseases with prevalent patient populations. For example, we shared at our 2023 R&D Day that we are working on multiple upregulation targets in hepatic diseases with patient populations into the millions.

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We are now more than ever seeing lots of success within this field with yourselves moving into the clinic as well as Ascidian Therapeutics. However, what do you see as the greatest bottleneck which remains for getting RNA editing therapeutics to those patients in need?

Ken: A key challenge for the genetic medicines field broadly is that technologies have advanced more rapidly than the universe of available targets. At Wave, we are working to overcome this by investing in machine learning, artificial intelligence, and large genetic datasets. At our R&D Day in 2023, we debuted the "Edit-verse," which leverages genetic datasets to gain insights into the editable gene-disease network, and proprietary deep learning models to identify new RNA editing targets and edit sites. With these tools, we will be able to advance first-in-class treatments that address diseases in new ways.

Ginnie: Additionally, delivery has been a challenge for this field, resulting in the use of LNPs or other complex delivery vehicles. We have solved for this differently by using proprietary chemistry modifications, like PN backbone chemistry, to enable our first clinical candidate, WVE-006,

and our other RNA editing programs to efficiently recruit ADAR enzymes and achieve high editing levels. WVE-006 and our other liver targets contain a GalNAc-conjugate – a highly specific and elegant delivery tool that is well-validated with multiple approved silencing therapeutics on the market. GalNAc enables the ease and convenience of subcutaneous dosing and effective and selective delivery to hepatocytes. It also offers a high degree of confidence of preclinical to clinical translation for WVE-006 and our other liver programs, since the entire dose is delivered reliably to the target organ.

In the past few months, we have continued to see exciting developments within the RNA editing field, recently, we heard about Stanford researchers discovering a new RNA-targeting CRISPR platform which can be used to improve existing cell therapies for cancer. What would you say have been the most exciting?

Cynthia: The most exciting advancement was Wave initiating the world's first RNA editing clinical program, which is for WVE-006. WVE-006 is our GalNAc-conjugated, subcutaneously delivered, RNA editing oligonucleotide that is uniquely designed to address AATD-related lung disease, liver disease, or both. Preclinically, we've shown AAT protein levels that exceed the thresholds for both the MZ and healthy MM populations, and we confirmed the functionality of this protein with the neutrophil elastase inhibition assay. Additionally, we saw decreases of lobular inflammation and reduction of liver aggregates. WVE-006 also prevented an increase in mitoses – or turnover – of hepatocytes, indicating improved hepatocyte survival.

Our RestorAATion clinical program is evaluating WVE-006 for AATD and includes healthy volunteers (RestorAATion-1), as well as patients who have the homozygous Pi*ZZ mutation (RestorAATion-2). It is designed to provide an efficient path to proof-of-mechanism as measured by restoration of wild-type alpha-1 antitrypsin (M-AAT) protein in serum. Our progress in dose-escalating healthy volunteers in RestorAAtion-1 enabled the quick identification of a starting dose level in RestorAATion-2 that, based on preclinical data, is expected to engage target in patients. With RestorAATion-2 now underway, we are on track to deliver expected proof-of-mechanism data in patients with AATD this year, which would represent the first-ever clinical demonstration of RNA editing and would be an important milestone for the alpha-1 community.

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With the above in mind, where do you expect to see the next breakthroughs happening in 2024/25?

Ginnie: We are in an exciting place to deliver expected proof-of-mechanism data in AATD patients in 2024. Beyond being a big moment for the field, these data would serve as proof-of-concept for our pipeline of wholly owned editing candidates. As shared in our 2023 R&D Day, we have used our proprietary Edit-verse to identify several new mRNA correction and upregulation targets, which leverage easily accessible biomarkers, offer efficient paths to proof-of-concept in humans, and represent areas of high unmet need and meaningful commercial opportunities. We plan to share new preclinical data for our advancing RNA editing programs in 2024.

What is Wave Life Sciences most looking forward to at the 5th RNA Editing Summit and why do you think it is important this event takes place?

Ginnie: The RNA Editing Summit is a great opportunity to share our latest research and insights as the first company to enter the clinic and a company pioneering new applications of RNA editing, as well as connect with attendees and hear about their latest research. This remains the only purely RNA editing-focused conference to our knowledge, so it is an important forum for this rapidly expanding field.

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As a leading company within the RNA editing community, what insights will you be sharing with our audience at the 5th RNA Editing Summit this June?

Cynthia: At Wave, I lead the WVE-006 clinical program, so I will be presenting on our preclinical data that support WVE-006 as best-in-class for AATD and will also provide an overview of the RestorAATion clinical program evaluating WVE-006.

Ken: Ginnie and I will be giving a combined talk that speaks to how we are mapping and leveraging the Edit-verse, as well as providing an overview of targets that Wave is evaluating to build a pipeline of high-impact RNA editing programs.