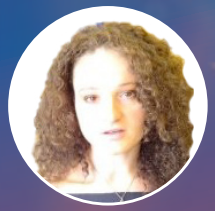
An Exclusive Interview With...

Paul Bolno
President & Chief Executive Officer



Paloma Giangrande
Vice President, Platform Discovery Sciences Biology

Wave Life Sciences (Nasdaq: WVE) is a clinical-stage genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases. Wave aspires to develop best-in-class medicines across multiple therapeutic modalities using PRISM, the company's proprietary discovery and drug development platform that enables the precise design, optimization, and production of stereopure oligonucleotides. Driven by a resolute sense of urgency, the Wave team is targeting a broad range of genetically defined diseases so that patients and families may realize a brighter future

www.wavelifesciences.com

3rd RNA Editing Summit 2022

Boston | April 5-7

Why is RNA editing such an area of current interest?

Paloma:

Over the past 10 years it has been recognised that DNA-based editing approaches present with many different challenges, including their general inability to re-administer, the potential for permanent and undesired off-target effects, and various manufacturing challenges. So, we saw an opportunity with an RNA editing approach to instead target the transcriptome and recruit editing proteins that already exist in the body, called ADAR enzymes, which naturally edit certain adenine (A) bases to inosine (I), which cells read as guanine (G). We are doing this with short, fully chemically modified oligonucleotides which use a simplified mode of delivery to the liver - the well understood GalNAc ligand. In this way, we are avoiding complex delivery vehicles like AAV or LNPs, which were for us a real drawback. By avoiding these vehicles, we have also demonstrated that we can remove GalNAc and deliver editing outside the liver. This gave us an opportunity to move an efficient base editing approach forward that's different from DNA-based approaches.

Paul:

While there has been a fascination with permanently editing the genome, one must recognize that there is a reason nature keeps DNA intact. A permanent change to a person's genome, particularly the risk of off-target editing, can have permanent deleterious effects.

Innovation in RNA therapeutics has created an opportunity for durable effects, infrequent dosing, and the opportunity re-dose when required. So, you don't need to manipulate DNA, and can stay focused on the RNA. At the end of the day you are still fixing where the problem is, which is the beauty of RNA base editing.

Additionally the ability to target single bases enables us to pursue diseases with different therapeutic goals, such as protein upregulation, restoration of wild-type protein, among other areas of biology.

How did you come to start focusing on RNA editing?

Paul:

We founded Wave on the principle of bringing rational drug design to the field of nucleic acids. As we thought about what's required in order to optimize RNA therapeutics, it was clear that one needed the capability to control the structural features of an oligonucleotide to provide the resolution necessary for designing and optimizing single drugs. The not only included controlling the stereochemistry of the oligonucleotide, but inventing new backbone modifications like our PN chemistry, that allowed for increases in potency, durability and nuclear trafficking.

The other component of our foundational scientific approach was a focus on engaging endogenous machinery with highly specific, rationally designed oligonucleotides. We improved the ability to engage RNase H and AGO2 for silencing, and splicing machinery for exon skipping. But to reach new target space and pursue a correction approach, we had to find a different enzyme. This is where ADAR came in, and it led to the creation of AIMers - our Ato-I RNA base editing oligonucleotides.."

Paloma:

This work began because one of our scientists recognized the potential of using our platform for doing therapeutic RNA editing. Over the next couple years, he and his team set out to generate both in-vitro and in vivo proof-of-concept, and they were the first in the field to successfully demonstrate RNA editing with ADAR in NHPs, which was recently published in Nature Biotechnology. This work really does stem from the ability of our PRISM platform to discover and develop much needed genetic oligonucleotide-based tools for treating many different diseases. We continue to set the bar high for the editing field in general. This is really a testament to how unique our platform is and the creativity of the entire Wave team.

How do AIMers differ to other RNA editing approaches?

Paloma:

Our AIMer technology was built from the ground up by our team. These are relatively short oligonucleotides, about 30 nucleotides or so. And they are fully chemically modified with our unique and proprietary chemistry, including novel PN backbone chemistry modifications that lead to increased potency, distribution, and durability preclinically, compared with oligonucleotides that only use PS/PO linkages. Today we've demonstrated in multiple pre-clinical studies that, unlike others in the field, we do not need complex delivery vehicles. This simplifies our approach and we have presented a lot of data showing that we can edit in many different cell types as well as deliver our AIMers to various tissues, including delivery to the CNS, kidney, and lung.

We demonstrated using transcriptomewide analysis that our AIMers are highly specific. The strong evidence or proof of the uniqueness of our platform is the massive amount of data that we generated and shared publicly, showing that our AIMers are potent and durable and they can be applied across many different types of diseases.

What is the opportunity of AIMers in the broader editing field?

Paul:

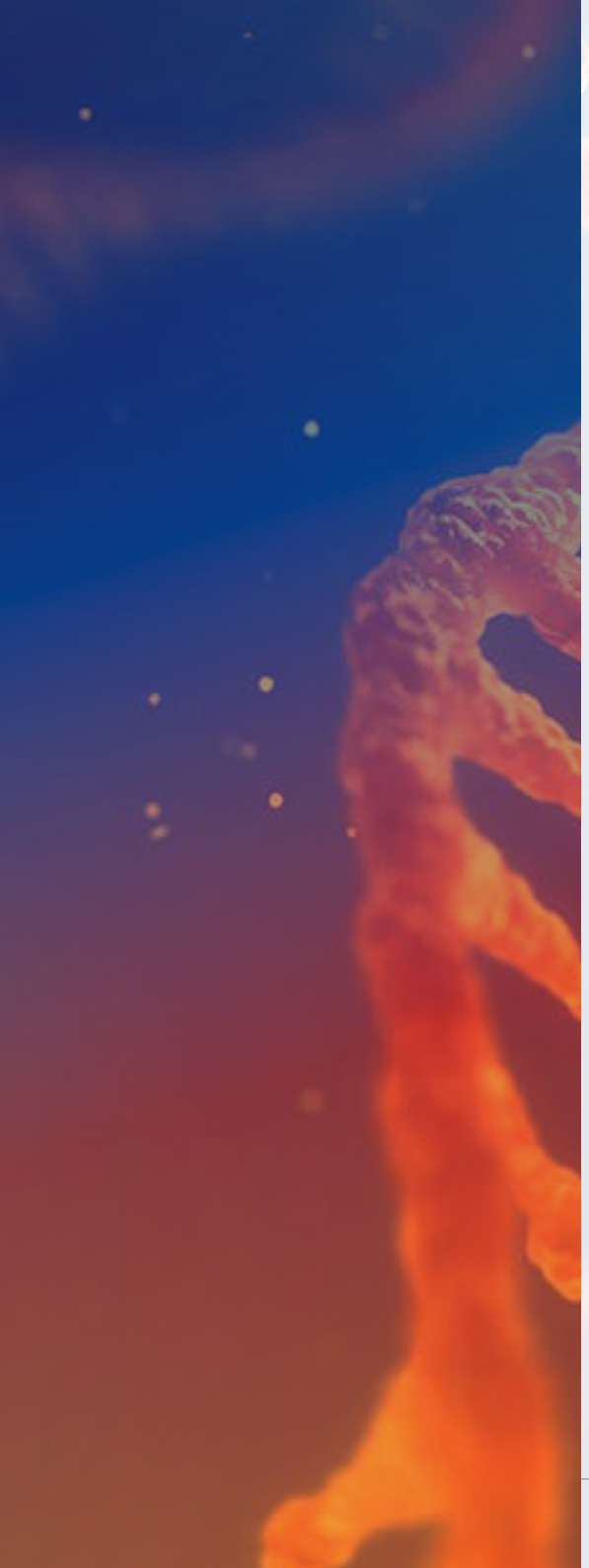
While correction of an underlying RNA mutation is the likely initial use for AIMers and RNA base editing, what's really exciting is how this new modality may address other areas of disease biology. There are a lot of opportunities to innovate on the biology side and address larger indications.

The RNA editing opportunity is believed to be quite broad, and we are just starting to understand the scope of diseases we may be able to address. We are initially focusing on the prospect of addressing genetically defined diseases, such as alpha-1 antitrypsin deficiency (AATD) where we already have generated preclinical proof-of-concept. But in the future, we expect to push new boundaries as we bring this tool forward. That's why meetings like the RNA

Editing Summit are so important - they connect people who are approaching editing from different fields of biology, tools and chemistry, giving us an opportunity to elevate the discussion in this quickly evolving field.

WAVE LIFE SCIENCES

Join Wave Life Sciences at the 3rd RNA Editing Summit in Boston, MA on April 5-7, 2022



What is the current status of the AATD AIMer program?

Paloma:

One thing to comment on before going into the status of our first AIMer program is how our approach differs from other approaches for AATD. Our AIMer editing approach addresses all the therapeutic needs for this disease with one molecule. By correcting the underlying genetic driver of the disease we are not only fixing the liver disease by creating or restoring the wild-type M-AAT protein in the liver itself, we are also fixing the lung disease by the secretion of this wild type, functional protein in the serum, thus benefiting both the liver and the lung.

So this is a really unique approach that can do both. We are currently working towards selecting our first clinical candidate and initiating IND enabling studies, which is expected in the third quarter of this year. So far, our data have demonstrated that we can achieve 50% editing of the mutated Z mRNA by day seven post administration with AIMers, which increases to about 60% with repeat dosing through 19 weeks,. We have shown that we can restore AAT protein well above the required therapeutic threshold. We've confirmed using mass spec that the protein we are making is truly the wild-type protein and not some other less functional isoform of the protein. Finally, we have shown that AIMer treatment reduces liver aggregates at 19 weeks with repeat dosing.

What's next after AATD?

Paloma:

With GalNAc conjugation we are now getting about 60% editing, getting high levels of protein in serum, and showing that the therapeutic effect is durable in an AATD model. These are all the features we want, not just for AATD but for a whole host of other diseases. So beyond AATD, we are building our portfolio of GalNAc conjugated AIMers for other hepatic targets - so going deeper within the liver.

The next piece that we are focused on is what happens without GalNAc - understanding where our oligonucleotides distribute and expanding our focus outside of hepatocytes to the CNS, for example. We also are interrogating other areas of biology - such as disrupting protein-protein interactions, and have shown data where AIMers disrupted the KEAP1-NRF2 interface in vitro.

Why are you partnering with the RNA Editing Summit?

Paul:

We're excited to be taking part in a meeting where the focus is on RNA editing and on the realization that this is a big space with countless opportunities to help patients and their families. This forum is bringing together leaders who are all approaching RNA editing with different chemistries and different areas of biology. Any time you bring that kind of diversity together, interesting ideas blossom and people learn from each other. This forum also allows leaders in the field to challenge each other and everybody attending benefits from that. At the end of the day all of us are trying to develop medicines to treat challenging and complex diseases. The question is - how do we work together to push this field forward? So I'm exciting to participate, it's going to be good fun.