Wave Life Sciences Announces Nature Biotechnology Publication Highlighting First RNA Base Editing in Non-Human Primates Using an Endogenous Enzyme

March 7, 2022

Published data demonstrate potent, durable, and specific editing and potential for therapeutic applications in liver using a subcutaneous GalNAc-conjugated oligonucleotide approach

Wave's foundational AIMer technology avoids limitations of other base editing approaches reliant on co-administration of exogenous enzymes

Wave continues to set new bars for RNA base editing across tissues and cell types; lead AIMer for AATD expected to initiate IND-enabling toxicology studies in Q3 2022

CAMBRIDGE, Mass., March 07, 2022 (GLOBE NEWSWIRE) -- Wave Life Sciences Ltd. (Nasdaq: WVE), a clinical-stage genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases, today announced the publication of preclinical proof-of-concept data for the company's novel ADAR-mediated RNA base editing modality in the journal *Nature Biotechnology*. Data reported include an *in vivo* study where Wave's GalNAc-conjugated A-to-I(G) RNA base editing oligonucleotides ("AIMers") yielded up to 50% editing of ACTB (Beta-actin) transcript in the liver of non-human primates (NHPs), with editing levels persisting as high as 40% for more than one month. This is the first scientific publication to report that RNA base editing in NHPs can be achieved with a simplified oligonucleotide approach. The paper, titled "Endogenous ADAR-mediated RNA editing in non-human primates using stereopure chemically modified oligonucleotides," is available here.

"Efficient *in vivo* DNA or RNA base editing has historically relied on co-administration of engineered exogenous enzymes such as CRISPR/Cas9 with lipid nanoparticles or viral vectors, complicating delivery and specificity. Our approach does not, and therefore this publication represents a significant step forward for the genetic medicines field," said Chandra Vargeese, PhD, Chief Technology Officer and Head of Platform Discovery Sciences at Wave Life Sciences. "The publication also summarizes foundational design principles that enabled us to achieve potent, durable editing with high specificity and exposure, using short chemically modified oligonucleotides with simplified delivery. Since the generation of these data, we have continued to evolve our AIMer designs, allowing us to further optimize editing efficiencies across multiple targets, cell types, and tissues, and establish versatile therapeutic platform technology. We are proud to be contributing these important learnings to the scientific community through this seminal publication in *Nature Biotechnology*."

AIMers are designed to correct single base mutations in an RNA transcript, thereby avoiding permanent changes to the genome that occur with DNA-targeting approaches. Rather than using an exogenous editing enzyme, AIMers recruit proteins that exist in the body, called ADAR enzymes, which naturally possess the ability to change an adenine (A) to an inosine (I), which cells read as guanine (G). This approach enables simplified delivery and avoids the risk of irreversible off-target effects of DNA-targeting approaches.

AIMers are short in length, fully chemically modified, and use novel chemistry, including proprietary PN backbone modifications and chiral control, that make them distinct from other ADAR-mediated editing approaches. As outlined in the *Nature Biotechnology* paper, AIMers can be taken up by several cell types with high editing efficiency under gymnotic conditions *in vitro* and are amenable to GalNAc conjugation, a validated ligand for clinical delivery to the liver.

Wave has also demonstrated in a multitude of preclinical studies that AIMers do not need complex delivery vehicles such as viral vectors or lipid nanoparticles to achieve durable editing in the liver, central nervous system (CNS), and other tissues, providing versatility in therapeutic applications. Beyond targeting the transcriptome to correct point mutations, Wave is also exploring the use of AIMers to treat non-genetic diseases through modulation of protein-protein interactions and recently provided proof-of-concept *in vitro* at the Deaminet 2022 conference.

In addition to reporting up to 50% editing of ACTB transcript in NHPs with subcutaneous administration, additional advances from the *Nature Biotechnology* publication include:

- AIMers are highly specific *in vitro* and *in vivo* based on transcriptome-wide analyses.
- In the NHP *in vivo* study there were no signs of hepatoxicity at 2-days post-dose when AIMer levels in the liver were high, with all animals exhibiting ALT and AST levels within or below the historical data range.
- There is an ample reservoir of ADAR activity in cells to support therapeutic use without disrupting the natural functions of ADAR enzymes in the body.
- Early-generation AIMers designed to correct the Z mutation in SERPINA1 transcript, which is the most common cause of alpha-1 antitrypsin deficiency (AATD), supported high levels of RNA editing, and this editing increased the amount of functional alpha-1 antitrypsin (AAT) protein secreted from primary hepatocytes *in vitro*. Wave has separately shared *in vivo* data for its AATD program, where AIMer treatment in a transgenic mouse model resulted in approximately 60% editing of SERPINA1 transcript and circulating AAT serum levels (18.5 uM) approximately five-fold greater than PBS-treated controls at 19 weeks. Wave has also shared histological analyses that indicate reduction of liver aggregates in a transgenic mouse model at 19 weeks with AIMer treatment.
- Several guiding principles for the design of AIMers were revealed through analysis of the relationship between chemical modifications and editing activity. These include that controlling backbone stereochemistry and the use of judiciously placed PN backbone modifications can improve editing activity, which are both features of Wave's proprietary PRISM™ platform.

"The vast potential therapeutic applications for AIMers, enabled by unique chemistry modifications and the creativity of Wave's scientists, and these compelling proof-of-concept data underscore the many reasons we are excited about this new therapeutic modality," said Paul Bolno, MD, MBA, President and Chief Executive Officer at Wave Life Sciences. "We are rapidly working towards selecting our first AIMer development candidate for AATD, with IND-enabling toxicology studies planned to initiate in the third quarter of this year. We also are expanding our discovery work in the CNS and liver, and we expect AIMers to become a significant component of our pipeline in the future. RNA base editing represents the next frontier of precision medicine and we have only begun to realize its potential. We look forward to contributing additional publications in the future as we continue

driving this science."

About AIMers
Adenosine deaminases acting on RNA (ADAR) enzymes are naturally occurring enzymes in humans which catalyze adenine (A) to inosine (I) changes in repetitive elements, microRNAs (miRNAs) and protein encoding transcripts. Wave's A-to-I RNA base editing oligonucleotides ("AIMers") are designed to recruit these ADAR enzymes to direct efficient and highly specific editing of RNA transcripts. Because I is read as G (guanine) by translational machinery, sequence-directed editing with ADAR has the potential to revert transcripts with single G-to-A point mutations that cause genetic diseases.

It is estimated that there are more than 32,000 pathogenic single nucleotide polymorphisms, of which about 50% may be ADAR amenable. In addition, A-to-I(G) editing could potentially address non-genetic diseases through modulation of post-translational modifications or protein-protein interactions.

About PRISM™
PRISM is Wave Life Sciences' proprietary discovery and drug development platform that enables genetically defined diseases to be targeted with stereopure oligonucleotides across multiple therapeutic modalities, including silencing, splicing, and editing. PRISM combines the company's unique ability to construct stereopure oligonucleotides with a deep understanding of how the interplay among oligonucleotide sequence, chemistry and backbone stereochemistry impacts key pharmacological properties. By exploring these interactions through iterative analysis of *in vitro* and *in vivo* outcomes and machine learning-driven predictive modeling, the company continues to define design principles that are deployed across programs to rapidly develop and manufacture clinical candidates that meet pre-defined product profiles.

About Wave Life Sciences
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. To find out more, please visit www.wavelifesciences.com and follow Wave on Twitter @WaveLifeSci.

Forward-Looking Statements
This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, our understanding of the incorporation of GalNAc-conjugated A-to-I(G) RNA base editing oligonucleotides (AIMers) and the anticipated therapeutic benefits thereof; our understanding of the impact of PN chemistry on our AIMers; the potential benefits of our AIMers compared with other RNA base editing approaches; the potential benefits of PRISM, including our AIMers, and our stereopure oligonucleotides compared with stereorandom oligonucleotides; and the anticipated timing of future development milestones for our lead AIMer program. The words "may," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "estimate," "predict," "project," "potential," "continue," "target" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release and actual results may differ materially from those indicated by these forward-looking statements as a result of these risks, uncertainties and important factors, including, without limitation, the risks and uncertainties described in the section entitled "Risk Factors" in Wave's most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC), as amended, and in other filings Wave makes with the SEC from time to time. Wave undertakes no obligation to update the information contained in this press release to reflect subsequently occurring events or circumstances.

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