



Wave Life Sciences Announces Two Papers in the Journal *Nucleic Acids Research* Describing How PN Backbone Chemistry Modifications Enhance the Pharmacological Effects of Oligonucleotides

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Wave paper on PN chemistry for silencing in the CNS, and the implications for oligonucleotides more broadly, designated as a Breakthrough Article by *Nucleic Acids Research*

Publications highlight the profound impact of PN chemistry on potency, distribution, and durability of effect in multiple preclinical models and across modalities; underscore the potential of Wave's ongoing clinical programs and pipeline, all of which utilize PN chemistry

First clinical data for PN chemistry-containing stereopure oligonucleotides expected in 2022

CAMBRIDGE, Mass., Feb. 02, 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 two publications in the journal *Nucleic Acids Research* supporting the incorporation of PN backbone chemistry modifications (PN chemistry) in stereopure oligonucleotides as a significant advancement for the therapeutic oligonucleotide field. In the multitude of *in vitro* and *in vivo* (animal) studies highlighted in the papers, PN chemistry dramatically improved potency, distribution, and durability of effect. The papers explore the use of PN chemistry in stereopure silencing oligonucleotides for central nervous system (CNS) diseases and stereopure splicing oligonucleotides for neuromuscular diseases. Wave currently has three ongoing clinical trials investigating PN chemistry-containing compounds for amyotrophic lateral sclerosis (ALS)/frontotemporal dementia (FTD), Duchenne muscular dystrophy (DMD) and Huntington's disease (HD).

The publication focused on PN chemistry for silencing in the CNS was also designated as a Breakthrough Article by the journal, which is awarded for high-impact studies answering long-standing questions in the field of nucleic acids research and/or opening up new areas and mechanistic hypotheses for investigation.

"These papers on PN chemistry – specifically phosphoryl guanidine linkages – demonstrate that we have identified an important new opportunity for optimizing therapeutic stereopure oligonucleotides," said Chandra Vargeese, PhD, Chief Technology Officer at Wave Life Sciences. "Wave was founded on the insight that chirality matters in oligonucleotides, just as it matters in small molecules. Rather than ignore the structural feature of stereochemistry, we developed the ability to control it and design single isomers, giving us the resolution necessary to better characterize structure-activity relationships and discover novel chemistry modifications aimed at improving potency, distribution and durability of effect. It was through our foundational science that we were able to uncover the potential of PN chemistry and deploy it across our pipeline and modalities. We're proud to be sharing these scientific contributions, which help to advance the field of genetic medicines."

Highlights from the Breakthrough Article on applying PN chemistry to stereopure silencing oligonucleotides ("[Impact of guanidine-containing backbone linkages on stereopure antisense oligonucleotides in the CNS](#)") include:

- Incorporation of PN linkages to a stereopure PS/PO oligonucleotide backbone increased potency of silencing in cultured neurons under free-uptake conditions 10-fold, compared with similarly-modified stereopure PS/PO-based molecules without PN linkages
- The increased potency resulting from incorporation of PN linkages translated *in vivo* in mouse CNS
 - PN chemistry also increased durability of silencing activity in mouse CNS
- Stereopure oligonucleotides with PN linkages were significantly more potent than stereorandom oligonucleotides with PN linkages, highlighting the importance of control of backbone stereochemistry in design of oligonucleotide therapeutics
- The paper also highlights the structure-activity relationship that underscores application of PN chemistry to antisense oligonucleotides

Highlights from the paper on applying PN chemistry to stereopure splicing oligonucleotides ("[Control of backbone chemistry and chirality boost oligonucleotide splice switching activity](#)") include:

- Chimeric skipping oligonucleotides with PN linkages promoted exon skipping and dystrophin restoration in the severe double-knock out (dKO) mouse model for DMD
 - Improved activity correlated with improved muscle exposure (*in vivo*) and muscle cell uptake / intracellular stability (*in vitro*)
- Oligonucleotides with PN linkages improved muscle function and increased lifespan in the dKO mouse model
 - Restored respiratory function to wild-type levels in multiple assays (tidal volume, minute volume, peak inspiratory flow, peak expiratory flow) in 6-week study
 - Improved survival from a median of 49 days (PBS) to a median >274 days (150 mg/kg weekly) and median >280 days (75 mg/kg biweekly)
 - Treated dKO mice in survival studies exhibited improved weight gain, biomarker signatures and skeletal muscle function
- The paper also illustrates the structure-activity relationship analysis that underscores Wave's stereopure exon skipping oligonucleotides

"The foundational work outlined in these publications resulted in our next generation of clinical candidates currently being dosed in three clinical trials and has been critical as we continue to build a robust research pipeline," said Michael Panzara, MD, MPH, Chief Medical Officer and Head of Therapeutics Discovery and Development at Wave Life Sciences. "The findings fuel our optimism for the clinical data we expect this year from the

ongoing studies of WVE-N531 in DMD, WVE-004 in C9orf72-associated ALS and FTD, and WVE-003 in HD.”

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 PN backbone chemistry modifications in stereopure oligonucleotides and the anticipated therapeutic benefits thereof for silencing and splicing modalities; our understanding of PN chemistry and its anticipated impacts on our pipeline; the potential benefits of PRISM and our stereopure oligonucleotides compared with stereorandom oligonucleotides; and the anticipated timing of data from our PN chemistry-containing stereopure oligonucleotides in our ongoing clinical trials. 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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