# Intellia Therapeutics' Preclinical Data Show Continued Progress in In Vivo Gene Editing With Systemic Lipid Nanoparticle Delivery of CRISPR/Cas9 components

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CAMBRIDGE, Mass., Aug. 18, 2016 (GLOBE NEWSWIRE) -- Intellia Therapeutics, Inc. (NASDAQ:NTLA), a leading genome editing company focused on the development of potentially curative therapeutics using CRISPR/Cas9 technology, presented preclinical data demonstrating *in vivo* gene editing using lipid nanoparticles (LNPs) to deliver CRISPR/Cas9. These data were presented at the 2016 meeting on *Genome Engineering: The CRISPR/Cas Revolution*, in Cold Spring Harbor, New York.

In several *in vitro* and *in vivo* preclinical studies, the data demonstrated:

- Editing efficiency in mouse liver of up to approximately 60 percent at the transthyretin (TTR) target site after a single intravenous administration, consistently across different lobes. This resulted in an associated decrease in serum TTR protein levels of up to approximately 80 percent;
- Dose-dependent editing by LNP delivery;
- Undetectable Cas9 mRNA and guide RNA (gRNA) in the liver at 72 hours post administration;
- Repair patterns in mouse liver cells *in vivo* being best predicted by primary mouse liver cells *in vitro*.

"Intellia has shown robust data that demonstrates the clinical potential of the LNP delivery of CRISPR components. With a single administration, we show significant editing at the target gene and a related decrease in target protein in serum," said David Morrissey, Ph.D., Chief Technology Officer, Intellia Therapeutics. "These early data also show that LNP delivery can lead to rapid clearance of the Cas9 and guide components from the liver, an important consideration for future clinical studies. Intellia continues to make further advances, and we would expect greater editing efficiency with continued optimization."

**Study Background**

The preclinical editing studies were designed to explore the use of lipid nanoparticles for delivery of CRISPR/Cas9 components to the liver in mice and to mediate editing of target DNA within hepatocytes. In general, for the LNPs in the studies, Cas9 mRNA was co-formulated with chemically synthesized gRNAs targeting the mouse TTR gene, and administered via one or two intravenous tail vein injections. Additional studies were performed to evaluate the impact on editing of variables including guide format, dosing regimen and dose escalation.

**About Intellia Therapeutics**

Intellia Therapeutics is a leading genome editing company, focused on the development of proprietary, potentially curative therapeutics using the CRISPR/Cas9 system. Intellia believes the CRISPR/Cas9 technology has the potential to transform medicine by permanently editing disease-associated genes in the human body with a single treatment course. Our combination of deep scientific, technical and clinical development experience, along with our leading intellectual property portfolio, puts us in a unique position to unlock broad therapeutic applications of the CRISPR/Cas9 technology and create a new class of therapeutic products. Learn more about Intellia Therapeutics and CRISPR/Cas9 at intelliatx.com; Follow us on Twitter @intelliatweets.

**Forward-Looking Statements**

*This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. These forward looking statements include, but are not limited to, statements regarding our ability to advance CRISPR/Cas9 into therapeutic products for severe and life-threatening diseases; the potential timing and advancement of our clinical trials; the impact of our collaborations with Novartis and Regeneron on our development programs; the potential indications we may pursue, including our sentinel indications; the potential timing of regulatory filings regarding our development programs; and potential commercialization opportunities for product candidates. Any forward-looking statements in this press release are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, the risk that any one or more of our product candidates will not be successfully developed and commercialized, the risk of cessation or delay of any of the ongoing or planned clinical trials and/or our development of our product candidates, the risk that the results of previously conducted studies involving similar product candidates will not be repeated or observed in ongoing or future studies involving current product candidates, the risk that our collaboration with Novartis or Regeneron will not continue or will not be successful, and risks related to our ability to protect and maintain our intellectual property position. For a discussion of other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in our most recent quarterly report on Form 10-Q filed with the Securities and Exchange Commission, as well as discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the Securities and Exchange Commission. All information in this press release is as of the date of the release, and Intellia Therapeutics undertakes no duty to update this information unless required by law.*

**Study Abstract**

ROBUST *IN VIVO* GENE EDITING IN MOUSE HEPATOCYTES WITH SYSTEMIC LIPID NANOPARTICLE DELIVERY OF CRISPR/CAS9 COMPONENTS

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There is considerable interest in the therapeutic potential of CRISPR/Cas9-mediated gene editing to treat a wide variety of genetic diseases; however, clinically viable delivery of CRISPR/Cas9 components presents an obvious challenge. Effective and safe delivery of CRISPR/Cas9 components, whether based on viral or non-viral delivery vehicles, would require specific targeting of a tissue or cell type; and brief half-life in order to minimize potential off-target activity and innate and humoral immune responses. In addition, the ability to re-administer the therapy to attain stable, therapeutically relevant levels of gene editing would be an advantage. With these requirements in mind, we have explored the use of lipid nanoparticles (LNPs) for delivery of CRISPR/Cas9 components to the liver to mediate editing of target DNA within hepatocytes. Cas9 mRNA and chemically synthesized gRNA specific to the mouse transthyretin gene (TTR) were co-formulated into LNPs, and administered to mice via intravenous tail vein injection. Various parameters were explored, including the nature of the guide RNA (sgRNA vs. dgRNA & chemical modification), the dosing regimen, and molecular strategy (single target site vs. two-target site micro-deletion). We found that the best results were obtained with a chemically modified single guide co-formulated with Cas9 mRNA. We were able to achieve a median dose-dependent editing of up to 55% of the gene copies in liver biopsies. A corresponding dose-dependent reduction of serum transthyretin protein levels was seen, with a decrease of up to 80%. The levels of editing across liver lobes were in general highly consistent. Notably, the DNA repair patterns in liver were distinctly different from those seen in cell lines using the same TTR-specific gRNA. These results demonstrate that therapeutically meaningful levels of *in vivo* CRISPR/Cas9-mediated gene editing can be obtained with a completely synthetic and scalable single-agent system, and suggest that the treatment of liver-based genetic disease with CRISPR/Cas9 will be clinically viable.

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