Regeneron Genetics Center® Publication in New England Journal of Medicine Identifies New Genetic Variant Providing Protection from Chronic Liver Disease

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TARRYTOWN, N.Y., March 21, 2018 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) today announced a publication in the *New England Journal of Medicine* identifying for the first time a variant in the *HSD17B13* gene that is associated with reduced risk of, or protection from, various chronic liver diseases for which there are currently no approved therapeutics. By analyzing extensive genetic sequencing data linked with electronic health records, researchers from the Regeneron Genetics Center (RGC) discovered a potential new therapeutic target to reduce the risk of chronic liver disease and progression to more advanced stages of disease, such as nonalcoholic steatohepatitis (NASH).

Specifically, researchers concluded that individuals with two copies of the loss-of-function variant in the *HSD17B13* gene, which encodes the hepatic lipid droplet protein hydroxysteroid 17-beta dehydrogenase 13, had 73 percent lower risk of alcoholic cirrhosis and 49 percent lower risk of nonalcoholic cirrhosis than individuals with two functioning copies of the gene. These individuals also had 53 percent lower risk of alcoholic liver disease and 30 percent lower risk of nonalcoholic liver disease than people with functioning copies of the gene. The variant was also associated with a reduced risk of NASH, suggesting that loss of *HSD17B13* function protects from progression to later, more clinically-impactful stages of liver disease.

Based on these findings, Regeneron today also announced a collaboration with Alnylam Pharmaceuticals, Inc. to discover RNAi therapeutics for this target.

"These findings further emphasize the importance of large-scale human genetics data in drug discovery, and represent yet another actionable breakthrough coming from the Regeneron Genetics Center," said George Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer of Regeneron. "Finding a new target for drug development has always been one of the hardest and most important things that we do in this business. Examples of previous human genetics successes include the breakthrough work by Hobbs and Cohen that led to the discovery of the *PCSK9* target for heart disease, eventually leading to an important new class of medicines. Today's publication demonstrates how our Regeneron Genetics Center uses large-scale, automated approaches to greatly expedite and expand our target discovery capabilities, as we work to deliver new medicines to patients in need."

Chronic liver disease and cirrhosis are leading causes of morbidity and mortality in the United States, accounting for over 38,000 deaths in 2014.[1] The most common precursors to cirrhosis are alcoholic liver disease, chronic hepatitis C and nonalcoholic fatty liver disease (NAFLD). About 3 to 12 percent of adults in the United States have NASH,[2] a more severe type of NAFLD, and prevalence is increasing due to rising rates of obesity.[3,4] There is a great need for new medicines that treat non-viral forms of chronic liver disease, as there are currently no approved drugs for these conditions.

"This genetic 'experiment of nature' has pinpointed a new target for the discovery of novel medicines that mimic the action of this variant and similarly reduce the risk of chronic liver diseases, leading causes of death in this country," said Aris Baras, M.D., Vice President at Regeneron and Head of the Regeneron Genetics Center. "This work would not have been possible without the entire Regeneron team, as well as our great collaborators at the Geisinger Health System, the University of Pennsylvania and the University of Texas Southwestern. These groups are not only providing world-class care to their patients today, but investing in long-term outcomes by supporting pioneering large-scale genetics research like this."

"The results of this study illustrate the power of human genetics to identify targets for pharmaceutical intervention, even for diseases that are not strictly genetic, and have few therapeutic options. The substantial protection against non-viral liver disease enjoyed by individuals with DNA sequence variations in HSD17B13 suggests that pharmacological inhibition of this enzyme may slow or prevent the progression of these disorders," said co-author Dr. Jonathan Cohen, Professor of Internal Medicine and with the Center for Human Nutrition and the Eugene McDermott Center for Human Growth and Development at UT Southwestern Medical Center.

Methodology and Additional Findings

The association between the *HSD17B13* variant and chronic liver disease was originally made by studying the exome sequence data and corresponding electronic health records of more than 46,544 participants in the DiscovEHR study population from the MyCode® Community Health Initiative at the Geisinger Health System (GHS). RGC scientists identified genetic variants associated with two common measures of liver health - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels - and then evaluated associations between the implicated genetic variants and prevalence and severity of chronic liver disease in these patients.

The ALT and AST association findings were replicated in analyses of three additional populations: 2,644 additional individuals from the DiscovEHR population who had undergone bariatric surgery, 1,357 individuals from the Dallas Heart Study and 8,526 individuals from the Penn Medicine Biobank. Since these cohorts are primarily made up of people of European ancestry, researchers also confirmed the chronic liver disease associations in more diverse populations: the findings were replicated in 517 people in the multi-ethnic Dallas Liver and Heart Studies and 439 Hispanic American children in the Dallas Pediatric Liver Study. Regeneron scientists then performed analyses of human liver tissue and conducted expansive target biology programs to confirm that the variant resulted in loss of *HSD17B13* protein expression and enzymatic function.

To evaluate for other clinical effects of the loss-of-function *HSD17B13* variant, RGC researchers scanned for associations with thousands of clinical diseases and measurements captured in electronic health records, finding that the only strong associations were with conditions related to chronic liver diseases. This real-world data indicates that genetic loss of *HSD17B13* function may be specific to reduction of chronic liver disease risk, which would be a positive safety consideration for potential therapeutics against this target.

About the Regeneron Genetics Center

The RGC is a fully integrated genomics program that spans early gene discovery and functional genomics and facilitates drug development. The primary goal of the RGC is to improve patient outcomes by identifying novel drug targets, clinical indications for development programs, and genomic biomarkers for pharmacogenomic applications. The RGC is tackling large scale sequencing and analytical approaches and has established numerous collaborations with leading human genetics researchers. To enable this large-scale sequencing and analysis program, the RGC utilizes fully-automated sample preparation and data processing, as well as cutting-edge cloud-based informatics. Through these efforts, the RGC is currently sequencing de-identified samples from patient volunteers at a rate of almost 250,000 unique exomes per year. The RGC has major collaborations with Geisinger Health System and the UK Biobank supporting their goal of sequencing 1,000,000 individuals linked to their comprehensive digital health records, plus many other major initiatives in disease specific-studies, founder populations and family based-studies.

About Regeneron Pharmaceuticals, Inc.
Regeneron (NASDAQ: REGN) is a leading biotechnology company that invents life-transforming medicines for people with serious diseases. Founded and led for 30 years by physician-scientists, our unique ability to repeatedly and consistently translate science into medicine has led to six FDA-approved treatments and numerous product candidates in development, all of which were homegrown in our laboratories. Our medicines and pipeline are designed to help patients with eye disease, heart disease, allergic and inflammatory diseases, pain, cancer, infectious diseases and rare diseases.

Regeneron is accelerating and improving the traditional drug development process through our proprietary *VelociSuite*® technologies, such as *VelocImmune*® which produces optimized fully-human antibodies, and ambitious research initiatives such as the Regeneron Genetics Center, which is conducting one of the largest genetics sequencing efforts in the world.

For additional information about the company, please visit www.regeneron.com or follow @Regeneron on Twitter.

Forward-Looking Statements and Use of Digital Media
This news release includes forward-looking statements that involve risks and uncertainties relating to future events and the future performance of Regeneron Pharmaceuticals, Inc. ("Regeneron" or the "Company"), and actual events or results may differ materially from these forward-looking statements. Words such as "anticipate," "expect," "intend," "plan," "believe," "seek," "estimate," variations of such words, and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements concern, and these risks and uncertainties include, among others, the nature, timing, and possible success and therapeutic applications of Regeneron's products, product candidates, and research and clinical programs now underway or planned; the likelihood, timing, and scope of possible regulatory approval and commercial launch of Regeneron's late-stage product candidates and new indications for marketed products; the extent to which the results from the research and development programs conducted by Regeneron or its collaborators (including the discovery discussed in this news release) may be replicated in subsequent studies and lead to therapeutic applications; unforeseen safety issues and possible liability resulting from the administration of products and product candidates in patients; serious complications or side effects in connection with the use of Regeneron's products and product candidates in clinical trials; coverage and reimbursement determinations by third-party payers, including Medicare, Medicaid, and pharmacy benefit management companies; ongoing regulatory obligations and oversight impacting Regeneron's marketed products, research and clinical programs, and business, including those relating to the enrollment, completion, and meeting of the relevant endpoints of post-approval studies; determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize Regeneron's products and product candidates; competing drugs and product candidates that may be superior to Regeneron's products and product candidates; uncertainty of market acceptance and commercial success of Regeneron's products and product candidates and the impact of studies (whether conducted by Regeneron or others and whether mandated or voluntary) on the commercial success of Regeneron's products and product candidates; the ability of Regeneron to manufacture and manage supply chains for multiple products and product candidates; unanticipated expenses; the costs of developing, producing, and selling products; the ability of Regeneron to meet any of its sales or other financial projections or guidance and changes to the assumptions underlying those projections or guidance; the potential for any license or collaboration agreement, including Regeneron's agreements with Sanofi, Bayer, and Teva Pharmaceutical Industries Ltd. (or their respective affiliated companies, as applicable), as well as Regeneron's collaboration with Alnylam Pharmaceuticals, Inc. referenced in this news release, to be cancelled or terminated without any product success; and risks associated with intellectual property of other parties and pending or future litigation relating thereto, including without limitation the patent litigation proceedings relating to Praluent® (alirocumab) Injection, the ultimate outcome of any such litigation proceedings, and the impact any of the foregoing may have on Regeneron's business, prospects, operating results, and financial condition. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2017. Any forward-looking statements are made based on management's current beliefs and judgment, and the reader is cautioned not to rely on any forward-looking statements made by Regeneron. Regeneron does not undertake any obligation to update publicly any forward-looking statement, including without limitation any financial projection or guidance, whether as a result of new information, future events, or otherwise.

Regeneron uses its media and investor relations website and social media outlets to publish important information about the Company, including information that may be deemed material to investors. Financial and other information about Regeneron is routinely posted and is accessible on Regeneron's media and investor relations website (http://newsroom.regeneron.com) and its Twitter feed (http://twitter.com/regeneron).

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