Regeneron Genetics Center Discovers GPR75 Gene Mutations that Protect Against Obesity

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Publication in* Science *reports that people with these protective mutations have 54% reduced risk of obesity

Regeneron used its VelociGene® technology to create mice with similar protective mutation that are resistant to obesity

Regeneron already creating potential therapeutics to fight obesity using its VelocImmune® technology and collaborator Alnylam's siRNA technology

Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced that scientists from the Regeneron Genetics Center® (RGC) have discovered rare genetic mutations in the *GPR75* gene associated with protection against obesity. As reported in *Science*, almost 650,000 people were sequenced to find rare individuals with this genetic 'superpower,' providing new insights into the genetic basis of obesity. Potential therapeutics mimicking these genetic superpowers are being developed at Regeneron, utilizing its *VelocImmune* technologies and novel technologies from collaborators such as Alnylam Pharmaceuticals, Inc.

It is estimated that more than one billion people could be suffering from obesity (body mass index [BMI] of 30 or higher) by 2030.[1,2] Working with research collaborators, RGC scientists found that individuals who have at least one inactive copy of the *GPR75* gene have lower BMI and, on average, tend to weigh about 12 pounds less and face a 54% lower risk of obesity than those without the mutation. Protective 'loss of function' mutations were found in about one of every 3,000 people sequenced.

"Discovering protective genetic superpowers, such as in *GPR75*, provides hope in combating global health challenges as complex and prevalent as obesity," said George D. Yancopoulos, M.D., Ph.D., President and Chief Scientific Officer at Regeneron. "Discovery of protective mutations – many of which have been made by the Regeneron Genetics Center in its eight-year history – will allow us to unlock the full potential of genetic medicine by instructing on where to deploy cutting-edge approaches like gene-editing, gene-silencing and viral vector technologies."

As part of the research that led to the finding, RGC scientists analyzed deidentified genetic and associated health data from 645,000 volunteers from the United Kingdom, U.S. and Mexico. The study, one of the Regeneron Genetics Center's largest to date, was conducted in collaboration with Geisinger Health System, New York Medical College, the Nuffield Department of Population Health at the University of Oxford and the National Autonomous University of Mexico (UNAM) using data from the Mexico City Prospective Study, Geisinger's MyCode Community Health Initiative and UK Biobank.

The Regeneron team, collaborating with the labs of Dr. Schwartzman and Dr. Garcia at New York Medical College, then validated the finding in mice that were genetically engineered using Regeneron's *VelociGene* technology to lack copies of the *GPR75* gene. Such mice gained 44% less weight than mice without the mutation when both groups were fed a high-fat diet.

"This is a potentially game-changing discovery that could improve the lives and health of millions of people dealing with obesity, for whom lasting interventions have often been elusive," said Christopher D. Still, D.O., Director for the Geisinger Obesity Research Institute at Geisinger Medical Center. "While the behavioral and environmental ties to obesity are well understood, the discovery of *GPR75* helps us put the puzzle pieces together to better understand the influence of genetics. Further studies and evaluation are needed to determine if reducing weight in this manner can also lower the risk of conditions commonly associated with high BMI, such as heart disease, diabetes, high blood pressure and fatty liver disease."

Building on Regeneron's strengths in genetics-driven drug discovery and development, Regeneron scientists are pursuing multiple therapeutic approaches to target *GPR75*, including through antibodies, small molecules and gene silencing.

"The discovery of *GPR75* is already enabling Regeneron and our collaborators to identify potential ways to safely replicate the effect of this mutation through novel therapeutic approaches," said Aris Baras, M.D., Senior Vice President at Regeneron and Head of the Regeneron Genetics Center. "This is the latest in a long line of protective human genetics discoveries that have fueled new therapeutics programs at Regeneron. The pace is only quickening, as we uncover more and more about the human genome and work to rapidly translate those discoveries to the development of new medicines."

About the Regeneron Genetics Center
The Regeneron Genetics Center LLC (RGC) is a wholly owned subsidiary of Regeneron Pharmaceuticals, Inc. that focuses on early gene discovery and functional genomics. 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.

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

Regeneron is accelerating and improving the traditional drug development process through our proprietary *VelociSuite*® technologies, such as *VelocImmune*®, which uses unique genetically humanized mice to produce optimized fully human antibodies and bispecific antibodies, and through 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 press 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 impact of SARS-CoV-2 (the virus that has caused the COVID-19 pandemic) on Regeneron's business and its employees, collaborators, and suppliers and other third parties on which Regeneron relies, Regeneron's and its collaborators' ability to continue to conduct research and clinical programs, Regeneron's ability to manage its supply chain, net product sales of products marketed or otherwise commercialized by Regeneron and/or its collaborators (collectively, "Regeneron's Products"), and the global economy; the nature, timing, and possible success and therapeutic applications of Regeneron's Products and product candidates being developed by Regeneron and/or its collaborators (collectively, "Regeneron's Product Candidates") and research and clinical programs now underway or planned, including without limitation the use of human genetics in Regeneron's research to, among other things, discover and develop potential therapeutics mimicking gene mutations (such as the GPR75 *gene mutations discussed in this press release); the extent to which the results from the research and development programs conducted by Regeneron and/or its collaborators (including those discussed in this press release) may be replicated in other studies and/or lead to advancement of product candidates to clinical trials, therapeutic applications, or regulatory approval; uncertainty of the utilization, market acceptance, and commercial success of Regeneron's Products and Regeneron's Product Candidates and the impact of studies (whether conducted by Regeneron or others and whether mandated or voluntary) on any of the foregoing; the likelihood, timing, and scope of possible regulatory approval and commercial launch of Regeneron's Product Candidates and new indications for Regeneron's Products; the ability of Regeneron's collaborators, suppliers, or other third parties (as applicable) to perform manufacturing, filling, finishing, packaging, labeling, distribution, and other steps related to Regeneron's Products and Regeneron's Product Candidates; the ability of Regeneron to manufacture and manage supply chains for multiple products and product candidates; safety issues resulting from the administration of Regeneron's Products and Regeneron's Product Candidates in patients, including serious complications or side effects in connection with the use of Regeneron's Products and Regeneron's Product Candidates in clinical trials; 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 Regeneron's Product Candidates; ongoing regulatory obligations and oversight impacting Regeneron's Products, research and clinical programs, and business, including those relating to patient privacy; the availability and extent of reimbursement of Regeneron's Products from third-party payers, including private payer healthcare and insurance programs, health maintenance organizations, pharmacy benefit management companies, and government programs such as Medicare and Medicaid; coverage and reimbursement determinations by such payers and new policies and procedures adopted by such payers; competing drugs and product candidates that may be superior to, or more cost effective than, Regeneron's Products and Regeneron's Product Candidates; unanticipated expenses; the costs of developing, producing, and selling products; the ability of Regeneron to meet any of its financial projections or guidance and changes to the assumptions underlying those projections or guidance; the potential for any license, collaboration, or supply 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 press release, to be cancelled or terminated; and risks associated with intellectual property of other parties and pending or future litigation relating thereto (including without limitation the patent litigation and other related proceedings relating to EYLEA® (aflibercept) Injection, Dupixent® (dupilumab), Praluent® (alirocumab), and REGEN-COV™ (casirivimab and imdevimab)), other litigation and other proceedings and government investigations relating to the Company and/or its operations, the ultimate outcome of any such proceedings and investigations, 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 U.S. Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2020 and its Form 10-Q for the quarterly period ended March 31, 2021. 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 or otherwise) 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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[1] "Global burden of obesity in 2005 and projections to 2030," *International Journal of Obesity*, Oct. 2, 2008, https://pubmed.ncbi.nlm.nih.gov/18607383/#:~:text=By%202030%2C%20the%20respective%20number,and%201.12%20billion%20obese%20individuals.

[2] "Obesity and Overweight," *World Health Organization*, June 9, 2021, https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.