PRESS RELEASE

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Advancing Genetic Disease Treatments and Pharmacogenetics: From Scientific Discovery to Medical Delivery

Scientists Present Latest Research on Novel Genetic Therapies and Effective Treatments at The American Society of Human Genetics 58th Annual Meeting

BETHESDA, MD – November 14, 2008 – Thousands of the world's top scientists and clinicians in the human genetics field will convene to present their latest research at the 58th Annual Meeting of The American Society of Human Genetics (ASHG) in Philadelphia, Pennsylvania on November 11-15, 2008.

A number of scientific presentations at the ASHG 2008 Annual Meeting will provide information about important new research findings that advance our current understanding of possible causes of genetic conditions. A number of these studies go a step further in their quest to translate knowledge gained from scientific research into novel genetic therapies that can be used to treat patients in clinical practice.

ASHG will host a press briefing session to highlight four of the top research presentations at the 2008 Annual Meeting that report findings on important breakthroughs in the successful treatment of disease through novel genetic therapies and treatments, and the management of health conditions through findings from pharmacogenetics research.

ASHG invites members of the media to attend this press briefing session on *"Novel Genetic Disease Treatments and Therapies: From Scientific Discovery to Medical Delivery,"* which will be held on Friday, November 14, 2008 at 11:15 a.m. in the ASHG Press Briefing Room, located on the third level of the Pennsylvania Convention Center. This session will feature exciting new scientific research on successful genetic disease treatments and therapies, as well as new pharmacogenetics research findings that provide insights into appropriate drug dosage based on genetic variants.

The presentations included in this press briefing will report on: the results of a genome-wide association scan for genetic determinants of warfarin dosage, breakthrough research on a new treatment that has the potential to be the first successful therapy for Huntington's Disease, a long-term study on a successful enzyme replacement therapy for children with Type I Gaucher Disease, and new research findings that offer important new clues that will facilitate more precise and compartment-specific cancer treatment options.

Brief summaries of the major research findings reported in these four abstracts are included below:

Genome-wide Association Scan for Genetic Determinants of Warfarin Dose

A growing number of geneticists are using genome-wide association studies (GWAS) to systematically search for and identify single nucleotide polymorphisms (SNPs), which are single base changes in the human DNA sequence that can cause differences in genetic characteristics. GWAS may also detect genes that are associated with a particular health condition, or with variation in patient response to prescribed drugs.

In this session, Ralph E. McGinnis, Ph.D., a Statistical Geneticist at the Wellcome Trust Sanger Institute (Cambridge, UK), will discuss the results of new research that that he and his colleagues have recently completed which extends this genome-wide association scan (GWAS) method to investigate the genetic aspects of drug response (pharmacogenetics) related to predicting appropriate warfarin dose.

Warfarin is the most widely prescribed drug used to reduce blood clotting in order to protect high-risk patients from experiencing a stroke, deep vein thrombosis, pulmonary embolism, heart attack, or other serious coronary malfunction. However, a combination of genetic and non-genetic factors can cause patients to exhibit 10- to 20-fold variation in the required dose (RD) of warfarin needed to achieve an adequate level of blood thinning, which means that initial prescribed doses may be too low (risking blood clots and/or failure to protect the patient from developing life-threatening health conditions, such as stroke or heart attack) or too high (risking over-anticoagulation and severe bleeding). Therefore, associated SNPs and genes that are related to dose variation requirements could be used to better estimate the proper warfarin dose based on a patient's genetic makeup, thereby reducing the risk of adverse events caused by inappropriate dosing.

McGinnis' research team were among the first to show that a polymorphism in the warfarin drug target VKORC1 accounts for a major portion (~30%) of the variance in RD, and they have recently evaluated 1,523 Swedish patients from the Warfarin Genetics (WARG) cohort in the largest study to date showing likely patient benefit from genetic forecasting of RD. In this study, the researchers found that the strongest signals were clustered around VKORC1 (the gene of the warfarin drug target), and the second strongest signals were located at SNPs clustering in the warfarin-metabolizing gene CYP2C9.

Mc Ginnis and colleagues conducted additional analyses that tested each GWAS SNP's influence on warfarin dose after adjusting for the influence of already known genetic (VKORC1, CYP2C9) and non-genetic (age, gender, etc.) factors. These analyses identified another statistical signal with genome-wide significance that corresponded to a SNP that changes the protein coding sequence of the CYP4F2 gene. This finding was confirmed in a study of 588 additional Swedish patients.

In summary, the current research results suggest that the proportion of dose variation explained by known genetic factors is approximately 29% (VKORC1), 11% (CYP2C9) and 1.5% (CYP4F2). Furthermore, by also taking into account the around 15% contribution of non-genetic factors such as age and gender, researchers can predict at least 50% of warfarin dose variation, making pre-treatment dose forecasting for individual patients a realistic possibility.

Ralph E. McGinnis, Ph.D., is a Statistical Geneticist at the Wellcome Trust Sanger Institute (Cambridge, UK) whose research focus is identifying genes and DNA variants that cause complex genetic disease or alter response to therapeutic drugs (pharmacogenetics). He has recently analyzed data for genome-wide or large-scale association studies of celiac disease, coronary artery disease, type 1 diabetes, and response to warfarin.

Induction of PGC-1 Alpha Expression in Huntington's Disease Transgenic Mice Rescues Neuronal Dysfunction and Neurodegeneration

Neurodegenerative diseases pose a considerable burden to our aging population. Huntington's disease (HD) is an inherited neurological disorder that affects as many as 40,000 people in the U.S. alone. HD causes degeneration of the brain, which results in involuntary movement disorder, cognitive decline, and ultimately death. Studies of HD and other related neurodegenerative disorders, such as Parkinson's

disease, have highlighted the importance of mitochondrial function and energy production in the maintenance of normal neural function. However, there is currently no known cure for this fatal disease.

Albert La Spada, M.D., Ph.D., FACMG, Associate Professor and Director of the Center for Neurogenetics and Neurotherapeutics at University of Washington, Seattle, and his research team have been instrumental in establishing a new paradigm for HD neurodegeneration by linking nuclear transcription interference with mitochondrial dysfunction at the level of the transcription co-activator PGC-1a – an important factor that regulates mitochondria.

In their latest work, Dr. LaSpada and his research group sought to determine if PGC-1a can ameliorate any clinical symptoms of HD by performing genetic studies in a mouse model of HD. Their findings indicate that increased PGC-1a action does improve neurological defects in HD mice and results in reduced amounts of protein aggregates – a key pathological feature of most neurodegenerative disorders.

Specifically, the current results indicate that PPARd (a peroxisome proliferator-activated receptor that is positively modulated by PGC1-a) interacts with the huntingtin protein, and altered function of PPARd contributes to HD neurodegeneration. If PPARd is involved in this neurological disease, then tractable therapies to boost PPARd would be immediately available, as two recent lines of investigation make PPARd an attractive therapeutic target: (1) highly selective and powerful pharmacological agonists for PPARd have been developed and are currently being studied in clinical trials in humans; and 2) PPARd mediates pro-survival signaling in response to retinoic acid, a compound that has been used for years to treat human patients with leukemia and brain tumors.

“My colleagues and I are very excited about the surprising results of our most recent research on Huntington’s disease, since the findings could ultimately lead to the first potential treatment for this currently fatal disease,” LaSpada said. “Furthermore, our findings suggest there are drugs that are already available and currently being used in human patients that could be possible new therapies for Huntington’s disease.”

Albert R. La Spada, M.D., Ph.D., FACMG, is Director of the Center for Neurogenetics and Neurotherapeutics and Associate Professor of Laboratory Medicine, Medicine (Medical Genetics), Pathology, and Neurology at the University of Washington, Seattle. La Spada's research efforts have uncovered a number of connections between pathways involved in transcription and neuron dysfunction. His current work focuses on investigating the molecular basis of neurodegenerative disease.

Eight-Year Clinical Outcomes of Enzyme Replacement Therapy in 884 Children with Type I Gaucher Disease

Gaucher disease is a rare genetic disorder that occurs when a person lacks an enzyme called glucocerebrosidase. The most common form of this disorder is type 1 Gaucher disease. Type 1 Gaucher disease can start at any age, but recently it has been shown that about half of all patients are diagnosed before 18 years of age. These patients have variable combinations of problems with anemia, low platelet counts (causing risk of bleeding), enlargement of abdominal organs (spleen and liver), bone pain and abnormal bones with increased risks of fractures, and often growth delay.

Since 1992, an intravenous enzyme replacement therapy (ERT) has been used to treat all type 1 Gaucher patients, as well as those Gaucher patients with no neurologic problems. Because Gaucher disease is a relatively rare condition, no single research center follows enough patients to be able to make statistically significant conclusions about the effectiveness of long-term enzyme replacement therapy. However, the Gaucher Registry includes multiple years of clinical data from more than 800 pediatric patients with type 1 Gaucher disease.

Hans C. Andersson, M.D., Director of the Hayward Genetics Center and Professor of Human Genetics at Tulane University Medical Center, will discuss research that he and his colleagues recently conducted to

investigate the long-term efficacy of enzyme replacement therapy in children with type 1 Gaucher Disease. In this study, Dr. Andersson's research team analyzed clinical response of 884 pediatric patients with type 1 Gaucher disease during treatment up to eight years. No study to date has ever described long-term outcomes in such a large, international group of pediatric patients.

The results of Andersson's research indicate that within eight years of ERT, most clinical measures studied in the patient cohort became normal or near normal. Over 35 percent of the patients had significant growth delay (shorter than 95 percent of age-matched children) at baseline; however, at the end of eight years of treatment, their growth had virtually normalized. The data also indicate that all patients with anemia were cured of this complication, and over 95 percent of patients had significant resolution of their low platelet count. Furthermore, liver and spleen volumes were dramatically reduced over the treatment period, and patient complaints of severe bone pain were significantly reduced after only two years of therapy.

"This study is the first of its kind to document the long-term effectiveness of enzyme replacement therapy in children with type 1 Gaucher disease," said Andersson. "This study should prove to be a very useful tool for pediatricians who can use these results as a guideline for tracking the progress of their patients over multiple years of treatment."

Hans C. Andersson, M.D., FACMG, is the Karen Gore Professor of Human Genetics and Director of the Hayward Genetics Center at Tulane University Medical School, where he directs the Biochemical Genetics Lab. He also serves as a Regional Coordinator for the International Collaborative Gaucher Group. Andersson's research has elucidated clinical features and pathophysiology of inherited metabolic genetic disorders.

Common and Cancer Type-Specific Loss-of-Heterozygosity (LOH) in the Tumor Stroma and Epithelium of 3 Carcinoma Types Associated with Clinical Outcome

A team of researchers led by Charis Eng, M.D., Ph.D., Chair and Director of Cleveland Clinic's Genomic Medicine Institute, has found that in-common genetic alterations in both cancerous cells and the surrounding normal-looking cells (called tumor microenvironment or stroma) play an important role in predicting and dictating the outcome of three cancer types: breast cancer (BC), prostate cancer (CaP) and head neck squamous cell carcinomas (HNSCC). The findings not only offer important clues into how a cancer and its micro-environment interact, but show that in-common biomarkers may be important for prognosis among several solid tumor types.

Eng's research team hypothesized that frequent genetic alterations are in-common in BC, CaP and HNSCC, but genetic alterations that are associated with clinicopathological features are unique for specific cancer types. The study analyzed tissue samples from 413 patients and evaluated the cancerous (epithelial) and the surrounding stroma.

The researchers found 15-genetic-marker profiles that were in-common for the three cancer types and are likely to simultaneously predict or explain the cancers. Of these genetic-markers, 11 were stromal-specific, two were epithelial-specific, and two were in both compartments (epithelium and stroma). They also found a genetic-marker that was strongly associated with tumor-grade in CaP and BC only, and another one was associated with nodal metastases in BC and HNSCC only, in both compartments.

"Furthering our understanding of how multiple genetic factors interact between cancer cells and its micro-environment, or stroma, will be a valuable tool for clinicians in predicting how a cancer might spread, as well as forecasting patient outcomes," Eng stated. "Importantly, fewer molecular targets for treatment or prevention across several common carcinomas will facilitate more precise and compartment-specific therapeutic options."

Charis Eng, M.D., Ph.D., is the Director and Chair of the Cleveland Clinic Genomic Medicine Institute, and Professor and Vice Chairman of the Department of Genetics at Case Western Reserve University School of Medicine. Dr. Eng currently serves on the ASHG's Board of Directors. She also serves as Chair of the Clinical Science Committee for the Personalized Medicine Coalition (PMC).

ABOUT THE AMERICAN SOCIETY OF HUMAN GENETICS

Founded in 1948, The American Society of Human Genetics (ASHG) is the primary professional membership organization for human genetics specialists worldwide. The nearly 8,000 members of ASHG include researchers, academicians, clinicians, laboratory practice professionals, genetic counselors, nurses and others involved in or with a special interest in human genetics.

The Society's mission is to serve research scientists, health professionals and the public by providing forums to: (1) share research results through the Annual Meeting and in *The American Journal of Human Genetics* (*AJHG*); (2) advance genetic research by advocating for research support; (3) educate future genetics professionals, health care providers, advocates, teachers, students and the general public about all aspects of human genetics; and (4) promote genetic services and support responsible social and scientific policies. For more information about ASHG, please visit http://www.ashg.org/.

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Please direct all media inquiries to ASHG Press Office, ASHG Communications Manager, via e-mail at press@ashg.org, or by phone at 301-634-7307 (o) or at 240-281-2386 (c). For all onsite media inquiries during the ASHG 2008 meeting, Ms. Long can be reached via cell phone at .

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