Clinic *for* Special Children®

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FOR IMMEDIATE RELEASE

GENE THERAPY FOR CLASSIC MAPLE SYRUP URINE DISEASE SHOWS PROMISE IN MICE AND COW MODELS

- Maple Syrup Urine Disease is a severe genetic disease with lifelong dietary formula or liver transplantation as the only treatments currently available
- Animal studies suggest one-time gene therapy for classic MSUD could be a promising treatment for patients with the condition

LANCASTER COUNTY, PA – In a first-of-its-kind study, researchers developed a dual-function gene replacement therapy that demonstrated restored metabolic activity in mice and a cow model of two common genetic forms of maple syrup urine disease (MSUD). MSUD is a severe inherited metabolic disorder in which the body cannot break down specific amino acids, which build up and become toxic to the brain. Current treatment options, lifelong dietary formula and protein restriction or liver transplantation, do not protect against the neurocognitive and psychiatric effects of the disease. The cow is the largest experimental animal to receive this gene therapy vector systemically to date and continues to demonstrate normal growth and development over two years after treatment, suggesting this gene therapy is a promising treatment for patients with classic MSUD. The paper was recently published by researchers from the Clinic for Special Children and the University of Massachusetts Chan Medical School in *Science Translational Medicine*.

The dual-function AAV9 gene replacement vector was developed to treat patients with biallelic mutations of MSUD in either the *BCKDHA* or *BCKDHB* genes, which cause infantile-onset, severe (“classic”) MSUD. The therapy was delivered via intravenous (IV) infusion in mice and cow models with the disease and targeted the cells of the liver, muscle, heart, and brain.

If left untreated, the MSUD mouse and cow models experienced metabolic crises and died within 10 days of birth. The gene therapy prevented early death and restored gene activity in mouse models with MSUD. They were able to eat a normal diet high in protein without the adverse effects of the disease. The treated cow also demonstrated normal survival and normal growth with an unrestricted diet high in protein that has durable effects over two years post-dosing.

"We believed gene therapy could be a breakthrough for patients with MSUD and, in August 2018, met on a cattle farm in Iowa to pursue that vision: to develop and test gene therapy in a unique animal model, a newborn calf with MSUD. In the years that followed, physicians at the Clinic for Special Children worked intently with scientists and veterinarians from UMass Chan Medical School to achieve that goal, drawing their inspiration from the hopes and struggles of the MSUD community. In the paper, the team describes safe and effective gene replacement in two different types of MSUD mice and the MSUD cow, the largest animal ever to receive systemic gene therapy. For people worldwide living with MSUD, this signifies major progress on the path to a brighter future," shares Dr. Kevin A. Strauss, Head of Therapeutic Development at the Clinic for Special Children.

Future studies will be needed to assess the efficacy and effects of higher vector doses and their impact on cognition, behavior, and neurochemistry. It will be important to determine the long-term restoration of amino acid metabolic activity in the brain, which distinguishes this treatment approach from the current option of liver transplantation.

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The research was conducted by a team including the study's first author Jiaming Wang from the Department of Genetic and Cellular Medicine, University of Massachusetts Chan Medical School, Worcester, MA, the study's collaborating authors Heather Gray-Edwards from the Department of Genetic and Cellular Medicine, University of Massachusetts Chan Medical School, Worcester, MA, and Tufts University Cummings School of Veterinary Medicine, North Grafton, MA, Guangping Gao from Department of

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About the Clinic for Special Children

The Clinic for Special Children is a non-profit organization located in Lancaster County, PA, that provides primary care and advanced laboratory services to children and adults who live with genetic or other complex medical disorders. Founded in 1989, the organization provides services to 1,700 individuals and is recognized as a world leader in translational and precision medicine. The organization is primarily supported through community fundraising events and donations. For more information, please visit www.ClinicforSpecialChildren.org

About Maple Syrup Urine Disease

Maple Syrup Urine Disease (MSUD) is a severe inherited metabolic disorder in which the body cannot process certain amino acids. MSUD is fatal without treatment and the only current available treatment options are strict dietary formula with protein restriction or liver transplantation. If left untreated, MSUD causes rapid and toxic build-up of amino acids and their derivatives in the brain which can cause brain swelling, coma, and death. The name ‘Maple Syrup Urine’ refers to the sweet odor in the urine of affected individuals. MSUD affects approximately 1 per 185,000 births worldwide and 1 per 380 births in the Old Order Mennonite population.