Moderna Publishes Preclinical Data in *Cell Reports* on mRNA Therapeutic to Treat Rare Liver Disease Methylmalonic Acidemia (MMA), A Disorder of Organic Acid Metabolism

--Repeat systemic dosing enabled liver expression of functional *hMUT* enzyme, significantly improving survival and weight gain in MMA mice--

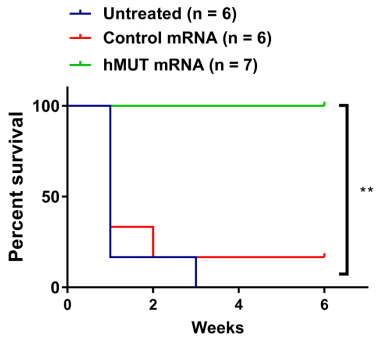
--No increased markers of liver toxicity or inflammation--

--Moderna continuing to advance MMA development candidate, mRNA-3704, toward clinical study--

Cambridge, Mass., December 19, 2017—Moderna Therapeutics, a clinical stage biotechnology company that is pioneering messenger RNA (mRNA) therapeutics and vaccines to create a new generation of transformative medicines for patients, today announced the publication of preclinical data supporting its first rare liver disease development program, an mRNA therapeutic for methylmalonic acidemia (MMA), a serious and often life-threatening organic acidemia.

The data, published online today in the journal *Cell Reports*, demonstrate that intravenous (IV) administration of an mRNA therapeutic encoding for human methylmalonyl-CoA mutase (*hMUT*), the enzyme most frequently mutated in MMA, enabled liver expression of *MUT* in MMA mouse models, leading to a significant reduction in methylmalonic acid, a substantial improvement in weight gain, and the complete survival of the full cohort of treated mice versus control group (see illustration below). Repeat IV dosing did not increase markers of liver toxicity or inflammation. The study was conducted in partnership with researchers in the Medical Genomics and Metabolic Genetics Branch of the National Human Genome Research Institute at the National Institutes of Health.

Survival curve of untreated, control mRNA and hMUT mRNA-treated mice



"Methylmalonic acidemia is a significant unmet need, and many children experience severe and often life-threatening metabolic crises due to a mutated (MUT) enzyme. The only effective treatment option today is liver and/or kidney transplantation. In contrast, our mRNA-based approach directly introduces

into the body's liver cells the genetic instructions they need to produce a functional MUT enzyme," said Paolo Martini, Ph.D., Moderna's Chief Scientific Officer, Rare Diseases, and the lead author on the publication. "These data give us an important early demonstration of our drug's ability to instigate MUT protein expression from within liver cells, which lowers methylmalonic acid levels and significantly improves outcomes in a preclinical setting. They also show our capability to systemically repeat dosing to the liver with a favorable safety profile."

Dr. Martini continued, "We are continuing to progress our MMA therapeutic development candidate, mRNA-3704, toward clinical study, and are driven by the acute and urgent need for an effective treatment option for these patients."

About the Study Findings

In the study, intravenous (IV) administration of an mRNA therapeutic encoding for human methylmalonyl-CoA mutase (*hMUT*), the enzyme most frequently mutated in MMA, was evaluated in two mouse models of methylmalonic acidemia (MMA) developed by Dr. Charles P. Venditti, M.D., Ph.D., Senior Investigator, Medical Genomics and Metabolic Genetics Branch, and Head, Organic Acid Research Section, National Human Genome Research Institute, National Institutes of Health, and his team. Dr. Venditti is also a corresponding author on the paper. The models recapitulated the more severe *mut*° subtype, where there is no liver enzyme activity, or the partial deficiency type of MMA, *mut*-, where there is some liver enzyme activity. The *hMUT* mRNA utilized one of Moderna's novel, proprietary delivery technologies, N2GL, which enables the delivery of mRNA drugs to hepatic cells and the ability to repeat dose. Both Moderna and NIH researchers conducted research for the study.

MUT plays an important role in metabolism. When MUT is deficient, toxic metabolites accumulate in the blood and urine, leading to a build-up of methylmalonic acid. This, in turn, causes severe and even deadly complications for patients, primarily children.

The researchers first evaluated a single IV bolus injection of *hMUT* mRNA. In both the *mut*° and *mut*- subtypes, a single IV bolus injection increased liver expression of a functional MUT enzyme, leading to a 75% and 85% reduction in plasma methylmalonic acid concentrations, respectively. The researchers observed acute metabolic correction after *hMUT* mRNA treatment, with plasma methylmalonic acid as well as methylmalonic acid in various tissues, including liver, heart, kidney, skeletal muscle and brain, acutely reduced.

The researchers also evaluated whether weekly IV injections of *hMUT* mRNA in the more severe *mut*° subtype could improve survival and correct biochemical and growth abnormalities that are a hallmark of the disorder. A cohort of mice receiving weekly IV injections of *hMUT* mRNA (n=7) for five weeks with an additional ten-day washout period were compared to cohorts of mice receiving control mRNA (n=6) or no treatment (phosphate buffered saline) (n=6). All of the mice treated with *hMUT* mRNA survived the entire duration of the study. In contrast, high mortality was observed in both the control and untreated cohorts, with only one control mouse surviving the entire duration of the study and no untreated mice surviving. Additionally, the treated mice thrived, with 40% more weight gain compared to the sole surviving mouse in the control group. Plasma methylmalonic acid levels in treated mice significantly decreased, by 62-89%, from base levels. The sole surviving mouse in the control group showed no metabolic response.

Repeat dosing of *hMUT* mRNA over the five-week treatment period did not increase markers of liver toxicity or inflammation and did not generate anti-drug antibodies against *hMUT*.

About Methylmalonic Acidemia and mRNA-3704

Methylmalonic acidemia, or MMA, is a rare, autosomal recessive organic acidemia/aciduria, most commonly (approximately 60% of cases) caused by a deficiency of the enzyme methylmalonic CoA mutase (MUT), due to a defective or missing MUT protein.

MMA is primarily a pediatric disease with onset in early infancy. The majority of patients with MMA have no functional MUT enzyme, which disrupts the metabolic pathway and leads to a build-up of toxic methylmalonic acid in the blood and urine. This acid accumulation causes, on average, three life-threatening metabolic crises per year. As a result, MMA is associated with significant mortality and morbidity, and there are no approved therapies. Standard of care includes dietary and palliative measures. Currently, liver and/or kidney transplant is the only effective treatment.

Moderna is developing an mRNA therapeutic, mRNA-3704, which directs cells in the liver to produce and express a functional MUT enzyme, restoring the metabolic pathway and reducing toxic acid build-up.

About Moderna Therapeutics

Moderna is a clinical stage pioneer of messenger RNA (mRNA) therapeutics and vaccines, an entirely new drug technology that directs the body's cells to produce intracellular or secreted proteins. With its breakthrough platform, Moderna is developing a new class of mRNA medicines for a wide range of diseases and conditions, in many cases by addressing currently undruggable targets. Moderna is developing its innovative mRNA medicines for infectious diseases, cancer (immuno-oncology), rare diseases, cardiovascular disease and pulmonary disease, through proprietary development and collaborations with strategic partners.

Headquartered in Cambridge, Mass., privately held Moderna currently has strategic agreements with AstraZeneca, Merck, and Vertex Pharmaceuticals, as well as the Defense Advanced Research Projects Agency (DARPA), an agency of the U.S. Department of Defense; the Biomedical Advanced Research and Development Authority (BARDA), a division of the Office of the Assistant Secretary for Preparedness and Response (ASPR) within the U.S. Department of Health and Human Services (HHS); and the Bill & Melinda Gates Foundation. To learn more, visit www.modernatx.com.

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