



MEDIA RELEASE

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CbIC Onlus, HCU Network America and the Organic Acidemia Association today announced the recipient of their first collaborative cobalamin research grant— awarding a research grant to the National Research Council's Institute of Biophysics in Palermo, Italy to identify potential treatment for cobalamin C (cbIC) deficiency. The research, led by Dr. Silvia Vilasi, aims to identify compounds that could potentially rescue MMACHC functional deficiency in cbIC disease. Dr. Vilasi is a researcher at the Institute of Biophysics (IBF) in the National Research Council, and has had a longstanding interest and involvement in the study of structure-function relationship of proteins involved in human pathologies. More recently she focused her interest in homocystinuria research.

Combined methylmalonic acidemia and hyperhomocysteinemia – cobalamin C subtype, more commonly known as cobalamin C (cbIC) is a rare autosomal recessive metabolic genetic disorder. CbIC disease is caused by more than sixty mutations in the gene coding for the MMACHC protein that transports and chemically transforms B12. Patients often present in infancy with megaloblastic anemia, lethargy, growth and developmental delays, cognitive impairment, seizures and progressive retinal deterioration. Late onset cbIC often presents with neuropathy or mental health disturbances.

The current treatment consists of hydroxocobalamin injections (a very specific form of B12) and betaine anhydrous. If a patient is symptomatic at the time of diagnosis, treatment will not reverse the clinical sequelae. Despite current treatment standards, many patients still become symptomatic. The exact incidence is unknown and varies globally. It is estimated that cobalamin C impacts at least 1 in 100,000 people worldwide with Italy being one of the countries with the highest known incidence. It has been given the classification of rare disease by the US Office of Diseases Research and is included as part of the newborn screening panels in many countries.

According to the principal investigator, Dr. Silvia Vilasi, the project aims to characterize and classify some of the most common cbIC variants of MMACHC protein based on the impact that specific mutation has on MMACHC molecular features, such as structure, stability, B12 binding properties and function. Based on this classification, MMACHC-specific molecules with potential therapeutic benefit and safety will be screened exploiting a structure-based bioinformatics approach. The idea is to find molecules able to bind the mutants and stabilize these protein variants in a conformation similar to the unmutated protein (wild type), recovering their function. The protein druggable sites will be targeted with several virtual libraries of drug-like molecules, giving priority to DrugBank library that includes EMA and FDA-approved molecules. 5-10 compounds from the bioinformatic experiments will be then experimentally validated, assessing their ability to restore functionality of proteins. The selected molecules could be precursors for further preclinical studies. Dr. Silvia Vilasi says "I am very happy and honoured to have the possibility to contribute to homocystinuria research and I am grateful to CbIC Onlus, HCU Network America and the Organic Acidemia Association for the trust they have placed in the project. The team I will coordinate with at IBF can leverage a wealth of facilities, multidisciplinary skills and backgrounds of the members participating in the project, from experimental biophysics, chemistry, cell biology, structural biology and structure-based

drug screening. Moreover, to achieve the proposed goals we will collaborate with Prof. Carlo Dionisi Vici, Head of Clinical and Research Unit of Metabolic Diseases at the Ospedale Pediatrico Bambino Gesù in Rome, who will have an important role in mentoring and guiding the experimental activities as the project is designed to be 'patient-centered'."

Rossella Brindisi, President of CbIC Onlus says, "It is a great pleasure to collaborate with HCU Network America and Organic Acidemia Association on this project. It is a good example of cooperation among different organizations spread out in different countries to support scientific research and family community. We hope it will pave the way for further common initiatives."

President of HCU Network America, Margie McGlynn says, "While HCU Network America's prior grants were awarded for research projects for potential new therapies for classical homocystinuria, we are pleased to collaborate with cbIC Onlus and the Organic Acidemia Association to support a grant focused on potential new therapies for cobalamin C disorder, which is consistent with the expanded focus of HCU Network America. We also hope this project will generate insights that can be applied in the future to other cobalamin disorders."

Organic Acidemia Executive Director, Kathy Stagni says, "The Organic Acidemia Association is happy to collaborate with HCU America and CbIC Onlus on this grant request. We feel fortunate and hopeful that researchers work toward the goal of better treatments for our cobalamin C families."

HCU Network America, the Organic Acidemia Association and CbIC Onlus thank their community of supporters whose contributions made this grant possible.

About CbIC Onlus

The CbIC Onlus, the Italian Association of Methylmalonic Acidemia with Homocystinuria cbIC type, was set up in March 2017, by the initiative of some parents of children affected by such disorder, with the purposeful intention to support scientific research and every initiative aimed at improving the quality of life of patients and their families.

Currently close to 80 families are associated with cbIC Onlus.

About HCU Network America:

HCU Network America is a 501c(3) non-profit organization founded in 2016 dedicated to helping patients and their families affected by Homocystinuria (HCU) and related disorders. The mission of the organization is to inform and provide resources for patients and families, create connections, influence state and federal policy, and support advancement of diagnosis and treatment for HCU and related disorders.

About the Organic Acidemia Association

The Organic Acidemia Association is a 501c(3) non-profit organization whose mission is to empower families and health care professionals with knowledge in organic acidemia metabolic disorders. We support early intervention through expanded newborn screening, solicit contributions and distribute funding that supports research toward improved treatment and eventual cures in the areas of Organic Acid disorders.