MEDIA RELEASE

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Today HCU Network America announced the third recipient of the CBS deficiency global grants program – awarding a research grant to the Newcastle University Biosciences Institute in Newcastle, United Kingdom to explore a potential avenue for treatment for homocystinuria due to cystathionine beta-synthase (CBS) deficiency. The research, led by Dr. Thomas McCorvie, aims to identify stabilizers or activators of the defective enzyme in CBS-deficient homocystinuria (HCU). Dr. McCorvie is a Senior Research Associate at the Newcastle University Biosciences Institute

Classical Homocystinuria (HCU) is a rare autosomal recessive metabolic genetic disorder. The disorder is caused by a faulty CBS enzyme leading to high levels of homocysteine and methionine. The severity of Classical HCU varies and depends on whether the faulty CBS enzyme is completely inactive or can still metabolize some homocysteine. Left untreated, HCU can lead to a range of health problems over time, affecting the eyes, skeleton, brain and blood vessels. Common consequences of untreated or uncontrolled individuals are lens dislocation, blood clots and strokes, and varying degrees of cognitive impairment.

There are two forms of HCU: a 'milder' form that responds to vitamin B_6 (pyridoxine) supplement and a more 'severe' pyridoxine non-responsive form. About 40% of individuals with CBS-deficient homocystinuria are pyridoxine responsive. People who do not respond adequately to pyridoxine need to be on a special diet that is low in protein and consequently low in methionine, as well as administration of a medication called betaine to help metabolize homocysteine. Medical formula is also given to provide non-methionine amino acids for those on a low protein diet. While effective, compliance with a low protein diet and medical formula is extremely difficult and is very often poor, especially in late diagnosed patients. If a safe and effective new treatment could result from this strategy, it could reduce the need for a low protein diet and formula.

While the exact incidence is unknown and varies globally, it is estimated that CBS-deficient homocystinuria impacts at least 1 in 200,000 people worldwide. It has been given the classification of a rare disease by the U.S. Office of Rare Diseases Research and is included as part of the newborn screening panel in many countries.

HCU Network America and HCU Network Australia launched the global grant program in 2017 as a joint initiative supported by a Scientific Advisory Board led by Dr. Viktor Kozich, Professor of Medical Genetics

at Charles University in Prague and Warren Kruger, Professor of Cancer Biology and Epigenetics program at Fox Chase Cancer Center, Philadelphia, PA. This grant call invited proposals for projects dedicated to assessing potential new therapies to treat HCU.

“Inherited mutations of Cystathionine Beta-Synthase (CBS) enzyme result in reducing its activity by destabilization and aggregation. There is precedent that small molecules which specifically bind to and stabilize CBS could restore mutant CBS activity by acting as a pharmacological chaperone (PC). Therefore, this project aims to screen for small molecules that bind to and stabilize CBS using fragment-based x-ray crystallography screening (XChem). XChem involves crystallizing the CBS protein hundreds to thousands of times and then soaking each crystal with a large library of fragments. Any small fragments that bind to CBS will be identified using x-ray crystallography and used as starting points to develop into larger molecules.”, said Dr. McCorvie.

“These potential binders will then be triaged against CBS and its disease mutants to determine if they act as PC molecules rescuing their functionality. The most promising small molecules can then be possible starting points for further preclinical studies in cell lines and animal models, and if successful can be developed as a PC therapy for classical homocystinuria.

I am incredibly honoured and excited that our proposal has been funded by the HCU Network America, as this builds on our previous work on the structural biology of CBS along with our goals to develop novel therapies for rare metabolic disorders. As such this research will leverage our group’s multi-disciplinary experience in biophysics, biochemistry, and structural-based drug screening along with guidance from our clinical contacts in the homocystinuria field.”

“We are pleased to support this research project to build upon the previous work on the crystal structure of the CBS enzyme by Drs. McCorvie and Yue, and we are hopeful that potential chaperone therapies can result from their work and be further developed into new treatments to support our patient community.” said Margie McGlynn, President of HCU Network America.

The funding from HCU Network America is through the HCU Network America’s Classical Research Fund and the Hempling Foundation for Homocystinuria Research, established in memory of Judy and Susie Hempling, two young girls from Buffalo, NY whose lives were cut short by HCU in the 1970s. HCU Network America would also like to thank the Bickelmann Family for their strong fundraising efforts that helped contribute to making this grant possible.

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.