A PROJECT OF THE GASLINI INSTITUTE OF GENOA WINS THE "SEED GRANT" OF ASSOCIAZIONE ITALIANA GLUT1, WITH THE SUPPORT OF FONDAZIONE TELETHON, TO STUDY GLUT1 DEFICIENCY

The "Seed Grant" combined the skills of the Fondazione Telethon with the work of the Associazione Italiana Glut1 to give new perspectives in research on this rare genetic disease.

Rome, 29 January 2020 - The winning project of the first "Seed Grant" call has been selected: the project, coordinated by prof. **Federico Zara**, of the U.O.C. of Medical Genetics of the Gaslini Institute, University of Genoa is focused on Glut1 deficiency syndrome. This pathology is characterized by epilepsy often refractory to pharmacological treatment, movement anomalies and cognitive disorders and is due to a defect in the transport of glucose in the brain.
The association that brings together the families of patients affected by this rare genetic disease, **Associazione Italiana Glut1**, has entrusted Fondazione Telethon to open and manage a research call with which to allocate the funds raised by the patient association, 50.000 euros: an “ad hoc” scientific commission was formed, made up of 4 researchers from the United States and Germany, which assessed the 13 project proposals received last November and selected the 3 most deserving. Most importantly, it was the association, with the support of Fondazione Telethon, to choose which project to actually finance among the "finalists", because it best met their needs.
In particular, the selected project aims to develop new molecular tools to promote the flow of glucose into the brain. In fact, patients with Glut1 deficiency syndrome have a genetic defect that leads to a malfunction of the "entrance door" for glucose, a fundamental source of energy for the brain, through the blood-brain barrier. Currently the only way in which the disease can be controlled is through the ketogenic diet, which causes the body to change its fuel source, replacing sugars with fats. However, in addition to being very demanding for families if not critical in the long term, the diet does not always manage to control all the symptoms: for this reason, research must identify alternative solutions.

“The project - explains prof. **Zara** - *aims to develop new molecules capable of increasing the permeability of the blood-brain barrier to glucose and of increasing the expression of the deficient transporter Glut1 and therefore of testing its effectiveness in an innovative experimental platform based on the use of patient cells . The project therefore responds to the growing demand for personalized medicine in the field of rare diseases".*

“This initiative is fundamental for our association. As a small association of patients and caregivers, fundraising is never easy, and every hard-earned cent needs to be spent rationally. And while one of our major goals is to support research, we realize that we can’t

conduct an independent assessment the true scientific value of research proposals on our own - said **Monica Lucente**, President of Associazione Italiana Glut1- *With this in mind, we reached out to Fondazione Telethon for support in launching the call for proposals, evaluating those that arrived, and in overseeing the administrative aspects now that the grant has been awarded. With the help of Telethon we can therefore guarantee our families and our donors that the funds, collected with great effort, will be spent in a manner consistent with our objectives. We are grateful for this opportunity and excited for the start of the research project. "*

"With the new Seed Grant project, Fondazione Telethon has set the goal of making its thirty-year experience available to associations of patients with rare diseases - said **Manuela Battaglia**, Head of Research of Telethon" - *It is a first important step, but the hope is that more and more associations will follow this same path, with an eye towards developing the best possible research, aware that only through processes with high standards of quality and excellence will it be possible to reap the benefits in terms of results" .*

Lay Summary of the winning project

The mammalian brain depends upon glucose as its main source of energy. However, glucose has only one single way to enter the brain, namely the Glut1 transporter present in the endothelium of brain capillaries. Brain endothelial cells form a tight Blood-Brain Barrier (BBB) that protects the brain from the ever-changing peripheral environment. The BBB allows the passage of molecules from plasma to brain only across endothelial cells through specific transporters, while extracellular spaces in between cells are sealed by tight junctions. Mutations in the gene encoding for Glut1 impair glucose transport to the brain, resulting in a severe neurological condition with seizures, intellectual disability and movement disorders. Since current treatments are largely ineffective, innovative therapies are in demand. Our main objective is to develop innovative tools to increase glucose transport across the BBB. We will follow two complementary strategies: (i) we will stimulate Glut1 synthesis by activating translation from the healthy copy of the Glut1 gene using non-coding RNAs; (ii) we will induce a transient BBB permeabilization using inhibitory peptides targeted to tight junctions to open the spaces between endothelial cells, letting glucose passively diffuse into the brain.

To test these innovative molecular tools, we will develop a model of the Glut1-deficient BBB using induced pluripotent stem cells obtained from Glut1 patients and differentiated in brain endothelium to mimic the patients' pathology. We expect to obtain a proof-of-concept of the ability of these strategies to rescue Glut1 deficiency in vitro, as a first step toward testing their therapeutic efficacy in vivo.

For more informations:

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