Title: Creatine Deficiency Syndrome: novel insight into brain function and therapeutic strategies

Abstract: Creatine Transporter Deficiency (CTD) is an X-linked inherited metabolic disorder presenting with cerebral creatine (Cr) deficiency, early intellectual disability, epilepsy and autistic-like behaviour. Although rare, CTD represents a major issue in health care, leading to a significant decrease of life expectancy and causing chronic illnesses with a large impact on patient quality of life and health-care system. There is no cure for this devastating disorder. Despite much knowledge about the natural history of CTD and the role of Cr in energy metabolism, little is known about the brain alterations underlying the impairment of multiple behavioural and cognitive domains in CTD. Resting on robust preliminary results, this project aims to explore how long-range and local brain circuits are affected by Cr depletion at different stages of disorder progression, and to devise gene therapy strategies to revert CTD-associated pathological defects and symptoms. By integrating imaging and electrophysiological techniques both in the mouse model and CTD patients, we will provide a unique characterization of brain morphological and neurofunctional alterations associated to CTD. Much of our efforts will be devoted to test a possible therapeutic strategy for CTD. Specifically, we will evaluate a gene therapy approach aimed to amend cellular dysfunction by exogenous provision of a functional copy of CrT gene in a well-established mouse model of CTD. We will exploit knowledge gained so far on the CTD mouse model to test this investigational product for the reinstatement of Cr and ATP physiological levels, the improvement of brain function, the suppression of epileptic phenotype and the recovery of a proper balance within neural circuits. We aim to provide evidence at the proof-of-concept level for the feasibility of CrT protein replacement in the mouse model and for the reversibility of CTD phenotype, laying the basis for future development of CTD gene therapy approaches.

References:

Keywords: creatine, intellectual disability, gene therapy

Contacts: LAURA BARONCELLI, IN-Pisa; laura.baroncelli@in.cnr.it
Website(s): http://www.in.cnr.it/index.php/it/9-people/136-laura-baroncelli2
Collaborations: Prof. Tommaso Pizzorusso (Department of Neuroscience, Psychology, Drug Research and Child Health NEUROFARBA, University of Florence, Institute of Neuroscience, CNR Pisa); Prof. Roberta Battini (Department of Developmental
Neuroscience, IRCCS Stella Maris Scientific Institute, Calambrone), Prof. Giovanni Cioni (Department of Developmental Neuroscience, IRCCS Stella Maris Scientific Institute, Calambrone), Prof. Vincenzo Leuzzi (Department of Paediatrics, Child Neurology and Psychiatry, Sapienza University of Rome); Dr. Alessandro Gozzi (IIT, Rovereto)


2017-in progress ‘Cyclocreatine treatment to creatine transporter knock out mice with, PK, PD, neurobehavioral and biomarker endpoints’. Granting Agency: LUMOS Pharma. Role in the project: PI