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CREATINE DEFICIENCY SYNDROME: NOVEL INSIGHT INTO BRAIN FUNCTION AND THERAPEUTIC STRATEGIES

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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 cognitve 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 reistatement 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 evicence 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.

La carenza del trasportatore di creatina (CTD) è una malattia metabolica ereditaria legata all'X che presenta carenza di creatina cerebrale (Cr), disabilità intellettiva precoce, epilessia e comportamento simile all'autismo. Sebbene rara, la CTD rappresenta un grave problema per l'assistenza sanitaria, portando a una significativa riduzione dell'aspettativa di vita e causando uno stato di patologia cronica con un elevato impatto sulla qualità di vita dei pazienti. Non esiste una cura per questa patologia devastante. Nonostante l'approfondita conoscenza del quadro clinico della CTD e del ruolo della Cr nel metabolismo energetico, si sa molto poco circa le alterazioni cerebrali alla base della compromissione di molteplici domini comportamentali e cognitivi nella CTD. Basandosi su solidi risultati preliminari, questo progetto ha lo scopo di esplorare come i circuiti cerebrali sono influenzati dalla deplezione di Cr in diverse fasi della progressione del disturbo e di elaborare strategie di terapia genica per contrastare i sintomi patologici associati alla CTD. Integrando tecniche di imaging ed elettrofisiologia sia nel modello murino che nei pazienti con CTD, forniremo una caratterizzazione unica delle alterazioni morfologiche e neurofunzionali del cervello associate alla CTD. Gran parte dei nostri sforzi saranno dedicati a testare una possibile strategia terapeutica per CTD. In particolare, valuteremo un approccio di terapia genica volto a modificare la disfunzione cellulare mediante la somministrazione esogena di una copia funzionale del gene CrT in un modello murino di CTD ben consolidato. Sfrutteremo le conoscenze acquisite finora sul modello di topo CTD per testare questo

prodotto sperimentale per il ripristino dei livelli fisiologici di Cr e ATP, il miglioramento della funzione cerebrale, la soppressione del fenotipo epilettico e il recupero di un adeguato equilibrio all'interno dei circuiti neurali. Miriamo a fornire risultati robusti sulla reversibilità del fenotipo CTD, gettando le basi per il futuro sviluppo di approcci di terapia genica per la CTD.

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Deficit del Trasportatore della Creatina

Coordinator: Laura Baroncelli
Partner: Alessandro Gozzi
Duration (N. Years): 3
Starting year: 2020

Telethon Project (nr):

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Disease Name:

Creatine Transporter Deficiency

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