Title: Metabolic interventions to heal FoxG1-related Rett syndrome

Abstract: Forkhead Box G1 (FoxG1) is a key gene for the correct development of cortical interneuron subtypes and connectivity patterns. Mutations in this gene have been recognized to cause a subset of cases of Rett Syndrome (RTT) a rare congenital autism spectrum disorder whose hallmarks are intellectual disability and motor abnormalities. Recently, heterozygous mutations in FoxG1 have been associated with RTT cases characterized by microcephaly, along with an early onset of neurological deficits, including autism-like features and epilepsy in both males and females. Of note, frequent and often drug-resistant epileptic seizures are a major determinant of the poor quality of life experienced by RTT patients and by their families.

By employing a transgenic mouse model for RTT, expressing a single null allele of FoxG1 (FoxG1-/- genotype), we have demonstrated dramatic alterations in the cortical balance between excitation and inhibition, correlating with altered synaptic transmission and generation of cortical and hippocampal epileptic seizures. Strikingly, we found that epilepsy in mice affected by FoxG1-related RTT can be cured by dietary administration of triheptanoin (TRI), a short-chain triglyceride. TRI is intracellularly metabolized to heptanoate, a short chain fatty acid, which replenishes Krebs cycle, thus acting as an anaplerotic compound.

We are currently investigating whether TRI can be used to ameliorate also the cognitive impairment observed in the FoxG1-/- RTT mouse model, by using a combination of behavioral tests, electrophysiological assays and cellular imaging.

We hope that our experiments will delineate a therapeutic strategy leading to a concrete improvement in the quality of life of patients and their families.

References:
- Cortical Seizures in FoxG1-/- Mice are Accompanied by Akt/S6 Overactivation, Excitation/Inhibition Imbalance and Impaired Synaptic Transmission
  Testa G, Olimpico F, Pancrazi L, Borello U, Cattaneo A, Caleo M, Costa M, Mainardi M.
  PMID: 31450553

- A triheptanoin-supplemented diet rescues hippocampal hyperexcitability and seizure susceptibility in FoxG1-/- mice.
  Testa G, Mainardi M, Olimpico F, Pancrazi L, Cattaneo A, Caleo M, Costa M.
  PMID: 30639390

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