Novel molecular targets for personalized treatment in epileptic encephalopathies

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Epileptic encephalopathies are clinical conditions in which the epileptic activity during brain maturation is the main causative factor of severe cognitive and behavioral impairments. The main features of Epileptic Encephalopathy include: (I) electroencephalographic (EEG) abnormalities, (II) seizures that are usually multi-form and resistant to current anticonvulsant treatment, (III) developmental delay or intellectual disability, (IV) sometimes early death. An increasing number of genes is implicated in the etiology of Epileptic Encephalopathy (EE). In particular, mutations in KCNQ2 (and more rarely, KCNQ3) genes encoding for voltage-dependent K+ channel subunits cause neonatal epilepsies with wide phenotypic heterogeneity. On the benign end of the spectrum is Benign Familial Neonatal Seizures (BFNS), a rare, autosomal-dominant epilepsy of newborns characterized by recurrent seizures that begin in the very first days of life and remit after a few weeks or months with mostly display normal interictal EEG, neuroimaging, and psychomotor development. On the severe end of the spectrum, KCNQ2 mutations have been recently described in neonates with pharmacoresistant seizures and psychomotor retardation, suppression-burst pattern at the EEG, and distinct neuroradiological features, thus defining a "KCNQ2 encephalopathy". The main hypothesis to explain epilepsy occurrence in individuals with familial or sporadic KCNQ2 or KCNQ3 mutations is that a loss-of-function (LOF) in channels comprising KCNQ2 subunits decreases the repolarizing reserve of excitatory neurons and causes neuronal hyperexcitability. However, some variants, including those associated with very severe clinical phenotypes, may also increase (rather than decrease) channel function, thereby producing gain-of-function (GOF) effects. The molecular basis for the striking heterogeneity in disease pathogenetic mechanisms and clinical manifestations of KCNQ2-related epilepsies is currently unknown, and no specific therapeutic approach capable of diminishing epilepsy burden and improving developmental outcomes exists for this very severely impacted patient population.

The aim of our work is to explore the functional consequences of KCNQ2 mutations associated to neonatal epilepsies, to expand the spectrum of molecular mechanisms responsible for disease pathogenesis in each individual/family by state-of-the-art biochemical, electrophysiological, computational, genetic, and in-silico structural modelling, and to investigate the pharmacological sensitivity of channels carrying each of these variant, in order to provide a rational basis for testing whether personalized treatment with KCNQ2 modulators may improve epileptic phenotype and developmental outcome in children affected with the most severe forms of KCNQ2-related epilepsy.

In this Symposium, we will describe: 1. The establishment of an informatics infrastructure for KCNQ2 encephalopathy research including patient registry, database, curation platform, and website; 2. The channel regulation by phosphatidyininositol-4,5-bisphosphate (PIP2) and its disruption by a KCNQ2 variant (R325G; Soldovieri et al., 2016), responsible for KCNQ2

encephalopathy; 3. The specific clinical presentation and outcome (also in term of clinical response to retigabine, a selective KCNQ2 activator) associated with two recurrent gain-of-function variants in the KCNQ2 gene (R198Q and R201Q) (Millichap et al., Neurol. Genet. 2:e96, 2016; Milichap et al., Epilepsia 2016; Mulkey et al., Epilepsia 2017).