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RestoreLeak

Accelerating Research on Neurodevelopmental Channelopathies: from Bench to Bedside

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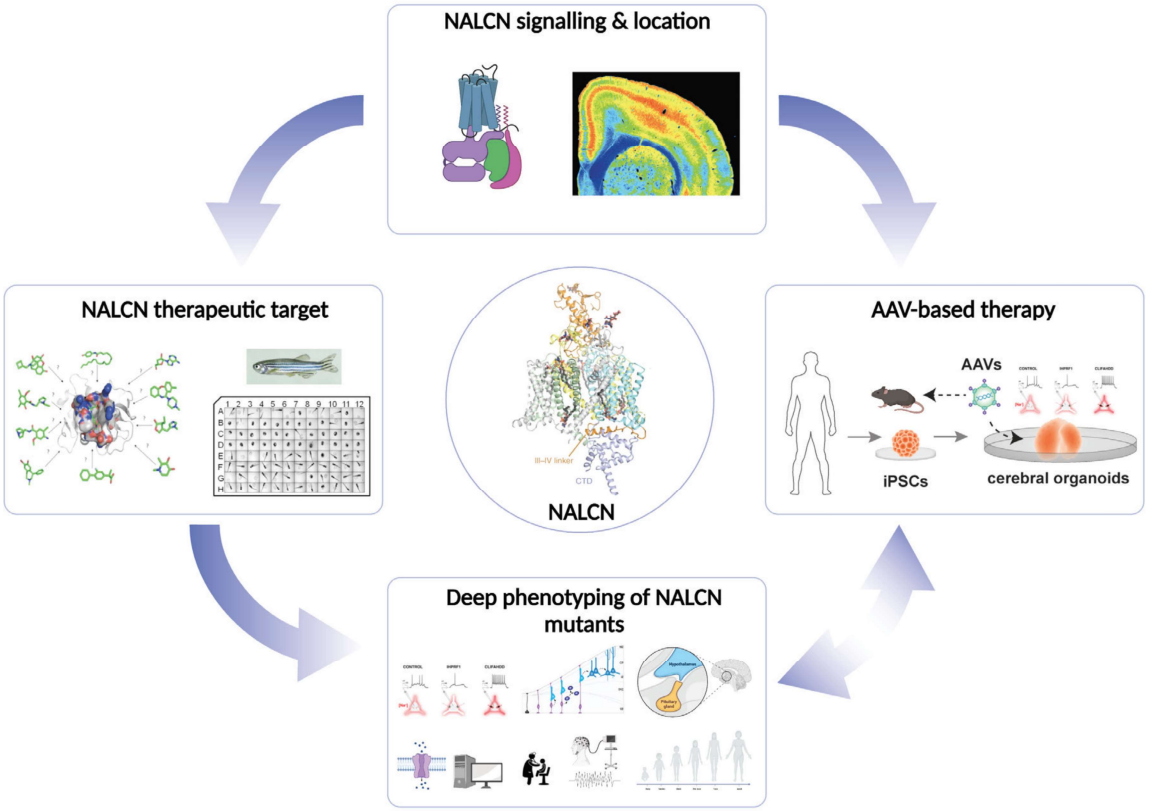
Several cell types, e.g., neurons and endocrine cells, exhibit electrical activity crucial for their physiological function. This electrical activity involves a complex interplay between different classes of specialized proteins. Any functional alteration of these proteins may, in humans, drive pathological states with devastating health consequences, including premature death. The present proposal focuses on the NALCN (Na+ leak channel) protein, a crucial regulator of cell electrical activity. Mutations in the NALCN gene were recently described in two ultra- rare and severe neurodevelopmental disorders referred to as the IHPRF1, for Infantile, Hypotonia, with Psychomotor Retardation and Characteristic Facies 1, inherited autosomal recessive syndrome affecting 40 patients from 23 families and the CLIFAHDD, for Congenital contractures of the Limbs and FAce, Hypotonia, and Developmental Delay, dominant syndrome which so far affects 45 patients with de novo mutations. Both syndromes display an onset early in infancy and may lead to premature death. The overall goal of the project is (i) to decipher molecular, cellular and circuit mechanisms involved in the etiology of these two pediatric diseases and (ii) to develop innovative and safe treatment options for patients. This will be achieved by (a) the combination of specific and complimentary know-hows and expertise from multiple laboratories across Europe, (b) the use of specific cell lines, patient cell derived preclinical models, such as induced pluripotent stem cells & brain organoids, and animal models. To maximize the chances of success, this project will rely on close collaboration between internationally recognized neuroscientists and neurologists in close association with the Libellas Foundation, a patient advocacy group (fundacionlibellas.org).


NALCN signalling & location
NALCN therapeutic target
NALCN
AAV-based therapy
AAVs
iPSCs
cerebral organoids
Deep phenotyping of NALCN mutants