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6th International Conference on

Brain Disorders and Therapeutics

July 01-02, 2019 | Paris, France

Therapeutic potential of targeting microtubule defects in a mouse model of CDKL5 Deficiency Disorder

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Mutations in the X-linked cyclin-dependent kinase-like 5 (CDKL5) cause CDKL5-deficiency disorder (CDD), a neurological pathology characterised by severe infantile seizures, intellectual disability, hypotonia, and impairment of motor, language and hand function skills. CDKL5-knockout (KO) mouse models recapitulate most features of the human disorder including impaired learning and memory. The absence of CDKL5 causes defective spine maturation that can at least in part explain the cognitive impairment of both CDKL5 patients and mouse models. The molecular basis for such defect is not clear but may partly depend on altered microtubule (MT) dynamics. Indeed, we recently demonstrated that CDKL5 regulates MT dynamics through CLIP170, a plus end binding protein the mutations of which are responsible for human intellectual disability. Our studies suggest that CLIP170 contributes significantly to the neuronal impairment of CDD and represent an important druggable target for patients with CDKL5 mutations. The neurosteorid pregnenolone (PREG) can directly bind and activate CLIP170. Here we present our data showing that its synthetic derivative pregnenolone-methyl-ether (PME) rescues CLIP170 functioning in CDKL5 deficient cells and normalizes neuroanatomic, molecular, and behavioural defects in a mouse model of CDD.

Speaker Biography

Kilstrup-Nielsen C has been working in the University of Insubria, Department of Biotechnology and Life Sciences Laboratory of Molecular Neurobiology.

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