CDKL5 Program of Excellence
Pilot Grant Program

Application Title: Innovative Strategy to Enhance the Efficiency of Gene Therapy for CDKL5 Disorder

PI: Elisabetta Ciani, PhD
Institution: University of Bologna

In theory, for a monogenic disease such as CDKL5 disorder, the delivery of a wild-type copy of the CDKL5 gene to cells which lack functional CDKL5 may represent the most effective approach. There are encouraging proof-ofconcept studies that demonstrate the potential for gene therapy, but also highlight significant caveats for treatment of brain diseases. The major caveat regards the low efficiency of gene delivery by viral vectors to the central nervous system (CNS) and the risk of toxic side effects connected with large vector doses. Moreover, the insertion of therapeutic genes into the genome can present considerable problems, such as the risk of insertional mutagenesis. We recently created an IgK-TATk-CDKL5 fusion construct. In view of the properties of the Igk-chain leader sequence polypeptide, the TATk-CDKL5 fusion protein produced by the infected cells can be secreted via constitutive secretory pathways. Importantly, due to the transduction properties of the TATk peptide, the secreted fusion protein can be internalized by cells. We demonstrated that, when internalized, the TATk-CDKL5 protein retains the activity of wild type CDKL5, as demonstrated by its ability to restore maturation of neurons lacking CDKL5 expression (patent pending WO/2015/128746). The innovative idea of this proposal is to enhance the efficiency and safety of a gene therapy for CDKL5 disorder by exploiting the unique properties of the Igk-TATk-CDKL5 gene and of the latest adeno-associated virus (AAV) vector that delivers therapeutic payloads to the brain neurons at high efficiency with minimal off-target effects through noninvasive intravenous (IV) vector administration. We expect the secreted TATk-CDKL5 protein, expressed by the infected brain cells, to locally diffuse and to be transduced into the neighboring neurons, thereby compensating for the lack of CDKL5 function (Fig. 1B). The comparison of the effects of a gene therapy with the CDKL5 gene (Fig. 1A) with that of the IgK-TATk-CDKL5 gene (Fig. 1B) in a Cdkl5 knockout (KO) mouse model will allow us to validate our hypothesis. A successful outcome of the proposed project will establish the proof-of-principle of an AAV vector-mediated gene therapy that exploits the unique properties of the Igk-TATk-CDKL5 gene as a novel, effective and safe therapeutic approach for the treatment of CDKL5 disorder.

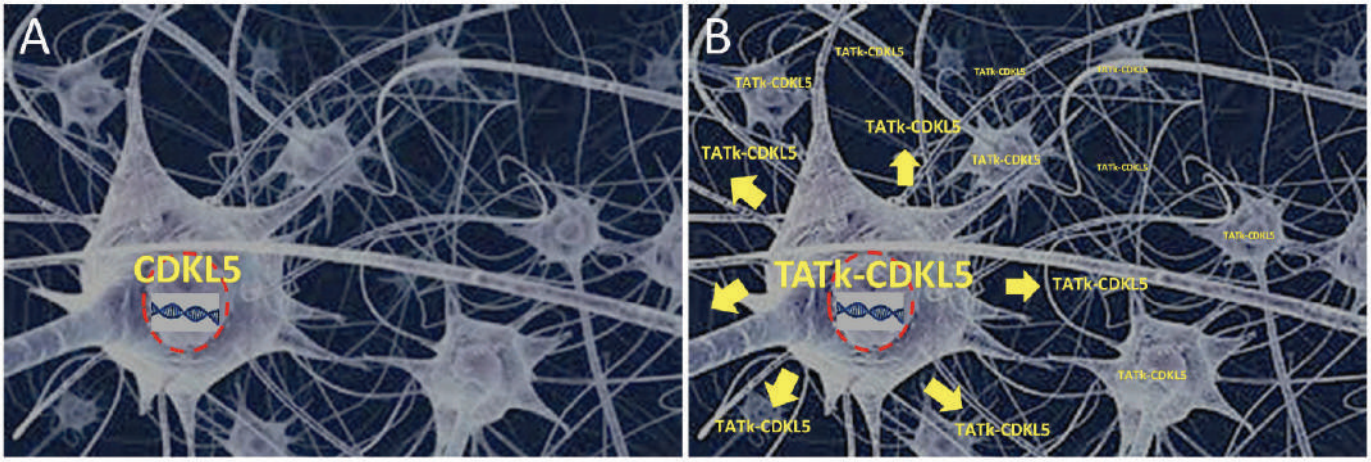
A
CDKL5
B
TATk-CDKL5
TATk-CDKL5
TATk-CDKL5
TATk-CDKL5
TATk-CDKL5
TATk-CDKL5
TATk-CDKL5
TATk-CDKL5
TATk-CDKL5
TATk-CDKL5
TATk-CDKL5
TATk-CDKL5

Figure 1