OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference and Exhibition on
Neurology & Therapeutics
June 17-19, 2013 Hilton Chicago/Northbrook, Chicago, USA

Protein transduction via PTD technology as a therapeutic approach of mitochondrial disorders

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Omics technologies, implemented by bioinformatic analysis, uncovered a large number of novel therapeutic targets. Protein therapy (as the direct delivery of the gene translational product itself) could be considered as a therapeutic approach of monogenetic disorders, provided that in cases of intracellular targets, protein therapeutics would "cross" the plasma membrane of the cells. Protein Transduction Domain Technology uses small peptides (PTDs) of less than 30aa in length, able to penetrate almost all biological membranes and carry on intracellularly a variety of cargos, including proteins. TAT is the most widely used PTD, an 11aa sequence derived from the protein TAT of the HIV-1.

"Primary" mitochondrial disorders, associated with defects of oxidative phosphorylation, affect organs with high energy demands, like brain (nerves), muscle and heart. There is no effective therapy for mitochondrial disorders, with a number of therapeutic approaches being under development. Since PTDs open for a variety of proteins the door to cells, PTDs in addition could open the door to subcellular organelles, like mitochondria. Our group applied the PTD technology as a protein therapeutic approach for the mitochondrial disorder "fatal infantile cardioncephalomyopathy and cytochrome c oxidase (COX) deficiency" due to mutations of the *SCO2* gene, encoding the Sco2 COX assembly protein, located in the inner mitochondrial membrane. Human recombinant TAT-L-Sco2-HA protein, administered exogenously in primary fibroblasts from SCO2 / COX deficient patients, resulted in enzymatic restoration of COX activity.

We propose the PTD-mediated Protein Replacement Therapy as a therapeutic approach of mitochondrial disorders, attributed to depleted or malfunctioned mitochondrial proteins.

Biography

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Main scientific interests

- Molecular mechanisms of action of antineoplastic agents [like anthracyclines (doxorubicin) and tyrosine kinase inhibitors (Imatinib)]
- Mitochondrial genetics and neurodegenerative disorders. Identification of SCO2 gene (AF177385; #604377) in Eric Schon's Lab, Columbia University, NYC, USA.
- Cloning, expression, purification and characterization of recombinant proteins
- PTD-mediated protein transduction into mammalian cells, as an alternative therapeutic approach for monogenetic disorders

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