SMA therapy approach

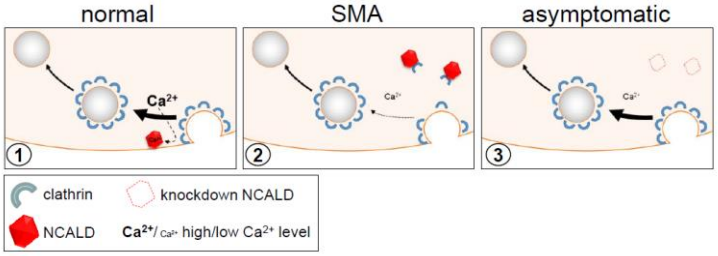
Down-regulation of NCALD in spinal muscular atrophy and diseases with a disturbed calcium homeostasis

Invention

Spinal muscular atrophy (SMA) is an autosomal recessive disorder based on the loss of the survival motor neuron 1 (SMN1) genes. The severity of the disease is inversely correlated with the copy number of the main disease modifying gene SMN2. In rare cases, siblings of SMA patients do not show SMA, although they carry exactly the same SMN1 and SMN2 gene status as their SMA affected relatives. So other genetic factors are able to fully protect homozygously SMN1-deleted individuals from developing SMA. The inventors found that this phenomenon might be caused by the overexpression of plastin 3, an actin-bundling protein, and/or low expression levels of the calcium sensing protein neurocalcin delta (NCALD).

In vitro and in vivo studies show that inhibitors of neurocalcin delta (NCALD) are suitable for treating and preventing such disorders in a patient. Said inhibitors are, likewise, effective tools for in vitro neuronal differentiation and maturation, and restoration of impaired endocytosis. Therefore, down-regulation of NCALD can revert the effect caused by the loss of SMN1. There are promising indications that a combination of an SMN2 targeted therapy with NCALD inhibitors not only reduce the symptoms of SMA patients but cure the disease as it is seen by relatives that have the same SMN1 and SMN2 gene status.

Based on that interaction, the inhibition of NCALD provides a tool to treat SMA and other neurodegenerative diseases in which disturbed calcium homeostasis plays a role, such as Parkinson and Alzheimer disease as well as amyotrophic lateral sclerosis.



Model: Inhibition of NCALD restores endocytosis and thereby synaptic vesicle recycling essential for neurotransmission at presynaptic level

Commercial Opportunities

Down-regulation of NCALD by e.g. siRNA or antisense oligonucleotides (ASOs) can be used to treat SMA and possibly other neurodegenerative diseases like Alzheimer. Potential application solely or as a combined therapy with SMN2 targeted drugs.

On behalf of the University of Cologne, PROvendis offers access to rights for commercial use as well as the opportunity for further co-development.

Current Status

In vivo studies provided evidence for a therapeutic effectiveness of NCALD down-regulation in SMA mice that express low SMN levels by restoring axon growth. In case of interest, we are pleased to inform you about the current status of the patent.

Relevant Publication

Wirth B, Garbes L, Riessland M. (2013) How genetic modifiers influence the phenotype of spinal muscular atrophy and suggest future therapeutic approaches. Curr. Opin. Genet. Dev. 23(3):330-8.

Ruiz et al. (2010) altered intracellular Ca2+ homeostasis in nerve terminals of severe spinal muscular atrophy in mice. J. Neurosci. 30(3):849-57.

An invention of the University of Cologne / University Medical Center.

Competitive Advantages

- A novel therapeutic approach to treat SMA and other neuro-degenerative disorders
- NCALD inhibitors might fully protect SMN1-deleted individuals
- New mode of action
- Combination with SMN2 drugs should be beneficial

Contact:

Ref. No. 3405
Dr. Constanze Vogel

PROvendis GmbH
Schlossstraße 11-15
45468 Muelheim an der Ruhr
Germany

Tel.: +49 (0) 208 94 105 41
Fax: +49 (0) 208 94 105 50
E-Mail: cv@provendis.info
Web: www.provendis.info