Innovative treatment of Alzheimer’s disease and related disorders - Concept for a somatic gene therapy

Project: 17013

Background /Medical Problem

Neurodegenerative disorders, namely Alzheimer’s disease (AD) and stroke giving rise to vascular dementia (VD) are most prominent. AD and stroke share a cell death pathway that is activated by unscheduled neuronal cell cycle re-entry and subsequent partial replication of DNA (see Figure 1). Moreover, the selective cell death of neurones which have replicated their DNA could be shown in AD recently. This directly proofs the link between cell cycle activation and cell death in neurons of the adult human central nervous system (CNS) and identifies the molecular control of cell cycle activation as therapeutic target.

Technology /Solution

The present therapeutic approach provides a vector which encodes a gene of the CDK4/CDK6 inhibitor of the INK4 family and a gene encoding a transactivator protein. This vector can be transferred into cells where it will exert its protective function to prevent cell death or to slow down progression of cell death by affecting the cell cycle regulation of targeted cells. The existing risks with gene therapy and specific challenges for gene therapy posed by the central nervous system will be met through viral or non-viral vectors for safe gene transfer, cell type specific recognition systems, cell-type specific expression system and controlled delivery by convection-enhanced delivery. The modular character of the gene therapeutic tools allows to adapt the above concept in alternative specifications for the treatment of a wide variety of other neurological disorders where unscheduled cell-cycle re-entry of cells is of critical importance such as Parkinson’s disease, stroke, amyotrophic lateral sclerosis or proliferative vitreoretinopathy.

Benefits

• Therapeutic concept of neuroprotection to slow down or even prevent cell death by neuron-specific targeting of the cell cycle
• Neuroprotective effects had been proven on in vivo models of ischemic cell death and excitotoxicity mimicking the effects of Aβ (see picture).
• High therapeutic efficacy and minimal or no side-effects based targeted gene transfer in combination with neuron-specific promoters and regulable gene silencer elements
• Anticipation to bring these therapeutic tools in a joined effort to a first clinical application within a framework of five years

AD or stroke will be in the direct focus of the first therapeutic application. The Approach will also be applicable to other neurodegenerative disorders and non-neuronal disorders with unscheduled cell-cycle activation, such as cancer or atherosclerosis.

Fig. 1: Major regulators of the activation of the cell cycle and its orderly progression are re-expressed in pyramidal neurons in Alzheimer’s disease prior to neurofibrillary degeneration.

Fig. 2: Ischemic cell death: Transgene expression protects against neurodegenerative cell death induced by ischemia (middle cerebral artery occlusion; MCAO). The mouse brain lesion volume is reduced by 50 – 70%.
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Development Status

Idea
- Gene therapeutic tools for the treatment of a wide variety of other neurological disorders

Demonstrator
- Neuroprotective effects had been proven on in vivo models of ischemic cell death and excitotoxicity mimicking the effects of Aβ (see Figure 2).

Prototype
- Prototype available for demonstration

Series Production

Intellectual Property Rights
- EP2620447 (B1); WO2010089122 (A3);

Cooperation Options
- License Agreement
- R&D Agreement
- Ownership Agreement

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