IMPROVED RETROGRADE LENTIVIRAL VECTORS FOR GENE THERAPY IN MOTOR NEURON DISEASES

Fact Sheet

Project information

IRLVGTMND
Grant agreement ID: 233147
Status
Closed project
Start date
1 April 2009
End date
31 August 2014

Funded under:
FP7-IDEAS-ERC

Overall budget:
€ 2 000 000
EU contribution
€ 2 000 000

Hosted by:
IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY AND MEDICINE
United Kingdom

Objective

Lentiviral vectors can be targeted to specific cell types by varying the envelope proteins, a process called pseudotyping. The rabies-G pseudotyped lentivectors are useful for distal targeting of neurons because they are retrogradely transported to the nucleus where they integrate and express the transgene, as first demonstrated by us. Motor neuron (MN) diseases are incurable neurodegenerative diseases causing progressive paralysis and premature death. Most amyotrophic lateral sclerosis (ALS) cases are sporadic, but there are rare inherited forms one of which being due to mutations in the superoxide dismutase (SOD1) gene. Spinal muscular atrophy (SMA) is the second commonest genetic disease affecting children and is due to mutations in the survival motor neuron (SMN1) gene. In mouse models for ALS (SOD1 mutant mouse) or SMA (SMNDelta7 mouse) when we delivered in various muscle groups rabies-G pseudotyped lentiviral vectors expressing either vascular endothelial growth factor or short interfering RNA targeted to a mutated SOD1 gene or the normal SMN1 gene we corrected motor defects and extended survival. Despite these successes, experiments with rabies-G pseudotyped vectors in non-human primates have failed to give good efficiency of transduction of MNs so as to translate this approach to the clinic. Also SMN-1 targeted replacement produced only a marginal increase in survival despite sparing MNs. In this grant we propose: 1) To investigate the molecular pathway of retrograde transport of the rabies-G lentiviral vectors. This might allow us to increase the efficacy of gene transfer with these vector systems. 2) To design novel lentiviral vectors with tropism to the neuromuscular junction (NMJ) so as to try to
increase the efficiency/specificity of gene transfer to MNs. 3) To utilise the new NMJ-targeted lentiviral vector derived in (2) to simultaneously deliver several neuroprotective proteins to MNs and test its efficacy in animal models of ALS and SMA.

Field of Science

/natural sciences/biological sciences/zoology/mammalogy/primatology

/medical and health sciences/medical biotechnology/genetic engineering/gene therapy

/natural sciences/biological sciences/genetics and heredity/mutation

/natural sciences/biological sciences/biochemistry/biomolecules/proteins

/social sciences/social and economic geography/transport

/social sciences/sociology/anthropology/physical anthropology

/medical and health sciences/basic medicine/neurology/amyotrophic lateral sclerosis

Programme(s)

FP7-IDEAS-ERC - Specific programme: "Ideas" implementing the Seventh Framework Programme of the European Community for research, technological development and demonstration activities (2007 to 2013)

Topic(s)

ERC-AG-LS7 - ERC Advanced Grant - Diagnostic tools, therapies and public health

Call for proposal

ERC-2008-AdG

See other projects for this call

Funding Scheme

ERC-AG - ERC Advanced Grant

Principal Investigator

Nicholas Mazarakis (Prof.)

Host institution
<table>
<thead>
<tr>
<th><strong>Beneciaries</strong> (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY AND MEDICINE</strong></td>
</tr>
<tr>
<td><strong>Address</strong></td>
</tr>
<tr>
<td>South Kensington Campus Exhibition Road Sw7 2az London</td>
</tr>
<tr>
<td><strong>United Kingdom</strong></td>
</tr>
<tr>
<td><strong>Principal Investigator</strong></td>
</tr>
<tr>
<td>Nicholas Mazarakis (Prof.)</td>
</tr>
</tbody>
</table>