Improved retrograde lentiviral vectors for gene therapy in motor neuron diseases

https://neurodegenerationresearch.eu/survey/improved-retrograde-lentiviral-vectors-for-gene-therapy-in-motor-neuron-diseases/

Title of project or programme

Improved retrograde lentiviral vectors for gene therapy in motor neuron diseases

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
Professor	Nicholas	Mazarakis		UK

Address of institution of lead PI

Institution	Imperial College London
Street Address	South Kensington Campus
City	London
Postcode	SW7 2AZ

Country

United Kingdom

Source of funding information

European Research Council

Total sum awarded (Euro)

2000000

Start date of award

01-04-2009

Total duration of award in months

60

The project/programme is most relevant to

- Motor neurone diseases
- Spinal muscular atrophy (SMA)

Keywords

Research abstract in English

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.

Lay summary