

Novel treatment for Huntington's Disease using zinc finger gene therapy

A novel gene therapy for Huntington's Disease that leverage zinc finger protein technology.

Proposed use

Novel zinc finger proteins, delivered to the brain through the use of AAV viral vectors, have been designed to efficiently and selectively repress the mutant huntingtin gene. *In vivo* data in an acute mouse model of Huntington's Disease shows sustained repression after a single dose, and restoration of motor co-ordination to levels comparable to those of healthy controls.

Technology overview

Huntington's disease (HD) is a dominantly inherited neurodegenerative disorder caused by expanded CAG (polyglutamine) repeats in the huntingtin (HTT) gene. There is currently no cure and a limited number of approved symptomatic treatments available to individuals with HD. Lowering mutant HTT reverses the disease phenotype in animal models and several approaches are in development that target the RNA or the mutated huntingtin protein, but none has yet proved to be effective or selective enough. Researchers at Imperial College London and the Centre for Genomic Regulation (CRG) have developed and validated *in vitro* and *in vivo* a new therapeutic approach that induces selective repression of the mutant HTT gene using synthetic zinc finger (ZF) proteins delivered to the brain using adeno-associated viral vectors (AAV). The first generation ZF construct mediated acute dose-dependent repression *in vivo* upon striatal injection in R6/2 mice, resulting in a reduction in mutant HTT protein aggregates and improvement of functional behaviour (reduced decline in rotarod performance and alleviation of claspings). A third generation ZF construct optimised for increased expression and persistence of the ZF protein in the brain mediates long-term mutant HTT repression to therapeutic relevant levels (at least 25% repression) *in vivo* after a single injection in R6/1 mice.

Intellectual property

Technology is covered by patents:

[WO20130493321A](#)

[US20160200781A1](#)

Benefits

- Therapy based on proprietary zinc finger protein technology – to date, the only clinically validated class of engineered DNA-binding proteins
- ZF construct design achieves specific binding to polyCAG/CTG repeats
- Selective for mutant HTT gene with no signs of repression of wild type HTT and limited risk of toxicity/non-specific binding
- Potentially more effective than other therapeutic approaches in development for HD (e.g. antisense oligonucleotides), tackling the challenge of trinucleotide expansion at the source (i.e. the defect at the DNA level)
- *In vivo* data in relevant disease models using well-established and clinically validated adeno-associated viral vectors as ZF delivery vehicle
- Sustained repression of mutant HTT observed from a single dose, suggesting potential for long-term curative treatment
- Potentially applicable to other polyglutamine (polyQ) disorders

Stuart Sims

Industry Partnerships and
Commercialisation – Natural
Sciences

e: s.sims@imperial.ac.uk

t: +44 (0)20 7594 3461

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