# 288 Novel treatment for Huntington's Disease

## Asset Overview

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| **Product Type** | Gene therapy |
| **Indication** | CNS Diseases |
| **Current Stage** | Lead Identification / optimization |
| **Target(MoA)** | Mutant HTT gene with no signs of repression of wild type HTT |
| **Brief Description** | Synthetic zinc finger (ZF) proteins can be targeted to desired DNA sequences and are useful tools for gene therapy. We recently developed a ZF transcription repressor (ZF-KOX1) able to bind to expanded DNA CAG-repeats in the huntingtin (HTT) gene, which are found in Huntington's disease (HD). This ZF acutely repressed mutant HTT expression in a mouse model of HD and delayed neurological symptoms (clasping) for up to 3 weeks. In the present work, we sought to develop a long-term single-injection gene therapy approach in the brain. |
| **Organization** | Imperial College London |

## Differentiation

□ **HD Market Will Exhibit Significant Growth Between 2014 and 2024**

- In the 2014 pharmaceutical sales for the HD market at approximately $252.6m across the 7MM (7MM; US, France, Germany, Italy, Spain, UK, and Japan)
- GlobalData expects this market to grow at a significant compound annual growth rate (CAGR) of 26.5% during the forecast period, to reach sales of $2,648.3M in 2024
- The greatest unmet need in HD is the development of a drug that will slow or halt the progression of the disease, or prevent the development of HD

□ **Engineering zinc fingers to bind new DNA sequences**

- Huntington's disease: expanded poly CAG repeats
- Zinc fingers target the mutation at its root in the DNA (to bind GCA, GCT (ie CAG)), consequently not allowing mutant HTT RNA transcripts - which are themselves toxic - ever to be transcribed (ASO targets existing toxic RNA)

□ **Opportunities for partnership**

- This approach latest gene expression constructs achieve long-term suppression of mutant HTT in mice from a single injection
- Unlike ASO, they have a generic approach to avoid targeting the short WT Huntingtin allele - which must not
- This approach could be expanded to treat other rare monogenic triplet expansion diseases

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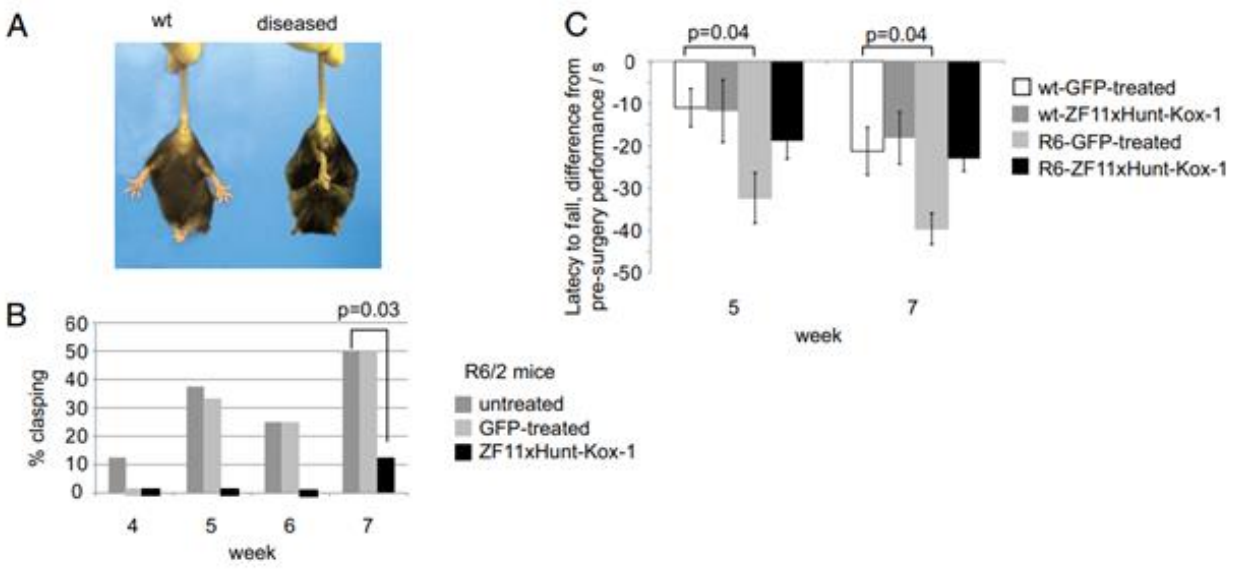
## Key Data

### Rescue of HD phenotypes with in vivo zinc finger treatment




(A) HD mice show a characteristic clasping behavior (diseased) corresponding to neurological pathology. (B) Clasping assay shows a significant improvement after zinc finger treatment in both hemispheres (P = 0.03). Only 1 in 8 zinc finger-treated mice displays symptoms by week 7, compared with 6 in 12 control mice. (C) Performance in the accelerating rotarod shows a clear decline with respect to presurgery levels in the GFP-injected R6/2 mice, whereas zinc finger-treated mice do not show a significant decline compared with wt mice.

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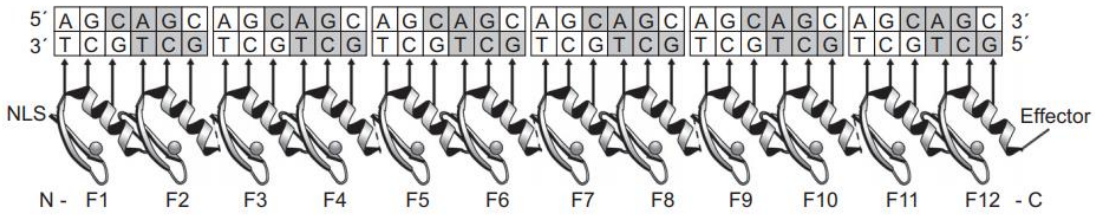
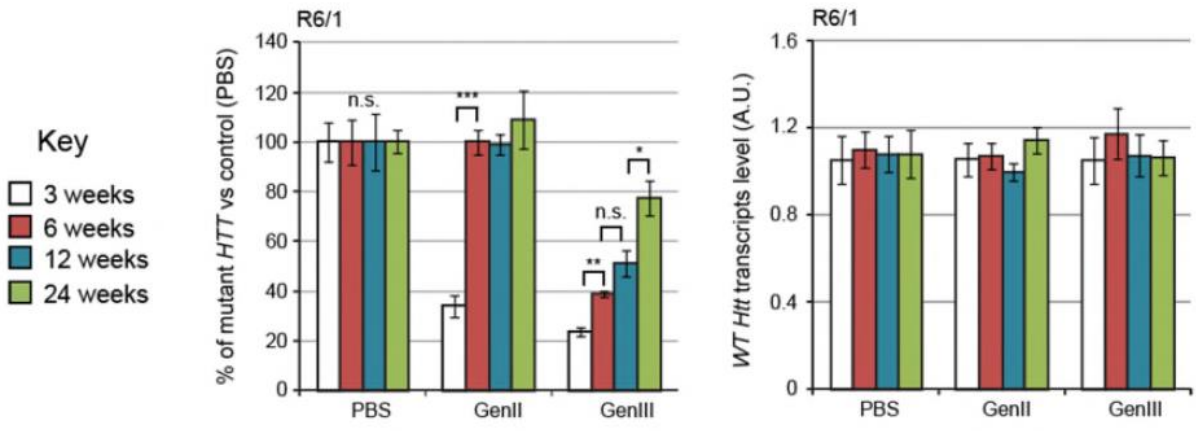
## Zinc fingers designed to bind poly-CAG




A twelve-finger array shows recognition helices contacting 5′-GCT-3′ bases on the lower DNA strand. Similar arrays of 4, 6, 12, or 18 zinc fingers were built (ZF4xHunt, ZF6xHunt, ZF12xHunt, and ZF18xHunt). Nuclear localization signals (NLS) and effectors (e.g., Kox-1 transcription repression domain) were added to N and C termini, respectively.

## Third generation (GenIII) constructs mediate long-term repression in whole brain samples after single intraventricular AAV injections




Left: At 3, 6, 12 and 24 weeks, respectively, AAV injection of GenIII resulted in 77%, 61%, 48% and 23% repression of mutant HTT in whole brain samples. Even 25% repression is expected to be within the therapeutic range and could be enhanced with higher viral dosages. Right: Other genes (including endogenous mouse WT Htt) are unaffected.

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## Intellectual Property

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| Patent No. | PCT-EP2011-068139<br>PCT-GB2016-053454 |
| Application Date | 2011.10.17<br>2016.11.04 |
| Status | Registered<br>Application Pending |
| Country | US, EP, AU<br>US, EP, AU, GB, CA |

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