Investigating molecular mechanisms

Using animal models, stem cells and human samples, we have discovered new molecular mechanisms that cause Huntington’s disease.

We have discovered that the highly pathogenic, aggregation-prone exon 1 HTT protein is generated by incomplete splicing. The level of exon 1 mRNA is proportional to CAG repeat length and present in all knock-in models of HD, and in HD post-mortem brains and fibroblast lines.

We have identified and verified new genetic modifiers of HD in DNA repair genes though studying the deeply-phenotyped TRACK-HD cohort. DNA mismatch repair is linked to somatic CAG repeat instability, which governs the level of incomplete HTT splicing. These new modifiers give us novel therapeutic targets in HD.

We have derived neural stem cell lines from our HD mouse models, which will be used to dissect the molecular mechanisms by which the seeding and polymerisation of HTT aggregation can be modulated.
Studying Huntington’s disease in patient tissues

Unique access to samples from HD patients to study mechanisms of disease in the human context

We study accessible HD patients’ cells and tissues ex vivo to yield important pathobiological insights.

There is growing evidence of shared molecular pathologies between the brain and periphery, as well as important changes in peripheral tissues of HD patients. For example, inflammation is altered in early disease both centrally by microglia, and by their peripheral equivalents, monocytes and macrophages.

New technologies let us differentiate patient-derived pluripotent stem cells into disease-relevant brain cells, including medium spiny neurons. These can be studied with high-content imaging and other techniques to examine many aspects of cellular pathobiology in the HD brain.

Subsequent ‘gene editing’ allows us to study the biological effects of genetic variants identified from large-scale genetic analyses of HD patients.
Biomarker development

Discovering new ways to predict and track Huntington’s disease to help develop and test new treatments

We need accurate ways to measure the progression of Huntington’s disease, so that we have a better idea of whether experimental treatments are working to prevent onset or slow progression in the brain.

We developed the first test that can measure the concentration of the mutant huntingtin protein in cerebrospinal fluid. This will be crucial in assessing whether ‘gene silencing’ treatments are working. Recently we discovered the first blood biomarker that can predict onset and progression of HD, and our HDClarity study is the first international cerebrospinal fluid study in HD.

Our landmark TRACK-HD study and its successor TrackOn-HD established the best imaging measures for running clinical trials and new ways of measuring the earliest brain changes in HD that help the brain compensate for the effects of the mutation.
Huntington’s disease drug development

Screening thousands of drugs for modifiers of huntingtin splicing, and improving drug delivery with engineered viruses

We have discovered that exon 1 of the huntingtin gene (HTT) does not always splice to exon 2 generating a small polyadenylated mRNA that is translated into the highly pathogenic exon 1 HTT protein.

In collaboration with the UCL Drug Development Institute, > 250,000 compounds (AstraZeneca) will be screened to identify molecules that correct this splicing deficit.

We use mouse models to validate therapeutic targets for HD by both pharmacological and genetic approaches, and for the preclinical testing of therapeutic strategies e.g. HDAC4 and HSF1.

In collaboration with Ben Deverman (Caltech), we are using AAV viruses that cross the blood brain barrier to expedite our target validation activities and for the delivery of therapeutic agents.
The first gene silencing trial

We are leading the first ever trial of a drug that targets Huntington’s disease at its source

The UCL Huntington’s Disease Centre is the lead site of the first ever ‘gene silencing’ or huntingtin-lowering trial and Professor Tabrizi is the trial’s Global Chief Investigator.

The trial is designed to test the safety of HTTRx, an antisense oligonucleotide (ASO) – a single strand of chemically-modified DNA designed to reduce production of the huntingtin protein without affecting other proteins.

Patients receive four injections into the spinal fluid at monthly intervals. The dose of drug has been increased several times and so far appears safe and well-tolerated. If successful, we hope a larger trial will follow.

Meanwhile our Wellcome-funded TREAT-HD study will use the trial to understand the mechanisms underlying neurodegeneration and recovery as well as studying the earliest changes in HD in our landmark Young Adult Study (HD-YAS).