The long-sought cure to Huntington's disease

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The current lack of a treatment proven effective against 'Huntington's disease' (HD) is leaving one in every 10 000 people with psychiatric, movement, feeding and communication problems that are very difficult to live with. An EU consortium believes it has found the long-sought after cure and is getting very close to its first preclinical studies.

For those who have been closely following research related to HD, the term 'zinc fingers' probably sounds familiar. In 2012, a group of researchers from Spain turned heads among stakeholders when they publically announced the successful use of synthetic zinc fingers—zinc proteins are known for their role in enabling cells to control the activity levels of different genes in our DNA—to fight Huntington's disease.

The zinc fingers were tested in genetically-engineered cells, HD patient cells and the brain cells of HD mice. In the latter, they managed to reduce the activity of the mutant form of the huntingtin gene by 50 % without any evidence of harmful effects. And unlike standard gene silencing, this solution is aiming directly at the DNA rather than the RNA message molecule.

The FINGERS4CURE (Zinc finger gene therapy in the brain for treating Huntington's disease) project picked up where this research effort had left off, by trying to make the expression of zinc fingers long enough to sustain a single-intervention, long-term therapy in humans.

Dr. Mark Isalan, Reader in Gene Network Engineering at Imperial College London and coordinator of FINGERS4CURE, discusses the

results of the project a few weeks ahead of its completion.

How do you explain the current absence of a cure for HD patients?

It should be noted that several treatments are in development, but clinical trials and safety testing are unfortunately taking a long time. Some promising clinical trials are just beginning.

HD is a distinctive disease that presents both advantages and difficulties for developing treatments. Compared to other neurodegenerative diseases, a main advantage is that it is a single gene disease—early mouse studies clearly showed that the disease can be stopped and reversed just by reducing expression of the mutant Huntingtin gene that causes toxic protein aggregates in the brain. The difficulties are that Huntingtin is expressed in many cell types and that it has to be suppressed for the lifetime of the patient. Another consideration is that patients have a second non-mutant copy of the gene and treatments should ideally leave this gene alone. The exact mechanisms through which the mutant huntingtin gene causes disease are not fully understood. This means that an ideal cure would cut off the problem at its source: by preventing the bad gene from ever being expressed in cells.

What kind of solution do you propose under this project?

We have spent the last ten years developing a genetic off-switch, called a zinc finger that specifically targets the bad mutant Huntingtin gene. The zinc finger sticks to DNA and switches off gene expression. Back in 2012, we were the first to show that we could deliver the zinc fingers to mice quite efficiently and that we could specifically turn off the bad gene. Excitingly, one injection halted neurological symptoms in

Huntington's mice for a couple of weeks. The problem at that stage was that the zinc finger effect did not last very long. The new FINGERS4CURE project aimed to overcome that problem.

You tested this new gene therapy on mice. Are you happy with its performance?

We are very excited by our latest results: we used the FINGERS4CURE project to optimise the specific design of our zinc finger to make it invisible to the host immune system, and to allow its expression for a much longer period of time. We are about to submit a new paper on this work, reporting how we can now achieve specific repression of mutant Huntingtin for a least 6 months after a single injection. For comparison, other therapeutic strategies, such as antisense oligonucleotides or siRNAs, act one level up from the DNA—at the level of RNA—and require more frequent infusions. Our long-term repression, which works at the root of expression, is a major step forward and required a lot of trial-and-error work.

How close would you say you are to testing this therapy on humans?

Based on the new generation constructs, we are edging closer. We feel more confident that the construct we have designed is the right one to progress into larger preclinical studies to understand factors such as safety, toxicology, the ideal dose and frequency of dosing to achieve the desired level and duration of repression. This would enable us to design and start a clinical study in patients. Our main barrier now is securing the quantum of funding for these extensive studies as well as an industrial partner who can help guide translation, product development and advanced clinical trials.

Speaking of which, where do you stand with your attempts to find this industrial partner?

This work has been a progressive journey from my work at the Centre for Genomic Regulation (CRG), in Barcelona, to my current lab at Imperial College London. The Technology Transfer Offices of both Institutions (TBDO for CRG and Imperial Innovations for Imperial College) are working together to approach potential partners now that we have these new results. Based on the fact that we can get long-term effects in vivo, we believe that we have something unique to offer in terms of a therapy.

When do you think patients could start benefitting from the project's outcomes?

It cannot be early enough. I am well aware of the unimaginable suffering currently borne by both patients and their families. The pace of the formal development process is often frustratingly slow, but this is unavoidable to ensure safety and efficacy. All I can say is that we will do our best to move this forward as quickly as possible.

More information: Project website: cordis.europa.eu/project/rcn/193795_en.html

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