Delivering therapy beyond the blood-brain barrier

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Brain diseases are particularly challenging to treat. Every substance that has to be delivered to the brain needs to overcome several obstacles, such as the blood-brain barrier—a system that prevents potentially dangerous substances, but also many drugs, to enter this organ—,to get to its target. This is true not only for drugs, but also for the viruses that many scientists think could be used as vehicles, or vectors. These would deliver functioning genes in the brain as a way to treat neurodegenerative diseases. Now, the EU-funded project BrainCAV, completed in 2013, has tried to develop and test one such vector in animals. Project coordinator Eric Kremer, director of research at the CNRS Institute of Molecular Genetics at Montpellier, in France, talks to youris.com about the strength of this approach and of its possible applications in the treatment of brain diseases.

How did you discover that the CAV-2 virus you were researching could infect neurons?

We started working with canine adenovirus type 2, or commonly referred to as CAV-2, back in 1994. CAV-2 is best known for its ability to infect the respiratory tract of dogs and give a mild cough. In the early 1990's, CAV-2 was the only nonhuman adenovirus that had been sequenced and well characterized. This was because an attenuated strain was used as a vaccine in dogs. The lab's initial idea was to use it for gene therapy for cystic fibrosis. However, we serendipitously found that CAV-2 vectors were very good at infecting neurons in the central

nervous system.

Why is this virus considered a good candidate for gene therapy of brain diseases?

Humans are constantly exposed to adenoviruses. We probably have five or ten adenoviruses circulating at any given time. The idea was to use a non-human adenovirus to prevent the neutralisation of the vector by the immune response in humans. CAV-2 vector also had some other interesting characteristics. When we injected it into the brain, we found that it preferentially infected neurons. Another characteristic is that it goes to numerous brain structures via the axons that project into the site of injection. In addition, one can put several genes or expression cassettes in it. Or alternatively very big genes.

What tests have you performed on the vector?

We incubated CAV-2 vectors in cells from almost every species imaginable and injected them into the brains of mice, rats, guinea pigs, dogs, lemurs and old and new world monkeys. We also tested the vector in human brain tissues. Then we created a vector to treat a rare orphan disease, mucopolysaccharidosis type VII (MPS VII), also called Sly syndrome. This affects the entire brain. There are only a few hundred documented cases of MPS VII. But it is a member of a larger group of diseases called mucopolysaccharidoses. What we did is put a good copy of the gene affected into the vector and tested it in the brains of mice and dogs with the disease.

For what other kind of diseases could CAV-2 vectors be used?

The options are only limited by our imagination. For the brain, many of

the other eleven mucopolysaccharidoses are potential targets. In parallel, we also hope to use it as a tool to understand brain diseases. For example, we have tried to create a primate model of Parkinson's disease. Our idea is that with CAV-2 vectors we could infect dopaminergic neurons, which are some of the neurons affected in Parkinson's disease. We could also express mutated Parkinson's disease-related genes and induce symptoms of the disease.

What is the next step?

Our idea at the moment is to continue with mucopolysaccharidosis, in particular type VII. We hope that once we have the proof of principle showing we can treat the neuropathology and the cognitive effects associated with the disease, we will then be able to produce a vector according to so called Good Manufacturing Practices—which are regulations for the production and use of vectors as drugs—and propose it as a therapy.

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