DNA nanoparticle gene therapy in brain

Dr David Yurek at the University of Kentucky, and his collaborator Dr Mark Cooper, a founder of Copernicus Therapeutics, Inc, are taking a novel approach to gene therapies in treating disorders of the brain. While the treatments for diseases such as Parkinson’s have developed, they have limited effectiveness and do not improve Parkinson’s natural history. This proficient team are applying their findings to discover innovative ways to overcome these limitations and improve Parkinson’s disease treatment.

Brain disorders are some of the most abundant, diverse and troublesome to treat physiological conditions clinicians encounter. Due to the complexity and inaccessibility of the brain, many of its associated disorders have suboptimal therapeutic options. Nonetheless, novel approaches such as gene therapy provide potential in overcoming these barriers.

Gene therapies directly target depleted levels or mutant forms of proteins within cells, often using parts of DNA known as ‘gene segments’ incorporated into viral vectors. However, in the case of neurons, delivering and expressing the normal gene is challenging because neurons are post-mitotic (they do not reproduce), and there is a danger of viral vector immune responses.

BREAKING THROUGH – NANOPARTICLES

Alongside Dr Mark Cooper of Copernicus Therapeutics, Inc., Dr Yurek has used non-viral gene therapy vectors developed at Copernicus to treat neurological diseases, including Parkinson’s. These vectors are compacted into rod-like DNA nanoparticles (DNPs), and with these Dr Yurek and his research team were able to express the transfected gene within neurons and astrocytes to levels one hundred times that of naked plasmid DNA. It is the small size (8–11 nm) of these DNPs and their stability in nuclease-rich environments that allow them to diffuse safely and efficiently to the nucleus through the nuclear membrane envelope – an essential process for gene therapy of post-mitotic cells. Studies have demonstrated localisation of transfected gene expression to injection sites, and have revealed stable protein levels up to one year after a single treatment.

Furthermore, DNPs have been demonstrated to exhibit much fewer inflammatory, toxicity and immune responses when compared to viral vector approaches, strengthening promise for their clinical application. Ultimately, Dr Yurek, Dr Cooper and researchers at Copernicus Therapeutics hope to develop this approach as a treatment for Parkinson’s disease (PD) and other degenerative brain disorders.

USES AND IMPROVEMENTS

During Dr Yurek’s and Dr Cooper’s studies investigating DNP performance and viability, the gene coding for glial cell line-derived neurotrophic factor (GDNF) was successfully transfected to cells of the rat striatum to produce overexpression of the protein – measured up to six months post-injection. Interestingly, GDNF has been shown to...
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What made you realise the potential of improving genetic therapies for brain disorders? Previous successful studies that used viral vectors as a means to transduce brain cells and overexpress therapeutic proteins provided the impetus to find an alternative and safer means to introduce therapeutic genes into brain cells. These nanoparticles have been found to be non-toxic when delivered to the lung of humans and when delivered to the nasal mucosa, lung, eye, and brain of animals.

Do you believe that DNP transfection alone can bring about marked improvements in Parkinson’s disease, enough for clinical use? Nanoparticles may provide a means to deliver therapeutic genes to brain cells at physiologically relevant levels. This may be very significant when one considers that high expression of therapeutic proteins can lead to adverse off-target effects and can lead to the generation of antibodies that subsequently diminish the effects of these therapeutic proteins. In terms of clinical efficacy, “bigger is not always better” and therefore low, sustained expression of therapeutic genes may provide better long-term outcomes.

Have you looked into the specifics of treating any other neurological disorder with this approach? What is the potential? We have demonstrated these nanoparticles target both neurons and astrocytes, which suggests that other neurodegenerative disorders such as Alzheimer’s disease or traumatic brain injury may benefit from nanoparticle gene therapy. One of the cell surface receptors for nanoparticles, the nucleolin, is highly expressed on the cell surface of some types of gliomas and therefore there may be some utility in using these nanoparticles to target brain tumours.

From these studies and your experience, can you see it being a smooth transition to DNP gene therapies in human cells? One of the challenges of translating animal studies to human studies is the ability to scale-up the delivery of the nanoparticles to affect the larger brain structures in humans. These challenges can be overcome by using multiple deliveries of nanoparticles into specific brain regions or by developing a mean for these nanoparticles to pass through the blood brain barrier at specific brain regions. Early data suggests this is possible using intranasal administration of DNA NPs.

How will your findings contribute to developing novel data, such as research techniques and methodologies? The use of gene therapy to express or knock-down (using RNA interference technology) genes of interest may prove useful in exploring and understanding numerous biological pathways important for neurological processes, including neural outgrowth and connectivity, myelination, cell-cell recognition, formation of neural synaptic units and synaptic plasticity.

Dr. Yurek received his Doctor of Philosophy degree in Physiology and Biophysics in 1987 from the University of Southern California. He completed his postdoctoral studies at the University of Rochester and is currently a Research Professor in the Department of Neurosurgery and a faculty member of the Nanobiotechnology Center at the University of Kentucky.

Dr. Cooper received his BA degree from Cornell University and his MD degree from Johns Hopkins University. He joined the faculty at Case Western Reserve University School of Medicine where he was an Associate Professor of Medicine, is a founding scientist of Nanobiotechnology Therapeutics, and is now Senior VP of Science and Medical Affairs at Copernicus.

Dr. Yurek works in collaboration with Dr Mark Cooper and Copernicus Therapeutics, Inc. to research the functions and efficacy of using nanoparticles as a gene therapy technique for a number of neurological disorders.

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BIO
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