news

Non-viral gene therapy lights up

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Safety concerns raised by the use of viruses to deliver genes to the inflamed lungs of cystic fibrosis patients have made non-viral approaches the field's leading therapeutic candidates. Among these non-viral gene therapy vectors are DNA nanoparticles, compacted DNA plasmids carrying the cystic fibrosis transmembrane regulator (CFTR) gene that have shown promise in a phase I clinical trial [1]. Now, researchers at Case Western Reserve University and Copernicus Therapeutics have developed a way to image the delivery, expression, and stability of these DNA nanoparticles, bringing light to this potential therapy (Figure 1).

A chronic condition needing continuous treatment

Cystic fibrosis, an autosomal recessive genetic disease, affects >70,000 people worldwide. Even with current therapy, which typically includes daily physiotherapy and aggressive treatment with antibiotics and anti-inflammatory drugs, most patients do not survive beyond their early 30s, says Deborah Gill, research lecturer at the University of Oxford, UK.

Although both viral and non-viral gene therapy showed initial promise, scientists soon found that the effectiveness of viral gene therapy diminished with the repeated administrations necessary to treat the disease. 'Gene therapy for cystic fibrosis must correct the cells of patients on an ongoing, repetitive basis so the patient's quality of life will improve and their lifespan increase,' explains Assem G. Ziady, assistant professor of pediatrics at Case Western Reserve University, USA.

Ziady and his colleagues at Case Western and Copernicus Therapeutics, a Cleveland, Ohio-based biotechnology company, have developed a non-viral gene therapy approach that delivers a copy of the CFTR gene to the airway of cystic fibrosis patients [2,3]. Called a 'DNA nanoparticle,' it consists of a plasmid that has been compacted with polyethylene glycol-substituted 30-mer lysine peptides. 'The [DNA nanoparticle's] small size facilitates its efficient uptake and expression,' says Mark J. Cooper, Senior Vice President of Science And Medical Affairs at Copernicus.

A Phase I clinical trial completed in 2004 found most patients had evidence of partial to complete correction for the CFTR gene, which produces a protein needed to correct the basic defect in cystic fibrosis cells, and no significant side effects [1]. 'Their approach offers a whole new strategy which hasn't been tested before,' says Gill, who works with a non-viral vector composed of plasma DNA complexed with a cationic lipid developed by Cambridge, Mass.-based Genzyme Corporation.

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Determining therapeutic doses by light

Most recently, the researchers have begun developing a technology that will enable them to locate DNA nanoparticles once they have been administered and measure the level of gene expression. Compacted DNA nanoparticles that contain a plasmid with the firefly luciferase gene – a reporter gene that produces light in the presence of its substrate, luciferin – were injected into mice trachea and followed using bioluminescent imaging [4] (Figure 1).

'Imaging allows you to do repeated studies on the same subject,' says Zhenghong Lee, assistant professor of radiology at Case Western. 'We can find out where the gene particles are expressed, the level of gene expression and the duration of gene expression.' Because the luciferase plasmid was designed to have a composition similar to the CFTR gene, the information that results will have direct implications for future clinical trials. 'You can use the imaging studies to gauge how often you need to give the nanoparticle cocktail to maintain efficacy of the drug over time in patients,' says Ziady.

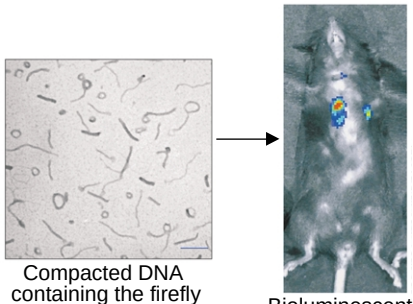

FIGURE 1

DNA nanoparticles containing the firefly luciferase gene release expressed in mouse lungs two days after administration. Image courtesy of A.G. Ziady of Case Western Reserve University.

The next step is to develop a tag for the CFTR gene that could be used to follow its expression *in vivo*. Gill says that to do so, the researchers face two challenges: developing a system that's sensitive enough to measure low levels of expression and to specify the cell type where the expression is occurring. 'If there were whole-body imaging systems that could give you that sensitivity, it would be fantastic,' she says.

References

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