Developing a gene therapy for cystic fibrosis airway disease

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Cystic Fibrosis (CF) is a life-long multi-organ genetic disease and should be an ideal candidate for a genetic therapy, but it has been over 20 years since the CFTR gene was discovered and despite significant advances no gene therapy is yet available for any aspect of CF.

Our group has focussed on developing practical methods to gene-correct CF lung disease that can be tested in animal models. Lung disease is an obvious target since it is the overwhelming cause of the progressive decline in quality of life and for the early death that often occurs from eventual lung failure.

We use a highly-modified HIV-1 viral vector to deliver the gene payload. During development a test (reporter) gene is used for investigation in normal animal models, subsequently the effect of delivering the corrective (CFTR) gene into CF transgenic animals is examined.

Amongst the major challenges that have delayed progress in the field we significantly developed techniques in two key areas using *in vivo* animal models: improved efficiency of airway gene transfer, and the ability to non-invasively image aspects of airway health.

We can now produce efficient airway gene transfer in intact animal airways, and enable long-term genetic correction of the electrophysiological defect in CF mouse airways. Unexpectedly, gene correction of only nasal airways in CF mice resulted in a substantial survival benefit, with treated CF mouse lifetimes more than doubling, to approach those of normal mice. The mechanism underlying this effect remains to be investigated.

The emergence of our novel *in vivo* measurement technique for examining airway and lung health in animal models has relied on use of synchrotron phase-contrast X-ray imaging. Changes in airway health markers such as mucociliary transit (MCT) and airway surface liquid (ASL) depth can now be examined. In the latter case we have recently obtained the first imaging data able to directly measure ASL depth and show that hypertonic saline aerosol treatment - a current clinical treatment for CF lung disease - increases ASL depth *in vivo* as predicted. An exciting development for understanding lung physiology in health and disease is our new-found ability to monitor lung function *via* X-ray in any region of the lung. Currently, only global measures of lung function (*i.e.* spirometry and derivatives) are available, and these are insensitive to the small areas of regional lung mucus obstruction and infection that establish CF disease early in life. The result is that initial CF lung disease – disease that later becomes irreversible – is difficult to detect and so be able to treat. Our goal here is to provide lung imaging tools to help make prevention a realistic option in CF lung disease treatment.

These recent advances in gene transfer effectiveness and in novel lung and airway imaging now provide us new tools to use in the continuing fight to prevent or effectively treat CF airway disease.