

## ***The Lancet Respiratory Medicine*: First trial of gene therapy for cystic fibrosis to show beneficial effect on lung function**

**\*\*Embargo: 00:01 [UK time] Friday 3 July, 2015\*\***

For the first time gene therapy for cystic fibrosis has shown a significant benefit in lung function compared with placebo, in a phase 2 randomised trial published in *The Lancet Respiratory Medicine* journal. The technique replaces the defective gene response for cystic fibrosis by using inhaled molecules of DNA to deliver a normal working copy of the gene to lung cells.

“Patients who received the gene therapy showed a significant, if modest, benefit in tests of lung function compared with the placebo group and there were no safety concerns,” said senior author Professor Eric Alton from the National Heart and Lung Institute at Imperial College London. “Whilst the effect was inconsistent, with some patients responding better than others, the results are encouraging.” [1]

Cystic fibrosis is a rare inherited disease caused by mutations in a single gene called cystic fibrosis transmembrane conductance regulator (CFTR) and affects 1 in every 2500 newborns in the UK and over 90000 people worldwide. Scientists have discovered around 2000 CFTR mutations so far. These mutations make the lining of the lungs secrete unusually thick mucus. This leads to recurrent life-threatening lung infections, which result in lung damage that causes 90% of deaths in people with cystic fibrosis.

Since the discovery of the genetic basis for cystic fibrosis in 1989, scientists have developed a variety of viral and non-viral vector systems for delivering a corrected CFTR gene back into lung cells. Despite expectations of a rapid breakthrough, no cystic fibrosis gene therapy trial so far has been able to show long-term clinical improvement.

Coordinated by the UK Cystic Fibrosis Gene Therapy Consortium [2], the two-year study involved 136 CF patients aged 12 years or older from across the UK. Participants were randomly assigned to either 5ml of nebulised (inhaled) pGM169/GL67A (gene therapy) or saline (placebo) at monthly intervals over 1 year. Lung function was evaluated using a common clinical measure of the volume of air forcibly exhaled in one second (FEV<sub>1</sub>).

After a year of treatment, in the 62 patients who received the gene therapy,

FEV<sub>1</sub> was 3.7% greater compared to placebo [3]. This was a result of stabilisation of respiratory function rather than an improvement. However, the effects were inconsistent, with some patients responding better than others. In particular, in the half of patients with the worst lung function at the start of the study, there was a doubling of the treatment effect, with changes in FEV<sub>1</sub> of 6.4%.

Overall, the gene therapy was well tolerated and patients in the treatment and placebo groups experienced similar rates of adverse events.

According to senior co-author Professor Stephen Hyde from the Gene Medicine Research Group at the University of Oxford, “Stabilisation of lung disease in itself is a worthwhile goal. We are actively pursuing further studies of non-viral gene therapy looking at different doses and combinations with other treatments, and more efficient vectors.” [1]

Senior co-author Dr Alastair Innes from Western General Hospital, Edinburgh, UK adds, “Publication of this trial is a landmark for cystic fibrosis patients and we are particularly grateful to the many patients across the UK who gave their time and effort to participate and make this collaborative venture a success.” [1]

#### NOTES TO EDITORS:

This study was funded by a partnership between the UK Medical Research Council (MRC) and the National Institute for Health Research (NIHR).

[1] Quotes direct from authors and cannot be found in text of Article.

[2] The UK Cystic Fibrosis Gene Therapy Consortium is a group of scientists and clinicians from Imperial College London, the Universities of Oxford and Edinburgh, the Royal Brompton and Harefield NHS Foundation Trust and NHS Lothian who have worked together for over fifteen years to develop gene therapy for CF supported by the Cystic Fibrosis Trust <http://www.cfgenetherapy.org.uk/index.php>

[3] The 95% confidence interval for the effect size is 0.1% to 7.3%. Thus, although the best estimate of the effect size is 3.7%, the data are consistent with the true effect size lying anywhere in the range 0.1% to 7.3%. This interval straddles values from no effect to clear clinical relevance.

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