



GENERATION OF A CLINICAL TRIAL PLASMID FOR CYSTIC FIBROSIS LUNG GENE THERAPY

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The UK Cystic Fibrosis Gene Therapy Consortium



<http://users.ox.ac.uk/~genemed>

<http://www.cfgenetherapy.org.uk>

Poster download available

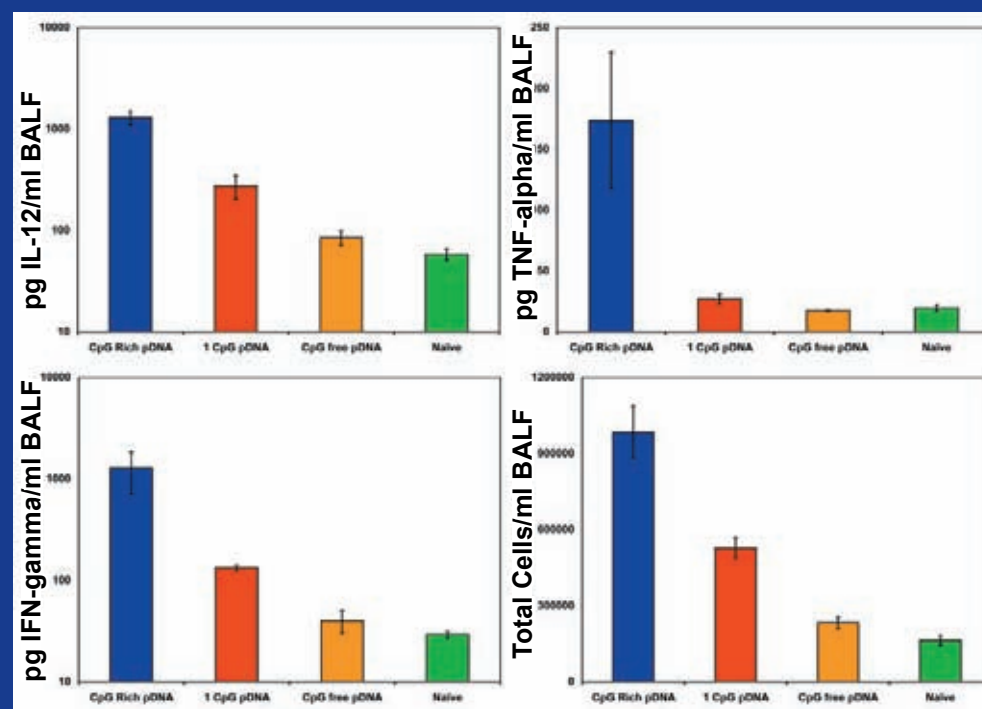
In 2008 the UK Cystic Fibrosis Gene Therapy Consortium will conduct its first clinical trials in the UK
This poster highlights some of the major landmarks of this research programme over the past 5 years

2004

PLASMID DNA DEVELOPMENT I

- First CpG-free plasmids introduced

 - GL67/pDNA instilled to mice (BALB/c, n=6)
 - BALF collected at 24 hours post dosing
 - BALF assayed for:-
 - IL-12
 - TNF-alpha
 - IFN-gamma
 - Total cells



- No inflammation from CpG-free plasmids
- CpG-rich pDNA result in high levels of all inflammatory markers
- 1-CpG plasmid results in intermediate response
- Response from CpG-free plasmid = naive mouse
- More details on Poster 1015

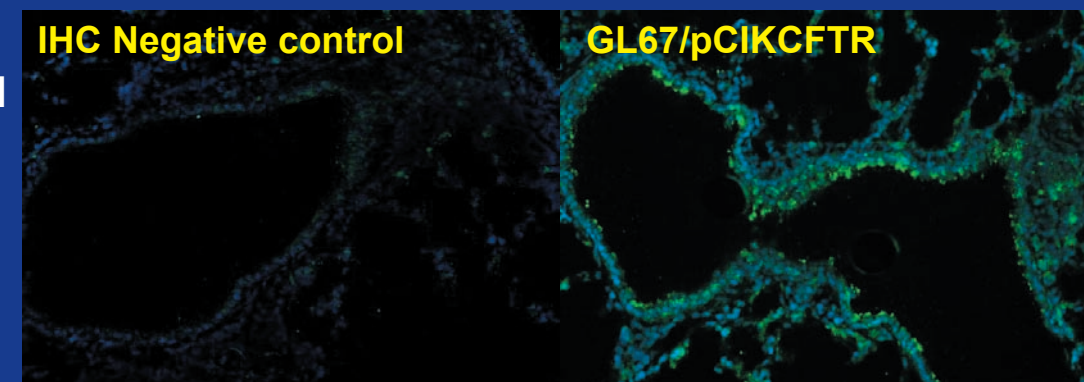
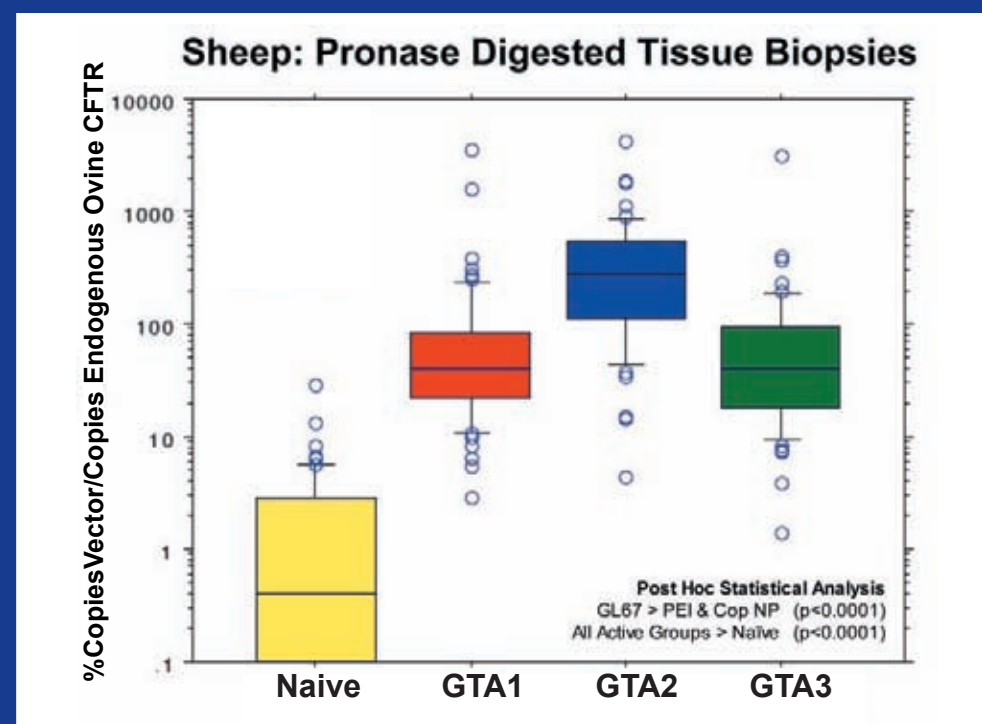
- 2004
- CpG-free plasmids developed for clinic

2005

PRODUCT EVALUATION STUDY

- Three GTAs evaluated in sheep aerosol model

 - GTA/pDNA aerosolised to sheep
 - Lung samples collected at 24 hours
 - Taqman RT-PCR for vector mRNA
 - Immunohistochemistry for human CFTR



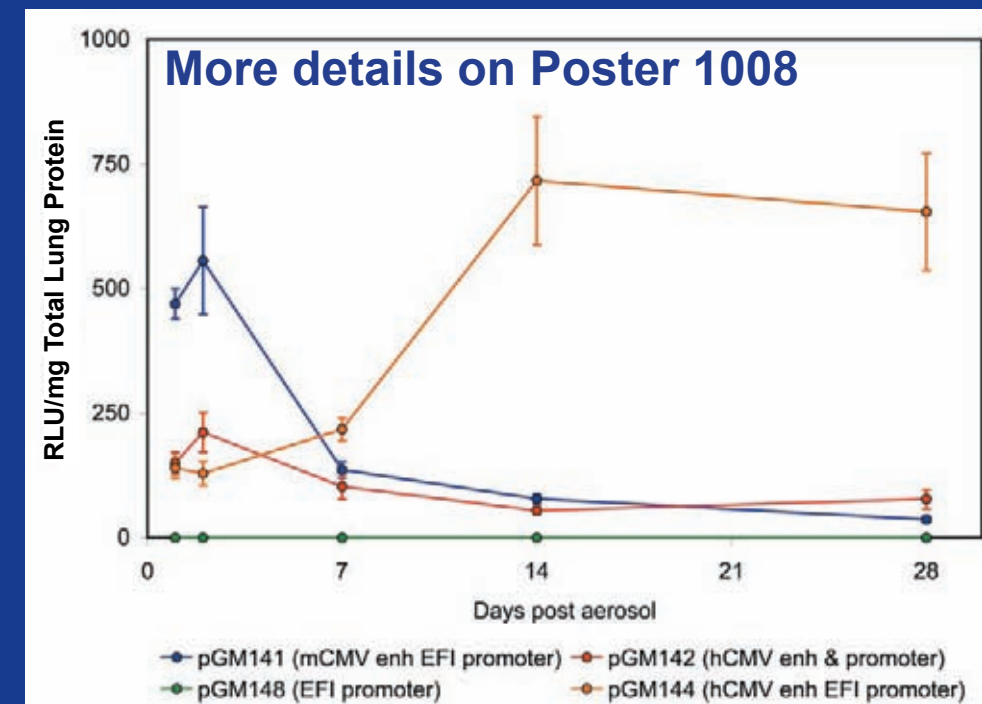
- GL67A was leading GTA from evaluation
- Highest epithelial specific Taqman RT-PCR
- Most CFTR positive cells in IHC studies

- 2005
- GL67A selected as clinical trial GTA

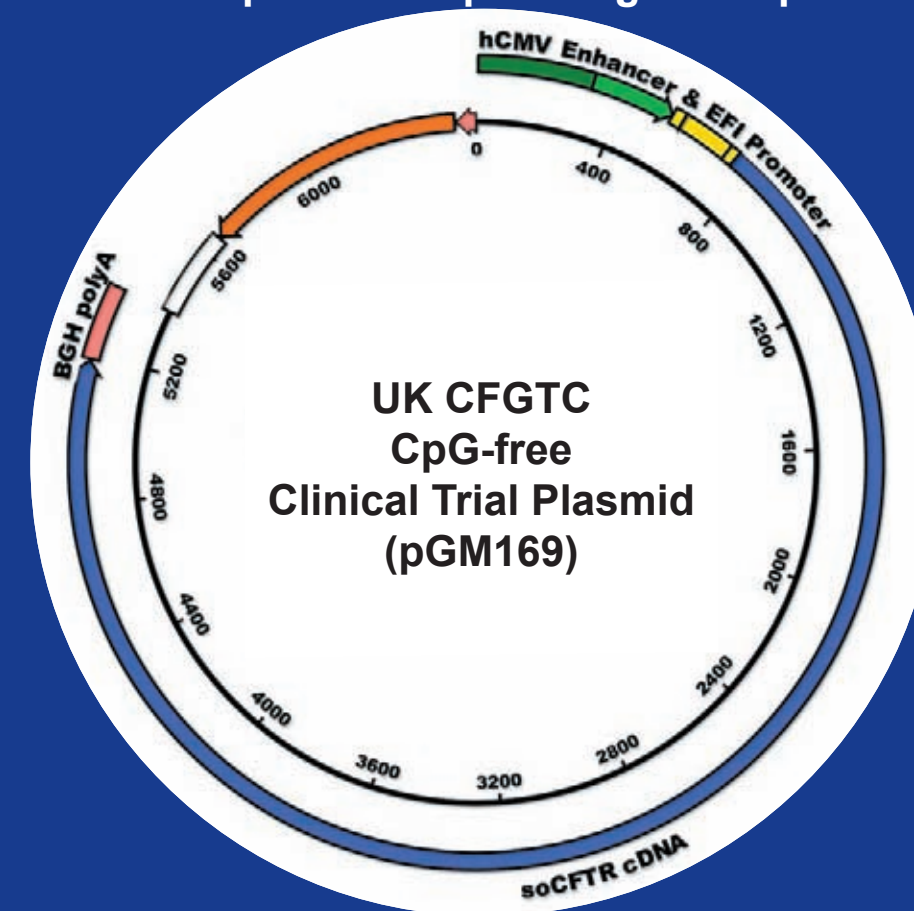
2006

PLASMID DEVELOPMENT II

- Plasmids with novel promoters produced
- Plasmids tested in GL67 aerosol model in mice



- Increased duration from CpG-free pDNA
- Plasmid with hCEFI promoter expresses for at least 1 month following aerosol of GL67/pDNA
- Clinical trial plasmid expressing CFTR produced



- 2006
- hCEFI promoter developed
- Clinical trial CFTR plasmids produced

2007

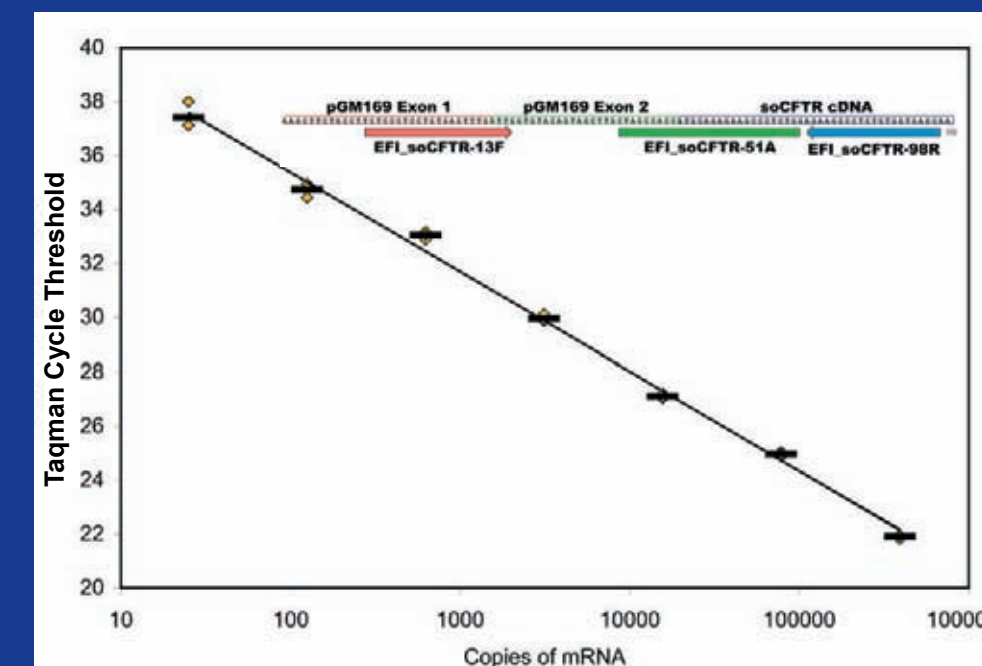
PRE-CLINICAL STUDIES

- Manufacturing of GMP materials
 - Clinical trial plasmid DNA
 - GL67A
- Evaluation of GMP products in sheep lung model



Development of a sensitive Taqman assay for the clinical trial plasmid

- 5' RACE confirmed mRNA splice site in plasmid
- Taqman assays tested on mRNA
- Standard curve of synthetic mRNA produced



- Clinical trial plasmid Taqman assay sensitive to 25 copies of mRNA

- 2007
- Final pre-clinical studies

2008

Q1: 2008: SINGLE-DOSE TRIAL

- GL67/pDNA aerosol administration to lung
- Dose escalation study to determine duration of expression
- Primary endpoints:- Taqman RT-PCR
Immunohistochemistry
Safety

Q4: 2008: MULTI-DOSE TRIAL

- Double blind placebo controlled multi-dose trial
- 12 X monthly administrations of GL67/pDNA or placebo to the lung
- Primary endpoints to assess clinical benefit



- The UK CFGTC is the unified research programme of the three leading gene therapy groups in the UK. It was established in 2001 on the initiative of the UK Cystic Fibrosis Trust.

- The member research groups are headed by Prof. David Porteous (University of Edinburgh), Drs Deborah Gill & Steve Hyde (University of Oxford) and Prof. Eric Alton (Imperial College in London)