Aerosol Delivery of Gene Therapeutics to the Lung

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Lung Gene Therapy

• Being developed for range of acute and chronic lung diseases
  Cystic fibrosis
  Cancer
  Alpha -1-antitrypsin deficiency

• Advantages of lung gene therapies
  Direct access to target cell population
  Non- invasive delivery via aerosol

• Cystic fibrosis as a paradigm for aerosol gene therapy
Cystic Fibrosis - CF

- Most common serious genetic disease in UK
  - In the UK: ~1:20 carriers
  - Worldwide: ~70,000 affected

- CF gene identified in 1989
  - Cystic Fibrosis Conductance Regulator (CFTR)
  - Epithelial Cl⁻ channel
  - Mutations result in dehydration of lung ASL and mucous
  - Chronic lung infection and inflammation
  - Median survival 31 years
Gene therapy for cystic fibrosis lung disease

- Target underlying CF defect
- Introduce functional cftr cDNA into appropriate lung cells
- Ciliated epithelial cells of conducting airways
Gene Replacement Therapy: How Do We Get The DNA Into The Cells?

- Modified virus vectors
  CFTR gene inserted into viral DNA

Initially high promise
Concerns with immunogenicity
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- Non-viral (synthetic) vectors
  Circular plasmid DNA carrying CFTR gene
  Compacted with liposomes/polymers
26 Phase I/II human GT trials to date (> 450 patients)
16 viral, 10 non-viral

Only 8 trials with aerosol delivery (5 viral, 3 non-viral)
Only 3 vectors aerosolised

Why so few vectors and why so few aerosol trials?
Jet nebuliser degradation of naked DNA

Open Circular (OC)

Supercolied Circular (SC)

Nebulisation time (mins)

Shear forces
Recirculation of material in reservoir

Molloy et al. Nucleic Acid Res 2004
Aerosolisation of GT complexes

- Formulation can confer protection
- Very few vectors “aerosolisable”
- Limited portfolio of aerosol gene therapy vectors
- Significant barrier to progress
Aerosol gene expression

- Gene expression inefficient
  - Few cells
  - Low levels

- Gene expression transient
  - Days / weeks

- Clinical delivery requires repeated treatments with high doses

- Improved efficiency essential for advances in aerosol gene therapy
Aerosol delivery efficiency

- Previous clinical trials using jet nebulisers
  Lung deposition 5 - 30%

- Vectors difficult and expensive to produce

- Wastage is prohibitive

- Need efficient delivery
Improved efficiency - cell entry

- Potential barriers
  - Mucous
  - Lung DNases
  - Macrophage clearance
  - Surfactant

- Vector uptake
  - Non-specific
  - Receptor mediated

- Nuclear transport
**Improved efficiency - vectorology**

- Improved gene therapy formulations
  - Higher overall expression
  - Longer duration
    - Promoter modification
    - Genomic integration
- Appropriate aerosol model systems
Model for aerosol gene therapy

- Which model?
- Mouse
  - Transgenic mice
  - Lung anatomy
  - Aerosol requirements
- Sheep / pig
  - Relevant size
  - No disease model
Where next?

• Improve efficacy of gene transfer agents
• Low-shear nebulisation
• Improve efficiency of delivery to target cells
• Identify barriers to vector uptake
• Appropriate animal model systems
• Development in the context of aerosol delivery
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