Cystic Fibrosis Gene Therapy - Where Are We?

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The Trials And Tribulations Of The
UK CF Gene Therapy Consortium

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**CF Gene Therapy**

*The Questions My Mother Asks*

- *How Is This Gene Therapy Thing Supposed To Work?*
- *Where Have You Got To?*
- *Why Does It Take So Long?*
- *Why Is It So Expensive?*
- *When Will It Be Available?*
- *Why Don’t You Visit More Often?*
• CF Genetics - A 5 Minute Crash Course
  Every Human Cell Contains Two Copies Of ~35,000 Genes
  Problems With Just One Of These Genes - CFTR Causes CF

• Mums, Dads & Children
  We Inherit One Copy Of Each Gene From Each Of Our Parents
  ~1:25 In The UK Is A CF Carrier - 1 Broken CFTR Gene
  Carriers Are Usually Healthy - No Knowledge They Have 1 Broken Copy
  If x2 Carriers Have Children Then 1:4 Chance Of Inheriting 2 Broken Copies

• If You Inherit Two Broken Copies Of CFTR Then You Will Have CF
  Severity Of Disease Can Vary
  >1600 Different Broken Forms, Some More Severe Than Others
  Most Common Broken Form - ΔF508 Thought To Be Severe
CFTR Controls The Volume Of The Fluid On The Surface Of The Lung

CFTR Protein Found Here

ASL Height
Mucus Movement Is Defective In CF

Non-CF vs CF

Non-CF: Mucus layer with NL of 60 μm/s

CF: Mucus layer with CF of 0 μm/s

NL: Neutral Layer

ASL: Airway Surface Layer

Na⁺, Cl⁻, H₂O: Ions and water transport
Defective Mucus Movement Leads To Cystic Fibrosis Lung Disease

Normal Airway

Obstructed CF Airway

Persistent Cycles Of Infection & Inflammation Lead To CF Lung Failure
How Is This CF Gene Therapy Thing Supposed To Work?

- Gene Repair

CFTR Gene Is Made From 250,000 Letters Of Genetic Code

In eg ΔF508 Just 3 Of These Are Missing

Find A Way To Add Back Just Those 3 Letters To All The Cells
How Is This CF Gene Therapy Thing Supposed To Work?

- **Gene Repair**
  
  CFTR Gene Is Made From 250,000 Letters Of Genetic Code
  
  In eg ΔF508 Just 3 Of These Are Missing
  
  Find A Way To Add Back Just Those 3 Letters To All The Cells

- **Gene Replacement**
  
  Make In A Test Tube A Correct Copy Of The CFTR Gene
  
  Find A Way To Add Back The Correct Copy To All The Cells
Gene Replacement Therapy: How Do We Get The DNA Into The Cells?

- Modified Virus Vectors
  CFTR Gene Inserted Into Viral DNA
  Compacting Viral Proteins And Lipids
Gene Replacement Therapy: How Do We Get The DNA Into The Cells?

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- Non-Viral (Synthetic) Vectors
  Synthetic DNA Circle Carrying CFTR Gene
  Compacting Liposomes
CF Gene Therapy: Clinical Experience

- Multiple Clinical Trials
  - Adenoviral Vectors
  - Adeno-Associated Virus
  - DNA Circle & Liposomes
CF Gene Therapy: Clinical Experience

- Multiple Clinical Trials
  Adenoviral Vectors
  Adeno-Associated Virus
  DNA Circle & Liposomes

- Broadly Similar Results
  Modest Gene Transfer
  Transient Correction Of CFTR Function
CF Gene Therapy: Clinical Experience

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CF Gene Therapy: Clinical Experience
Lung Delivery

Partial Correction ~25%
Transient ~ 1 Week
Mild Flu-Like Symptoms
Make CF Gene Therapy Work Better!

UK Cystic Fibrosis Gene Therapy Consortium

- Edinburgh
  - Chris Boyd
  - Alastair Innes
  - David Porteous

- London
  - Eric Alton
  - Jane Davies
  - Uta Griesenbach

- Oxford
  - Deborah Gill
  - Stephen Hyde

- CF Trust
  - Rosie Barnes
  - Stuart Elborn
  - Alan Larsen
  - Jim Littlewood

www.cfgenetherapy.org.uk

Make CF Gene Therapy Work Better!
CF Gene Therapy
Why Does It Take So Long?

- Wave 1

Find The “Best Buy” Gene Therapy Vector For The Lung
CF Gene Therapy
Why Does It Take So Long?

- Wave 1
  - Find the “Best Buy” Gene Therapy Vector for the Lung

- The Initial Screen
  - Test commercial & academic vectors for improved activity
  - Vectors tested in extensive mouse & sheep studies
  - Winner = pGM169 Circle of DNA / GL67A Liposomes

- Pharmaceutical Development
  - Manufacturable to cGMP
  - Stable >2 years under pharmacy conditions
Best DNA Circle & Liposome Directs
Sustained Mouse Lung Transgene Expression
CF Gene Therapy
Why Does It Take So Long?
CF Gene Therapy
Why Does It Take So Long?

- Pharmaceutical Manufacturing + Nebuliser Selection
CF Gene Therapy
Why Does It Take So Long?
UK Clinical Trials Toolkit

Key to Symbols

- Specific for trials within Directive's scope
- Relevant to all trials

Funding Secured

Is the trial within the scope of the UK Regulations?

R&D Consultation

Peer Review

Obtain EudraCT Number

Unique Trial number

Identify Sponsor(s)

Final Protocol

Ethics Submission

Approvals & Permissions Obtained

CTA Submission

Final Trial Management Documentation

Checklist Before Seeking Approval

To Trial Management & Closure Map

GCP (Management & Monitoring)

Trial Documentation

Trial Supplies

Pharmacovigilance

Research Question

Sponsorship

Funding Proposal (If Required)

Protocol Development

R&D Submission

UK Cystic Fibrosis Trust

UK Cystic Fibrosis Gene Therapy Consortium

Cystic Fibrosis Trust

UK Cystic Fibrosis Gene Therapy Consortium
UK CF Gene Therapy Consortium
Clinical Trials Programme

- **Run-In Study**  
  Jan 2008 - December 2010
  
  200 CF Patients  Age 10+
  ~2 Year  Longitudinal Clinical Measurements
  7 “Super Annual Visits” With Lots Of New Tests
  2 Day Stay In Southampton

Identify Optimal Patients And Assays
For Long Duration Gene Therapy Trial

Can Deliver  Can Measure
UK CF Gene Therapy Consortium
Clinical Trials Programme

- **Multiple Dose Gene Therapy Trial**  
  Jan 2011 - July 2012
  Select 100 CF Patients From The Run-In Study (Age 12+)
  50 Gene Therapy Treatment, 50 Placebo
  12 Months Of Gene Therapy Treatment (x1/month)
  Lots Of Tests At Each Monthly Visit (Best Tests From Run-In)

**Actually Trying To Find Out If Gene Therapy Makes You Better**
UK CF Gene Therapy Consortium
Clinical Trials Programme

- Single Dose ‘Pilot’ Trial
  Is The New Gene Therapy Formulation Safe?

27 CF Patients
Bronchoscopy Pre & Day 2 (n=12)
Pre & Day 14 (n=12)

Started Mid February, Now On Patient 4
Possible Outcomes

- Most Get Better Or Stop Getting Worse

- Small Or Variable Benefit

- No Benefit
Most Get Better Or Stop Getting Worse

- How Will We Get The Drug To The Patients?
  Pharmaceutical Partner
  Large Multi-Centre Clinical Trial
  All UK CF Centres Small & Large Invited To Take Part
  Europe & USA

- What Will Be The Scientific Challenges?
  Need To Manufacture Greater Quantities
  Need To Jump Higher Regulatory Hurdles (More Paperwork…)
Small Or Variable Benefit

• How Much Benefit Is Worthwhile?
  Low Dose Asprin (50mg) - Prevention
  High Dose Asprin (600mg) - Cure

• What Does This Mean For Gene Therapy?
  Low Benefit May = Prevention
  May Need A Higher Benefit (Higher Dose Or Wave 2) = Cure
No Benefit

• Have Done As Much As We Can With Wave 1
  Learned The Principles
  Know Where We Stand

• Wave 2 Drug Development
  Standard Pharmaceutical Company Approach
  Have Been Doing A Limited Amount Of Research To Facilitate
Wave 2 Gene Transfer Vector Development

Wave 1

Wave 2
UK CF Gene Therapy Consortium
Wave 2 Research Programme

- Continuing Pre-Clinical Development
  ‘Wave 1’ (Best Currently Available) Product In Clinical Trials
  Identify Novel ‘Wave 2’ Product With Improved Efficacy/Duration
  Viral & Non-Vial Products Under Evaluation.  
F/HN Lentivirus Example:

F/HN SIV Mouse Nose Studies In Collaboration With:
UK CF Gene Therapy Consortium
Wave 2 Research Programme

- Continuing Pre-Clinical Development
  ‘Wave 1’ (Best Currently Available) Product In Clinical Trials
  Identify Novel ‘Wave 2’ Product With Improved Efficacy/Duration
  Viral & Non-Vial Products Under Evaluation.

**cPEI Example:**
Cystic Fibrosis Gene Therapy
Where Are We?

• What Has The Consortium Been Doing?
  World’s Biggest Trial For Getting Better

• Why Does It Take So Long?
  Major Problem With Being Cutting Edge

• Why Is It So Expensive?
  It Is… A Lot Of Jobs Means A Lot Of People
  It Isn’t… Not Compared To Those Of A Pharmaceutical Company

• When Will It Be Available For My Child?
Thank You