The New Cystic Fibrosis Treatments: Genetic Benefits, Barriers and Breakthroughs

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Cystic Fibrosis (CF)

• Caused by a gene defect in the CFTR gene
  – Incorrect chloride ion flow out of the cell
  – Secondarily, other ion flows are defective
    • Sodium, bicarbonate
  – Associated water balance altered, surface dehydrates
  – Mucus builds up, is not cleared properly
    • Infection, inflammation, lung destruction
  – Typically slow. But relentless…
Lung disease controls lives: Both length, and quality

Normal Lung

CF Lung

10-40 years
2000 different CFTR mutations

**Cellular function**

- **Surface:** CFTR in action (or not)
- **Cytoplasm:** Build and transport the CFTR protein
- **Nucleus:** Creation point for CFTR

**Mutation Classes**

- Class I
- Class II
- Class III
- Class IV
- Class V
- Class VI

=6 mutation classes
Genetic technology has unraveled the genetic (and physiological) basis of CF

New and highly effective treatments, and potentially prevention, are the result

1. Target specific CFTR mutations / mutation type
   • Drugs developed to target those specific CFTR issues
     • = Only effective for certain CFTR gene mutations

2. Direct gene therapy
   • Add in the correct CF gene, to overcome the problems of the defective CF gene by providing fully-functional CFTR
Treatments and benefits

• Traditional “general” treatments for all with CF: treat the effects of the disease
  – Hypertonic saline (inhaled salty water)
  – Antibiotics (aerosols, pills, intravenous)
  – Physiotherapy (move stuck mucus out of the lungs)

• Median survival greatly improved
  – With combined CF clinical-care advances across nutrition (gut), lung, pancreas, liver, etc.,
  – 1950s: 1 year; 2014: 40 years
  – (But - better survival is not necessarily better Quality of Life)
Current “general” treatments (the specific mutation is irrelevant, treatment is for symptoms)

<table>
<thead>
<tr>
<th>Category</th>
<th>Pre-clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>To Patients</th>
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<td>Inhaled Levofloxacin</td>
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https://tools.cff.org/research/drugdevelopmentpipeline/
Genetically-focussed treatments

• ~ Last 5 years
  – Specific mutations, in certain mutation classes
  – Treat the **causes** of the disease within the cell
    • Target specific steps in the CFTR production pathway
    • Identify useful compounds via High Throughput Screening (HTS)
    • Cell cultures -> animal models -> human trials
    • Produce a drug
      – Currently short effects = daily (+) use
Personalised Medicine for Cystic Fibrosis: drugs that target the effects of specific mutation types

https://tools.cff.org/research/drugdevelopmentpipeline/
Drug Sites of Action

Cellular function

Surface: CFTR in action (or not)

Cytoplasm: build and transport the CFTR protein

Nucleus: creation point for CFTR

Kalydeco (Ivacaftor)

Orkambi (Lumacaftor plus Ivacaftor)

Ataluren
The best treatment so far: Kalydeco
Some key findings: Kalydeco (Ivacaftor)

- Improved weight
- Reduced hospital visits
- Reduced bacterial in the lung
- Reduced antibiotic needs

Improved Lung Function: 10%

- AND
  - Taken by mouth – provides benefits for many CF organ systems
Barriers, for some patients

• If ‘unlucky’ with your CF:
  – When, or will, your mutation type be treatable?

• Daily or more drug regimen, for your lifetime
  – A small price to pay for good lungs?

• Pricing - astonishing..
  – A$ 300,000 – $A 350,000 (for Vertex “Kalydeco”)?
  – Per person. Per year.

• Long term effects (good and bad) not known
Other gene-based options

• From the USA CF Foundation
  – Stated Aim: “A one-time cure for CF”
    • CEO: Preston Campbell, 2015
  – Very unlikely that enough individual drugs can be found for all the ~2000 CF mutations

• How do we support all the CF children born with, and young CF adults living with, the ‘wrong’ CF mutations?
Gene Therapy for CF

• Gene Therapy

• *Deliver the correct gene to the defective cells in the airway, to return proper cell functioning*
  – CF mutation type does not matter
  – Very long development road – started 1989

• UK: 2015: First successful clinical trial
  – “Good” CFTR gene delivered within liposomes
UK Gene Therapy trial

- Single dose, each month, for 12 months
  - Improved lung health (~4%)
  - No safety concerns
  - New studies to test multiple doses

Lung health improved
Better CF lung gene therapy..

- UK, USA, and Adelaide - Virus-based vectors (carriers)
  - ~1000 times more effective than liposome carriers (cell and animal data)
  - Potential for months -> years of benefit after dosing
- Adelaide: unique method to target airway stem cells
  - To provide persisting benefit after dosing
- Clinical trials for virus vectors - next 5 years
- Challenges for all
  - Production of the vectors harder, more expensive
  - Funding more research – all of us here today!
  - Funding the treatments – v. large initial cost
    - Governments, insurers, families, individuals
Genetic Benefits, Barriers and Breakthroughs

• Cystic Fibrosis
  – **Benefit** of our understanding the genetics of CF
    • Now paying off in effective new treatments
  – **Barriers** - some overcome; new ones appear
    • Ability to live well *with* CF is improving. For some.
    • Long-term effectiveness and unwanted effects not yet known
  – **Breakthroughs** – are real, not usual media hype
    • Substantial (for CF) improvements in lung (and other) health
    • Basic research, technology have been crucial
    • Clinical translation has then enabled new treatments
Acknowledgements

• NHMRC
• USA CF Foundation
• CF Australia
• WCH Foundation
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• Robinson Research Institute, Univ of Adelaide
• Centre for Stem Cell Research, Univ of Adelaide

• Cure4CF Foundation
  – Scott Group of Companies
  – Fay Fuller Foundation
  – Australian Executor Trustees
  – Coopers Brewery Foundation
  – Hacket Foundation
  – Hosking Foundation
  – Variety Club SA

• Individual contributors

• Commercial research links
  – Parion, USA
  – Pharmaxis, Australia
End
Gene therapies work

Gene therapy gets approval for ‘bubble kids’ in world first

A genetic therapy that lasts for years has been approved to treat a potentially fatal immune disorder that makes children need to be isolated from infection.

Looking for a long-term solution
Klaus Guldbrandsen/Science Photo Library

By Andy Coghill

“We nearly lost him twice,” says Kelly Gillion of her son Zeus, who was diagnosed with the potentially fatal condition ADA-SCID in the first weeks of his life.

A Glaxo Smith-Kline Product.
(1) FUNCTIONAL CLASSIFICATION

Class of mutation

<table>
<thead>
<tr>
<th>Molecular defect</th>
<th>No synthesis</th>
<th>Block in processing</th>
<th>Block in regulation</th>
<th>Reduced conductance</th>
<th>Reduced synthesis</th>
<th>Reduced half-life</th>
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<tbody>
<tr>
<td>Normal</td>
<td>Cl⁻ Cl⁻ Cl⁻ Cl⁻</td>
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<tr>
<td>Functional abnormality</td>
<td>Protein is not synthesized</td>
<td>Folding defect</td>
<td>Channel opening defect</td>
<td>Ion transport defect</td>
<td>Decreased protein synthesis</td>
<td>Decreased half-life of the protein</td>
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<tr>
<td>Main mutations</td>
<td>Gly542X Trp128X Arg553X Ile607del Arg560Thr</td>
<td>Phe508del Asn1303Lys Gly551Ser Ser549Asn</td>
<td>Gly551Asp Gly178Arg Gly551Ser Ser549Asn</td>
<td>Arg117His Arg347Pro Arg17Cys Arg334Trp</td>
<td>3849+10kbC→T 2789+5G→A 3120+1G→A 5T</td>
<td>4326delTC Gln1412X 4279insA</td>
</tr>
</tbody>
</table>

(2) CLINICAL CLASSIFICATION

Severe (A)       Broad-spectrum (A/B)       or       Mild

Unknown or uncertain clinical relevance (D)
CF: a rule of thumb...
Tubes block with mucus
The CF Protein: *Cystic Fibrosis Transmembrane Conductance Regulator* (CFTR)

- **Functions** – salt balance
  - Chloride channel
  - Bicarbonate channel
  - Regulates sodium channel
  - Lung is most affected

Modified from image provided by Dr Michael Boyle, Johns Hopkins CF Centre, USA
How CFTR channel operation affects airways

Video courtesy of Dr Michael Boyle and the CFF, USA
**Personalised Medicine** for Cystic Fibrosis: drugs that target the effects of specific mutation types

- Potentiator
- Corrector plus potentiator
- Corrector
- Corrector
- Potentiator
- Corrects misfolding, + Orkambi for more and better to surface
- Repair RNA

https://tools.cff.org/research/drugdevelopmentpipeline/
Benefits

• For the first time, knowing the type of (CF) gene mutation makes a huge difference in your treatment
  – Personalised Medicine is here in CF
  – Disease in other organs also improved here

• If you are ‘lucky’ with CF, you can now be treated far better than previously imagined
  – Up to 10% better lung function is a revolution in CF!
  – The next drugs have been less effective
  – Combination drugs can improve benefits