A personalised approach to Cystic Fibrosis

Professor Adam Jaffe
School of Women’s and Children’s Health

A personalised approach to Cystic Fibrosis

Adam Jaffe

John Beveridge Professor of Paediatrics
Respiratory Consultant
Sydney Children’s Hospital, Randwick
Cystic Fibrosis

- Commonest AR gene in Caucasians
- 1:25 carrier
- 1:2500 - 3000 babies
- 3000 patients in Australia
- 70,000 world-wide
- 2000 gene mutations
  - 150 disease causing
Ion Transport

Normal Cell

CF Cell

Sodium

Chloride

Water

CFTR
Cystic Fibrosis Gene

↓

Abnormal CFTR

↓

Abnormal Salt Concentration

↓

Inflammation  Infection  Thick Sputum

↓

Lung Damage
WHAT'S HAPPENING IN THE CELL

MUTATION EXAMPLES

% of people with CF who have at least one mutation in that class

22%

No mutation

G542X
W1282X
R553X
aka "nonsense mutations, splice mutations or deletions"

88%

F508del
N1303K
I507del

6%

G551D
S549N
aka "gating mutations"

6%

D1152H
R347P
R117H

5%

3849+10kbc→T
2789+5G→A
A455E

Cl−

Airway surface

Mature CFTR channel

Newly folded CFTR

Ribosome

Full-length RNA

Cell nucleus

DNA

Cl−

Mature CFTR channel

Channel gate does not open

Misfolded CFTR

Unstable, shortened RNA

Faulty channel

Not enough CFTR

Incorrect RNA
14 year old boy

16 year old sister

Same genotype
Both do no treatment
THE GLI SPIROMETRY REFERENCE EQUATIONS INFLUENCE THE APPARENT RATE OF DECLINE IN FEV1 AMONG CHILDREN AND ADOLESCENTS WITH CYSTIC FIBROSIS

G Davies, A Aurora, A McDonald, A Prasad, D Bilton, S Stocks, S Stanojevic, UCL Institute of Child Health, London, UK; Hospital for Sick Children, Toronto, Canada; Great Ormond Street Hospital for Children, London, UK; Royal Brompton Hospital, London, UK

10.1136/thoraxjnl-2014-206260.72
 Genome-wide association meta-analysis identifies five modifier loci of lung disease severity in cystic fibrosis

Harriet Corvol\textsuperscript{1,2}, Scott M. Blackman\textsuperscript{3}, Pierre-Yves Boëlle\textsuperscript{2,4}, Paul J. Gallins\textsuperscript{5}, Rhonda G. Pace\textsuperscript{6}, Jaclyn R. Stonebraker\textsuperscript{6}, Frank J. Accurso\textsuperscript{7,8,9}, Annick Clement\textsuperscript{1,2}, Joseph M. Collaco\textsuperscript{10}, Hong Dang\textsuperscript{6}, Anthony T. Dang\textsuperscript{6}, Arianna Franca\textsuperscript{11}, Jiafen Gong\textsuperscript{12}, Loic Guillot\textsuperscript{1}, Katherine Keenan\textsuperscript{13}, Weili Li\textsuperscript{12}, Fan Lin\textsuperscript{12}, Michael V. Patrone\textsuperscript{6}, Karen S. Raraigh\textsuperscript{11}, Lei Sun\textsuperscript{14,15}, Yi-Hui Zhou\textsuperscript{16}, Wanda K. O’Neal\textsuperscript{6}, Marci K. Sontag\textsuperscript{7,8,9}, Hara Levy\textsuperscript{17}, Peter R. Durie\textsuperscript{13,18}, Johanna M. Rommens\textsuperscript{12,19}, Mitchell L. Drumm\textsuperscript{20}, Fred A. Wright\textsuperscript{21,22}, Lisa J. Strug\textsuperscript{12,15}, Garry R. Cutting\textsuperscript{11,23} & Michael R. Knowles\textsuperscript{5}
Treatment approaches

- Antibiotics
- Nutrition
- Airway clearance
New treatment approaches
One size fits all

Cystic Fibrosis Gene

Abnormal CFTR

Abnormal Salt Concentration

Inflammation  Infection  Thick Sputum

Lung Damage
Cystic Fibrosis Foundation 2017
Potential therapies for CFTR mutations

Potentiators are drugs that help open the CFTR channel at the cell surface and increase chloride transport.

Correctors are drugs that help the defective CFTR protein fold properly so that it can move to the cell surface.

Read-through compounds aim to allow full-length CFTR protein to be made, even when the RNA contains a mutation telling the ribosome to stop.

RNA therapies aim to either fix the incorrect instructions in defective RNA, or provide normal RNA directly to the cell.
High throughput screening

- Chemical library with 100s of thousands of chemicals
- Screening test or assay for chemicals with desired ACTIVITY against TARGET: “Hits”
- “Hits” are analyzed and optimized for drug development
>12 years of age

150mg BD Ivacaftor v placebo

N=84
Approved by PBS January 2015
>1 G551D mutation

$270 000 per year
No effect in F508del
Orkambi
-Ivacaftor (VX770, potentiator)
-Lumacaftor (VX809, corrector)
Distribution of Change in ppFEV1 at Day 29 With VX-440 Triple Combination in $F508_{del}/MF$ Patients

Courtesy of Vertex
How can we predict response?
This scientist is building miniature guts, livers, and lungs that could save your life one day
Rectal biopsy

Crypt isolation

Proliferation, de novo stem cell formation and budding

Day 0  Day 1  Day 3  Day 5  Day 7  ~Day 10

Wnt
Budding
Wnt
Budding

Internal lumen
crypt-like structures

CFTR: apical membrane

Feeder cells (Wnt3-a, Noggin, Rospondin) donated by Rob De Vries (Hubrecht), Jeff Beekman (UMCutrecht) and Calvn Cuo (stanford)
CF AVATAR Research Studies

Individual A

+ VX-770 (Ivacaftor)

Individual B

+ VX-770 (Ivacaftor)
FDA News Release

FDA expands approved use of Kalydeco to treat additional mutations of cystic fibrosis

Laboratory evidence used to support efficacy

For Immediate Release

May 17, 2017

Release

The U.S. Food and Drug Administration today expanded the approved use of Kalydeco (ivacaftor) for treating cystic fibrosis. The approval triples the number of rare gene mutations that the drug can now treat, expanding the indication from the treatment of 10 mutations, to 33. The agency based its decision, in part, on the results of laboratory testing which it used in conjunction with evidence from earlier human clinical trials. The approach provides a pathway for adding additional, rare mutations of the disease, based on laboratory data.
## PBAC Decision July 2017

### JULY 2017 PBAC OUTCOMES – SUBSEQUENT DECISIONS NOT TO RECOMMEND

<table>
<thead>
<tr>
<th>DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION</th>
<th>TGA INDICATION</th>
<th>CURRENT PBS LISTING</th>
<th>LISTING REQUESTED BY SPONSOR / PURPOSE OF SUBMISSION</th>
<th>PBAC OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUMACAFTOR with IVACAFTOR</td>
<td>ORKAMBI 200/125 mg is indicated for the treatment of people aged 12 years or older who are homozygous for the F508del mutation in the CFTR gene</td>
<td>Resubmission to request a Section 100 (Budget Specialised Drug Program)</td>
<td>Lumacaftor with ivacaftor was not recommended by the PBAC for listing on the PBS for the treatment of patients with cystic fibrosis (CF) aged 12 years or older who are homozygous for the F508del mutation in the CFTR gene on the basis of uncertainty around the longer term impact of lumacaftor/ivacaftor on lung function and survival beyond 2 years of treatment and unacceptable cost effectiveness at the requested price.</td>
<td></td>
</tr>
<tr>
<td>Tablet containing lumacaftor 200 mg with ivacaftor 125 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orkambi®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertex Pharmaceuticals (Australia) Pty Ltd</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New listing</td>
<td></td>
<td></td>
<td>(Major Submission)</td>
<td></td>
</tr>
</tbody>
</table>

Lumacaftor with ivacaftor was not recommended by the PBAC for listing on the PBS for the treatment of patients with cystic fibrosis (CF) aged 12 years or older who are homozygous for the F508del mutation in the CFTR gene on the basis of uncertainty around the longer term impact of lumacaftor/ivacaftor on lung function and survival beyond 2 years of treatment and unacceptable cost effectiveness at the requested price.

- Randomised trials presented by the resubmission, a patient treated with lumacaftor/ivacaftor could expect to have one fewer pulmonary exacerbation over 2.5 years, and one fewer hospitalisation due to pulmonary exacerbation over 3 years. The PBAC therefore considered that the claim of superior comparative effectiveness was reasonable.
Organoids Proposed to Screen Patients for High-Priced Drugs

Dutch scientists want to create mini-organs for all 1,500 cystic fibrosis patients in the Netherlands.

by Antonio Regalado    June 29, 2017

Last week, Dutch scientists approached the ministry with a proposal to grow such mini-organs in their laboratories, using cells obtained from all 1,500 Dutch cystic fibrosis patients. That way, they say, Orkambi and other costly drugs can be tested in the lab to see if they’ll be effective in a particular patient. Eventually, the drug would be paid for only if a patient's organoid responds.
EU H2020 grant for unique HIT-CYSTIC FIBROSIS project

Original Article

The CF Canada-Sick Kids Program in individual CF therapy: A resource for the advancement of personalized medicine in CF

Paul D.W. Eckford a, Jacqueline McCormack a, Lise Munsie b, Gengming He c, Sanja Stanojevic d, Sergio L. Pereira e, Karen Ho e, Julie Avolio d,f, Claire Bartlett d, Jin Ye Yang g, Amy P. Wong g, Leigh Wellhauser a, Ling Jun Huan a, Jia Xin Jiang a, Hong Ouyang d, Kai Du a, Michelle Klingel d, Lianna Kyriakopoulou h, Tanja Gonska d,i, Theo J. Moraes d,f, Lisa J. Strug c,e,d, Janet Rossant g,k, Felix Ratjen d,f,i, Christine E. Bear a,m,n,*
Personalised CFTR Pharmacotherapeutic Response Testing and Therapy in CF

- 38 year old man
- F508del/Ser1159Pro (poorly characterized mutation)
- Nasal spheroids and airway liquid interface monolayer
- Ivacaftor Lumicaftor responses
  - CFTR-dependent swelling
  - Short circuit potential difference
Response to Ivacaftor and Lumicaftor

Before | After
---|---
No Treatment |  
Ivacaftor + Lumicaftor |  
Ivacaftor Alone |  
Lumicaftor Alone |  

CAMP-induced short-circuit current (A/cm²)

Normal range

Clinical response following Orkambi

Sweat test

Lung Function
Welcome to the miCF Research Centre.

Cystic Fibrosis (CF) is the most common life-threatening genetic disorder affecting Australian children.

CF affects all parts of the body, but mainly damages the lungs and digestive system. Over time, the lungs become increasingly affected by inflammation and respiratory function is significantly reduced. There are a number of treatments available to reduce the problems caused by the condition, but average life expectancy is ultimately compromised. At present there is no cure.

Here at the Centre, and with your support, we have two main aims: to fast track research aimed at finding a cure, and to raise awareness of Cystic Fibrosis in the community.

So join us, and invest in a future free from Cystic Fibrosis.
‘the previous prediction of a median survival of >50 years of age for individuals born in 2000 continues to look realistic, even in the absence of proven effective therapy’

Dodge JA ERJ 2007;29:522
Summary
Thanks to
Dr Shafagh Waters

Collaborators
Prof. Kevin Morris (COH, USA)
Prof. Margarida Amaral (U Lisboa)
Prof. Stephen Stick (Telethon)
A.Prof. Anthony Kicic (Telethon)
Dr. Wallace Bridge (UNSW)
A.Prof. Noel Whitaker (UNSW)

Our Team

www.cysticfobrosiscentre.org.au
I'm worried that health care has become too impersonal, Doc.

Nonsense... just relax and lie back on the bar code scanner.