School of Women's and Children's Health

A personalised approach to Cystic Fibrosis

Adam Jaffe

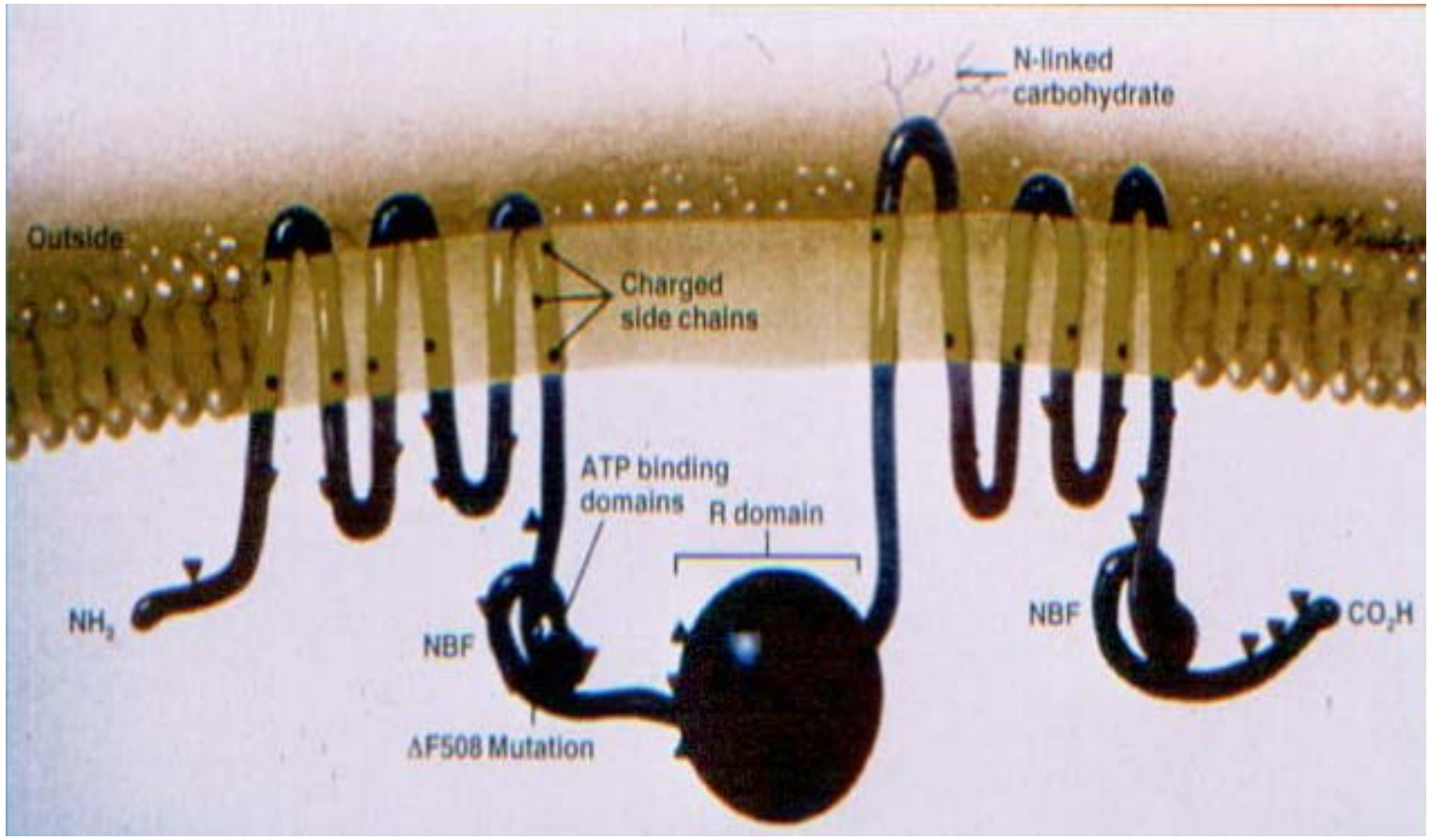
John Beveridge Professor of Paediatrics

Respiratory Consultant

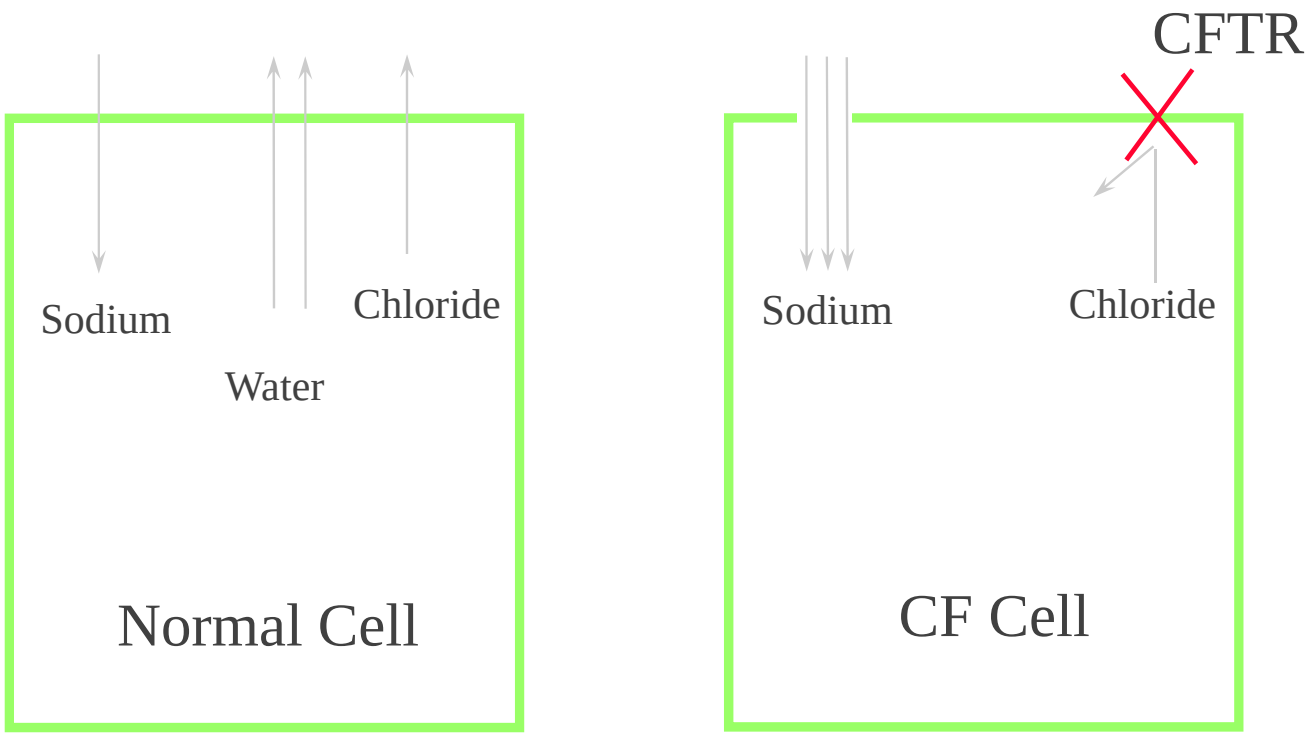
Sydney Children's Hospital, Randwick

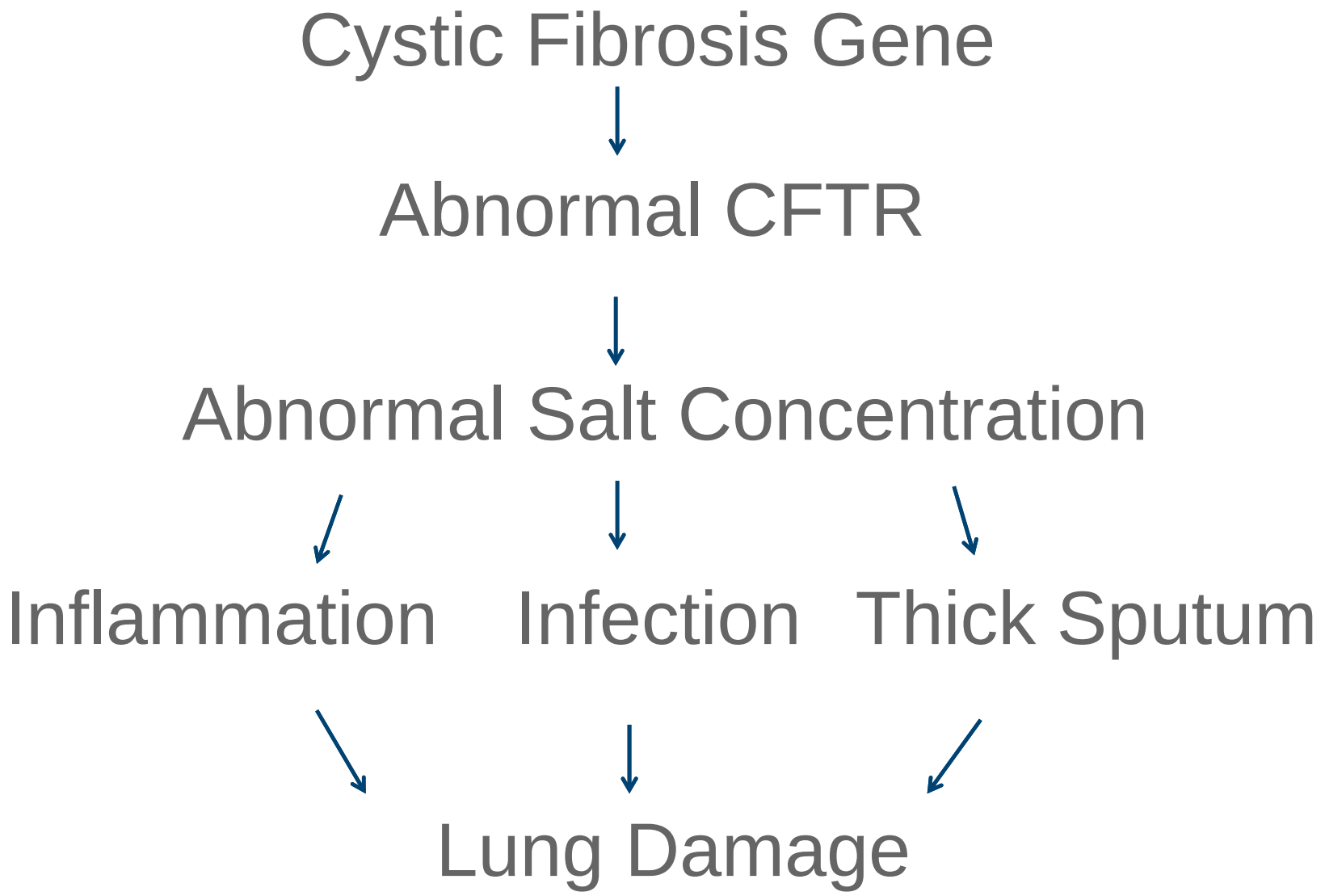
Cystic Fibrosis

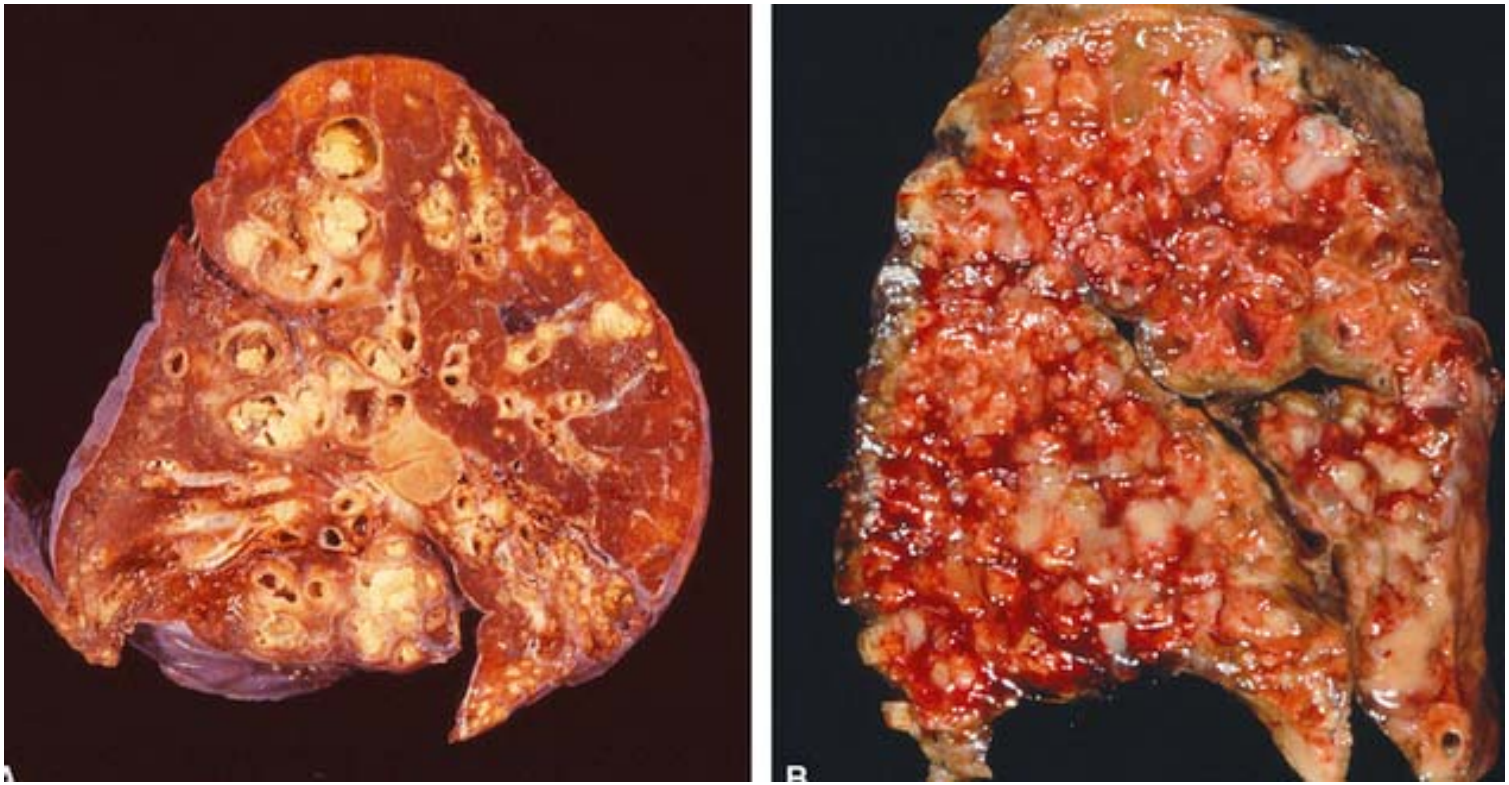
- Commonest AR gene in Caucasians
- 1:25 carrier
- 1:2500 -3000 babies
- 3000 patients in Australia
- 70 000 world-wide
- 2000 gene mutations
  - 150 disease causing


N-linked
carbohydrate
Outside
Charged
side chains
ATP binding
domains
R domain
NH_3
NBF
NBF
CO_2H
ΔF508 Mutation

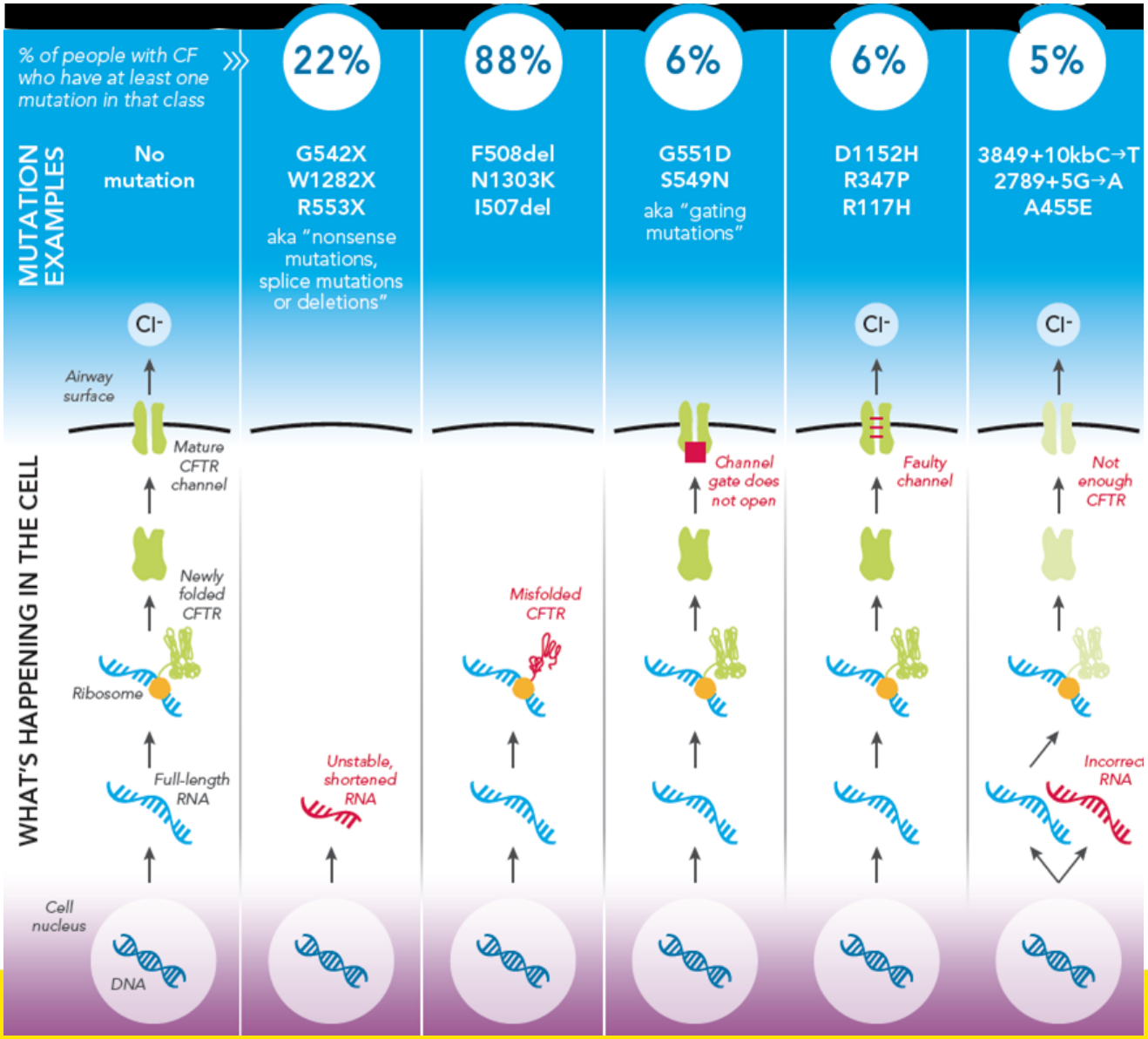
Ion Transport

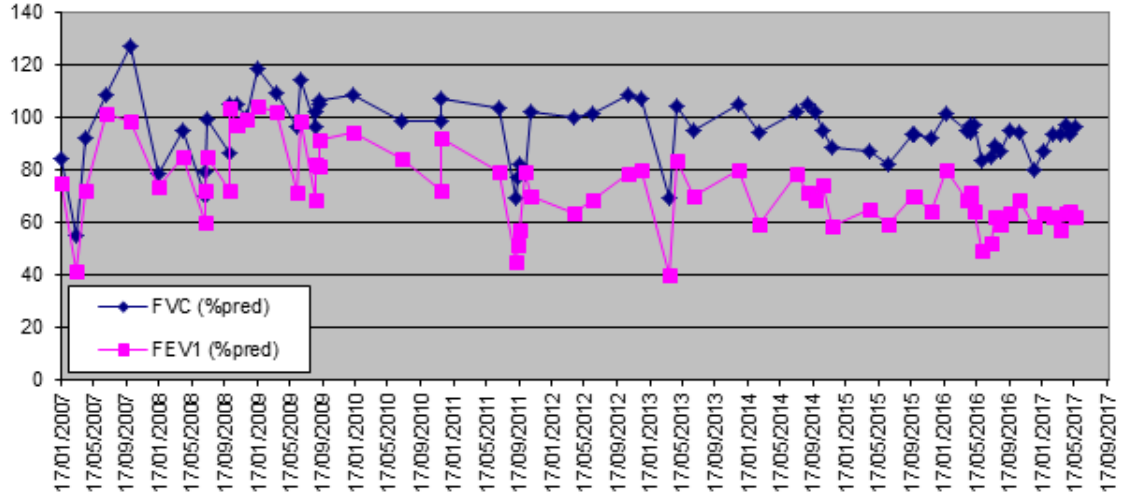



Cystic Fibrosis Gene
Abnormal CFTR
Abnormal Salt Concentration
Inflammation
Infection
Thick Sputum
Lung Damage

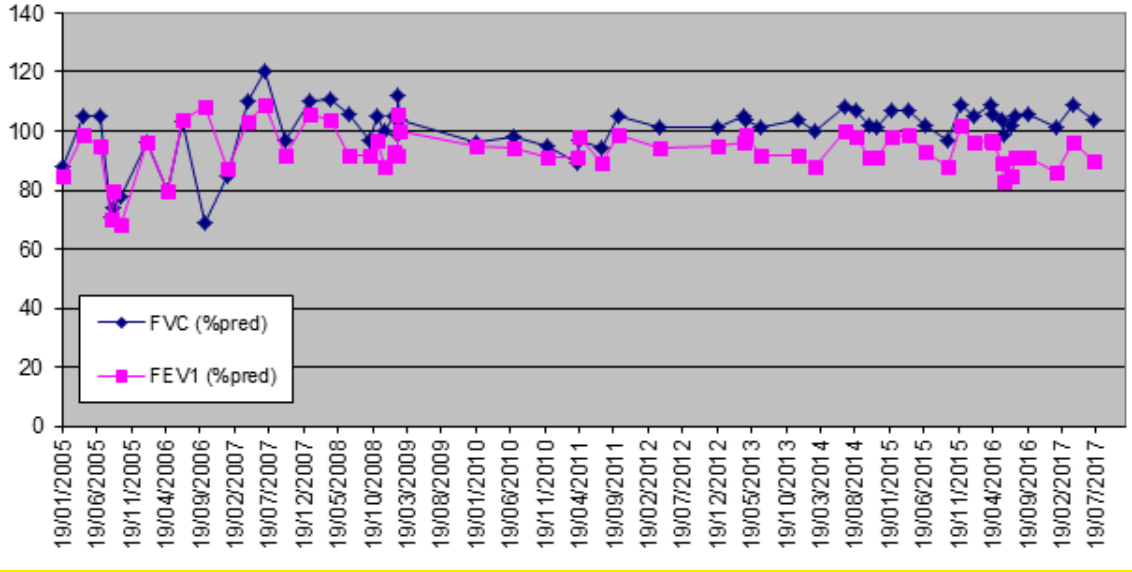


13 year old


% of people with CF who have at least one mutation in that class
22%
88%
6%
6%
5%
MUTATION EXAMPLES
No mutation
G542X
W1282X
R553X
aka "nonsense mutations, splice mutations or deletions"
F508del
N1303K
I507del
G551D
S549N
aka "gating mutations"
D1152H
R347P
R117H
3849+10kbC→T
2789+5G→A
A455E
Cl-
Airway surface
Mature CFTR channel
Channel gate does not open
Faulty channel
Not enough CFTR
WHAT'S HAPPENING IN THE CELL
Newly folded CFTR
Misfolded CFTR
Ribosome
Full-length RNA
Unstable, shortened RNA
Incorrect RNA
Cell nucleus
DNA



14 year old boy



16 year old sister

Same genotype
Both do no treatment

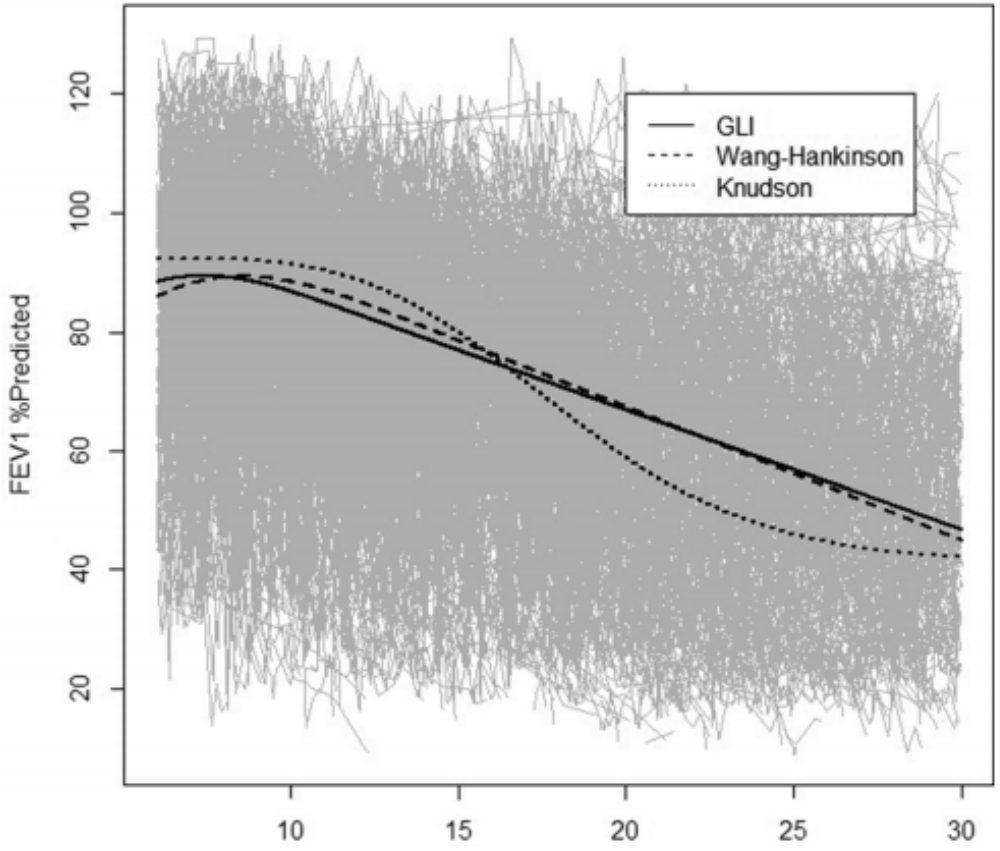
UNSW SYDNEY

S66

THE GLI SPIROMETRY REFERENCE EQUATIONS INFLUENCE THE APPARENT RATE OF DECLINE IN FEV1 AMONG CHILDREN AND ADOLESCENTS WITH CYSTIC FIBROSIS

[1]G Davies, [1]P Aurora, [2]A McDonald, [3]A Prasad, [4]D Bilton, [1]J Stocks, [2]S Stanojevic. *[1]UCL Institute of Child Health, London, UK; [2]Hospital for Sick Children, Toronto, Canada; [3]Great Ormond Street Hospital for Children, London, UK; [4]Royal Brompton Hospital, London, UK*

10.1136/thoraxjnl-2014-206260.72



nature COMMUNICATIONS

ARTICLE

Received 9 Jan 2015 | Accepted 17 Aug 2015 | Published 29 Sep 2015

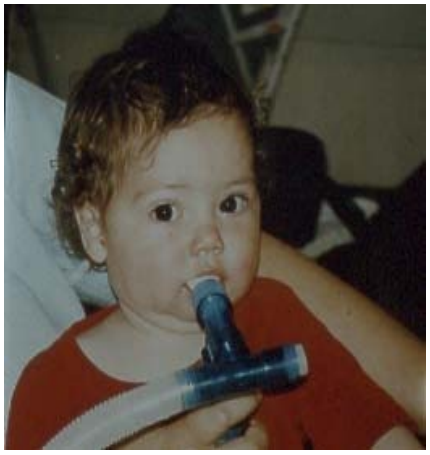
DOI: 10.1038/ncomms9382 OPEN

Genome-wide association meta-analysis identifies five modifier loci of lung disease severity in cystic fibrosis

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

Treatment approaches

- Antibiotics
- Nutrition
- Airway clearance



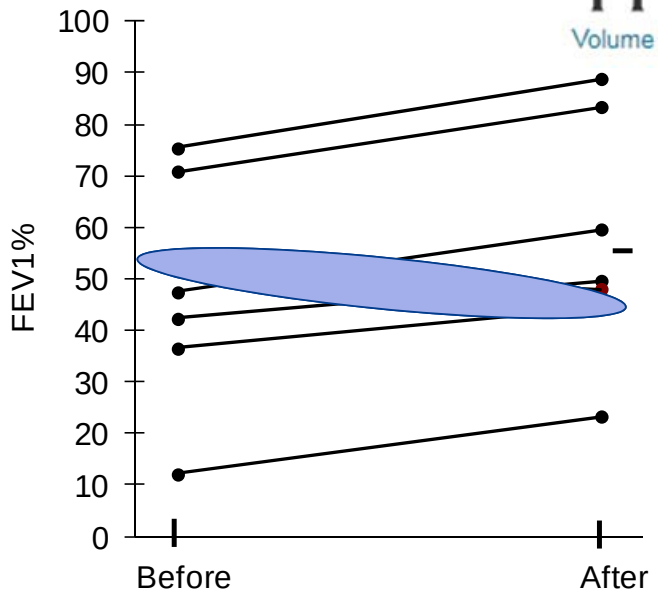
Long-term azithromycin may improve lung function in children with cystic fibrosis

Adam Jaffé [a]

[a] Department of Respiratory Paediatrics, Royal Brompton Hospital, London SW3 6NP, UK

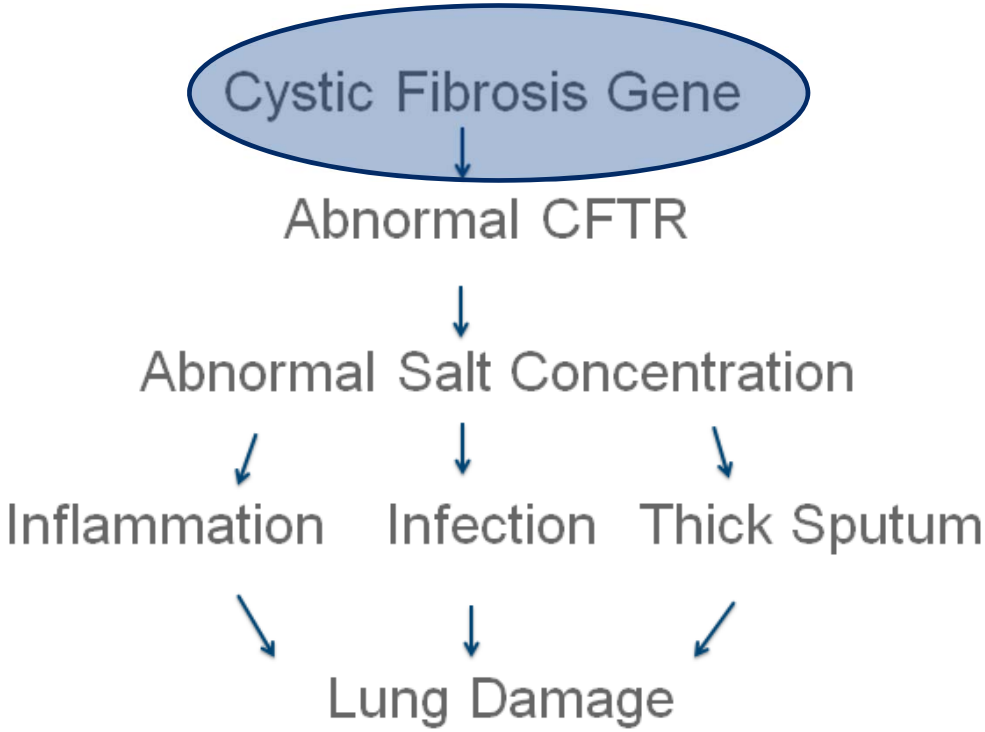
Jackie Francis, Mark Rosenthal, Andrew Bush

THE LANCET
Volume 351, Issue 9100, 7 February 1998, Page 420

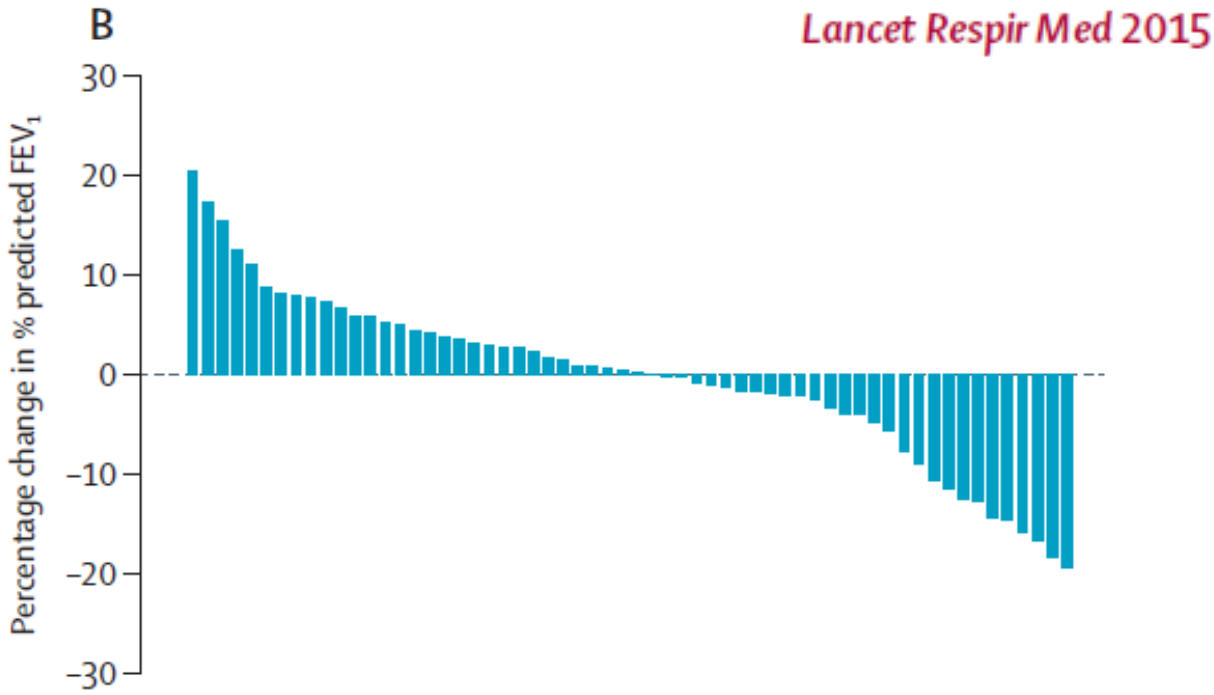


New treatment approaches

One size fits all



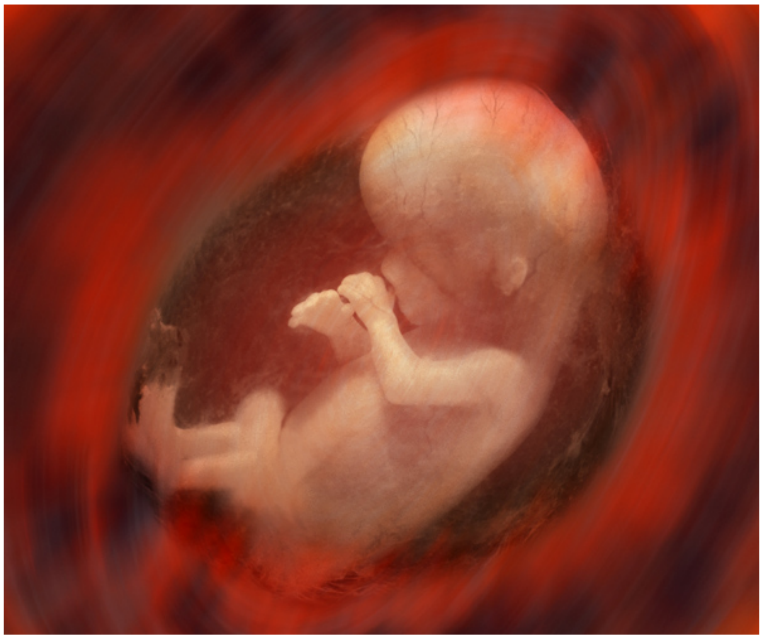
Repeated nebulisation of non-viral *CFTR* gene therapy in patients with cystic fibrosis: a randomised, double-blind, placebo-controlled, phase 2b trial



New treatment approaches

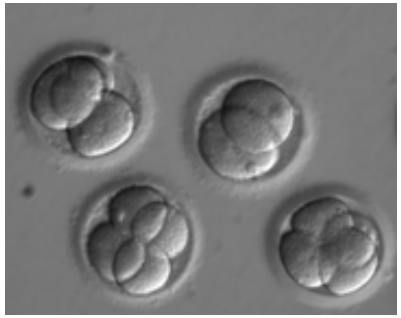
One size fits all

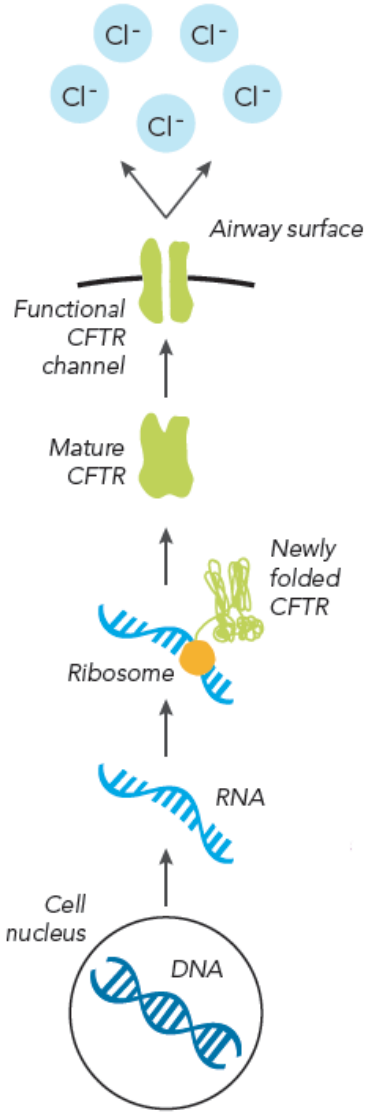
CRISPR vs. Hypertophic Cardiomyopathy: Embryo Gets Clean Genes



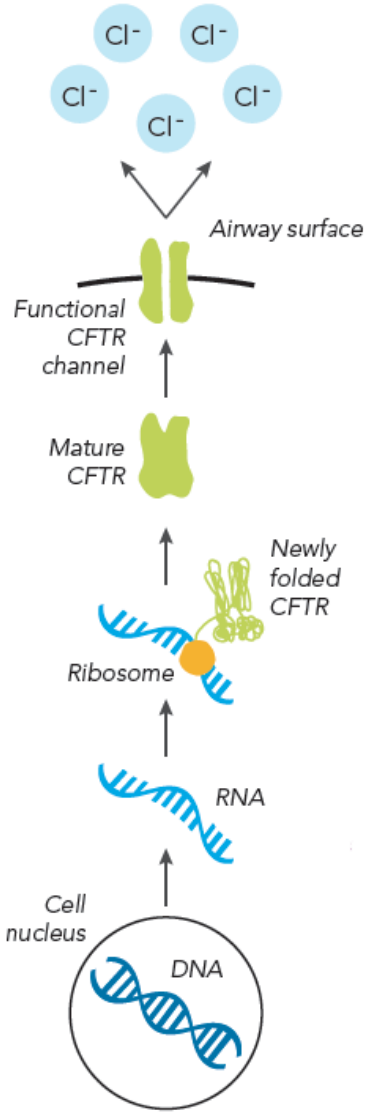
(Dreamstime)

By Clyde Hughes | Thursday, 03 Aug 2017 11:28 AM





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.

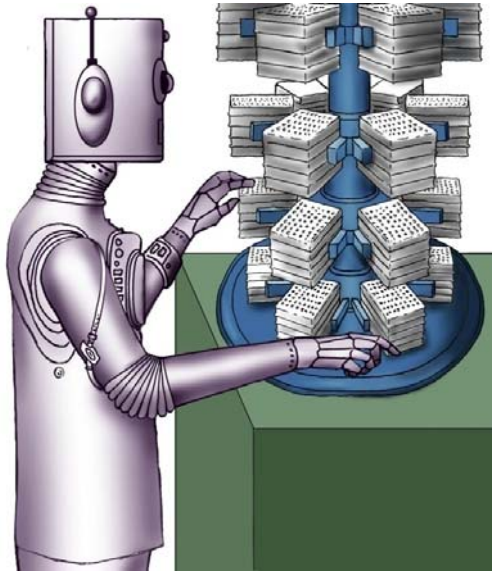
Correctors are drugs that help the defective CFTR protein fold properly so that it can move to the cell surface.

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.

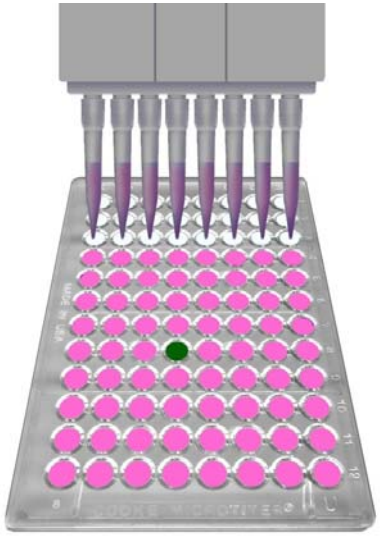
RNA therapies aim to either fix the incorrect instructions in defective RNA, or provide normal RNA directly to the cell.

CFF 2017

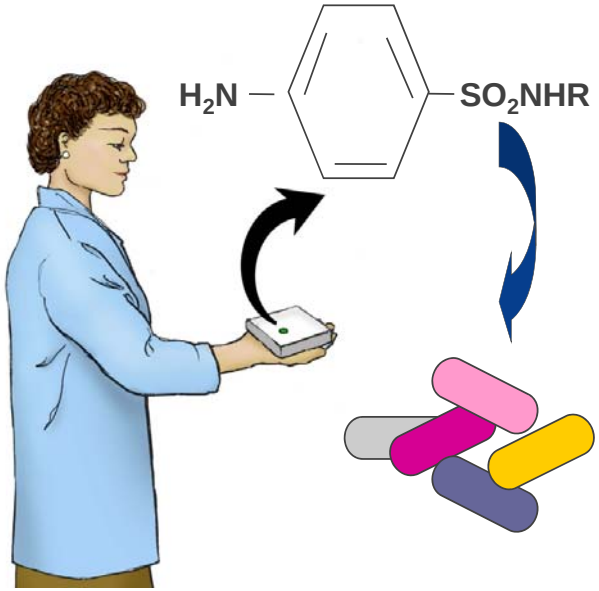
High throughput screening



Chemical library with 100s of thousands of chemicals

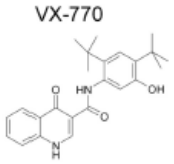


Screening test or assay for chemicals with desired ACTIVITY against TARGET: “Hits”



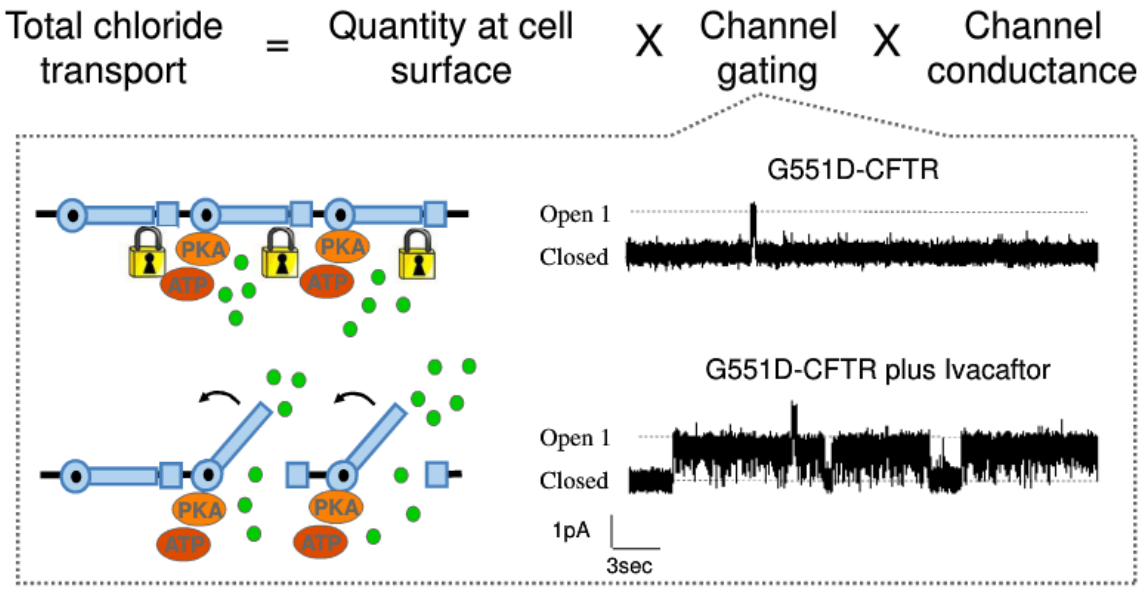
“Hits” are analyzed and optimized for drug development

VX-770



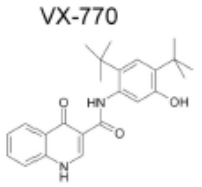
Ivacaftor (VX-770 aka Kalydeco) is a CFTR potentiator

In vitro enhanced G551D-CFTR and other mutant CFTR forms with defective channel gating



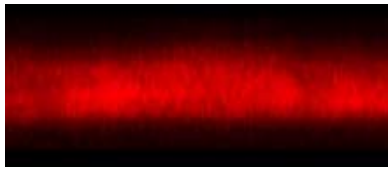
Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770

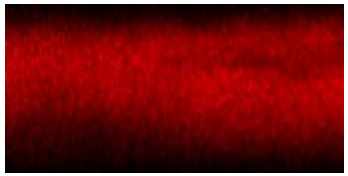
Fredrick Van Goor[a,1], Sabine Hadida[a], Peter D. J. Grootenhuis[a], Bill Burton[a], Dong Cao[a], Tim Neuberger[a], Amanda Turnbull[a], Ashvani Singh[a], John Joubran[a], Anna Hazlewood[a], Jinglan Zhou[a], Jason McCartney[a], Vijayalaksmi Arumugam[a], Caroline Decker[a], Jennifer Yang[a], Chris Young[a], Eric R. Olson[b], Jeffery J. Wine[c], Raymond A. Frizzell[d], Melissa Ashlock[e], and Paul Negulescu[a]

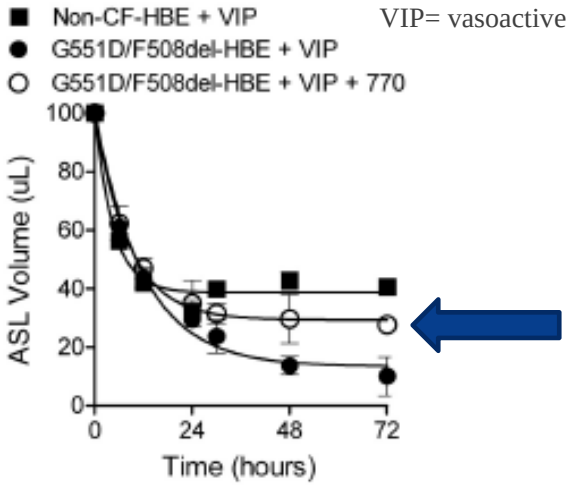


PNAS 2009

Increases airway surface liquid



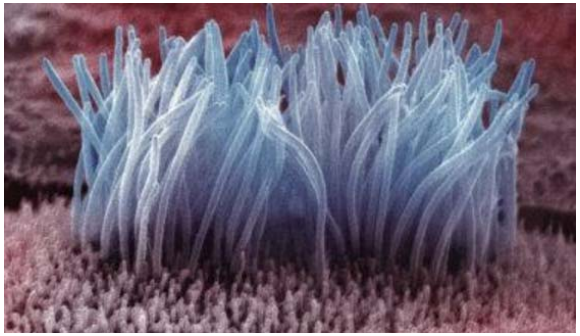


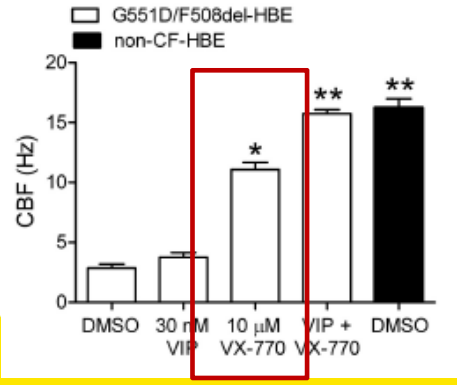


VIP= vasoactive intestinal peptide

VX-770

Increases CBF to normal





UNSW SYDNEY

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 3, 2011 VOL. 365 NO. 18

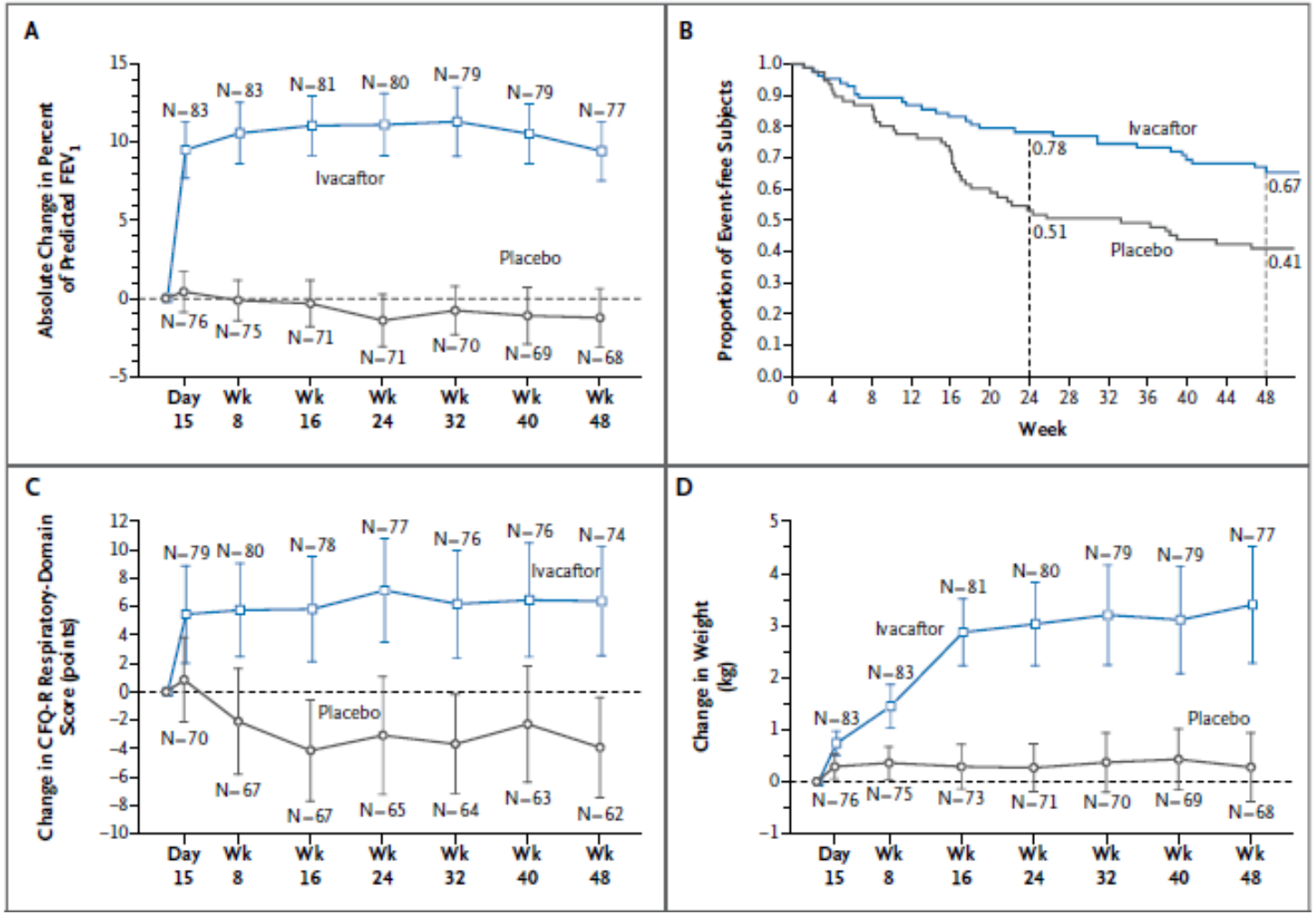
A CFTR Potentiator in Patients with Cystic Fibrosis and the *G551D* Mutation

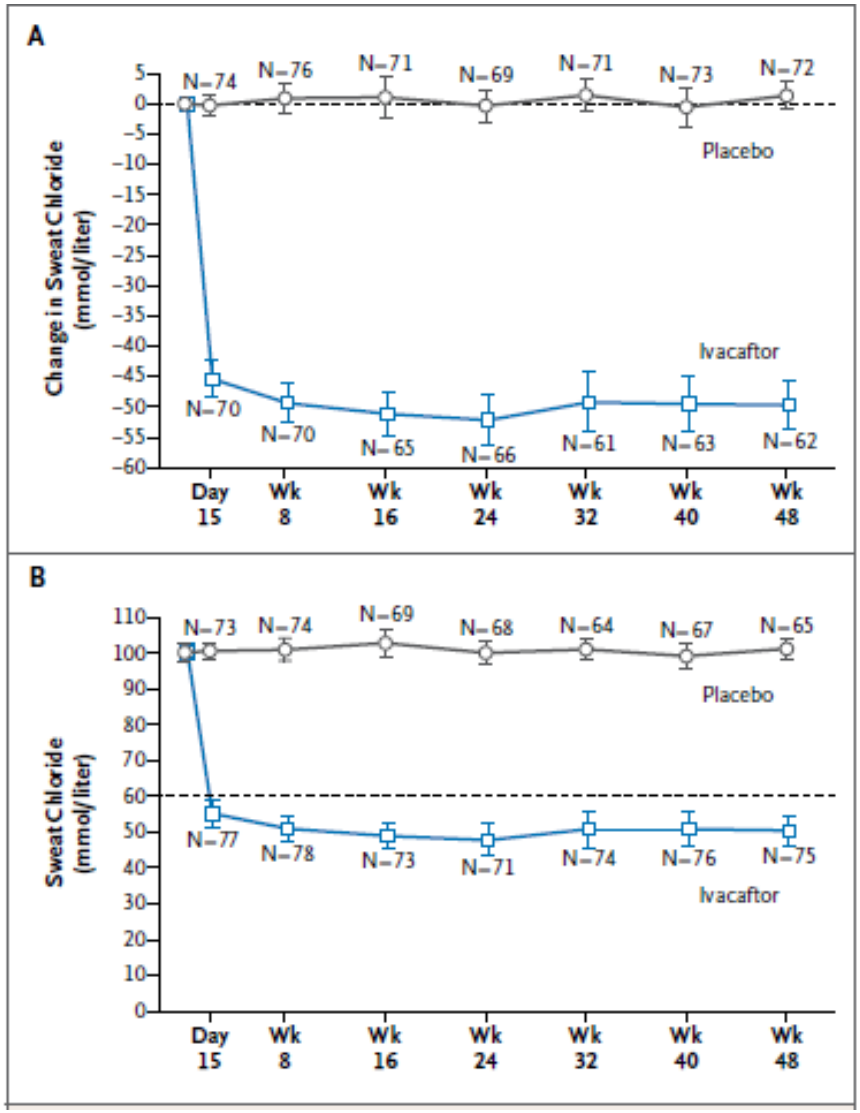
Bonnie W. Ramsey, M.D., Jane Davies, M.D., M.B., Ch.B., N. Gerard McElvaney, M.D., Elizabeth Tullis, M.D., Scott C. Bell, M.B., B.S., M.D., Pavel Dřevínek, M.D., Matthias Griese, M.D., Edward F. McKone, M.D., Claire E. Wainwright, M.D., M.B., B.S., Michael W. Konstan, M.D., Richard Moss, M.D., Felix Ratjen, M.D., Ph.D., Isabelle Sermet-Gaudelus, M.D., Ph.D., Steven M. Rowe, M.D., M.S.P.H., Qunming Dong, Ph.D., Sally Rodriguez, Ph.D., Karl Yen, M.D., Claudia Ordoñez, M.D., and J. Stuart Elborn, M.D., for the VX08-770-102 Study Group*

>12 years of age

150mg BD Ivacaftor v placebo

N=84


A
Absolute Change in Percent of Predicted FEV1
Ivacaftor
Placebo
N–83 N–83 N–81 N–80 N–79 N–79 N–77
N–76 N–75 N–71 N–71 N–70 N–69 N–68
Day 15
Wk 8
Wk 16
Wk 24
Wk 32
Wk 40
Wk 48
B
Proportion of Event-free Subjects
Ivacaftor
Placebo
0.78
0.51
0.67
0.41
Week
C
Change in CFQ-R Respiratory-Domain Score (points)
Ivacaftor
Placebo
N–79 N–80 N–78 N–77 N–76 N–76 N–74
N–70 N–67 N–67 N–65 N–64 N–63 N–62
D
Change in Weight (kg)
Ivacaftor
Placebo
N–83 N–83 N–81 N–80 N–79 N–79 N–77
N–76 N–75 N–73 N–71 N–70 N–69 N–68


A
Change in Sweat Chloride (mmol/liter)
5
0
−5
−10
−15
−20
−25
−30
−35
−40
−45
−50
−55
−60
N−74
N−76
N−71
N−69
N−71
N−73
N−72
Placebo
Ivacaftor
N−70
N−70
N−65
N−66
N−61
N−63
N−62
Day 15
Wk 8
Wk 16
Wk 24
Wk 32
Wk 40
Wk 48
B
Sweat Chloride (mmol/liter)
110
100
90
80
70
60
50
40
30
20
10
0
N−73
N−74
N−69
N−68
N−64
N−67
N−65
Placebo
N−77
N−78
N−73
N−71
N−74
N−76
N−75
Ivacaftor
Day 15
Wk 8
Wk 16
Wk 24
Wk 32
Wk 40
Wk 48

Approved by PBS January 2015
>1 G551D mutation

$270 000 per year

CHEST Original Research

CYSTIC FIBROSIS

Ivacaftor in Subjects With Cystic Fibrosis Who Are Homozygous for the *F508del-CFTR* Mutation

*Patrick A. Flume, MD, FCCP; Theodore G. Liou, MD, FCCP; Drucy S. Borowitz, MD; Haihong Li, PhD; Karl Yen, MD; Claudia L. Ordoñez, MD; and David E. Geller, MD; for the VX08-770-104 Study Group**

Background: **Ivacaftor (VX-770) is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator that was approved in the United States for the treatment of cystic fibrosis (CF) in patients ≥ 6 years of age who have a G551D mutation; however, the most prevalent disease-causing *CFTR* mutation, F508del, causes a different functional defect. The objectives of this study were to evaluate the safety of ivacaftor in a larger population and for a longer time period than tested previously and to assess the efficacy of ivacaftor in subjects with CF who are homozygous for *F508del-CFTR*.**

Methods: **This was a phase 2 study with a 16-week randomized (4:1), double-blind, placebo-controlled period (part A) and an open-label extension (part B) for subjects who met prespecified criteria.**

Results: **Part A: The safety profile of ivacaftor was comparable to that of the placebo. The overall adverse event frequency was similar in the ivacaftor (87.5%) and placebo (89.3%) groups through 16 weeks. The difference in the change of FEV_1 % predicted from baseline through week 16 (primary end point) between the ivacaftor and placebo groups was 1.7% ($P = .15$). Sweat chloride, a biomarker of CFTR activity, showed a small reduction in the ivacaftor vs placebo groups of −2.9 mmol/L ($P = .04$) from baseline through week 16. Part B: No new safety signals were identified. The changes in FEV_1 or sweat chloride in part A were not sustained with ivacaftor treatment from week 16 to week 40.**

Conclusions: **These results expand the safety information for ivacaftor and support its continued evaluation. Lack of a clinical effect suggests that a CFTR potentiator alone is not an effective therapeutic approach for patients who have CF and are homozygous for *F508del-CFTR*.**

Trial registry: **ClinicalTrials.gov; No.: NCT00953706; URL: www.clinicaltrials.gov.**

CHEST 2012; 142(3):718–724

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; HBE = human bronchial epithelial; ULN = upper limit of normal

No effect in F508del

Efficacy and safety of lumacaftor and ivacaftor in patients aged 6–11 years with cystic fibrosis homozygous for *F508del-CFTR*: a randomised, placebo-controlled, phase 3 trial

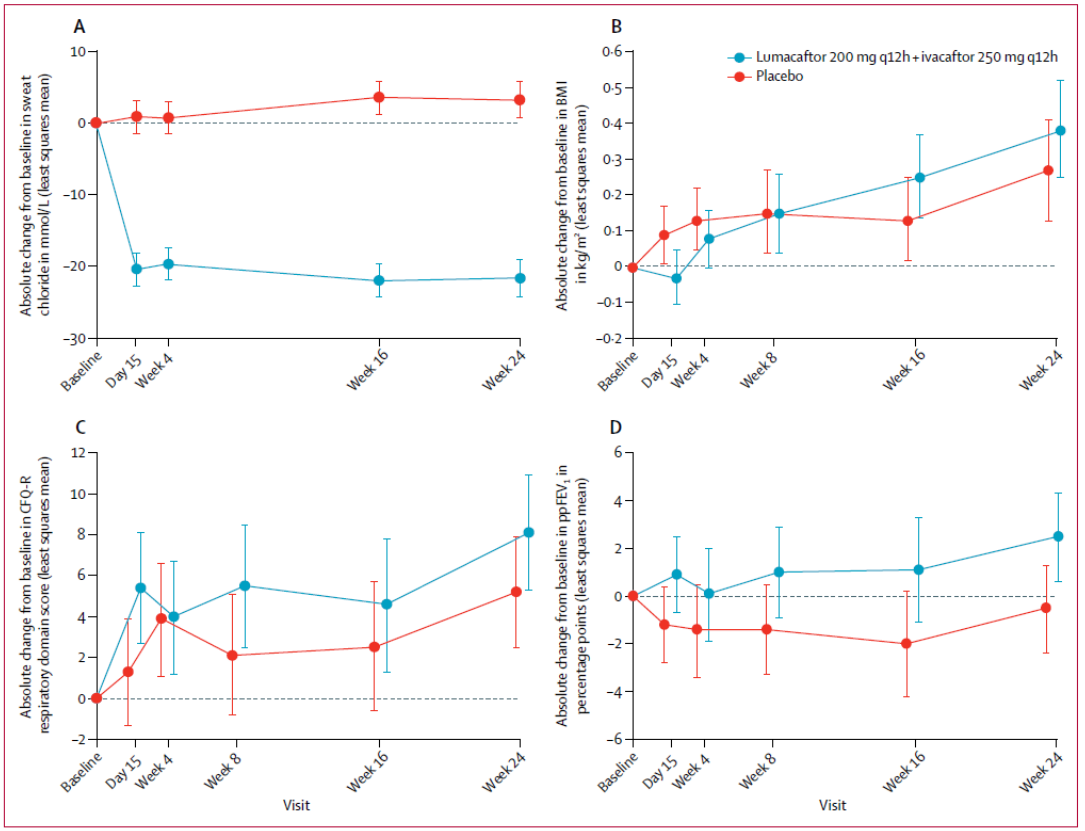
Lancet Respir Med 2017; 5: 557–67

*Felix Ratjen, Christopher Hug, Gautham Marigowda, Simon Tian, Xiaohong Huang, Sanja Stanojevic, Carlos E Milla, Paul D Robinson, David Waltz, Jane C Davies, on behalf of the VX14-809-109 investigator group**

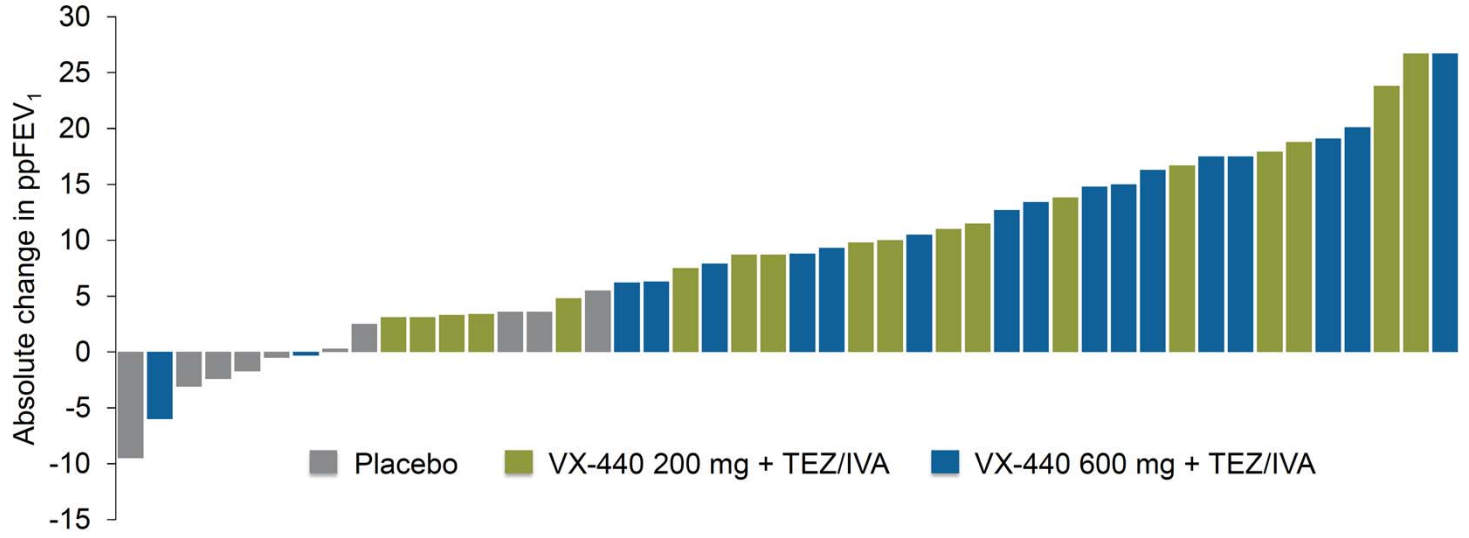
Orkambi

-Ivacaftor (VX770, potentiator)

-Lumacaftor (VX809, corrector)

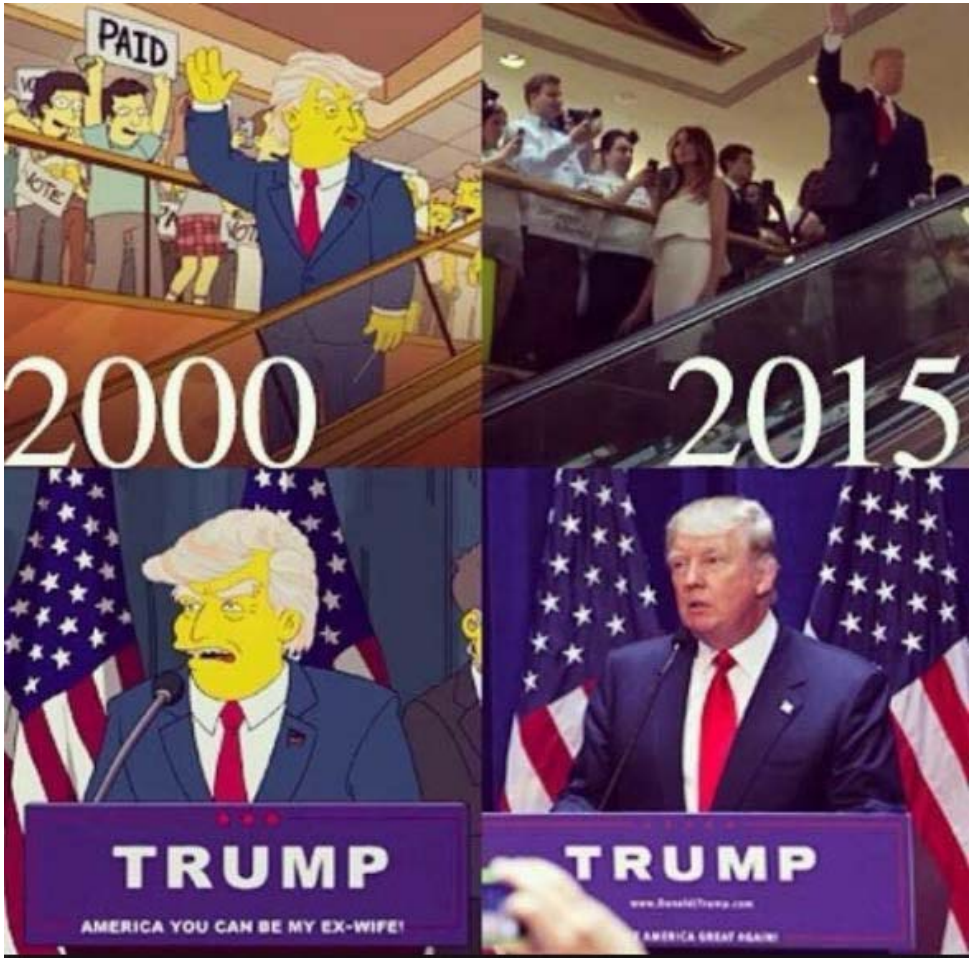


Distribution of Change in ppFEV1 at Day 29 With VX-440 Triple Combination in *F508del*/MF Patients



Courtesy of Vertex

How can we predict response?



A basic biologist at heart, Clevers says he never expected his findings to benefit patients.

SANDER HEEZ

SHARE

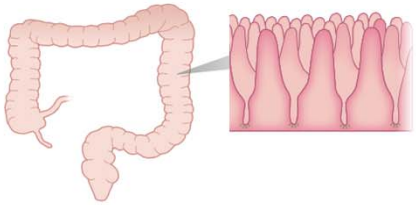
2K

This scientist is building miniature guts, livers, and lungs that could save your life one day

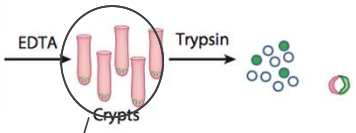
By Gunjan Sinha | Aug. 23, 2017 , 9:00 AM

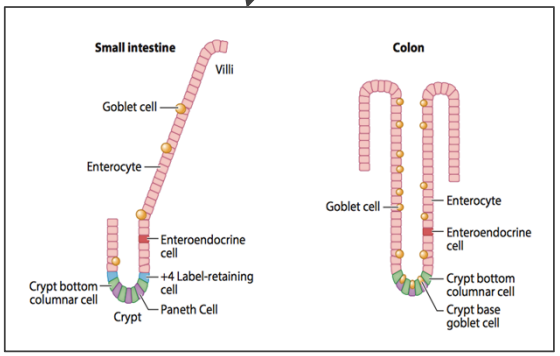
Crypt Isolation and Organoid Culture

Rectal biopsy

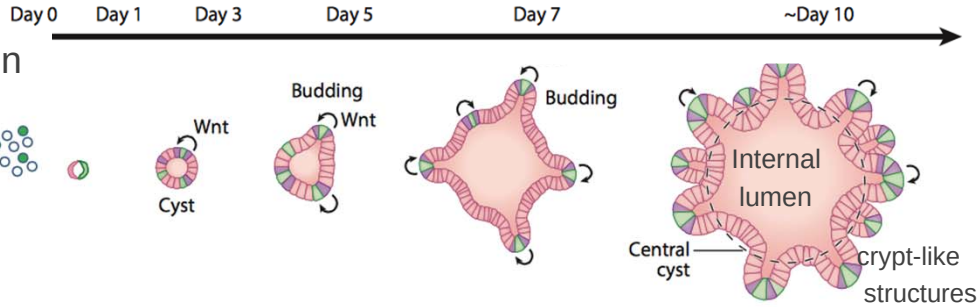


Crypt isolation

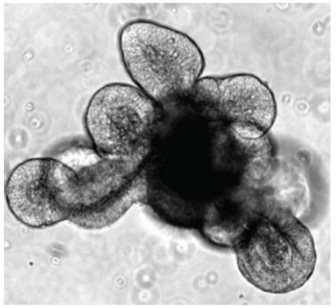


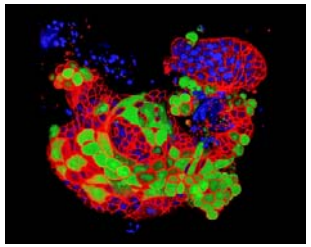


Proliferation, de novo stem cell formation and budding



CFTR: apical membrane

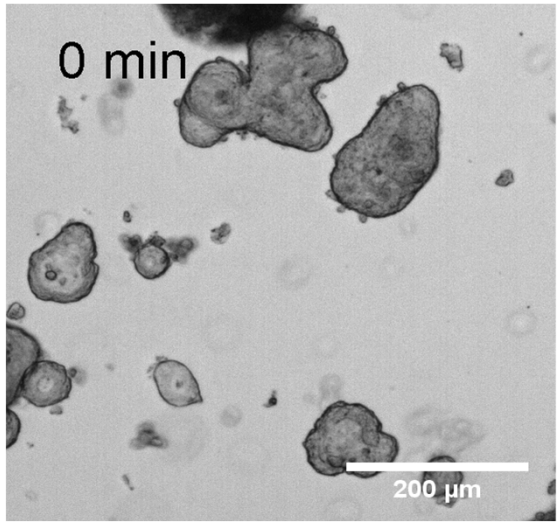




Passaging
Drug screening
Personalized treatments
Molecular assays
Biobanking

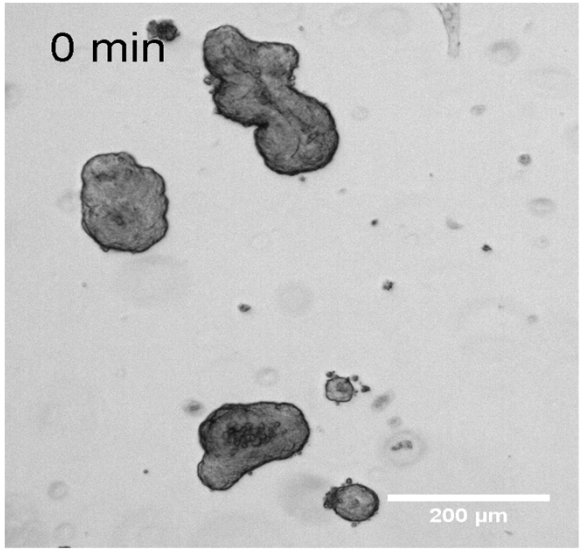
Feeder cells (Wnt3-a, Noggin, Rospondin) donated by
Rob De Vries (Hubrecht), Jeff Beekman (UMCutrecht) and Calvn Cuo (stanford)

CF AVATAR_ Research Studies



+ VX-770 (Ivacaftor)

Individual A



+ VX-770 (Ivacaftor)

Individual B

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

DRUG NAME, FORM(S), STRENGTH(S), SPONSOR, TYPE OF SUBMISSION	TGA INDICATION	CURRENT PBS LISTING	LISTING REQUESTED BY SPONSOR / PURPOSE OF SUBMISSION	PBAC OUTCOME
			Sponsor's comments	Novo Nordisk looks forward to working with the PBAC to determine the best approach to make Victoza® available for Australians with Type 2 Diabetes who would benefit from this product.
LUMACAFTOR with IVACAFTOR Tablet containing lumacaftor 200 mg with ivacaftor 125 mg Orkambi® Vertex Pharmaceuticals (Australia) Pty Ltd New listing (Major Submission)	ORKAMBI 200/125 is indicated for the treatme fibrosis age 12 who are the F50 the CF	LUMACAFTOR with IVACAFTOR is not	Resubmission to request a Section 100 (Highly Specialised Drugs Program)	Lumacaftor with ivacaftor was not recommended by the PBAC for listing on the PBS for the treatment of patients
			rate of deterioration over time.	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 a pulmonary exacerbation over 3 years. The PBAC therefore considered that the claim of superior comparative effectiveness was reasonable.

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.

The way forward

ELSEVIER

Journal of Clinical Epidemiology 66 (2013) S21−S28

Journal of Clinical Epidemiology

Single-patient (n-of-1) trials: a pragmatic clinical decision methodology for patient-centered comparative effectiveness research

Naihua Duan[a,*], Richard L. Kravitz[b], Christopher H. Schmid[c]

[a]*Division of Biostatistics, Department of Psychiatry, Columbia University, 1051 Riverside Drive, Unit 48, New York, NY 10032, USA*
[b]*Division of General Medicine, Department of Internal Medicine, University of California, Davis, 4150 V. Street, Suite 2400 PSSB, Sacramento, CA 95817, USA*
[c]*Center for Evidence-Based Medicine, Department of Biostatistics, School of Public Health, Brown University, 121 S Main Street, Box G-S121-8, Providence, RI 02912, USA*

Accepted 22 April 2013

The n-of-1 clinical trial: the ultimate strategy for individualizing medicine?

Elizabeth O Lillie[1,2], **Bradley Patay**[1,2], **Joel Diamant**[1,2], **Brian Issell**[1,2], **Eric J Topol**[1,2,3,4], and **Nicholas J Schork**[1,2,3,†]

[1] Scripps Health, La Jolla, CA 92037, USA

[2] The Scripps Translational Science Institute, La Jolla, CA 92037, USA

[3] The Scripps Research Institute, La Jolla, CA 92047, USA

[4] The West Wireless Health Institute, La Jolla, CA 92037, USA

Per Med. 2011 March ; 8(2): 161–173. doi:10.2217/pme.11.7.

Rewriting Life

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

ELSEVIER

Journal of Cystic Fibrosis xx (2018) xxx – xxx

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

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,j], Janet Rossant [g,k], Felix Ratjen [d,f,l], Christine E. Bear [a,m,n,*]

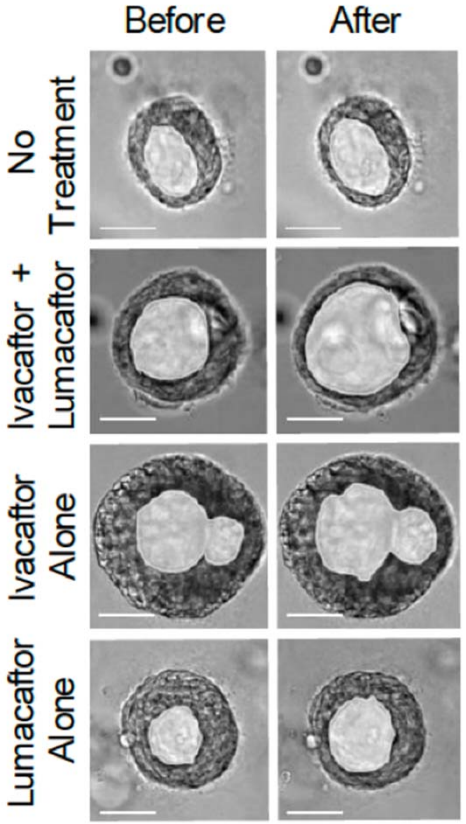
UNSW SYDNEY

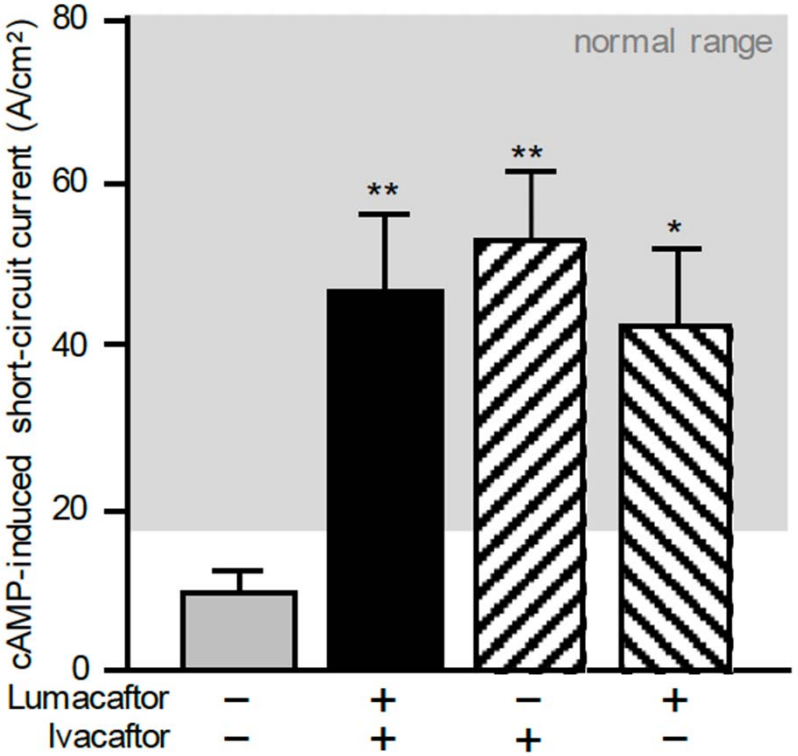
Personalised CFTR Pharamacotherapeutic Response Testing and Therapy in CF

- 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

McCarthy C et al ERJ March 21, 2018 doi: 10.1183/13993003.02457-2017

Response to Ivacaftor and Lumicaftor





McCarthy C et al ERJ March 21, 2018 doi: 10.1183/13993003.02457-2017

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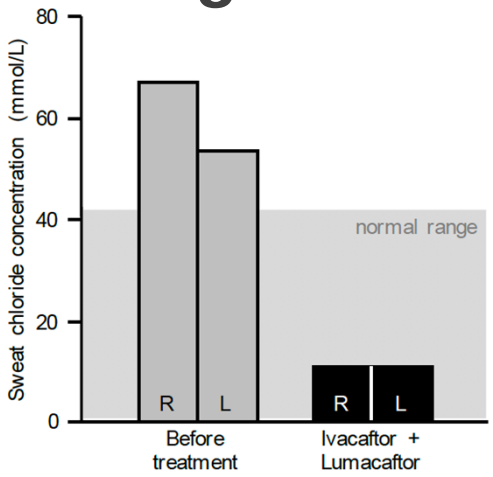
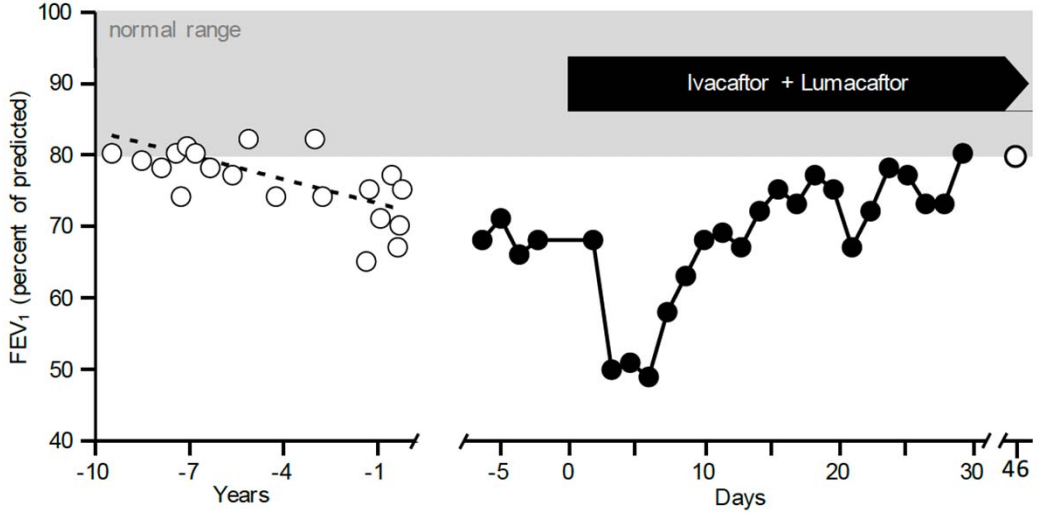
Clinical response following Orkambi

Sweat test



Lung Function



McCarthy C et al ERJ March 21, 2018 doi: 10.1183/13993003.02457-2017

UNSW SYDNEY

The Sydney children's Hospitals Network
care, advocacy, research, education

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miCF Research Centre

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.

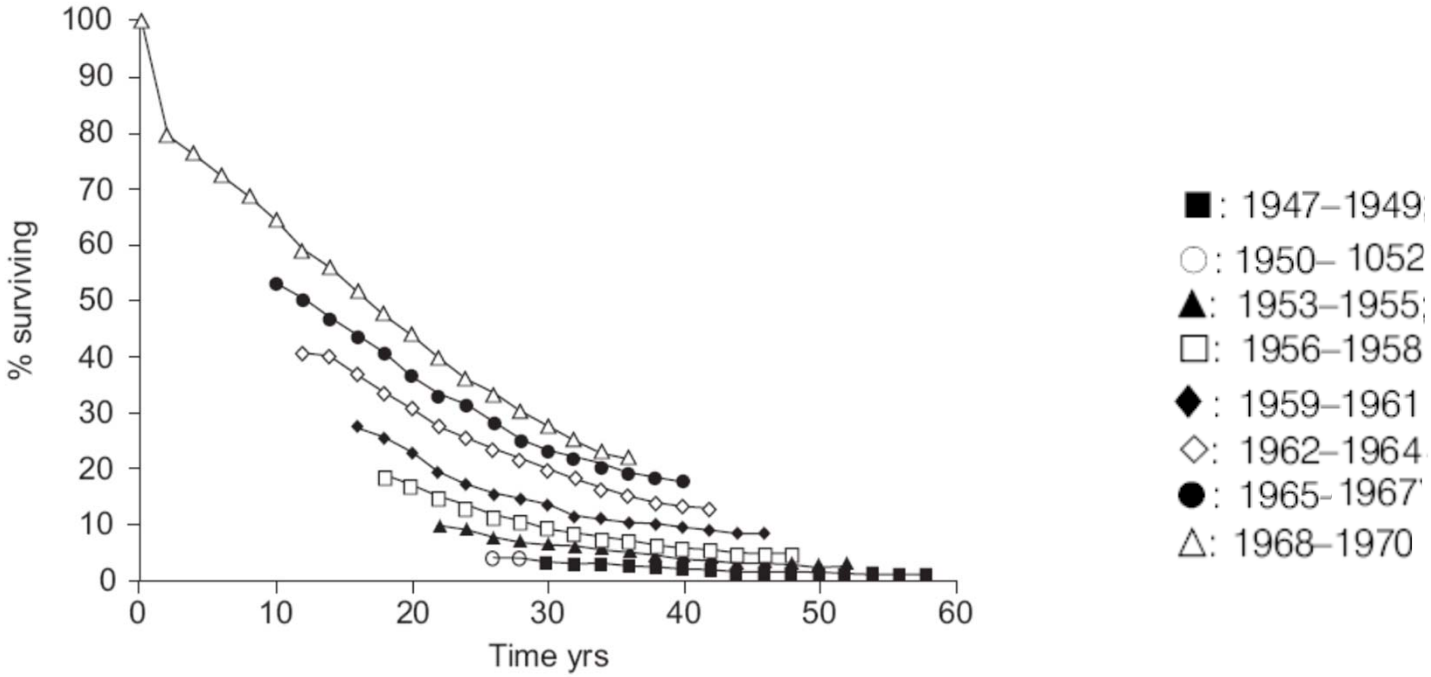
So join us, and invest in a future free from Cystic Fibrosis.

- About Cystic Fibrosis
- Our research
- Our team

www.cysticfibrosiscentre.org.au

UNSW SYDNEY

Summary



‘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

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)

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.
2229901055
Rob Rogers / Pittsburgh Post-Gazette