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2ND AAPS DRUG DISCOVERY AND DEVELOPMENT INTERFACE (DDDI) REGIONAL MEETING

Optimization of Drug Candidates:
Recent Perspectives on Risks/Strategies and Changing Landscape From Small Molecules to Biologicals at The Discovery-Development Interface

August 4, 2017
8:00am – 4:30pm
University of Maryland, Baltimore
Baltimore, MD

Discussion topics include:

- Industry Trends for NCE vs NBE Drug Candidate Transitions
- Academic Collaborations Enhancing Drug Discovery and Early Development
- Population Pharmacokinetics
- Formulation Support in Drug Discovery

Additional information will be available soon at: www.aaps.org

Catch up on Last Year's Design and Delivery Symposium

January 28	The Importance of Drug-Target Kinetics in Drug Design	Robert Copeland - Epizyme, Inc Dan Erlanson - Carmot Therapeutics
February 25	Long-Acting Injectable Medications: Strategies and Mechanistic Considerations	Jules Remenar - Alkermes Annette Bak - Merck
March 31	Modified Release Formulations for Solubility Starved Compounds	Mengwei Hu - Merck John Morrison - BMS
April 28	*The Medicinal Chemist of Tomorrow (Special Topic)*	Joel Barrish - Achillion Ravi Nargund - Merck Molly Schmid - Tech Coast Angels
May 19	Design of Deliverable Macrocycles	Scott Lokey - UC Santa Cruz Nicholas Meanwell - BMS
June 23	Dreaming Big and Thinking Small: Applying Medicinal Chemistry Strategy to Antibody-Drug-Conjugates	L. Nathan Tumey - Pfizer Peter Senter - Seattle Genetics
July 28	Nucleic Acids Therapeutics: Making Sense of Antisense Oligonucleotides	Punit Seth - Ionis Richard Olson - BMS
August 18	Crystallography as a Drug Design and Delivery Tool (Special Topic)	Robert Wenslow - Crystal Pharmatech Vincent Stoll - Abbvie Andrew Brunskill - Merck
September 29	Dealing with Reactive Drug Metabolites in Drug Discovery: Can We Predict Toxicities of Drug Candidates that form Reactive Metabolites?	Deepak Dalvie - Pfizer Frederick Peter Guengerich - Vanderbilt University
October 27	Rational Design of Small Molecules Targeting RNA	Matt Disney - Scripps Rl Florida Amanda Garner - University of Michigan
November 10	Cell Penetrating Peptides to Improve Cellular Drug Uptake	Dehua Pei - The Ohio State University Scott Hart - Bristol-Myers Squibb

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2017 Drug Design and Delivery Symposium

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Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
May 2017						
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31	Notes:		

"Anti-Infectives: Rational Approaches to the Design and Optimization" *Jason Sello, Brown University*

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Thursday, April 27, 2017

Being A Successful Scientist: Lessons in Self-Fulfillment

Darren Griffin, Professor of Genetics, University of Kent, UK

Patricia Simpson, Director of Academic Advising and Career Services, School of Chemical Sciences, University of Illinois at Urbana-Champaign

Thursday, May 4, 2017

Insourcing and Outsourcing in R&D: *Trends in the Pharma Industry*

Session 4 of the Industrial Science Series

Michael P. Trova, Senior Vice President, Drug Discovery, Albany Molecular Research Inc.

Michael McCoy, Assistant Managing Editor for Business, *Chemical & Engineering News*

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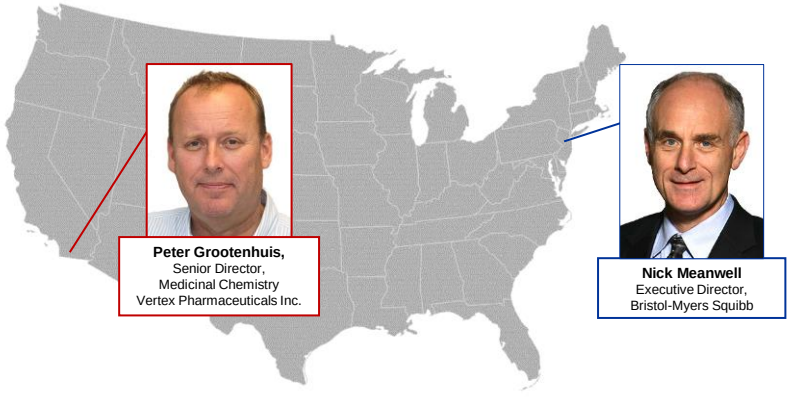
2017 Drug Design and Delivery Symposium

"Cystic Fibrosis: Discovery of CFTR Modulators"



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Cystic Fibrosis: Discovery of CFTR Modulators

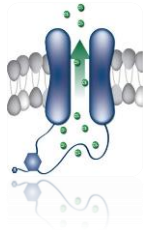
Peter Grootenhuis, PhD
Senior Director, Medicinal Chemistry
Vertex Pharmaceuticals Incorporated
San Diego, CA

American Chemical Society Webinar, April 20, 2017

Outline

1. Cystic fibrosis: The disease

2. CFTR as a drug discovery target



3. Discovery of ivacaftor, a CFTR potentiator

4. Conclusions and perspective

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1) Cystic Fibrosis: The Disease

- Rare genetic disease that affects ~75,000 children and adults in the US and Europe[1]
- CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene
- Of the ~2000 *CFTR* mutations identified, *F508del-CFTR* is the most common CF-causing mutation
- Although clinical manifestations occur throughout the body, lung disease is the main cause of death[2]

1. Cystic Fibrosis Foundation Patient Registry. 2013 Annual Data Report. Bethesda, MD: CFF; 2014;
2. O'Sullivan BP, Freedman, SD. *Lancet*. 2009;373:1891-1904.
3. Reviewed in Van Goor F et al. *Top Med Chem*. 2008;3:91-120.

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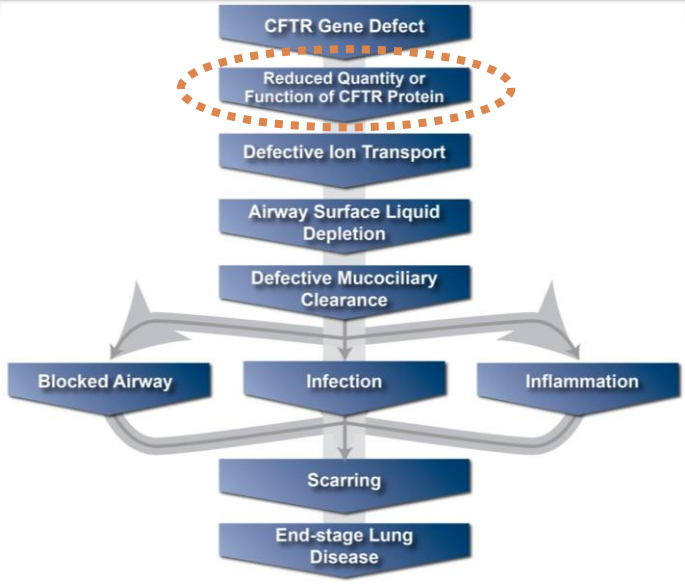
Pathophysiologic Cascade in CF Lung Disease



Reviewed in Van Goor F et al. *Top Med Chem*. 2008;3:91-120.

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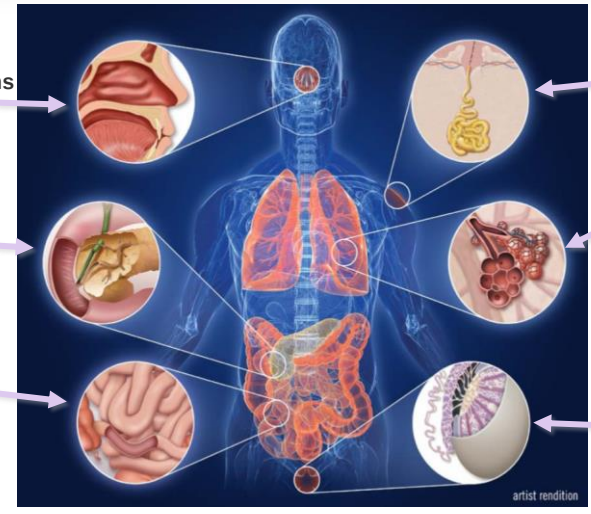
CF is a Multi Organ-Disease



Ramsey B et al. *J Allergy Clin Immunol*. 1992;90:547-552; Moskowitz SM et al. *Genet Med*. 2008;10:851-868;
Welsh MJ et al. Cystic Fibrosis: membrane transport disorders. In: Valle D et al, eds. *The Online Metabolic & Moleclar Bases of Inherited Disease*. The McGraw-Hill Companies Inc; 2004: part 21, chap 201. www.ommbid.com.

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From the Life of a Typical CF Patient

18th C German/Swiss literature:
"Woe is the child who tastes salty from a kiss on the brow, for he is cursed and soon must die"

- Diagnosed as infant
- High burden of disease:
  - Frequent hospitalization to treat reoccurring lung infection and inflammation
  - Daily drug regimen (50-75 pills/day)
    - Antibiotics, bronchodilators, DNAse enzymes, hypertonic saline, pancreatic enzymes
    - Airway clearance therapy
  - Lung transplantation
  - Median life expectancy: 41 years

Cystic Fibrosis Foundation Patient Registry. 2013 Annual Data Report. Bethesda, MD: CFF; 2014.

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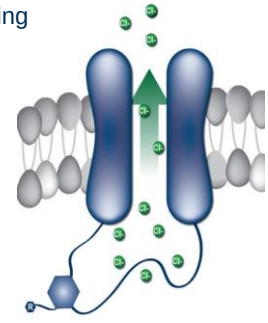
2) CFTR as a Drug Target

- Gene discovered in 1989
- 1480 aa ATP-binding ABC protein, regulated by cAMP-dependent protein kinase A and ATP
- Expressed in apical membrane of epithelia
- CFTR functions as a chloride channel
- F508del most common mutation (~90% of CF patients)
  - Primarily affects CFTR folding and trafficking
- G551D is a gating mutation
  - 4-5% of patients



Rommens JM et al. *Science*. 1989;245:1059-1065.

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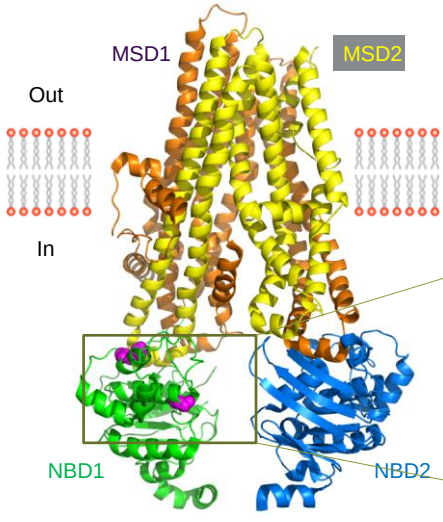
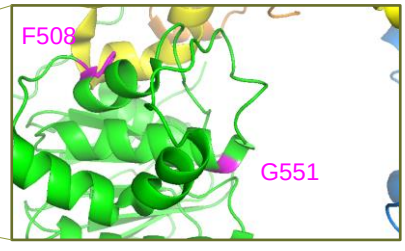
CFTR Structure: First Cryo EM Structure



PDB: 5UAR zebrafish (shown)
5UAK human (not shown)

Represents closed form of channel



Zhang Z, Chen J, *Cell*. 2016;167:1586

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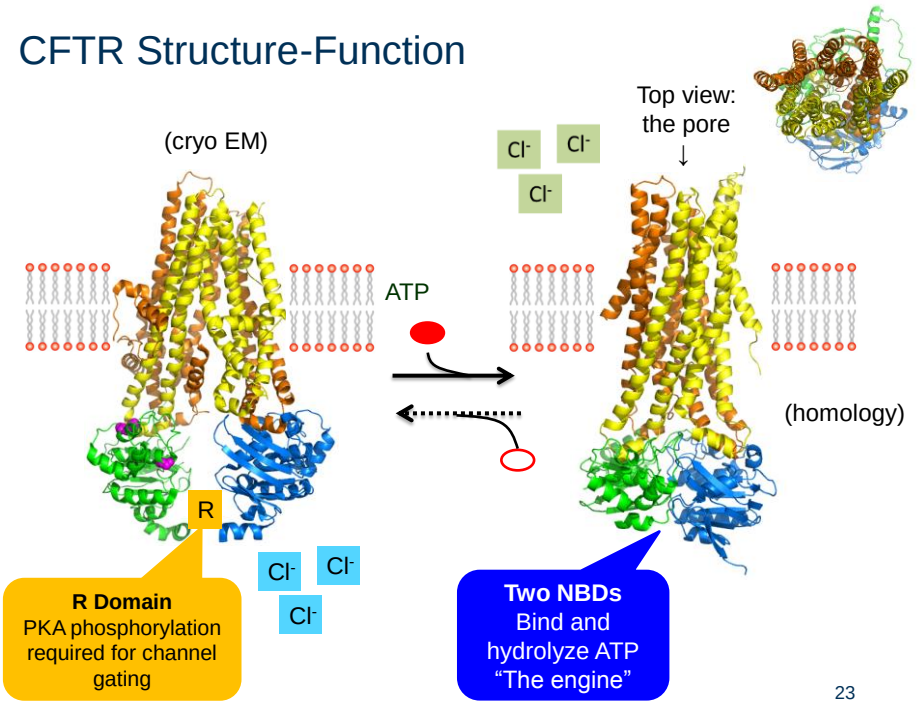
CFTR Structure-Function



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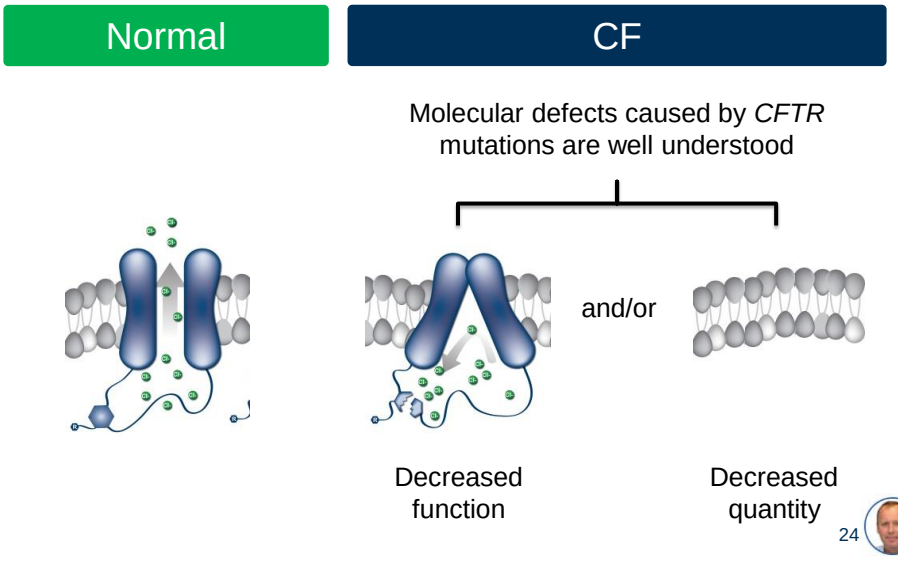
CF Is Caused by Molecular Defects in the CFTR Chloride Ion Channel



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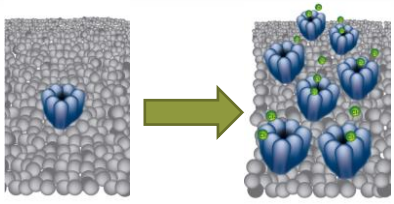
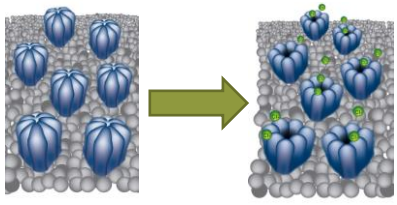
CFTR Modulators Increase the Quantity and Function of CFTR at the Cell Surface



CFTR Correctors

Facilitate increased chloride transport by increasing the quantity of CFTR delivered to the cell surface

e.g., Lumacaftor (VX-809)



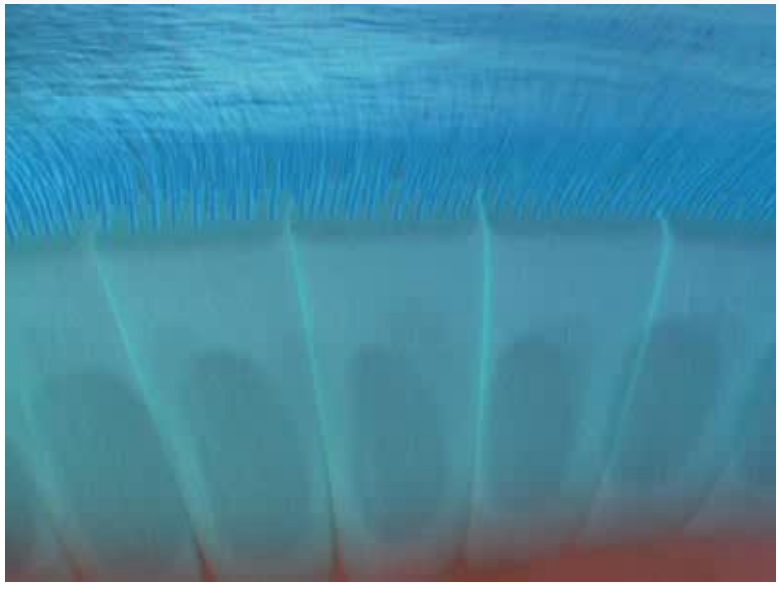
CFTR Potentiators

Facilitate increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface

e.g., Ivacaftor (VX-770)

Total CFTR Activity= **Surface density** x **Open probability** x Conductance

25



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Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

Which statement is INCORRECT?

- **A)** A potentiator increases the open probability of the CFTR channel
- **B)** Potentiators and correctors can be used in combination to enhance mutant CFTR function
- **C)** G551D-CFTR is a so-called gating mutation
- **D)** Most CF patients have gating mutations

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Key Questions During 1998-2002 Period

- Is it possible to modulate CFTR presence and/or function with small molecules?
- How to identify small molecule CFTR modulators?
- What is the best way to biologically profile modulators?
- What efficacy level in biological assays do we need to see to expect clinical efficacy?
- What is the desired profile of a CFTR modulator drug?

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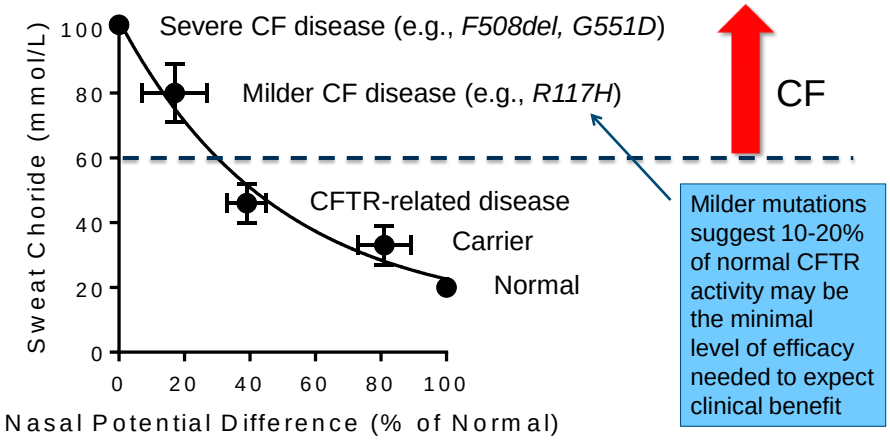
Level of CFTR Dysfunction Linked to Disease Phenotype



Accurso FJ et al. *J Cyst Fibros.* 2014;13:139-147, ; Strausbaugh SD, Davis PB. *Clin Chest Med.* 200;28:279-88; McKone EF, et al. *Chest.* 2006;130:1441-7; McKone EF, et al. *Lancet.* 2003;361:1671-6; Noone PG, et al. *Gastroenterology.* 2001;121:1310-9; Noone PG, et al. *Am J Respir Crit Care Med.* 2000;162:1919-24; Davis PB, et al. *Am J Respir Crit Care Med.* 1996;154:1229-56..

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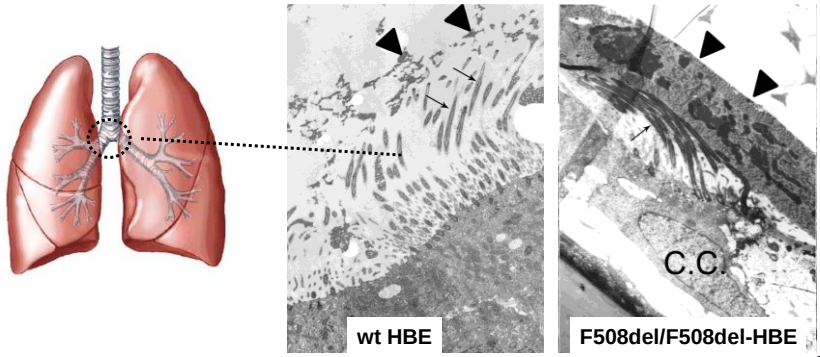
Human Bronchial Epithelial Cultures

- Cultured bronchial epithelia isolated from human tissue
- Differentiated epithelia show the same defective ion transport as observed in vivo
- Used as the pharmacology model for Vertex CFTR modulators



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Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

How would you start a CFTR modulator program?

- **A)** Determine the 3D structure of CFTR and apply structure-based design
- **B)** Take a lead from the scientific or patent literature as a starting point
- **C)** Do HTS using phenotypic assays
- **D)** Try to repurpose existing drugs or advanced clinical candidates

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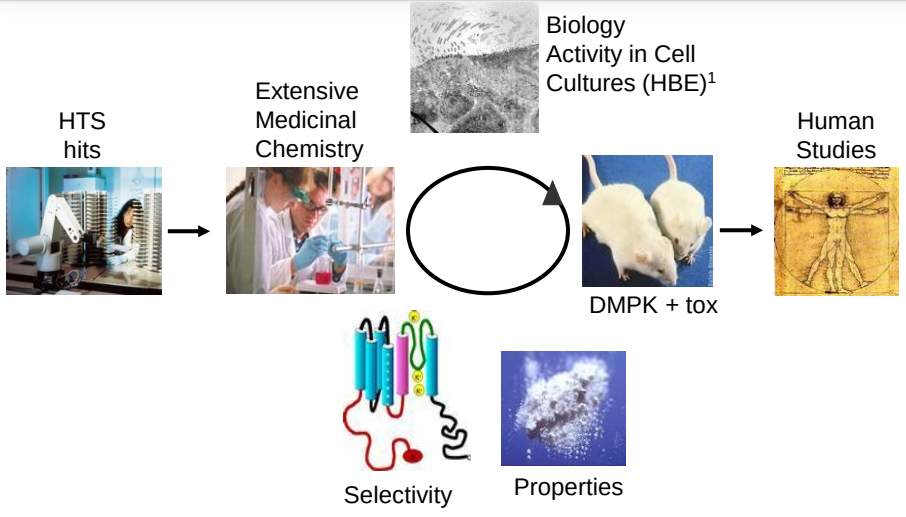
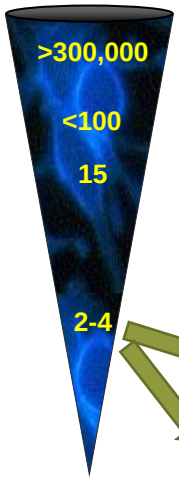
3) Discovery of CFTR Potentiator Ivacaftor



Human Bronchial Epithelial Cells (HBE)

32

Multiple HTS Campaigns for CFTR Modulator Hits

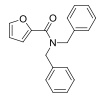


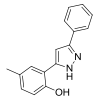
HTS in membrane potential assays of various cells over-expressing F508del CFTR including 3T3, FRT

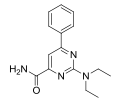
Confirmed hits

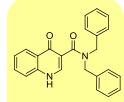
Secondary assays
- i. Patch-clamp assays
- ii. Selectivity and cell viability
- iii. CF-HBE in Ussing chamber

Potentiators: 4 scaffolds

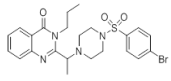

VRT-084

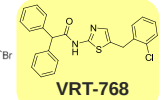

VRT-532


VRT-931


VRT-484

Correctors: 2 scaffolds


VRT-422


VRT-768

HBE, human bronchial epithelial cells; HTS, high throughput screening.

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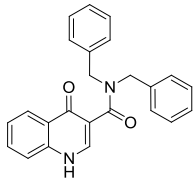
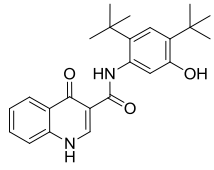
From Hit to Drug: Extensive Medicinal Chemistry and SAR Efforts Required

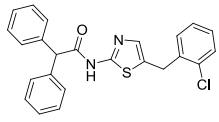


H2L,LO, Med.Chem.

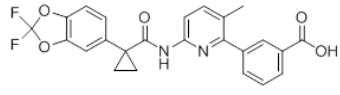


VRT-484 (Hit)
HBE EC_{50} 1.5 μM

Ivacaftor (VX-770)
HBE EC_{50} 0.022 μM



H2L,LO, Med.Chem.



VRT-768 (Hit)
HBE EC_{50} 2.5 μM
Efficacy <1% normal

Lumacaftor (VX-809)
HBE EC_{50} 0.06 μM
Efficacy 15% of normal

EC_{50}, half maximal effective concentration; SAR, structure-activity relationship.
Van Goor F et al. *Proc Natl Acad Sci U S A.* 2009;106:18825-18830.
Van Goor F et al. *Proc Natl Acad Sci U S A.* 2011;108:18843-18848.

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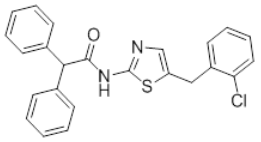
Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



C logP = 6.9
Fsp3 = 0.08

What do you think when you see this hit?

- **A)** Compounds like this should not be in a screening deck
- **B)** Hit optimization will be a nightmare
- **C)** Let's continue screening for more lead-like hits
- **D)** Great. Let's start hit-to-lead optimization

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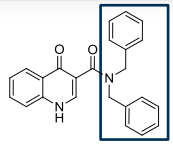
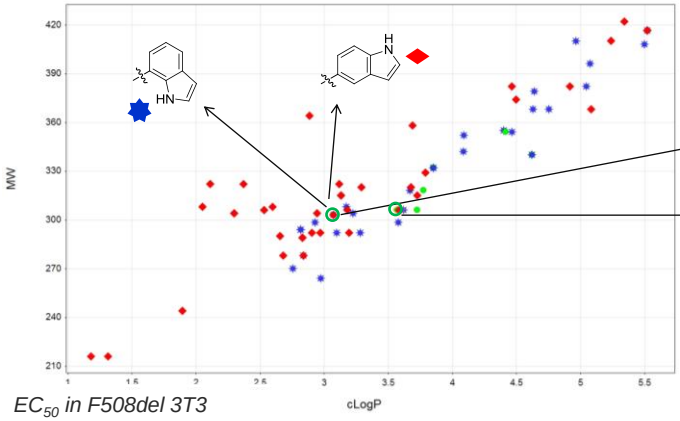
Potentiator Hit: Amide Exploration Led To Potency Improvements

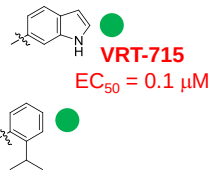
- Synthesized in a small library of ~70 analogs that included
  - Primary and secondary amines
  - Aliphatic, aromatic and heterocyclic amines



VRT-484
EC_{50} = 2.1 μM



EC_{50} in F508del 3T3



VRT-715
EC_{50} = 0.1 μM

- 0.1 ≤ EC_{50} < 0.5 μM
- 0.5 ≤ EC_{50} ≤ 5 μM
- EC_{50} > 5 μM

Hadida S et al, *J.Med.Chem.* 2014;57:9776-9795.
Hadida S et al, *Ann.Rep.Med.Chem.* 2014;*49*:383-398.

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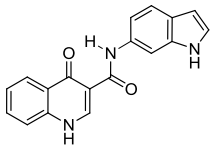
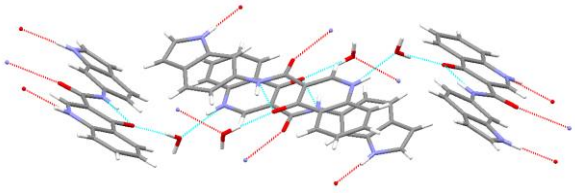
VRT-715: Good Activity But Poor Properties



VRT-715

EC_{50}= 0.1 μM F508del 3T3

EC_{50}= 0.05 μM F508del HBE



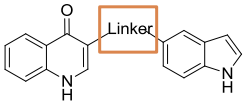
Extensive H-bonding and stacking in crystal structure: poor solubility (not detectable)

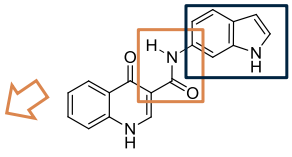
High iv Cl in rats and dogs

Hadida S et al, *J.Med.Chem.* 2014;57:9776-9795.
Hadida S et al, *Ann.Rep.Med.Chem.* 2014;*49*:383-398.

MedChem Strategy Around VRT-715

Linker modifications





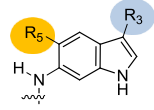
VRT-715

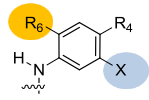
EC_{50}= 0.1 μM F508del 3T3

EC_{50}= 0.05 μM F508del HBE

EC_{50} in F508del 3T3

Amine modifications





X= NH_2, hydrogen bound donors, aniline bioisosteres

Linker	EC_{50} (μM)
-CONH-	0.1 μM
-CO_2-	19% @ 30 μM*
-SO_2NH-	1% @ 30 μM*
-CH_2NH-	1% @ 30 μM*
-NHCO-	8% @ 30 μM*

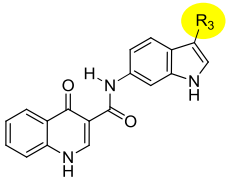
% activity of VRT-532 @ 30 μM

Hadida S et al, *J.Med.Chem.* 2014;57:9776-9795.
Hadida S et al, *Ann.Rep.Med.Chem.* 2014;*49*:383-398.

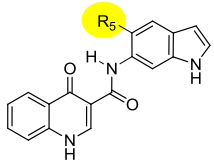
Amide SAR: Bicyclic Analogs

EC_{50} in F508del 3T3

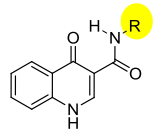
Lipophilic substituents at indole positions 3 and 5 improve potency

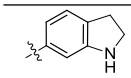
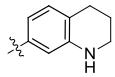
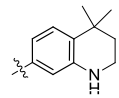


R_3	EC_{50}(μM)
-H (VRT-715)	0.1
-CN	2.8
-Me	0.3
-*t*Bu	0.02



R_5	EC_{50} (μM)
-H (VRT-715)	0.1
-F	0.3
$-CF_3$	0.04
-*t*Bu	0.01



R	EC_{50} (μM)
	0.4
	0.8
	0.05

- Alkyl substitutions detrimental at indole position 7, tolerated at 2 and 4

Hadida S et al, *J.Med.Chem.* 2014;57:9776-9795.
Hadida S et al, *Ann.Rep.Med.Chem.* 2014;*49*:383-398.

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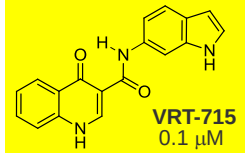
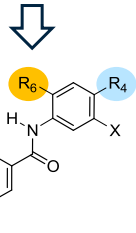
Amide SAR: Monocyclic Analogs

EC_{50} in F508del 3T3

Multiple chemotypes show sub-micromolar activity





R_4	R_6	X	EC_{50} (μM)
-Et	*-H*	*$-NH_2$*	*1.7*
-tBu	*-H*	*$-NH_2$*	*0.1*
-H	*-tBu*	*$-NH_2$*	*0.5*
-*t*Bu	-H	-H	0.1
-*t*Bu	-H	-F	0.1
-*t*Bu	-H	$-NHCO_2CH_3$	3.5
-*t*Bu	-H	$-SO_2NH_2$	5.1
-*t*Bu	-H	-OH	0.003
-*t*Bu	-F	-OH	0.002
-*t*Bu	$-CF_3$	-OH	0.003
-*t*Bu	-*t*Bu	-OH	0.003

1700-fold !!!

Hadida S et al, *J.Med.Chem.* 2014;57:9776-9795.
Hadida S et al, *Ann.Rep.Med.Chem.* 2014;*49*:383-398.

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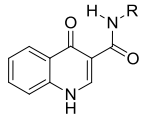
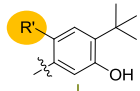
Discovery of VX-770 (Ivacaftor)



F508del



R	R'= H	R'= F	R'= CF_3	R'= tBu
EC_{50} 3T3 (nM)	3	2	3	3
EC_{50} HBE (nM)	5	45	22	22
Rat iv PK				
Cl (ml/min/Kg)	86	63	18	5.5
$t_{1/2}$ (hr)	0.7	1.1	2.9	9.5
Vss (L/Kg)	2.9	2.9	3.2	3.6

Hadida S et al, *J.Med.Chem.* 2014;57:9776-9795.
Hadida S et al, *Ann.Rep.Med.Chem.* 2014;*49*:383-398.

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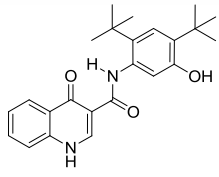
VX-770 (Ivacaftor) Has a Favorable Animal PK Profile



	iv			po
Species	Cl (mL/min/kg)	$t_{1/2}$ (hr)	Vss (L/kg)	%F
Mouse	20.0	1.3	2.8	ND
Rat	5.5	9.5	3.6	55
Dog	0.7	13	0.7	43
Monkey	7.4	6.7	2.2	ND

ND, not determined
Hadida S et al, *J.Med.Chem.* 2014;57:9776-9795.
Hadida S et al, *Ann.Rep.Med.Chem.* 2014;*49*:383-398.

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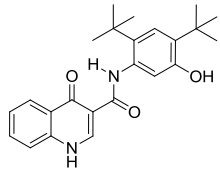
Discovery of VX-770 (Ivacaftor)



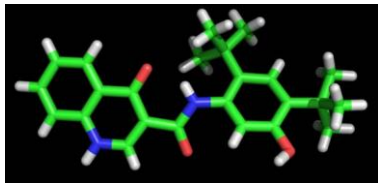
Analogs with EC_{50} < 100 nM

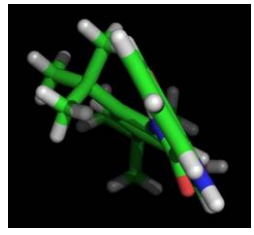
Activity in F508 and G551D HBE cells

in vitro ADME and selectivity

In vivo PK

VX-770 (Ivacaftor)





Hadida S et al, *J.Med.Chem.* 2014;57:9776-9795.
Hadida S et al, *Ann.Rep.Med.Chem.* 2014;*49*:383-398.

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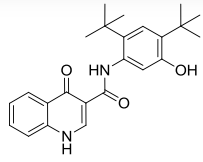
Ivacaftor Preclinical Profile



- Potentiator, not activator
- In vitro activity against multiple genotypes[1,2]
  - On residual CFTR in F508del/F508del HBE: 22 nM
  - G551D/F508del HBE: 236 nM
- In vitro selectivity
- >99% plasma protein binding
- Favorable oral pharmacokinetics in rodents and non-rodents

1. Van Goor F et al. *Proc Natl Acad Sci U S A.* 2009;106:18825-18830
2. Yu H et al. *J Cyst Fibros*. 2012;11:237-245.

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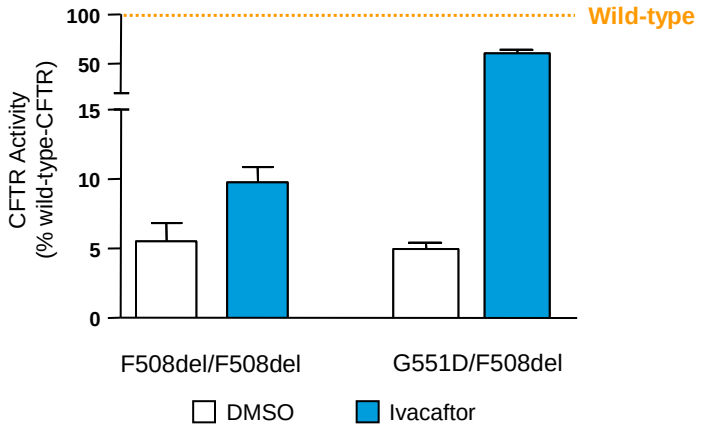
Ivacaftor Increases G551D-CFTR Function In Vitro

Ussing chamber studies using G551D/F508del-HBE



DMSO, dimethyl sulfoxide.
Van Goor F et al. *Proc Natl Acad Sci U S A*. 2009;3:18825-18830.

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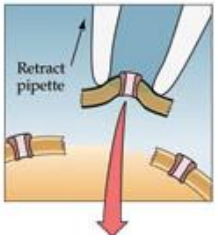
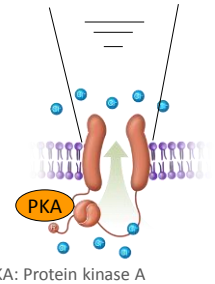
Direct Measurement of CFTR Channel Gating

Single-channel, patch-clamp technique





PKA: Protein kinase A

Channel open probability
Measure of the fraction of time the channel is open

Current amplitude
Measure of channel conductance

Normal CFTR

Patch clamp: electrophysiology technique that allows the study of a single or multiple ion channels in cells (developed in late 1970s)

Reviewed in Van Goor F et al. *Top Med Chem*. 2008;3:91-120.

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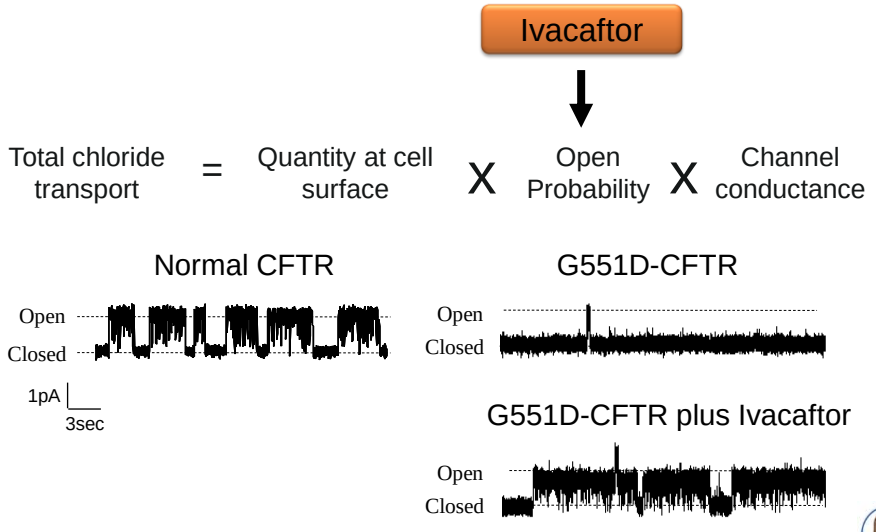
Ivacaftor Increases the Channel Open Probability of G551D-CFTR Expressed in Cultured Cells



Reviewed in Van Goor F et al. *Top Med Chem*. 2008;3:91-120.

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Ivacaftor Increased Cilia Beating in G551D/F508delHBE

Defective CFTR Function

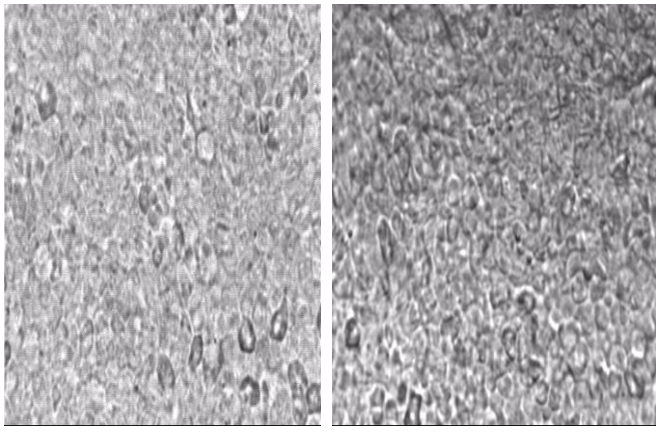
↓

Decreased Cl^- flux
Increased Na^+ flux

↓

Airway Dehydration
Reduced Cilia Beating

DMSO-Treated → (5 days) Ivacaftor-Treated



4.0 ± 0.4 Hz

16.0 ± 0.3 Hz

Cilia Beat Frequency

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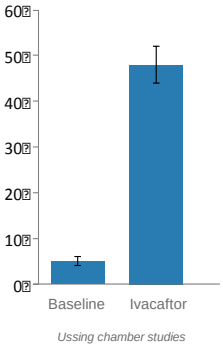
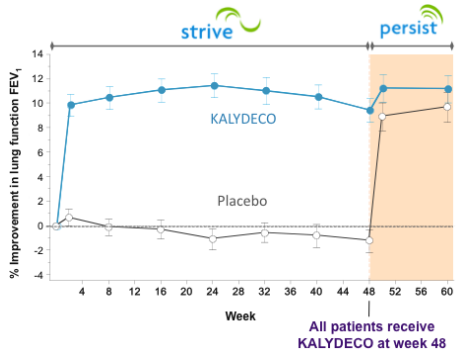
Effect of Ivacaftor *in Vitro* Translated to Effect in People with *G551D* Mutation

Cultured G551D-HBE[1]
~50% normal with ivacaftor



CF Patients with G551D[2]
+10.5% Mean Within-Group Absolute FEV_1 Improvement



1. Goor F et al. *Proc Natl Acad Sci U S A*. 2009;3:18825-18830.
2. McKone E et al. *Lancet Respir Med*. 2014;2(11):902-910.

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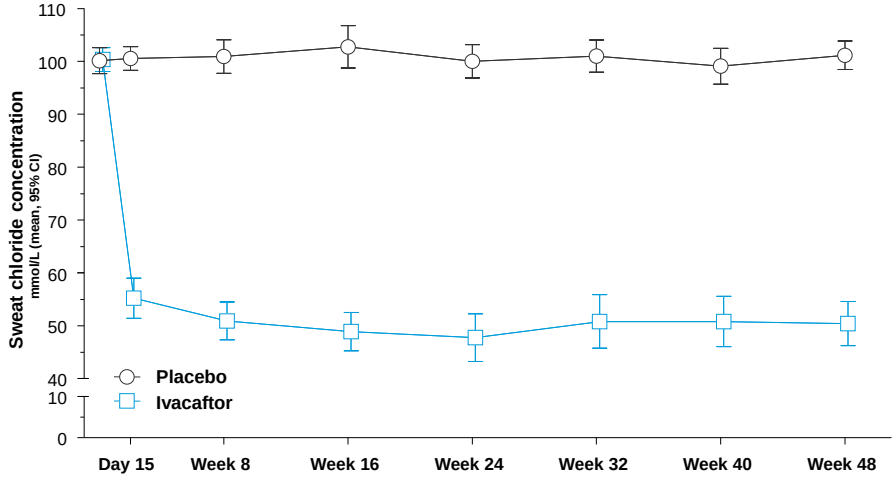
Ivacaftor Reduced Sweat Chloride Concentrations in People with CF who have the G551D Gating Mutation



Ramsey B et al. *N Engl J Med*. 2011;365:1663-1672.

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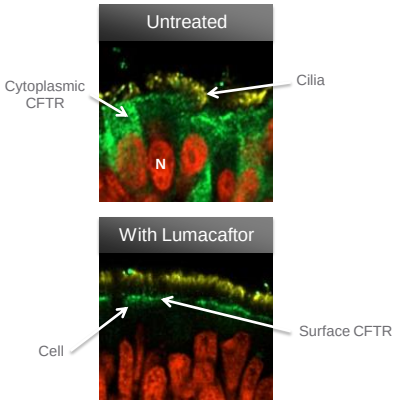
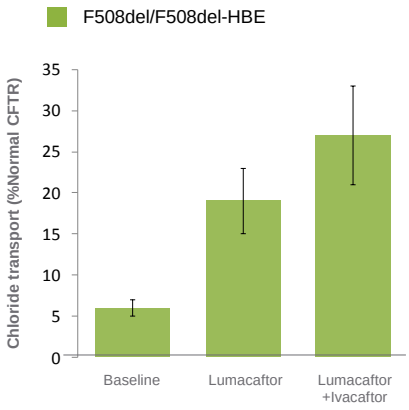
Ivacaftor Potentiates *F508del-CFTR* Delivered to the Cell Surface by Lumacaftor

Cultured F508del/F508del-HBE



Data from 4 Donor Bronchi



Chronic treatment with lumacaftor (3 µM) and/or ivacaftor (100 nM) in Ussing chamber studies

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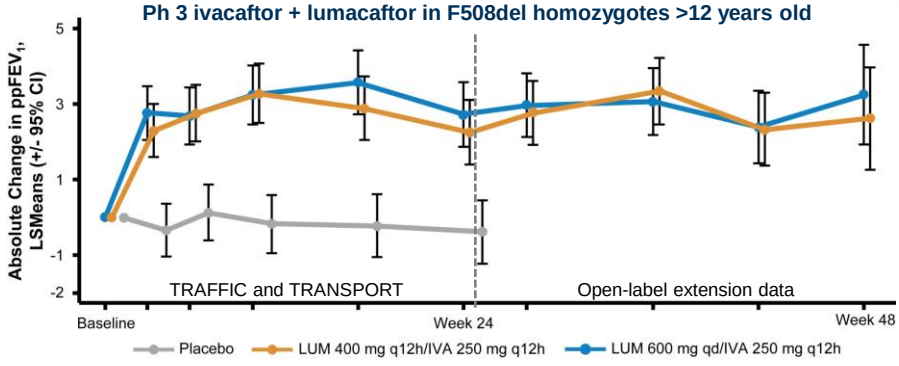
Lumacaftor + Ivacaftor Produced Significant Clinical Benefits in People with 2 Copies of F508del

Ph 3 ivacaftor + lumacaftor in F508del homozygotes >12 years old



Source: Wainwright C., "Effect of lumacaftor in combination with ivacaftor in patients with CF who are homozygous for F508del-CFTR: Phase 3 TRAFFIC and TRANSPORT studies." NACF meeting, Atlanta, GA. October 10, 2014; Data for 26% of participants available through 48 weeks

- Statistically significant and clinically meaningful improvement in lung function
- Significant improvement in multiple secondary endpoints
  - Pulmonary exacerbations (Reduced by 30 – 39%)
  - Hospitalizations related to pulmonary exacerbations (39 – 61% reduction)
  - BMI (+0.24 – 0.28 kg/m^2 treatment difference in 24 weeks)
- Generally well tolerated; The most common adverse events, regardless of treatment group, were infective pulmonary exacerbation, cough, headache and increased sputum.

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4) Conclusions & Future Perspectives

- Ivacaftor (Kalydeco®) FDA approval in 2012
  Lumacaftor/ivacaftor combo (Orkambi®) FDA approval in 2015
- Misfolded mutant CFTR is 'fixable' by small molecules
- Open mind required when looking for CFTR modulators:
  "Rules are, by nature, barriers to innovation" (G. Mueller)
  "Rules are not laws, but guidelines " (N. Meanwell)
- Human bronchial epithelia to date appear to be predictive for clinical outcomes
- Currently in clinical evaluation: novel correctors that will be part of a triple combination treatment with the goal to enhance and expand clinical benefit towards all F508del heterozygote CF patients

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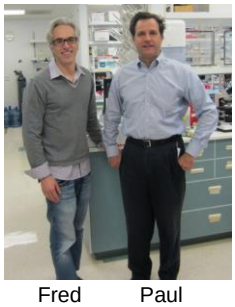
Acknowledgements



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Cystic Fibrosis Foundation

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Darren Griffin, Professor of Genetics, University of Kent, UK

Patricia Simpson, Director of Academic Advising and Career Services, School of Chemical Sciences, University of Illinois at Urbana-Champaign

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Session 4 of the Industrial Science Series

Michael P. Trova, Senior Vice President, Drug Discovery, Albany Molecular Research Inc.

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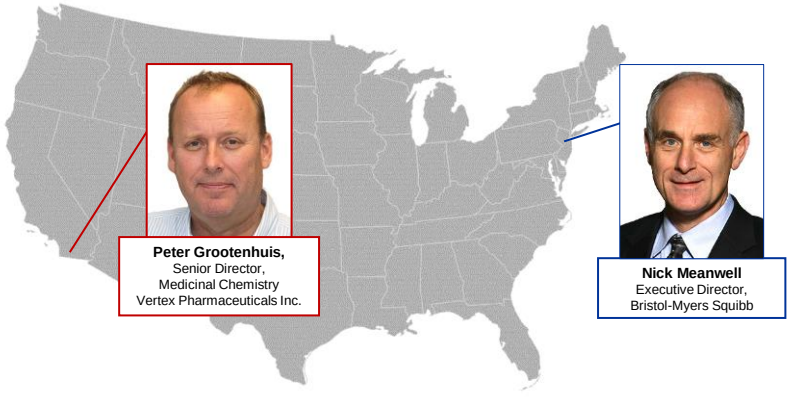

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Baltimore, MD

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- Academic Collaborations Enhancing Drug Discovery and Early Development
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Patricia Simpson, Director of Academic Advising and Career Services, School of Chemical Sciences, University of Illinois at Urbana-Champaign

Thursday, May 4, 2017

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Session 4 of the Industrial Science Series

Michael P. Trova, Senior Vice President, Drug Discovery, Albany Molecular Research Inc.

Michael McCoy, Assistant Managing Editor for Business, *Chemical & Engineering News*

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