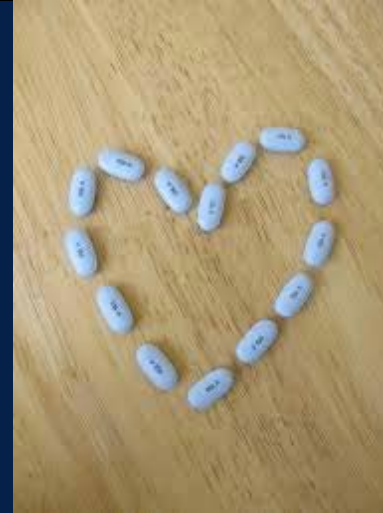
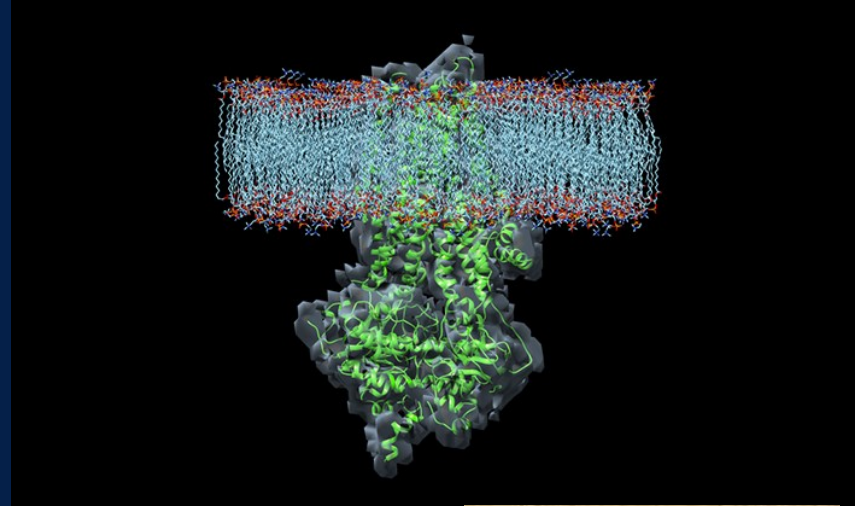


# Cystic Fibrosis: Updates in New Therapeutics

Elizabeth Gibb MD  
Pediatric Pulmonary Medicine  
January 27, 2018



# Overview

- Cystic Fibrosis manifestations and survival
- History of Development of CF Therapeutics
- CFTR Mutations
- CFTR Modulators
  - Ivacaftor, Lumacaftor/Ivacaftor, Tezacaftor/Ivacaftor
  - Next generation CFTR modulators
- Other therapeutics in the pipeline
  - Mucociliary clearance
  - Anti-inflammatory
  - Anti-infective
  - Nutritional/GI

# A Case

- 12 year old Latina female with pancreatic insufficient Cystic Fibrosis.
- Genetics:
  - S549N and 1811+1.6kbA->G
- In the past year, FEV1 has been 33 to 39% of normal
- 8 admissions (117 days) in the past 2 years for pulmonary exacerbations
- BMI of 19.2 kg/m<sup>2</sup>



# Manifestations of Cystic Fibrosis

## General

- Growth failure (malabsorption)
- Vitamin deficiency states (vitamins A, D, E, K)

## Nose and sinuses

- Nasal polyps
- Sinusitis

## Liver

- Hepatic steatosis
- Portal hypertension

## Gallbladder

- Biliary cirrhosis
- Neonatal obstructive jaundice
- Cholelithiasis

## Bone

- Hypertrophic osteoarthropathy
  - Clubbing
- Arthritis
- Osteoporosis

## Intestines

- Meconium ileus
- Meconium peritonitis
- Rectal prolapse
- Intussusception
- Volvulus
- Fibrosing colonopathy (strictures)
- Appendicitis
- Intestinal atresia
- Distal intestinal obstruction syndrome
- Inguinal hernia

## Lungs

- Bronchiectasis
- Bronchitis
- Bronchiolitis
- Pneumonia
- Atelectasis
- Hemoptysis
- Pneumothorax
- Reactive airway disease
- Cor pulmonale
- Respiratory failure
- Mucoid impaction of the bronchi
- Allergic bronchopulmonary aspergillosis

## Heart

- Right ventricular hypertrophy
- Pulmonary artery dilation

## Spleen

- Hypersplenism

## Stomach

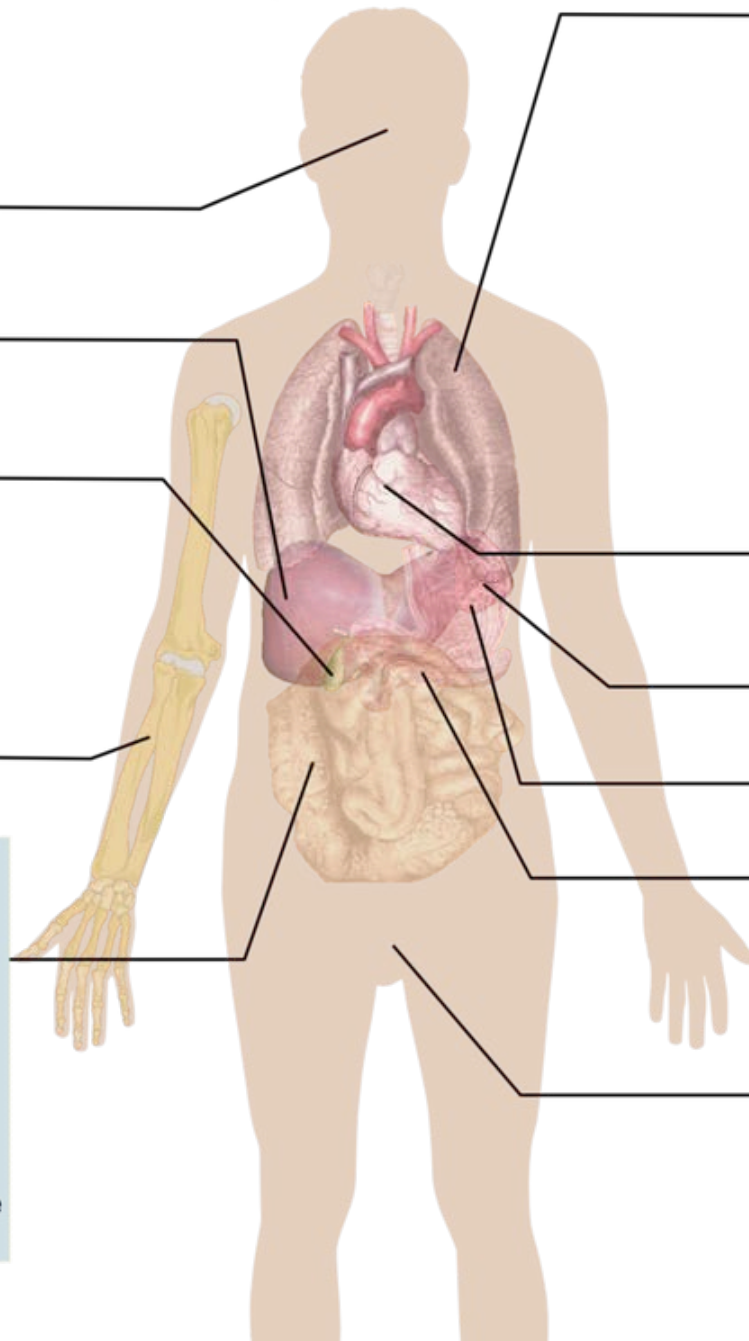
- GERD

## Pancreas

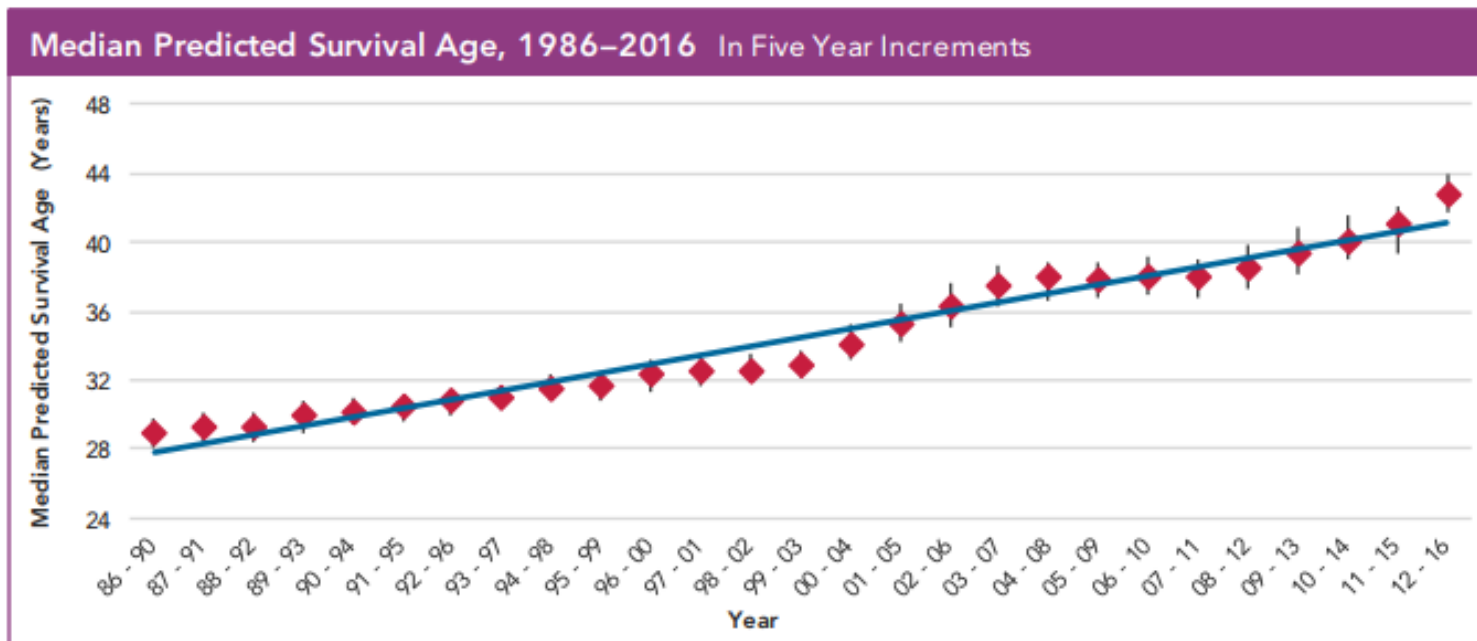
- Pancreatitis
- Insulin deficiency
- Symptomatic hyperglycemia
- Diabetes

## Reproductive

- Infertility (aspermia, Absence of vas deferens)
- Amenorrhea
- Delayed puberty



# CF Survival Continues to Improve – BUT



*\*Using the currently recommended method for calculating median predicted survival.*

# ... We Have More To Do To Advance Quality of Care

## Intervene Earlier

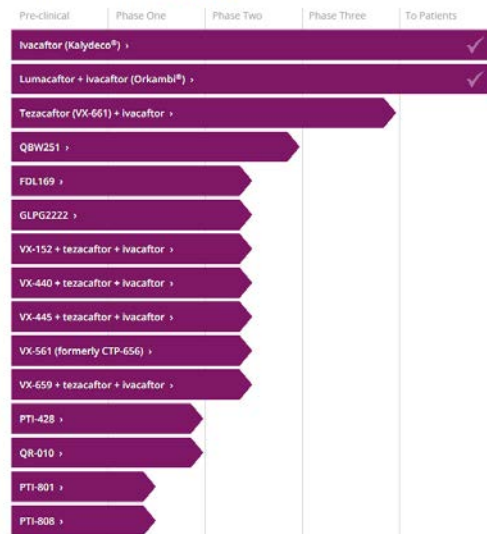
- Diagnose CF earlier (newborn screening)
- Target CF lung disease before symptoms occur
- Target genetics to optimize pulmonary and nutritional status
- Prevent bronchiectasis and loss of lung function
- Promote good nutrition

## Develop Comprehensive Treatment Plan (CTP) from Early Age

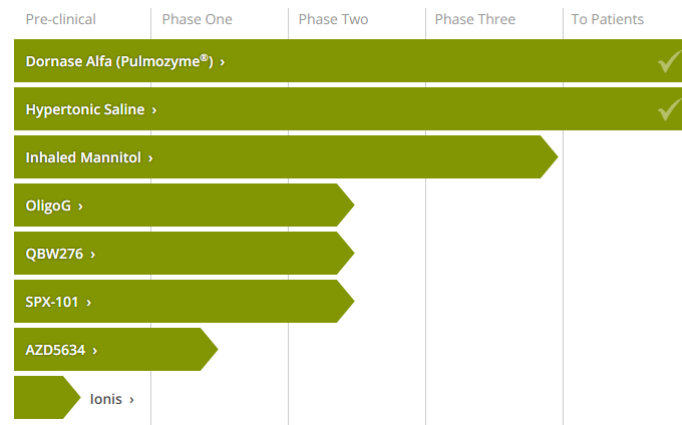
- Address comorbidities
- Add exercise to CTP
- Address adherence
- Plan transition to adult care

# CF Drug Development Pipeline in 2018

## Restore CFTR Function [Learn more >](#)



## Mucociliary Clearance [Learn more >](#)



## Anti-Inflammatory [Learn more >](#)



## Nutritional-GI-Other [Learn more >](#)



## Anti-Infective [Learn more >](#)



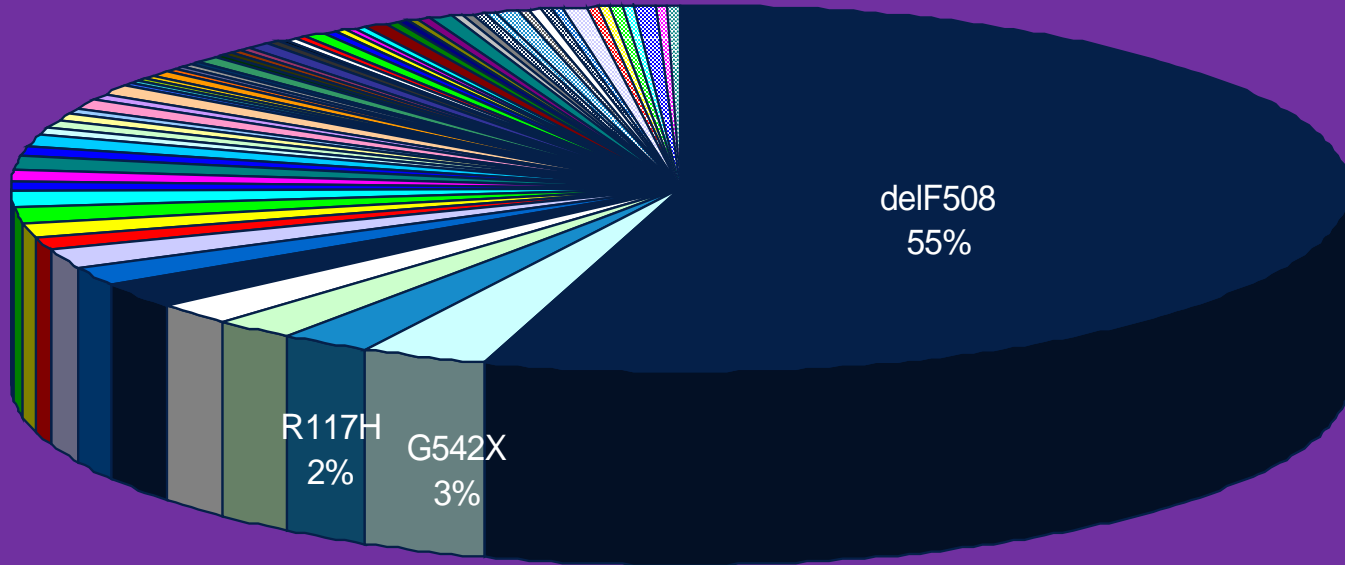


# History

- 1989: Discovery of defective CF gene and its protein product (CFTR)
- 1993: Dornase alfa - first drug developed specifically for CF.
- 1997: Inhaled tobramycin - first aerosolized antibiotic designed for CF.
- 2002: Chronic azithromycin shown to improve CF lung health.
- 2003: Discovery of 3-dimensional structure of a portion of the CFTR protein
- 2004: Inhaled hypertonic saline
- 2010: Inhaled aztreonam



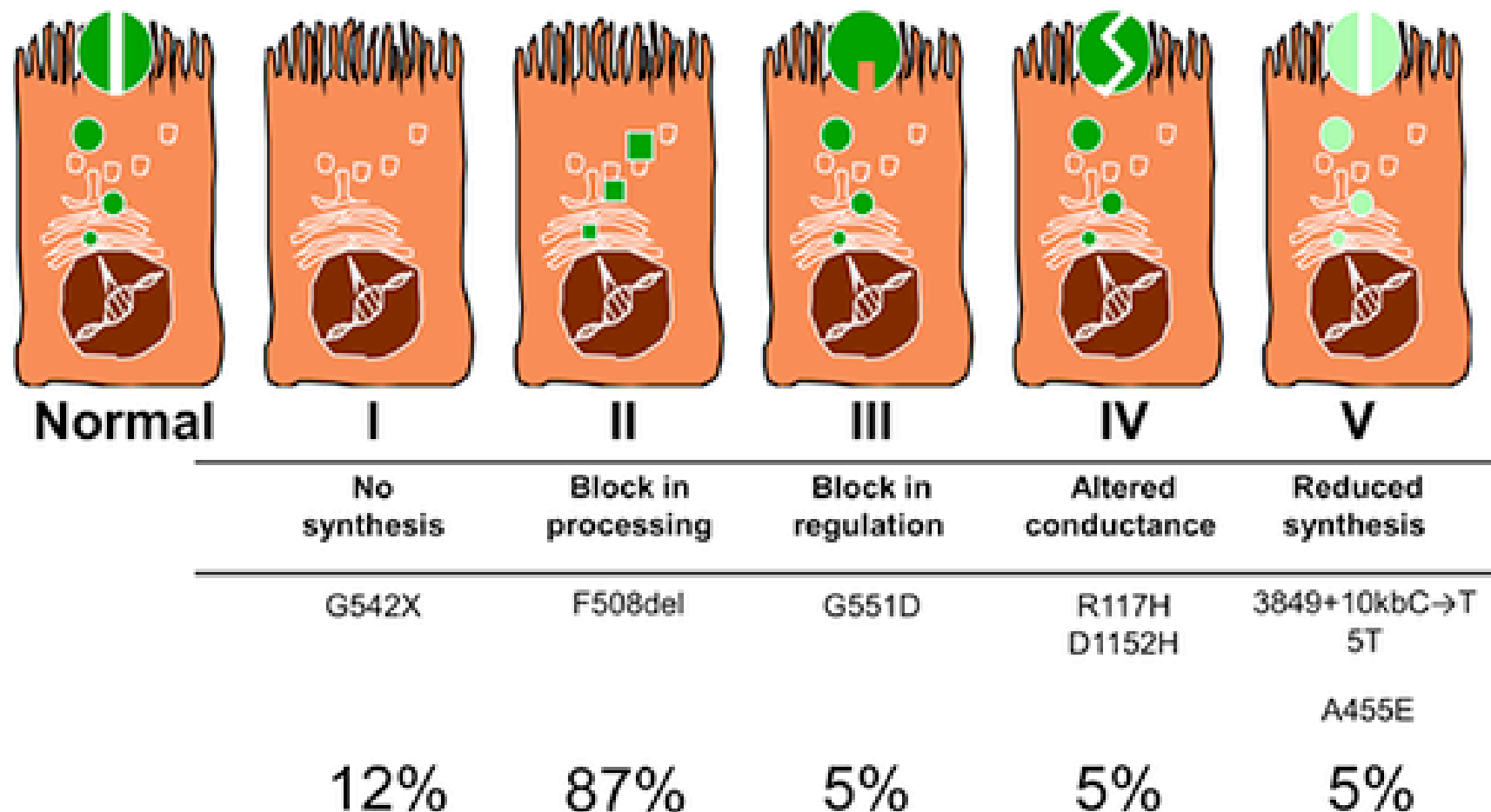
# CFTR mutations



delF508	G542X	R117H	1288insTA	G551D
R75X	TG125T	W1282X	D1152H	L206W
N1303K	S945L	3120+1G>A	3272-26A>G	663delT
S549N	W1089X	1248+1G>A	2307insA	3849+10kbC>T
406-1G>A	delI507	R1162X	TG135T	1874insT
1952_2035del84	2055del9>A	2105-2117del13insAGAAA	2183AA>G	2789+5G>A
296+28A>G	3199del6	3876delA	5'UTR-20G>C*	5'UTR-316A>G*
5'UTR-755C>T	621+1G>T	711+1G>T	712-1G>T	A349V
A559T	c.2686-2687insT*	D513G	delF311	E1371X
E60X	F1016S	F1052V	F1107L*	G85E
K162E	L102R	L323P*	L997F	p.K114del*
P205S	P67L	R117C	R31C	R352Q
R352W	R553X	R785X	S1118F	S1235R
TG115T	V754M	W1204X(3744G>A)	Y1092X(C>A)	Y913X
Y917C				

# CFTR

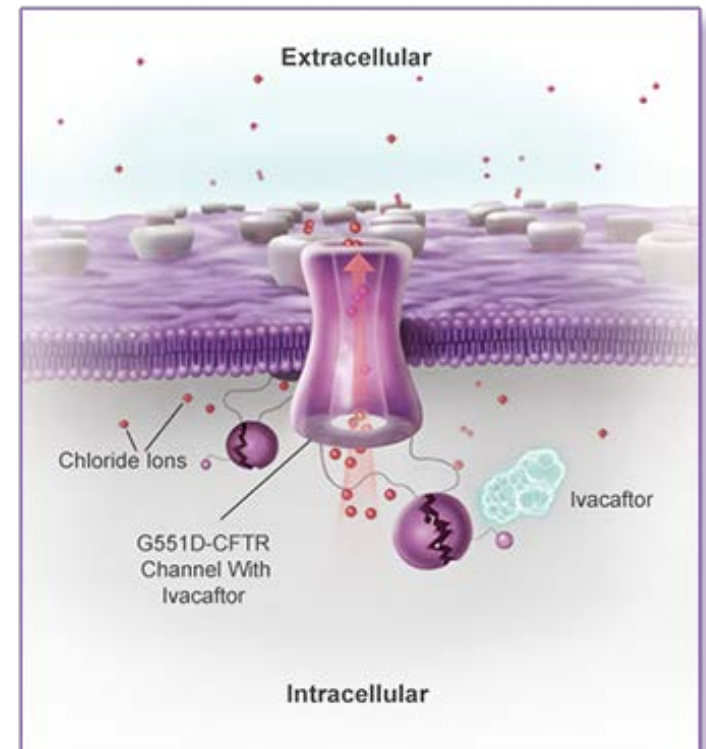
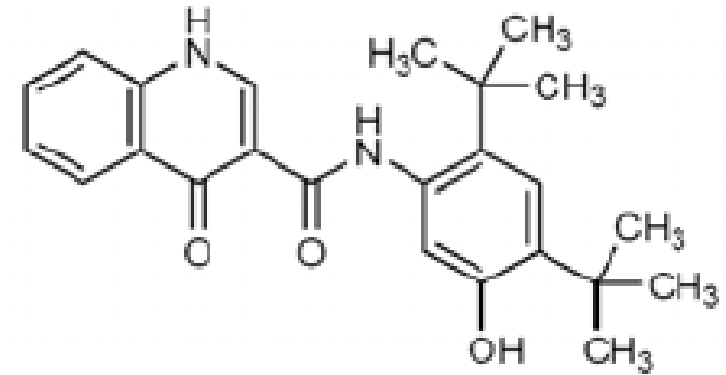
## *Classes of Mutations*



# Ivacaftor

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- CFTR Potentiator
- Increases time that activated CFTR channel remains open
- Increases the movement of salt and water through the channel, across the epithelium



# History Ivacaftor

- 2006: Ivacaftor (formerly VX-770) enters clinical trials.
- 2008: Phase 2 studies of ivacaftor in people with the G551D.
- 2012: Approved for ages 6 and older with the G551D mutation.
- 2014: Approved for ages 2 and older with one of 10 CFTR mutations.
- 2017: Approved for ages 2 and older who have at least one of 38 CFTR mutations
- 2018: Studies in infants 0-2 are ongoing

# Ivacaftor Approved Mutations

## Gating Mutations

G551D	G1244E
G1349D	G178R
G551S	S1251N
S1255P	S549N
S549R	

## Residual Function Mutations

E56K	R347H	A1067T
P67L	R352Q	G1069R
R74W	A455E	R1070Q
D110E	D579G	R1070W
D110H	S945L	F1074L
R117C	S977F	D1152H
E193K	F1052V	D1270N
L206W	K1060T	

## Splice Mutations

3849+10kbC->T	3272-26A->G	E831X
2789+5G->A	711+3A->G	

## Conducting Mutation

R117H
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# Clinical Benefits of Ivacaftor

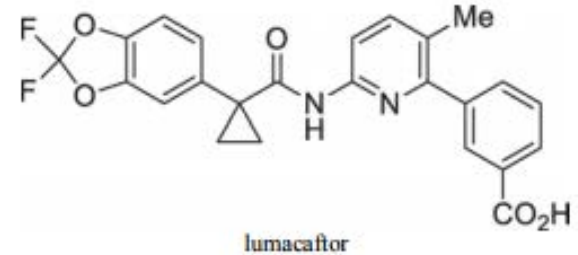
Results from STRIVE, ENVISION, PERSIST studies

- Improved pulmonary function and reduced rate of pulmonary exacerbations<sup>1,2</sup>
- Less frequent infection with *Pseudomonas*<sup>3</sup>
- Improved glucose tolerance, sustained weight gain, and better growth in children<sup>4</sup>
- Benefit is seen across age and disease severity groups and is sustained after prolonged use

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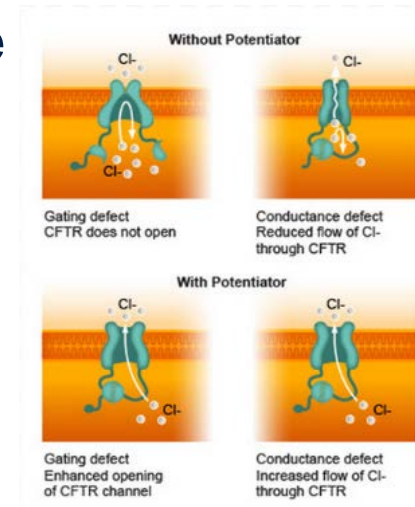
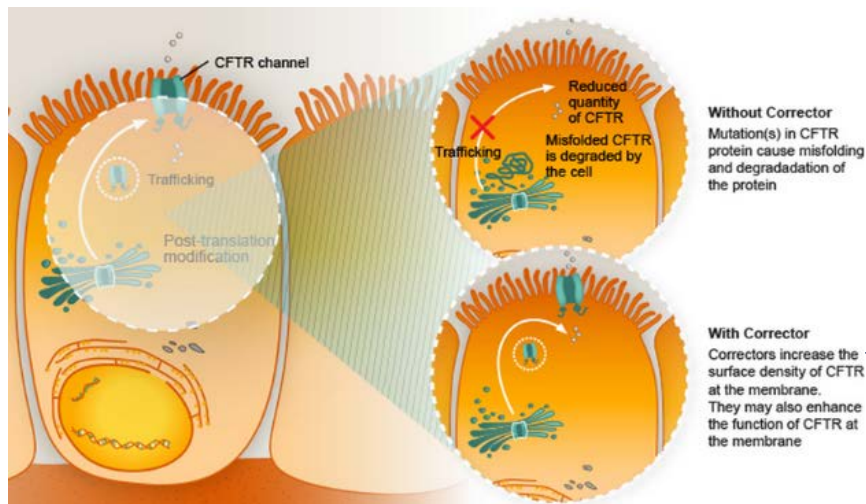
1) Ramsey, et al. *N Engl J Med*. 2011;365:1663-72. 2) Davies, et al. *Am J Respir Crit Care Med*. 2013;187(11):1219-25. 3) Heltshe, et al. *Clin Infect Dis*. 2015;60(5):703-12. 4) McKone, et al. *Lancet Respir Med*. 2014;2(11):902-10.

# Lumacaftor / Ivacaftor



## ■ Two Step Mechanism of Action

- Corrector (Lumacaftor) allows CFTR to move to the cell surface
  - Prevents degradation of abnormal protein in the ER
  - Increasing the amount of CFTR at the cell surface
- Potentiator (Ivacaftor) increases channel opening





# History of Lumacaftor/Ivacaftor



- 2015: Approved for people ages 12 and older with CF who have two copies F508del.
- 2016: Approval extended to children with CF ages 6 to 11 who have two copies of the F508del.
- 2018: A phase 3 study in ongoing in children aged 2-5 years with two copies of the F508del.

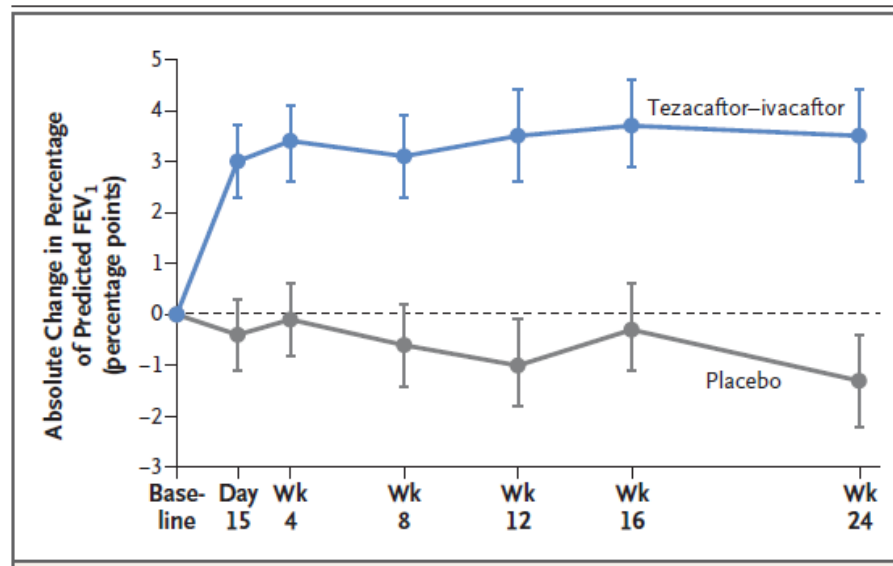
# Clinical benefits of Lumacaftor/Ivacaftor

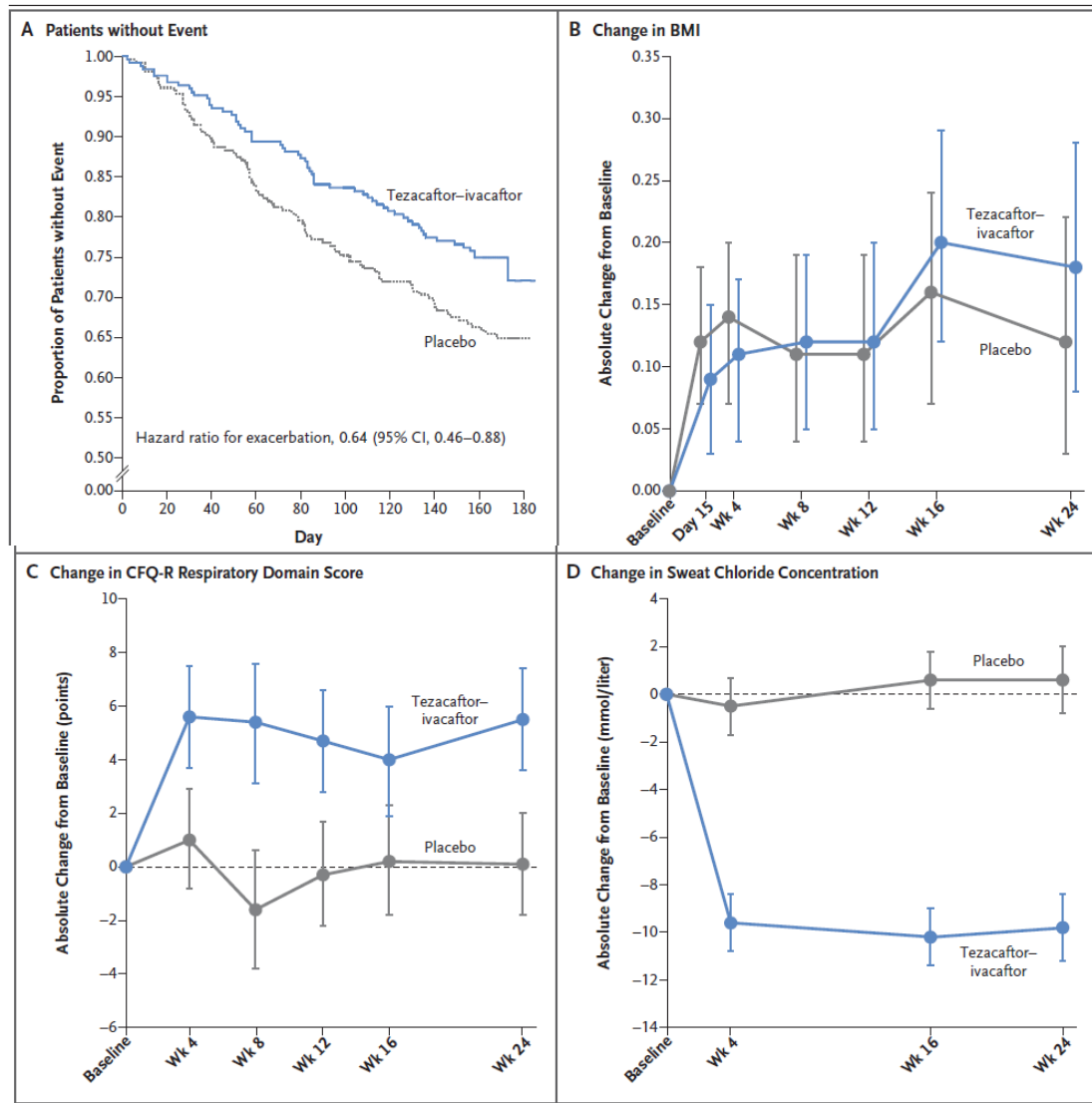
## Results from TRAFFIC/TRANSPORT /PROGRESS

- Improved pulmonary function and reduced rate of pulmonary exacerbations
- Improved weight gain
- Benefits continue to be observed with longer-term treatment
- 42% slower rate of ppFEV1 decline than matched registry controls

# CFTR Modulators Of the Future: Tezacaftor-Ivacaftor

- 2017: Two Phase 3 clinical trials of another corrector (tezacaftor = VX-661) in combination with ivacaftor demonstrate positive results for people with two copies of the F508del (Taylor-Cousar et al, 2017) AND those who have one F508del mutation and a second mutation that results in residual function (Rowe et al, 2017).





# CFTR Modulators Of the Future: Next Generation Modulators

- 2017: Phase 1 and Phase 2 Clinical Trials
- Next-generation modulator (VX-440, VX-152, VX-659) + ivacaftor + tezacaftor
- Improve CFTR folding and increase the amount of CFTR trafficked to the cell surface
- Promising results in people with
  - Two copies of the F508del
  - One F508del mutation and a second mutation that results in minimal function (ex nonsense mutations, G542X)

**4-Week Efficacy Data in *F508del*/Min Patients:** Part 1 of the study evaluated the triple combination for four weeks in 47 patients who have one *F508del* mutation and one minimal function mutation (11 in placebo, 18 in VX-440 200mg and 18 in VX-440 600mg). A summary of the within-group lung function and sweat chloride data is provided below:

#### VX-440 in *F508del*/Min Patients

Mean Absolute Within-Group Change From Baseline Through Day 29*	Mean Absolute Within-Group Change in ppFEV <sub>1</sub> (percentage points)	Mean Absolute Within-Group Change in Sweat Chloride (mmol/L)
Triple placebo	+1.4 (p=0.4908)	+1.6 (p=0.6800)
VX-440 (200mg q12h) + tezacaftor (50mg q12h or 100mg QD) + ivacaftor (150mg q12h)	+10.0 (p < 0.0001)	-20.7 (p < 0.0001)
VX-440 (600mg q12h) + tezacaftor (50mg q12h) + ivacaftor (300mg q12h)	+12.0 (p < 0.0001)	-33.1 (p < 0.0001)

\* all p-values are within group p-values based on mixed effect models; values expressed as 'Through Day 29' are the average of Day 15 and Day 29 measures

A secondary endpoint in the study measured mean absolute change in the respiratory domain of CFQ-R, a validated patient-reported outcome tool, at Day 29. In this study, the mean absolute improvements for patients with a minimal function mutation who received the triple combination were 18.3 points (VX-440 200mg) and 20.7 points (VX-440 600mg). The improvement for those who received placebo was 2.2 points.

**4-Week Efficacy Data in *F508del*/*F508del* Patients:** Part 2 of the study is ongoing to evaluate the addition of VX-440 for four weeks in 26 patients who have two copies of the *F508del* mutation, who were already receiving the combination of tezacaftor and ivacaftor (6 in placebo and 20 in VX-440 600mg). In this part of the study, all participants received four weeks of treatment with tezacaftor and ivacaftor and were then randomized to the addition of VX-440 or placebo for four additional weeks. A summary of the within-group lung function and sweat chloride data for the triple combination treatment period, from baseline (end of the 4-week tezacaftor/ivacaftor run-in period), is provided below:

#### VX-440 in *F508del*/*F508del* Patients

Mean Absolute Within-Group Change From Baseline Through Day 29*	Mean Absolute Within-Group Change in ppFEV <sub>1</sub> (percentage points)	Mean Absolute Within-Group Change in Sweat Chloride (mmol/L)
Placebo + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	-2.5 (p=0.2755)	+2.1 (p=0.7385)
VX-440 (600mg q12h) + tezacaftor (50mg q12h) + ivacaftor (300mg q12h)	+9.5 (p < 0.0001)	-31.3 (p < 0.0001)

\* all p-values are within group p-values based on mixed effect models; values expressed as 'Through Day 29' are the average of Day 15 and Day 29 measures

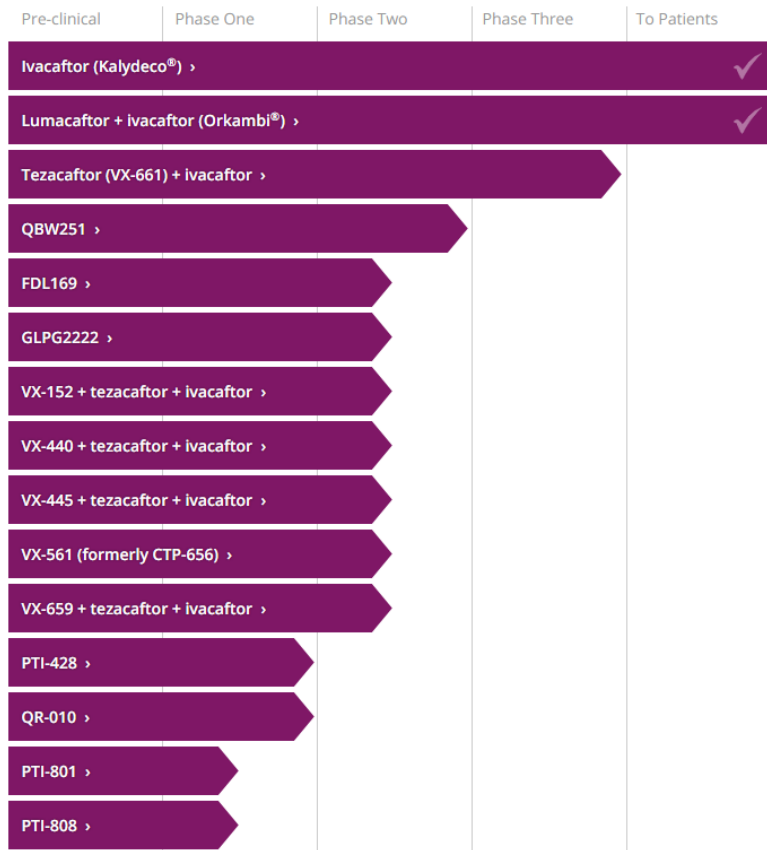
# Future

- With over 2000 mutations there will need to be more drugs developed to target each one
- Some mutations may need 3 or more drugs!!!
- 2018: More Phase 2 and Phase 3 trials and studies in adults and children are underway
- Individualized medicine, N of 1 trials



# CF Drug Development Pipeline in 2018

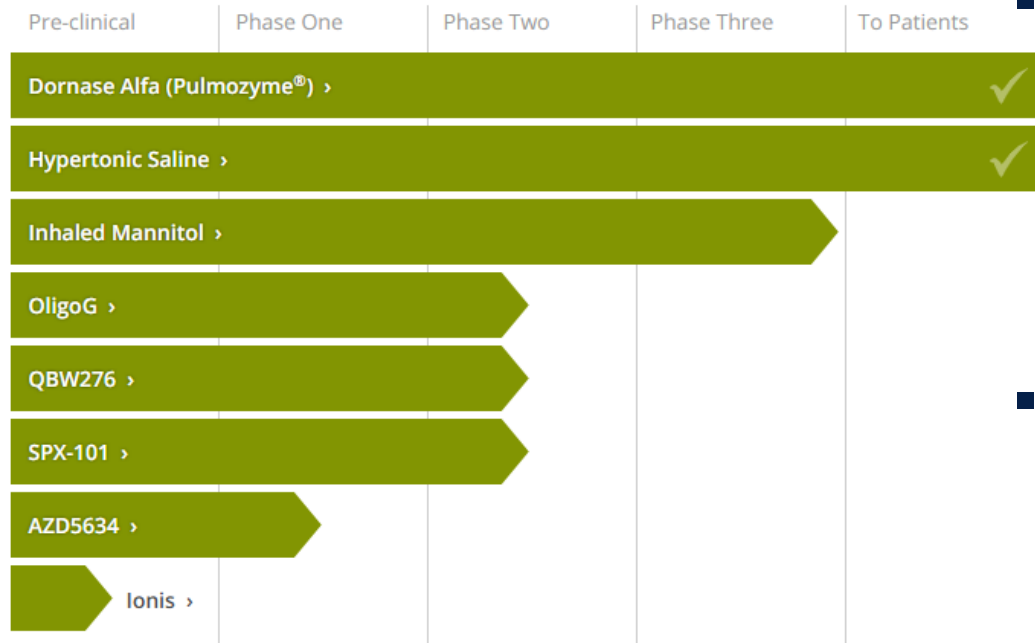
Restore CFTR Function | [Learn more >](#)



- New correctors
- New potentiators
- PTI-428 - Amplifiers - increase the amount of CFTR protein in the cell. This makes more CFTR protein available for other therapies, such as ivacaftor and lumacaftor, to work on.
- QR-010 is an inhaled oligonucleotide designed to repair CFTR-encoded mRNA

# CF Drug Development Pipeline in 2018

## Mucociliary Clearance [Learn more >](#)



- Bronchitol is an inhaled dry powder form of mannitol (a naturally occurring osmotic agent), which works by drawing water into the airways.
- OligoG is a dry powder drug that has been shown to decrease the thickness of mucus in the lungs
- QBW276 , SPX-101 and AZD5634 are designed to block the function of the sodium (Na+) channel found in the lungs, to help maintain fluid in airways.

# CF Drug Development Pipeline in 2018

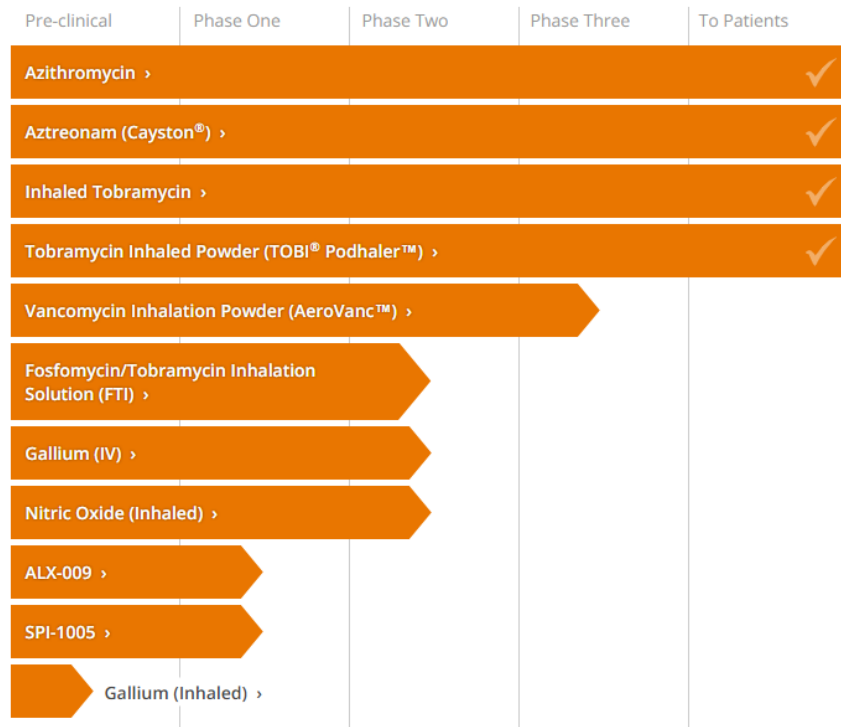
## Anti-Inflammatory [Learn more >](#)



- JBT-101 is an endocannabinoid-mimetic
- CTX-4430 reduces production of leukotriene B4 (LTB4)
- LAU-7b is a retinoid related to vitamin A.

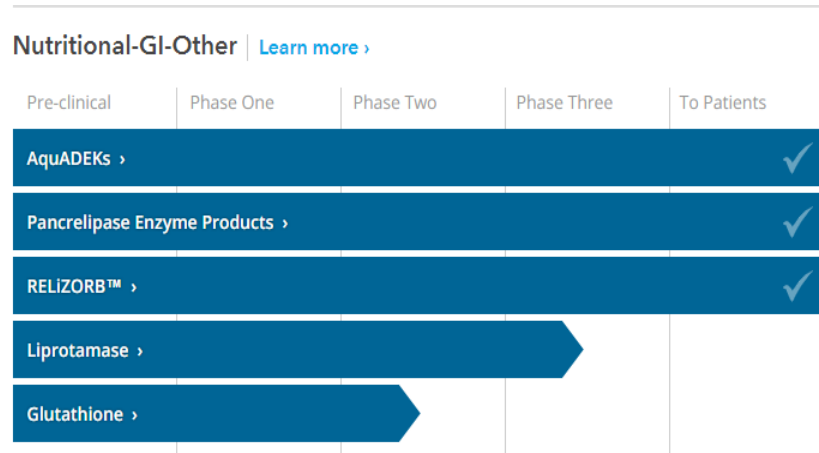
# CF Drug Development Pipeline in 2018

## Anti-Infective [Learn more >](#)



- Gallium is a molecule, nearly identical to iron, that disrupts iron-dependent biological processes and has been shown to kill antibiotic-resistant strains of *Pseudomonas aeruginosa*
- SPI-1005 may protect inner ear damage from use of aminoglycoside antibiotics

# CF Drug Development Pipeline in 2018



- Liprotamase (Sollpura) is a pancreatic enzyme replacement that is not prepared from animal sources.
- Oral glutathione is an anti-oxidant which may improve growth and decrease gut inflammation in children with CF.

# A Case

- 12 year old Latina female with pancreatic insufficient Cystic Fibrosis.
- Genetics:
  - S549N - a class III (gating) mutation
  - 1811+1.6kbA->G – a class I mutation
- In the past year, FEV1 has been 33 to 39% of normal
- 8 admissions (117 days) in the past 2 years for pulmonary exacerbations
- BMI of 19.2 kg/m<sup>2</sup>



# After Ivacaftor

- Sweat test decreased from 95 to 19 mmol/L
- FEV1 increased from 33% to 57% in 1 month
- BMI increased from 19.2 to 21.7 kg/m<sup>2</sup> in 1 month
- Symptoms improved
- No baseline cough
- Participating in gym class and dancing without shortness of breath
- 5 years later...Currently applying to college



# Summary

- CF survival is improving but there is more to be done
- There are over 2000 CFTR mutations, with different effects on the CFTR channel
- CFTR Modulators are targeting these different types of CFTR mutations and can be life changing for affected patients
- Next generation CFTR modulators may be able to help a wider variety of patients
- Cystic Fibrosis Foundation website has information on drugs in the CF pipeline and trials which are enrolling

# Acknowledgements

- Ngoc Ly
- Meghan McGarry
- Mary Ellen Kleinhenz
- Dennis Nielson
- Diana Dawson
- My CF Care Teams in Oakland and San Francisco



# References

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- Cystic Fibrosis Foundation
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  - <https://www.cff.org/trials/pipeline>
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# References

## ▪ Ivacaftor

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- Davies, et al. Am J Respir Crit Care Med. 2013;187(11):1219-25.
- Heltshe, et al. Clin Infect Dis. 2015;60(5):703-12.
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## ▪ Tezacaftor/Ivacaftor

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- 
- Rowe et al. N Engl J Med. 2017 Nov 23;377(21):2024-2035. doi: 10.1056/NEJMoa1709847. Epub 2017 Nov 3.



**UCSF Benioff Children's Hospitals**

- In the Phase 2 clinical trial of VX-152 in combination with ivacaftor and tezacaftor (VX-661), the 10 participants in the study with a single F508del mutation who received the 200 mg dose of VX-152 had a 9.7 percent increase in lung function and a decrease in sweat chloride of 14.1 after two weeks of treatment. The 10 participants in the study who have two copies of the F508del mutation who received the 200 mg dose of VX-152 had a 7.3 percent increase in lung function and a decrease in sweat chloride of 20.9 after two weeks of treatment.
- In the Phase 1 clinical trial of VX-659 in combination with ivacaftor and tezacaftor (VX-661), participants in the study with a single F508del mutation who received the 120 mg dose of VX-659 had a 9.6 percent increase in lung function and decrease in sweat chloride of 41.6 after two weeks of treatment.
- Data from the trials, along with results from another study expected to begin later this year, will help Vertex decide which next-generation modulator candidate or candidates to move forward into Phase 3 studies in early 2018.

### About the VX-152 Phase 2 Study

This ongoing Phase 2 randomized, double-blind study is evaluating VX-152 (100mg, 200mg and 300mg q12h) in combination with tezacaftor and ivacaftor in people with CF ages 18 and older who have one *F508del* mutation and one minimal function mutation and in people who have two copies of the *F508del* mutation. The primary objective is safety and tolerability. Secondary endpoints include mean absolute change in ppFEV<sub>1</sub> and change in sweat chloride. Data reported today are from the 100mg and 200mg arms of the study in people who have one *F508del* mutation and one minimal function mutation and from the 200mg arm in people who have two copies of the *F508del* mutation.

**Overall Safety Data:** In the study, the triple combination regimen was generally well tolerated. The majority of adverse events were mild or moderate. The most common adverse events (> 10%), regardless of treatment group, were cough, sputum increased, infective pulmonary exacerbation, productive cough, diarrhea and fatigue. There was one discontinuation due to an adverse event in the triple combination treatment groups (pneumonia in the VX-152 200mg group) and none in the control groups.

**2-Week Initial Efficacy Data in *F508del*/Min Patients:** In Part 1 of the study, the triple combination was evaluated for two weeks in 21 patients ages 18 and older who have one *F508del* mutation and one minimal function mutation (5 in combined placebo, 6 in VX-152 100mg and 10 in VX-152 200mg). A summary of the initial within-group lung function and sweat chloride data (secondary endpoints) from the VX-152 100mg and 200mg dose groups is provided below:

#### VX-152 in *F508del*/Min Patients

Observed Mean Absolute Within-Group Change from Baseline at Day 15*	Observed Mean Absolute Within-Group Change in ppFEV <sub>1</sub> (percentage points)	Observed Mean Absolute Within-Group Change in Sweat Chloride (mmol/L)
Triple placebo	-0.9 (p=0.6245)	+1.0 (p=0.5659)
VX-152 (100mg q12h) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+5.6 (p=0.0135)	-19.6 (p=0.0004)
VX-152 (200mg q12h) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+9.7 (p=0.0017)	-14.1 (p=0.0219)

\* p-values presented are within-group p-values based on 1 sample t-test; an efficacy analysis using mixed effect models will be conducted following completion of an additional cohort of patients currently being treated in the study

This part of the study is ongoing to evaluate the triple combination of VX-152 (300mg q12h), tezacaftor and ivacaftor in patients with one *F508del* mutation and one minimal function mutation. These data are expected later in 2017.

**2-Week Initial Efficacy Data in *F508del*/*F508del* Patients:** Part 2 of the study is ongoing to evaluate the addition of VX-152 for two weeks in 14 patients ages 18 and older who have two copies of the *F508del* mutation, who were already receiving the combination of tezacaftor and ivacaftor (4 in placebo and 10 in VX-152 200mg). A summary of the initial within-group lung function and sweat chloride data (secondary endpoints) for the triple combination treatment period, from baseline (end of the 4-week tezacaftor/ivacaftor run-in period), is provided below:

#### VX-152 in *F508del*/*F508del* Patients

Observed Mean Absolute Within-Group Change from Baseline at Day 15*	Observed Mean Absolute Within-Group Change in ppFEV <sub>1</sub> (percentage points)	Observed Mean Absolute Within-Group Change in Sweat Chloride (mmol/L)
Placebo + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	-1.4 (p=0.2773)	+3.4 (p=0.1212)
VX-152 (200mg q12h) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+7.3 (p=0.0354)	-20.9 (p=0.0010)

\* p-values presented are within-group p-values based on 1 sample t-test; an efficacy analysis using mixed effect models will be conducted following completion of an additional cohort of patients currently being treated in the study