CLINICAL EXPERIENCE OF CFTR MODULATION AND NEW THERAPEIES IN THE PIPELINE

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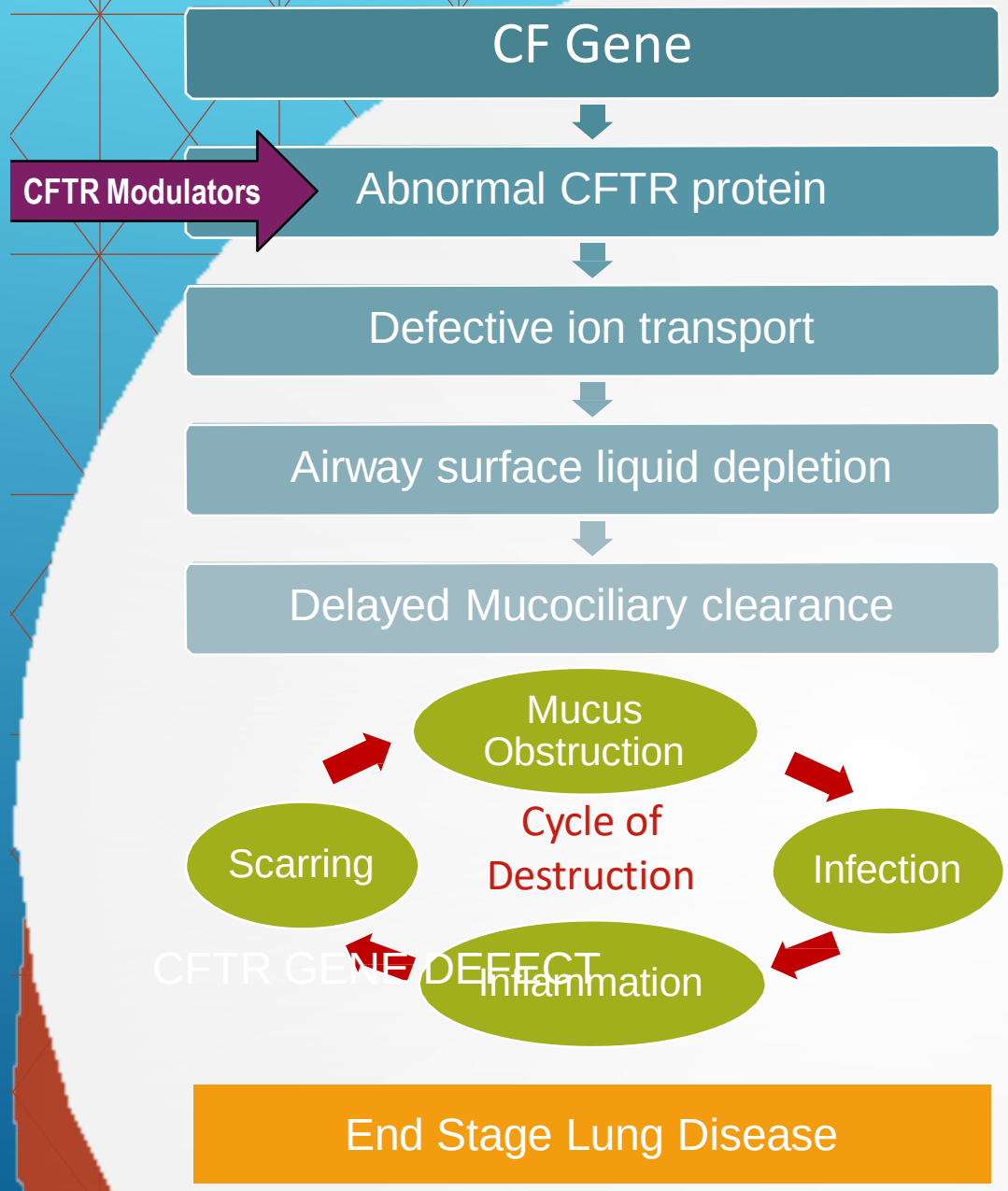
ANN ARBOR, MICHIGAN, USA

Pathophysiology of Cystic Fibrosis

CFTR Modulators



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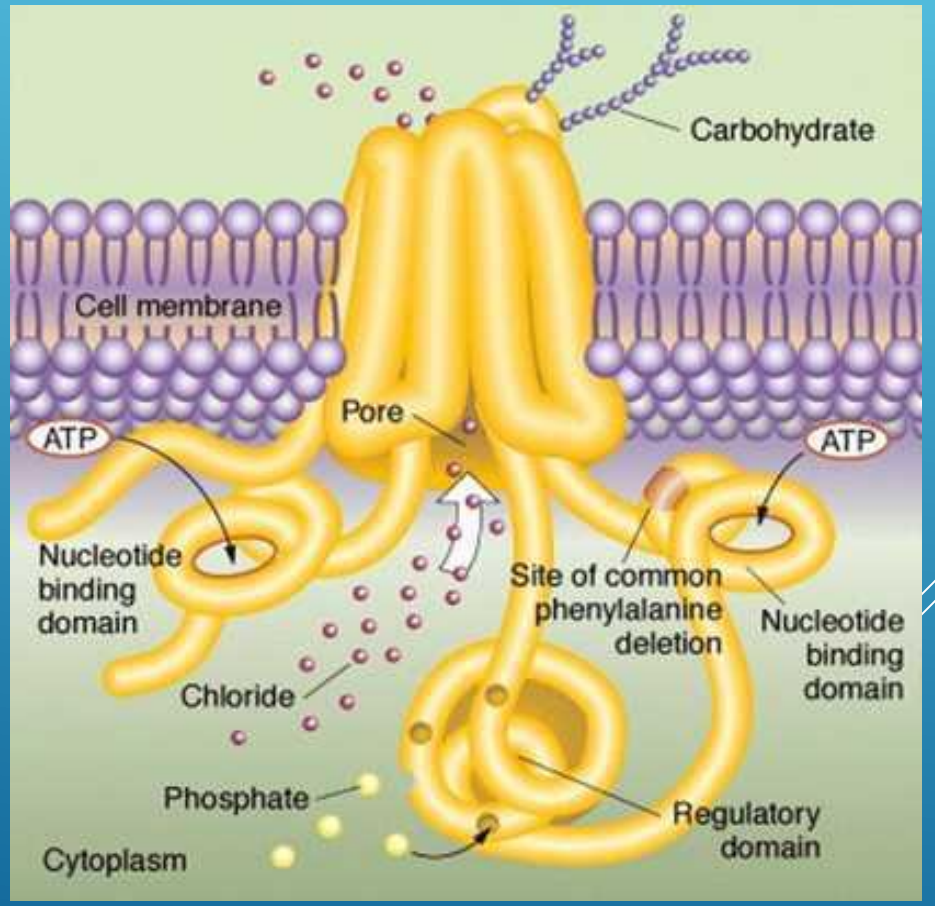
CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR (CFTR)

- Functions
  - Chloride Channel
  - Bicarbonate Channel
  - Regulates ENaC



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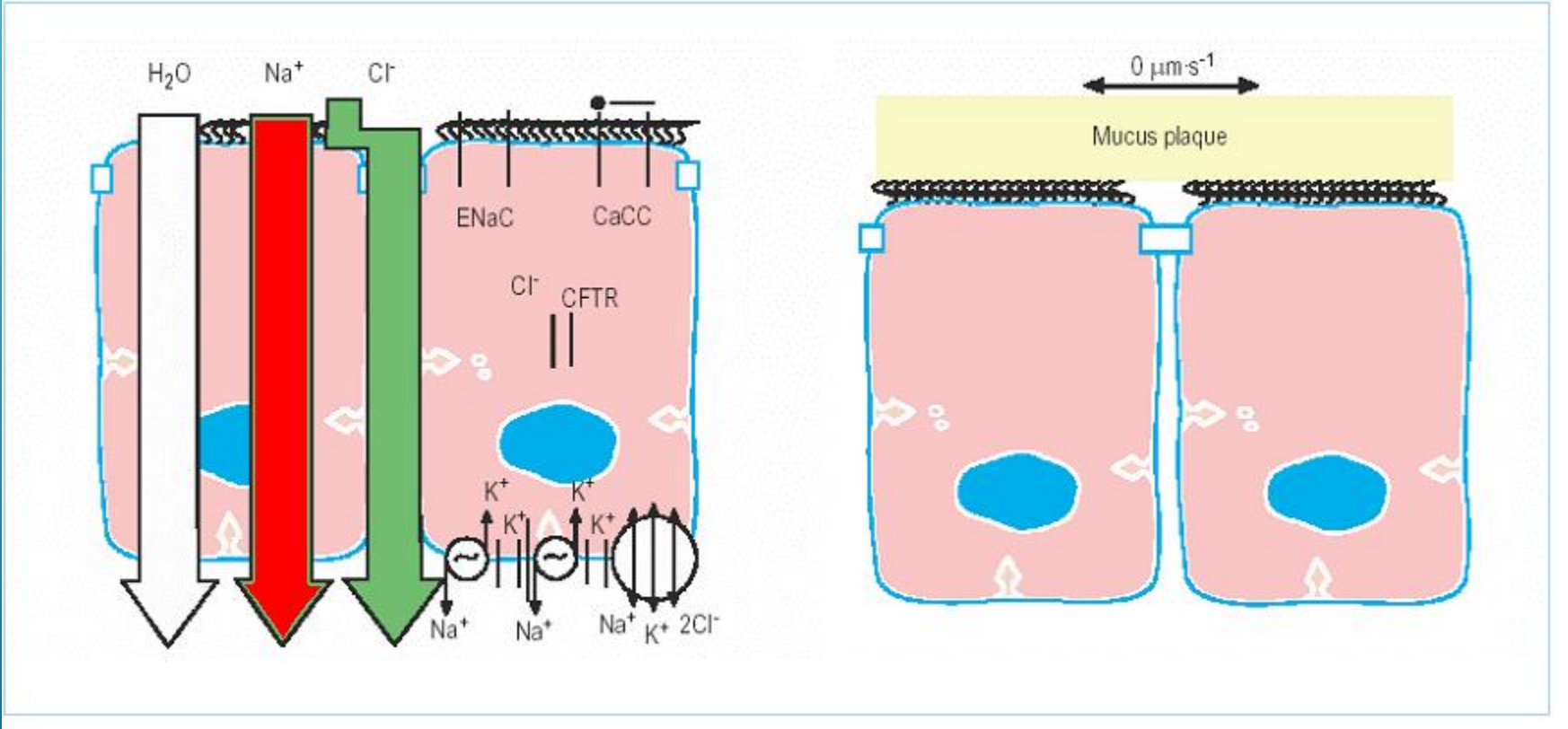
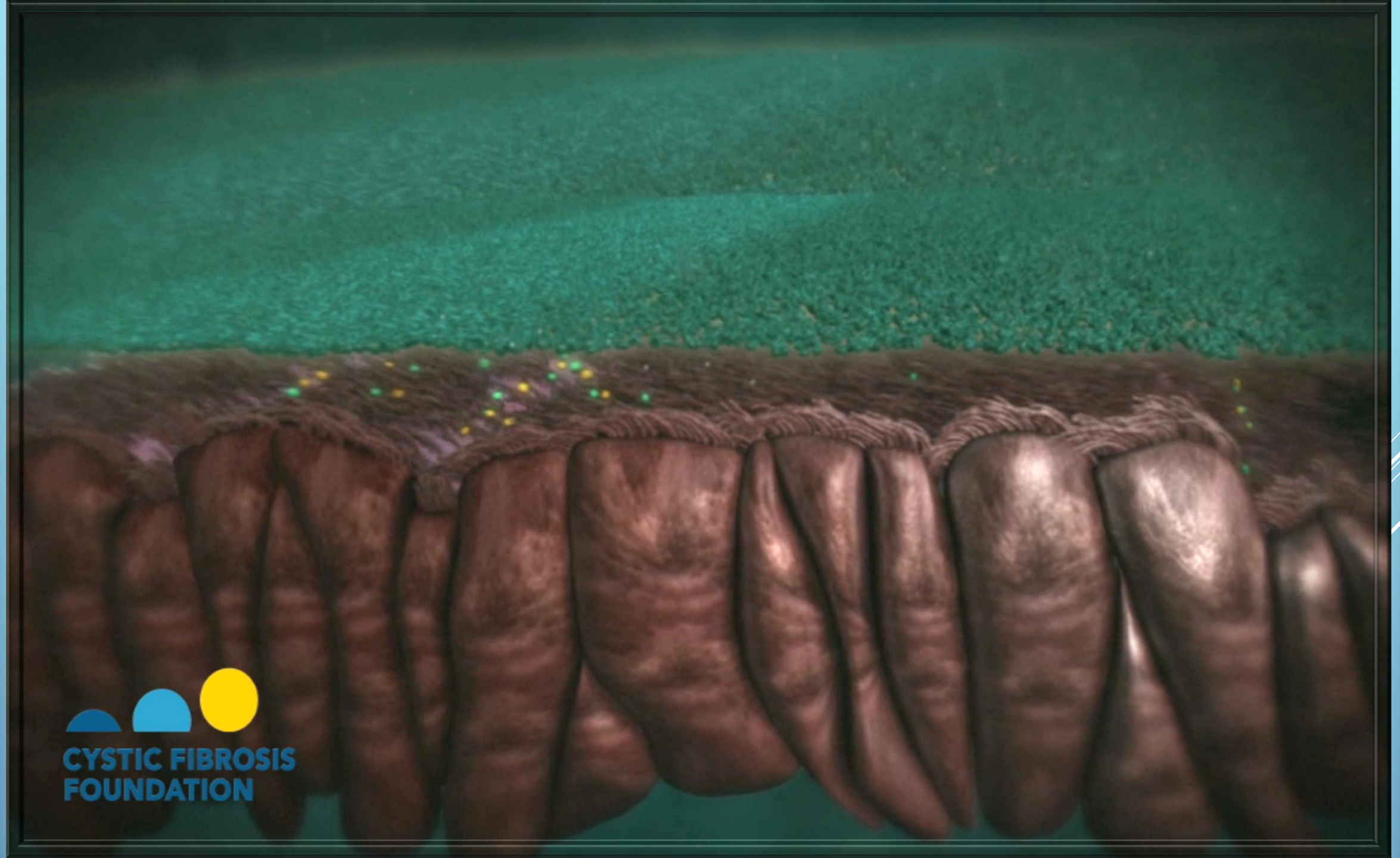
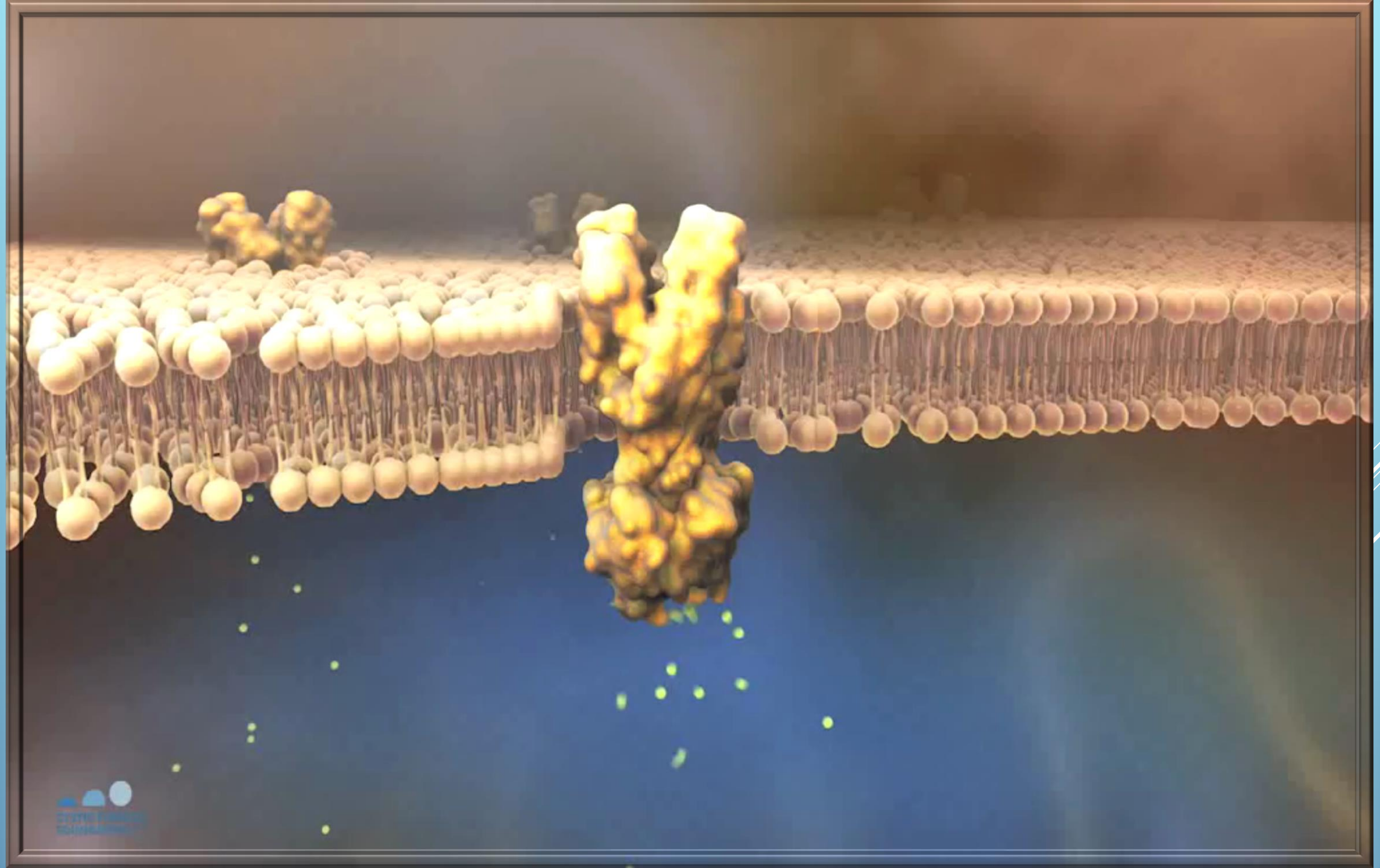
ABNORMAL ION TRANSPORT AND MUCUS STASIS IN CF



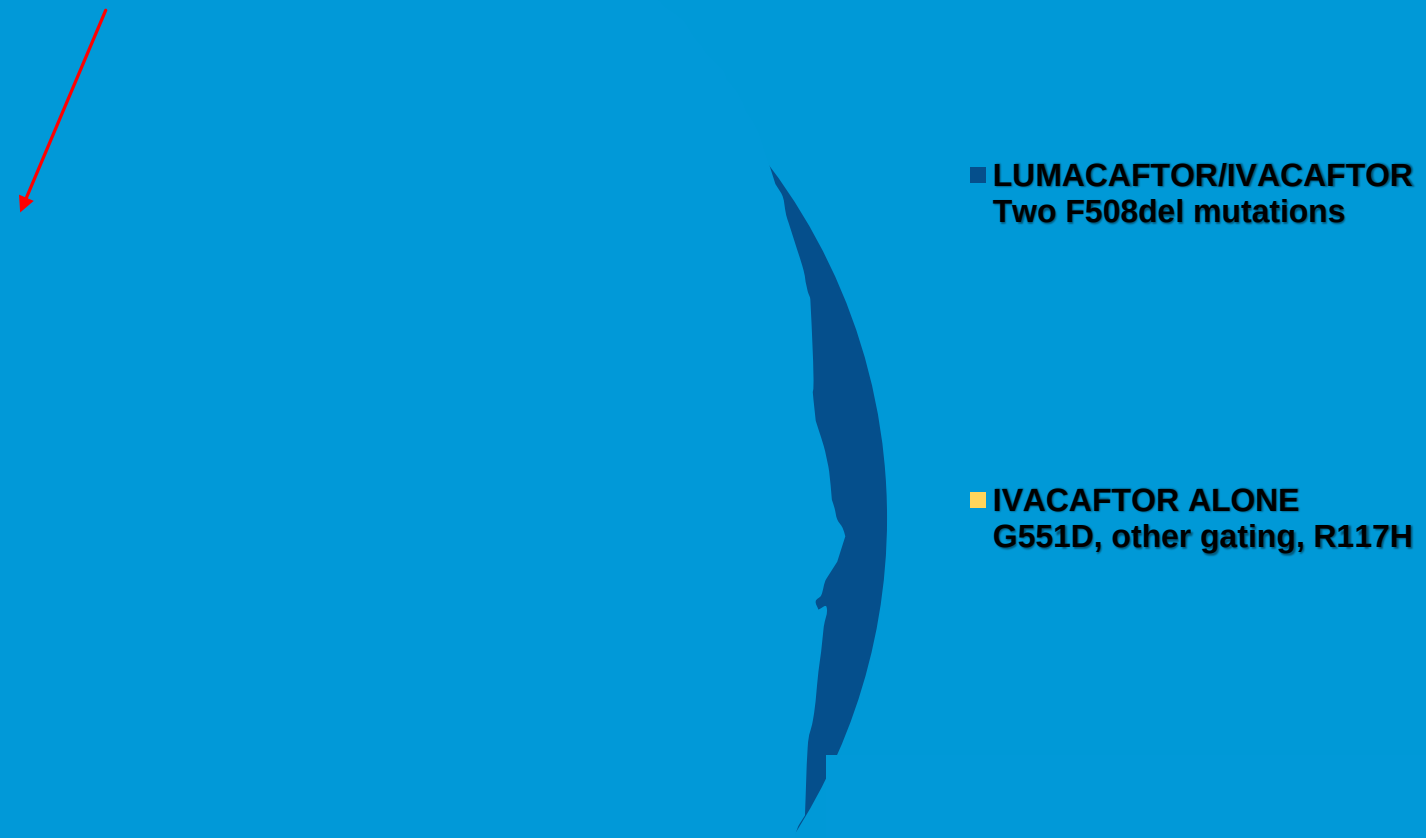
CaCC: Ca^{2+}-activated "alternative" Cl^- channel; ENaC: epithelial Na^+ channel

Boucher RC. *Eur Respir J*. 2004.


CYSTIC FIBROSIS
FOUNDATION



CFTR Modulators at the End of 2016



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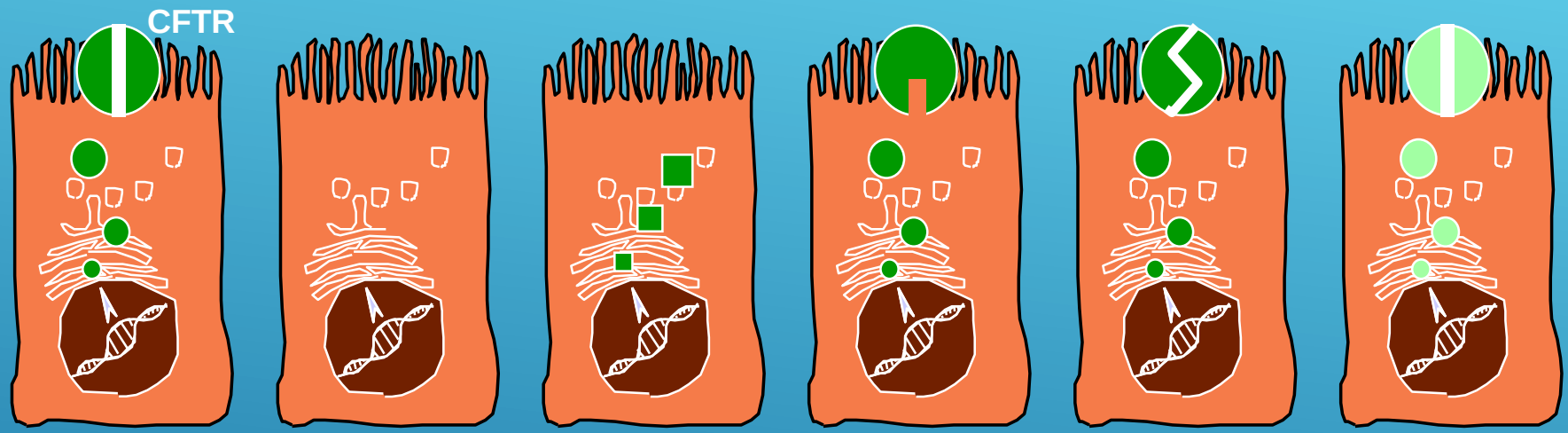
MOLECULAR CONSEQUENCES OF CFTR MUTATIONS



Normal	I	II	III	IV	V
	No synthesis	Block in processing	Block in regulation	Altered conductance	Reduced synthesis
	Nonsense G542X	AA deletion ΔF508	Missense G551D	Missense R117H	Missense A455E
	Frameshift 394delTT				Alternative splicing 3849+10kbC→T
	Splice junction 1717-1G→A				

Vankeerberghen A, et al. *J Cyst Fibros.* 2002.
http://www.genet.sickkids.on.ca/cftr/

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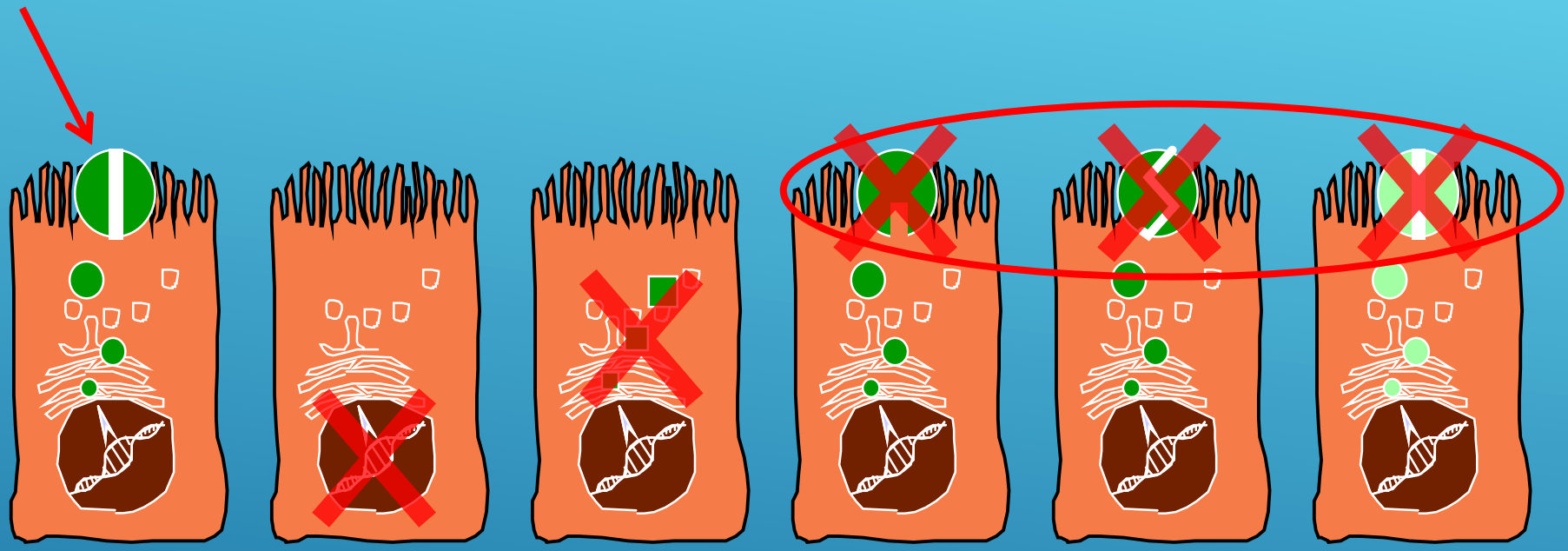
Understanding the Complexity of CFTR & the Classes of *CFTR* Mutations



	No synthesis	Block in processing	Block in gating	Altered conductance	Reduced synthesis
	G542X	F508del	G551D	D1152H	3849+10kbC–>T
% of patients with an allele in this class	12%	87%	5%	5%	5%

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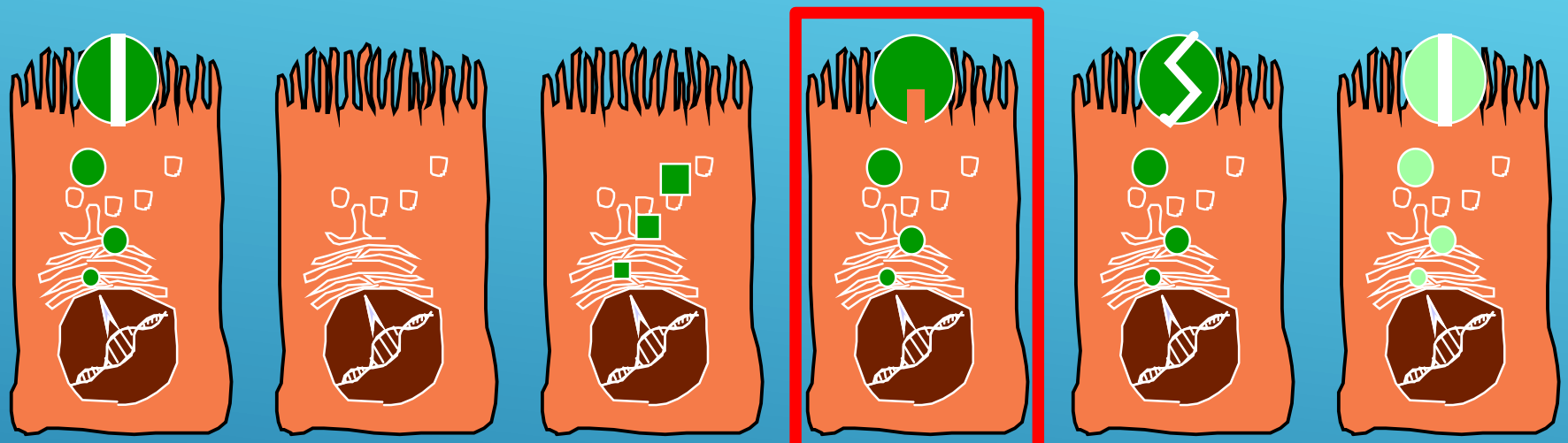
Identifying Ivacaftor and Demonstrating Benefit in G551D



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IVACAFTOR

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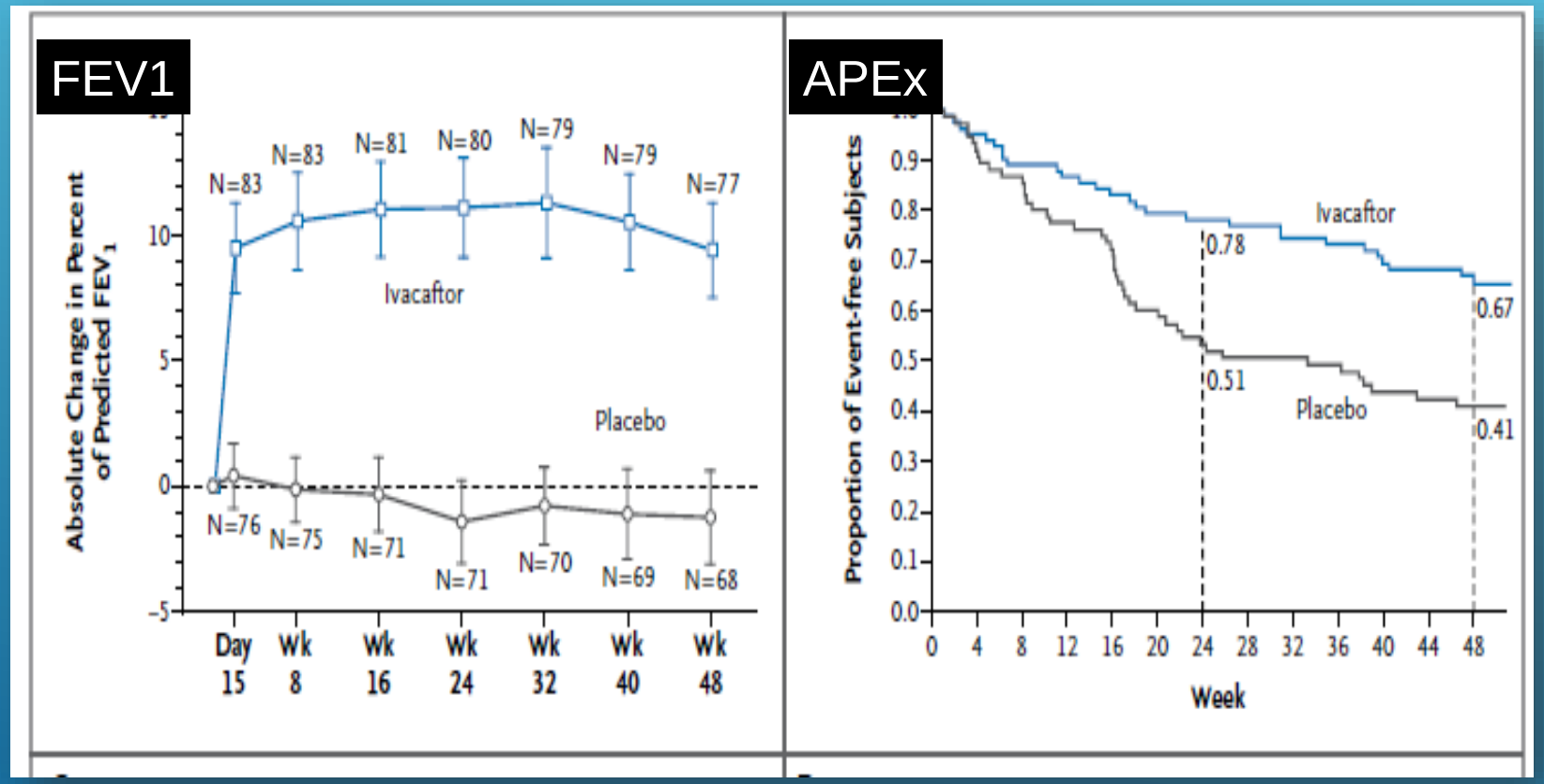
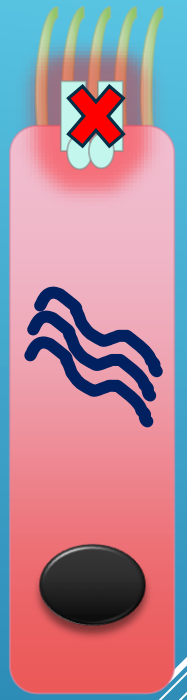
IVACAFTOR FOR GATING MUTATIONS

G551D patients: STRIVE results: N=161 (>12 yr); FEV_1 = 63.6%; RDBPC





Class 3 gating

A new 'benchmark'

Ramsey, B et al. *New Engl J Med* (2011), 365: 1663-1672

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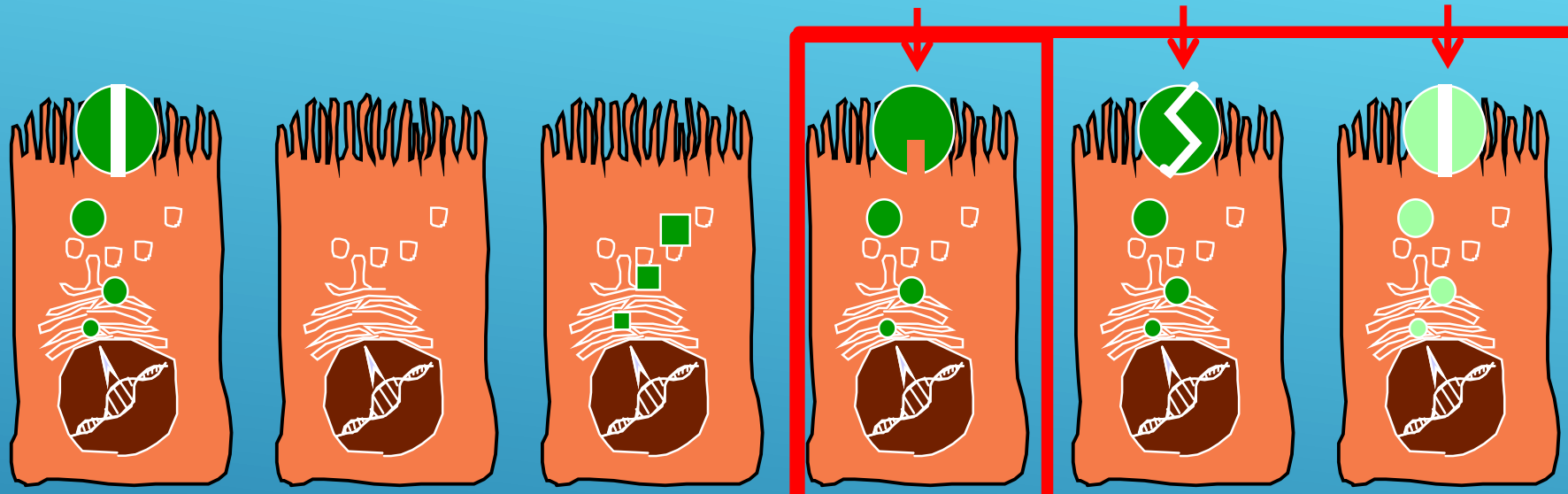
Classes of CFTR Mutations



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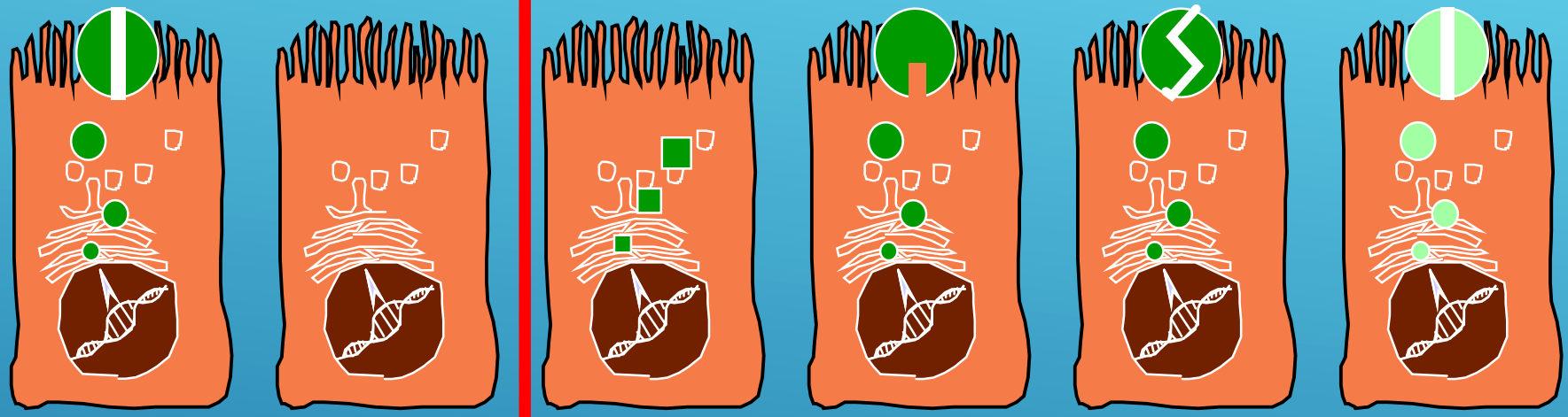

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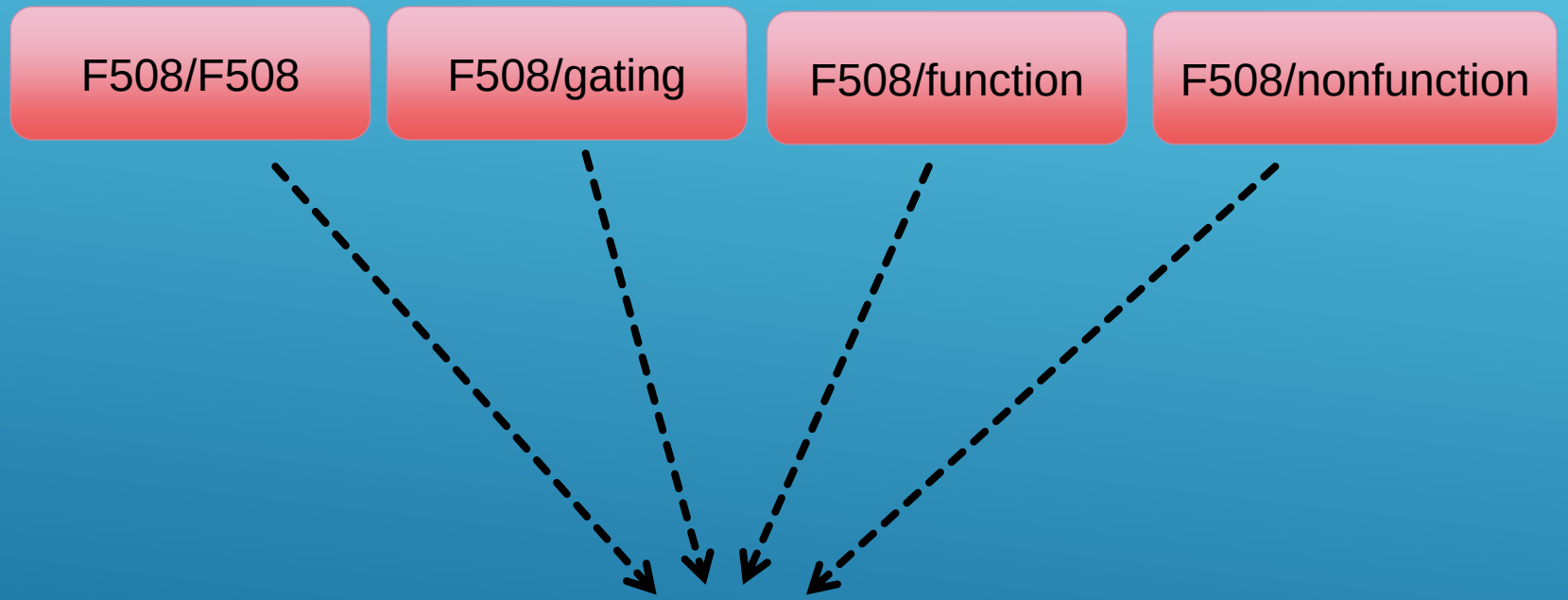
DEVELOPMENT OF CO-THERAPIES

VX-661 phase 3 program (Vertex)



Different designs, common co-therapy

www.clinicaltrials.gov

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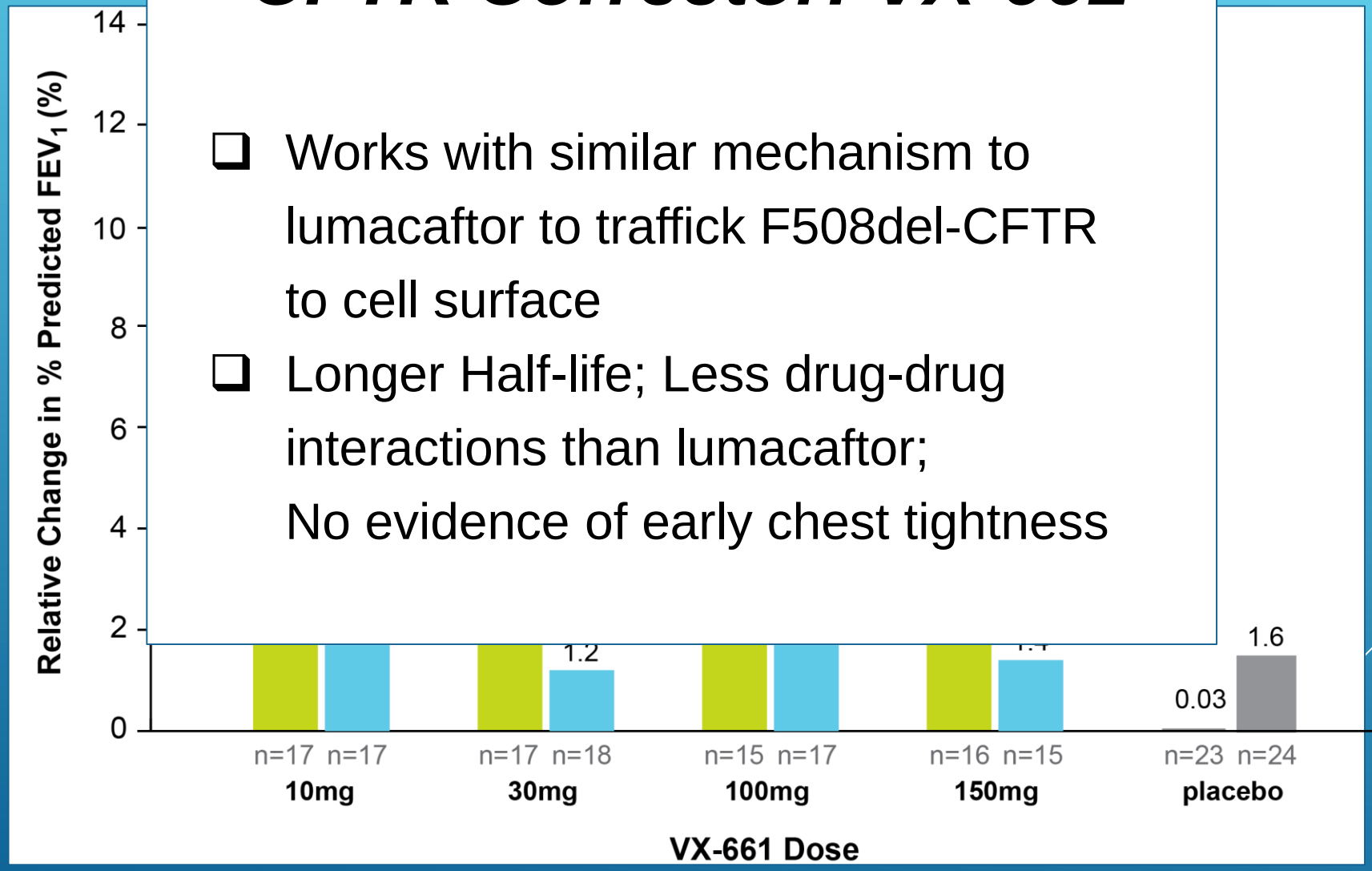
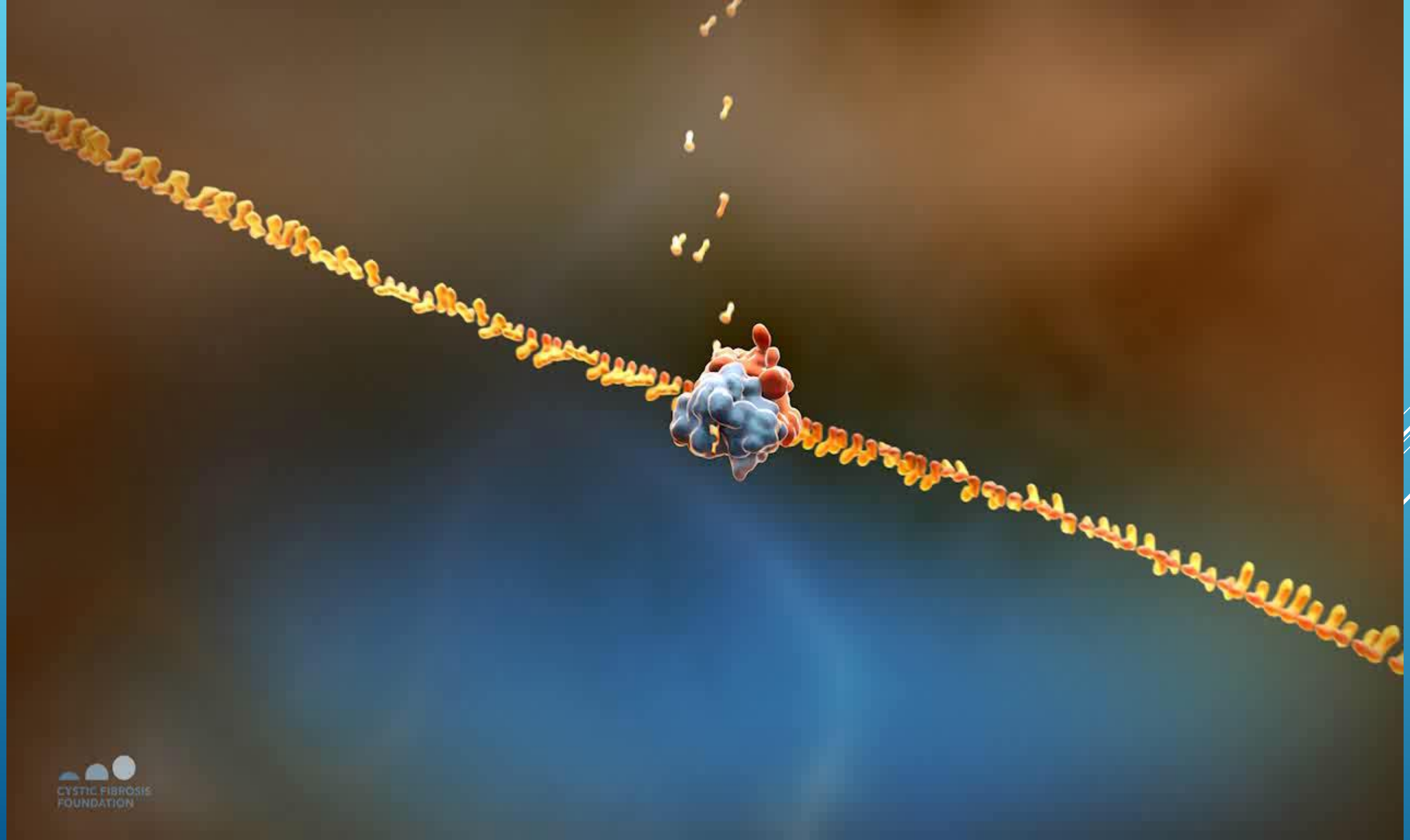
EFFECT OF 28 DAYS OF VX-661/ IVACAFTOR ON ES

CFTR Corrector: VX-661

- Works with similar mechanism to lumacaftor to traffick F508del-CFTR to cell surface
- Longer Half-life; Less drug-drug interactions than lumacaftor;
  No evidence of early chest tightness



Donaldson, Pilewski….Rodman, et al. ECFS 2013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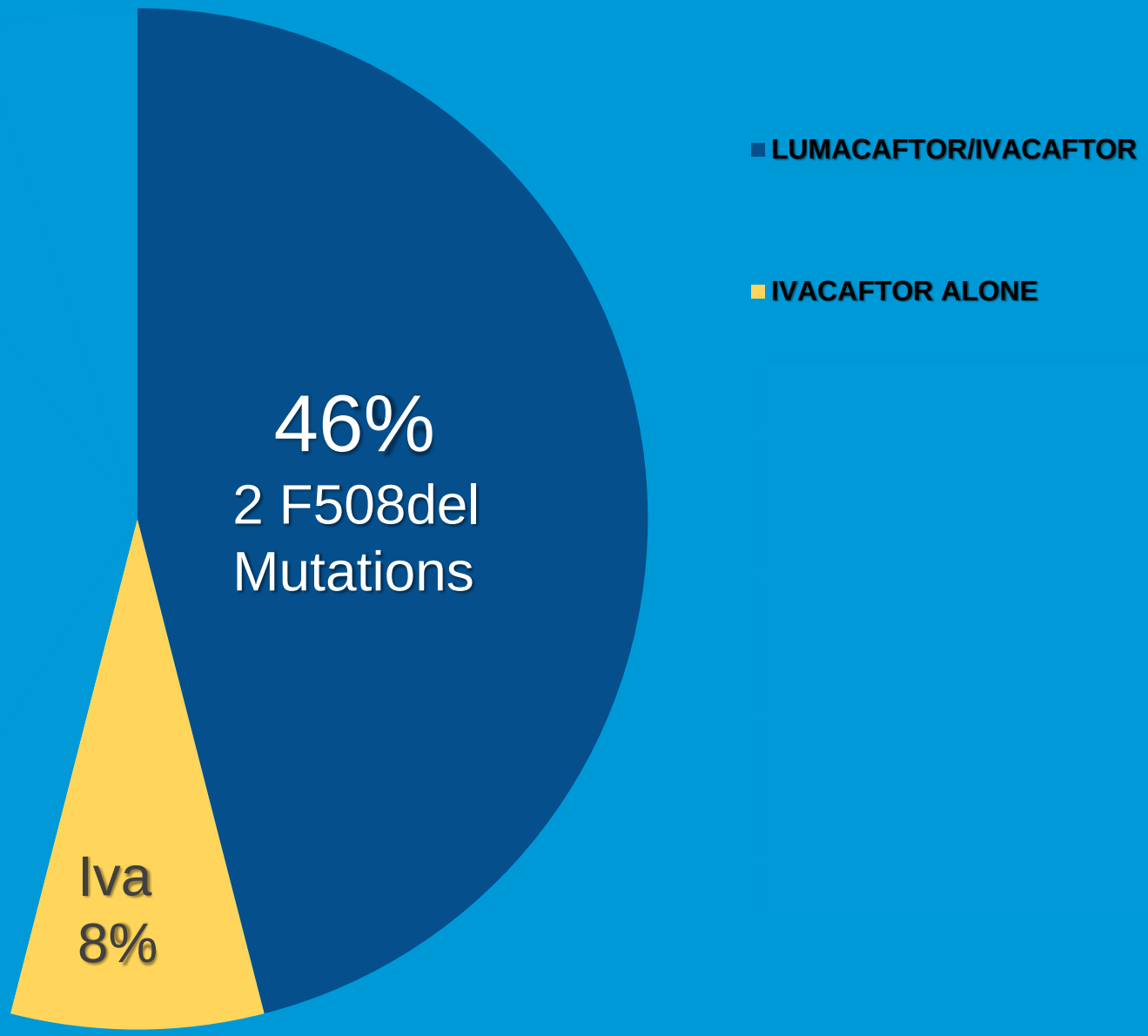
Getting to 100%: How to Address the Remaining 46%



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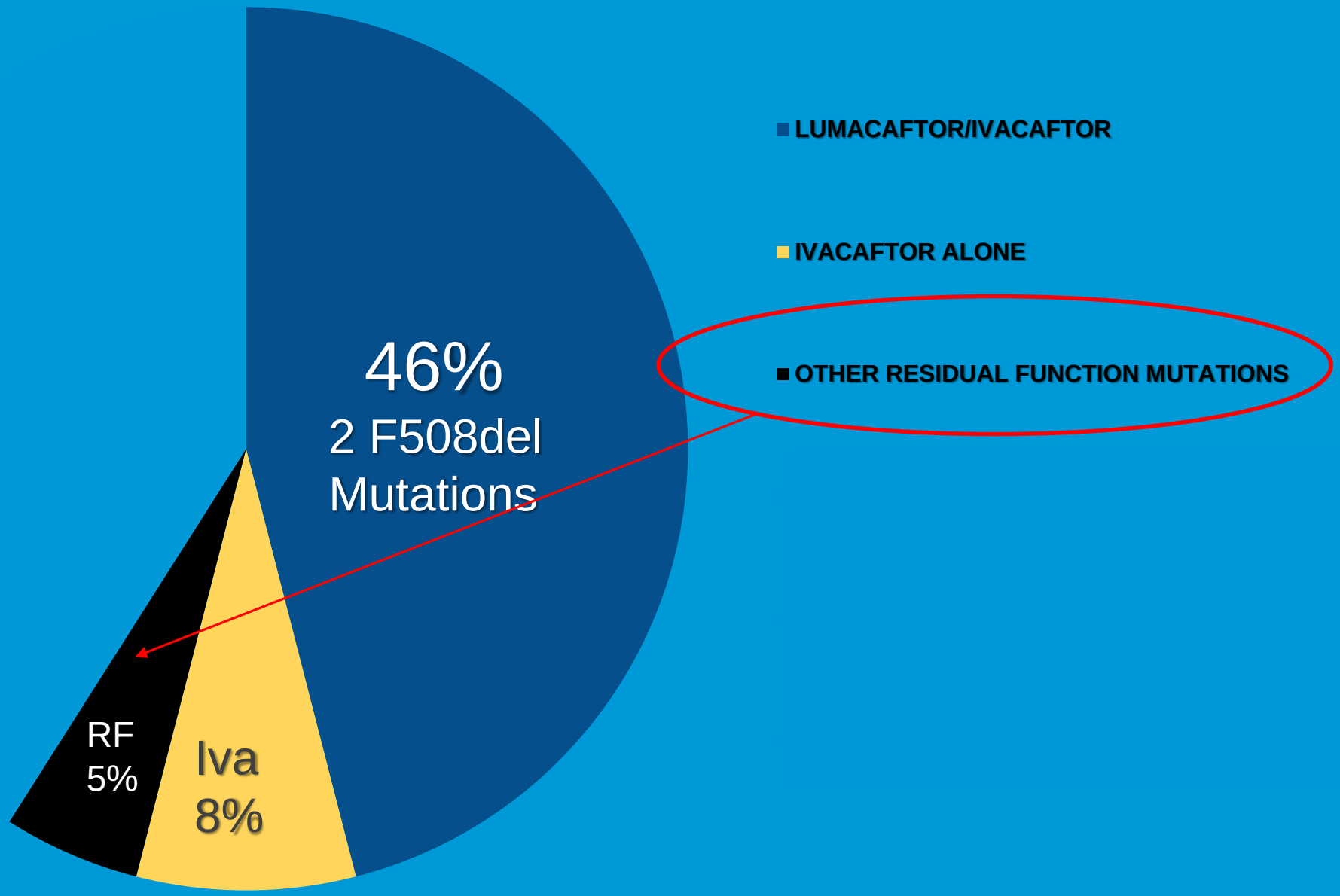

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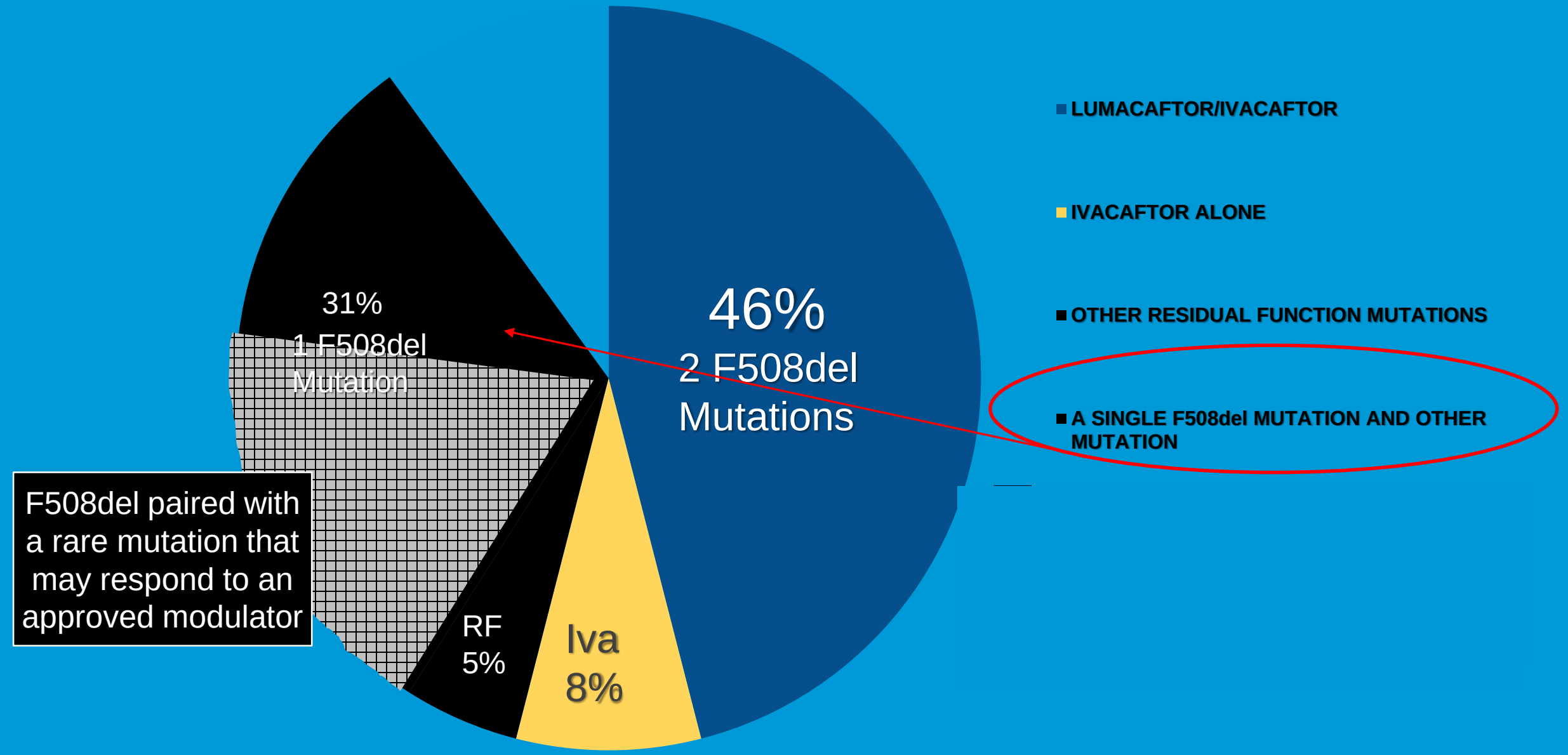

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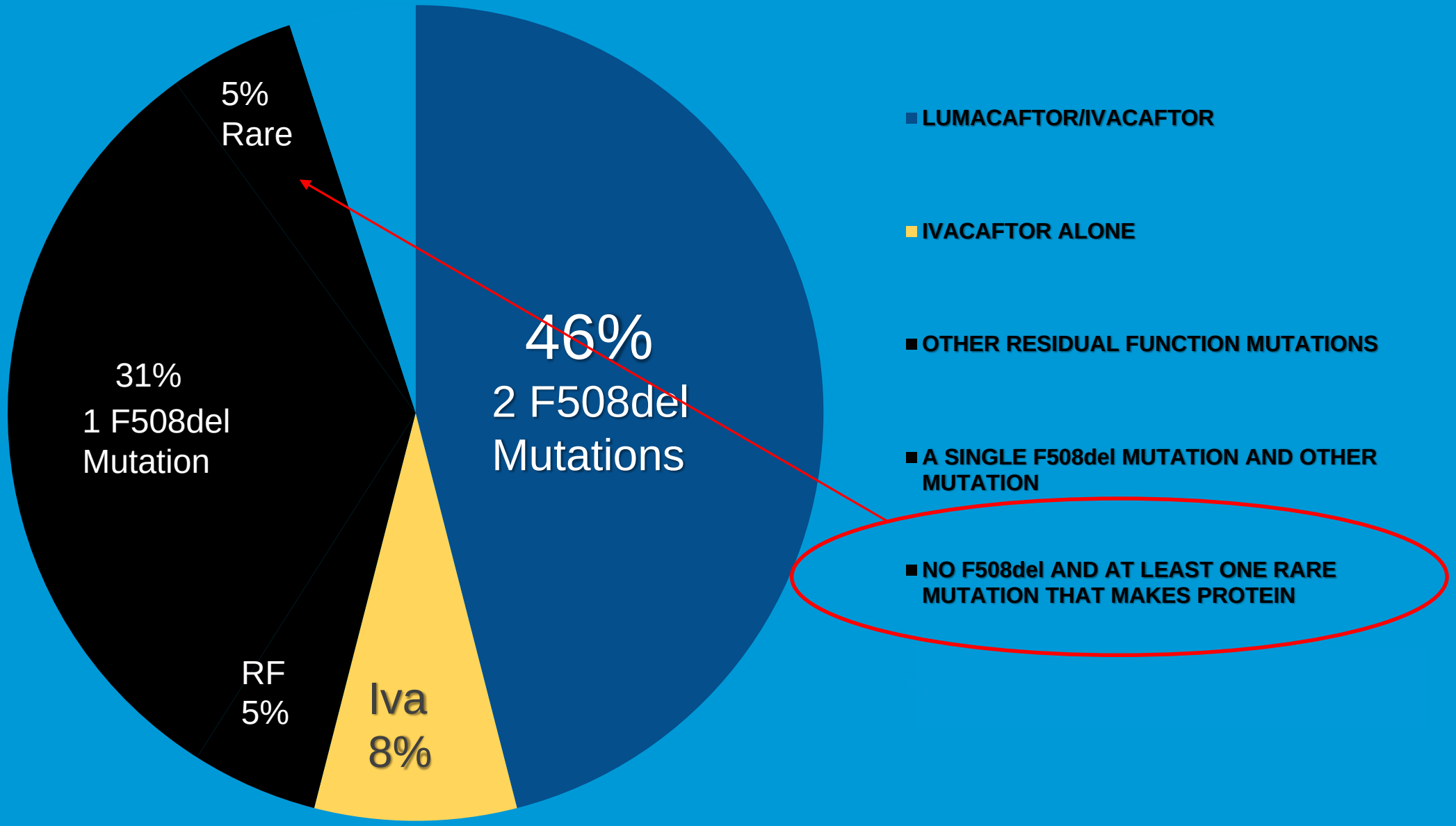

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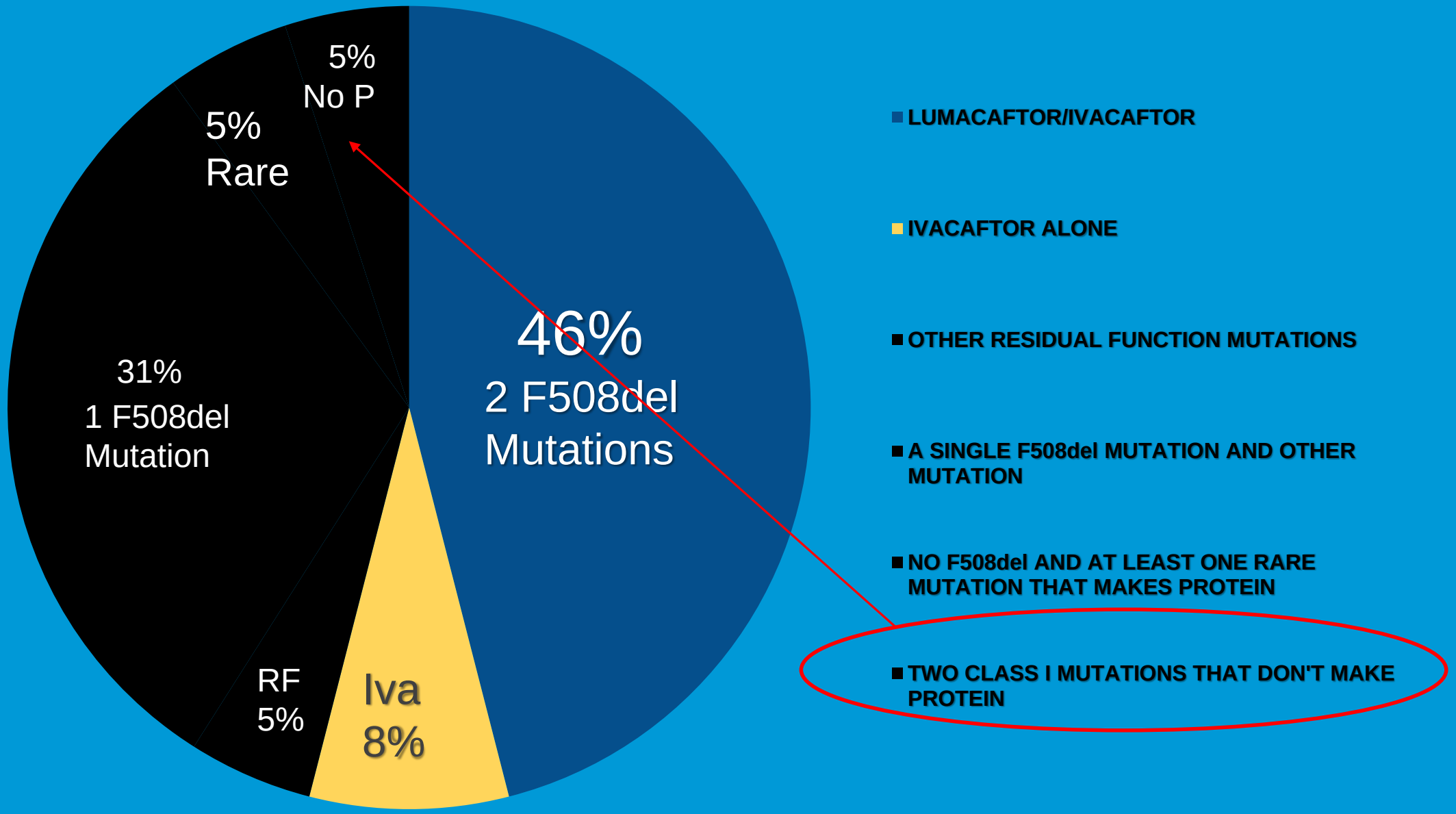

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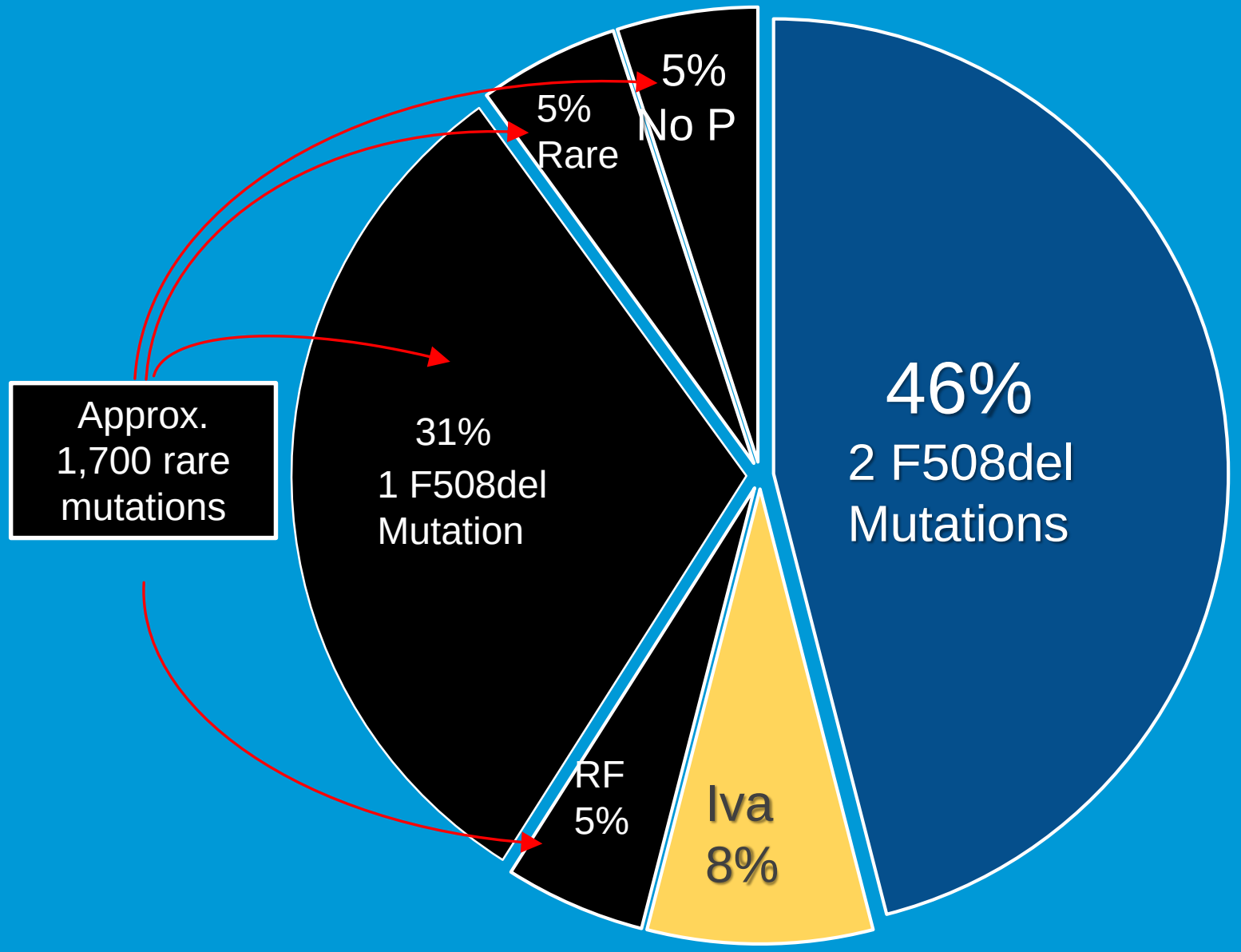


- **LUMACAFTOR/IVACAFTOR**
- **IVACAFTOR ALONE**
- **OTHER RESIDUAL FUNCTION MUTATIONS**
- **A SINGLE F508del MUTATION AND OTHER MUTATION**
- **NO F508del AND AT LEAST ONE RARE MUTATION THAT MAKES PROTEIN**
- **TWO CLASS I MUTATIONS THAT DON'T MAKE PROTEIN**

The Challenge of Rare Mutations

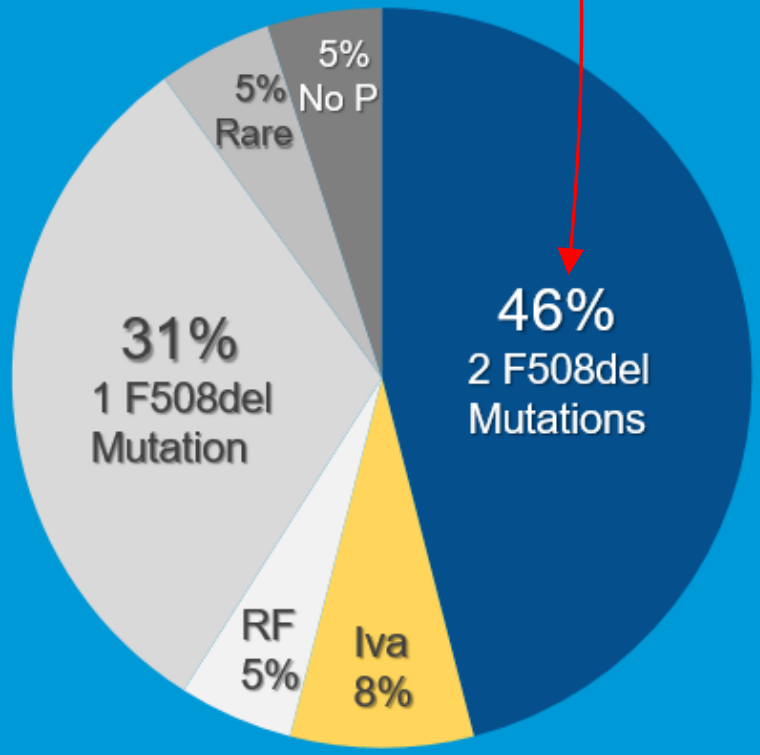
- There are over 1,000 *CFTR* mutations which five or less people with CF in the world carry.[1]

- Traditional clinical trials designs are not possible for these rare mutations.

[1] *CFTR2* database; Garry Cutting and Karen Raraigh

Modulator Needs Headed Into 2017

1) Better therapies for those already on modulators
2) Residual function mutations treatment
3) Ability to assess rare mutations
4) Single F508del mutation treatment
5) Class I mutations treatment



March 2017:

Tezacaftor/Ivacaftor likely

an improved version of

Lumacaftor/Ivacaftor

for those with two F508del mutations.

2017: A Breakthrough Year for Modulators

1) Better therapies for those already on modulators

2) Residual function mutations treatment

3) Ability to assess rare mutations

4) Single F508del mutation treatment

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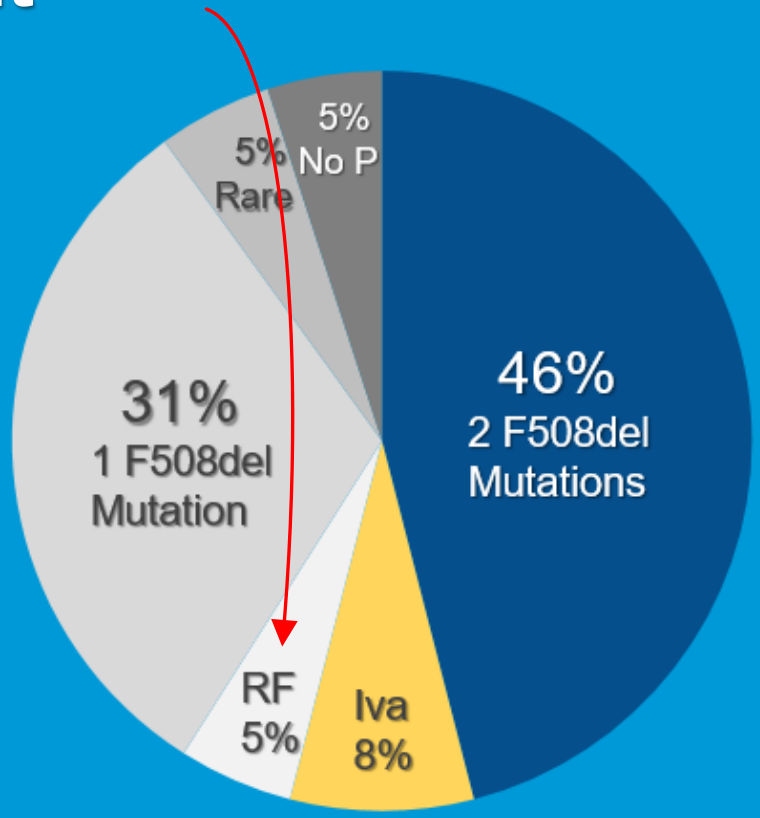


May 2017: FDA Approves Ivacaftor for 23 Missense Residual Function Mutations

E56K	G178R	S549R	K1060T	G1244E
P67L	E193K	G551D	A1067T	S1251N
R74W	L206W	G551S	G1069R	S1255P
D110E	R347H	D579G	R1070Q	D1270N
D110H	R352Q	S945L	R1070W	G1349D
R117C	A455E	S977F	F1074L	
R117H	S549N	F1052V	D1152H	[redacted]

August 2017: FDA Approves Ivacaftor for Five Additional Splice Residual Function Mutations

E56K	G178R	S549R	K1060T	G1244E	3272-26A->G
P67L	E193K	G551D	A1067T	S1251N	711+3A->G
R74W	L206W	G551S	G1069R	S1255P	E831X
D110E	R347H	D579G	R1070Q	D1270N	
D110H	R352Q	S945L	R1070W	G1349D	
R117C	A455E	S977F	F1074L	3849+10kbC->T	
R117H	S549N	F1052V	D1152H	2789+5G->A	

FDA Opens the Door to Use of In-Vitro Testing to Assess Rare Mutations Modulator Response

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.

FDA Press Release
May 17, 2017

FDA decision opens a

new era of personalized CF medicine,

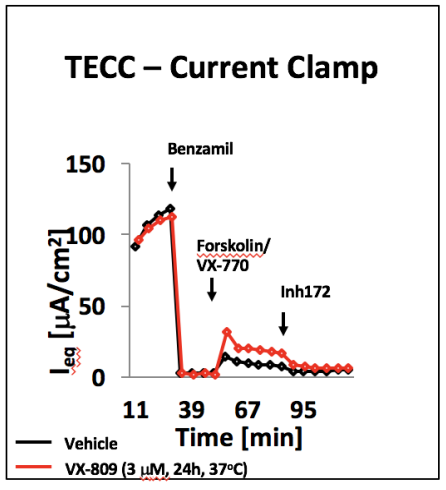
allowing *laboratory* evaluation

of rare *CFTR* mutations

unable to be studied in clinical trials.

Theratyping:

Laboratory testing of *CFTR* mutations using cell lines to determine which available modulators they respond to



Theratyping:

Do CF cells with the mutation in question respond to a specific modulator or combination of modulators?

For those with one Ivacaftor-approved residual function mutation *and* one F508del mutation, Tezacaftor/Ivacaftor likely more beneficial than Ivacaftor alone.

Much Work Still to Do for Single F508del

- Lumacaftor/Ivacaftor (Orkambi) and Tezacaftor/Ivacaftor only showed benefit in those with **two** F508del mutations
- Study of Tezacaftor/Ivacaftor in patients with a single F508del and a second mutation that does not make protein
  - Enrolled 150 participants
  - Stopped by DSMB after 8 weeks of therapy for futility

Highly Effective Next-Generation CFTR Modulator Combination Therapy

- Vertex next-gen molecules: **VX-152, VX-440, VX-659, VX-445**
- Combine with Tezacaftor and Ivacaftor for 3-drug combination
- Other companies:
  - Sanofi Genzyme
  - AbbVie
  - Proteostasis Therapeutics, Inc.
  - Novartis
  - Flatley Discovery Lab
  - Reata Pharmaceuticals

Next-Gen Modulator Programs: What's Next?

- Data consistent for VX-152, VX-440, and VX-659
- VX-445 now in early trials and moving forward
- Final trial data will allow selection of best candidate(s)
- **Pivotal next-gen Phase 3 program(s) to begin mid-2018**

- Other companies also planning combination trials in 2018: Abbvie/Galapagos, Proteostasis, Flatley Labs

CFF is Absolutely Committed to Developing Highly Effective Therapy for the Last 5%

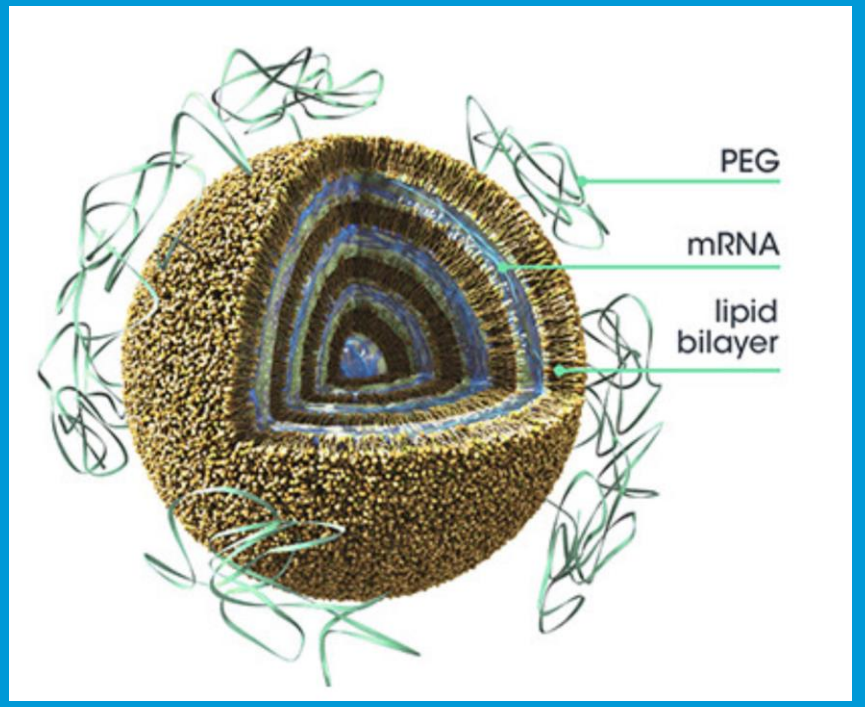
Strategies: stop mutation readthrough, RNA delivery and repair, DNA delivery and expression, gene editing and stem cells

- Evaluated over 100 projects in these areas in the last two years; funded 50
- **Partnership with Southern Research Institute/University of Alabama**
  - Screening of 750,000 compounds for new readthrough agents
- **CFFT Laboratory,** Lexington, Mass. (>35 scientists)
  - More than 50% of effort is directed toward therapy for the last 5%
  - Screening 200,000 compounds for new readthrough agents
- **Pharma partnerships:** Arcturus, Ionis, Recode, 4D Molecular, Sangamo

Coming Soon: CFTR RNA Delivery and Repair

RNA delivery

- Translate bio
- Delivery of CFTR mRNA
- Clinical trial 2018



RNA repair

- ProQR
- QR-010 – demonstrated POC in two F508del mutations
- Mutation-specific repair of common stop mutations

Modulator Needs Headed Into 2017

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2) Treatment for residual function mutations
3) Ability to assess rare mutations
4) Single F508del mutation treatment
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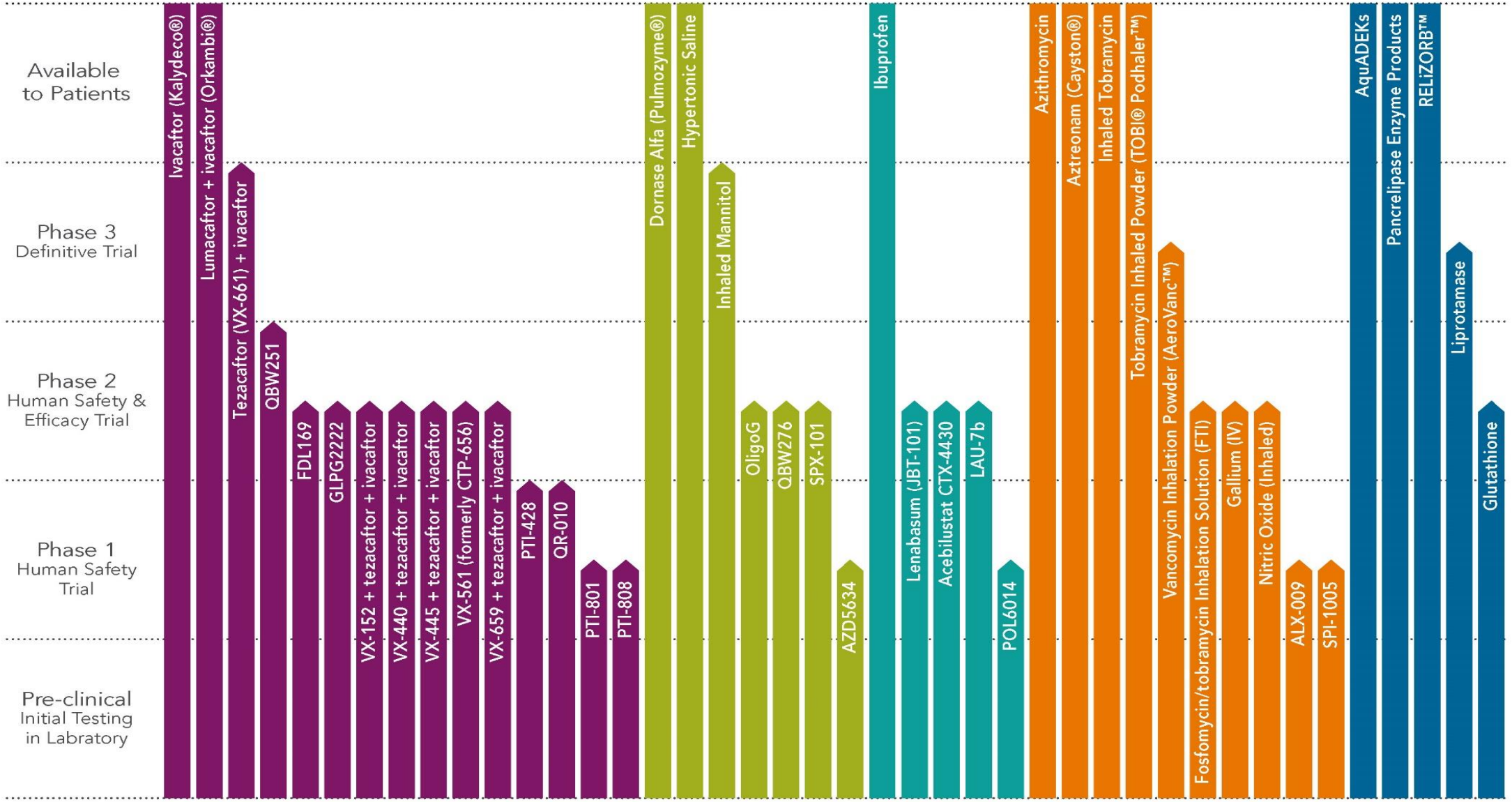
Drug Development Pipeline

11/20/2017



CYSTIC FIBROSIS FOUNDATION
ADDING TOMORROWS

THANK YOU