Galápagos abbvie

# The way forward in drug testing is mutation specific

Katja Conrath, PhD
Therapeutic Area Head

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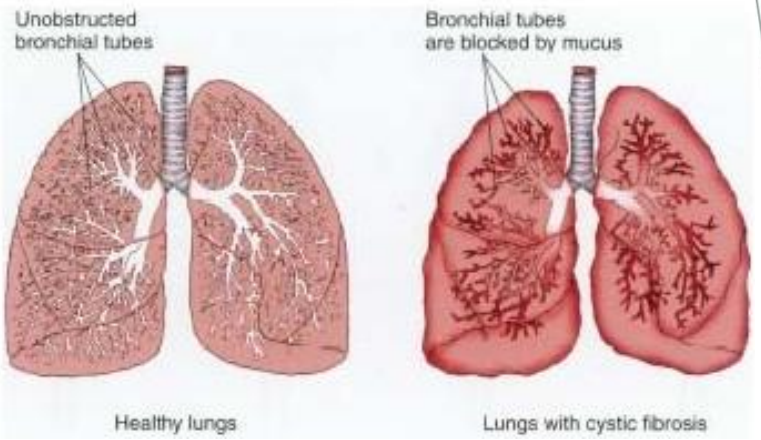
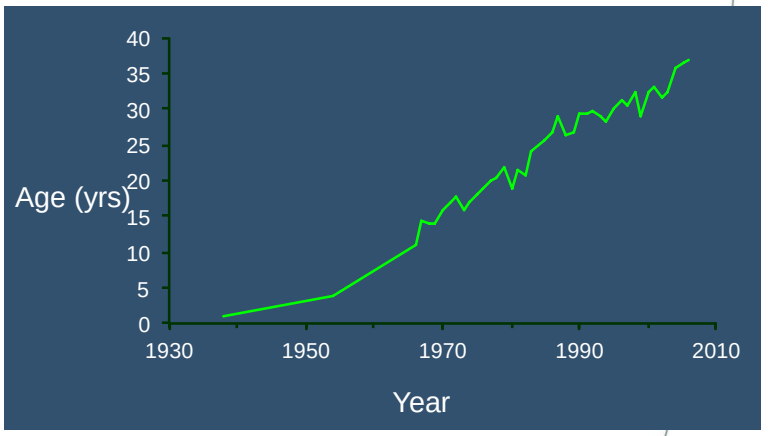
# Cystic Fibrosis (CF) Disease Overview

## An Orphan Disease, with a high unmet need

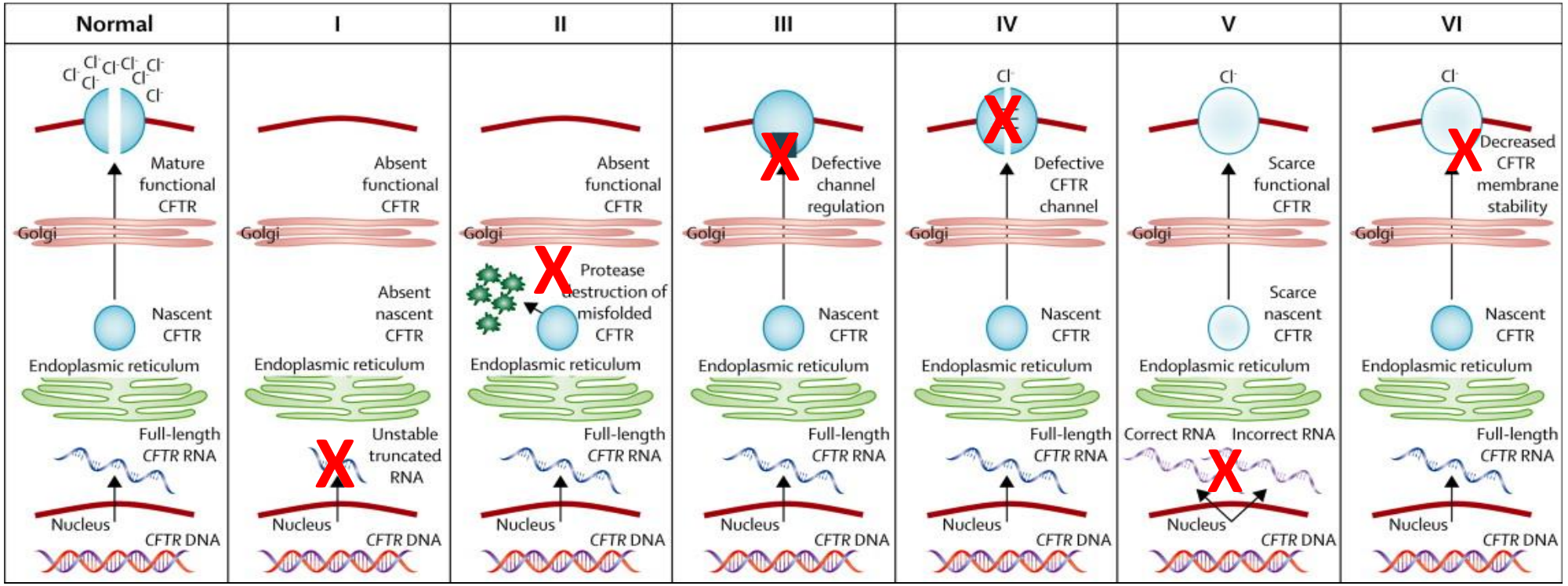
- CF is a recessive genetic disease
  - Over 1900 mutations identified
  - Lead to absent, deficient, or dysfunction of CFTR
- Affects ~ 70,000-90,000 people worldwide
- Predicted median survival ~ 35 years
- Current therapies are palliative in nature
- Kalydeco is the only disease-modifying therapy
  - Only about 4% of patients




Predicted Median Survival



# CFTR Mutations Fit Into 6 Classes



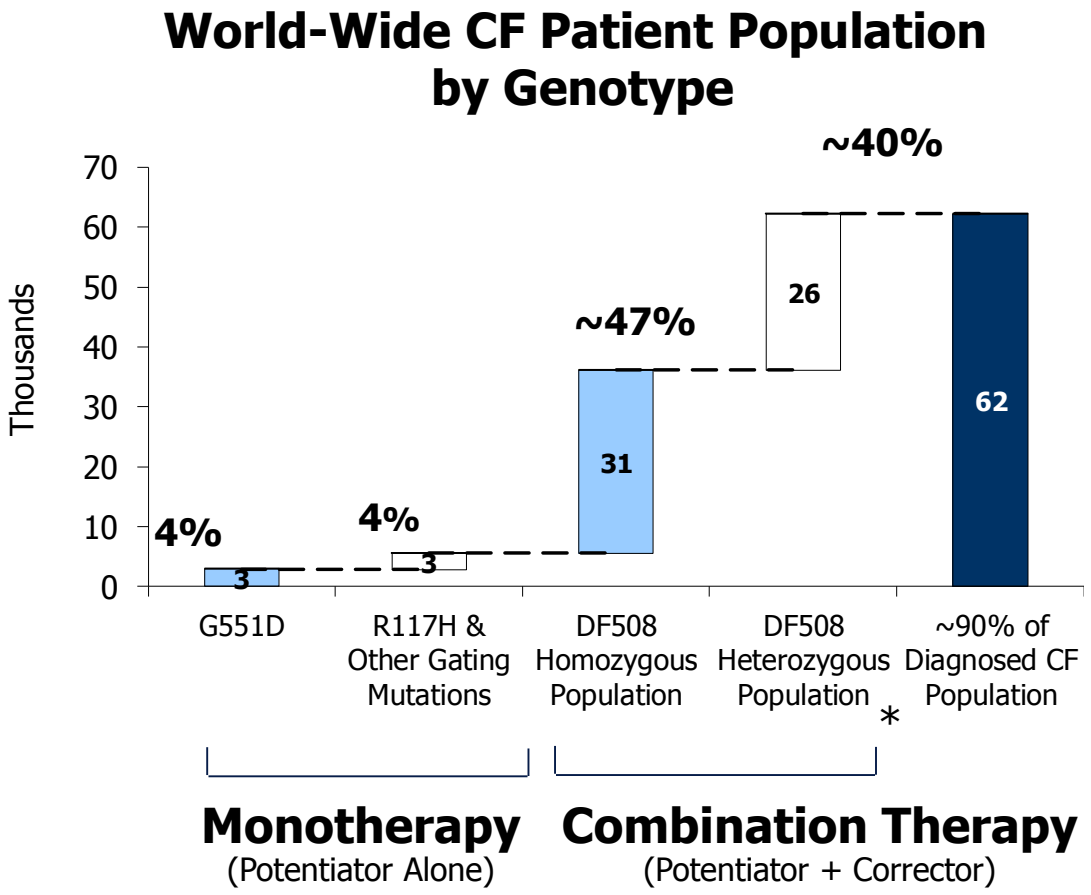

Normal | Synthesis | Maturation | Regulation | Conductance | Quantity (↓ number) | Quantity (stability)

'Severe' mutations
~96% of patients

'Mild' mutations

Source: Boyle, M.P. and De Boeck, K.
The Lancet Respiratory Medicine 2013; 1:158-163

# Most patients have ΔF508 mutation




According to CF Foundation: ~70,000 CF patients worldwide

**= Clinical PoC obtained; primary populations of interest**

**= Clinical PoC not yet obtained; represents potential upside**

*ΔF508 heterozygous CF patients have one copy of the ΔF508 mutation and one copy of another a deleterious CFTR mutation; CF is a recessive disease

Source: CF Foundation 2011 Annual Patient Registry Report; Decision Resources Patient Base; IPD Database

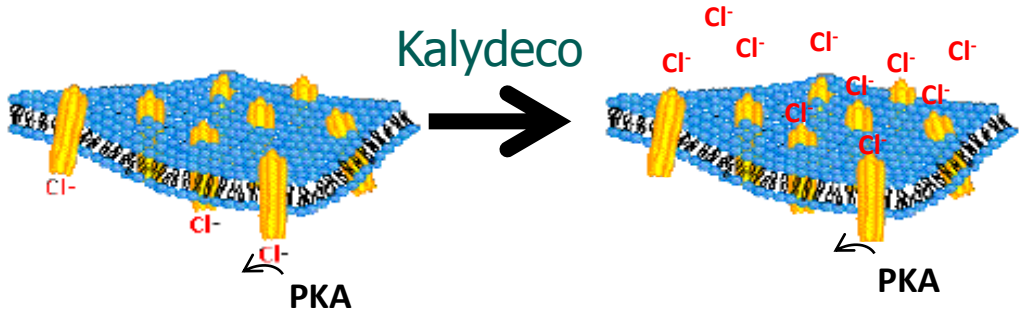
# Therapies for most severe mutations

## Two approaches to fix CFTR

Functional Defects (Class III / IV)

Potentiators restore the flow of ions through activated CFTR

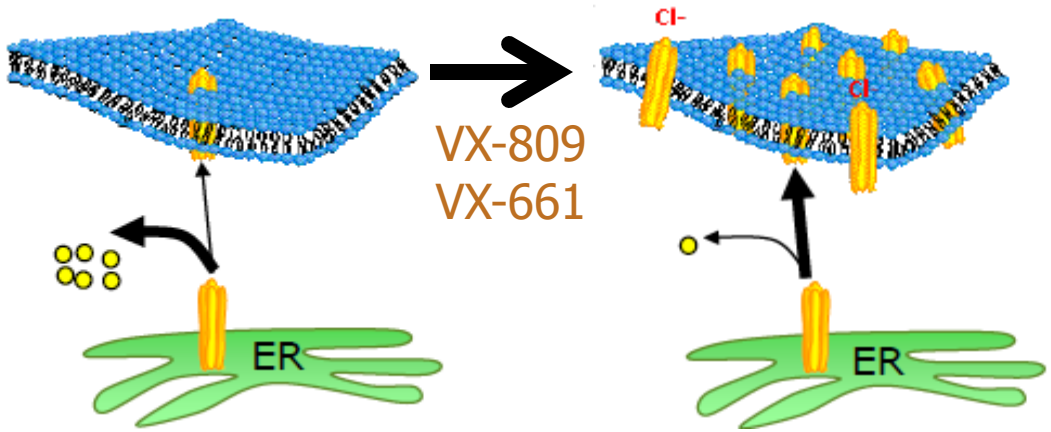
- 1 approved agent




Maturation Defect (Class II)

Correctors restore the processing of CFTR from the ER to the surface

- No approved agents
- 2 in development




Adapted from Dr. Scott Donaldson's Plenary Session (NACFC, 2013)

# CF Pipeline: CFTR Modulators

| Preclinical | Phase 1 | Phase 2 | Phase 3 | Registration |
|---|---|---|---|---|
| DF508 Mutation Correctors or Combos<br>Pfizer, Proteostasis, Genzyme, Reata, Parion, Flatley Discovery Labs, Bayer, Novartis | N6022<br>(S-nitrosoglutathione)<br>N30 Pharmaceuticals | pGM169/GL67A<br>Imperial Coll London | Ataluren<br>(formerly PTC124)<br>PTC Therapeutics<br>+ CFF Therapeutics | **On Market**<br>Kalydeco (ivacaftor, VX-770) approved Jan 2012 for G5521D, expanded in 2014 to include 8 more CF gating mutations |
| McGill/GSK collaboration (gene therapy) | | VX-661+/- ivacaftor<br>Vertex | VX-809+/- ivacaftor<br>Vertex | |
| Galapagos/AbbVie<br>pre-clinical candidate potentiator and correctors | | ivacaftor (R117H)<br>Vertex | VX-770 (LT tx)<br>Vertex | |
| CFTR-001<br>(biomarker dev – pilot study)<br>CF Therapeutics Dev Network | | | | |
| dF508 RNA repair<br>ProQR Therapeutics | | | | |

**Mode of Action**

- =CFTR Modulator
- =Gene Therapy
- =RNA Repair

Sources: CF Foundation Drug Pipeline, Company websites

# CFTR modulators

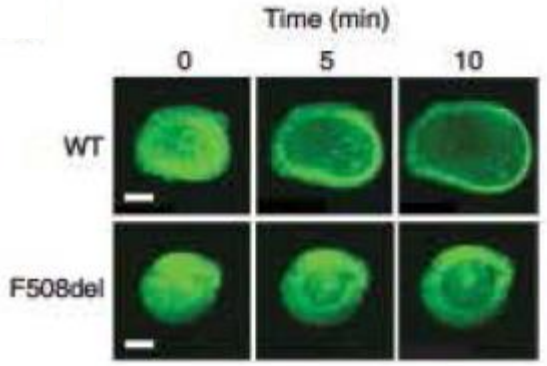
| Class I | Class II | Class III | Class IV |
|---|---|---|---|
| Corrector for Class I | Corrector for Class II | Potentiator A | Potentiator A |

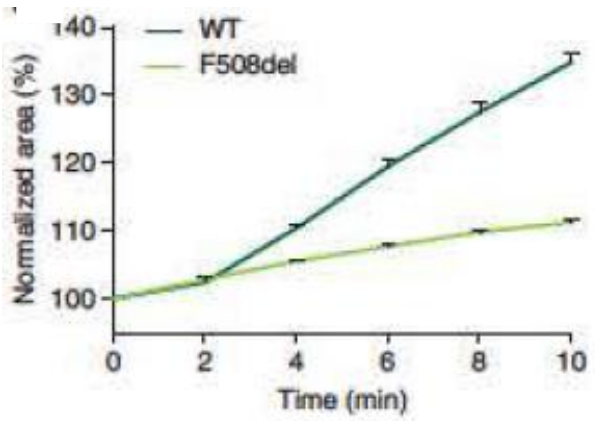
Is this enough?

Is this enough for all patients in same class?
Does genetic background influence efficacy?

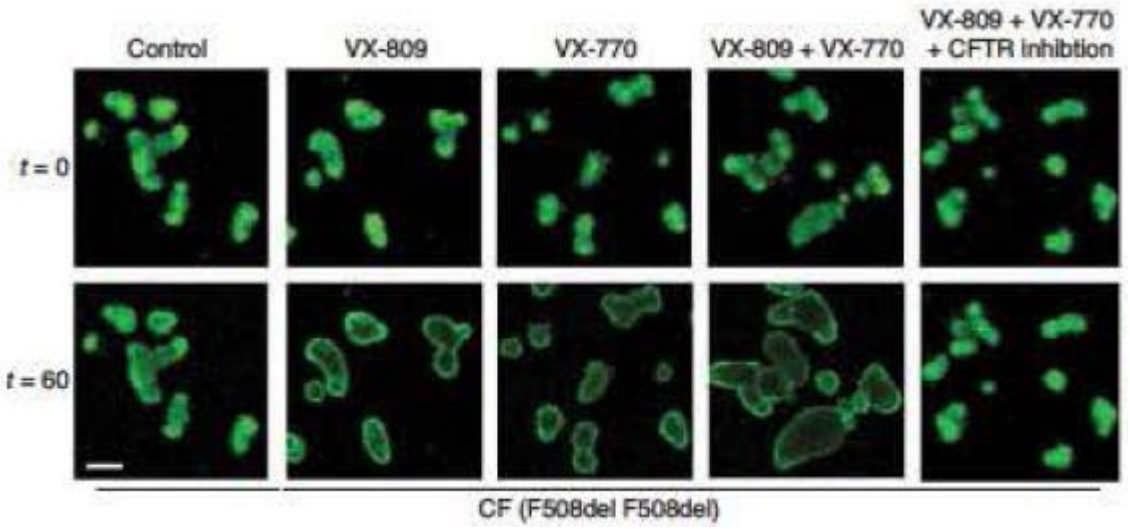
| | | | |
|---|---|---|---|
| Corrector for Class I | Corrector A for Class II | Potentiator A | Potentiator A |
| Potentiator A | Corrector B for Class II | Potentiator B | Potentiator B |
| OR | OR | OR | |
| Corrector for Class I | Corrector A for Class II | Potentiator B | |
| Potentiator B | Corrector B for Class II | | |
| | Potentiator A or B | | |

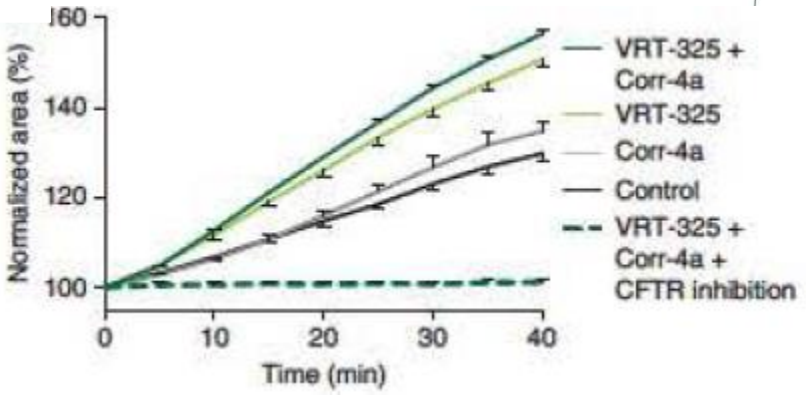
# Organoids
## Patient derived material




- CFTR specific signal in organoids derived from intestinal biopsies
- CFTR present at apical side in organoid



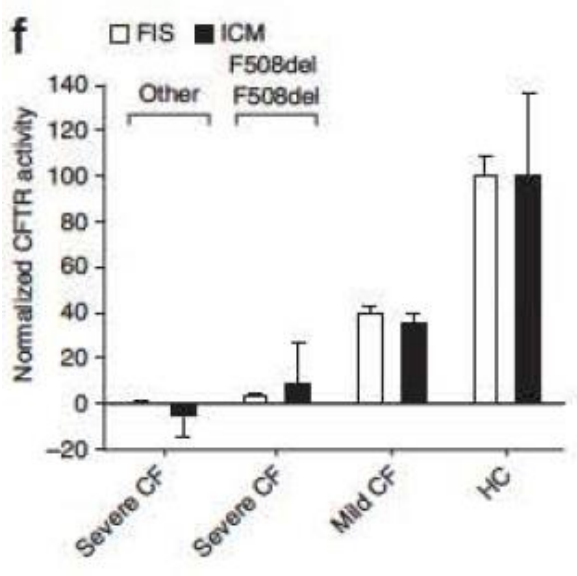






Source: Dekkers *et al.,* Nature Medicine, 2013

# Organoids
## Can be derived from all genotypes

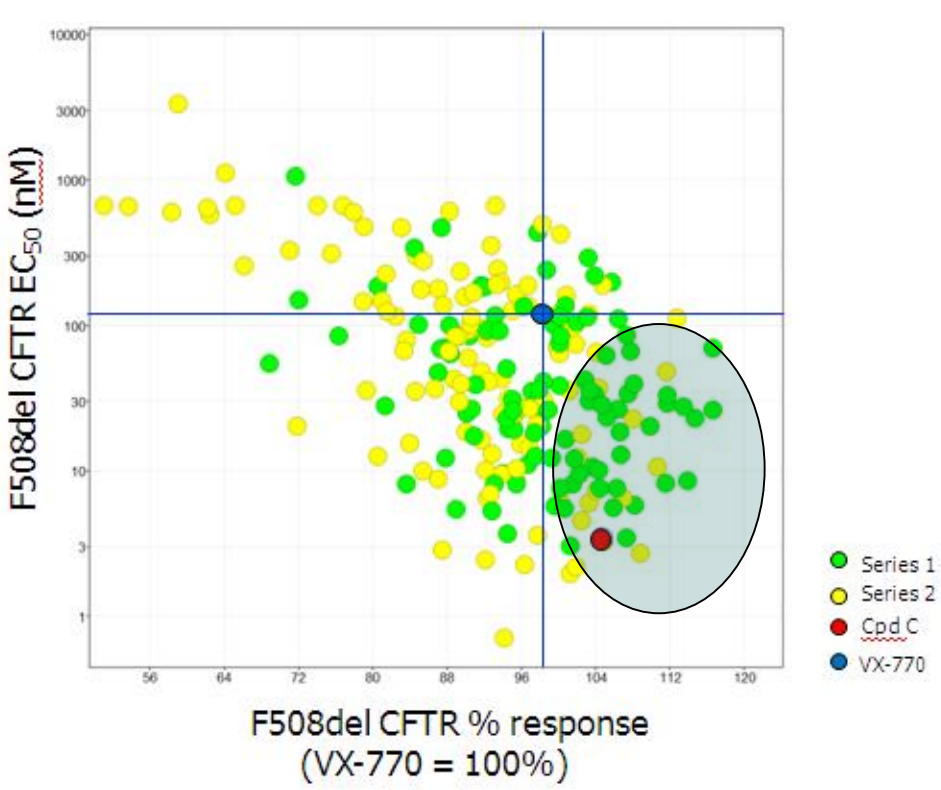
- The team of J. Beekman has shown that isolation and generation of organoids derived from different patient genotypes is feasible and can be used for measuring FIS or RLS
- Specific drug combinations can be evaluated in each of these patient derived organoids and identification of the best combination set can be determined using this method

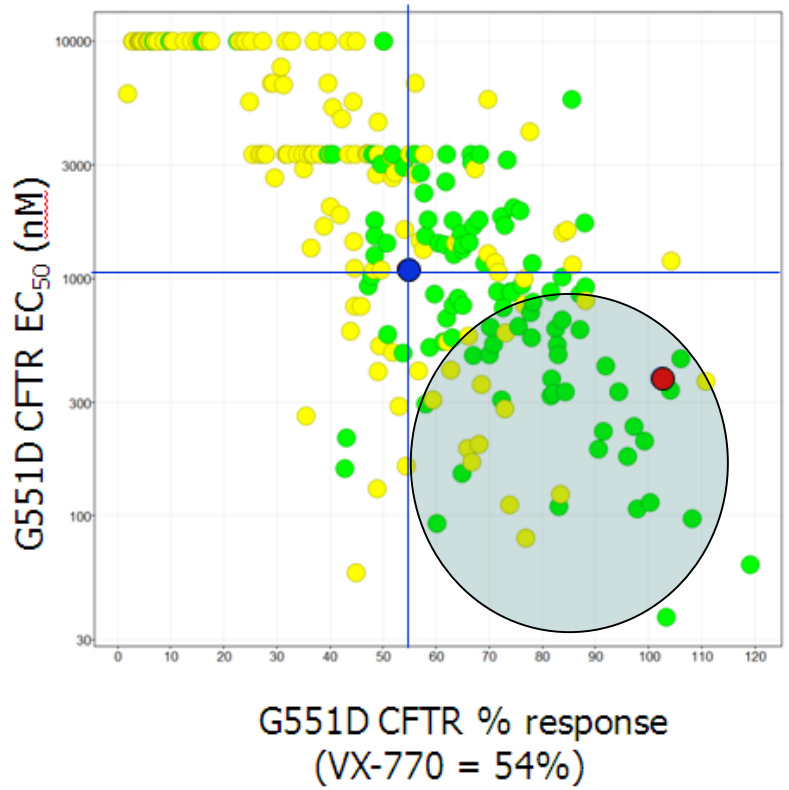



Steps towards personalized medicine for CF set

# Novel potentiators
## Activity and Efficacy on F508del and G551D CFTR

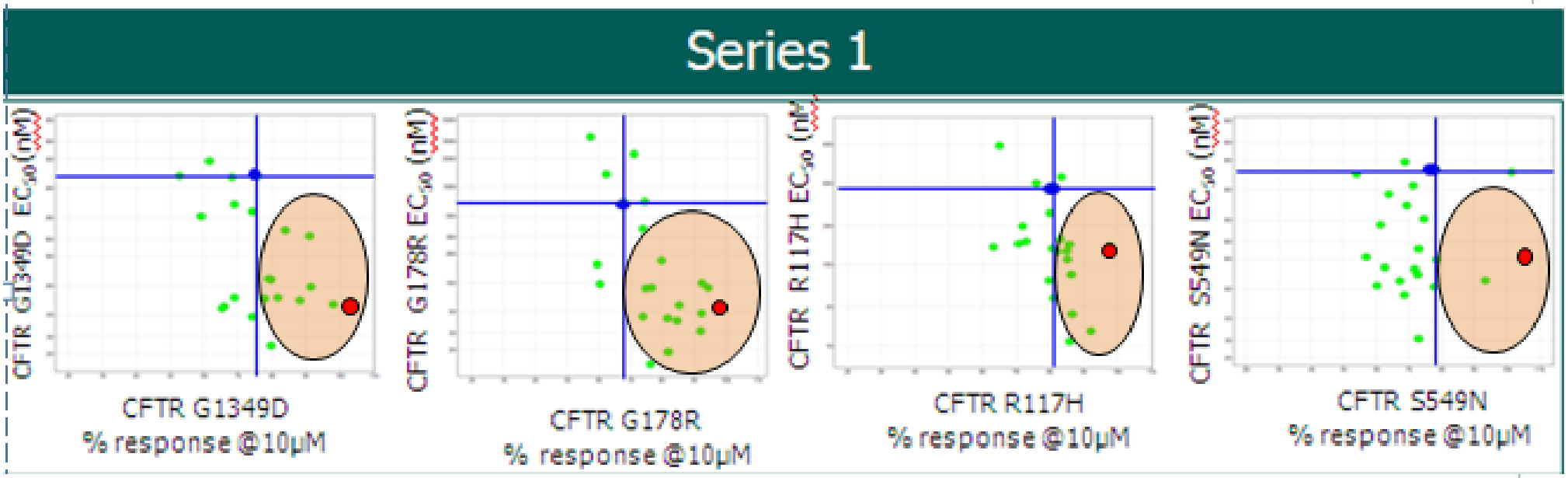
- Potentiators are very potent and improve CFTR channel opening to a high extent



# Novel potentiators

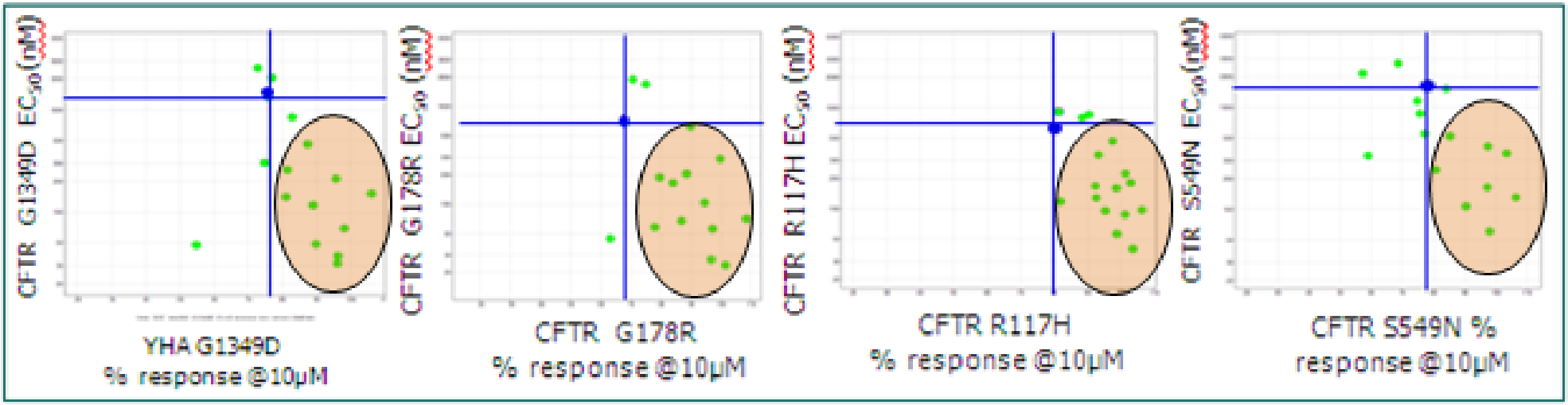
## Activity on other CFTR mutants



# Novel potentiators

## Activity on other CFTR mutants

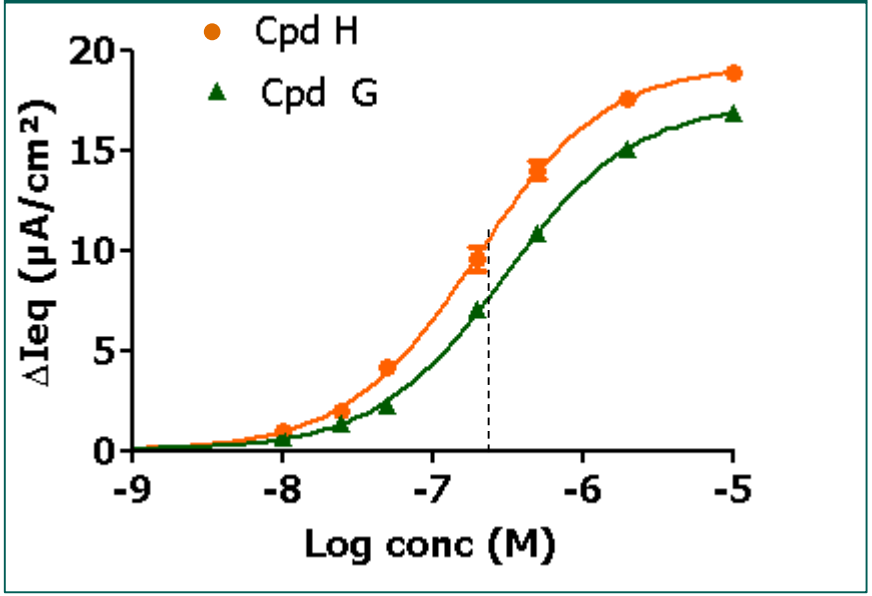
### Series 2



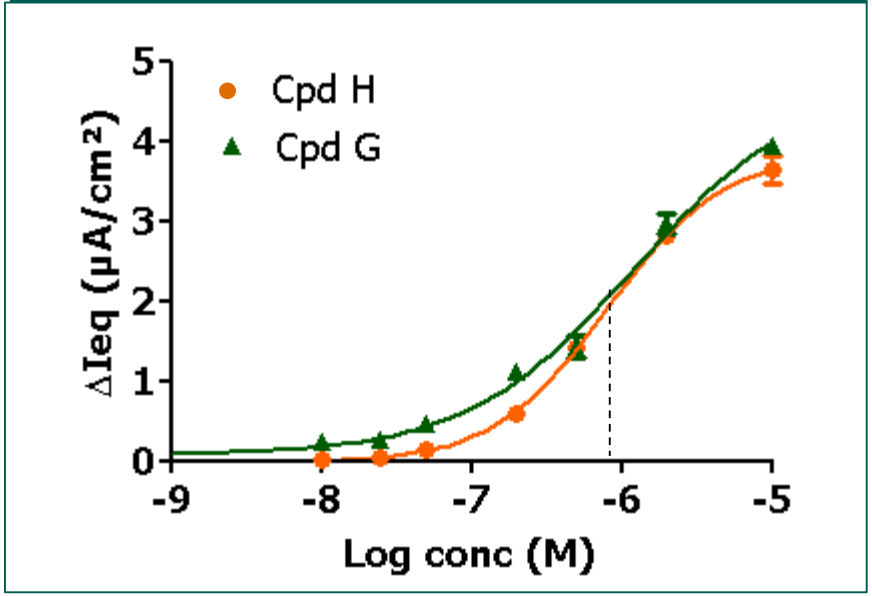
# Novel potentiators
## Activity in FRT cells

- FRT G551D cell line can be used to rank compounds for activity before going into primary G551D/ F508del cells

### FRT-G551D High expressor



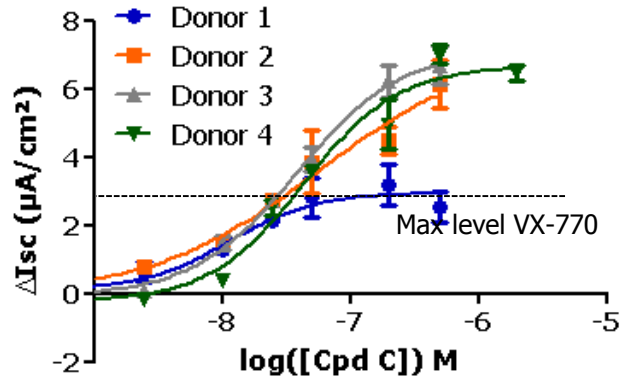

### FRT-G551D Low expressor



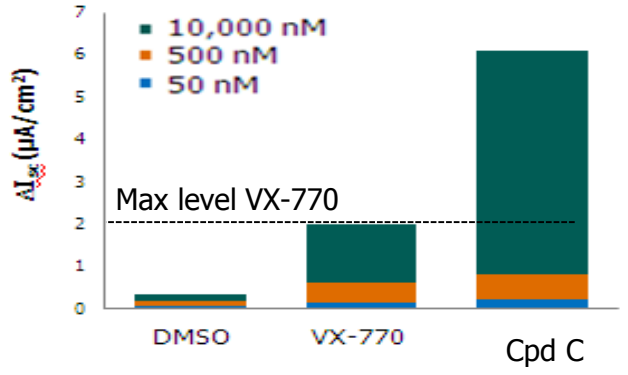
# Novel potentiators
## Translation into primary cells

- Activity of potentiators is confirmed into primary cells derived from patients

**F508del/ F508del HBE**




**G551D/ F508del HBE**

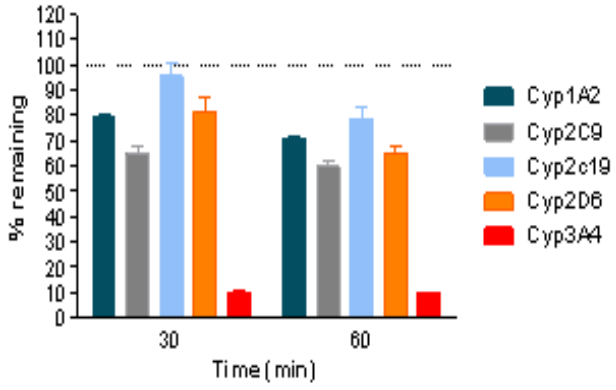



Novel potentiators can open CFTR channels to higher extent than VX-770

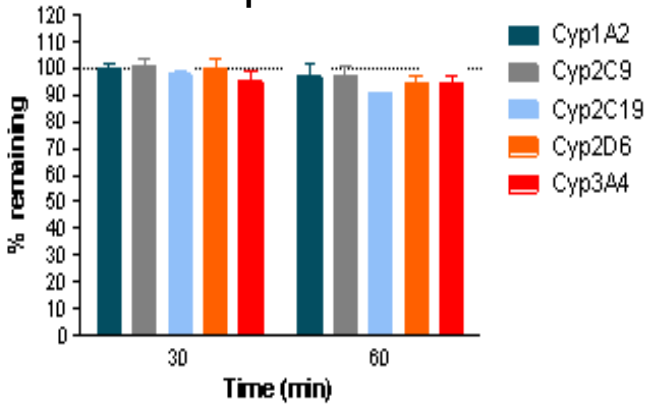
# Novel potentiators

- Good ADME profile present in series
  - Compounds with no DDI liabilities identified within series
    - No CYP induction liability
  - Good exposure achievable in various species
  - Compounds with low or no CYP conversion present in series

VX-770




Compound C




Source: Conrath *et al.*, Poster 41, NACFC 2013, Salt Lake City

# CFTR Modulators
## Summary

- Several strategies feasible to address cause of CF depending on class of mutation
  - Optimal combination for each genetic background can be different
  - Room for different modulators (potentiators and correctors) with different characteristics to be developed for treatment of all CF patients
  - Need for technologies to assess optimal combination for each patients – organoids as an example

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