



Children's Hospital

Organoids, the road to personalized and optimal care for patients with Cystic Fibrosis

Harry Heijerman

University Medical Center Utrecht

The Netherlands



University Medical Center Utrecht

Disclosures :

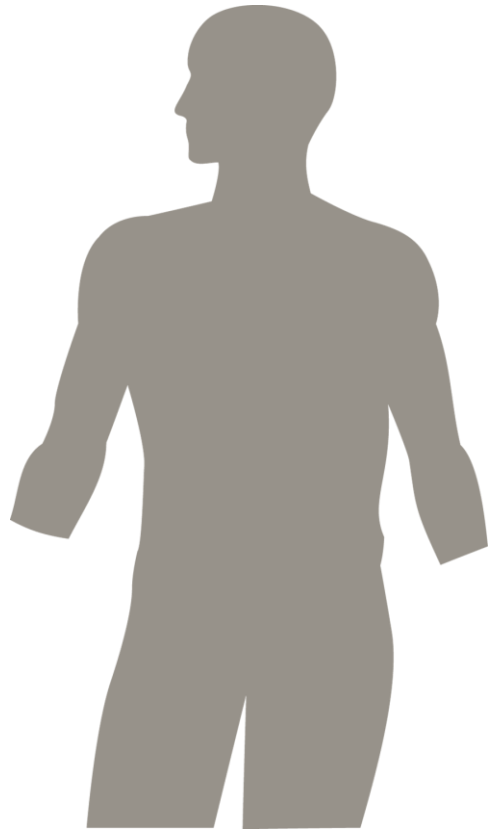
Grants/Research Support: Gilead, Novartis, GSK, Vertex

Speakers Bureau/Honoraria: PTC, Novartis, Vertex, Raptor, Gilead

Consulting Fees: Vertex, Raptor, PTC, Gilead

Personalized medicine is the future of
cystic fibrosis treatment

CF disease modeling using organoids

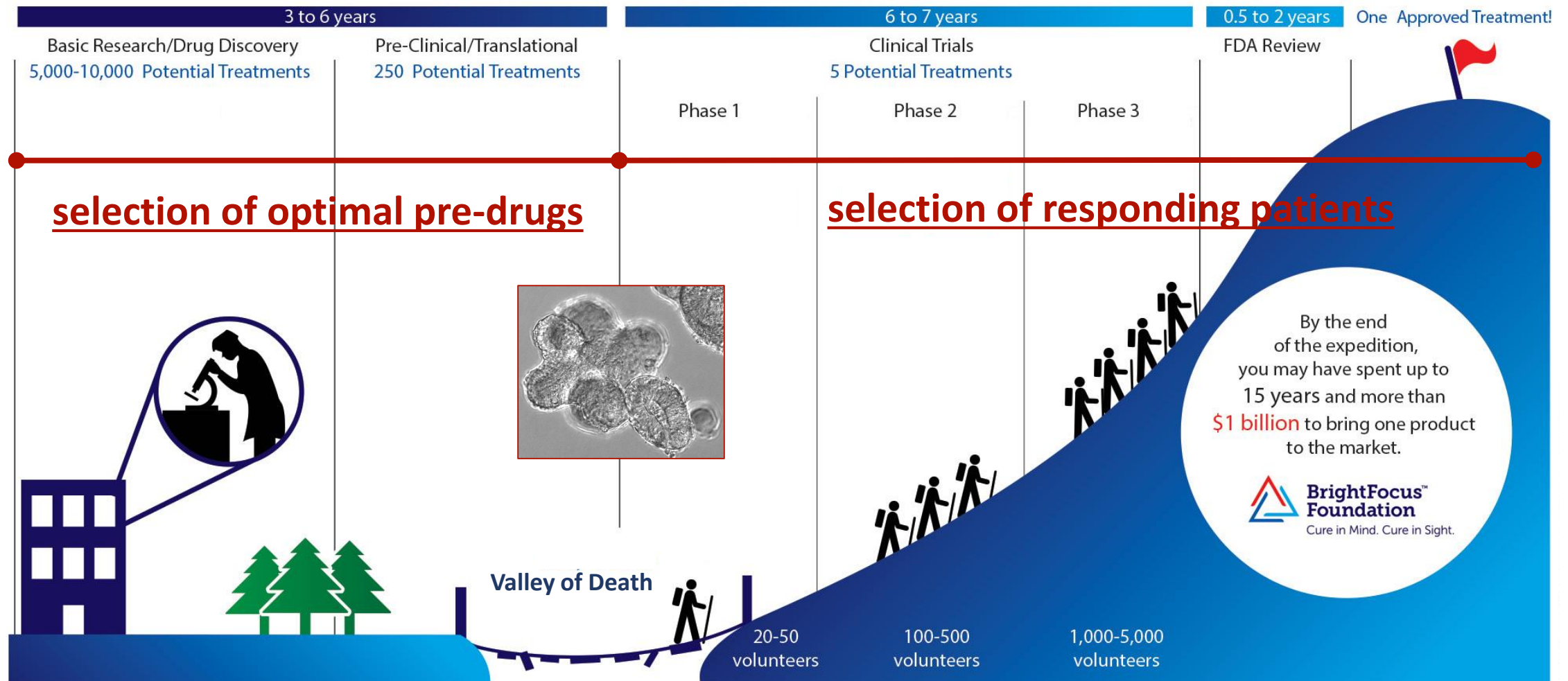


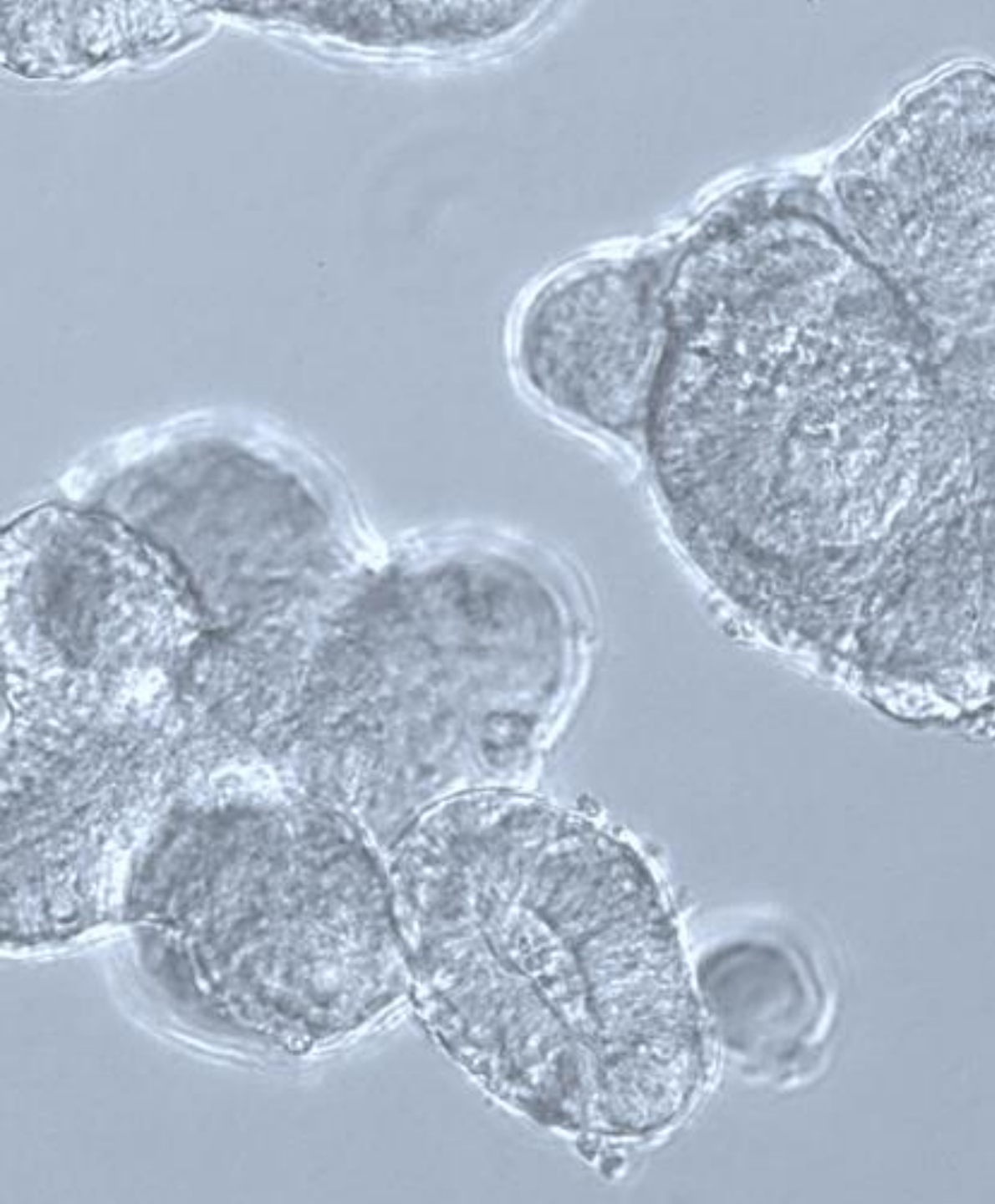
subject



Drug development and clinical application

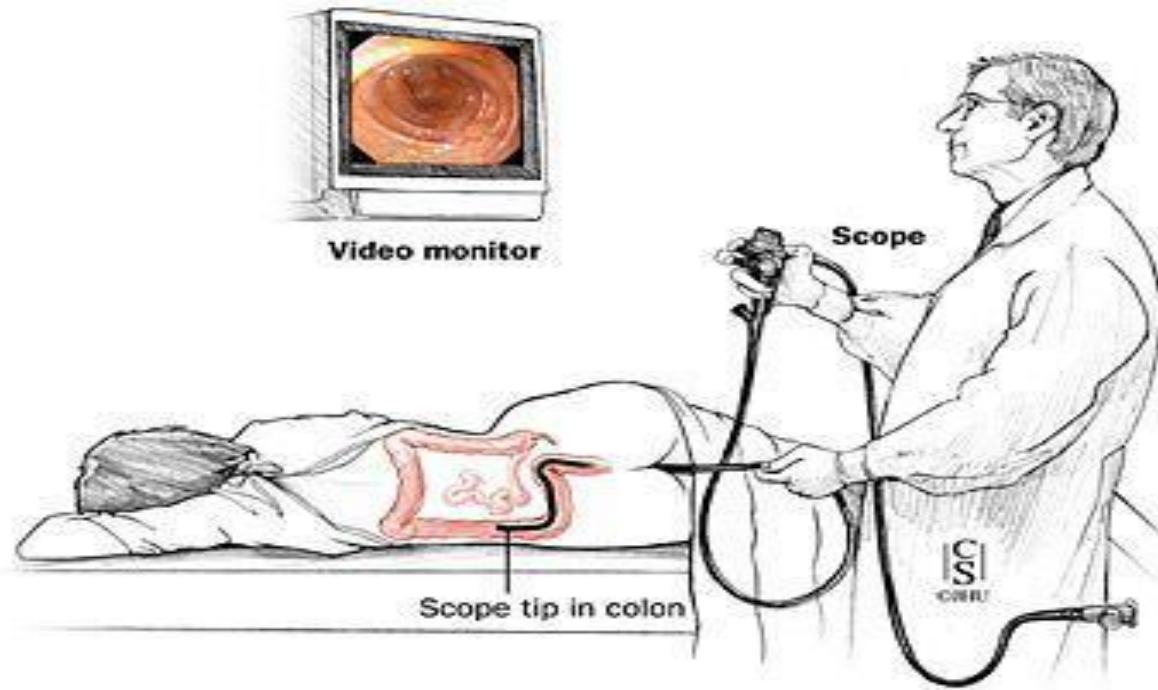
FROM GROUP-BASED MEDICINE TO PERSONALIZED MEDICINE





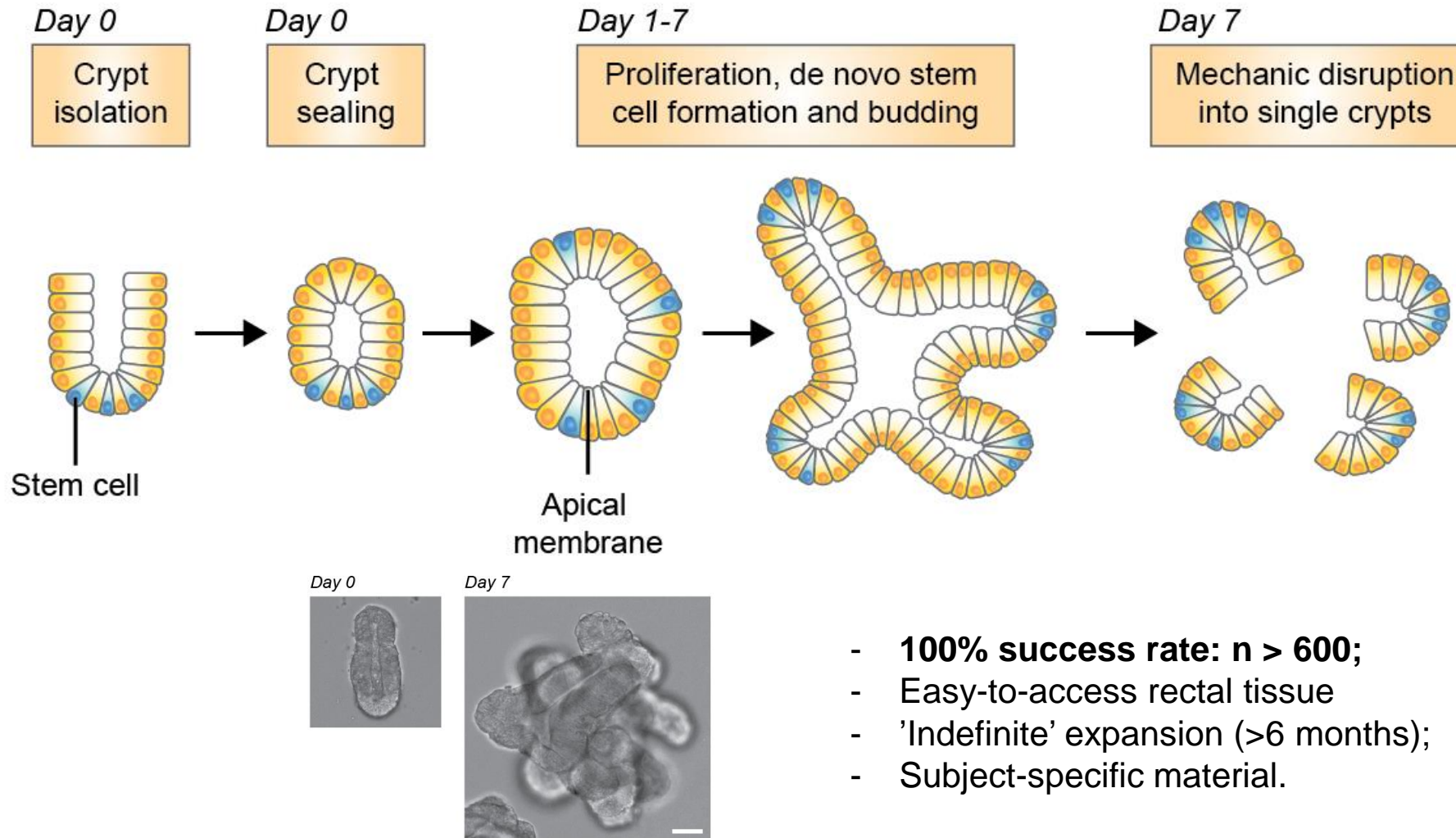
APPLICATIONS OF ORGANOIDS IN CF RESEARCH

Organoids = minigut



This morning I had rectal biopsies taken for the HIT CF study. No need for preparation and no pain at all, the only problem was that I had to get out of bed early.....

Organoids to model CF disease



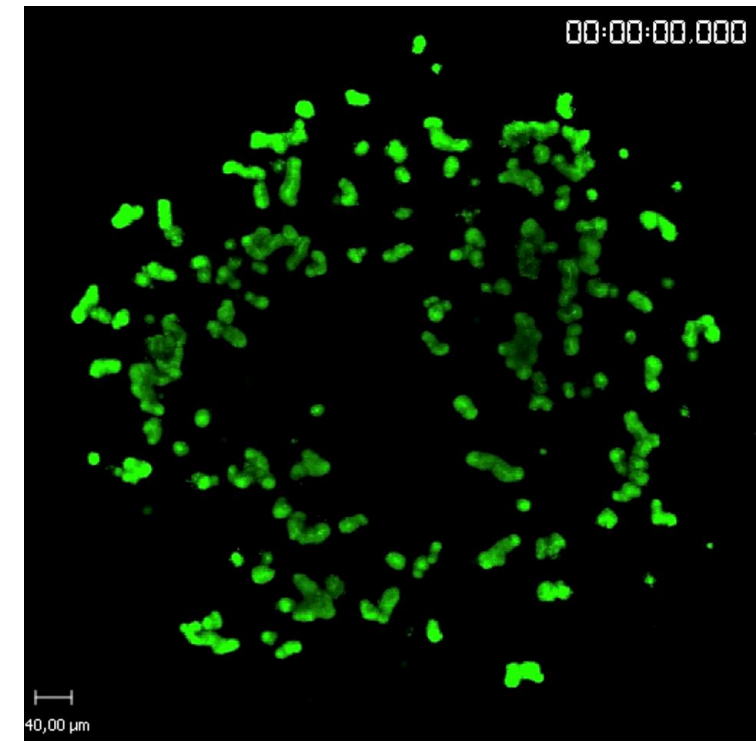
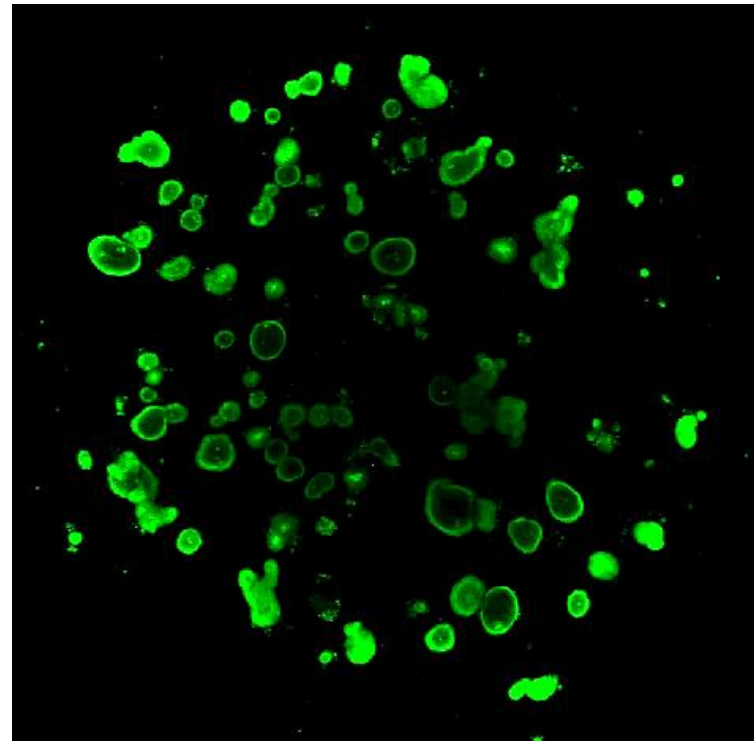
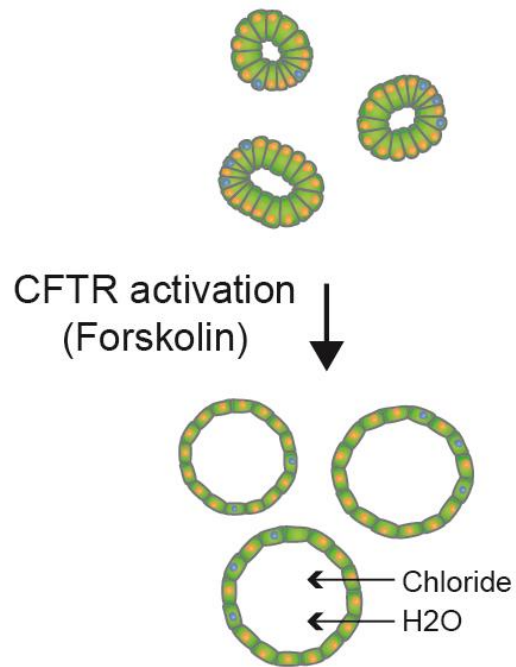
- **100% success rate: n > 600;**
- Easy-to-access rectal tissue
- 'Indefinite' expansion (>6 months);
- Subject-specific material.

Forskolin-induced swelling (FIS) assay

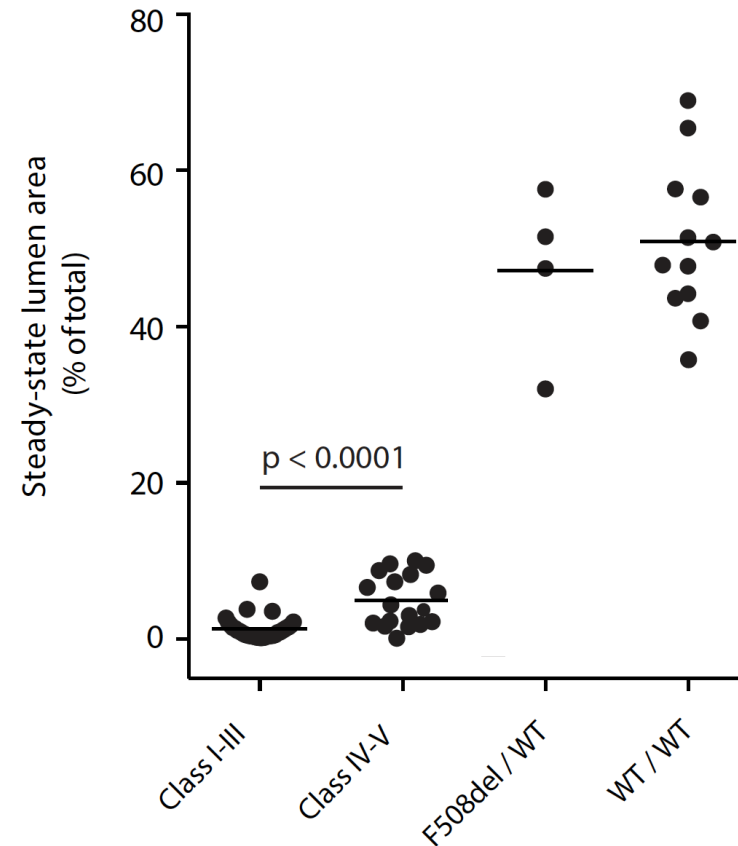
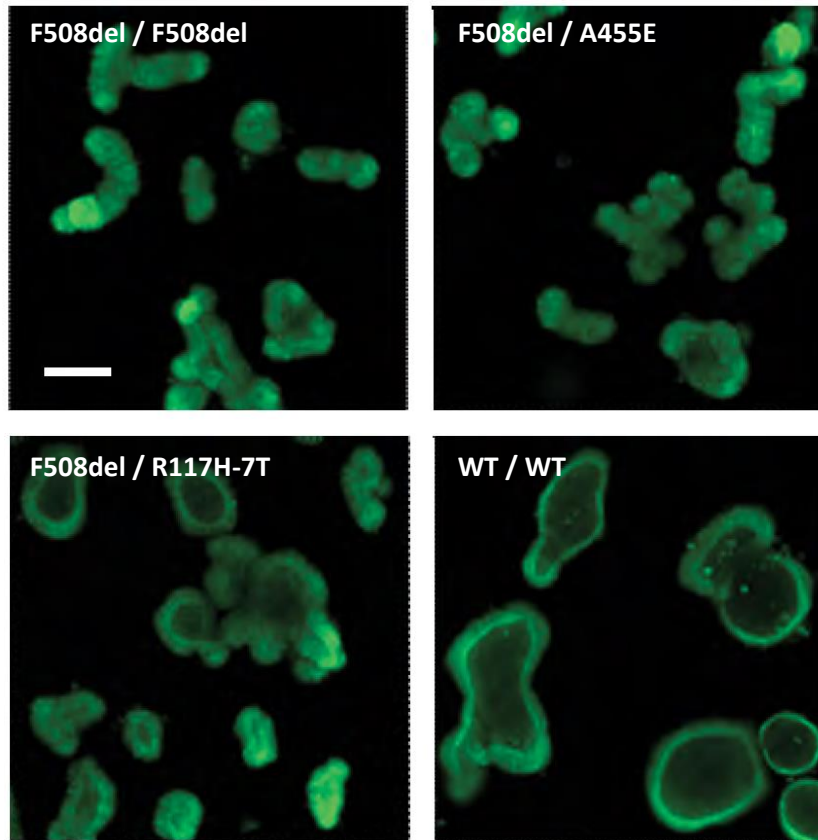
FLUID SECRETION IS FULLY CFTR-DEPENDENT

wt / wt

F508del / F508del



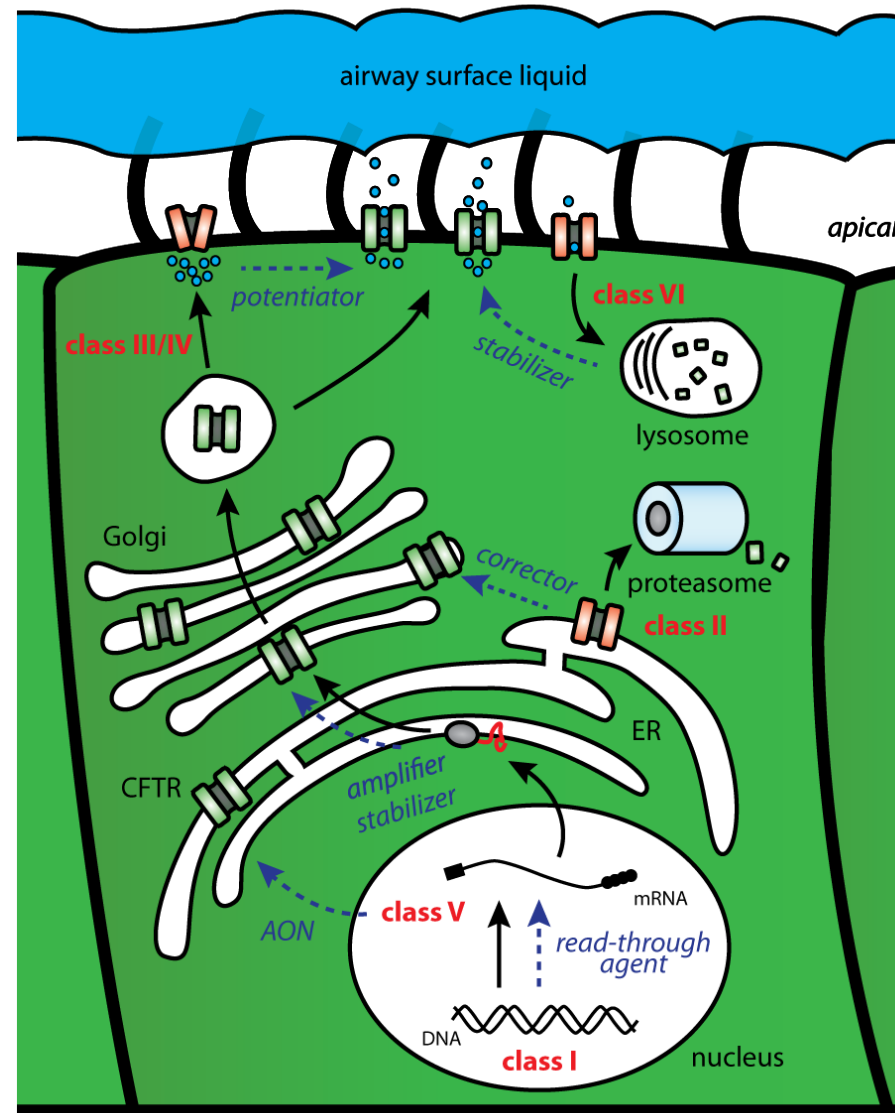
Different phenotypes of Healthy Controls and CF organoids



Steady-state lumen area discriminates between healthy and CF subjects

More than 2,000 *CFTR* mutations cause CF

- Class I:** Non-functional protein synthesis;
- Class II:** Impaired folding and trafficking;
- Class III:** Defective regulation/gating;
- Class IV:** Impaired conductivity;
- Class V:** Reduced levels;
- Class VI:** Reduced stability.



Available CFTR-restoring drugs:

KALYDECO®: potentiator

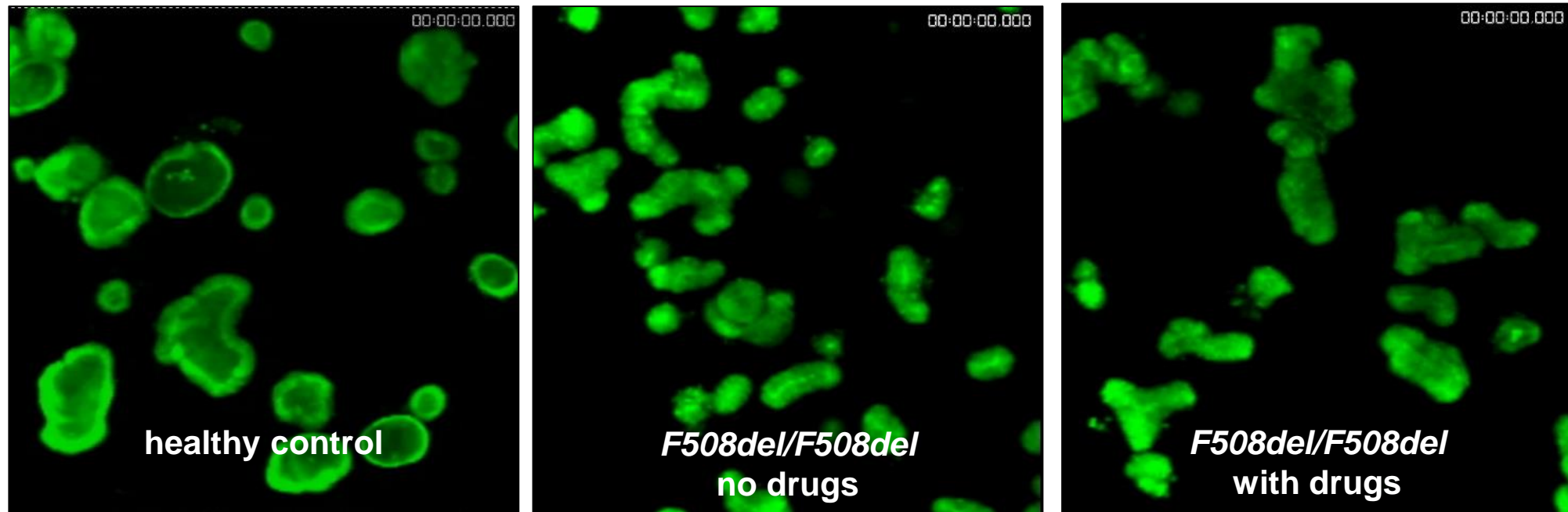
ORKAMBI®: potentiator/corrector



Effective for ~50% of CF subjects

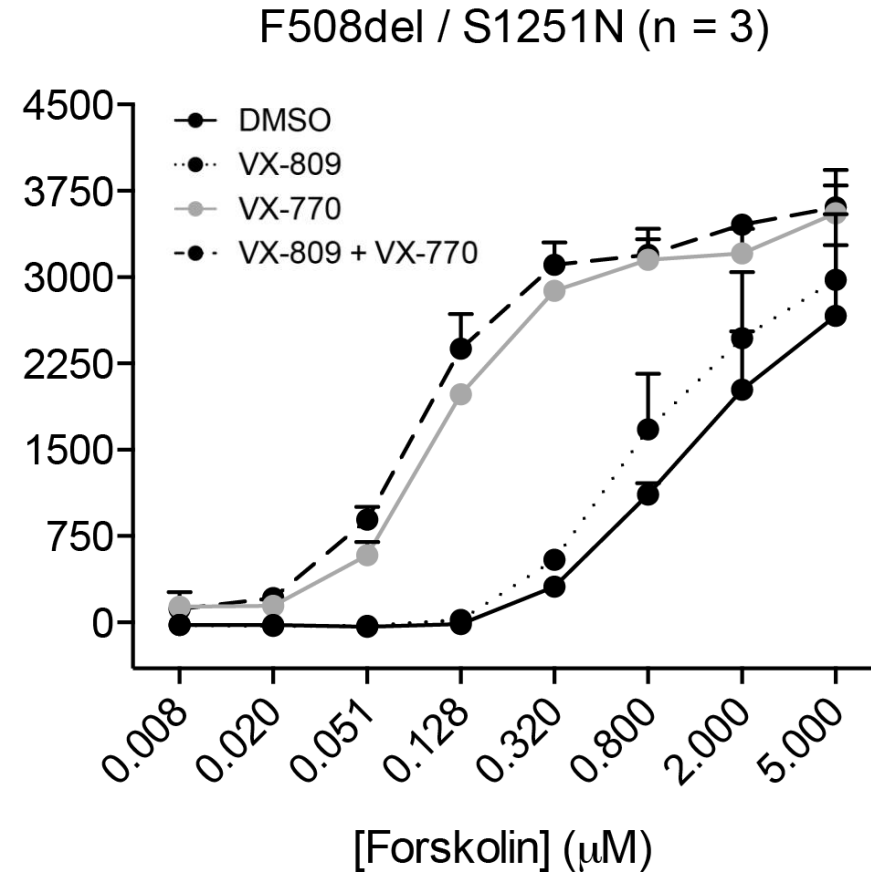
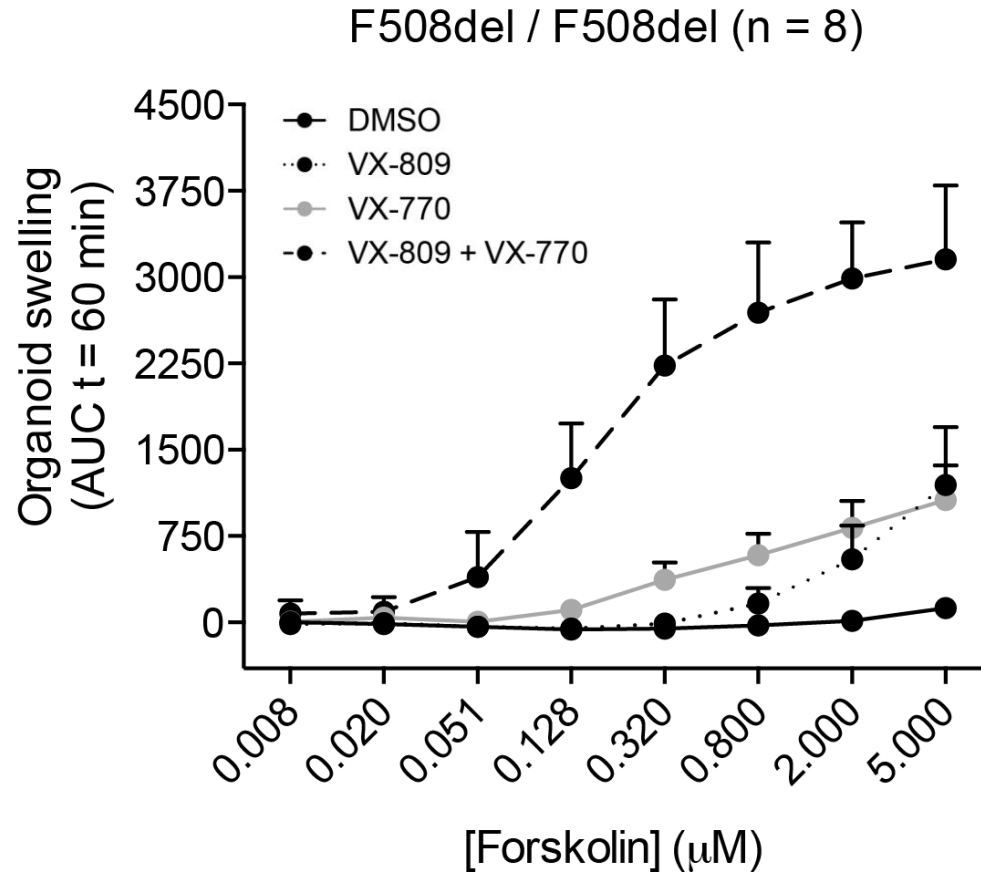
Epithelial fluid secretion assay

INDIVIDUAL ASSESMENT OF CFTR MODULATORS



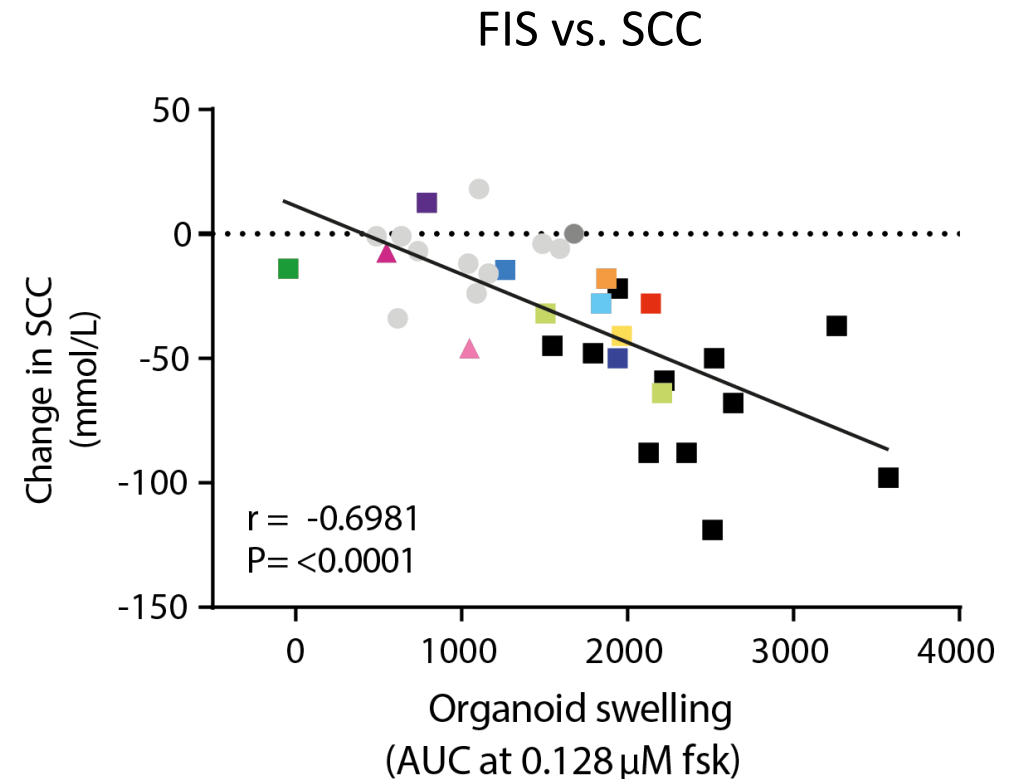
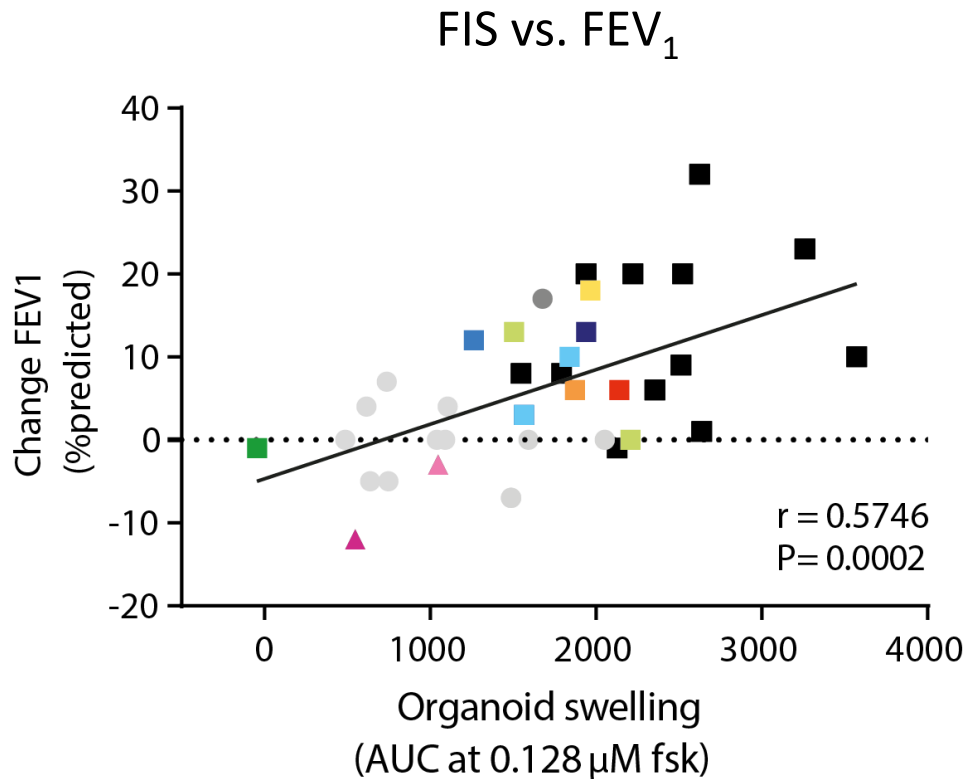
Forskolin-induced swelling (FIS) assay

RESIDUAL FUNCTION AND RESPONSE TO THERAPY



Pulmonary function (FEV) is a poor individual
drug response indicator

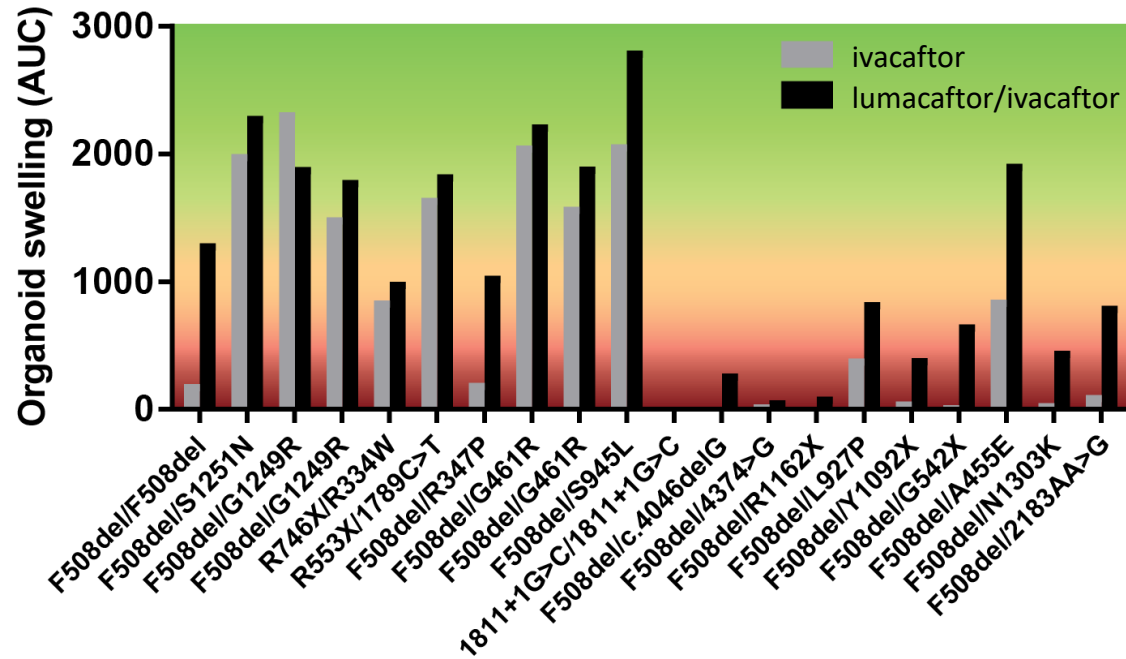
Correlation of organoid swelling with biomarkers



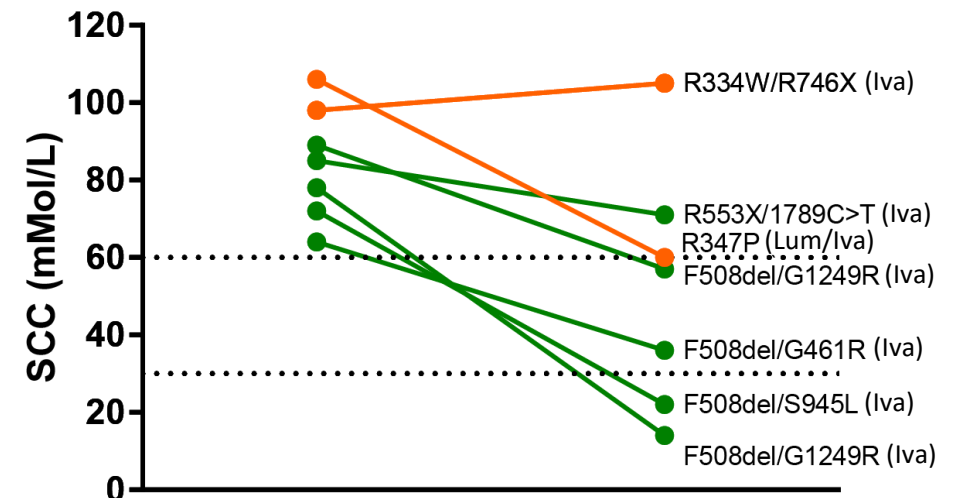
FIS responses correlate with clinical trial data

Selection of clinical responders using organoids

Organoid response of individual patients at 0.128 μ M Forskolin

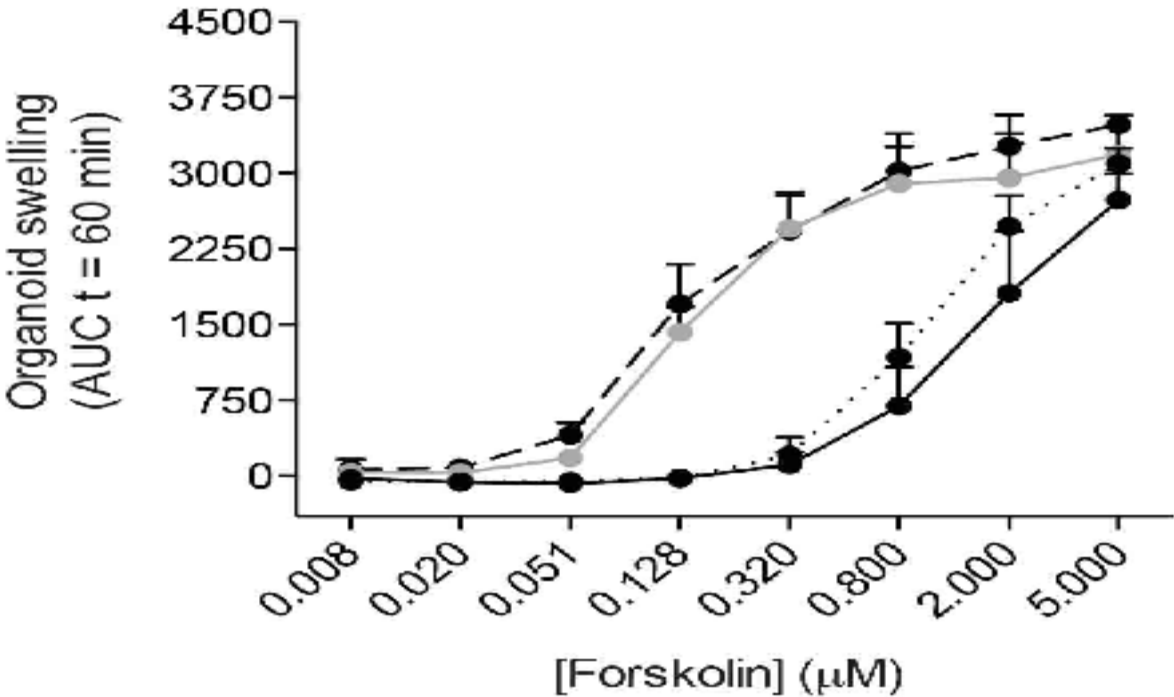


Individual SCC change after 4 weeks treatment



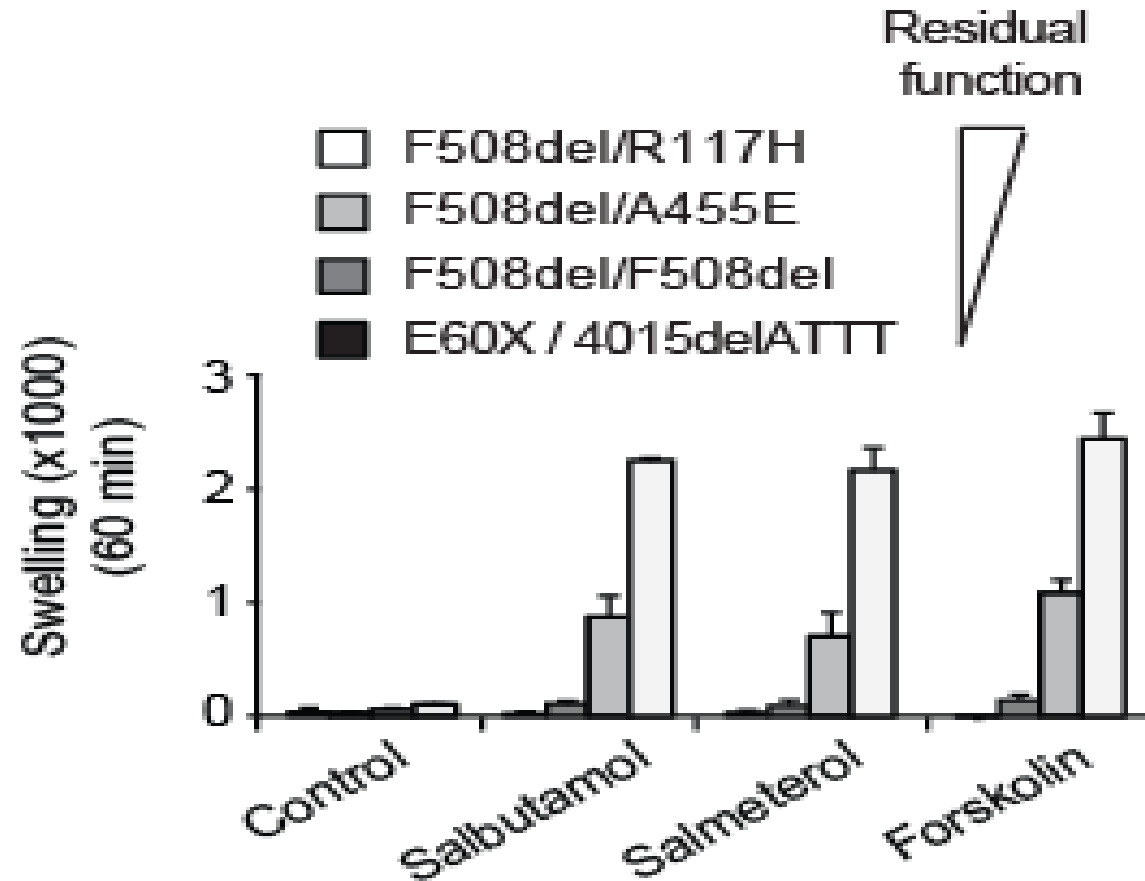
Proof-of-principle of organoid-based assays in selection of clinical responders to ivacaftor and orkambi with rare mutations

— DMSO
.... VX-809
— VX-770
-- VX-809 + VX-770



	Female		
	39		
	Baseline	4 weeks Ivacaftor	4 week washout
Weight	66.5	67.2	67.5
FEV1	52	65	59
Raw	144	95	125
SweatCL	89	57	91

Never forget what you already have.....



ABBA study



39 yr dF508/A455E

LF: 62% 74%

LG: 50kg 53kg

4 weeks oral salbutamol
3 x 4mg

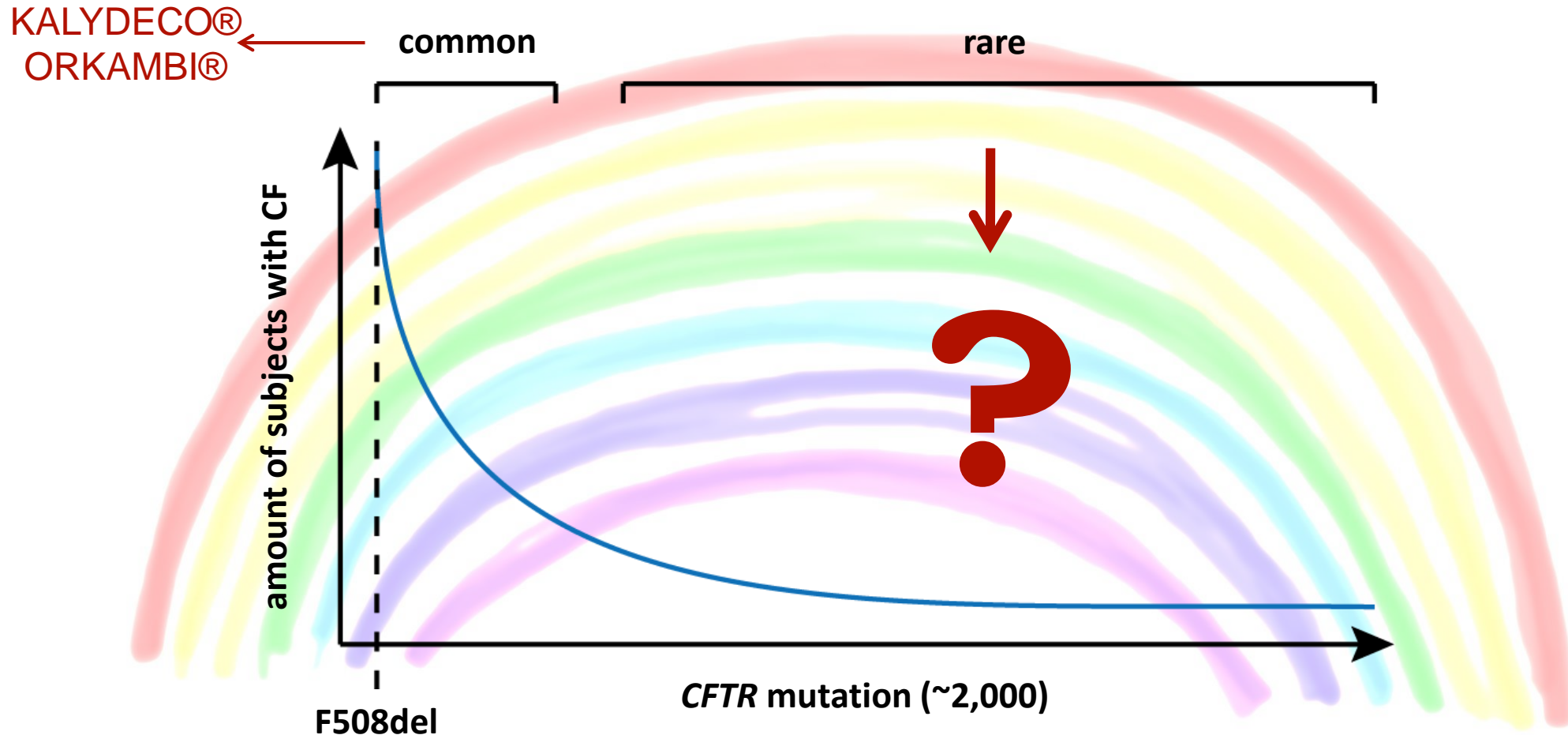
Conclusions part 1

Organoid swelling is a fully CFTR dependent readout

Organoid swelling is restored by CFTR modulators

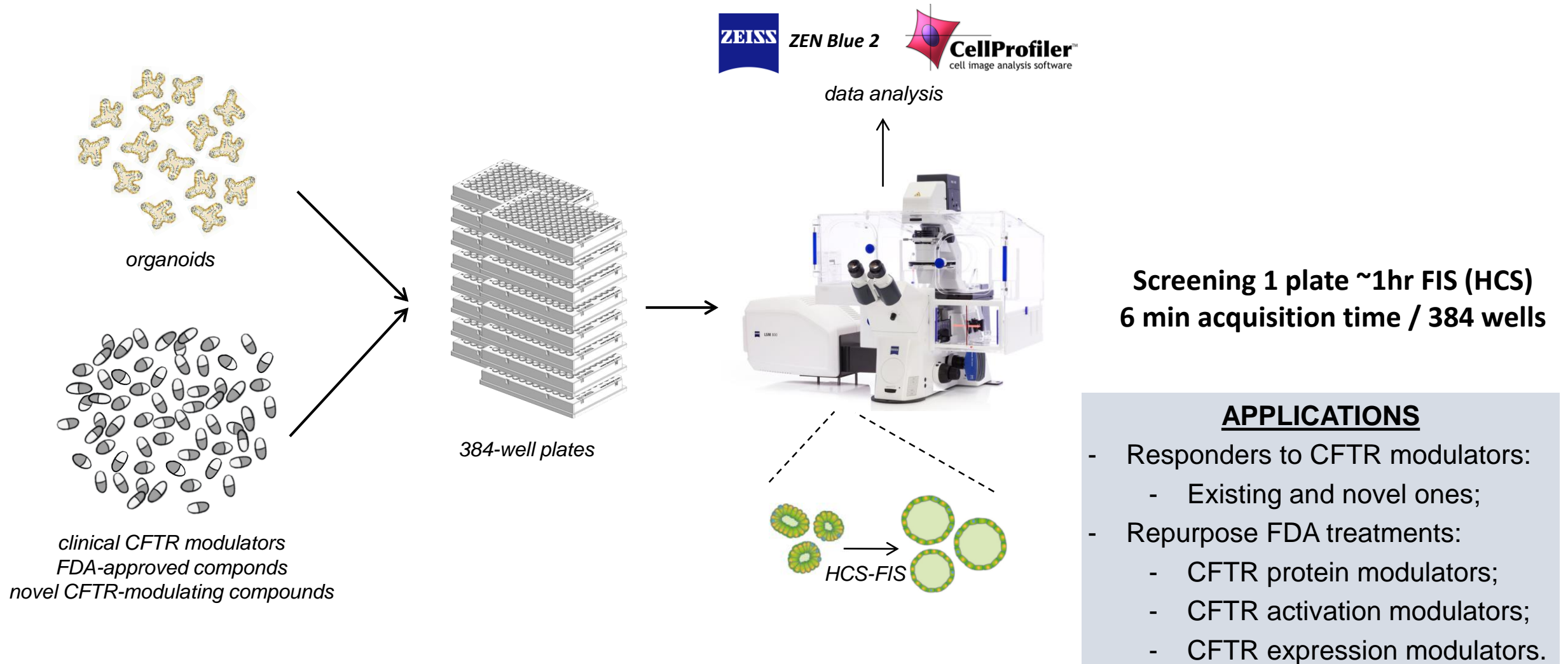
Organoid swelling correlates with individual clinical response indicators

Individual drug screening in subjects with rare mutations



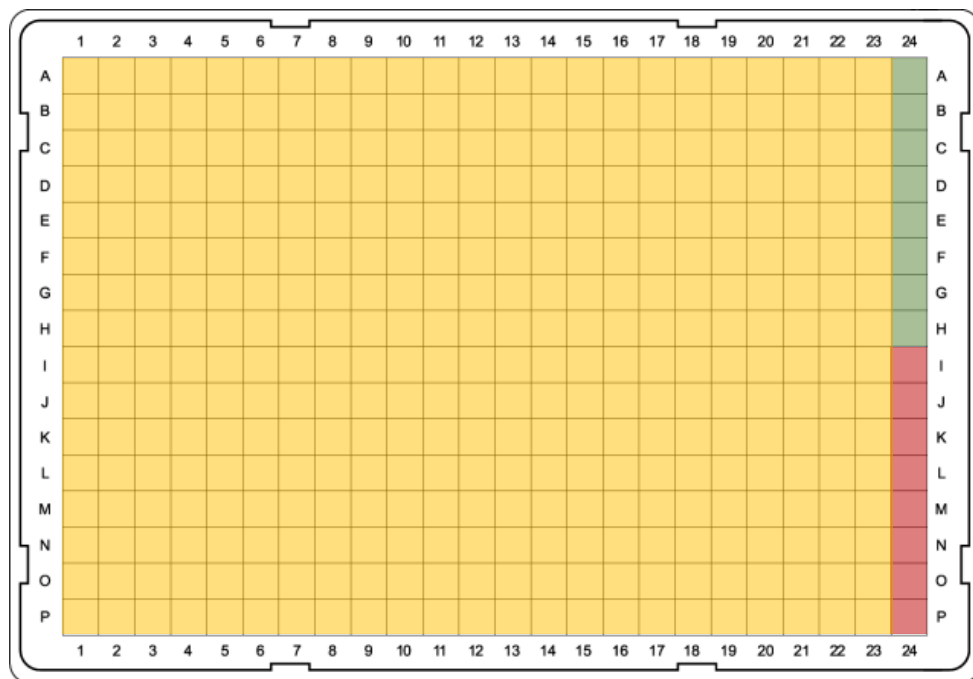
Identification of novel CFTR-restoring compounds for CF patients with an extremely rare *CFTR* mutation

High-content FIS screening assay (HCS-FIS)

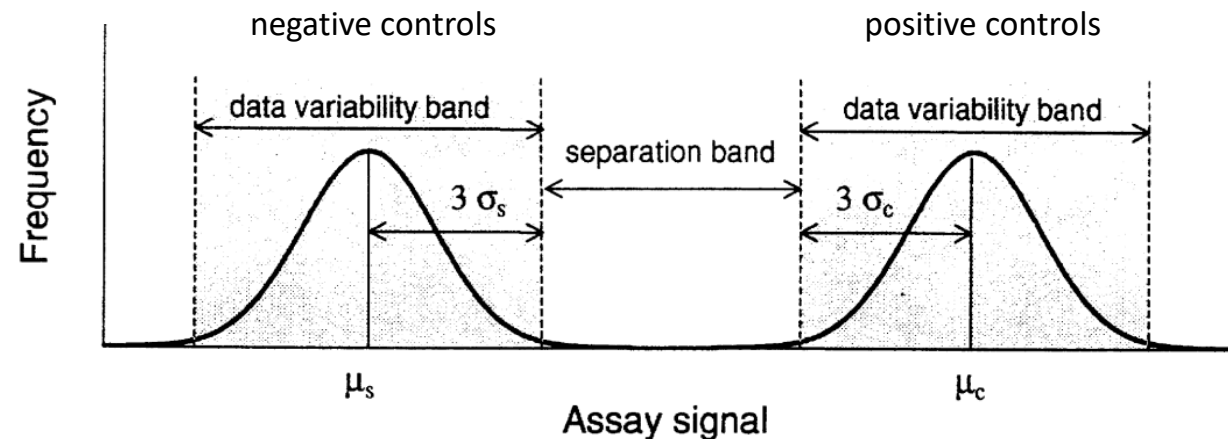


Quality of HCS-FIS screening platforms

384-well plate layout HCS-FIS

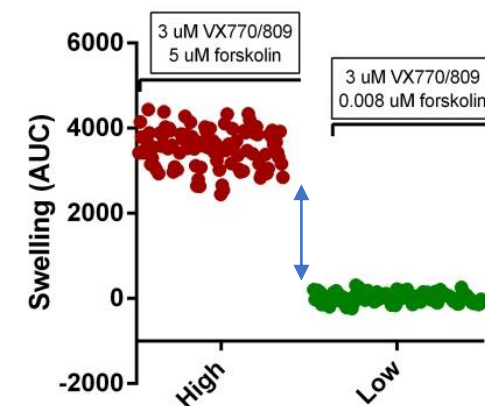


- 8 positive control samples;
- 8 negative control samples;
- 368 test samples.



mean (μ), standard deviation (σ)

- | | | |
|-------------------|---|------------------------|
| $1 > Z' \geq 0,5$ | → | excellent assay |
| $0,5 > Z' > 0$ | → | marginal assay (n = 3) |
| $Z' = 0$ | → | yes/no assay |
| $Z' < 0$ | → | unreliable assay |



HCS-FIS has average Z'-factor of 0,54



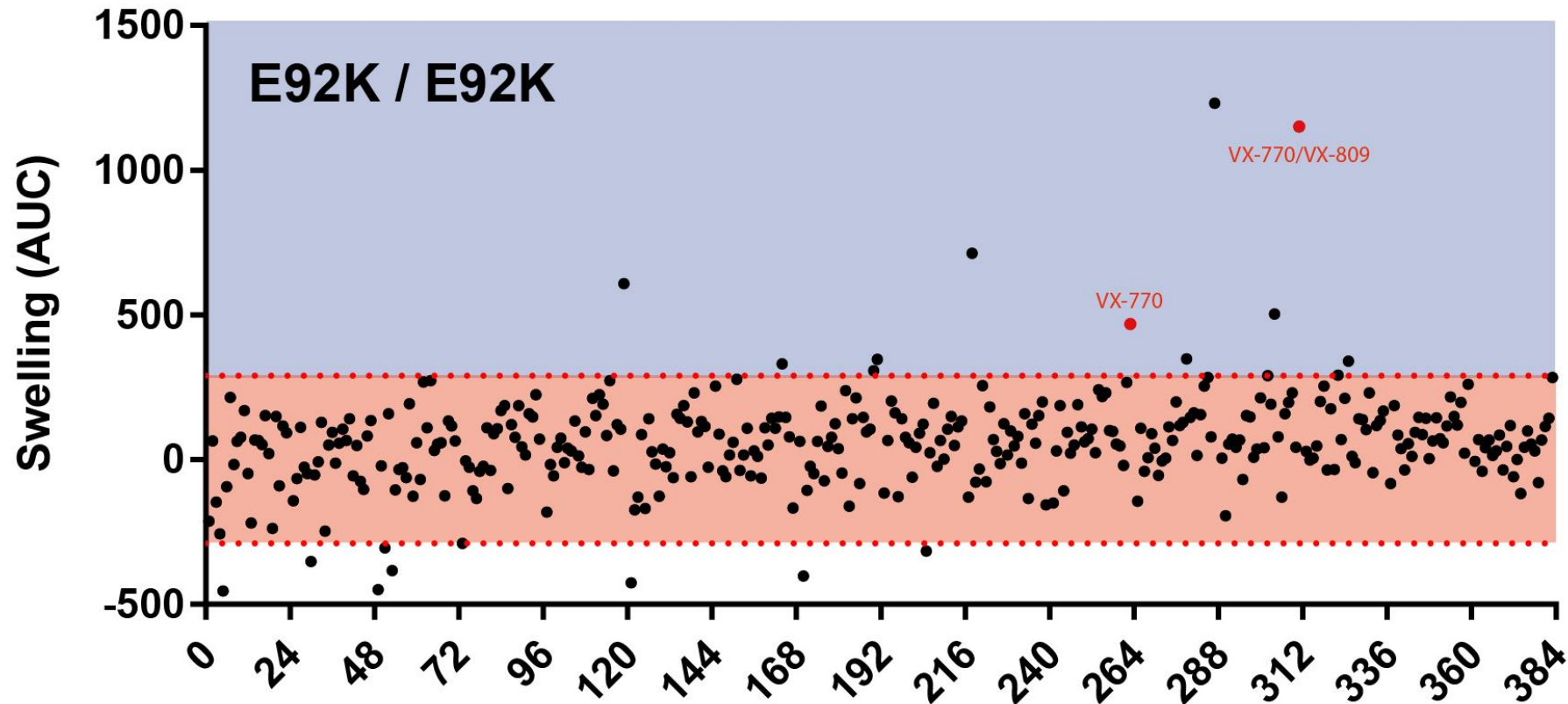
RAD
TECHNOLOGY

MULTIFLO|FX
washer dispenser

Biotek

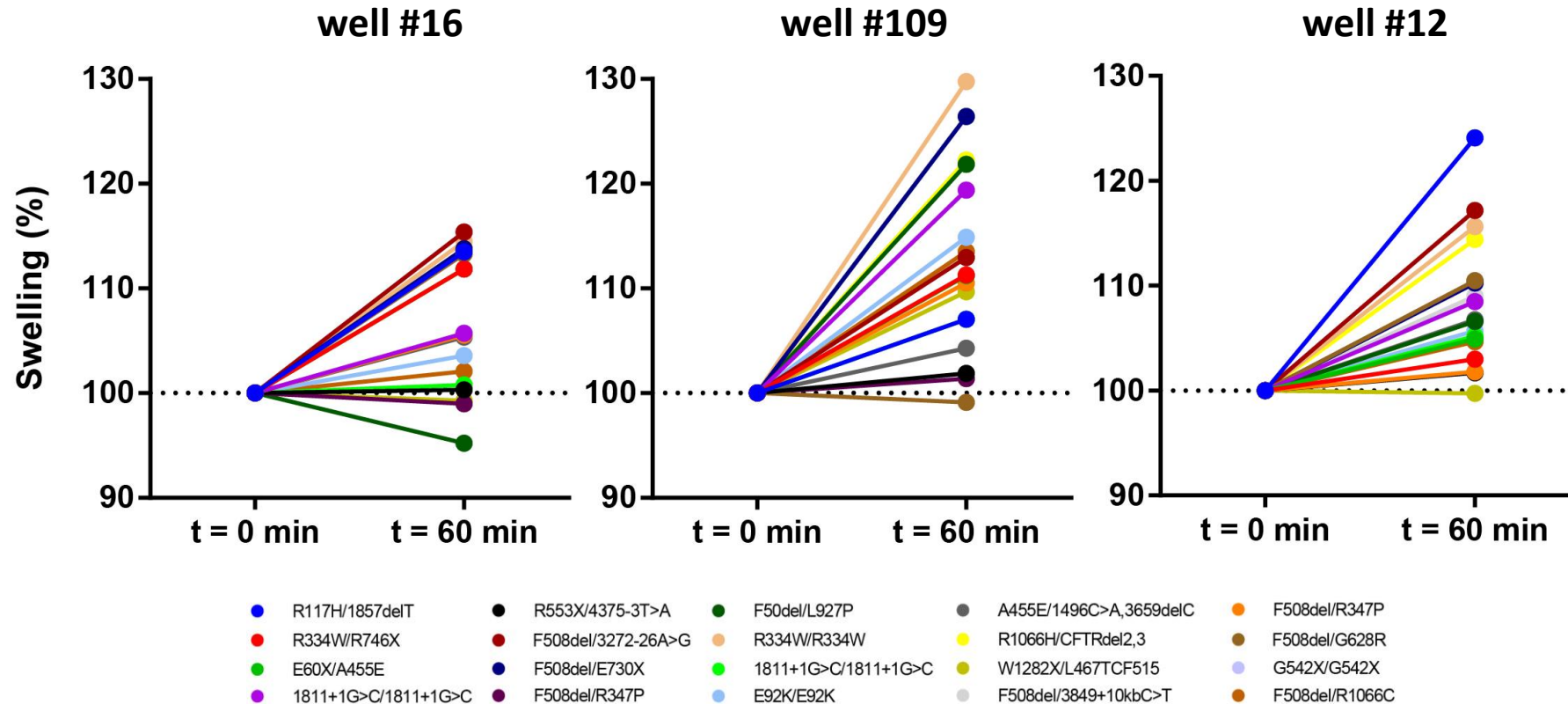


Identifying HTs using HCS-FIS screening platform



Repurposing of existing clinically available drugs is a very promising strategy to identify novel CFTR-restoring compounds

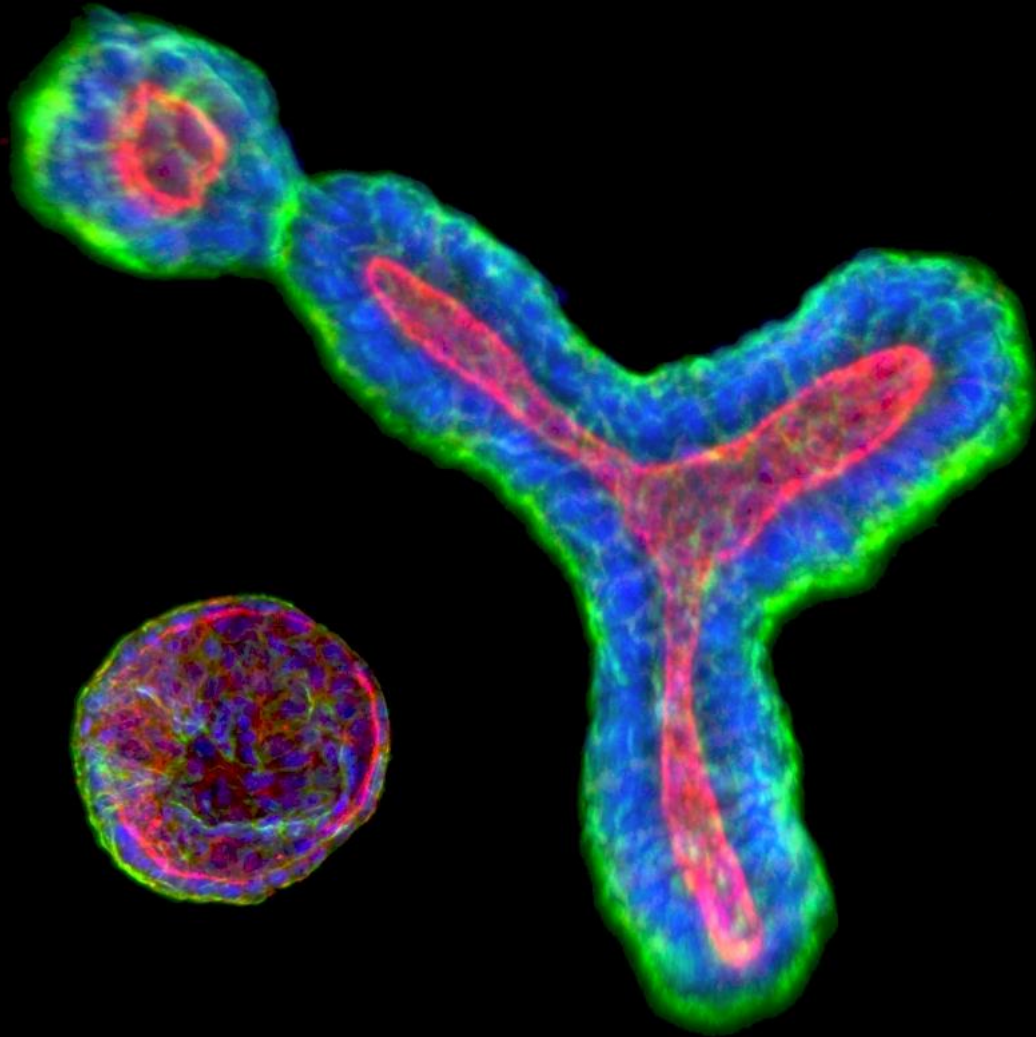
Drug responses are CFTR genotype specific



Overall conclusions

- **A first example that prospective drug testing using a patient-derived adult stem cell biobank can guide clinical decision making;**
- **Fully CFTR-dependent *in vitro* readout translates to (individual) clinical phenotypes;**
- **We made fast progress – robustness of system.**

Acknowledgements



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