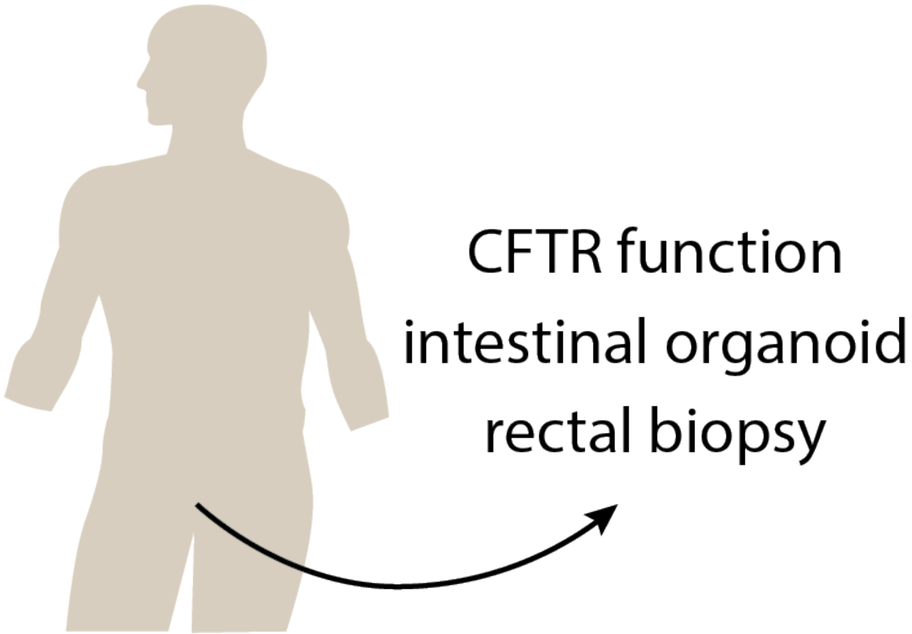
Children's Hospital

The role of intestinal organoid function for evaluation of CFTR modulators

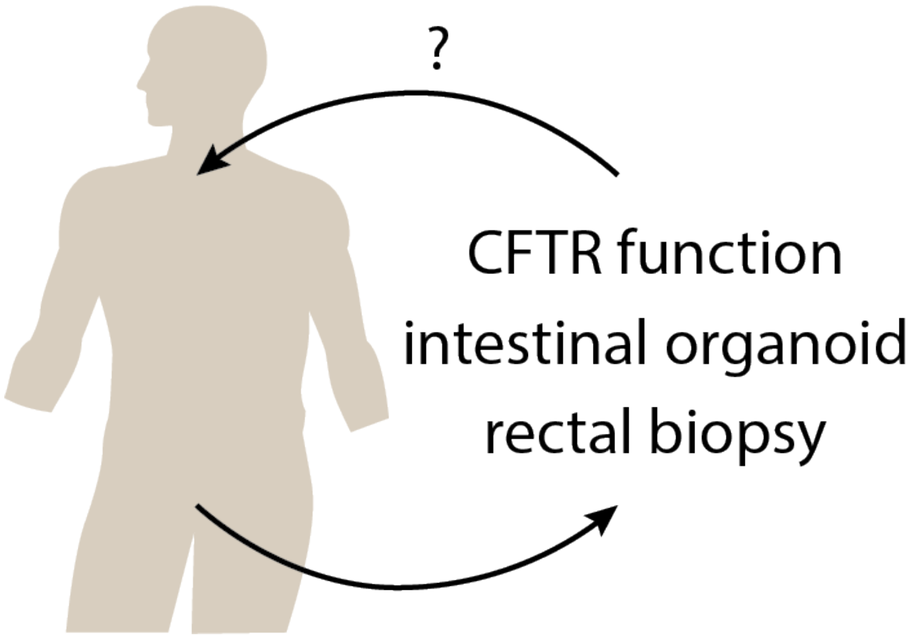
Laboratory of Translational Immunology

University Medical Center Utrecht

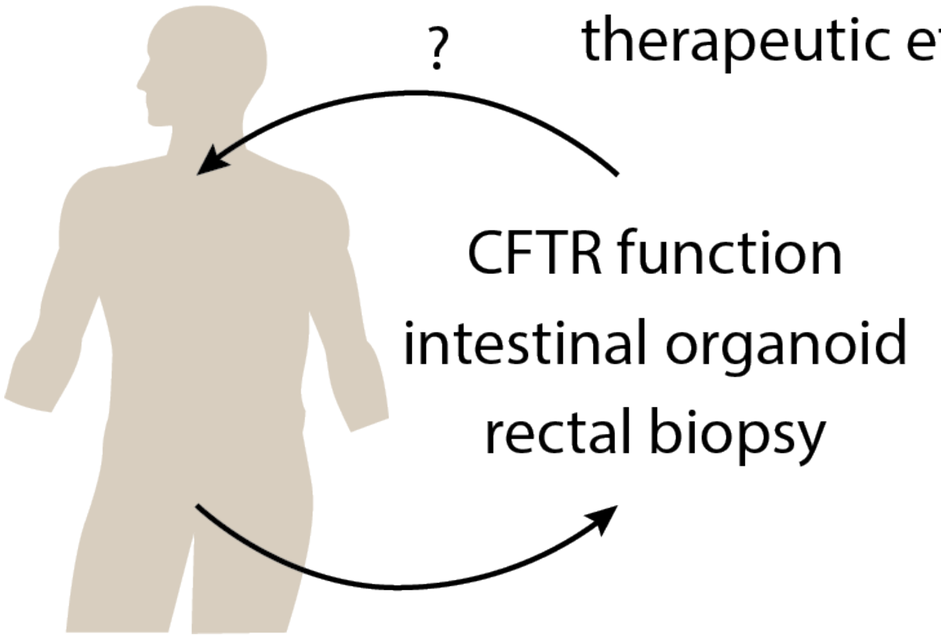
Intestinal organoids for CF disease modeling



Intestinal organoids for CF disease modeling



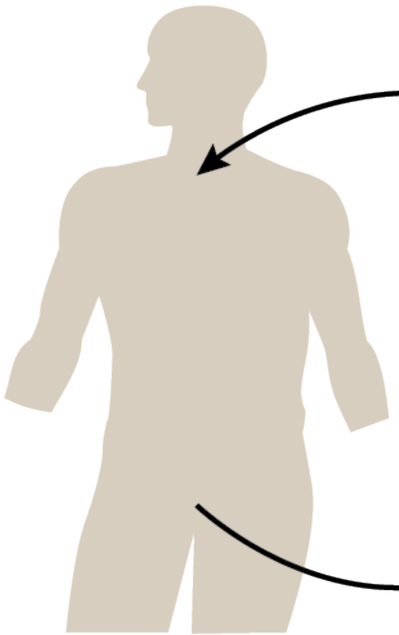
Intestinal organoids for CF disease modeling



disease progression - CFTR residual function

therapeutic efficacy - in vitro response to drugs

Intestinal organoids for CF disease modeling



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disease progression - CFTR residual function

therapeutic efficacy - in vitro response to drugs

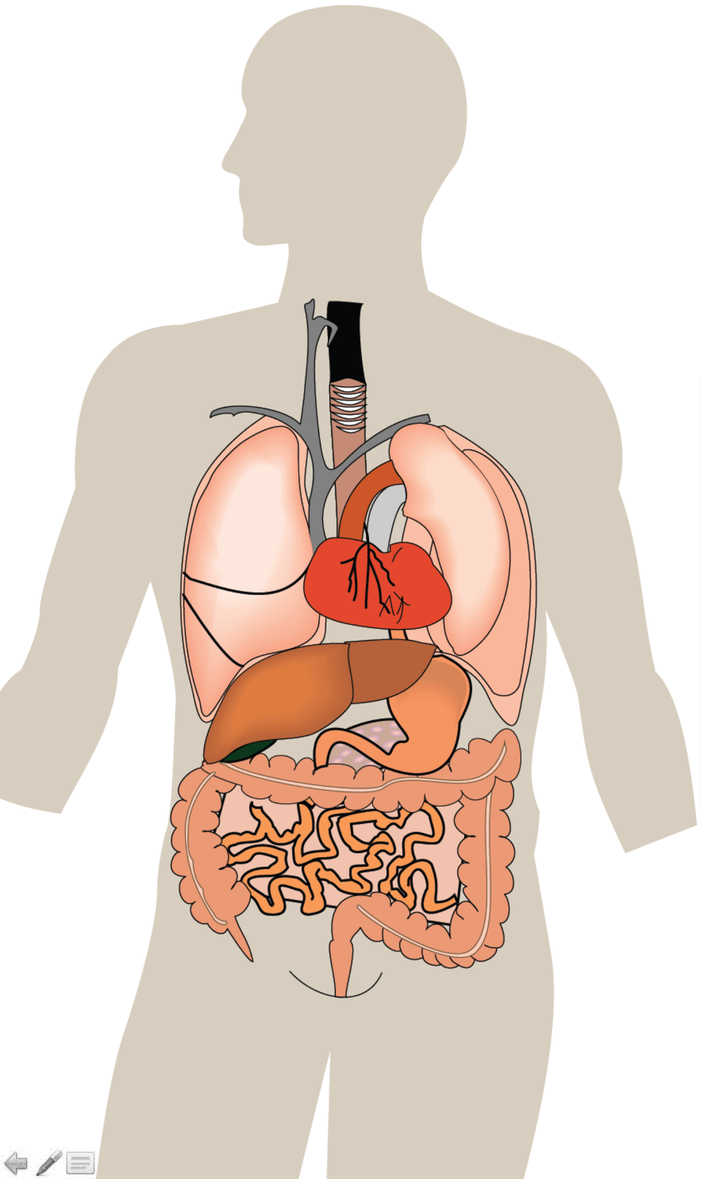
CFTR function

intestinal organoid ⟷ CFTR genotyping

rectal biopsy

airway primary cultures

(Individual) drug efficacy



+ CFTR protein restoring drugs
(VX770 / VX809)

(Individual) efficacy

Pharmacodynamics
What does a drug do to a body?

Pharmacokinetics
What does a body do with a drug?

CFTR genotyping
Ex vivo primary cells

Benefits of organoid cell cultures

- Rectal biopsy: relatively easily accessible (painless, w/o hemorroids)

- Robust and ‘easy’ culture: ~250 donors (40 CFTR genotypes) - start of shipped biopsies within 3-4 days - self-organize

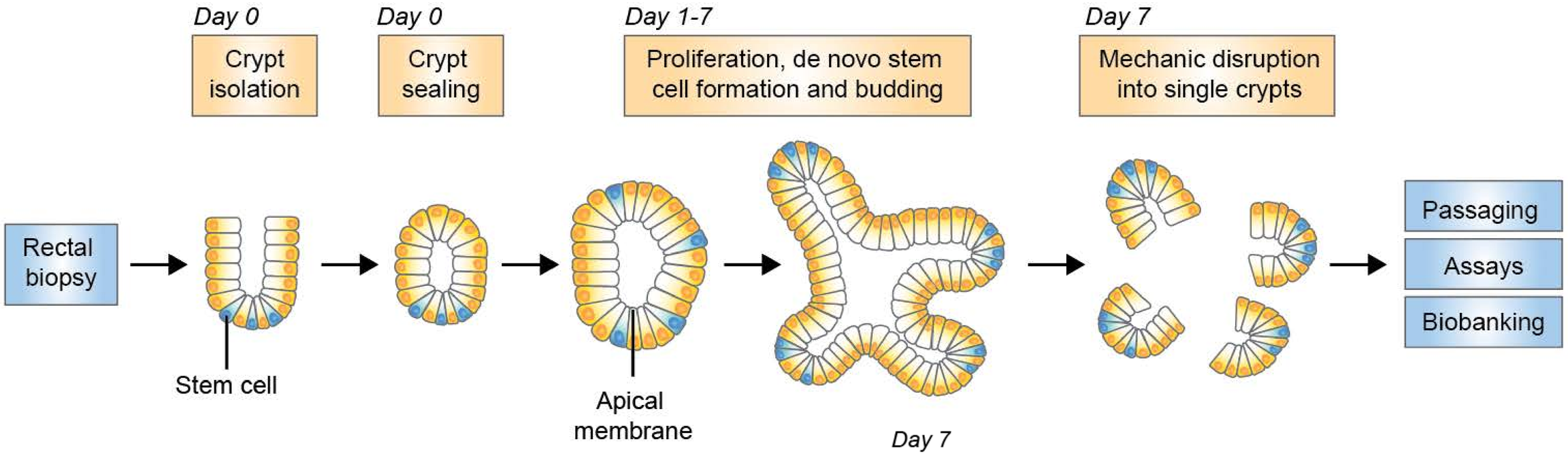
- Stem cells: expansion and biobanking

- New technology

- Impact of ex vivo culture and culture components variability

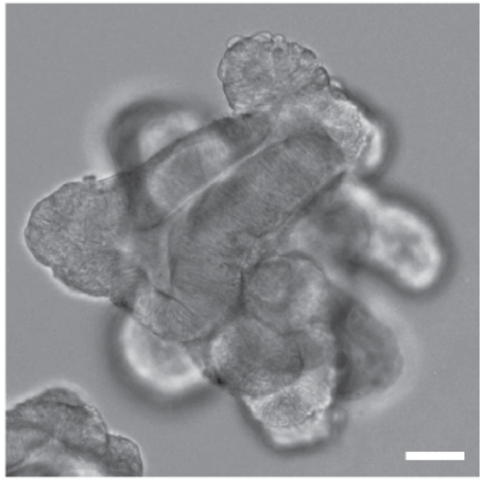
- Intestinal origin

Intestinal organoids



Day 0

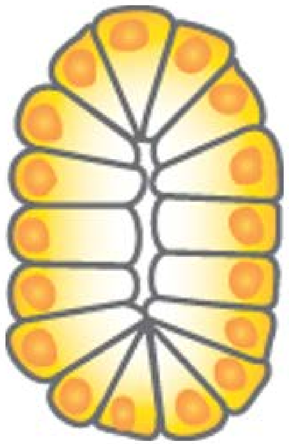
Day 7



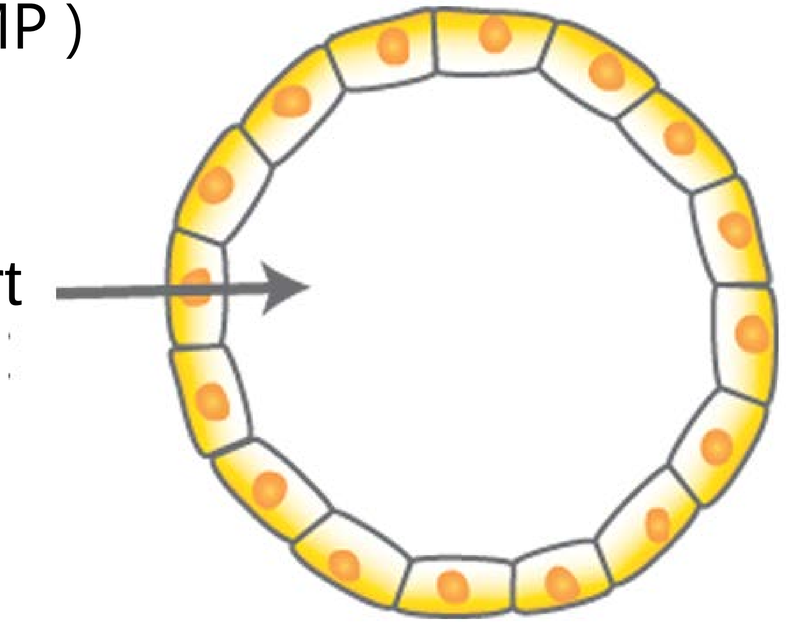
Dekkers et al Nature Medicine, 2013
Dekkers *et al*. Rare Diseases, 2013

cAMP-driven fluid secretion in organoids is CFTR-dependent

Forskolin /
Cholera toxin +
(cAMP)

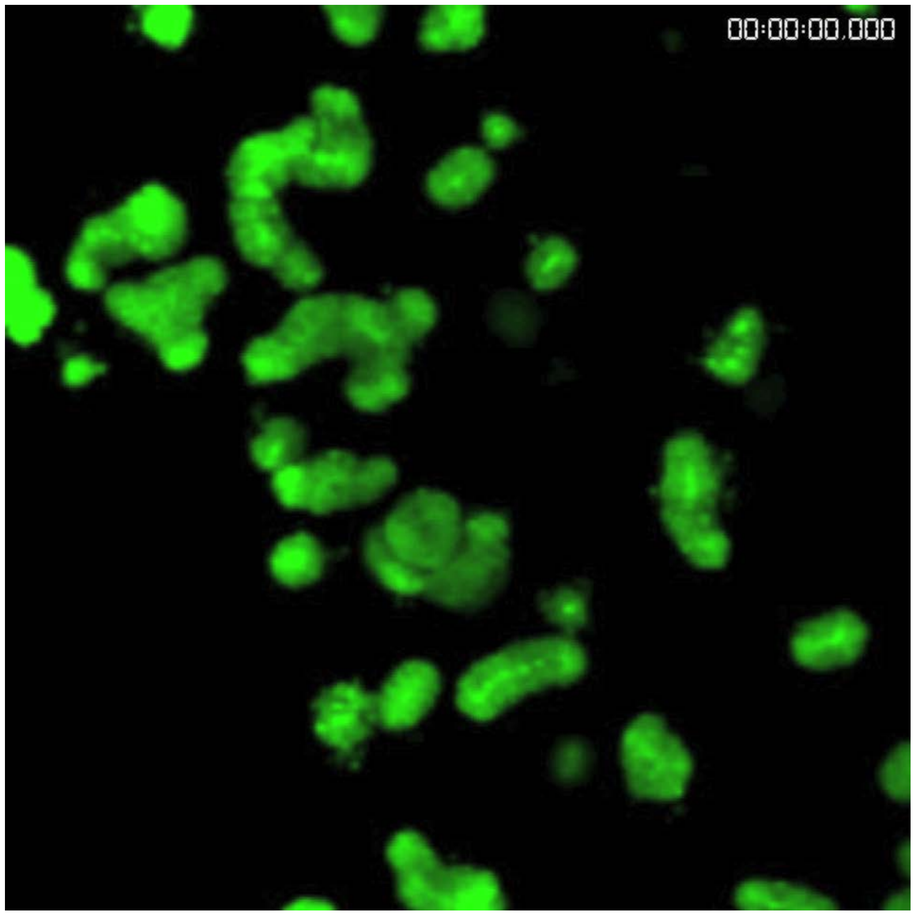


Fluid transport

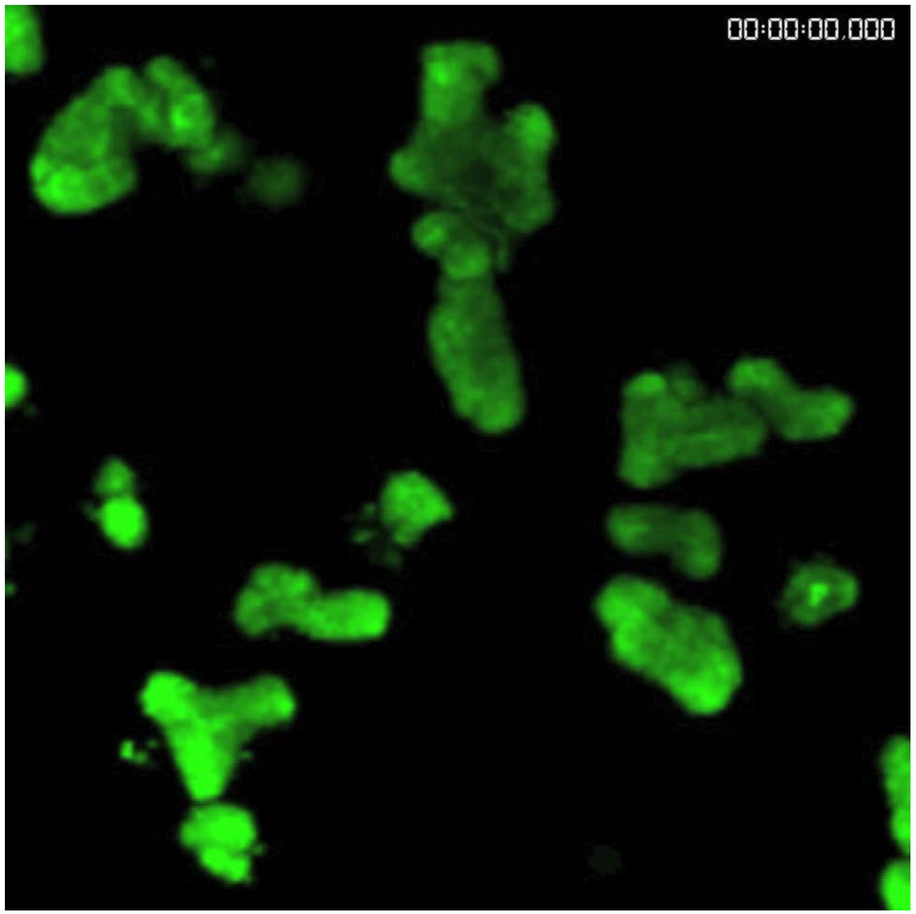


CFTR-directed therapy in organoids

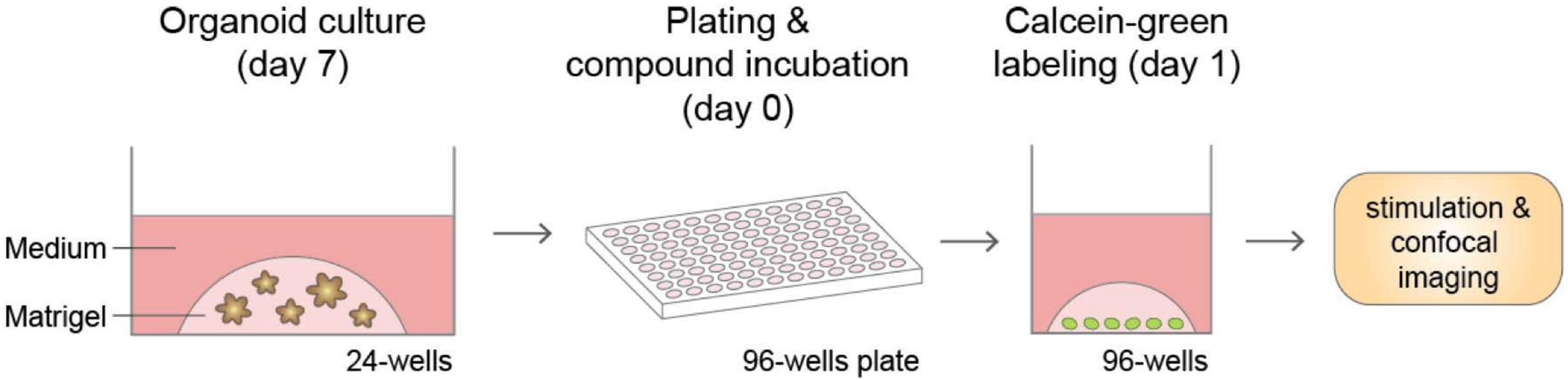
F508del / F508del



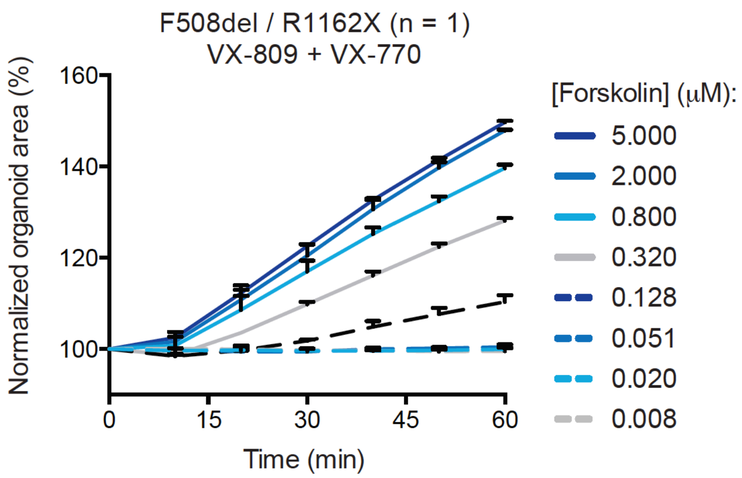
F508del / F508del +
CFTR directed therapy

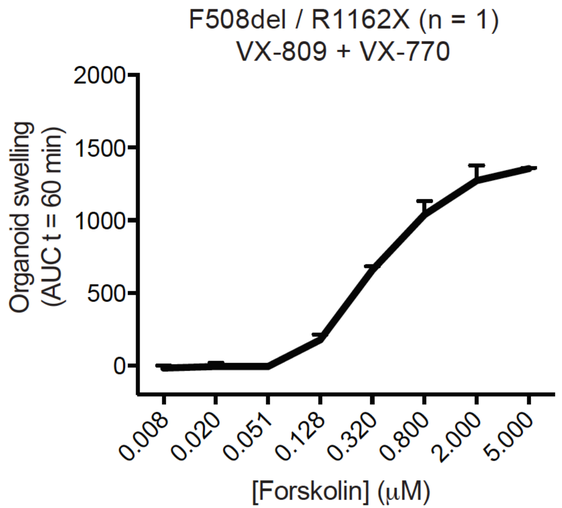


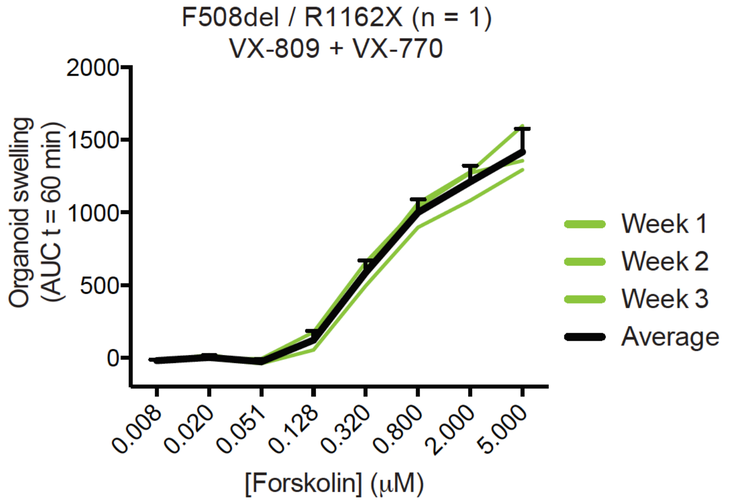
CFTR function measurement: FIS



Typing a patient function using organoids



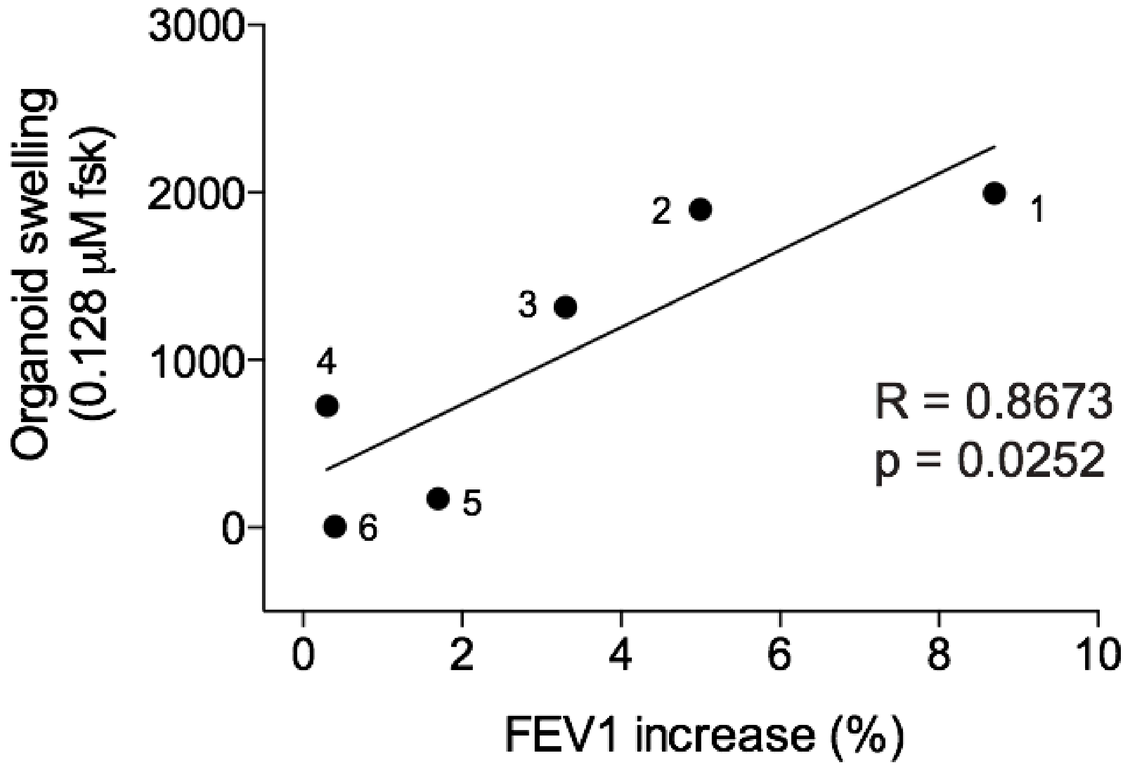




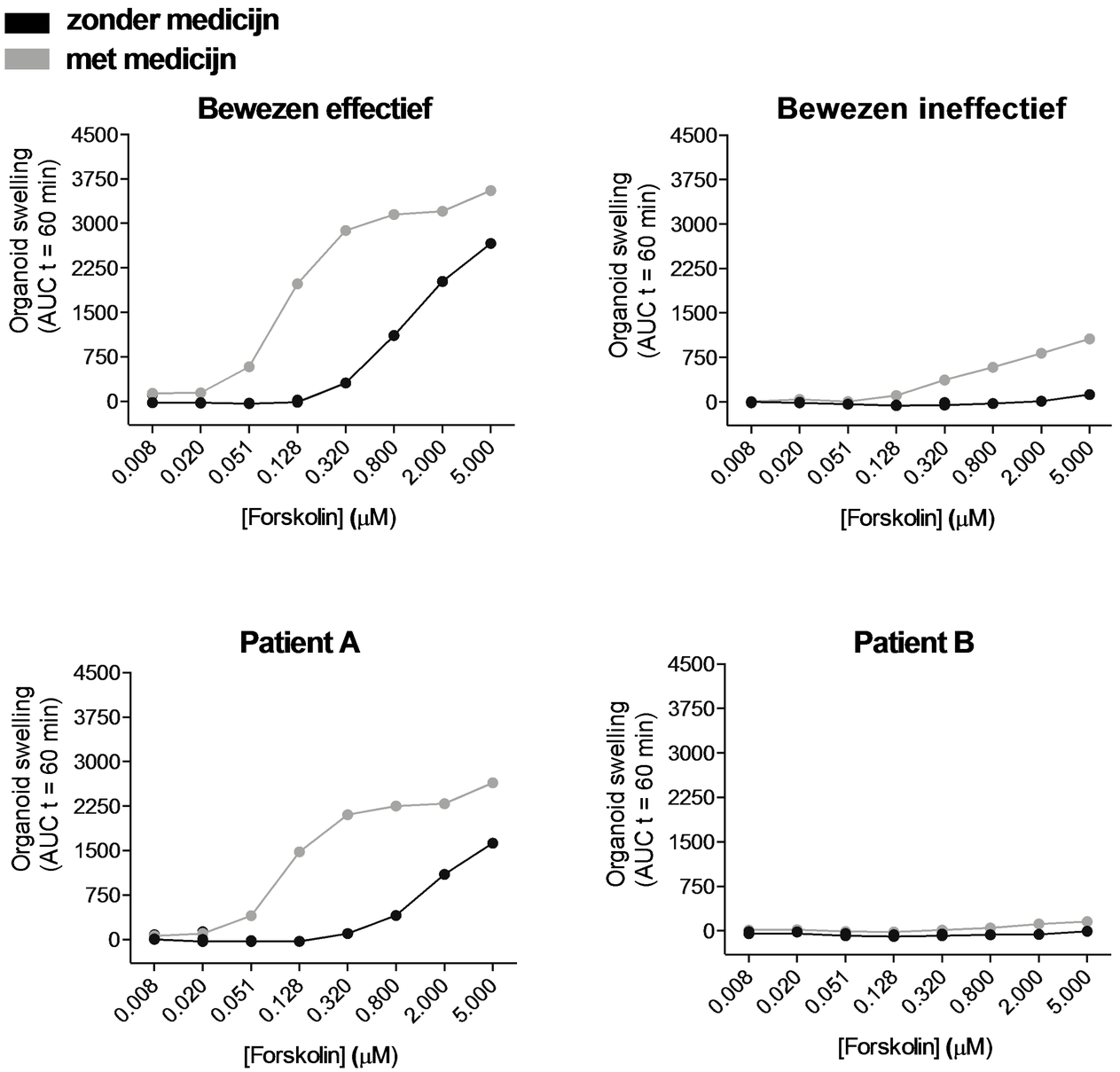
8 x 3: 24 wells
4 drug conditions
(-,770, 809, 770+809)
96 wells: 1 plate

Organoid responses and FEV1 (published data)

	Treatment	Phase	*CFTR* genotype	Lung function increase[c]
1	VX-770	III	S1251N / other	8.7% (p<0.0001)
2	VX-770	III	R117H-5T/7T / other	5.0% (p=0.01)
3	VX-809 + VX-770	III	F508del / F508del	3.3% (p<0.0001)
4	VX-809 + VX-770	II	F508del / other[b]	0.3% (NS)
5	VX-770	II	F508del / F508del	1.7% (NS)
6	VX-809	IIa	F508del / F508del	0.40% (NS)



Identifying potential responders



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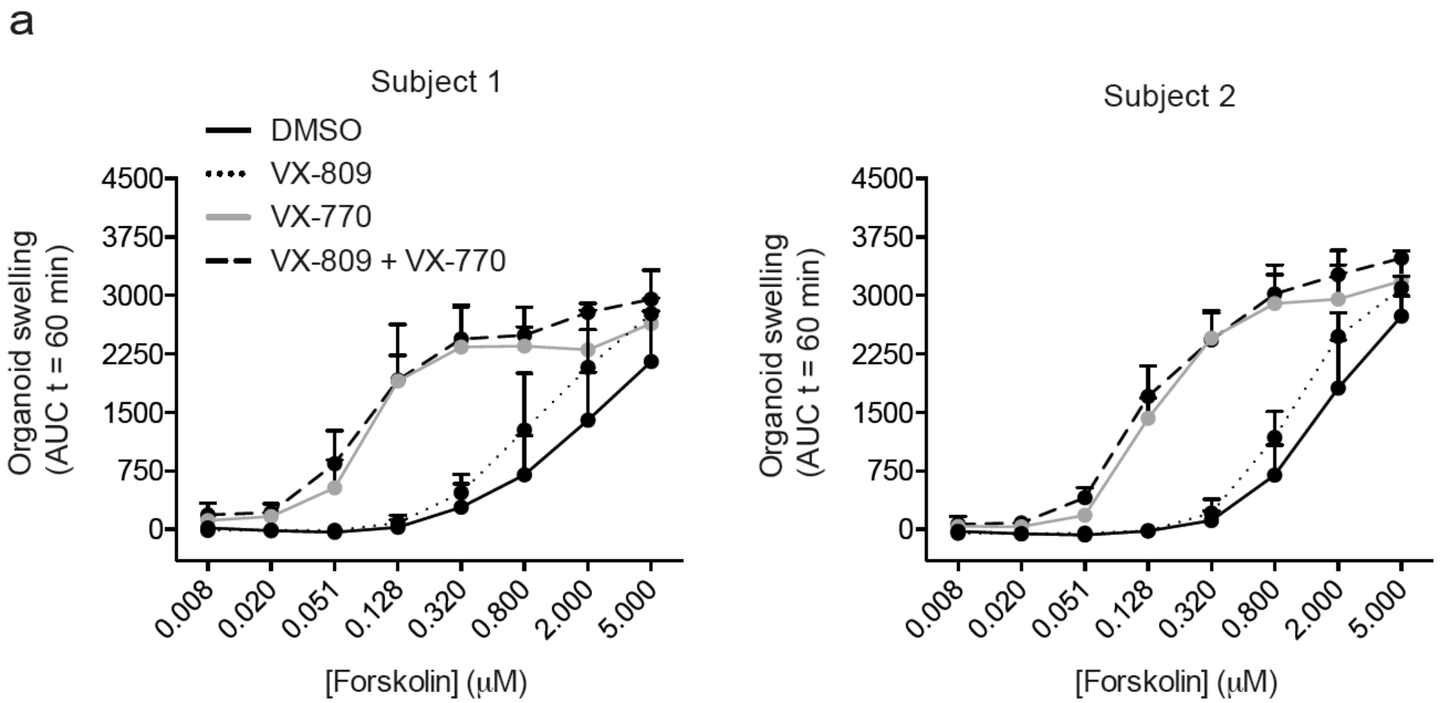
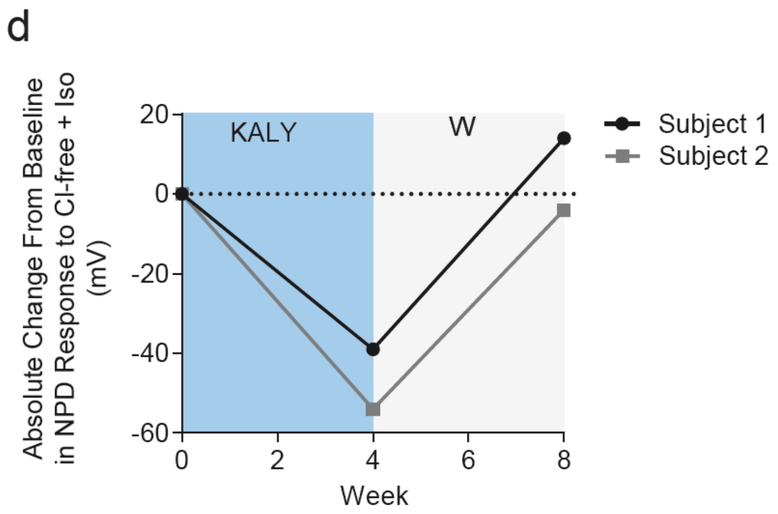
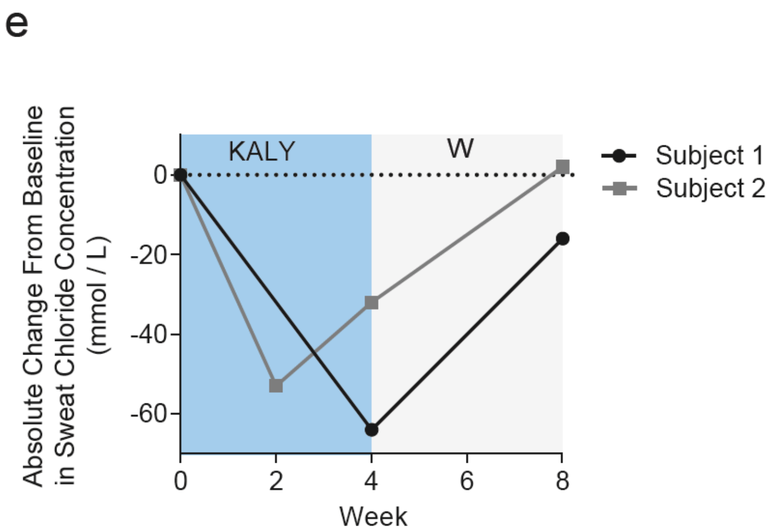
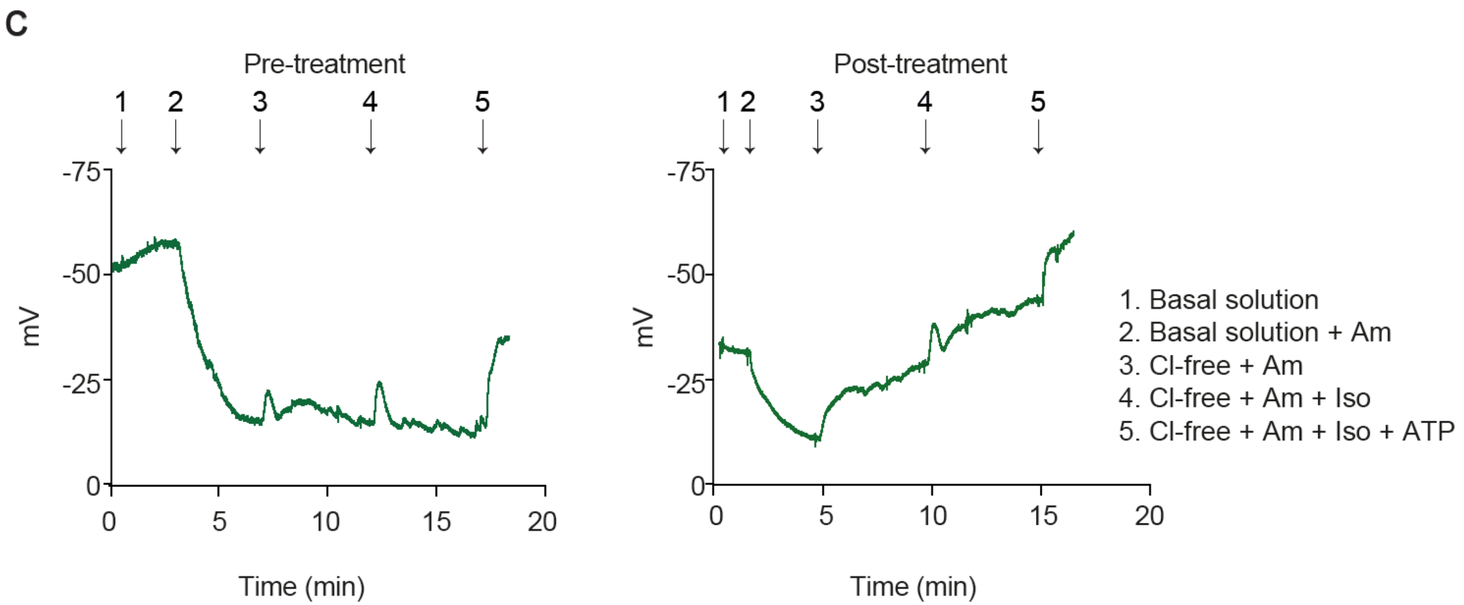

a
Subject 1
DMSO
VX-809
VX-770
VX-809 + VX-770
Organoid swelling (AUC t = 60 min)
4500
3750
3000
2250
1500
750
0
0.008
0.020
0.051
0.128
0.320
0.800
2.000
5.000
[Forskolin] (μM)
Subject 2
Organoid swelling (AUC t = 60 min)
4500
3750
3000
2250
1500
750
0
0.008
0.020
0.051
0.128
0.320
0.800
2.000
5.000
[Forskolin] (μM)

CFTR biomarker response is very consistent

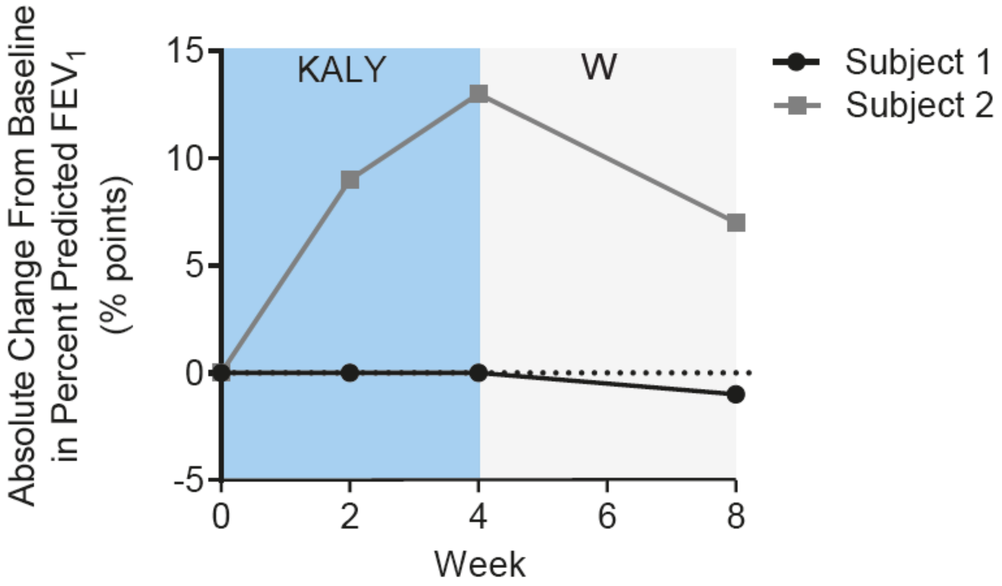




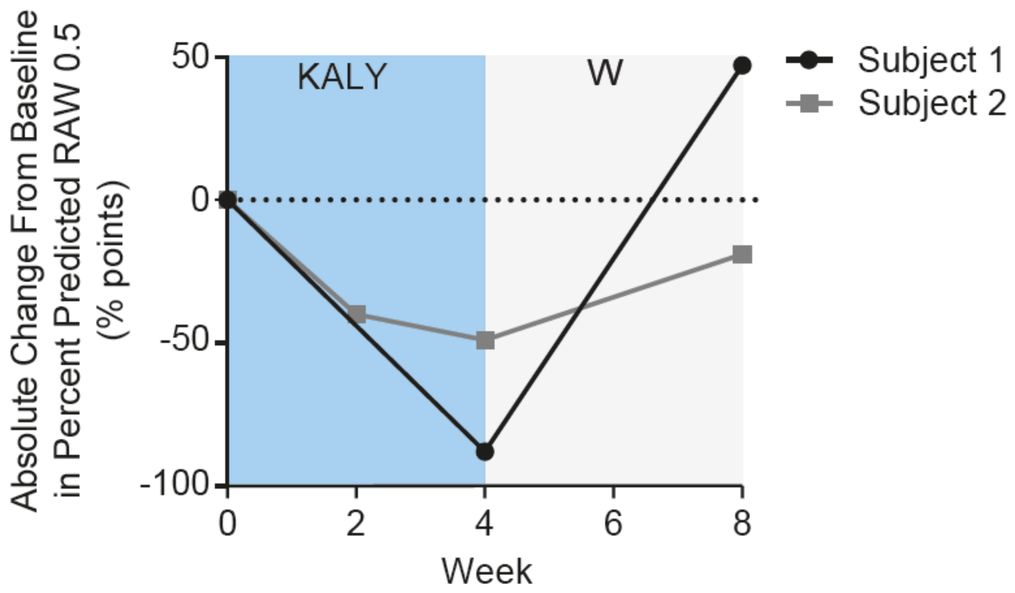


Airway parameters

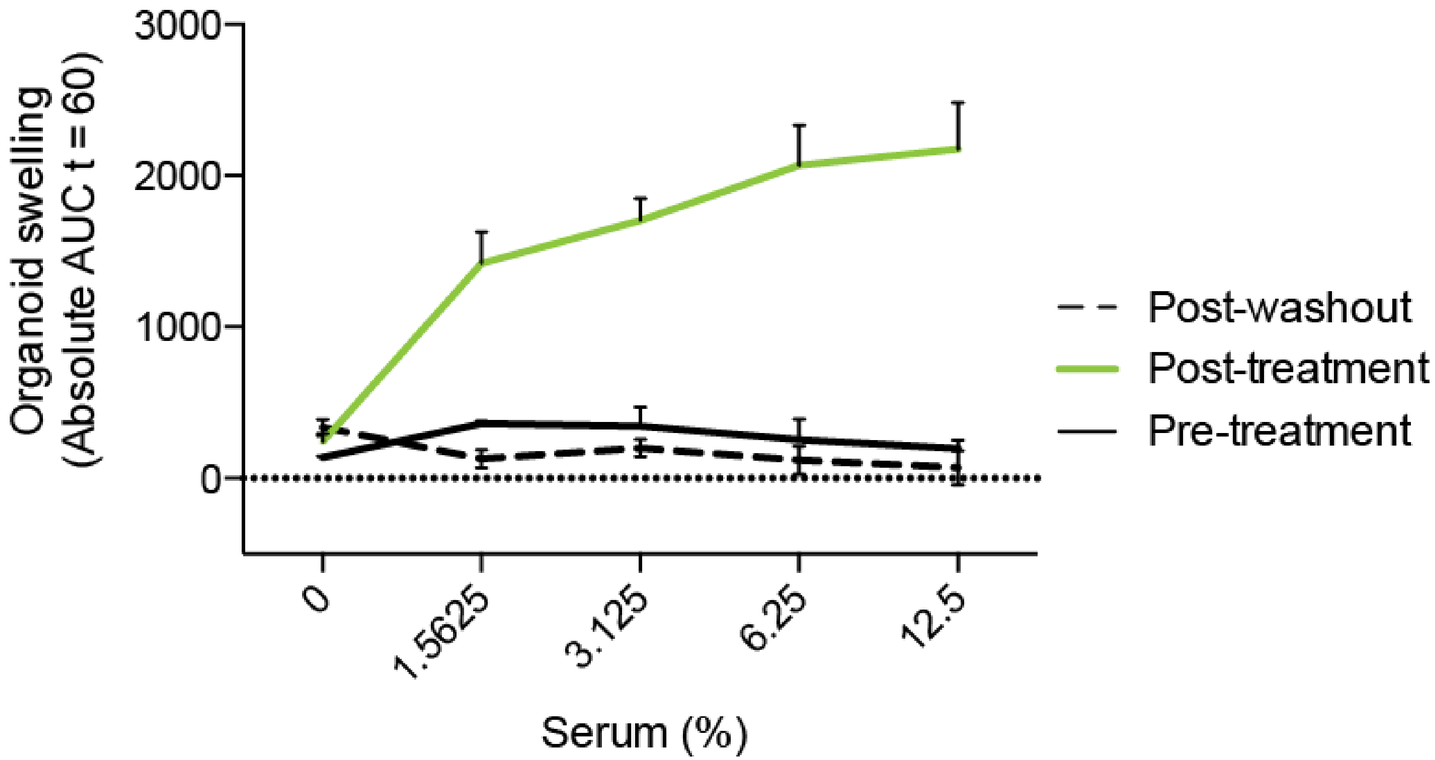
FEV1



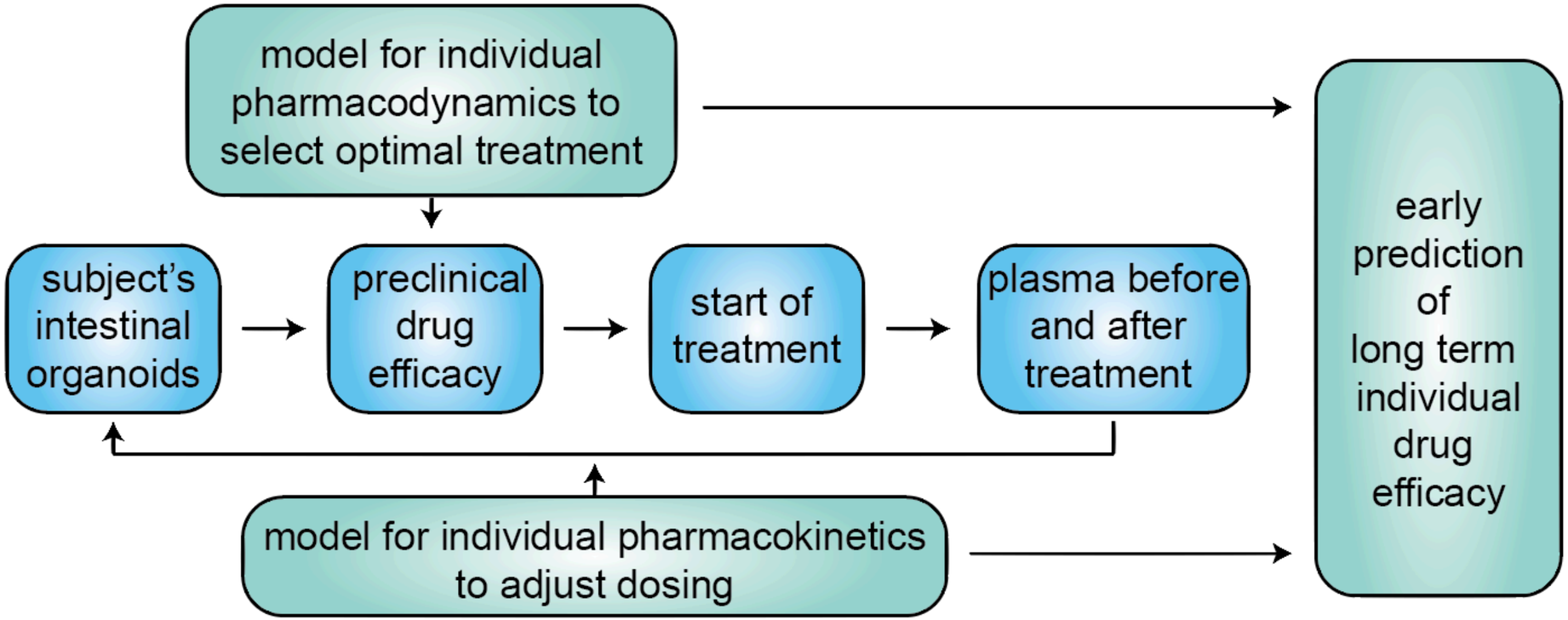
RAW0.5



Pharmacokinetic parameter: VX770 in blood



Intestinal organoids and individual drug readout



Conclusions and Discussion

Characterization of unknown genotypes (rare mutations)

additional tool (preclinical / serum endpoint)
standardization (shipping to central lab is possible)
grey zone?

Genotypes vs individuals

exclude subjects from treatment?
can we increase individual drug efficacy through dosaging?
future: identify optimal combination?

How to define a clinical responder?

- relation between in vitro and in vivo CFTR biomarkers >
(in vitro) CFTR biomarker and multi-origin disease phenotype
- prophylactic treatments or not?