université de BORDEAUX

13èmes JS
de la SFM (2019)

C·H·U Hôpitaux de Bordeaux

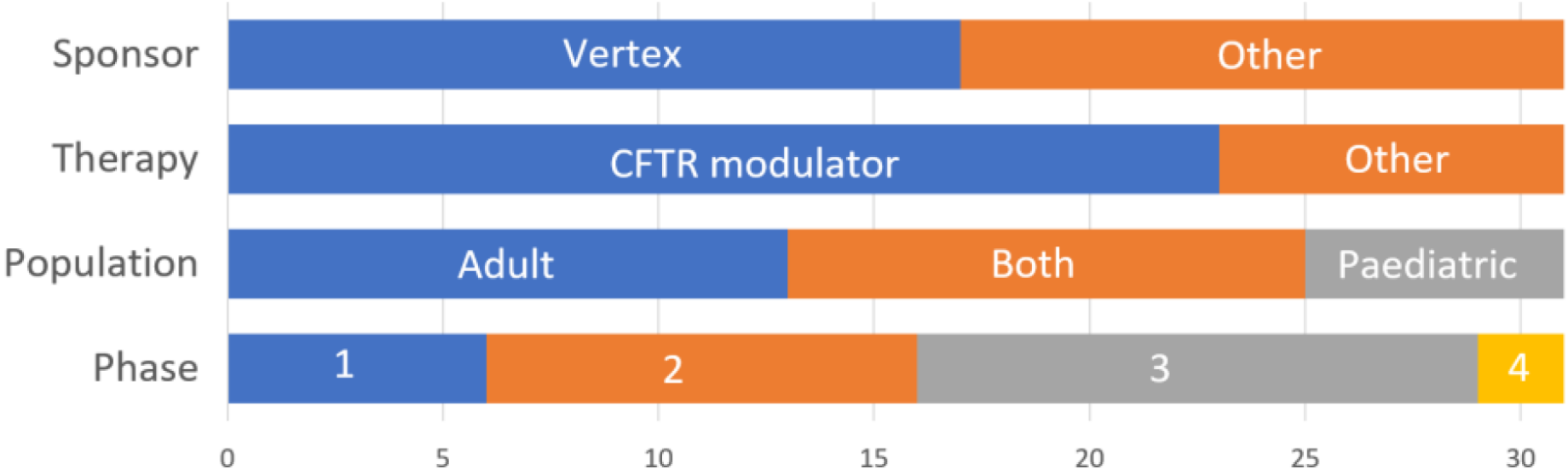
# Projet européen HIT-CF (H2020)

ANALYSE DE LA REPONSE DES ORGANOÏDES INTESTINAUX DE PATIENTS A DIFFERENTS MODULATEURS DE CFTR, AFIN DE SELECTIONNER LES PARTICIPANTS A DE FUTURES ETUDES CLINIQUES

Pr Michael FAYON, MD PhD MSc
Dr Julie MACEY, MD

# ECFS – CTN

## Study characteristics

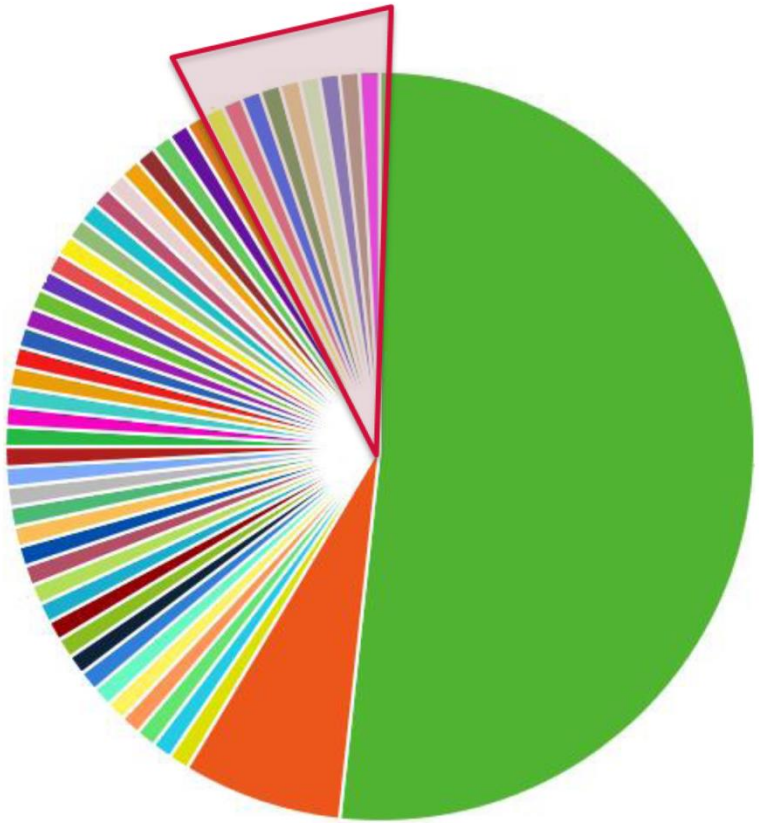



Caracteristiques des 31 études en cours (Nov 2017 à Nov 2018)

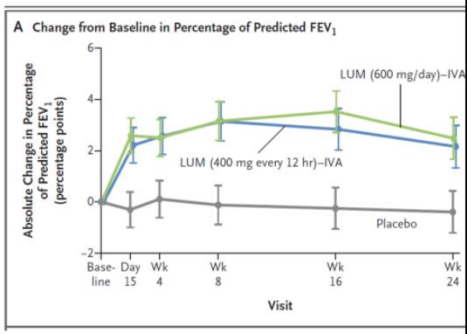
# CF Patient Population: > 2000 CFTR mutations

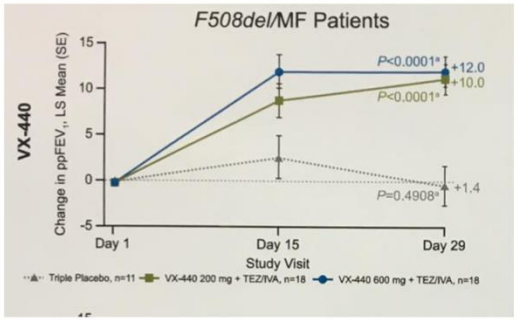
## Ultra-rare CF

F508del heterozygous

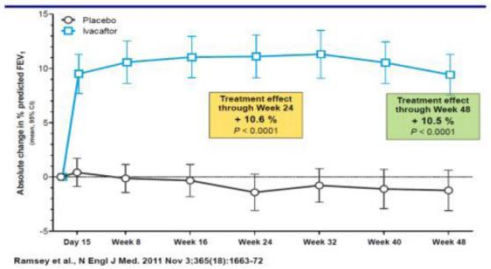


F508del/F508del




Gating



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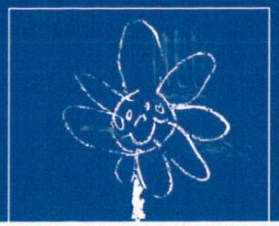
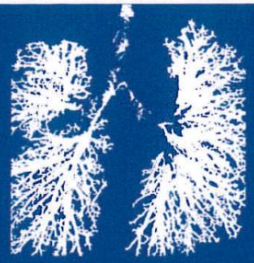


# PEDIATRIC PULMONOLOGY

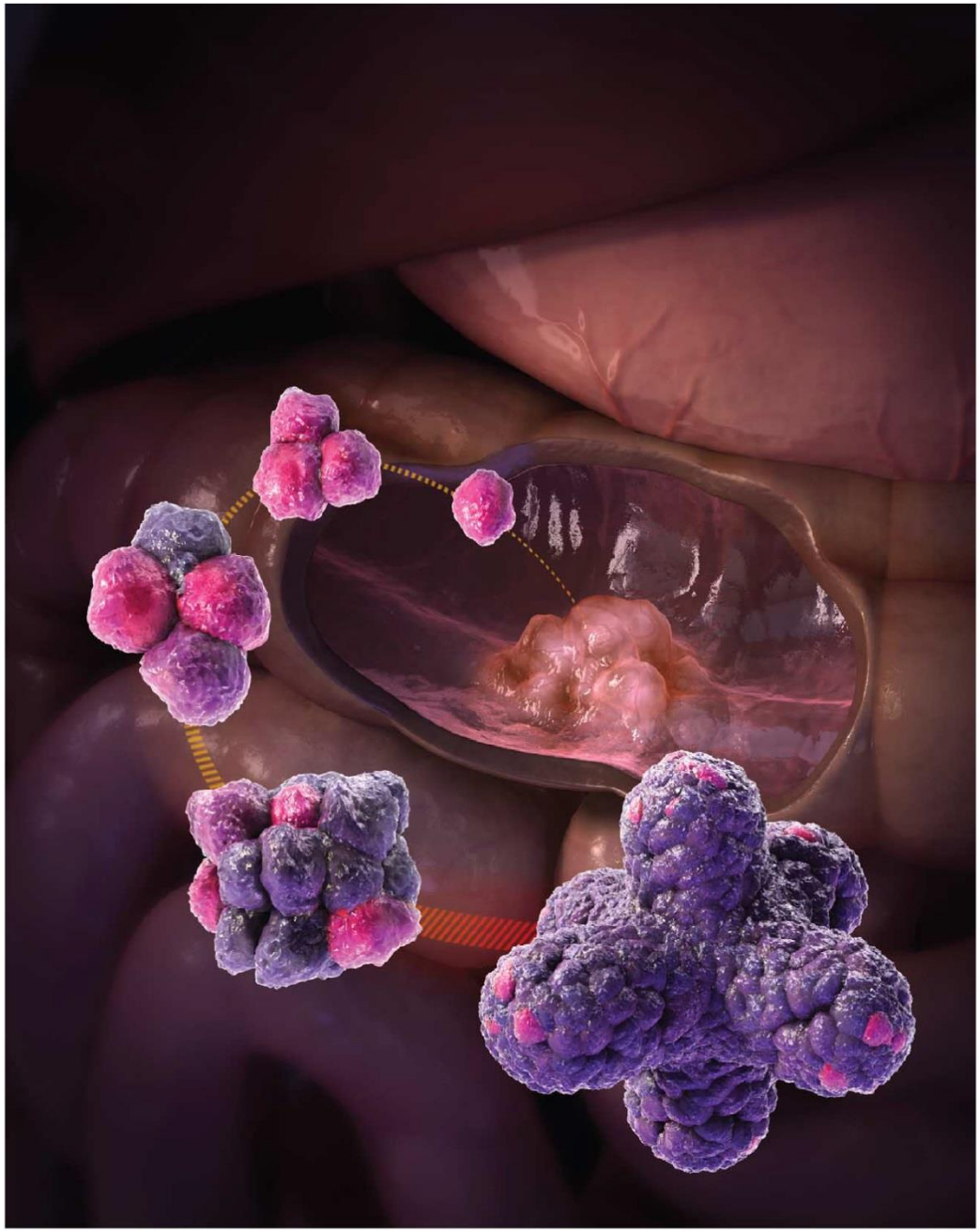


## Remaining Barriers to Normalcy in Cystic Fibrosis IV

Guest Editors:
Thomas Murphy
Terry Noah

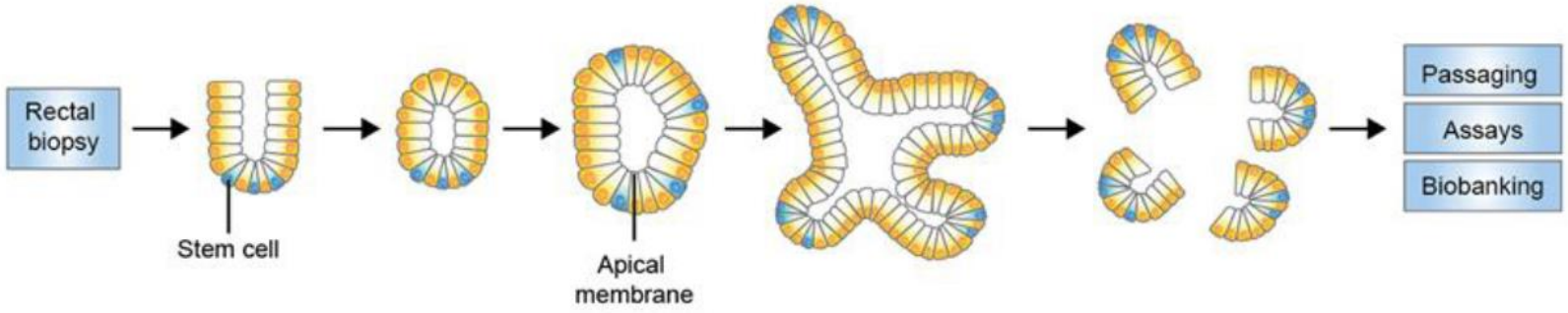
# HIT-Project : Objectif principal

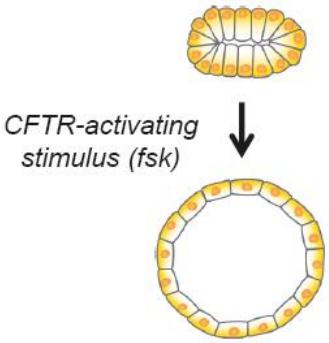
- L'identification des **meilleurs répondeurs** cliniques potentiels, et aussi des **moins bons répondeurs** (patients témoins), aux **nouveaux modulateurs** du CFTR, à partir **d'organoïdes intestinaux** unique et spécifique à chaque patient, lors les tests **de screening *in vitro***



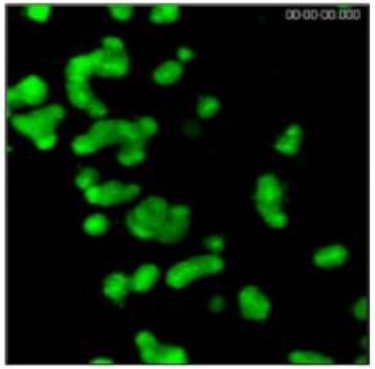
Bredenoord 2017

# The organoid model

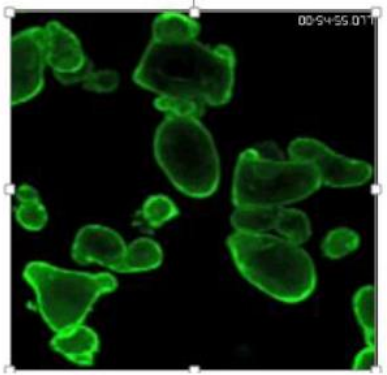



F508del/F508del



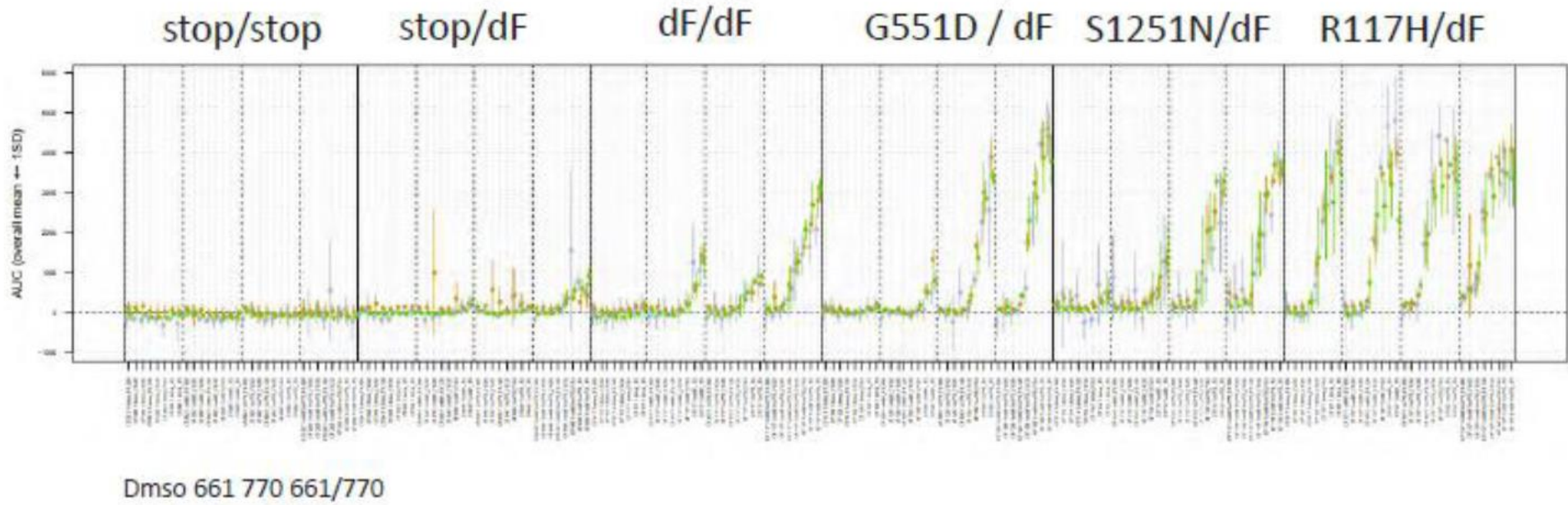
F508del/F508del
Lumacaftor/Ivacaftor



Le modèle des organoïdes

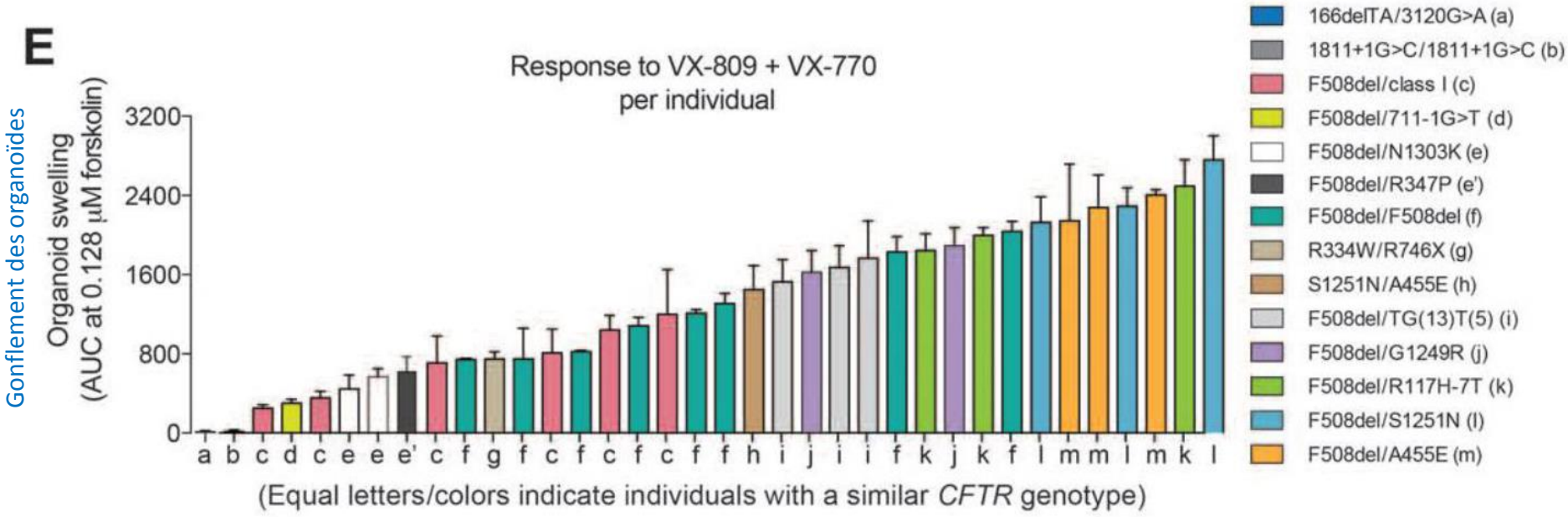
*Dekkers et al, Nature Medicine, 2013*

# Relative size increases




Augmentation relative de taille

# Drug response differs per individual



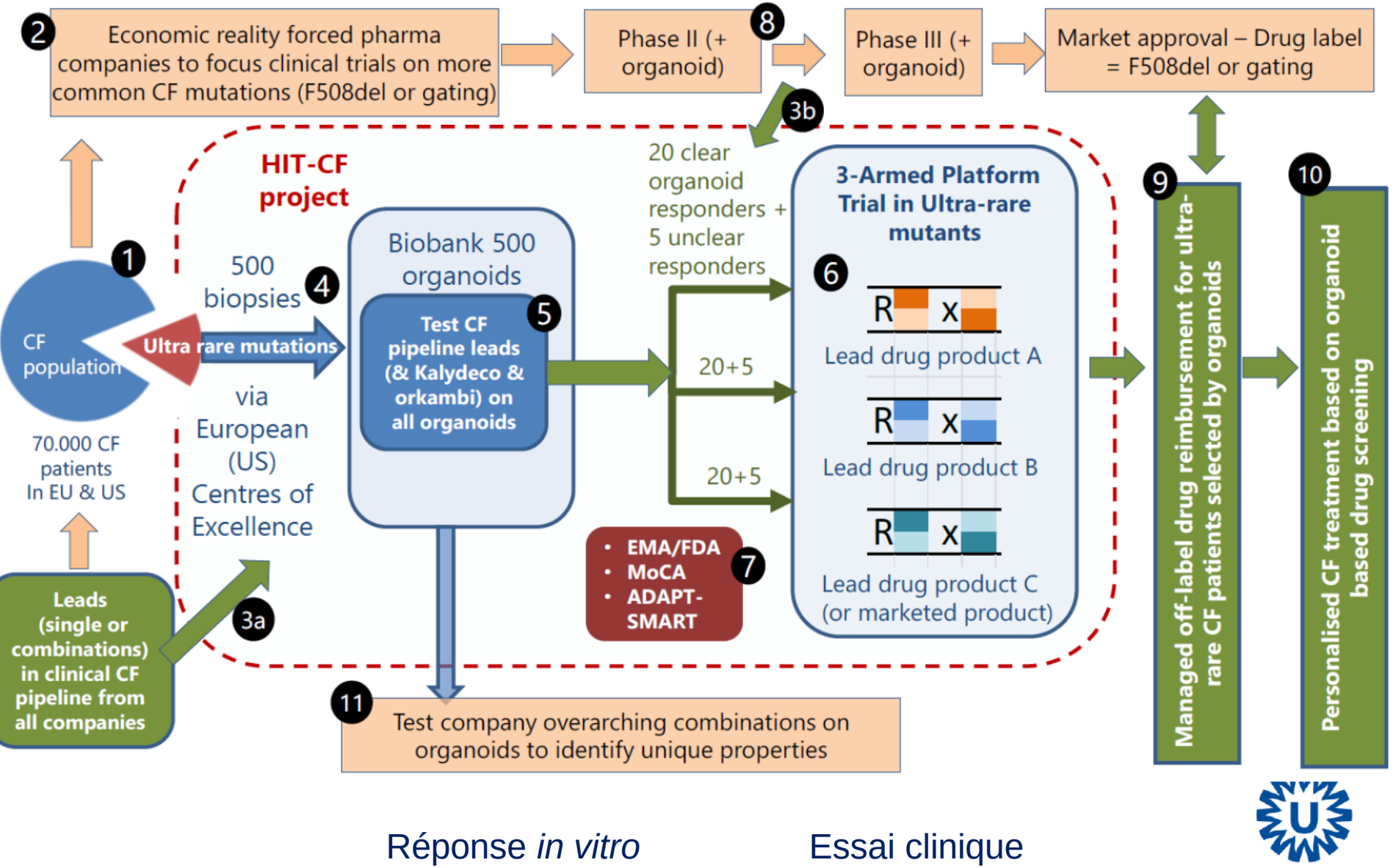

Chaque lettre / code couleur correspond à des individus
ayant un génotype CFTR similaire

La réponse aux agents pharmacologique varie selon les individus

*Dekkers et al, Sci Transl Med, 2016*

# Buts du projet

- Rendre accessible des modulateurs du CFTR aux patients ayant des mutations rares
- Traiter de façon personnalisée la Mucoviscidose
- Constitution d'une « Biobanque » facilement accessible, pour conduire des études ultérieures



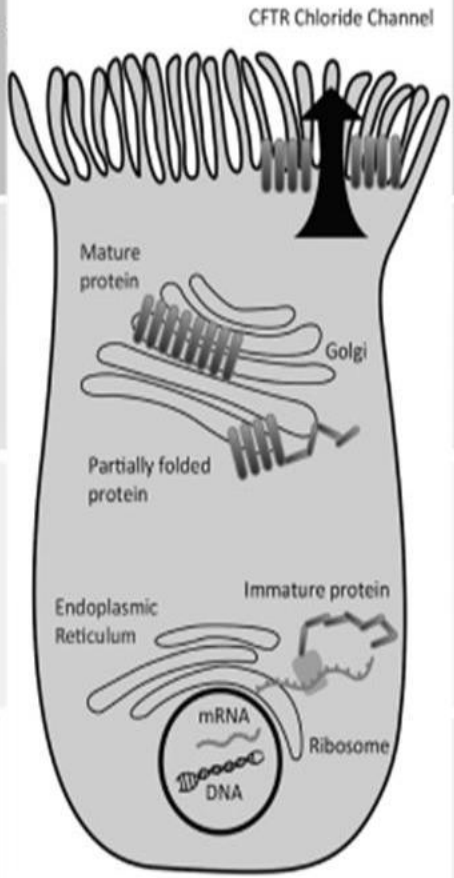

Réponse *in vitro* Essai clinique

POTENTIATORS

CORRECTORS

AMPLIFIERS

READ THROUGH




Potentiators, such as ivacaftor, act by increasing the opening time of the CFTR channel resulting in higher ion flow.

PTI-808, GLPG-1837, FDL

Correctors, such as lumacaftor, are thought to facilitate the processing of mutated CFTR protein substrate leading to improved delivery to the cell membrane.

PTI-801, GLPG-2222, 2737, FDL

Amplifiers selectively increase the amount of immature CFTR protein in the cell providing additional substrate for correctors and potentiators to act upon.

PTI-428

Read through agents enable ribosomes to pass by non-sense mutations, so CFTR protein can be produced in patients with X-mutations

ELX-O2

FLATLEY DISCOVERY LAB
SEEKING a CURE for CYSTIC FIBROSIS

abbvie

pti PROTEOSTASIS THERAPEUTICS, INC.

ELO
Eloxx Pharmaceuticals

# Consequences of new partners

- 500 ultrarare mutations
  - Estimated 450 non-STOP and 50 STOP mutations
- Decided 100 extra non-STOP and 100 extra STOP mutations
- Adaptation of exclusion criteria

550 mutations Non-STOP
150 mutations STOP

# Inclusion/exclusion

- Age > 16/18 years
- SCC > 60 mmol/L

**Non-Incluable (en l'absence)**

≥ 1

- Subjects that will not be covered by current programs:

  Those with **at least one** of the following CFTR-mutations:

  F508del, G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H, A455E, 3849+10kbC>T

- Subjects that are not ultra-rare:

  Those with **a combination of any two** of the following mutations:

Combinaison de 2 mutations

G542X, ~~R553X, W1282X, R1162X, E60X, Q493X~~, 1717-1G>A, 621+1G>T, 3120+1G>A, 1898+1G->A, CFTRdele2,3 and 2183AA->G

## Forceps biopsy

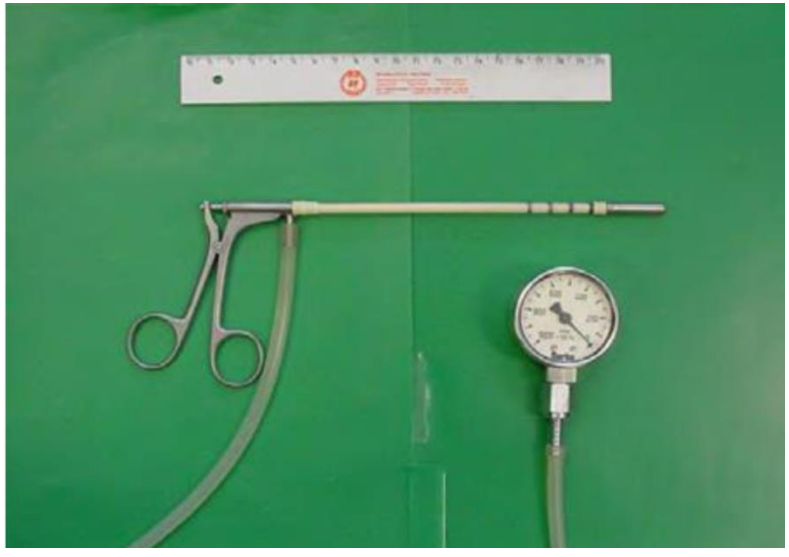
- Common procedure for gastroenterologists
- Obtained during sigmoidoscopy
- Not painful
- Success rate organoid generation 92% (until 48h after procedure)

*Formation à distance*

## Rectal Suction Biopsy

- Also used for ICM biopsies
- No endoscopy needed
- Not painful
- Quality of biopsies depends on experience

(UMCU: 95% success rate organoid generation)



# Exclusion criteria

- History of any comorbidity reviewed at the Screening Visit that, in the opinion of the investigator, might pose an additional risk in potentially administering study drug to the subject. For example, a history of cirrhosis with portal hypertension

- History of lung transplantation

*These comorbidities will eventually prevent patients from entering the 2nd stage clinical trials*

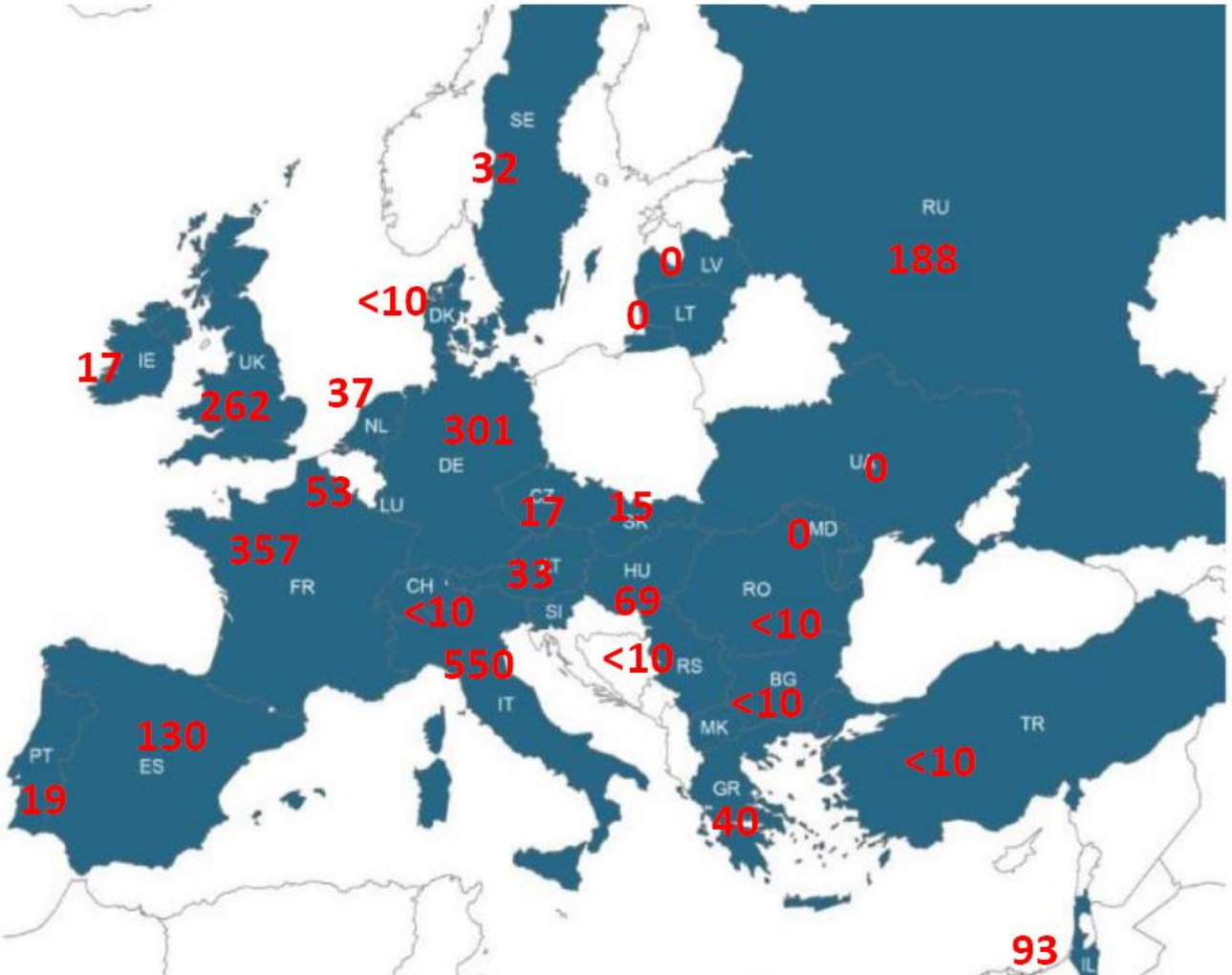
# Taille de l'étude

- N = 500 patients au total
- 150 pour France

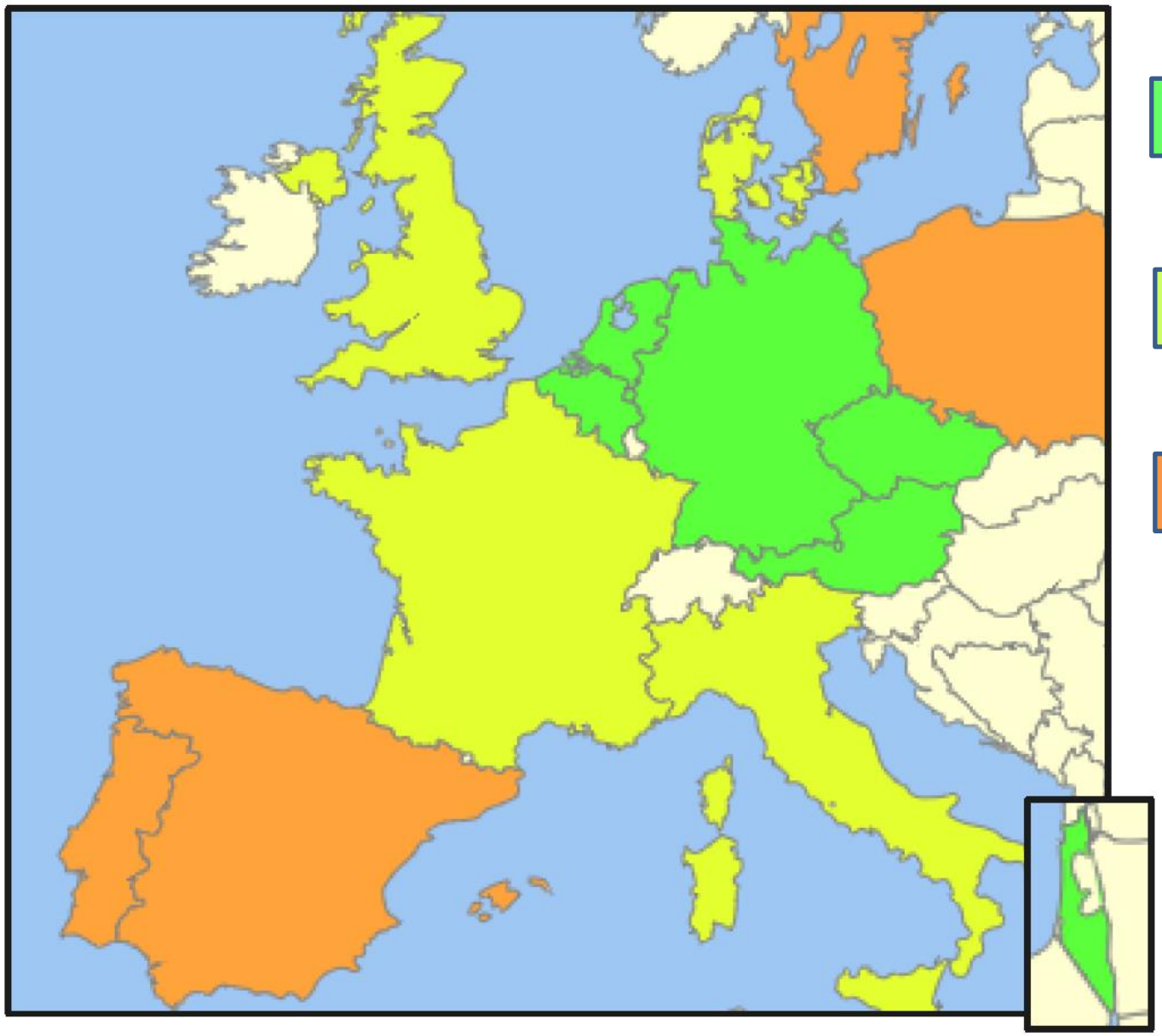
Durée de la période d'inclusion : 18 mois
Durée de participation de chaque participant : 1 journée
Durée de l'étude :  19 mois

# Patient localization based on ECFS-PR data

**Total eligible patients: 2027**



# 3. Update per country



Inclusion

Imminent

A venir

# En France

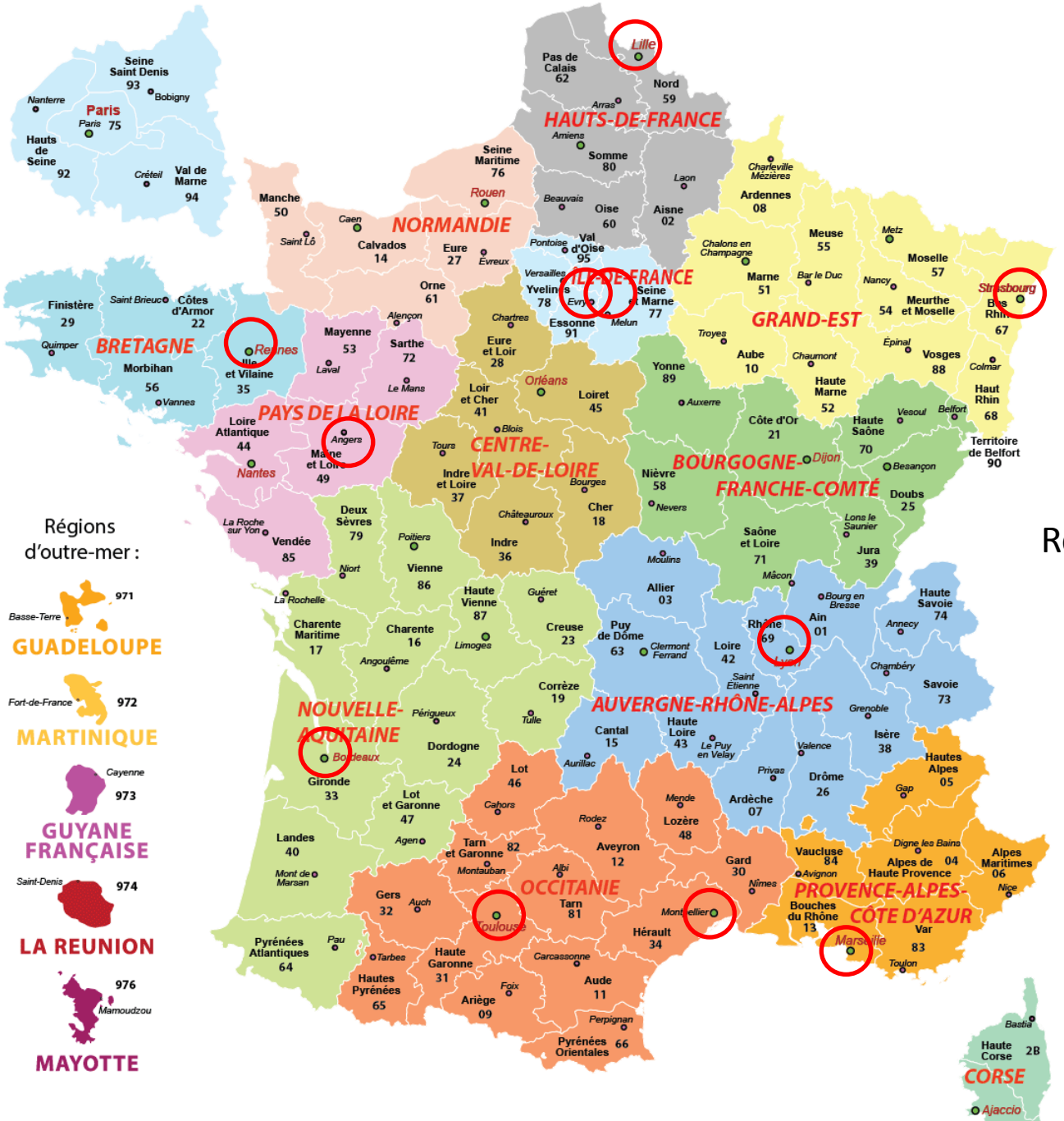
## Registre français
DE LA MUCOVISCIDOSE

VAINCRE LA MUCOVISCIDOSE


CRCM
Centre de Ressources et de Compétences de la Mucoviscidose

CRCM
Centre de Ressources et de Compétences de la Mucoviscidose

CRCM
Centre de Ressources et de Compétences de la Mucoviscidose




11 centres
150 patients
(275 éligibles)

Remboursement des frais de déplacement*

VAINCRE LA MUCOVISCIDOSE

*pour les patients référés vers un CRCM qui n'est pas leur CRCM habituel

# 3. France: 11 sites across France


**ANSM**

> 18 ans

Pince jetable uniquement

**CPP**

Informations complémentaires

devenir des biopsies et des organoïdes

**Inclusions**

juin 2019


**Les Patients**

**Vaincre la Mucoviscidose** PNRC : Anna Ronayette, Paola de Carli, les membres

Registre : Lydie Lemonnier, Clémence Dehillotte

**SFM** Stéphane Mazur, Isabelle Durieu

**Centres Investigateurs** CRCMs, Gastro-Entérologues

**DRCI Bordeaux** Aurore Capelli

Sophie Regueme

Caroline Bouyssou-Cellier

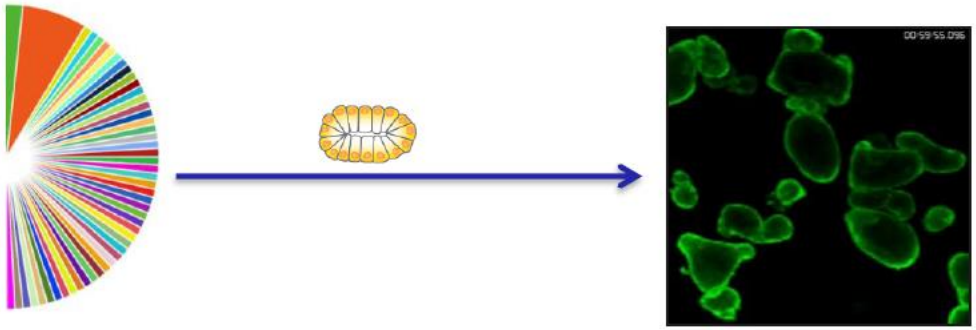
**HUB** Utrecht, Louvain, Lisbonne

# Two clinical stages

**1.**

Collect 500 biopsies from European CF-patients

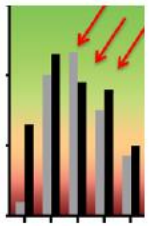
Test drugs of three pharmaceutical companies on these organoids

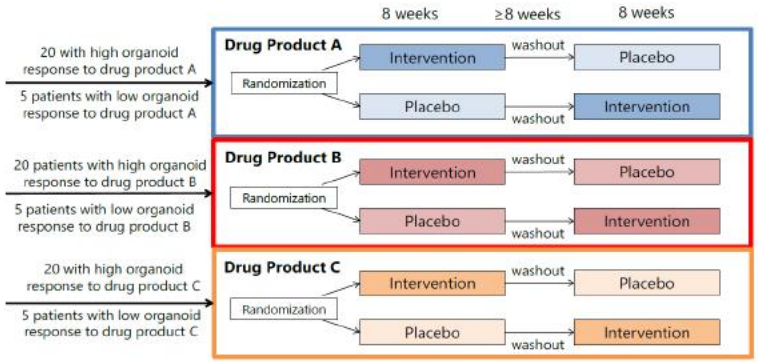


**2.**

Select the best responders per drug

Execute 3 double-blinded, placebo-controlled cross-over clinical trials

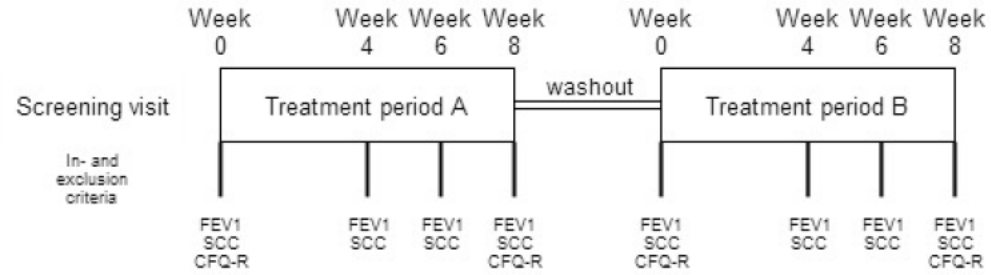




# Starting trial design

- Placebo-controlled crossover design
  - Decreasing the influence of within-patient variability
  - Decreasing the influence of between-patient variance

- Repeated measurements
  - Decreasing the influence of within-patient variability



# ***Critères d'inclusions***

*(pour la première étape : biopsie rectale)*

- Patient masculin ou féminin âgés de 16 ans ou plus
- -chez qui un diagnostic de mucoviscidose a déjà été porté par un test de la sueur dont la concentration en ions chlorure était supérieur à 60 mmol/L
- -en l'absence d'une mutation pour laquelle un médicament modulateur du CFTR est actuellement disponible, ou des mutations classe 1 avec une fréquence d'allèle >0.2% selon la base de données CFTR2.

# Inclusion criteria

- Confirmed diagnosis of CF, **both** of the following:
  - One or more phenotypic features **or** history of CF in sibling **or** positive newborn screening result
  - **SCC >60 mmol/L**

- Adult* on the date of informed consent for biopsy taking. Younger patients will not be included due to extensive and long-term safety data needed before a trial in younger paediatric patients is considered safe.

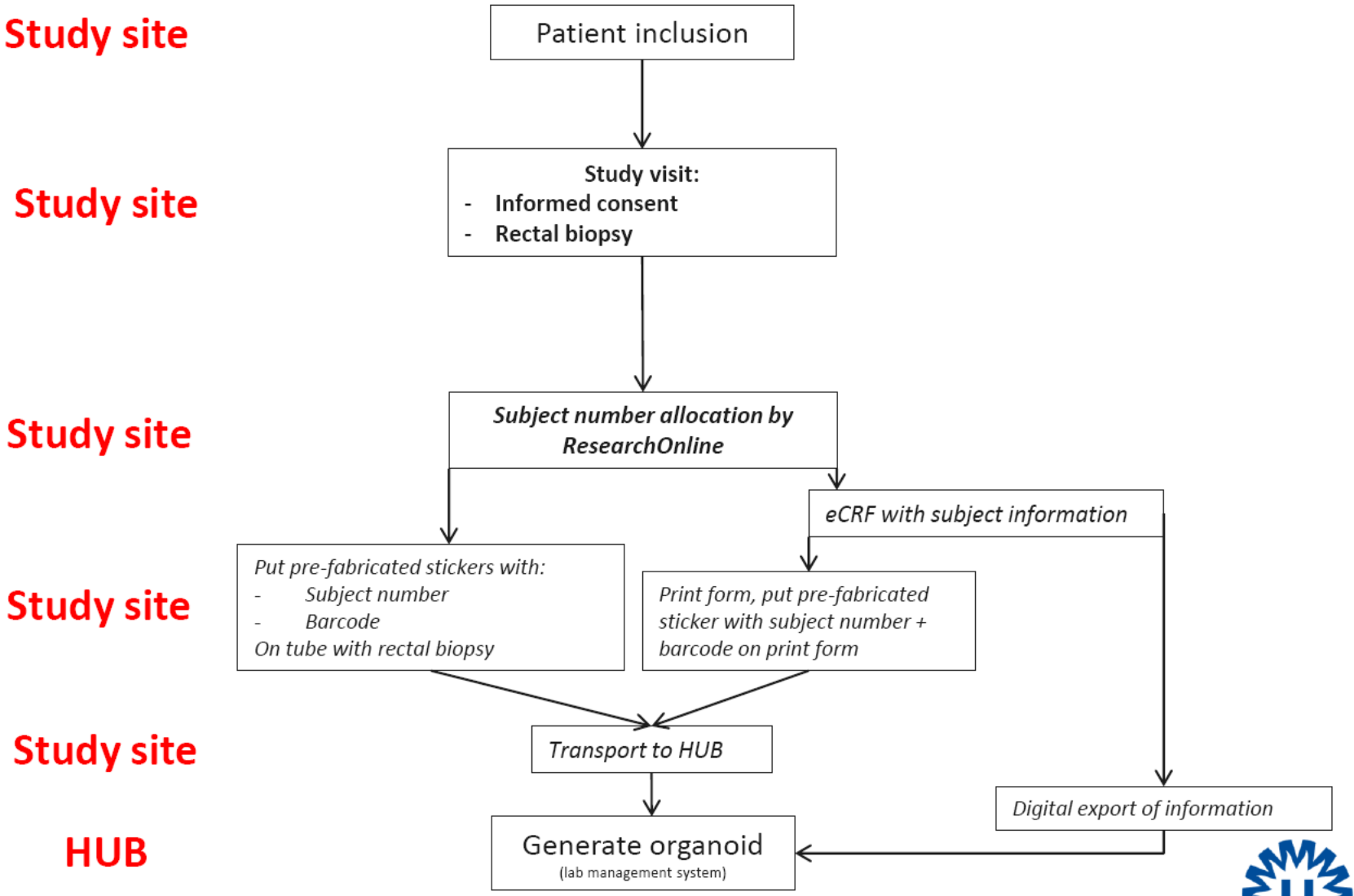
**16 or 18 years depending on country-specific ethical regulations*

# 1. What have we achieved so far

- All countries selected (12)
- Potential 34 sites
- Germany and Austria will refer patients to NL
- 8 countries Ethical Approval
- All other countries are preparing EC submission or are in submission
- 19 inclusions in study
- New partners in consortium: amendment current protocol

Wilhelmina Children's Hospital

# Logistics of Organoid Study



# Biobank organization