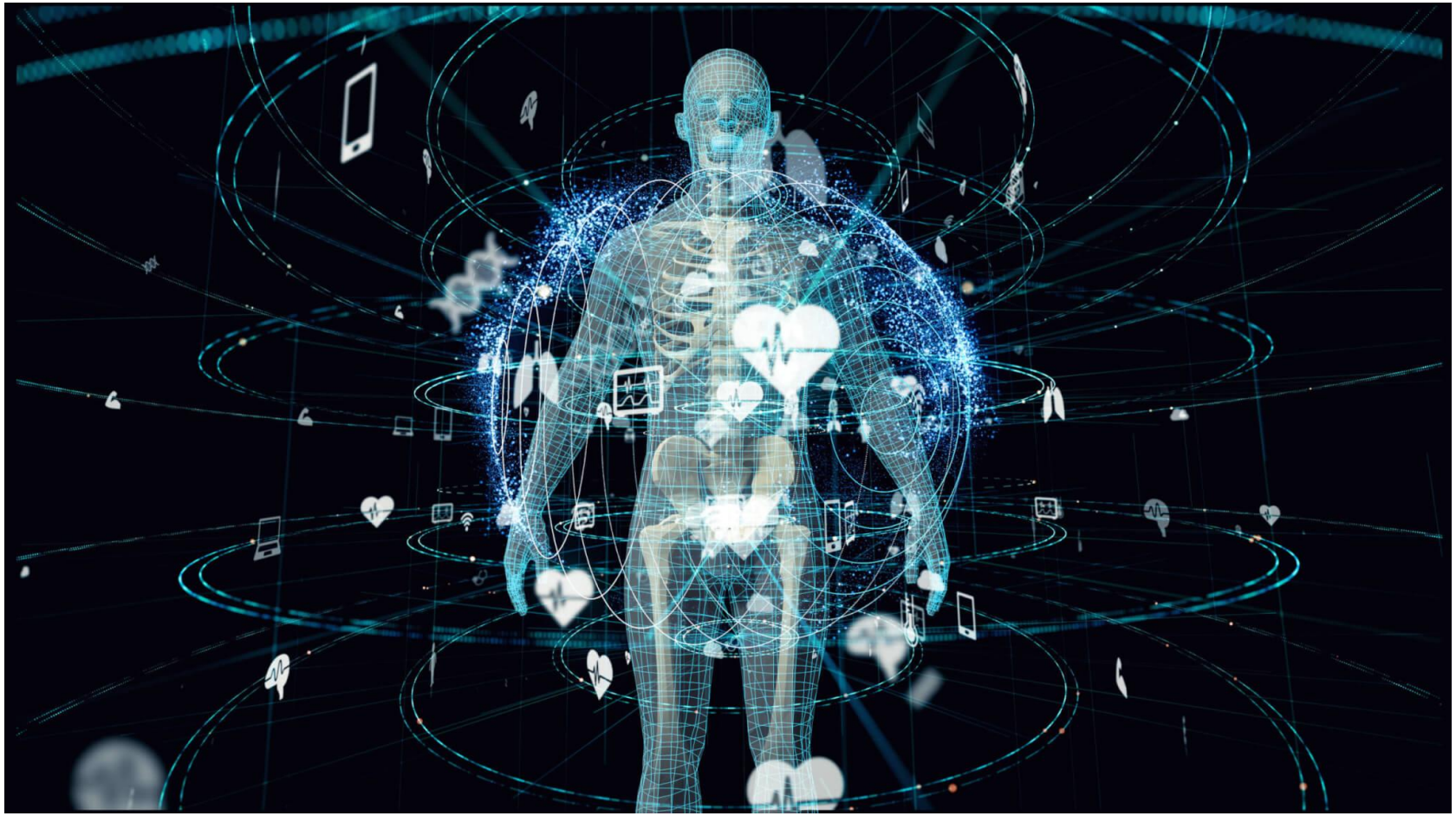
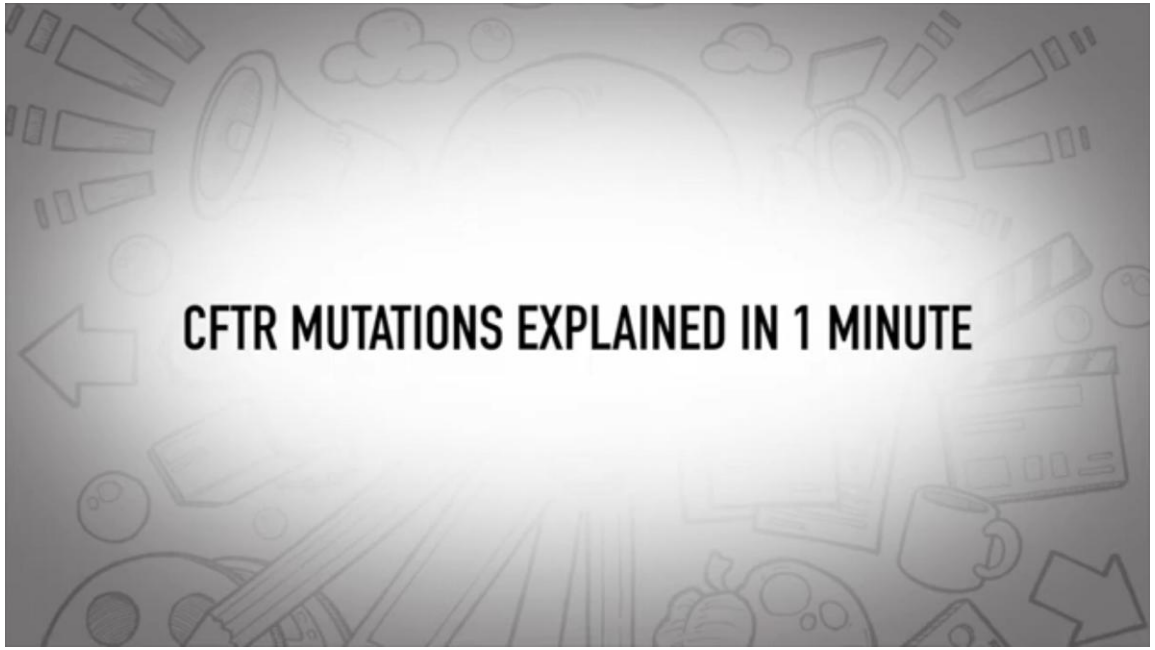
# Personalized medicine: a trade-off between throughput and personalization of treatment



# Cystic Fibrosis: a multisystem genetic disorder




Mutations in CFTR lead to mucus accumulation

**Lungs**

- Cough
- Wheezing
- microbial infections

**Pancreas to small intestine**

- Foul-smelling, greasy stools
- poor weight gain and growth

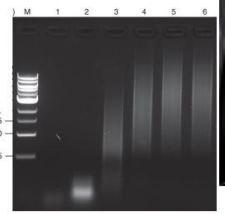
# Treating the causes…

## First cystic fibrosis treatment ever : 5 YEARS RECORD timing from an idea to making an innovative medicine in clinical practice !

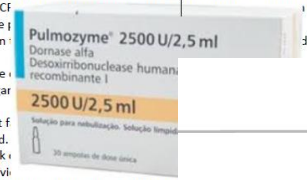
Genentech
*A Member of the Roche Group*

CYSTIC FIBROSIS FOUNDATION

5 years from bench (molecular biology) to bedside : a world record !




**Pulmozyme-the first new treatment approach for cystic fibrosis** in 30 years-was developed through a collaborative effort by Genentech, the CF Foundation, CF centers in North America, and the FDA. It is a bioengineered drug: The human protein deoxyribonuclease was isolated and synthesized in the lab at the cost of "several hundred million dollars," according to Genentech's **March, 1988**: Genentech researcher **Dr. Steven Shak** was observing the blood-thinning drug TPA (Activase®)as it dissolved blood clots, and developed the idea to engineer an enzyme that would dissolve mucus plugs in the lungs of CF [illegible] that DNase




down DNA

[illegible] the FDA unanimously approved [illegible]
[illegible]nt populations of CF patients not

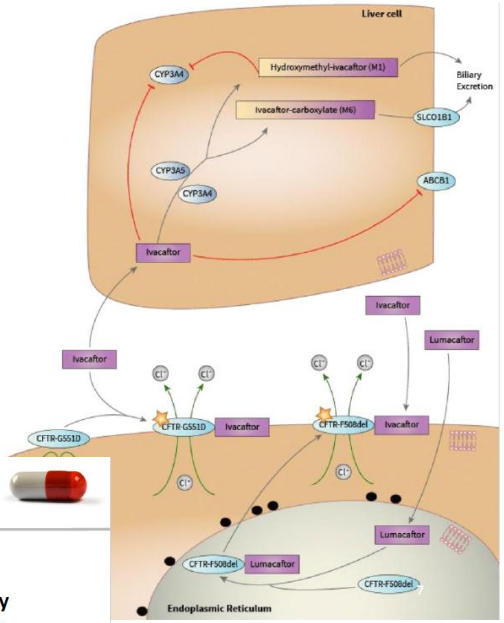
## Cystic fibrosis – CFTR allosteric modulator : a paradigm change treatment for CF patients

### Ivacaftor

- Selective potentiator of CFTR by stabilizing its open state ( Allosteric modulator that stabilize the open state of CFTR)
- Metabolized by CYP3A4 and CYP3A5

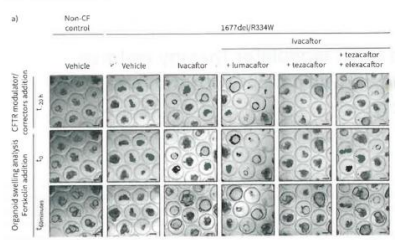
### Lumacaftor

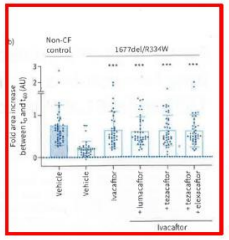
- Corrector




Nathalie Brandenberg
PhD MBA CEO

## Organoids for all seasons – whose tissue not included ? Breaking news : organoids enable patient compliance



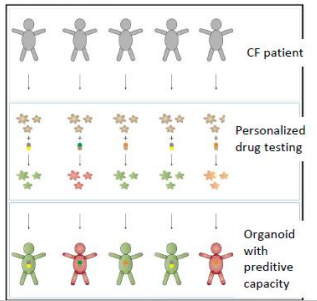




**Rectal organoid-guided CFTR modulator therapy restores lung function in a cystic fibrosis patient with the rare 1677delTA/R334W genotype**

### Rectal Organoids Enable Personalized Treatment of Cystic Fibrosis

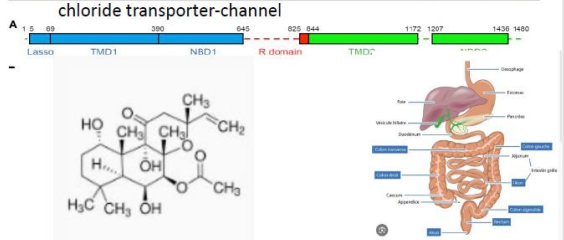
Gitte Berkers,[1] Peter van Mourik,[1] Annelotte M. Vonk,[1,2] Evelien Kruisselbrink,[1,2] Johanna F. Dekkers,[3] [illegible] Jasper S. Diikema.[1]

Graphical Abstract




Mitropoulou G ...and Brandenberg N. 2022 Eur Respir J. 60:2201341

cystic fibrosis transmembrane conductance regulator (CFTR), a chloride transporter-channel



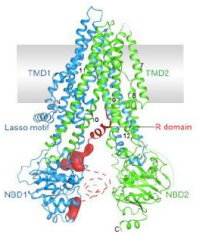





...Based on our results, we obtained health insurance coverage for this patient reporting significant improvement of respiratory symptoms...

## Cystic fibrosis – first tri-therapy frp CF patients : a paradigm change


Trikafta : triple combo : elexacaftor/tezacaftor/ivacaftor



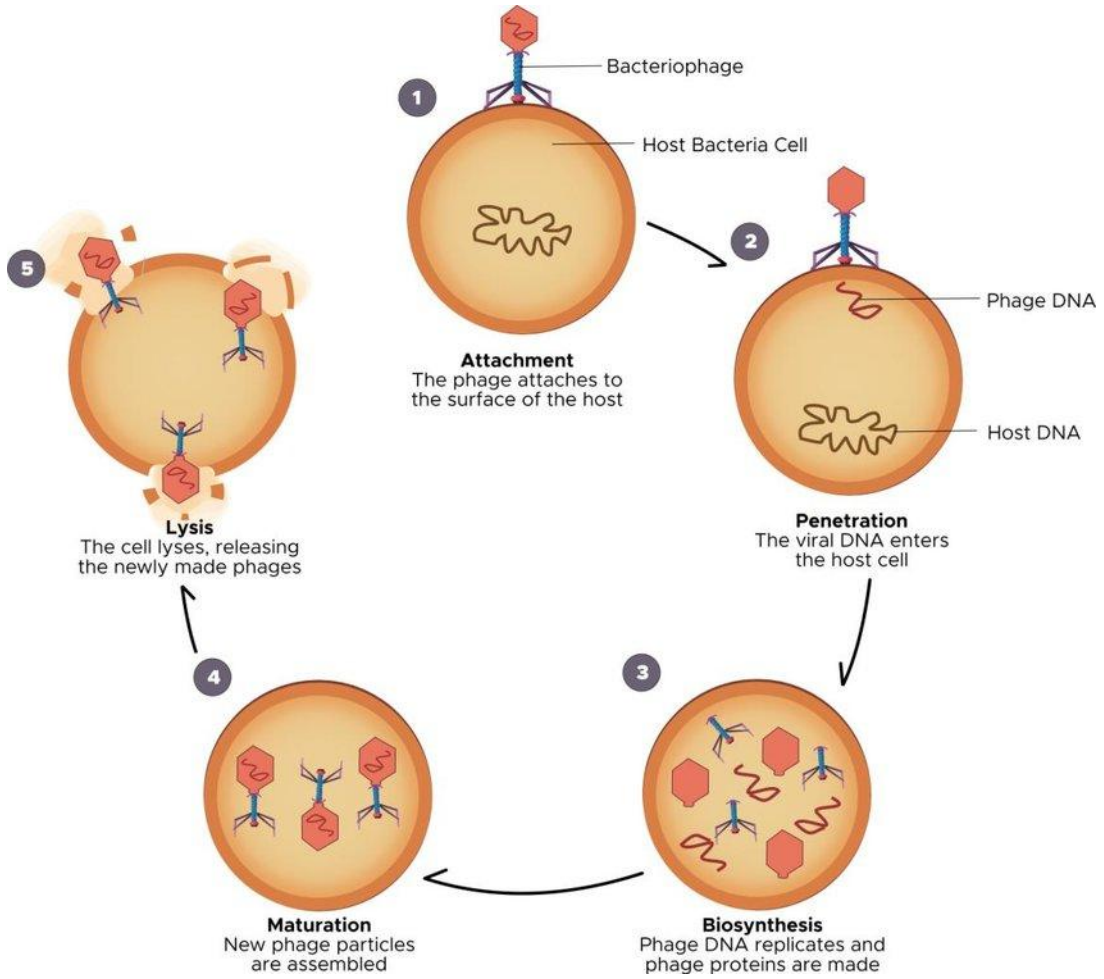

**Vertex breakthrough : CFTR allosteric modulators in tri-therapy show a real benefit for CF patients (game changer (!) with even different mutations that represent 90% of the CF population ! FDA approval in 2019**

# …vs treating the consequences

*Pseudomonas aeruginosa*

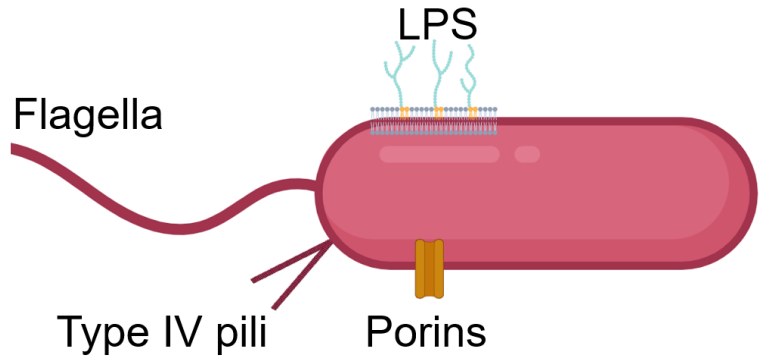
- Gram – opportunistic pathogen
- Highly virulent, biofilm
- Resistant to antibiotics

# Phage therapy is a promising solution




Adesanya et al., 2020

**Phages most common receptors**



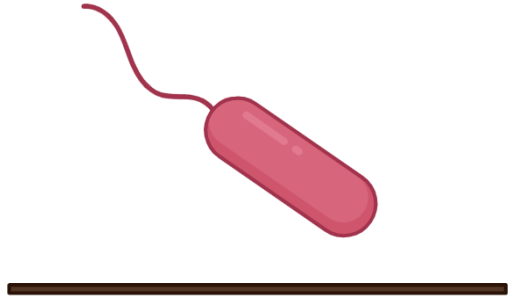

✓ safe, small effective dose, effective against ab-resistant strains, easy administration

X high specificity, lack of high-quality screening and production, phage clearance

# Bacterial physiology influences phage infectivity

***P. aeruginosa* in LB medium**

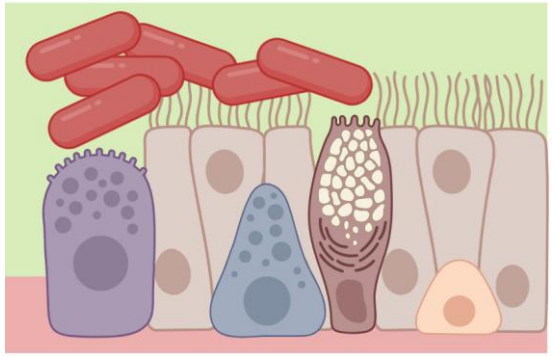
Planktonic

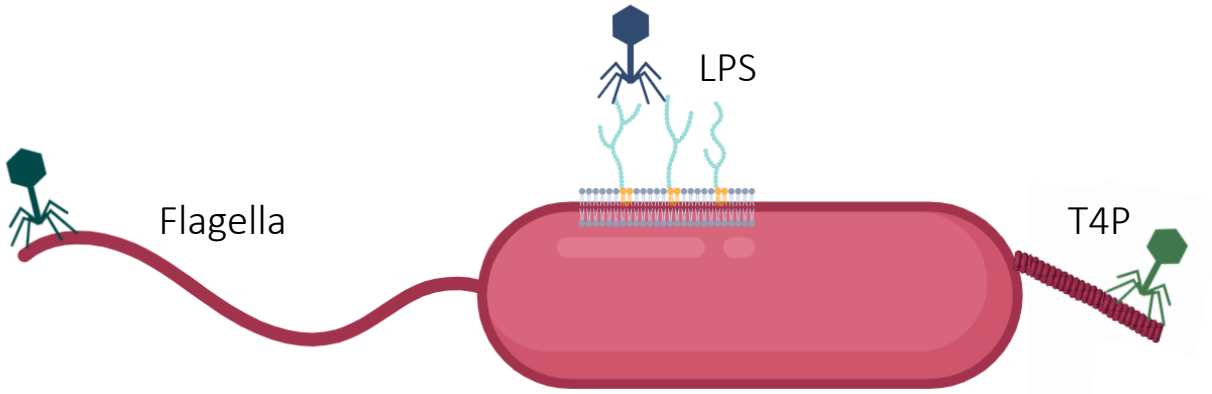


***P. aeruginosa* on agar surface**

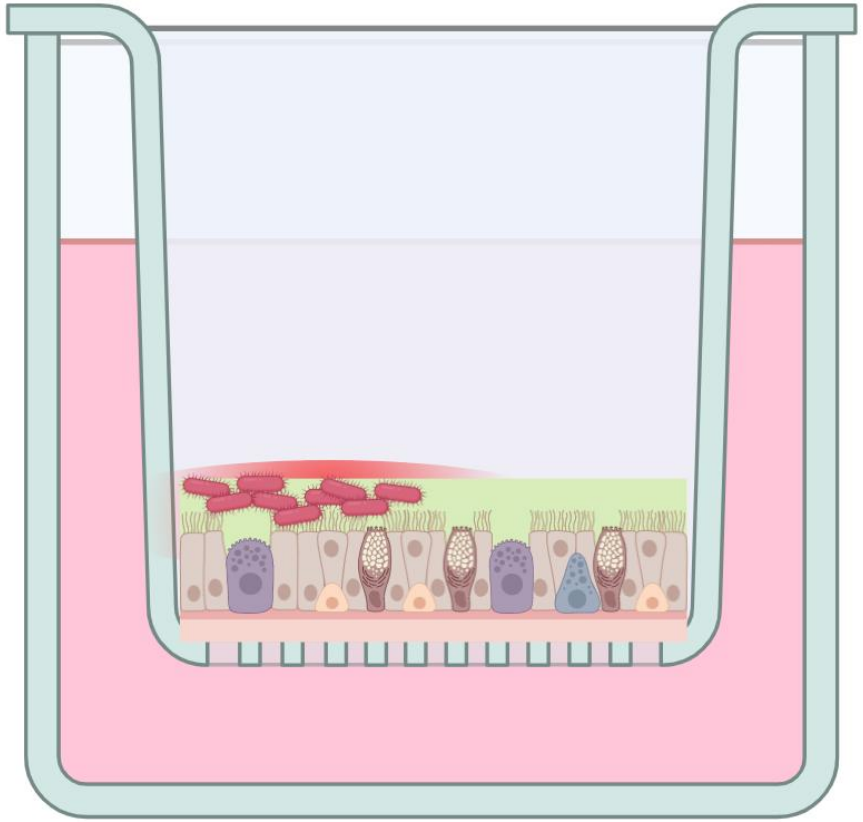
Sessile

***P. aeruginosa* on lung epithelium**





# Lung transwell as a reliable system



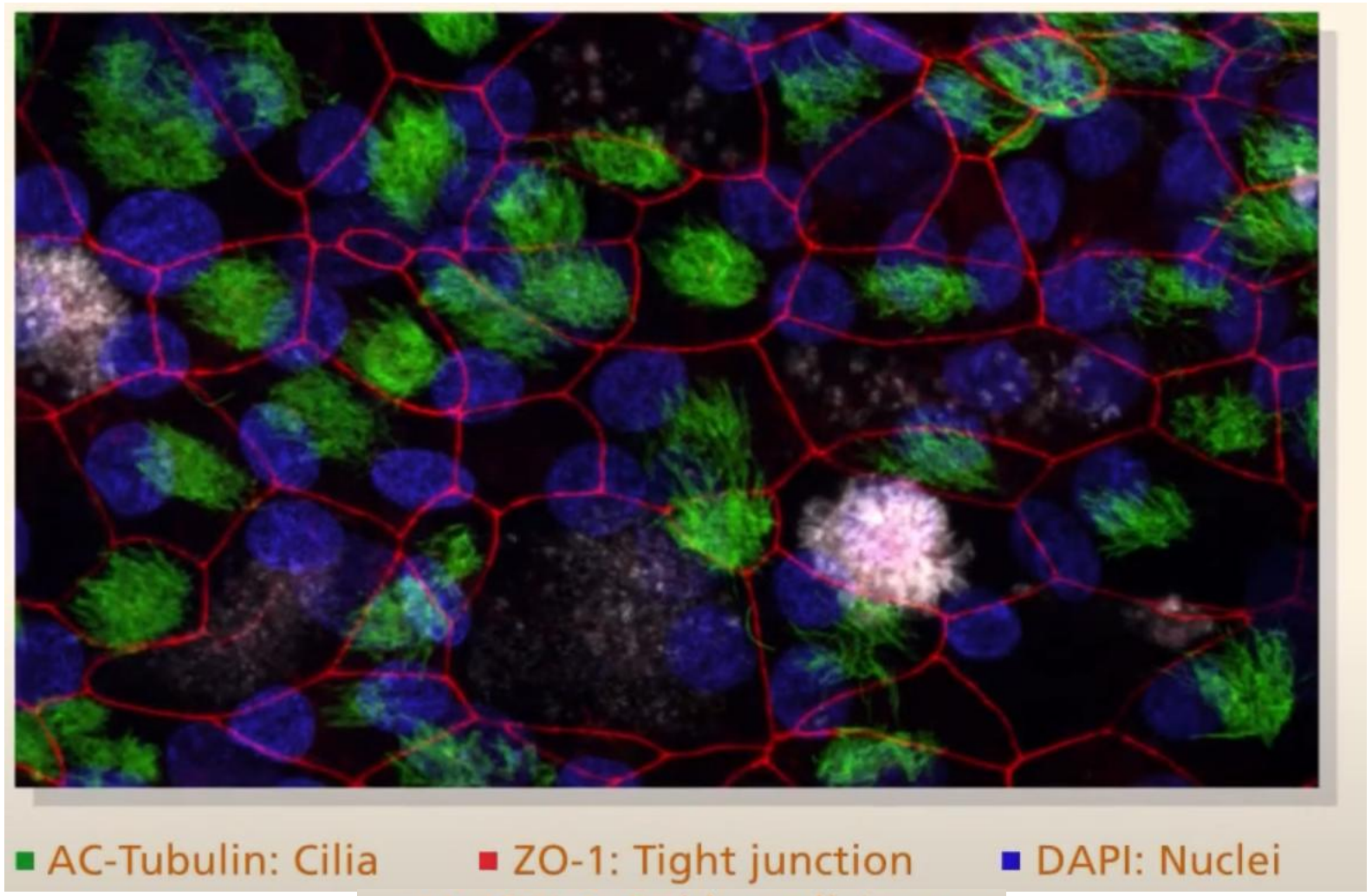
- Air-liquid interface
- Basal, Goblet, ciliated cells
- It mimics infected lung conditions

*P. aeruginosa* adapts to the mucosal surface Meirelles, 2024

**Phage efficacy differs in the mucosal environment**

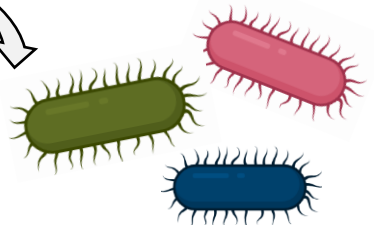
**A bacterial infection model that closely mimics patient conditions for effective phages selection**

# Lung transwell as a reliable system



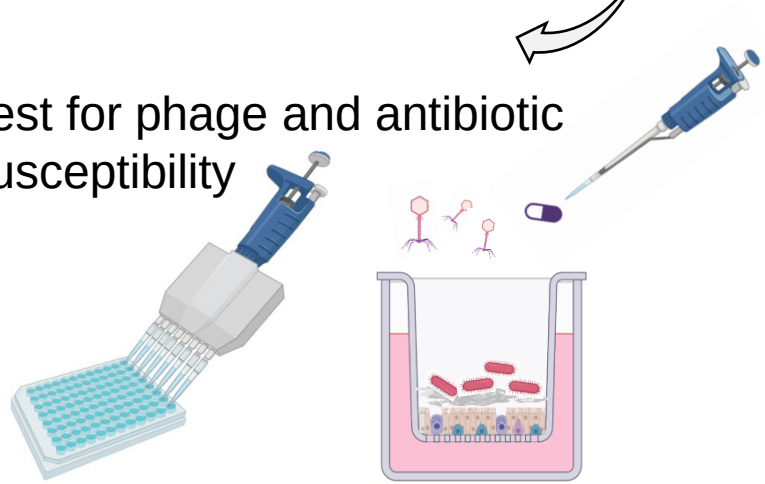
# Personalized medicine cycle

Sputum from patient

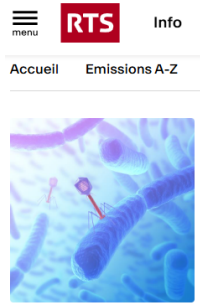


Isolate clinical strains

Test for phage and antibiotic susceptibility



Administer phage + antibiotic



menu RTS Info Sport Culture TV & Streaming

Accueil Emissions A-Z Chaines

Sciences

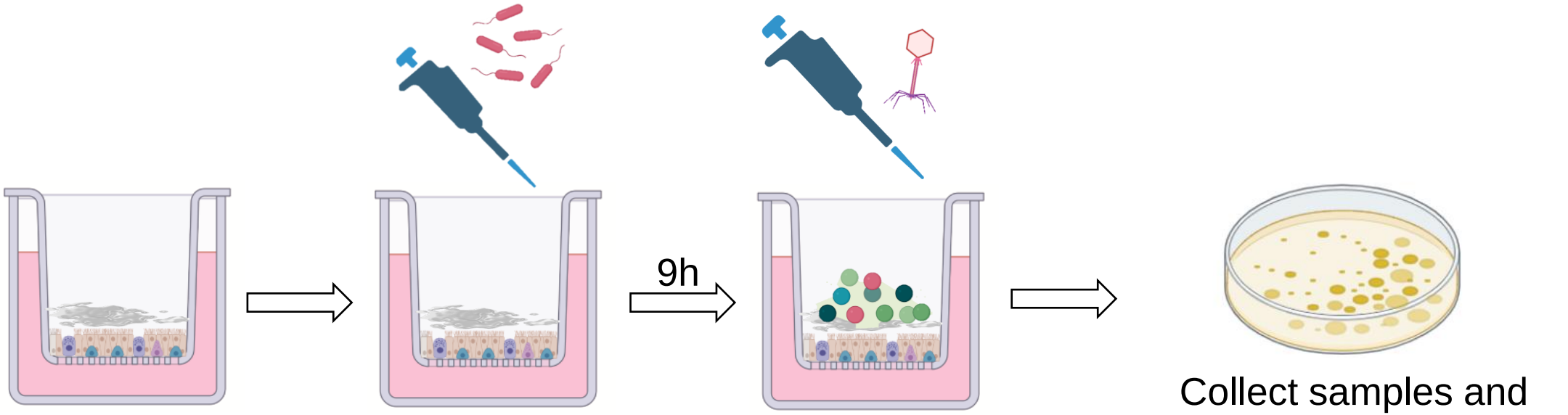
## Un patient sauvé de la mort par des phages

Mettre en pause Partager Télécharger

La phagothérapie, une méthode visant à utiliser des virus pour cibler et éliminer des bactéries résistantes aux antibiotiques sans nuire aux cellules humaines, a récemment été testée avec succès aux Hôpitaux universitaires de Genève. Ce procédé offre une lueur d'espoir dans un contexte où de plus en plus de bactéries développent une résistance aux antibiotiques.
Une équipe des Hôpitaux universitaires de Genève a récemment utilisé cette méthode pour traiter un patient atteint d'une grave infection pulmonaire, une première en Suisse.

Cécile Guérin a recueilli le témoignage du patient, José Vidal, et nous explique les détails de cette méthode en compagnie de Gregory Resch des Laboratoires des bactériophages et phagothérapie (CHUV) et Christian Vandelden, médecin adjoint au service des maladies infectieuses (HUG).

# How to mimic real infections

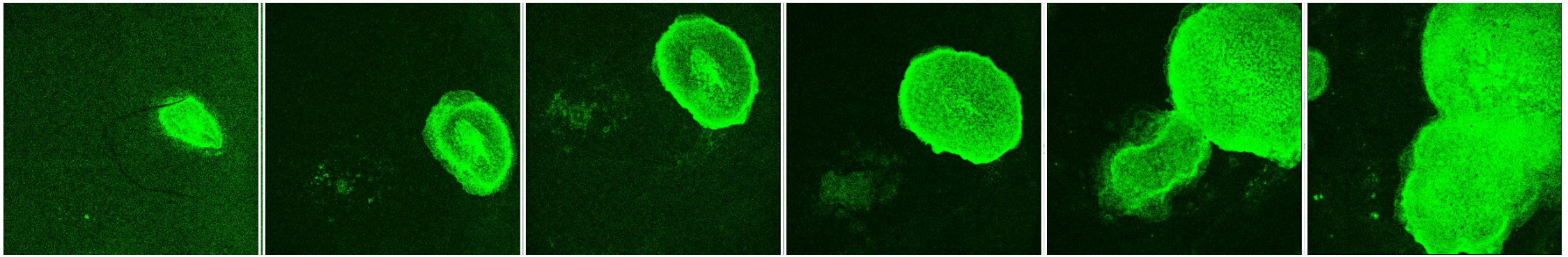



Over 1.5 months

Bacterial infection

Phage infection

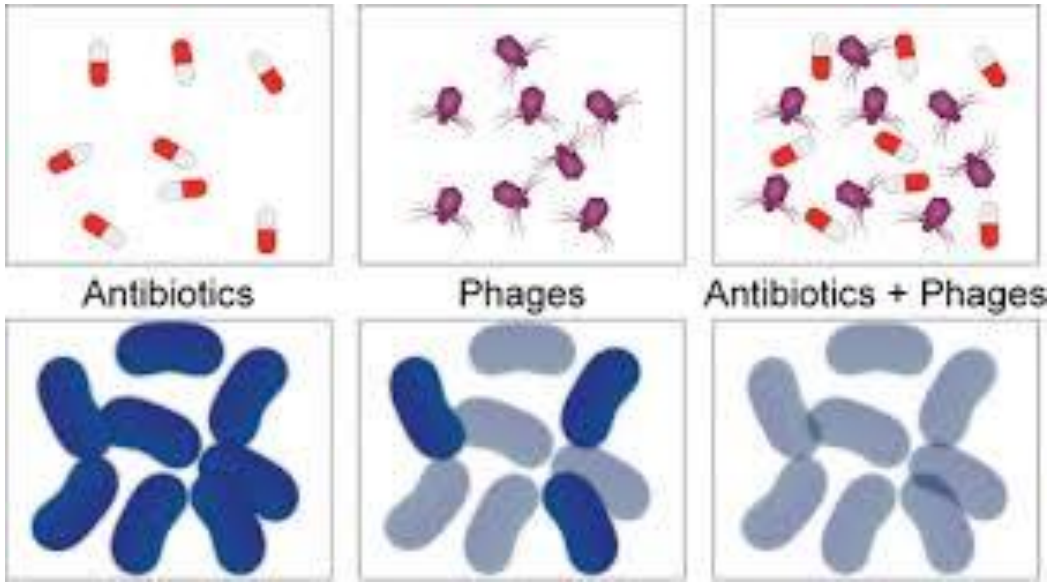
Collect samples and plate for CFU at different t points

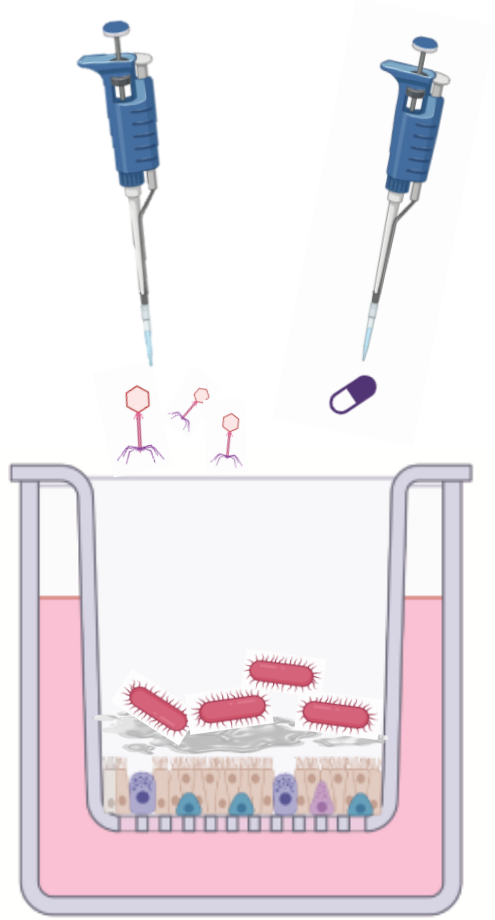


5h p.i. 7h p.i. 8h p.i. 9h p.i. 11h p.i. 13h p.i.

# Even further towards clinical conditions…

Test the **combination of phages and antibiotics**



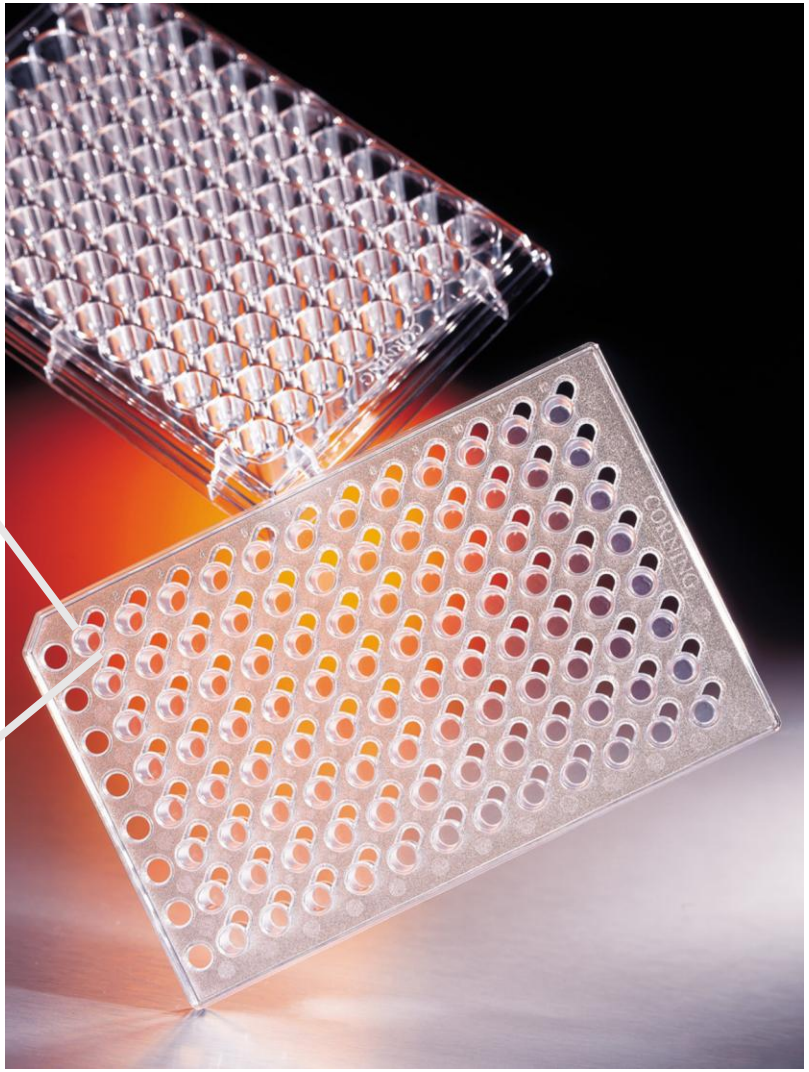



Hypothesis: phage infection can resensitize to antibiotic and sequential combination of phage and antibiotic can eradicate infection better than phage or antibiotic provided alone

# Towards high-throughput

**96-well transwell**

Potentially, each well a different donor, drug, concentration, combination, etc...



# Conclusions

**Personalization:**

- Lung transwell organoids from tissue derived from the patient
- Bacterial strains isolated from the patient

**Throughput:**

- Test more drugs combinations:
  - CFTR modulators
  - Antibiotics
  - Phages
  - Mucolytics
- Test more dosages
- Test drugs on more bacterial strains

**Thanks a lot for your attention!**