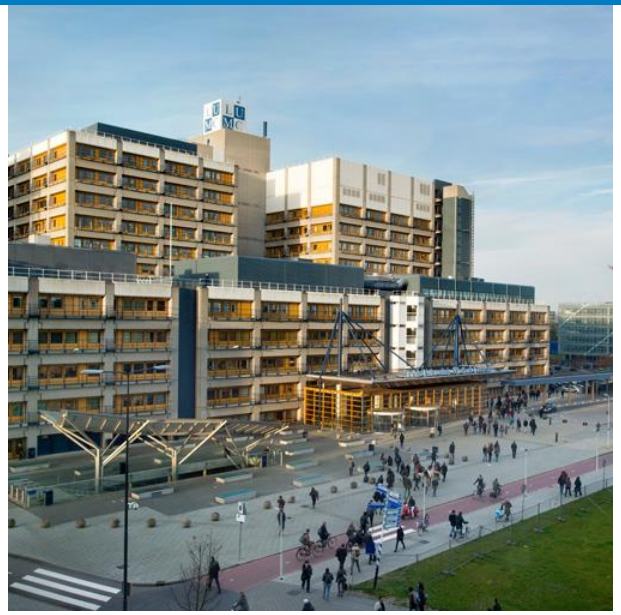
Leiden University
Medical Center

Overcoming the gaps in non-animal approaches in COVID-19 research

The role of non-animal approaches in COVID-19 related research
Intergroup on the welfare & conservation of animals
20 May 2020



Pieter S. Hiemstra

Department of Pulmonology
Leiden University Medical Center
Leiden, The Netherlands

nature
https://doi.org/10.1038/s41586-020-2312-y
Accelerated Article Preview

The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice

DOI: 10.1002/ame2.12108
SHORT COMMUNICATION

Age-related rhesus macaque models of COVID-19

nature
https://doi.org/10.1038/s41586-020-2324-7
Accelerated Article Preview

Respiratory disease in rhesus macaques inoculated with SARS-CoV-2

What do we aim to model?

Infection of the upper airways

Transmission of virus

Spread to lower airways

Development of **severe** COVID-19:

- Alveolar inflammation and injury
- Cardiovascular effects/thrombosis
- Involvement of other organs: gut, kidney, brain?

Long-term consequences of COVID-19:

Development of structural alterations/scarring (fibrosis) of the lungs

Immune response

Inflammation and tissue injury

Coagulation & blood vessel involvement

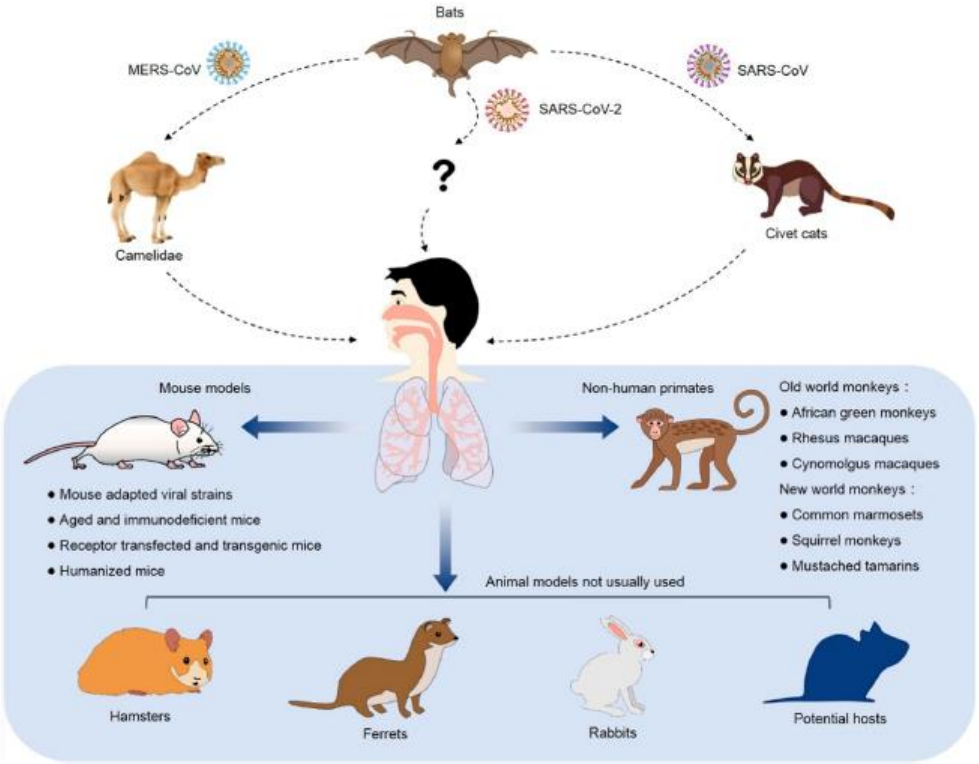
Impairment of organ function

Animal models of COVID-19

- Animal models allow studying the complex pathogenesis and multi-organ involvement of COVID-19
- Vaccine development, evaluating antiviral drugs and development of novel drugs to treat acute and long-term consequences of COVID-19

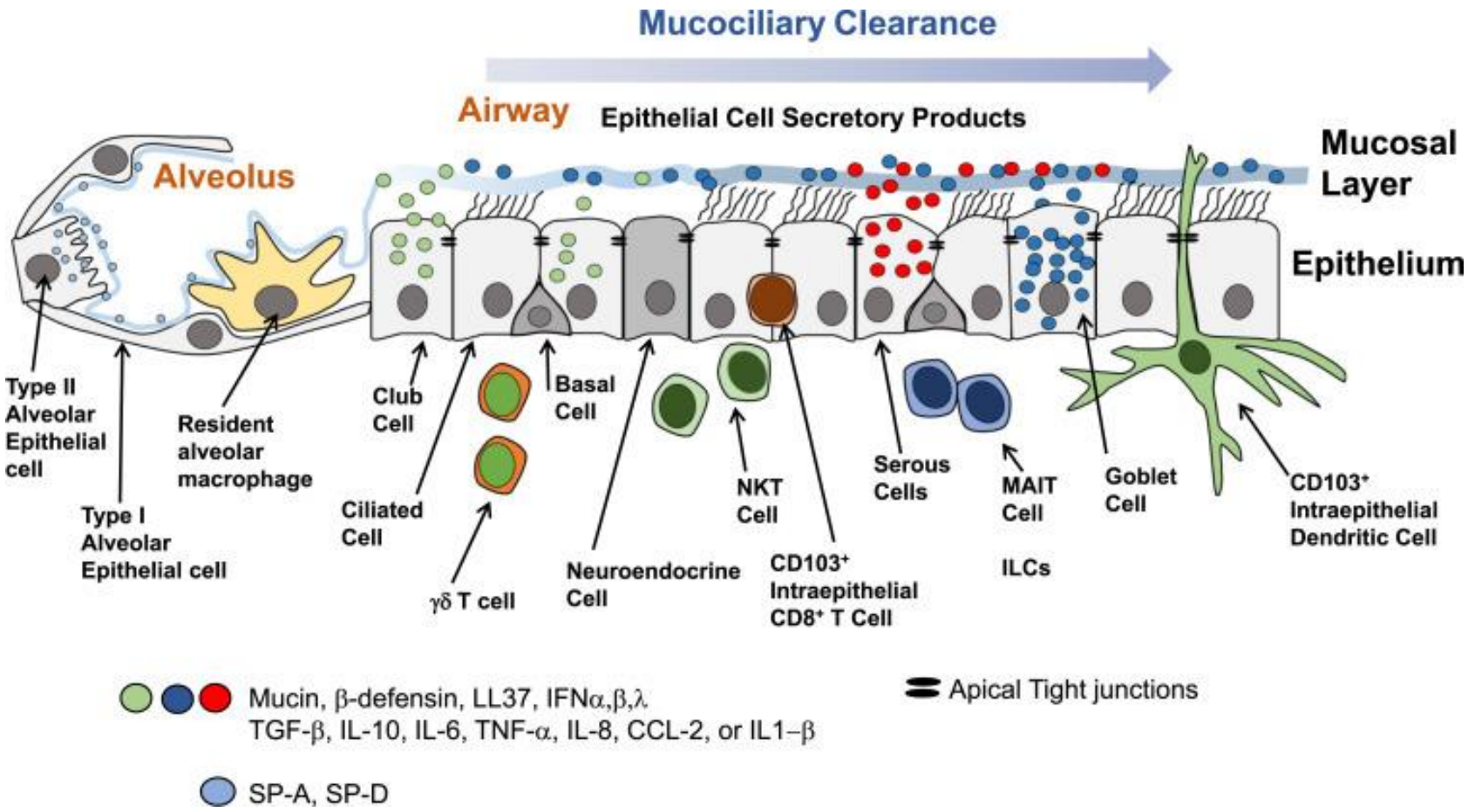
Limitations:

- Mice vs human ACE2: need for hACE2 transgenic mice
  - But: ferrets and rhesus macaques are infected
- Development of severe viral pneumonia with alveolar injury and ARDS-like features
- Modelling of risk factors, such as age & obesity



Yuan et al, Emerg Microbes Infect 2020

Epithelial host defense: a complex interplay between various cell types



Denney and Ho, Biomed J 2018

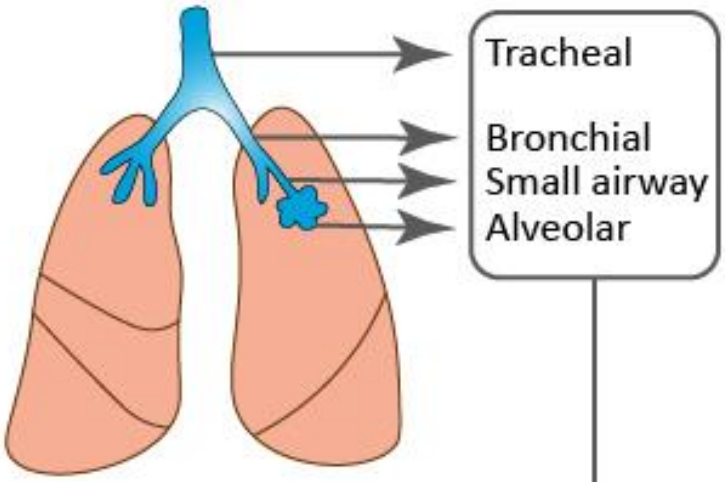
Cell culture models of COVID-19

- Aim of *in vitro* models is to create the **relevant microenvironment** because mimicking the whole body is not yet feasible

- **Matching the (cellular) element**s of this microenvironment **with the research question** is essential

- Which models are available, and which are the gaps?

Culture models to study lung epithelial cells



Tracheal

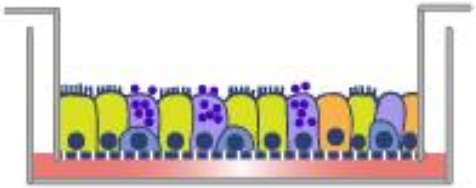
Bronchial
Small airway
Alveolar

Organ-culture:

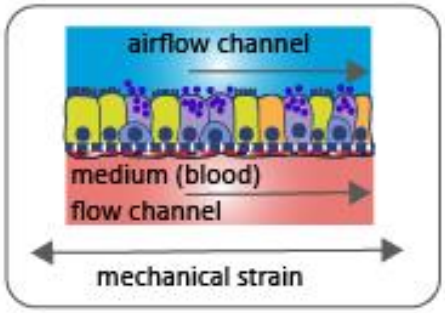
- Precision-cut lung slices
- Ex-vivo human lungs

Submerged culture

Air-liquid interface



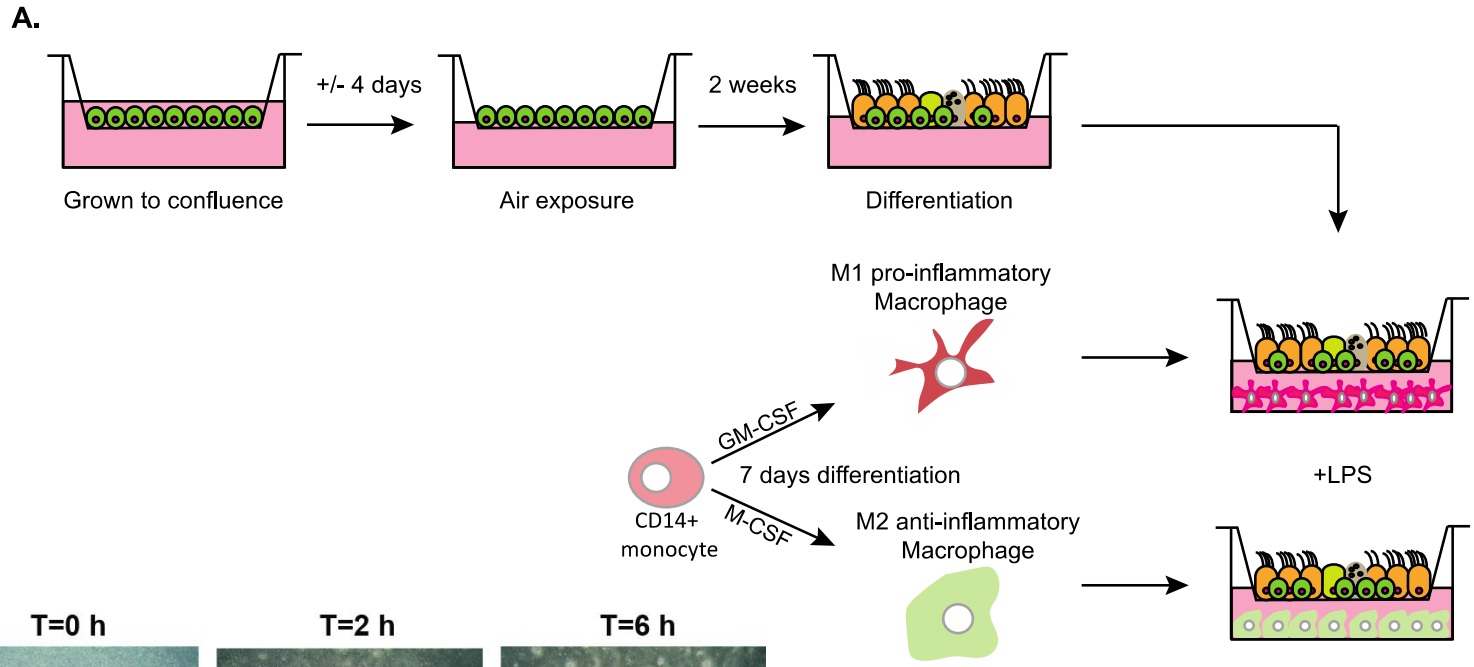
Lung-on-chip

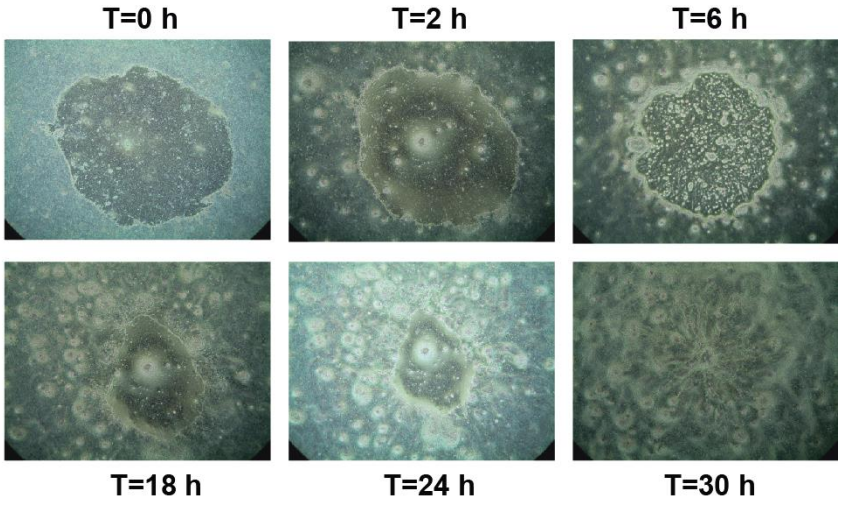


Organoid

Hiemstra *et al.* Eur Resp J 2019

Model for studying effect of macrophages on airway epithelial repair



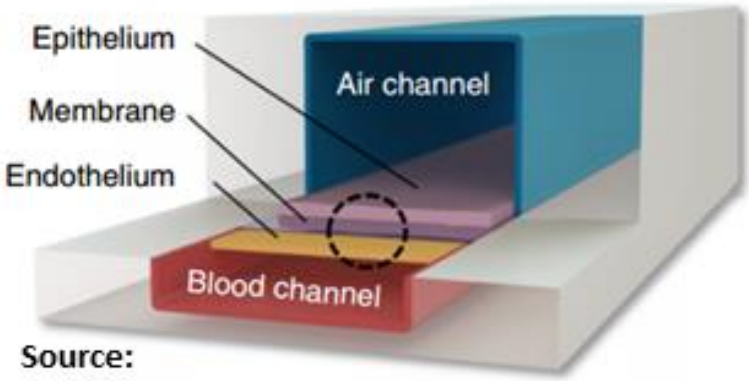


Van Riet et al, Khedoe, J Innate Immun 2020

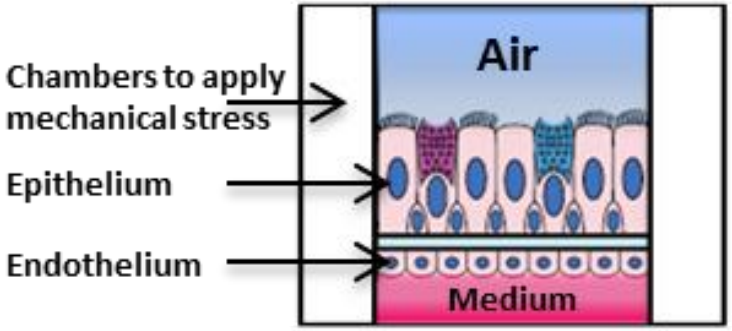
Organ-on-Chip/microfluidics models

- Chips: in-house/collaboration/commercial
- Fluidics e.g. pump system
- Complex cell cultures

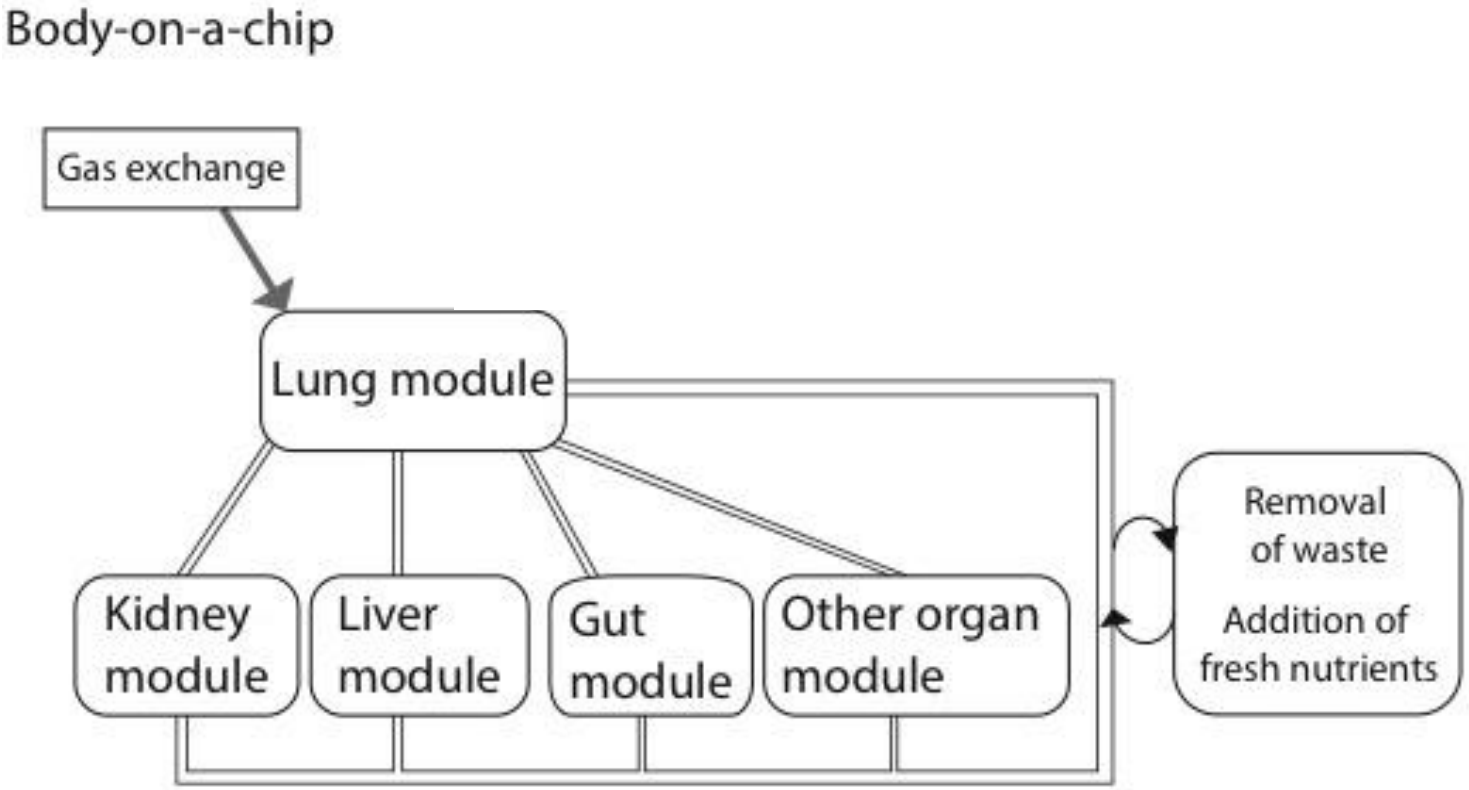
Various Organ-on-Chip platforms are available, each with specific strengths and weaknesses



Source:
Benam et al, *Nat. Methods*, 2015



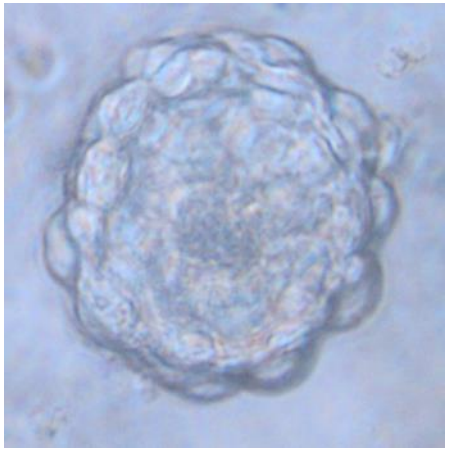
Coupling various Organ-on-Chip models to develop a Body-on-Chip

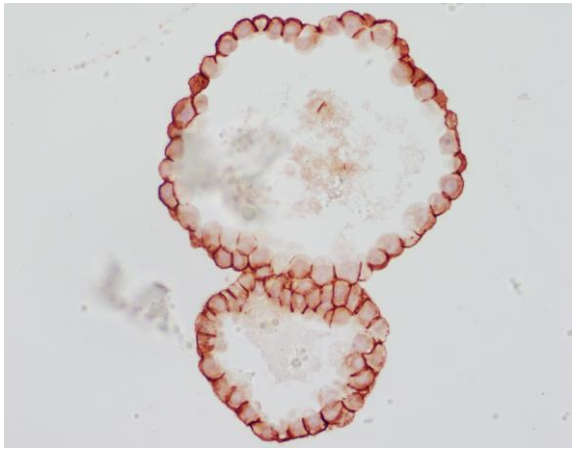


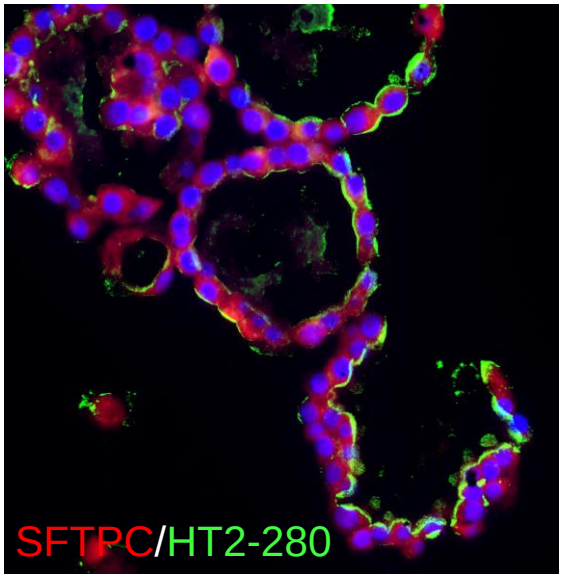
Hiemstra et al,
Toxicology in vitro, 2018

Organoids/spheroids

Definition: cultured structures that consist of *multiple organ-specific cell types*, exhibit some of the *functions* of the organ it models, and in which the cells are *grouped and spatially organized similar to an organ*

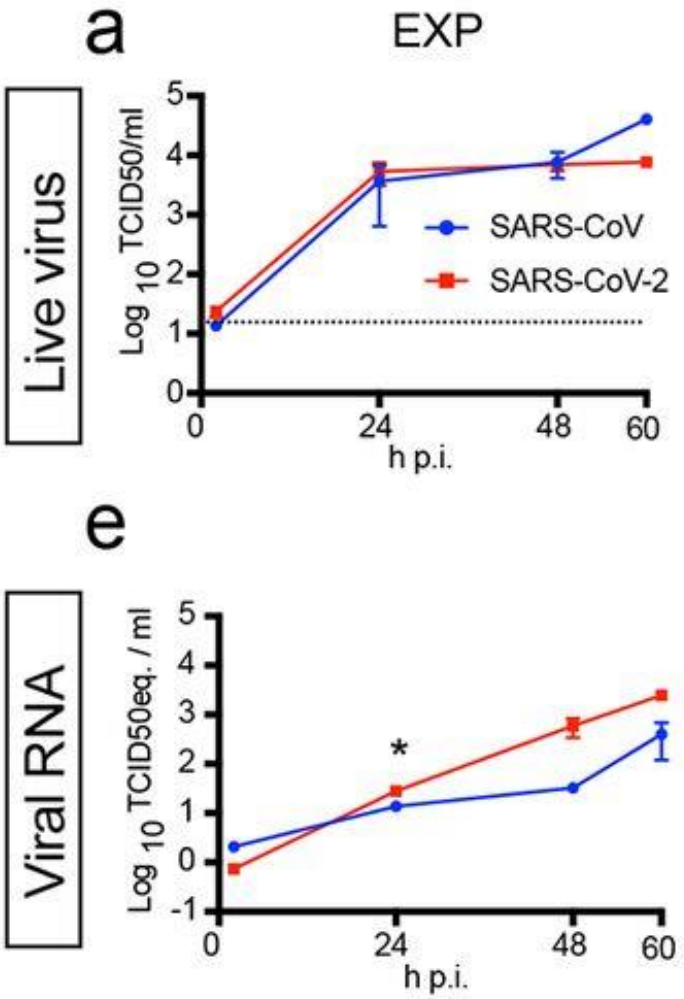






Alveolar

Replication of SARS-CoV-2 in human airway and intestinal organoids



Comparison of infection of intestinal organoids with SARS-CoV and SARS-CoV-2

Mart M. Lamers et al. Science 2020;science.abc1669

Conclusions

State-of-the-art **newly developed culture models** allow studying important aspects of COVID-19 disease

Limitations/gaps relate to:

- Use of and access to cells (primary cells versus cell lines, lung and blood)
  - ➢ increased use of *primary cells* (COVID-19 patients) and *hiPSC*
- Many models composed of single or two cell types (e.g. epithelial cells and macrophages)
  - ➢ more tailormade models composed of *various cell types* constructed based on research question
- Mimicking effects of air & blood flow, and mechanics of breathing
  - ➢ included in *Organ-on-Chip* models
- Cell-cell interactions in a tissue-structure related environment
  - ➢ *organoids*
- Interactions between organs
  - ➢ Body-on-Chip

Leiden University
Medical Center

E-mail: p.s.hiemstra@lumc.nl

Twitter: LUMC PulmoScience Laboratory @LungLabLeiden