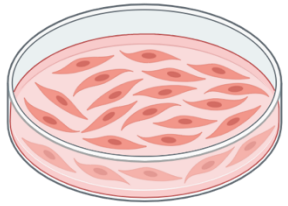
KU LEUVEN

ESRR
European Society of Radiopharmacy & Radiochemistry

Organoids: Tiny Models, Big Impact.

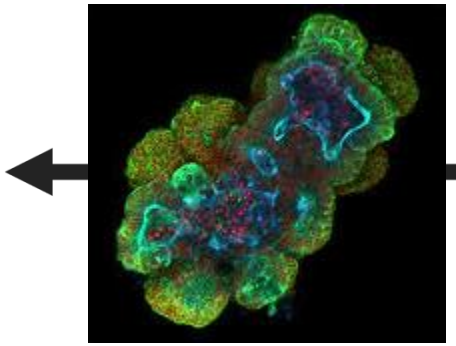
Emma Laporte, PhD

The translational gap between humans and available preclinical models



2D cell culture

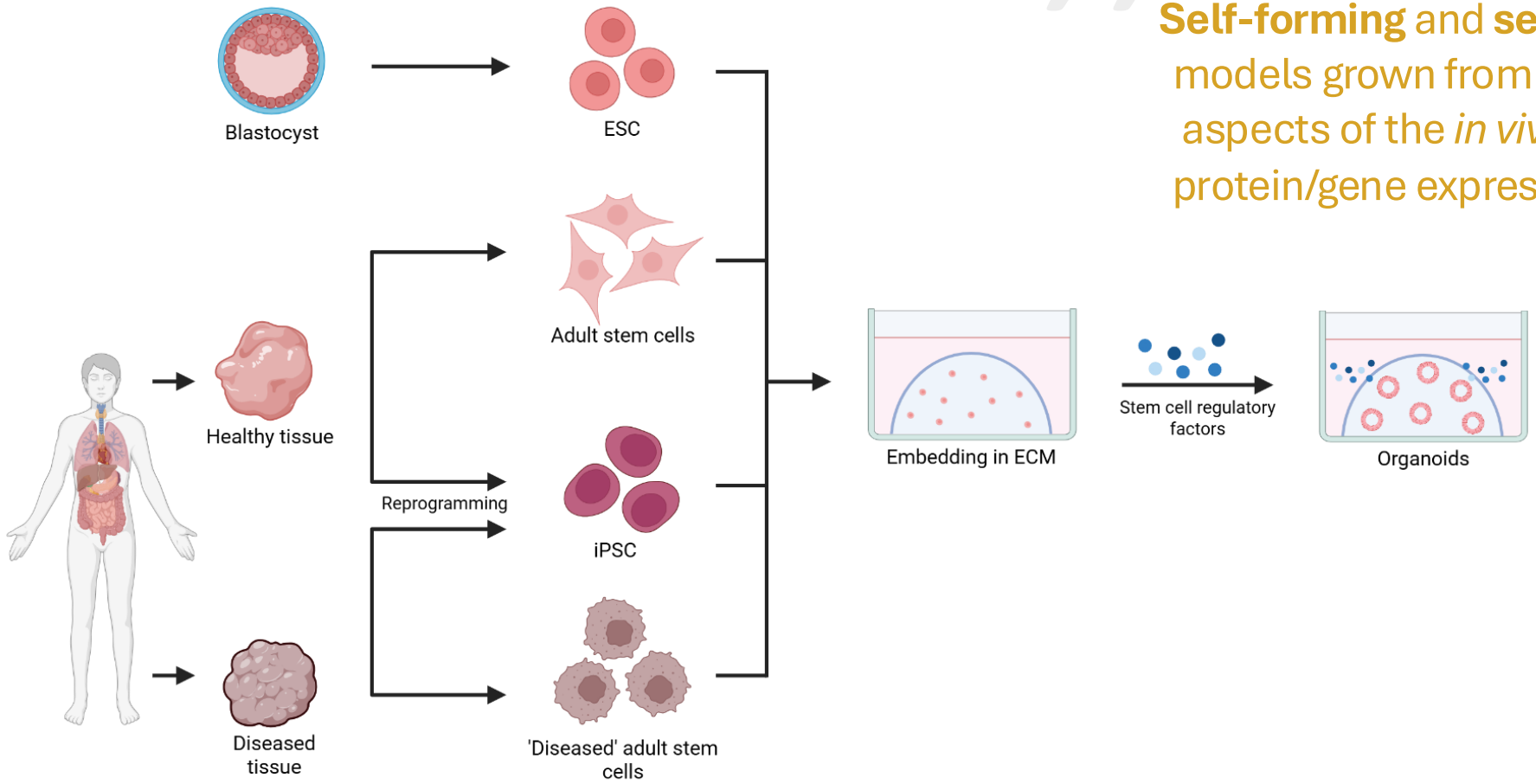
Animal models



3D human organoid models

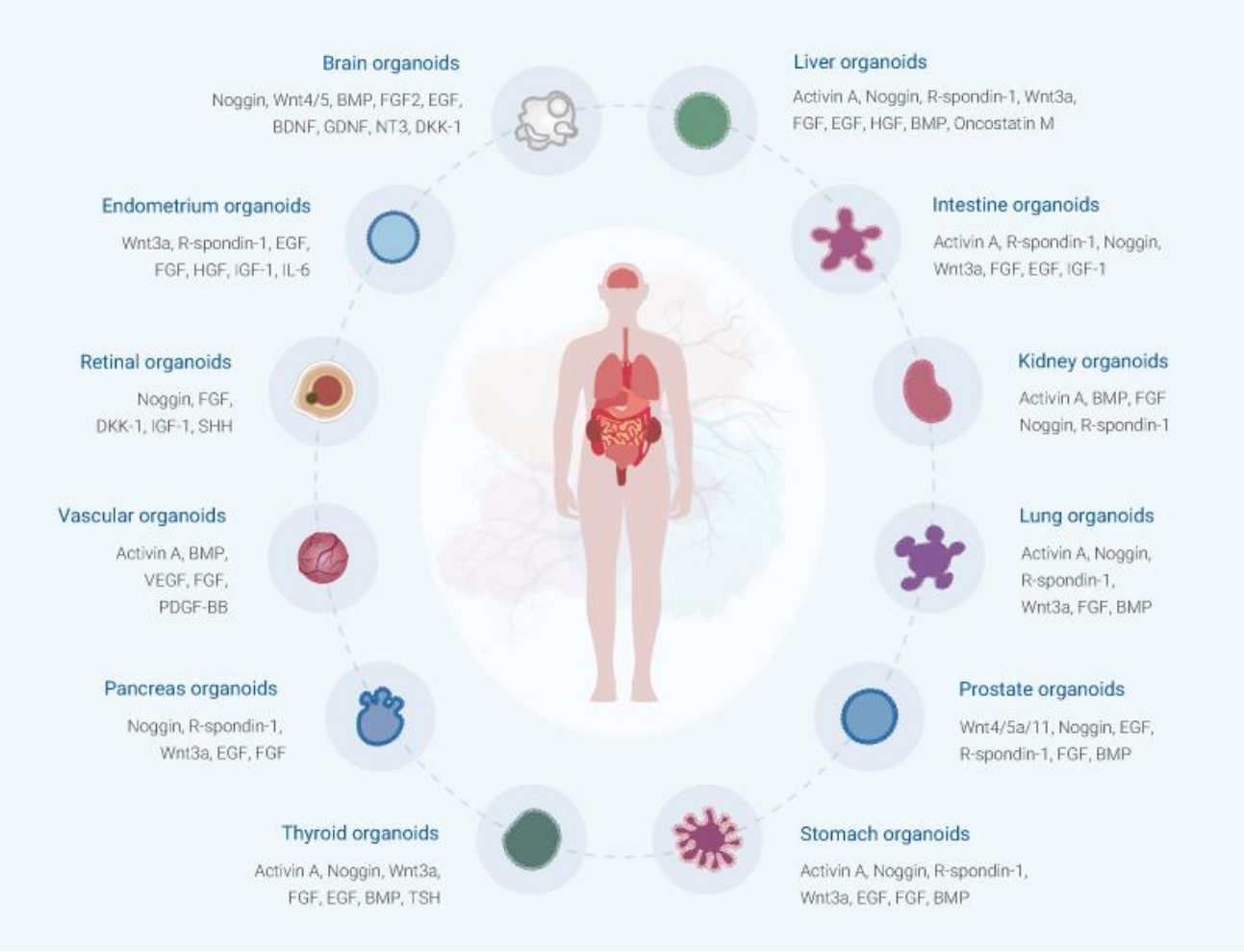
Human population

Organoids: general concept



Self-forming and **self-organizing** 3D organ models grown from stem cells that mimic aspects of the *in vivo* tissue architecture, protein/gene expression and functionality.

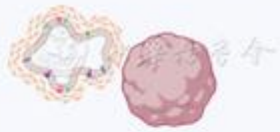
Organoids: general concept



Lung organoids

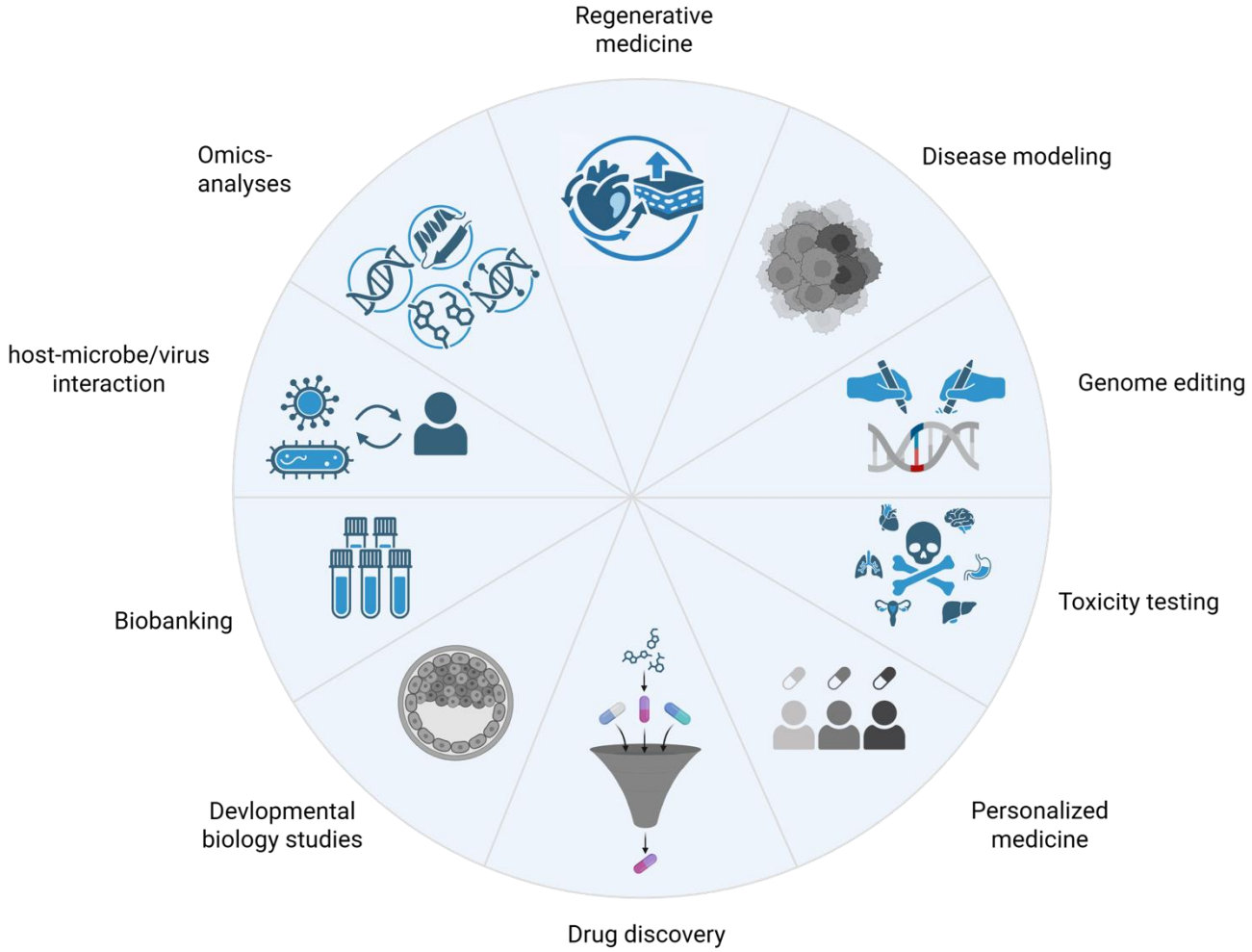
Zhou et al., *PNAS* (2018)

Organoids: (dis)advantages

✖ Not suitable ● Partly suitable ✔ Best suitable				
	2D cell culture	**Mus musculus**	**Non-human primates**	**Human organoids**
Physiological similarity to human	●	●	●	✔
Physiological complexity	✖	✔	✔	✔
Simple and easy accessibility	✔	✖	✖	●
Relative cost	✔	●	●	✔
High-throughput screening	✔	✖	✖	✔

Sun, et al. 2023

Organoids: applications



Organoids: applications – drug discovery

Target Discovery › **Lead Identification** › **Lead Optimization** › **Preclinical Safety** › **Clinical Trials**

Develop disease models that recapitulate patient genetics and epigenetics to validate drug targets

Examine the toxicity and efficacy of potential candidates to identify a lead with the highest therapeutic index

Evaluate and improve the efficacy of a preidentified lead to optimize its functionality

Anticipate the potential toxicity of a preidentified lead across multiple organ systems

Perform co-clinical trials with organoids from patients enrolled in clinical trials to precisely stratify and tailor treatments

HUB ORGANOIDS is now part of

Organoids: applications – drug discovery

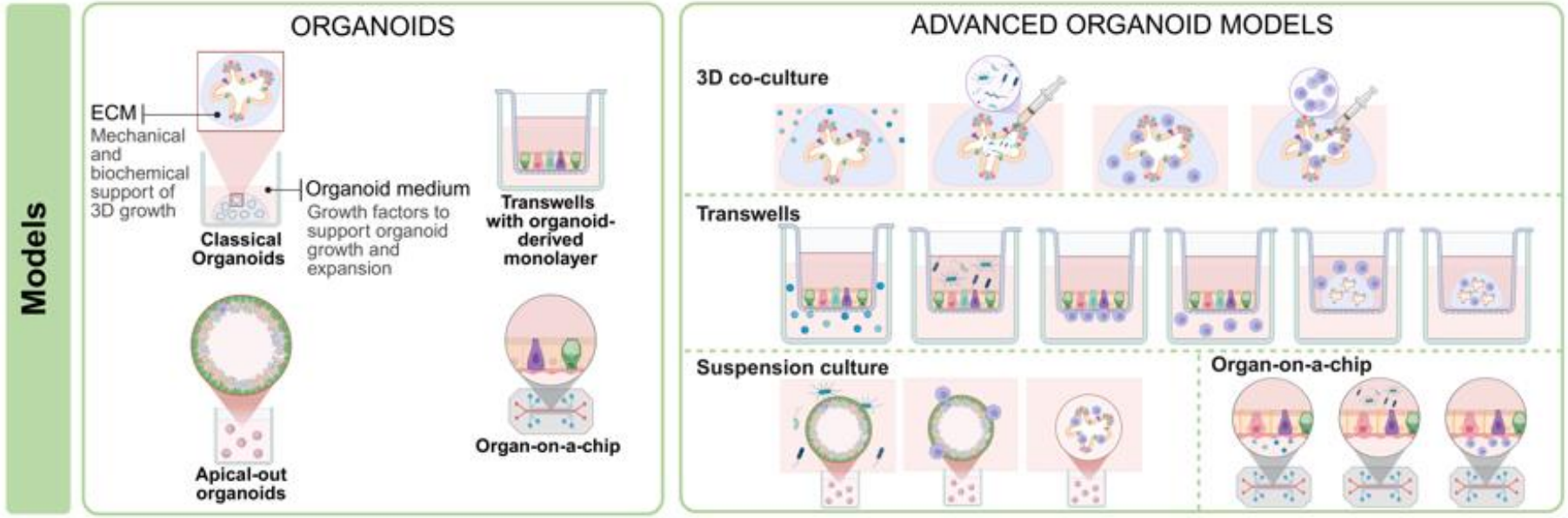
FDA NEWS RELEASE

FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs

- Human-Based Lab Models: The FDA will promote the use of lab-grown human "organoids" and organ-on-a-chip systems that mimic human organs – such as liver, heart, and immune organs – to test drug safety. These experiments can reveal toxic effects that could easily go undetected in animals, providing a more direct window into human responses.

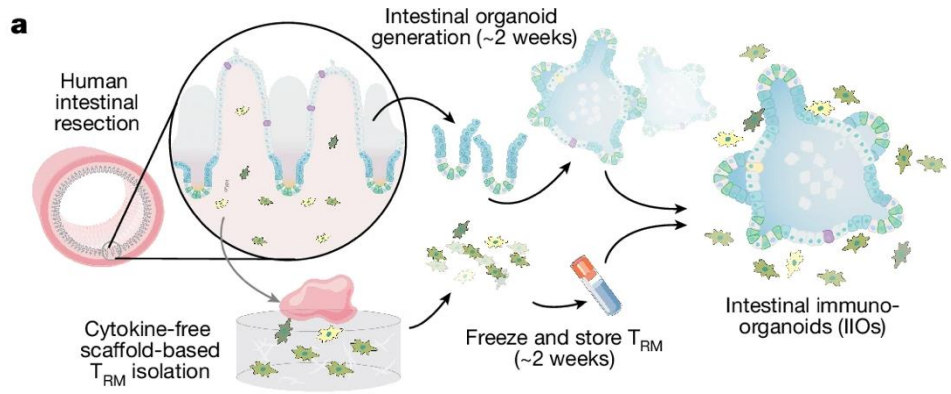
Increasing the complexity

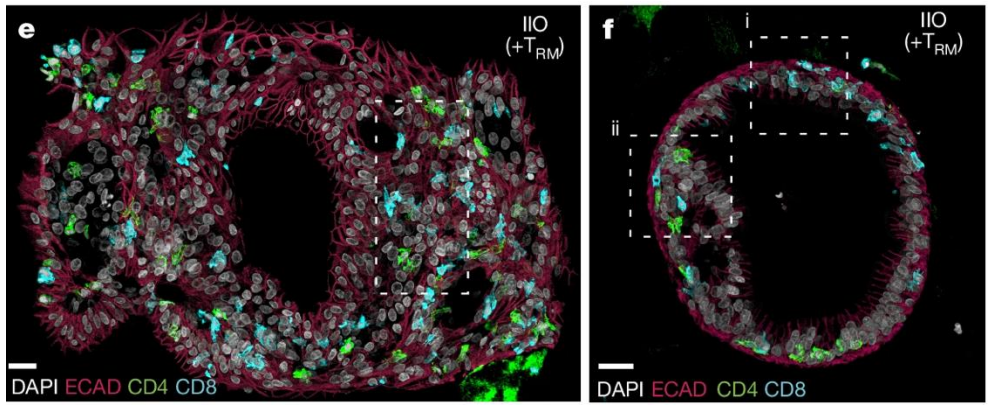
- Co-cultures
- On chip
- Bioprinting



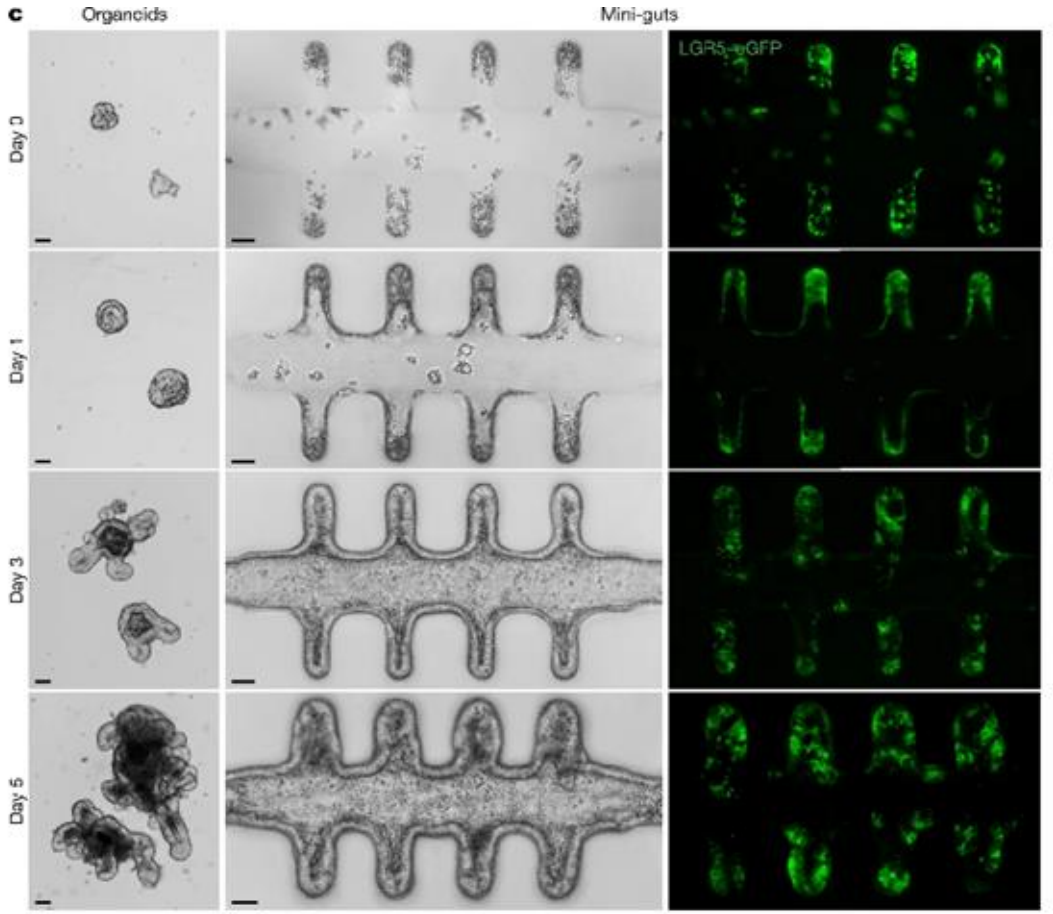
De Moor, et al. *Unpublished*. (2026)

Increasing the complexity





Recaldin et al. *Nature* (2024)

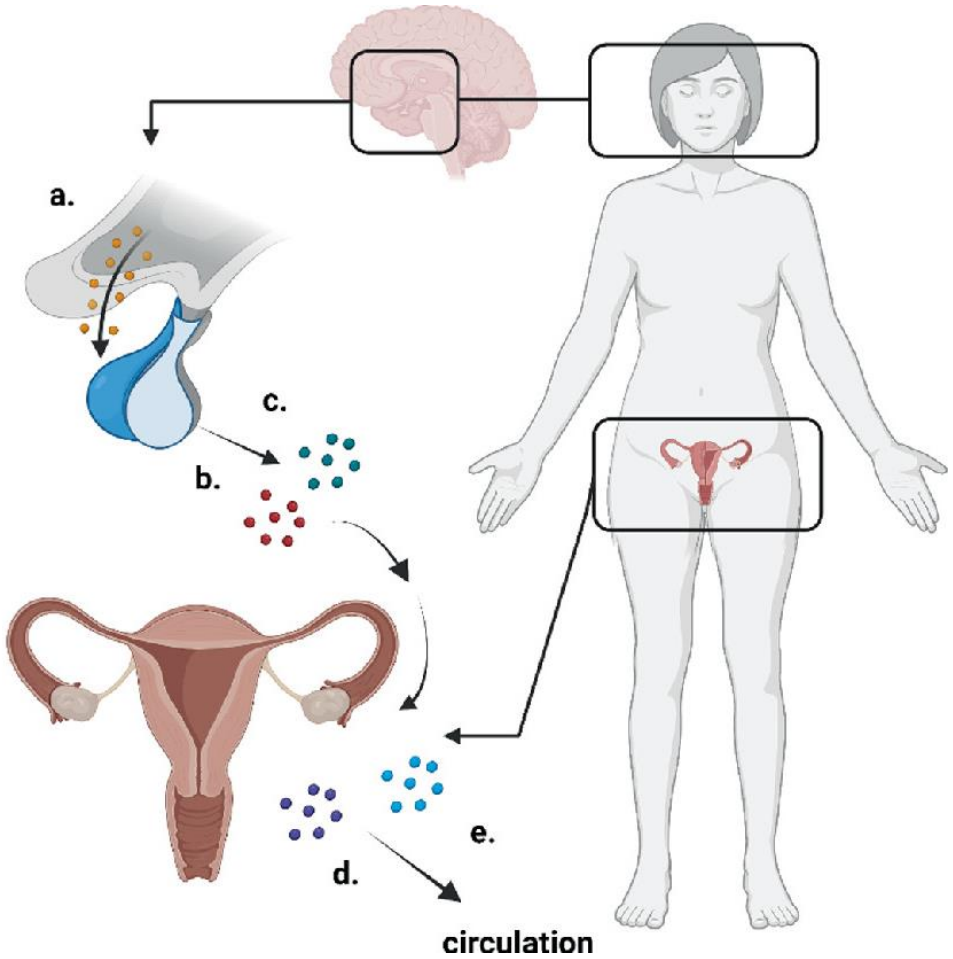


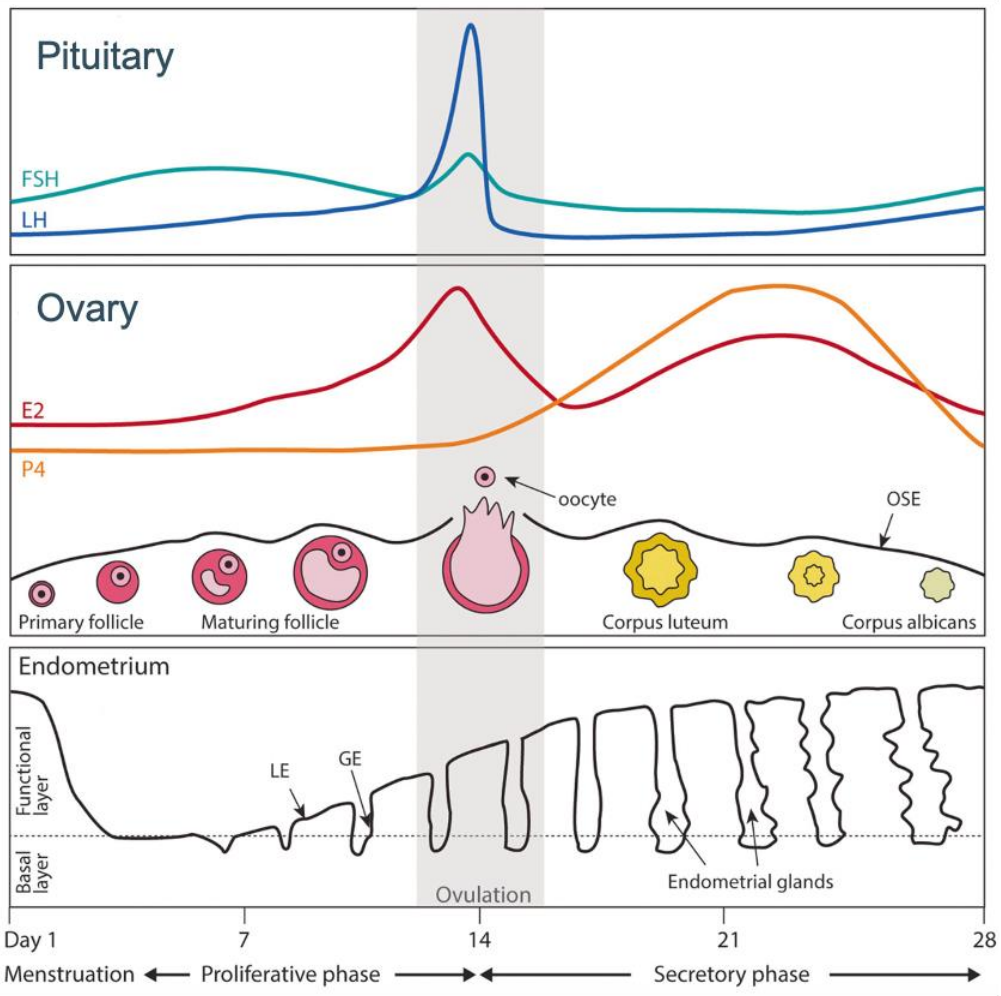
Nikolaev et al. *Nature* (2020)

Organoid modeling @Vankelcom Lab

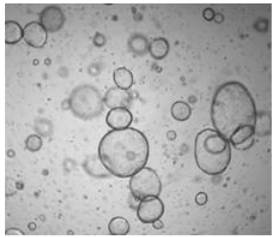
- Modeling the (reproductive) endocrine axis
  - Hypothalamus
  - Pituitary
  - Ovary
  - **Endometrium**
- Disease modeling – focus on Women's Health
  - **Endometriosis**
  - **Endometrial cancer**
  - PCOS

Modeling the (reproductive) endocrine axis



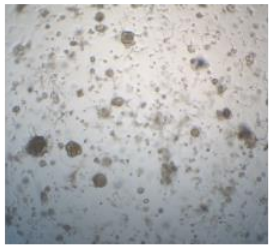


Pituitary Organoid



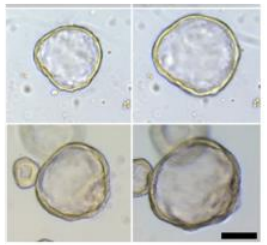
Vennekens et.al (2021)

Ovarian Organoid



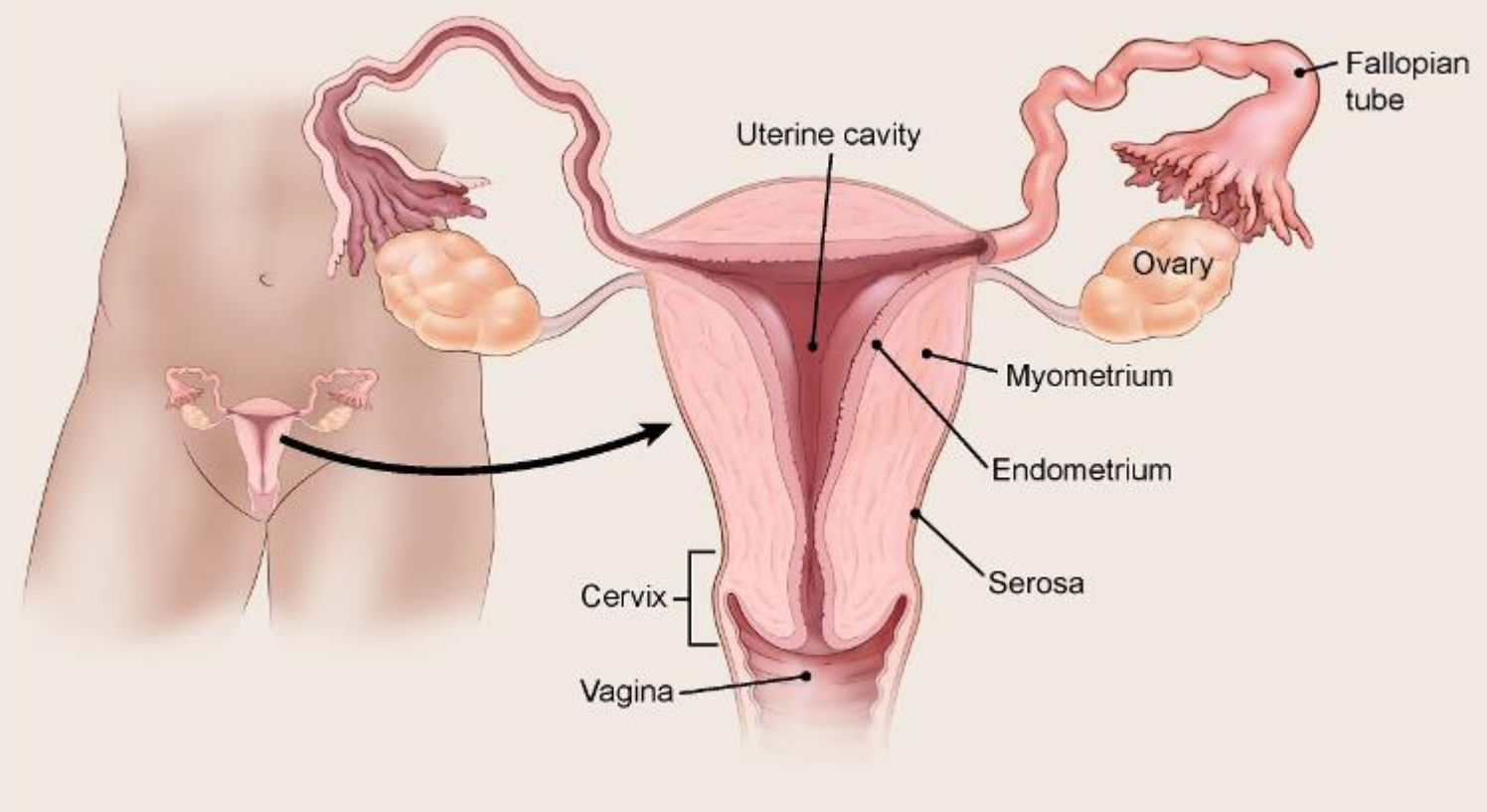
Unpublished data

Endometrium Organoid

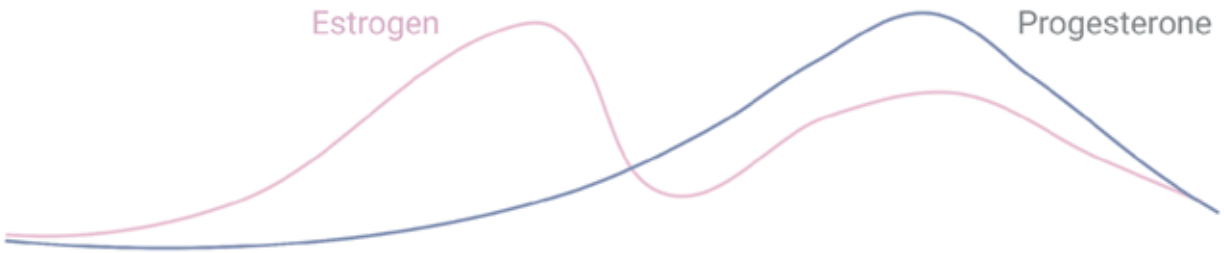


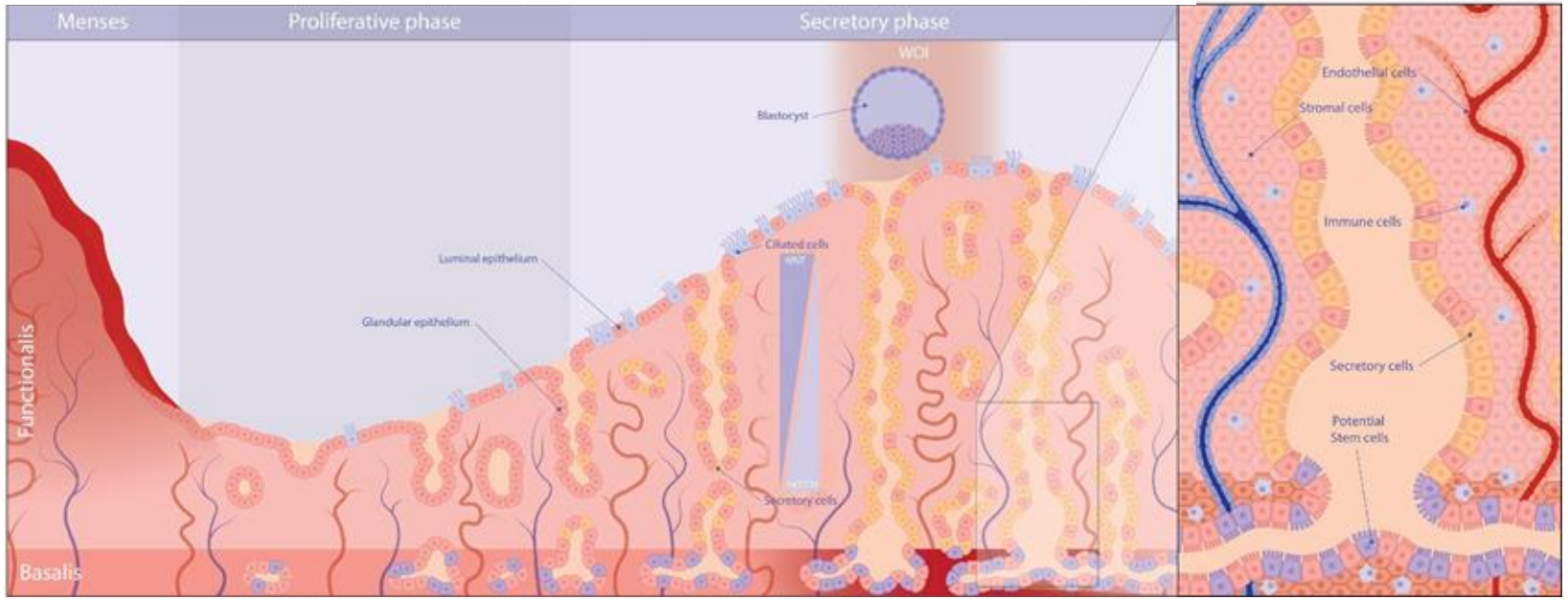
Boretto et.al (2019)

Endometrium: intro



Endometrium: intro





- Estrogen (E2)-driven proliferation
- Progesterone (P4)-induced maturation
- E2 + P4 = window of implantation

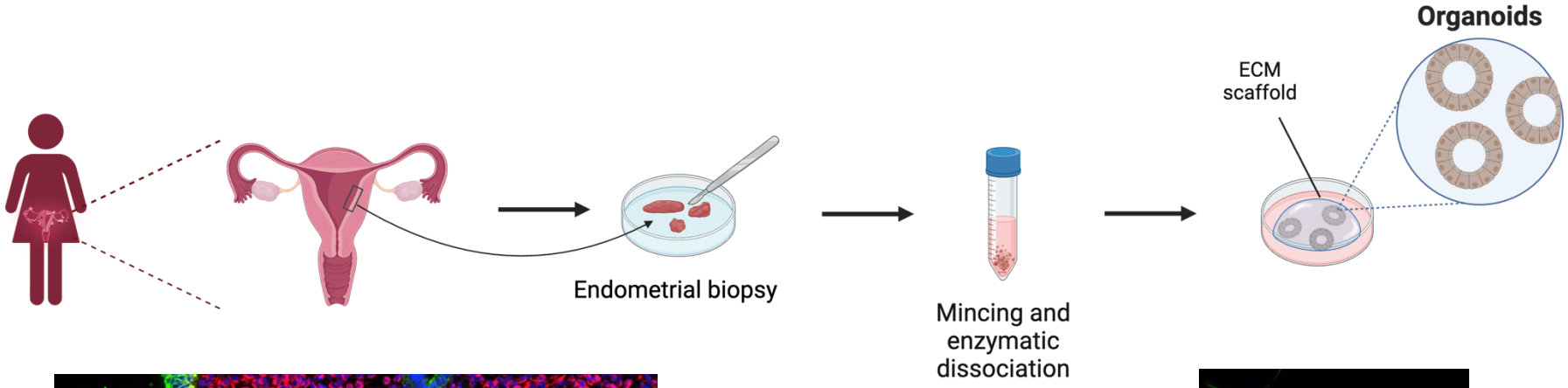
Maenhoudt *et al*. Journal of Personalized Medicine. (2022)

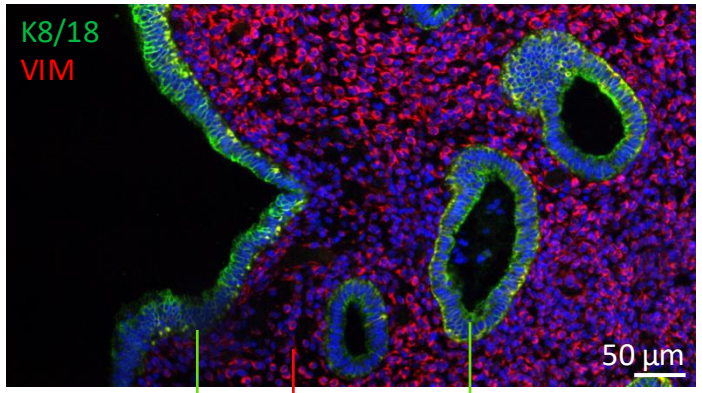
Endometrium: research models

Primary endometrial cells	Immortalized cell lines	Mouse models	Non-human primates
			
• Limited expansion • Lose hormonal regulation *in vitro* • No biobanking/drug screening platforms	• Poor biological relevance • Carcinoma-derived • No hormonal regulation	• Species-specific differences • Don't menstruate • Ethical issues	• Expensive • Difficult to maintain • Ethical issues

→ **High need for a more appropriate model**

Endometrial organoids: development

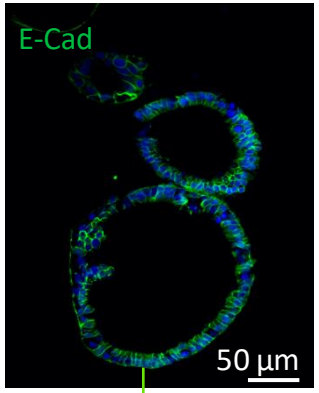




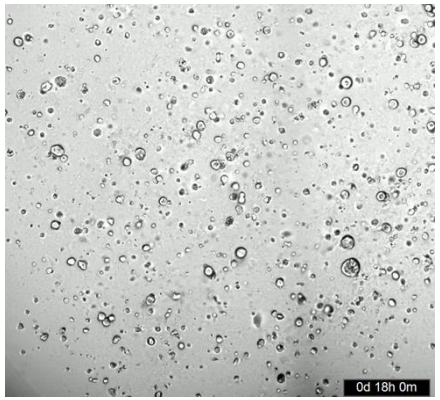
Epithelial cells (Luminal)

Stromal cells

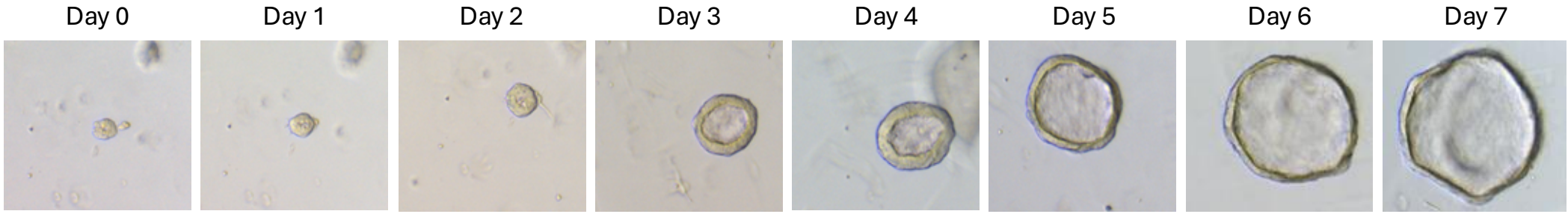
Epithelial cells (Glandular)



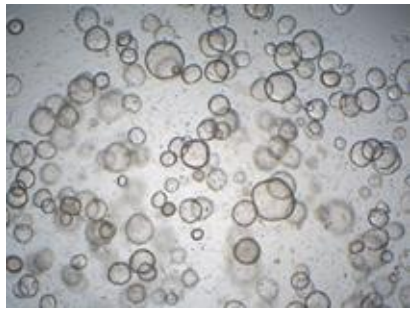
Epithelial cells



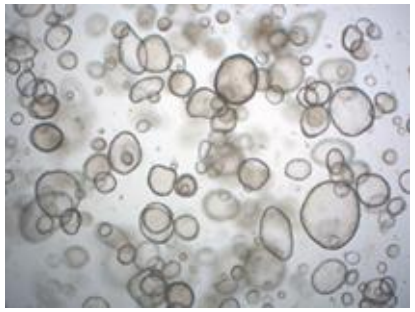
Endometrial organoids: development



Early passage

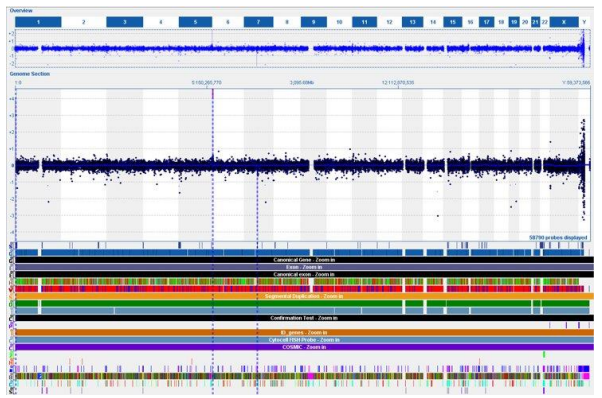


Late passage



Early passage

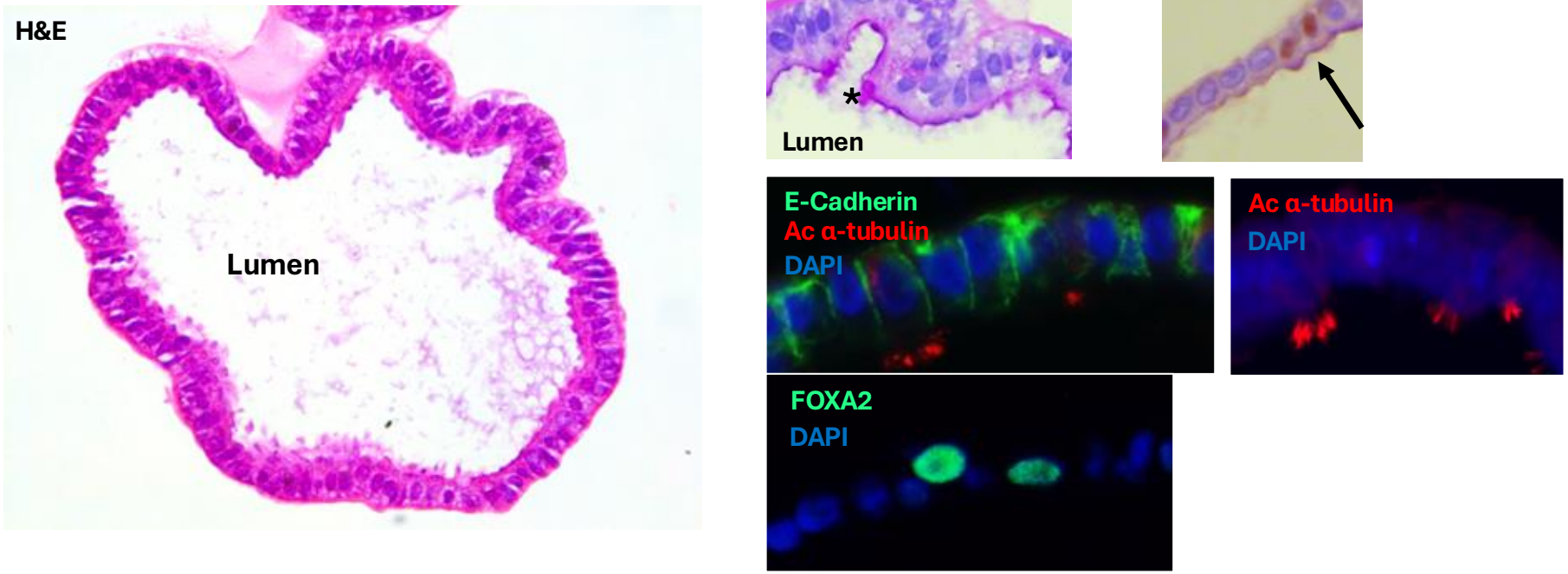
Late passage



→ Long-term, genomically stable organoids can be established from human healthy endometrium

Boretto, et al. *Development*. (2017)

Endometrial organoids: characterization

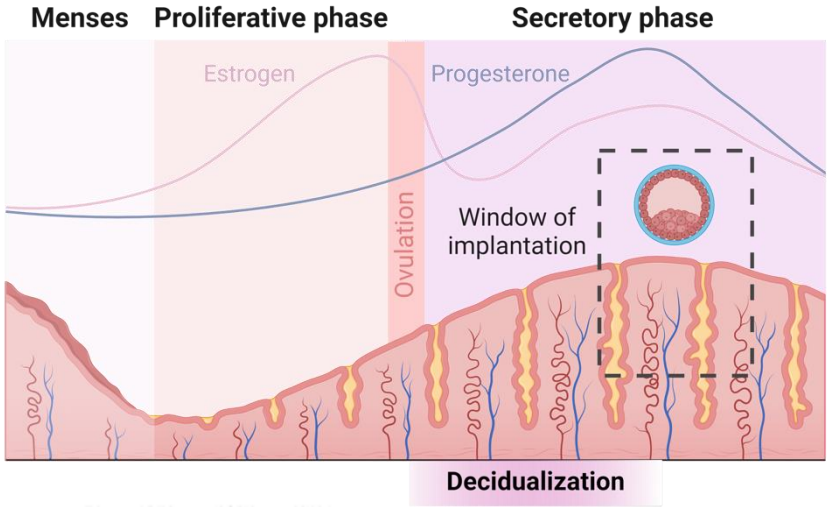


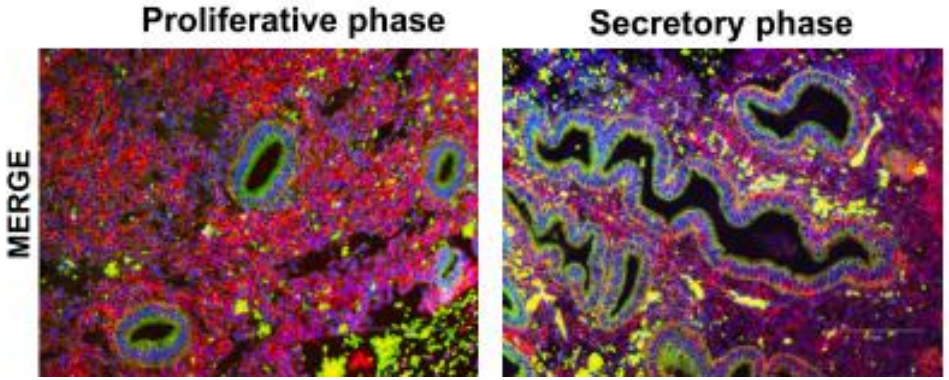
→ **Endometrial organoids recapitulate expression of endometrial markers**

Boretto, et al. *Development*. (2017)

Endometrial organoids: functionality

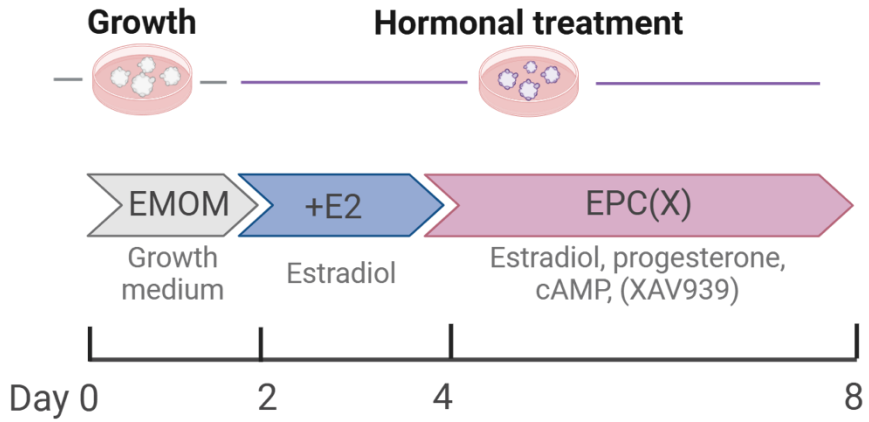
In vivo





Gnecco et al., *Med*. (2023)

In vitro

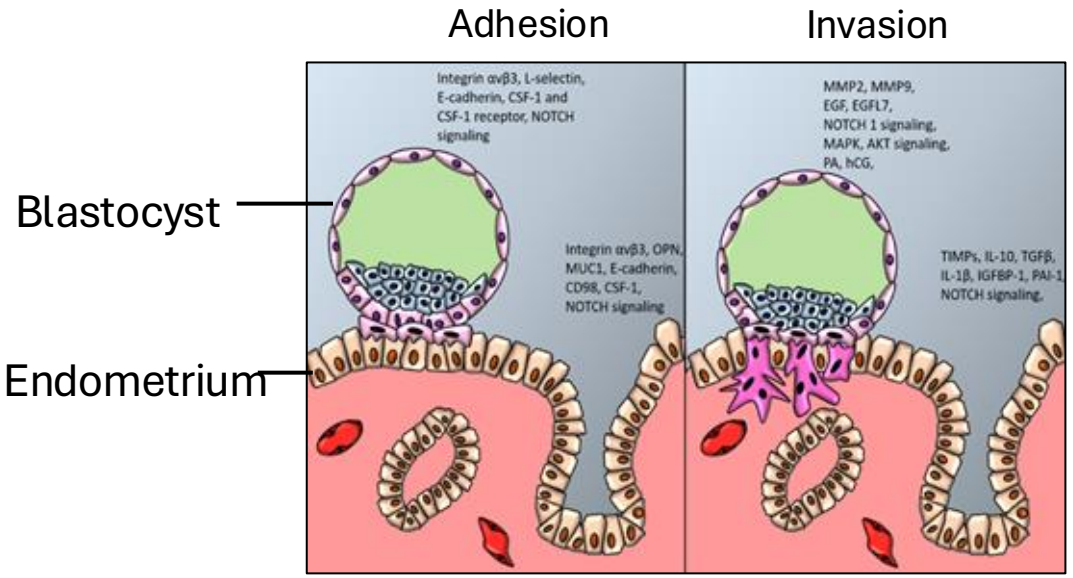


Boretto, et al. *Development.* (2017)

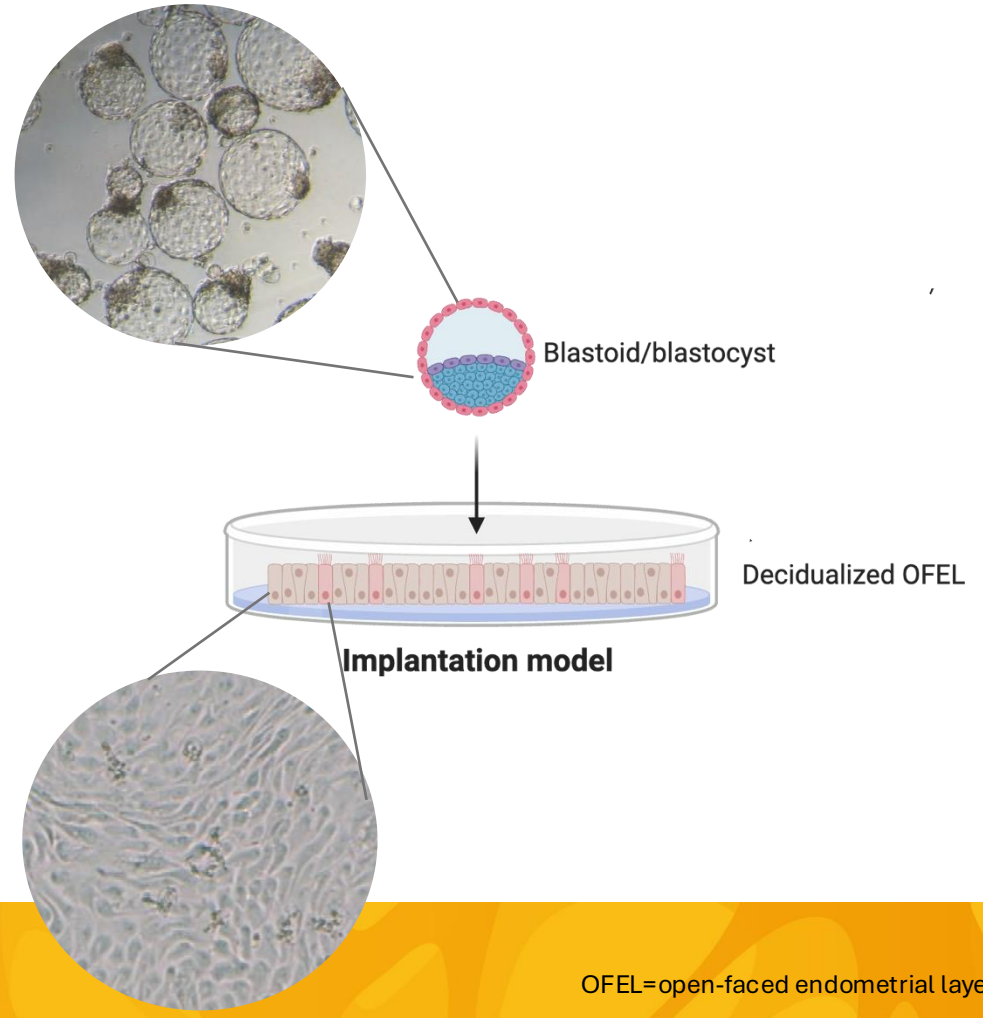
→ **Endometrial organoids recapitulate the menstrual cycle**

Endometrial organoids: functionality

In vivo

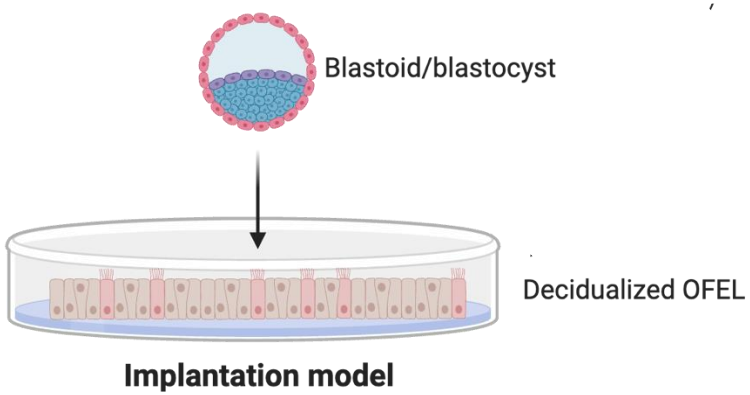


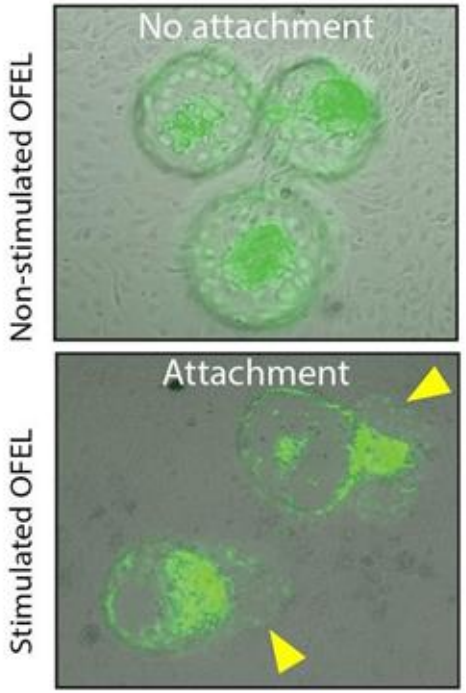
In vitro

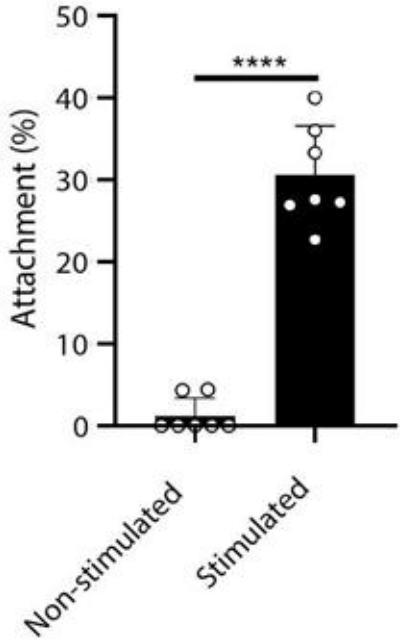


OFEL=open-faced endometrial layer

Endometrial organoids: functionality



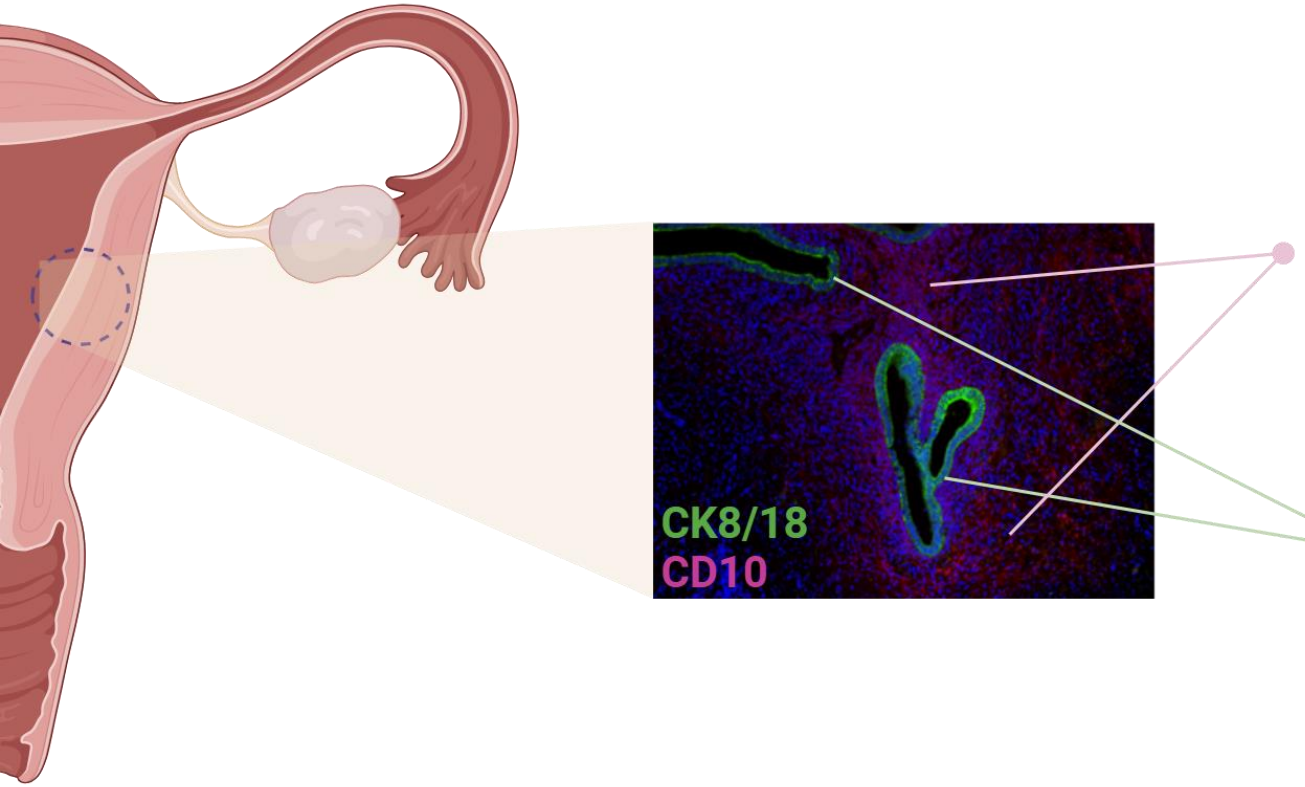




→ **Endometrial organoids can facilitate implantation**

Kagawa et al., *Nature*. (2022)
OFEL=open-faced endometrial layer

Endometrial assembloids

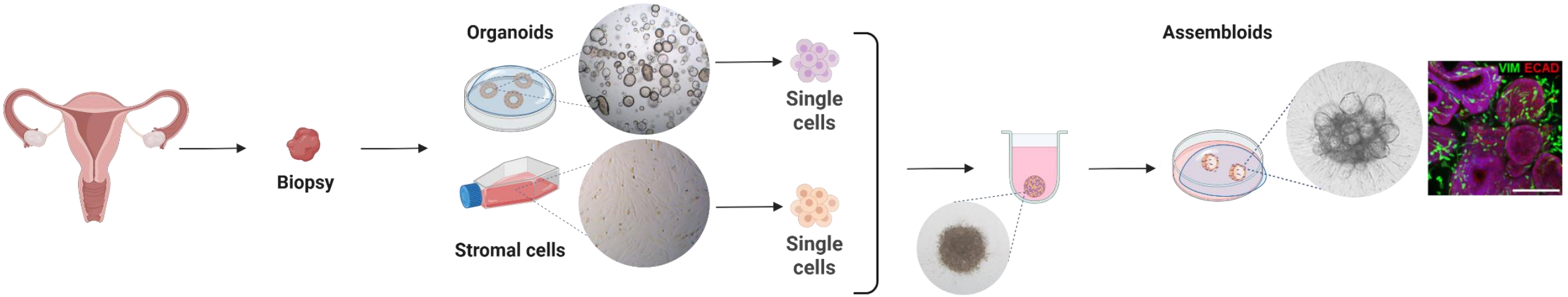


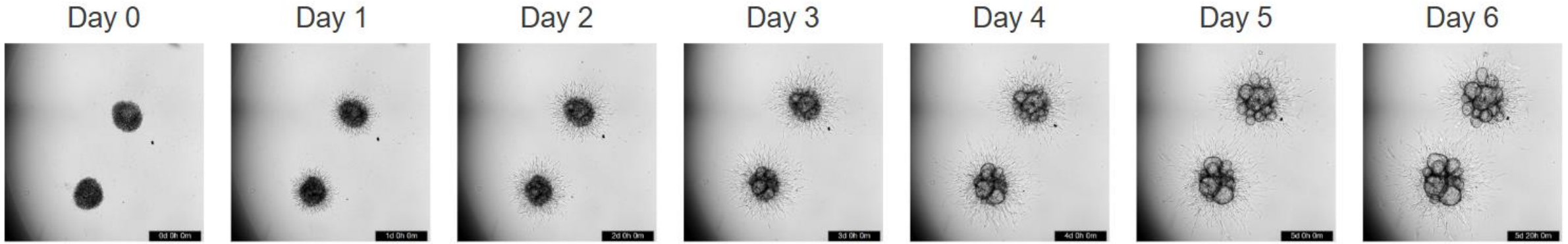
Endometrial type
stroma
Mesenchymal cells

Endometrial gland
Epithelial cells

Epithelial - niche crosstalk
- growth
- proliferation
- inflammation

Endometrial assembloids

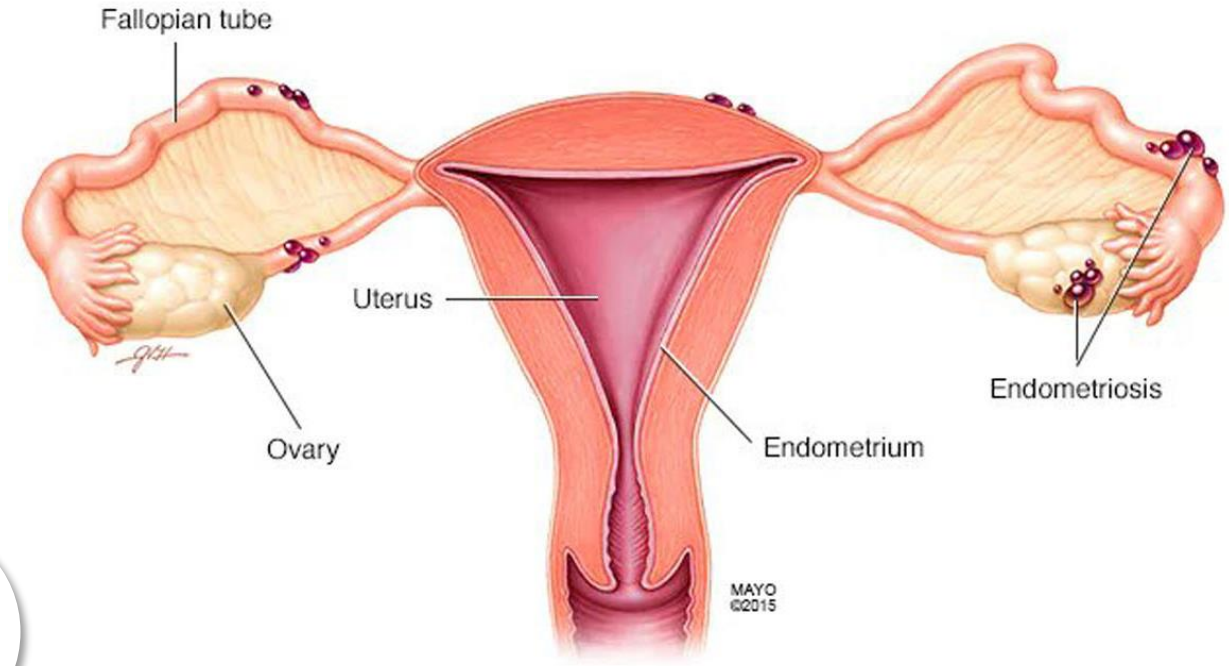




Laporte, Lorente Martin, De Moor, et al. *Unpublished*.

Disease modeling: **endometriosis**

- Chronic pelvic pain
- Severe menstrual cramps
- Painful intercourse
- Infertility



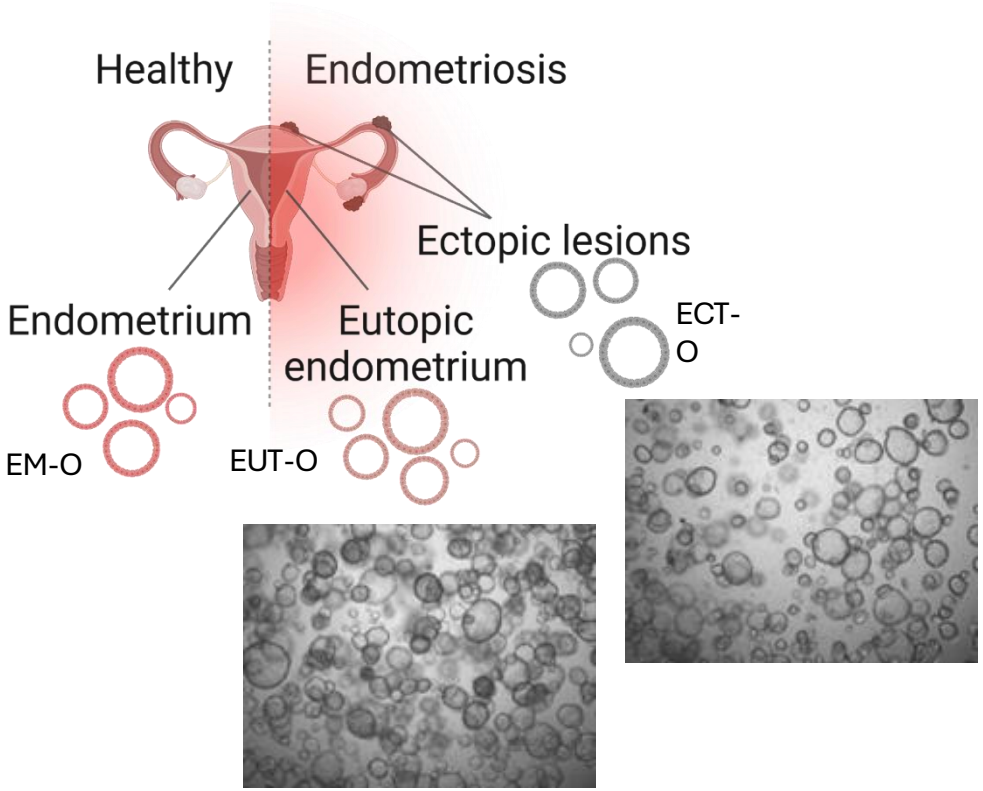
Chronic disease

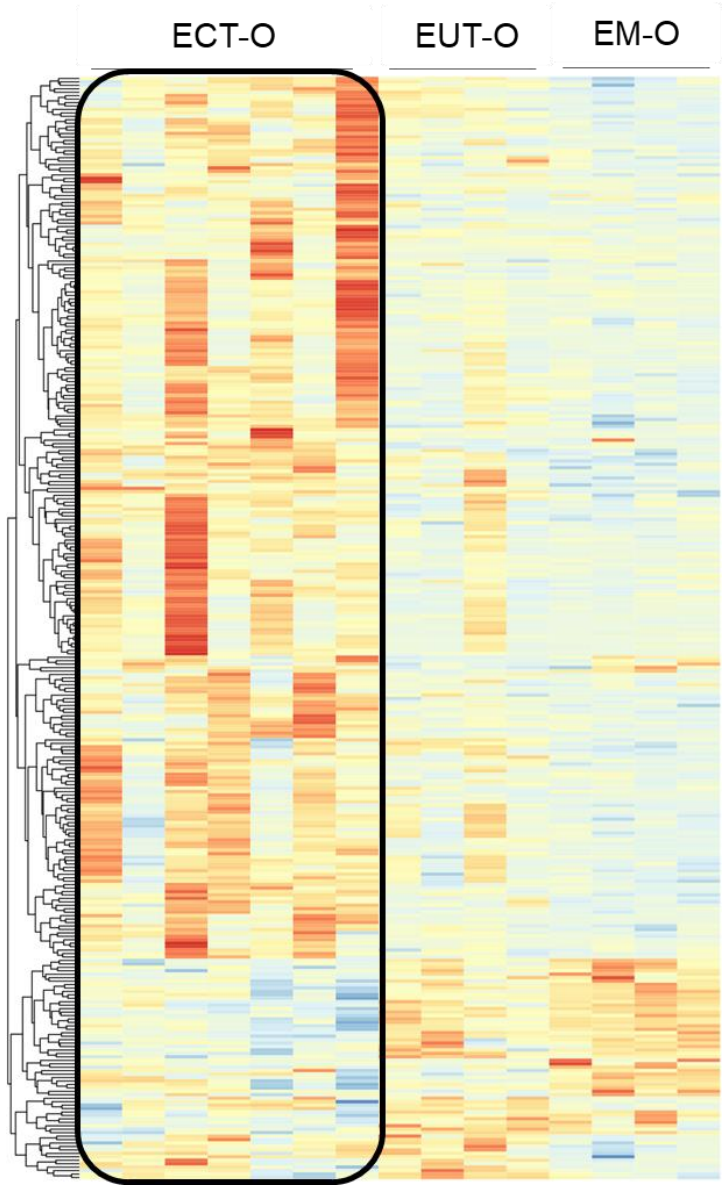
High unmet need

Global issue

190M women

Disease modeling: **endometriosis**



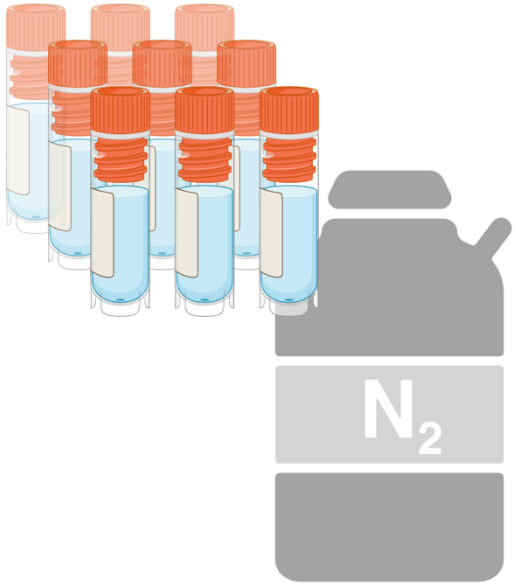


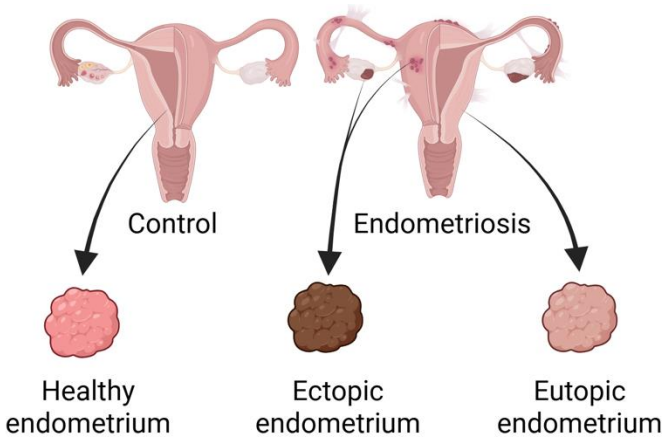
Boretto, et al. *Nat Cel Bio*. (2019)

Disease modeling: **endometriosis biobank**

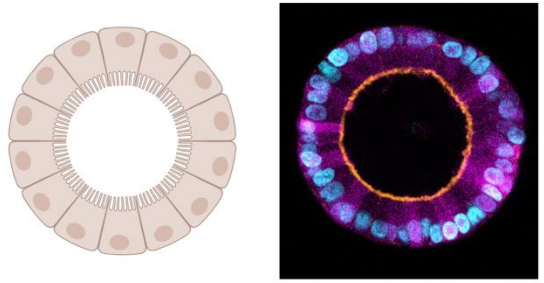
250+ women

Biobank





400+ samples



70+ organoid lines

KU LEUVEN

BioInnovation Institute

GynQura Therapeutics

ESRR European Society of Radiopharmacy & Radiochemistry

Revolutionizing the treatment of endometriosis

Target identification

Integrated omics analyses

Target validation

Organoid-based phenotypic read-outs

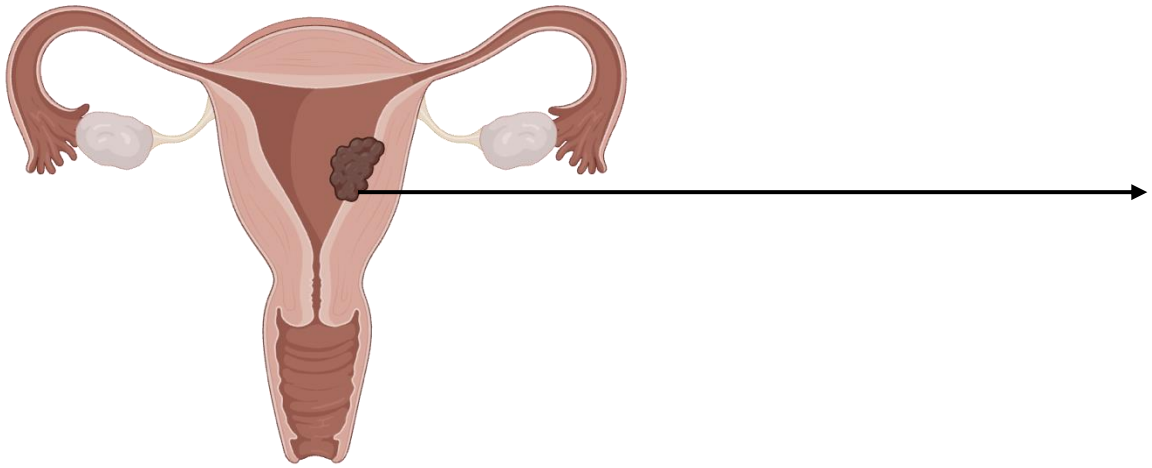
Therapeutic screening

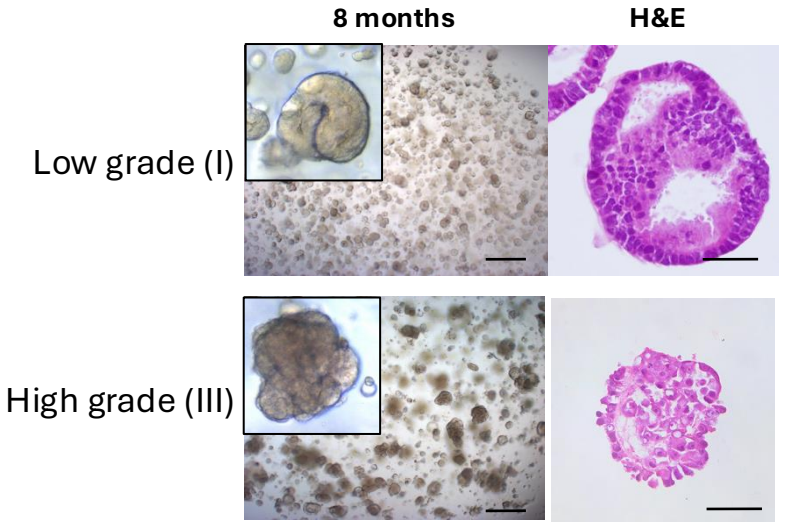
Fully automated organoid screening platform

Organoids are used during **key steps** of the **drug discovery process**

Disease modeling: **endometrial cancer**

- Most common gynecological malignancy
- Rising incidence and mortality
- High recurrence rates
- Limited treatment options

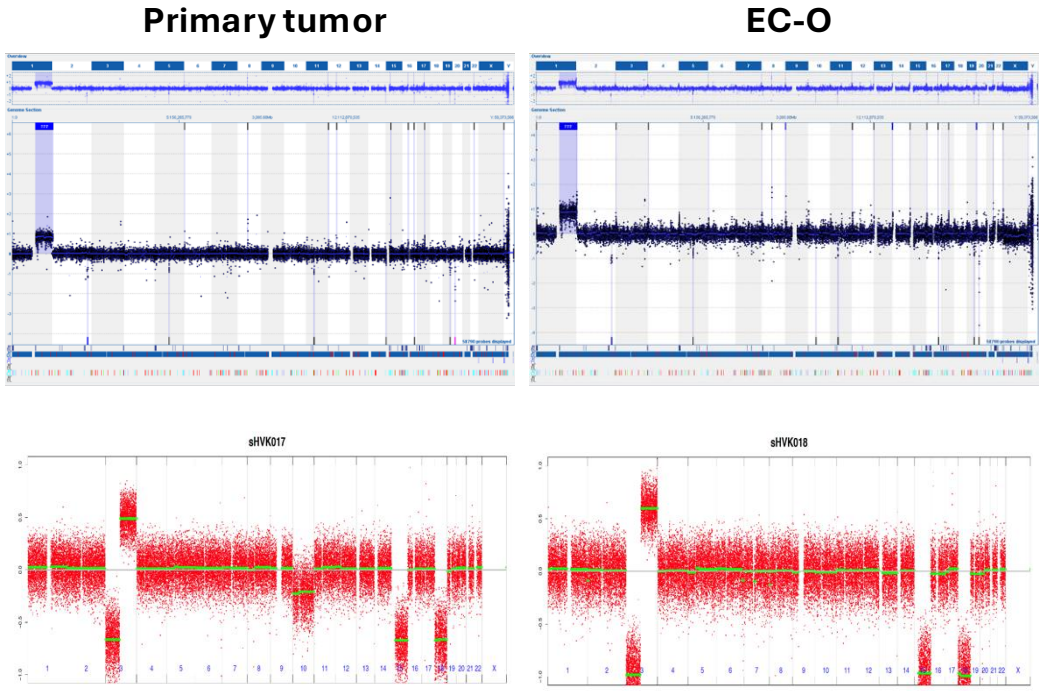




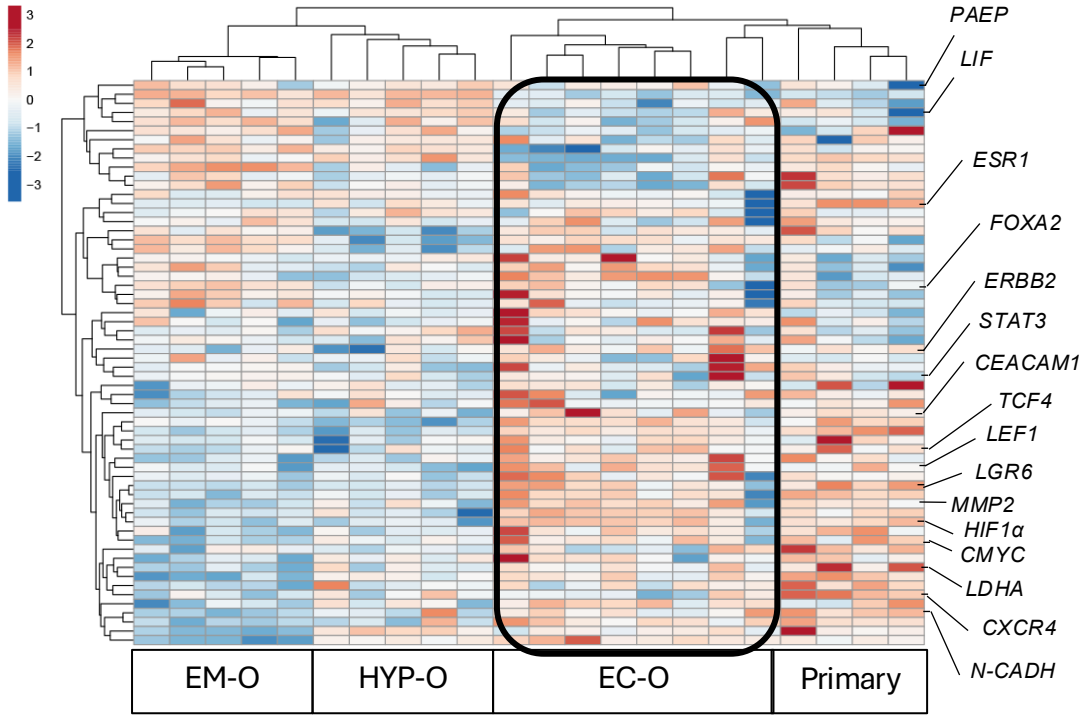
Boretto, *et al. Nature Cell Biology*. (2019)

Disease modeling: **endometrial cancer**

Array CGH

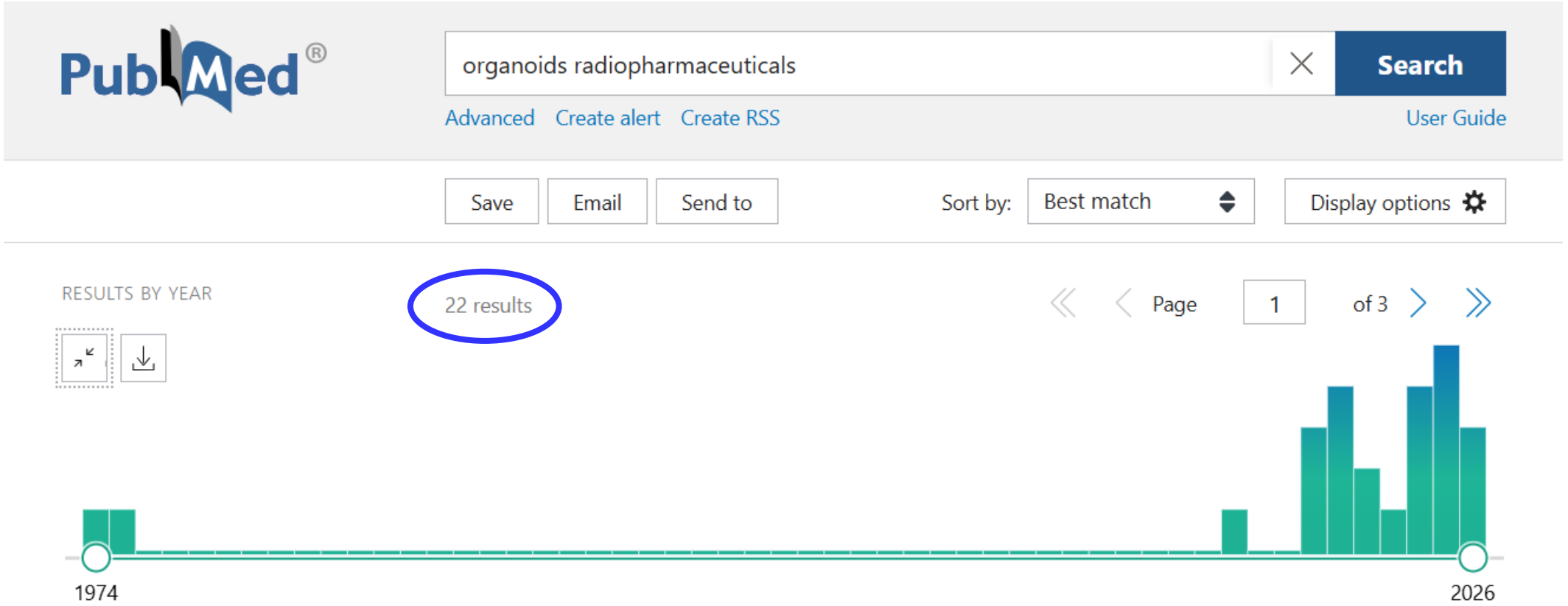


Bulk RNA-seq



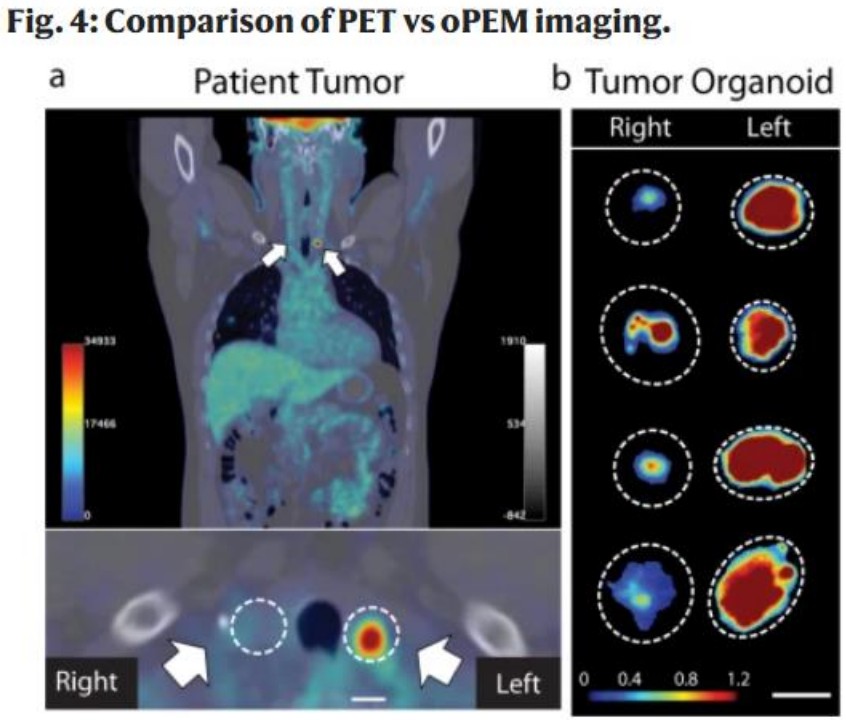
Boretto, *et al*. Nature Cell Biology 2019
EC-O = endometrial cancer organoid

Organoids & radiopharmaceuticals



Organoids & radiopharmaceuticals

- Image clinical radiotracers
- Validate radiopharmaceutical targets
- Predict patient-specific radiation response
- Study radiation biology mechanisms
- Assess normal-tissue toxicity
- Enable theranostic development pipelines



Khan, et al. *Nat Com.* (2021)

oPEM = Positron-Emission Microscopy of Organoids

Thank you!

Lab of Tissue Plasticity
Prof. Dr. Hugo Vankelecom
Ellen De Pauw, PhD
Silke De Vriendt
Amber De Moor
Celine Bueds
Mengjie Wei
Berkehür Abaylı
Beau Gommers
Ana Lorente Martín
Lixian Liu
Ulrieke Van Gestel
Fien Vermeire
Lotte Lievens
& previous members

Lluis lab
Prof. Dr. Frederic Lluis Vinas
Tijs Vanhessche
Gwenny Cosemans

UZ Leuven
Prof. Dr. Carla Tomassetti
Prof. Dr. Arne Vanhie
Dr. Celine Bafort
Prof. Dr. Sharon Lie Fong
Prof. Dr. Lieven Dupont
Prof. Dr. Els Van Niewenhuysen

Contributing patients

GynQura team
Panagiota Kakni, PhD
Diede Cresens
Paolo Cardile, PhD
Frauke Christ, PhD
Maj Hedtjärn, PhD

Images created with BioRender.com