



NIH Office of Research on Women's Health (ORWH)

The Female Reproductive Microphysiologic System

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#ResearchForWomen

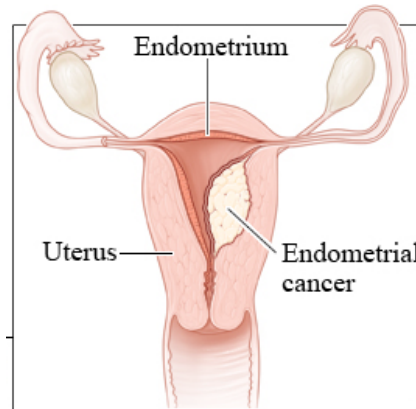
Kim Lab: Understanding Development and Growth of Uterine Diseases

Sex Hormones, Obesity, Genetics, Race

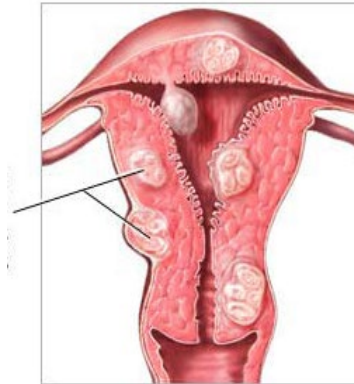
Northwestern
University



Endometriosis

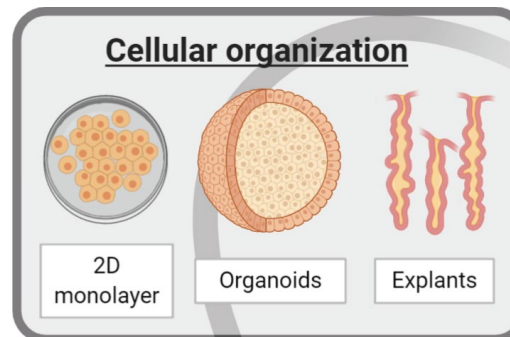
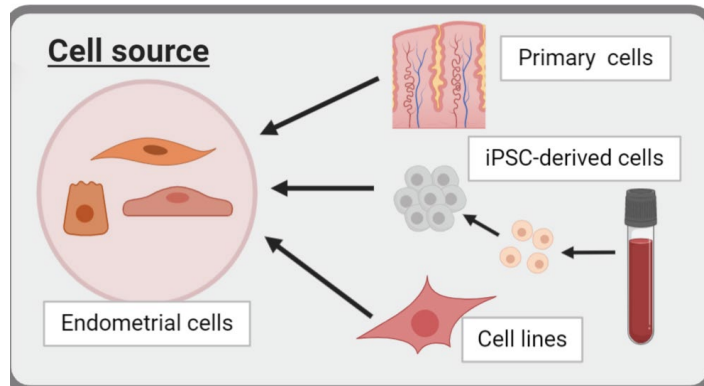


Endometrial Cancer



Uterine fibroids

In vitro physiological modeling



Medicine is **FAILING** Women's Health



Toxicity with new drugs



Menopause



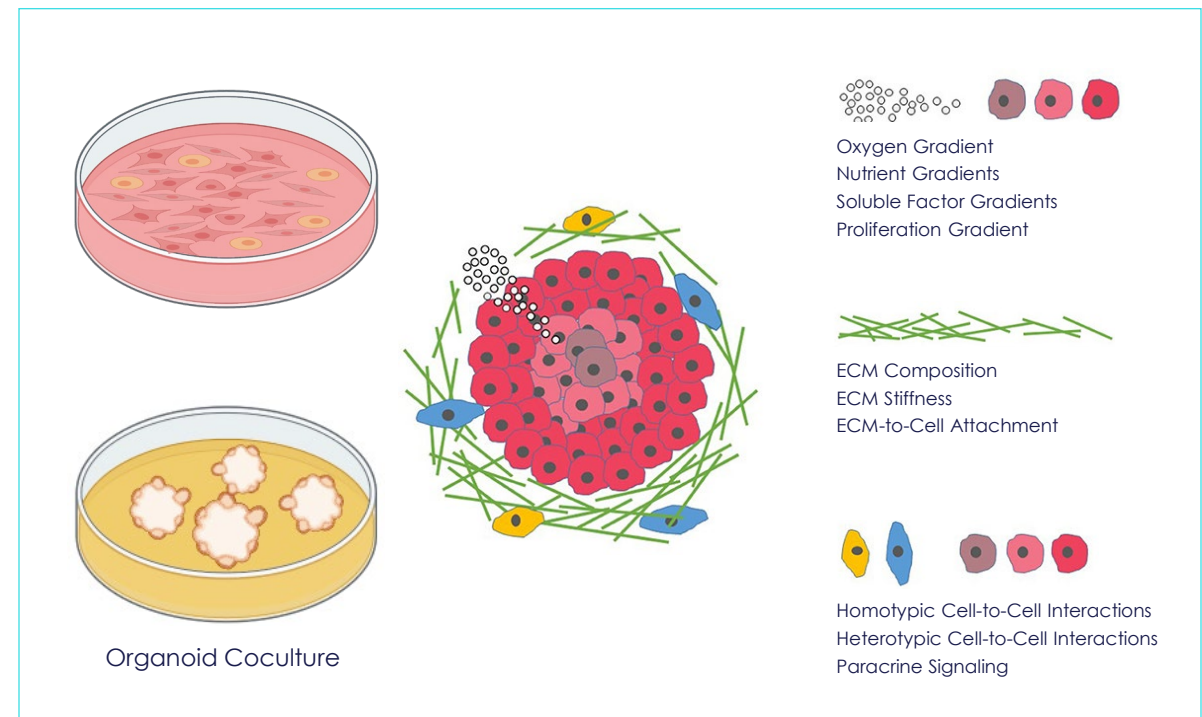
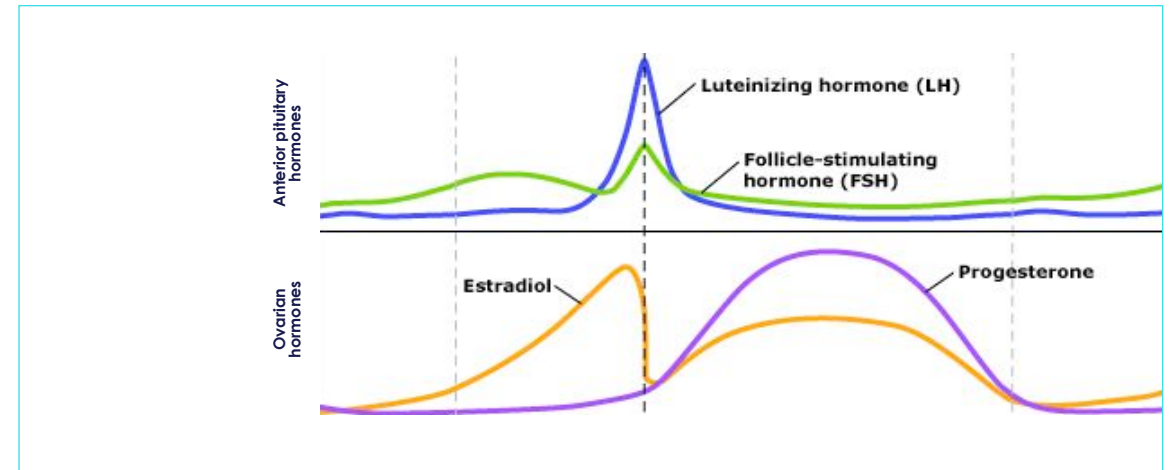
Gynecologic diseases



Age-related fertility

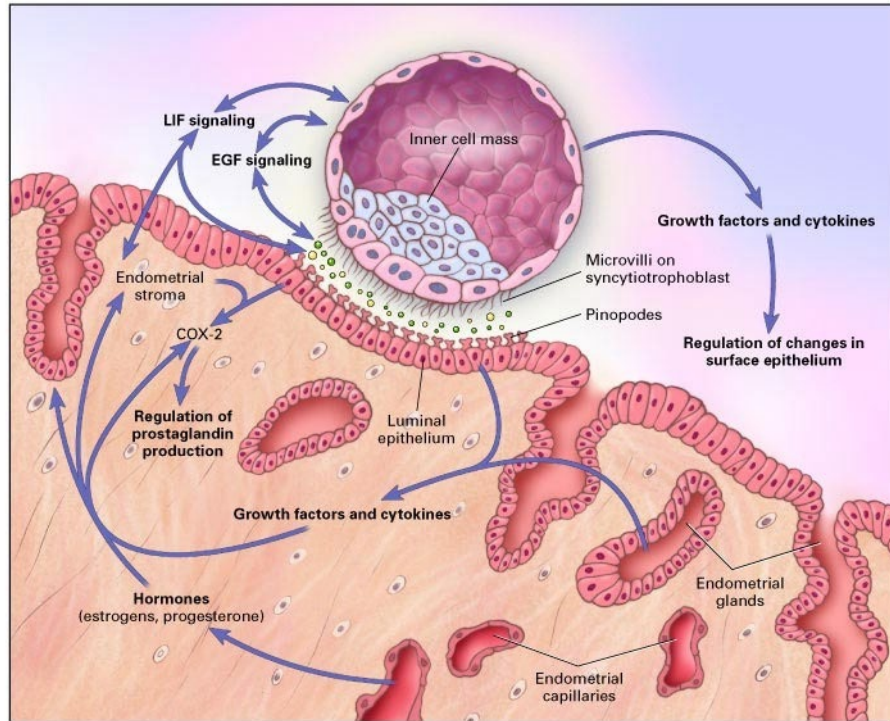


Conventional *in vitro* systems do not accurately represent the complexity of female physiology



Understanding the Biology of the Endometrium

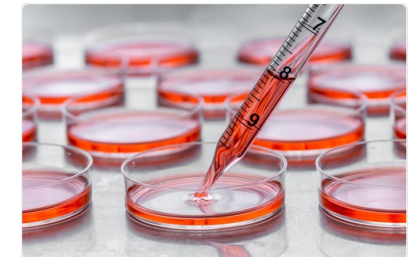
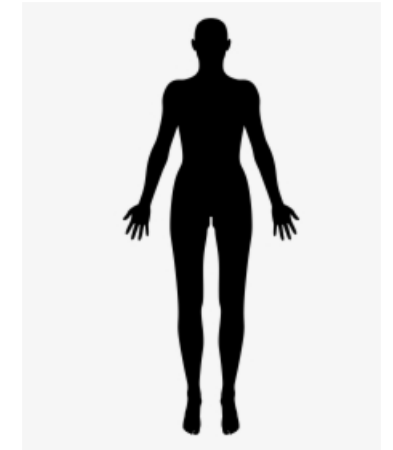
Implantation & Establishment of Pregnancy



Norwitz et al (NEJM 2001)

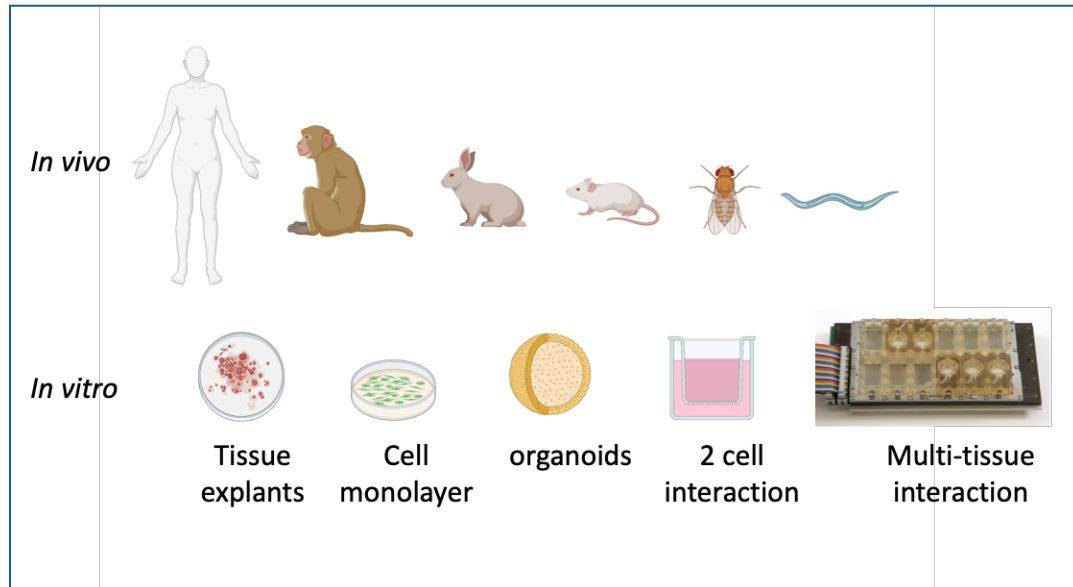
Diseases of the Endometrium

- Endometriosis
- Endometrial Hyperplasia
- Endometrial Cancer
- Adenomyosis
- Dysmenorrhea
- Menorrhagia



Models of the Female Reproductive System – Why is it important?

Models matter



Limitations in Research of the Female Reproductive Tract

- Ethical
- Species differences
- Hormones are complicated

Sex Differences in Drug response

- Preclinical and clinical research have been done in males
- 8 of the 10 drugs were pulled from the market

Challenges to studying Reproductive Diseases

Human
reproductive
tract is unique

Lack of
physiologic in
vivo models

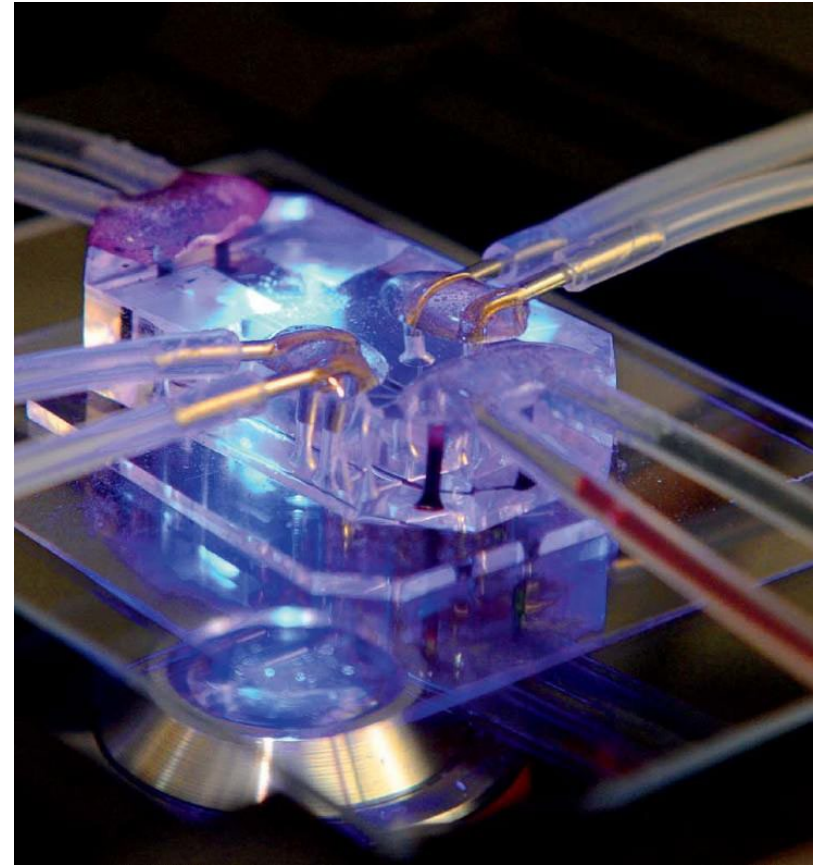
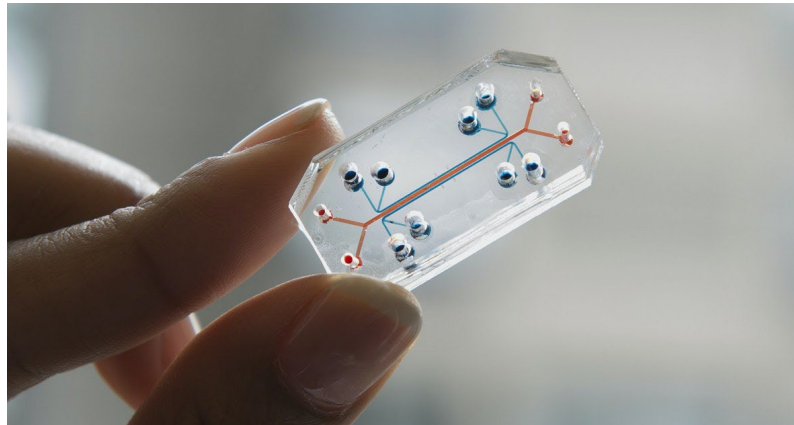
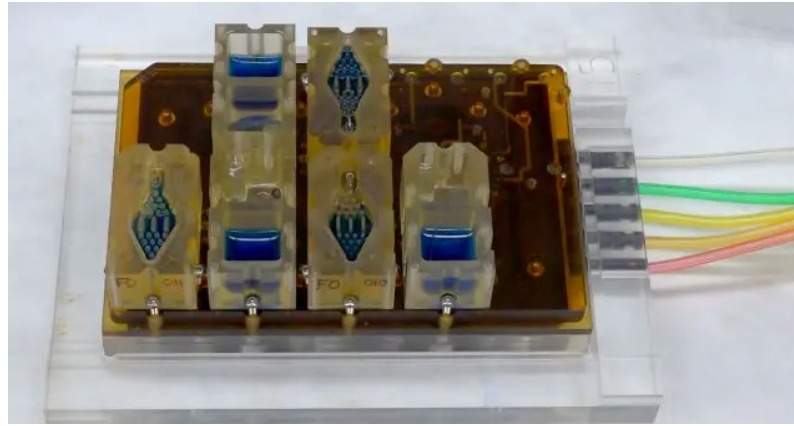
Hormones are
complex

Challenges

Yield of tissue
is limiting

Current in
vitro models
are simple

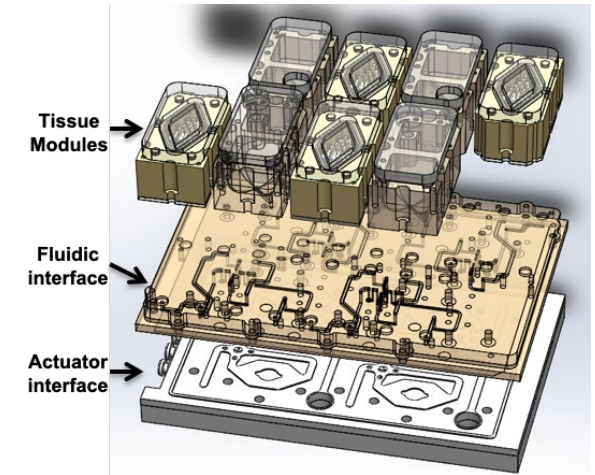
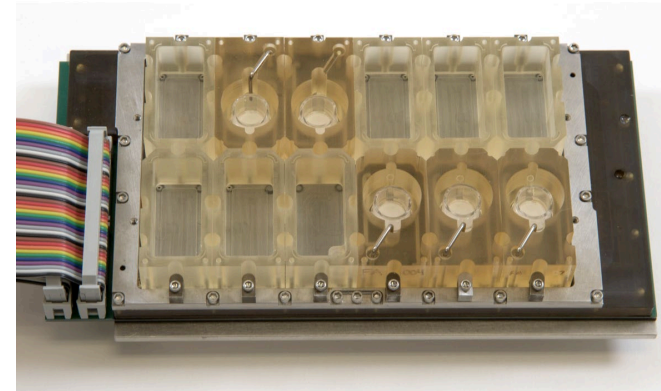
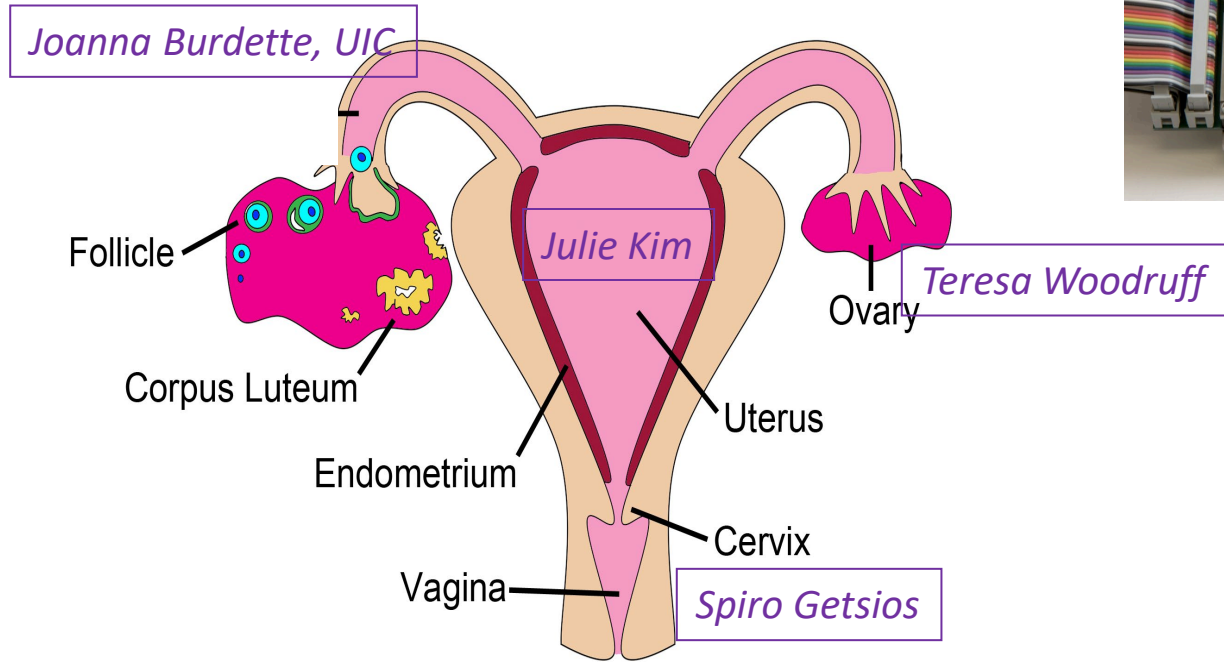




Organs-on-a-chip NIH Tissue Chip Consortium



EVATAR: The Mother of Microphysiological Systems

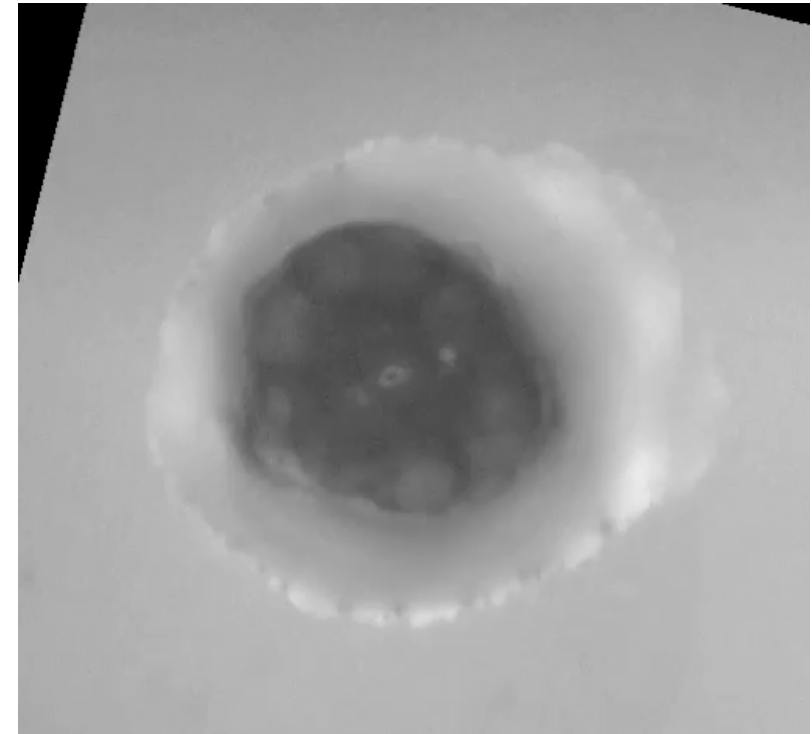
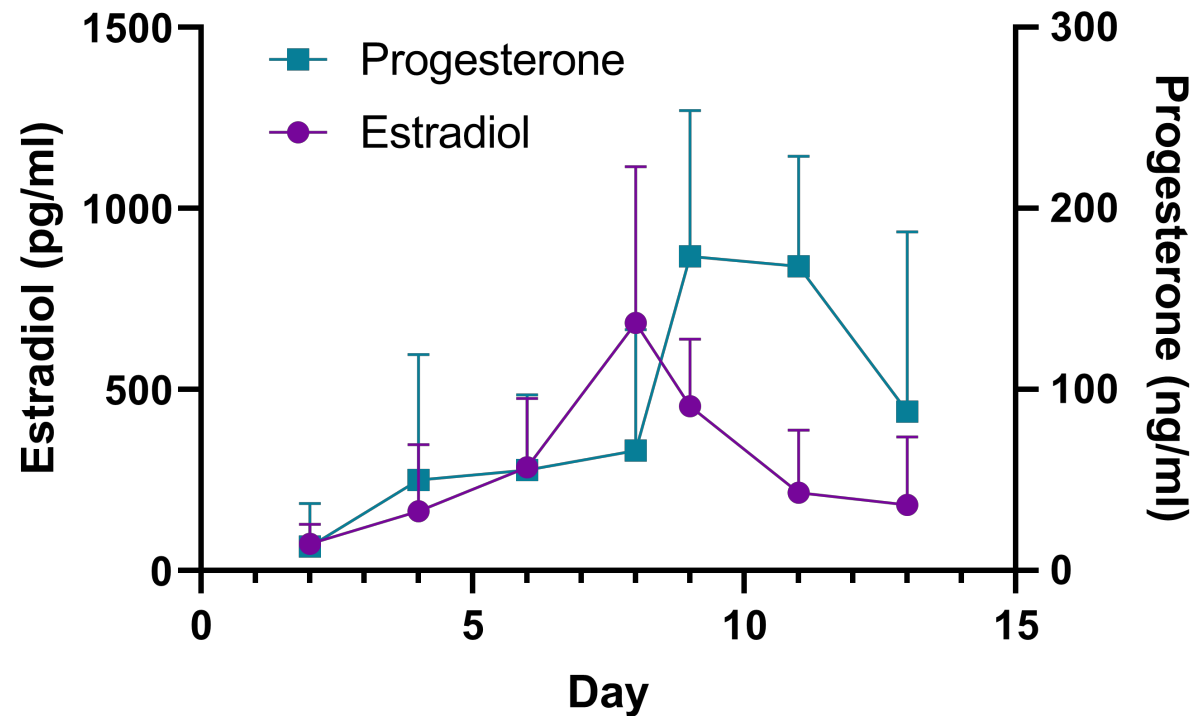


- **Materials:** can be sterilized, non-toxic to cells/follicles, do not bind hormones;
- **Pumping pattern:** computer program controlled.

Jeffrey T. Borenstein
Jonathan R. Coppeta
Brett C. Isenberg



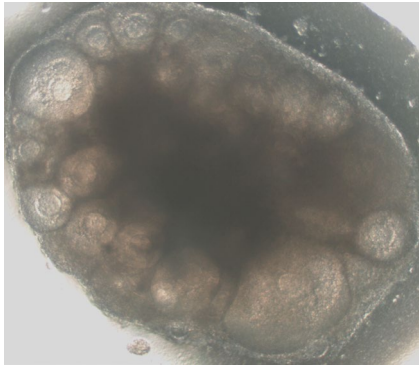
Ovary growth and hormone secretion in vitro



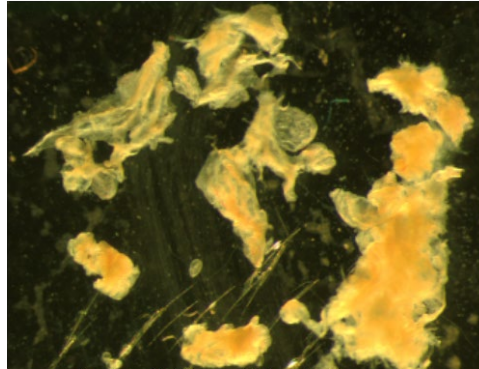
Hormone production from mouse ovaries is similar to human menstrual cycle

EVATAR – Multi-organ Female Reproductive Tract

Mouse ovary

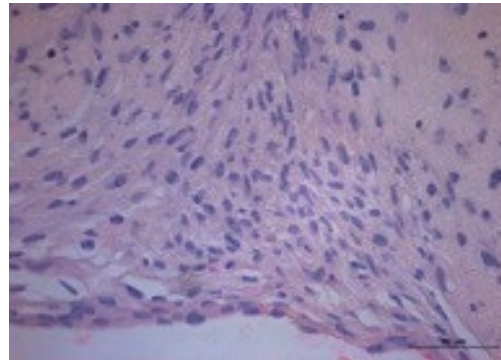


Human Fallopian tissue

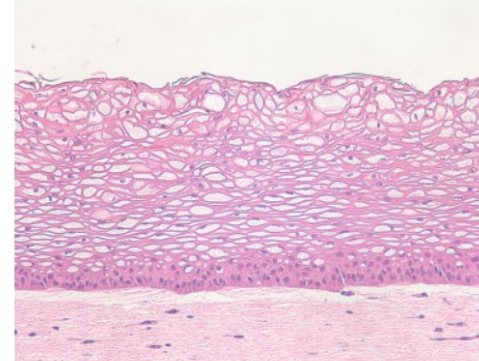


Epithelial layer

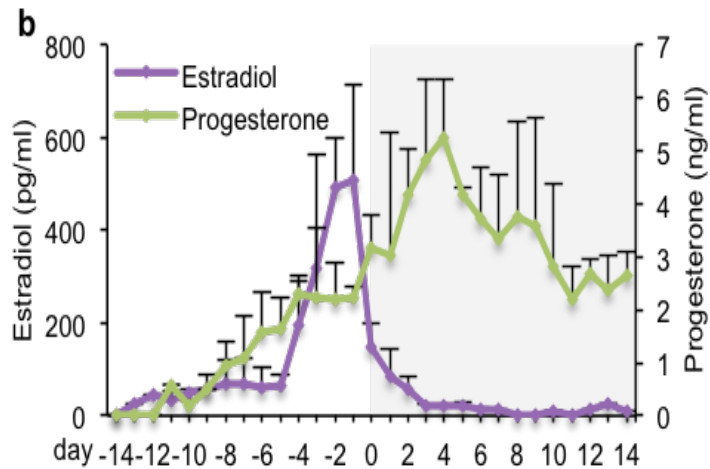
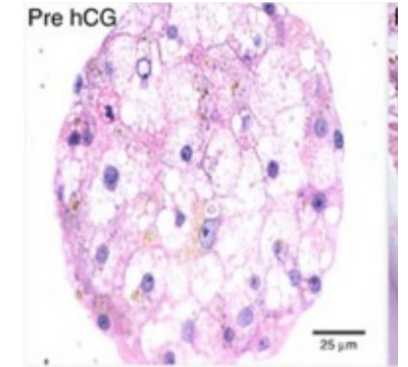
Human Recellularized Endometrium



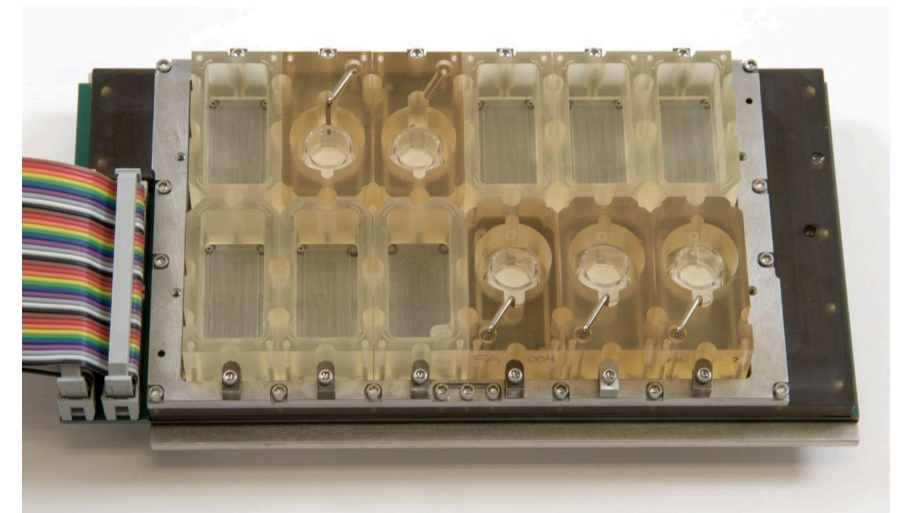
Engineered Human Ectocervix



Human liver microtissues



- One media
- Tissue longevity over 28 days
- Functional response to hormones



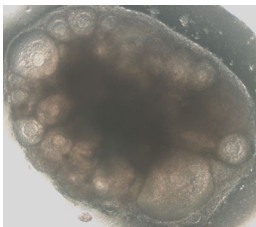
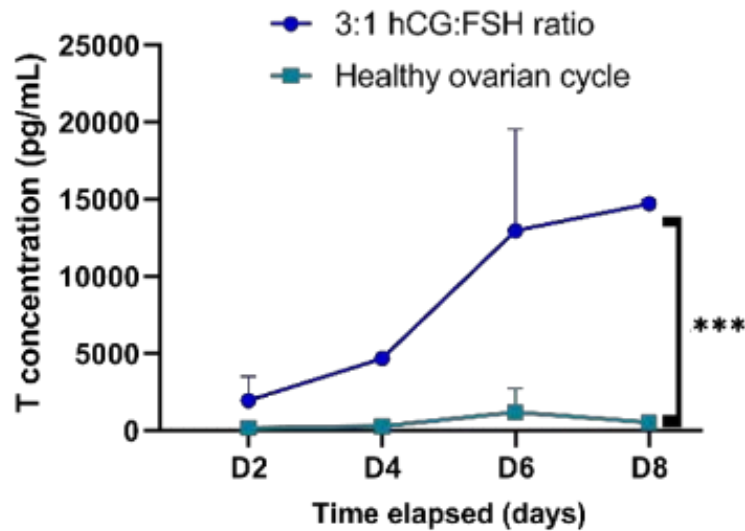


(Video credit © Sam Palahnuk)

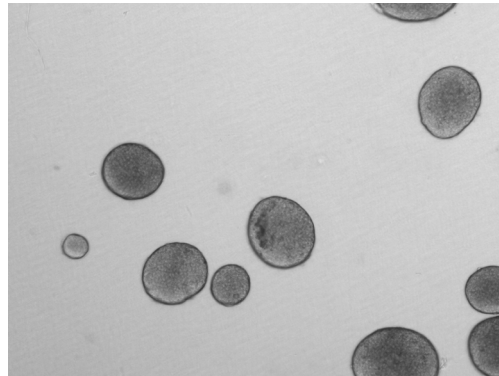
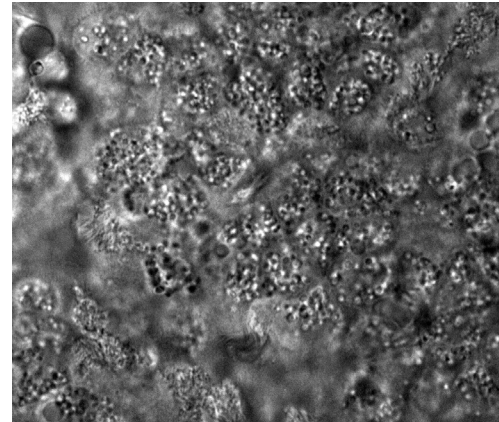
Biomedical Visualization program at University of Illinois Chicago

Polycystic Ovarian Syndrome in Lattice

Hyperandrogenic Ovary

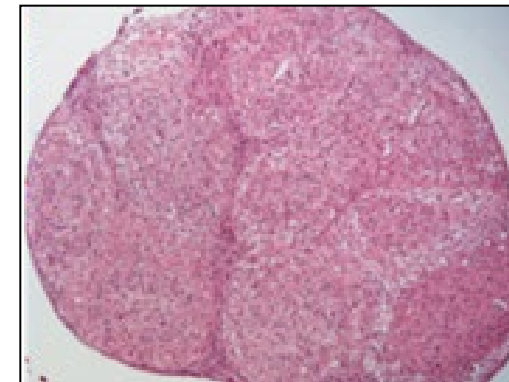
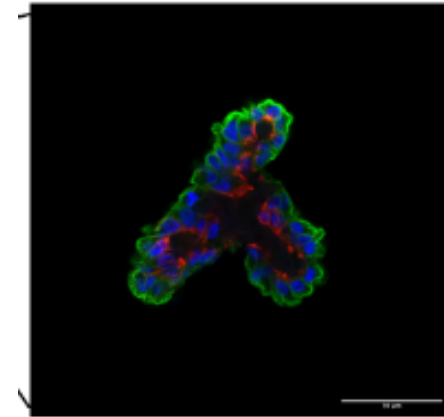


Fallopian Tube explants



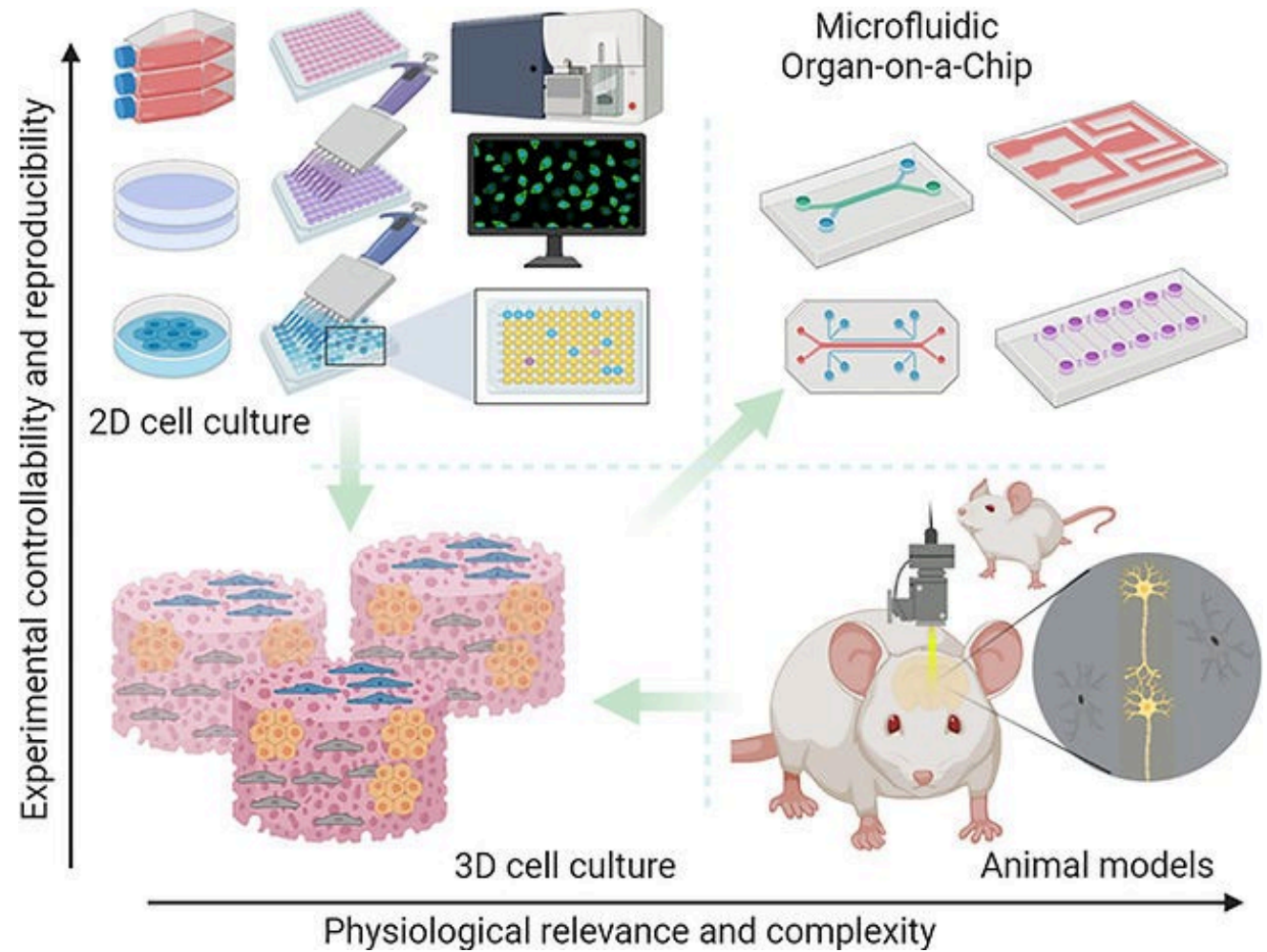
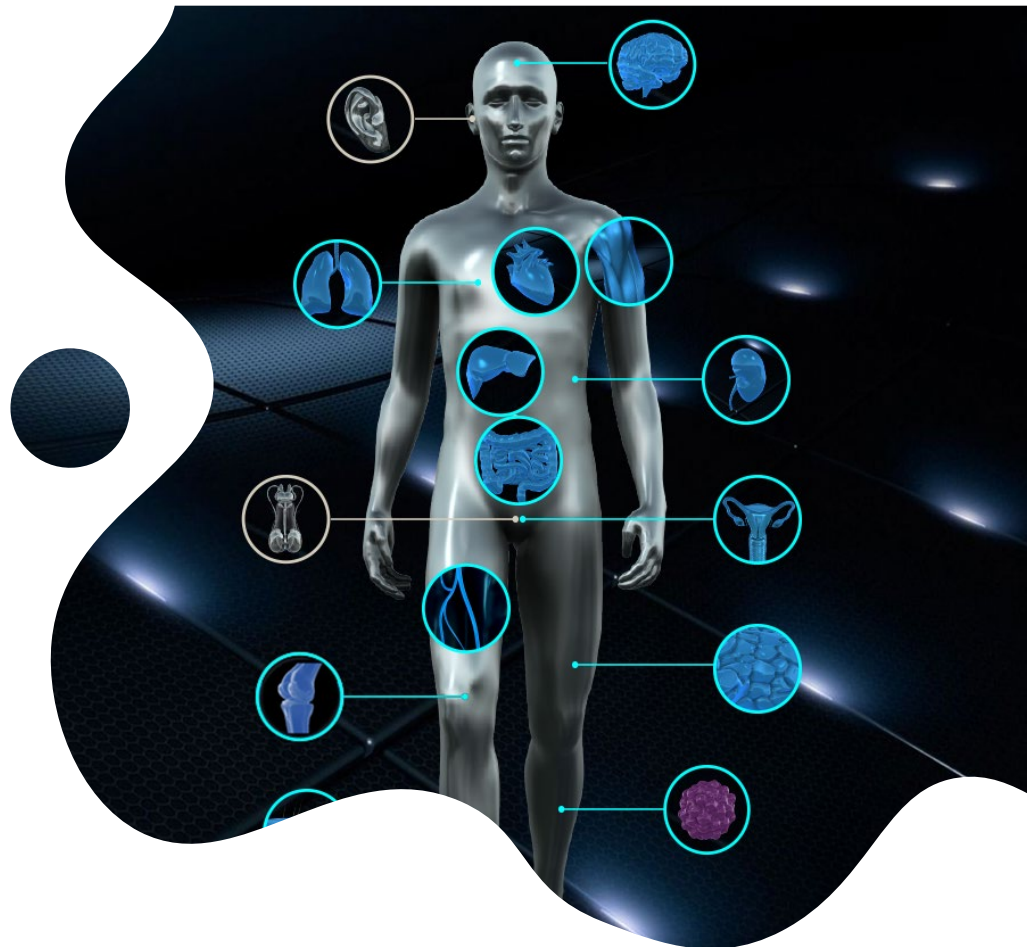
Pancreatic islets

Endometrial organoids



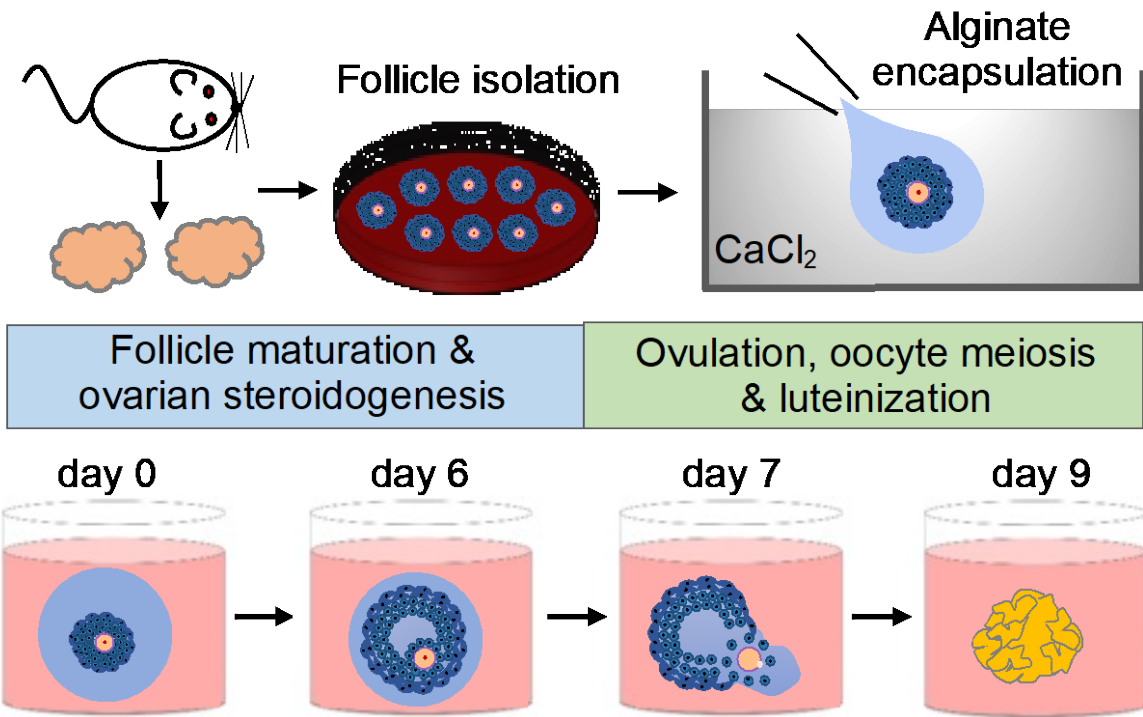
Adipocyte Spheroids

Tools and Models for Drug Testing



Ma et al, Trends Pharmacol Sci. 2021

Repro Tox screen using ovarian follicles



Clinical drugs



Bisphenol analogues



Flame retardants



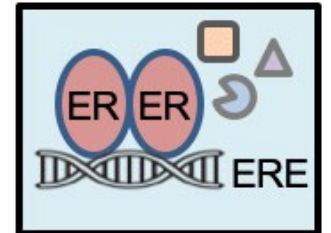
Per- and polyfluoroalkyl substances (PFAS)



Micro or nano-plastics



Harmful algal bloom toxins

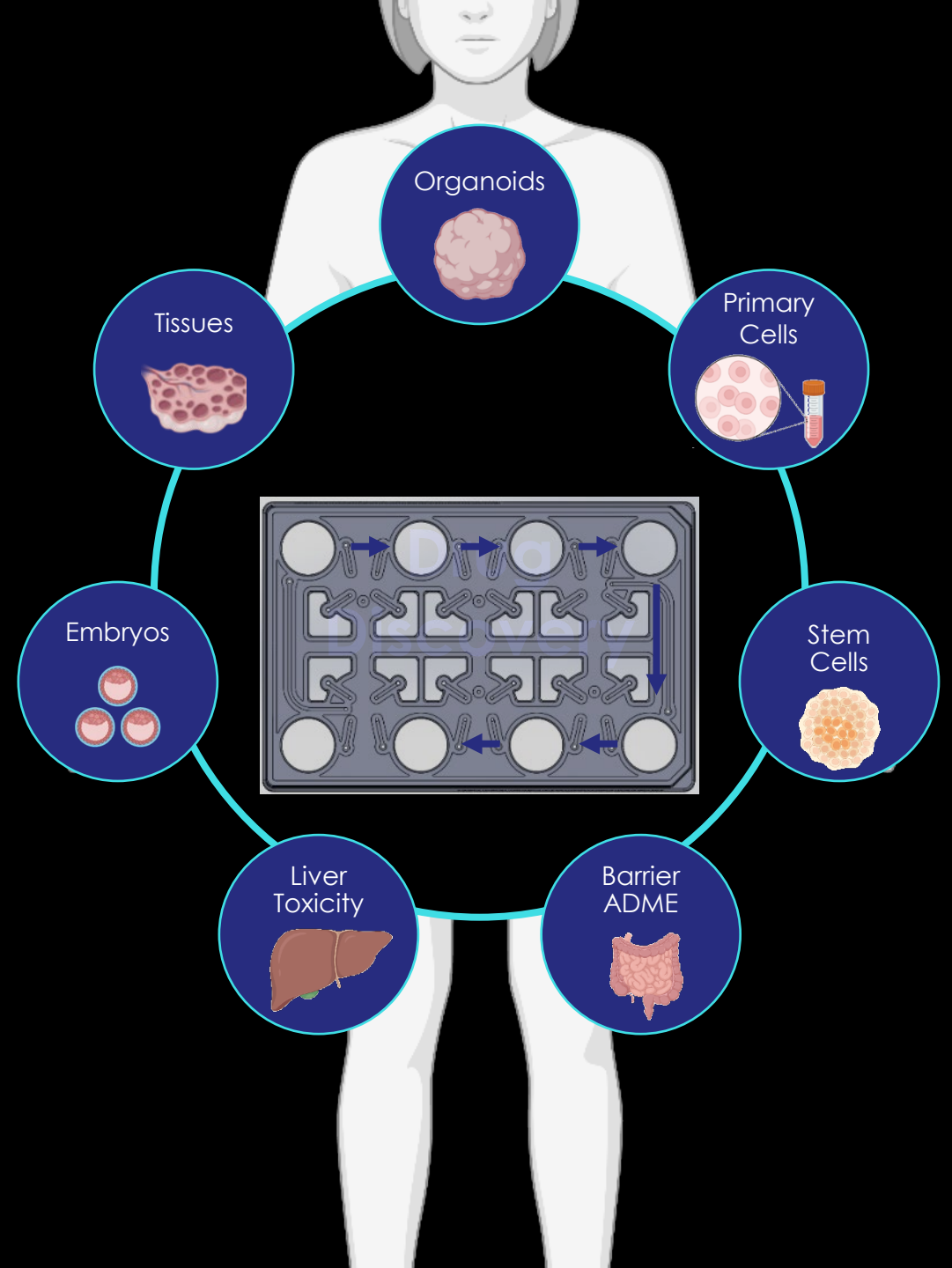


Estrogen receptor modulators



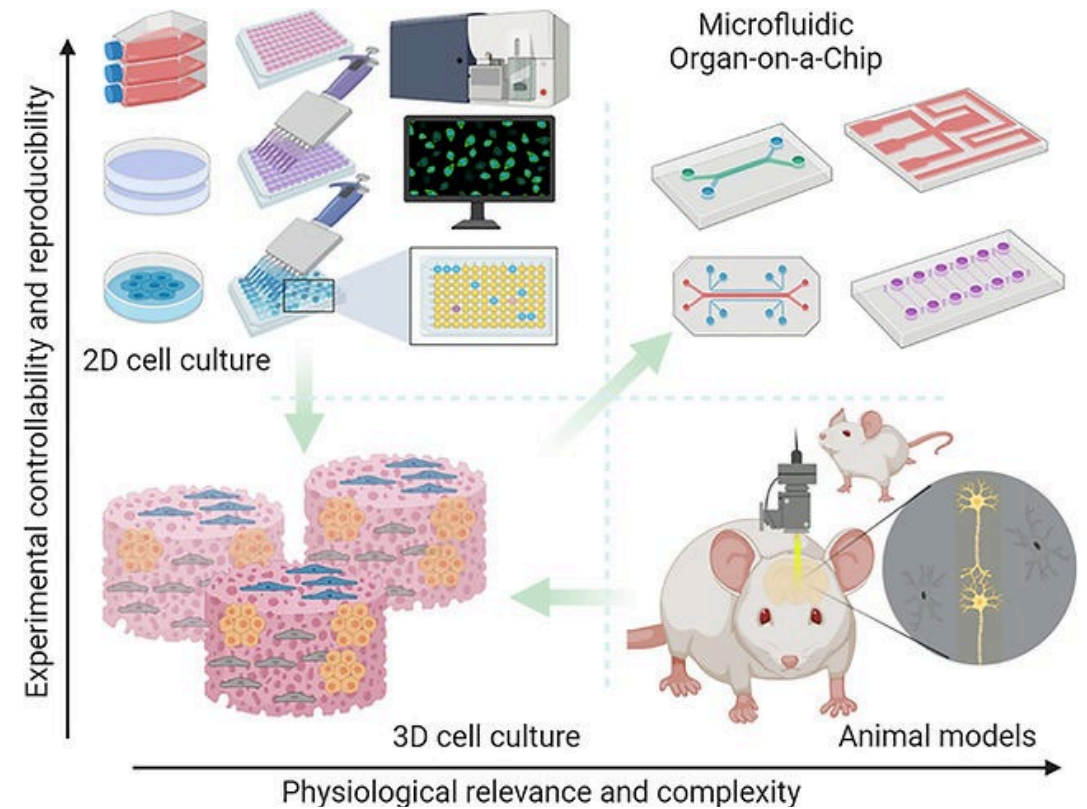
Translation to Human Health

- Importance of sex hormones
- Importance of systemic interactions
- A more complex and physiologic system for drug testing



Challenges in the Research

- Appropriate physiological cultures
- Organoids/spheroids – how many cell types
- Tissue availability –surgery schedules
- Coordinating tissues depending on availability
- Scalability
- Real time monitoring for health of cultures



Ma et al, Trends Pharmacol Sci. 2021

Challenges in commercialization

- Which market? Is there a demand?
 - Provide the data
- Usability – simple, inexpensive, plug and play
- Commercial partners
- Funders

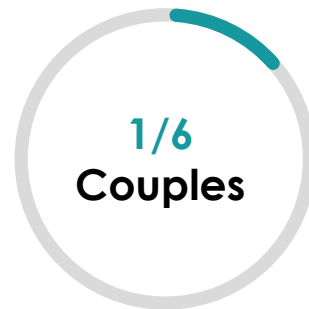
Research and Drug Testing in Reproductive Health

Menopause



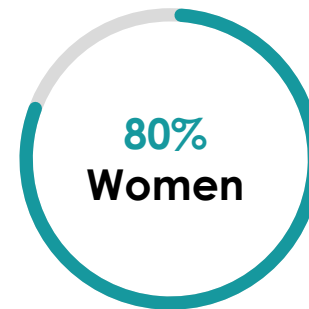
\$17B
Market

Fertility
Treatment



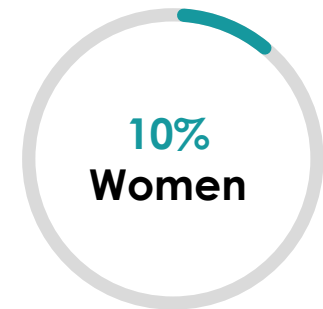
\$23B
Market Size

Uterine
Fibroids



\$34B
Impact

Endometriosis



\$78B
Impact

Acknowledgements



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