

Breaking barriers in endometriosis: from 3D microphysiological models to combination therapies

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University of Bern, Switzerland

u^b

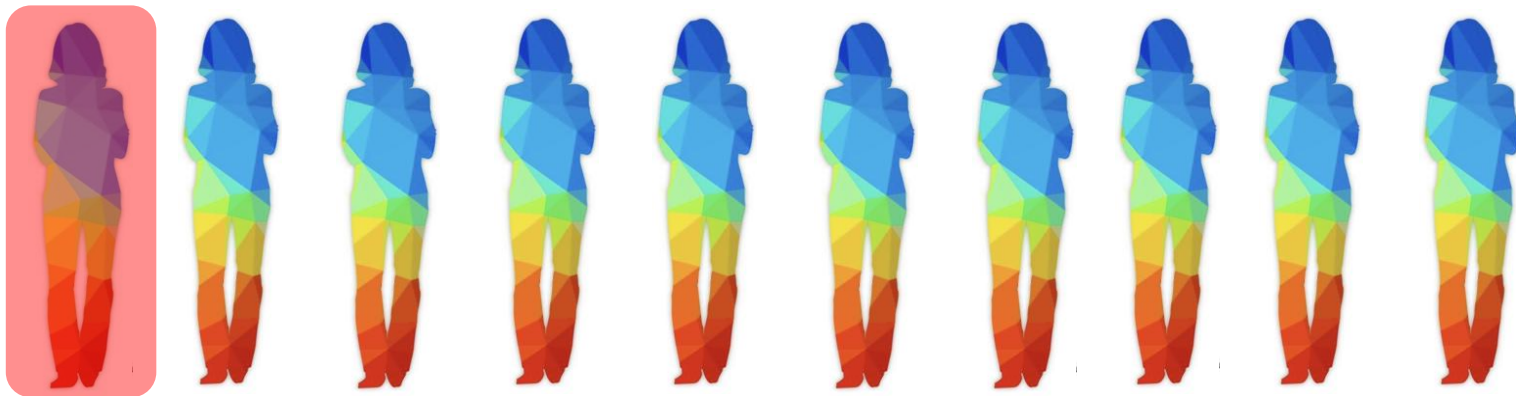
b
UNIVERSITÄT
BERN



PHILADELPHIA, PA
JULY 13-18, 2025

**NEXT-GENERATION
DELIVERY INNOVATIONS**

Endometriosis: the silent disease



190 million women & individuals assigned female at birth worldwide

7–10 years between the
symptom onset and
confirmed diagnosis

Source: WHO

Endometriosis: Symptoms

Symptoms



Pain



Heavy and painful periods



Fatigue, depression



Infertility

PNAS

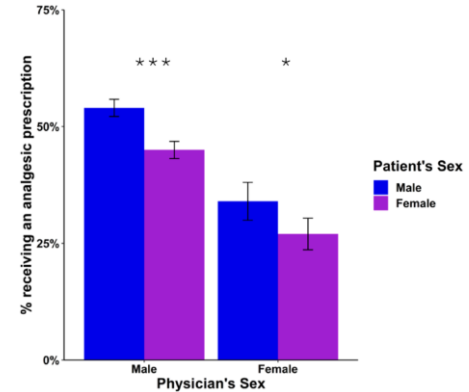
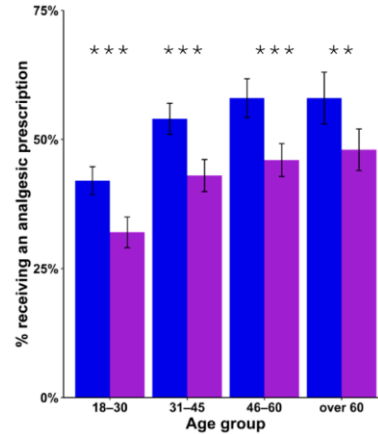
RESEARCH ARTICLE

PSYCHOLOGICAL AND COGNITIVE SCIENCES
MEDICAL SCIENCES

Sex bias in pain management decisions

Mika Guzikovits^{a,b,1}, Tom Gordon-Hecker^{c,1}, David Rehtman^d, Shaden Salameh^d, Salomon Israel^e, Moses Shayo^{b,f,g}, David Gozal^h, Anat Perry^g, Alex Gileles-Hillel^{h,k,2}, and Shoham Choshen-Hillel^{h,b,2,3}

Likelihood of receiving an analgesic prescription by patient's sex (N = 17,576)



Guzikevits et al, *PNAS* (2024) 121:e2401331121



Endometriosis: Symptoms

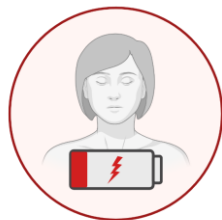
Symptoms



Pain



Heavy and
painful periods



Fatigue,
depression



Infertility

PNAS

RESEARCH ARTICLE

PSYCHOLOGICAL AND COGNITIVE SCIENCES
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Sex bias in pain management decisions

Mika Guzikovits^{a,b,1}, Tom Gordon-Hecker^{c,1}, David Rehtman^d, Shaden Salameh^d, Salomon Israel^e, Moses Shayo^{b,f,g}, David Gozal^h, Anat Perry^g, Alex Gileles-Hillel^{h,k,2}, and Shoham Choshen-Hillel^{a,b,2,3}

nature genetics

Article

<https://doi.org/10.1038/s41588-023-01323-z>

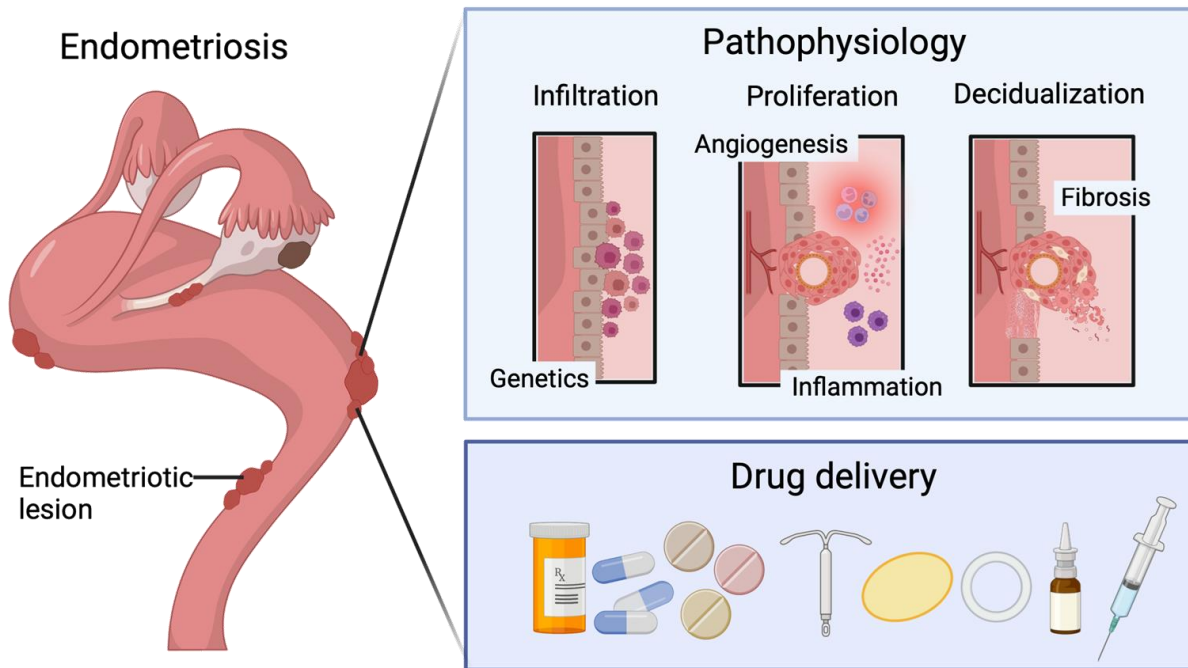
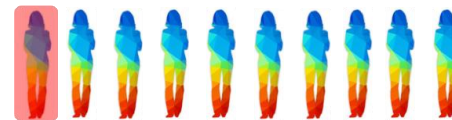
The genetic basis of endometriosis and comorbidity with other pain and inflammatory conditions

Significant genetic correlations between endometriosis and 11 **pain conditions**, including migraine, back and multisite chronic pain, as well as **inflammatory conditions**, including asthma and osteoarthritis

Guzikevits et al, *PNAS* (2024) 121:e2401331121

Rahmioglu et al, *Nat Genet* (2023) 55:423-436

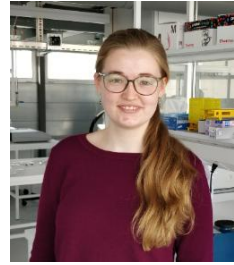
Endometriosis: the silent disease



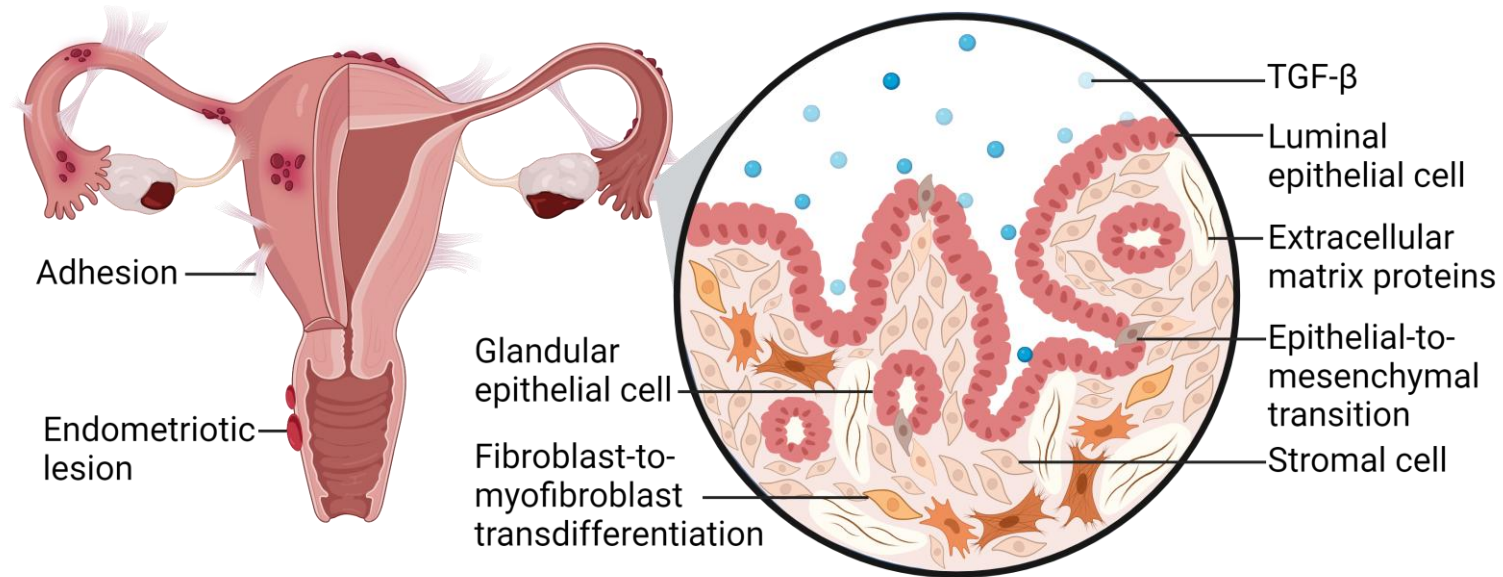
Teworte and Luciani, *Helv. Chim. Acta* (2023) 106:e202200132

Fibrosis in endometriosis

Cyclical repeated tissue injury and repair leads to scarring, fibrosis, and adhesions

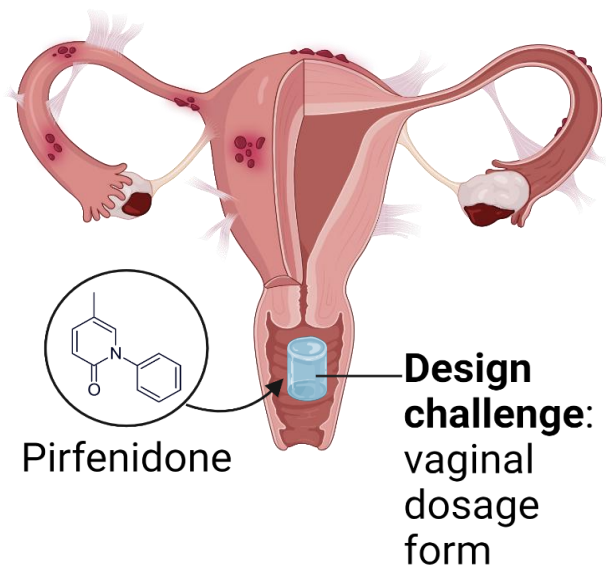


Dr. Sarah Teworte

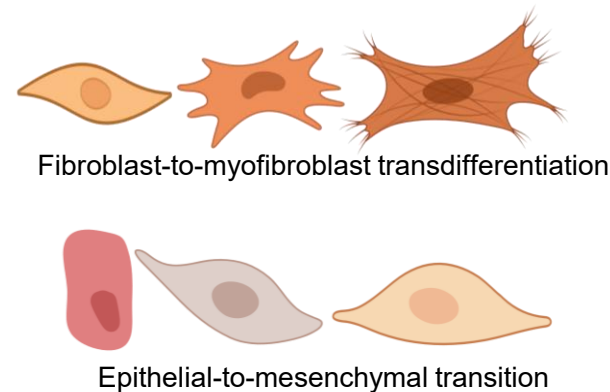


Fibrosis in endometriosis

Formulation development

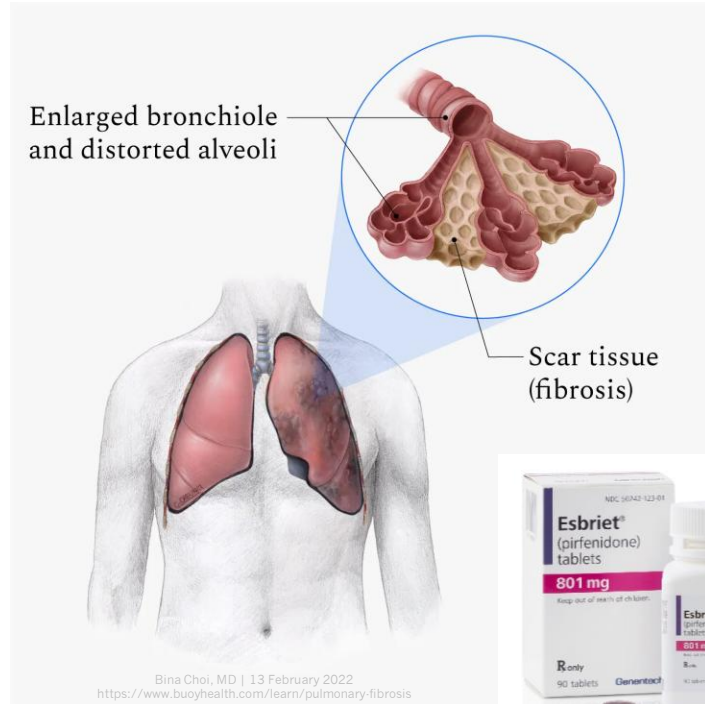


In vitro disease modelling

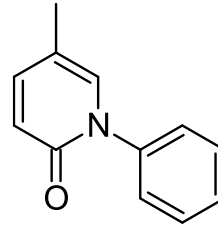


**Screening tool to test
antifibrotic drug candidates**

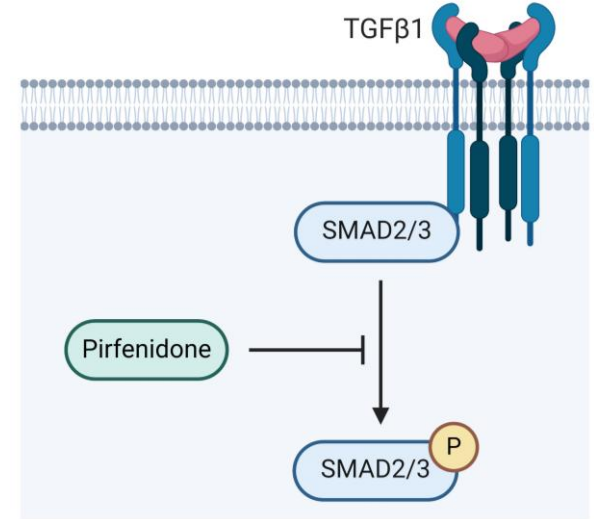
Repurposing pirfenidone



Pirfenidone



185 g/mol
logP 1.9

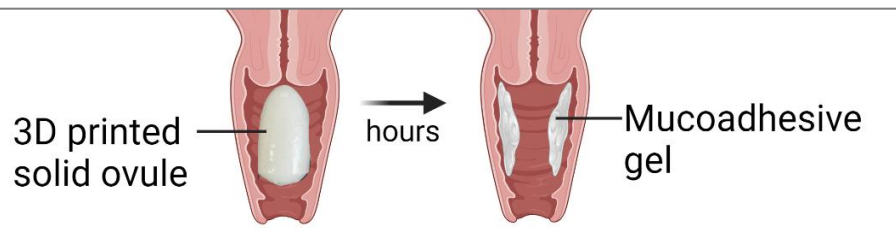


Tablets for oral intake

~70% of patients experience adverse drug reactions

Fibrosis in endometriosis

Formulation development



3D printed ovules



Quality requirements

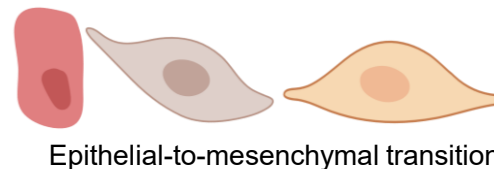


Controlled drug release



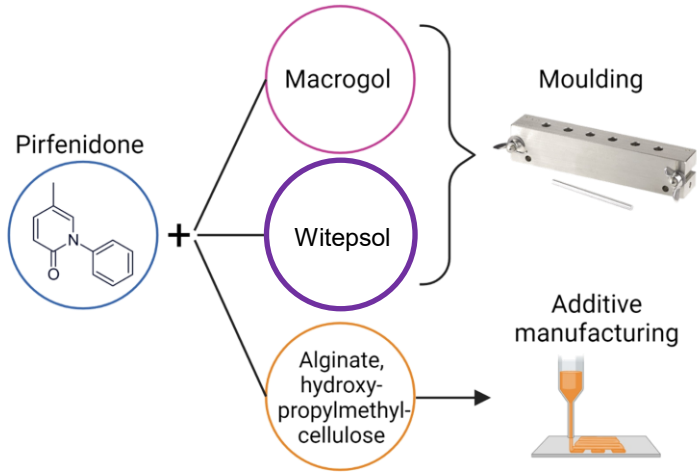
Mucoadhesion → long residence time

In vitro disease modelling

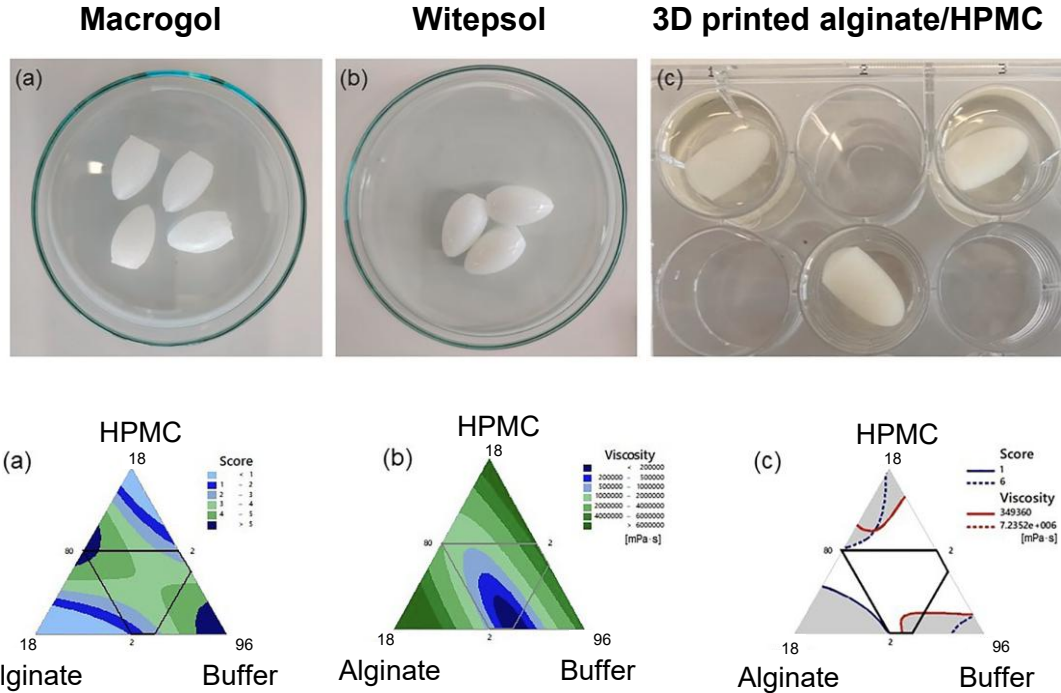


**Screening tool to test
antifibrotic drug candidates**

3D printed mucoadhesive ovules

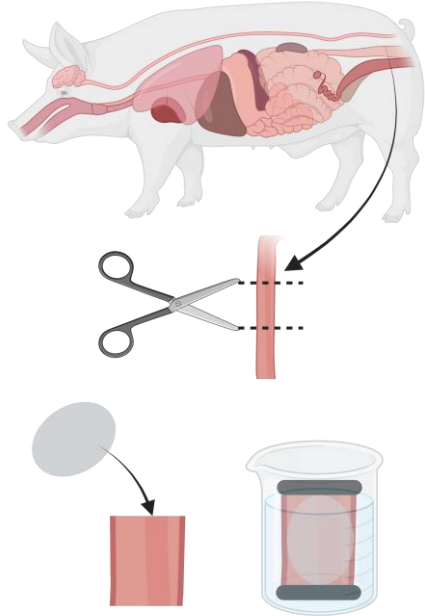


HMPC: Hydroxypropyl methylcellulose



Teworte et al. *Eur. J. Pharm. Sci.* (2023) 188:106501

Ex vivo mucoadhesion



3 h



Macrolog



Wittepsol



3D printed

16 h



3D printed

Towards biorelevant *in vitro* tests

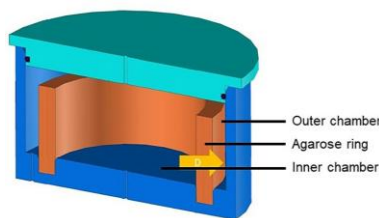
Shake flask



Model

- Volume
- Phases of menstrual cycle

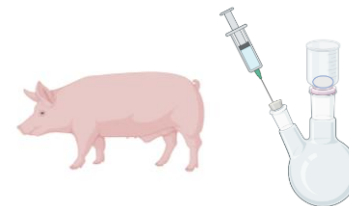
Agarose ring



Model

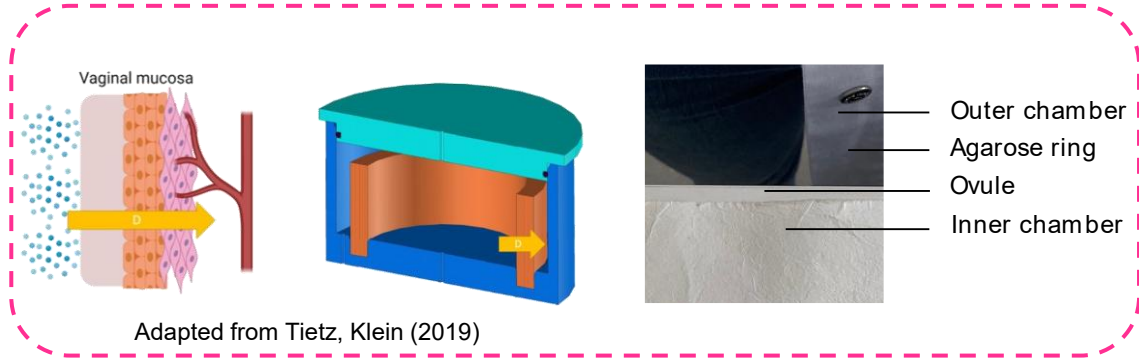
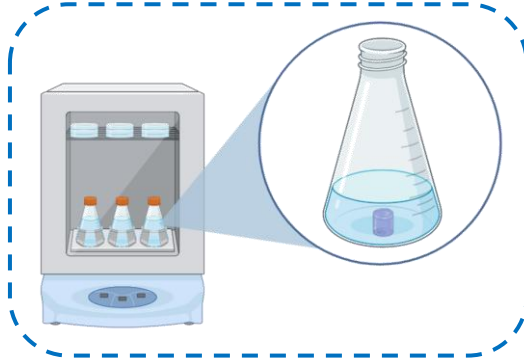
- Phases of menstrual cycle

Ex vivo

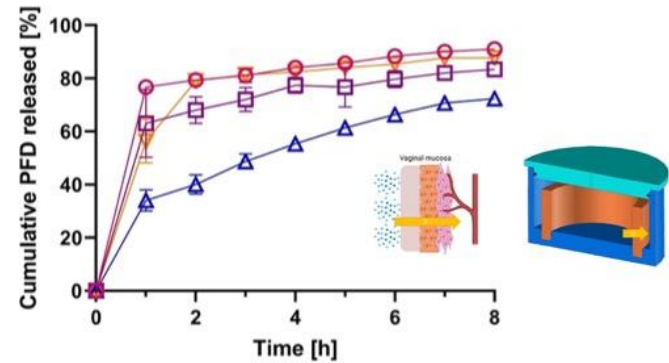
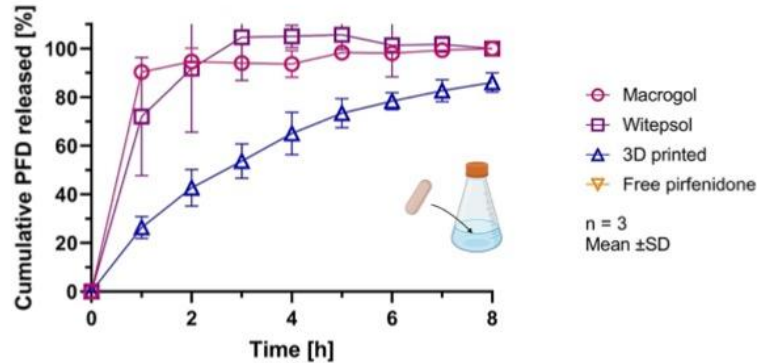


- Design setup
- Develop a protocol for quantification of drug in tissue

Release assays

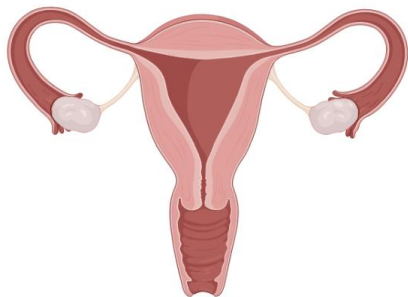


Adapted from Tietz, Klein (2019)



Teworte, ..., Luciani (2023) *Eur. J. Pharm. Sci.* 188:106501

What to consider to reach biorelevance?



Cervical mucus:

- Mucins
- Albumin

2 g/day

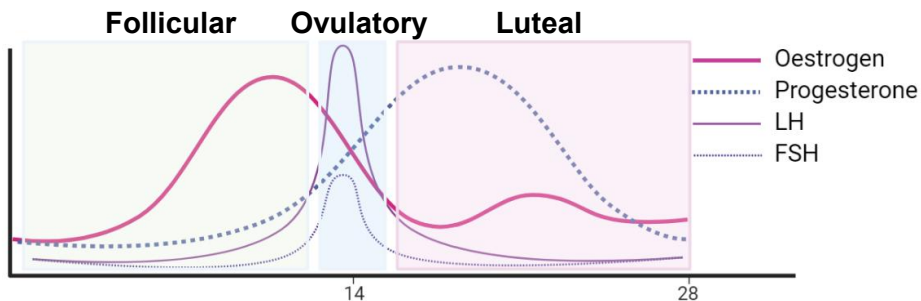
Vaginal fluid:

- Glucose
- Sodium Chloride
- Lactic acid
- pH 4

0.1-0.5 mL/day

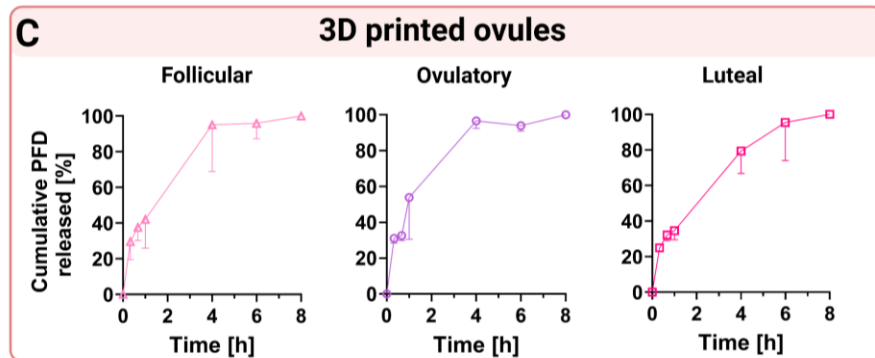
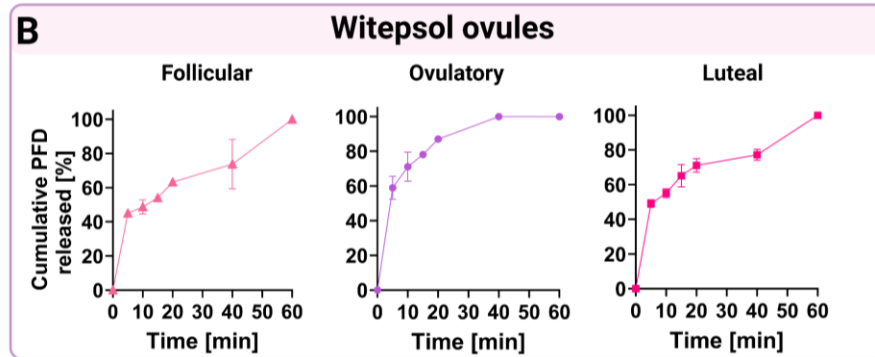
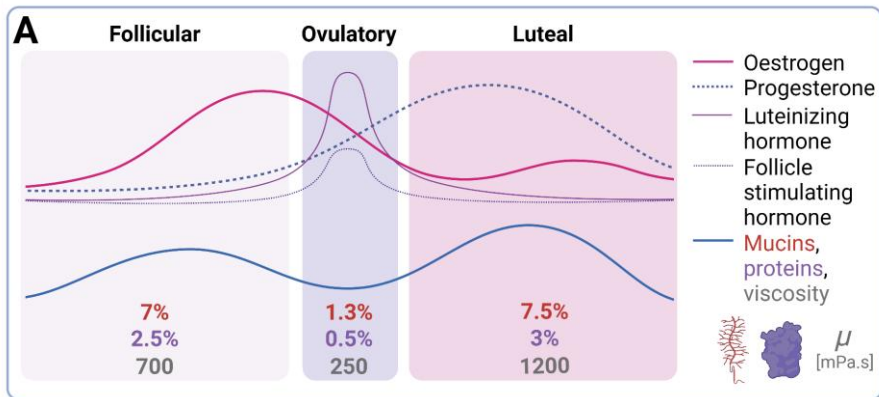
Parameters to consider

- Fluid components
- Volume
- Viscosity
- pH
- Temperature

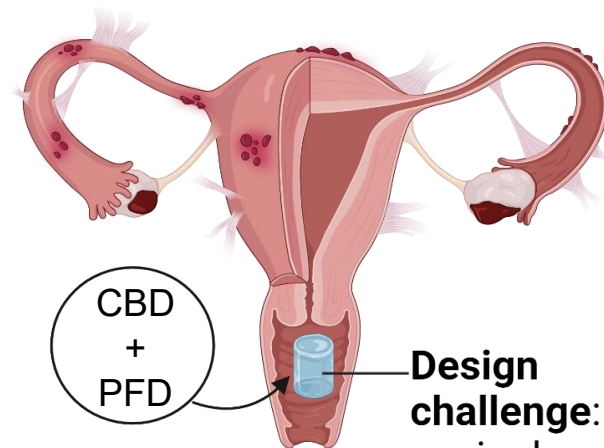
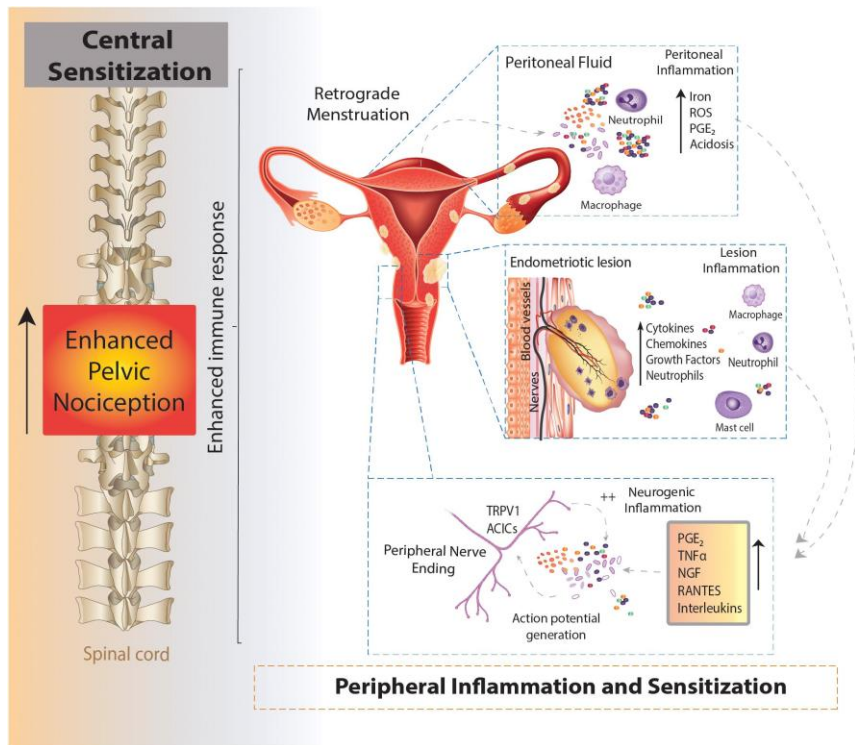


**Poor quality of data
available in the
literature!**

Effect of the simulated vaginal fluid



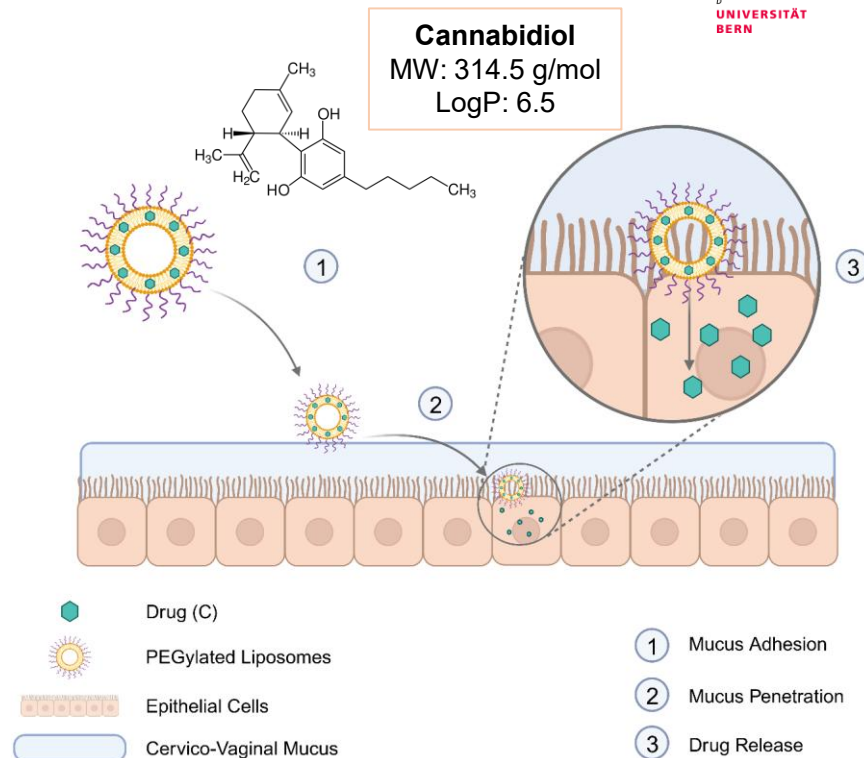
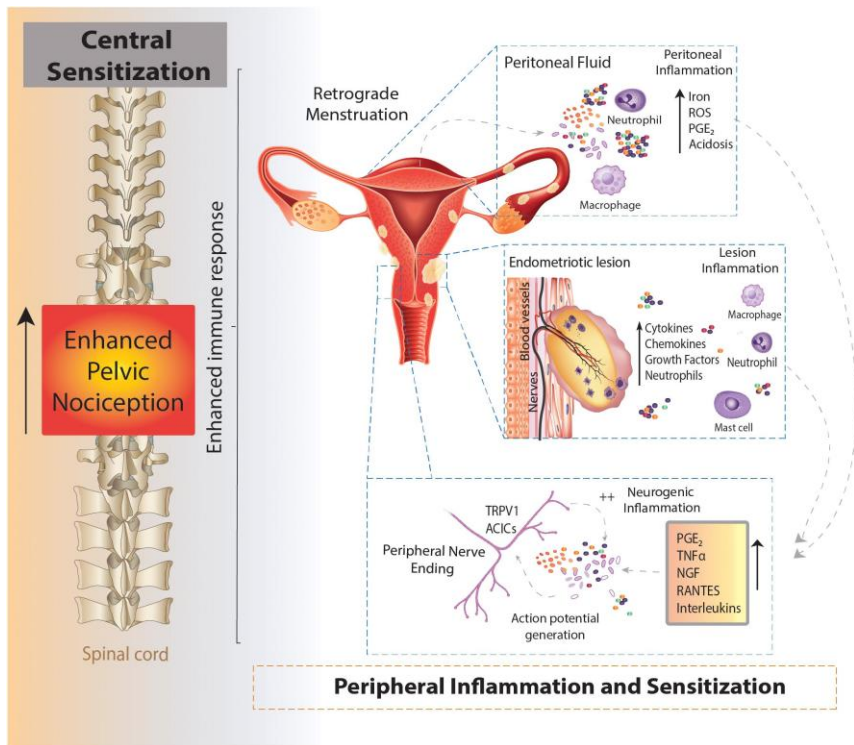
Managing fibrosis AND pain in endometriosis



CBD: Cannabidiol
PFD: Pirfeidone

From Maddern et al. *Front Cell Neurosci* (2020) 6:14:590823

Managing fibrosis AND pain in endometriosis



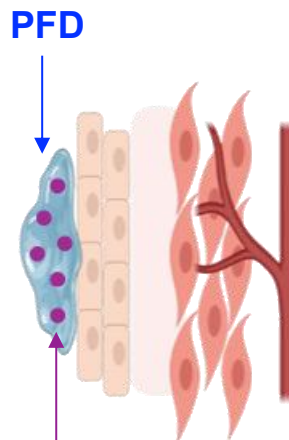
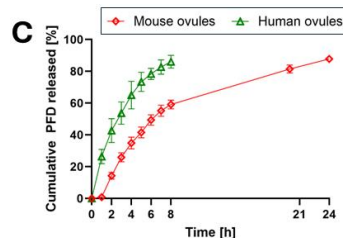
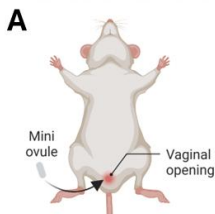
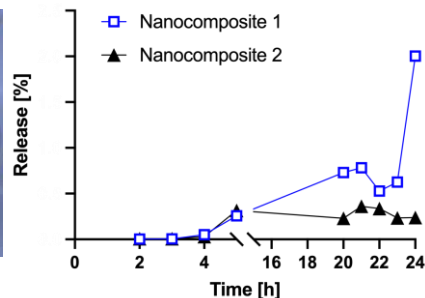
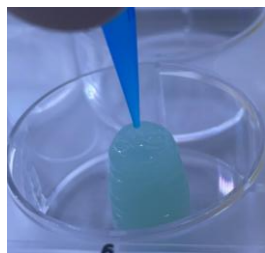
From Maddern et al. *Front Cell Neurosci* (2020) 6:14:590823

Combination therapy for fibrosis and pain



Neslihan Salar

Vaginal pessaries

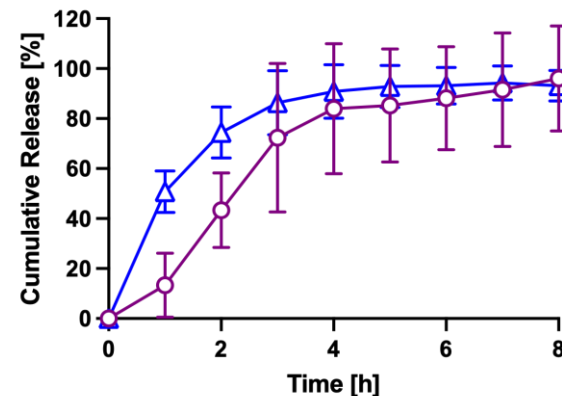


Liposomal
CBD

CBD: Cannabidiol
PFD: Pirfenidone

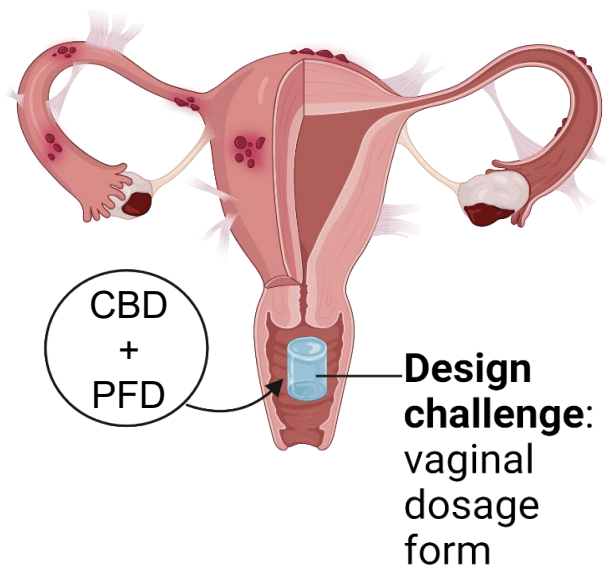
n=3, Mean $\pm$ SD

Vaginal gel

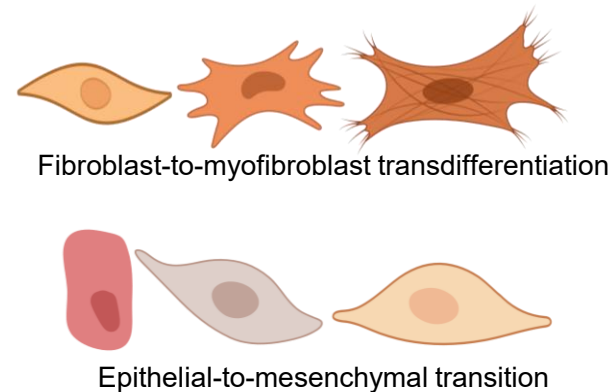


Fibrosis in endometriosis

Formulation development



In vitro disease modelling



**Screening tool to test
antifibrotic drug candidates**

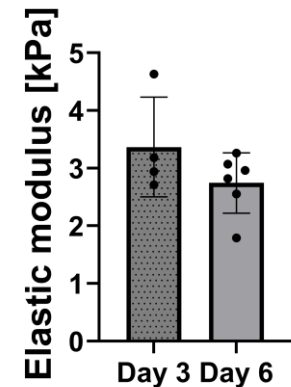
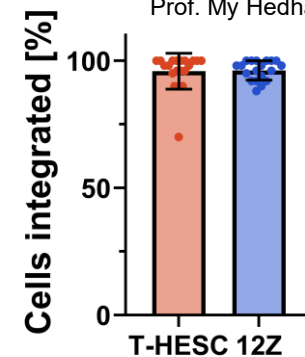
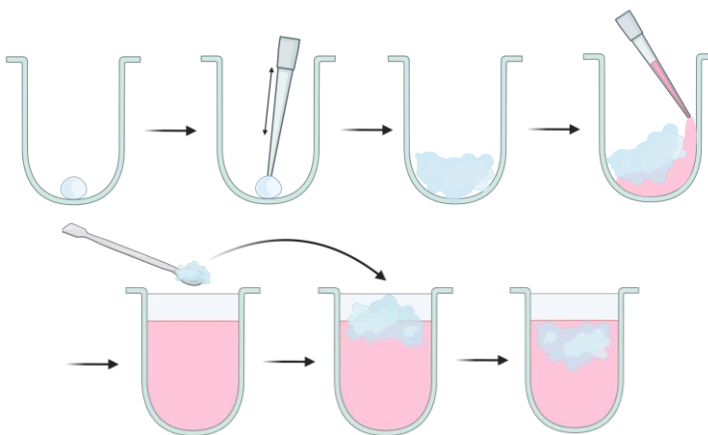
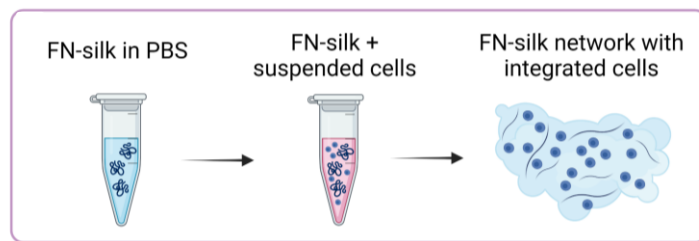
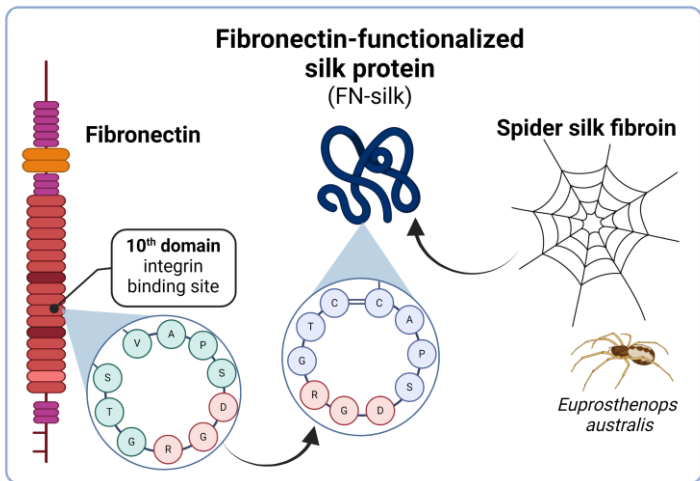
Fibronectin (FN)-silk networks



Prof. My Hedhammar



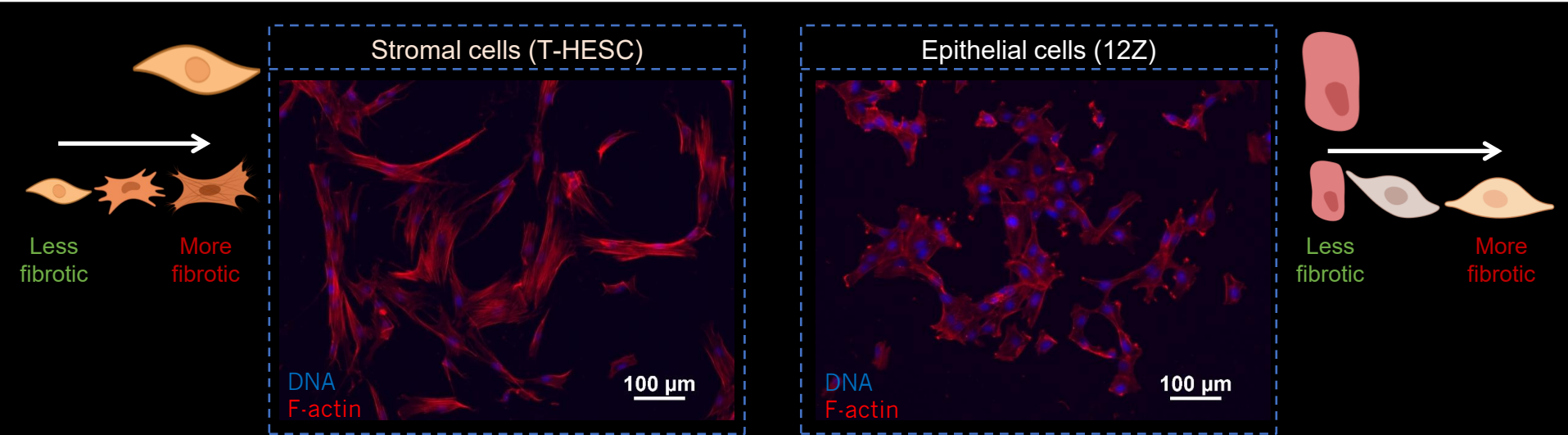
Fibronectin-functionalized silk protein (FN-silk)



Methodology adapted from Johansson, Widhe *et al.* 2019 and Collodet *et al.* 2023

Designing an *in vitro* model of fibrosis in endometriosis

- **Stromal** and **epithelial** cells
- Tissue-relevant **microenvironment**
- Maintain cell **viability** in 3D
- Recapitulate **physiological behaviour** in relation to fibrosis



Cell metabolic activity in 3D

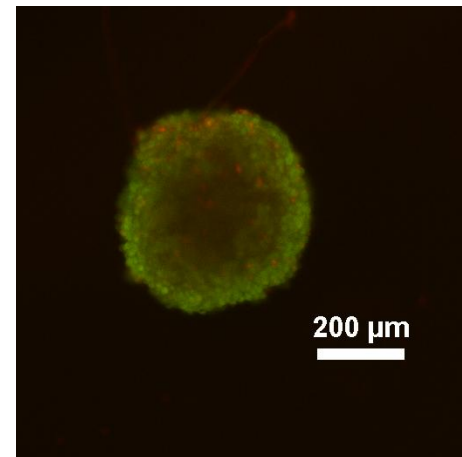
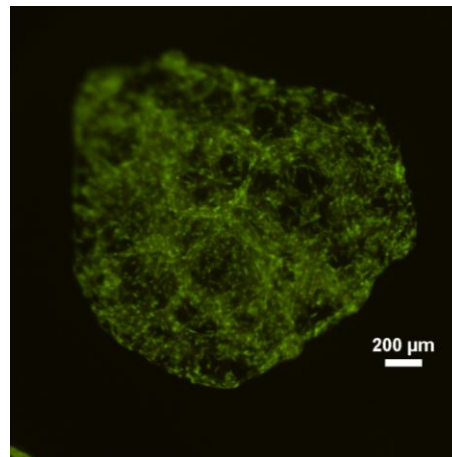
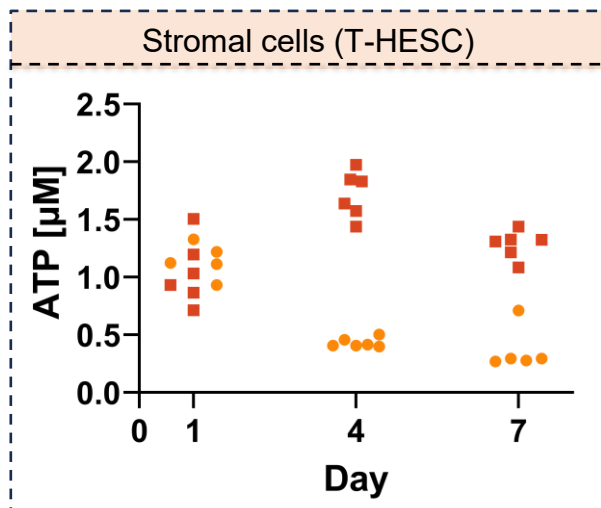


vs.



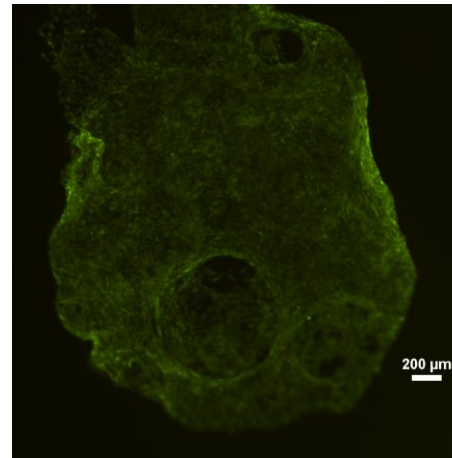
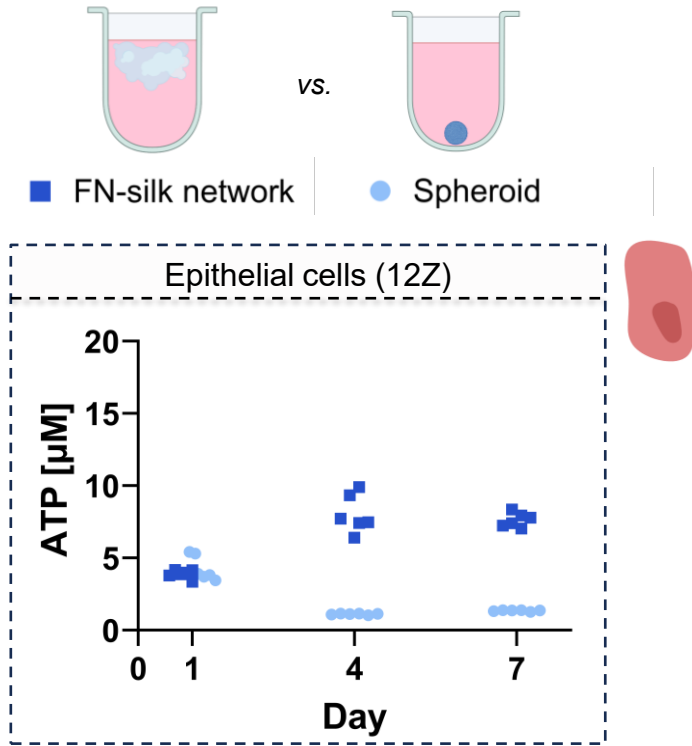
■ FN-silk network

● Spheroid

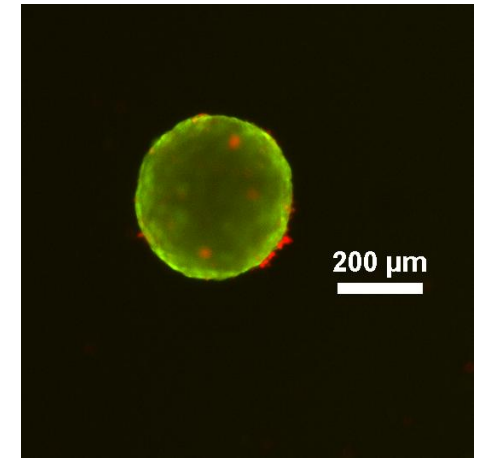


Live Dead

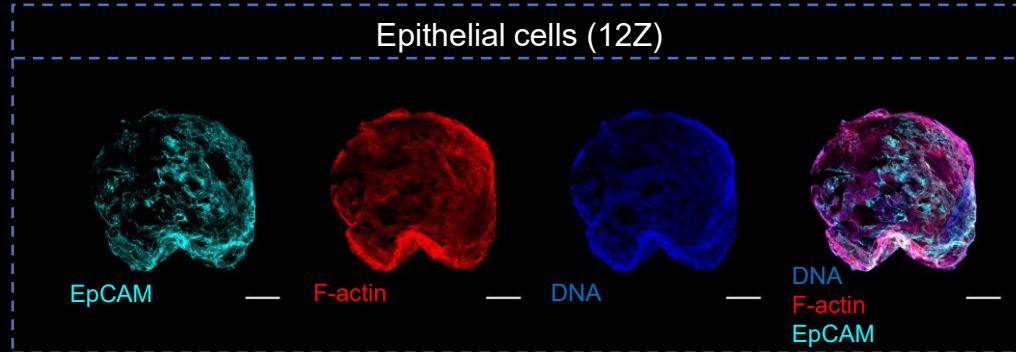
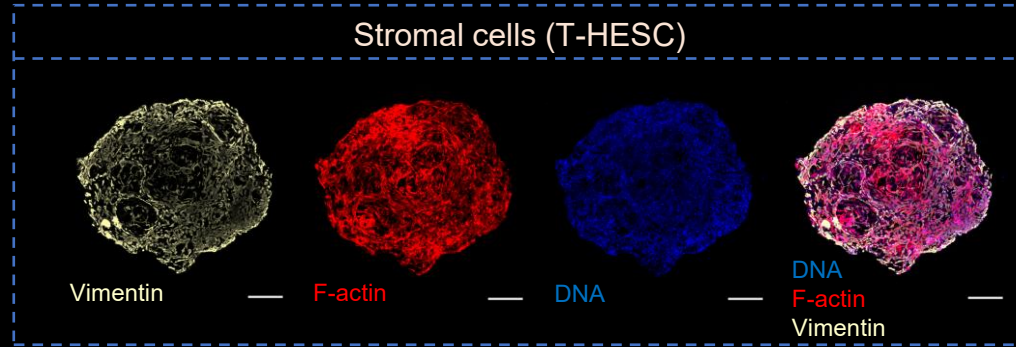
Cell metabolic activity in 3D



Live Dead



Morphology of FN-silk networks

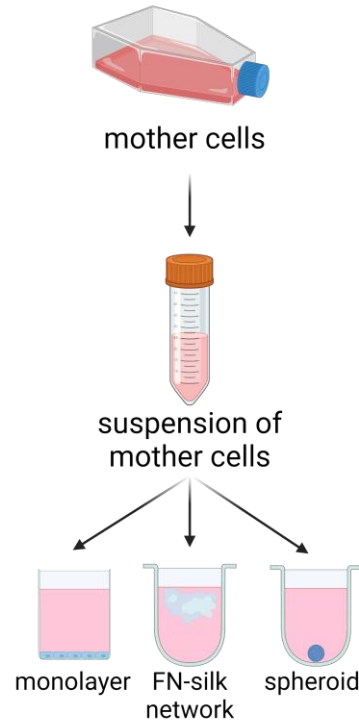


Scale bars, 500 μ m

EpCAM, epithelial cell adhesion molecule

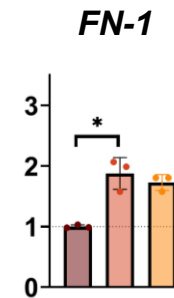
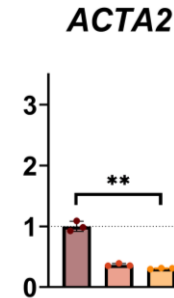
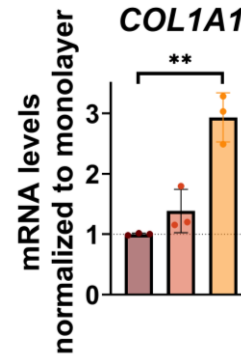
Effect of culture format on fibrotic markers

Fibroblast-to-myofibroblast transdifferentiation



COL1A1 ↓
ACTA2 ↓
FN-1 ↓

COL1A1 ↑
ACTA2 ↑
FN-1 ↑



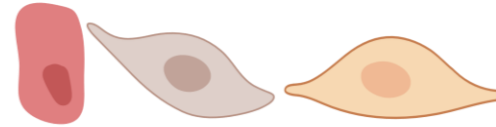
● Monolayer ● FN-silk network ● Spheroid

Modelling fibrosis: response to TGF- β 1



COL1A1 ↓
ACTA2 ↓
FN-1 ↓

COL1A1 ↑
ACTA2 ↑
FN-1 ↑

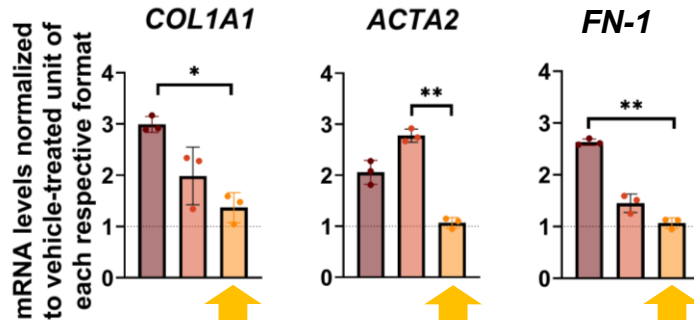


SNAI1 ↓
CDH1 ↑
CDH2 ↓

SNAI1 ↑
CDH1 ↓
CDH2 ↑

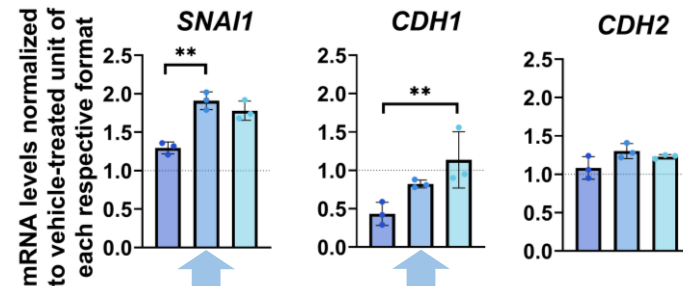
Stromal cells (T-HESC)

● Monolayer ● FN-silk network ● Spheroid



Epithelial cells (12Z)

● Monolayer ● FN-silk network ● Spheroid

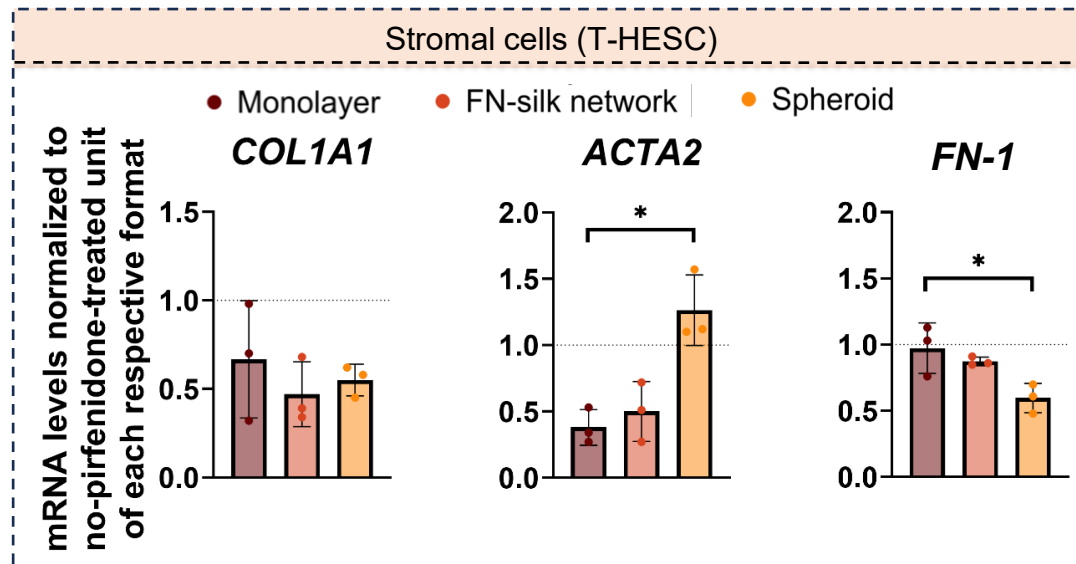
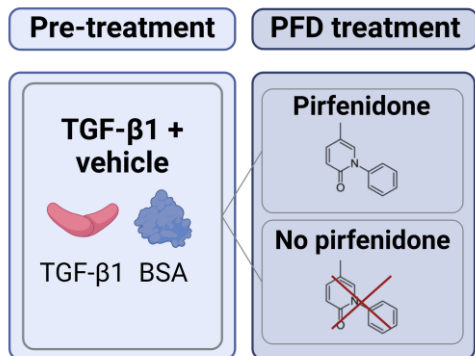


Testing pirfenidone

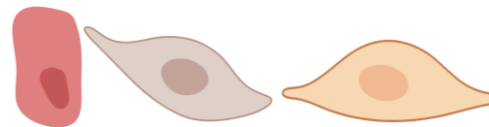


COL1A1 ↓
ACTA2 ↓
FN-1 ↓

COL1A1 ↑
ACTA2 ↑
FN-1 ↑



Testing pirfenidone



SNAI1 ↓
CDH1 ↑
CDH2 ↓

SNAI1 ↑
CDH1 ↓
CDH2 ↑

Epithelial cells (12Z)

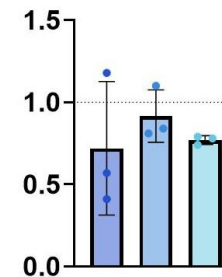
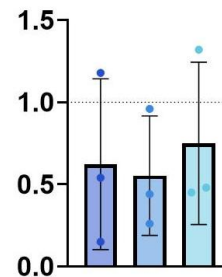
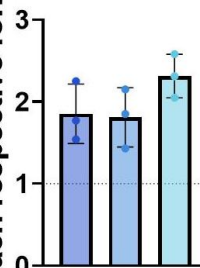
● Monolayer ● FN-silk network ● Spheroid

mRNA levels normalized to
no-pirfenidone-treated unit
of each respective format

SNAI1

CDH1

CDH2



Pre-treatment

PFD treatment

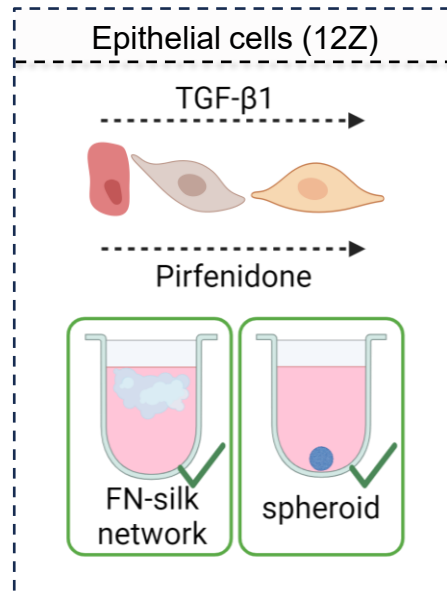
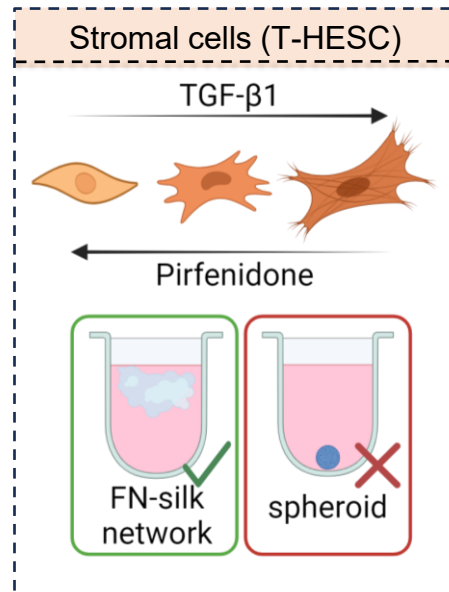
TGF-β1 +
vehicle

TGF-β1 BSA

Pirfenidone

No pirfenidone

Our 3D cell model: present & future



In progress / Next

- Co-culture
- Primary cells
- Intercellular communication
- Identification of markers
- *In vivo validation*
- *Testing new compounds*



Center for Extracellular Vesicles Research

<https://evr.unibe.ch>

Acknowledgements



CURRENT MEMBERS

Dr. Simone Aleandri

Dr. Gregor Bordon

Dr. Cristina Zivko

Dr. Tiziana Cremona

Rafaela Gazzi

Remo Eugster

Assumpta Widak

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Proteomics Core Facility

FACS Core Facility

MIC Microscopy Center



Prof. My Hedhammar
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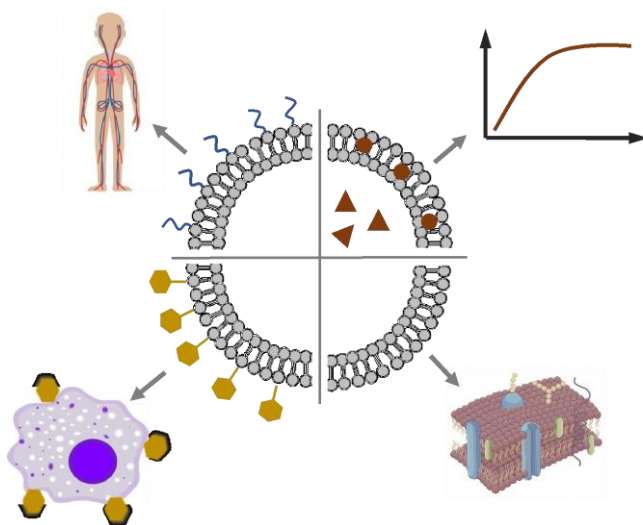
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PHILADELPHIA, PA
JULY 13-18, 2025

**NEXT-GENERATION
DELIVERY INNOVATIONS**



Bluesky: @luciani-lab.bsky.social

<https://lucianiresearch.com>

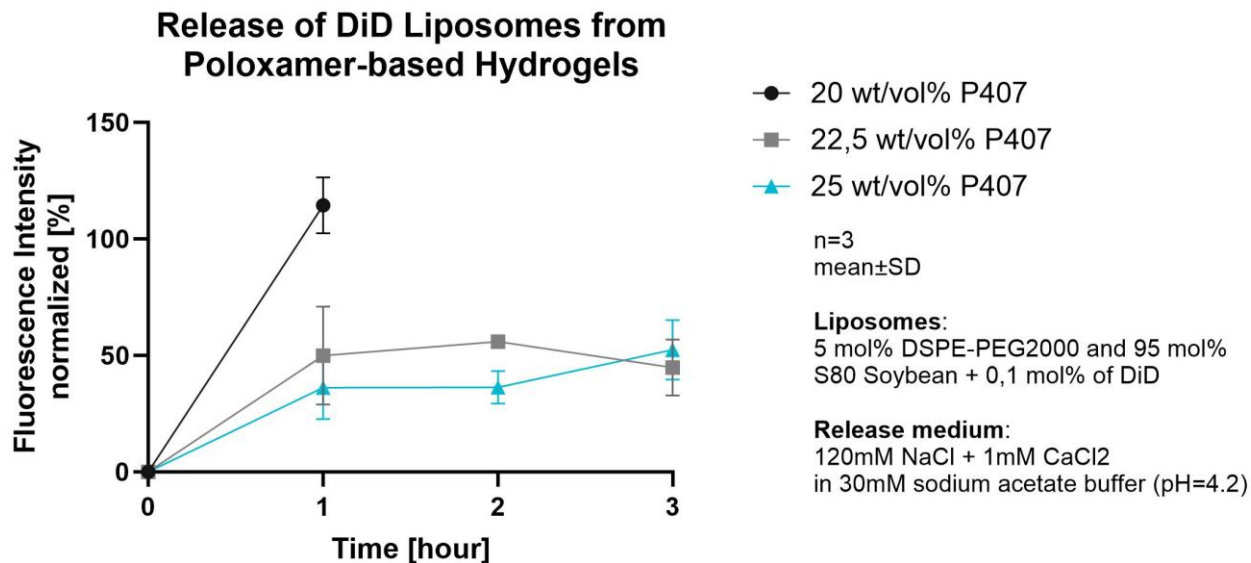
Thank you for your attention!



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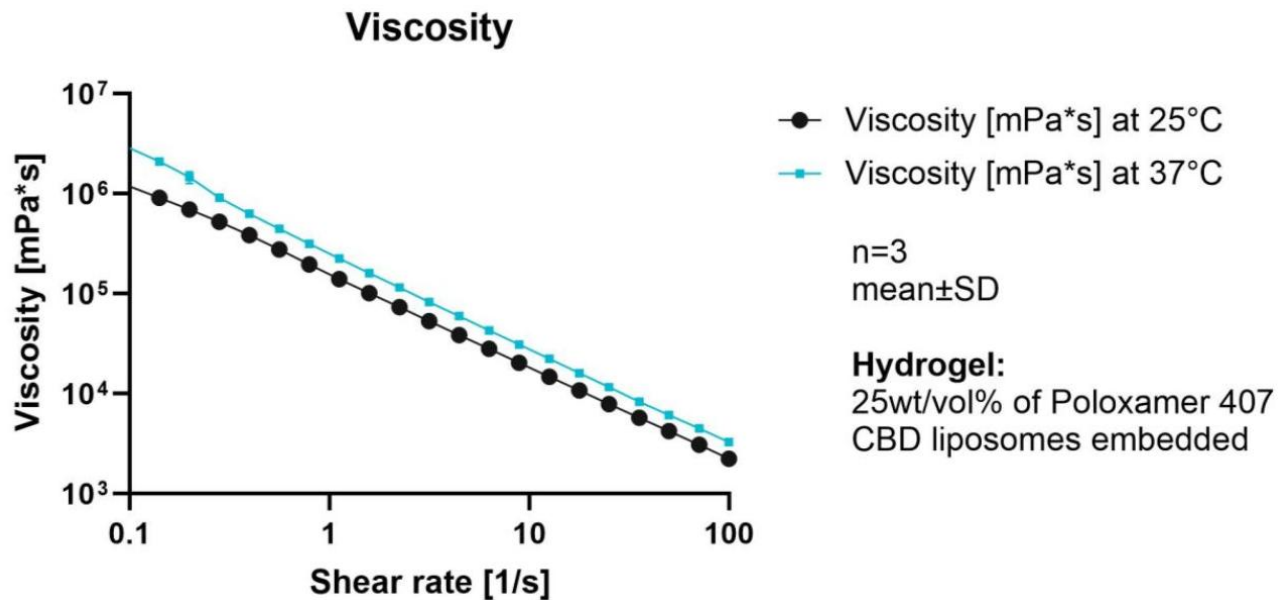
**NEXT-GENERATION
DELIVERY INNOVATIONS**

Liposome release from hydrogel



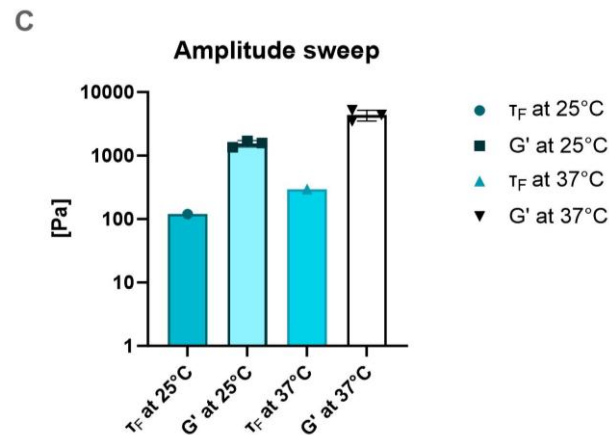
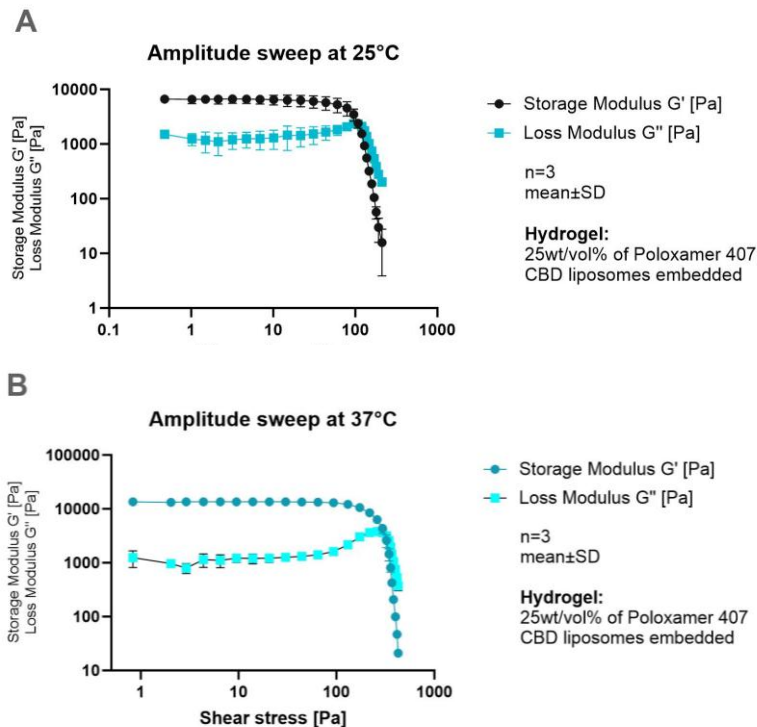
Ana Lucic, unpublished data

Shear-thinning behaviour of the liposomal gel



Ana Lucic, unpublished data

Rheological characterization hydrogel



G' and T_F increase due to thermo-gelling properties of Poloxamer 407

Angular frequency, $\omega = 10 \text{ s}^{-1}$
Shear strain range (γ) = 0.01 – 100%

Ana Lucic, unpublished data