Advanced Biomaterials: Tissue Engineering & Bioprinting for Reproductive Science & Medicine

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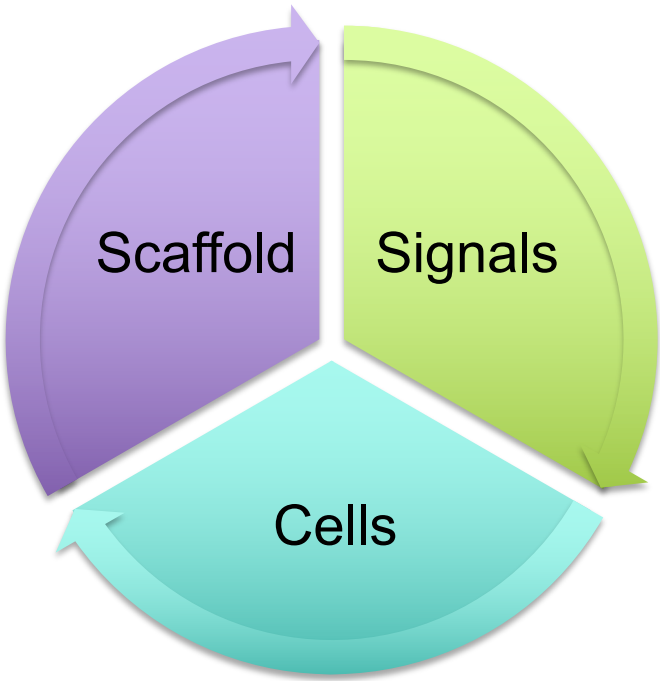
November 15, 2018

Oncofertility Consortium Annual Meeting

Tissue Engineering Paradigm

metal
ceramic
synthetic
hydrogel
ECM component
tissue-derived

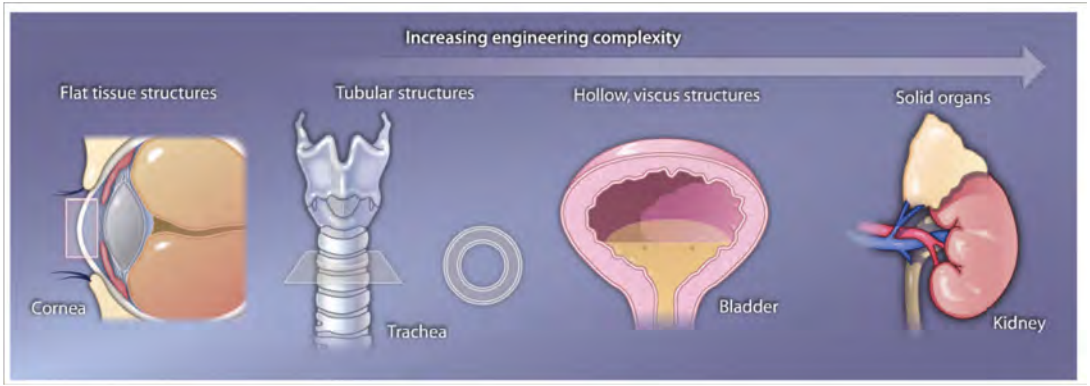


biomechanical
growth factors
proteins
chemokines
RNAs
small molecules
serum
hormones

autologous, allogeneic, xenogenic, MSCs, iPSCs

Progress in Tissue Engineering

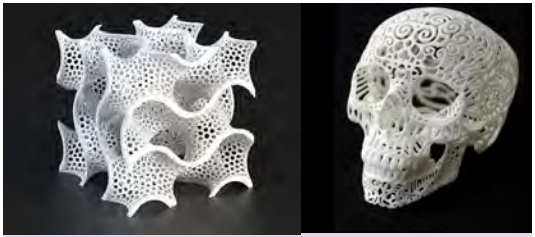
Only structural



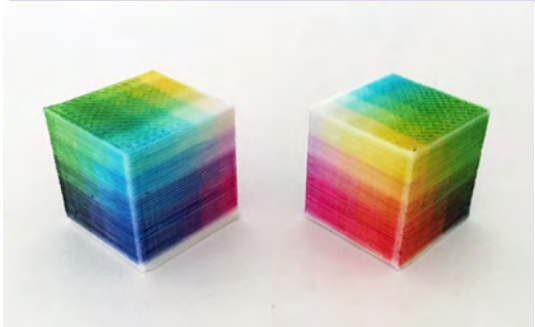
… is limited by our ability to fabricate complex, heterogeneous scaffolds that mimic native tissue

REF: Atala et al, *Sci Transl Med* (2012)

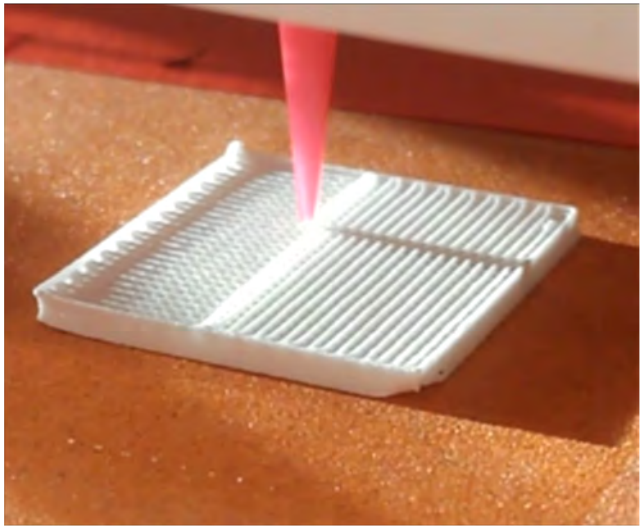
3D printing as an advanced manufacturing platform

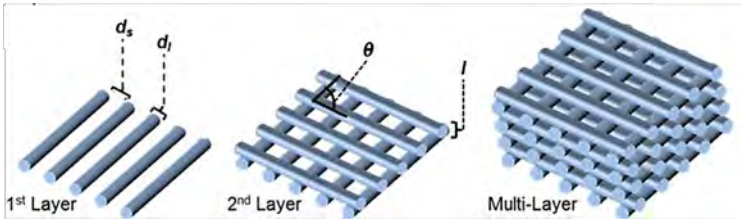


complex and precise



multi-material, heterogeneous



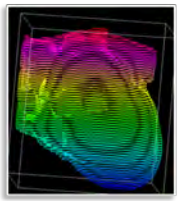


Direct Extrusion 3D Printing

Video by Adam Jakus, PhD

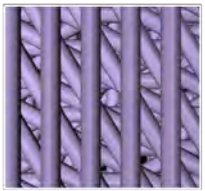
Bioprinting process flow

CAD Model → Custom or obtained from a 3D scan



Slice

Layer thickness dependent on material and nozzle type



Assign Micropore Structure

Pore architecture is designed to be relevant to particular cell/tissue/organ type

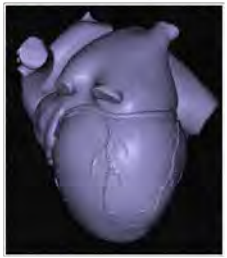
Material "Ink" Preparation

Varies greatly depending on material. Inks must meet certain criteria for bioplotting

3D-Print

Parameters used for 3D printing are highly material dependent and must be optimized for each material

Final Object



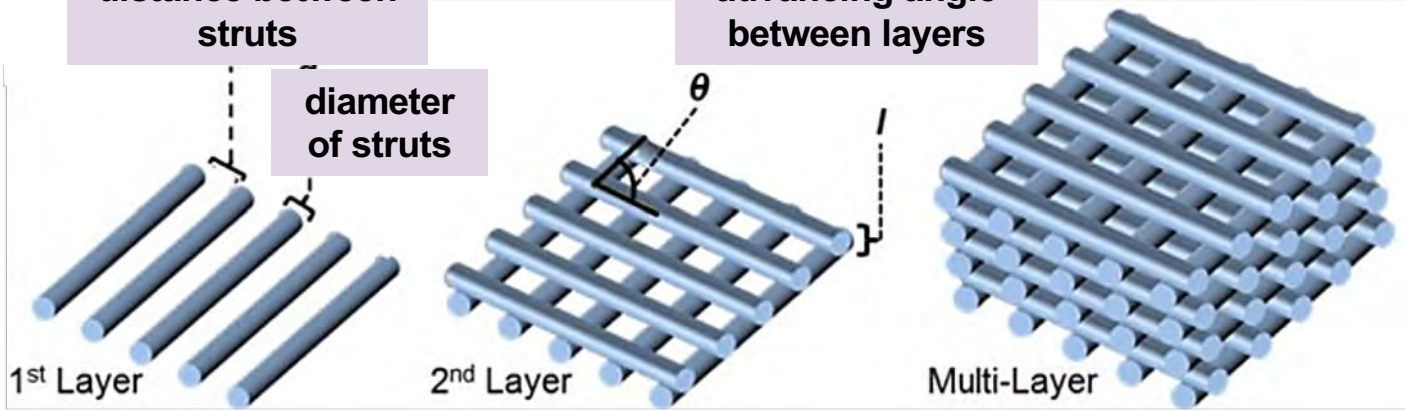
3D printed scaffold architecture: design variables

previous porous scaffolds

pore size: distance between struts

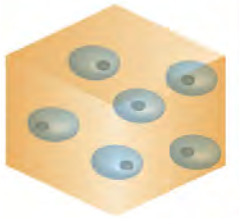
diameter of struts

pore geometry: advancing angle between layers



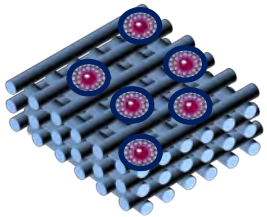
Case Study in 3D Printed Scaffolds: Bioprosthetic Ovary

Encapsulation



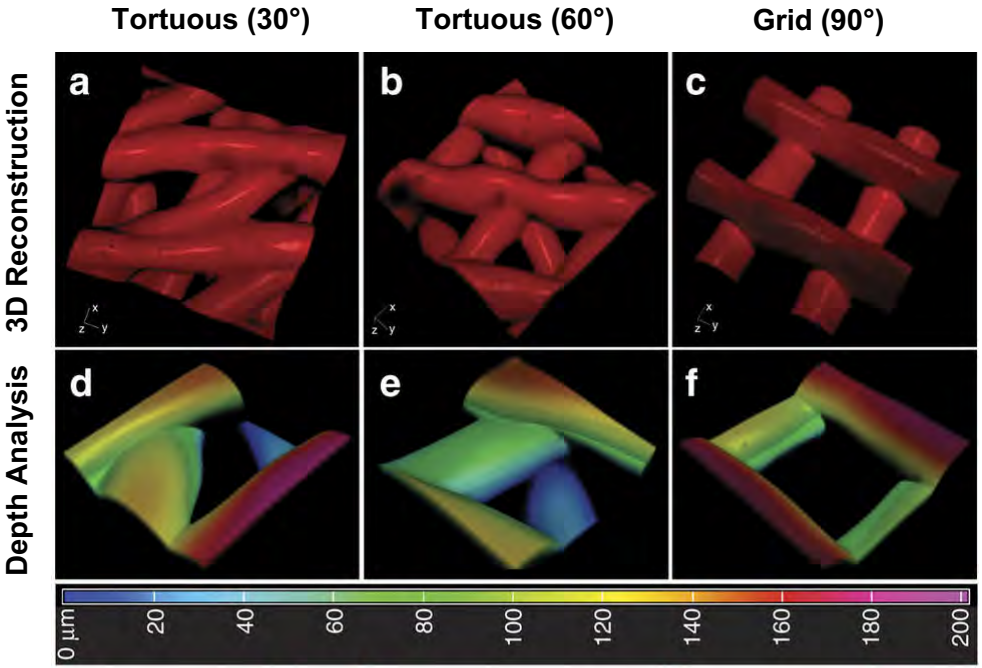
- ✓ Provide 3D support to follicles
- X Release of ovulated eggs and vascularization dependent on rapid degradation (days).
- X Degradation and mechanical properties coupled and result in very weak hydrogels.
- X Construct size limited by diffusion.

3D Printed Scaffold



- ✓ Provide a 3D microenvironment to support to follicle health
- ✓ Open porosity allows for the release of ovulated eggs and vascular infiltration
- ✓ Mechanically robust for surgical implantation and long-term grafting
- ✓ Easy to scale-up size of engineered tissue to meet patient needs

Tortuous scaffolds provide more depth than grid scaffold



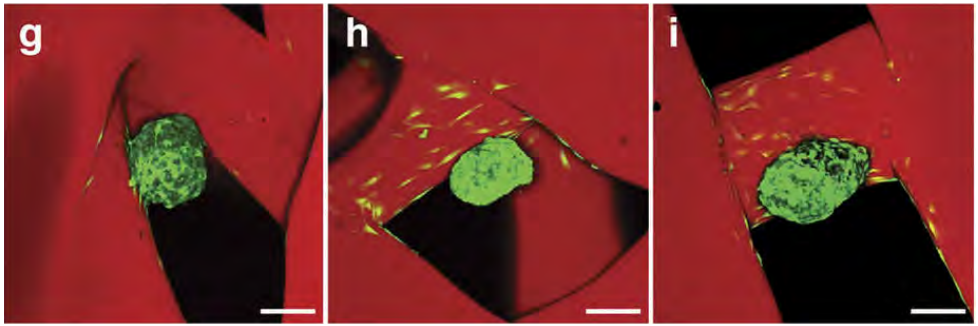
Laronda and Rutz, *Nature Comm* (2017)

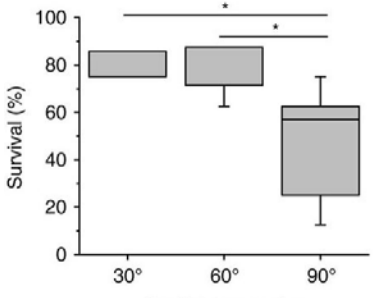
Follicles seeded in 3DP scaffolds

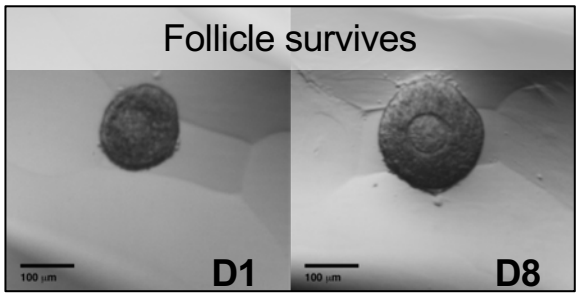
contact struts

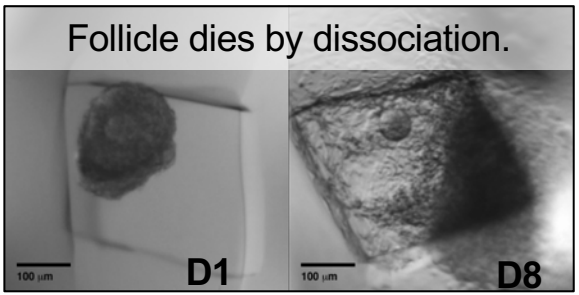
Tortuous (30°) **Tortuous (60°)** **Grid (90°)**

follicle/gelatin







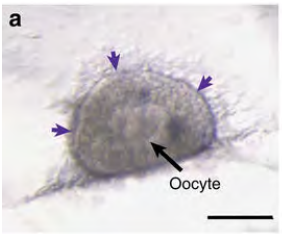


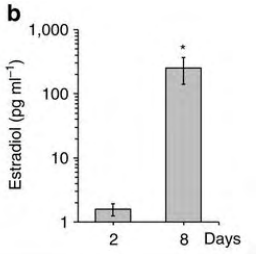
contacting 2 or more struts **contacting only 1 strut**

Laronda and Rutz, *Nature Comm* (2017)

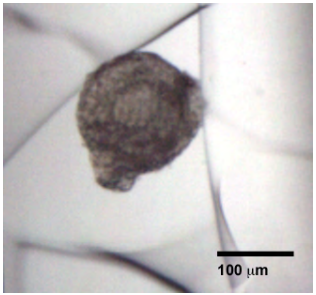
Follicles seeded in 3DP scaffolds function *in vitro*

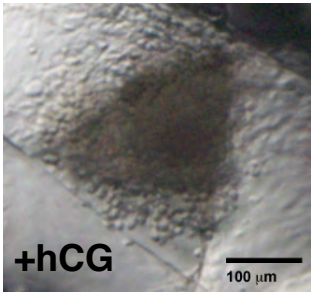
3βHSD expression

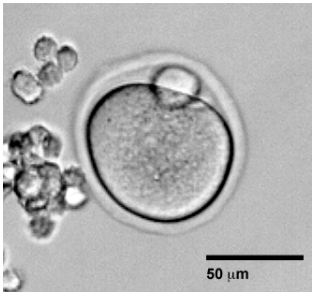




estradiol secretion

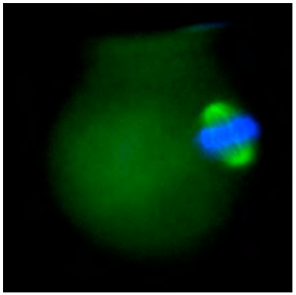






fully mature MII eggs

Microtubules / DNA

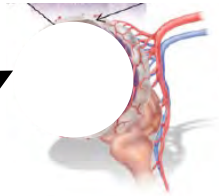


normal spindle morphology

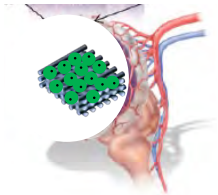
Laronda and Rutz, *Nature Comm* (2017)

GFP+ follicle-seeded 3DP scaffolds for intrabursal implantation

adult NSG female

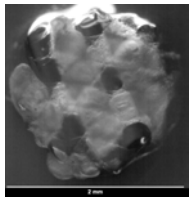


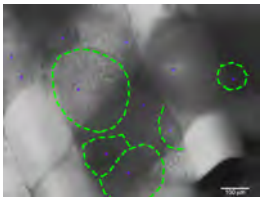
1. Ovarian tissue is removed



40-50 GFP+ follicles

2. bioprosthetic ovary implanted



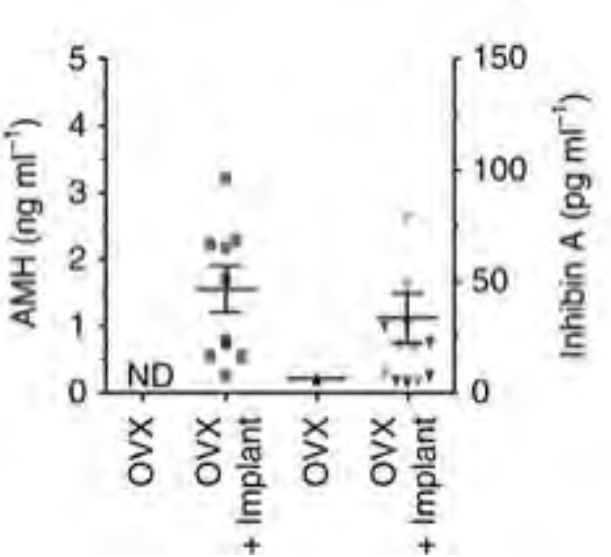


follicles seeded into scaffold and cultured prior to transplant

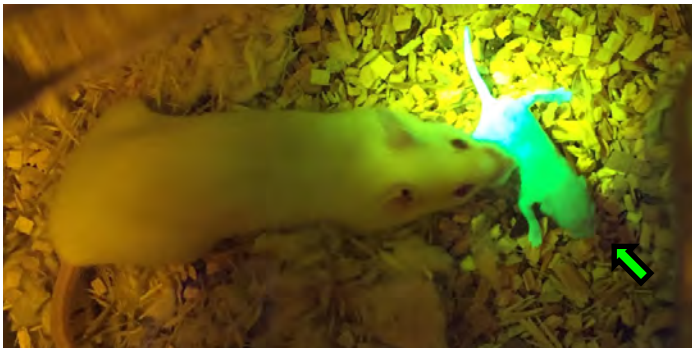
bioprosthetic ovary = GFP+ follicles on 3D printed gelatin scaffold

Laronda and Rutz, *Nature Comm* (2017)

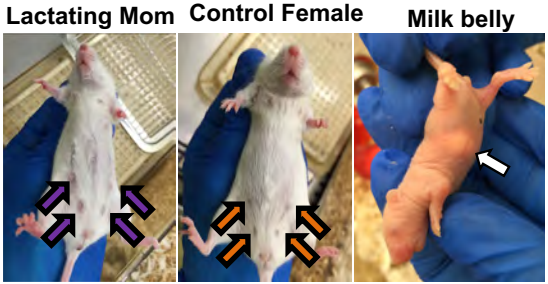
The bioprosthetic ovary restores ovarian function in mice



hormone secretion

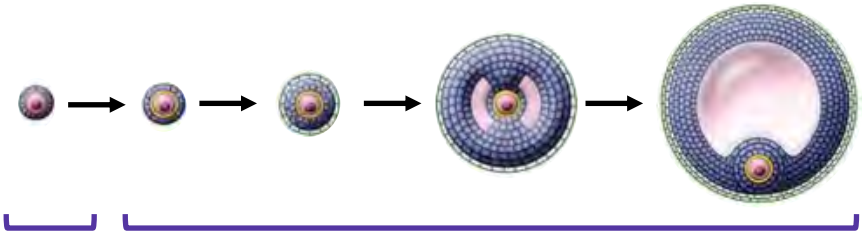


fertility through natural mating



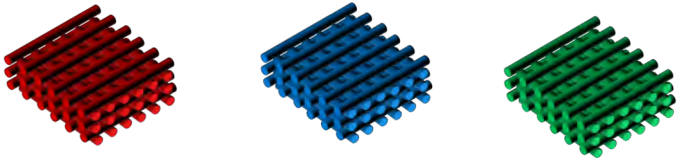
Laronda and Rutz, *Nature Comm* (2017)

Next-generation ovarian bioprosthetic:
bioinspired compartmentalization



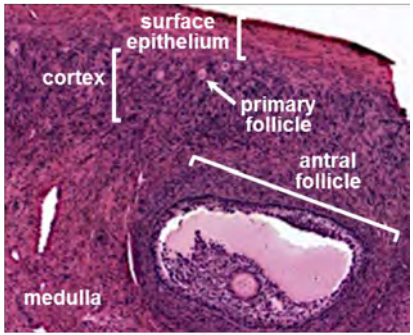
cortex
rigid
quiescent

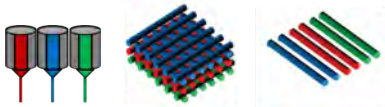
medulla
soft
growing



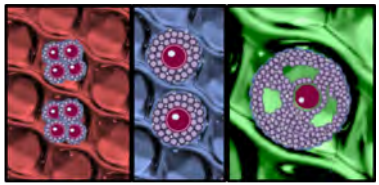
stiffness

pore size

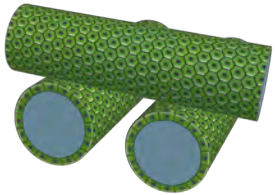


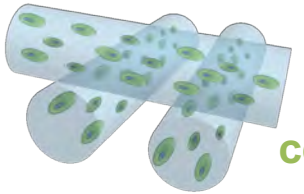


multi-material printing
designer bioinks
cell printing



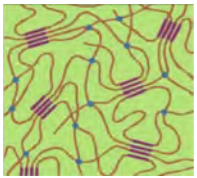
traditional 3DP scaffold
top-seeded





bioprinted scaffold
cell-encapsulating

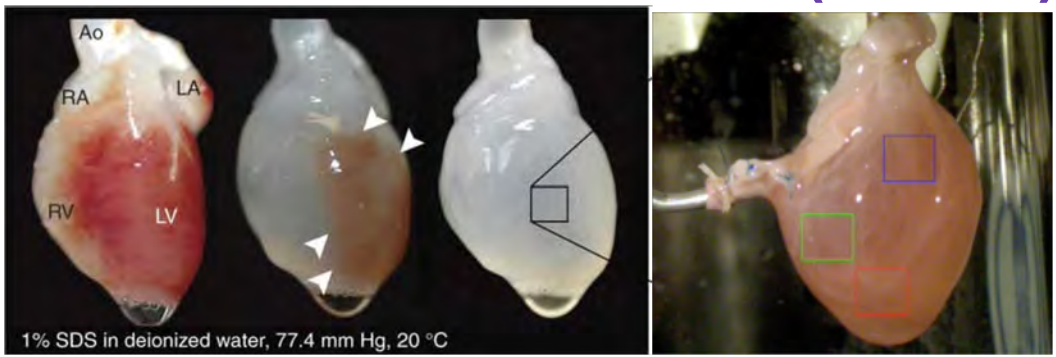
Cell-encapsulating biomaterial inks = “bioinks”



Cells + Hydrogel + Bioprinter = Bioprinted tissue or organ

3D filament images courtesy of Phillip Lewis

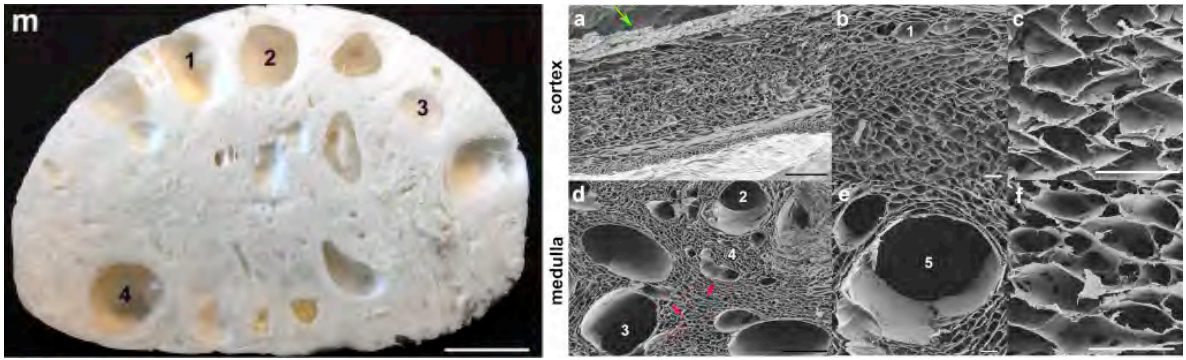
Beyond bioinspired: decellularized extracellular matrix (dECM)

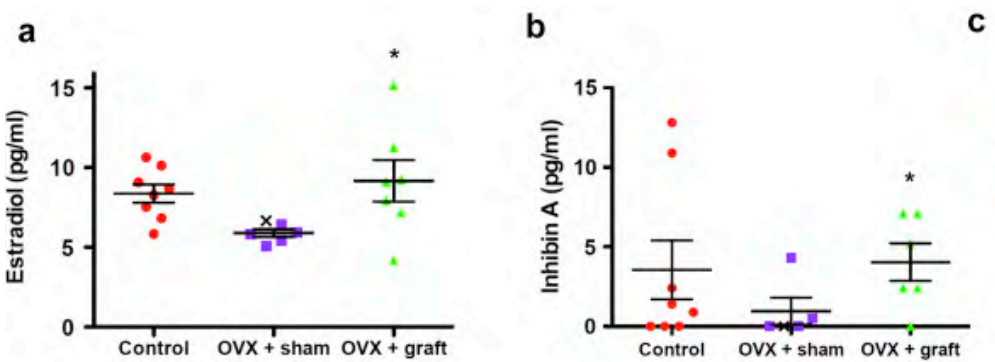


- Composed of native ECM molecules and tissue architecture
- Biodegradable and biocompatible
- Compatible with xenogenic donor organs
- Can be recellularized (?)

REF: Ott et al, *Nature Medicine,* 2008.

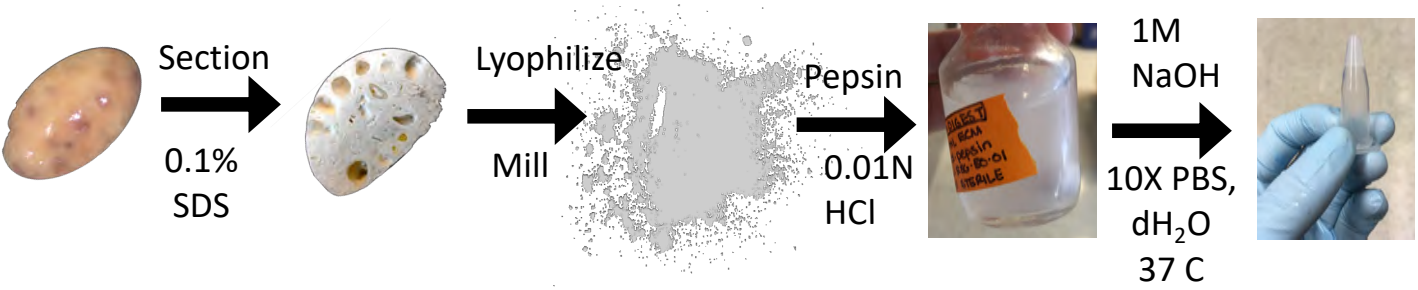
Initiation of puberty in mice following decellularized ovary transplant



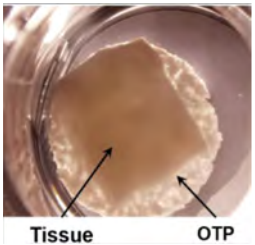


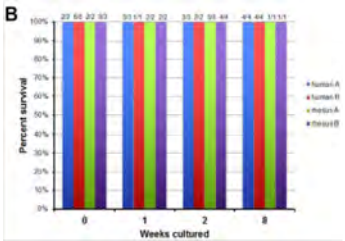
REF: Laronda et al, *Biomaterials* (2015).

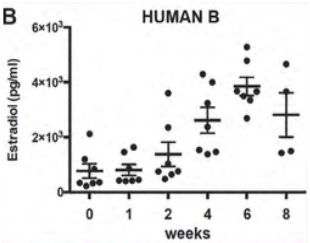
dECM derived hydrogels

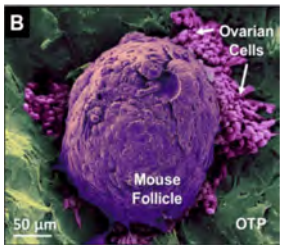


"Tissue Papers": dECM/PLGA composites









REF: Jakus et al, *Adv Functional Materials* (2017).