A 3D Printed Ovarian Bioprosthesis Restores Estrous Cyclicity and Supports Natural Ovulation, Live Birth and Lactation

Program: Late-Breaking Abstracts
Session: LB-OR01-Late-Breaking Oral Session- Basic
Basic/Translational

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Impact: Patients who face primary gonadal insufficiency due to disease treatment, or as a result of genetic causes, have limited options for long-term endocrine and fertility support. Our objective is to create an ovary bioprosthesis that can restore function. We have implanted a bioinspired, scalable 3D printed scaffold of a material with FDA-approved uses in an ovariectomized mouse that models human disease.

Results: We invented a new method for printing gelatin, a collagen-derived biomaterial, into self-supporting ovary bioprosthesis scaffolds with bioinspired pore structures and a stiffness after cross-linking (~30 kPa) similar to that of the ovary (5-20 kPa). We tested several 3D architectures to optimize ovarian follicle survival and function. Our criteria were to maintain high mechanical properties for surgical handling while creating space from scaffold porosity to enable follicle expansion, ovulation, vascularization and transport of follicle paracrine signals. Our intersecting 30° and 60° advancing angle designs, supported folliculogenesis significantly more than scaffolds created with a 90° advancing angle containing through-pores (30°, 78.6% ±3.6; 60°, 75.9% ±4.0; 90°, 48.5% ±8.3 survival p=0.01). The 30° and 60° scaffolds supported 2 or more follicle contacts more than the 90° scaffolds, and were essential for sustained follicle health in culture (74.3% ±6.5 survival with 2+ contacts; 33.2% ±11.3 with 1, p=0.01). Follicles were not only supported by but also interacted with the struts as they robustly expressed vinculin, a focal adhesion protein. The length of cell spreading across struts was significantly less with more contacts, enabling the follicle's spheroid structure to persist (average contact length when contacting 1 strut 198.7mm ±42.8; 2 104.8mm ±14.0; 3 59.5mm ±5.4; $p<0.01$). Follicles within 30° and 60° scaffolds stained positive for 3bHSD, released estradiol and, upon exposure to hCG, ovulated and released MII eggs through the open porosity without mechanical or enzymatic manipulation of the follicle or scaffold. The ovary bioprosthesis consisted of the down-selected 60° scaffold and GFP-positive quiescent and small murine follicles. The bioprostheses were implanted into the native organ site in ovariectomized GFP-negative mice. These bioprostheses supported vascular infiltration without the addition of angiogenic factors, restored the estrous cycle and produced live offspring. These healthy offspring were supported by the lactating implant recipient mother until weaning.

Summary: These data underscore the importance of the bioactive scaffold architecture in supporting folliculogenesis and demonstrate a functional ovary bioprosthesis. This research reaches beyond the current state of tissue engineering toward developing a common scheme for complex soft tissue replacement through bioinspired-manufacturing of bioactive scaffolds.

Nothing to Disclose: MML, ALR, SX, KAW, RNS, TKW