Functional and Tunable Biomimetics for Reproductive Tissue Engineering

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Ovarian follicles are multicellular aggregates in the ovary responsible for a woman's fertility and ovarian endocrine function. Currently, young women and prepubertal girls diagnosed with cancer and facing cytotoxic treatments have limited options to preserve their fertility, resulting in depletion of the non-renewable ovarian reserve and premature ovarian insufficiency (POI). POI results in sterility, along with consequences of lost ovarian endocrine function: premature osteopenia, muscle wasting, and cardiovascular diseases. The unique challenges associated with fertility preservation in females are primarily due to limited and non-renewable ovarian reserve. Technologies for the cryopreservation of eggs or embryos available for adult patients are not suitable for prepubertal patients or adult patients with hormone- and time-sensitive cancers. Additionally, none of the clinically available fertility preservation options can restore the lost ovarian endocrine function and none are suitable for children and young adults.

Patients at risk and prepubertal girls can undergo ovarian tissue cryopreservation prior to beginning of cytotoxic treatments. This ovarian tissue typically contains thousands of early-stage primordial and primary follicles, which carry the potential to restore fertility, yet have been challenging to mature *in vitro* or *in vivo*. We, and others, have demonstrated that three-dimensional biomimetic constructs promote tissue regeneration and restore biological function. We aim to create artificial constructs that support healthy follicle growth and development outside the body and after transplantation by combining approaches from engineering, materials, chemistry and life sciences. For example, to obtain fertilizable oocytes from small follicles cultured *in vitro* we created a culture system for multiple follicles that recapitulates well-choreographed synchronized signaling events, involving soluble cytokines and transcription factor activation necessary for follicle maturation. Resulting mature oocytes can be stored for future fertilization and used for assisted reproduction. For restoration of lost endocrine function in patients with POI we designed an immunoisolating capsule able to support the physiological function of the implanted allogeneic ovarian tissue and protect the allograft from immune rejection. We demonstrated that non-vascularized ovarian tissue encapsulated in a hydrogel-based capsule responds to endogenous stimuli and secretes ovarian hormones that reach systemic circulation by diffusion to restore cyclic ovarian function in ovariectomized mice. Results from our research will provide insights into follicle development and help bridge the gap to support the use of cryopreserved ovarian tissue for fertility and ovarian endocrine function restoration.