Novel in Vitro Model to Grow and Culture the Culture the Ovaries Outside the Body
Product Design Specifications
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Function:

Oftentimes female patients lose their reproductive capabilities as a consequence of having cancer or from undergoing cancer chemotherapy. Research has shown that doxorubicin (DXR) chemotherapy causes ovarian insult, ultimately leading to ovarian failure. Currently, no systems exist to grow adult ovaries in vitro to test chemotherapy toxicity and protection. This situation greatly limits ovarian research. A system to test the effects of the chemotherapy agent DXR on the ovaries needs to be developed. This project will establish a novel ex-vivo ovary culture system to maintain cell viability in order to facilitate assessment of chemotherapy toxicity and protection. The device will utilize ovarian vasculature, providing the ovary with necessary nutrition in a physiologically accurate manner to prevent necrosis. The fluid flow rates and pressure of the infusion lines will be adjusted to physiological conditions to ensure ovarian health. The ovary scaffold will be contained within a sealed environment capable of maintaining internal sterility and cell viability.

Design Process

Upon ample research into the ovarian physiology, tissue culture, and ovarian tissue culture it was concluded that the design would be best served by analyzing two distinct divisions of the design – biological scale and bioreactor/culturing technique. Thus, two separate, different design matrices were created to analyze each part of the design independently. The first decision was determining the biological scale that we would be culturing. A biological scale was chosen that was both plausible and relevant to the problem statement. The second decision involved researching the biological scale chosen and then developing a design for a bioreactor based on that research. The design alternatives were each evaluated and given a score in relevant categories weighted based on importance. The design alternatives were then compared in a design matrix and the design that scored the highest was pursued further.

Biological Scale

Design Alternative 1: Follicle Culture

- Various three-dimensional (3D) in vitro culture systems are been developed
- Chemical and physical properties of the biomaterial must been extensively critiqued
    - Properties such as elasticity, rigidity, and diffusion [1].
- Current models for 3D culture include follicle cluster
    - Encapsulation in a matrix
    - Suspension culture
    - Serial culture
    - Microfluidic culture
- Viability for up to 14 days
- Little clinical and physiological relevance

Design Alternative 2: Ovarian Tissue

- Extracellular matrix (ECM) is very advantageous in ovarian culture
    - Ability to maintain the three-dimensional organization of the follicle [2].
    - Using natural ECM has also shown to significantly increase the viability of follicle cells and increase the growth of many other cell types [3].
- The desire to study follicle cells in their natural environment
- Limits the complexity of the design
- The culture of human ovarian cortical tissue has been achieved using either slices or cubes of tissue [4].

Design Alternative 3: Complete Ovary

- Culture entire cow ovary
    - On average 35x25x15 mm [5]
    - More pronounced features
- Significant clinical and physiological relevance
    - Relatable to human ovaries (can be scaled down for future testing)
- Very difficult
    - Complete ovaries have never been cultured

Biological Scale				
Factors	**Weight**	**Follicle Cluster**	**Ovarian Tissue**	**Complete Ovary**
Feasibility	30	27	23	22
Clinical Relevance	30	18	22	30
Ease of Culturing	20	18	15	15
Consistency	15	12	10	15
Cost	5	3	4	5
TOTAL POINTS	**100**	**78**	**74**	**87**

Bioreactor/Culturing Technique

Design Alternative 1: "Balloon" Method

- Interior of the ovary will be removed
- Interior chamber (thin layer spherical layer) that will fill with medium to provide nutrients to the inner parts of the ovary
    - Input tube
    - Multiple output tubes (one below and multiple on sides of sphere)
    - Provides structural support
- Entire ovary will be placed in large chamber that will be filled with medium
    - Input and output pump

Design Alternative 2: Intravenous Method

- Utilize the vasculature of the ovary that is already in place
- Cannula will be put into major veins and arties for input and output of medium
    - Will provide nutrients to the interior of the ovary
        - Artery = inflow
        - Vein = outflow
    - Use pump to regulate flow and pressure to replicate physiological conditions
- Entire ovary will be placed in large chamber that will be filled with medium

Design Alternative 3: Direct Perfusion

- Remove interior of ovary to allow diffusion of medium and nutrients
    - Increase diffusion rate
- Medium flow directly through the pores of the scaffold
- Enhances mass transfer not only at periphery but also within internal pores [6]
- Widely used in tissue engineering

Bioreactor/Culturing Technique				
Factors	**Weight**	**"Balloon" Method**	**Intravenous Method**	**Direct Perfusion Bioreactor**
Cell Viability	20	15	18	10
Physiological Accuracy	20	15	20	13
Ease of Use	15	13	12	14
Biocompatibility	15	14	14	14
Repeatability	10	7	9	8
Versatility	10	6	8	3
Cost	5	3	2	4
Ease of Assembly	5	2	2	4
TOTAL POINTS	**100**	**75**	**85**	**70**

References

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