ARTIFICIAL OVARIES

Activity Packet

Carnegie Mellon University - Department of Biomedical Engineering

Note: This educational resource was developed as a project by the Carnegie Mellon student Meghan McGraw for the summer 2020 course, Experiential Learning through Projects [99-520], inspired by a project completed by student Carolyn Bolz in the spring of 2020. Editing and additional project development was also completed by Claire Kenny.

Background

Making artificial ovaries is a relatively new (~2015 - present) technology that is still in animal trials. The creation of artificial ovaries aims to restore or create fertility in those who are infertile, as well as balance hormones. It has been tested in mice, where some were able to ovulate and produce viable offspring, showing promise for being able to be used in humans in the future, although some major issues remain in making them accessible for human use ("Researchers Create").

Students will learn how to think like engineers--they will be able to identify a problem (ovarian pathophysiology and infertility) and explore viable solutions (tissue engineering and artificial ovaries) to it based on constraints (ovarian anatomy and physiology). It is recommended for a high school audience with general biology knowledge (anatomy and physiology is also useful, but not required).

There are three activities included--a lecture, a sugar crystal biomaterials activity, and an interactive ovarian histology lab. While doing all three provides students with the most complete knowledge of the field, they can be done separately. From the lecture students will gain a 'bird's eye view' of all aspects of creating an artificial ovary. The sugar crystal activity will allow students to make a familiar craft with an analogy to the components of tissue engineering. An optional competition to see who can grow the largest sugar crystals can be held and related back to the process of trying to successfully grow cells on scaffolds. The ovarian histology lab allows students to examine normal functioning ovarian tissue, as well as diseased tissue that requires engineering interventions. Supplemental worksheets for the sugar crystals and histology lab as well as vocab quizzes are also included.

Objectives

After these activities, students should be able to:

Lecture

- Demonstrate knowledge of basic ovarian anatomy and physiology
    - Name stages of the ovarian cycle
- Name and describe conditions that cause ovarian damage
- Identify the stages of tissue engineering
    - Name each component of an artificial ovary and describe how each serve to help solve infertility problems
- Discuss who can benefit from artificial ovaries
- Discuss the ethical questions that go into consideration with new technology

Sugar Crystal Biomaterials

- Name the components required to make an artificial ovary and briefly describe their purpose
- Compare and contrast sugar crystal making to growing cells

Interactive Ovarian Histology Lab

- Define histology and explain why it is useful for understanding ovarian anatomy
- Name, define, and draw stages of the ovarian cycle
- Name conditions that affect ovarian tissue and describe some of the histological characteristics of the conditions

Materials

Lecture

- Projector
- A computer able to display PowerPoint slides

Sugar Crystal Biomaterials

*Note: The following resources are enough for 16 individual students. This can be done in teams to save resources. *

- 24 cups of sugar (with extra sugar for seeding)
- 8 cups of water
- 16 pipe cleaners
- 16 pencils
- Tape
- 16 cups (Note: glass cups or Mason Jars are best. However, plastic cups may be substituted)

- Paper towels
- Stovetop (or anything that will bring water to a boil)
- Saucepan (or anything that can fit the volume of water and can withstand heat)
- Food dye
- Sharpies
- Student Worksheet for each student

Optional:

- Small scale
- Weigh paper

Interactive Ovarian Histology Lab

- Computer
- PowerPoint file
- Student worksheets for each student

Safety Considerations

Lecture

There are no consequential safety concerns in relation to the activity.

Sugar Crystal Biomaterials

The water will need to be brought to a boil. Do not let students handle the hot water or the cups after the water has been added to them. Do not let students eat the sugar crystals.

Virtual Ovarian Histology Lab

There are no consequential safety concerns in relation to the activity.

Vocabulary

Note: The following are terms students may be unfamiliar with. They are not required to know all of them. Depending on the classroom environment, it is the educator's decision on how many terms that the students should know. The definitions were drawn from the sources named at the end of this packet.

Lecture and Kahoot

1. Biocompatibility - the property of a material being compatible with tissue Bioreactor- a chamber for cells to grow in
2. Chemotherapy - a drug treatment with chemicals to kill fast-growing cells
3. Decellularization - stripping the cells off of the extracellular matrix (ECM)
4. Endometriosis - a condition where uterine tissue grows outside the uterus
5. Estrogen - signals the buildup on the uterine lining; a surge in this leads to ovulation
6. Fertility - the ability to produce offspring
7. Fertilization - union of a sperm and an egg
8. Follicle - an ovum and the cells around it
9. Menstrual Cycle - the process of ovulation and menstruation; broken into three phases
10. Oocyte - the cell that develops into an egg
11. Ovaries - a female reproductive organ that is responsible for producing and releasing eggs, estrogen, and progesterone
12. Ovulation - the release of an egg from the ovary
13. Ovum - a mature egg
14. Polycystic Ovary Syndrome (PCOS) - a condition where follicular growth is arrested and the developing follicle turns into a large fibrotic 'cyst'
15. Progesterone - a hormone released by the ovary (corpus luteum) that maintains the uterine lining in preparation for fertilization
16. Radiation - using high energy waves to kill cancer cells
17. Reproductive system - all organs involved in sexual reproduction
18. Scaffold - a structures where cells can grow
19. Tissue Engineering - combining scaffolds, cells, and other biologically active molecules into functional tissues

Extra:

1. Androgens - male hormones
2. Corpus Luteum - the remainder of the follicle structure--maintains high progesterone levels
3. Cortex - the area of the ovaries that contains follicles and connective tissue
4. Endocrine system - organs and glands that make hormones
5. Epithelial cells - cells that cover tissue
6. Follicle-Stimulating Hormone (FSH) - helps stimulate the growth of eggs
7. Follicular Phase - the phase in which the follicle matures before ovulation
8. Integrins-proteins on a cell that attach it to the environment
9. Luteal Phase - the phase in which the corpus luteum maintains the uterine lining in preparation for pregnancy
10. Luteinizing Hormone (LH) - a surge in this hormone triggers ovulation
11. Medulla - in the center of the ovary
12. Oogenesis - the development of eggs into viable gametes that are fertilizable
13. Pituitary - an endocrine gland responsible for secreting hormones

Sugar Crystal Biomaterials

1. Biocompatibility- the property of a material being compatible with tissue
2. Bioreactor- a chamber for cells to grow in
3. Decellularization- stripping the cells off of the extracellular matrix (ECM)
4. Oocyte- the cell that develops into an egg
5. Scaffold- a structures where cells can grow

Virtual Histology Lab

1. Corpus Albicans - the stage where the corpus luteum is degrading after LH levels fall
2. Corpus Luteum - the remainder of the follicle structure--maintains high progesterone levels
3. Endometriosis - a condition where uterine tissue grows outside

the uterus

4. Estrogen - signals the buildup on the uterine lining; a surge in this leads to ovulation
5. Fertility - the ability to produce offspring
6. Follicle - an ovum and the cells around it
7. Histology - study of cells microscopically
8. Oocyte - the cell that develops into an egg
9. Ovulation - the release of an egg from the ovary
10. Ovum - a mature egg
11. Primary Follicle - the beginning stage of the menstrual cycle for the egg 6
12. Primordial Follicle - dormant egg cells and the granulosa cells around them
13. Progesterone - a hormone released by the ovary (corpus luteum) that maintains the uterine lining in preparation for fertilization
14. Secondary Follicle - in this stage, the antrum begins to form
15. Tertiary Follicle- in this phase, the zona granulosa separates from the corona radiata

Extra:

1. Antrum - a fluid filled sack
2. Chemotherapy - a drug treatment with chemicals to kill fast-growing cells
3. Corona Radiata - when ovulated, an egg has this surrounding it
4. Cortex- the area of the ovaries that contains follicles and connective tissue
5. Cytotoxic - poisonous to cells
6. Epithelial cells - cells that cover tissue
7. Estradiol - a precursor to estrogen
8. Follicle-Stimulating Hormone (FSH) - helps stimulate the growth of eggs
9. Glycoprotein - a sugar protein that is used for cellular recognition
10. Granulosa cells - cells that surround the developing egg--eventually convert androgens into estradiol

11. Granulosa Lutein cells - in the corpus luteum, these cells surround a blood clot located where the egg was previously located
12. Lipid - fat
13. Luteinized - process of lipid accumulation and formation of the corpus luteum
14. Luteinizing Hormone (LH) - a surge in this hormone triggers ovulation
15. Metastasize - a tumor spreading to other parts of the body
16. Radiation - using high energy waves to kill cancer cells
17. Squamous - flat cells
18. Stroma - the supportive tissue of an organ
19. Theca cells - produce androgens
20. Tumor - abnormal cell grow (neoplasm)
21. Vascularization - the presence of blood vessels
22. Zona pellucida - recognition coating for sperm cells

Procedure

Lecture

Note: The lecture can be distributed to students for independent remote learning.

1. Review the PowerPoint slides and slide guide to become familiar with the terms and topics used in the slides.
2. Present a lecture to students using the PowerPoint slides. They are welcome to (and should be encouraged to) take notes.

Sugar Crystals Biomaterials

Note: This activity can be done remotely if students have access to the materials and a parent is available to help them.

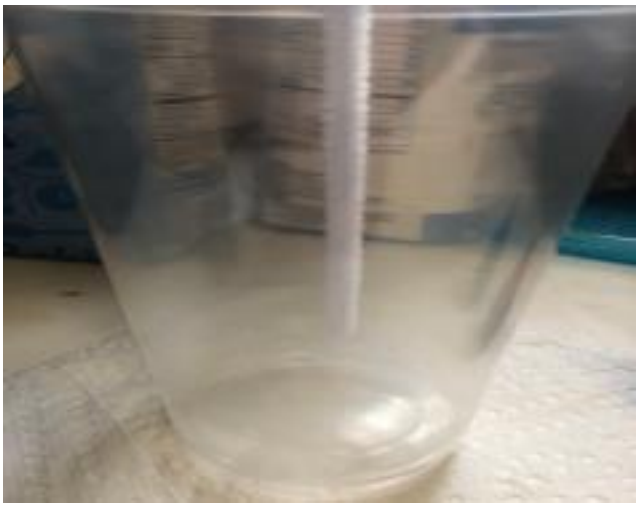
1. Print out the supplemental worksheet for students from the website, listed under *Sugar Crystals Biomaterials*.

2. Gather materials. The instructor should give the cups/Mason jars, pencils, Sharpies, and pipe cleaners to the students.

3. Bring water to a boil in the saucepan.

4. Add sugar little by little, mixing continuously to help sugar dissolve. Add food coloring and stir.

5. Take off heat, letting rest for 10 minutes.
6. Simultaneously, students should:
   a. Put their name on a cup.
   b. Take a pipe cleaner, dip it in water, and coat it in sugar.
   c. Measure out the amount of pipe cleaner needed to get almost to the bottom of the cup and wrap the rest of the pipe cleaner around the pencil. The sugared side should be in the cup.
   d. Place cups on a tray in a safe area.



7. Pour sugared water into each cup, almost filling to the top.

8. Cover the top of each cup with a paper towel.
9. Wait 3-5 days to take the pipe cleaners out of the water.
10. After leaving the sugar crystals to set, give students the worksheet and let them match the components of tissue engineering to those of sugar crystals.

Optional:

11. Conclude with the discussion questions, listed on the website under *Additional Resources.*
12. After letting the sugar crystals set, take them out and let them dry for a few

minutes.

13. Place weighing paper on a scale, and tare the scale.
14. Weigh each person's or team's sugar crystals, using and taring new piece of weighing paper each time. Have the students record the weight on their worksheet. A winner (or winners) can be declared by seeing which sugar crystals grew the largest. A prize can be distributed to the winner(s).

Interactive Ovarian Histology Lab

Note: This activity can be done remotely.

1. Print out the supplemental worksheets
2. Open the Virtual Histology Lab PowerPoint
3. Go through the "How to Play" instructions with the students
4. Let students complete the activity
5. Students can turn in the worksheet for grading

Additional Resources

1. **Ovarian Histology -- An article showing and explaining every stage of the ovarian cycle.**
   Histology@Yale. medcell.med.yale.edu/histology/ovary_follicle.php.

2. **Detailed Ovarian Anatomy -- An article providing information on female reproductive anatomy.**
   Sokol, E."Clinical Anatomy of the Uterus, Fallopian Tubes, and Ovaries." Glowm, July 2010, https://www.glowm.com/section_view/heading/Clinical+Anatomy+of+the+Uterus,+Fallopian+Tubes,+and+Ovaries/item/1

3. **Infertility -- An article listing causes of female infertility**.
   "What Causes Female Infertility?."
   https://web.stanford.edu/class/siw198q/websites/reprotech/New%20Ways%20of%20Making%20Babies/Causefem.htm

4. **Menstrual Cycle -- Articles going through the phases of the menstrual cycle.**
   Wakim, S. and Grewal, M. '22.7: Menstrual Cycle.' *Biology LibreTexts*, Libretexts, 16 June 2020, https://bio.libretexts.org/Bookshelves/Human_Biology/Book:_Human_Biology_(Wakim_and_Grewal)/22: Reproductive_System/22.07:_Menstrual_Cycle

   Watson, S. 'Stages of Menstrual Cycle." Healthline, 23 October 2010, https://www.healthline.com/health/womens-health/stages-of-menstrual-cycle

5. **Endometriosis -- An article explaining every aspect of endometriosis.**

Han, L. and Garcia, R. “Endometriosis.” Pathology Outlines, 16 March 2020, http://www.pathologyoutlines.com/topic/uterusendometriosis.html

6. **Polycystic Ovary Syndrome -- An article going through all aspects of endometriosis.**

“Polycystic ovary syndrome.” *Genetics Home Reference*, NIH. https://ghr.nlm.nih.gov/condition/polycystic-ovary-syndrome

7. **Cancer and Fertility -- The first article explains the impact that cancer and cancer treatments have on females. The second article describes a way to prevent the spread of ovarian cancer cells.**

“How Cancer and Cancer Treatment Can Affect Fertility in Females.” American Cancer Society, 6 February 2020. https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/fertility-and-sexual-side-effects/fertility-and-women-with-cancer/How-cancer-treatments-affect-fertility.html

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8. **Artificial Ovaries -- These articles explain the current strides being made in artificial ovary development.**

Mullin, E. “Bioengineered Ovaries Can Survive in Mice. Humans Are Next.” Medium, 20 September 2018. https://medium.com/neodotlife/artificial-ovaries-f84ecc7beb6a

“Mouse implanted with ovaries made by 3D printer gives birth, offering new hope for infertile women.” National Post, 18 May 2017, https://nationalpost.com/health/mouse-implanted-with-ovaries-made-by-3d-printer - gives-birth-offering-new-hope-for-infertile-women/

“Researchers create prosthetic ovaries using gelatin and a 3D printer.” National Post, 16 May 2017, https://www.ctvnews.ca/health/researchers-create-prosthetic-ovaries-using- gelatin-and-a-3d-printer-1.3415835

9. **Scientific Papers of Artificial Ovaries - -Articles describing the methods used to create artificial ovaries**.

Dolmans, M. and Amorim, C. “FERTILITY PRESERVATION:Construction and use of artificial ovaries” *Reproduction*, BioScientifica, 12 November 2019, https://rep.bioscientifica.com/view/journals/rep/158/5/REP-18-0536.xml

Kim, J., Perez, A., Claflin, J., David, A., Zhou, H., and Shikanov, A. “Synthetic hydrogel supports the function and regeneration of artificial ovarian tissue in mice.” Nature, 7 July 2016, https://www.nature.com/articles/npjregenmed201610

10. **The Patent for Artificial Ovaries--The current patent for artificial ovaries.**
"US10479980B2 – Artificial ovary. https://patents.google.com/patent/US10479980B2/en

Next Generations Science Standards Alignment

HS-ETS1-1. Analyze a major global challenge to specify qualitative and quantitative criteria and constraints for solutions that account for societal needs and wants.

HS-ETS1-2. Design a solution to a complex real-world problem by breaking it down into smaller, more manageable problems that can be solved through engineering.

Authors

Lesson idea from Carolyn Botz, final product developed by Meghan McGraw as a project for 99-520O Development of Biomedical Engineering Educational Outreach Activities for Middle and High School Audiences

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