Gas and Liquid Gradient Bioreactor to Mimic Tumor Microenvironment

Sex in Biomedical Research: A Case Study of Organ-on-a-Chip As Undone Science

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By

Emma Lunn

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Technical Team Members: Elizabeth Wood, Evan Clark

On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

ADVISORS

Sean Ferguson, Department of Engineering and Society

Dr. Tom Genetta, Department of Radiation Oncology

Introduction

Sex/gender bias in biomedical research contributes to decreased health outcomes for women (Plevkova et al., 2021). Women have historically been excluded from biomedical research in basic, preclinical, and clinical study settings (Medicine et al., 2001). In 1977, the FDA set guidelines explicitly excluding premenopausal women from clinical trials (K. A. Liu & Mager, 2016). This was reversed by the Revitalization Act of 1993, when the NIH mandated the inclusion of women in clinical research for the first time (K. A. Liu & Mager, 2016). Yet, medical research that uses in vivo animal models and in vitro models continues to exclude females (Heidari et al., 2016). A review of biomedical research conducted in 2012 found that 80% of animal model studies that reported sex used all males and 71% of cell studies that reported sex used all males (Yoon et al., 2014). Researchers continue to overwhelmingly use males in studies to "avoid variability" thought to be associated with female hormones, even though it has been shown that there is no significant difference in variability between all-male and all-female studies (Plevkova et al., 2021). Without valid justification, the results from majority or all-male studies are extrapolated to include females. This underrepresentation prevents researchers from understanding how a drug or treatment will affect female physiology, which can lead to worse outcomes for female populations (Heidari et al., 2016). Moreover, medical conditions that exclusively or predominantly affect female populations are under-researched, and thus many are not well understood (Lee, 2018; Medicine et al., 1994). This has created a gap in knowledge between men's health and women's health (Heidari et al., 2016).

Traditionally, it is difficult to model female physiology like hormone levels within the context of an in vitro system (Nawroth et al., 2018). Recent innovations in organ-on-chip

technologies and microfluidic devices have made it possible to model complex and specific microenvironments. This has provided a great opportunity for the expansion of women's health to in vitro research because of the increased ability to control the physiology of the system, making it easier to induce female-specific conditions. There have been studies that have used this to close gaps in recent years, but this innovation is still under-used for women's health applications (Nawroth et al., 2018). The most widely funded organ-on-chip technologies focus on non-sex-specific organs and minimally consider the impacts of female-specific physiology on these systems (Wu et al., 2020).

The technical portion of this paper focuses on the design and fabrication of a microfluidic device technology that can be used to mimic a tumor microenvironment more accurately. This technology has the potential to allow for researchers to model female-specific physiology in tumor growth. In this way, the technical portion of the paper is linked to the STS portion, which investigates gender and sex in biomedical applications. The STS portion of the paper will use the undone science framework to examine how counterpublics influence women's health research.

Technical Topic

Cancer remains one of the leading causes of deaths across the globe, despite worldwide efforts to research cancer biology and develop therapies (*Cancer Facts & Figures 2021*, 1930; Sung et al., 2021). One major barrier to cancer research is inaccuracy of in vitro tumor microenvironment modeling, which prevents researchers from efficiently screening anticancer drugs (X. Liu et al., 2021). Currently, data on proliferation, differentiation, and migratory capacity of cells is obtained through the use of traditional, labor-intensive tissue culture methods (X. Liu et al., 2021). These methods subject cells to static conditions of fixed temperature,

atmosphere, and media compositions, acquiring a molecular/biochemical/histological “snapshot” of a dynamic cellular response (Byrne et al., 2014; Rogers et al., 2018). These methods are extremely limited in their ability to replicate one of their most critical aspects of tumor microenvironments: the presence of multiple overlapping gas (NO, O2, etc.) and solute (growth factors, cytokines, nutrients, etc.) gradients (Rogers et al., 2018; Sleeboom et al., 2018). There is a need to develop a more accurate understanding of cell behavior in tumor microenvironments and in response to various therapeutics.

The ultimate goal of this project is to design and validate a novel bioreactor that will allow for more accurate in vitro simulation of the dynamic tumor microenvironment. I have worked with my team, made up of two BME undergraduate peers, and our technical advisor, Dr. Tom Genetta, from the Radiation Oncology Department at UVA to determine specific needs of the device. My team and I have researched prior art and designed a CAD model of the bioreactor using Fusion360. We have combined two distinct, gradient-generating technologies into a single device which will enable the delivery of simultaneous gradients of both gas and liquid solutes to cultured cells. The device will apply an oxygen gradient to a 2D cancer cell culture in order to mimic the hypoxic environment of a 3D tumor. The standard method of oxygen gradient application is through the use of gas cylinders. These cylinders are large, bulky, and require sophisticated instrumentation. Instead, we plan to use an oxygen generating chemical reaction to produce the oxygen gradient based on the success of this method in recent research (Chiang et al., 2017). I worked with Dr. Guilford, BME Professor and Assistant Dean, to 3D print an initial prototype of the device. We will test the efficiency of this prototype to deliver gas and solute gradients and iterate our design based on these results.

Next, our team will move to the validation phase. We plan to use our device to apply multiple gradients at varying concentrations such as nutrients, growth factors, and cytokines, to determine how they affect the cancer cells. We also plan on administering the anti-cancer drug, Olaparib, to the cell culture as a solute gradient in order to measure its efficiency over a broad range of conditions. By fluorescently tagging specific gene products, we will be able to monitor cellular responses to the various solute gradients in real-time. One gene product we are interested in is the hypoxia-regulated transcription factors HIF-1a and HIF-2a. The HIF-1 gene is activated in low oxygen environments, such as in a tumor, and leads to increased angiogenesis. This increases oxygen supply to the area and allows for the tumor to grow and spread (Laderoute et al., 2006). By monitoring HIF-1a and HIF-2a levels within an oxygen gradient, we hope to learn more about how tumors develop and metastasize.

STS Topic

Introduction

Sex/gender bias in biomedical research contributes to decreased health outcomes for women (Plevkova et al., 2021). Women and non-human female models have been historically excluded from biomedical research (Plevkova et al., 2021). Male-only cells, tissue cultures, and animal models are seen as the convention in studies, even those that focus on predominantly female conditions (Blanchard et al., 1995; Plevkova et al., 2021). In 1977, the FDA set guidelines explicitly excluding premenopausal women from clinical trials (K. A. Liu & Mager, 2016). This was reversed by the Revitalization Act of 1993, when the NIH mandated the inclusion of women in clinical research for the first time (K. A. Liu & Mager, 2016). Yet, medical research that uses in vivo animal models and in vitro models continues to exclude females (Heidari et al., 2016). A review of biomedical research conducted in 2012 found that 80% of animal model studies that reported sex used all males and 71% of cell studies that reported sex used all males (Yoon et al., 2014). This may be due to convenience and cost-effectiveness (Blanchard et al., 1995). However, this is problematic because women report higher rates of adverse effects from drugs when the research on the drug is conducted on a predominantly male population (Plevkova et al., 2021).

Use of male-only models has also been rationalized as a method to maintain heterogeneity, avoiding variance associated with female reproductive system hormones (Plevkova et al., 2021). Many sex differences in cellular responses can be traced to direct or indirect effects of hormones associated with reproductive organs (Medicine et al., 2001). However, hormones do not solely account for differing responses to drugs in males and females

(Medicine et al., 1994). Other contributing factors include physiological sex differences like body weight, length, surface area, total body water, and extracellular/intracellular water (Medicine et al., 2001). Pharmacokinetic and pharmocodynmaic sex differences like drug absorption, distrubution, metabolism, and elimination are also contributing factors (Medicine et al., 2001). Without valid justification, the results from majority or all-male studies are extrapolated to include females. This underrepresentation prevents researchers from understanding how a drug or treatment will affect female physiology, which can lead to worse outcomes for female populations (Heidari et al., 2016).

For example, the mortality rate due to cardiovascular disease is significantly higher in women, despite its incidence being lower (Gao et al., 2019). Since cardiac disease presents differently in men and women, it is commonly under-recognized in women and the treatment strategies used are not as aggressive (Maas & Appelman, 2010). Additionally, due to the underrepresentation of women in clinical trials, the treatments proven effective for cardiovascular disease may be less effective for women (Maas & Appelman, 2010). Other diseases and conditions in which sex differences are known include autoimmune diseases, cancer, depression, diabetes, obesity, and infectious diseases (*What Is Women's Health Research? | Office of Research on Women's Health*, n.d.). Therefore, sex should be an important variable to consider in biomedcial research (Medicine et al., 2001).

Moreover, medical conditions that exclusively or predominantly affect female populations are often under-researched, and thus many are not well understood (Lee, 2018; Medicine et al., 1994). For example, multiple sclerosis (MS), a disease that impacts the brain and spinal cord, predominantly affects women and its symptoms were thought to be hysteria up until the 20th century (Mirin, 2021). In current times, federal funding for MS is still less than the

amount of its disease burden (Mirin, 2021). This has created a gap in knowledge between men's health and women's health (Heidari et al., 2016).

Gender and sex in biomedical sciences is a topic that has been studied in a variety of ways by many STS scholars, women scientists, and feminist advocates. The framework selected for this study is undone science, a theoretical integration of science and technology studies and social movement studies popularized by David Hess (Frickel et al., 2010; Hess, 2016). Undone science describes areas of research that have been recognized by civil society as needing more research but are underfunded, incomplete, or ignored. This framework rests on the assumption that there is a systematic tendency for scientific research to reflect cultural assumptions and interests of elite groups, however, there is room for research that supports social movement perspectives due to division among elites, differences in social movement organizations, diverse funding sources, and autonomy in the scientific field (Frickel et al., 2010).

Government Funding

With increased pressure from feminist advocacy groups and more female representation in STEM fields, there has been change in policy over the past three decades that mandates inclusion and encourages research on women's health through federal funding. In 1990, the Society for Women's Health Research (SWHR) was founded by Dr. Florence Haseltine, who worked at the NIH, to advocate for the inclusion of women and minorities in clinical trials at both the NIH and the Food and Drug Administration (FDA). This goal was ultimately achieved with the reversal of the 1977 FDA guidelines that excluded premenopausal women from clinical studies and the introduction of the NIH's Revitalization Act of 1993, which mandated inclusion of women and minorities in clinical trials. Additionally, the NIH established the Office of

Research on Women's Health (ORWH) in 1990 and the FDA established the Office of Women's Health (OWH) in 1994. The primary goals of ORWH and OWH are increasing scientific inquiry in women's health areas, providing direction on policy that relates to women's health, and promoting inclusion of women in clinical studies.

The SWHR has continued to work towards closing gaps in women's health by promotoing research on biological sex differences in disease and influencing policy. In 2016, with support from the SWHR, the NIH implemented a policy called Sex as a Biological Variable (SABV). This policy recommends researchers carefully consider the role sex may play when designing studies and requires researchers to provide justification for single-sex studies (*NOT-OD-15-102: Consideration of Sex as a Biological Variable in NIH-Funded Research*, n.d.). In 2019, a study was done to evaluate how this policy has changed the proportion of female models used in biomedical research (Woitowich et al., 2020). The study highlighted the sex used in studies across multiple discplines in 2009 compared to 2019. The results showed significant progress towards inclusion: both sex studies increased from 28% to 49%, male-only studies decreased from 33% to 27%, and unspecified sex studies decreased from 16% to 6% (Woitowich et al., 2020). However, 27% of both sex studies did not provide a description of the sample size by sex, and the percentage of both sex studies that performed sex-based analyses decreased from 50% to 42% (Woitowich et al., 2020). With no description of the sample size by sex, it is plausible that female representation in both sex studies is lacking. The decrease in sex-based analyses is partciularly concerning as a major part of the motivation behind the Sex as a Biological Variable policy was to increase knowledge about sex differences.

Additionally, many single-sex studies still did not provide justification for doing so. The justification provided for male-only studies included prior knowledge of sex-differences, the

potential for increased experimental variability, experimental conditions which limited the use of both sexes, and difficulties in animal husbandry (Woitowich et al., 2020). The idea that there is a potential for increased experimental variability with inclusion of women has been proved incorrect and is a flawed research practice (*Inclusion of Females Does Not Increase Variability in Rodent Research Studies - ScienceDirect*, n.d.). Experimental conditions which limited the use of both sexes could denote high cost and increased time, which opposes the SABV recommendation to include both sexes despite these constraints. Further studies need to be done to evaluate how the SABV policy has affected inclusion in biomedical research.

Female researchers are more likely than their male counterparts to include female samples and to perform sex-based analyses (Nielsen et al., 2017; Sugimoto et al., 2019). Studies that report sex and perform sex-based analyses are associated with being published in lower impact journals (Murrar et al., 2021; Sugimoto et al., 2019). Women are less likely to be published in high-impact journals, and articles published in high-impact journals are cited less when the primary or senior author is a woman as opposed to a man (Chatterjee & Werner, 2021). In academia, the impact of scholarly work is extremely important for career advancement. Therefore, the association between women authors and low impact acts as a barrier to women becoming primary/senior authors, achieving tenure, acquiring funding for research, and being promoted to leadership positions (Chatterjee & Werner, 2021). This issue is expected to become exaggerated in the midst of the COVID-19 pandemic. Women may face barriers to academic productivity as schools and businesses shift to operating from home and women scientists carry a larger share of household and family-care responsibilities compared to their male counterparts (Woitowich et al., 2021). If women submit fewer abstracts to journals, the percentage of articles authored by women and the percentage of both sex studies are likely to decrease. This would

prevent progress towards equality in biomedical sciences. The combination of promoting the professional advancement of women in scientific research and the inclusion of female participants in studies is essential to increase knowledge about women's health.

Over the past two decades, women have received increased funding from the NIH. The percentage of research grants awarded to women has increased from 24% in 2000 to 35% in 2020 (*NIH Data Book - Data by Gender*, n.d.). The percentage of R01-equivalent grants awarded to women increased from 22% to 32% (*NIH Data Book - Data by Gender*, n.d.). The difference in average size of research grant funds between men and women has decreased from $60,631 in 1998 (constant dollars, 1998) to $40,671 in 2018 (constant dollars, 1998) (*NIH Data Book - Data by Gender*, n.d.). Although this gap has shrunk, the average funds men are awarded is still significantly higher than that of their female counterparts. The fraction of women among PIs also has increased over recent years, but remains unequal. The percentage of female PIs of NIH research grants increased from 34% in 2016 to 37% in 2020 (*NIH Data Book - Data by Gender*, n.d.). Strategies need to be developed and implemented to promote more equality among biomedical researchers.

Non-Profit Organizations

In addition to the NIH, many private organizations and wealthy individuals also fund research projects. These groups often fill in the gaps of unknown science by funding areas of research that have public awareness, but have not received a large amount of funding from the government. Organizations in particular are commonly formed to help a particular cause. They function not only to provide funds to researchers, but also to raise awareness about the condition to the public, as well as to advocate at the governmental level to increase funding in their area.

For example, endometriosis, a painful and chronic condition wherein the lining uterus grows outside the uterus, remains widely underfunded and under researched (As-Sanie et al., 2019). This may be due to a number of factors including: clinical gender bias, inequities in the treatment of pain based on gender, and social stigma surrounding endometriosis symptoms like infertility, menstruation irregularities, and bowel issues (*BMJ Open*, n.d.; Liaudat et al., n.d.). Due to the lack of knowledge and innovation around this problem space, the diagnosis and treatment options for endometriosis are limited (As-Sanie et al., 2019). Although in the past many women did not seek medical care for endometriosis due to social stigma or lack of education, it is now known to affect 10% of women, therefore awareness about the condition is growing among the public (Shafrir et al., 2018). In 2014, a non-profit organization called the Endometriosis Foundation of America (EndoFound) was founded to address the gap in research on endometriosis (*About Us*, 2020). This organization currently is offering grants up to $25,000 to scientists who want to focus on learning more about endometriosis (*Research Grants - Endometriosis Foundation of America | Research | Weill Cornell Medicine*, n.d.). In 2019, EndoFund helped form the Congressional Endometriosis Caucus to support increased federal funding towards endometriosis research . In March 2022, EndoFound finally was successful in helping HR 2471, the FY22 Consolidated Appropriations Act, pass in the Senate (*Endometriosis Research Funding Bill Passed in Congress*, 2022). The HR 2471 is a piece of legislation that increases the federal funding to the National Institute of Child Health and Human Development (NICHD) by $92 million (*Endometriosis Research Funding Bill Passed in Congress*, 2022). Therefore, the NICHD now has the ability to increase federal funding towards endometriosis. This demonstrates how public awareness and non-profit organizations can impact federal funding and help to decrease health disparities.

Training of Healthcare Professionals

Fueled by public concern that medical students were not receiving adequate training on women's health, in 1993 Congress called for the Office of Research on Women's Health at the National Institutes of Health (NIH), the Health Resources and Services Administration (HRSA), and the Public Health Service Office on Women's Health to evaluate the extent to which women's health is addressed in medical school curricula (Henrich et al., 2008). From 1994-1995, the Association of American Medical Colleges (AAMC) conducted a survey to gather this data. The results showed that there was a wide variation in women's health curricula across the 95 schools that were captured in the survey (Silverton, 1999). The survey found that almost all medical schools taught about sexual and reproductive function, medical interviewing and examination skills, and diagnostic tests specific to women (Silverton, 1999). However, few schools taught sex/gender-specific information on leading causes of death and disability in women or on chronic medical disorders that disproportionately affect women (Silverton, 1999). Furthermore, only 14% of schools had a women's health curriculum, 28% offered a clinical rotation in women's health distinct from an OB/GYN clerkship, and 10% had an office/program whose purpose was to incorporate women's health into the curriculum (Silverton, 1999). This study showed that there was a need for a more uniform incorporation of women's health into the curriculum.

In 1996, federal funding was allocated to develop a comprehensive medical curriculum for academic medical centers across the US (Henrich et al., 2008). In 2000, the Association of Professors of Gynecology and Obstetrics (APGO) and the Women's Healthcare Education Office (WHEO) released two guidance documents on incorporating women's health into the medical school cirriciculum: *Women's Health Care Competencies for Medical Students:Taking Steps to Include Sex and Gender Differences in the Curriculum* and *Women's health care competencies*

for medical students (APGO Women's Healthcare Education Office., 2000; APGO Women's Healthcare Education Office, 2000). The same year, the National Centers of Excellence in Women's Health Program (CoE) created an overarching model for academic health centers that incorporated recommendations on women's health research, teaching, clinical care, public education and outreach, and career advancement for women (Gwinner et al., 2000).

A decade later, in 2004, a study was conducted to reevaluate what women's health and gender-specific information was incorporated into the medical school curriculum (Henrich & Viscoli, 2006). Using data gathered by the AAMC, this study found that only half of the schools taught at least 11 of the 18 recommended women's health topics and less than 30% of schools included any gender-specific information in their curricula (Henrich & Viscoli, 2006). Only nine of the 95 schools surveyed met criteria for an interdisciplinary women's health course/clerkship (Henrich & Viscoli, 2006). The study found that having a designated women's health program was positively associated with inclusion of women's health and gender-specific information (Henrich & Viscoli, 2006). Despite the APGO defining competencies and providing guidance on how to incorporate these into the curriculum, the implementation across medical schools was deficient. This shows that along with tools, more oversight is needed in order to drive change.

In 2005, in collaboration with the organizations listed on the 1993 congressional directive, the American Women's Medical Association (AWMA), an organization dedicated to the advancement of women in medicine, surveyed medical students from all 125 allopathic schools on what women's health/gender-specific information students felt was incorporated into the curriculum (Henrich et al., 2008). This added a new perspective to the AAMC's data that surveyed school administrators in the previous studies mentioned. The results of the study showed that there was only brief to moderate coverage of most women's health/gender-specific

topics in the curriculum (Henrich et al., 2008). The category that received the least coverage was the influence of sex and gender differences in common medical conditions (Henrich et al., 2008). This is concerning since it has been proven that sex and gender have an influence on many medical conditions, yet most medical students are not made aware of this research. Other categories that received low ratings include gender identification, sexuality, interpersonal violence, and certain reproductive topics (Henrich & Viscoli, 2006). AJOG and other organizations with influence over the curriculum of medical schools should place an emphasis on incorporating these low-coverage topics. Additionally, medical school administrators should hire and retain faculty that are knowledgeable about these subject areas so that students can be adequately taught these topics.

The 2015 National Healthcare Quality and Disparities Report (QDR), a study performed under the National Quality Strategy (NQS) established by the Affordable Care Act, found that women were less likely than men to report good patient-provider communication and having medical needs addressed (Moore et al., 2018). The QDR also showed that 83% of health disparities between men and women remained constant between 2000 and 2013 (Moore et al., 2018). The areas that require the most attention in women's health were identified to be cardiovascular disease, behavioral health, and access to care (Moore et al., 2018). Although there has been focus on improving medical education in women's health areas since 1995, gaps still remain between women and men in terms of clinical care and health outcomes. It is extremely important to continue to study the ways in which care and outcomes differ between men and women so training of healthcare professionals can be enhanced accordingly. It will take time, advocacy, and continued changes in training for these health disparities to be reduced.

Case Study: Organ-on-chip

Traditionally, it is difficult to model female physiology like hormone levels within the context of an in vitro system (Nawroth et al., 2018). Recent innovations in organ-on-chip technologies and microfluidic devices have made it possible to model complex and specific microenvironments. The development of organ-on-chip technologies has the potential to be a more predictive model of normal physiology and drug testing as compared to animal models or 2D in vitro models (Low et al., 2021). One study showed that 80% of drugs tested with animal models fail clinical trials due to the lack of reproducibility in humans (Low et al., 2021). Organ-on-chip technologies also may be used for personalized medicine in the future because cells taken from a patient can be used to test drug effectiveness and proper dosage for that individual (Ashammakhi & Elzagheid, 2018). This has provided a great opportunity for the expansion of women's health to in vitro research because of the increased ability to control the physiology of the system, making it easier to induce female-specific conditions. The use of female cells in organ-on-chip technologies should be encouraged for all tissue/disease models, as it could help increase knowledge about sex differences in many conditions. The 2016 NIH policy that encourages researchers to consider sex a biological variable in their studies applies to this emerging field of research. There have been studies that have used this to close gaps in recent years, but this innovation is still under-used for women's health applications (Nawroth et al., 2018). The most widely funded organ-on-chip technologies focus on non-sex-specific organs and minimally consider the impacts of female-specific physiology on these systems (Wu et al., 2020).

Additionally, there is great potential for organ-on-chip technologies to close gaps in knowledge in conditions solely or predominantly affecting women. For example, modeling the

placenta and fetal membrane is currently very difficult because of the lack of human subjects and limited reproducibility in animal models (Richardson et al., 2020). Organ-on-chip technologies could be used to better mimic the placental and fetal membrane tissues. This would help researchers learn more about fetal-maternal communication and factors that influence preterm labor (Richardson et al., 2020). It would also provide a safe and more accurate model to test new therapeutics (Richardson et al., 2020).

In 2017, the NIH awarded $15 million to support the development of organ-on-chip technologies as part of the Tissue Chip for Disease Modeling and Efficacy Testing program (*NIH Awards $15 Million to Support Development of 3-D Human Tissue Models*, 2017). One of the collaborators of the project is the NIH Office of Research on Women's Health. However, only one out of thirteen of the projects that received funding focused on a condition relevant to women's health, and only two out of thirteen of these projects included a woman as one of the primary investigators (*NIH Awards $15 Million to Support Development of 3-D Human Tissue Models*, 2017). The most heavily funded and thus most advanced organ-on-chip technologies include lung, liver, intestine, heart, and kidney (Wu et al., 2020). Dr. Woodruff's lab remains the sole NIH-funded lab that focuses on the development of the female reproductive system on a chip (Meet Chip, 2015). One explanation for this is researchers who focus on conditions that solely or disproportionately affect women often struggle to gain funding, the knowledge may become stigmatized, and the researchers may lose credibility (Frickel et al., 2010). Overall, there still remains a significant amount of work to be done to close these knowledge gaps and improve healthcare for women.

Next Steps

- Technical Next Steps:
    - Produce a final 3D printed model of bioreactor (End of Semester)
        - Iterate CAD design based on results of benchtop testing of initial prototype
    - Quantitatively measure solute and gas concentrations within the microenvironment
        - Produce a mathematical model of dissolved solute flow through the bioreactor based on the placement of baffles within the structure and

determine how the delivery of each respective gradient affects the other. (End of Semester)

        - Develop a system which accurately measures molecular concentrations and flow rate within the bioreactor in real-time without disturbing the gradients and while maintaining a sealed, sterile environment. (Early Next Semester)
    - Test the bioreactor with cancer cells and evaluate various phenotypic changes (End of Year)
        - culture cancerous cells within the bioreactor that have been transfected so as to produce oxygen dependent fluorescent proteins to allow for real-time evaluation of the intracellular environment.
        - Subject the cells to anti-cancer therapeutics in order to determine the efficiency of these drugs in a more accurate tumor microenvironment.
- STS Next Steps:
    - Continue to gather literature in the following areas:
        - Undone science
        - Organ on chip technology applications in women's health
        - Government and private organization funding information
    - Summarize and synthesize this literature to provide convincing evidence
    - Address in more depth the connection between STS and technical side
    - Solidify and strengthen argument using evidence and appropriate style
    - Dig more into potential solutions to this problem based on literature
    - Identify weaknesses of the framework used

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