Manufacture and Validation of Advanced Cell Culture Inserts
(Technical Paper)

Organ Transplantation During COVID-19: How the Pandemic Altered the Transplant System's Operation
(STS Paper)

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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.

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Prospectus

Introduction

Operations of the United States (US) healthcare system have been negatively impacted by the Coronavirus SARS-CoV-2 (COVID-19) pandemic (Iyengar et al., 2020). In general, patients are more hesitant to receive non-emergency medical care; and healthcare systems struggle to provide adequate staffing and manage equipment supply chain shortages (Iyengar et al., 2020). One healthcare sub-system that could greatly suffer from the pandemic, due to its already fragile state, is the organ transplant system. Prior to the pandemic, organ demand was already much greater than the supply, ethical concerns in terms of donors were present, and the system lacked efficiency (Beyar, 2011; Chopra & Sureshkumar, 2015; Das & Lerner, 2007). The system's shortcomings motivate the research of alternatives to solid organ transplants that could increase opportunities for patients to receive organ failure treatment, such as developing tissue engineered organs for transplantation, however these potential alternatives are still in development.

In order for the tissue engineering of organs for use in transplant situations to become feasible, biomedical researchers must be able to best mimic the structure and function of these organs. Developing technology that will promote biomimetic tissue formation in the laboratory will allow for better models to be used for analysis and tissue engineering applications. Developing a biodegradable membrane that is optimized towards a certain cell type differentiation for cell culture inserts is an important step towards generating improved tissue models. The technical project will focus on developing a degradable membrane optimized for skeletal muscle tissue modeling.

After a system altering occurrence, such as the COVID-19 pandemic, it is important to understand how the organ transplant system in the US has been affected and to identify what new stress is added to different components of that system. System alterations and their impacts are identified by analyzing the ways the sociotechnical systems within organ transplantation impact how the COVID-19 pandemic has influenced the organ transplant system's operation. Recognizing the added stress on these sociotechnical systems will help the transplant system assess the current safety concerns and priorities, for both the patients and their medical teams, and proceed their operations in fashion that they deem safe. The STS project will then analyze the effectiveness of the sociotechnical systems that impact how the COVID-19 pandemic influences organ transplantation.

Technical Project – Manufacture and Validation of Advanced Cell Culture Inserts

Cell culture refers to growing cells in a laboratory under conditions similar to that of the body (Segeritz & Vallier, 2017). When culturing cells for research, it is important to place the cells in an environment that imitates the structural framework that cells build around themselves, called extracellular matrix (ECM). The ECM's structure influences how the cells grow, move, and behave, therefore replicating the ECM allows one to accurately model the tissue's structure and function (Yue, 2014). Most commonly, cell culture is performed by placing the cells on cell culture plates or flasks, or by suspending the cells in a solution. However, these techniques do not provide the cells with the three-dimensional structure and support that their ECM provides. Lacking this support can hinder the cell's ability to interact with nearby cells and properly form tissue and organs. An innovative product in cell culture which addresses the need for cells to grow in an ECM-like environment outside the body is the cell culture insert plate (CCIP). CCIPs consist of a device which can be inserted into a well on a cell culture plate, and holds a membrane inside the well which mimics cellular ECM. CCIPs allow for cells to grow on the top and bottom of the membrane, allowing for the formation of multiple two-dimensional layers of cells that can simulate a basic tissue structure (*Millicell® Cell Culture Inserts & Plates*, n.d.). While there are commercially available CCIPs, these options only have non-degradable membranes. Thus, there is a need for CCIPs which contain degradable membranes, as this will allow the cells in culture to produce their own ECM to replace the degrading membrane, further improving the ability to mimic how cells grow in the body (Mhatre et al., 2021).

Luna Innovations (Luna) in Charlottesville, VA developed a novel CCIP which demonstrated the feasibility of CCIPs with degradable membranes. However, these membranes must now be optimized to promote cell proliferation and differentiation down desirable cell lineage. For the proposed technical project, the research team plans to design an optimized membrane, for insertion into Luna's CCIP, to promote the growth of muscle cells. The membrane will be fabricated through electrospinning a combination of chemicals to generate a porous mesh of fibers. The chemical makeup, fiber density, fiber thickness, pore size, overall membrane thickness, and degradation rate will be altered to optimize the membrane to mimic the environmental properties which muscle cells desire. The membrane prototypes will then be tested to validate their functionality by culturing an immortal mouse muscle cell line, C2C12 cells, on the membranes. These cultured membranes will be analyzed to determine the cell viability and whether muscle cell behavior is present. Further optimization to the membranes will be performed based on testing results. Further downstream in the project, the optimized membranes will also be validated through culturing human muscle cells on them. The optimized membrane research will then be used as justification for bringing the optimized membranes to market for use in musculoskeletal research as an improved skeletal muscle tissue model for tissue culture applications.

STS Project – Organ Transplantation During COVID-19: How the Pandemic Altered the Transplant System's Operation

Since the beginning of the COVID-19 pandemic, the organ transplant system has been working hard to keep the system's actors safe from infection, while also continuing to provide care for patients in need of transplants (Michaels et al., 2020). This balancing act of performing transplants with a novel respiratory illness present nearly everywhere has led to additional stress being placed on the transplant system. There are less donor organs available, fewer transplantations occur, and scheduled transplantations must be delayed (Michaels et al., 2020; *Recommendations and Guidance for Organ Donor Testing*, 2021). COVID-19, along with these changes in the transplant system, impact both organ donors and recipients, along with their respective caregivers, families, and medical teams. Also impacted by the system are the organs themselves, the spread of COVID-19 infections, the risk of decisions in regard to transplantations, and the mentality of the mentioned stakeholders. These stakeholders currently must weigh the risks between transplantation at the time of a pandemic and delaying, or not performing, transplantation by considering these artifacts (Michaels et al., 2020). Therefore, it is important to further research these adjustments currently happening in the organ transplant field in order to answer the question: "how effective are the sociotechnical systems that impact how the COVID-19 pandemic influences organ transplantation?" These sociotechnical systems provide the interactions between the humans, technologies, and the environment of the transplant system (Baxter & Sommerville, 2011). Identification of these systems' roles can help stakeholders navigate their decisions in regard to transplantation, especially at a time of uncertainty about associated risks and minimal published information related to health and safety.

The research question will be answered utilizing the frameworks of Risk Analysis and Social Construction of Technology (SCOT). Risk analysis is the determination of acceptable levels of risk in a system, as well as the compensation when harm is caused by the risk (Mythen, 2004). A system, like the transplant system, utilizes Risk Analysis to protect its stakeholders from dangers within the system. These risks are identified through the relations of definition, which are "basic principles underlying industrial production, law, science, opportunities for the public and for policy" (Mythen, 2004). By finding a balance between all the components of the system which the relations of definition include, one can find stability and decrease the risk potential in the system. Utilizing this framework will be useful in understanding how the risk of COVID-19 infection altered the operations of the organ transplant system. One limitation of Risk Analysis is the difficulty to analyze emerging risks when the background knowledge is limited (Aven, 2016). This limitation must be considered when answering the research question as the COVID-19 pandemic produced many emerging risks, though referencing former epidemics may help to overcome this limitation.

SCOT is the analysis of how society shapes technology. Analysis using the SCOT framework has five guiding components: interpretive flexibility, relevant social groups, closure and stabilization, wider context, and the technological frame (Klein & Kleinmann, 2002). These components allow for a structured system with multiple potential designs which satisfy all stakeholders. Looking at the organ transplant system through these components will explain how organ transplants are affected by the COVID-19 pandemic. The framework does have some shortcomings in terms of the analysis of power dynamics and the structure of systems, though the latter is addressed, in part, through the technological frame component added to SCOT analysis (Klein & Kleinmann, 2002). These shortcomings will be acknowledged while analyzing the research question, and the utilization of the Risk Analysis framework in conjunction with SCOT will help prevent these shortcomings from being exploited.

The research question: "how effective are the sociotechnical systems that impact how the COVID-19 pandemic influences organ transplantation?" will be analyzed and answered using the discourse analysis method. This methodology requires utilizing a wealth of different types of resources to determine the connections and contradictions between sources on the topic in order to strengthen the analysis (Powers, 2001). Information will be gathered from sources such as literature reviews, informational documents for stakeholders, informational videos, and American Society of Transplantation (AST) town hall recordings. Keywords that will be used to collect this information will include "organ transplant during COVID-19," "changes in transplants," "organ donors with COVID-19," and "effects of COVID-19 on organ transplants." I plan to use broad search engines such as Google Scholar, as well as more specific databases such as PubMed, ClinicalKey, and SAGE Journals while performing my research. I also plan to use the AST's resource page and the American Journal of Transplantation's "COVID-19 & Transplantation" resource page to find videos, town hall recordings, and more COVID-19 and transplant related literature. Through this research, I hope to find information about what components of the transplant system have been altered due to COVID-19, stakeholders' mentalities on the pandemic influencing the transplant system, and how risks in transplantation are being assessed as the pandemic progresses. The analysis of the diverse resources available on organ transplantation during the COVID-19 pandemic will aim to provide the answer as to how the sociotechnical systems within organ transplantation are impacting how the pandemic affects the functioning of the transplant system in return.

Conclusion

The technical problem and societal research question both aim to promote improvement and innovation in the organ transplant system. The design of membranes which better promote the development of biomimetic tissue modeling allows researchers to overcome a massive hurdle in the tissue engineering field: inaccurate research models. Better modeling techniques, which mimic the three-dimensional structures of tissues can improve testing accuracy and expand the research capabilities of those in the tissue engineering field, contributing to the development of tissue engineered organs for transplantation in the future. In contrast, the identification of the effectiveness of the sociotechnical systems which impact how COVID-19 has altered transplant operations has the opportunity to improve the organ transplant system currently. Identifying how effective transplant centers' efforts in balancing the priorities of safety from COVID-19 infection versus safety from one's failing organ will highlight the sociotechnical systems which are most important to the success of transplant operation in the current environment. This allows the system to implement operational adjustments that best address the stakeholders' priorities during the current health crisis.

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