Undergraduate Thesis Prospectus

Assessing Microvascular Cell Behavior in an in vitro PEG-DA Hydrogel Cell Culture Assay of Idiopathic Pulmonary Fibrosis (IPF)

(Technical Report)

Addressing Inequality in American Healthcare: How Agencies Have Advocated for Reducing Healthcare Disparities

(STS Research Paper)

A Thesis Prospectus
presented to the faculty of
School of Engineering and Applied Science
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by

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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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STS advisor: Peter Norton, Department of Engineering and Society

General Research Problem

How can incidence of chronic lung diseases be reduced?

Chronic lung diseases like chronic obstructive pulmonary disease (COPD), asthma, and idiopathic pulmonary fibrosis (IPF) impact around 550 million people worldwide (GBD, 2020). These conditions are often marked by inflammation that makes breathing and lung oxygen exchange difficult. This is uncomfortable for patients and results in low blood oxygen levels that prevent normal bodily functioning. The causes and mechanisms of these conditions are not well understood, so many lack a cure. Treatments focus on alleviating discomfort from symptoms, but ultimately 4 million people will die from a chronic lung disease annually (GBD, 2020). Incidence of chronic lung disease cases is increasing and projected to continue increasing without intervention (Chen et al., 1999). If nothing is done, annual death toll is expected to rise. How can the incidence, and subsequent death toll, of chronic lung diseases be reduced? A lack of research on the cause and progression of chronic lung diseases is perhaps the greatest catalyst for this rise in cases.

Understanding Idiopathic Pulmonary Fibrosis (IPF)

How can we better understand the progression of IPF?

Cell types like endothelial cells, fibroblasts, and pericytes reside around the lung capillaries and communicate to maintain homeostasis. In IPF, this homeostasis is somehow disrupted, and an overactive wound healing response causes excess creation of extracellular matrix (ECM) components, like proteins and sugars. The ECM is the non-cellular part of tissue responsible for scaffolding, but excess components can cause scarring. In IPF, this scarring thickens lung tissue, making breathing and oxygen uptake difficult. This condition affects around

100,000 Americans, with around 40,000 new cases each year (ATS, 2000), and patients generally survive 2-5 years after diagnosis. The causes of IPF are not widely understood, though research speculates that genetic and environmental factors both contribute (Maher et al., 2007). Partially due to this lack of causal understanding there is no cure for IPF, and treatments focus on mitigating symptoms to increase patient comfort. Understanding what is happening at a cellular level during the progression of IPF can guide future treatment development by creating a targeted approach that inhibits these contributing factors.

Our goal is to understand how microenvironmental changes from IPF affects behavior of lung cells. Current IPF research focuses on understanding contributing factors because these must be discovered before cure development. Modeling IPF conditions outside the body using biomaterials or tissue scaffolds is a common way to research what happens at a cellular level (Degryse et al., 2015). Biomaterials like hydrogels have been studied because they can be easily tuned to mimic the physical properties of native lung tissue, like stiffness. This research has failed to recapitulate IPF or positively identify causes, but one theory is that microenvironmental cues cause endothelial cells and pericytes to produce the excess ECM components seen in IPF. Our project could fill the knowledge gap and guide future research by testing this theory and potentially identifying a source of ECM component overproduction.

Dr. Shayn Peirce-Cottler in the biomedical engineering department will advise this capstone project. I will collaborate with fourth year undergraduate student Tara Tavakol and graduate student Julie Leonard-Duke. This project completion will rely on coordination with Dr. Lakeshia Taite in the chemical engineering department for hydrogel supply.

This project will use an established polyethylene glycol (PEG) hydrogel system of varying stiffness to model the increase in lung stiffness from IPF; 2 kPa for normal tissue, 10 kPa

for IPF progression, and 20 kPa for IPF. We will also vary the presence of growth factors found in IPF progression, like vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). Altering these conditions in a controlled environment allows us to observe the effects on cell behavior and how these may contribute to IPF progression. We will encapsulate human umbilical vein endothelial cells (HUVEC) and HUVEC-pericyte co-cultures in our hydrogel system. These cell types were chosen due to their presence in the lungs and ability to create ECM components. Samples will be cultured for one or two weeks then fixed and immunostained with fluorescent secondary antibodies to tag specific cellular components. Image processing program ImageJ will quantify morphological changes from Leica Thunder fluorescent microscopy images of samples. We will conduct a minimum of three trials per condition, with 4 samples in each trial. Data across conditions will be compared and changes in cell behavior and interactions will be noted.

We aim to gain quantitative data on how physical and chemical environmental factors impact morphology and behavior of HUVECs and pericytes. If notable changes are quantified, these cells may play a key role in the progression of IPF, which is something the field has not yet identified. This information could guide treatment development that prevents the cellular changes that cause the scar tissue formation seen in IPF.

The Gaps in Access to American Health Care

How have social groups advocated for reducing health disparities?

Health disparities are measured in differences in prevalence, incidence, and mortality rates of health conditions amongst social groups. Racial and ethnic disparities are the most salient, with racial minority groups seeing greater rates of chronic disease and premature death

than whites (NAS, 2017). It was not until the late 1990s that the term “health disparities” was coined and debates emerged over achieving “health equity” (Braveman, 2006). From this, social groups focused on bridging these gaps in healthcare access and quality emerged. How have these groups advocated for better health outcomes for racial and ethnic minority groups?

Researchers have explored the causes of health disparities and methods and motivations for mitigating the consequences. For example, Ozaki et al. (2022) found that intervention by pharmacists can reduce health disparities, while Arrieta et al. (2008) argue that a multidisciplinary approach is necessary to reduce inequalities, with support from economics, policy making, education, and social work. Major et al. (2013) propose that interactions between and among diverse social groups may contribute to group health differences, emphasizing the need for effective group education to minimize disparities. Much of this research introduces theories for mitigation, not solutions. All studies lack wide-scale quantitative data on health disparity mitigation by the methods introduced, but they all agree that reducing health disparities will require a large systemic change involving many parties. The greatest perpetrator of health disparities is a lack of awareness and education on the issue.

Important participants include research groups seeking more diverse and representative healthcare data. For example, the National Institutes of Health (NIH) launched the All of Us Research Program to gather health-related data from 1 million diverse American volunteers to “help build one of the most diverse health databases in history” (AOURP, 2022). The Center for Health Equity Research and Promotion (CHERP) helps to fund university healthcare research focused on more diverse participants, with the hope to “reduce disparities in health and health care in vulnerable populations” (CHERP, 2022). The Robert Wood Johnson Foundation launched the National Commission to Transform Public Health Data Systems to “reimagine how

health data are collected, shared, and used and identify what public and private investments are needed to advance health equity" (NCHE, 2021).

Some participant groups promote access to resources. The Asian and Pacific Islander American Health Forum (APIAHF) provides grants, training, and technical assistance to Asian Americans who want to work in healthcare policy. APIAHF is heavily involved in the politics of health disparities and informs community members of healthcare related legislation, emphasizing that "health equity must be the overarching goal against which any policy is benchmarked" (APIAHF, 2022). Allies for Reaching Community Health Equity (ARCHE) runs Health Equity Design Labs that bring together individuals and healthcare workers to address disparities and methods for mitigation (ARCHE, 2022).

Other participant groups emphasize the need for fostering communication among diverse groups. The Health Equity Leadership and Exchange Network (HELEN) is a collaboration between hospitals, medical schools, and other advocacies. Their goal is to create a "national network designed to bolster leadership and the exchange of ideas and information among communities of color" (HELEN, 2022). Community-Campus Partnerships for Health (CCPH) aims to connect communities and academic institutions to "emphasize partnership approaches to health" (CCPH, 2022).

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