Microdevice Enabling Long-term *in vitro* Study of Biofabricated Constructs
(Technical Paper)

The Role of Psychological Wellness in Type 1 Diabetes Management
(STS Paper)

A Thesis Prospectus
In STS 4500
Presented to
The Faculty of the
School of Engineering and Applied Science
University of Virginia
In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science in Biomedical Engineering

By
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October 27, 2022

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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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Introduction

People with diabetes are two to three times more likely to experience depression than people without diabetes (CDC, 2021b). The symptoms of depression can make it extremely difficult to execute the steps necessary to maintain healthy blood glucose levels and avoid diabetes complications such as heart disease and nerve damage. The hemoglobin A1C test is one of the key indicators and measures of diabetes diagnosis and management. It measures an individual's average blood sugar levels over the past three months, and the normal range is below 5.7% while the diabetic range is 6.5% or above. An A1C level of 7.0% or higher indicates increased risk of diabetes complications (CDC, 2018). 50% of US adults diagnosed with diabetes have an A1C value of 7.0% or higher, indicating unsuccessful disease management (*National Diabetes Statistics Report 2020. Estimates of Diabetes and Its Burden in the United States.*, 2020). The connection between psychological health and diabetes management is one that should be further studied and taken into account when designing treatment plans for diabetic patients. The standard of diabetes care must shift to improve disease management through providing medical, psychological, and social care. The proposed research paper will analyze the effect of psychological health on diabetes management and suggest possible amendments to current treatment standards.

The technical project outlined in this prospectus aims to design and fabricate a microfluidic device to hold and stabilize granular hydrogel for long-term *in vitro* research of complex cellular systems. The focus of this project is to use various biomaterials to further the field of tissue and disease modeling. The creation of this novel device will enable researchers to harness the dynamic properties of granular hydrogels in three-dimensional systems and help to model complex physiological systems such as organoids. This device must be able to hold small

amounts of granular hydrogels in place to allow for stable cell culture for at least seven days, and will be constructed using established PDMS fabrication techniques (Friend & Yeo, 2010).

Technical Project

Hydrogels are three-dimensional networks of hydrophilic polymers which have various applications within the field of biomedical engineering, including biosensors, drug delivery vectors, and matrices for cells in tissue engineering (Chai et al., 2017). Advancements in the field of biomaterials have allowed researchers to move beyond decellularized extracellular matrix scaffolds, which are poorly chemically defined and allow for limited tunability and reproducibility, and towards the fabrication of engineered matrices where the biochemical and biophysical properties can be specifically chosen and optimized (Kratochvil et al., 2019). The hydrogels traditionally used for these applications demonstrate poor cell motility and generation of tissue structure, and it can be difficult to control the material properties. Granular hydrogels, a subset of hydrogels that are composed of hydrogel microparticles (HMPs), are capable of demonstrating injectable, self-assembling, shear-thinning, and self-healing properties (Riley et al., 2019). These hydrogels are formed by the packing of HMPs, introducing varying porosities depending on the shape and size of particles and their density per volume. Introducing porosity to these material applications promotes a more rapid exchange of reactants, nutrients, and waste. Granular hydrogels have shown potential for improved cellular infiltration and subsequent tissue remodeling *in vitro* (Riley et al., 2019).

Granular hydrogels are incredibly dynamic in nature because the particles are not crosslinked to one another. This makes them difficult to study long-term in traditional cell culture, as the exchange of media during cell culture causes surface erosion of the particles. Surface erosion alters the volume of the hydrogel and limits the ability to control material

properties. In turn, this limits the ability to integrate cells and create tissue and disease models. The goal of this capstone project is to design, prototype, build, and iterate upon a microfluidics device made of polydimethylsiloxane (PDMS) that will allow small amounts, on the order of microliters, of a modified hyaluronic acid granular hydrogel to be maintained in stable culture over time. PDMS is commonly used biomaterial due to key properties including its ability to integrate surface modifications, molds that can replicate nanoscale features, high biocompatibility, cost efficiency, non-toxic, well-established protocol, and clear appearance (Friend & Yeo, 2010; Miranda et al., 2021).

There are two specific aims to be accomplished within this project: the creation of a single-well microdevice from PDMS to hold and stabilize granular hydrogel for long-term *in vitro* research, and validation that culture conditions in the device maintain cell viability. To accomplish these aims, first computer-aided design software will be used to design a single-well model that can be 3D printed as the negative to form the microdevice. Then PDMS fabrication techniques (Friend & Yeo, 2010) will be used to build the device and a membrane lid to hold the materials in place and allow for the transport of cell culture media will be created. To test the efficacy of the device, hydrogel swelling will be measured during the introduction media, and the device and its lid will be redesigned accordingly to allow for sufficient compliance to swelling. To validate that the device maintains cell viability human umbilical vein endothelial cells (HUVECs) will be cultured, mixed with the HMPs, and placed into the device. Cell viability after a seven day period will be determined using LIVE/DEAD staining technique. If successful, this project will create a foundation and protocol for the construction and implementation of a new kind of microdevice, and will serve as an essential step forward in the field of biomaterials, specifically in the use of granular hydrogels in tissue and disease modeling.

STS Topic

Type 1 Diabetes (T1D) is a chronic autoimmune disorder in which the pancreas is unable to produce insulin, resulting in the body being unable to metabolize glucose (*Type 1 Diabetes - Symptoms and Causes - Mayo Clinic*, n.d.) Over time, many serious complications may arise from the fluctuation of blood glucose levels or from consistent high blood sugar, known as hyperglycemia. Mismanaged diabetes can result in heart and blood vessel disease, nerve damage, kidney damage, eye damage, and diabetics are also more susceptible to serious complications of other illnesses, such as pneumonia (CDC, 2021a). Managing diabetes requires constant surveillance of blood glucose levels, carbohydrate intake, activity level, and countless other factors that can influence a patient's condition. Diabetes is a very physically and emotionally demanding condition, and the psychological burden is magnified by the social implications of having this disease. The term "diabetes distress" has been coined to address the specific phenomenon of the emotional and psychological difficulties of living as a T1D patient. While the burden of disease management can negatively impact one's emotional state, it has also been shown that diabetes distress is associated with poor self-management (Fenwick et al., 2018). The physical and psychological tolls of T1D cannot be separated from one another, as each informs the other. For this reason, it is important to reconfigure standard diabetes treatment plans to include psychological care and social resources.

The conceptual framework of the wicked problem will be used to analyze and understand the factors that contribute to mental health concerns in T1D patients as well as to provide a base on which to propose a possible solution in the form of a change in standard disease treatment. The concept of a wicked problem allows one to draw attention to and specifically address the complications and challenges of complex social and technical problems. Among the

characteristics of wicked problems are how the constraints of the problem change over time and how stakeholders have differing ways of understanding the problem at hand (Termeer et al., 2019). The problem itself is difficult to define, as is demonstrated in the difficulty of defining the specific and concrete problem with current diabetes treatment that creates such high rates of depression and poor disease management. In order to begin to untangle the relationship between diabetes and mental health, the various actors and stakeholders and their perspectives must be considered. These groups include the patients themselves and all of the medical professionals they receive care from, which may include primary care physicians, endocrinologists, and psychiatrists or other mental health workers, as well as close family and friends of the patient, their community, and broader society as a whole. What makes the issue of poor diabetes management due to psychological distress such a difficult issue to take on is the fact that living with diabetes comes with a myriad of psychosocial implications that may not be fully understood by these groups, even by the patients themselves (Nefs et al., 2012).

Common critiques of the concept of wicked problems center on the inherent difficulty of both defining the problem and proposing a solution (Turnbull & Hoppe, 2018). A particular criticism of the framework poses the question of whether defining a problem as wicked actually has any analytical use or provides new insights on how to address the issue (Termeer et al., 2019). Despite these criticisms, this framework provides a way to analyze complex problems without attempting to simplify them and without ignoring certain stakeholders or factors. In response to the criticism of the difficulty of creating solutions to wicked problems, Nancy Roberts, a scholar in Wicked Problems and Organization Studies, had identified three specific strategies to work with wicked problems: authoritative, competitive, and collaborative (Roberts, 2000). While each of these proposed approaches has their own pros and cons, they demonstrate

that these problems can be worked through with the goal of finding solutions, and a wicked problem diagnosis is not the end of analysis or understanding.

Research Question

How does the psychological condition of Type 1 Diabetes patients impact their ability to manage the disease, and how can standard treatment plans change to take this connection into account and improve disease management?

Methods

To answer this research question, the methodologies of wicked problem framing and literature review will be used. Wicked problem framing refers to a method of gathering information and evidence to reveal connections between the issue and its potential causes that might not be obvious at first glance. In the context of this research paper, this framework will be used to understand the connections between patients with mental health concerns and their diabetes management and how the current standard of diabetes care addresses mental health and social concerns. Wicked problem framing allows this material to be synthesized with the understanding that the relationship between these aspects and stakeholders are very complex, and thus should be approached with the goal to re-interpret the information that is already available.

The information to support this analysis will be collected via the method of literature review. This method will be used to conduct a study of existing secondary sources of relevant topics, in order to address and analyze the current discourse on this topic. The topics that will be researched include background on T1D pathology, statistics related to both diabetes management and mental health prevalence among T1D patients in the US, current standards of diabetic care, psychological intervention programs for patients with poor disease management, and proposed changes to the standard of care for diabetes patients.

Conclusion

This prospectus details an investigation of the contribution of psychosocial factors on Type 1 Diabetes management as well as the design, fabrication, and implementation of a novel microfluidic device to be used for long-term cell culture. The device created for the technical deliverable will serve to further the field of biomaterials research and tissue and disease modeling by creating a novel way to use granular hydrogels for in vitro research. This will allow the desirable properties of the hydrogels to be fully utilized while maintaining form and resisting erosion and degradation.

Investigating the connection between psychological well-being and T1D management will allow for a more in-depth understanding of what it means to live as a T1D patient, and will shed light on what resources must be available to patients in order to ensure the highest quality of treatment with the greatest chance of successful outcomes.

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