Encapsulation of Dissociated Beta Cells within MAP Scaffold for Type 1 Diabetes Therapy

(Technical Paper)

Building Transparency in the Scientific Community

(STS Paper)

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Alessia Randazzo

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Capstone Technical Project Team Members
Alessia Randazzo
Jonathan Daniel

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

Signature _____ Date 12/5/21
Alessia Randazzo

Approved _____ Date 12/9/21
Don Griffin, PhD , Department of Biomedical Engineering

Approved _____ Date 12/9/21
STS Advisor, Richard D. Jacques

Alessia Randazzo

STS Thesis Project Prospectus

Introduction

How can treatment for Type 1 Diabetes be optimized in terms of function and affordability?

Type 1 diabetes (T1D) is caused by the autoimmune destruction of the insulin-producing islet cells in the pancreas. T1D patients can administer exogenous insulin to regulate blood glucose fluctuations, however, insulin is expensive and incapable of fully restoring glucose regulation functionalities. In 2015, the global cost of medical care for diabetes was the equivalent of $1.3 trillion U.S. dollars (*Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030 | Diabetes Care*, n.d.). By 2030, the global cost is expected to surpass $2.1 trillion. In the United States, 25% of health care dollars are spent on treatment and care for diabetes, and as of 2017, this amounted to approximately $237 billion (American Diabetes Association, 2018; Riddle & Herman, 2018). Indirect costs of diabetic care include lost revenue from work absences, reduced work productivity, and inability to work. Insulin detemir (IDet) is a commonly used treatment for type 1 and type 2 diabetes that lasts for only *24 hours* (*Insulin Detemir*, n.d.; Suh & Aagren, 2011). The retail price for five syringes is $146.99. This is not a cost that can be easily afforded by all people. Therefore, there is a clinical need to develop a long-term treatment for T1D that can restore endogenous insulin secretion and be afforded by all people, regardless of socioeconomic class.

In recent research, transplantation of donor islet cells has been used to regulate endogenous insulin secretion in response to blood glucose levels. However, the transplantation site is highly inflammatory, which may result in significant islet mortality. Hydrogel encapsulation is a promising method to protect islets from the immune system, though the lack of porosity and

tunability inhibit the ingrowth of supporting vasculature (Mao et al., 2017). The technical project outlined in this prospectus aims to create an alternative solution to T1D that allows for the recovered functionality of insulin-producing beta cells. The STS research topic will focus on why there is a lack of trust in novel scientific developments, such as the SARS-CoV vaccine, and what we can do, as a scientific community, to resolve any concerns.

Technical Project Description

How can biomaterials and microengineering be combined to create an effective therapeutic for Type 1 Diabetes?

Microporous annealed particle (MAP) gel is composed of highly concentrated hydrogel microspheres that are assembled *in situ* and covalently bonded to form a macroscale material with open pore geometry (pores >10 μm) (Griffin et al., 2015). Dissociated islet cells can be encapsulated within individual MAP hydrogel microspheres using microfluidics, and the resulting porous scaffold allows for ingrowth of blood vessels to promote long-term cell viability (Koh et al., 2019). Doing so will allow for the sustainable and autonomous production of insulin after treatment, without the need for daily expensive injections of insulin that fail to recover the body's inability to produce insulin.

The objective of the technical section is to create a cell therapy therapeutic that will regenerate insulin-producing cells in diabetic patients and restore the ability to autonomously produce insulin. The team will begin this by first designing a microfluidic strategy to encapsulate and store islet cells within MAP gel to use for T1D cell therapy applications (Fig. 1). To accomplish this, the team will first optimize the MAP gel polymer solution and microfluidic flow rates to create a hydrogel capable of cell encapsulation and cell viability maintenance. To show

feasibility, we have already encapsulated fluorescent microspheres, similarly sized to islet cells, at 33% efficiency (Fig. 2). However, optimizations will be needed to improve this, which will be achieved by adjusting flow rate speeds of MAP gel in the microfluidic device and increasing microsphere concentration. We will then determine an efficient strategy for freezing and thawing the islet cells to ensure they remain viable in order to be stored and used in clinical settings. This will be done by experimenting with different freezing media and growth factors to retain viability, tested with live/dead stains. These islet cells need to be readily available at hospitals to offer treatment for people whenever needed, and so it is crucial that the treatment is able to be safely stored without losing efficacy. We will assess functionality through ELISA assays to prove the overall success and clinical significance of the cell encapsulation and protocol design. Once these components have been fully optimized, studies will move *in vivo* to quantify the success of the encapsulated islet cells in inducing insulin-production in live diabetic rats.

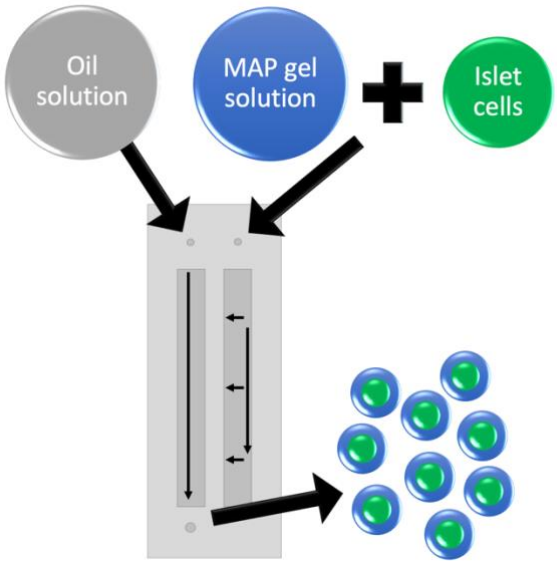

Figure 1: Schematic of microfluidic design used to create MAP gel particles for technical project. A gel solution including islet cells will enter one channel of the device and pinch off to form individual gel particles due to the pinching off from the oil solution entering in the other channel.

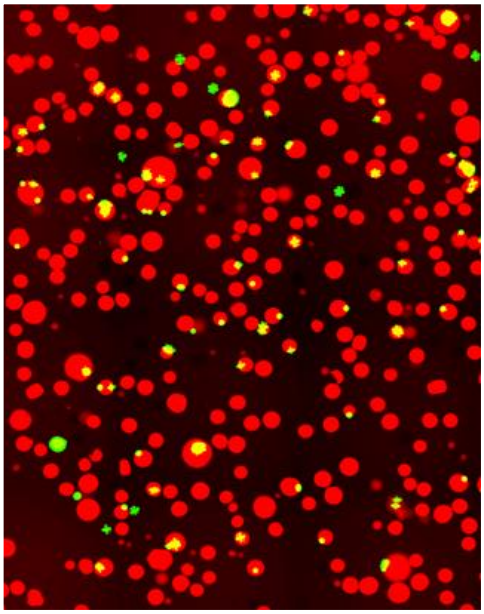

Figure 2: 33% encapsulation of fluorescent microspheres (green) in MAP gel (red) by a microfluidic device.

The technical project will cover two semesters as

part of the BME 4063 and BME 4064 courses. The team will work together every weekday to continue experimentation and, on a weekly basis, privately discuss the progress of the project and how any protocols may be improved. Biweekly, we will meet with our project advisor, Dr. Don Griffin of the Biomedical Engineering Department to present current progress, bring up any challenges we have encountered, and gather ideas for further direction and various improvements. The team also consists of a graduate student in Dr. Griffin's lab, Colleen Roosa, who is available to us on a regular basis to provide assistance and guidance with everyday tasks and issues.

I joined Dr. Griffin and his team in solving this medical issue at the start of August 2021. Though I had no experience working with microfluidics, I have spent years working with biomaterials and designing experiments to recover muscle fiber functionality in volumetric muscle loss injuries, where the body loses muscle to a point where it is unable to autonomously regenerate it on its own. I'm fascinated by biomedical research that involves rehabilitation after the loss of a function, whether it is related to orthopedic or pancreatic function. During my time in Dr. Griffin's lab, I have gained skills in using microfluidics, developing and purifying the gel, and using rheology to test mechanical properties, like MAP gel viscoelasticity. I learned that, as a novel biomaterial, MAP gel has numerous advantages over other standard biomaterials, and has the potential to be used in a number of other biomedical applications.

STS Project Details

What concerns do people retain about the SARS-CoV vaccines and how can we resolve these for the improved health and safety of the public?

In spite of the success of numerous novel engineered therapeutics to provide solutions for a variety of biomedical problems, there will always be a number of ethical and safety concerns

surrounding the use of cell therapies, biomaterials, tissue engineering, or anything deemed "unnatural" to a lay person. There is a plethora of myths about developments in the science and engineering industry. Particularly targeting the SARS-CoV pandemic, when the first vaccines were being released, many were concerned by the short time period it took for the vaccines to be approved, in spite of every vaccine having to check off all of the boxes before being distributed to the public. People thought that the mRNA vaccines would alter one's DNA and result in cancer, or they thought it contained toxic ingredients and would lead to worsened health (*10 Common Vaccine Myths Busted*, n.d.). Others firmly believe that any vaccine will put you at risk for autism. The goal of my STS research is to better understand these concerns and how they are founded in order to induce higher vaccination rates and improve the safety of the general public.

As we come to a plateau in SARS-CoV vaccination rates, but continue to have new cases and deaths every day, it is imperative that we figure out why people do not want the vaccine and how we can better educate them on the urgency of being vaccinated for the safety and well-being of those who are at risk. Of all unvaccinated Americans, 80% of them say they will probably or definitely not receive the vaccine, and 64% of them have little or no confidence that the vaccines are effective against variants (*AP-NORC Poll*, 2021). This contrasts starkly with the 86% of vaccinated Americans that have at least some level of confidence in the success of the vaccines. Numerous papers have been published supporting the efficacy of the vaccines and boosters, indicating excellent safety profiles and showing substantial declines in infection after rapid vaccine rollouts (Amirlak et al., n.d.; Milman et al., 2021; Vitiello et al., 2021). So why are people still doubting vaccines?

A study brings forth some thoughts and misleading statistics that people use to argue the inefficiency of vaccines. As is with every vaccine for any virus we have encountered, when

someone is vaccinated for SARS-CoV-2, they are still able to show symptoms and infect others. However, for a vaccinated person, the frequency at which the virus transmits is 2-4 times lower compared to the rate in an unvaccinated person (Callaway, 2021). Studies have been conducted to hypothesize the reason behind these lowered transmission rates, suggesting that in vaccinated individuals, the virus is coated in antibodies, preventing it from spreading to others. Misleading statistics may show that some vaccinated people continue to die due to the virus, however, this data is typically skewed and does not explain the context, which may include pre-existing conditions that are already be weakening the immune system, such as cancer. Despite this information that is readily available, people continue to not trust FDA-approved and mass distributed vaccines.

To better understand why people continue to be skeptical of the vaccines, an epidemiological survey will be conducted to further understand people's perceptions on SARS-CoV, the variants, the vaccines, and the boosters. Vaccinated and unvaccinated people will be surveyed, and after initial thoughts are recorded, they will be presented with published research explaining the virus, how people are infected, how the vaccine is developed, the success rates of the vaccine in preventing further transmission, and any recorded long-term side effects of the vaccines, in any. After this influx of information, the groups will, once again, be asked the same questions. This survey will not only assess people's thoughts on the vaccine and virus, but it will also test the efficacy of different educational methods we can use to better inform people about the situation at hand.

Conclusion

While the scientific community comes close to solving various biomedical problems we experience today, all of it will be of naught if the people we are trying to help have little trust in our developments and research. My team has faith in the success of our design to encapsulate dissociated islet cells for the treatment of type 1 diabetes, and when we move onto clinical trials, every checkbox and more will be filled out to ensure the safety and efficacy of our products. We are striving to create safe, efficient, and affordable options for people suffering from T1D, and I feel it is a human's right to receive treatment for a disease if one is readily available, regardless of the cost. Transparency in the scientific community can be difficult, but it is necessary to implement. It's the reason many people refuse to receive the SARS-CoV vaccine, and it is an issue that needs to be addressed.

Word count: 1907

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