Growth Factor-Loaded MAP Gel to Improve Diabetic Foot Wound Healing
(Technical Paper)

Scientific Discovery and the Diabetic Patient: How the Past Century Has Transformed Our Understanding of Diabetes
(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

Introduction

Millions of people across the United States are affected by diabetes: a population that is expected to grow 1.5-fold in the next decade and a problem with lacking solutions (Wild, Roglic, Green, Sicree, & King, 2004). Over the past century, scientific breakthroughs in the diabetic research and pharmaceutical communities have provided critical understanding of the mechanisms of diabetes and consequently shaped the treatment and lives of diabetic patients. Prior to modern developments in the understanding and treatment of diabetes, patients faced the threat of poor quality of life and even fatality (White, 2014). Advancements made by researchers and pharmaceutical companies such as Eli Lilly and Genentech have altered treatment approaches and patient outcomes, shifting scientific practice and assumptions along with it (Quianzon & Cheikh, 2012; White, 2014). An analysis of how these research developments contributed to and shaped the scientific community, pharmaceutical industry, and diabetic patient will deepen the understanding of the power of scientific understanding and innovation in diabetes.

Up to 15% of the current 16 million diabetic patients in the United States suffer from diabetic foot ulcers (DFUs), a potentially fatal condition and unmet clinical need (Margolis et al., 2011). DFUs can result from a variety of factors and have a range of physical and psychological side effects, making them difficult to treat (Pop & Almquist, 2017). An ideal wound healing environment for chronic wounds include tissue integration, cell migration, and vascularization, results of biological agents and cues that traditional treatments do not provide (Liu & Velazquez, 2008). Researchers have started to investigate biomaterials as a promising tool in creating successful wound healing environments (Pop & Almquist, 2017). Microporous Annealed Particle (MAP) gel specifically is proving to be a promising solution over other non-porous hydrogels as

it decreases healing time and inflammation and increases tissue integration and cellular network formation (Griffin, Weaver, Scumpia, Di Carlo, & Segura, 2015). While MAP gel is a promising wound healing candidate, it currently lacks the optimization needed to enhance regeneration in a chronic wound setting. Creating a formulation that includes a chemotactic agent such as EGF will further accelerate wound healing and increase cellular activity (Mandial, Gupta, & Sharma, 2015).

The past 100 years have seen immense change in the scientific realm of diabetes, from the understanding and management of insulin to treatments of conditions such as diabetic foot ulcers. An investigation into the shifts in understanding and resulting treatment of diabetes will showcase the societal effects on the industry and the patient. A technical study of a novel DFU treatment using MAP hydrogels and growth factors could impact the millions suffering significantly. Together, the importance of scientific research and consequent innovation will be emphasized through historical analysis and technical study.

Technical Topic (Capstone)

Millions of diabetic patients suffer from diabetic foot ulcers, a condition lacking a clinical solution. Over 16 million people in the United States have diabetes, a number that expands to 200 million across the globe. Up to 15% of those affected by diabetes also suffer from diabetic foot ulcers (DFUs) (Margolis et al., 2011). Patients with DFUs experience numerous risks from decreased mobility, sleep deprivation, depression, anxiety, and amputation (Pop & Almquist, 2017). Further, patients with amputations resulting from DFUs have a five-year mortality rate, comparable to those of prostate and breast cancer (Robbins et al., 2008). The diabetic population is growing with an anticipated global population of 366 million by 2030 (Margolis et al., 2011; Wild et al., 2004). With this rapid growth, DFUs are a largely unmet clinical need as the options

for clinical treatment are sparse and inadequate. These wounds are difficult to treat because of the range of factors that contribute to DFUs. Current options for treatment span tissue removal, negative pressure therapy, and topical applications (Margolis et al., 2011; Pop & Almquist, 2017). However, these therapies are still ineffective for a substantial fraction of the patient population (Pop & Almquist, 2017).

Traditional treatments lack the biological cues and stimulatory agents that provide an ideal wound healing environment (Pop & Almquist, 2017). Hindered blood flow and impaired local neovascularization often delay the healing of DFUs, increasing the chances of infection and further complications. With chronic wound healing, such as DFUs, integration that allows for the development of the extracellular matrix, cell migration, and proliferation is critical (Liu & Velazquez, 2008). Specifically, the promotion of angiogenesis at the wound site could be crucial to diabetic wound closure (Liu & Velazquez, 2008). Each wound site varies in its composition and requirements for tissue regeneration, calling for a robust and tunable treatment (Griffin et al., 2015).

Recently, researchers in the chronic and diabetic wound healing field have been focusing on the use of biomaterials to create an optimal wound healing environment (Pop & Almquist, 2017). These microstructures enable bioactivity and stimulate natural tissue repair through their cell-binding and controllable degradation capabilities (Pop & Almquist, 2017). Microporous Annealed Particle, or MAP, gel provides a microporous and tunably degradable wound healing environment that promotes cellular network formation and vascularization (Griffin et al., 2015). MAP gel has proven to be a more successful alternative over other non-porous hydrogel alternatives as it accelerates wound healing, decreases inflammation, increases integration with healthy tissue, and encourages the formation of cellular networks when compared to competing

non-porous hydrogels (Griffin et al., 2015). Therefore, the overall goal of this proposed project is to continue to build upon the success that MAP gel has already achieved in order to continue to advance the best possible solution to the unmet clinical need of diabetic wound healing.

While MAP hydrogel promotes an initial pro-healing microenvironment which is effective in healthy wounds, it lacks the optimization necessary for enhancing regeneration in a chronic wound setting. Including a chemotactic agent, such as EGF, will accelerate tissue integration within the MAP gel. Chemotactic agents have been shown to improve healing by promoting faster wound closure and attraction of cells to the wound site (Mandial et al., 2015). The combined impact of MAP gel on tissue integration and wound closure along with EGF's promotion of epidermal tissue growth in dermal wounds will create an ideal dermal wound treatment. The overarching goal of our project is to develop a MAP-EGF formulation that can be applied in a murine wound healing model. Together, Meghan McDermott and Regan Ellis will run a number of *in vitro* experiments in Fall 2019, followed by an *in vivo* study upon completion of the *in vitro* tests in Spring 2020. The MAP-EGF formulation will be developed by first optimizing the concentration of EGF loaded into the MAP gel that will elicit a significant cell response in Fall 2019. Then, the loading and release of EGF from the MAP gel will be characterized using an ELISA to better understand the amount of growth factor released into the wound setting causing cell interactions. Finally, evaluating the effects of lyophilization on the cell migration and loading and release of EGF will indicate the feasibility of stably storing the MAP gel in a freeze-dried state. Once these steps have been completed, a mouse study will be initiated in Spring of 2020.

STS Topic

Diabetes is the third leading cause of death behind heart disease and cancer in the United States (Ladisch & Kohlmann, 1992). Over 200 million people suffer from diabetes worldwide (Margolis et al., 2011). While cases of diabetes date back centuries, as far as in ancient Egyptian civilization, foundational understanding and medical treatments were not obtained until the 20th century (Quianzon & Cheikh, 2012). Due to the nonexistence of diabetic pharmaceuticals, type 1 diabetes was typically fatal until the 1920s when Frederick Banting created the first insulin injection (White, 2014). Banting isolated insulin from animal pancreases through a process that combined ground-up beef pancreas with alcohol at a one-to-one ratio. Through an agreement with Eli Lilly, this concoction of insulin arrived on the market in 1923 (White, 2014).

While a major and life-saving advancement, patients still required multiple injections throughout the day and night to prevent a stunt in growth, among other conditions (Ladisch & Kohlmann, 1992). The first extended release insulin became commercially available 13 years later in 1936, yet inefficient methods of harvesting insulin from animal pancreases were still in use (White, 2014). A second critical development in the treatment of diabetes came in 1978 when Genentech successfully manufactured the first recombinant DNA human insulin known as Humulin (Evans, Buckland, & Lefer, 2006; Quianzon & Cheikh, 2012). As a model of human insulin, this product had less of a risk of immunological reaction than its animal-derived counterpart (Ladisch & Kohlmann, 1992; Landgraf & Sandow, 2016). Over the span of just 55 years, the diabetic world went from having no pharmacological agents to many.

As a prominent cause of death in the U.S. whose treatments have rocketed from non-existence to an over $30 billion global market, an in-depth investigation into the key scientific discoveries and decisions will provide further understanding into how diabetic stakeholders today were shaped (Heinemann, 2016). In order to thoroughly and meaningfully analyze the

impact of these developments on the diabetic patient, effected stakeholders, artifacts, and technological, social theories must be identified. The stakeholders in this assessment span the entirety of the drug pipeline from discovery to use, including scientists, corporations and academic institutions contributing to and benefiting from the researchers' findings, and the patients themselves. The primary artifacts are the drugs themselves, but the focus of this evaluation will be on the institutions. While the developed drugs are key results of the innovations being discussed, an evaluation of the stakeholders will provide more insight into the impact.

Utilizing the perspective of the paradigm shift theory will provide insight into how the major breakthroughs in the field of medical research and pharmaceutical development implemented a shift in the perspectives and practices of scientists, ultimately impacting the pharmaceutical industry and the diabetic patient. In Thomas Kuhn's theory of paradigm shifts, a paradigm embodies the recurrent practices and applications of a group, both abstract and concrete. Further, Kuhn observes that the assumptions of paradigms shape science. Paradigm shift theory, therefore, comes about when a community accepts a new framework and implements it in their field of study (Kuhn, n.d.). These paradigms "require the reconstruction of prior assumptions and the re-evaluation of prior facts" (Pajares, n.d.). In this way, a fundamental change in a scientist's way of thinking, application, and interpretation of concepts shifts. Criticism of the paradigm shift theory arises from skepticism of the degree of novelty in these paradigms. Famed professor Fenwick English argues that the "new theories" implementing paradigm shifts are nothing more than rebranded "old theories" (English, 2001). Thus, the paradigm is continuously re-centered, not changing in scope nor influence at all, causing them to

miss Kuhn's own definition of a paradigm shift. Still, this theory frames the study by aiding in evaluating the impact of approach-altering discoveries on multiple stakeholders.

An investigation into how the production and understanding of diabetic treatment changed over the past century will help tell the story of diabetes' image and impact in society. The scientific advancements and the effected quality of life for the patient is relevant to many, as one-third of Americans either have or are at risk of developing diabetes mellitus (Burke, Sherr, & Lipman, 2014). Our understanding of the disease has deepened, but the risk of disease has increased as well. In evaluating the progression of how companies manufacture treatments and how society understands and handles diabetes consequently, the impact of pharmaceutical developments on society will be better understood.

Research Question and Methods

How did scientific breakthroughs in the understanding of diabetes affect treatment approaches and consequently shape the lives of diabetic patients over the course of the 20th century? To address this question, historical case studies will be implemented to connect events in the scientific world to the changes in patients' lives. Historical case study research helps explain the role of events in shaping a group, in this case the diabetic patient, over time by investigating the dynamics between specific occurrences and resulting effects. This evaluation is achieved through the formation of specifically structured questions and in-depth, holistic analysis of the results over a certain timeframe (Harrison, Birks, Franklin, & Mills, 2017).

Research developments on the topic of diabetes throughout the 20th century will be evaluated in comparison to the changes in the clinical approaches and treatments of diabetic patients. The impact of two specific events, Eli Lilly's commercialization of insulin and Genentech's development of synthetic human insulin, will be investigated and compared with

shifts in the treatment and quality of life of patients. A variety of accounts will be systematically and chronologically organized to evaluate the dynamics between these two innovations and the impact on patients.

Conclusion

The diabetic world, from the scientists to the patients, has seen dramatic transformation over the last century. Through the lens of historical case studies, an investigation of the scientific breakthroughs in diabetic research throughout this time will be connected to consequent pharmaceutical developments and changes to patients' lives. This investigation will show how scientific discoveries, specifically those related to the development of insulin, impact entire industries and patient groups, causing fundamental change in approaches and thought. This societal shift goes hand-in-hand with the impact of technical developments in the world of DFUs. Understanding of the needs for an ideal wound healing environment can lead to a finetuned development of a therapeutic solution. The technical development of MAP gel loaded and optimized with growth factor will provide a tailored solution to wound healing in DFUs, creating an environment that addresses the needs of chronic wound environments with the encouragement of vascularization and cell migration, among other benefits. This provides an encouraging wound healing environment that will decrease recovery time and improve tissue integration, reducing the risks associated with DFUs. Diabetes impacts millions and its scope is only growing, yet significant innovations both in pharmaceutical agents and tissue engineered treatments will help provide understanding and groundwork for future solutions.

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