"Bugs For Drugs": Encapsulation of a Cooperative Bacterial Consortia as a Therapeutic to Resolve Recurrent *C. difficile* Infection

Analysis of Factors Contributing to and Impeding the Success of Biotherapeutic VOWST

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 and Bachelor of Science in Engineering Science

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December 6, 2023

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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

Clostridioides difficile infection (CDI) is a bacterial infection caused by the highly contagious *Clostridioides difficile (C. diff)* bacterium. Commonly occuring in healthcare settings after antibiotic treatment for another illness, CDI is debilitating to not only patients, but also the healthcare system as a whole. Patients who contract *C. diff* suffer with diarrhea and colitis (inflamation of the large intestine) that can often be very severe and in some cases, fatal. Older and immunocompromised patients are higher risk and generally are more severely impacted. Incidence is high, with about 500,000 cases a year, leading to a hefty yearly healthcare burden of nearly $4 billion (Viswanathan et al., 2010).

One notably awful characteristic of CDI is the very high rates of recurrence. Although there is a variety of current treatment options available, there is a scarcity of options that are both accessible and effective in preventing recurrent infections. Antibiotics continue to disrupt the gut microbiome, which leads to continued dysbiosis and recurrence (Shen & Surawicz, 2008; Viswanathan et al., 2010). Fecal microbiota transplant (FMT), while a good, more effective alternative that restores a healthy gut microbiome and prevents recurrence, usually requires a procedure, and can be expensive, inaccessible, and unappealing to for patients (*Fecal Transplant*, 2022).

To address these current shortcomings in treatment options for CDI, I propose a technical project for the development of an orally administered microbial therapeutic to treat CDI and prevent recurrence. This therapeutic would deliver a community of healthy bacteria to the large intestine to restore a healthy gut microbiome, in a way that is not only as effective as FMT, but more convenient and accessible for patients and clinicians.

Although this project is fundamentally based on scientific research and development, there are also many non-technical aspects that will directly and indirectly impact its development and eventual implementation. Healthcare itself is very sociotechnical: it is intrinsically scientific, but also incredibly sensitive, and socially complex, and inseverable from economics. Failure to take account of both technical and non-technical influential factors will hinder completion of the end goal, as medicine is heavily regulated, debated, and deeply personal. For a therapeutic to be approved and accepted for clinical use, it needs to not only work, but also consider regulatory impositions and perspectives of the end-users (patients and clinicians).

To further understand the complexity of the sociotechnical system surrounding the development and use of live biotherapuetics, I will draw on the STS framework of Actor-Network theory (ANT) to investigate the social, technical, and natural actors present and their relationships with one another in the success of VOWST. VOWST is an FMT therapuetic used to prevent recurrent CDI, and is the first FDA-approved orally administered live biotherapuetic (*NOW APPROVED | VOWST™ (Fecal Microbiota Spores, Live-Brpk) Capsules*, n.d.). This investigation will assist in determining important actors for future consideration that can disrupt or support the success of novel biotherapeutics.

In what follows, I elaborate on the aforementioned technical project and STS research project, with the goal of addressing the overarching sociotechnical issue that is the lack of adequate treatment for *C. diff* infections. By exploring the actors and corresponding network contributing (positively and negatively) to the recent and ongoing success of a similar live biotherapeutic, I will gain context that will be helpful to consider in decision-making to spur my technical project to a similar success.

Technical Research Project Proposal

C. diff infection is major issue in healthcare globally, it as a healthcare-associated infection with high incidence and mortality, especially among high-risk populations. CDI also poses a unique problem due to its cyclical nature, causing reccurent infections that further contribute to the spread of infection, lower patient quality of life, and overall healthcare burden (Viswanathan et al., 2010). Furthermore, CDI is deeply intertwined with multiple overarching problems in the field, such as the stigmatizaiton and misunderstanding of digestive illnesses, and the overprescription and misuse of antibiotics leading to antimicrobial resistance (Ranallo et al., 2021).

In most cases, healthy gut bacteria prevent *C. diff* from colonizing, but when broad-spectrum antibiotics are used to treat other health conditions or a patient is immunocompromised, the normal flora is disrupted, increasing susceptibility to *C. diff* infection. Those who contract *C. diff* usually face an onslaught of serious, painful gastrointestinal symptoms that can significantly impact their lives. This is especially true for patients with recurrent CDI (rCDI), as they can fight a persistent, repeated cycle of infections for months or even years. rCDI is common: around 1 in 6 CDI patients will contract it again in the 2-8 weeks following recovery (Viswanathan et al., 2010).

Typical treatments for CDI involve narrow-spectrum antibiotics, which cause continued dysbiosis of the gut's microbiome. making recovery more difficult and contributing to high relapse rates (Shen & Surawicz, 2008). Recently, fecal microbiota transplants have had high success rates in treating recurrent CDI, as they introduce a healthy community of microbes to the colon to help restabilize the microbiota. However, this requires a the acquisition of fecal sample from a healthy donor, and often is done through a procedure (colonoscopy) (*Fecal Transplant*,

2022). Overall, FMT can be expensive, inaccessible, and unappealing to patients, especially those from higher risk populations. With these deficiencies in the current treatment options, there is a large need for a more accessible and affordable treatment for recurrent CDI that can restore healthy microbiota by re-establishing natural colonization resistance.

This technological project aims to meet this need by developing a biotherapeutic that will use a similar mechanism of action to FMT but improves upon the current impracticalities of FMT. This includes the elimination of the need for donor feces, increase in administration simplicity to benefit both patients and clinicians, and design that caters specifically to older patient's difficulty with swallowing pills.

To achieve this, the biotherapeutic developed will encapsulate a predefined, "healthy" consortia of anaerobic bacteria for ingestion and subsequent delivery to the large intestine. The specific community of bacteria is a cooperative consortium determined by previous work as able to return the gut microbiota to a healthy balance following colonization by *C. diff*, consequently ending the cycle of recurrent CDI (Jenior et al., 2023). The final form of the therapeutic will be a sort of film that dissolves in saliva, and the encapsulation method developed will keep the bacteria alive and contained until they reach the large intestine.

This will be completed in a series of sequential developmental steps. The success of each step is verified with an appropriate assay upon completion before moving onto the next step. First, a hydrogel material system will be determined that will be used as the basis for the encapsulation, followed by the development of encapsulation methods, fine-tuning to the specific bacteria. Once defined, then a material and method for "bundling" the encapsulated method into a film to form a single therapeutic will be developed. Finally, the therapeutic's efficacy will be tested and analyzed using rodent models, and the therapeutic will be refined based on the results.

Within each step outlined, the design process will be iterative, therefore, intermittent outcomes will be continually observed inform the next course of action. This project will be completed by a team of two students over the course of two semesters within the biomedical engineering department at the University of Virginia.

Although this is likely beyond the scope of the year-long capstone project, the eventual goal for the larger project is to advance the therapeutic to clinical trials and eventually, get it approved for use and use it to treat patients.

Initial data used to conceptualize and plan this technical project has been compiled through previous work and research completed by the larger project team. Any other information needed throughout the processes will be obtained via literature review of relevant scholarly articles and discussion with professors, clinicians, and other experts who work at the University of Virginia.

STS Research Project Proposal

In April 2023, the U.S. Food and Drug Administration (FDA) approved VOWST as a therapeutic to prevent the recurrence of CDI. It is the first orally-administered microbiota based therapeutic approved by the FDA, and only the second live biotherapeutic approved for medicinal administration. Now, VOWST is actively being marketed and prescribed to treat patients (United States Food and Drug Administration, 2023).

The development, testing, and approval processes for VOWST took over a decade. This undertaking eventually led to success in approval from the FDA, however, it was not always direct and clear. There were various challenges and supports that arose along the way from a

wide variety of sources, some of which persist now as the therapeutic is being marketed and used clinically (*Here's a Timeline of Seres' 12-Year Trek to One of the First Microbiome Drugs*, 2023; Jain et al., n.d.).

Much of the discourse surrounding the factors that affected the development and approval of VOWST is heavily from a technical, and occasionally economic, viewpoint. In conversation about the process, most obstacles and/or successes discussed are purely scientific, such as clinical trial results, microbiological interactions, etc. Seres Therapeutics' economic support from Nestlé Health is also usually mentioned as a contributor to the therapeutic's approval. However. the only social contributor to VOWST's development journey regularly mentioned is the FDA and the regulatory hurdles it imparts on drug and biologic development for approval, however, even this is very technical by nature (*Seres Therapeutics and Nestlé Health Science Announce FDA Approval of VOWST™ (Fecal Microbiota Spores, Live-Brpk) for Prevention of Recurrence of C. Difficile Infection in Adults Following Antibacterial Treatment for Recurrent CDI | Seres Therapeutics*, n.d.; *Seres' Vowst Wins FDA First-Ever Approval for Oral Microbiome Therapeutic*, n.d.; United States Food and Drug Administration, 2022).

This largely technical and economic viewpoint neglects to consider many vital elements of the larger "network" that had influences on VOWST's development and eventual approval. Although the process itself was very scientific and technical, following the FDA's drug-approval processes, the FDA and Nestlé Health were not the only entities that had a hand in spurring or hindering these processes. Most anything related to healthcare usually is influenced heavily by society from many angles in a very complex manner, including VOWST. End-users usually determine success, and a large portion of the end users for drugs and therapeutics such as these are patients with non-technical backgrounds. Understanding the non-technical factors that

impacted VOWST's development and current market is vital to fully understand the past, present, and future of VOWST. This is especially important to look forward, as it will be critical for decision-making that spurs continued growth and success and pursuit of the end goal: a better method for rCDI resolution.

I plan to examine and determine how various factors, as well as the relationships between them, played roles throughout the various developmental and current on-market phases of VOWST. I maintain that although technical and economic factors contributed heavily to these processes, there are additional, often unrecognized social, natural, economic, and other factors that were and are very interconnected in the case of VOWST. Such factors undoubtedly hold a lot of influence over the biotherapeutic's success. These include social factors such as patient and clinician feelings about feces-related treatments, natural actors such as the gastrointestinal system, human physiology, and antibiotic resistance, and economic factors such as market competitors (*Patient Attitudes Toward the Use of Fecal Microbiota Transplantation in the Treatment of Recurrent Clostridium Difficile Infection | Clinical Infectious Diseases | Oxford Academic*, n.d.; United States Food and Drug Administration, 2022). I will determine the specifics of how the various factors interact and have impacted VOWST's and each other through further investigation utilizing the science, technology, and society (STS) framework of actor-network theory (ANT) to provide support and structure for my analysis.

ANT regards the various, diverse entities that interact within a sociotechnical system as "actors" in a network and analyzes the dynamics of the network by focusing on the relationships between actors (Cressman, 2009). Technologies themselves can exist as both a network and an actor. According to ANT, actors are recruited to the network and associated together by a "network builder" for a common purpose, such as developing a treatment for CDI (Callon,

1984). As it is particularly relevant in this case, I will also be paying attention to "rogue" actors that do not work cooperatively with other actors for the "common goal" of the network, but rather, against them. While there were a lot of actors in the network assembled by engineers to develop VOWST that worked to reach approval and success on the market, there are assuredly also rogue actors, such as strict regulations on therapeutics and potential for pathogen transmission, that introduced obstacles to impede success (*Seres Therapeutics and Nestlé Health Science Announce FDA Approval of VOWST™ (Fecal Microbiota Spores, Live-Brpk) for Prevention of Recurrence of C. Difficile Infection in Adults Following Antibacterial Treatment for Recurrent CDI | Seres Therapeutics*, n.d.). ANT defines and examines each of these actors alone and as they interact with one another to understand the system as a whole.

To perform this investigation, I will analyze a variety of different online sources, including scholarly journal articles and literature, news articles, product websites, recorded video interviews with clinicians, engineers, and other experts, first person accounts from patients, discussion boards, etc.

Conclusion

Together, the technical and STS research projects defined in the prospectus will take action to address the complex, sociotechnical challenge present in healthcare due to *C. diff*. The technical project will develop and deliver an alternative treatment method for CDI in the form of a wholistically effective and accessible biotherapeutic that improves upon the inadequacies of currently available treatments. The ANT analysis of VOWST's developmental path and eventual success will help to define what sorts of "actors" and interactions between actors impacted the

VOWST both positively and negatively, creating a more complete understanding of how the network surrounding the development of a biotherapeutic can contribute to its success or failure. This knowledge will be used to inform decision making in the technical project, altogether supporting the ultimate goal of resolving the issues caused by *C. diff*.

Word count: 2,331 (including in-text citations)

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