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Thank You to Our Members!

From President Tim Bloomquist

It is with great pleasure that I welcome you to the Fall 2023 edition of the Surfaces in Biomaterials SurFACTS newsletter.

Participating in the Surfaces in Biomaterials Foundation has been a longstanding goal of mine since I started at SurModics, Inc. post college. However, it took some time before a good friend of mine encouraged me to deepen my involvement. Beginning with my role as a Session Chair in Park City, I progressed to positions such as Secretary, President-Elect, and now, as the President. As we are all aware, there have been struggles along the way. I extend my heartfelt gratitude to Landon Nash and Rob Diller for their guidance through the past two years, ensuring we got together in Portland and San Diego to start rebuilding the foundation's momentum. As we navigate this pivotal year, I am reaching out to seek your support to ensure our long-term viability.

The Biointerface 2023 event in San Diego was a wonderful experience, providing an opportunity to connect with industry professionals, reconnect with friends within the group, and establish new connections.

It remains a rare occasion on the calendar where we can get to know each other and foster deeper relationships that often lead to exciting breakthroughs.

Looking ahead, the entire SIBF Board is eagerly anticipating the 2024 BioInterface Workshop and Symposium in Minneapolis, MN, on the campus of the University of Minnesota-Twin Cities at the McNamara Alumni Center in Memorial Hall from October 2nd to 4th, 2024. Bringing the Symposium back to Minneapolis, where it all started back in 1991, holds special significance. The program is in its early stages, and we encourage you to reach out to any SIBF Board members if you are interested in chairing a session in the biomaterials/surface science fields, becoming an exhibitor, or sponsoring any component of the 2024 BioInterface event. You can find more details about these opportunities on our website: www.surfaces.org.

On behalf of the Surfaces in Biomaterials Foundation, I extend my best wishes to you and your families for a prosperous 2024. Please stay tuned for upcoming SurFACTS newsletters, BioInterface 2024 updates, and other SIBF events.

The Development of a "Turn On" Nitric Oxide Antibiotic Material to Coat Orthopedic Medical Devices

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While the technological advances of the medical device industry have revolutionized the quality of healthcare available to patients, implantable devices remain one of the leading causes of nosocomial infections.[1,2] Approximately 60-70% of infections acquired in hospitals are associated with medical devices.[3] Additionally, while preventative strategies help reduce infection rates, the introduction of an abiotic material into a biological space initiates a healing process that inevitably creates a periprosthetic environment conducive to biofilm formation.[1]

Biofilms are difficult to both detect and treat, and can form days or even years after an implant is inserted into a patient.[4-6] The increased resistance of biofilms to common antibiotics can lead to chronic infections, which are correlated with long term morbidity, and increased economic burden.[7] Techniques such as loading materials with antibiotics have been explored to minimize bacterial infections associated with implanted devices.[1,8] However, while the loaded materials provide an increased localized concentration of antibiotics for months, the material has a finite amount of antibiotic to release, and an infection still might occur once the antibiotic stores have been depleted.[8]

A prodrug is a biologically inactive compound that can be enzymatically activated to produce a drug. This research seeks to synthesize and characterize an antibiotic prodrug that is "turned on" by the target bacteria. The proposed design includes the controlled release of a unique antibiotic into the local environment by the enzymatic removal of a molecular cap. The goal of this project is to incorporate this novel prodrug into an orthopedic medical device coating that selectively releases the antibiotic when an infection occurs, potentially reserving the antibiotic stores for years until needed (Figure 1). This work is currently ongoing, and a provisional patent has been filed on this innovation.

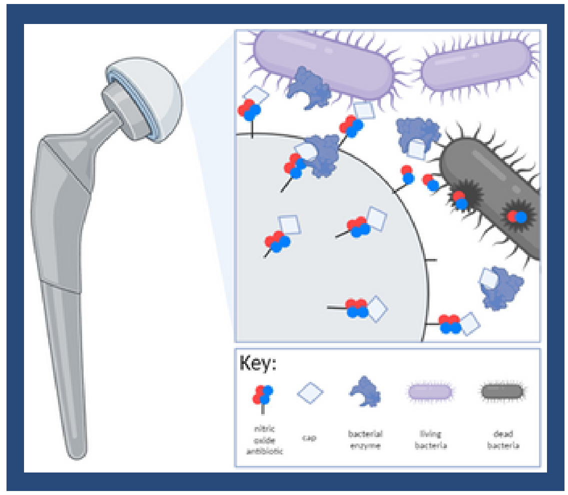

Figure 1. Schematic figure illustrating how target bacteria releases enzymes that "turn on" the antibiotic material coating orthopedic medical devices.

The unique antibiotic that is incorporated into this enzyme-activated prodrug is nitric oxide. In 1992, nitric oxide was named "molecule of the year" due to the radical gas molecule's numerous physiological and pathological functions.[9] Since then, nitric oxide's protective,

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regulatory and deleterious effects have been studied at length and it has been explored as an anticancer, anticoagulant, and antibiotic.[10-13]

Nitric oxide has demonstrated its effectiveness as an antibiotic. In fact, previous studies have shown that even resistant bacteria are sensitive to nitric oxide's antibacterial properties, and do not evolve resistance after weeks of selective pressure.[14] It is hypothesized that this is because nitric oxide's free radical nature induces both oxidative and nitrosative stress within the bacteria.[15]

One concern with antibiotic loaded materials is their potential to exacerbate bacterial resistance. Resistant bacteria are more likely to be isolated from medical devices made of antibiotic loaded materials than non-loaded materials.[8,16,17] However, due to the various mechanisms of cytotoxicity that nitric oxide presents to bacteria, multiple simultaneous mutations would have to occur for bacterial survival, protecting against resistance development. Therefore, nitric oxide shows great promise as a robust antibiotic that is even effective against resistant bacteria.

However, due to the gaseous nature of nitric oxide, delivering the molecule to its intended site can be difficult. A nitric oxide donor, in this case a diazeniumdiolate, will be used to store nitric oxide within the material.

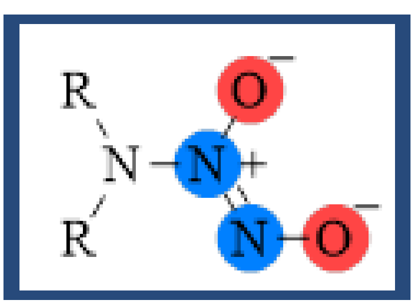

Figure 2. Generic chemical structure of a diazeniumdiolate, a type of nitric oxide donor.

Diazeniumdiolates are stable solids, activated in physiological conditions, that release two equivalents of nitric oxide per one equivalent of diazeniumdiolate making them a good candidate for the prodrug (Figure 2).[18,19]

However, while being loaded with a biologically active and robust antibiotic is beneficial, what differentiates this design from other loaded materials is its ability to store the antibiotic until bacteria are present. This will be done by utilizing a molecular cap that can only be removed by bacterial enzymes (Figure 3).

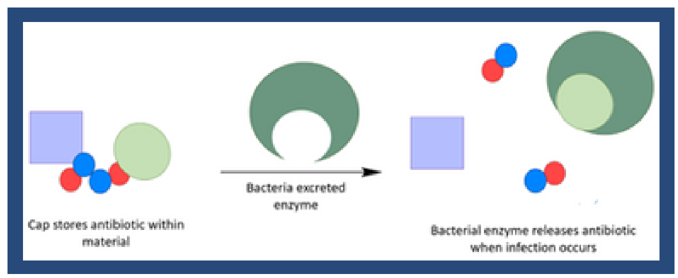

Figure 3. Schematic illustration of a bacterial enzyme removing the molecular cap, thus inducing antibiotic release.

At the cellular level, when a bacterial infection is starting, enzymes are being released into the environment surrounding the infection site.[20] These enzymes are released by the bacteria to initiate the infection.[21] However, the cap is designed so that these excreted enzymes will target and remove the cap, releasing nitric oxide, and thus killing the bacteria. The cap is bacteria-specific, in this case targeting *Staphylococcus aureus* as it is a prominent cause of nosocomial infections, especially with critically ill patients.[22,23]

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Thus far, work has been focused on the synthesis and characterization of the prodrug (Figure 4).

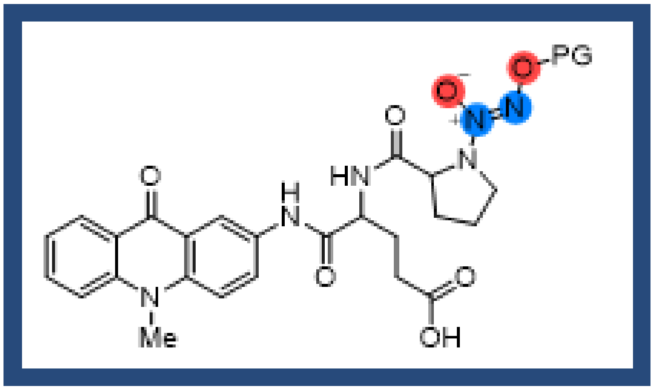

Figure 4. Chemical structure of proposed antibiotic prodrug.

The first four steps of the synthesis modify an acridone fluorescing detector with a *S. aureus* specific dipeptide. The dipeptide is comprised of glutamic acid, which detects the target bacteria, and proline, which is the site of diazeniumdiolate loading. Detection of the bacteria is visibly observed through a fluorescent color change from blue to green. This color change is solely for research purposes, and illustrates when bacterial enzymes are interacting with the prodrug (Figure 5). The fifth step of the synthesis loads the diazeniumdiolate onto proline, and the final step would be to add a cap, finishing the prodrug synthesis.

Immediate next steps will focus on exploring the efficacy of various caps to identify a cap that only releases nitric oxide after desired enzymatic activity. These experiments are crucial to ensure that nitric oxide release is controlled by bacterial enzymes alone.

Once a cap has been identified, finishing the synthesis of the proposed prodrug, the focus of this project will pivot to the incorporation of the prodrug into a polymer material. Future work will test the antibacterial properties of the loaded material, ideally characterizing a material that lowers bacterial cell viability, thus treating infections caused by implanted medical devices and lowering patient morbidity and mortality.

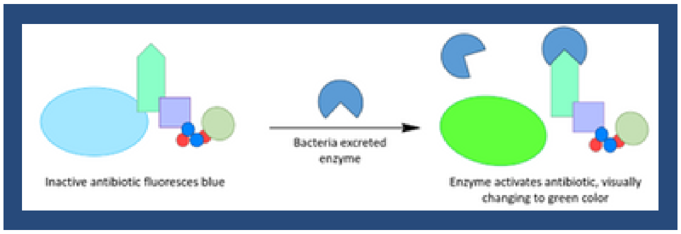

Figure 5. Schematic illustration of how a bacterial enzyme interacts with the prodrug, initiating a color change that allows for enzymatic activity to be easily monitored.

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Unlocking the Future of Medical Device Coatings: ISurTec's Trailblazing Journey

At ISurTec, Excellence Knows No Bounds
Since its inception in 2004, ISurTec has been at the forefront of innovation in the biotechnology sector, setting a benchmark for excellence and driving advancements in medical device coatings. As a privately held, family-owned business with an impressive portfolio of over 19 U.S. patents, we take pride in our legacy of exceptional service to the industry.

A Proven Track Record
We are privileged to serve more than 100 medical devices worldwide, offering specialized expertise in reagents, coatings, and comprehensive R&D support. Our remarkable journey spans over 15 years, during which we've cultivated deep industry experience, making us a trusted partner for enhancing medical devices.

Your Gateway to Excellence: Feasibility Studies
At ISurTec, we kick off projects with a commitment to excellence through our thorough feasibility studies. Our process allows you to coat your devices, test them as needed, and rely on our expertise to take your innovations to new heights. We specialize in working with a range of materials, including PEBAX, Silicone, Nylon, SST, and Polyurethane, ensuring that your devices meet and exceed industry standards.

Leading the Way in Coating Technologies
Our coatings are designed to provide substantial improvements in lubricity, achieving a remarkable 0.01-0.03 coefficient of friction (COF). ISurTec's coatings are known for their thin, durable quality, with a thickness of 5-10 microns when wet. These coatings have earned FDA Masterfile status and are biocompatible, assuring you of the highest standards in safety and performance.

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The ISurTec Advantage

What sets ISurTec apart is our commitment to being small, agile, and responsive. This approach allows us to adapt quickly to your unique needs and provide tailored solutions that meet your specific requirements. With our flexible pricing options, you can access our cutting-edge expertise without compromising on quality or budget.

Innovation Meets Experience

ISurTec is not just about innovation; it's about innovation backed by experience. With more than 15 years of internal experience in the medical device industry, our team brings a wealth of knowledge to the table. We understand the complexities and nuances of your industry, ensuring that our coatings and solutions are designed to meet the challenges you face

In conclusion, ISurTec is proud to be your partner in advancing medical device technologies. With our rich history of innovation, deep industry experience, and unwavering commitment to excellence, we stand ready to help you create the medical devices of the future. Together, let's take a step closer to a healthier and more efficient world.

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Mentorship Program

Surfaces in Biomaterials is hosting a **mentorship program**. The goal is to build a professional relationship between mentor and mentees. Once matched, mentors and mentees can create a timeline to meet virtually. The goal is to meet twice in the first month and then at least once a month for a total of six months.

Please sign up to start your mentorship.

SurFACTS in Biomaterials is the official publication of the Foundation and is dedicated to serving industrial engineers, research scientists, and academicians working on the field of biomaterials, biomedial devices, or diagnostic research.

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