Design Brief

Next-gen bioremediation: regenerable lipopolysaccharide vesicles for uranium sequestration*

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Nuclear power plants serve as potent sources of alternative energy. However, atomic energy generates harmful byproducts through the release of irradiated substances, such as uranium. Exposure to heightened levels of ionizing radiation from uranium can damage cells, impair organ functionality, and, in sufficient quantities, act as a carcinogen. Lead-lined storage containers can store uranium until radioactive decay functions; nevertheless, lead in itself can cause harmful health and neurodegenerative effects, and the substance itself remains a potential danger when stored in mass quantities. Our study showcases a novel, highly scalable way to reduce radiation pollution by means of synthetic biology-based bioremediation. We leverage proteins characterized in the bacterial strain Geobacter sulfurreducens (Geobacter), which produce a lipopolysaccharide (LPS) vesicle that traps uranium and prevents it from entering and damaging a cell's contents. On this basis, our system uses Escherichia coli (E. coli) and a pBAD inducible promoter system to express genes transformed from Geobacter to efficiently provide the bioremediation effects sought. The sequences are further modified with Nickel-NTA (Ni-NTA) tags to allow for purification of the product, and a Sterile Alpha Motif (SAM) for embedding within materials to construct vesicles necessary for capturing uranium deposits. Ease of production through the E. coli-based system ensures capabilities for mass production, and the embedding structure enables the LPS vesicle structure to be regenerated after usage for continuous utilization of the product in safely dispersing and remediating uranium waste. Our approach will aid in nuclear facilities and the creation of devices geared towards radiation protection. Moreover, this study elaborates upon a simple yet effective methodology for designing and applying protein systems through techniques in synthetic biology for potent, wide-scale waste remediation.

Keywords: *Geobacter*, pBAD operon, lipopolysaccharide, uranium, bioremediation

Irradiated materials have dangerous, carcinogenic effects when they come into contact with biological compounds. By penetrating the cell barrier, substances that emit ionizing radiation, such as uranium, which can damage DNA, kill cells, and cause irreparable damage to organ structures (Mohan and Chopra, 2022). In addition to devastating immediate effects ranging from bone marrow failure to cardiovascular disorders, contact with radioactive material increases the risk of certain cancers to individuals later in life, and has been shown to have some effects on progeny (Kamiya et al., 2015).

Despite associated health risks due to the

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radioactive byproducts generated, nuclear power presents a potent substitute to more traditional energy types. Nuclear energy produces fewer greenhouse gas emissions than fossil fuels and is currently integrated as a form of clean energy by global bodies (Sadekin et al., 2019). Nuclear facilities are a source of nearly three-fourths of the annual power generated in some developed countries, such as France (EBSCO Information Services, 2023). Over the next couple of decades, increasing numbers of developing nations will be weighing investments into the power source for their infrastructure, and established economies into whether they should take on clean energy alternatives (Ibrahim et al., 2023). To prevent reliance on fossil fuels, it is critical to implement efficient and safe means of utilizing renewable energy, such as nuclear power, without negative consequences.

Current technological processes of abating radioactivity include shielding harmful uranium byproducts behind lead-laden containers until natural radioactive decay occurs over billions of years (Craft et al., 2004). These methodologies, effective in very limited quantities, are not suitable for increasing the usage of nuclear facilities to produce energy. The United States, unlike France, only sources around 19% of its annual power requirements from nuclear plants (Davis, 2012) and still has over 700,000 metric tons of depleted uranium in storage (U.S. Nuclear Regulatory Commission, 2010). Diverting resources to store increasingly large quantities of uranium, which has a decay rate measured in geological time scales, is not practical for continued development. Neither is using lead as a storage mechanism, which has been shown to bring about harmful neuropsychological effects and functional decline in humans (Mason et al., 2014).

Alternative means to abate the effects of ionizing radiation have been evinced by certain specialized organisms (Somu et al., 2022). By assembling specialized lipopolysaccharide (LPS) tendrils, the bacterial strain *Geobacter* prevents harmful substances from penetrating its membrane and remediates the element through reduction reactions in vesicles (Clark et al., 2021). In doing so, *Geobacter* uses targeted proteins for vesicle assembly in environmental conditions where humans would not usually be able to function. Though LPS vesicles in themselves can harm human health (Bell et al., 2019), these effects can be neutralized by both biological and synthetic mechanisms and are not nearly as long-lasting as uranium in its natural state (Pfalzgraff et al., 2019; Huang and Zhou, 2023).

This study proposes a harvesting mechanism for characterized LPS vesicles, constructing proteins found in *Geobacter* based on the principles of synthetic biology. These proteins, which normally allow the bacterium to survive in harmful conditions, can also be applied to construct devices with embedded vesicle constructs that reduce levels of uranium deposit. Rather than purely focusing on materials and time-based decay, this study takes a proactive approach to the problem of uranium deposits by proposing a means for producing, purifying, and embedding *Geobacter*-sourced proteins whose product mineralizes uranium into devices for targeted bioremediation. Leveraging the already characterized group of proteins that form the LPS vesicles, we propose a means to purify large quantities of these proteins, embed them in materials, and create a system wherein regenerable LPS vesicles ensure the decontamination of uranium waste before it poses a health risk.

Systems level

The principal objective of this research is to develop an organism that can serve to effectively remove and neutralize radioactive substances, particularly uranium, from contaminated environments. This novel bioremediation mechanism acts through a system employed by *Geobacter* bacteria. *Geobacter* can survive in radiation-contaminated environments that are toxic to other organisms. It produces LPS vesicles that can bind, trap, and neutralize uranium, leaving behind the comparatively less harmful vesicle as a byproduct, before the harmful radioactive substance can penetrate the cell wall (Clark et al, 2021). Using such a process, our study's system utilizes *E. coli*, both due to its high availability and faster doubling time, as a chassis to express such

LPS radiation prevention genes found in *Geobacter* bacteria and mass produce the vesicle-creating proteins. Upon the expression of its recombinant DNA, *E. coli* develops the same lipopolysaccharide vesicles as those seen in *Geobacter,* capable of performing the same radiation-controlling tasks **(Fig. 1)**.

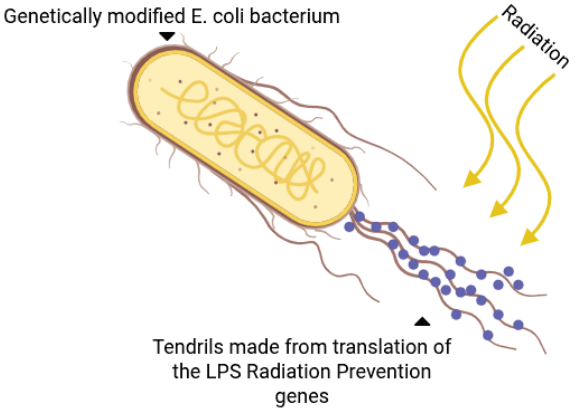

Figure 1. E. coli bacterium genetically modified to acquire uranium-neutralizing abilities.

Device level

For our system, we selected the pBAD operon system, explicitly chosen for its many beneficial properties and commonality in synthetic biology. Indeed, much research has been conducted on this operon system. It is a segment of the *araBAD* operon, which assists in the metabolism of L-arabinose sugar in various species of bacteria. The *araBAD* operon consists of three genes—*araA*, *araB*, and *araD*—which encode together to produce the enzymes necessary for the metabolism of L-arabinose in *E. coli*. The expression of *araBAD* is controlled by the regulatory gene *araC*, which is responsive to the levels of L-arabinose sugar present in determining whether to act as an activator (in the presence of high amounts of L-arabinose) or as an inhibitor (in the presence of low amounts of L-arabinose). Such a controlled system regulates the gene expression of interest in the adjacent pBAD operon (**Fig. 2**) (Guzman et al, 1995). The araC protein coded for by the *araC* regulatory gene acts as a transcription factor (TF) controlling the expression of our gene of interest, which in this case is the LPS Radiation Prevention gene group, coding for the radiation-capturing vesicles identified in *Geobacter*. TFs can quickly respond to environmental changes in many organisms and in many circumstances. Thus, the precise control of the pBAD operon by the *araBAD* system makes it useful for the expression of environmentally active proteins to respond to radiation with comparatively less harmful products. In our case, LPS may have a myriad of negative effects in humans and other large mammals, including possible inflammatory responses, brain and nervous system damage (Ekland et al., 2006), and endothelial damage (Bannerman et al., 2003); nevertheless, the fundamental goal of preventing the uptick of longer lasting and more potentially damaging radiation is achieved as a result.

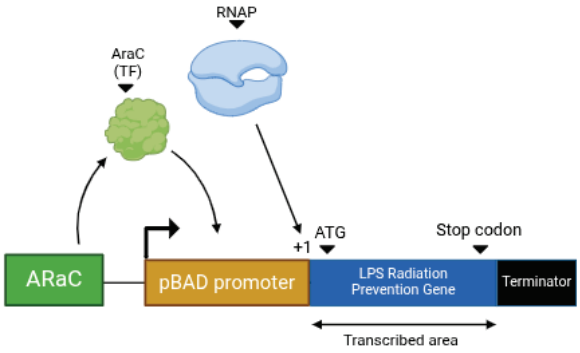

Figure 2. LPS expression gene circuit.

Nickel-nitrilotriacetic acid (Ni-NTA) is a type of resin often used to purify proteins. It is constructed when nitrilotriacetic acid (NTA) (**Fig. 3A**) binds to Ni^{2+} ions. It effectively purifies proteins tagged with a string of histidine residues (**Fig. 3A**). Essentially, Ni-NTA acts as an affinity chromatography system, a system often used to separate a complex mixture through differences in binding interactions between the individual compounds in the mixture. In this case, Ni-NTA binds to proteins engineered to have histidine tags, leaving behind other untagged proteins to be separated from the rest of the sample. Through this methodology, the DNA coding for production for the LPS-vesicle producing proteins may be further modified and purified to produce a selected mixture containing only

the proteins of interest (Spriestersbach, et al., 2015).

A Sterile Alpha Motif (SAM) is a small domain found in some proteins that allows proteins to effectively bind together, forming groups to carry out specific functions within the cells of the body. Each SAM is made of several alpha helices in the protein, a structure that allows it to bind to other SAM domains or to other proteins (**Fig. 3B**). The noted ability of an SAM to even bind to several non-SAM containing proteins and RNA makes its usage applicable to a wider variety of situations as well (Kim et al., 2003). For our research, an SAM is used to bind and embed our synthesized and purified proteins in the constructed vesicles needed to capture uranium (**Fig. 3C**). This embedding process allows for the regeneration of the structure and the continuous use of the product, thereby allowing for the cleanup of uranium-contaminated areas.

*Modification with the Nickel-NTA tag (**Fig. 3A**) for purification, and SAM (**Fig. 3B**) for ease of embedding (**Fig. 3C**) allows for the construction of a device that enables bioremediation using the characterized proteins.*

Parts level

This research project utilizes the pBAD promoter, crucial in regulating the expression of its gene, to facilitate the transcription of our genetic circuit. As mentioned in previous sections, the promoter is sensitive to the careful management of the *araC* regulatory gene, found further upstream on the DNA strand. When L-arabinose is present, it binds to *araC* and facilitates changes in the gene to produce the araC protein. When this protein is produced, it may bind to the pBAD promoter to recruit RNA polymerase (RNAP), initiating transcription of the lipopolysaccharide (LPS) genes. The LPS genes include a group of over twenty genes that, when expressed in our chassis's phenotype, codes for the crucial vesicles involved in the trapping and neutralization of uranium. A terminator signals the end of the LPS genes and initiates the breaking off of RNAP, halting transcription further down the DNA strand (**Fig. 2**).

Upstream to the coding sequence on the LPS genes typically lies a ribosome binding site (RBS), which facilitates the binding of the messenger RNA (mRNA) to the cell ribosomes in order to begin translation of the mRNA into proteins and eventually into bioremediating vesicles.

Safety

Our research involves the construction of LPS vesicles, through the transcription and translation of a group of LPS genes coding for such uranium-neutralizing proteins. While biological and synthetic mechanisms exist to remediate their effects as well (Huang and Zhou, 2023), LPS vesicles can be extremely toxic, capable of causing health complications and even death (Bell et al., 2019). Therefore, constructed bioremediation devices cannot be used in direct contact with organisms to help those already suffering from radiation poisoning. Instead, to ensure no harmful contact occurs, such devices may only be used in contained environments, such as certain areas of nuclear facilities, and to clean up traditional, lead-lined storage containers.

A principal concern of this research is the inability to test our system, both due to the toxicity and low public availability of

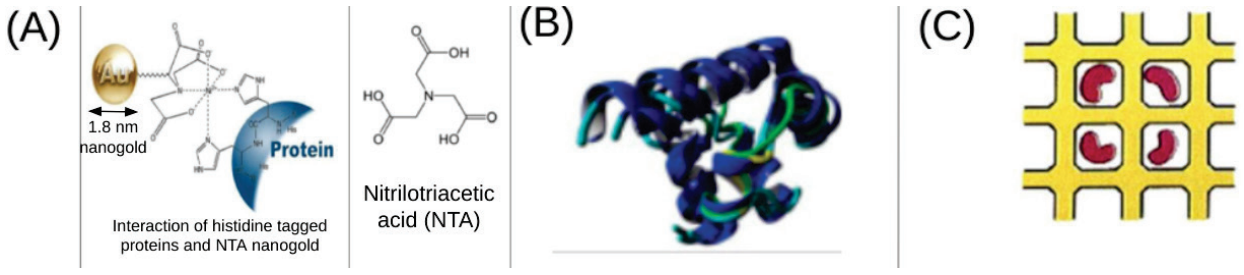

Figure 3. Purification of LPS-produced proteins, and protein embedding using an SAM domain.

radioactive materials. Uranium, as a toxic chemical, can cause a multitude of harmful bodily changes when ingested, such as adverse effects on the kidneys and other organs. Furthermore, the decay of uranium produces alpha particles, which, once in the body, can lead to other health complications such as cancer (CDC, 2024). Therefore, when handling uranium, investigators should follow established procedures set by Federal standards to ensure proper handling (United States Department of Energy, 2024).

Discussions

This work presents a design for creating an innovative system for radiation bioremediation using synthetic biology. The focus of this study is on developing a structured, modular approach that can be applied to future environmental remediation challenges. Specific biologically sourced proteins exhibit the ability to absorb or dissipate radiation, which makes them promising candidates for integration into protective and remediating structures (Homaei et al., 2013). By embedding these proteins within durable matrices, like polymers, we could develop adaptive materials with applications ranging from environmental clean-up to nuclear safety and potentially medical imaging.

This design proposes a novel approach to radiation bioremediation by producing bioremediating vesicles for uranium decontamination. Building upon prior work showing that *Geobacter* produces LPS vesicles capable of sequestering uranium to protect cellular contents (Clark et al., 2021), this study modified the genetic circuit in *E. coli* with the *Geobacter*-derived genes to accomplish this pathway. Embedding this enzyme within a SAM domain increases its structural stability, ensuring consistent functionality in bioremediation processes.

The genetic circuit provides a platform that could be extended to other remediation systems as well. Another example of this pathway would involve the potent problem of plastic pollutants, which have become a significant problem due to overproduction (MacLeod et al., 2021). Using an enzyme, serine hydrolase, which dissolves plastics, sourced from select worm species (Xu, 2020), the same means of enzyme production and embedding could be accomplished. We can further generalize this platform by incorporating other enzymes and bioremediating proteins for different target pollutants. The modular nature of the genetic circuit and SAM-embedding strategy allows for flexibility in design and the potential to address a wide range of environmental contaminants. This extension could involve substituting different protein domains or modifying the vesicle structure to tailor the system to specific use cases.

The primary application of this approach is environmental, focusing on cleaning up uranium deposits and other radioactive contaminants. By leveraging the SAM-embedding strategy, this methodology presents a structured and efficient pathway for addressing radioactive waste, making bioremediation more precise and adaptable. Beyond radiation remediation, this concept could extend to tackling waste management. This could contribute to a cleaner, more efficient industrial disposal process. With proper application, SAM-embedded proteins could facilitate controlled degradation mechanisms for pollutants, improving waste breakdown strategies.

Despite its promise, the current work is a conceptual framework that requires further development. The system has not yet been tested; several constraints must be addressed before practical implementation. Stability, effectiveness, and durability over the long term must be carefully evaluated to ensure that proteins maintain their functionality under real-world conditions. Additional focus must be placed on the safe embedding of the SAM-based system within designed materials and providing components for vesicle construction to ensure it remains effective and regenerable across multiple uses. These steps are necessary to confirm that the designed structure yields a viable product suitable for bioremediation.

Next steps

Future work will focus on validating and optimizing the SAM-embedded protein system for bioremediation applications.

Immediate next steps include empirically testing the pBAD operon transformation of genes encoding vesicle-producing proteins. Once protein production and purification are established, stability, effectiveness, and long-term durability of the proteins under simulated environmental conditions will be examined. Assessments will determine whether the embedded proteins maintain functionality when exposed to varying stresses, such as temperature shifts and chemicals designed to remove LPS contaminants to fully cleanse the proposed uranium container. Additional work could also expand the system's capabilities by exploring the integration of different bioremediating proteins into the genetic circuit. These activities will help refine the robustness and adaptability of the platform, moving towards practical environmental applications such as waste clean-up and broader pollutant management.

Author contributions

A. F. wrote the System, Device, Parts, and Safety sections; E. G. wrote the Discussion section; and H. S. composed the Abstract and Background sections, and created the video. A. F. and H. S. edited the manuscript. A. F. designed the figures based on H. S.'s design. While H. S. led the group, all members collaborated in developing the project design, attending meetings, and contributing to the final manuscript for publication.

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