Polymeric Synthetic Oxygen Carriers for Transfusion at the Location of Injury

An Analysis of the Ethical and Sociotechnical Context of Biotechnology in the Military-Industrial Complex

A Thesis Prospectus

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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

In the wake of World War II, of which he was a military hero and key figure, and following a greatly unpopular Truman presidency, General Dwight Eisenhower easily won the presidency in 1952 (McAuliffe, 1981; McInerny, 1981). In strong contrast (or perhaps strong agreement) with his decorated military career, Eisenhower's term in office was defined by peace and stability (Kinnard, 1977). In his 1961 farewell address, while also acknowledging the necessity of it, Eisenhower famously warned of the dangers of the "permanent armaments industry of vast proportions" that arose after WWII, in the looming shadow of the Cold War (Eisenhower, 1961). He coined this phenomenon the "military-industrial complex." Additionally, Eisenhower acknowledged and warned of the expanding intersection between the federal government and scientific research in the midst of the current "technological revolution" of the last few decades (Eisenhower, 1961). Nearly two decades later, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research published the Belmont Report. Following the establishment of the Nuremberg Code and multiple cases of bioethical malpractice in the United States (Beecher, 1966; Brandt, 1978; International Military Tribunal, 1949), it had become clear that an updated legal framework for bioethics was necessary (Friesen et al., 2017). The authors of the Belmont Report outlined three basic principles for ethical research: respect for persons, beneficence, and justice. While these principles have become canonical guidelines for human biomedical research in the United States, critics of the Belmont Report claim that the report is limited in scope and may no longer be applicable (Friesen et al., 2017; Nagai et al., 2022; Sidiqui and Sharp, 2021). Strikingly, the increasing conflation of biomedical research with the military industrial complex has led to increasing focus on the development and analysis of military medical ethics since the turn of the century (Bailey et al., 2022; Gross, 2013). Biomedical research and the subsequent creation of biomedical technologies for military applications is a complex and increasingly relevant domain of scientific research, with many open ethical and sociotechnical questions.

Technical research project

During excessive blood loss, hemorrhagic shock can occur if tissues do not receive adequate amounts of oxygen (Cannon, 2018). As a result, intracellular lactic acid and oxygen radical concentrations increase, leading to widespread inflammation and eventually cell death across the body (Cannon, 2018). The leading cause of death in Americans aged 46 and under is hemorrhage due to physical trauma; as such, research into methods of rapidly controlling hemorrhagic shock is particularly important, especially for military healthcare (Cap et al., 2018). Whole blood transfusion can be an effective hemorrhage treatment, but blood has a relatively short shelf-life of 35 days and supply can often fall below demand due to sourcing difficulties (Huish et al., 2019). Additionally, the red blood cells in the donor blood must match the patient's anti-A/anti-B antibodies to prevent an adverse immune response (Chambers et al., 2019). In order to combat these challenges, the goal of this project is to develop a safe, effective, shelf-stable alternative for blood that has a substantial oxygen delivery capacity and increases patient survival. Perfluorocarbons are small molecules with high oxygen dissolving capabilities, but are not stable during lyophilization and while inert, may have some adverse effects in vivo (Grandjean and Clapp, 2014; Lee, 2018). Thus, polymer nanoparticles will be employed to encapsulate the perfluorocarbons and ensure their stability in both a dried state and in the body. The polymer nanoparticles will be synthesized using emulsification-solvent evaporation and lyophilized into a dry powder, to be reconstituted in sterile water before administration to the patient at the location of trauma.

Firstly, this project aims to design and test a nanoparticle capable of significantly increasing the dissolved oxygen capacity. Multiple iterations of nanoparticles, using varying polymers and perfluorocarbons, will be tested for oxygen carrying abilities. Parameters regarding the synthesis of the nanoparticles, such as sonication time/energy and organic solvent fraction, will be tested as well. Using the Foxy FOSPOR-R O2 sensor (Ocean Insights) to measure fluorophore quenching by dissolved oxygen, we will determine the oxygen capacity of the different formulations and synthesis parameters under both oxygenated and ambient conditions.

Secondly, this project aims to characterize the stability of the nanoparticles after lyophilization and resuspension. To efficiently store and transport the nanoparticles, we plan to lyophilize the nanoparticles to be reconstituted at the point of care. Thus, we will test the yield of nanoparticles after lyophilization and the shelf life of nanoparticles in a dry powder form. We will also use dynamic light scattering (DLS) to characterize the size of the nanoparticles before and after lyophilization to determine if any major changes in morphology occurred during the drying process.

Thirdly, the project will use the nanoparticles to demonstrate a significant improvement in survival times in a murine hemorrhagic shock model. For *in vivo* testing, our collaborator, Dr. Mangino at Virginia Commonwealth University, will use a model by which hemorrhage will be induced in the mouse via controlled arterial bleeding. Hemorrhagic shock will be quantified by plasma lactate concentration. After reaching a sufficient plasma lactate concentration, a solution containing the sample will be infused into circulation over periods of time ranging from 1 to 15 minutes. Data gathered by Dr. Mangino will be important for iteration of the nanoparticle formulation to ensure no adverse interactions occur in the murine models while validating that significantly increasing the dissolved oxygen capacity of the blood corresponds to an increase in mean survival time.

Creating a synthetic oxygen carrier to be used in a blood substitute represents a significant improvement over the current standard treatment for hemorrhage. Given the severe mortality rates of hemorrhagic shock due to physical trauma, this work is of vital importance in both civilian and military settings. The rapid deployment of hemorrhage control shifts the timeline of treatment; prehospital whole blood transfusion reduces mortality, yet this option is not always available to paramedics or emergency medical technicians (Braverman et al., 2021; Kuaver et al., 2006). The polymer nanoparticles in a synthetic blood substitute will achieve similar reductions in mortality without the significant complications in sourcing, blood type matching, storage, and transportation that are associated with using whole blood.

STS research project

The 2023 North Atlantic Treaty Organization (NATO) Science and Technology Trends Report asserts that, in relation to potential implications for NATO operations and capabilities, technology will be increasingly sourced from the commercial sector (i.e., dual-use technologies) (NATO, 2023). The report also labels biotechnology and technology related to human enhancement as emergent technologies:

> "Emerging technologies represent *creative destruction*, as originally described by the economist J. Schumpeter, and are characterised by the potential of shifting paradigms. The term emerging indicates novel scientific discoveries in the early stages of development, technologies that embody an uncertain and risky nature, and insecurity of their potential impact on military capability." (p. 57)

Modern biologically-derived or centered technologies and innovations, including those that improve the body and biological functions beyond baseline performance (human enhancement), are expected to greatly displace outdated biotechnologies in the next two decades (hence the term "creative destruction"). Citing the impacts of a post-information revolution world, the novelty of many areas of biotechnological research, and "physical, biological, ethical, legal, and moral constraints," NATO highlights the unique complications associated with military biomedical research (p. 64). However, nations with access to superior biotechnologies are poised to establish (or further maintain) military dominance (Malet, 2014). QuikClot, a novel hemostatic agent adopted by the U.S. military for use in Iraq, proved to be highly effective in reducing American combat fatalities over previous conflicts, demonstrating the tangible benefits of investment in biomedical technologies (Malet, 2014; Rhee et al., 2008; Welch et al., 2020). With a yearly budget of over 4 billion dollars, the Pentagon's Defense Advanced Research Projects Agency focuses on funding novel research with military applications (Reardon, 2015). Especially in the last two decades, DARPA has funded research in health and survivability of soldiers, human enhancement, food, infectious disease, and novel bioweaponry (Bickford, 2019; Malet, 2014; Rasmussen et al., 2020). In comparison to other scientific epistemologies, that of engineering is exceptionally intertwined with military research, as both engineering research and military research are typically considered applied or need-driven research (as opposed to basic research) (Melson, 2003; Nieusma and Blue, 2012; Rasmussen et al., 2020).

Thus, biomedical engineers find themselves squarely in the center of one of this century's most substantial ethical and sociotechnical affairs. This work aims to study how Biomedical Engineering, as a field primarily focused on medical advancements, differs from other engineering disciplines in technology and ethics in the context of the military industrial complex.

Due to the fast-paced yet novel nature of biotechnology research in the military and the complications of human health research, biomedical engineering holds a rather unique position in the military industrial complex compared to other engineering disciplines. The creation of biomedical technologies by biomedical engineers for military use is certainly entangled with the broader social, economic, political, and ethical context of the military industrial complex as a whole. With that in mind, this study will analyze where biomedical engineering breaks free from that context in ways that other engineering disciplines do not, as well as the distinctive social, economic, political, and ethical problems that biomedical engineering introduces to the equation.

To analyze the greater implications of the development of any technology, one must first analyze the technology itself. Many biomedical technologies are dual-use, meaning they have both civilian and military applications. For example, the same autoinjector provided to soldiers to administer nerve agent antidotes forms the basis of the EpiPen (Newark, 2007; Sherkow and Zettler, 2021). Maintaining a secure tether to civilian industry may help promote innovation and economic growth (Gansler, 1988), but the lines between civilian and military industry are also becoming increasingly blurred (Mahfoud et al. 2018), which has lengthy implications regarding the creation of such technologies, especially technologies with potentially malevolent uses. Dual-use research is therefore a topic of concern for researchers in the biomedical sciences who may have ethical objections to the advancement of those malevolent technologies (Ashcheulova and Ambrosova, 2019; Oltmann, 2014; Resnik et al., 2011). This study will assess the extent to which biomedical engineering research is dual-use, as well as how dual-use biomedical technologies differ from dual-use technologies of other engineering disciplines.

Beyond any given technology, the ethics and underlying politics of the creation and use of that technology must be properly considered and studied (Winner, 1980). Many researchers have either studied or developed a framework for military bioethics (Bailey et al., 2022; Gross, 2013; Have, 2023; Mehlman and Corley, 2014), yet the rapid pace of development of novel biotechnologies makes such studies difficult. Additionally, a service member is not representative of an average patient; informed consent and refusal may not work in a scenario where the patient must follow orders (Benjamin, 2016), such as when the Department of Defense implemented a mandatory anthrax vaccine despite concerns from service members (Katz, 2001; Pica-Branco and Hudak, 2008). Furthermore, public policy is an even slower endeavor, meaning laws and regulations surrounding biotechnology are often severely outdated. This study will provide an analysis of the specific ways in which biomedical engineering and military bioethics influence one another, and how current understandings of military bioethics and the surrounding policies may require significant overhauls in approach to accommodate the "biotech revolution in military affairs" we find ourselves entrenched in (Malet, 2014, p. 320).

Conclusion

In the decades following President Eisenhower's farewell address and the publication of the Belmont Report, the need for better understanding of the sociotechnical implication of biomedical research in the military industrial complex has become increasingly vital. In the face of the incredible dynamicity characteristic of both biomedical sciences and military affairs, we cannot rely on a patchwork comprehension of bioethics, the military industrial complex, and engineering. Instead, a perspective that is able to successfully synthesize those intersecting areas into a single analysis of biomedical engineering in the military industrial complex will serve to better prepare us for the unforseeable challenges that will surely arise as biomedical technology continues to improve in such a revolutionary manner.

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