Thesis Project Portfolio

Design of a Pembrolizumab Manufacturing Plant Utilizing a Perfusion Bioreactor and Precipitation Chromatography

(Technical Report)

Key Causes of Monoclonal Antibody Access Limitations

(STS Research Paper)

An Undergraduate Thesis

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Sociotechnical Synthesis

Monoclonal antibodies are used to treat many diseases including cancer, asthma, rheumatoid arthritis, and multiple sclerosis. The first therapeutic monoclonal antibody product, muromonab-CD3 (Orthochlone OKT3), was produced in 1986 and was used to prevent kidney transplant rejection. In 2015, sales of monoclonal antibodies were estimated to increase by $20 billion per year with over 30 monoclonal antibodies approved by the FDA for human treatment. During this time, sources estimated at least 70 monoclonal antibody products to be developed by 2020 with world-wide sales exceeding $125 billion. However, in 2019, sales of monoclonal antibodies were much greater than estimated, approximately $163 billion, making up 60 percent of the total $230 billion biopharmaceutical revenue; over 139 monoclonal antibody products were produced by 2020.

This data shows the rapid advancement in monoclonal antibody production over the past 30 years and its dominance in the pharmaceutical industry today. My technical project describes the design of a manufacturing plant for a particular monoclonal antibody, pembrolizumab, also known as Keytruda, to assist with its growing demand. My team and I utilize process intensification methods to reduce the cost and energy required for pembrolizumab production. In relation to my STS project, my technical project offers solutions to improve access to monoclonal antibodies; a more efficient production method of pembrolizumab will increase the affordability for patients, increasing global access. My STS research question is: “What are the leading issues that prevent access to monoclonal antibodies?” I analyze the social and technological factors in monoclonal antibody access and its relation to society using the actor-network theory.

Pembrolizumab is a monoclonal antibody manufactured by Merck & Co that can be used to treat various conditions such as advanced melanoma, lung, bladder, stomach, and colon

cancers. Pembrolizumab usage by colon cancer patients decreased the risk of death by 38% as opposed to chemotherapy treatment alone. In 2021, pembrolizumab was the 4th highest selling pharmaceutical on the market. Pembrolizumab offers oncological benefits as opposed to chemotherapy treatment, such as increased efficacy and reduced negative side effects. However, monoclonal antibodies including pembrolizumab are insufficiently accessible in low to middle income countries (LMICs) due to differences in global regulations, a lack of government and manufacturer awareness towards registering monoclonal antibodies, and a lack of healthcare infrastructure required for monoclonal antibody production. The high cost of monoclonal antibodies leads to these barriers in both LMICs and underprivileged regions of high-income countries. With Merck's pembrolizumab patent due to expire in 2028, it is an opportune time to develop a cheaper alternative production process to the current one.

The technical project contains a detailed design of a more efficient pembrolizumab manufacturing plant utilizing continuous process conditions. Operating with perfusion or continuous bioreactors instead of the traditional batch bioreactors allows for increased product quality and productivity. Currently, the most expensive part of the monoclonal antibody production process are chromatography methods used to separate and purify the final protein product; many chromatography methods have been explored to optimize chromatography cost, including continuous antibody precipitation. Therefore, our design includes protein expression from Chinese Hamster Ovary (CHO) cells utilizing fed-batch scale up followed by a perfusion bioreactor. This will be followed by precipitation chromatography supplemented by other continuous filtration methods for product purification. Our design process includes formulation requirements and final packaging for patient delivery.

A study in Thailand found that lower respiratory infections were the leading cause of hospitalization with over 1.4 million children hospitalized between 2015 and 2019, most between the ages of 1 and 5; approximately 10% of these hospitalizations were the result of a respiratory syncytial virus (RSV). RSV is a leading cause of acute lower respiratory tract infections in infants and inhabitants of low- and middle-income countries (LMICs). Currently, there are no vaccines available for treatment of RSV in infants, but there are RSV monoclonal antibodies available. However, an approved RSV monoclonal antibody, palivizumab, is expensive and requires monthly administration which prevents access to LMICs. As shown, low affordability is a leading cause of limited access to monoclonal antibodies. In my STS research paper, I describe alternative production methods that have been explored by experts to reduce the costs of these monoclonal antibodies and make them more affordable. I use history and literature reviews as my STS methods of focus in which I explore the history of process development, treatment conditions, and shipping/storage limitations. I use case studies related to COVID-19, Henrietta Lacks, and government authorizations to describe various ethical limitations.