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

An Intersectional Causal Analysis of Racial Disparities in Inflammatory Disease Prevalence of Cancer Alley, Louisiana

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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

Since the first was commercialized in 1986, monoclonal antibodies (mAbs) have been on the rise as highly effective and target-specific immunotherapy alternatives to traditional oncological treatments, such as chemotherapy (Lu et al., 2020). MAbs comprised nearly 50% of all therapeutic protein sales as of 2010 and have grown further in demand to $168.70 billion in sales in 2021 (Lu et al., 2020**;** The Business Research Company, 2022). Unfortunately, the profitability of these life-saving therapeutics comes at the expense of their accessibility to economically disadvantaged communities (Wellcome, 2020). This effect is at least partially attributable to the focus of pharmaceutical companies on the robustness of their processes in the FDA approval process over resource efficiency and cost reduction (Wang, 2021).

Medical inequity, particularly regarding cancer treatment, stems from a multitude of nuanced social factors as well. For example, St. John the Baptist Parish is part of the corridor of counties in Louisiana appropriately named 'Cancer Alley' that is home to nearly 25% of the total petrochemical production in the US (Mizutani, 2019). The first to settle in the area was the DuPont chloroprene plant located in St. John the Baptist Parish, LA – a historically Black county since the formal end of slavery in 1865 (Mizutani, 2019). The region surrounding the plant now bears a cancer rate over 1.5 times the average within the continental US, where Black communities disproportionately face the brunt of the inflammatory disease (James et al., 2012; Mizutani, 2019). Past research has individually addressed the roles of environmental injustice, medical discrimination, and historic legislative discrimination in this disparity; however, these linear perspectives diminish the complexity in which the sources of racial health disparities interweave with and strengthen one another (Terrell & St. Julien, 2022).

To enable equitable access and execution of healthcare, the network of structural racism underlying discriminatory policies and practices must be uprooted, and the pharmaceutical industry must aspire to a new cost-efficient standard for high-efficacy drugs, such as mAbs. My group and I intend to divert the complacency towards mAb production by proposing a continuous, intensified approach to production of the cancer therapeutic pembrolizumab. I then aim to analyze the disparities in inflammatory diseases, including cancer and Covid-19, in the region as a collective product of intersecting societal factors, focusing on the DuPont plant's inception and impacts in St. John the Baptist Parish as a case study using the lenses of Actor-Network Theory (ANT) and Technological Momentum.

Technical Project

Antibodies help the body fight against infections and diseases; monoclonal antibodies are single antibody clones that can be artificially replicated for large scale production and treatment for specific diseases (Carter, 2021; Daintith, 2010). They can be used for cancer treatment by specifically targeting cancer cells to destroy them, block cells from multiplying, or to deliver other treatments, such as chemotherapy (Cleveland Clinic, 2022). As of 2021, cancer is one of the leading causes of death in the United States (CDC, 2021). Pembrolizumab (Keytruda), is a monoclonal antibody manufactured by Merck & Co as a treatment for advanced melanoma, lung, bladder, stomach and colon cancers (Merck & Co., 2019). It averaged a 38% reduction in risk of death due to cancer versus chemotherapy, and it drew 17.2 billion dollars in sales in 2021 alone, the fourth highest sales of all pharmaceuticals on the market (Dunleavy, 2022; Merck, 2020).

While pembrolizumab offers oncological benefits over chemotherapy, such as increased efficacy and reduced negative side effects, mAbs 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 mAbs, and a lack of healthcare infrastructure required for mAb production (Reck et al., 2016; Wellcome, 2020). The high cost of mAbs leads to these barriers in both LMICs and underprivileged regions of high-income countries (Wellcome, 2020).

In June 2020, the FDA approved pembrolizumab as the first-line treatment for people with two different types of colorectal cancer. This is the first immunotherapy approved as a first-line treatment in the US, which would be administered to people without chemotherapy. With the pembrolizumab patent due to expire in 2028, it is an opportune time to develop a cheaper alternative process to the current one (Hagen, 2021).

We plan to design a more efficient pembrolizumab manufacturing plant. Operating with perfusion or continuous bioreactors instead of batch bioreactors allows for increased product quality and productivity (Yang et al., 2019). Currently, the most expensive part of the process is the chromatography used to separate and purify the final protein product; many chromatography methods have been explored to optimize chromatography cost, including continuous antibody precipitation (Burgstaller et al., 2019). We will utilize Chinese Hamster Ovary (CHO) cells to express pembrolizumab in a perfusion reactor and precipitation chromatography supplemented by other continuous filtration methods for product purification.

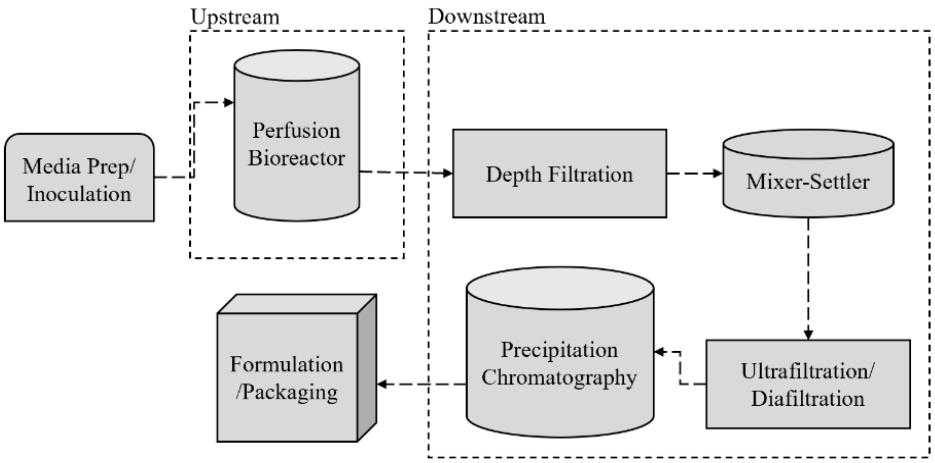

Figure 1. General Process Flow Diagram for Continuous mAb production (Kornecki et al., 2019).

The general mAb production process can be described by several stages of processing: fermentation, purification, formulation, and fill/finish. Fermentation uses bioreactors to grow CHO cells to produce the active ingredient. Purification processes use filtration methods such as chromatography columns and membrane-based separations to isolate the active ingredient from impurities after fermentation. Formulation adds excipients to aid in transport, patient delivery, and stability of the drug substance. Following filtration, to ensure patient safety and drug purity, the drug product is filled into a vial or syringe and packaged as a final product. We will design these elements and the utilities and disposal systems needed for a pharmaceutical manufacturing site (Kelley, 2009).

We will design the facility to produce 1400 kg of pembrolizumab annually to provide approximately 7 million doses, accounting for 20% of the 2024 projected demand, as users of pembrolizumab are projected to double (Liu, 2022). This growth in demand is driven by pembrolizumab's continued market lead in treating lung, gastric, and kidney cancers with the potential for use in early-stage treatment around surgery (Dunleavy, 2022).

Matlab and Aspen Plus V11 will be used as a process simulation tool to design our equipment and to obtain appropriate material and energy balances. This design process will take place over two semesters in a team of five people as a part of CHE 4474 and CHE 4476. We plan to work fluidly as a team on all parts: upstream, downstream, formulation, WFI production, and packaging. We will meet weekly to analyze progress.

STS Project

In 1969, the residents of St. John the Baptist Parish, Louisiana had their first encounter with the petrochemical giant, DuPont. The 55.7% African American county was considered a prime location for a new chloroprene production plant due to its proximity to the Mississippi River and its low property values (Hersher, 2018; Louisiana Department of Health, 2021). Chloroprene is a key component in the production of the synthetic rubber, neoprene – a flexible and waterproof material used in boots, phone cases, and an abundance of other consumer products (Hersher, 2018). 41 years after DuPont launched its chloroprene facility, the EPA deemed the chemical "a likely human carcinogen" (Hersher, 2018) and in February of 2018, "multiple air monitors showed concentrations more than 150 times higher than the IRIS value" (Hersher, 2018) of 0.2 in St. John the Baptist Parish. Evidence suggests that its presence in the locality is continuing to grow. The communities of Cancer Alley have historically endured a cancer rate that is 700 times the national average and now face disparately high rates of severe Covid-19 symptoms and Covid-19-based deaths, where the majority of cases are borne by predominantly Black communities (Hersher, 2018; Louisiana Department of Health, 2021; Mizutani, 2019).

Rather than framing the overwhelming rates of Covid-19 infections and inflammatory diseases in St. John the Baptist Parish as purely environmental injustice matters or purely

medical discrimination, I will argue that the stresses of racial capitalism, which is defined as the neglect of impoverished communities of color based on their race and economically disposable status, predisposes the immune systems of Black St. John the Baptist Parish residents to a weakened response against Covid-19 on a biological level. The amplified attack Covid-19 has imparted thus far on St. John the Baptist Parish is a reflection of structural racism that has origins at least as early as the period of slavery in the US. Racial capitalism then drives the environmental injustice enacted by petrochemical corporations like DuPont, which exacerbates Covid-19 symptoms (Mizutani, 2019). Neglecting this comprehensive perspective fails to fully challenge the underlying system of factors enabling health disparities faced by Black people in Cancer Alley and limits scientists' and medical practitioners' capacities to understand the health issues in Black people as a non-linear compounding record of historic, environmental, and medical discrimination in the US.

I will employ both Actor-Network Theory (ANT) and Technological Momentum to illuminate the ways in which the DuPont chloroprene plant and surrounding chemical plants of Cancer Alley have propagated this network of discriminatory actors into a racial disparity of Covid-19 and inflammatory disease impacts in the region. ANT will contribute a view of both human and non-human sources of influence as active contributors to the state of the technology within the context of society, which will aid in emphasizing the diverse set of factors causing systematic health inequity (Latour, 1992). These actors make up a network, in this case for chloroprene production by DuPont in Cancer Alley, which is brought together by network builders - the plant engineers or designers.

Technological Momentum pushes back against the extremes of Social Constructionism of Technology and Technological Determinism by asserting that a technology initially conforms to

the society in which it's made, but as it accrues physical land, infrastructure, stakeholders, employees, and more for its development, it increasingly controls society (Hughes, 2000). Technological Momentum will highlight how a chemical plant can take the social values of its surroundings at its origins and propel them into a much greater network of systemic discrimination as it accumulates political and economic gravity over time (Alexander, 2010).

To undertake this analysis, I will utilize data from the Louisiana Department of Health, which contains county-by-county rates of cancer, Covid-19 infections, and vaccinations. I will also employ data from studies elucidating the historic and contemporary employment rates of people of color in the chemical plants in Cancer Alley, population rates, air pollution rates, and rates of poverty in the region.

Conclusion

This proposal calls for technical and social solutions to the racial and socioeconomic disparity in cancer prevalence and treatment. My teammates and I will aim to reconcile these disparities through cost-saving process intensification of the bioreactor, filtration, and chromatography skids within pembrolizumab production. Transitioning these steps into a continuous process from batch will be the first push in redirecting the momentum of mAb production as a whole from a focus on robustness to emphasizing accessibility. Individually assessing the progression of the DuPont chemical plant in Cancer Alley from its inception to its finalized state through the lenses of technological momentum and actor-network theory will support my team's goal of designing a sustainable and ethical mAb plant. This will elucidate the complex network of government actions, economic forces, and historic systems that influence plant engineering decisions and enable us to clearly anticipate the long-term impact of our design choices.

Word Count: 1850

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