Undergraduate Thesis Prospectus

Design of a Monoclonal Antibody Manufacturing Genentech Facility in the United States to Continuously Produce Herceptin, a HER2+ Breast Cancer Treatment

(technical research project in Chemical Engineering)

How Teachers Accommodate Neurodiverse Students in U.S. Schools

(sociotechnical research project)

by

Joseph Letteri

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technical project collaborators:

Geoffrey Burns
Molly Caveney
David Lee
Morgan Pellegrin

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.
Joseph Letteri

Technical advisor: Eric W. Anderson, Department of Chemical Engineering

STS advisor: Peter Norton, Department of Engineering and Society

General Research Problem

How may inequities of access be diminished?

In healthy societies, social services such as healthcare and schooling are both effective and accessible. Institutions within such a society are guided by norms that are consistent with these values. Organizations owe their successes in part to their institutional norms. Such norms may have contributed to the success of researchers at UCLA Cancer Center and Genentech Herceptin, who inadvertently developed a monoclonal antibody useful in treating breast cancer, during a collective effort to develop a cure for cancer by altering oncogene expression. (Mukherjee, 2010, 463-69) In 2020 about 1.8 million people in the U.S. will be diagnosed with cancer; breast cancer will account for about 15 percent of such cases (NCI, 2020). By 2016 about 2.3 million eligible patients had been treated with Herceptin. Herceptin is expensive; the overall high out-of-pocket price of cancer treatment is about $30,000 (Kantarjian, 2014). By designing a process to continuously produce Herceptin at a higher rate, we hope to cut costs and thereby improve access.

Problems of access also afflict public education in the United States. TAccording to Forshay (199, p. 277), a successful education system ultimately guides students toward a realization of their human potentiality. Socially constructed limitations, such as “disability,” may obstruct this educational path. Less than half (46 percent) of U.S. working-age adults with learning disabilities are employed, compared to 71 percent of adults without learning disabilities (NCLD, 2019). When school systems fail segments of the population they serve, such as students who learn differently, they contribute to burdens on other social institutions, such as healthcare, incarceration, and social services.

Design of a Monoclonal Antibody Manufacturing Genentech Facility in the United States to Continuously Produce Herceptin, a HER2+ Breast Cancer Treatment

How can the production rate of Herceptin be increased to expand its access to patients?

Cancer is the second leading cause of death in the U.S., and the number of cases is only increasing due to a growing and aging population. With this rise comes an increase in the need for pharmaceutical technology and therapeutics (*CDC - Expected New Cancer Cases and Deaths in 2020*, 2019). Monoclonal antibodies (mAbs) are important therapeutics that are among the best selling drugs. They treat a wide array of deadly diseases from cancers to autoimmune disorders. Antibodies present an acute specificity for their target antigens, and they have the potential to recognize and bind to a small region of the antigen. Binding to the HER2 antigens causes cell growth arrest and allows rapid recognition by specialized components of the immune system. The global mAb market is projected to generate $300 million in revenue by 2025 (Lu et al., 2020).

In 2019, Herceptin, a mAb, was the 6th highest selling drug in the U.S. with approximately $7 billion in sales (Pharmaceutical Technology*, 2019*). Herceptin is the brand name for trastuzumab, which is a mAb used to treat HER2+ cancer. It targets the HER2+ receptor to fight tumor cell growth for breast and stomach cancer. Within the immune system, trastuzumab acts via interactions with effector cells which are relatively short-lived activated cells that defend the body in an immune response (Chartrain & Chu, 2008). The mAb forms a complex with a membrane protein, which prompts various mechanisms that may lead to the destruction of the targeted cell via cell lysis or triggering apoptosis, a pre-programmed self-destruction pathway.

Genentech developed and manufactures Herceptin. It was originally approved to treat metastatic breast cancer in 1998, and it was then approved to treat early breast cancer in 2006

and stomach cancer in 2010 (Genentech, 2019). Potential future approvals for other diseases or patient segments will increase the demand for Herceptin and require Genentech to increase its manufacturing capabilities. Genentech's U.S. patent for Herceptin expired June 2019. This allows competing biopharmaceutical companies to produce Herceptin biosimilars and compete for market share. Amgen, Pfizer, Merck and Samsung Bioepis, Celltrion and Teva, and Mylan and Biocon have approved trastuzumab drugs (RAPS, 2019). Genentech must improve its manufacturing process to effectively compete with the emerging biosimilars.

The proposed project seeks to design a manufacturing facility in the United States to continuously produce Herceptin. The framing of the project will be from the perspective of Genentech to improve their manufacturing process internally. Genentech has an established main cell bank engineered to successfully express trastuzumab and an optimized culture media recipe. The scope of the project will include process design of the large scale upstream and downstream bioprocessing of Herceptin. The upstream process consists of CHO cell culture and synthesis of the target protein, and the downstream process consists of multiple methods of purification and formulation of the protein into a drug substance or product. Unlike previous production designs that have utilized batch or fed-batch bioreactors, the proposed project will adopt perfusion as a technique for continuous upstream cell culturing. The downstream bioprocess design will use various continuous centrifugation, homogenization, and chromatography technologies. A schematic overview of the upstream and downstream processes for mAb production is shown in Figure 1. Our proposed design will not use fed-batch reactors like Figure 1, but the depicted flowchart is a useful schematic overview for the production process.

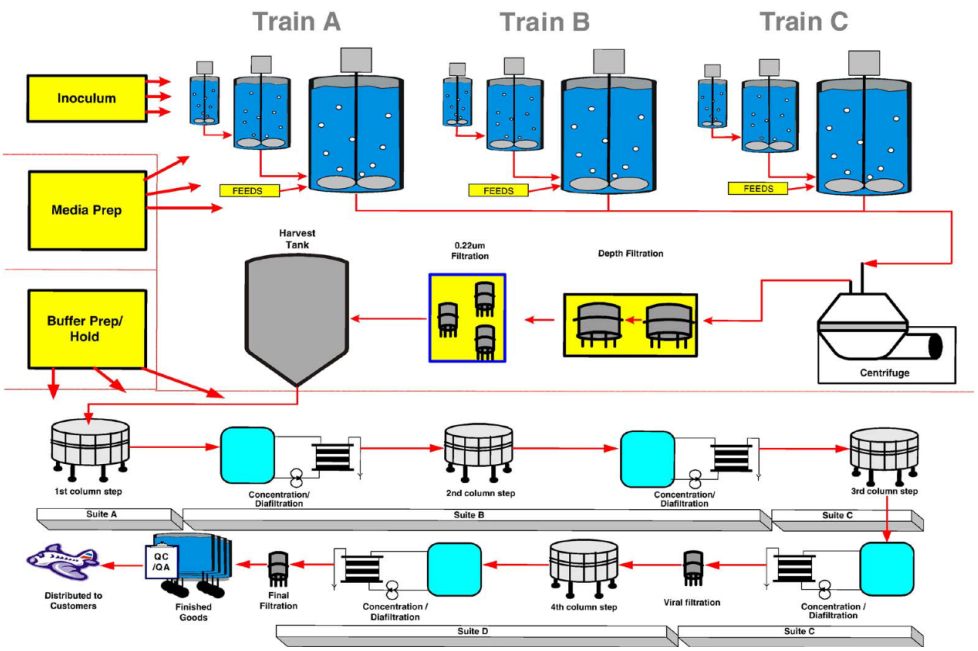

Figure 1: (Birch, J. R., & Racher, A. J. (2006). Antibody production. *Advanced Drug Delivery Reviews*. *58*(5–6), 671–685. https://doi.org/10.1016/j.addr.2005.12.006)

Bioreactor design will be studied extensively because bioreactor controls are one of the most important and well-defined areas of mammalian cell culture, encompassing pH, temperature, O_2, CO_2, and agitation controls (Chartrain & Chu, 2008). Although a batch process is simple and easy to implement, it is commonly difficult to provide sufficient nutrients in the medium without generating disproportional levels of waste product or obtaining toxic levels of some components. The purpose of incorporating perfusion bioreactors into the upstream process design is to maintain cell growth and minimize the time required to shut down and start up the bioreactor for cleaning and maintenance. As opposed to batch or semi-batch fermentation, perfusion bioreactors maintain high concentrations of viable cells. This is done by continuously introducing fresh media and nutrients while continuously removing spent media, dead cells, and product. Birch and Racher (2006) showed that perfusion bioreactors can create a throughput of antibody approximately 10 times higher than that of a batch or fed-batch system. Perfusion bioreactors lead to relatively large and consistent product generation, as shown in Figure 2.

Figure 2 shows that the viable cell concentration stays high in the perfusion reactor while it drops in the batch and fed-batch reactors. The time scale is 2-3 months of product generation for perfusion compared to 4-7 days for batch and 12-30 days for fed-batch. This is a significant difference in the amount of product being produced, which has serious economic implications. Other factors that contribute heavily to the pricing of therapeutic mAbs are costs associated with development time, cultivation medium, purification resins, and general facilities. Our designed plant will consider these factors.

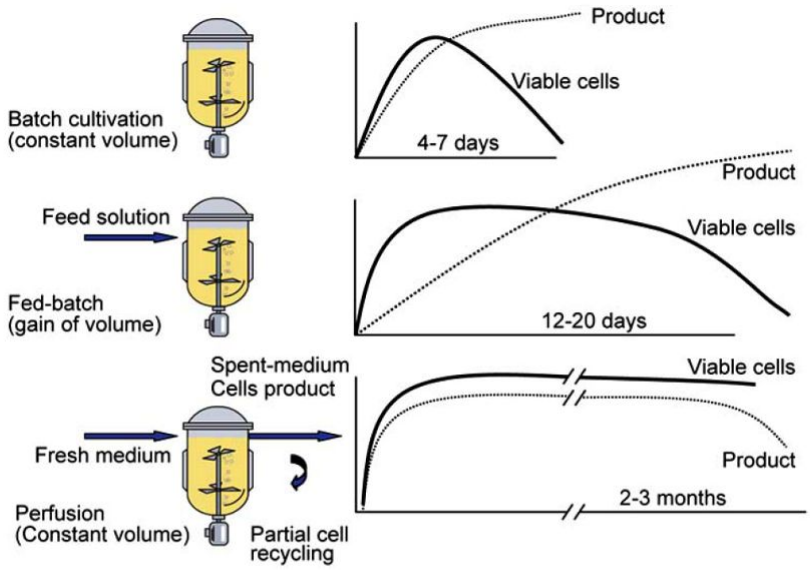

Figure 2: mAb production processes (Lu, R.-M., Hwang, Y.-C., Liu, I.-J., Lee, C.-C., Tsai, H.-Z., Li, H.-J., & Wu, H.-C. (2020). Development of therapeutic antibodies for the treatment of diseases. *Journal of Biomedical Science*, *27*(1), 1. https://doi.org/10.1186/s12929-019-0592-z)

A typical perfusion bioreactor design is shown in Figure 3. It's important to note that not shown in the figure, cell bleed is often from the concentrated stream being returned to the bioreactor. This design is more complex than the current batch or fed-batch bioreactors, but the payoff in production is significant. The feed, cell bleed, and cell recycle lines must be run in

balance to keep the bioreactor running with viable cells. The cell retention device must be designed to avoid any product degradation.

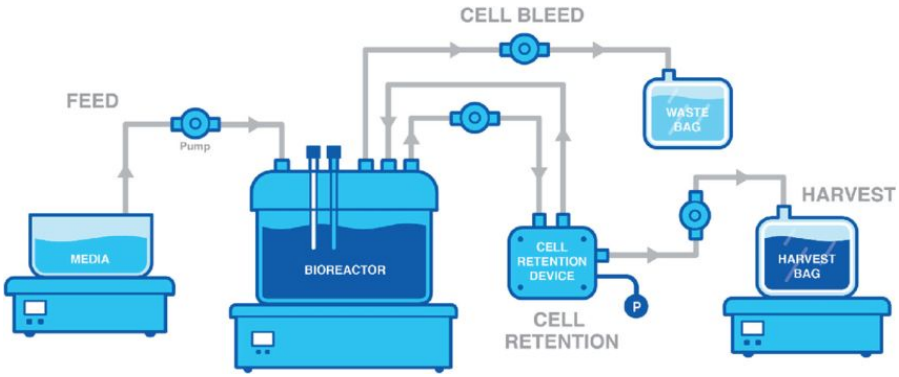

Figure 3: Typical Perfusion Bioreactor (Bausch, M., Schultheiss, C., & Sieck, J. (2018). Recommendations for Comparison of Productivity Between Fed-Batch and Perfusion Processes. *Biotechnology Journal*, *14*, 1700721. https://doi.org/10.1002/biot.201700721.)

By optimizing the individual unit operations involved in the upstream and downstream bioprocesses and incorporating continuous technologies into the process design, this project will increase manufacturing efficiency by reducing maintenance costs and time between production runs.

A continuous manufacturing process is relatively new to the mAbs space. The first mAb to be produced by a fully continuous process received approval for clinical trials in February 2019 (GEN, 2019). Continuous manufacturing benefits include higher productivity, higher cost effectiveness, greater consistency, and a smaller environmental footprint (Yang et al., 2020). These benefits will allow the mAbs to be produced at lower costs, which can lead to lower pricing and increased accessibility for patients who depend on them (Yang et al., 2019). Biosimilars have shorter FDA approval timelines and less investment in research because the original drug exists as a foundation, so they can typically be priced lower than the original drug. For Genentech's Herceptin to be competitively priced with biosimilars, Herceptin must be manufactured at a lower cost. This shift from fed batch to continuous represents a major change

that should be of interest to all pharmaceutical companies, especially those with drugs in a newly competitive space.

Matlab and Excel will be our main forms of technical analysis, as we can create and model our hypothetical process scenario. Aspen will also be used in conjunction with Excel to perform an energy and cost analysis. The design data for cell growth will be obtained from a 2009 study of *Perfusion mammalian cell culture for recombinant protein manufacturing – A critical review* (Bielser et al., 2018) and data for mAb production rates can be obtained from *A Study of Monoclonal Antibody-Producing CHO Cell Lines: What Makes a Stable High Producer?* (Chusainow et al., 2009)**.** An important part of the downstream manufacturing process is chromatography. We will use the patent *A Highly Efficient Process Of Purification And Production Of Recombinant Trastuzumab,* which provides example affinity chromatography runs with exact measurements and results, to guide our chromatography analysis (Patell et al., 2011). The physical property data for trastuzumab will be obtained from Drug Bank (*Trastuzumab*, n.d.). Material balances will be performed around each unit operation - specifically the group will hone in on the perfusion bioreactor. Professor Carta, Professor Prpich, and Professor King will be consulted for design input due to their industry and research experience. We will have a weekly meeting on Wednesdays at 3:30 p.m. as a "check-in" to discuss what work has been done and what work needs to be completed. Here, we will treat it as an in-depth presentation so all group members can thoroughly understand the work that has been done. This will also be the main form of "check-ins" to ensure all group members are working efficiently and on the tasks that they set out to complete. We will assign weekly tasks to individuals. For the larger tasks, we will split up into groups of 2 or 3 to assure a manageable workload and provide multiple perspectives and sources of information. We will be sure to hold

each other accountable for late or sub-par work, but we will always be understanding if a conflict comes up or a group member needs more help. Our main form of communication will be through text messaging. We will utilize the resources and time provided in CHE4438 and CHE4476 and meet with Professor Anderson for advice throughout the school year.

How Teachers Accommodate Neurodiverse Students in U.S. Schools

In U.S. schools, how do teachers accommodate neurodivergent students?

In U.S. schools, neurodivergent students are at a disadvantage. Although 91 percent of neurotypical students earn high school diplomas, only 68 percent of neurodivergent students do (NCLD, 2019). Official diagnoses of neurodivergent conditions, such as ADHD, dyslexia, and dyscalculia, were approved in the second half of the twentieth century. Advocacies for the neurodivergent were established in the 1980s. ADHD, the most common neurodivergent condition, is medically and legally recognized as a treatable disorder, affecting about 9 percent of children and about 4 percent of adults (CHADD, 2020).

Classroom accommodations for neurodivergent children have been scarce. Harrison (2020) reviewed and evaluated accommodation methods. Parents can markedly improve student outcomes (Van der Oord, 2020). Researchers have critically reexamined teachers' methods of evaluating neurodivergent students' behavior and academic performance (Iznardo, 2020). More social interventions, such as mentorship programs and support groups, have been introduced and evaluated. Mentoring can improve neurodivergent students' mental health (Haft, 2019).

Advocacies for the neurodivergent serve as their intermediaries with the legal system, and fight for the policies and the resources neurodivergent people need (NCLD, 2019). Parents of children with learning disabilities often endure more stress than other parents; they may

therefore become advocates for their children (Dyson,1996). Because younger students with learning disabilities may be disruptive in class, teachers may develop an antagonism toward them (Dyson, 1996). Physicians are not always well prepared to guide parents of neurodivergent children. In primary care, only about two thirds of physicians feel comfortable in recommending evaluations for learning needs, and only 52 percent of healthcare professionals feel confident in identifying learning and attention issues (NCLD, 2019).

Teachers are challenged in teaching neurodiverse students, as they believe they need to provide them with individualized learning plans in addition to instructing their entire class. First year teacher Lauren Acree states: “I had to figure out how to make a day work for each of them. Making my classroom work in one way was not going to meet the needs of each of them. And if I wasn’t meeting their needs, we had lots of behavioral issues. But instead of kind of casting that on them, I felt like: Okay, what can I do to set them up for success? (Fofaria, 2019)” Other teachers believe that common classroom conditions can become detrimental to students with attention deficits. Educator Kate Garnett claims, “Students with learning disabilities are among the most vulnerable-at chronic risk for "not learning" under the aforementioned conditions, for long-term academic and social problems, and for lifelong debilitating side-effects of their classroom experiences.” College level educators can observe the effects of neurodiverse students creating false labels for themselves as a result of poor learning experiences early on. Stanford University Math Professor Jo Boaler writes, “There are many problems with the procedural approach to mathematics that emphasizes memorization of methods, instead of deep understanding. Students come to believe they are “not a math person” and that they are incapable.”

References

Birch, J. R., & Racher, A. J. (2006). Antibody production. *Advanced Drug Delivery Reviews*, *58*(5–6), 671–685. https://doi.org/10.1016/j.addr.2005.12.006

Boaler, J. (2019, February 28). A Better Way to Teach Students with Learning Disabilities. https://time.com/5539300/learning-disabilities-special-education-math-teachers-parents-students/

CDC (2019, Jan. 31). U.S. Centers for Disease Control and Prevention. Expected New Cancer Cases and Deaths in 2020.

Chartrain, M., & Chu, L. (2008). Development and production of commercial therapeutic monoclonal antibodies in Mammalian cell expression systems: An overview of the current upstream technologies. *Current Pharmaceutical Biotechnology*, *9*(6), 447–467.

Chusainow, J., Yang, Y. S., Yeo, J. H. M., Toh, P. C., Asvadi, P., Wong, N. S. C., & Yap, M. G. S. (2009). A study of monoclonal antibody-producing CHO cell lines: What makes a stable high producer? *Biotechnology and Bioengineering*, *102*(4), 1182–1196.

Dhanasekharan, K., Berdugo-Davis C., Xiaoming L., Richey, C., Segu, Z., Vinci V., Calabrese, D., LeFourn, V., & Girod, P.A. 2015, April 14). Rapid Development and Scale-Up of Biosimilar Trastuzumab: A Case Study of Integrated Cell Line and Process Development. BioProcess International.

DrugBank (n.d.). Trastuzumab.

Dyson, L. L. (1996). The Experiences of Families of Children with Learning Disabilities: Parental Stress, Family Functioning, and Sibling Self-Concept. *Journal of Learning Disabilities*, *29*(3).

Fofaria, R. (2019, April 19). Teachers eager to gain better understanding of learning differences. https://www.ednc.org/teachers-eager-to-gain-better-understanding-of-learning-differences/

Forshay, A. W. (1991). THE CURRICULUM MATRIX: TRANSCENDENCE AND MATHEMATICS. *Journal of Curriculum and Supervision*, *6*(4), 277-293.

Garnett, K. (2017, November 15). What Are Classrooms Like for Students with Learning Disabilities? Retrieved December 14, 2020, from https://www.readingrockets.org/article/what-are-classrooms-students-learning-disabilities

GEN (2019, Sep. 24). First mAb Produced via Fully Continuous Biomanufacturing. Genetic Engineering and Biotechnology News.

Genentech (n.d.). What is Herceptin (trastuzumab) for HER2+ Cancer? Genentch.

Haft, S. (2019). Impact of mentoring on socio‐emotional and mental health outcomes of youth with learning disabilities and attention‐deficit hyperactivity disorder. *Child and Adolescent Mental Health*, *24*(4).

Kantarjian, H. (2014). High Cancer Drug Prices in the United States: Reasons and Proposed Solutions. *Journal of Oncology Practice*, *10*(4).

Li, F., Vijayasankaran, N., Shen, A. Y., Kiss, R., & Amanullah, A. (2010). Cell culture processes for monoclonal antibody production. *MAbs*, *2*(5), 466–479.

Lu, R.-M., Hwang, Y.-C., Liu, I.-J., Lee, C.-C., Tsai, H.-Z., Li, H.-J., & Wu, H.-C. (2020). Development of therapeutic antibodies for the treatment of diseases. *Journal of Biomedical Science*, *27*(1), 1.

Miller, S. (2019, April 9). *Social Institutions*. Social Instututions (Stanford Encyclopedia of Philosophy). https://plato.stanford.edu/entries/social-institutions/#TelAccIns

Mukherjee, S. (2010). *The Emperor of All Maladies*. Scribner.

Müller, V. (2018). Long-term trastuzumab (Herceptin) treatment in a continuation study of patients with HER2-positive breast cancer or HER2-positive gastric cancer. *BMC Cancer*, *18*(295).

National Cancer Institute. (2020). *Cancer Stat Facts: Female Breast Cancer*. Female Breast Cancer - Cancer Stat Facts. https://seer.cancer.gov/statfacts/html/breast.html

National Center for Learning Disabilities. (2019, June 24). *Why Now? Why Us?: Inclusive 21st Century Learning*. Why Now? Why Us?: Inclusive 21st Century Learning. https://www.ncld.org/research/why-now-why-us/

Patell, V. M., Guzder, S. N., Maity, S., & Shekar, S. (2011). *A highly efficient process of purification and production of recombinant trastuzumab* (World Intellectual Property Organization Patent No. WO2011015920A2). https://patents.google.com/patent/WO2011015920A2/en

Pharmaceutical Technology (2019, May 21). Top-selling prescription drugs by revenue: Ranking the top ten. (2019, May 21). Pharmaceutical Technology.

RAPS (2019). Regulatory Affairs Professional Society. FDA Approves 20th Biosimilar, 5th for Roche's Herceptin.

Shukla, A. A., & Thömmes, J. (2010). Recent advances in large-scale production of monoclonal antibodies and related proteins. *Trends in Biotechnology*, *28*(5), 253–261.

Yang, O., Prabhu, S., & Ierapetritou, M. (2019). Comparison between Batch and Continuous Monoclonal Antibody Production and Economic Analysis. *Industrial & Engineering Chemistry Research*, *58*(15), 5851–5863.

Yang, O., Qadan, M., & Ierapetritou, M. (2020). Economic Analysis of Batch and Continuous Biopharmaceutical Antibody Production: A Review. *Journal of Pharmaceutical Innovation*, *15*(1), 182–200.