Engineering and Gene Therapy: A Distinct Exploration of the Engineering Process through Viral Vector Production

81F Forge

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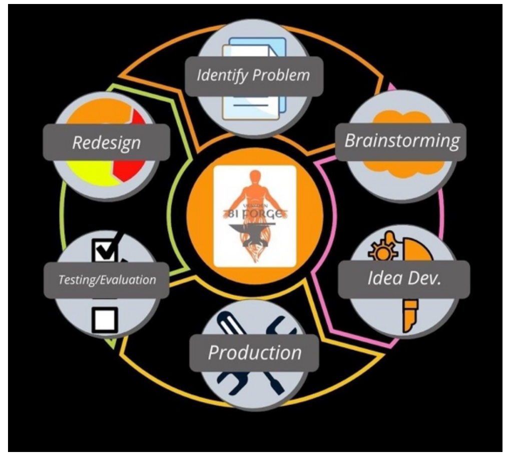
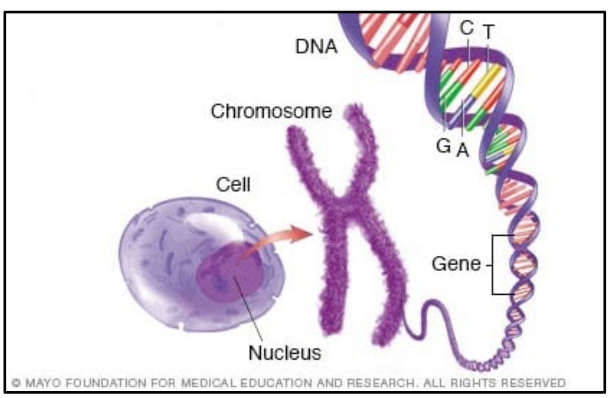
Throughout our years as 81F Forge, it is undeniable how vital the engineering design process has been in our understanding of solving problems in robotics. This process has not only allowed us to succeed in creating effective robots, but has also deepened our appreciation of how the world functions. It is incredible that such a simple process undergirds the way our society functions; from the buildings we occupy to the machines that construct cars, the design process is an icon of societal advancement in assembling the world we live in. Similar to our process, professionals in gene therapy utilize the engineering design process to solve certain problems.



Our Engineering Design Process

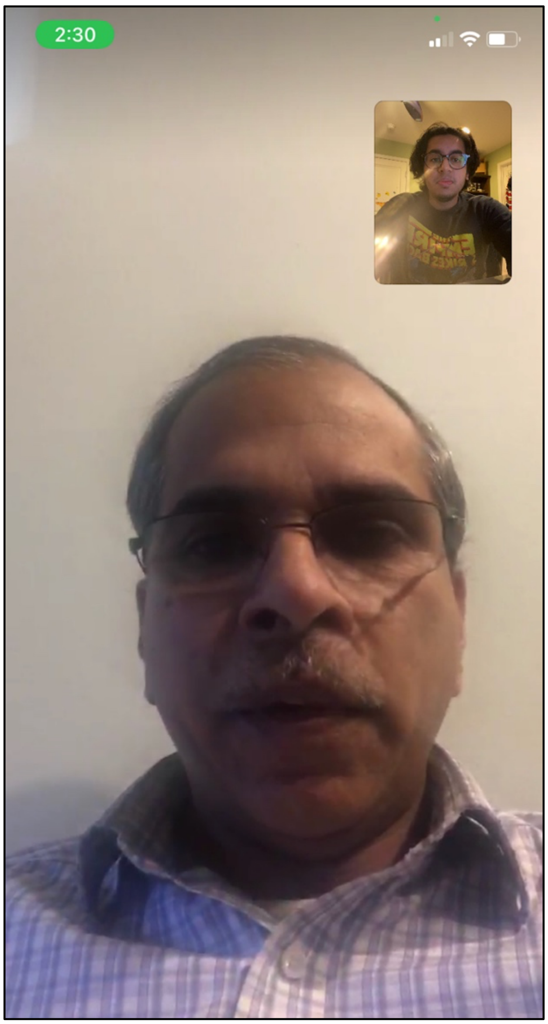
We desired to explore beyond engineering, and the Career Readiness Online Challenge provided us the opportunity to do so. With our scientific interests in biology as a guide, we satisfied our thirst for knowledge by learning how the design process impacts gene therapy. Gene therapy is a therapeutic strategy using genetic engineering techniques to treat diseases. Genes-constructed from DNA–a biological blueprint–constitute an organism's growth and its characteristics, so if there is a genetic defect or symptoms of a disease, gene therapy can correct them with the deliberate introduction of necessary genes into an organism. There are two types of gene therapy: germline and somatic. Germline gene therapy refers to introducing genes into reproductive cells in order to correct defects that could be present in successive generations,



while somatic gene therapy introduces genes into tissues or cells to treat abnormal genes (Petechuk & Cobb, 2014).

In 1968, virus-mediated gene transfer became viable after foreign genetic material could be transferred into cells with the use of viruses. However, until 1980, non-viral methods such as microinjection and calcium phosphate precipitation were used for gene delivery. Non-viral methods possessed advantages such as large-scale production and low host immunogenicity– the magnitude of an immune response (*What Does*, 2020)–but they resulted in decreased levels of transfection–implementation of "foreign nucleic acids into cells to produce genetically modified cells" (Kim, 2010)–and gene expression, lowering overall therapeutic efficiency (Toda, 2020). This turning point in gene therapy represented the genesis of viral vectors, molecular delivery trucks derived from viruses that naturally invade specific cells in an attempt to transport genes. Ranging from artificial retroviruses to adenoviruses that can infect non-dividing cells, vectors have been developed to become successful. For example, in 2008, the AAV2/2 (AAV = adeno-associated viral) vector delivered the *RPE65* gene into retinal pigment epithelial cells, resulting in clinical benefits and no adverse reactions in an attempt to treat Leber's Congenital Amaurosis (LCA)–a visual disorder that impacts the retina (*Leber Congenital*, n.d.)–in phase I/II clinical trials (Toda, 2020).

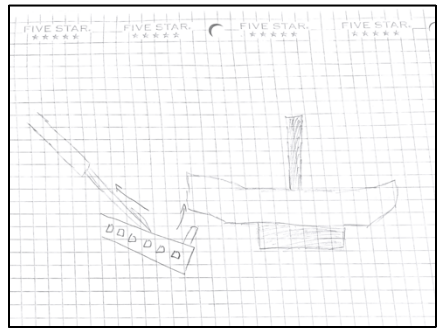
In order to discover more about viral vectors, we consulted with Samir Acharya, the Associate Director of Product Development at Andelyn Biosciences, through an online video call. Andelyn Biosciences is a gene therapy organization that fulfills its mission to accelerate "the development and manufacturing of innovative therapies to bring more treatments to more patients" with their 20+ year expertise in manufacturing viral vectors (Andelyn Biosciences, n.d.). With his team, Dr. Acharya focuses on producing specific processes for AAV vectors for clients. For example, he devises exact solutions that insert genes into viruses, and then finds methods to purify the virus containing the gene (this is an example of them using the scientific method to solve biological issues). We studied Dr. Acharya's position and company as it provided us with further information to learn about gene therapy. Dr. Acharya became an outlet of guidance, so selecting his career allowed us to view how the design process is utilized under a biological discipline through a professional lens–an opportunity that cannot be experienced via a generic informational website. Before contacting Dr. Acharya, our team thoroughly explored the Andelyn Biosciences website to verify if this company could offer guidance on viral vectors. Fortunately, after reviewing its *Clinical Manufacturing* page, we confirmed that contacting Andelyn Biosciences would yield beneficial information regarding our analysis into viral vector production. The company provides "clients with a broad range of viral vector manufacturing platforms and solutions, including AAV and Lentiviral



Dr. Acharya and 81F on call discussing viral vectors adherent and suspension systems" (Andelyn Biosciences, n.d.), solidifying its credibility with respect to our career readiness initiative.

Initially, we determined that Dr. Acharya applies the engineering design process in a different approach than we do. Dr. Acharya analyzes the use of single-use technologies such as shake flasks and rocking bioreactor bags–systems that yield better infectivity rates of vectors compared to stainless steel systems (Challener, 2021)–with the design process, but with a crucial factor: communication with the companies who create them. When responding to a question regarding the engineering design process, Dr. Acharya answered, "Design process is done in conjunction with the companies who make them… If the problem is there in the design of the machine, then we talk to the company who made it." He highlighted how the designs of instruments are critical, and in a professional setting, he and his company must fulfill "validation"–their version of testing and evaluation (S. Acharya, lecture, n.d.). In this scenario, they must apply the design process to critique improper single-use systems; as they revise prototypes from other companies, they must communicate these changes. When compared to our use of the design process, we converse independently amongst ourselves. For Dr. Acharya, he not only follows the design process in establishing the best single-use system, but he must communicate the changes to a third party. This extra step of communication is necessary in achieving his goals and is indicative of work in a professional setting. Communication is imperative in uniting people from different backgrounds in order to create a product.

Conversely, Dr. Acharya also applies the engineering design process in a similar manner with troubleshooting. Dr. Acharya stressed documentation; if a problem arises in vector production or technology use, they "go back because everything is saved." Each step and detail in the manufacturing process is documented, which helps with troubleshooting. Dr. Acharya noted that "If there is a problem, it is obligated upon us to resolve it… discuss it, propose a solution, and mitigate the problem by solving it… And then saying 'OK, these are the things that when we changed, the problems never arose'… it has to be a full circle; we have to explain that," (S. Acharya, lecture, n.d.). Similar to their use of the design process, we as 81F utilize the process to solve problems in the same exact manner. For example, our first robot iteration for the 2021-2022 VRC Game *Tipping Point* utilized a pneumatics-based



Dragger Design

"dragger" that allowed our robot to possess a third mobile goal. However, the dragger contacted

Dragger (dragging red goal)

the field, interfering with base movement. With the design process, we discussed this issue and proposed a solution of a simple stopper. After reviewing our notebook, it was clear that we did not completely define the limitations of the dragger in our *Brainstorming* section, so it was significant that we followed the design process to devise a solution. As Dr. Acharya outlined, we completed a "full circle" in relation to the design process. Although Dr. Acharya completes this cycle with gene therapy, it is undisputable how extensive the design process is. It is inspiring that high school students can use the design process similarly to professionals in diverse backgrounds to solve problems.

Dragger with stopper

We are grateful to have had the chance to explore gene therapy with Dr. Acharya. This opportunity let us discover our curiosities and it allowed us to learn beyond the VEX environment. Participating in VEX has equipped us with essential skills such as collaboration and critical thinking–skills that will develop us into leaders in our future careers. Not only that, but VEX has taught us the importance of communication. If it were not for communication, we might not have contacted Dr. Acharya in order to learn about gene therapy. Most importantly, participating in VEX allows us to help younger students in robotics through our VEXMEN Student Mentor program. When we were in middle schoolers, high school teams would aid us in learning about robotics. With this mentor program, we are able to emulate this experience for younger students all while teaching ourselves the value of education in encouraging learners. Our experiences in helping others will only help as we prepare ourselves to join careers in STEM fields that strive to better society.

VEXMEN mentors above set up scrimmage for all teams to practice and learn before competition (Not pictured: Vansh and Colin took this picture)

As we progress through the season, we hope to incorporate what we learned from this Career Readiness Initiative to the best of our capabilities. With this initiative, we

Our Team
From Left: Ayush, Suhaas, Vikash, Colin, Vansh

learned that we can always go above and beyond in learning about engineering, and that engineering impacts the world in a multitude of ways!

References

Acharya, S. (Presenter). (n.d.). *Gene therapy discussion with Dr. Acharya (Vex Paper)*. Lecture presented in Chester Springs.

Informal presentation through video call to help young high school robotics team understand application of design process in the field of gene therapy

[Andelyn Biosciences]. (n.d.). Andelynbio.com. Retrieved January 15, 2022, from https://andelynbio.com/about-us/

[Andelyn Biosciences logo]. (n.d.). Nationwidechildrens.org. https://www.nationwidechildrens.org/-/media/2ee1c6097969441e89b76d2c947fafa5.ashx

Challener, C. A. (2021, August). Single-Use technologies prove effective for viral vector process development: The benefits of single-use technologies for upstream viral-vector processes clearly outweigh their disadvantages. *Biopharm International*, *34*(8), 12+.

[DNA, gene, and chromosome depiction]. (n.d.). Mayoclinic.org. https://www.mayoclinic.org/-/media/kcms/gbs/patient-consumer/images/2013/11/19/10/05/ds00549-your-genes-chromosomes-and-dna.jpg

Forge, 8. (n.d.). [81F forge design process].

Kim, T. K. (2010, June 13). *Mammalian cell transfection: The present and the future*. ncbi.nlm.nih.gov. Retrieved January 15, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2911531/

Leber congenital amaurosis. (n.d.). Medlineplus.gov. Retrieved January 15, 2022, from https://medlineplus.gov/genetics/condition/leber-congenital-amaurosis/

Petechuk, D., & Cobb, B. (2014). Gene therapy. In K. L. Lerner & B. W. Lerner (Eds.), *The gale encyclopedia of science* (5th ed.). Gale.

Toda, M. (2020, September 8). [Historic overview of genetic engineering technologies for human gene therapy]. Ncbi.nlm.nih.gov. Retrieved January 15, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7555159/#B6

What does immunogenicity mean in the context of COVID-19 vaccines? (2020, November 19). Astrazeneca.org. Retrieved January 15, 2022, from https://www.astrazeneca.com/what-science-can-do/topics/disease-understanding/what-does-immunogenicity-mean-in-the-context-of-covid-19-vaccines.html

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