The Triple Helix at Johns Hopkins University

Science In Society Review

PUSHING THE LIMITS

BIOENGINEERING

3D PRINTED TRANSPLANTS

page 11

ASTROBIOLOGY

POLYEXTREME ALIEN MICROBES

page 17

NEUROSCIENCE

UPLOADING THE MIND

page 30

Spring 2019

About The Triple Helix

The Triple Helix is an international network of undergraduate students that focuses on the dynamic relationship between science, society, and law. We aim to promote education and critical thinking about current developments in science and the implications of these issues within a broader societal framework. The flagship journal of the Triple Helix is the Science in Society Review, which features articles that tackle scientific issues from any interdisciplinary lens including business, law, and ethics. In addition to these publications, the Triple Helix also hosts discussions, lectures, and conferences throughout the semester, so there is always something to look forward to!

For more information please visit :

www.thetriplehelixjhu.weebly.com
www.facebook.com/thetriplehelix

Our Team

Note From The Editors

Dear Readers,

Welcome to the 2019 edition of Science in Society Review! This year, we have turned our attention to the ever-progressing nature of science and medicine. Inherent in this revolution is pushing-- and breaking past-- limits.

In this modern era, medicine and science are intertwined with technology, social and cultural dynamics, and ethics. The boundaries we break every day are certainly rousing, giving rise to questions on every subject from genetics to the relationship of immigration and race with science. Just decades ago, the idea of growing mini-brains or engaging in artificial intelligence or applying the study of endoliths to astrobiology was the stuff of science fiction. These exciting breakthroughs offer solutions, hope, and knowledge to the world through drug and technology development. However, as we explore the prospects of reprogramming viruses or uploading brains to software, we must continue to question the varied implications of progress-- both inviting and dangerous.

In what follows, you will find pieces exploring revolutionary and modern advancements in science, and what those changes mean for our communities, scientists, patients, and society in general. These pieces serve to foster discussion not only about the successes we have had, but also the necessary changes we need to make and questions we need to ask. Our hope is that they compel you to contemplate the limits of science, and how far we should push them. We encourage you to read, share, and think about the conversations our writers have engaged in to make your own contributions to the interdisciplinary scientific revolution.

Naomi Doshi and Ananya Reddy
Editors-in-Chief, 2019

Table of Contents

The Human Brain in a Dish?: Advancements in Cerebral Organoids

Benjamin Fry

ABSTRACT

Imagine a world in which the brain, the most complex and least understood organ in the human body, could be copied and grown in a petri dish for scientific experimentation. All it would take is a blood sample and in a few short steps, an individualized copy of a person's brain could be made. It seems that in recent years, what once may have been believed to be purely science fiction is inching ever closer to reality. In this essay, I will analyze a new technology that researchers of many disciplines are using to study the brain known as cerebral organoid culture. These 'mini-brains', created from human skin or cartilage samples, provide a new way of studying the brain that have benefits compared to traditional, 2-dimensional methods of observing living body structures. With this technology, researchers are able to experiment with human nervous tissue that is a much closer representation of what can be found in nature. Furthermore, Cerebral Organoids can act as representations of the person whose cells they were developed from, thus providing excellent potential for use in personalized medicine. Despite many potential benefits, this technology poses a few notable limitations and ethical dilemmas that must be considered before mass adoption.

For decades scientists have worked to unravel the mysteries of the human brain. Since well before the term "neuron" was coined in 1891[1] to the Human Connectome Project, today's international effort to map the connections between the brain's billions of neurons,[2] the brain has fascinated scientists, and it is not hard to see why. After all, at a basic level you are your brain. Despite this, soon ethicists may have to decide exactly at what point in development a brain becomes a person. Traditionally, neuroscientists have been held back in their research by ethical considerations when studying the brain.

Figure 1. Cerebral organoids grown in a petri dish. Spheres are ~4mm in diameter.

Because of these restrictions, researchers often need to use animal models or scanning techniques such as fMRI and DTI tractography to look at the brain's activity and the connections between its parts rather than directly manipulating brains themselves.

However, in the past few years, scientists have made strides to develop a new form of brain-study that may hold the key to understanding the development of neuropsychiatric disorders such as schizophrenia and autism spectrum disorder. [3] Cerebral organoids (Commonly referred to as 'mini-brains' in popsci articles) are 3-dimensional clusters of cortical human brain tissue created from induced pluripotent stem cells (iPSCs). These mini-brains have advantages over the techniques mentioned earlier because scientists can perform experiments on human neurons and observe development in conditions much closer to what they would observe in the body. Researchers no longer have to extrapolate information from animal models or construct images from complicated brain scans; instead, they can look directly at an area of interest in real human nervous tissue. Since cerebral organoids are developed from the cells that compose the human neuroectoderm (a layer of cells present in development that differentiate into the nervous system), they contain the same cells as the adult brain (excluding microglia and endothelial cells). [4] Despite their miniature size (only around 4mm in diameter [10]), mini-brains retain the same function and histological organization as human brain cells in vivo. In their current state, the possibility of these structures experiencing consciousness is remote due to their small size, and lack of vasculature when compared to the adult human brain. However, medical ethicists have begun exploring the implications of this research as it is not impossible that in the next few years technology could advance to growing these organoids at larger scales with higher functions. [10] This paper will explore what this cellular culture technique is, its current and future uses, and the ethics of using it to study human disease.

"Researchers no longer have to extrapolate information from animal models or construct images from complicated brain scans; instead, they can look directly at an area of interest in real human nervous tissue"

Previously, when researchers studied human neurons in vitro, 2-dimensional cultures of iPSCs were directed to differentiate into one specific type of cell. With this technique it is hard to study the neural connections between different brain regions or cell types as only one is grown. [10] Because organoids mimic the structure and development of the brain itself, they give a much closer approximation of how the cells appear naturally in the body.

To create an organoid is fairly straightforward. First, Human Pluripotent Stem Cells must be created from a sample of fibroblasts, skin cells, or blood cells obtained from the individual whose brain is being studied. These cells are then exposed to genetically engineered viruses which induce them into reverting back to stem cells through the presence of reprogramming factors such as OCT4, SOX2, MYC, and KLF4 (proteins that function in the renewal of stem cells during development).[8] Once iPSCs have been obtained, the cells are plated and allowed to grow in the presence of chemicals and nutrients that push them toward developing into the cells found in the human neuroectoderm. The cells are then placed in Matrigel, a hydrogel that mimics the conditions of a developing embryo in nature[8]. Matrigel is what allows the cells to take on the complex, 3-dimensional structure that is characteristic of mini-brains. The cells are then placed into an orbital incubator at body temperature where the flow of the nutrient-rich fluid they have been suspended in mimics the flow of blood in the body.[6]

Cerebral organoids also allow scientists to study interactions between different regions. Once an organoid is grown to mimic a specific part of the brain, it is possible to combine it with an organoid that mimics another region. The process of combining brain regions that had initially been grown separately results in what are referred to as brain assembloids, which according to Dr. Nita Farahany, a prominent scholar studying the intersection of ethics and biological sciences at Duke University, "can then have interconnections between the regions, so that you can actually have electrical activity that occurs across the different regions."[10] However, there are some limitations to using these organoids as models for the brain. The current method for developing cerebral organoids does not have an analog to the surrounding fetal tissue needed to guide the parts of the mini-brains to the positions that they would be in within a living organism. Because the neurons lack the cellular guides provided by nature, they arrange in more randomized ways. To use an analogy, mini-brains approximate life in a similar way to a work by Picasso, when the human brain is represented most accurately as a Rembrandt. Writing about the development of organoids in their current state, Dr. Madeline Lancaster, a researcher at the University of Cambridge, claims, "the different brain regions [develop to be] a bit jumbled, kind of like how a toddler might try to build a toy spacecraft with the solar panels backwards and the detection equipment upside down… So, just like the toddler-built toy spacecraft doesn't work, like the toy that it should, our organoids don't think like a brain."[7] Despite not being a perfect representation of human anatomy, researchers looking to study a specific brain region are still able to locate that region based off of its cellular characteristics. It simply may be in the wrong place. Interestingly, in recent months, 3D printing techniques

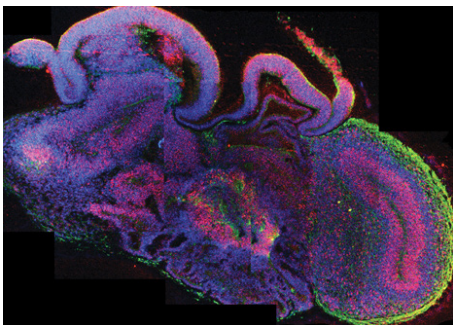


Figure 2. Sectioned and stained view of organoid

have solved some of the problems associated with the traditional method for cerebral organoid creation. While the traditional technique allowed the cultured cells to arrange themselves semi-randomly, by using 3D printers and a 'hydrogel-based bio-ink', cell layers can be placed in exactly the way they would be in the body. [11] Currently, this technology does have some drawbacks. 3D printed organoids are limited to smaller sizes of around 1 mm and have only been known to survive for around 2 months. This is compared to the 4mm and 6-12 month life span of organoids grown with standard techniques. [11] Excitingly, 3D printed organoids can be created in around 5 minutes compared to the month-long process usually associated with organoid development. [11] This technique of organoid creation improves the accessibility of organoids and opens their creation up to plenty of future research.

Currently, organoid culture techniques are being used to study diseases that have been hard to replicate in animal models and those that are difficult to ethically study in humans. Microcephaly was the first such disease to be studied with cerebral organoids. [4] Patients with mutations in a gene called Nde1 present with the microcephaly phenotype. However, when mouse models are designed to have the same Nde1 mutation that causes microcephaly in humans, they have an extremely small to no microcephalic phenotype. [6] Because of this, mouse models proved to be ineffective at representing microcephaly and researchers needed to find another way to study it without crossing ethical lines. Cerebral organoids grown from a severely microcephalic patient's fibroblasts proved to be an effective method of replicating microcephaly in vitro. [8] Researchers studying neuropsychiatric conditions such as autism and schizophrenia are also looking to cerebral organoids to model the disorders. As the field of genomics advances alongside neuroscience, researchers are finding that more and more of these neuropsychiatric disorders "involve heterogeneous combinations of many alleles of small effect, which are extremely difficult to recreate in animal models". [3] In the case of conditions like autism and schizophrenia that cannot be linked to one specific gene mutation, organoids grown from the cells of patients with these conditions allow researchers to directly observe what may make a brain schizophrenic or autistic. The fields of developmental biology and regenerative medicine stand to benefit from the study of organoids as well due to their approximation of nature.

Furthermore, organoids can be used to act as a sort of 'avatar' for a patient suffering from a particular disease. [9] With this technology, if a researcher wants to determine what kind of drug will work most effectively to treat a particular patient's condition, they can take a cell sample from the patient, induce the cells to form iPSCs, and create a cerebral organoid that models the patient's brain structures which were created as a result of their individual DNA. The organoids then become 'avatars' in the sense that doctors looking for the most effective drugs to treat a disease can experiment first on the organoids rather than the patient. This could also allow multiple drugs to be tested

at once ensuring that the most effective ones are chosen. This is an especially revolutionary technology in the field of oncology where in the future, specific tumors could be grown as organoids outside of a patient's body and an effective treatment plan can be developed by experimenting with their cells rather than their bodies. [9] Moreover, for congenital diseases, researchers can potentially experiment on patients' cells with CRISPR-CAS complexes to further revolutionize personalized medicine by selectively removing defective genes in vitro long before ever trying it in vivo. [9]

Due to the nature of the subject matter, it is clear that ethicists need to be involved to help guide the development of this technology. As mentioned earlier, there is a very slim chance that one day researchers will be able to create mini-brains that could ever potentially experience consciousness. The possibility is viewed as, "extremely remote," but, according to Dr. Nita Farahany, "the mere fact that it is remote, rather than impossible creates the need for us to have the conversation now about greater research that unpacks consciousness---whether or not we can detect it and if so, how we might address that". [10]

By implanting human cerebral organoids into mice, we have already begun raising questions that will need to be answered before we ever even approach creating a sentient being. Such questions are: How do we define human? At what stage of life does something deserve rights or protections? and do humans have any place 'playing God' in this manner? When creating human-mouse chimeras, these questions seem more important than ever. In a recent experiment that implanted human organoids into mouse brains, the researchers observed that the organoids grew blood vessels and projected their axons deep into the mouse brains as if they had developed with the brain itself. [10] Essentially, the scientists made the mice ever so slightly closer to being human. Furthermore, now that researchers are growing more and more human brain tissue in the lab, there comes about a question of whether it is appropriate to simply dispose of the experiments using the standardized procedures, or if specimens such as human-mouse or human-chimpanzee chimeras should be given "special treatment at the end of a study". [10] Despite these questions of ethics, researchers and ethicists like Farahany believe that it would be inherently unethical in itself to stop research in this field due to these concerns. [10] It is clear to see why---the potential impact of this technology on improving our understanding of topics such as disease treatment, developmental biology, and neuroscience is massive. However, it is important for us to trod carefully. As large as the benefit to society could be, there is just as large a potential risk inherent in the future development of what we may create.

In conclusion, the development and use of cerebral organoids as miniature representations of the human brain has the potential to make an incredible impact on many different fields of study that center on the human brain. Using a relatively simple technique, researchers can now create miniature,

3-dimensional representations of the human brain that provide researchers much closer approximations to the organization of nervous tissue in the brain Techniques have not yet found a way to replicate the structure of the brain in vivo perfectly. However, these advances are is not outside the realm of possibility for the future and advances such as 3D printing technologies may hold the key to unlocking them. Organoids have already been used to study diseases such as schizophrenia and autism spectrum disorder, which have been very difficult to ethically study in animals and in living humans in the past. This technology is not without its own ethical implications, though, and it is likely that a large amount of discourse on the subject and many years will pass long before humans ever come close to replicating a brain in the lab. Developments like these are what makes today a wonderful time to be a scientist. While these advance may not be ready to replace pre-existing techniques of brain study, they are certainly pushing the boundaries of what we once thought was possible.

References

[1] Jabr, F. (2012, May 14). Know Your Neurons: The Discovery and Naming of the Neuron. Retrieved from https://blogs.scientificamerican.com/brainwaves/know-your-neurons-the-discovery-and-naming-of-the-neuron/

[2] Human Connectome Project. (n.d.). Retrieved November 15, 2018, from http://www.humanconnectomeproject.org/about/

[3] Quadrato, G., Brown, J., & Arlotta, P. (2016, October 26). The promises and challenges of human brain organoids as models of neuropsychiatric disease. Retrieved November, 2018, from https://www.nature.com/articles/nm.4214

[4] Marsoner, F., Koch, P., & Ladewig, J. (2018, June 07). Cortical organoids: Why all this hype? Retrieved November, 2018, from https://www.sciencedirect.com/science/article/pii/S0959437X18300522?via=ihub

[5] Staerk, J., Dawlaty, M. M., Gao, Q., Maetzel, D., Hanna, J., Sommer, C. A., Mostoslavsky, G., … Jaenisch, R. (2010). Reprogramming of human peripheral blood cells to induced pluripotent stem cells. Cell stem cell, 7(1), 20-4. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2917234/

[6] iBiology. (2017, September 20). Jurgen Knoblich (IMBA) 2: Modeling Human Brain Development in 3D Organoid Culture [Video file]. Retrieved from https://www.youtube.com/wat ch?v=WrsPhkpooUQ

[7] TEDx Talks. (2015, November 30). Growing mini brains to discover what makes us human | Madeline Lancaster | TEDxCERN [Video file]. Retrieved from https://www.youtube.com/watch?v=EjiWRINEatQ

[8] Lancaster, M. A., Renner, M., Martin, C., Wenzel, D., Bicknell, L. S., Hurles, M. E., . . . Knoblich, J. A. (2013, August 28). Cerebral organoids model human brain development and microcephaly. Retrieved from https://www.nature.com/articles/nature12517

[9] International Society for Stem Cell Research (ISSCR). (2017, July 23). "Organoids: What is the Science and What are the Clinical Applications?" [Video file]. Retrieved from https://www.youtube.com/watch?v=SuthgBZqBk0&t=2275s

[10] Farahany, N. A., Greely, H. T., Hyman, S., Koch, C., Grady, C., Pașca, S. P., . . . Song, H. (2018, April 25). The ethics of experimenting with human brain tissue. Retrieved from https://www.nature.com/articles/d41586-018-04813-x

[11] Yeager, A. (2018, August 1). As Brain Organoids Mature, Ethical Questions Arise. Retrieved From https://www.the-scientist.com/infographics/infographic--how-to-make-a-brain-organoid-64534

Using 3D Printing to Create Realistic Models of Organs

Ashley Tsang, Vani Kumar

ABSTRACT

While 3D printing was originally used to promote easy prototyping, its usages have spread to 3D printing entire organs. There are many processes of 3D printing currently being developed. The most popular being the extrusion method, which is constantly being improved by the medical community. The method is still relatively new; however, doctors and researchers have made impressive strides in printing tissue and organs. Therefore, this success in 3D bioprinting of tissues and cartilage has opened up possibilities for human organ transplants. This ability to increase the opportunities for organ implants counters the argument that bioprinting may exacerbate socioeconomic inequalities as bioprinting would create more opportunity for those waiting years for an implant. Though 3D bioprinting raises other several ethical implications, its long-term benefits and potential indicate its worthy development.

In 2012, a group of doctors from the University of Michigan encountered a baby born with tracheobronchomalacia, a rare condition where the airway tissues are weakened, affecting his ability to breathe and regularly triggering cardiac and pulmonary arrest. The physicians were tasked with determining a solution to repair or replace his tissue in a high-risk and delicate setting, so they turned to 3D bioprinting, a method that can turn a scan or model on a computer into a physical biological product. Using the process of 3D printing for materials, the team first scanned the baby's chest to create a map of his affected airways. From there, they created and printed a specialized splint that would be sewn around his airway to hold it open, allowing his breathing to become normalized. This splint, made of biological material, expanded as the baby grew, allowed for new cells to form over it, and dissolved after it was no longer needed. Seven years later, this boy is still healthy.

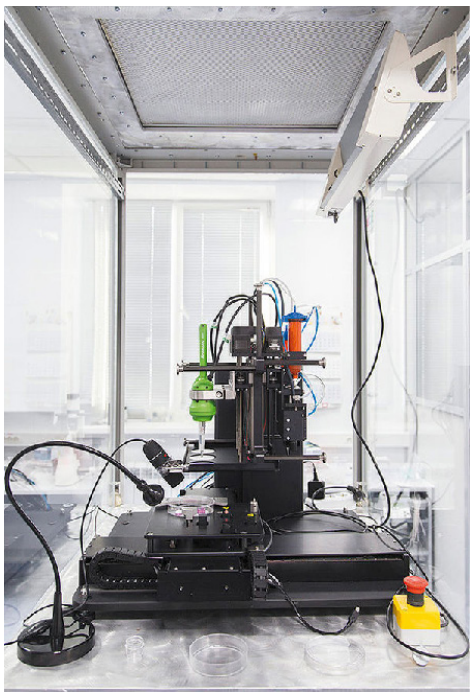


Figure 1. Bioprinter from the Russian company 3D Bioprinting Solutions which uses a variation of extrusion 3D printing to generate human tissue.[8]

The first form of 3D printing was stereolithography, invented by Charles Hull in 1984. In this process, liquid photopolymer, an acrylic based material, is targeted by a UV light, which causes the liquid to harden into plastic in the shape that the light hits.[1] This process was used layer by layer to "print" a 3D object. While very expensive at the time, 3D printing has become widely accessible and available now, mainly for prototyping purposes. Because of its customizability, 3D printing is an efficient and cheap way to test a new idea at a very fundamental and basic level.

In the early 2000s, surgeons were using collagen and synthetic polymers to model inner human anatomy. Before this, only human or animal subjects could be studied and tested on, which made this field of research important and popular. Dr. Anthony Atala, a research fellow in 1990 at the Children's Hospital in Boston, was part of this trend as he was working to creating homegrown bladders. The idea was to build scaffolds that were composed of collagen and synthetic polymer, and then layer them with the patient's cells so they could grow into usable bladders.[2] While Atala and his team were not the first to work on this aspect of tissue engineering, they were the first to spawn substantial cell growth using new cells from the base of the bladder.[3] Once his team was able to produce a successful protocol for creating these bladders, the next obstacle was mass manufacturing of these kinds of scaffolds as creating them by hand was a tedious process. Atala continued to work on this problem at Wake Forest Baptist Medical Center in 2004. Here, he first started experimenting with 3D printing, initially using an inkjet printer to print these customized scaffolds, speeding up the process considerably. This breakthrough expanded to other aspects of anatomy, particularly flourishing in orthopedics. Because of its customizability in terms of both shape and material, 3D printing expanded into other areas of medicine, particularly medical devices. For example, it has become popular for making patient-specific devices, including jigs for spinal instrumentations and total knee arthroplasty. Prior to using 3D printing to mold these devices out of porous polymeric materials, metal structures had to be devised using complex techniques to fit the specific geometries required by the procedures. Due to this complexity, these systems were not very effective or affordable. However 3D printing gives them the capability to be both.[4]

"3D printing expanded into other areas of medicine, particularly medical devices"

Atala was not the only one to see the benefits of 3D printing. Since his breakthrough, many companies and research institutions have been working on perfecting the technique. Organovo was the first company to successfully 3D print tissue. The company, founded in 2007, has since been dedicated to designing and creating functional 3D printed cell tissue. Building on Atala's rudimentary inkjet printer system, the company designed bioinks that contain the building blocks for cells. Hydrogel components are used in the layering of the tissue to ensure that the tissue is "printed" in the correct formation. In 2013, Organovo created the first bioprinted liver tissue in the world and even claimed that they would create a functioning liver by the end of 2014. Alas, while Organovo has since completed many models of various liver tissues and implanted some in vitro, they have yet to complete a full liver model.

Figure 2. A surgeon performing an organ transplant.[11]

Organovo, while the first to successfully print tissue, is only one of many who are working on mechanisms for 3D printing tissue. The main principle behind 3D printing tissue is devising some kind of bioink which is ejected into shapes and layered to form the tissue, as explained above. Extrusion is the simplest method which utilizes hydrogels, as they allow the cells to be printed at a low temperature, allowing them to survive, while also providing them with flexibility to be molded. However, this benefit is also a major flaw. Due to its fluidity, these cells are also unable to withstand the loads of normal cell tissue, so in order to increase stability, more cells have to be added to the hydrogels, making them more viscous and not as easily manageable. The other types are inkjet, stereolithography, and laser-assisted printing, which each have their own flaws. Therefore, extrusion has been the most popular form of 3D printing due to its accessibility and relative ease compared to the other types, so many researchers have been focusing on maximizing its potential. For example, researchers in the Netherlands are using melt electrospinning writing, which puts polyesters in an electric field to generate fibers that reinforce the hydrogel.

This employment of 3D printing has transformed the way doctors and researchers are approaching human transplants. Currently, the process of transplanting is very grueling due to the complexities of the process, which involve obtaining consent from patients without coercion, selecting patients for the transplant through a fair process, and ensuring that enough organs are available for use. The limiting factor for organ transplants is, by far, the insufficient number of organ donations. One reason for this is that there is currently no monetary

incentive for being an organ donor due to the National Organ Transplant Act of 1984, which banned the selling and purchase of organs. This act was instituted because of concerns that economically disabled people would be coerced into selling their organs. Also, only people who could afford buying organs would be able to have access to them, which would also widen the socio-economic gap.

While the current law protects potential donors, it also means that about 20 people die every day because of the lack of available organs to transplant. Therefore, 3D printing has the potential to increase the overall availability of organs to the public. While there are still concerns that only the wealthy would be able to afford 3D printed organs, one of the benefits is that people will not be targeted for their organs. While the U.S. does its best to control organ donations, the organ black market is still thriving. Brokers involved in the business team up with funeral homes to harvest the organs of people before they are buried or cremated, but they also sometimes harvest from living people who are either compensated or, in the worst case, kidnapped. 3D printing would divert the wealthy from this dangerous and cruel black market to a safer and more legitimate alternative for everyone. Another issue debated in the topic of 3D bioprinting is the social stratification of bioprinting. Because the technology of bioprinting is advanced and fairly new, the cost of procedure is high, only allowing it to be accessible and beneficial to those of higher socioeconomic status. While bioprinting proves to show promise in transforming human transplants, its mere accessibility to the upper-class prevents this procedure from revolutionizing and transforming the entire field. Additionally, similar to the implications of gene-editing therapies, upper-class members may exploit this procedure for own personal or materialistic gain, not to address medical problems. For example, in the future, it may be possible to transplant a heart to improve fitness even if the person had no problems with their original heart. Those of lower socioeconomic status who are in critical need for bioprinting procedures may be prevented from receiving it due to those of higher status who may simply seek to improve themselves slightly. However, the current waitlist for kidney patients is over 120,000 people with roughly 3,000 added to the list each month. The median wait time for a transplant is 3.6 years and 13 people die daily waiting for an implant. These significant numbers indicate a need for change and the addition of bioprinted organs have the ability to do so. Though personalized medicine is expensive and will likely be accessible to wealthy

"If we can print organs individually, what's stopping us from printing all of the organs and assembling a person?"

groups, having this procedure will decrease the number of people on waitlists and result in a greater chance for all others to receive necessary treatment. [14]

While we are still not at the point where we can 3D print full organs, it is now only a question of when and not how can we do it. Therefore, if we can print organs individually, what's stopping us from printing all of the organs and assembling a person? This idea has similar ethical implications as cloning, so let's look at what the differences are and what this means for humanity. [15]

In his book, *Never Let Me Go,* Kazuo Ishiguro imagines a world where cloning is possible, but only by cloning a person. Therefore, clones are made with the sole purpose of harvesting their organs later on. 3D printing works in the opposite way, where organs can be made for transplants, but can then be put together to create a human. In the book, these clones are raised in boarding schools where they spend all of their time cultivating the arts as the government is trying to determine whether the clones have souls and can therefore be considered humans. Clones are made from existing humans so it would be easier to accept that a clone is human. However a 3D printed person would be constructed entirely by machinery. So would this "human" even be human or would it be considered a robot by our standards? Well, for current 3D printing mechanisms, real cells are used as the seed and then the mechanism multiplies them using various techniques as explained before, so the products are not entirely manmade. Therefore, a more accurate comparison would be the monster in Mary Shelley's *Frankenstein*, which is an amalgam of human body parts. If the original cells for all of the organs came from the same person, then this new person could be thought of a clone. Otherwise, this "human" would be the descendent of multiple different people, but unlike Frankenstein, it could exist at the same time as the people from which it was derived. Another way we could think of this situation is by considering a person who, over time, gets every removable organ replaced. Is this person who has gotten all of their organs replaced still considered as the same person? If the initial seed cells are coming from the same person, it may be easy to reason that the answer is yes, but how about for the situation in which the seed cells come from somewhere else? In that case, the answer may still be yes as long as the essence of the person is not being replaced, which most people consider to be the brain. While brain transplants are not possible, this may not be an issue, but in a future where they were, this would be an interesting question to consider as well. Thankfully, the human body is very complicated and there is still much to learn about it, so by the time we are able to actual 3D print humans or perform brain transplants, we will also know more about how 3D printed organs perform in humans as well what makes a human, human.

Though 3D bioprinting presents several socioethical implications regarding equality, the possibility of human cloning, and safety, this process is still in development and the long-term benefits outweigh the uncertainties and possible implications.

References

[1] Goldberg, D. (2018, April 13). History of 3D Printing: It's Older Than You Are (That Is, If You're Under 30). Redshift. Retrieved from https://www.autodesk.com/redshift/history-of-3d-printing/

[2] Whitaker, M The history of 3D printing in healthcare. Retrieved from https://publishing.rcseng.ac.uk/doi/pdf/10.1308/147363514X13990346756481

[3] (2006). The Organ Farmer. Popular Science. Retrieved from https://books.google.com/books?id=2J3KBui1OEsC&pg=PA101#v=onepage&q&f=false

[4] (2018). Golish, S. R., Kurtz, S. M., Boyan, B. D. Can 3D Printing Revolutionize Orthopaedic Devices? American Academy of Orthopaedic Surgeons.

[5] Bioprinting Process. Organovo Retrieved from https://organovo.com/science-technology/bioprinting-process/

[6] Whitaker, M The history of 3D printing in healthcare. Retrieved from https://publishing.rcseng.ac.uk/doi/pdf/10.1308/147363514X13990346756481

[7] File:Printer 3D Bioprinting Solutions.jpg Retrieved from https://commons.wikimedia.org/wiki/File:Printer_3D_Bioprinting_Solutions.jpg

[8] 3D Bioprinting Solutions Retrieved from https://bioprinting.ru/about-lab/

[9] (2018, July 2) Bilby, E. 3D-printed living tissues could spell the end of arthritis. Horizon Magazine. Retrieved from https://horizon-magazine.eu/article/3d-printed-living-tissues-could-spell-end-arthritis.html

[10] (2018, June) Derakhshanfara, S., Mbelecka, R., Xu, K., Zhang, X., Zhong, W., Xing, M. 3D bio printing for biomedical devices and tissue engineering: A review of recent trends and advances. Bioactive Materials. Retrieved from https://www.sciencedirect.com/science/article/pii/S2452199X17301068

[11] (2011, October 23) File:Dr. Ehtuish Performing An Organ Transplant.jpg. Retrieved from https://commons.wikimedia.org/wiki/File:Dr._Ehtuish_Performing_An_Organ_Transplant..jpg

[12] Facts and Myths. American Transplant Foundation. Retrieved from https://www.americantransplantfoundation.org/about-transplant/facts-and-myths/

[13] (2013, Nov 13). Archer, D. Body Snatchers: Organ Harvesting For Profit. Psychology Today. Retrieved from https://www.psychologytoday.com/us/blog/reading-between-the-headlines/201311/body-snatchers-organ-harvesting-profit

[14] (2018). Patuzzo, S., Goracci, G., Gasperini, L. et al. Sci Eng Ethics 24: 335. Retrieved from https://link.springer.com/article/10.1007/s11948-017-9918-y#citeas

[15] (2017, March 21). Haddow, G., Vermeulen, N. So, What is Not to Like about 3D Bioprinting? Journal of Medical Ethics. Retrieved from https://blogs.bmj.com/medical-ethics/2017/03/21/so-what-is-not-to-like-about-3d-bioprinting/

Polyextreme Microbes and their Implications on Astrobiology

Bayleigh Murray, Amber Zhou

ABSTRACT

Extremophiles are organisms that can adapt to desiccation, extreme pressures, high temperatures, or other conditions known to hinder the development and sustenance of life. Most extremophiles are microbes that can use their unique, microenvironments to their advantage. Endolithic organisms are a prime example of this. Endoliths are rock dwelling organisms that hide in the pore space of rocks, exploiting moisture and shielding themselves from damaging radiation. Understanding the adaptations of endolithic communities is crucial for the advancement of astrobiology, which has impacts throughout scientific institutions & society as a whole.

In hyperarid deserts, endolithic microbial communities are comprised largely of cyanobacteria and archaea (with archaea representing a larger portion of the population). Cyanobacteria are photosynthetic, blue-green bacteria. Their presence is recorded in some of the oldest rocks on Earth (~3.5 billion years old) and they are responsible for the planet's first known mass extinction, the Great Oxygenation Event, that eventually led to the evolution of the aerobic organisms we see today. Archaea is an entirely different domain of life. Because they are also prokaryotic, they eluded early taxonomists and were grouped in with bacteria, creating a two-domain system of life (Eukarya & Prokarya). It wasn't until 1977 that sequencing of the 16s ribosomal RNA gene, performed by Carl Woese and George Fox, suggested that not all prokaryotes were the same. This lead to their classification as archaebacteria, and eventually, molecular differences in metabolism and cell wall structure revealed that archaea were best classified as a distinct domain. This led to the currently accepted three-domain system of Eukarya, Bacteria, & Archaea.

Figure 1. Image of the Atacama Dessert Courtesy of Dr. Jocelyne DiRuggiero.

Cyanobacteria and archaea have been incredibly important historically,

permanently altering the evolution of life on Earth and changing the way life is classified at the broadest level, and they continue to challenge our assumptions about the living world today. Both taxonomic groups are especially hardy and exist at the limits of life on Earth. Understanding their adaptations to extreme environments is crucial to the advancement of burgeoning studies in astrobiology, and can not only help scientists predict what life might be able to evolve on "uninhabitable" planets, but also change the social landscape of scientists and non-specialists alike.

Astrobiological advancements can come from looking up at the stars or closely examining the ground. According to Dr. Jocelyne DiRuggiero, a microbial ecologist at Johns Hopkins University, "Endoliths are 'islands of life' in an otherwise almost barren landscape; there are no plants or animals, and microorganisms in the soil are dormant for the most part, waiting for the next rain. This means that if we want to look for life, or most likely remnants of life, in places like Mars, we should look inside rocks, and in particular evaporitic rocks (halite, gypsum) because it was the last place for life as the planet was getting drier."

Dr. DiRuggiero's lab studies endolithic archaea and cyanobacteria at the limits of life. In her own words, the lab uses extremophiles, "as magnifying loops to address fundamental processes in biology such as adaptive mechanisms of extremophiles to environmental stresses and the mechanisms that generate and maintain microbial diversity," she explained. In the lab, she grows isolated microbes from several different rock and mineral types in deserts widely considered to be the most challenging polyextreme environments. Here, the microbes must constantly battle high amounts of radiation, salinity, and very little available water, yet the populations they form are not insignificant in size.

"Without knowing what to look for, life in rocks can easily be overlooked"

The study of endolithic life can inform the criteria astrobiologists use for in their pursuit of life on other planets and can alter our expectations of what that life might look like. The search for life shouldn't end with the search for oceans of liquid water. Endolithic communities show that life can survive on small amounts of water and that water may be trapped in the pore spaces of rocks made from evaporite minerals. They also demonstrate just how closely we may have to look in order to determine whether an environment is truly abiotic. Cyanobacteria and archaea can live inside cracks and fissures, bury themselves in pore spaces, or cocoon themselves on the underside of rocks. Without knowing

what to look for, life in rocks can easily be overlooked. [1,2]

Studying life in extreme habitats requires a multidisciplinary approach. The adaptation of cyanobacteria to varying light conditions is a great example of how physical observations can lead to biological discoveries. Photosynthesis converts light energy into chemical energy and is predominantly studied in photosynthesizers found on the surface of the Earth, where white light reigns supreme. But in some environments, like endolithic communities and microbial mats, the light spectrum looks different than it does on the surface.[8] Adaptations in light absorbing chlorophyll reveal how these communities adapt. The most common form of chlorophyll is chlorophyll-a. Some species of cyanobacteria possess enzymes that allow them to remodel their photosystems and make novel pigments in response to light that creeps into the infrared. The chlorophyll produced by this remodeling can absorb wavelengths that chlorophyll-a cannot, pushing the boundary of visible light photosynthesis. [3] This challenges one of the oldest assumptions about life: that it requires visible light to exist, and forces scientists to reevaluate environments on other planets that were thought to be permanently sterile. [4,5] The great amount of interdisciplinary collaboration needed to conduct studies like these serves to unify the sciences and deepen our understanding of the natural world.

Understanding life more deeply often takes us to the molecular level, which isn't a scale many individuals interact with. In polyextreme environments, one of the biggest threats at the molecular level is oxidative stress, a disruption in the balance of reactive oxygen species that threatens to destroy DNA and proteins. [6] Recent advances in the study of oxidation stress focus on the role of small, non-coding RNAs found in cells. In salt-tolerant haloarchaea, which are more resistant to oxidative stress than microbes that prefer more moderate environments, there are hundreds of sRNAs that showed differential expression in response to oxidative stress induced in the lab. [7] The specific role they play is still being elucidated, but the existence of small scale, molecular adaptation calls attention to how science can be most effectively communicated. The outcomes of astrobiology will alter our understanding of the origins of life and the Earth's uniqueness. Therefore, it is incredibly important for all individuals to be able to consider what scientific and exploratory decisions are being made and by whom, and for scientific institutions to consider cultural understandings of life when attempting to garner support for their work.

Polyextreme organisms deepen our understanding of life. By studying the adaptations of the smallest, yet most enduring organisms, astrobiologists can develop an understanding of how life evolves and survives on Earth. If we are to advance our search for life, and better understand what life is and how it evolves and survives on earth, it is imperative that we study these rare, and 'peculiar' adaptations. Astrobiological outcomes change our understanding of scale, call attention to the need for responsible science communication, and forge new collaborations between scientific

disciplines. No matter future research reveals it is crucial to consider social, cultural, and political landscapes that will be affected by these discoveries.

Figure 2. Photosynthetic organisms colonizing a halite rock in Salar Grande, Atacama Dessert. Image Courtesy of Dr. Joceylene DiRuggiero.

References

[1] Wierzchos J., Casero C., Artieda O., Ascaso C. 2018. Endolithic microbial habitats as refuges for life in polyextreme environment of the Atacama Desert. Current Opinion in Microbiology. DOI: 10.1016/j.mib.2018.01.003

[2] Wierzchos J., Ascaso C., McKay C. 2006. Endolithic Cyanobacteria in Halite Rocks from the Hyper arid Core of the Atacama Desert. Astrobiology. DOI: 10.1089/ast.2006.6.415

[3] Gan F., Shen G., and Bryant D. 2015. Occurrence of Far-Red Light Photoacclimation (FaRLiP) in Diverse Cyanobacteria. Life. DOI:10.3390/life5010004

[4] Badshah S., Mabkhot Y., Al-Showiman S. 2017. Photosynthesis at the far-red region of the spectrum in Acaryochloris marina. Biological Research. DOI: 10.1186/s40659-017-0120-0

[5] Airs R.L., Temperton B., Sambles C., Farnham G., Skill S.C., Llewellyn C.A. 2014. Chlorophyll f and chlorophyll d are produced in the cyanobacterium Chlorogloeopsis fritschii when cultured under natural light and near-infrared radiation. FEBS Letters. DOI: 10.1016/j.feb slet.2014.08.026

[6] Martindale J.L., Holbrook N.J. 2002. Cellular response to oxidative stress: signaling for suicide and survival. J Cell Physiol. DOI: 10.1002/jcp.10119

[7]Gelsinger, D. and DiRuggiero, J. 2018. Transcriptional Landscape and Regulatory Roles of Small Noncoding RNAs in the Oxidative Stress Response of the Haloarchaeon Haloferax volcanii. J Bact DOI: 10.1128/JB.00779-17

[8] Meslier V., Casero M.C., Dailey M., Wierzchos J., Ascaso C., Artieda O., McCullough P. R., Di Ruggiero J. 2018. Fundamental drivers for endolithic microbial community assemblies in the hyperarid Atacama Desert. Environmental Microbiology. DOI: 10.1111/1462-2920.14106

Preventing the Aging of Neurons can Lead the Way to the Continued Extension of Human Life Expectancy

Eric Lynch

ABSTRACT

A research team has recently discovered that transplanting bone marrow from young mice into older mice can reduce aging in specific brain cells. This study has implications for the prevention of neurological diseases like Alzheimer's and Parkinson's. Along with this comes the continuing possibility of living longer lives, and maybe one day of living forever. Such implications also carry ethical weight in a society where some view death as a necessary part of life and where medical treatments are still not available to everyone.

The quest for eternal life has been a focus of storytellers, explorers, and even scientists for all of history. The fountain of youth has still not been discovered, but methods of age prevention are being tested by scientists with promising results. Recently, a study from Cedars-Sinai Medical Center has revealed that a bone marrow transplant can reverse some aging in mice.[1] An interesting study on its own, most people still just want to know if there are any implications for similar forms of treatment in human beings. The research team experimented with mice of different ages, specifically using a group of 4-month old mice and a group of 18-month old mice. The researchers transplanted bone marrow from the 4-month old mice to some of the 18-month old mice. For comparison, they also transplanted bone marrow from some of the 18-month old mice to other 18-month old mice. The researchers also kept a control group of 18-month old mice that received no transplant at all. A test consisting of several cognitive tasks was performed on the mice six months after the initial transplants. Activity levels were observed, pain-based fear was tested to observe memory in the hippocampus and amygdala, and a maze was introduced to test learning

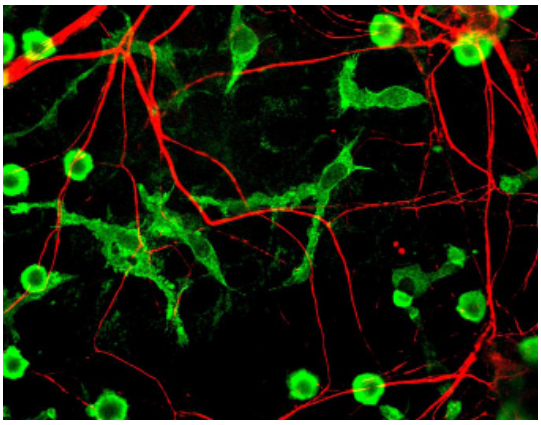


Figure 1. Neurons and microglia[5]

and a maze was introduced to test learning and memory. The researches put the mice into an unfamiliar environment and simply observed their behavior. The group of mice that had received transplants from the young mice were much more active and did more exploring than the other two groups of mice. This observation led the researchers to look at the effects of this transplant on the hippocampus to design the next two tests, as the hippocampus is often correlated with this explorative tendency.

To isolate the hippocampal activity, the researches conducted two different tests that were focused on fear. The researchers placed the mice into a specific place and gave them an electric shock. They then put the mice back in that location and observed. The method used to determine their memory of the event was how long the mice froze when initially placed down. The mice that received the transplants from the young mice froze for a significantly longer time than the other two groups. This indicates that these mice remembered the previous shock better than the two other groups. This type of memory heavily involves the hippocampus.

In contrast, the researchers carried out a similar experiment that used audio cues instead of a location. This would test for memory associated with the amygdala instead of the hippocampus. In this test, there was no significant difference between the three groups. The last test they carried out was a maze. They carried out the experiment twice. The first time, the mice with the bone marrow from the young mice made fewer mistakes than the other too groups, but not by a very significant margin. The researchers waited two days and repeated the experiment. This time, the mice with the one marrow from the younger mice performed much better than the other two groups. When they moved the location of the exit, the results were similar; the mice with the bone marrow from the younger mice performed similarly the first time, but when repeated later outperformed the others.

"Curing, or more likely, preventing these diseases would fundamentally change not only the length of the human life, but also the quality of life among older people"

From these tests, the researchers concluded that the transplanting of bone marrow from younger mice into older mice preserves the mice's hippocampus-associated memory. To gain further results, the researchers went in and looked at the mice's brains to examine the numbers of neurons and synapses. When they observed CA3, a dorsal region in the mouse hippocampus, they noticed that the mice with the bone marrow from the younger

mice had not lost as many neurons as the other two groups had. Those numbers were not incredibly significant, however, and many other brain regions found no conclusive differences as well. However, the researchers then looked at synapses and found significantly more synapses in the mice with the bone marrow from the young mice. This synaptic breakdown usually occurs before the neuronal breakdown, so it makes sense that the synaptic differences would be more apparent after only 6 months.

One last detail they discover is that the mice with the bone marrow from the young mice had noticeable difference in their microglia, a certain type of cell in the brain normally responsible for removing or repairing damaged cells.[2] The researchers were able to infer that the microglia possibly cause the breakdown of synapses by being overactive but having young blood in the body inhibits this activity. This gives a little more insight into the exact mechanism occurring in the mice brains. The study ultimately concludes that the bone marrow transplant from young mice into older mice prevents aging in the hippocampus by inhibiting synaptic breakdown by microglia.

In their conclusion, the researchers briefly discuss the human implications of this method of treatment for neural diseases such as Alzheimer's disease. They note that regular plasma transplantation is already occurring to treat Alzheimer's patients. However, these are done weekly, whereas the bone marrow in this experiment worked for six months, possibly indicating longer-term effects are possible. The researchers think that the procedure would be too risky to try on humans with current technology, but hope that in the near future, special care and advancements can be used to make it work out.[3] They hope treatment like this could be used not only in Alzheimer's patients, but also for other neurological disorders like Parkinson's.

Currently, there is no way to know for sure if this type of treatment would have any similar effects if tried on humans. The only way to determine this will be future testing. The results from the experiment, specifically the mechanisms by which the transplant inhibited aging, show no obvious signs that this cannot translate in some capacity to human beings. Except for the technological and safety barrier that is currently limiting this being used, it's certainly exciting to imagine what this could mean for the future.[4]

Even if this specific treatment option is not implemented soon, this study has still given lots of insight into why hippocampal memory declines with age. Now, other research teams can look into overactive microglia and the synapses in the brain to see if there are additional ways to inhibit this aging process specifically.

Those with family histories of diseases like Alzheimer's or Parkinson's could undergo some kind of treatment to prevent possible onsets of these diseases. However, nothing in this study really indicates some kind of cure. It doesn't seem like reversing the effects of Alzheimer's will be possible in the near future. Once the synapses are broken down and missing, they cannot be

simply rebuilt using the current knowledge and technology that exists right now. Of course, that doesn't discredit anything discovered here, as the ability to prevent Alzheimer's or similar neurological diseases would be an incredibly feat of medical science and would vastly improve the quality of life of those who are at risk for developing it. Hopefully, the base that this study has established can be further explored and such prevention can become a reality.

This test obviously has not provided a cure for aging, nor will it allow for eternal life. But age-related neurological diseases like Parkinson's and Alzheimer's are certainly in the way of expanding the human lifespan. Curing, or more likely, preventing, these diseases would fundamentally change not only the length of the human life, but also the quality of life among older people. Heart disease, cancer, and neurological disorders are all leading causes of death in the United States and being able to prevent any one of these would help countless people live longer lives.

When people discuss eternal life, they often don't think about it in this medicinal and scientific way. The ethics of living forever have been seen as complicated, but it's rare that someone would be opposed to finding cures for deadly diseases. If humans are to come anywhere close to eternal life, it will not be through a magic pill, it will be through eliminating the things that prevent eternal life: the things that kill people. The term eternal life can certainly be provocative, but upon a closer inspection, the form it may one day be realized in is not very controversial.

Hopefully, whatever such treatment arises becomes available to as many people as possible. In the United States there is already an issue with the cost of medical treatment and its accessibility to poorer people. If the treatment were to be in any way similar to the kind discussed in this study, it would necessitate a blood marrow donor of a pretty specific age. Organ and blood donations are always in short supply, so this treatment would be no different. This is a dangerous transplant with current technology already, and combined with the scarcity of donors, this treatment would likely be unavailable to most poor people in America. They would certainly not be the first ones on the list to get this treatment. Since this is preventative and not a cure, some may find it easier to deny poor people access to it as there is already a chance the person may never develop a neurological disease anyway.

But hopefully this is not the case. Medical discoveries are infinitely more impactful when they can be used to help as many people as possible. As powerful as its impact could be on a select few people, it would be much better to spread its implementation far and wide. The politics of healthcare must be quick to catch up to medical advancements to ensure that even treatments like this that might ordinarily be expensive are widely available and affordable. If humans are to take a crack at achieving eternal life, it cannot be for the rich alone.

References

[1] Robitzski, D. (2019, February 21). New data: Bone marrow transplants prevent aging. Retrieved from https://futurism.com/bone-marrow-transplants-prevent-aging

[2] Microglial function in the Healthy Brain. (n.d.). Retrieved from https://faculty.sites.uci.edu/kimgreen/bio/microglia-in-the-healthy-brain/

[3] Das, M. M., Godoy, M., Chen, S., Moser, V. A., Avalos, P., Roxas, K. M., . . . Goodridge, H. S. (2019, February 20). Young bone marrow transplantation preserves learning and memory in old mice. Retrieved from https://www.nature.com/articles/s42003-019-0298-5#Abs1

[4] Cedars-Sinai Medical Center. (2019, February 20). Young bone marrow rejuvenates aging mouse brains: Transplanting marrow from young lab mice to old mice preserves memory and learning skills. ScienceDaily. Retrieved from www.sciencedaily.com/releases/2019/02/190220103341.html

[5] Shaw, G. (2005, July 25). File:Microglia and neurons.jpg. Retrieved from https://commons.wikimedia.org/wiki/File:Microglia_and_neurons.jpg

Synthetic Virology: Engineering a Future of Uncertainty

Hilina Seifu

ABSTRACT

This article discusses the new and growing field of synthetic virology and whether the research opportunities it creates should be feared or welcomed.

What do you think of when you hear the word "synthetic"? Is it artificial intelligence? Prosthetics? Or is it...viruses? Little vehicles of destruction and death (as they are often portrayed), modified and enhanced to do their job that much better. When that job is solely to infiltrate cells and kill them in the name of their own replication, is this portrayal of viruses really so shocking? So, then, you might ask yourself, "Why on Earth would anyone want to synthesize these things?"

The relatively new field of synthetic virology isn't really about the creation of viruses so much as the reprogramming of viruses as nanodevices that can be controlled. [4] Viruses are uniquely useful because their relative simplicity makes them easy to study and characterize genomically; this means modification and replication of their genetic structure and function is not a difficult task. [4] Replacing harmless viral DNA with human genes that could allow scientists to deliver healthy copies of human genes to cells and bodies that lack properly-functioning versions of these genes. [9] Thinking ambitiously, this genetic modification would allow future scientists to, " ...prevent or cure infectious diseases, cure genetic deficiencies by delivering genes or treat cancer..." [3]

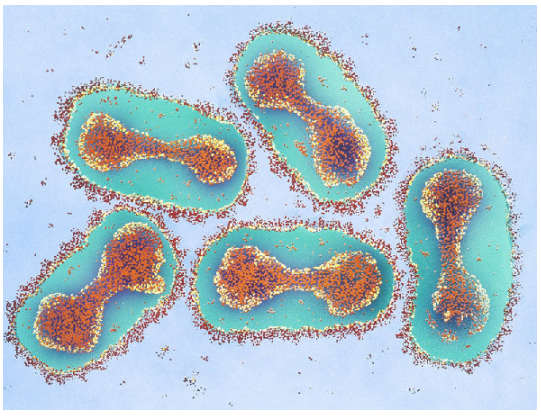


Figure 1. Smallpox virus, the real target of the resurrected horsepox. Bjornberg, C. (n.d.). Smallpox Virus

Synthetic virology is not just some futuristic dream. Scientists for the past few decades have been harnessing viruses to deliver genes into host cells. [5] Viruses used in gene therapy have been instrumental in treating viral infections such as herpes by deleting malicous viral genomes to alter viral replications in a safe way. [6]

If viral modification can be so instrumental in the treatment of disease and possibly cancer, is there reason to fear it?

Characterized by high fever and iconic rashes and sores, the world was happy to officially declare the fatal smallpox eradicated in 1980 ("Smallpox"). Smallpox no longer occurs naturally, and the only two remaining samples are safely tucked away in a secure lab in the U.S. and in Russia, never to be worried about again, at least, until recently. [3] In 2017, Canadian researcher David Evans and his team synthesized horsepox, the once-extinct cousin to smallpox, for the low price of $100,000. Evans' intention was to synthesize a safer version of the smallpox vaccine. The fear lies not in the spread of horsepox, but in the fact that scientists have the ability to create potentially deadly viruses from scratch[3, 1]. One hundred thousand dollars is a relatively cheap price to pay for the power to potentially devastate humanity, so the question remains: do we have something to fear from Evans' experiments? The fear lies in terrorists knowing the formula for viral creation and modification and cooking up a terrifyingly effective new brand of bioterrorism. Following news of Evans' creation, some critics believed that, "...making horsepox in the lab has endangered the public by basically revealing the recipe for how any lab could manufacture smallpox as a bioweapon." [3] Many even fought against publication to keep Evans' methods a secret.

"If viral modification can be so instrumental in the treatment of disease and possibly cancer, is there reason to fear it?"

Certainly, Evans' experiment has created a lot of fear within the scientific community as the threat of bioterrorism \increased with each new development. One of the primary concerns is the ease with which Evans' experiments can be recreated with different, deadlier viruses. The information is readily available, as the genomes of nearly all mammalian viruses are available in a database. Furthermore, Evans' process of synthesizing a virus is relatively simple with some background. Evans' experiment means that any terrorist or criminal with the right know-how could be able to create, resurrect, or modify powerful and destructive viruses. The US National Academy of Sciences recognizes synthetic biology and its connection to bioweapons as a threat of highest concern. "It requires some expertise,but it's something that's relatively easy to do, and that is why it tops the list" said Michael Imperiale, chair of the Academy's report committee. [7]

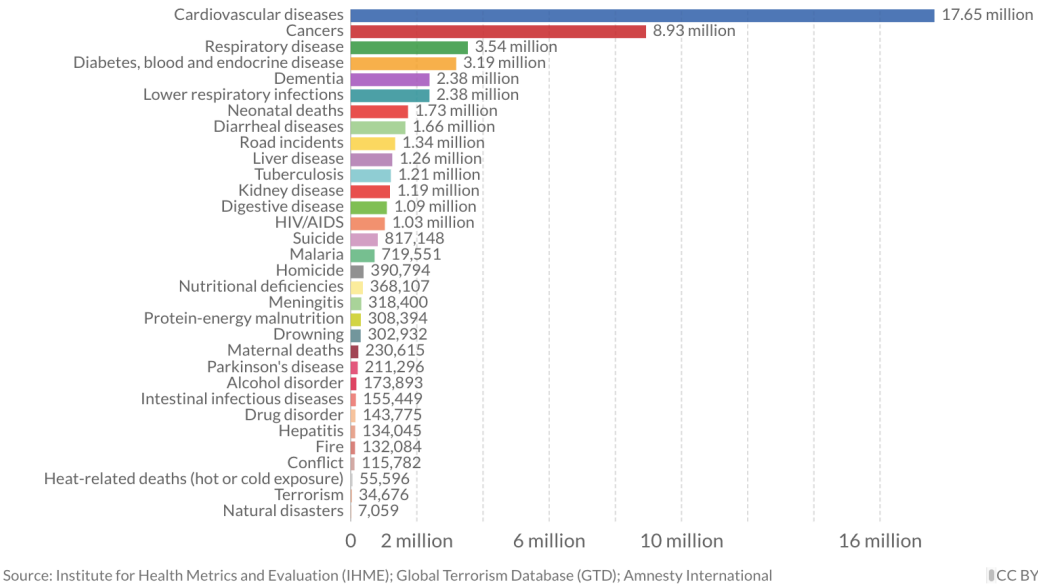


Figure 2. Graph of the leading causes of death worldwide. Many of which could be reduced with further study into and application of the field of synthetic virology, such as cancer and viral infections. Reprinted from "Causes of Death," by Ritchie, H., & Roser, M, Feb 2018. Retrieved from https://ourworldindata.org/causes-of-death

But these are just possibilities. As of now, it is too soon to know the effects of Evans' experiments; questions that remain include whether or not people will take advantage of his findings, whether they will be successful in recreating his experiment, and whether their own experiments have any impact. At this point, all anyone can do is predict.

However, one thing is known: how useful synthetic virology could prove to be in the future. It certainly increases the risk of the creation of bioweapons, but it also creates more possibilities for healing, in previously unimagined capacities. Scientists are currently in the process of reprogramming viruses to fit important needs, such as cancer and a number of cardiovascular diseases. These would become activated when they encounter particular enzymes, like extracellular proteases which are present in diseases characterized by inflammation. [5]

Additionally, bioterrorism is not restricted to synthetic biology. Even now, the Center for Disease Control stockpiles samples of the smallpox vaccine in the event that smallpox ever gets out and gets used as a bioweapon. [3] Synthetic virology may promote bioterrorism, but it can also defend against the world's already existing bioweapons. Synthetic virology has a number of benefits, yet its potential harms are just hypothetical. There is no clear idea of how or if it will ever be used for bioterrorism. To let fear limit development clashes fundamentally with human nature. Every day, people get into cars with a 1/100 chance of killing them. Dangerous house pets such as snakes kill about 20,000 people annually. Illnesses like influenza can kill about 50,000 people per year. [2] Still, people persevere. People continue to compete

in street races, cuddle up to their boa constrictors, and refuse flu shots. Humanity is defined by persistence, often through much worse odds, and human nature will not allow the field of synthetic virology to end now, while there is still so much potential and we have so many unanswered questions. Furthermore, if any virus were to destroy humanity, it likely would not be synthetic viruses, but the natural ones we already face, like Ebola. [8] As the Bubonic Plague, Spanish Flu, and a number of other nasty diseases have shown, humanity has a tendency to bounce back. With synthetic virology, maybe humanity can subvert these tragedies.

References

[1] Branswell, H. (July 7, 2017). Scientists Recreate and Extinct Virus, Triggering New Warnings About Controversial Research. Retrieved from https://www.statnews.com/2017/07/07/smallpox-relative-extinct/

[2] Geggel, L. (Feb 9, 2016). The Odds of Dying. Retrieved from https://www.livescience.com/3780-odds-dying.html

[3] Greenfieldboyce, N. (Feb 17, 2018). Did Pox Virus Research Put Potential Profits Ahead of Public Safety? Retrieved from https://www.npr.org/sections/health-shots/2018/02/17/585385308/did-pox-virus-research-put-potential-profits-ahead-of-public-safety.

[4] Guenther, CM., Kyupers BE., Lam, MT., Robinson, TM., Zhao, J., & Suh, J. (Sep 4, 2014). Synthetic Virology: Engineering Viruses for Gene Delivery. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25195922

[5] Junghae, S. (Dec 2, 2016). Synthetic Virology: Reprogramming Viruses into Controllable Nanodevices [Abstract]. (n.d.). Retrieved from http://www.bme.uh.edu/research/seminar/201612/synthetic-virology-reprogramming-viruses-controllable-nanodevices

[6] Nayerossadat, N., Maesah, T., Ali PA. (July 6, 2012). Viral and Nonviral Delivery Systems for Gene Delivery [Abstract]. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/?term=Maedeh%20T%5BAuthor%5D&cauthor=true&cauthor_uid=23210086

[7] Sample, I. (June 19, 2018). Synthetic Biology Raises Risk of New Bioweapons, US Report Warns. Retrieved from https://www.theguardian.com/science/2018/jun/19/urgent-need-to-prepare-for-manmade-virus-attacks-says-us-government-report

[8] Singer, E. (May 30, 2006). The Dangers of Synthetic Biology. Retrieved from https://www.technologyreview.com/s/405882/the-dangers-of-synthetic-biology/Smallpox. (n.d.). Retrieved from https://www.cdc.gov/smallpox/index.html

[9] Weidman, C. (Jan 9, 2018). Viruses, Not All Are Bad for You. Retrieved from http://sitn. hms.harvard.edu/flash/2018/viruses-not-all-are-bad-for-you/

[10] Wimmer, E., Mueller, S., Tumpey, TM., Taubenberger, JK. (Dec 27, 2009). Synthetic Viruses: a New Opportunity to Understand and Prevent Viral Disease. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2819212/

Uploading the Mind: The Basics and Ethics of Whole Brain Emulation

Michelle Ng Perez, Rachel Cohen

ABSTRACT

Whole brain emulation (WBE), or "mind uploading", is the process of copying the functions of a brain onto a software, resulting in an emulation that can essentially simulate the processing of the original brain. Though only a hypothetical process now, technological advances and extensive research promise the actualization of WBE. This technology can be used to further understand how the brain works and to preserve human minds in software after their biological bodies fail. However, there are many ethical complications in attempting to perfect and use WBE.

The main question is: can you upload your mind to a computer? If you run the computer simulation, can that simulation be identified as you? These are questions that arise when considering whole brain emulation, the hypothetical process of creating a one-to-one model of the human brain in a computer. There are several reasons why WBE is a common goal for many researchers and scientists. As knowledge in the various fields of neuroscience, computer science, and engineering grow, the world inches closer to the reality of WBE. We must grapple with serious ethical and philosophical obstacles before attempting WBE and making it a widespread process. Some of these roadblocks include experimentation on animals and humans, and the moral status of an emulation.

WBE sounds like science fiction. However, with rapid technological advances in various fields in neuroscience and engineering as well as the passionate drive to continue research on the human brain and artificial intelligence, it may not be too far-fetched. The field of computational neuroscience has already made great strides in attempting to accurately model neurons and brain systems. The brain functions like a computer, processing and responding to information in a rapid fashion that can often be analyzed mathematically. For example, the action potential—a neuron's basic function and mode of communication—is an all-or-nothing phenomenon that is analogous to the binary code of a computer. There are many proposed methods of achieving a successful whole brain emulation that rely on the mathematical nature of the brain. These methods involve a transfer from biological to digital processing, from the brain to the computer, that is either instantaneous or gradual. In instantaneous transfer, a brain is

scanned and destroyed at the same time that its information is transmitted to a computer. [1] This is a destructive method. On the other hand, gradual transfer takes more time. An example of a gradual transfer is the replacement of each piece of the brain with a neural prosthetic device until all parts of the brain is computerized.[2] Researchers and proponents of WBE have created projects to expand upon these methods in scientific details in order to foster the science of WBE. Such projects include the Blue Brain Project, DARPA's SyNAPSE (Systems of Neuromorphic Adaptive Plastic Scalable Electronics) program, and the nonprofit organization Carboncopies. Why attempt WBE? One practical reason is that it would help explain how the brain works. Brain emulation would make significant contributions to neuroscience research that will allow for an ideal subject for neuroscientific experimentation and study. For example, controlled simulations of damage to the brain, such as a stroke, could be created using the emulation to see how the brain would respond to certain stimuli or treatments. It would also further research in computational neuroscience and help progress artificial intelligence. A more philosophical reason is to enable people's minds to exist as a computer after their bodies perish. WBE would enable a kind of "digital immortality" that could push the limits of human biology and help people to continue to live after their organic bodies fail them.[3] However, this potential power carries great ethical concern. The pursuit of making WBE possible would require experimentation on animals and humans that may induce suffering and even death. Scientists would have to use in vivo preparations as well as in vitro experiments to compare with the in models. As scientists inevitably move their experiments from nematode worms to primates to humans, the process becomes more charged with ethical problems.[4]

"WBE would enable a kind of 'digital immortality' that could push the limits of human biology and help people to continue to live after their organic bodies fail them"

Another issue is how to obtain informed consent from people to become an emulation. Destructive transfer—leading to the destruction of the original brain—would be an unusual case of assisted suicide. It would carry the same ethical considerations as physician assisted suicide, with the additional weight that the subjects would be ending their lives for the sake of science rather than to escape pain (as in the case of physician-assisted suicide). These human experiments would also go against regulations of research outlined in the Nuremberg Code of World War II.[5] For instance, the fourth point of the Nuremberg Code states: "The experiment should be so conducted as to avoid all unnecessary

unnecessary physical and mental suffering and injury." [6] For the first of the WBE experiments involving human subjects, the risks of suffering, injury, and death may be too great for the slim chance of success. Nondestructive transfer would be an even trickier subject we must deal with, as the risks and benefits of WBE in this case would be more unclear in the first of the WBE trials with human subjects.

Figure 1. WBE relies on the notion that the functions of the brain and of computers are very similar. For example, an action potential can be seen as a sort of binary code.

If WBE is perfected, and the entire physiology of a human brain can be virtually uploaded to a computer, would the resulting emulation have the same identity or consciousness as the original person? This question is important when considering the philosophical implications of WBE and its promise to allow us to somehow overcome biological death. The definition of "personal identity" and even "personhood" is a rich topic in philosophy, and how one approaches the identity issue of WBE depends on one's opinions on this topic. Some view one's mind and identity as an immaterial soul, while others focus on how neurons physically instantiate the mind or how a "person" consists of one's memories and cognitive abilities. Some even think that the notion of a "self" is an illusion; that "there is no survival because there is no person". [1]

One view of the matter is that if consciousness and intentionality, essential factors of our identity, are not transferred to the computer, then we won't be able to survive WBE after all. Many philosophers argue that there's something about the human brain that makes it fundamentally different than computers. While we think of the right answers, a computer would only process the right outputs by running a program that humans created. For example, there may be a distinction between a computer manipulating symbols to arrive at a checkmate in a chess game and the genuine reasoning of a person's brain to get the same result. Though this distinction is somewhat abstract, many philosophers think that intentionality plays an important role. The argument is that a computer's output can never be wholly intentional on the computer's part, and so the computer would not have a consciousness regardless of how powerful it is technologically.[7] Though we may model the many neurological functions of the brain as accurately as we can, genuine human consciousness is instantiated by something more profound that cannot be replicated technologically.

If the resulting emulation would contain a consciousness comparable to that of a human, it would probably have the same moral rights as a human would. After all, the emulation is you, with all your conscious abilities, memories, and intentions, just substantiated by different materials. This poses

another ethical issue about how to treat emulations, especially since the first emulation resulting from successful WBE would most likely be created for the sole purpose of study and experimentation. One proposal is the "Principle of Assuming the Most" (PAM), in which researchers assume that "any emulated system could have the same mental properties as the original system and treat it correspondingly". [5] This means that a system of good practice for the treatment of emulated animals and humans must be developed, similar to that of the treatment of biological animals and humans that already exists. WBE has the potential to make many useful contributions to science and artificial intelligence. It may even have the power to help humanity overcome death. However, in pursuit of this promising technology, the world must be wary of letting technological progress surpass its current understanding of ethics and philosophy. The issues inherent in the technology must be handled so that human morals are not lost to computers.

Figure 2. How is a computer winning a chess game different from a person winning? Is there a difference at all? Successful WBE requires the transfer of all the cognitive capacities, such as decision-making and intentionality, that make us who we are.

References

[1] Corabi, Joseph., and Schneider, Susan. "If You Upload, Will You Survive?." Intelligence Unbound: The Future of Uploaded and Machine Minds, edited by Russell Blackford and Damien Broder ick. John Wiley & Sons, Inc., 2014, 134-135. Web. 22 October 2018.

[2] Frequently Asked Questions. Carboncopies. https://carboncopies.org/faq/

[3] Bostrom, Nick., and Sandberg, Anders. "Whole Brain Emulation: A Roadmap." Technical Report #2008-3. Future of Humanity Institute, Oxford University, 2008, 5. Web. 22 October 2018.

[4] Sandberg, Anders. "Ethics of brain emulations." Journal of Experimental & Theoretical Artificial Intelligence, 2014. Vol. 26, No. 3, 439-457. 440-441. Web. 23 October 2018.

[5] Sandberg, Anders. "Being Nice to Software Animals and Babies." Intelligence Unbound: The Future of Uploaded and Machine Minds, edited by Russell Blackford and Damien Broderick. John Wiley & Sons, Inc., 2014, 290-296. Web. 22 October 2018.

[6] Office of NIH History. "Laws Related to the Protection of Human Subjects: The Nuremberg Code." Web. 8 February 2019. https://history.nih.gov/about/timelines/nuremberg.html

[7] Agar, Nicholas. "On the Prudential Irrationality of Mind Uploading." Intelligence Unbound: The Future of Uploaded and Machine Minds, edited by Russell Blackford and Damien Broderick. John Wiley & Sons, Inc., 2014, 156. Web. 22 October 2018.

Health is Happiness

Selena Kim

ABSTRACT

Junk food is very mainstream and is considered an instant stress reliever, which is an underlying reason that people are blinded by the fact that it is not good for physical or mental health. In this article, the reasons that people continue to opt out for "unhealthier" options in food are discussed, and we look at the effects junk food has on mental and physical health. Junk and fast foods lack essential nutrients, and when a person is depleted of those nutrients, mental distress may build up as a result. On the other hand, a healthy diet triggers a positive cycle linked with increased dopamine levels and eventually better mental health.

When given the keyword "food," junk food is one of the most commonly thought of foods. Ranging anywhere from chips at your local convenience store or takeout from your favorite fast food place, junk food is one of the most idealized foods these days because of how convenient and cheap it is. Especially in modern day America, it doesn't take much for one's diet to become centered around junk food. Take exhibit A, for example. Jane is in her 40s and works at a demanding law firm in Manhattan. She has to get to work by 9 AM so she skips breakfast. By 12 PM, she realizes how swamped she is with work that she steps outside for a quick breather and gets a pizza from one of the food trucks. It's oily and greasy but she doesn't mind because it's quick and cheap. To overcome the afternoon slump, she snacks on a bag of salted chips. She's working in the office late as per usual plus she's on a tight financial budget, so she gets Chinese takeout, which of course, is heavy in sodium and oil. This is Jane's diet. She simply doesn't have time to prepare healthy meals in advance, or to even think about the quality of her food. Despite junk food being tasty, studies show that eating it on a regular basis can increase heart disease,

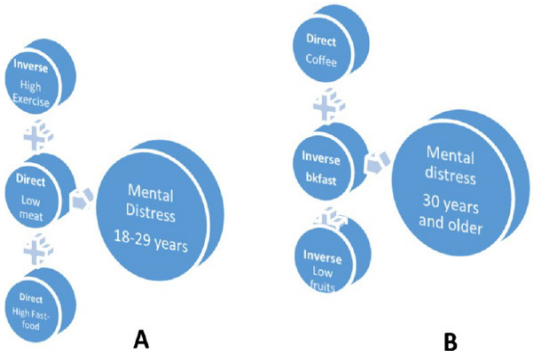


Figure 1. The relationships between high exercise, low meat, high fast food, coffee, breakfast, and low fruits on young adults (Group A) vs. mature adults (GroupB)

cause type 2 diabetes, damage your liver, impair digestion—just to name a few detrimental effects.[4] More recently, it is shown that consuming junk food over a long period of time can lead to psychological distress. Fast food consumers are aware of this, but why don't they change their diet? It's convenient, cheap, and tasty. The level of instant gratification consumers get from junk food is so high that they fail to consider long-term downsides.

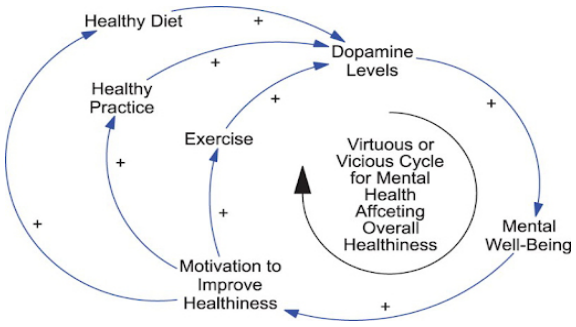
We tend to crave junk food because it is high in sugar, which releases neurons like dopamine, noradrenaline, and serotonin, known as the feel-good hormones. The mind takes note of what made us so happy, and the next time we feel down, we're reminded of how a certain junk food satisfied us at the time. Sugar addiction can be subtle because it is embodied within the foods we eat and often goes unnoticed. This explains why we tend to crave unhealthy foods high in sugar rather than something healthy, and why comfort foods are associated with fast foods. It is a temporary stress-reliever and releases the "happy" chemicals in our brain.

Apart from reasons that induce instant gratification, it is also hard to eat healthy on a budget. Junk foods tend to be cheaper since the price is on par with the quality of the food. This reason works for those who want to save money, which is a big majority of the population. Some may think that a couple dollars more to get healthier foods isn't that much, but food system doesn't seem to support that. For example, adding any type of protein (chicken, tofu, shrimp, etc.) to some meals in restaurants costs extra money, which works against the notion of healthy eating. If customers are essentially "forced" to pay extra to make their meals taste better, we can't avoid the fact that some people may end up opting out to cheaper options like a hot dog or sandwich. Additionally, organic foods, which some people strongly believe that it is the healthier option to foods, are more expensive than non-organic foods. The general trend here seems to be that eating healthier costs extra money that not everyone is willing or able to spend. Food is not necessarily the first thing on one's mind when facing any type of financial issues.

"Sugar addiction can be subtle because it is embodied within the foods we eat and often goes unnoticed"

The Loma Linda University Adventist Health Sciences Center in California conducted a study of 240,000 telephone survey found that "nearly 17 percent of California adults are likely to suffer from mental illness -- 13.2 percent with moderate psychological distress and 3.7 percent with severe psychological distress."[3] The team's findings indicated that "dietary

interventions for people with mental illness should especially target young adults, those with less than 12 years of education, and obese individuals."



The figure above is from a study in 2017 and shows that fast food has a direct relationship with mental distress. This makes sense because fast food lacks essential nutrients and is high in saturated, trans- and omega-6 fatty acids. Over time, these fatty acids are conducive to low-grade inflammation (LGI), which is associated with symptoms of anxiety and depression. The study also states that "dietary omega-6 fatty acid (linoleic acid; 18:2n-6) is metabolized systemically into arachidonic acid (20:4n-6), a precursor for prostaglandins PGE2."[1] Therefore, if fast food is consumed frequently, it may result in mental distress due to buildup of LGI and a lack of essential nutrients. Studies show that while an unhealthy diet cannot necessarily "create" distress, it is possible to aggravate one's distress.[2] People often experience stress in life from factors like work, relationships, or academics. However, this stress could be greatly reduced by adjusting one's diet. The same study from 2017 shows that a cycle of a healthy diet, healthy practice, and exercise increase dopamine levels, which ultimately promote mental well-being.

Society needs to be more cognizant of how much their life can be affected by a healthy or unhealthy diet. The base of people consuming an unhealthy diet mainly stems from the lack of proof and physical evidence of how detrimental an unhealthy diet can be to the body.

References

[1] Begdache, Lina. "Assessment of Dietary Factors, Dietary Practices and Exercise on Mental Distress in Young Adults versus Matured Adults: A Cross-Sectional Study." Taylor & Francis, 11 Dec. 2017, www.tandfonline.com/doi/full/10.1080/1028415X.2017.1411875.

[2] Hare, Holly Van. "Fast Food Really Can Cause Mental Distress, Study Says." The Daily Meal, 18 Dec. 2017, www.thedailymeal.com/healthy-eating/fast-food-mental-distress-study/121817.

[3] "Junk Food Is Linked to Both Moderate and Severe Psychological Distress." ScienceDaily, ScienceDaily, 21 Feb. 2019, www.sciencedaily.com/releases/2019/02/190221111701.htm.

[4] Rupavate, Shraddha. "10 Reasons Junk Food Is Bad for Your Health." 10 Reasons Junk Food Is Bad for Your Health, 3 Nov. 2014, www.msn.com/en-in/news/other/10-reasons-junk-food-is-bad-for-your-health/ar-AAbPYz.

[5] Verma, Prakhar. "Craving Junk Food? Here Are The 2 Most Common Reasons." Fit Yourself Club, Fit Yourself Club, 21 Jan. 2018,fityourself.club/craving-junk-food-here-are-the-2-most-common-reasons-ba6b5a343afd.

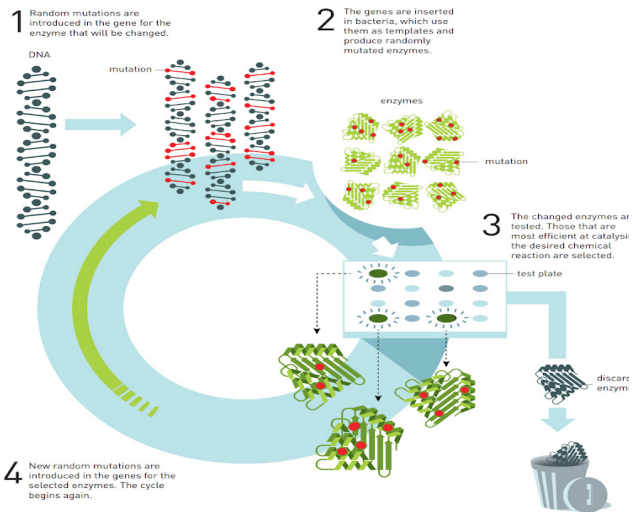
The Evolving Potential of Proteins

William Shao

ABSTRACT

Proteins, in addition to serving as building blocks for the human body, have found essential roles in medicine and industry. They serve as the driving force behind both manufacturing processes and treatments of debilitating disease, simultaneously pushing the envelopes of multiple scientific disciplines. The natural desire to better harness the protein framework's potential has resulted in remarkable progress within the nascent field of protein engineering. Directed evolution, the spearhead of this pioneering wave of innovation, should serve as a learning opportunity for scientists still using the antiquated scientific thought process.

Proteins are some of the most ubiquitous and important building blocks of life. These molecules serve in roles ranging from the seemingly mundane task of forming our skin and hair to the critical one of transporting oxygen in our blood. The existence of functional proteins is indeed a testament to the power of nature, as it is estimated to take more than one quadrillion (10^{15}) years for a protein to accrue the necessary mutations to acquire a new function. [1] No other molecule yet discovered, synthetic or natural, can perform the functions of proteins nearly as well. This realization has motivated scientists to build upon the existing framework offered by nature, giving rise to the field of protein engineering.

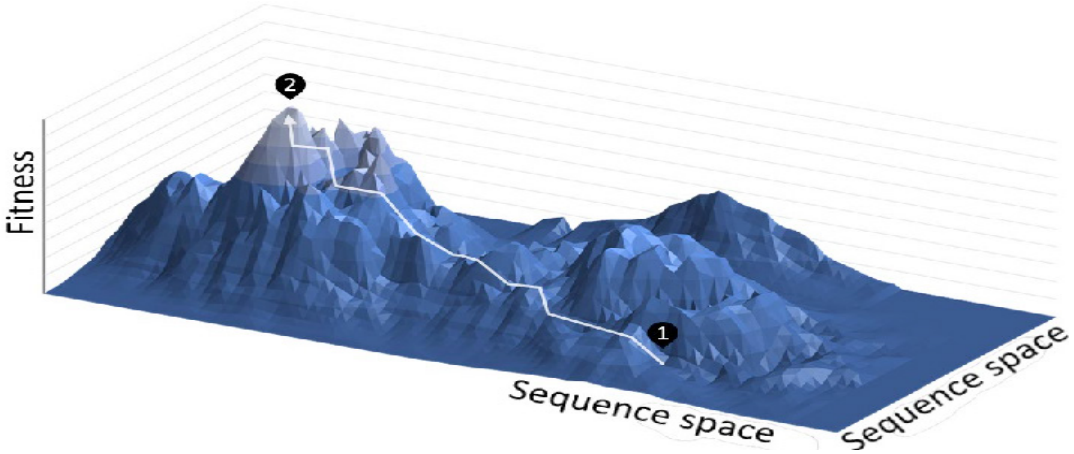


The field of protein engineering developed in the 20th century with a goal similar to most other engineering disciplines of the time: to follow the conventional method of designing and innovating using existing knowledge. However, very little was known about the details of protein synthesis. This glaring gap in scientific knowledgeintimidated most scientists and hindered the efforts of those willing to step up to the challenge. To this day, the landscape of protein synthesis is still largely unexplored

despite the efforts of biochemistry researchers throughout history. As the progress of rational design stalled, protein engineers began turning to the idea of directed evolution: accelerating nature's in-house design process to create more effective – and sometimes novel – proteins.

The theory behind directed evolution was first introduced by Nobel Prize-winning chemist Manfred Eigen in 1984, who proposed inducing mutations in existing proteins and then screening these for desired phenotypes in an iterative process dubbed the "evolutionary machine". [2] About a decade later, Frances H. Arnold of the California Institute of Technology successfully applied Eigen's theory to subtilisin E, a protein commonly added to detergents to aid in removing stains. [3, 4] Based on her colloquial logic of "you don't get a racehorse from a donkey", Arnold began her process by selecting a suitable enzyme for her goal. [5] She then created a DNA-sequence library from subsets of the sequence where mutations would likely result in phenotypical changes, based on experimental evidence and rational design. [2] After identifying the necessary criteria for assessing the fitness of the protein, she began the iterative process of inducing mutations through error-prone PCR and screening the proteins. [2] Using this method, she created a competent subtilisin E variant capable of 256 times the activity level of the original enzyme after only three generations of compounded mutations. [6] When she performed post-experiment analysis of the new protein, she found the presence of a combination of 10 different mutations, demonstrating the potency of directed evolution when used in coordination with elements of rational design [6] For this pioneering experiment

"By targeting the core molecular mechanisms through which food is created, protein engineering proves to be an enormously powerful tool which can ease the burden society's growth is imposing upon itself"



and for her following work, Frances H. Arnold of the California Institute of Technology recieved the Nobel Prize in Chemistry in 2018. Even in rational design experiments, directed evolution is now accepted as a necessary component in "a final optimisation step" – in no small measure due to Arnold. [2] Currently, the method of directed evolution is the most common protein engineering strategy alongside rational design, and is continuously being refined in labs around the world.

The proof-of-concept for directed evolution has led to far-reaching impacts on various industries, all of which have found uses for different types of proteins. Proteases and lipases are used in detergents to clean protein-based stains, biofuels can be created through alcohol synthesis pathways utilizing enzymes found in E. coli bacteria, and protein-based pharmaceutical compounds are used to treat diseases such as metastatic cancer and macular degeneration. [2, 7,8] These are but a few of the numerous applications of proteins, showing just how versatile and prevalent they are in our daily lives. The tangible effects of protein engineering can already be seen in, improved efficiency of industrial chemical reactions, immunotherapeutic drugs with milder side-effects, and environmental-friendly reactions using novel biocatalysts which produce less waste. [9]

Perhaps most importantly, protein engineering has the potential to determine the future of agriculture. It is estimated that by 2050 we will have a total world population of over 9 billion people, presenting an enormous challenge to the agricultural industry as it is now. [10] Jonathan Foley, director of the Institute on the Environment at the University of Minnesota, presents his plan on how to tackle the challenge of ramping up food production in his "Five-Step Plan to Feed the World". [10] Steps 1 and 2 are to freeze our agricultural footprint and grow more on existing farmland – both of which protein engineering is pertinent to. To accomplish these first two steps, scientists have been working to improve the inefficient Rubisco protein in plants. [11] Rubisco is responsible for carbon fixation within plants, allowing for the generation of biomass and thus food. Yet this protein is hampered by its tendency to fix oxygen, an alternate biochemical pathway that is functionally worthless to humans. [11] If Rubisco could be altered mutagenically to favor the carbon fixation pathway, crop yields should improve. The major roadblock to applying protein engineering to Rubisco has been the difficulty in expressing the Rubisco enzyme in a functional form within bacteria. In 2017, a team at the Max Planck Institute of Biochemistry finally overcame this obstacle, opening the way for other researchers to begin applying the method of directed evolution to Rubisco. [12] Other proteins that are good candidates for improvement include Cry1Ac, an insecticidal toxin, and EPSPS, an enzyme important to amino acid production. [13] By targeting the core molecular mechanisms through which food is created, protein engineering proves to be an enormously powerful tool which can ease the burden society's growth is imposing upon itself.

Despite being a relatively young field, scientists have already demonstrated that protein engineering is a force to be reckoned with when it comes in societal impact. The success of the field makes protein engineering an excellent case study for the scientific world: great breakthroughs can arise from basic concepts, with a little help from creativity. Borrowing the traditionally biological concept of evolution enabled protein engineers to utilize their knowledge of chemistry to an unprecedented extent. It follows logically that researchers from other fields also have much to gain from deriving inspiration from distant disciplines. As Frances Arnold so succinctly puts it at the end of her Nobel Prize acceptance speech: "By marrying these different fields, it's like you're in a goldmine of possibilities".[5] Scientists are slowly learning to look beyond the wealth of knowledge they hold in their narrowly focused specialties, and trying their hand at intertwining the different threads of science to form better solutions to increasingly complex problems. Evolution has helped us unlock the potential of proteins. Perhaps cross-disciplinary creativity can do the same for science.

References

[1] Gauger, A. (2018, October 04). It's Not "Evolution" - A Nobel Prize for Engineering Enzymes. Re trieved from https://evolutionnews.org/2018/10/its-not-evolution-a-nobel-prize-award-for-en gineering-enzymes/

[2] Directed Evolution of Enzymes and Binding Proteins. (2018, October 03). Retrieved from https:// www.nobelprize.org/uploads/2018/10/advanced-chemistryprize-2018.pdf.

[3] Crabb, W. D. (n.d.). Subtilisin: Commercially Relevant Model for Large-Scale Enzyme Production. Retrieved from https://pubs.acs.org/doi/abs/10.1021/bk-1991-0460.ch007

[4] Press release: The Nobel Prize in Chemistry 2018. (2018, October 03). Retrieved from https://www. nobelprize.org/prizes/chemistry/2018/press-release/

[5] Prize, N. (2018, December 08). Retrieved from https://www.youtube.com/watch?v=6hOZ5e0g9Uo

[6] Fernholm, A. (2018, October 03). A (r)evolution in chemistry (C. Barnes, Trans.). Retrieved from https://www.nobelprize.org/uploads/2018/10/popular-chemistryprize2018.pdf

[7] Tide Detergent Ingredients A to Z. (n.d.). Retrieved from https://tide.com/en-us/ingredients/tide-de tergent-ingredients-a-to-z

[8] Lagassé, H. D., Alexaki, A., Simhadri, V. L., Katagiri, N. H., Jankowski, W., Sauna, Z. E., & Kim chi-Sarfaty, C. (n.d.). Recent advances in (therapeutic protein) drug development. Retrieved from https://f1000research.com/articles/6-113/v1

[9] Kapoor, S., Rafiq, A., & Sharma, S. (2017, April 13). Protein engineering and its applications in food industry. Retrieved from https://www.tandfonline.com/doi/pdf/10.1080/10408398.2014.92204 3?needAccess=true

[10] Foley, J. (n.d.). A Five-Step Plan to Feed the World. Retrieved from https://www.nationalgeograph ic.com/foodfeatures/feeding-9-billion/

[11] Society, M. (2017, December 08). The future of crop engineering . Retrieved from https://phys.org/ news/2017-12-future-crop.html

[12] Aigner, H., Wilson, R. H., Bracher, A., Calisse, L., Bhat, J. Y., Hartl, F. U., & Hayer-Hartl, M. (2017). Plant RuBisCo assembly in E. coli with five chloroplast chaperones including BSD2. Science, 358(6368), 1272-1278. doi:10.1126/science.aap9221

[13] Engqvist, M. K., & Rabe, K. S. (2019). Applications of Protein Engineering and Directed Evolution in Plant Research. Plant Physiology,179(3), 907-917. doi:10.1104/pp.18.01534

America's Immigration Conundrum: A Practical and Philosophical Discussion with Illegal Immigrant-turned-Neurosurgeon Dr. Alfredo Quiñones-Hinojosa

Gugan Raghuraman, Teja Yeramosu

ABSTRACT

In what follows, we will explore both pragmatic and philosophical arguments raised by pro- and anti-immigration groups, and explore an inspirational and humbling interview with Dr. Alfredo Quiñones-Hinojosa, an illegal immigrant from Mexico who is now a world-renowned neurosurgeon, researcher, author, and the Chair of Neurologic Surgery at the Mayo Clinic.

The plaque on the Statue of Liberty, a universal symbol of freedom, democracy, and the American Dream, reads, "'*Keep, ancient lands, your storied pomp!' cries she with silent lips. 'Give me your tired, your poor, your huddled masses yearning to breathe free, the wretched refuse of your teeming shore. Send these, the homeless, tempest-tost to me, I lift my lamp beside the golden door!*'"[1] These optimistic sentiments are reminiscent of a century-old America, where the overall denial rate for immigration at Ellis Island – an 1892-1954 immigration checkpoint for millions of individuals from Africa, Asia, and Europe – was around 2% (immigrants from Latin America traveled by land and did not need a checkpoint).[2] In 2018, the US Citizenship and Immigration Services agency reported that the denial rate was 11.3% – a whopping 36% increase from 8.3% in 2016.[3] This should come as no shock amid the Trump administration's attempts to "crack down on illegal border crossings, increase deportations, cut the number of refugees allowed into the United States and make it harder for migrants to claim asylum"[4] and the "zero-tolerance policy"[5] that "separated thousands of migrant children from their parents in an effort to deter Cen-

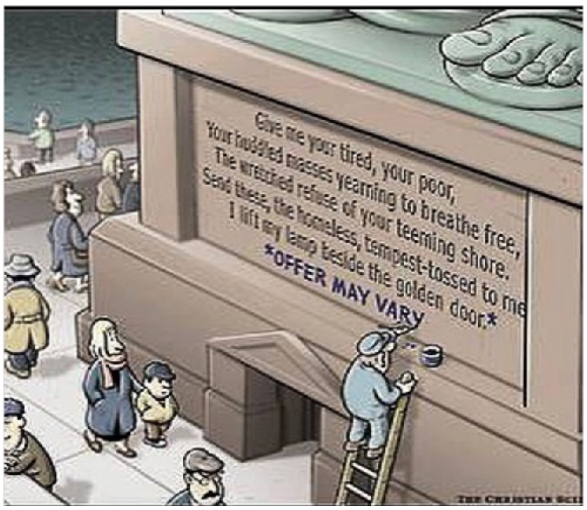


Figure 1. A satirical take on the Plaque on the Statue of Liberty, and immigration at-large, in contemporary times

tral American families from trying to seek refuge in the United States."[4]

To understand an issue and find objective, evidence-based solutions, one must first consider all the various perspectives to the problem at-hand. First, we will briefly explore some of the most common arguments from the anti-immigration stance. The most frequent claim against immigration is that immigrants will lower wages and take available jobs, in turn hurting the poor the most and increasing economic inequality.[6] The logic behind this is that unskilled immigrants will take low-paying jobs, given the assumption that this wage is probably higher than the opportunity available from where they came. Another argument is that immigrants will abuse taxpayer money and take advantage of welfare benefits.[6] The rationale here is that they will use more public benefits than what they would provide back to the state. Lastly, more socially-oriented contentions are that immigrants won't assimilate into the larger society well, are more prone to crime, and increase the risk of terrorism.[6] Although these claims may seem intuitive or rational at first glance, they have all been disproved with data-driven results and research.[6]

Macroscopically, libertarianism is a particularly relevant moral and political philosophy here, which "argues in favor of a strong presumption of letting people engage freely in mutually consensual activity and on minimizing coercion in society."[7] In other words, people should be able to do what they want as long as it is "mutually consensual" and not coercive. Following this pro-immigration line of reasoning, the freedom of movement should be a fundamental right of any individual, or group of individuals, as long as it does not infringe on others' rights.[8] An anti-immigration response to libertarianism is that migration violates "collective property rights", which states that any territory of a nation-state that is not owned privately is owned "collectively" by the people, with the, theoretically representative, government making the citizens' decisions.[9] Those who own and/or have property rights to a piece of land can allow or forbid anyone they please without justification.[9]

"The world needs people who are willing to make great sacrifices and the world will appreciate what you are doing"

However, this anti-immigration response is fundamentally rooted in a socially constructed idea of "property rights" and proves to only be mildly relevant. Put another way, "owning" land or preventing others from encroaching one's land is borne from human-made ideas of capitalism, whereas the freedom, ability, or right to move is objectively embedded in our DNA and biology as motor skills. Socially constructed ideas, like capitalism and socialism, are extensively

debated to decide which is the best for human welfare, but nonetheless have no objective basis and are only as valid as each other. On the other hand, one cannot deny our biological ability to move around wherever physically possible. In addition to conceding to this common-sense response, this "collective property rights" argument does not hold against the pro-immigration corollaries of other popular philosophies, such as utilitarianism, which emphasizes maximizing utility (happiness) for the greatest number of people, and egalitarianism, which states that all humans are created morally equal and should be treated as such.[9] In both cases, allowing individuals to do what they please, including freedom of movement, is morally just, as long as 1) the actions maximize the happiness of the most people, and 2) everyone is treated equally, respectively. These various philosophical ideas and rationales primarily lend support to the pro-immigration stance. Contrarily, the more practical and data-driven facet of the pro-immigration position typically consists of responses to novel anti-immigration arguments. Numbers and evidence speak to the real impact of immigrants, which strongly disprove the aforementioned anti-immigration contentions – all hyperlinked in the cited source.[6]

Ultimately, though, it is easy to forget that, regardless of race, ethnicity, socioeconomic class, gender, or other divisions, we are all humans, experiencing the beautiful opportunity of life, granted to us by the universe against all odds, one day at a time. The human experience, connection, and empathy for which we live can be overshadowed by a shroud of rationality and numbers, albeit both support the pro-immigration stance. Dr. Quiñones-Hinojosa's journey is awe-inspiring. The following conversation exploring his early life, hardships, immigration experience, work, accomplishments, and recommendations for the future of healthcare and immigration is essential in understanding the unique struggle and perspective of an individual who decides to migrate illegally, a situation arising from centuries of global inequality and injustice.

Gugan Raghuraman (GR): How has your early life influenced your work?

Dr. Quiñones-Hinojosa (Dr. Q): Well, I have no doubt that I am today because of who I was yesterday. Yesterday, that means in the past, as a young kid, growing up in a very poor area of Mexico, really with a poor family. My parents had no education. I was a kid who was extraordinarily curious, and I would get into a lot of trouble I'll tell you as a little boy, and my parents somehow seeked out a way to channel that energy into positive energy. Now I look back to my past, and my mother was very young – she was 19 when she had me – and she was able to keep me entertained and engaged in school. Somehow, they inculcated in me that if I learned, things were going to turn around. And, to be honest with you, it's not like I knew it – as you know, I came to this country by the time I was 19 years old as an illegal migrant farm worker, and I didn't have an education and ended up getting an education in the United States, but I would

say that those principles of my childhood, which you know, you work hard and you have a good time doing it. My family and my kids, they never questioned what I was doing. All the way from when I was 14 years old – the very first time that I decided that I was going to leave Mexico to come to the United States to work and bring a little bit of money back. My parents, they knew that this was a very dangerous situation – that I was going to cross the border illegally, that a lot of people die in this journey, in this track, but I think that they realized at that point they couldn't physically or emotionally, you know, stop me from this – because I had a dream. I had a dream that I was going to make better the years of my own life, and that I was going to change the world, and I still have that dream. When I was a kid, I was a dreamer, you know, and I continue to be a dreamer. I have big, big dreams. I had them as a kid. Some people confuse that with arrogance, and I always say there's a fine line between confidence and arrogance, and the key is not to cross it. And, when you cross it, you better step back. So that's how my childhood, to be honest with you – intense experiences on April 14th, 1989. Seeing my little sister die in 1971 of diarrhea, you can only imagine how those experiences can change one's life. Seeing my father battling with alcoholism, you know, depression. Now that I look back, I understand it, but at the time, I couldn't really understand it. I was trying to make sense of it. Those experiences, they must, in one way or another, shape your DNA.

GR: What are your views on immigration in America (being an illegal immigrant yourself before you obtained US citizenship)?

Dr. Q: This is a country that was built on the backs of immigrants from all over the world for hundreds of years. I feel that immigration is part of a natural process and that as long as there is disparity and a bifurcation of classes around the world, there is always going to be a need to pursue a dream, in our case, we call it the American Dream. And as long as the United States is as wonderful of a country as it is, there are always going to be people who are going to want to pursue the American Dream, and I think that we should be proud of it. So my view is that it is a necessary part of society that we need to figure out a way to better build bridges rather than building barriers. How do we make it better for our colleagues in America, for instance, the continent of North America, down south of the border, in Mexico and Latin America? I'm saying that it's not only the responsibility of the people down south but also our responsibility to make it better for them so that they don't have a need or a necessity to say "I don't need to move up north to the United States." So my views are that we can certainly improve, that we can make it better for ourselves, here in the United States, that we can make it better for the rest of the world, and that we do need to build bridges rather than barriers. And those bridges happen between people, between institutions, between countries, and the glue that puts them all together is dreams, and ideas. And when you share those

things, I think that you have an opportunity to make the world a better place.

GR: What advice would you offer recent immigrants who may be in a similar situation as you were?

Dr. Q: My advice for recent immigrants is that don't lose sight of the reason why you came to this country. You came to this country because it's a beautiful country. You came to this country because this is, in my opinion, the most beautiful country in the world, and I'm not saying you don't love your own country, I love Mexico, I'm never going to stop being Mexican, I love my people, but I also recognize that this country is a land of opportunity. Don't lose track of the fact that this country has opened its doors to many millions and millions of immigrants, and sure sometimes we get discouraged because of what we hear, in the political arena for example, but don't lose track that at the end of the day this country is filled with wonderful people, the most philanthropic and the most unique people in the world, and we are part of this dream. So don't lose track of it, keep the dream alive, keep working hard, and getting an education. Keep making this world a better place, keep building bridges from the United States to the rest of the world.

GR: How did your non-traditional background influence the experiences that you had in medical school?

Dr. Q: I would say that my background influenced my experience at Harvard Medical School in a simple way. I couldn't understand it at the time. It was in 1994 when I got accepted into Harvard Medical School and just seven years prior, in 1987, I was an illegal migrant worker. So my prior experiences influenced my experience in medical school in such a way that it made me into a sponge. I was basically absorbing every single thing that was coming my way. And when you are poor, and you came into this United States and you were homeless, and you live out there in the middle of nowhere, in a three-wheeler motor cycle, and you were out there getting wet at night when it was raining because you don't have a roof over your head, you can only imagine that when you're at a place like Harvard Medical School, you think that you are in heaven. You are grateful for every single thing that comes your way. You finish 24 hours a day at work, and you welcome it, because at least you have a job. You finish 48 hours without sleep, you welcome it because you know that once you go home, you have a roof over your head. You go many hours without food because you're working and don't have enough money, you welcome it, because at least you see a light at the end of the tunnel. You know that eventually you'll get food and a place to sleep. And all those things, there is no doubt that your prior experiences influence the way you feel about an institution, and I was grateful, and continued to be grateful because Harvard opened its doors to me, and I hope that I am slowly paying

it back to this county, all the wonderful things this country has done for me.

GR: You're significantly involved in the neuro-oncology and neurosurgery fields. What drew you to the field, and what impacts has your research had on society?

Dr. Q: What drew me to the field of brain surgery, was my infinite desire to understand an unexplored frontier. As a little boy I used to watch Star Trek, and I used to watch this Captain Kirk and Spock going into space and exploring the universe, and I was fascinated by that universe outside. When I began to explore neuroscience, I began to realize that we have an amazing universe inside and we can basically put our hands on it and that you're given a gift every time you operate because you are able to put your hands on that universe. And just like Captain Kirk and Spock went out and explored the stars in the universe, you are able to do the same when doing surgery or research. So I got drawn into it because I wanted to be part of history, I wanted to be part of that exploratory team that was going to give us more answers about how the brain worked. And that's exactly how I began to do research. Our work has been able to offer a new way of thinking about the brain. We can understand that the brain does have cells that can renew, thanks to some of the work I have been a part of when I was a resident. We understand that the brain has this capacity of recovery and thus there is plasticity in the brain. We understand that cells from other parts of the body can be used as Trojan horses, that we can engineer with nanoparticles or with viruses and put them back in patients. And these cells can have a significant impact on humans, the brain, and in curing brain cancer. I would say those are the kind of contributions that our group has given to society and the world.

GR: What gives you the courage to operate in a region many neurosurgeons dare not to - the insula [the insular cortex, or insula, is a difficult-to-operate region located deep within the brain]?

Dr. Q: The insula is a tiger territory and there is a handful of surgeons within the United States that operate in that area, and I am one of them. This area is extraordinarily dangerous and the weight you have on your shoulders when you are operating there is tremendous. And that is extraordinarily powerful. What gives me the courage is my patients. I look at them and I realize that if I don't venture in, then they will not even have the opportunity to fight cancer. So I used to think I was in the business of doing brain surgery, but I realized over the past five years that I am actually in the business of giving patients hope, through my work and through brain surgery.

GR: I read that your relocation to Mayo Clinic was in part to establish it as the go-to medical center for the Southeast United States and Latin America. What made you interested in this cause and group of people? (and is this

your ability to identify with this population group because of your own ethnicity and history?)

Dr. Q: I would say Mayo is at the pinnacle of healthcare and of patient care. There is no identity crisis in Mayo – they know they are the best at taking care of patients. So the only place I ever felt could match my infinite desire to take care of patients and to be the best surgeon I could be is Mayo Clinic. When the opportunity came, I decided to take it. The truth is that they are extraordinarily committed to the health of the world and building bridges with the rest of the world and specifically with Latin America, and that was an unparalleled match opportunity to build the bridges between the Mayo Clinic and Florida to the rest of the world and specifically to Latin America. They believe in the vision and the mission, and they have resources allocated to be able to do that, unlike any other institution, Mayo gives more money to research than any other institution. Whatever profits they have, they put it back into this mission of building bridges to the rest of the world. And Latin America is a priority because if you understand the United States you will understand that sometime down the road, one out of every four people will be of Latin American origin, so they wanted to be ahead of the game and wanted to create a center that would be able to communicate specifically with the rest of the world and most importantly with Latin America.

GR: What is your most impactful or memorable patient interaction? (or which types of patients do you tend to remember the most?)

Dr. Q: Every memory, every patient is memorable in my mind. The ones that leave a little bit of a scar, the ones that are almost always on your mind, are the ones that do not do well. Patients are like your children, so it is impossible to have a favorite. Every patient takes a little bit away from you. The ones that do well, they make you very happy. The ones that do poorly, they make you very sad, and take you more out of your life. I have had cases where the outcome has been poor, and I have tried to learn my lessons from them. For example, some cases in the insula have had complications and had be doubting myself, but then I realized if I don't venture out there who will?

GR: What is your biggest motivator?

Dr. Q: My biggest motivator has evolved over time. When I first came to the United States, it was my desire to make something out of my life. When I was in residency, it was my children who kept me going. When I was a junior attending, it was my patients. And today, I think the thing that has kept everything together like a glue has been the dream of changing the world.

GR: What are your opinions on the American medical system? (The process and efficiency/lack-of efficiency in training future doctors with necessary skills and personality traits, financial aspects, ability to reach all critical patients)

Dr. Q: I think that the American medical system is the best system in the world. My only concern is that we're a little bit spoiled. We spend a lot. We are not very fiscally responsible, and this is one of the reasons why I started my foundation (BRAIN foundation). I wanted to build bridges. I wanted to go around the world and learn from those who do more with much less. Because I think some of those lessons we can bring back to the United States and learn how to practice better medicine while being more fiscally responsible. I also wanted to appreciate how those who have little do so much, and how we can give them more hope. I wanted to go out there and build this bridge of communication so that the world would know that the United States cares for them. So my opinion of the American medical system is that it is the best in the world, no question about it, but I think that we can make it better. We can become more fiscally responsible, we can teach our medical students how to communicate with patients better, how to empathize with patients, because that is as important as the amount of knowledge that you have while taking care of that patient, because sometimes what the patient is looking for is not necessarily medications, not necessarily surgical procedures, but just you putting your hand on their shoulder, looking at them in the eyes, and telling them I'm going to take care of you, and I believe in your pain. I am here to support you. That's all they ask for many times, and its more than just science and medicine, it's an art.

GR: Where do you hope to see science and medicine in the future?

Dr. Q: I'm hoping that the science and the medicine in the future will be utilized to build bridges between people, between institutions, between nations. I'm hoping that we will be able to provide a better balanced approach to healthcare, where we are fiscally responsible, where we can actually enjoy our lives and our quality of life for a long time.

GR: Our publication is primarily for undergraduates. Do you have any advice for students (i.e. work-life balance, future careers, etc.)?

Dr. Q: My advice is balance your life. You have to find a passion and when times are difficult and you're studying late at night for a final and taking exams, you have to

Figure 2. Pictured above, Gugan (left) with Dr. Quiñones-Hinojosa (right)

put it into perspective. Don't forget that at the end of the day you're doing all these things because you want to become a better human being, because the world needs you. The world needs people who are willing to make great sacrifices and the world will appreciate what you are doing.

References

[1] "The New Colossus." National Parks Service, U.S. Department of the Interior, 31 Jan. 2018, www.nps.gov/stli/learn/historyculture/colossus.htm

[2] Naik, Vipul. "Ellis Island and Keyhole Solutions." Open Borders: The Case, 17 Mar. 2016, openborders.info/blog/ellis-island-and-keyhole-solutions/.

[3] Bier, David. "Immigration Application Denial Rates Jump 37% Under Trump." Cato Institute, 15 Nov. 2018, www.cato.org/blog/immigration-application-denials-jump-37-percent-under-trump.

[4] Michael. "Anti-Immigration Groups See Trump's Calls for More Legal Immigrants as a Betrayal." The New York Times, The New York Times, 9 Mar. 2019, www.nytimes.com/2019/03/08/us/politics/trump-anti-immigration-groups-betrayal.html.

[5] Sands, Geneva, and Catherine E. Shoichet. "Five Takeaways from Wednesday's Hearings on Immigration and Family Separation." CNN, Cable News Network, 7 Mar. 2019, www.cnn.com/2019/03/06/politics/immigration-nielsen-hearing-takeaways/index.html.

[6] Nowrasteh, Alex. "15 Common Arguments against Immigration, Addressed | Alex Nowrasteh." FEE, Foundation for Economic Education, 11 Aug. 2016, fee.org/articles/15-common-arguments-against-immigration-addressed/.

[7] "Libertarian Case for Open Borders." Open Borders: The Case, 12 Feb. 2015, openborders.info/libertarian/.

[8] "US-Specific pro-Immigration Arguments." Open Borders: The Case, 26 July 2015, openborders.info/us-specific-pro-immigration-arguments/.

[9] "Collective Property Rights." Open Borders: The Case, 27 Oct. 2012, openborders.info/collective-property-rights/.2

[10] Mandell, Nina. "Ronda Rousey Quotes Statue of Liberty Plaque to Protest Immigration Policy." USA Today, Gannett Satellite Information Network, 29 Jan. 2017, ftw.usatoday.com/2017/01/ronda-rousey-trump-immigration.

jhu@thetriplehelix.org

