Berkeley Medical Journal

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Meet the editors

Berkeley Medical Journal is a student-run semesterly medical journal at UC Berkeley that explores current biomedical, political, and ethical research in the medical health field.

Meera Nagpal
Editor in Chief

As a science enthusiast and seasoned writer, Meera Nagpal has found her passion in the pages of the Berkeley Medical Journal. Meera is a senior at UC Berkeley studying Molecular and Cellular Biology with a minor in Data Science. She's interested in the interdisciplinary aspects of health; in particular, the intersection of health and technology, as well as a community-based perspective on health equity. She currently does research at UCSF on developing a machine learning model for diagnosing diabetic nephropathy. As an advocate for sexual health, she is teaches a class on sexual health and works with the Tang Center to bring safer sex resources to the student body. She volunteers at the Down Syndrome Clinic at Benioff Children's Hospital and the Lifelong Trust Clinic with the goal of bringing quality care and resources to underserved populations. In her free time, she enjoys binging fantasy novels and taking many naps.

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Ankita Chatterjee is a third-year Integrative Biology major who is also minoring in Creative Writing. She conducts research on interneuron proliferation, migration, and death at the Alvarez-Buylla Laboratory at UCSF. On campus, she is the co-founder and president of Alzheimer's Association at Berkeley and writes for the Weekender at Daily Cal. She loves writing short fiction, poetry, and screenplays; watching movies; and learning the electric guitar in her free time.

Niharika Desaraju
Editor

Niharika Desaraju is a third year Bioengineering major who is minoring in Computer Science. She currently does research on Multiple Sclerosis at the Henry Roland Laboratory at UCSF and on gene expression at the Berkeley Institute of Data Science. She's an active member of the social engineering sorority, Phi Sigma Rho, and is also a writer for Spoon University. In her free time she loves to watch TV shows and movies with her friends and cook.

Shivani Sundaram
Editor

Shivani Sundaram is a third-year pre-med student studying Molecular & Cellular Biology. She currently does research at the Miller Lab, where she investigates the genetic determinants of tooth development, and the Whiteman Lab, where she determines the genes responsible for toxin resistance in flies and how it affects their fitness. She is also a medical assistant at UCSF and the Marketing Director of the American Medical Student Association at Berkeley. In her free time, she enjoys reading books, plays, and biographies; watching movies, and teaching herself to play the piano.

Sana Desai
Editor

Sana Desai is a first year student who is passionate about human biology, the humanities, and the fascinating questions that arise at their intersections. Writing and editing for the Berkeley Medical Journal has been a unique opportunity to combine her scientific interests with her love of writing. She hopes to major in Public Health or Biology and minor in English, eventually taking her education and practice of public service, medicine, and literary composition to the next level as a doctor and novelist.

Doris Ma
Editor

Doris Ma is a third-year pre-vet student studying Integrative Biology. She currently does research at the Hlusko lab, CT scanning and visualizing turtle skulls to explore the adaptive radiation of turtle morphology. She is also a surgical assistant volunteer at House Rabbit Society and fosters animals that need special care in her home. When she's not cooking, she's traveling the world in search of delicious food.

Annie Zheng
Designer

Annie Zheng recently graduated from UC Berkeley with a degree in civil engineering. Her involvement in UC Berkeley's design community led her to a career in product design. Building meaningful products that empower people excites her, and she looks forward to exploring how design can be used to make technology more accessible to everyone. In her free time, she loves to explore new food places, try new recipes, and watch documentaries.

DEFNE YIGCI

A device to potentially control seizures and tremors: WAND

Implanting a chip in people's brains might have seemed like science fiction five years ago, but scientists are working on a device to help with several neurological disorders.

Researchers from the department of Electrical Engineering and Computer Science and the Helen Wills Neuroscience Institute at the University of California, Berkeley have created a 128-channel, closed-loop, Wireless Artifact-free Neuromodulation Device, WAND. In a research paper published in the Nature Biomedical Issue on the 31st of in December, 2018, researchers explain how this device might potentially become the standard of care for diseases like Parkinson's or epilepsy.

Scientists have been hoping to create an autonomous device that is autonomous, can learn and adapt to the electrical signals preceding seizures or tremors for years. With these new advancements, researchers might finally be close to achieving this goal. The mechanism behind WAND makes use of a neural interface technology and utilizes electrical stimulation modalities as well as neural recording. By stimulating the brain and recording electrical signals at the same time, the goal is to create a system that will learn how to interpret brain waves and respond to it autonomously. In other words, researchers are hoping to create a closed loop system that can function on its own to treat tremors and seizures.

Essentially, the aim is to treat "a variety of neurological conditions by dynamically delivering and adjusting therapeutic electrical stimulation in response to a patient's neural state". At the moment, the target population includes epilepsy and Parkinson's patients as the device is being used to control seizures and tremors. For both diseases, the idea of using neuromodulation devices to treat symptoms have been around for a while now. Although treatment techniques such as deep brain stimulation seem to be implementing this same idea of monitoring brain waves and sending signals, no single device has been able to do these

simultaneously. Another problem for treating tremors and seizures using brain stimulation stems from the fact that electrical signs that are preceding tremors or seizures can be very subtle and challenging hard to catch. Moreover On top of that, with neuro-stimulator devices producing larger electrical impulses, it becomes even more difficult for the device to differentiate between an artificially induced electrical impulse and a brain wave.

When we look at the standard treatment with deep brain stimulation, we see that it basically employs two devices in two different locations on the brain. One of the devices measures the brain activity and the other sends electrical impulses in order to reduce tremors or seizures. Technically, the device measuring brain activity can analyze the impact of the artificially generated electrical impulses. However, this does not give us a full picture regarding the effect of the neuro-stimulator induced electrical impulse on the brain. The commonly used system of engaging two devices is almost like measuring the effect of a ripple in a pond (Berkeley News). The electrical signal that is delivered is like a rock falling into a pond making a splash and a ripple effect. The device that measures brain activity, however, is not located on the exact spot where the splash happens but rather on one of the outer circles of the ripple. So, realistically currently used devices do not measure the impact of the splash but instead monitors the ripple.

Additionally, other devices that are currently in use, only have 8 closed loop systems while WAND has 128. This is the primary reason why WAND can achieve both tasks at the same time. In effect, this implies that WAND has an incredible
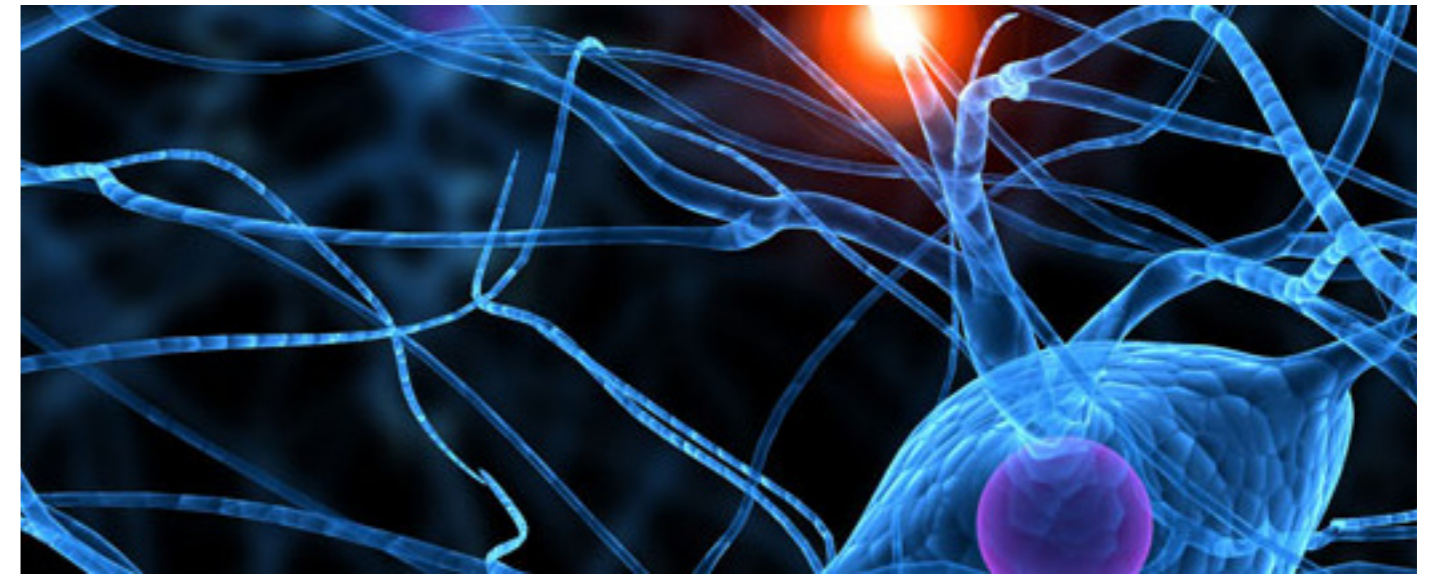
What differentiates WAND from any other neuro-stimulator is that WAND is a single device that can accomplish both tasks, recording brain waves and sending electrical impulses, meaning that the source of the splash as well as the measurement device are located at the same place.

potential for improvement with little adjustments and opens up many whole new possibilities for clinical research and treatment techniques neurological disorders.

Although it might take years before doctors can implement these devices in patients' brains, the device fundamentally makes it possible for a neural interface platform technology to significantly advance neuroscientific discovery as well as preclinical investigations of stimulation-based therapeutic interventions. It's important to note that the device differs from others not only because it can operate in a much more precise way, but also makes it possible to provide effective on demand therapy for patients, reduces side effects, has an extended battery life in wireless devices, and gives accurate estimations of neural biomarkers.

To demonstrate this, researchers first tested the quality of recordings made using WAND. Then, they went on to "establish a baseline for neuromodulation experiments" and performed

what they called a "self-paced, center-out joystick task". The main point of this experiment was to detect and delay neural activity that was related to motor functions. The experiments were conducted on rhesus macaques and researchers tried to establish the effectiveness of the device by monitoring the recognition and delay of specific arm movements on the rhesus macaques. After a certain time had passed, the WAND device was able to pick up neural signals that were occurring in preparation of motion and deliver electrical stimulation. In effect, the device was able to delay motion in the rhesus macaques.

The findings were interesting because although this was not the first time a neuro-stimulation device was able to delay motion, it was the first time that it was done autonomously by a close-looped, wireless system. Researchers believe that [insert quote from interview about future of neurological diseases/ medicine/ this technology].

SHERRY WU

A Closer Look into the HIV Life Cycle: Hijacking the Host Cell

Around every 9.5 minutes, one person in the United States is newly infected with human immunodeficiency virus (HIV) (Center of Disease Control and Prevention). The rapid rate at which HIV propagates is extremely alarming, hinting at the significant role that this virus plays on a larger scale.

Photo by Robina Weermeijer on Unsplash

In fact, globally, an estimated 37 million people are currently infected with HIV. Thanks to many breakthroughs in research, the number of people dying from AIDS as a result of HIV is significantly lower than the peak year of 2004. However, the sizable impact that HIV has on human lives is still undeniably present. This impact is felt much more heavily in some areas of the world, like sub-Saharan Africa. According to Avert, a global HIV and AIDS organization, more than half of the people in hospital beds in this region have some HIV-related condition. Thus, effective prevention and treatment of HIV is crucial to human wellbeing all over the world. There is already a breadth of information on the transmission of the virus. However, there is little understanding of the molecular mechanisms involved. Studying and clarifying such mechanisms provides vital insights on the HIV life cycle that may reveal many potential strategies to more effectively avert and restrain HIV infection, improving human health globally.

One of the most critical steps of HIV infection is the release of newly formed virions out of the host cell, where the virions can begin infecting more cells, furthering the malady. Research in the past century on this process has shown that HIV cannot carry this step out on its own. The virus can only escape out of the host cell by hijacking one of the host cell's innate systems: the ESCRT system. The ESCRT system is a collection of proteins in human cells that allow the cell to transport material outside of the cell. Although HIV's recruitment of these ESCRT proteins has been discovered, a mechanistic understanding of this process has not yet been reached. The Hurley Lab in the department of Molecular & Cell Biology at UC Berkeley is currently working towards clarifying this phenomenon, recognizing the great potential applications that it has on the world of health and medicine.

Reaching an understanding of how HIV recruits ESCRT proteins presents many potential directions of developing HIV treatments. Because it is known that ESCRT proteins are required in the HIV life cycle, inhibiting the ESCRT proteins seems like a potential treatment for HIV. However, King Cada, PhD candidate in the Hurley and Bustamante labs at UC Berkeley, points out the caveat that ESCRT proteins are essential to normal cell function, so inhibiting them would obstruct human cells along with HIV. Instead, Cada suggests another promising treatment: delaying, rather than inhibiting, the ESCRT proteins. "The actual timing of when these proteins are recruited to the sites of where the viruses are forming is very very important;" says Cada. "If there is any sort of delay [in recruitment], the viruses that escape from the plasma membrane become non-infectious." Cada explains that if the exact mechanism of ESCRT recruitment is understood, "we can design a drug that 'tricks' the ESCRT proteins", presenting them with other tasks so that they do not immediately arrive at the site of the budding virions. By doing so, ESCRT recruitment is delayed, and the cell to cell spread of HIV is deterred as the virus is rendered non-infectious. These insights offered by Cada display the importance of understanding the exact mechanism of HIV replication. Perhaps, after this mechanism is clarified, more effective HIV treatments will be developed, and global HIV and AIDS rates will decrease significantly. We look forward to a future where HIV can be as easily treated and as unthreatening as the common cold.
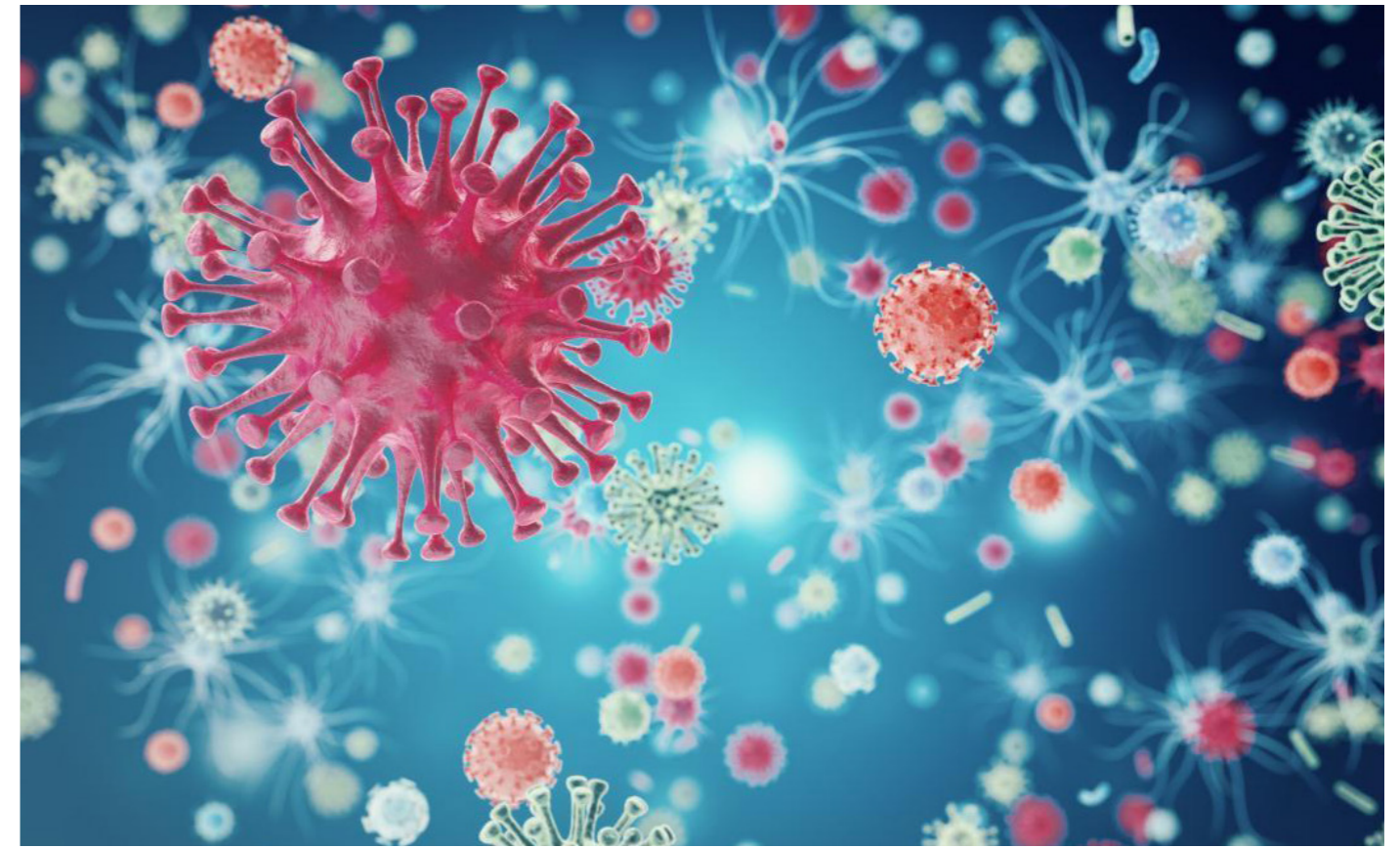
SHERRY WU

Does our Eye Tell the Truth: Mathematical computation to account for 3-D Error

The human eye is deceiving; everything we see is not how it necessarily is. We've all seen one too many optical illusions to prove this. This is a known fact, but what does that entail?

In the past, researchers have diverted their focus to 2-D eye error, creating mathematical models to explain eye tendencies. Scientists have been looking at 2-D error to establish how humans misinterpret speed, direction, and clarity. However, now the focus has switched to 3-D perception. A mathematical model to explain 3-D error would account for practical advancements in determining danger in traffic situations to sports vision. But this is more difficult than it seems.

In 2002, the first mathematical model for 2-D error was created after years of trying to explain the reason why humans don't comprehend information they see accurately. The Bayesian Mathematical Framework was used for these models and determined several factors in 2-D perception: speed is underestimated in low contrast environments and other factors in vision knowledge. Bayesian mathematical framework focuses on determining the probability of an event, in this case perception error, based on a specific list of factors.

3-D motion, however, is more complex. It involves lateral motion bias, direction of motion, and large variety of viewing settings such as changing backgrounds, peripheral vision distraction, etc. Lateral bias, which is how we misinterpret what we see in the x plane, has been researched frequently because of the ability to measure this with ease. Researchers have also attempted to recreate real life scenarios and measure with multiple factors that may affect misperception. However, these are limited, and it is difficult to factor in so many variables without a substantial mathematical model.

Emily Cooper, a research professor at UC Berkeley, and her team consisting of members from University of Wisconsin, Princeton University, and Dartmouth College, took on the task of creating a mathematical model to represent 3-D vision error. Their goal was to combine the multiple aspects of vision into a model to explain the common naturalistic misperceptions that commonly occur due to stimulus distance, contrast, geometric considerations, and optimal inference. Cooper's team decided to derive a Bayesian mathematical model and test it. To test their model, Cooper and her team conducted three separate experiments involving observers indicating the direction of miscellaneous objects randomly chosen in orientation and direction in the x-z plane. Experiment one centered around stimuli projected from a macintosh computer through an Oculus Rift DK I VR System. The virtual reality headset measured the overall movement of the head: including yaw, pitch, and roll of the head. Participants watched a room with a white sphere, or stimulus, at the center of the room. The stimulus would move in random directions. The stimulus was presented in three various contrasts: 100%, 15%, and 7.5%. Participants then placed a flat white paddle at an angle and location so that it would hit the white sphere perpendicularly after the stimulus disappeared from view. The intention of this was to take a measurement of what direction the subject would perceive the stimulus to go. The participants completed 12-15 practice trials with the experimenter, and then concluded a self paced block with random contrasts.

The experiment led Cooper's team to observe two factors that played a role in participant error: the contrast of the stimulus and the distance between the observer and the stimulus. Using positive values for the z plane errors, or medial errors, and negative values for the x plane errors, or lateral errors, in the paddle placement, Cooper's team used this data to determine where the eye had

Photo by Robina Weermeijer on Unsplash

more error. Using the previously derived formula, the results were compared against calculated predicted error values. The mathematical model seemingly accurately incorporated distance and contrast into the formula.

Cooper's team set up a secondary experiment to verify their findings in the first by eliminating the virtual reality portion. Using a CRT, cathode Ray Tube Display, three subjects proceeded to do the same test with a stereoscope, a device that combines two images taken at two different angles to create one 3-D image. Similarly to the last setup there was a stimulus, except this time instead of one sphere, there was a line of spheres. Subjects placed a paddle perpendicularly to the line. The contrasts varied in the same way: half the stimulus dots were darker or brighter than the background. The experiment validated the results of the first experiment, resulting in the same outcomes.

However, one more aspect of the experiment was not addressed: does the model work from different locations? Cooper's team set up an additional experiment with 21 members of the University of Wisconsin community. The apparatus was set up similarly, however, there were three locations for stimuli: one in the center, and two 20 degrees left or right of the center. Subjects were not allowed to move their head, but were allowed to move their eyes; this allowed for difference in the 3-D space and not to the retina. The participants each completed 360 trials with stimuli always at full contrast. Using the mathematical model once again, the experiment intended to record the mean angular error, motion in depth direction confusions (z plane), and lateral direction confusions (x plane).

The mathematical model proved to be very close to accurate in its predictions compared to the actual values. Experiments 1 and 2 proved that inaccuracy, or noise, increased as the contrast decreased. Both the model and the experiment proved that the contrast is not linearly proportional to the error, meaning that error increases more quickly at lower contrasts. Results also showed that as participants accurately understood the lateral movement, the depth movement was less accurate, and vice versa. Lateral confusion seemed to be less common, but was nonetheless affected by viewing distance and contrast.

While the model seems to explain the majority of 3-D perception aspects, it does not explain why observers perceive something as incoming or

Photo by Andrea Piacquadio from Pexels

receding. This is the next step in mathematical derivation. Seeing that the experiment was always done in a controlled setting, applying this to real world scenarios is another important step in finding the benefits of this information.

Scientists hope to use this information to advance sport vision science, a growing new concentration. This mathematical model could give a running back more information on the incoming ball, or a golfer more practical information on the distance of the course. In a more practical sense, this information can be used for determining the safety of various driving conditions such as rain, snow, haze, fog, or night driving. Technology and new regulations can be created to help eliminate the amount of car crashes we see in these types of weather conditions. Creating this model is a first step into the possibility of research allowing us to actually see what is going on around us.

KEN HINH

The Capabilities of Robotic Surgeries and Cancer

Novel surgical techniques that can treat cancer patients are constantly emerging every single day. One such technique, robotic surgery, has been used to operate on patients with different types of cancers, ranging from cervical cancer to skin cancer.

Photo by Jonathan Borba from Pexels

Robotic surgery is a particularly useful type of surgery because it is minimally invasive, meaning that surgeons can operate on patients with tiny incisions, and has proved effective for all other types of surgery that it has been applied to. However, recent studies on the effectiveness of robotic surgery have revealed that it has not been more effective than traditional surgical techniques in removing tumors. In addition, the Food and Drug Administration (FDA) warns that there is a lack of evidence on both the safety and effectiveness of such techniques.

Ever since the first robotic surgery, conducted in 1984, this surgical technique has developed and advanced tremendously to be more precise and safe for operating on humans. In principle, robotic surgery involves complex mechanical arms, which are controlled by a computer, that can mimic surgical procedures, all while being controlled by a human surgeon that monitors the procedure from a computer screen. Even though there have been advances in robotic surgery in recent years, the FDA has still not recommended the use of this technique to be used on any cancer-related treatments because of its inherent lack of safety. Despite this pronouncement, surgeons have continued to utilize this technique for various cancer-related surgeries because the FDA has approved the technique for use in other types of surgeries.

However, it has also been found that robotic surgery accounts for four times the number of cervical cancer recurrences than traditional surgeries or abdominal radical hysterectomies, the latter of which is normally used for treating cervical cancer. This study undermines the effectiveness of robotic surgery for cervical cancer in which traditional surgery would fully remove the cervical cancer cells. Even more, a second study conducted by the National Institutes of
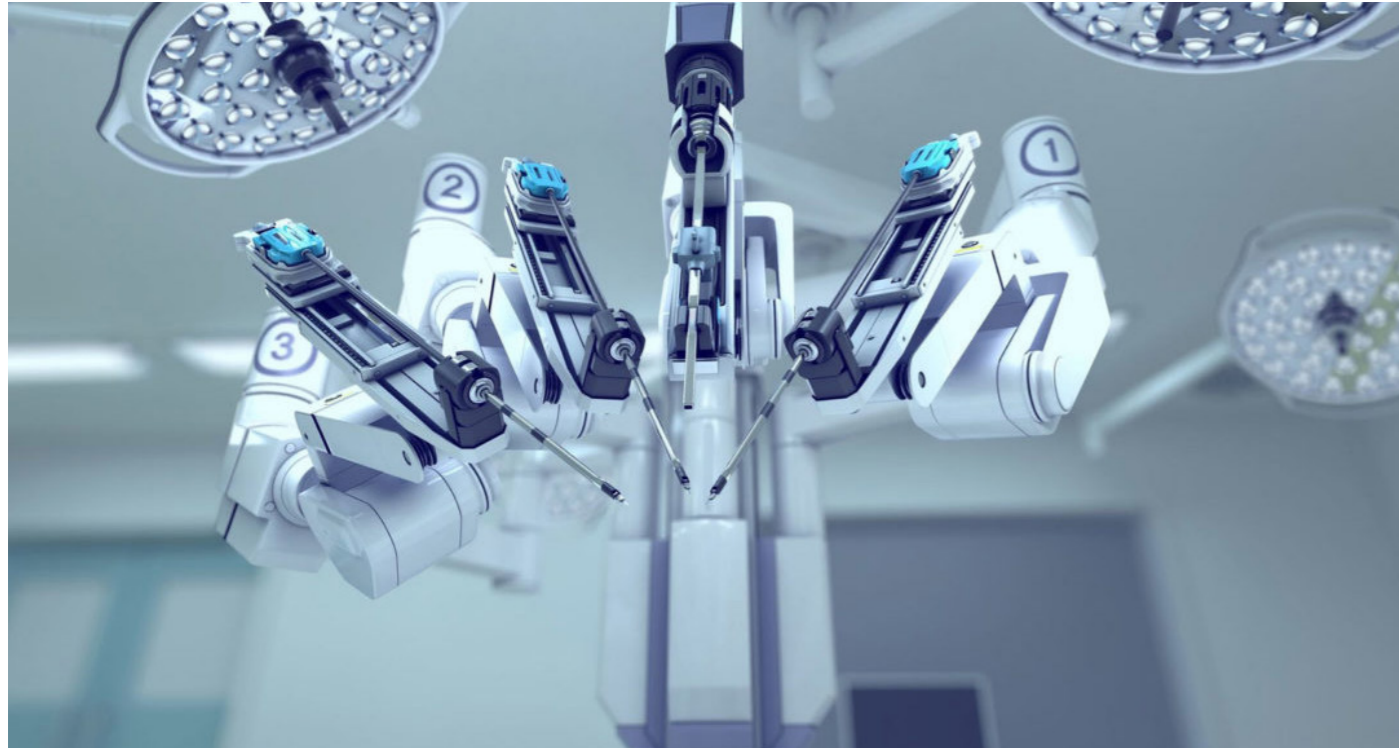
Photo from Greenlight Medical

Health (NIH) revealed that there was a 4% lower survival rate for patients who had undergone minimally invasive surgery as opposed to traditional surgery.

One theory for why robotic surgical techniques have been less effective than expected is that the mechanical arms of the robot could be spreading some of the cancer cells that it could not remove. Another theory supports the inadvertent spread of cancer cells through the use of carbon dioxide in robotic surgery; carbon dioxide is pumped into the operating cavity to allow the instruments more room to work in, which could unintentionally spread cancer cells within the artificially expanding area.

To address the ineffectiveness of robotic surgery, scientists and engineers have been advancing the precision and effectiveness of these procedures. One such advancement is with the assistance of a Smart Tissue Autonomous Robot, a new robotics technology which utilizes more intricate arm control with eight degrees of motion. With the advancement in the accuracy of robotic surgery, the rate of recurrence for cancer patients may decrease. In the current market and state of robotic surgery, policymakers need to re-evaluate the effectiveness of these techniques and impose stricter regulations. Alternatively, surgeons should consider performing traditional surgeries

as opposed to robotic surgery as it is safer and more effective at removing tumors.

Ultimately, as technological advances improve in the surgical field, there may be an increased need for regulation and oversight of the capabilities of these tools. With an estimated 1.7 million people being diagnosed with cancer in the U.S. alone every year, the race against cancer affects many of us. Robotic surgery will most likely be an important technology for future generations and the ongoing race against cancer. In the meantime, surgeons will need to stick to traditional procedures while humanity waits for the next big robotic advancement.

VIMATHI GUMMALLA

Genetically Engineered T-Cells: The Challenges and Possibilities of Treating Brain Tumors

Photo by Drew Hays on Unsplash

Immunotherapy is a rising field in medical health, in which treatment boosts the body's own natural defenses to fight disease. However, one specific area that continues to complicate this innovative treatment is the brain.

To simplify this problem, scientists created T-cell therapy, in which a patient's T-cells are genetically altered to have a specific function. Earlier this year, the Okada Lab at the University of California, San Francisco studied the success of these genetically engineered T-cells. Their goal was to describe immunotherapy in a brain tumor setting. As Postdoctoral Scholar Dr. Polly Chuntova explains, "our ability to engineer and manipulate such a small object, as T-cells are even smaller than normal cells, is truly amazing." Their findings not only illustrate a number of key challenges but also demonstrate a promising approach to a personalized and less invasive treatment, especially in the brain.

In this study, the lab focused on glioblastomas (GBM), a highly aggressive, invasive, and violent tumor that originates in the brain but spreads to other parts of the body. Since patients with GBMs live an average only fifteen months after diagnosis, GBM is characterized as one of the most common aggressive cancers. Once diagnosed, patients often undergo tumor resection, during which the maximum amount of tissue that is safe to cut out is directly removed from the tumor site and treatment is continued with radiotherapy and chemotherapy. Although these treatments generally show positive results in reducing tumor growth, they carry many dangerous side-effects because the radiation and chemicals from the treatment can spread to healthier parts of the body. Additionally, GBMs responds poorly to both treatments, so there still remains a high likelihood of recurrence. For these reasons, scientists agree that finding a treatment that directly targets the tumor site is necessary and urgent.

It was this necessity that engendered the field of immunotherapy. In general, immunotherapy includes techniques ranging from vaccines to human-made antibodies to altered T-cells, but there exists a limited number of hands-on and personalized procedures. The general procedure is to directly insert an altered

protein or cell into the site and let the patient's own immune system adapt to it. This way, an overflow of chemicals or radiation found in past treatments is minimized. In treating most cancers, genetically-altered T-cells is the most successful and reliant method to utilize. Specifically, Dr. Chuntova's study utilizes chimeric antigen receptor (CAR) T-cell therapy to treat GBM. This is a type of immunotherapeutic procedure in which doctors collect and use the patient's T-cells to treat their cancer. Naturally, the role of T-cells is to destroy any detected infected cells; genetically engineered T-cells harness the same power, but they target only the tumor. The procedure involves collection and isolation of the T-cells from a sample of the patient's blood, genetic modification of the cells to produce specific CAR receptors on their surface, and infusion of the new CAR T-cells in the bloodstream. The receptors can now easily recognize the target, kill the tumor cells, and ideally destroy the cancer.

Though the general cure is outlined, immunotherapy for GBM has its own set of challenges. Firstly, the brain is a part of the body like no other. It is a highly sensitive organ, so any procedure that damages its tissue could have serious and irreversible consequences. In this research, the key challenges include infiltrating the blood-brain barrier, facilitating immunosuppression at the tumor site, and ensuring antigen heterogeneity. The blood-brain barrier (BBB) is a semi-permeable border around the brain that prevents bacteria and toxins in the blood from entering. In doing so, the BBB also blocks out lymphocytes that could potentially kill the tumor. Interestingly, the BBB is still intact in areas where the cancer cells infiltrate the normal brain tissue, so it is apparently possible for cells to pass through. The challenge is to ensure that the CAR T-cells are a part of those selected cells and can actually reach the tumor site within the brain. Second, tumors often use a process known as immunosuppression,

where the tumor builds a microenvironment that enables the growth of cancer cells while halting that of T-cells. Therefore, engineered T-cells must be able to survive this environment.

Lastly, due to antigen heterogeneity, antigens are too diverse for scientists to know which one is best to bind to. Antigens are foreign substances, in this case signals from tumor cells, that trigger

antigens that is tumor-specific.

Due to limited evidence of CAR T-cell therapy, the paper discussed four different trials, but two in particular showed significant results. In one, scientists treated 10 GBM patients who had EGFRvIII-specific CAR T-cells infused through their veins. EGFRvIII is an epidermal growth factor receptor previously found to be over-expressed in GBM patients, but not in normal

responded positively. Unfortunately, the CAR T-cells did not infiltrate the barrier and remained only on the outer rim of the tumor site. As such, the need to develop new methods still exists. Even though all four clinical trials demonstrated positive profiles, the data further emphasized the continued challenges among successful CAR T-cell therapy for GBM.

Working to develop an effective immunotherapy treatment is a very long and complex process. Postdoctoral Scholar Dr. Bindu Hedge says that "when moving forward, they have to consider the different aspects at once and tackle the challenges all together." With more challenges comes a greater motivation to innovate and invent new technologies. The future of immunotherapy for GBM is full of creative and advanced solutions.
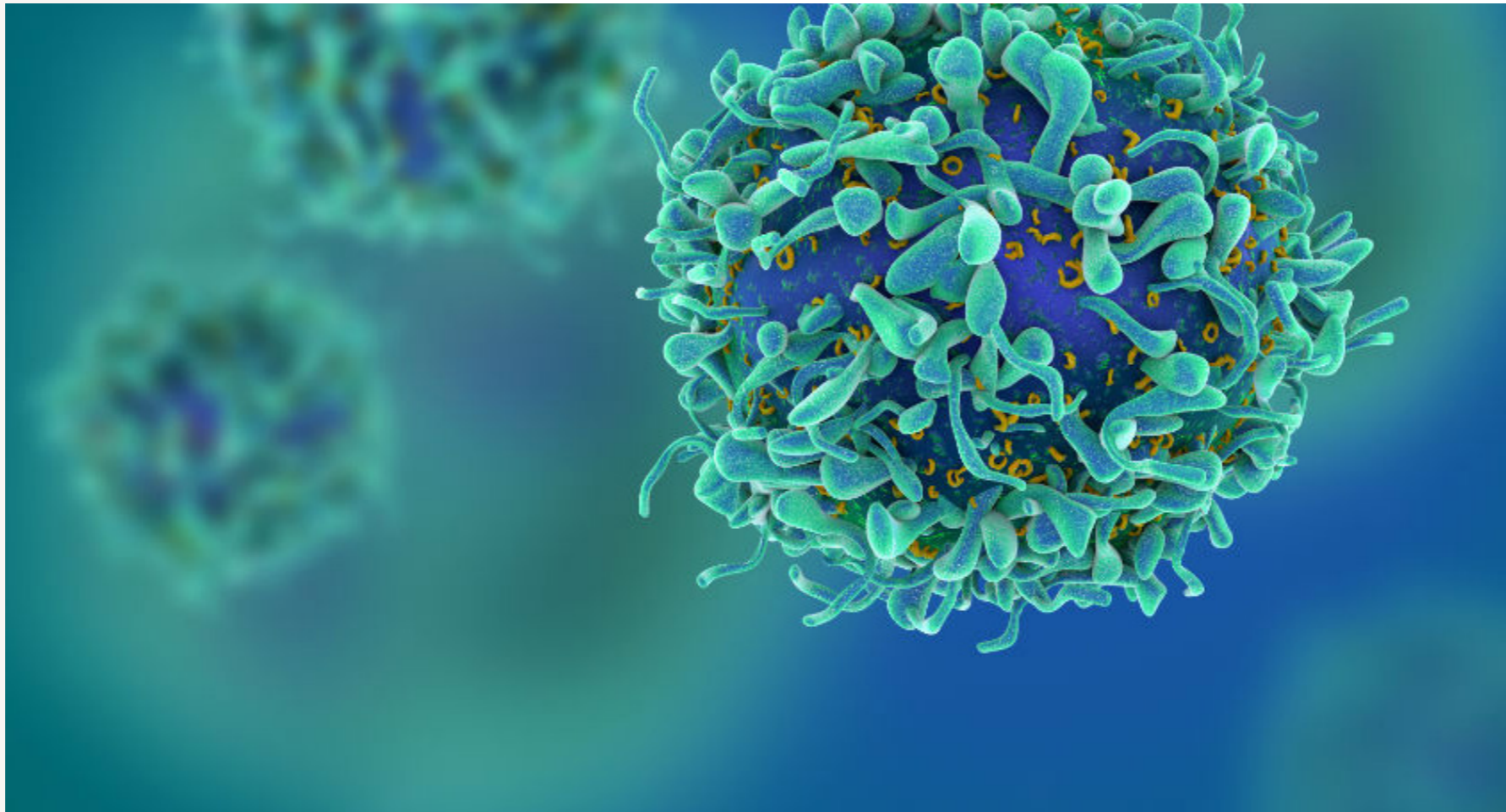

Photo from BioInformant

the immune system to produce antibodies that recognize and kill the cell the antigens are on. Tracking antigens is important because each is like an identification tag for a drug or mechanism to easily target. The key challenge in this study and the technology it uses is finding the right antigen that lies only on tumor cells. If the antigen is not specific to cancer cells, then the T-cells might also attack healthy cells. Therefore, the current goal of this study is to explore the availability of such antigens and their success with the genetically engineered T-cells. As Kira M. Downey, a junior specialist at the Okada lab, shared, "the most exciting part of CAR T-cell technology is that we are now trying to hit more than one targets," to then come up with a kind of combination of

tissue. The same mutation was researched to enhance resistance to both chemotherapy and radiotherapy. Throughout the trial, the team collected data and saw counteractive results in only one patient; also, none of the patients suffered off-tumor toxicities, which is when the cells start to attack healthy cells expressing the same target antigen. This meant that the CAR T-cells successfully entered the bloodstream, passed through the BBB, and reached the tumor site, which overall, decreased the expression of EGFRvIII in tumor cells.

In another trial, the epidermal growth factor receptor called HER2 was targeted. This trial was done on 17 GBM patients, and 8 of them

MING PEI

Consumer Inertia in Healthcare Industry and its Impact

Ben Handel is assistant professor at UC Berkeley. He specializes in Industrial Organization and Health Economics. This report is based on his paper published at the Hamilton Project: Getting the Most From Marketplaces: Smart Policies on Health Insurance Choice and his paper "Adverse Selection and Inertia in Health Insurance Markets: When Nudging Hurts."

People often have great difficulty choosing the best healthcare plan and treatment because of the limited healthcare price transparency and the energy cost. Professor Ben Handel at UC Berkeley used data from a large employer-sponsored insurance system and conducted research to find that consumer inertia causes an average employee to forgo $2032 annually. Professor Handel also found that many people tend to stay with their default option even if it's not the optimal plan for them. Consumer inertia explains that "customers just tend to put up with poor service and results, as long as it doesn't get too bad" (Shephyken). Because consumers are mostly not very well informed, consumer inertia in the healthcare industry has generated a welfare loss.

This consumer inertia comes from many aspects of complexities in the healthcare industry. Firstly, there is no standard price for a certain surgery. Different hospitals set their own prices. Prices also depend on the negotiated contract between hospitals and insurance companies. These contracts will determine how much insurance companies can reimburse hospitals. From the patient's side, the amount they pay out of pocket will depend on their deductible, copay and coinsurance. These factors make it harder to set a price on a certain medical treatment. Secondly, different patients will go through different medical procedures, which makes it difficult to settle the price before the whole procedure is done. Thirdly, it's hard to change customers' mindset to let them know that the healthcare industry is no different from the other marketplaces.

For example, once a person decides to accept a treatment by their physician, it's more likely that they will choose the insurance plan based on his physician's recommendation. Physicians' decisions are very influential. However, very few people will spend lots of time comparing between different physicians, like what they would do when buying a new car. Getting a different insurance plan often means changing to another doctor, which is undesirable. Despite the lack of transparency driven by the market, legislations don't largely support price transparency. Providers, insurers and drug makers are not willing to disclose prices. The Affordable Care Act added another layer of complexity to consumer inertia: tax and subsidy. The Affordable Care Act also requires consumers to automatically enroll in their current healthcare plan next year if they don't tend to make any changes to their current plan, which makes consumers more sticky to the current plan. These different factors all contribute to the existence and continuity of consumer inertia in the healthcare industry.

Despite the consumer inertia, consumers all want more information on the quality and prices of the service they receive. Investors pour a lot money into healthcare transparency companies; for example, Kaiser has a price estimator tool. However, there is a relatively small audience who know and utilize the existence of these agencies

Photo by Michael Berdyugin on

and their price estimator tools.

While price transparency seems favorable and beneficial for both consumers and the industry, it may also incur adverse selection problems in a macroeconomics perspective. Adverse selection in healthcare market means that sick people tend to invest more in their insurance plans while healthy people want to opt out of their expensive health plans, which will lead to a pool of insured people who are mostly sick people. This will lead to higher premiums for consumers and greater financial risks for insurance companies. Professor Handel finds that if consumer inertia is reduced, adverse selection would be more likely to increase and less risk adjustment between the sick and healthy people will be made. So ultimately, whether consumers should be well informed about the marketplace is still under discussion. Data shows patients with high deductibles are more likely to shop and compare different insurances. But in his study, Professor Handel finds that patients who face a high deductible will not shop for a better deal, but instead, will use less healthcare. High deductibles do help to lower overall healthcare expenditure, but they may also lead to sicker patients rather than smarter shoppers.

Overall, we see consumer inertia existing commonly in the current healthcare industry, revealing the necessity of letting consumers be more informed about what is happening in the market. But whether we should reduce consumer inertia and what kind of reform government should carry on is still open to discussion.

ALINA DAS

Mental Health Neglect and Associated Stigmas in University Settings

Photo by Segopotso Makhutja from Pexels

Depression is the leading cause of disability worldwide, affecting over 300 million people across the globe. One in four people between the ages of 18 and 24 have a diagnosable mental illness (World Health Organization, 2018). Despite its immense contribution to the overall global burden of disease, mental illness remains largely circumvented in matters of public discourse, health care priorities, and legislative agendas. Of these arenas in which mental health issues persist unaddressed, none is more concerning than the sphere of college campuses. A nationwide survey of college students found that nearly 33% of students reported feeling so depressed it was difficult for them to function (NIH, 2014). As mental health issues become ever more prevalent on university campuses, affecting student's health and academic success, several patterns and contradictions arise. Despite the undeniable presence of mental illness such as depression and anxiety, mental health issues remain largely

neglected and consequently stigmatized.

A landmark study published in January of 2018 in the Journal of Social Science & Medicine utilized a unique dataset of over 60,000 students from 75 American college and university campuses from 2009 to 2015. The authors investigated the contextualization of mental health stigma on these campuses, focusing on the different levels at which stigma can operate. The authors present three main levels of stigma that are commonly accepted: micro- (self-stigma), meso- (public stigma), and macro- (structural stigma) levels. However, there is scholarly dispute surrounding the level at which public stigma operates. Many scholars maintain that public stigma is primarily formed at the individual level as an innate response to what "most people" think. This study criticizes this perspective as ignoring local and community context, asserting that public stigma must be measured at the proper level of analysis in order to fully understand its true mechanisms and impact.

The study focused on three main associations: public stigma against mental health treatment and formal treatment-seeking behaviors (medication, therapy, or counseling), public stigma and informal treatment-seeking behaviors, and public stigma against mental health and self-reports of / screens for mental health conditions. The primary dataset was the Healthy Minds Study (HMS), an annual online survey including random samples

of over 100 colleges and universities. The HMS collects data on depression, anxiety, substance abuse, and treatment-seeking behaviors. The primary independent variable of interest was a mean score on a mental health stigma scale out of five, calculated for each individual school.

The authors conducted a multivariate analysis which included six controls for school type (public or private), school size, housing type, and type of institutional program (excluding professional and specialized programs such as art and medical schools). They performed a multilevel logistic regression and created a model including 21 dependent variables to examine four different mental health outcomes: medication use, counseling and therapy visits, self-reports and screens for mental health conditions, and informal support. These four outcomes were defined by five binary variables: depression, anxiety, suicidal ideation, self-injury, and presence of any mental health condition.

Photo by Finn on Unsplash

The study found that all four mental health outcomes varied significantly by school. Prevalence of any mental health condition ranged from 25% to 50%. Medication use, counseling or therapy, and informal support had means of 10%, 11%, and 29%, respectively. The logistic regression revealed that school-level stigma was negatively associated with reporting suicidal

ideation and self-injury. There was no association found between school-level stigma scores and screens for depression or anxiety. This means that students on campuses with higher school-level mean stigma scale scores are less likely to report thoughts of suicide or self-injurious behavior.

To further examine mental health stigmas from a medical perspective, I chose to interview Dr. State, who is the Chair and Head of the Psychology Department at UCSF Parnassus. He has been practicing for several decades. Dr. State discussed the challenges in the field of psychiatry at length. He began by dissecting the shortcomings of the healthcare system, which make it difficult for those with psychiatric issues to receive proper care. "Everything about psychiatry's broken in the healthcare system. You're lucky enough if none of your family members or close friends require serious psychiatric care," State lamented. He explained that with or without decent insurance, it's nearly impossible to find a psychiatrist available. "Psychiatrists cannot afford to live on what insurance companies have decided they're willing to pay for psychiatric services, so that's pushed people outside of the system."

State continued to discuss that although the deinstitutionalization of mental illness had good intentions, there was no system of outpatient care put in place to compensate. He explained, "What ended up happening was that the psychiatric system has ended up in the streets and in the jails. The largest provider of healthcare in the United States is the criminal justice system; the largest clinic in the United States for psychiatric treatment is the Cook County Jail in Chicago. Can you imagine any other medical specialty saying that? This has been an area in which society has turned its back on people who are really seriously ill. There's still a tremendous amount of stigma."

State articulated the prevailing widespread failure to recognize mental illnesses as true medical issues, explaining how the phenomenon contributes to the stigma of shame: "We live in San Francisco where people are supposed to be very forward-thinking. We say that it's okay to have a mental illness, but people feel that... admitting it is [admitting to] weakness. It's like cancer was 50 years ago, when it was shameful to say the word. People often don't want to say that they, or their children, have a psychiatric illness. It's more acceptable to say, 'My kid has cancer,' than 'My kid has schizophrenia.'"

SHIVANI SUNDARAM

The Modern Space Odyssey: Curing Radiation Damage from Space Travel

Photo by Vincent Beneche on Unsplash

The idea of one day traveling through outer space has captured the attention and imaginations of many in recent decades. Since the moon landing, space travel as a concept has become nearly synonymous with humanity's potential. While the rapid expansion of technology has certainly made recent years exciting for those working towards space travel, it is important to keep in mind that with new territory comes new health risks. For example, previous research has shown that astronauts are exposed to cosmic rays equivalent to 1000 times the radiation one would experience on Earth. This radiation exposure significantly damages the brain's microglia, which essentially serve as the immune system for the central nervous system. While microglia normally produce cells that remove foreign particles, radiation damage causes them to hyperactivate and actually attack the brain itself.

Researchers at the Rosi Lab at the University of California, San Francisco, published a paper in May 2018 in which they discovered further consequences of being exposed to this level of radiation. The results showed brain inflammation, problems with memory, social interaction, and increased levels of anxiety. In conjunction with the Rosi Lab, researchers at Loma Linda University have developed a drug called PLX5622 that encourages the brain to replace the irritable, radiation-exposed microglia with new microglia, effectively curing the once-thought permanent damage to the brain done by radiation.

In the second phase of this experiment, researchers treated these irradiated mice with the drug PLX5622 that they synthesized in tangent with a pharmaceutical company. When they again administered the memory task to irradiated mice, they noticed that the mice performed much like the original control group. When they again
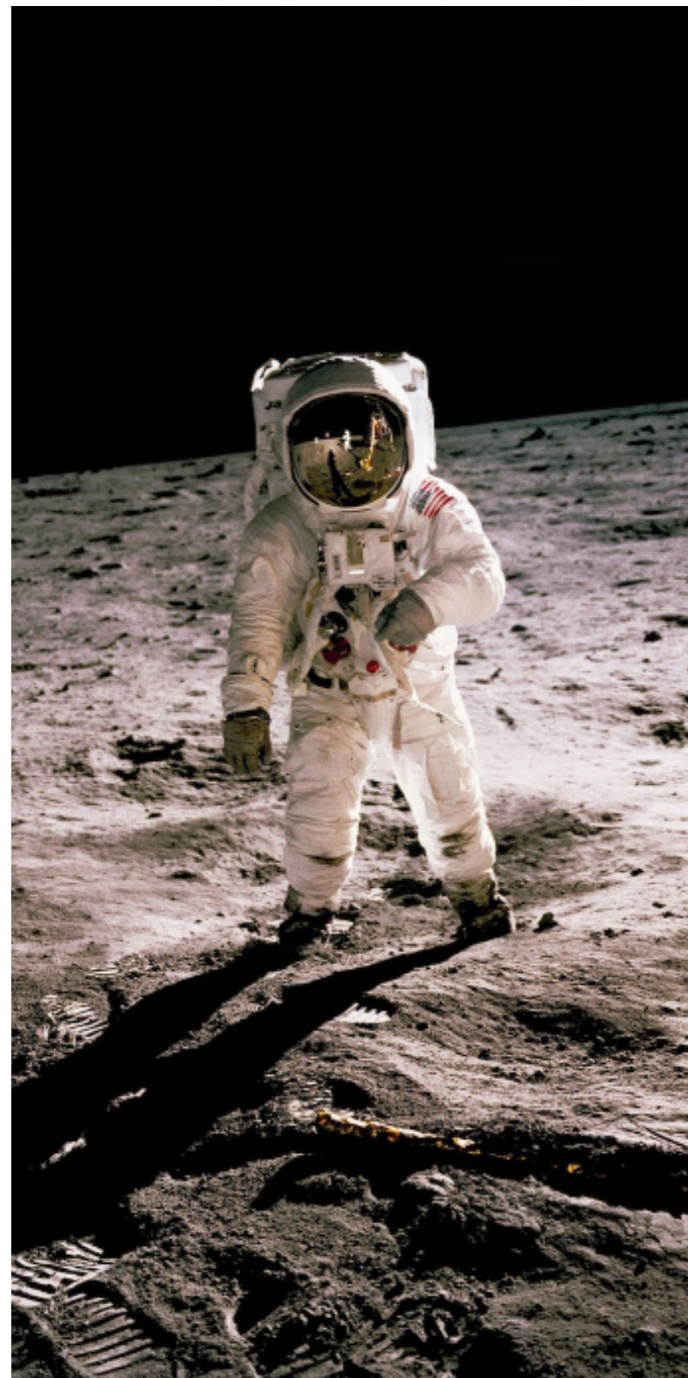

Photo by History in HD on Unsplash

dissected their white matter, they observed that the mice's microglia looked normal. They concluded that PLX5622 had forced the brains to replaceIn addition, they noticed that even after several weeks the mice were still healthy, suggesting that the drug's effects persist through large periods of time.

These findings have huge implications for the future of space travel as the risk of microglia damage can be substantially reduced. On a related note, the brain damage caused by space radiation is similar to other neurodegenerative disorders, such as Alzheimer's and Parkinson's. and that done by radiation therapy that doctors now use to treat cancer. Although the causes of these disorders are not specifically known, they have been linked to microglia-driven brain inflammation. Thus, researchers hypothesize that PLX5622 may also be able to ameliorate the damaging effects of radiation therapy and dementia disorders. This connection is extremely important because these diseases affect a relatively large proportion of the population and currently have no cure. Therefore, although this study has immediate applications for space travel, it also can be important in the field of medicine to design treatments for prevalent diseases like cancer and dementia.

KYLE MCGREGOR

Novel Target for Neural Recovery Discovered

Everyday, over two thousand people in the United States will have a stroke. Strokes have become frighteningly common; they are now the fifth leading cause of death in the United States.

Although the majority of strokes do not result in immediate death, they still cause significant brain trauma. As such, stroke is the number one leading cause of long-term disability and many of those suffering will never fully recover. In a world where modern medical technology has eradicated polio and used CRISPR to manipulate our very DNA, healing a damaged brain seems to be a tough egg to crack.

However, recent research suggests that a gene that's been studied for HIV therapy could be linked to neural recovery after stroke. Neurology researchers at UCLA found a connection in mice between the expressed CCR5 protein and increased inflammation in the brain, which hampers recovery. In their study, published in Cell this February, they knocked out the expression of this protein with either drugs or gene therapy and observed how it helped the brain readily make new connections between neurons in post-stroke mice. Given the permanent nature of the damage caused by brain trauma, a new therapy that can recover or even reverse this damage would be life changing for the thousands of stroke victims seen a year.

Stroke is characterized by a lack of blood flow to a part of the brain, typically via a blood clot causing impaired blood flow or heavy bleeding. In the areas of the brain where this loss of blood flow occurs, many of the localized cells are starved of precious oxygen and die. It is then no surprise that the effects of a stroke can be catastrophic; large sections of the brain can die and the function that they previously carried out is seriously impaired, if not lost. Most current treatment options focus on either prevention of the stroke in the first place or rehabilitation after the fact.No options currently exist to actively heal or regenerate the damaged brain tissue.

The Cell study, authored by UCLA postdoctoral researcher Mary T. Joy and others, found the first real biological target to enable this recovery. They showed that after a traumatic brain injury,

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levels of CCR5 gene expression in mice soared: and stayed high for weeks. When the researchers halted the production of the CCR5 protein, they saw promising results. The mice had better motor control of their legs and were able to complete complex tasks faster, such as going through a maze. On a cellular level, cell samples showed that their brains were making new connections between neurons and any biological markers that indicate the growth and repair of neurons were observed in higher levels. Increased levels of growth promoting genes, specific changes in GABA activity, and remapping of cortical connections in the brain are all markers that were identified in mouse studies following CCR5 downregulation. These results seem to support another study from 2016 (Zhou et al) that showed improved cognitive capabilities after similar treatment post traumatic brain injury.

While CCR5's role in the brain is not well understood, its other roles are not new to medicine. It is a protein that appears on the surface of various immune cells throughout the body and acts as a receptor for certain types of cell-to-cell signaling. It's most notable use thus far has been in the field of HIV treatment and anti-retroviral therapy. It was first noticed because a small minority of people carry a genetic mutation that disrupts the gene that is responsible for CCR5 production. Because HIV relies on CCR5 as an entry point into immune cells, people with the mutated gene are far more resistant to infection by certain strains of HIV than those without. Luckily, FDA-approved pharmaceuticals that are effective CCR5 antagonists already, such as maraviroc, originally created for AIDS and HIV patients in 2007.

Joy's study shows the capability of drugs such as maraviroc to enhance the brain's natural response to brain damage. However, her study only experimentally tested those responses in mice, and as shown in many Alzheimer's Disease clinical trials, neurological treatments often do not carry over from animals to human. However, when Joy and and her colleagues analyzed a previous observational study on stroke outcomes in humans, they found more promising results. The Tel Aviv Brain Acute Stroke Cohort, or TABASCO study by Ben-assayag and others, followed 446 stroke patients at the Tel Aviv Sourasky Medical Center and measured their recovery post-stroke through cognitive tests. Joy and her colleagues screened these patients for the CCR5 mutation that was known to infer resistance to HIV-1 and wanted to see if it would display the same enhanced brain recovery that was shown in mice. After finding 68 carriers of this mutation, they were determined to have scored better in all metrics; The delta NIH stroke scale was used to determine recovery, and carriers were observed to have better recovered motor skill, language ability, and sensory recovery compared to non carriers, all of which reached clinical significance.

So not only was CCR5 determined to be an accurate and effective target for brain recovery in mouse models, but Joy's analysis of the human TABASCO study likely links her animal findings to humans, providing the groundwork for a future clinical trial based in CCR5 downregulation.

And although this research does not promise a be-all end-all cure for damage after stroke and brain injury, it certainly provides hope for the future and a step in the right direction. The brain is perhaps the least understood organ in the human body and as countries around the world undergo demographic transition, aging populations, and increased lifespans, our inability to treat traumatic brain injury will only become more apparent. If humans as a species ever hope to continue the advancement of modern medicine and keep pushing the boundaries of our lifespan, at some point the brain must be further understood. The simple fact remains that you can technically get a new kidneys, lungs, or even a heart - but you can never get a new brain.

KYLE MCGREGOR

Potential New Treatment for Diabetes – No Needles This

The dream of many diabetic patients might soon become reality: New research suggests that scientists might be close to finding a new treatment for diabetes that doesn't involve insulin shots –or any needle as a matter of fact.

CBS News estimates that globally there are 371 million people have diabetes, half of them being undiagnosed. Once the pancreas stops producing insulin or if the pancreas does not produce enough insulin, these diabetic patients are compelled to take pills or insulin shots on a daily basis. New research conducted by the University of Lincoln, UK, was published in February 2019, and shows that "pancreatic cells that don't normally produce insulin can be modified to do so". Using this new technique, researchers were able to control blood sugar levels in mice.

The research is based on understanding the mechanisms behind diabetes. There are several factors that can lead to diabetes, like genetics or environmental factors. In essence however, diabetes occurs from the destruction of a single kind of insulin-producing cell –called the B-cell or the beta cell- in the pancreas. In type 1 diabetes, the patient's immune system attacks beta-cells and in type 2 diabetes, beta-cells simply do not produce enough insulin or the body becomes resistant to insulin.

Previous studies had shown that when beta-cells are depleted or do not function well, another kind of pancreatic cells, alpha-cells, start acting more "beta-like". In a healthy patient alpha-cells –or A-cells- produce glucagon which is a hormone that increases the blood glucose levels. However, when beta-cells are destroyed, alpha-cells start producing insulin Researchers had then established that, "two proteins that control gene expression seemed to have an important role in

Photo by Karolina Grabowska from Pexels

Photo by Matt Chesin on Unsplash

coaxing α-cells to produce insulin in mice: Pdx1 and MafA".

Going off of these findings, a group of researchers led my Pedro Herrera at the University of Geneva, Switzerland, tried to "reprogram" alpha-cells in order to make them produce insulin. They introduced the two genes Pdx1 and MafA to the DNA of the alpha-cells and examined the production of insulin and obtained a promising result: waiting a single week had increased the production of insulin of the treated alpha-cells had increased the production of insulin by forty percent. Then, in order to evaluate the impact of these cells on the blood sugar levels of mice, they implanted the cell grafts to diabetic mice. They saw that the blood sugar levels dropped to normal levels after the graft was made, but rose back up when the grafts were removed.

The dream, Herrera says, is to find a drug that can switch the identity of α-cells. The developments are promising and researchers are working to solidify their findings with additional research. In the meantime, it would not be wrong to say that in a couple of years the finding of this research could improve the life quality of diabetic patients to a great extent.

When asked about this research, Inês Cebola,

a biologist at Imperial College London who specializes in pancreatic cells, is intrigued that pancreatic cells can be convinced to produce insulin without actually becoming proper β-cells. Diego Balboa Alonso, an islet biologist at the Centre for Genomic Regulation in Barcelona, agrees. The latest work demonstrates that there is much more plasticity in the hormonal system of the human pancreas than was previously thought, he says.

KEN HINH

CasX enzymes comprise a distinct family of RNA-guided genome editors

Photo from the New Scientist

Advancements in genetic engineering have skyrocketed in the past seven years, especially with the emergence of the renowned genome editing tool, CRISPR-Cas9. This unique technology has been used to edit the DNA of plants, animals, and bacteria, suggesting its utility and potential value to a wide variety of organisms. The CRISPR-Cas system is a system innate to prokaryotes that functions as an adaptive immunity against the invasion of foreign nucleic acids, such as those present within bacteriophages. The CRISPR-Cas has many more specific functions that can be divided into three types. The genes associated with the Cas (CRISPR-Associated System) used in each functional type are distinct. Of all the types, the second type, type II, has been the most extensively studied by researchers as it confers the key gene-editing ability to CRISPR-Cas9. Within this system, the introduction of a specific protein, Cas9, allows the CRISPR system to, prospectively, cut the DNA of any genome at any desired location.

However, on the basis of specificity and delivery of the genetic engineering tool, the CRISPR-Cas9 system has the potential to be greatly improved. Within the past two years, UC Berkeley scientists have discovered the CasX protein, found in only the smallest bacteria, sharing many characteristics with the Cas9 protein. Physically, CasX is smaller and shaped differently than Cas 12 and Cas9, and functionally, it is an excellent gene editor. While Cas9 has been a geneticist's dream, it has had some shortcomings in terms of efficiency, selectivity, and specificity. However, the new and improved CasX aims to fix many of its predecessors' failings. Though it is similar in function to Cas9/12, CasX evolved independently. Overall, due to its origin, molecular make-up, and size, the CasX protein can be used for efficient genetic engineering over the Cas 9 protein.

In regards to CasX's unique origins, the protein's molecular makeup and shape reveals that there is no common ancestor between CasX and Cas9. While Cas9 usually comes from bacteria that already reside inside the human body, CasX is derived from bacteria that does not commonly inhabit the human body. Since humans have been exposed to the bacteria that Cas9 is defrocked from, the human immune response could potentially impede therapies that use Cas9. However, because CasX is derived from bacteria that aren't usually associated with human infections, human bodies will have had no prior exposure to CasX therapies and thus won't destroy the protein before it has time to therapeutically edit the human genome. By analyzing the unique domains of CasX that have similar roles to Cas9, scientists will be able to better understand how CasX can interact with the body to treat disease.

One of the most significant features of the CasX protein is its efficient delivery into the target cell or organ. To insert the CasX protein into a target cell, scientists must use a molecular delivery mechanism, in this case, the carrier virus Adeno-Associated Virus (AAV). Since AAV can only deliver relatively small substances, CasX, as it is smaller than Cas9, is more efficient for viral vector delivery. Moreover, the AAV does not have sufficient carrying capacity, carrying the smaller CasX protein is better for garnering additional genome editing accessories. In fact, CasX was recently discovered to be 40% smaller than Cas9, which is promising for the improved efficiency of the CasX system. In addition, with various in vivo genome editing experiments in multiple trials, researchers have shown that CasX proteins have greater cellular delivery efficiency than Cas9 proteins.

Furthermore, successful experiments have been performed on some mammals, such as pigs and mice, using CRISPR-CasX to inhibit certain genes and to treat genetic diseases. In the future, the CRISPR CasX system, with its superior efficiency and targeting, could replace the Cas9 system in having a greater influence on the advancement of biotechnology. With time and hard work by researchers, the advancement of the CRISPR CasX system, and genome editing technologies in general, has great potential to create comprehensive cures for any genetic disease, unveiling a light at the end of the tunnel in the world of genetic disorders and beyond.

MING PEI

Will high-dose influenza vaccines be more effective for patients?

Julia Thornton Snider is a lecturer who teaches Health Economics at UC Berkeley. Dr. Snider focuses on Health Economics and Policy. This feature report is based on her work published in 2018: "Relative vaccine effectiveness of high-dose versus standard-dose influenza vaccines among Veterans Health Administration patients." and interviews with her.

The relative effectiveness of vaccines is a valuable parameter to be examined to help with health decision-making, particularly due to increasingly dire seasonal influenza epidemics breaking out every year. Influenza epidemics result in infections, and can also make existing chronic diseases more severe, especially for seniors, who often have chronic diseases and are more vulnerable to influenza epidemics. Therefore, influenza vaccines are introduced in order to mitigate the healthcare burden on annual influenza epidemics. New vaccines are introduced to the market every year, and different doses may have different effects on patients. Recent research by Professor Snider and her colleagues on the analysis of relative effectiveness of high and low doses of vaccines finds the relationship between the hospitalization of patients and high and standard doses influenza vaccines they receive in the Veterans Health Administration. Researchers ultimately found that high-dose influenza vaccines are more effective than standard-dose ones in terms of preventing influenza or pneumonia-associated hospitalizations, cardiorespiratory hospitalizations, and all-cause hospitalizations (Snider).

Having randomized control trials is vital in finding the relationship between doses and

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hospitalization. According to Professor Snider, because there is a tendency that doctors may give high dose vaccines to patients who have severe pre-existing diseases, an instrument variable which is directly related to doses but indirectly related to hospitalization should be used in a linear regression analysis. In this experiment, researchers successfully used the facility as the instrument variable for the study. Some facilities have access to high dose vaccines while the others don't have such access. Senior patients who get diagnosed in these hospitals with a supply of high-dose vaccines are more likely to use high-dose vaccines. On the other hand, some other hospitals may not have access to high-dose vaccines, so they must use only standard-dose vaccines.

Patients A and B are seniors who have similar health conditions. If patient A gets treatment in hospital A, they may get high-dose vaccines just because the hospital has a reserve of high-dose vaccines. Patient B doesn't get high-dose vaccines because hospital B only has standard-dose vaccines. By introducing the facility as the instrument variable, researchers get rid themselves of the interdependence of the factor of high-dose vaccine with hospitalization. During their study, researchers also separated vaccine recipients into four groups based on the reasons they are hospitalized. The four groups were: All-cause hospitalization; hospitalizations primarily caused by a cardiorespiratory event; influenza or pneumonia associated hospitalizations; and

hospitalizations primarily caused by urinary tract infection. Because influenza may increase the risk of chronic diseases in different ways, it was necessary to separate patients into different groups. The urinary tract infection group acted as a control group because influenza is not related to urinary tract infection at all.

This research found that high-dose influenza vaccination of senior veterans reduced hospitalization, which, explained by Professor Snider, is an indicator of whether an individual will be hospitalized. In particular, cardiorespiratory-associated hospitalization received 18% more benefits from applying high-dose vaccines, and

influenza/pneumonia-associated hospitalizations received 14% more benefits. The benefits of high-dose vaccination was evident and consistent across different seasons.

Since this study was conducted in different influenza seasons, one of the limitations is that the result may be influenced by the severity of influenza seasons and virus types. Therefore, researchers plan to reinvestigate in a timely fashion. Since influenza epidemic is a heavy economic burden for the United States and many people are estimated to die from respiratory and circulatory complications associated with seasonal influenza virus infections (Snider), the findings from this study have profound

and practical meanings in terms of a solution. These findings help practitioners prescribe the right dose of influenza vaccines to patients who have different diseases. It also helps to know the relative effectiveness of high-dose influenza vaccines to standard-dose influenza vaccines.

SASHA NIKITINSKA

Microbiome Interactions: Bacteria that Shape Life

There are 39 trillion bacteria in a human body. These microbiome interactions are vital in influencing the physiology and fitness of a host. Microbiomes are groups of microorganisms in an environment, such as a plant or animal. How much of an impact does bacteria really have on animals or humans? A research team at UC Berkeley decided to find out.

Using an animal that is easy to reproduce and observe, Alison Gould, lead researcher from University of California's Department of Molecular and Cell Biology, chose the Drosophila melanogaster, or common fruit fly, to test on. In the past, research on flies showed that germ free flies live longer. Host fitness involves multiple factors including lifespan, fertility, and development time. Fitness was measured by these three attributes by sorting the flies into groups based on bacteria. There are five major bacteria groups in fruit flies and only located in the gut. Gould's team made thirty combinations of these bacteria and placed these groups into germ-free flies that were created by sterilizing the embryos. Tests were done to measure fitness as well as presence and abundance of the bacteria.

Results showed that lifespan was indeed cut down by the bacteria. While groups of 100 flies ranged from containing 1 species to all 5, the germ free flies still lived the longest. All 5 species resulted in the lowest life span, the Germ free life span was approximately 20% longer than the typical fly. But what was surprising was that the number of bacterial species was correlated with life span, and gradually increased lifespan with fewer species. While life span decreased, female flies experienced an increase in fecundity, or fertility. So what does this say about fitness?

The team compiled their information and found that as fecundity and lifespan traded off, the fitness stayed consistent. This also confirms why many species lose their fecundity later in life, so that they can extend their lifespan.

Secondary observations on Gould's research also showed that bacteria added late into a flies life will not increase its fecundity. This showed researchers that the physiological changes done by the bacteria are primarily done earlier in life. To continue this research, tests were also done to determine phenotype of fitness traits based on the bacteria. Results showed that the phenotype of development time and fecundity was completely predictable based on the combinations.

As more questions were asked and the researchers delved deeper, they found that bacterial interactions become much more complex on the fly than originally thought. Observations on abundance, interactions, and live bacteria came with many conditional factors. As a next step, Gould's team hopes to use this model of complexity to deepen the understanding of microbiomes as research will continue in this area. We can move forward to ask bigger questions: is human fertility tied to these microbiome interactions, Which bacteria play more important roles in humans, and are there ways to mimic ideal microbiomes in humans for optimal health?

SHERRY WU

The Switch between Cell Antiviral versus Antibacterial Defense

Though centuries have passed, the battle with tuberculosis (TB) is not over yet. Nobel Prize winner Robert Koch first identified the bacillus causing TB in 1882. However, TB is still one of the top 10 causes of death worldwide; it kills more people globally than any other infection.

According to the World Health Organization, in 2017 10 million people fell ill with TB, out of which 1.6 million died. TB is extremely contagious and is spread through the mundane actions of sneezing, coughing, and even talking. The first and only TB vaccine, bacillus Calmette-Guerin (BCG), was discovered by Albert Calmette and Camille Guerin in 1906. However, BCG offers very limited protection against TB, allowing TB to persist as a very alarming and impactful pathogen

Photo from Live Science

towards human health. Despite its significance, little is known about the mechanisms TB utilizes to develop and spread. Fortunately, recent discoveries by researchers in the department of Molecular and Cell Biology at UC Berkeley have

shined light on these mechanisms. These new understandings hint at opportunities to optimize vaccines and to explore new treatment methods to push forward humanity's battle against TB.

TB infection begins when the airborne Mycobacterium tuberculosis (Mtb) bacteria is inhaled by a human host. Inside the host body, Mtb is detected as a foreign cell and is met with macrophages, white blood cells that are a part of the body's first line of defense. Macrophages perform their function by engulfing the Mtb bacteria and storing it inside a membrane that will lead to its digestion. However, despite the antibacterial defense mechanisms of the macrophages, Mtb is still able to proliferate and to spread infection. The question is, how does Mtb continue to thrive under these harsh conditions?

The Cox lab at UC Berkeley set out to tackle this question, emerging with remarkable findings that provide new potential approaches of battling TB. Knowing that many other bacterial pathogens hinder host cell function by secreting proteins that interact with the host cell's proteins, researchers analyzed the protein-protein interactions (PPIs) between Mtb and its host cell. To do so, they employed a technique, affinity tag purification with mass spectroscopy (AP-MS), which allows researchers to isolate certain proteins and to examine their interplay with other

proteins. After mapping hundreds of Mtb-host cell PPIs, the lab identified the key interaction between the LpqN protein, secreted by Mtb, and the CBL host cell protein. CBL is a protein whose function limits Mtb growth, but LpqN blocks the normal functioning of CBL, allowing Mtb to undergo bacterial replication, effectively advancing the infection.

Through further analysis of this PPI, the Cox lab elucidated the pivotal role of CBL in combating pathogens. As viruses and bacteria are two types of pathogens, specific cells of the immune system have two types of responses targeted towards each pathogen, and the Cox lab found that CBL acts as a toggle between these responses.

The CBL protein signals the cell to switch between its antiviral and antibacterial responses, allowing the immune system to employ more specialized and effective defense mechanisms. In the case of Mtb, this remarkable function is undermined, as the PPI between LpqN and CBL causes CBL to erroneously switch "off" the antibacterial response and turn "on" the antiviral response, generating less effective defense mechanisms. By suppressing the host cell's expression of the antibacterial response, Mtb has the opportunity to grow, proliferate, and infect other cells.

This new understanding of the mechanisms behind Mtb infection provides new potential approaches to treating TB. Rather than targeting the bacteria itself, developing new drug therapies that target host proteins or PPIs may prove to be more effective treatments. Perhaps new vaccinations developed on this basis could provide much more protection than the current BCG vaccine. On a grander scale, this new approach could be applied to other pathogens as well, pushing forth a new wave of research on the pathogen-host cell PPIs and how they can play into the development of novel treatments. In addition, shifting the focus to the host cell rather than the pathogen creates the potential for more generalized treatments. For example, targeting a host cell protein involved in common PPI pathways may allow researchers to develop drugs that are effective against multiple pathogens. All in all, these discoveries open up new doors in the fight against infections and diseases, with great potential to improve human health on the global scale.

KYLE MCGREGOR

The New Antibiotics: Phage Therapy and Why it Works

Imagine a world without antibiotics: people die from small cuts that become infected, surgery is severely limited, and seemingly mild things like strep throat become fatal. We tend to forget the dangers of bacteria when we can always go to a doctor and be prescribed penicillin by the handful. However, if we aren't careful, we may be sorely reminded of that reality.

Antibiotic resistance has been a considerable problem since the inception of penicillin by Alexander Fleming in 1928. The discovery at the time was groundbreaking, offering a novel way to fight many bacteria by extracting penicillin from fungal mold colonies. However, this didn't last forever, and within 20 years some bacteria became resistant. The same trend has continued until today - new antibiotics are discovered and soon after new bacterial strains appear that are unphased, such as infamous MRSA. This is where bacteriophage therapy comes in - rather than exploiting physical weaknesses in bacteria, phage therapy utilizes viruses that actively hunt and kill bacteria. While bacteriophage therapy isn't new, it seems to be regaining the spotlight as resistance becomes a bigger and bigger problem - in fact, the FDA just approved the first clinical trial for intravenous phage therapy at UCSD Medical School in February.

But if bacteria can become resistant to antibiotics, couldn't they do the same with bacteriophages? Not exactly, and the answer lies in how bacteria deal with each threat.

Penicillin works by interfering with a critical property of all bacteria – their cell wall. This wall acts as a shield of armor for every bacterium, protecting them from toxins, and before antibiotics, many methods of treatment. This cell wall is made of a substance called peptidoglycan, a mesh-like polymer that forms hard to break networks – like a little wall of Kevlar around

Photo by Mark Fletcher-Brown on Unsplash

the bacteria. Penicillin works by attacking the center of the peptidoglycan network, a chemical structure called the beta-lactam ring. Once this structure is dismantled, the cell wall layer of bacteria unravels and falls apart – ridding it of its protective Kevlar shell and killing it. Because only bacteria, and not human cells, have this specific cell wall and mesh-network, Penicillin only kills bacteria and spares human cells.

However, because bacteria randomly mutate, they evolved resistance by essentially hardening this beta-lactam ring – rendering penicillin ineffective. Soon after, we made a new antibiotic, methicillin and not long after, some bacteria become immune to it. The same story with oxacillin, ampicillin, and so on and so forth until today, where we have about 24 different antibiotic classes in use today.

The problem is that we can't keep making new antibiotics forever - and some bacteria are already winning this arms race. Even now, some strains of MRSA, Methicillin Resistant Staphylococcus Aureus or flesh eating bacteria, are virtually immune to every antibiotic medicine can offer.

This is where bacteriophage therapy offers a unique solution and a completely new way to fight off infection: instead of competing in the same antibiotic arms race with bacteria that we've been doing, we leverage naturally occurring viruses to kill the bacteria for us.

Your first thought when you hear 'virus' probably conjures up bad memories of the flu and at first, sounds like more of something bad than something good. A bacteriophage is simply a normal virus, but instead of infecting humans or animals, it infects other bacteria.

The way they work is both simple and a little terrifying. Bacteriophages, which are an order of magnitude smaller than bacteria, work by latching onto a bacterium and using a needle-like appendage to pierce their cell wall and inject

their own DNA. They hijack the nucleus-control-center of the bacterium and force it to make more and more viruses until the bacterium actually explodes (technically the term is lyses, but that's not as flashy) and the process starts again.

Using viruses to fight infection has a few distinct advantages over antibiotics. Firstly, they are incredibly specific. One species of phage will likely only ever hunt one species of bacteria. In contrast, antibiotics kill broad amounts of different bacteria, potentially harming the beneficial bacteria in your body. It's like using a silver bullet instead of a shotgun – you only affect what you need to.

Secondly, when a bacterium develops immunity to a certain phage therapy it will most likely lose its ability to protect itself from certain antibiotics. Think of it like this - every time a bacterium evolves resistance, it needs to build a little bit more cellular machinery against a threat - like how it hardened its Kevlar vest against penicillin. But phages use a whole different mechanism to enter the cell and a bacterium can only have so much protective machinery at once. So while sole use of one treatment or the other may not be effective, the combination of both might be a one-two punch that a species of bacteria simply can't counter.

However, as promising as this may seem, you're likely not going to go into your doctor's office anytime soon and get prescribed Pfizer-brand phages. As of now, the problem lies in finding, identifying, and producing very specific phages for bacterial pathogens – each of which is, at least right now, a time consuming, expensive process.

But the potential is there. And as the arms race between antibiotics and bacteria progresses and we continue to see MRSA cases rise, we will likely be forced to look for alternatives if we don't want modern medicine to be sling-shotted back 80 years into the past. As of now, that alternative is most likely phage therapy. Alexander Fleming did the world a great favor when he discovered antibiotics 91 years ago, but now it's our turn to make phage therapy a viable option.

SHIVANI SUNDARAM

Promoting Cancer Suicide: Inhibiting the Protein Responsible for Cancer

Throughout history, the disease that most captured the imagination of authors, the horror of the populace, and the interest of medical researchers has been cancer. While research into this disease has grabbed journal headlines for decades, a constitutive cure seems far off because it has varied causes, tumor cells rapidly mutate, and because tumors generally become resistant to drugs in a relatively short period of time.

One of the most common lung cancers is non-small-cell lung adenocarcinoma, which induces tumor growth in the cells that normally secrete mucus in the lung lining. Because most of these cancers involve a protein called EGFR, which controls the expression of growth factors and signals cell division, researchers have attempted to synthesize drugs that specifically target this protein; however, in all cases, the tumor cells eventually acquire resistance after a few months. After several experiments, researchers have now discovered the protein responsible for this resistance, offering the chance to effectively block cancer drug resistance once and for all.

Researchers at the University of California, San Francisco in the lab of Dr. Khyati Shah recently published a study in the journal "Nature Medicine" in January 2019 in which they discuss their discovery of a protein called Aurora Kinase A, which cancer cells activate in the presence of such drugs. Therefore, regardless of high drug doses, the cell will continue to grow in response to epidermal growth factors. In their experiment, the researchers used both EGFR and Aurora Kinase A inhibitors to simultaneously target EGFR and Aurora Kinase A, which destroyed the cancer cells. Thus, the targeted mechanism of this drug may actually be able to cure non-small cell lung adenocarcinomas and potentially other cancers as well.

The normal function of cells is highly controlled to ensure that they grow, operate, and divide in a way that is healthy for the rest of the body. To achieve this, these cells use certain checkpoints to make sure routine cell growth and division occur at the appropriate time; the absence of
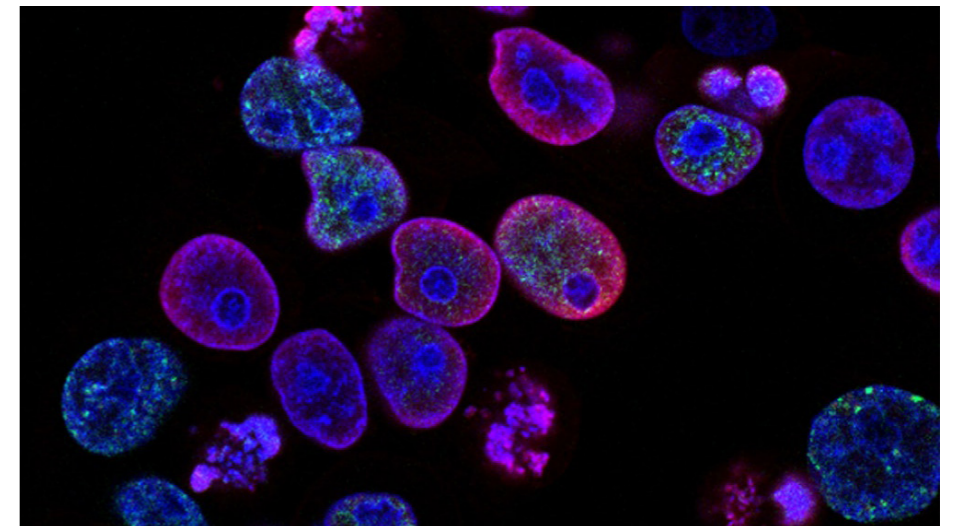

Photo by National Cancer Institute on Unsplash

these checkpoints causes the cell to self-destruct in a process called apoptosis. However, when a cell is mutated so that it cannot abide by these checkpoints, the cell and its progeny rapidly grow and divide and accumulate mutations that inhibit the apoptotic pathway. This leads to the tumor formation that is characteristic of cancer.

Normally, a protein known as epidermal growth factor (EGF) initiates growth in these cells by binding to epidermal growth factor receptors (EGFR) found on cellular membranes, which in

turn relay this signal to affect growth mechanisms. According to Dr. Khyati Shah, 35% of patients with non-small-cell lung adenocarcinomas have mutations in these EGFRs, causing excessive EGFR signaling. Therefore, regardless of the amount of EGFs present, the cell will grow disproportionately. In an effort to stop tumor growth in non-small-cell lung cancer, previous researchers synthesized drugs, such as rociletinib and osimertinib, to inhibit EGFRs and stop downstream proliferation. While such treatments are initially successful, according to Dr. Shah, over 95% of patients develop resistance after 12-15 months. However, the exact way they acquired this resistance has been unknown for a long time.

Researchers at UCSF, after very targeted experiments, discovered this mechanism. They generated several cancer cell lines that were resistant to either rociletinib or osimertinib. When they were administered to cells at ten times the concentration needed to neutralize a normal cell, they became resistant after an average of nine days. In addition, they discovered that despite the varied mutations in each cell line, all had mutations in this EGFR pathway that halted apoptosis. This suggests that this is a common characteristic and cause of this particular lung cancer. To determine the cause of the EGFR mutant, researchers systematically screened all the proteins in these cells for a property known as synergy. This metric quantifies how important a particular protein is for cell survival and how its presence or absence affects other cellular pathways. During this search, they found that a protein known as Aurora Kinase A (AURKA) displayed the highest degree of synergy, as its presence alone ensures the survival of 90% of tumor cells. In addition, they learned that when a tumor cell chemically senses that EGFR is being inhibited by drugs, it activates AURKA, which will independently inhibit apoptosis; therefore, no matter how much EGFR inhibitor is present, the cell will continue to grow because of the actions of AURKA.

In an effort to create a sophisticated and conclusive drug for these cancer cells, researchers used a method known as combination treatment, in which they administered either rociletinib or osimertinib inhibitor in addition to MLN8237, an extremely potent AURKA inhibitor. They found that with this two-pronged approach, the once-resistant tumor cells slowed in their rate of cell proliferation and a higher proportion of them died. In addition, this strong reduction in tumor size was sustained for as many as seventy days, much more than the initial nine it took for them to acquire resistance. Dr. Shah remarks that "combination therapy, while relatively new in treating adenocarcinomas, shows great promise in vivo, and we believe that similar results will be replicated in human trials."

In this way, the discovery of AURKA and its subsequent inhibition marks an important step in the treatment of cancer. These experiments have shown why many times cancer drugs have failed to have any lasting cures, ultimately causing many patients go into remission. In addition, many patients with these EGFR mutations also fail to respond to common cancer treatments, making this particular therapy highly important. In fact, Dr. Shah and her colleagues, including those at the company that created the AURKA inhibitor, are currently working to set up clinical trials to test the efficacy of this treatment plan on human subjects that can potentially, "provide an effective treatment plan for people who normally do not respond to immunotherapy and chemotherapy, significantly improving their chances of survival."

Although research in this experiment was done on a very particular strain and type of cancer, AURKA is a cell module that is present in every cell of the body because it is fundamentally critical for cell survival. Therefore, future drugs and clinical trials developed will not only target lung cancer, but will also open up avenues for treatment of various other cancers as well. In addition, this research will not only allow us to further investigate the microscopic causes of cancer, but will also help us understand more about how a general cell functions in various environments. Ultimately, the research done by Dr. Shah and her colleagues on using AURKA to cause tumor cell death brings us closer to eradicating cancer, a disease that many people have aptly referred to as the emperor of maladies.