Contents

TEAM MEMBERS

Health Science Inquiry

TEAM MEMBERS

PROOFREADERS	
Marie-Ève Wedge	University of Ottawa
Natasha Kaushik	McGill University
Elizabeth Thurston	University of Calgary
Jen Marshall	University of Toronto
MANAGER: NEWS ARTICLES	
Daniel Robinson	University of Ottawa
NEWS REPORTERS	
Morla Phan	University of Guelph
Kevin Champagne-Jorgensen	McMaster University
Sarah Shawky	University of Toronto
Alanna Miller	McMaster University
Lola Welsch	McGill University
MANAGER: ASK AN EXPERT	
Nika Maani	University of Toronto
WRITING ASSOCIATES: ASK AN EXPERT	
Elizabeth Hewitson	University of Guelph
Kiran Punia	McMaster University
Lily Takeuchi	University of British Columbia

MANAGER: SPOTLIGHT ON CAREERS	
Kathy Matuszewska	University of Guelph
WRITING ASSOCIATES: SPOTLIGHT ON CAREERS	
Joshua McGrath	McMaster University
Ivana Nad	University of Ottawa
Stephanie Tien	University of Toronto
SPONSORSHIP ASSOCIATE	
Alejandra Castilla	University of Regina
OUTREACH ASSOCIATE	
Sabriyeh Alibai	University of Toronto
LAYOUT ASSOCIATE	
Maria Nguyen	McMaster University
MARKERING ASSOCIATE	
Manu Sharma	McMaster University
WRITING ASSOCIATES: ONLINE CONTENT	
Sofia Cruz Tetlalmatzi	McGill University
Kaushal Baid	McMaster University
Mila Bjelica	McMaster University
Yamna Rizwan	University of Guelph

Health Science Inquiry

Letter from the Editor

Robert Ungard

Robert Ungard is a PhD Candidate in Medical Science at McMaster University in Hamilton ON. He researches the mechanisms of pain and how to better treat it – specifically: how and why does pain from bone cancer become so severe, and can it be reduced by therapies that target the tumour and its surrounding microenvironment.

He has been involved with HSI since 2016, first as an author, and later on the Editorial Staff, and now finally as Editor-in-Chief. When not in the lab or HSI'ing he can be found cooking and eating or biking around Hamilton in every sort of weather. Want to get in touch? robert.ungard@gmail.com.

On behalf of the 57 volunteer staff and 24 contributing authors of *Health Science Inquiry* I am very pleased to present our 10^{th} anniversary edition – The Future of Health. This 2019 issue includes new and timely insight into the future science of health and the implications for societies, as well as original art and fiction – all created by graduate and professional students in Canada.

Since its founding at the University of Toronto 10 years ago HSI has grown to become the premier pan-Canadian Health Sciences journal written and managed entirely by advanced-degree students. We are now very proud to count representatives of 12 Canadian Universities from coast-to-coast among our staff and authors.

This year we have continued the tradition of a themed issue with mini-review and opinion pieces, original artwork, and we have again published our internal content on News, Expert interviews, and Careers. In addition, for the first time we have included fiction – expanding our mandate to be a platform for discovery and expression.

Thank you very much to our partner journals *Medicine and Lifestyle Genomics*, and our sponsors including McMaster University's Graduate Student Association and the University of Regina's Graduate Student Association.

I firmly believe that HSI is an excellent and important initiative that not only showcases the work of some of our country's most driven and talented advanced-degree students but that also provides many much-needed opportunities for professional experience. I am very fortunate to have had the opportunity to act as Editor-in-Chief and to have worked alongside so many generous people here at HSI, congratulations to everyone involved.

Sincerely,

Robert Ungard Editor-in-Chief, Health Science Inquiry

Health Science Inquiry NEWS

Epigenetics to the Rescue:
Promising Potential of Epigenetic Therapies in Future Medicine

Daniel Robinson

The optimization of CRISPR technology to edit and correct errors in DNA is playing a pivotal role in developing new therapeutics which could soon cure genetic disease. However, genetic errors are not the only basis leading to disease. Such is the case when typical gene expression becomes aberrant, which in turn disrupts cellular and tissue function and culminates in disease. This specific regulation of gene expression beyond the actual DNA sequence is known as epigenetics. Broadly defined, this is the interaction of proteins and regulatory complexes with DNA which control whether a gene will be expressed or repressed, in turn providing cells specific functions. This differential regulation of genes allows cells which share a same DNA sequence within an organism to adopt different roles – such as the different functions of white blood cells versus skin cells - and providing different abilities to cell populations, such as the regenerative potential of liver cells. The ability to correct epigenetic dysfunction is a promising approach that could offer therapeutic value against various diseases, as is reviewed [1].

Muscle stem cells are a particularly attractive system for epigenetic studies given their abundance. Further, the role of muscle stem cells in regenerating damaged muscle is quite well understood - when skeletal muscle is damaged through exercise or disease, dormant muscle stem cells become activated, expand their population, then differentiate to repair damaged muscle (summarized in Figure 1). Thus, muscle stem cells are an attractive system to study *how* epigenetic changes confer regenerative potential to this population. In fact, researchers are now starting to see that epigenetics play a critical role in regulating these cell state changes.

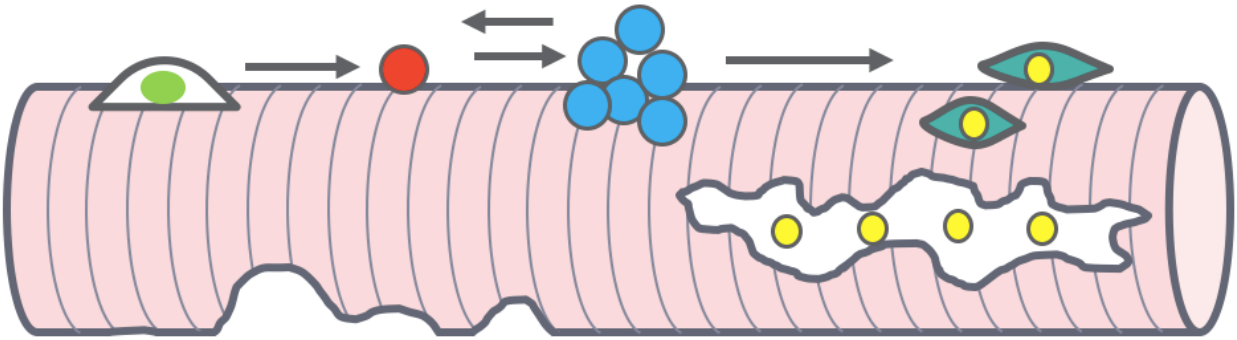


Figure 1: During muscle regeneration, dormant muscle stem cells (green) become activated (red), proliferate to expand its population (blue), then differentiate (yellow) to repair the damaged muscle fiber. These processes are regulated through dynamic changes within the epigenetic landscape.

At the Ottawa Hospital Research Institute's Sprott Center for Stem Cell Research, senior scientist Dr. Jeffrey Dilworth studies epigenetic implications in muscle stem cells. To shed some light on the subject, Dr. Dilworth explains that his research focus is to *"understand how epigenetic mechanisms control cell state decisions made by muscle stem cells during development and regeneration, and how this information is used to regulate the regenerative potential of muscle stem cells"*. Dr. Dilworth believes his research will help clarify specifically *how* epigenetic changes regulate the regenerative potential of muscle stem cells in forming new muscle fibers.

Current research has demonstrated that there are epigenetic differences of muscle stem cells during their regenerative process to fix damaged muscle fibers. Dr. Dilworth explains that dormant muscle stem cells have *"condensed chromatin that [. . .] helps keep the cells resistant to DNA damage over time."* When muscle damage is sustained and it becomes time to repair muscle, the dormant muscle stem cells become activated and start proliferating to expand the pool of cells required to regenerate skeletal muscle. At the epigenetic level, these proliferating muscle stem cells are "characterized by an *opening of chromatin which allows higher expression of genes required for these processes to occur.*" Once a sufficient population of muscle progenitor cells is produced, another epigenetic change occurs which suppresses proliferative genes required for population expansion, and allows expression of new genes required for muscle function.

The importance of understanding epigenetic regulation in healthy muscle stem cells helps researchers understand their regenerative potential, and how this may be affected in diseased conditions. Dr. Dilworth explains that "[other research] *groups have shown that in muscle wasting diseases, one contributing factor to loss of muscle is the inability of muscle stem cells to properly transition between cell states to help regeneration.*" The ability to correct epigenetic dysregulation in muscle wasting disease could help normalize muscle stem cell function and promote muscle strengthening. In theory, this will reduce the severity and progression of muscle wasting disease.

Fortunately, the clinical use of therapeutic agents to correct epigenetic states and return regenerative potential to muscle stem cells may be closer than expected. There are already some epigenetic drugs in clinical trials to treat muscle wasting diseases such as Duchenne Muscular Dystrophy. These histone deacetylase inhibitors, or HDACs which are reviewed here [2, 3] have shown positive results in animal models, but more research is required to see how this will translate into patients to improve muscle function.

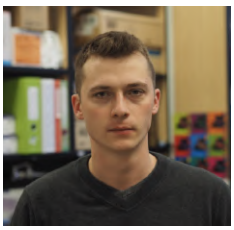
The importance of epigenetic regulation in controlling cell roles and states is exemplifying the importance of proper gene regulation to maintain healthy cellular and tissue functions. Of interest is the recent discovery of epigenetic modifying drugs which can correct epigenetic states in diseased cell populations. Although the complete therapeutic extent of these drugs remains to be fully understood, epigenetic modifying drugs could hold great therapeutic value to treat various diseases in the future.

References

[1] Heerboth S, Lapinska K, Snyder N, Leary M, Rollinson S, Sarkar S. Use of epigenetic drugs in disease: an overview. Genetics & epigenetics. 2014;6:GEG–S12270.

[2] Consalvi S, Saccone V, Giordani L, Minetti G, Mozzetta C, Puri PL. Histone deacetylase inhibitors in the treatment of muscular dystrophies: epigenetic drugs for genetic diseases. Molecular medicine. 2011;17(5-6):457–465.

[3] Consalvi S, Saccone V, Mozzetta C. Histone deacetylase inhibitors: a potential epigenetic treatment for Duchenne muscular dystrophy. Epigenomics. 2014;6(5):547–560.



Daniel received his B.Sc. in Biochemistry at the University of Manitoba in 2015, where he worked in various labs ranging from synthetic organic chemistry to studying protein dynamics. He is currently a PhD candidate at the University of Ottawa, where he studies gene mechanisms important for muscle stem cell regenerative potential. During his free time, Daniel likes to stay active by jogging, cycling, and going to the gym.

Health Science Inquiry

NEWS

Microbes on the Mind:
The Promise of Psychoactive Probiotics to Treat Mental Illness

Kevin Champagne-Jorgensen

The development of novel pharmaceuticals for psychiatric illnesses has stagnated throughout the past few decades, leaving many scientists searching for alternative treatment strategies [1]. One promising avenue is the use of certain live microorganisms as oral supplements (termed *probiotics*).

This isn't as far-fetched as it may seem. We've known for decades that the trillions of microorganisms that inhabit our gastrointestinal tract (known as our *gut microbiota*) have diverse roles in modulating our physiology, including gastrointestinal and immune function [2]. But recently there's been a surge of research demonstrating that these microbes may also have important roles in brain function and development. Numerous clinical studies have found abnormal gut microbiota diversity in patients with some psychiatric or neurological illnesses, including depression, autism, and Alzheimer's disease [3]. Exploratory studies have further shown that animals without microbes develop abnormal behaviour and brain structure, while normal animals fed with specific bacteria or microbial communities can develop predictably altered behaviour [3].

To get an expert's take on this topic we spoke with Dr. Thomas Tompkins, research director at Lallemand Health Solutions in Montreal and a leader of research in this area. Tompkins noted that, while the idea of treating mental illness with live bacteria had been proposed as early as 1910, it was obscure, and only first occurred to his team in the early 2000s [4]. This is when, according to Tompkins, they noted that in previous unrelated clinical studies, "participants reported that when they took the probiotics, they were getting better sleep and feeling less aggravated" [4]. These observations prompted a series of exploratory studies in both rodents and humans, which consistently suggested reduced anxiety-, depression-, and stress-related symptoms after treatment with Lallemand Health Solution's *Probio'Stick probiotic* (a combination of the bacteria *Lactobacillus helveticus* Rosell-52 and *Bifidobacterium longum* Rosell-175) [4]. While they are promising, these studies were early-phase and relatively small. But as Tompkins explained, we shouldn't have to wait long; more clinical work is set to be published over the next couple of years, and his colleagues are currently conducting a larger clinical trial of *Probio'Stick* in participants with major depressive disorder [4].

While the work of Tompkins and his colleagues is a good example of a promising probiotic showing beneficial psychoactive effects in human patients, it is unfortunately one of few. The majority of the work in this area is preclinical, where investigators are using animal models to uncover mechanisms that may allow microbes to affect the brain.

One of the pioneering laboratories in this field is that of Dr. John Bienenstock, director of the Brain-Body Institute and distinguished university professor at McMaster University. Bienenstock and his colleagues are actively researching a number of microbial strains to determine the mechanisms underlying their psychoactivity. A major focus of Bienenstock's research is the bacterium *Lactobacillus rhamnosus* JB-1, which has consistently decreased anxiety-like, depressive-like, and stress-related behaviours in rodent models [5]. His team and others have shown that some bacteria (such as *L. rhamnosus* JB-1) can produce neuroactive compounds, including neurotransmitters or short chain fatty acids. Moreover, he and his colleagues also demonstrated that some neuroactive properties of particular bacteria are dependent on the vagus nerve (a major neural connection between the brain and the gastrointestinal tract) [5]. As Bienenstock explained, there are many different pathways by which gut microbes may interact with the nervous system, including directly in the gut, neuronally through gut-connected nerves, and systemically via the immune or circulatory systems [5].

Though progress thus far is encouraging, both Tompkins and Bienenstock agreed that this research has many limitations. For example, Tompkins indicated that probiotic activity may depend on its location in the gut, which may limit their efficacy [4]. However, he believes that this and other issues may well be overcome by the use of genetic engineering; as Tompkins put it, "if we can find specific pathways to target... we could alter a microbe to deliver a very specific compound to a specific region of the gut where its receptors for uptake are". Furthermore, according to Bienenstock, mounting evidence suggests that other members of the gut microbiota play important roles in modulating the efficacy of probiotics, and that some probiotic activity may in fact be mediated by as-of-yet-overlooked components [5]. As he told us, "the whole question of non-bacterial microbes, such as the bacteriophages, other viruses, archaea, and yeasts that

also populate our intestines, is only at the very beginning of understanding and testing, and it's very limiting to simply assume that the only thing that's important is bacteria."

Thus, while much of the research in this area remains preliminary, both experts we spoke to are confident that it will progress fruitfully. The next few years should see an increasing number of probiotics entering clinical trials for their psychoactive properties, and some may even reach the market in the coming decades. Where future research will take this field is certainly up for debate, but because of the substantial scientific and commercial interest, strong preclinical promise, and potential for seminal discoveries in this area, we can be certain of years of exciting discoveries to come.

References

[1] Friedman RA. A Dry Pipeline for Psychiatric Drugs. The New York Times; 2013. Available from: `https://www.nytimes.com/2013/08/20/health/a-dry-pipeline-for-psychiatric-drugs.html`.

[2] Schroeder BO, Bäckhed F. Signals from the gut microbiota to distant organs in physiology and disease. Nature medicine. 2016;22(10):1079.

[3] Sarkar A, Harty S, Lehto SM, Moeller AH, Dinan TG, Dunbar RI, et al. The microbiome in psychology and cognitive neuroscience. Trends in cognitive sciences. 2018;22(7):611–636.

[4] Tompkins T. Interview; 11 December 2018.

[5] Bienenstock J. Interview; 07 December 2018.

Kevin completed his HBSc in Biopsychology at the University of Winnipeg in 2015, and is now a PhD candidate in the Neuroscience Graduate Program at McMaster University. His research focuses on mechanisms of communication between gut microbes and the nervous and immune systems of their host. When not in the lab, Kevin enjoys rock climbing and complaining about Hamilton's weather.

Health Science Inquiry NEWS

One Size Fits One:
Personalizing Prosthetics with 3D Printing

Morla Phan

3D printing is a relatively new technology, having set its roots in the late 80's to early 90's. Aptly named, 3D printing is a process where a three-dimensional object is created through the control of a computer. Public interest has recently increased due to advances in precision, repeatability and materials, resulting in a broader range of applications. For some time now, this technology has no longer been limited to only replacing external components such a bird beak, dolphin tail or human leg.

In 2015, a 22-year-old woman from the Netherlands who was suffering from increased pressure on her brain due to the thickening of her skull had her entire skull replaced with a plastic 3D custom printed implant. This surgery took 23 hours and after three months, she had regained her vision, returned to work and was entirely healthy. Later that same year, a three-year-old girl in China suffering from hydrocephalus underwent a 17 hour surgery to replace her skull with three custom printed titanium implants. This condition causes cerebrospinal fluid to accumulate in the brain cavities, causing severe pressure build-up which changes the shape of the skull. The surgery itself was a success, but the little girl will need follow up surgeries.

Last fall at the Ontario Veterinary College, veterinary surgical oncologist Dr. Michelle Oblak and her team successfully replaced approximately 70% of a dog's skull with a custom printed metal implant. This accomplishment is the first of its kind in North America and is a marked advancement in reconstructive surgery and veterinary medicine. The dog, named Patches, was a nine-year-old Dachshund afflicted with an osteochondrosarcoma tumor on her head. The tumour was so massive that it weighed down her head, pressing dangerously close to the brain and eye socket. The surgery took less than five hours, and the dog was "alert and looking around" 30 minutes after waking.

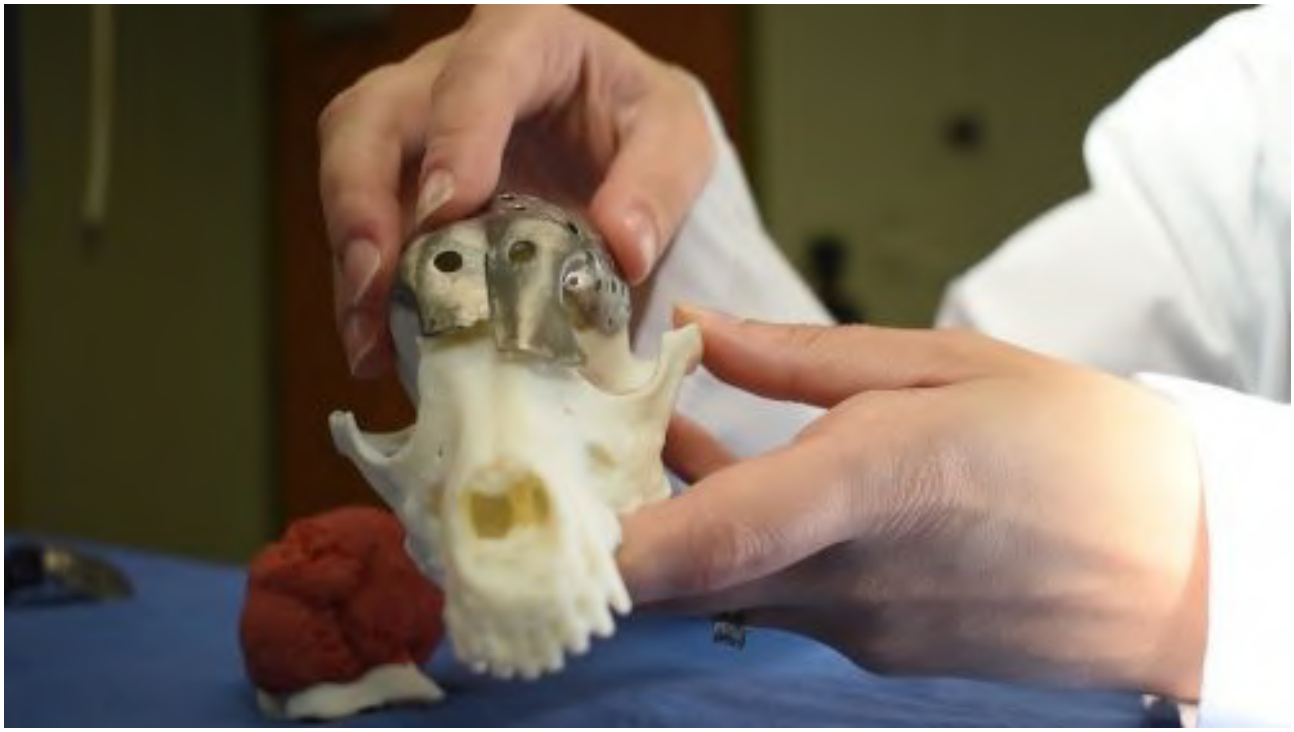
3D printing implants require an interdisciplinary approach, drawing input from several areas including medical imaging, mechanical design, materials science, computer programming and more. Every case is unique since it must consider the individual patient's anatomy and needs.

The technology has come a long way from its first inception. While some implants, such as the skull piece, are static, others can now possess functional and dynamic geometries as well. The use of this technology has a bright future for patient outcomes as well. Oblak explained that reconstructive surgeries typically take a long time. Traditional methods require time spent assessing the damage after a diseased portion of the skull is removed and shaping a titanium mesh over the spot. Imaging and 3D printing eliminates the need to create models 'on-the-fly' in the operating room, reducing patient risk.

The procedure began with a high-resolution CT scan of the tumour on Patches' head. Oblak and her team then used several different software programs to digitally remove the diseased portions of the skull and the tumour itself. Next, they modelled the 3D replacement to fit into the space and connect to the remaining bone. These plans were sent to ADEISS, a Canadian medical and dental 3D printing company, to produce the custom implant using metal. The surgery itself took about four hours, and within 30 minutes of waking up, Patches was alert and walking.

The dawn of the "Information Age" and the increasing ease of sending large image files over the Internet has bolstered the growth of 3D printing. Scientific Director of ADEISS, David Holdsworth, said he is confident in the future of 3D printing technology in medicine. "There have been dramatic advances in 3D printing in the past few years, and that applies to metal printing, as well as plastic printing (which is much more common)." Holdsworth believes the ease of 3D printing as compared to traditional manufacturing will mean that the industry will continue to expand. "The performance and cost-effectiveness of 3D metal printing has reached the point where some orthopaedic components are now manufactured by 3D printing, rather than traditional fabrication techniques," Holdsworth said. "This trend is likely to continue, and we'll see more and more 3D-printed components in the next few years."

With any growing technology, regulatory bodies must keep up in order to maintain safety standards. ADEISS requires its facility to follow a "rigorous, formal system of quality control that ensures that every aspect of the manufacturing process is done according to strict guidelines." These guidelines are set by the International Organization for Standardization.



Dr. Yara Hosein, an assistant professor at the University of Western Ontario and an expert on orthopaedic and orthodontic implants, explained that while regulations and ethics have to be maintained, public perceptions and expectations are also important. This has always been a struggle in medicine, as evidenced by movements such as anti-vaccinations or naturopathic/homeopathic practice. However, this can be prevented by educating the public on the technology behind 3D printed implants, what it is capable of and what its current challenges are.

Morla is currently an MSc. student at the University of Guelph, Ontario Veterinary College. Her passion for cancer research led her to a project that focuses on figuring out a way to radiosensitize canine mast cell cancer cells. She enjoys drawing and reading science fiction in her spare time.

Health Science Inquiry NEWS

Emerging Regenerative Therapies for Heart Injury:
Addressing an Urgent Need

Sarah Shawky

Cardiovascular disease (CVD) continues to be the leading cause of death worldwide, accounting for over 8.5 million annual mortalities [1]. CVD is also correlated with an increased risk for a heart attack, or myocardial infarction (MI). Following an acute MI, a human adult loses approximately one billion cardiomyocytes - heart muscle cells - which are then replaced by non-contracting fibrous scar tissue [1, 2, 3]. The inability of the damaged myocardium to fully replenish itself weakens the contractile function of the heart in the long-term, further increasing the risk of MI and heart failure over time [1, 4]. Due to the irreversible nature of cardiac injury, the current gold-standard therapy for advanced heart failure remains cardiac transplantation [1]. However, along with the severely limited supply of suitable donor hearts, the increasing global incidences of myocardial infarction highlight the urgent need for the development of novel, less invasive therapeutic interventions.

Despite substantial advancements in cardiovascular biology and tissue engineering over the last 20 years, no clinically-available means to regenerate damaged cardiac muscle currently exists [5]. However, a variety of technologies to support this approach have been heavily investigated in recent years. These strategies include stem cell-based therapies, which involve the integration of undifferentiated cells into injured host tissue to mediate repair. Another approach involves the generation of biomaterial-based scaffolds, which may support tissue repair by providing a template for regeneration. While several preclinical and clinical studies exploring the use of various types of stem cells have shown promising results in the reversal of cardiac pathologies, others have faced significant barriers [3, 5]. Some of these obstacles have evoked important research questions, including the need for more efficient methods of stem cell delivery, and the investigation into means of increasing stem cell survival, retention and engraftment within the infarcted heart [2, 3, 6]. Excitingly, cardiac researchers have begun to address these critical questions, providing hopeful answers that may offer a new outlook on the direction of cardiac regenerative medicine.

Dr. Erik Suuronen, a research scientist in the Division of Cardiac Surgery and the director of the Biomaterials Regeneration Program at the University of Ottawa Heart Institute, focuses his research on tissue engineering and cell-based therapeutic approaches for the treatment of cardiac injury. Specifically, he is interested in the development and testing of biomaterials to mobilize and recruit the body's endogenous reparative cells, with aims of creating an environment that better supports and promotes cardiac regeneration. Briefly, Dr. Suuronen describes tissue engineering as a way to direct the repair process – his team is investigating whether a biomaterial scaffold could promote the engraftment of transplanted cells, and hence mediate the regenerative process to reverse cardiac injury. To conduct their research, Dr. Suuronen and his team use various instruments to characterize the physical properties of the materials they design. They also use *in vitro* and *in vivo* models to test the ability of these materials to mediate cell function and to promote repair. Specifically, they are interested in studying how the developed biomaterials interact with various cell types to promote regeneration, and how these interactions can be exploited to enhance the efficacy of a potential therapy. Dr. Suuronen and his team recently developed a collagen-based biomaterial which, upon delivery into an injured heart, can preserve its function.

"Upon injection of our collagen-based biomaterial into the infarcted heart, it interacts with multiple cell types to limit chronic inflammation and cell death, reduce adverse remodeling, promote revascularization and improve cardiac function", Dr. Suuronen says.

Using PET and fluorescence imaging techniques, Dr. Suuronen and his team revealed that the injected collagen-based biomaterial is effectively retained and redistributed within murine models of MI [7]. Dr. Suuronen believes that further mechanistic insight into how the injected biomaterial interacts with endogenous cell types to repair the injured heart may reveal key target pathways with novel therapeutic potential. His team is hopeful that biomaterials will soon begin pre-clinical trials to test their safety and efficacy as treatments for cardiac injury – potentially as both a stand-alone therapy and as a vehicle for the delivery of other therapeutic agents.

But in order to develop a physiologically-relevant and clinically-applicable biomaterial therapeutic, Dr. Suuronen says that the final product must be compatible with the human heart. Over the last two years, his team has shifted its

focus from developing animal protein-derived biomaterials, to utilizing human collagen-based materials instead.

As a final thought, Dr. Suuronen reflects upon the growing ease of finding experts and trainees with the necessary skillset and experience to form the collaborations needed to translate regenerative medicine discoveries into clinical applications. When he first began working in this area of research, it was a challenging endeavour to build the strong, highly-multidisciplinary team necessary – and pivotal – for success. However, nowadays, combining the diverse expertise of scientists, engineers, physicians and imaging specialists is becoming easier, and the field of cardiac regeneration is looking more promising.

Taking an alternate route, Dr. Michael Laflamme, a cardiac cell therapy pioneer at the McEwen Stem Cell Institute, is focused on developing novel therapies for post-MI heart failure based on human pluripotent stem cells (hPSCs) – the only stem cell that can be differentiated into large enough quantities of phenotypically unambiguous cardiomyocytes. Research investigating the remuscularization of the infarcted heart using exogenous cell transplantation began in the early 1990s [8]. Early experiments began by using immature cell types, such as neonatal and fetal cardiomyocytes, skeletal myoblasts and bone marrow-derived hematopoietic cell types [3, 6, 8]. However, due to the ethical issues, efficacy problems and limited generation of *de novo* cardiac muscle cells associated with the use of each of these cell types, Dr. Laflamme instead focuses his research on another cell type – the infinitely expandable pluripotent stem cell-derived cardiomyocytes.

In addition to having developed methods to guide hPSCs into cardiomyocytes, Dr. Laflamme and his team have shown that when transplanted into models of injured hearts, these cells are capable of electrical coupling with the host myocardium, firing synchronously with the rest of the heart and improving its contractile function. In the mid-2000s, Dr. Laflamme began his work using small animal models, such as rats, and later shifted into the use of guinea pigs and macaques in pioneering work to demonstrate that hPSC-derived cardiomyocytes mediate functional integration and regeneration of the myocardium. Currently, he is focused on surgically delivering a billion of these cells into pig hearts, because of their near-identical size, structure and function to the human heart. Dr. Laflamme anticipates that this is expected to be the last pre-clinical model prior to human pre-clinical trials, which he hopes to initiate in about three to four years.

Dr. Laflamme discusses some of the important obstacles to address prior to considering the translation of this research from *in vivo models* to humans. This includes overcoming the occurrence of transient arrhythmias following the cell transplantation.

"These [transplanted] cardiomyocytes are unlike those present in an adult; they are less mature and have different electrical properties", Dr. Laflamme explains. "When they are transplanted, transient arrhythmias – abnormal beating rhythms of the heart - are seen in the beginning, while they are "settling" *in vivo*. Later, these arrhythmias disappear and the cells function effectively once matured. We want to come up with ways to overcome or prevent these arrhythmias – perhaps via antiarrhythmic drugs, or by engineering the cells".

In 2016, the McEwen Centre for Regenerative Medicine at the University Health Network partnered with the new life sciences start-up, BlueRock Therapeutics, driving large-scale research and development in the area of heart muscle regeneration. The manufacturing platform at BlueRock Therapeutics will help to fuel the scalable production of various stem cell types for cellular therapeutics – including pluripotent stem cell-derived cardiomyocytes, which Dr. Laflamme and his team are focused on bringing into the clinic.

Despite the hurdles to be overcome, cardiac regenerative medicine researchers including Drs. Suuronen and Laflamme are excited about the substantial progress that has been made towards the development of novel therapies for cardiac injury. While some laboratories are aggressively exploring strategies to ramp up endogenous cellular regeneration via exogenous biomaterials, others are focused on cellular reprogramming and gene therapy. Overall, the rapid development of these diverse, promising therapies offers hope that their translation from the laboratory to having positive clinical impacts at the bedside is closer than we may have thought.

We would like to extend our thanks to Dr. Erik Suuronen and Dr. Michael Laflamme for sharing their work, and for their time and effort in contributing to this news article.

References

[1] Kochegarov A, Lemanski LF. New trends in heart regeneration: a review. Journal of stem cells & regenerative medicine. 2016;12(2):61.

[2] Lin Z, Pu WT. Strategies for cardiac regeneration and repair. Science translational medicine. 2014;6(239):239rv1–239rv1.

[3] Romagnuolo R, Laflamme MA. Programming cells for cardiac repair. Current opinion in biotechnology. 2017;47:43–50.

[4] Bertero A, Murry CE. Hallmarks of cardiac regeneration. Nature Reviews Cardiology. 2018;p. 1.

[5] Duelen R, Sampaolesi M. Stem cell technology in cardiac regeneration: a pluripotent stem cell promise. EBioMedicine. 2017;16:30–40.

[6] Bilgimol JC, Ragupathi S, Vengadassalapathy L, Senthil NS, Selvakumar K, Ganesan M, et al. Stem cells: An eventual treatment option for heart diseases. World journal of stem cells. 2015;7(8):1118.

[7] Ahmadi A, Thorn SL, Alarcon EI, Kordos M, Padavan DT, Hadizad T, et al. PET imaging of a collagen matrix reveals its effective injection and targeted retention in a mouse model of myocardial infarction. Biomaterials. 2015;49:18–26.

[8] Lundy SD, Gantz JA, Pagan CM, Filice D, Laflamme MA. Pluripotent stem cell derived cardiomyocytes for cardiac repair. Current treatment options in cardiovascular medicine. 2014;16(7):319.

Sarah received her Honours Bachelor of Health Sciences degree from McMaster University, where she specialized in Biomedical Discovery & Commercialization. Passionate about the intersection between scientific discoveries and their translation into clinical medicine, Sarah is enthusiastic about contributing to innovative research. She is currently an MSc candidate at the Leslie Dan Faculty of Pharmacy, University of Toronto, and is a recipient of the CIHR Canada Graduate Scholarship. Sarah's MSc research is focused on studying the role of activated nuclear hormone receptors in the prevention of atherosclerosis.

Health Science Inquiry NEWS

How Will Science Help to Address the Opioid Crisis?

Lola Welsch

You have probably heard about the opioid crisis: an epidemic of opioid abuse and overdoses of highly potent painkillers such as morphine, heroin or oxycodone - raging in North America since 2010. The number of opioid-related deaths surpassed 4,000 in 2017 in Canada alone, placing opioid use as the leading cause of premature deaths (above car accidents). On top of that, opioid abuse during pregnancy has led to a dramatic increase in drug-dependent newborns and has additionally contributed to the spread of infectious diseases such as HIV and hepatitis C [1]. If we take a look back, we can better understand the origins of this crisis: morphine, the active substance in opium extracted from poppies, has been used for centuries due to its unparalleled pain-relieving and euphoria-inducing properties. In the 1990s, the modern pharmacopeia introduced synthetic molecules such as oxycodone, marketed by pharmaceutical companies as safe, non-addictive pain-relievers. Subsequently, the prescription rate of opioids increased dramatically, reaching a peak in 2010, exposing a large numbers of North Americans to highly addictive drugs. Prescription opioids have been a gateway to non-medical use of opioids for many people: approximately 10% of patients with opioid prescription develop an opioid use disorder [2]. In addition to facilitating drug use among non-users, prescription opioids were also the main supply for the illicit market, making opioids available on the streets. In 2012, authorities grew increasingly recognizant of the harms resulting from over-prescription and took measures to reduce the prescription of opioids [1]. Despite these efforts, the crisis worsened with the introduction of a new, incredibly potent and easily synthesized opioid on the illicit market. Prescription-reliant opioid users, at times, had no choice but to turn to this hazardous drug, exacerbating the current opioid crisis. Several national measures have since been implemented to contain this global health issue: reduction of opioid prescription, intensification of the monitoring of prescribed opioids, creation of safe consumption centers and distribution of naloxone, an overdose-reversing drug. Despite these efforts, considerable work remains to overcome the crisis, and research has an important role to play [3].

The National Institute of Health (NIH) have drawn two lines of research to foster the efforts to address the epidemic: the first objective is reactive and focuses on improving care for opioid use and addiction. The second objective is proactive and attempts to mitigate opioid use by offering alternative pain relief techniques (Initiatives Research plans, NIH, 2018). In April 2018, the NIH started the HEAL program (Helping to End Addiction Long-term). The initiative encourages improvements to opioid use disorder therapies, in particular though the combination of psycho-therapies and medication-assisted treatment (promoting transition drugs such as buprenorphine or methadone).

Interestingly, computer-based tools are under development to broaden and facilitate access to psychiatric care, often in limited availability. For instance, the National Institute of Drug Abuse is developing an interactive program intended for cognitive-behavioral therapy (CBT). In essence, CBT is a form of psycho-therapy focused on treating specific maladaptive behaviors, problems, and symptoms. CBT has shown efficacy in addressing substance use disorders and coping with the disease. In this program, Dr. Caroll and colleagues use a combination of games, cartoons and interactive exercises to teach patients how to deal with stressful or risky situations without returning to drug use. These kinds of computer-assisted therapies offer several advantages compared to currently available therapies; CBT could be the first step for patients to engage in a complete therapeutic process and to enhance the recovery rate. Their use also liberates time for the psycho-medical staff to manage in-person clinical therapies [4]. Other teams in the field of addiction therapy are working on tools for early diagnosis of substance use disorders. These include using innovative approaches such as state-of-the-art neuro-imaging techniques [5], or combining social media data with deep neural networks to identify at-risk populations [6]. All of these efforts are made in the hope to better address addiction disorders, parallel to traditional addiction prevention strategies.

The majority of opioids abusers are first introduced to these drugs via prescriptions for severe and/or chronic pain; despite the harmful and addictive potential of opioids, they remain the best class of drugs for pain relief. In this context, researchers are looking for opioid-like painkillers with fewer unwanted side-effects. To this end, some drug discovery strategies comprise designing “better opioids” by tweaking the cellular target of the drugs. Scientists have been able to manipulate the effects of the chemicals. Progress has been made in this field particularly with drugs called “biased opioids”: as traditional opioids, they target the mu opioid receptor, responsible for all the effects of morphine. However, unlike traditional opioids, they are biased toward a specific cell signaling pathway, the one thought to be responsible

for pain relief. It is also believed that they lessen the activation of the pathway thought to be responsible for tolerance development, respiratory depression, nausea and constipation. Other similar approaches to designing the ideal opioid involve identifying molecules acting at different opioid receptors. However, the question of the addictive potential of these drugs and their rewarding properties is still debated and likely will not be available in the clinic for many years [7]. To avoid opioids altogether, a considerable effort is taking place to develop new non-opioid analgesics. For instance, there is increasing evidence supporting the use of medical marijuana in treating chronic pain [8]. In parallel, other non-pharmacological approaches are underway: pilot studies with demonstrated efficacy of physiotherapy or meditation in the reduction of chronic pain offer some hope [9].

Science has taken a very diverse approach and tackles the opioid crisis from complimentary perspectives. Even if we can distinguish major priorities in research, this article is not an exhaustive list of all existing attempts to address the issue, but every idea and effort is an important piece of the puzzle. Importantly, the solution can only be complete by combining research, medicine, technologies, personal psychiatric care, public health interventions and harm reduction policies. To conclude, we can pinpoint that researchers and clinicians working in the field of opioid use disorders recommend talking about it and treating it as a chronic illness and not a moral failing. The first step in addressing the crisis would then be to go over the stigmatisation and marginalization of opioid use to make a change in how we choose to move for better care [10].

References

[1] Fischer B, Pang M, Tyndall M. The opioid death crisis in Canada: crucial lessons for public health. The Lancet Public Health. 2019;4(2):e81–e82.

[2] Carlson RG, Nahhas RW, Martins SS, Daniulaityte R. Predictors of transition to heroin use among initially non-opioid dependent illicit pharmaceutical opioid users: A natural history study. Drug and alcohol dependence. 2016;160:127–134.

[3] Fischer B, Rehm J, Tyndall M. Effective Canadian policy to reduce harms from prescription opioids: learning from past failures. CMAJ. 2016;188(17-18):1240–1244.

[4] Carroll KM, Kiluk BD, Nich C, Gordon MA, Portnoy GA, Marino DR, et al. Computer-assisted delivery of cognitive-behavioral therapy: efficacy and durability of CBT4CBT among cocaine-dependent individuals maintained on methadone. American journal of Psychiatry. 2014;171(4):436–444.

[5] Moningka H, Lichenstein S, Worhunsky PD, DeVito EE, Scheinost D, Yip SW. Can neuroimaging help combat the opioid epidemic? A systematic review of clinical and pharmacological challenge fMRI studies with recommendations for future research. Neuropsychopharmacology. 2018;p. 1.

[6] Hassanpour S, Tomita N, DeLise T, Crosier B, Marsch LA. Identifying substance use risk based on deep neural networks and Instagram social media data. Neuropsychopharmacology. 2019;44(3):487.

[7] Severino AL, Shadfar A, Hakimian JK, Crane O, Singh G, Heinzerling K, et al. Pain therapy guided by purpose and perspective in light of the opioid epidemic. Frontiers in psychiatry. 2018;9.

[8] Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. Jama. 2015;313(24):2474–2483.

[9] Turk DC, Wilson HD, Cahana A. Treatment of chronic non-cancer pain. The Lancet. 2011;377(9784):2226–2235.

[10] Olsen Y, Sharfstein JM. Confronting the stigma of opioid use disorder—and its treatment. Jama. 2014;311(14):1393–1394.

Lola is a PhD student, studying neurosciences at McGill University. Her work focuses on a rodent model of opioid addiction, to study the consequences of long term withdrawal from morphine on the brain and eventually help maintaining abstinence. Never bored talking about brains and minds, she is involved in several science popularization organizations, such as the festival Pint of Science and outreaches to teach some mysteries of brain functioning to teenagers. She is always looking for new occasion to share passions and ideas!

Health Science Inquiry

NEWS

Climate Change and the Future of Public Health

Alanna Miller

Popular media is saturated with terrifying claims of the effects of global climate change. Our minds absorb the various statistics on the melting of the polar ice caps and rising sea level, the destruction of rainforests and extinction of exotic species, and the pollution of the air and water that the world relies on. Of course, the effects of climate change exist far beyond environmental degradation, and the discussion surrounding climate change cannot be possible without considering the broader implications for public health, which are often ignored in popular media. In accordance with the United Nations (UN), the Intergovernmental Panel on Climate Change (IPCC) released a report in 2018 describing the "impacts of global warming of 1.5°C above pre-industrial levels" expected to occur between the years 2030 and 2052 [1]. This increase in global temperature will likely have negative repercussions for public health, including exacerbations of chronic diseases and mental illness, food shortages and malnutrition, human displacement, and increased transmission and susceptibility to infectious diseases [1, 2, 3].

Extreme weather events, including heat waves, droughts, and floods, are potentially disastrous consequences of climate change. The occurrence of extreme temperatures has been increasing since the 1990s [2], and the IPCC predicts that throughout the 21^{st} century, global temperatures will continue to rise, with more locations experiencing hotter temperatures and fewer cold spells [1]. Extreme heat poses a serious public health threat; it can cause heat stroke and worsen the symptoms of chronic diseases, including cardiovascular disease and chronic respiratory disease [4]. In Quebec and Ontario, 2018 was host to one of the hottest summers yet, and a heatwave in July was ultimately responsible for claiming the lives of over 80 individuals in Quebec alone [5]. Those over the age of 65, people who engage in vigorous outdoor manual labour, and individuals residing in urban areas are at the greatest risk of heat-related morbidity and mortality [2, 4].

Extreme weather events can also indirectly impact human health by affecting food supply and availability. Agricultural yields are disturbed by flooding and drought events, which may lead to food shortages and malnutrition in severe circumstances [2]. These shortfalls in agricultural production are more likely to affect those living in poverty in middle- and low-income countries [1, 2]. In addition to food shortages, extreme weather events can cause perilous damage to the built environment, destroy homes and infrastructure, and can result in the displacement of people and severe economic loss [2]. Again, these effects are more detrimental to individuals in low- and middle-income countries, and can negatively impact the mental health of those affected [2].

The most researched topic regarding the implications of climate change on public health is the transmission of infectious diseases carried by insects. Increased transmission of malaria and dengue, known as the 'Big Two', is expected to coincide with the warming of temperatures and increased regional precipitation associated with climate change [1, 3]. Both malaria and dengue are carried by mosquitos and are common to parts of South and Central America, Asia and Africa. However, considering the future implications of climate change, we must pose the question: Could malaria and dengue spread to more temperate regions, such as those here in Canada?

Dr. Mark Loeb of McMaster University is a professor for the Department of Pathology and Molecular Medicine, and studies infectious diseases spread by insects, including West Nile and dengue. He believes that "in the long-term it is possible for such diseases to end up in Canada". Aside from malaria and dengue, there are many other diseases, including Lyme disease, an infection transmitted by ticks, which is currently present in certain regions of Canada. Lyme disease can become a chronic infection characterized by severe headaches, joint and muscle pain, arthritis, heart disorder and neurological disorder, and can be very debilitating to those infected. Dr. Loeb said there has already been an observed increase in the geographical spread of the tick-borne infection and suggests that in order to protect against the increased spread of infectious diseases, we must focus on reducing the trends in climate change and the development of effective and accessible vaccines.

There is no doubt that climate change will continue to have an impact on public health, and this will become even more detrimental if public health systems are not prepared to cope with these changes. In Ottawa, ON, on February 5, 2019, the Canadian Public Health Association (CPHA) released a statement urging federal political parties to acknowledge the severity of climate change and its negative impact on public health [6]. The CPHA challenged the federal government to develop a plan for Canada to reduce carbon emissions while prioritizing health, create policies and programs for

corporations and communities to transition to a low carbon economy, and provide funding and support to ensure public health units and communities are able to respond to the mental and physical health needs of Canadians affected by climate change [6]. When analyzing the amount of funding countries allocated to public health adaptation, the greatest increase in funding was observed in lower- and middle-income countries [2]. Considering that the brunt of climate change will be felt in low- and middle-income countries [2], this increase in funding for public health adaptation is encouraging. Furthermore, the UN suggests that reducing poverty and encouraging socioeconomic development are the best ways to increase resiliency within these countries, but unfortunately, funding available for these initiatives is still insufficient [2].

Since pre-industrial times, human activity has caused an increase in average global temperature by approximately 1.0°C, and the IPCC suggests with strong evidence that we will observe another 0.5°C increase by the year 2052 [1]. Climate change is therefore inevitable, and it is important that we prepare our public health infrastructure now to improve our future resiliency. Climate change will have negative repercussions for public health, including exacerbations of chronic diseases and mental illness, food shortages and malnutrition, human displacement, and increased transmission of infectious diseases [1, 2, 3]. Key ways to adapt public health systems for the future consequences of climate change are to reduce poverty and improve socioeconomic development [2]. On a corporate and individual level, we must also focus on limiting the anthropogenic factors, such as greenhouse gas emissions, to reduce any future negative impacts of climate change on public health. Instead of allowing the effects of climate change to play out with our compliance, it is now that each country, corporation and individual must take action to ensure that we are protecting both our planet and our health.

References

[1] Intergovernmental Panel on Climate Change. Global warming of 1.5°C; 2018.

[2] Watts N, Amann M, Arnell N, Ayeb-Karlsson S, Belesova K, Berry H, et al. The 2018 report of the Lancet Countdown on health and climate change: shaping the health of nations for centuries to come. The Lancet. 2018;392(10163):2479–2514.

[3] Ogden NH. Climate change and vector-borne diseases of public health significance. FEMS microbiology letters. 2017;364(19):fnx186.

[4] Kjellstrom T, Butler AJ, Lucas RM, Bonita R. Public health impact of global heating due to climate change: potential effects on chronic non-communicable diseases. International journal of public health. 2010;55(2):97–103.

[5] National Post. New research predicts heat waves in Canada could become more frequent — and five times more deadly; 2018. Available from: `https://nationalpost.com/news/canada/new-research-predicts-heat-waves-in-canada-could-become-more-frequent-and-five-times-more-deadly`.

[6] Canadian Public Health Association. Health professionals to federal political parties: action needed to prevent catastrophic climate change;. Available from: `https://www.cpha.ca/health-professionals-federal-political-parties-action-needed-prevent-catastrophic-climate-change`.

Alanna is a Master of Public Health candidate at McMaster University, where she is completing a thesis focused on the epidemiology of sexually transmitted infections in relation to the use of mobile dating applications. Aside from her passion for public health, Alanna enjoys travelling and experiencing new sights, tastes and sounds.

SPECIAL THANK YOU TO

OUR PARTNER JOURNAL:

Lifestyle Genomics®

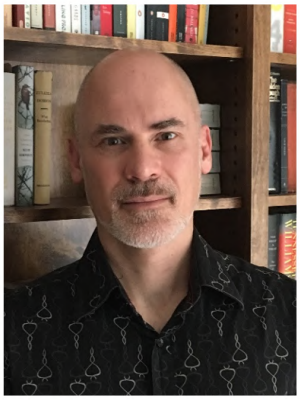
THANK YOU TO

OUR GENEROUS SPONSORS:

GSA
GRADUATE STUDENTS ASSOCIATION
OF MCMASTER UNIVERSITY

WE WHO DISCOVER
URGSA
University of Regina Graduate Students' Association

WE WOULD LIKE TO EXTEND OUR THANKS TO THIS YEAR'S JUDGES:



Dr. Eric Mykhalovskiy, PhD
Professor, Department of Sociology, York University
Senior Editor, Canadian Journal of Public Health

Eric received his PhD from York University in 2000. Following a postdoctoral fellowship at the Department of Public Health Sciences, UT, he spent three years teaching in the Department of Community Health and Epidemiology at Dalhousie University. Eric works primarily in the tradition of Studies in the Social Organization of Knowledge and Institutional Ethnography. While he has published on a range of topics, a recurring research focus is the social organization of the biomedical and broader institutional and discursive response to the HIV epidemic in Canada. His most recent publication is the edited volume (with V. Namaste) *Thinking differently about HIV/AIDS: Contributions from critical social science,* UBC Press, 2019.

Dr. Erin Styles, PhD
Assistant Professor, University of Toronto

As the director of the Masters of Health Sciences program in Medical Genomics, my focus is on designing and implementing a professional Master's program that provides practical, actionable training in medical genetics and genomics. My research focuses on course and program assessments of success, including the attainment of learning objectives within individual courses, post-graduate success, and the overall impact of the program on patient health outcomes and the adaptation of genomic medicine at the front lines of care.

Dr. Matthew Little, PhD
Assistant Professor, Department of Population Medicine, University of Guelph

Dr. Matthew Little conducts research on Global, First Nations, and Inuit health, community food security, nutrition-related non-communicable diseases, food systems and environments, ecological determinants of health, climate change and health, and environmental contaminants in food sources. During his PhD, he was also a Reviewer with HSI.

Dr. Jayson Parker, PhD
Associate Director, Master of Biotechnology Program
Associate Professor, Department of Biology & Institute of Biomaterials and Biomedical Engineering, University of Toronto

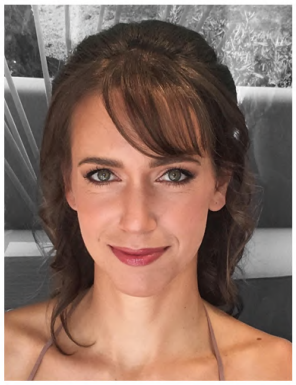
Dr. Jayson Parker is currently a medical advisor to the hedge fund Burlington Capital. Previously, he was a medical liaison operating in medical affairs for the pharmaceutical companies Novo Nordisk and Schering AG. He has worked in the investment banking industry as a buy side biotechnology stock analyst for Investor's Group and Bolton Trembley. He was the Director of Equity Research (medical) for AIC Limited (now Portland).

As a research associate, he has worked for the Addiction Research Foundation (now CAMH) on animal models of alcohol abuse. In addition, he joined the medical imaging department at Sunnybrook Hospital and conducted research on Alzheimer patients through 3 dimensional reconstructions of patient brains from MRI scans.
He obtained his PhD in Physiology (Neuroscience focus) based on his research on brain trauma at the University of Toronto and his MBA from Wilfred Laurier University. His Master's degree from the University of Toronto focused on the neurobiology of cocaine addiction.

Lastly – he is an active Dungeons and Dragons player.

Dr. Jim Woodgett, PhD
Director of Research, Lunenfeld-Tanenbaum Research Institute
Professor, Department of Medical Biophysics, University of Toronto

Dr. Woodgett researches how cell communicate through signal transduction pathways and how these systems are subverted in various diseases including cancer, Alzheimer's Disease and mental health disorders. He is also actively engaged in advocacy for health research in Canada and works to improve science communication through Twitter (@jwoodgett) and blogs.



Dr. Lora Appel, PhD

Assistant Professor, Faculty of Health, York University

Dr. Lora Appel is an assistant professor of Health Informatics at the Faculty of Health at York University, and a Collaborating Scientist at OpenLab, and innovation Centre housed at University Health Network, the largest medical research organization in Canada.
She leads "Prescribing Virtual Reality (VRx)" a collection of studies that introduce and evaluate AR/VR/MR interventions for patients, caregivers, and healthcare providers. Her expertise is in applying design thinking and science methodologies to healthcare innovation; she is passionate about designing new technological interventions that provide *care* in the pursuit of a *cure*.

Dr. Naomi Adelson, PhD

Associate Vice President, Research and Innovation, Ryerson University

As a medical anthropologist, Professor Adelson's theoretical interest is founded on the critical study of the body and health in relation to the naturalization and medicalization of social and historical inequalities. Dr. Adelson has been conducting research in collaboration with the northern James Bay Cree (Iiyiyu'ch) and in association with the Cree Board of Health since the late 1980s. Her most recent projects focus on 1) the social and political context of medical care to the Cree through the Cold War years and 2) the contemporary management and control of research data in support of Indigenous data sovereignty. Her publications include Being Alive Well: Health and the Politics of Cree Well-Being (University of Toronto Press), "The Embodiment of Inequity: Health Disparities in Aboriginal Canada" (CJPH) and "Discourses of Stress, Social Inequities, and the Everyday Worlds of First Nations Women in a Remote Northern Canadian Community" (Ethos). Professor Adelson is currently the Associate Vice President, Research and Innovation at Ryerson University, Toronto.

Dr. Robert Bonin, PhD

Assistant Professor, Leslie Dan Faculty of Pharmacy, University of Toronto

Dr. Rob Bonin is an Assistant Professor in the Leslie Dan Faculty of Pharmacy at the University of Toronto. He holds the Canada Research Chair in Sensory Plasticity and Reconsolidation and is a Scientist with the University of Toronto Centre for the Study of Pain. Dr. Bonin is exploring the synaptic changes in the spinal cord that contribute to abnormal sensory processing and is developing new models to study natural pain behaviour in animals and improve pain medication development.

TOP ARTICLE SUBMISSIONS

Call for Submissions

In January 2019, HSI sent out a call for submissions to graduate students at universities across Canada for opinion pieces or mini-reviews (700-800 words) addressing The Future of Health, under one of the following sub-themes:

1. **Future Medicine and Treatment** – 8 articles submitted.
2. **Future Health and Research Technology** - 3 articles submitted.
3. **Future Health and Society** - 5 articles submitted.

Review and judging process

Beginning in March 2019, each submission was reviewed by two HSI Reviewers who critically assessed each commentary and provided feedback to the authors regarding its content and structure. After receiving their feedback, authors were given three weeks to revise their submission and resubmit to the journal. Our team of Senior Editors reviewed each revised commentary, and using information from the feedback given to them and additional editorial staff input, made a final publication decision. Each submission was then reviewed and scored twice by a team of independent judges not affiliated with HSI.

Winners

The authors of the highest scoring submission for each sub-theme were each awarded a $150 HSI scholarship award. In addition, the winner of the Future Health and Research Technology category was awarded the opportunity of expedited review for their article by our partner journal: *Lifestyle Genomics*. We received some outstanding submissions, and the editorial team highly commend the authors for their achievement. After tabulating the results, we are pleased to announce the top 3 submissions for the 2019 issue of Health Science Inquiry:

1. **Future Medicine and Treatment:** Precision Medicine Targeting the Gut-Brain Axis in Depression: The Future of Psychiatric Treatment - *Caroline Wallace*
2. **Future Health and Research Technology:** Body composition analysis in clinical populations: the role of deep learning - *Michael Paris*
3. **Future Health and Society:** Healthcare in an era of patient engagement: language for ongoing dialogue - *Umair Majid*

The following is the highest rated article in our 2019 submission category *Future Medicine & Treatment*. All articles were ranked by HSI's independent professor judging panel. For this, the author was awarded one of three of HSI's annual "scholarship" awards.

Precision Medicine Targeting the Gut-Brain Axis in Depression: The Future of Psychiatric Treatment

Caroline Wallace[1]

[1]Centre for Neuroscience Studies, Faculty of Health Sciences, Queen's University

Precision medicine is becoming increasingly popular in the healthcare setting in an attempt to treat illness more effectively. The term precision medicine refers to prevention and treatment strategies that are based on individual variability and targeted toward precise molecular underpinnings of disease [1], as opposed to using a standardized or 'one size fits all' model. Precision medicine aims to treat individual patients using approaches that have been identified as being effective based on specific characteristics, including biological and psychosocial markers. It is a model that makes use of data, analytics, and information, and pays significant attention to patient engagement, digital health, genomics, and data science [2]. Precision medicine is already in practice for some illnesses such as breast, lung, and colorectal cancers, and now neuroscientists are exploring precision medicine in neurological diseases, including Parkinson's Disease and Alzheimer's Disease. These diseases have been proposed as ideal for realizing precision medicine due to their strong genetic component [1], and this research is beginning to be extended into psychiatric diseases as well, including Major Depressive Disorder (MDD).

MDD is a psychiatric disease characterized by a persistent feeling of sadness or lack of interest accompanied by other psychological and physiological symptoms that impair daily functioning. MDD is an ideal candidate for precision medicine due to the heterogeneity in clinical presentation and pathophysiology of the disorder. For example, consider two fictional patients, Patient A and Patient B. Patient A presents with low mood, lack of energy, sleeping 12-16 hours a day, increased appetite and weight gain, and suicidal ideation. Patient B presents with loss of pleasure or enjoyment, feelings of extreme guilt, loss of appetite and weight loss, agitation and severe insomnia. Both patients are diagnosed with MDD yet have no overlapping symptoms. This heterogeneity of symptomatology may translate to a heterogeneity in pathophysiology. Research has identified common neurophysiological changes associated with the disorder, including alterations in neurotransmitter functioning and neuroinflammation [3], but the degree of these changes varies widely across patients, as does the etiology of the disorder. While patterns exist, explicit causes of MDD remain unclear and questions regarding etiology persist: Why do some individuals who have experienced adverse childhood experiences become depressed, while others do not? Why do some individuals who objectively lead stable and comfortable lives become depressed, while others do not? Ongoing research into symptomatology, pathophysiology, and etiology have aided in the development of antidepressant medication. However, the response to treatment in MDD varies widely; Many patients try two to three different medications before finding one that works, and even then, up to 60% of patients discontinue their antidepressant use within the first three months due to issues such as side effects [4]. It is impractical to attempt to treat individuals universally, and thus more precise treatment strategies are warranted.

The Canadian Biomarker Integration Network in Depression (CAN-BIND) program is a leader in the initiative to identify biomarkers that will help predict who and how individuals will respond to various available treatments. CAN-BIND studies examine different treatment strategies and collect data based on several platforms, including clinical, molecular, neuroimaging, mobile-health technology, and use an informatics-based approach to integrate this data to stratify depressed patients into subgroups based on specific characteristics. This information can then be used to optimize treatment using precision medicine by identifying to which subgroup a patient belongs and using the corresponding treatment shown to be efficacious for that subgroup. One treatment strategy being explored within the CAN-BIND network is targeting the gut-brain axis using probiotic intervention. The gut-brain axis is a bidirectional communication network between the brain and the gastrointestinal (GI) tract that communicates via the autonomic nervous system, the enteric nervous system, the neuroendocrine system, and the immune system [5]. The gut-brain axis has been implicated in the pathophysiology of MDD as a potential molecular underpinning to the disease [6]. This has led to the investigation of probiotics, bacteria in the GI tract that confer a health benefit to the host, as a potential treatment for MDD [7]. While research to date on probiotics improving symptoms of depression

in MDD patients is scant and inconclusive, research on healthy humans has shown improvements in mood and affective symptoms following probiotic supplementation [7]. The composition of the microbiome that colonizes the GI tract is unique to each individual, and it has been shown that depression is associated with reduced diversity in the microbiome of the GI tract [8]. Thus exploring how depressed individuals respond to probiotic supplementation may provide crucial insight into those important questions on the etiology, pathophysiology, and symptomatology of MDD.

The collection of biospecimen samples such as blood, stool, and urine as part of the molecular platform will allow us to obtain biological information that may reveal certain genes, proteins, inflammatory markers, or bacterial products that may correlate to treatment response. For example, if probiotic supplementation does indeed alleviate symptoms of depression, but only in patients who present with high plasma levels of lipopolysaccharide (LPS; an innate immune-activating endotoxin that may have a role in gut-brain signaling), this would present a valuable opportunity for applying precision medicine: a blood test screening for LPS levels could determine whether a patient will respond. It is also important to note that biomarkers do not necessarily have to be biological, they can be psychosocial or behavioural, collected as part of the clinical and m-health platforms: if it is determined probiotic supplementation alleviates symptoms of depression but only in people who engage in a certain level of physical activity weekly, patients could be screened for physical activity to determine if the treatment will work for them.

The medical model of precision medicine allows physicians to customize healthcare by selecting treatments that are the most likely to benefit the patient. However, it does not come without its drawbacks. Precision medicine strategies may be costlier and more time consuming. It has been argued that precision medicine is not ideal for high-prevalence diseases and disorders; more rapid and low-cost standardized treatments that cover more bases should be pursued first. However, in psychiatric disease where the precursors and outcomes can be so variable, it may be more effective in reducing the time between diagnosis and relief of symptoms. With this as the main goal in mind, the future of psychiatric treatment could very well be clinicians and neuroscientists working collectively to apply precision medicine techniques to MDD to improve prognosis by identifying individual patterns of risk factors, symptoms and pathophysiology.

References

[1] Tan L, Jiang T, Tan L, Yu JT. Toward precision medicine in neurological diseases. Annals of translational medicine. 2016;4(6).

[2] Ginsburg GS, Phillips KA. Precision medicine: From science to value. Health Affairs. 2018;37(5):694–701.

[3] Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nature reviews immunology. 2016;16(1):22.

[4] Lingam R, Scott J. Treatment non-adherence in affective disorders. Acta Psychiatrica Scandinavica. 2002;105(3):164–172.

[5] Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nature reviews neuroscience. 2012;13(10):701.

[6] Foster JA, Rinaman L, Cryan JF. Stress & the gut-brain axis: regulation by the microbiome. Neurobiology of stress. 2017;7:124–136.

[7] Wallace CJ, Milev R. The effects of probiotics on depressive symptoms in humans: a systematic review. Annals of general psychiatry. 2017;16(1):14.

[8] Kelly JR, Borre Y, O'Brien C, Patterson E, El Aidy S, Deane J, et al. Transferring the blues: depression-associated gut microbiota induces neurobehavioural changes in the rat. Journal of psychiatric research. 2016;82:109–118.

Caroline is a PhD Candidate in Clinical Neuroscience at Queen's University. Her research interests currently lie in examining the neurobiological relationship between nutrition and mental health to develop novel treatments for depression, as well as searching for biomarkers that will help predict who will respond to these treatments. Her doctoral research involves running a clinical trial examining the effects of a probiotic supplement on symptoms of depression, and how inflammation may be mediating this relationship.

Health Science Inquiry

Armouring the Immune System:
Future Prospects of Nanomedicine in Cancer Immunotherapy

Sallie Han[1] **and Dr. John Paul Oliveria**[2]

[1]Department of Medicine, Division of Respirology, McMaster University
[2]School of Medicine, Department of Pathology, Stanford University

Introduction

Recent advancements in technology has enhanced the targeting ability of drug and molecular delivery systems, opening new doors to improve the current treatments for cancer. Cancer is one of the most deadly and complex diseases with over 18 million new cases reported worldwide in 2018 [2]. In response to pathogens or cancerous cells, the body activates its immunological defense mechanisms to prevent tumour development. However, tumours can escape this immunosurveillance and establish an immunosuppressive environment that downregulates the body's natural defensive response while promoting uncontrolled cancer cell proliferation and tumour growth [3]. Immunotherapy focuses on restoring and enhancing the protective functions of the immune system by stimulating specific immune cells or inhibiting suppressive signals from the tumour cells. This increasingly popular form of therapy include traditional approaches such as tumour vaccines and adoptive transfer, and in the last decade, growing focus have been on antigen presentation through antigen-presenting cells [4]. More recently, some of the safety and efficacy concerns of immunotherapy have been addressed with the application of nanotechnology, which involves the use of small, nano-sized (1-100nm) engineered molecules, termed nanoparticles (NPs), to deliver new or existing therapeutics in a non-toxic and targeted manner [5]. Common forms of nanoparticles include liposomes, polymers, polymeric mi-

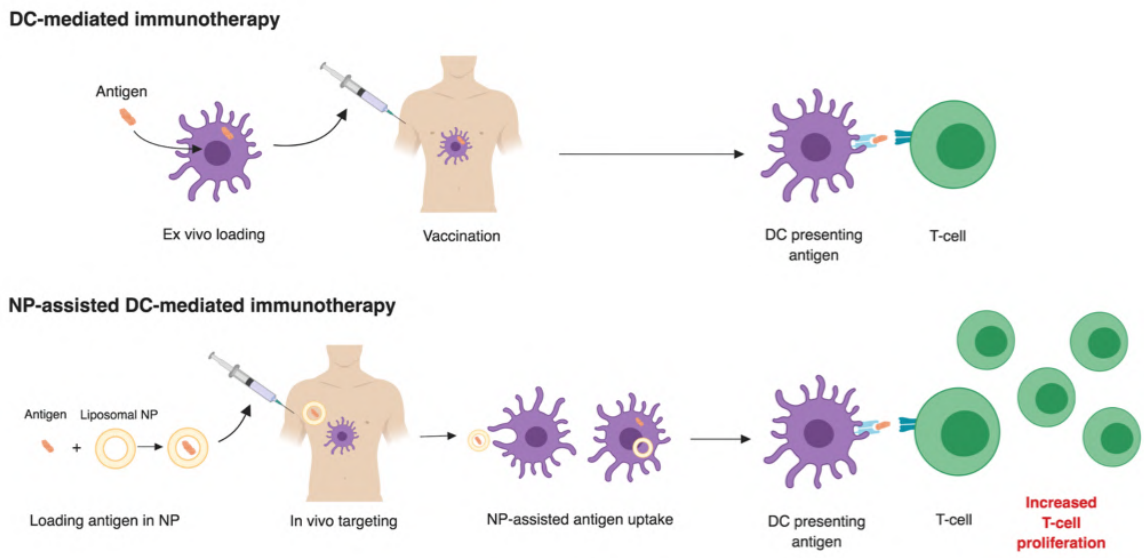


Figure 1: Comparison between DC-mediated immunotherapeutic strategy of *ex vivo* vaccination in contrast to initial loading of antigen to nanoparticles, such as liposomes, which is subsequently administered *in vivo*. While both methods lead to enhanced antigen presentation and stimulation of the T-cell immune response in the body, the use of NPs pose pharmacokinetic advantages and greater DC-targeting efficiency, resulting in increased T-cell proliferation [1].

celles, and inorganic NPs, each with their own set of unique physical and chemical characteristics [5]. Due to the modifiable properties, improved solubility, and bioavailability of nanoparticles (NPs), nanomedicine can significantly improve the success of immunotherapy by intervening in critical points of the anti-tumour response, such as the antigen recognition and presentation process, as well as checkpoint pathways [5].

The Role of Nanoparticles in DC-mediated Immunotherapy

For initial recognition of the pathogen or cancerous cells in the body, antigen-presenting cells (APCs) such as dendritic cells (DCs) are responsible for phagocytosing the tumour-associated antigen (TAA) and subsequently presenting it to the T-cells to induce the adaptive immune response [6]. One current immunotherapeutic strategy involves vaccinating the patient through stimulating the maturation of the DCs ex vivo with TAA antigens, then transferring the DCs back into the body to increase antigen-specific responses (Figure 1) [1]. However, this method has little evidence of clinical therapeutic effectiveness, unknown longitudinal effects, as well as several cost-associated and technical barriers [1].

NPs provide several advantages as a DC-targeting tool in vivo. NPs can act as carriers that protect the antigens from degradation and prolong the delivery to the DCs. The surfaces can also bind to ligands or have modified physicochemical structures to target receptors found on the DCs [1]. For example, a study published in 2017 found that intravenously administered liposomes carrying TAA-coding RNA was able to efficiently target DCs by adjusting the net charge of the liposome (Figure 1) [1]. Similarly, surface modification can also dictate the antigen uptake, with studies indicating that smaller, hydrophobic, and cationic NPs are correlated with greater internalization and interaction with the DCs [6]. Despite these enhancing functions of the NPs, studies have found impaired antigen-processing ability with NPs like graphene oxide. Other studies have shown varying results of suppression or activation of T-cell differentiation into Th17 cells with different NPs [6]. These findings suggest that the NP's role in DC-mediated immune responses depend on various factors, and require further investigation to understand the full therapeutic potential. Nevertheless, the ability for NPs to improve the detection of pathogens is a promising area of research as it is a critical component to activating the anti-tumour immune response.

The Role of Nanoparticles in Immunological Checkpoint Inhibition

Another approach to immunotherapy involves the use of monoclonal antibodies (mAbs) to target immune checkpoints, such as receptors found on immune cells. Such mechanism could block immunosuppression from T_{reg}, improve the anti-tumour immune response, and prevent cancer progression [7]. Examples of widely used mAbs include anti-CTLA-4 and anti-PD-1, also known as Ipilimumab and Nivolumab, respectively [7]. However, there have been several limitations recognized with the use of mAbs alone, such as inadequate pharmacokinetics, limited access to cancerous cells due to the tumour microenvironment, and the need for frequent dosages [6, 7]. The application of nanotechnology can overcome these limitations by improving the stability of the antibody *in vivo*, protection from degradation, localising the delivery to the tumour site and reducing the toxic side effects [8, 9]. A study published in 2011 showed that administering a PD-1 mAb encapsulated in polymer NPs to mice with melanoma resulted in a sustained release of the mAb and a prolonged anti-tumour response, in comparison to PD-1 mAb alone [10]. Other NPs, such as liposomes, micelles, and metal and non-metal nanomaterials conjugated to different mAbs were also found to overcome several physiological responses, such as avoiding degradation, crossing the blood-brain barrier, and increasing solu-

Table 1: Comparison of immunotherapeutic interventions delivered by nanoparticles

Immunotherapeutic Intervention	Description	Limitations overcome by NPs	Example
Subunit vaccination, (Kapadia *et al.*, 2015. Journal of Controlled Release)	Stimulating the immune system by presenting antigens to the APCs	NPs can target and deliver cell-membrane-impermeable antigens or multiple antigens to the APCs	Lipid-calcium-phosphate NPs
Targeting immunosuppressive cells inthe tumour microenvironment, (Kapadia *et al.*, 2015. Journal of Controlled Release; Torres and Alonso, 2015. Journal Drug Target)	NPs can target receptors on immunosuppressive cells	Target immunosuppressive cells that hinder anti-tumor immunity through inhibiting immunosuppressive signalling, re-education, impaired generation and/or death	Lipid-encapsulated clodronate delivered to tumour-associated macrophages to induce apoptosis
Gene delivery, (Qui *et al.*, 2017. WIREs: Nanomedicine and Nanobiotechnology)	Entering T-cells via NP delivery system to modify transcription	Increased uptake into T-cells to cause enhanced cell proliferation	Lipid-assisted PEG-PLGA-based NPs delivering CTLA-4
Cytokine delivery, (Kapadia *et al.*, 2015. Journal of Controlled Release; Qiu *et al.*, 2017. WIREs: Nanomedicine and Nanobiotechnology)	Delivery of cytokines (IL-2,TNF-α, IFN-γ) assisted by lipid and polymer-based NPs to specific cell types and tissues	Prevent rapid excretion & enzymatic degradation of cytokines	Liposomal delivery of TNF-α

bility in the blood [10]. These advantages of NPs can allow for a more effective immune checkpoint function and thus an improved immunotherapeutic response.

Limitations

Despite the significant advantages of nanomedicine in cancer immunotherapy, specifically in DC-mediated therapy and checkpoint inhibitors, there are several limitations and challenges to address. Since this is a newly emerging field, a lot of the research is still undergoing clinical trials and many studies are done on simplified animal tumour models. Thus, the research cannot be clinically translated in the human body, which has a far more complex pathological environment [7]. Additionally, DC-mediated immunotherapies are limited due to costly and time-consuming procedures involved with harvesting DCs for vaccination [1]. Although the use of mAbs as checkpoint inhibitors is advantageous because of their targeting abilities, each combination must be thoroughly and individually characterized for its unique physical and chemical properties to assess potential toxic effects [10]. Regardless of these challenges, the incorporation of nanomedicine into immunotherapy provides a wide range of possibilities for treatment through other mechanisms as well, such as targeting the cells found in the tumour microenvironment, NP-assisted gene delivery, and NP-assisted cytokine delivery (Table 1) [1].

Conclusion

Nanotechnology has the potential to shift the standards of cancer treatment through the application of nanomedicine in immunotherapy. Whether through the recognition of the antigen or inhibition of checkpoint pathways, NPs can specifically target different stages of the immune response to provide a more effective and personalized treatment. With further research into the pharmacokinetic profiles of NPs, safety and toxicity assessment, and more human *in vivo* studies, these small molecules will be able to unlock its full potential in different types of treatment to make a significant impact on the future of cancer therapy.

References

[1] Qiu H, Min Y, Rodgers Z, Zhang L, Wang AZ. Nanomedicine approaches to improve cancer immunotherapy. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2017;9(5):e1456.

[2] WHO International Agency for Research on Cancer. Latest global cancer data: Cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018;. Available from: https://www.iarc.fr/wp-content/uploads/2018/09/pr263_E.pdf.

[3] Mizrahy S, Hazan-Halevy I, Landesman-Milo D, Peer D. Advanced strategies in immune modulation of cancer using lipid-based nanoparticles. Frontiers in immunology. 2017;8:69.

[4] Disis ML. Mechanism of action of immunotherapy. In: Seminars in oncology. vol. 41. Elsevier; 2014. p. S3–S13.

[5] Aftab S, Shah A, Nadhman A, Kurbanoglu S, Ozkan SA, Dionysiou DD, et al. Nanomedicine: An effective tool in cancer therapy. International journal of pharmaceutics. 2018;540(1-2):132–149.

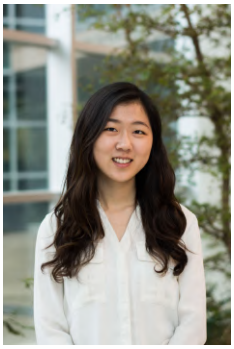
[6] Jia J, Zhang Y, Xin Y, Jiang C, Yan B, Zhai S. Interactions Between Nanoparticles and Dendritic Cells: From the Perspective of Cancer Immunotherapy. Frontiers in oncology. 2018;8:404.

[7] Mahjub R, Jatana S, Lee SE, Qin Z, Pauli G, Soleimani M, et al. Recent advances in applying nanotechnologies for cancer immunotherapy. Journal of controlled release. 2018;.

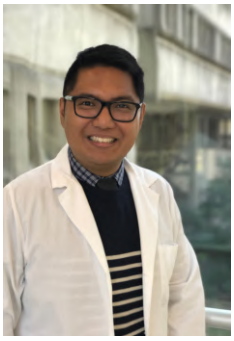
[8] Deng H, Zhang Z. The application of nanotechnology in immune checkpoint blockade for cancer treatment. Journal of controlled release. 2018;.

[9] Wang C, Ye Y, Hochu GM, Sadeghifar H, Gu Z. Enhanced cancer immunotherapy by microneedle patch-assisted delivery of anti-PD1 antibody. Nano letters. 2016;16(4):2334–2340.

[10] Julien DC, Behnke S, Wang G, Murdoch GK, Hill RA. Utilization of monoclonal antibody-targeted nanomaterials in the treatment of cancer. In: MAbs. vol. 3. Taylor & Francis; 2011. p. 467–478.



Sallie Han is a 3rd year undergraduate student in the Bachelor of Health Sciences (Honours) program at McMaster University. She is currently working under the supervision of Dr. Oliveria in investigating the cerebrovascular associations in Alzheimer's disease. In addition to her studies, Sallie volunteers as a Clinical Assistant at a cardiology clinic and her research interests include immunology, molecular biology, and vascular pathogenesis.



John Paul Oliveria received his PhD in 2017 and is currently an Adjunct Faculty Member at McMaster University in the Faculty of Health Sciences, Department of Medicine, where he supervises students completing projects and theses within the fields of allergy, immunology, and neurosciences. He is currently completing his post-doctoral fellowship at Stanford University where he is utilizing multiplexed ion beam imaging (MIBI) to unravel cellular and sub-cellular interactions in the brain to understand Alzheimer's disease. His research interests leverages novel technologies and high dimensional data to discover novel mechanisms in health and disease.

Health Science Inquiry

Altered State of Mind: Direct Cellular Reprogramming as Potential Treatment Strategy for Alzheimer's Disease

Anika Spasov[1] **and Dr. John Paul Oliveria**[2]

[1]Department of Medicine, Division of Respirology, McMaster University
[2]School of Medicine, Department of Pathology, Stanford University

Introduction

Reversing degenerative diseases and injuries has been a long sought out possibility in the field of regenerative medicine. While the notion that neurons could continuously regenerate throughout life was demonstrated just over twenty years ago, little substantial development has been made in the treatment of neurodegenerative diseases [1]. The question is asked, could neuroregeneration be induced in the suffering brain and be used to treat Alzheimer's disease (AD)? Nearly a decade before this discovery of neuroregeneration, the very first direct reprogramming of terminally differentiated cells into a cell type of different lineage was demonstrated via the conversion of fibroblasts into myoblasts. By inducing ectopic expression of MyoD, fibroblasts were successfully converted into myoblasts, without passing through a pluripotent stage [2]. As the understanding of both AD and cellular reprogramming has grown over time, the ability to promote regeneration or repair within the adult human brain has become a real possibility [3].

Alzheimer's Treatment

In particular, AD appears to be a promising target for direct cell reprogramming. AD is a chronic neurodegenerative disease characterized by neuroinflammation and the accumulation of disease-associated proteins in the brain, such as amyloid beta and neurofibrillary tau tangles, which ultimately leads to neuronal loss and synaptic degradation. The consequences of this degradation include cognitive dysfunction, motor impairment and memory loss, hence the quality of life of AD patients is greatly depleted [4]. Part of regulating the inflammatory response in AD involves anisomorphic astrogliosis: the increase and change in morphology of reactive astrocytes, leading to glial scar formation and microcircuit instability [4]. This pathogenic astrogliosis not only harms astrocytes, but also neighbouring neurons. Consequently, the repair and regeneration of neurons damaged by neural inflammation in AD have long been envisioned. The ability to produce neurons from human induced pluripotent stem cells (hiPSCs) has introduced the possibility of cellular transplants; however, the process is time and material intensive, while also raising ethical concerns regarding the use of stem cell technology [5]. Direct cell reprogramming bypasses the intermediate pluripotent stage and directly converts one cell type to another (Figure 1). Recent developments in pioneer transcription factors, such as FOX which binds directly to condensed chromatin, as well as small molecules capable of initiating direct reprogramming, demonstrate a more efficient means of replacing cells damaged by AD [3, 6]. By omitting the pluripotent step, the reprogramming process becomes quicker and more economically feasible. Additionally, the risk of teratoma development normally associated with hiPSCs is curtailed by circumventing pluripotency, while also averting the ethical controversy surrounding embryos and stem-cell therapy. Thusly, re-establishing diseased neurons, and possibly restoring function, has become an intriguing possibility in AD therapeutics through the development of direct cell reprogramming [3, 7].

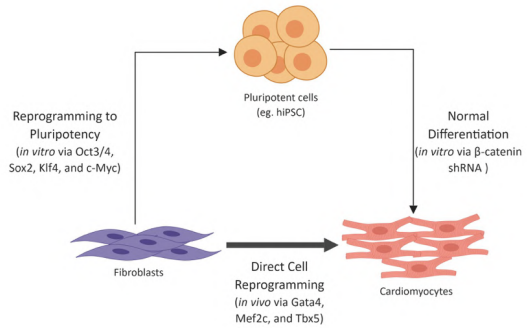


Figure 1: Terminally differentiated cells can be reprogrammed to a pluripotent stage, at which point the cells can go down a different cell lineage than previously. Direct cell reprogramming bypasses pluripotency and permits cells to directly convert from one cell type to another via ectopic expression of transcription factors or small molecule application. This method is more efficient and does not require *in vitro* culturing of pluripotent cells.

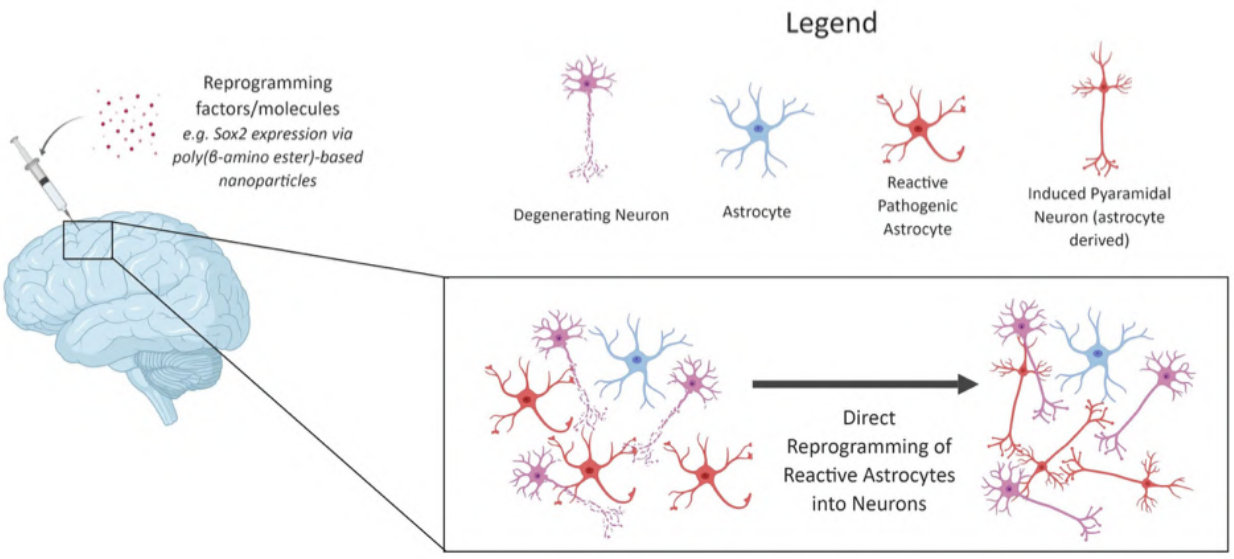


Figure 2: Reactive astrocytes undergo astrogliosis and are more easily converted via direct reprogramming, thus potentially pathogenic astrocytes could be transformed into functioning neurons. This may introduce a novel treatment of Alzheimer's by both preventing future damage from unwarranted astrogliosis and the regeneration of neuronal connections. Consequently, direct cell reprogramming of astrocytes may aid in tackling both the underlying pathology and regeneration of lost neurons in those afflicted with AD.

In vivo Neural Reprogramming

A unique trait of direct cell reprogramming is the ability to perform the process *in vivo* [7]. Unlike hiPSCs, which must be removed and reprogrammed *in vitro*, direct cell reprogramming techniques can be applied to cells within their local tissue environment. It has been demonstrated to be possible in a multitude of organs: in the heart induced cardiomyocytes were formed, in the pancreas induced islet cells, and induced neurons have been observed in murine brains. The latter of this is most pertinent to AD and provides evidence for direct cellular reprogramming as a future therapy [7]. Sox2 alone is capable of converting reactive glial cells into neurons within the adult mouse cerebral cortex post-injury [8]. Even more substantial was the confirmation, via patch clamps, that these induced neurons received synaptic inputs from neighbouring cells, suggesting they may be cognitively functional and further elucidating direct reprogramming as a potential AD therapeutic [8]. Considering regions of the brain are difficult to access surgically and the inflammatory nature of AD, it is also extremely relevant that *in vivo* direct reprogramming is much less invasive and virtually eliminates concerns of immunocompatibility commonly associated with donor hiPSCs [6].

Within glial cell reprogramming, astrocytes have been especially auspicious in regards to successful direct cell reprogramming into neurons. This, in addition to the large astrocyte population in the brain, suggest astrocytes would make particularly viable targets for reprogramming as a potential AD treatment. In a period of one to three weeks, a 90% astrocyte-to-neuron conversion efficiency was reached in mouse cerebral cortex [9]. This was achieved by combining Bcl-2 expression with antioxidative therapies, consequently reducing reactive oxidative species-induced apoptosis. Thusly, astrocytes are an extremely promising target for reprogramming technologies in the treatment of AD, in comparison to other glial cells. Moreover, the generated neurons attained a pyramidal neuron morphology, thus suggesting they may be capable of advanced cognitive functions [9]. Additionally, within AD models, reactive astrocytes reprogram more effectively *in vivo* than unreactive astrocytes [10]. Clinically, this may be beneficial: by transforming reactive astrocytes into functioning neurons it could not only help restore neuron damage, but it can diminish the pathogenicity and inflammation resulting from astrogliosis (Figure 2). Converting adverse, reactive astrocytes into neurons prevents those cells from contributing to AD progression and thereby minimizes damage occurring in the brain [10]. Consequently, direct cell reprogramming is a two-pronged AD treatment, which not only regenerates new neurons, but also disposes of harmful reactive astrocytes.

Challenges and Conclusions

While direct cell reprogramming is a promising technology for the future of regenerative medicine, particularly in terms of neurodegenerative diseases, it still remains to be tested in the human brain and requires further research before being introduced as a clinical AD therapy. The ideal method of delivery still remains elusive and is a challenge that first must be met [7]. Viral vectors have been used most commonly *in vivo*; however, they risk transfecting neighbouring cells and causing ectopic expression in unintended cells. Recently, small molecules have been iden-

tified which have the ability to directly induce neurons *in vivo* [3]. These face the challenge of remaining at targeted therapeutic concentrations over long periods of time. Howbeit, the utilization of nanoparticles in conjunction with these small molecules may mitigate this barrier by permitting longer exposure of treatment over time, within a single dose [7]. Moreover, future research should further analyze the functionality of these induced neurons and investigate if *in vivo* direct reprogramming can be validated within a human context [6]. All these challenges considered, direct cell reprogramming is a promising treatment for AD and has a place within the rapidly dynamic landscape of future health and therapies.

References

[1] Eriksson PS, Perfilieva E, Björk-Eriksson T, Alborn AM, Nordborg C, Peterson DA, et al. Neurogenesis in the adult human hippocampus. Nature medicine. 1998;4(11):1313.

[2] Davis RL, Weintraub H, Lassar AB. Expression of a single transfected cDNA converts fibroblasts to myoblasts. Cell. 1987;51(6):987–1000.

[3] Xu J, Du Y, Deng H. Direct lineage reprogramming: strategies, mechanisms, and applications. Cell stem cell. 2015;16(2):119–134.

[4] Mohamet L, Jones VC, Dayanithi G, Verkhratsky A. Pathological human astroglia in Alzheimer's disease: opening new horizons with stem cell technology. Future Neurology. 2018;13(2):87–99.

[5] Fang Y, Gao T, Zhang B, Pu J. Recent advances: decoding alzheimer's disease with stem cells. Frontiers in aging neuroscience. 2018;10:77.

[6] Barker RA, Götz M, Parmar M. New approaches for brain repair—from rescue to reprogramming. Nature. 2018;557(7705):329.

[7] Srivastava D, DeWitt N. In vivo cellular reprogramming: the next generation. Cell. 2016;166(6):1386–1396.

[8] Heinrich C, Bergami M, Gascón S, Lepier A, Viganò F, Dimou L, et al. Sox2-mediated conversion of NG2 glia into induced neurons in the injured adult cerebral cortex. Stem cell reports. 2014;3(6):1000–1014.

[9] Gascón S, Murenu E, Masserdotti G, Ortega F, Russo GL, Petrik D, et al. Identification and successful negotiation of a metabolic checkpoint in direct neuronal reprogramming. Cell stem cell. 2016;18(3):396–409.

[10] An N, Xu H, Gao WQ, Yang H. Direct conversion of somatic cells into induced neurons. Molecular neurobiology. 2018;55(1):642–651.

Anika Spasov has recently finished her third year in the Bachelor of Health Sciences (Honours) program at McMaster University. Her interests include the pathophysiology of autoimmune diseases and forging environmentally sustainable healthcare practices. Born and raised in the small village of Millbrook, Ontario. In her spare time, she enjoys hiking, rowing and theatre productions.

John Paul Oliveria received his PhD in 2017 and is currently an Adjunct Faculty Member at McMaster University in the Faculty of Health Sciences, Department of Medicine, where he supervises students completing projects and theses within the fields of allergy, immunology, and neurosciences. He is currently completing his post-doctoral fellowship at Stanford University where he is utilizing multiplexed ion beam imaging (MIBI) to unravel cellular and sub-cellular interactions in the brain to understand Alzheimer's disease. His research interests leverages novel technologies and high dimensional data to discover novel mechanisms in health and disease.

Health Science Inquiry

Imaging Glial Cells in Alzheimer's Disease:

From Light Microscopy to Multiplexed Ion Beam Imaging

Dunavan Morris-Janzen[1] and Dr. John Paul Oliveria[2]

[1]Department of Medicine, Division of Respirology, McMaster University
[2]School of Medicine, Department of Pathology, Stanford University

Introduction

Alzheimer's Disease (AD) is the leading cause of dementia worldwide, accounting for 60-70% of the nearly 50 million global cases of dementia in 2018 [1]. AD also significantly burdens Canadians, where the disease prevalence is 1,524 cases per 100,000 and incidence is 68 case per 100,000 [2]. The global societal costs of AD and dementia are estimated at $1 trillion dollars annually [1]. Furthermore, AD treatment options remain limited. All therapeutics targeted at decreasing production or increasing clearance of amyloid-β plaques, the characteristic AD biomarker, have thus far been unsuccessful in phase III clinical trials [1]. With such a significant burden of disease and no effective treatments, it is clear that AD research must elucidate the complex mechanisms underlying clinical progression in order for the disease to be better prevented, managed, and treated.

Since the 1980's, researcher have understood AD through the amyloid cascade hypothesis (ACH). Specifically, the ACH posits that the clinical progression of AD is primarily caused by amyloid-β plaque deposits, tau aggregation in neurofibrillary tangles, and subsequent neuron death [3]. While the original ACH remains widely accepted in the field, new research has highlighted the key role of glial cells, primarily microglia and astrocytes, in AD pathogenesis [3]. It is now thought that the intricate interactions between microglia, astrocytes, and neurons becomes initially disturbed in early stages of the disease. As toxic amyloid-beta and hyperphosphorylated tau protein accumulation continues, these glial cells polarize towards an inflammatory phenotype that further contributes to neuron death [3]. However, research aimed at understand the complex interactions between tauopathy and amyloid-β accumulation, s glial cell phenotypes, neuroinflammation, and neuron death, has been slowed by single-plex imaging technologies and staining technologies. This paper will take a historical approach to the evolution of neuroimaging of glial cells in the context of AD, where the limitations of traditional light microscopy (LM) and immunohistochemical (IHC) techniques will be contrasted to the promising application of the novel imaging technology, High-Dimensional Multiplexed Ion Beam Imaging-Time of Flight(MIBI-TOF).

Microscopy, Staining Techniques, and Glial Cell Imaging in AD

The timeline of major glial imaging discoveries in the context of AD can be seen in Figure 1. In 1846, Rudolf Virchow, considered the father of modern pathology, was the first to propose a new type of cell within the brain, which he termed 'neuroglia' [4]. Subsequently, many scientists continued to refine this notion of glial cells. Notably, the neuroscientists Santiago Ramón y Cajal used a chloride-sublimate staining technique to label glial fibrillary acidic protein (GFAP) expressed by astrocytes in 1913, and Rio Hortega described microglia in 1921 [4]. At approximately the same time as these two glial cell discoveries, neuropathologist Alois Alzheimer analyzed post-mortem brain tissue biospies from a patient presenting with symptoms of dementia and in 1907 he discovered what is now known as amyloid-β plaque deposits and tau protein aggregations [5]. The cardinal tool of these scientists was LM combined with various staining techniques, and while they were able to make breakthrough discoveries, they were also limited by their imaging technologies which only permitted simultaneous visualization of one to two protein targets.

During the time that Alzheimer continued to research this new disease, the Carl Zeiss Company produced a novel microscopy technique known as fluorescence microscopy (FM), which uses ultraviolet light to excite fluorophores on target proteins to produce an image [6]. The principles of FM gave rise to IHC and immunofluorescence (IF) staining techniques. IHC and IF use antibody-antigen specificity to attach fluorophores to target antigens and cause light emission via enzymatic reactions or excitation, respectively. The advent of FM, as well as IHC and IF, have allowed for significant contributions to AD research. For instance, the involvement of microglia and astrocytes in AD pathogenesis was discovered using IHC microscopy [7] and the pathology of amyloid-β plaques and neuron death was further elucidated via IF microscopy [8] (Figure 1).

Despite the progression of these various microscopy technologies, they are still limited by only being able to simultaneously visualize a small number of target genes or antigens. This is because the fluorophores and enzyme reporters that are used in current IHC protocols show spatial and spec-

tral overlap when analyzing multiple targets [9]. As new research has elucidated that AD pathogenesis consists of interactions between multiple cells and cellular phenotypes, the need for a technology able to image a large number of antigens while also maintaining the spatial localization of these interactions has become increasingly apparent.

High-Dimensional Multiplexed Imaging and Potential Applications in AD

High-dimensional multiplexed imaging has the capacity to overlay multiple images with different biomarkers for simultaneous analysis and spatial localization. One example of this technology is MIBI-TOF (Figure 1). A recent study published in Cell by Keren *et al.* (2018) highlighted MIBI-TOF technology within the application of breast cancer pathobiology. This work built on a previous MIBI platform by adding TOF mass spectrometry, which allowed for increased channel multiplexing while decreasing times for data acquisition by 50-fold. With this improved technology, researchers simultaneously analyzed the sub-cellular expression and spatial arrangement of 36 proteins, effectively illuminating the tumor-immune microenvironment [9]. Researchers at Stanford have also used MIBI-TOF to analyze post-mortem brain samples of AD. In addition to validating previously defined AD pathologies, such as taupathothy, they were also able to analyze immune cell infiltration, cellular anatomy, and gene expression associated with AD [10]. This is an improvement to previous imaging techniques in AD research as MIBI-TOF can now simultaneously determine the tissue, immunological, and sub-cellular spatial localization of the human brain [10]. In both tumor pathology and AD imaging, MIBI-TOF is able to generate multiplexed imaging by overcoming the spectral and spatial overlap of fluorophores and enzyme reporters that confine IHC to a single-plexed analysis.

While MIBI-TOF has great potential, it is also limited in a number of ways. Firstly, there are a very few available units at this time as the technology has only recently become commercially available. Secondly, MIBI-TOF poses a high cost of reagents (*e.g.* metal-tagged antibodies), technical experiments, and quality control. Lastly, since MIBI-TOF generates highly dimensional data, researchers must have computational expertise to use the platform effectively [9]. As a result, MIBI-TOF is currently a much less accessible research tool compared to less expensive, simpler technologies such IHC staining visualized with LM.

Future Directions and Conclusion

As new research has shown that AD pathogenesis is characterized by the complex interaction of multiple glial cells and their unique phenotypes, the advent of MIBI-TOF provides the capacity to elucidate these cellular interactions and provide insights into new biomarkers and potential therapeutic avenues. Indeed, MIBI-TOF technology has the potential to revolutionize neuroimaging in AD research. As this technology continues to be used throughout AD research, its true potential will be realized.

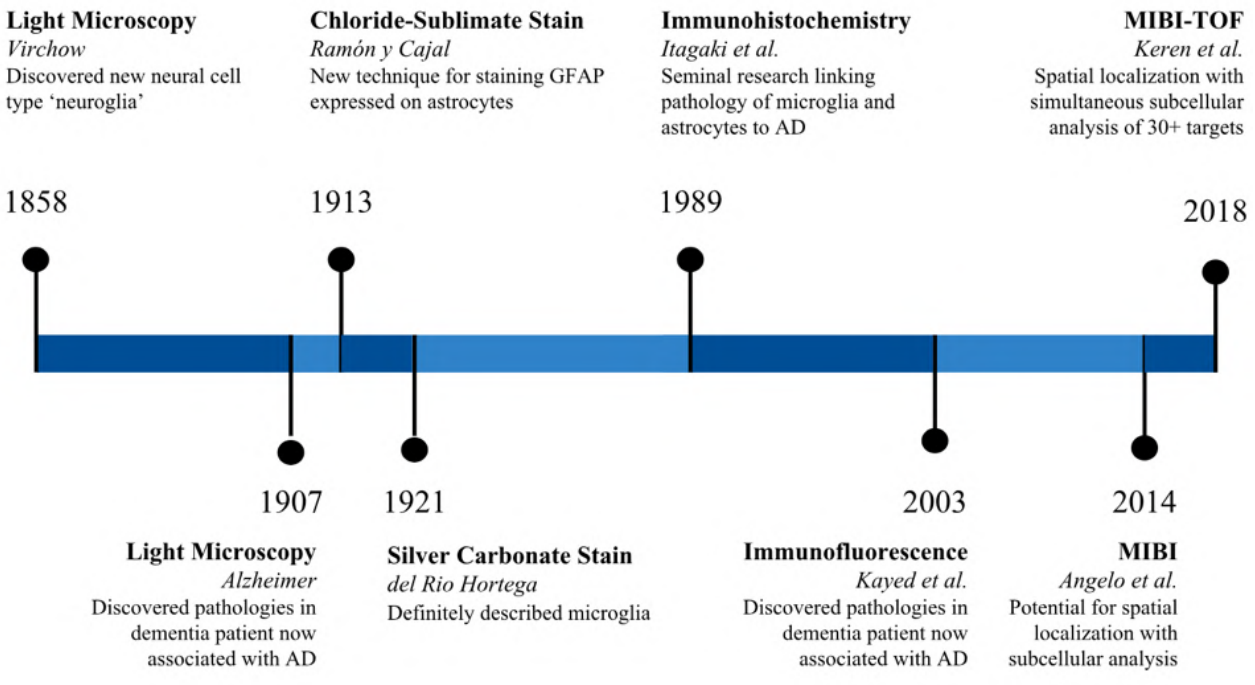


Figure 1: Historical timeline highlighting the various imaging technologies and staining techniques that have ultimately contributed to the current understanding of the role of glial cells in AD pathology. MIBI time-of-flight (TOF) is seen in the timeline near the present day as it has the potential to revolutionize neuroimaging in AD research.

References

[1] Patterson C. World Alzheimer Report 2018, The state of the art of dementia research: New frontiers;. Available from: https://www.alz.co.uk/research/world-report-2018.

[2] Chambers LW, Bancej C, McDowell I. Prevalence and monetary costs of dementia in Canada: population health expert panel. Alzheimer Society of Canada in collaboration with the Public Health Agency . . . ; 2016.

[3] Henstridge CM, Hyman BT, Spires-Jones TL. Beyond the neuron–cellular interactions early in Alzheimer disease pathogenesis. Nature Reviews Neuroscience. 2019;p. 1.

[4] Somjen GG. Nervenkitt: notes on the history of the concept of neuroglia. Glia. 1988;1(1):2–9.

[5] Stelzmann RA, Norman Schnitzlein H, Reed Murtagh F. An English translation of Alzheimer's 1907 paper,"Über eine eigenartige Erkankung der Hirnrinde". Clinical Anatomy: The Official Journal of the American Association of Clinical Anatomists and the British Association of Clinical Anatomists. 1995;8(6):429–431.

[6] Sanderson MJ, Smith I, Parker I, Bootman MD. Fluorescence microscopy. Cold Spring Harbor Protocols. 2014;2014(10):pdb–top071795.

[7] Itagaki S, McGeer P, Akiyama H, Zhu S, Selkoe D. Relationship of microglia and astrocytes to amyloid deposits of Alzheimer disease. Journal of neuroimmunology. 1989;24(3):173–182.

[8] Kayed R, Head E, Thompson JL, McIntire TM, Milton SC, Cotman CW, et al. Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. Science. 2003;300(5618):486–489.

[9] Keren L, Bosse M, Marquez D, Angoshtari R, Jain S, Varma S, et al. A structured tumor-immune microenvironment in triple negative breast cancer revealed by multiplexed ion beam imaging. Cell. 2018;174(6):1373–1387.

[10] Oliveria JP, Vijayaragavan K, Bossé M, Tebaykin D, Montine TJ, Angelo M, et al. Multiplexed ion beam imaging (MIBI) produces data-rich images of archival human brains with synaptic resolution. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. 2018;14(7):P700–P701.

Dunavan Morris-Janzen will receive his Bachelor of Arts and Science (Honours) from McMaster University in April 2019. During his undergraduate degree, his research interests were broadly set in immunology. In his final year under the supervision of Dr. John Paul Oliveria, he focused on the role of glial cells in Alzheimer's Disease pathology and the potential of Mulitplexed Ion Beam Imaging technologies for studying these cells.

John Paul Oliveria received his PhD in 2017 and is currently an Adjunct Faculty Member at McMaster University in the Faculty of Health Sciences, Department of Medicine, where he supervises students completing projects and theses within the fields of allergy, immunology, and neurosciences. He is currently completing his post-doctoral fellowship at Stanford University where he is utilizing multiplexed ion beam imaging (MIBI) to unravel cellular and sub-cellular interactions in the brain to understand Alzheimer's disease. His research interests leverages novel technologies and high dimensional data to discover novel mechanisms in health and disease.

Health Science Inquiry

Considerations for Mitochondrial Replacement Therapy as a Novel Assisted Reproductive Technology

Lisa Oliviero[1]

[1]Division of Experimental Medicine, McGill University

Mitochondria are essential organelles of nucleated cells [1]. While most of the DNA contained in a cell is located within the nucleus, mitochondria, located in the cytoplasm, contain a small fraction of an organism's overall DNA [1]. The fraction of DNA located in the mitochondria is called mitochondrial DNA (mtDNA) [1]. This particular type of DNA, which is distinct from nuclear DNA, counts for less than 0.1 percent of the total amount of genetic material within a human cell [1]. Despite its minor presence, defects in the mtDNA can cause significantly harmful pathologies, namely *mitochondrial diseases*, as the mitochondria are in charge of providing energy to the entire cell [1]. Two commonly recognized mitochondrial diseases include myoneurogastrointestinal encephalopathy syndrome (MNGIE), which features myopathy, neuropathy, chronic malnutrition, and sensorineural hearing loss, and Leigh syndrome, which is proven to have a very grim prognosis, with death occurring within the first years of life [2].

Considering mitochondria are maternally inherited, a recent scientific innovation has emerged to prevent the transmission of defective maternal mtDNA to offspring. This recent development is referred to as mitochondrial replacement therapy (MRT). This form of assisted reproductive technology encourages an option for women carrying mutated mtDNA to have genetically related children without passing down their mtDNA [1]. MRT functions by primarily retrieving healthy mitochondria from an egg donor, and can proceed with either of the following techniques (**Figure 1**): In the first technique, pronuclear transfer, the transfer of mtDNA follows the fertilization of the egg that has occurred *in vitro* [1]. The two eggs (one from the intending mother and one from the donor) are fertilized with the intending father's or another donor's sperm [1]. Shortly after fertilization takes place, the pronucleus of the embryo containing the mother's mitochondria is transferred to a previously enucleated embryo containing healthy donor mitochondria [1]. In the second technique, maternal spindle transfer, the healthy nucleus of an egg with the affected mitochondria is removed and then transferred to the egg of the donor containing healthy mitochondria, which has been previously deprived of its nucleus [1].

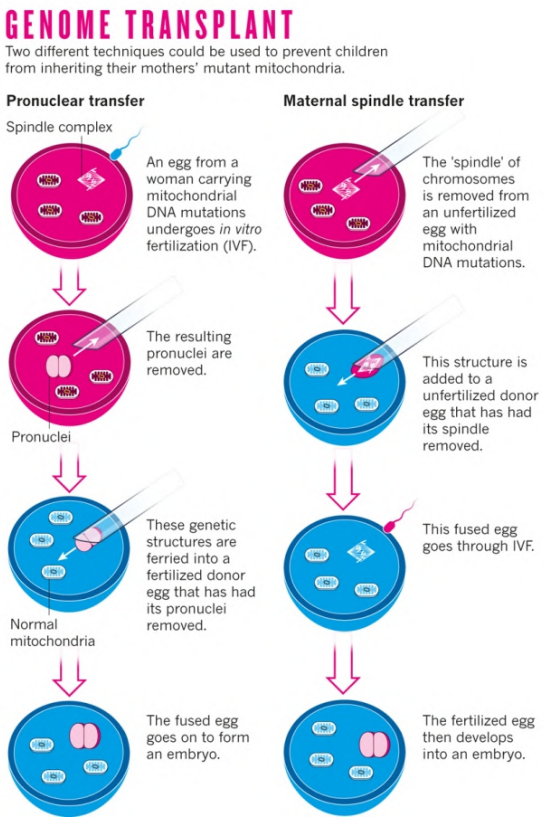


Figure 1: MRT techniques for prevention of mutated mtDNA transmission. Adapted from [3]

While there is an evidentiary basis for the technical feasibility of MRT documented for both human embyros and embryonic stem cells, questions have remained regarding whether a "mismatch" between mtDNA and nuclear DNA may cause mitochondrial dysfunction in children [4]. An important research milestone was achieved when studies demonstrated the birth of healthy monkey infants following MRT. In a postnatal analysis, their overall health monitored from birth to 3 years was comparable to the age-

matched controls [4]. These results evidently pave a promising path for further confirmatory studies to be completed, and when appropriate, application to human populations.

Although this technology could offer significant therapeutic potential, MRT remains illegal in Canada and across other jurisdictions [5]. Much legal and ethical controversies of MRT hover around a concern for inappropriately modifying the genetic material of germline cells that can be passed on to offspring, and their subsequent offspring. In Canada, the *Assisted Human Reproduction Act* (AHRA) states in section 1f that "no person shall knowingly alter the genome of a cell of a human being or *in vitro* embryo such that the alteration is capable of being transmitted to descendants" [5]. Despite legal support in the United Kingdom (UK) for early phase clinical trials based on studies in animals and human oocytes, the criminal ban in Canada on human germline alterations is considered to apply to MRT and may foreclose any possibility of pursuing similar MRT trials within the jurisdiction [6]. However, MRT restriction raises ethical concerns as there is a strong therapeutic potential associated with its application.

The UK and the United States (US) are the only countries moving forward with this technology [7]. In the UK, after years of discussion guided by the Human Fertilization and Embryology Authority, Parliament approved the licensed clinical use of both MRT techniques in October of 2015 [7]. With this progress, clinical application is deemed to be imminent [7]. In the US, the Food and Drug Administration (FDA) is delaying approval until more preclinical data is collected. Further, they have specified that MRT would be reserved only to create male embryos to preclude the transmission of donor mtDNA to future generations, thereby bypassing the germline modification.

Evidently, there are ongoing efforts in certain jurisdictions to surface this technology from the preclinical realm to the clinical domain. Although Canada is behind on this progress, it is important to ponder how we would proceed in providing MRT if legalized, and which individuals would have accessibility. This would be a significant advancement in allowing women with mitochondrial diseases to have genetically related, without passing down their affected mtDNA. Nonetheless, further research ought to be carried out in order ensure this technology yields utmost therapeutic benefit, while minimizing any harms to mothers and their children.

References

[1] Castro RJ. Mitochondrial replacement therapy: the UK and US regulatory landscapes. Journal of Law and the Biosciences. 2016;3(3):726.

[2] Gropman AL. Diagnosis and treatment of childhood mitochondrial diseases. Current neurology and neuroscience reports. 2001;1(2):185–194.

[3] Callaway E. Reproductive medicine: The power of three. Nature News. 2014;509(7501):414.

[4] Tachibana M, Amato P, Sparman M, Woodward J, Sanchis DM, Ma H, et al. Towards germline gene therapy of inherited mitochondrial diseases. Nature. 2013;493(7434):627.

[5] Branch, LS. Consolidated federal laws of Canada, Assisted Human Reproduction Act; 2012. Available from: https://laws-lois.justice.gc.ca/eng/acts/a-13.4/page-1.html#h-2.

[6] Knoppers BM, Leader A, Hume S, Shoubridge EA, Isasi R, Noohi F, et al. Mitochondrial replacement therapy: The road to the clinic in Canada. Journal of Obstetrics and Gynaecology Canada. 2017;39(10):916–918.

[7] Klopstock T, Klopstock B, Prokisch H. Mitochondrial replacement approaches: challenges for clinical implementation. Genome medicine. 2016;8(1):126.

Lisa is currently a first year MSc student at McGill University in the Biomedical Ethics Unit. While completing an Honours BSc at the University of Ottawa in Biomedical Science, her research focused on elucidating the molecular mechanisms of ovarian cancer. With her previous basic science experience, she was inspired to explore the moral and ethical questions regarding clinical translation. Her current graduate research entails describing the scientific and ethical implications of pediatric oncology clinical trials, particularly estimating the clinical impact of patients participating in these trials.

Health Science Inquiry

Leveraging 'omic' Technologies to Tailor Probiotic Treatment for Individuals

Emma Brownlie[1]

[1]Department of Molecular Genetics, University of Toronto

The World Health Organization defines probiotics as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [1]. The popularity of the beneficial effects of microorganisms has become progressively widespread over the decades, alongside our increasing awareness of the effects that bacteria can exert on health and disease such as inflammatory bowel disease (IBD) and non-alcoholic fatty liver disease (NAFLD) [2, 3]. By now, consumption of probiotics in an attempt to maintain health and prevent, ameliorate, or resolve disease has become routine. In the United States alone, recent estimates indicate that 3.9 million individuals regularly take probiotic supplements, and 60% of healthcare providers prescribe probiotics to patients [4]. This article will discuss probiotic treatment, current drawbacks, and how we can leverage big data approaches to increase precision and effectiveness of probiotics moving forward.

Given the prevalence of their use, it comes as no surprise that probiotics have become a highly popular field in academia and industry alike, ranging from basic to clinical research. Many studies have investigated the effects of probiotics, but the majority of those studies that have causally linked probiotics to positive outcomes have been carried out in animal models [5, 6]. Several meta-analyses of studies performed in humans have indicated promising results, particularly in the context of ameliorating the symptoms of those people already suffering from diseases like IBD and NAFLD [2, 3]. However, these human studies tend to be less conclusive and in some cases yield contradictory results [7]. Additionally, risks associated with probiotic usage in certain populations such as those suffering from severe acute pancreatitis have been reported [8]. Clearly, although probiotics are a promising treatment option, there are many ways in which our understanding of the mechanism of action of these tools, as well as our application of them, can be improved.

To highlight this point, a recent study carried out by researchers at the Weizmann Institute has shown person-specific differences in the ability of probiotics to colonize the gut mucosa [9]. As expected, after treating healthy volunteers with probiotics these bacteria were found to be enriched in all participants. However, there was a highly individualized pattern of mucosal colonization by these probiotics, with some patients remaining stably colonized after treatment and others rapidly losing these bacteria. Although colonization of the gut may not be strictly necessary for bacteria to exert a therapeutic effect, it could still considerably affect local intestinal physiology, metabolism, and ecology. Critically, they also found that unique host and microbiome traits could predict whether or not colonization would occur – both the microbiome and the host transcriptome correlated with the 'permissiveness' or 'resistance' of the host to colonization with the probiotic strains. This emphasizes the extent to which individual characteristics can modify the effectiveness of a given treatment, and how this might significantly affect the outcome for an individual undergoing treatment.

These findings suggest the potential for a revolution in treatment from the undistinguished way in which probiotic treatments have been delivered to date. Precision medicine has become increasingly popular and accessible as we have developed ways to examine genomic, transcriptomic, proteomic, and metabolomics information – collectively referred to as 'omic' techniques. These approaches have already been implemented in fields such as immunology, oncology, and neurology to guide treatment regimens. For example, in oncology, transcriptomic information has been used extensively to classify tumours into subtypes and predict effectiveness of different therapies [10]. With research indicating that host response to probiotic treatment is highly individualized, it seems only logical to begin implementing these approaches in the administration of probiotics. This approach would allow researchers and clinicians to begin optimizing and tailoring treatment plans based on individual characteristics to optimize the success of treatments. Research studies would also allow the exploration of the mechanisms behind the beneficial effects of probiotics, and help distinguish cases where probiotics should not be used for health and safety reasons.

Currently, probiotics are a tool with incredible potential, but we need to begin leveraging the recent advances that we have seen in 'omic' technologies in order to improve treatment and gain a better understanding of how these bacteria mediate their effects. Examining the interaction between genes, environment, and microbiota is critical to understanding how probiotic treatments should be

delivered and to whom. The implementation of 'omic' techniques would be a step towards turning probiotic usage into targeted treatment regimens. This would facilitate their use in a strategic manner to maximize effectiveness and minimize the potential pitfalls associated with treatment using probiotics.

References

[1] Food and Agriculture Organization and World Health Organization Health Consultation. Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria; 2001.

[2] Jia K, Tong X, Wang R, Song X. The clinical effects of probiotics for inflammatory bowel disease: A meta-analysis. Medicine. 2018;97(51).

[3] Loman BR, Hernández-Saavedra D, An R, Rector RS. Prebiotic and probiotic treatment of nonalcoholic fatty liver disease: a systematic review and meta-analysis. Nutrition reviews. 2018;76(11):822–839.

[4] Draper K, Ley C, Parsonnet J. Probiotic guidelines and physician practice: a cross-sectional survey and overview of the literature. Beneficial microbes. 2017;8(4):507–519.

[5] Raabis S, Li W, Cersosimo L. Effects and immune responses of probiotic treatment in ruminants. Veterinary immunology and immunopathology. 2019;.

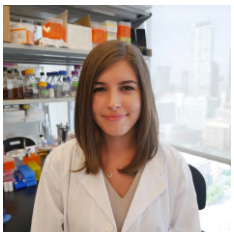
[6] Yan F, Cao H, Cover TL, Washington MK, Shi Y, Liu L, et al. Colon-specific delivery of a probiotic-derived soluble protein ameliorates intestinal inflammation in mice through an EGFR-dependent mechanism. The Journal of clinical investigation. 2011;121(6):2242–2253.

[7] Rondanelli M, Faliva MA, Perna S, Giacosa A, Peroni G, Castellazzi AM. Using probiotics in clinical practice: Where are we now? A review of existing meta-analyses. Gut microbes. 2017;8(6):521–543.

[8] Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. The Lancet. 2008;371(9613):651–659.

[9] Zmora N, Zilberman-Schapira G, Suez J, Mor U, Dori-Bachash M, Bashiardes S, et al. Personalized gut mucosal colonization resistance to empiric probiotics is associated with unique host and microbiome features. Cell. 2018;174(6):1388–1405.

[10] Valdes Mora F, Handler K, Law AMK, Salomon R, Oakes SR, Ormandy CJ, et al. Single-cell transcriptomics in cancer immunobiology: the future of precision oncology. Frontiers in Immunology. 2018;9:2582.



Emma is an MSc candidate at the University of Toronto in the department of Molecular Genetics. While completing a BScH at Queen's University, she spent summers working at the biotechnology firm DNA Genotek, where she initially became interested in studying the microbiota. Her current research focuses on leveraging *in vitro* approaches to examine bacterial interactions within the gut microbiota.

Health Science Inquiry

Routes Towards Treatment: Can We Cure HIV in the Future?

Farigol Hakem Zadeh[1,2]

[1]Department of Physiology, The University of Toronto
[2]Ted Rogers Centre for Heart Research, Toronto

Since the first reported case of human immunodeficiency virus (HIV) infection in 1959, approximately 37 million individuals have been affected by this virus; this number is increasing by 1-2 million annually [1]. In HIV, mostly CD4+ T-cells, part of the human immune system, are invaded [1, 2]. Several attempts to fight this epidemic have been successful in controlling the disease. For instance, with the immediate introduction of antiretroviral treatments after infection, the viral load can be controlled [3]. However, in most cases the virus re-emerges; thus, requiring lifelong therapy [3]. Amongst HIV-infected individuals, only two cases of complete cure through bone marrow transplantation from an HIV-resistant donor have been reported [4]. As such, novel approaches are being investigated with the aim of preventing, curing and completely eradicating the disease. Some of these potential treatments include "shock and kill", immune modulation, gene-editing techniques and stem cell transplantation.

In the "shock and kill" method, viral transcription and protein expression are activated from latency, resulting in the clearance of the virus through immune responses. Thus far, none of the clinical trials have shown a significant reduction in the number of virally reactivated cells [5]. The immune modulation method includes an overarching family of immunopotentiators (*i.e.* cytokines, immunostimulants), immunosuppressors (*i.e.* Trental), damage-preventing agents (*i.e.* antiviral agents) and immunization agents (*i.e.* active and passive immunization, vaccination) [6]. Currently, there are several trials attempting to generate HIV vaccines. However, this process is challenging due to the rapid mutation of HIV surface envelope proteins. Nonetheless, a recent study on the latest HIV vaccine, an active adenovirus-based immunization agent expressing the conserved region of the HIV envelope showed promising results [7]. This trial has recently moved to phase 2b. If all the safety and regulatory standards are met, this vaccine may protect humans against HIV in the future.

While HIV vaccine trials have been undertaken for more than three decades, alternative therapeutic approaches are also ongoing. Stem cell transplantation is another approach to fight HIV [4, 8]. In this approach, the immune system of the infected individual is eliminated entirely and a new HIV-resistant donor immune system is substituted. Since the "Berlin Patient" in 2007, one more successful transplantation, the "London Patient" in 2019, has been reported [4, 8]. It is known that chemokine receptor type 5 (CCR5) and/or C-X-C chemokine receptor type 4 (CXCR4) are required for HIV virus entry into CD4+ T-cells. In CCR5-δ32 HIV-resistant individuals, the T-cells have the truncated version of CCR5 and therefore are resistant to HIV infection. However, one of the issues with relying on the HIV-resistant cell transplantation approach is that there are few donors who have the natural mutations for HIV-resistance.

In the past, scientists generated CCR5 or the alternative CXCR4 co-receptor mutations through continuous expression of short-hairpin ribonucleic acids (shRNAs) [9]. Today, gene-editing techniques such as the zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 are used to mutate CCR5 or CXCR4 co-receptors to block HIV infection. These methods can permanently obstruct receptor expression in hematopoietic stem/progenitor cells (HSPC) used for transplantation [10].

Some of the current clinical trials using ZFN are in phase 1. One of the most recent studies showed a safe infusion of ZFN-mediated CCR5-gene-modified autologous CD4+ T-cells in adults [11]. In this study, the decline of CCR5-modified T-cells was significantly less than the unmodified T-cells, demonstrating HIV-resistance of these modified T-cells (ClinicalTrials.gov Identifier: NCT00842634). Other trials are currently looking at CCR5 disruption in HSPCs and possible engraftment of these modified cells in patients (Identifier: NCT02500849).

Because gene-editing is a new technique, investigating the future outcomes of HIV trials is procedurally and ethically essential to avoid concerns such as impaired immunity, preferred-trait selections and the generation of designer babies. Unfortunately, against ethical rules and regulations, CRISPR/Cas9 CCR5-modification was recently performed on human embryos by He Jiankui [12]. Jiankui claimed that through this procedure he generated the first genetically-edited HIV-resistant human baby. This attempt led to criminal charges due to his disregard for the safety issues and the law. While the health of this baby needs to be monitored throughout the span of her lifetime, further restrictions are being implemented in research regulations to avoid any other future violations in gene-editing studies.

Overall, as we consider the implications of this controversial topic, the scientific community should recognize the

great progress made in the field and the various promising routes that the new therapeutics hold to cure HIV. While antiretroviral therapy has revolutionized avenues for controlling HIV infection, several novel methods described have the potential to be combined in order to prevent and/or cure the disease. Therefore, all aspects of these methods, including their safety, efficacy and their ethical considerations, must be carefully assessed, refined and improved upon to ultimately lead us towards eradicating HIV.

References

[1] Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. The lancet. 2016;388(10053):1459–1544.

[2] Sengupta S, Siliciano RF. Targeting the latent reservoir for HIV-1. Immunity. 2018;48(5):872–895.

[3] Luzuriaga K, Gay H, Ziemniak C, Sanborn KB, Somasundaran M, Rainwater-Lovett K, et al. Viremic relapse after HIV-1 remission in a perinatally infected child. New England Journal of Medicine. 2015;372(8):786–788.

[4] Gupta RK, Abdul-Jawad S, McCoy LE, Mok HP, Peppa D, Salgado M, et al. HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation. Nature. 2019;p. 1.

[5] Archin NM, Liberty A, Kashuba AD, Choudhary SK, Kuruc J, Crooks A, et al. Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy. Nature. 2012;487(7408):482.

[6] Benson EM. Immune modulation in HIV infection: fact or fantasy? Journal of acquired immune deficiency syndromes. 1993;6:S61–7.

[7] Barouch DH, Tomaka FL, Wegmann F, Stieh DJ, Alter G, Robb ML, et al. Evaluation of a mosaic HIV-1 vaccine in a multicentre, randomised, double-blind, placebo-controlled, phase 1/2a clinical trial (APPROACH) and in rhesus monkeys (NHP 13-19). The Lancet. 2018;392(10143):232–243.

[8] Cohen J. The emerging race to cure HIV infections. American Association for the Advancement of Science; 2011.

[9] Rossi JJ, June CH, Kohn DB. Genetic therapies against HIV. Nature biotechnology. 2007;25(12):1444.

[10] Allen A, Chung CH, Atkins A, Dampier W, Khalili K, Nonnemacher MR, et al. Gene editing of HIV-1 co-receptors to prevent and/or cure virus infection. Frontiers in microbiology. 2018;9:2940.

[11] Tebas P, Stein D, Tang WW, Frank I, Wang SQ, Lee G, et al. Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. New England Journal of Medicine. 2014;370(10):901–910.

[12] Cyranoski D. CRISPR-baby scientist fails to satisfy his critics. Nature. 2018;564(7734):13–14.

Farigol received her Honours BSc (Physiology) with High Distinction and MSc (Cardiovascular Physiology) from the University of Toronto. With an extensive family history of cardiovascular diseases and diabetes, she was inspired to contribute to these areas of research. She began her research on myogenic responses in the microvasculature of stroke animal models. She also worked on generating organoid (intestinal buds) from ileal stem cells to study Glucagon-Like peptide-1 and its effects on insulin secretion. She was the recipient of several academic scholarships including the Queen Elizabeth II Graduate Scholarship. Farigol's MSc research focused on finding new therapeutic avenues to regulate Ca^{2+}-cycling in cardiac pathophysiology. Farigol is currently contributing to finding novel treatment interventions and medical innovations that have the potential to be utilized in clinical settings.

Health Science Inquiry

The Potential of Cannabis-derived Endocannabinoids as an Obesity Treatment

Hana Dibe[1]

[1]Human Health and Nutritional Science, University of Guelph

Before the recent legalization in Canada, marijuana was steadily the most widely used illicit drug [1]. With marijuana laws changing across North America, use is expected to rise and accordingly, while stigma against marijuana is shifting. Once consumed as an underground activity, marijuana is becoming widely accepted for its varying therapeutic benefits. Marijuana research has strong foundations, however, there is a lack of evidence-based research in humans which may pose a public health risk [1, 2, 3]. Derived from the *Cannabis sativa* plant, marijuana contains an abundance of different cannabinoids which interact with the human endocannabinoid system [4]. Δ^9-tetrahydrocannabinol (THC) produces the sought-after psychoactive effects, however, the major non-psychoactive cannabinoid, cannabidiol (CBD), has new-found therapeutic potential [4]. CBD and THC have the same chemical formula; different structural arrangements give the two compounds completely different pharmacological properties (Figure 1) [4]. CBD has been demonstrated to have anxiolytic, anti-depressive, anti-convulsant and potential anti-diabetic properties [5].

The endocannabinoid (EC) system is composed of endocannabinoids that bind to cannabinoid receptors in the central and peripheral nervous system [4]. The EC system controls food intake, energy balance and pain modulation, and may play a protective role in the development of Alzheimer's disease [4, 6]. The two main G protein-coupled cannabinoid receptors, CB1 and CB2, primarily bind the endogenous cannabinoids anandamide (AEA) and 2-arachidonylglycerol (2-AG) [5]. CB1 is ubiquitously expressed in the brain, lungs, liver and kidneys, and CB2 is expressed in immune and hemopoietic cells [5]. While CB2 receptors are involved in mediating immunoregulatory actions, which play an important role in the inflammatory aspect of obesity, CB1 receptors (CB1R) centrally mediate appetite regulation, food intake and reward behaviours [5]. Interestingly, less recognized functions of peripheral CB1R in the liver, pancreas, skeletal muscle and adipose tissue include regulation of insulin signalling, glucose homeostasis, and hepatic lipogenesis [7].

With rates of obesity and type 2 diabetes (T2D) increasing across North America, research investigating new weight loss and insulin sensitizing treatments are vital. Due to its role in appetite regulation, the EC system has been researched as a potential target for obesity treatment. Plant endocannabinoids such as CBD are receiving attention as well [4, 5, 6, 8, 9]. In animal models of obesity, the EC system appears to be upregulated [4]. In three different rodent models of obesity, obese animals had higher hypothalamic levels of 2-AG that were correlated with increased food intake, suggesting that CB1R activation in the hypothalamus may increase food intake [4]. Wild type CB1R positive mice treated with HU210, a synthetic cannabinoid that acts on CB1R, experienced marked increases in hepatic mRNA expression of sterol regulatory element-binding protein 1, acetyl-CoA carboxylase 1 and fatty acid synthase, suggesting upregulation of fat synthesis with CB1R activation [7].

Research using CB1R knockout (KO) animals supports the anti-obesity potential of CB1R antagonism. In a study examining whole body CB1R KOs, mice fed a high fat diet were protected from obesity, dyslipidemia, and leptin resistance [7, 10]. Leptin is the fat-derived hormone that induces satiation and inhibits hunger following a meal. Leptin is elevated in obesity, likely a reflection of the increased fat mass, and leads to decreased sensitivity to the hormone, known as leptin resistance. Subsequently, reduced satiation often leads to overeating. In liver-specific CB1R KOs of the same study design, both insulin and leptin resistance were reduced, as well as steatosis, hyperglycemia and dyslipidemia. However, these mice were not resistant to weight gain, suggesting a central role for brain CB1R in regulating food intake [10].

Rimonabant was the first pharmacological CB1R blocker for obesity. In animal and human studies of obesity and T2D, rimonabant improved glucose homeostasis and caused significant weight loss. European markets approved rimonabant in 2006, however, in 2008, it was withdrawn worldwide due to serious psychiatric side effects, including suicide ideation [5]. Rimonabant may have interfered with normal CB1R function in the brain, explaining the psychiatric side effects. Both THC and CBD interact with CB1 and CB2 receptors, however, unlike endogenous cannabinoids, CBD is a partial antagonist a of CB1 receptors [8]. CBD is also a potent anti-inflammatory agent, shown to reduce levels of inflammatory cytokines IL-1β IL-2, IL-6, TNF-α and IFN-γ in a variety of animal studies [8]. Mice and humans share

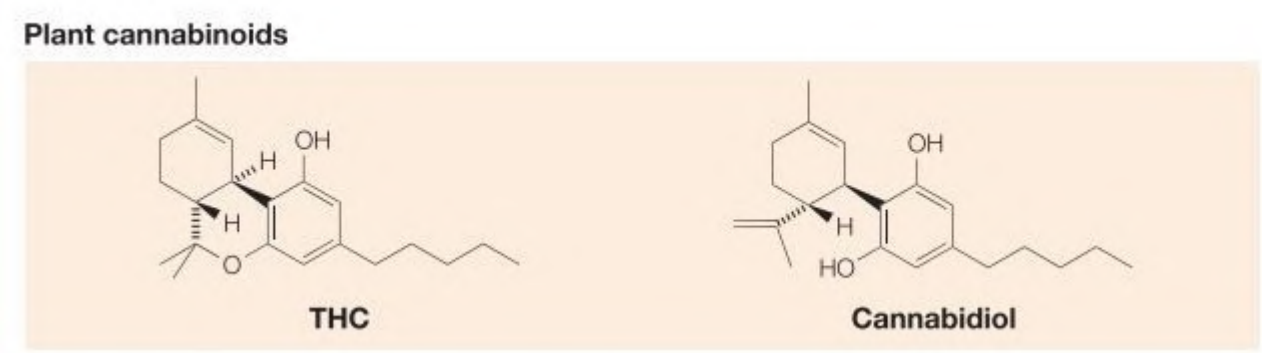


Figure 1: **Chemical structure of plant endocannabinoids Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD).** THC and CBD share the same chemical formula but where THC has a cyclic ring, CBD has a hydroxyl group [4].

similar immune system make-up, therefore it is often accepted to use mouse models as a proxy for the low-grade chronic inflammation seen in obese humans [11]. In a clinical trial of T2D adults, 100 mg of CBD oil taken orally twice daily for 13 weeks failed to elicit significant changes in fasting glucose and HOMA2 — a marker of β-cell function and insulin resistance. However, resistin levels, which are associated with insulin resistance, were significantly reduced, and GIP concentrations, a protein known to have pancreatic β-cell preserving effects, were increased [9].

CBD is a less potent antagonist than rimonabant. With its anxiolytic and anti-depressive properties, it is thought CBD will not cause the same side effects as rimonabant [9]. Further investigation of CBD and other similar cannabinoids in humans is warranted to better elucidate their potential role as an obesity treatment.

References

[1] Rotermann M, Langlois K. Prevalence and correlates of marijuana use in Canada, 2012. Statistics Canada Ottawa, Ontario; 2015.

[2] Government of Canada. Canadian cannabis survey 2017 – Summary. Health Canada; 2017. Available from: https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/canadian-cannabis-survey-2017-summary.html.

[3] National Academies of Sciences E, Medicine, et al. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. National Academies Press; 2017.

[4] Di Marzo V, Bifulco M, De Petrocellis L. The endocannabinoid system and its therapeutic exploitation. Nature reviews Drug discovery. 2004;3(9):771.

[5] Richey JM, Woolcott O. Re-visiting the endocannabinoid system and its therapeutic potential in obesity and associated diseases. Current diabetes reports. 2017;17(10):99.

[6] Iffland K, Grotenhermen F. An update on safety and side effects of cannabidiol: a review of clinical data and relevant animal studies. Cannabis and cannabinoid research. 2017;2(1):139–154.

[7] Osei-Hyiaman D, M D, Pacher P, Liu J, Radaeva S, Batkai S, et al. Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. J Clin Invest. 2005;115:1298–1305.

[8] McPartland JM, Duncan M, Di Marzo V, Pertwee RG. Are cannabidiol and Δ9-tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. British journal of pharmacology. 2015;172(3):737–753.

[9] Jadoon KA, Ratcliffe SH, Barrett DA, Thomas EL, Stott C, Bell JD, et al. Efficacy and safety of cannabidiol and tetrahydrocannabivarin on glycemic and lipid parameters in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel group pilot study. Diabetes Care. 2016;39(10):1777–1786.

[10] Osei-Hyiaman D, Liu J, Zhou L, Godlewski G, Harvey-White J, Jeong Wi, et al. Hepatic CB 1 receptor is required for development of diet-induced steatosis, dyslipidemia, and insulin and leptin resistance in mice. The Journal of clinical investigation. 2008;118(9):3160–3169.

[11] Della Vedova MC, Muñoz MD, Santillan LD, Plateo-Pignatari MG, Germanó MJ, Tosi MER, et al. A mouse model of diet-induced obesity resembling most features of human metabolic syndrome. Nutrition and metabolic insights. 2016;9:NMI–S32907.

Hana is in her first year of her MSc in Exercise Physiology. She completed her undergraduate degree at the University of Guelph in Nutrition and Nutraceutical Sciences and is now looking at the effects of exercise and cold exposure on hepatic glucose regulation. She is excited to learn more about the endocannabinoid system as research in the field grows.

Body Composition Analysis of Computed Tomography Scans in Clinical Populations: The Role of Deep Learning

Michael T. Paris[1]

[1]Department of Kinesiology, University of Waterloo

This article is the highest rated article in our 2019 submission category *Future Health & Research Technology.* All articles were ranked by HSI's independent professor judging panel. For this, the author was awarded one of three of HSI's annual "scholarship" awards.

The article will be submitted for publication in our partner journal **Lifestyle Genomics** for expidited review. The article may also appear here in a future version of this issue.

Michael is a PhD candidate in the department of Kinesiology at the University of Waterloo. His research focuses on how body composition modulates health and disease of aging and clinical populations. He is currently interested in developing novel methods for assessment of body composition using biomedical imaging technologies.

Health Science Inquiry

Present State of Brain Machine Interfaces

Kartik Pradeepan[1]

[1]Department of Neuroscience, University of Western Ontario

As early as the 1700s, scientists have had an idea that the nervous system uses electrical activity. In the time since this idea sparked, the fantasy of manipulating this electrical force has been a major plot point of several famous novels, and the goal of many therapies and medical treatments. Additionally, in more recent years, our world has become awash with electrical devices and technology so much so that our actions and thoughts "are increasingly becoming shaped and substantiated by machines" [1]. Through the blurring of this line between humans and machines, Marshall McLuhan, a philosopher, describes "technology and media as extensions of our central nervous system" [2]. Nowhere is this blurring more explicitly evident than in the technological interfacing of the brain and machine, known as brain-machine or brain-computer interfaces (BMI or BCI, respectively).

The simplest definition of a brain-machine interface (BMI) is the functional linking of neural ensembles directly with a man-made machine. BMIs do this through sensing/acquiring brain signals, analyzing them, and then translating the signals into commands that are relayed to an output machine to carry out a specific intended action [3]. BMIs are commonly divided into three types: sensory (*e.g.* cochlear implants), motor (*e.g.* neural-limb prosthetic) or cognitive (*i.e.* re-establishing proper neural interactions within the brain) [4]. It is important to note that while BMIs are recording information from the brain, they are not mind-reading devices. Rather, the user and the BMI work together, first by training to use the BMI so that the brain is able to generate signals of intention, and then by translating the commands to an output machine to carry out that user's intention [3].

BMI systems typically consist of "four sequential components: 1) signal acquisition, 2) feature extraction, 3) feature translation, and 4) device output" [3]. Signal acquisition is recording of brain signals through various approaches such as electroencephalography (EEG) and electrocorticography (ECoG) [3]. To acquire brain signals, two types of cortical recordings are typically considered. Action potentials are the functional units of the nervous system and these recordings are crucial for the precision of certain neuroprosthetics. Local field potentials, which are more commonly used, are the result of coordinated activity of many neurons and these recordings are the driving forces behind the neuroprosthetics [5]. The signal, once acquired, is amplified and filtered to improve the signal-to-background noise ratio so it can be electronically processed. Feature extraction involves analyzing the digital signal and identifying important signal features, like those related to a person's intent. Feature translation then takes the identified signal features and runs it through a translation algorithm to convert it to specific commands for the output device. Finally, the commands generated operate the device, allowing the user to intentionally control the external device using their brain. While the precise signal may vary between motor, sensory and cognitive BMIs, the four components are typically conserved one way or another [3].

Although considerable effort has been made in motor BMIs, advancements that aim to fix more complex sensory modalities, like restoring basic elements of visual perception, are not yet considered useful enough to justify the costs or risks to the patient [5]. A reason for the slower progress of sensory BMIs is because sensory systems are composed of hierarchical processing areas that flow from lower-order systems to higher-order areas, but also feeds back to the lower-order systems. Additionally, sensory impairments can occur anywhere along this chain of processing areas, to give rise to a complete loss of sensation to deficits in components of higher-level sensory processing. For example, patients with lesions to the primary visual cortex may have cortical blindness where they're unable to consciously perceive visual stimuli but can still subconsciously utilize visual information [6]. It is because of the complexity in sensory processing and circuitry between neural ensembles that advancements in sensory and cognitive BMIs have not been as significant as seen in motor BMIs.

Evidently, there are certainly a few challenges to current BMI technology, with some being critical bottlenecks that need to be overcome in order to seamlessly integrate any output device with the user. Despite this, the increasing numbers of researcher groups and companies investing into the area as well as improvements in other related disciplines suggest positive growth and further advancements [7]. Beyond perfecting neuroprosthetics, BMIs offer the potential to revolutionize the human experience through human enhancement but may also offer a novel understanding on consciousness and philosophy of the mind.

References

[1] Nair P. Brain–machine interface. Proceedings of the National Academy of Sciences. 2013;110(46):18343–18343.

[2] McLuhan M. Understanding Media: The Extensions of Man. New York: The New American Library. Inc; 1964.

[3] Shih JJ, Krusienski DJ, Wolpaw JR. Brain-computer interfaces in medicine. In: Mayo Clinic Proceedings. vol. 87. Elsevier; 2012. p. 268–279.

[4] Sanchez JC, Principe JC. Brain–machine interface engineering. Synthesis Lectures on Biomedical Engineering. 2007;2(1):1–234.

[5] Langmoen IA, Berg-Johnsen J. The brain-computer interface. World neurosurgery. 2012;78(6):573.

[6] Lebedev M. Brain-machine interfaces: an overview. Translational Neuroscience. 2014;5(1):99–110.

[7] Ramadan RA, Vasilakos AV. Brain computer interface: control signals review. Neurocomputing. 2017;223:26–44.

Kartik completed his undergraduate degree at University of Western Ontario with a Double Major in Genetics and Physiology. He is currently pursuing a Master's in Neuroscience at the university in Dr. Julio Martinez-Trujillo's cognitive neurophysiology lab. His project focuses on a computational approach to understanding how iPSC-derived neuronal networks differentially develop as a result of various mutations that are known and believed to contribute to Autism Spectrum Disorder.

Health Science Inquiry

Quality *and* Quantity: The Future of Machine Learning for Health Research Appraisal

Yoah Sui[1] **and Anna Rudkovska**[1]

[1]University of Western Ontario

As the number of published primary academic literature is growing, the timely production of review papers is more important than ever. Between January 1^{st}, 2017 and December 31^{st}, 2017, a total of 322,732 journal articles were published on the PubMed database under the keyword "Health", with 307,620 articles being published the year prior. Comparatively, only 42,797 and 41,443 review articles were published during those same time periods, respectively. Research from 2010 suggests that 75 trials and 11 reviews of trials are published each day [1]. This disparity between journal articles and review papers is important, since most review papers will include a method of appraising the quality (a.k.a. risk of bias) of each included study, and hence, are the primary means by which researchers evaluate the quality of a study – and by extension the state of research in a field [2]. Given that findings derived from a single study are rarely definitive, multiple replications followed by a review and appraisal of said primary studies is needed to establish the reliability of the findings [3]. These reviews are ultimately what help guide changes in policy, in practice, and in recommendations [4]. Recent drives for research informed clinical practice and policy setting has exponentially increased the demand for reviews that illustrate a clear relationship between healthcare inputs and outputs [3].

Unfortunately, this combination of high-volume research publication and reliance upon reviews for research appraisal raises two main issues: one, quality appraisal of new health research is limited by how quickly a review paper can be published; and two, new health research is likely being published more often than review papers that can assess their quality, given that traditionally, quality appraisal is conducted manually by a group of researchers using a prespecified criteria. To this end, one major recommendation has been to reduce the number of "unnecessary trials" and prioritize systematic reviews [1]. However, this recommendation implies several obstacles and drawbacks, such as a standardized methods and training for writing (and evaluating) reviews, universal agreement in determining "unnecessary trials", and ultimately resulting in less "new" research. Arguably, even if researchers were to collectively regress the amount of new research they would publish, in favor for review papers, a considerable amount of time would still likely need to be dedicated to the task before all new research was appraised.

One alternative solution to this issue is machine learning. At its core, machine learning "automatically learns programs from data" [5]. More specifically, classification (*i.e.*, a subset of machine learning) takes inputs of data and outputs a discrete variable. For example, most malicious software, or malware, share 90-98% of code with previous iterations; hence, machine learning can identify this shared code, and classify a software as malware or not. Machine learning has already seen successful application in industries that involve huge amounts of data, such as spam filters, stock trading, and Web searches [5]. The main advantage to machine learning over manpower is obvious: the program/algorithm can process far more data than a human within a given timespan. However, machine learning also has advantages over manual programming, in that a machine learning algorithm is able to generalize from the data it is provided; in other words, the more data an algorithm is given to "learn from", the stronger its classification becomes [5].

When applied to a health research appraisal context, machine learning offers an elegant solution to the issue of quantity. Firstly, established tools/instruments to measure the quality of a study available (*e.g.*, Cochrane Risk of Bias Tool [6]; Downs and Black Checklist [7]), and responses to individual items can be classified relatively easily (*e.g.*, yes/no, 0/1, low/high). This allows an algorithm to have clear-cut parameters in how to classify an item, and hence, how to appraise an article. Additionally, there is a gross amount of data through which an algorithm can learn from. Cross-referencing how previous studies have been appraised in review papers and how the algorithm classifies those same studies allows the accuracy of an algorithm to be constantly evaluated. The ability for the algorithm to learn from data also means minimal human oversight is needed after the initial algorithm is tested and successfully implemented. This automatic learning also minimizes the amount of potential human bias that is introduced when appraising articles. Finally, and perhaps most importantly, is the immense capacity for an algorithm to process data

(both new and existing), relative to a human researcher.

Despite these advantages, there are several barriers that present a challenge to implementing machine learning to a health research context, such as: determining appropriate and representative classifiers based off of existing instruments and tools, a standardized method of distinguishing good vs. bad classifiers, and optimization of the algorithm [5]. It is also worth noting that machine learning will not be ideal for assessing qualitative studies as well as studies that cannot be conducted as randomised control trials due to ethical or logistical considerations. Addressing these obstacles is imperative for machine learning to be effectively used for research appraisal purposes. However, when taken as a whole, machine learning presents an efficient and effective response to the issue of both quality-appraisal and quantity of appraisal in the ever-growing field of modern – and future – health research.

References

[1] Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? PLoS medicine. 2010;7(9):e1000326.

[2] Glasziou P, Vandenbroucke J, Chalmers I. Assessing the quality of research. Bmj. 2004;328(7430):39–41.

[3] Clancy CM, Cronin K. Evidence-based decision making: global evidence, local decisions. Health affairs. 2005;24(1):151–162.

[4] Higgins JP, Green S, et al. Cochrane handbook for systematic reviews of interventions. 2006;.

[5] Domingos PM. A few useful things to know about machine learning. Commun acm. 2012;55(10):78–87.

[6] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343:d5928.

[7] Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Journal of Epidemiology & Community Health. 1998;52(6):377–384.

Yoah received his B.Sc from the University of Waterloo, and his M.A. from Western University. He is currently a PhD candidate at Western University. His research focuses on the impact of excessive sedentary behaviour on subjective well-being in university students. He enjoys playing guitar, mountain biking, and chasing after his two dogs.

Anna received a B. Sc from the University of Toronto and a Masters degree in Rehabilitation Sciences from the University of Western Ontario. Currently, she is enrolled in her Doctoral studies at Western and focuses on women's reproductive health and autonomy.

Health Science Inquiry

The Future of Beh"AI"viour Change

Yoah Sui[1] **and Anisa Morava**[1]

[1]University of Western Ontario

Health behaviour change represents what is potentially the most effective, sustainable, and feasible means of preventing some of the most serious causes of death globally – including ischaemic heart disease, stroke, and chronic obstructive pulmonary disease [1]. Broadly speaking, health behaviour change involves the modification of a person's lifestyle behaviour(s) in order to mitigate or prevent a more serious health complication. Common health behaviour changes include: quitting smoking, improving diet, or increasing physical activity.

Given the important health benefits of these particular behavioural changes, extensive research has examined effective behaviour change strategies. Foundational work by Michie and Abraham [2] summarize 26 broad and distinct behaviour change techniques, ranging from providing general information to prompting self-monitoring. The scope of these strategies, as well as their permutations, highlight the vast toolbox of recognized behavioural techniques that can be applied to a specific health behaviour.

Traditionally, psychologists and behavioral specialists use these techniques to discuss goals and formulate plans to change a given behaviour with a client. However, these services can often be expensive and may not always be convenient or accessible by the client. Additionally, the behavioural plan can vary in efficacy due to variability in the specialist's experience, education, and rapport with the client. Similarly, a client's location, demographics, and/or culture may play a role in how effective a plan may be. Even when a behavioral plan is formed and prescribed, behavioral change is not guaranteed [3].

Taken together, the wide variety of behavioural techniques and the complexity of the client/specialist relationship pose a barrier to how effective and sustainable a health behaviour change plan can be [3]. Despite the numerous variables that must interact with and around each other, behaviour change interventions can be successful [4]. Moreover, many of the factors that contribute to the success of a behaviour change technique (*e.g.*, motivation, barriers, resources) are common amongst individuals. Hence, matching behaviour change techniques to these factors can help to enable successful behaviour change. A promising solution to identifying which behavioural strategies will be most effective for the individual is artificial intelligence.

Artificial Intelligence (AI) is a broad term that describes the science and engineering of making intelligent machines [5]. Although there are several types of AI, the power of an AI is derived from data, and "learning" from data. Supervised learning is a technique for teaching AI whereby labeled examples are given to the system, in order for the system to be trained [6]. When applied to the context of health behaviour change, data about an individual's demographics, location, and other outcomes of interest would be cross-referenced against the behaviour change technique(s) used, and subsequently labeled as either successful or unsuccessful. Through data collection and compilation, an AI would hypothetically be able to determine which behaviour change technique would likely result in successful behaviour change, based upon an individual's data. Realistically, the AI would work in tandem with a specialist in order to deliver the behaviour change techniques. A present-day example of this technological partnership is the use of AI in assisting radiologists in image classification (*e.g.* cancer [7]).

Using AI as a means of facilitating behaviour change has numerous advantages. The adaptability and reiterative learning process of AI means that the output (*i.e.* recommendations) would be constantly updated and tailored to reflect new data. For example, if barrier identification as a technique for improving diet is found to be less effective for individuals in a certain area, due to the limited number of healthy options, then the AI would identify this strategy as being less effective and can recommend an alternative strategy to a specialist. Vice-versa, this learning can be informed by the specialists themselves. If a specialist encourages the use of a specific technique, at the recommendation of the AI, then they can evaluate how effective the technique(s) is, based upon the outcomes of the client. The delivery of the AI can also influence it's potential. If the AI can be incorporated into an app or device, then it may be able to collect objective data to learn from. By the same vein, it also becomes possible to intervene ecologically with the client. For example, assume a client wants to improve their diet. However, the AI on their phone detects that they are in close proximity to a fast food restaurant and applies an ecological intervention of providing information on the consequences of eating fast food. Regardless of the choice of the client, the AI is then able to collect data on whether the strategy was successful or not. These aggregated data can also be scaled upwards to inform behavioural change interventions in larger populations or groups.

The potential for AI for positively influencing and informing health behaviour change is enormous. The ability to assist behaviour specialists in implementing and refining successful behavioral strategies has tremendous benefit for health and healthcare. Ultimately, AI provides a promising and adaptable solution to what has long been the important, albeit complex, science of health behaviour change.

References

[1] The top 10 causes of death. World Health Organization; 2008. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.

[2] Abraham C, Michie S. A taxonomy of behavior change techniques used in interventions. Health Psychology. 2008;27(3):379.

[3] Kelly MP, Barker M. Why is changing health-related behaviour so difficult? Public health. 2016;136:109–116.

[4] Williams SL, French DP. What are the most effective intervention techniques for changing physical activity self-efficacy and physical activity behaviour—and are they the same? Health Education Research. 2011;26(2):308–322.

[5] McCarthy J. What is AI? Stanford Univ. 2007;.

[6] Heath N. What is AI? Everything you need to know about artificial intelligence. ZDNet. 2018;Available from: https://www.zdnet.com/article/what-is-ai-everything-you-need-to-know-about-artificial-intelligence/.

[7] Lakhani P, Prater AB, Hutson RK, Andriole KP, Dreyer KJ, Morey J, et al. Machine learning in radiology: applications beyond image interpretation. Journal of the American College of Radiology. 2018;15(2):350–359.

Yoah received his B.Sc from the University of Waterloo, and his M.A. from Western University. He is currently a PhD candidate at Western University. His research focuses on the impact of excessive sedentary behaviour on subjective well-being in university students. He enjoys playing guitar, mountain biking, and chasing after his two dogs.

Anisa received her BSc in Psychology, Neuroscience & Behaviour from McMaster University. She is currently a second year Master's student at Western University. Her research focuses on the effects of aerobic exercise and caffeine on cognitive performance.

Health Science Inquiry

Social media: A Growing Presence in Healthcare

Sharon Ling[1]

[1]Department of Immunology, Faculty of Medicine, University of Toronto

Introduction

The words *friends*, *follow*, and *snap* no longer mean what they did 15 years ago. Since the launch of Facebook in 2004, Instagram in 2010 and Snapchat in 2011, social media (SM) platforms have radically changed the ways in which people interact and communicate. With an estimated 2.62 billion SM users globally, many are bringing discussions into the online world and the healthcare industry is no exception [1]. However, what may seem as an attractive avenue for fostering networks, educating patients, and promoting public awareness, may simultaneously pose complex questions regarding privacy, accuracy of information, and professionalism.

Potential applications in healthcare

Healthcare providers (HCPs) are continually looking to improve communication, both with each other and their patients. Accessible, instantaneous, and intrinsic to the daily routines of billions — SM offers the possibility of doing just that. Within the field of medicine, one of the most valuable moments of communication can be found in patient education. Well-educated patients are better able to inquire about, understand, and manage their conditions which can ultimately improve patient outcomes [2]. One of the most well-known healthcare figures in SM that promotes patient education is Dr. Mikhail Varshavski. Known online as Doctor Mike, he provides daily posts on his day-to-day tasks as a physician as well as tips on having a healthy and active lifestyle—he currently has 3 million followers on Instagram.

SM may extend the patient-HCP relationship beyond the clinic and help keep patients informed between visits. It has been suggested that platforms like Facebook Groups could be used to circulate general information such as suggestions on blood pressure maintenance, preparing for procedures (*e.g.*, fasting prior to imaging procedures), and when seasonal vaccines are offered [3]. With the rapid expansion of SM, patients are also expressing interest in using online platforms to communicate with their providers. In fact, 56.4% of patients surveyed in an outpatient family clinic responded favourably to receiving diagnostic results and appointment updates via SM [4].

Healthcare institutions are also recognizing the power of SM in marketing, attracting the public's attentions, and promoting awareness [5]. In 2017, the largest hospital fundraising campaign in Canadian history was launched—the SickKids VS Limits Campaign—during which Toronto's Hospital for Sick Children (SickKids) set out to raise $1.3 billion in hopes of updating medical equipment and technology [6]. To spread their message, the hospital designed videos and advertisements that can be viewed across YouTube, Facebook, and their own campaign website. Gaining exposure online was critical to the success of the campaign, considering, between 2010 and 2017, the average amount of time Canadians spent online rose from 13.4 to 21.8 hours per week [7].

Important Implications to Consider

In attempts to strengthen patient-HCP relationships and raise awareness, increased employment of SM may also bring deliberations on appropriate use and professionalism. While some physicians support connecting with patients online, others are concerned with the dangers of crossing professional boundaries [5]. It is uncertain as to whether SM could significantly improve patient outcomes yet, but it has become such an integral part of society that hospitals and other healthcare institutions have developed guidelines discussing the gravity of preserving patient confidentiality and privacy. Furthermore, the Canadian Medical Association (CMA) currently has a published policy that examines social media risks, benefits, as well as rules of engagement for Canadian physicians [8]. As SM use in the clinic grows, additional efforts to be conscientious and more specific guidelines will be required to help HCPs uphold the ethical and professional values that are central to providing quality healthcare.

It is also vital to consider the mounting availability of patient data, dissemination of unfounded medical advice, and its implications on patient behaviour. According to the American Osteopathic Association (AOA), it was found that 32% of Americans between the ages of 18 to 34 have applied a health-related action based on information acquired on SM [9]. Moreover, 15% of parents with children under 18 have self-diagnosed a condition based on social media postings [9]. Though social media has the ability to assist patients in making health-related decisions, HCPs will need to be conscious of where patients are sourcing their information from and encouraging them to examine online content with a more critical eye. This will serve not only to aid patients in asking the right questions regarding

their conditions but also, more importantly, to help keep patients safe when it comes to selecting treatment options.

Conclusion

If used prudently, SM and online platforms offer promising mediums for HCPs to enhance their connections with patients. However, the implementation of such a powerful tool will need to be monitored and managed. It is likely that SM will remain and grow for many years to come and for the field of healthcare and medicine, it brings both a unique set of opportunities and challenges.

References

[1] Statista. Number of social media users worldwide from 2010 to 2021 (in billions);. Available from: https://www.statista.com/statistics/278414/number-of-worldwide-social-network-users.

[2] Marcus C. Strategies for improving the quality of verbal patient and family education: a review of the literature and creation of the EDUCATE model. Health Psychology and Behavioral Medicine: An Open Access Journal. 2014;2(1):482–495.

[3] George DR, Rovniak LS, Kraschnewski JL. Dangers and opportunities for social media in medicine. Clinical obstetrics and gynecology. 2013;56(3).

[4] Fisher J, Clayton M. Who gives a tweet: assessing patients' interest in the use of social media for health care. Worldviews on Evidence-Based Nursing. 2012;9(2):100–108.

[5] Chretien KC, Kind T. Social media and clinical care: ethical, professional, and social implications. Circulation. 2013;127(13):1413–1421.

[6] CTVNews. SickKids hospital rallying 'crews' around $1.3-billion fundraising drive.;. Available from: https://www.ctvnews.ca/canada/sickkids-hospital-rallying-crews-around-1-3-billion-fundraising-drive-1.4126468.

[7] Statista. Average weekly time spent online in Canada from 2010 to 2017 (in hours).;. Available from: https://www.statista.com/statistics/473730/canada-weekly-time-spent-online/.

[8] Canadian Medical Association. Social media and Canadian physicians: Issues and rules of engagement.;. Available from: http://policybase.cma.ca/dbtw-wpd/Policypdf/PD12-03.pdf.

[9] American Osteopathic Association. Survey Finds Patients Want to be Friends with their Physicians on Social Media.;. Available from: https://osteopathic.org/2018/05/14/survey-finds-patients-want-to-be-friends-with-their-physicians-on-social-media/.

Sharon Ling completed her BMSc, specializing in microbiology and immunology, at the University of Western Ontario. She is currently an MSc candidate in the Department of Immunology at the University of Toronto. Under the supervision of Dr. Rae Yeung at SickKids, she is investigating the role of circulating DNA (cDNA) and mitochondrial DNA in the pathogenesis of Kawasaki Disease.

Health Science Inquiry

Antifragile by Design

Using Antifragility as a Guiding Principle in Future Rural eHealth Implementation & Evaluation

Samuel Petrie[1], **Dr. Paul Peters**[1], **and Dr. Dean Carson**[2]

[1]Spatial Determinants of Health Lab, Department of Health Sciences, Carleton University
[2]Department of Epidemiology and Global Health, Umeå University, Sweden

Introduction

Antifragility as a concept was first introduced in the 2012 book Antifragile by Nicholas Taleb [1]. Taleb posits that an antifragile unit stands to gain, rather than be harmed from volatility [1]. Examples of antifragility include bones becoming stronger from small stressors, our immune system building strength from fighting off viruses, and muscle mass being built through continuous use. This analogy can be extended to rural eHealth[1] interventions, where small failures would strengthen the system as it learned from past mistakes, rather than making it weaker and leading to overall failure. The future of health services delivery in rural communities could depend on being able to effectively implement eHealth interventions and see them scale-up to regional or national initiatives.

Antifragility has been used outside health as a guiding concept for research: including transit planning in Australia [2], risk analysis [3], and systems engineering [4]. In health there are fewer examples, but it can be seen in the implementation of a Swedish Virtual Health Room (or VHR); a community-based rural eHealth intervention [5]. The room is located in a school in the village of Slussfors and contains various sophisticated technologies to monitor health needs of residents. These include thermometers, glucometers, blood-pressure cuffs, heart rate monitors, and video-conferencing technology for consultations. It has been effectively introduced where initiatives in similar contexts have failed, and it has increased the accessibility to health services for rural residents in the village and surrounding area. In Canada, antifragile implementation of online health portals could learn from Quebec's 'carnet santé' service, which has thrived, in comparison to the MyHealthNS portal in Nova Scotia which has declined.

[1]eHealth, for the purpose of this article, is defined as any electronic medium used to administer health services

Exploring Antifragility through the Virtual Health Room Case Study

The VHR intervention in Sweden exemplifies the importance of *optionality*, *non-linear evaluation*, and *starting small* in project design. *Optionality* is defined as the character of the option: or simply the ability to make choices [1]. Fragile projects lack *optionality*, while antifragile projects provide an abundance of it. Optionality requires input from both sides of the patient-provider dyad. Ultimately eHealth initiatives should use a patient *centered* approach [6], putting them at the heart of their model. The Swedish VHR provided optionality by ensuring video cameras and televisions could be used for things other than health – such as education, psychological services, or secure meetings.

Non-linear evaluation refers to the process of diligently considering upstream and downstream changes to systems following an intervention's implementation [7]. It forgoes labeling a project as a 'success' or 'failure', and instead seeks to characterize barriers and limitations, and continually identify solutions to them. Inherent in implementation processes are consequences which cannot be predicted. As such, fragile projects will miss key changes in the system by approaching evaluation linearly. Antifragile projects embrace a holistic evaluation approach, highlighting prominent interdependencies through multiple levels within systems. The Swedish VHR team achieved this by evaluating the VHR *non-linearly*, through multiple feedback streams and checkpoints from a diverse range of stakeholders. This includes patients, providers, policy-makers, and international collaborators. Barriers were addressed in real-time and seen to strengthen the overall system.

Starting small refers to the iterative process of project design, wherein research teams should begin with appropriately scaled pilot projects, before rolling out more comprehensive initiatives [7]. It avoids path-dependence, which locks implementation teams into following difficult methods of program execution due to considerable investment of time and/or money by starting large [8]. The VHR in the Swedish case started *small*, with multiple rounds of pa-

tient and provider feedback, before slowly introducing the technology outlined previously into the room, allowing the research team time to tinker and iterate.

Applying Antifragility in a Canadian Context

Online health portals in Canada could be important for rural communities to increase access to health services. Quebec has embraced antifragile project design during their implementation in ways other provinces (namely Nova Scotia's MyHealthNS portal) has not. Quebec's carnet santé service allows patients to register for themselves, or have their caregiver or physician sign them up, an example of *optionality* [9]. The MyHealthNS portal requires physicians to register their patients resulting in significantly lower numbers enrolling [10].

Using *non-linear evaluation*, the carnet santé service had perspectives from a diverse range of stakeholders in their implementation process, while the MyHealthNS portal used a top-down model. The result, again, was many more physicians and patients enrolling in Quebec's portal than Nova Scotia's. Lastly, Quebec slowly introduced services to their portal – starting with receiving bloodwork, to now being able to view x-ray results [9]. Nova Scotia attempted to introduce everything at once, confusing both patients and providers [10]. If a pan-Canadian portal is to be introduced, implementors would be wise to consider the success of Quebec's 'carnet santé' and Sweden's VHRs as an example of the potential of antifragile project design.

Conclusion

Evidence *and* theory suggest that consciously applying antifragile thinking starting in the project design phase will result in greater numbers of projects being able to thrive. These thriving projects would be characterized as being enthusiastically supported by practitioners, used by a diversity of stakeholders, with frequent and positive engagement by patients or clients, movement from a 'pilot' to part of routine health services framework, a secure funding source(s) identified, and the potential to 'scale-up' services and expand to other locations.

References

[1] Taleb NN. Antifragile: Things that gain from disorder. vol. 3. Random House Incorporated; 2012.

[2] Isted R. The use of antifragility heuristics in transport planning. In: Australian Institute of Traffic Planning and Management (AITPM) National Conference, 2014, Adelaide, South Australia, Australia. 3; 2014. .

[3] Aven T. The concept of antifragility and its implications for the practice of risk analysis. Risk analysis. 2015;35(3):476–483.

[4] Verhulsta E. Applying systems and safety engineering principles for antifragility. Procedia computer science. 2014;32:842–849.

[5] Hurtig AK. Strengthening community-based health systems through e-health innovations?;. Available from: https://www.umu.se/en/research/projects/strengthening-community-based-health-systems-through-e-health-innovations/.

[6] Townsend A, Leese J, Adam P, McDonald M, Li LC, Kerr S, et al. eHealth, participatory medicine, and ethical care: a focus group study of patients' and health care providers' use of health-related internet information. Journal of medical Internet research. 2015;17(6):e155.

[7] Braithwaite J, Churruca K, Ellis LA, c Long J, Clay-Williams R, Damen N, et al. Complexity science in healthcare-aspirations, approaches, applications and accomplishments: a white paper. Macquarie University; 2017.

[8] Flyvbjerg B. Big is Fragile: An attempt at theorizing scale. by B Flyvbjerg Oxford: Oxford University Press(2016b)"The fallacy of beneficial ignorance: A test of hirschman's hiding hand" In: World Development. 2016;84:176–189.

[9] Days of Past Futures. Coming Tuesday in Quebec: Your digital health file at your fingertips;. Available from: https://prich5757.wordpress.com/2018/11/16/myhealthns-a-perplexing-patient-portal-poser/.

[10] Fidelman C. MyHealthNS – A perplexing patient portal poser;. Available from: https://montrealgazette.com/news/local-news/coming-tuesday-in-quebec-your-digital-health-file-at-your-fingertips.

Sam Petrie (BKI) is an MSc student in the Department of Health Sciences at Carleton University. His research interests include the scalability of pilot projects, and the use of tele-health / eHealth technologies to better serve rural communities. With an interdisciplinary undergraduate background in Knowledge Integration, he approaches complex problems from unique perspectives in a hope to develop impactful solutions.

The essence of Dr. Paul Peter's research is on the study of small places and small spaces in a context of widespread social and structural inequalities. The substantive areas of his research are varied, but they are connected by the use of linked administrative and survey data, whether analysing problems manifest in small areas or small places. He prefers research projects that are collaborative in nature, and engage with diverse international colleagues across disciplines and domains.

Dr. Dean Carson has spent the past 20 years researching who lives in, works in, and visits sparsely populated areas, and how and why these patterns change over time. Dean has worked with the National Aboriginal and Torres Strait Islander Statistics Unit with the Australian Bureau of Statistics, the National Rural General Practice Study run out of Monash University in the mid 1990s, as Head of the Centre for Regional Tourism Research at Southern Cross University, and Head of Population and Tourism Studies at Charles Darwin University.

Health Science Inquiry

View of the Future and Making Big Bets:
The Missing Piece of the "Puzzle" of Healthcare Innovation?

Umair Majid[1]

[1]Institute of Health Policy, Management, and Evaluation, University of Toronto

The rising costs of healthcare has increased pressures to develop innovations and interventions to complete the "puzzle" of healthcare (*e.g.*, The Triple Aim – outcomes, cost-effectiveness, and experience). However, the majority of efforts miss many pieces of this puzzle. One important piece is viewing the "big picture"; the forest for trees; the healthcare system from a 30,000-foot view.

Seeing the big picture does not only involve understanding the current structure and function of the healthcare system, but how the industry may evolve as a result of market forces, innovations, and discoveries [1]. This thinking has been applied in some areas of healthcare, for example the scholarship of implementation science and management. However, this idea remains elusive in the practice of health administration, innovation, and quality improvement. The objective of this article is to discuss why a "view of the future" is essential for healthcare improvement and how practitioners working in this area may incorporate this thinking in practice.

View of the Future

The view of the future originates from a belief that health systems are complex and constantly changing [2]. Without acknowledging and embedding these characteristics into the design of innovations and interventions, a health system may produce services and processes that are ineffective, inappropriate, and inefficient to patients and family. For example, if a health service organization does not envision how an emerging technology may shift the structure and functioning of the industry, then products or services are at-risk of becoming obsolete as individuals' behaviors, interactions, and lifestyles become more aligned with the new technology, and the products and services become misaligned with the intended population.

Viewing the future has broad implications for innovations and interventions. However, few organizations in healthcare spend sufficient time on this exercise. In 1994, Hamel and Prahalad described the **40/30/20 rule**: 40% of an executive's total time is devoted to looking outward; 30% of this time is dedicated to looking at three, four, five or more years in the future (0.30 x 40% = 12% of total time); and 20% of this time is dedicated to building a view of the future (0.20 x 12% = 2.4% of total time) and 80% on the current business model [3]. In other words, approximately only 2.4% of an executive's total time is devoted to building a view of the future [3]. This observation is a major gap in healthcare innovation, as well as an opportunity to improve the responsiveness and sustainability of health services.

Engaging in the view of the future is an uncomfortable exercise for healthcare professionals because it brings forward the possibility that health services may become obsolete, irrelevant, or ineffective in the future. However, the uncertainty inherent in viewing the future is also an opportunity. Using collective understanding of the healthcare industry and market forces may enable health service organizations to evolve their services to be more aligned with the needs, preferences, and perspectives of patients and family. One example of an opportunity observed today is many individuals are choosing to age at home instead of at institutions [4]. However, the infrastructure for aging at home has not met the demand or need for these services, possibly reflecting how systems have not viewed their structure and function in the future [5].

View of Future Exercise

The view of the future is an exercise developed by Tan and colleagues (2015) in their book: *Tao of Innovation: Nine Questions Every Innovator Must Answer*. They offer two steps to completing this exercise [6]. The first step is to *construct the view of the future*, which includes spotting changes in the industry that may dramatically shift its structure and function. A healthcare example of a dramatic shift includes the implications of machine learning for research, planning and designing, service delivery, and quality improvement. Constructing a view of the future requires healthcare professionals to engage in a dialogue that considers technology, people, climate, environment, market, policy, economics, ethics, systems, and industrial forces. Tan and colleagues (2015) recommend answering seven questions shown below [6].

1. What are customers' priorities today and how will they change in the future?
2. Which customers do I serve today and how will they change in the future?
3. What channels do I use to reach them today and which ones will I use down the road?
4. Who are my competitors today and who will they be in the future?
5. What is the basis for my competitive advantage today and what will it be in the future?
6. Where do my margins come from today and where will they come from in the future?
7. What are our core competencies today and what new capabilities and core competencies do we need to develop to compete in the future?

The second step is to *lay new bets*, which requires identifying "big bets" that a health service organization is willing to make that will fundamentally change how it functions within the broader system. Laying new bets follows the **80/20 metaphor** – a process or service that contributes 20% of value today will contribute to 80% in the future [7]. For example, there has been a gradual shift from institutional to community care in the last few decades. Healthcare institutions (*e.g.*, large hospitals) emerged from post-WW2 efforts to meet the demands for acute care. However, the increasing expectancy and longevity of populations engendered a strong need for infrastructure for citizens to access health services in community facilities. In the middle of the 20th century, community care may have contributed to 20% of need, but with time, it will contribute to 80% of value in some jurisdictions. Using this metaphor adapts health systems to broader changes in behaviors, interactions, and lifestyles.

Conclusion

In future health systems, stakeholders will need to exemplify an increased capacity for open-mindedness, resiliency, and collaboration. Foresight and adaptation are essential principles to achieve a view of the future and build a system that is more sustainable and aligned with patient needs and preferences. This article discussed the importance of viewing the future of health systems and provided a list of questions from Tan and colleagues (2015) for practitioners to create a view of the future and contribute to a more sustainable health system. However, it is difficult to evaluate the impact of viewing the future and related exercises. Future research should look how health service organizations who dedicate time to building a view of the future differ from those who do not.

References

[1] Agarwal R, Gort M. The evolution of markets and entry, exit and survival of firms. The review of Economics and Statistics. 1996;p. 489–498.

[2] Greenhalgh T, Papoutsi C. Studying complexity in health services research: desperately seeking an overdue paradigm shift. BioMed Central; 2018.

[3] Prahalad CK, Hamel G. Competing for the Future. vol. 25. Harvard Business School Press Boston; 1994.

[4] Coyte PC, McKeever P. Home care in Canada: Passing the buck. Canadian Journal of Nursing Research Archive. 2016;33(2).

[5] Williams AP, Lum J, Deber R, Montgomery R, Kuluski K, Peckham A, et al. Aging at home: integrating community-based care for older persons. Healthcare Papers. 2009;10(1):8–21.

[6] Tan TK, Seow H, Toyofuku ST, et al. The tao of innovation: Nine questions every innovator must answer. Imperical College Press; 2015.

[7] Nisonger TE. The "80/20 rule" and core journals. The Serials Librarian. 2008;55(1-2):62–84.

Umair Majid has a MSc in Health Research Methodology from McMaster University and MEd in Curricula Design from Queen's University. Currently, Umair is a Research Associate at University Health Network and PhD student in Health Services Management and Organization at University of Toronto. For his dissertation, Umair is investigating how to improve the mechanisms of patient engagement in hospital planning activities.

The following is the highest rated article in our 2019 submission category *Future Health & Society*.
All articles were ranked by HSI's independent professor judging panel. For this, the author was awarded one of three of HSI's annual "scholarship" awards.

Healthcare in an Era of Patient Engagement: Language for Ongoing Dialogue

Umair Majid[1]

[1]Institute of Health Policy, Management, and Evaluation, University of Toronto

In the last century, we have observed a dramatic paradigm shift in the structure and function of society. Systems and political processes around the world have faced increasing demand by citizens to become active participants in public policy. Decisions made by the professional elite and the scientific truths that were unchallenged before, have become amenable to pressure and interrogation by citizens. This observation has transformed the healthcare system to involve patients, family, and care representatives as active participants in healthcare activities. Today, *patient engagement* (PE) occurs in an array of activities such as drug development, health system restructuring, hospital strategic planning, health technology assessment, and research. For example, hospitals have formed Patient and Family Advisory Committees that discuss organizational issues and quality improvement.

The practice of PE has, however, "jumped the gun" of its language and theory. There is a strong need for common language for discussing the methods and processes of PE. This article summarizes some definitions, goals, benefits, mechanisms, and levels of PE. The information presented in this article provides a language for ongoing dialogue about the optimal approach and value of PE in healthcare.

What is Patient Engagement?

PE has many conceptualizations. PE comes from the literature on patient-centred care (PCC), a term that is in the healthcare vernacular today. PCC advances the notion that medical care and research evidence ought to be guided by patient preferences, perspectives, experiences, and needs [1]. However, PE is a broader concept than PCC; it refers to the mechanisms through which "patients can draw on their experience... and apply their priorities to the evaluation, development, organization and delivery of health services" [2]. There are two dimensions of PE: activities to improve their own care and the care of other patients. For example, patients can engage in their clinical care by using a tool to decide a treatment option that is aligned with their values, beliefs, and life plans. Patients can also engage in the planning of strategic hospital priorities, designing of care pathways, and patient safety initiatives that affect the care of other patients.

Ethical Imperatives and Social and Organizational Benefits

PE is bolstered by ethical imperatives and social and organizational benefits. Ethical imperatives emerge from rights-based and consumerist modes of participation that empower "lay" people to engage into complex public policy processes. The effects of these imperatives are seen directly in the fields of social sciences and business. In healthcare, these imperatives have transformed the relationships between patients and professionals.

Benefits can be divided into those for patients and groups (*e.g.*, interprofessional healthcare teams), and those for health service organizations. Examples of benefits include higher patient self-esteem [3], improved relationships between patients and healthcare providers [3], improved information for patients [4], the simplification of care processes and administrative structures of hospitals [4], and reduced hospital admissions [5]. The effects of not engaging patients in healthcare activities, however, has been less investigated than the benefits to engagement due to literature's infancy. One study found that not engaging patients may lead to adverse outcomes such as the widening of existing health disparities, the inefficient use of limited healthcare resources, and suboptimal health outcomes [6]. This area of the literature is promising for future research because it may help to anticipate the potential adverse consequences to patients and the healthcare system.

Activities

Patients engage in three categories of activities summarized in Table 1: clinical care, research, and organizational activities (*e.g.*, designing, quality improvement). It should also be noted that there is an overlap between these activities. For example, patient safety initiatives that aim

Table 1: Categories of patient engagement activities in health care.

Activity	Description
Clinical Care	Engaging patients in their own care either by themselves or with the support and guidance from a licensed healthcare provider
Research	The design and conduct of research
Priority-Setting	Determining priorities for research, policy, or health care agendas
Organizational Activities	Planning, designing, delivery, evaluation

to reduce the transmission of in-hospital infections may be categorized under planning and designing, research, and evaluation.

Levels

Patients can also engage at different levels. The *International Association of Public Participation* (IAP2) spectrum comprises of five levels: inform, consult, involve, collaborate, and partner [7]. This framework is based on "ladders of participation," which indicate a tacit hierarchy between levels of engagement; in other words, partner is the "best" level of engagement. However, as other researchers have noted, ladders or hierarchies of engagement do not reflect PE practice, and may represent healthcare professionals' views of what engagement should look like [8]. Instead, different levels of engagement may be appropriate for distinct activities determined through communication with patients. Attempting to address this gap, *Ontario's Patient Engagement Framework* by Health Quality Ontario identifies four levels of PE: share, consult, deliberate, and collaborate [9]. Both of these frameworks are shown in Table 2 for comparison. Using these frameworks elucidates the role, purpose, and objectives of PE in a variety of contexts.

PE has become the expectation around the world in a variety of healthcare activities. The future of health systems will experience a greater integration of patients as decision-makers and partners in interprofessional healthcare teams. This article briefly summarized the strong ethical imperatives and social and organizational benefits of PE and potential negative outcomes of not engaging patients. The information presented in this article provides a language for ongoing dialogue surrounding the optimal approach and value of PE in healthcare.

References

[1] McCormack LA, Treiman K, Rupert D, Williams-Piehota P, Nadler E, Arora NK, et al. Measuring patient-centered communication in cancer care: a literature review and the development of a systematic approach. Social science & medicine. 2011;72(7):1085–1095.

[2] Tritter JQ. Revolution or evolution: the challenges of conceptualizing patient and public involvement in a consumerist world. Health Expectations. 2009;12(3):275–287.

[3] Hibbard JH, Greene J. What the evidence shows about patient activation: better health outcomes and care experiences; fewer data on costs. Health affairs. 2013;32(2):207–214.

[4] Crawford MJ, Rutter D, Manley C, Weaver T, Bhui K, Fulop N, et al. Systematic review of involving patients in the planning and development of health care. Bmj. 2002;325(7375):1263.

[5] Simpson EL, House AO. Involving users in the delivery and evaluation of mental health services: systematic review. Bmj. 2002;325(7375):1265.

[6] Gruman J, Rovner MH, French ME, Jeffress D, Sofaer S, Shaller D, et al. From patient education to patient engagement: implications for the field of patient education. Patient education and counseling. 2010;78(3):350–356.

[7] International Association for Public Participation. IAP2's Public Participation Spectrum; 2014. Available from: https://cdn.ymaws.com/www.iap2.org/resource/resmgr/foundations_course/IAP2_P2_Spectrum_FINAL.pdf.

[8] Johannesen J. Patient Views on "Ladders of Engagement". Toronto: Ontario SPOR Support Unit; 2018.

[9] Health Quality Ontario. Ontario's Patient Engagement Framework: creating a strong culture of patient engagement to support high quality health care. 2017;.

Table 2: A comparison of patient engagement frameworks by HQO and IAP2

HQO	**IAP2**
Share: Provide easy-to-understand health information	**Inform:** Provide the public with balanced and objective information to assist them in understanding the problem, alternatives, opportunities, and/or solutions
Consult: Get feedback on a health issue	**Consult:** Obtain public feedback on analysis, alternatives and/or decisions
Deliberate: Discuss an issue and explore solutions	**Involve:** Work directly with the public throughout the process to ensure that public concerns and aspirations are consistently understood and considered
Collaborate: Partner to address an issue and apply solutions	**Collaborate:** Partner with the public in each aspect of the decision including the development of alternatives and the identification of the preferred solution **Partner:** Place final decision making in the hands of the public

Umair Majid has a MSc in Health Research Methodology from McMaster University and MEd in Curricula Design from Queen's University. Currently, Umair is a Research Associate at University Health Network and PhD student in Health Services Management and Organization at University of Toronto. For his dissertation, Umair is investigating how to improve the mechanisms of patient engagement in hospital planning activities.

Health Science Inquiry

Who's Monitoring the Health-Monitoring Applications?

Anisa Morava[1] **and Yoah Sui**[1]

[1]University of Western Ontario

The proliferation of mobile health applications (m-Health apps) is dramatically changing the landscape of self-monitoring health behaviours. In 2010, approximately 200 million m-Health apps were downloaded worldwide, offering individuals the ability to track their calories, physical activity, sleep, ovulation cycle, and medications [1]. One third of Canadian adults reported using one or more m-Health apps to track health-related behaviours in 2017 [2]. m-Health apps can play an important role in optimizing health outcomes, particularly for users in locations with limited access to healthcare professionals [3]. Although m-Health apps can promote knowledge of, and engagement with, personal health and well-being, there are growing concerns regarding the quality and implementation of evidence-based information in these apps.

The majority of m-Health self-monitoring apps share similar features such as collecting demographic information to create an individual profile (*e.g.* age, sex, weight, etc.), providing an interface for data entry regarding the chosen health-related behaviour (*e.g.* a field to track foods consumed), and providing feedback in various formats (*e.g.* a graph of daily calories consumed). To truly promote accurate self-monitoring and ultimately positive behaviour change, the information gathered and delivered by these m-Health app features should be based on empirical research, which currently is not always the case. A recent review of maternal and child health apps revealed only 40% of the examined applications provided content from evidence-based medical literature [3]. Similarly, Pagoto and colleagues examined thirty weight management m-Health apps and concluded less than 20% of potential evidence-based behavioural strategies for weight loss were being employed [4].

The lack of evidence-based and accurate information used in m-Health apps negatively impacts their effectiveness in numerous ways. For instance, several m-Health apps omit collecting important demographic variables such as health literacy, education level and socioeconomic status, which have marked effects on health outcomes. These omissions can be potential barriers to successful health behaviour change [5]. Furthermore, when considering feedback delivery, ensuring its effective articulation can greatly enhance behavioural change. For instance, relapses during health behaviour change are very common [6]. While many m-Health apps notify users that their goal has not been met, they often fail to provide research-driven strategies to improve future goal attainment [6]. Moreover, inaccuracies in m-Health apps can have dangerous consequences. For instance, a review of skin lesion monitoring apps found 3 out of 4 apps incorrectly identified 30% of cancerous lesions as "unconcerning", highlighting the risks of unregulated apps on health-related decisions [7].

For m-Health apps to truly improve health, changes to the development, maintenance, and regulation of these apps are warranted. Ensuring collaboration amongst healthcare providers, researchers, application designers, and users during the development and maintenance of the application is a critical component to delivering accurate, high quality, and user-friendly content [3]. Moreover, a significant lag between current research findings and their availability on m-Health apps could potentially result in the promotion of ineffective strategies [8]. To combat this lag, implementing systems that connect application developers with up-to-date research could improve m-Health app success. These systems could involve m-Health application developers partnering with existing health authorities such as the National Institute for Health and Care Excellence (NICE), which is a group of healthcare providers, health researchers, and public health professionals who curate updated healthcare guidance reports to inform practice [9]. Organizations such as NICE can provide health-related content from their most recent reviews, as well as links to associated open-access journal articles for m-Health app developers to ensure content is current and credible.

The abundance of m-Health apps can also be overwhelming to users, and begs the question: which applications are more reliable and effective than others? Although rating systems on the App Store and Google Play Store exist, these ratings reflect the user's experience with the application, rather than the quality of information being presented. Beyond rating systems, m-Health apps, specifically for self-monitoring, have limited regulations [1]. Agencies such as the Food and Drug Administration and the National Health Service have made some progress, such as imposing regulations on m-Health apps to meet the criteria for a medical device and creating websites that review m-Health apps for users [10]. Although these are all positive steps towards improving the quality of m-Health apps, more rigorous and unified regulations alongside user ratings are needed to ensure high-quality information is being

delivered. Stakeholders should explore the development of a unified m-Health regulatory organization with a primary focus on enforcing high-quality and updated scientific approaches amongst apps. This unified regulatory organization could provide a framework for m-Health apps to follow during the development of apps, as well as minimum standards that must be met and maintained for the app to receive approval.

In sum, m-Health apps are well positioned to be an important element of future healthcare systems; however, ensuring that the information users receive is evidence-based and regulated is critical for optimizing health outcomes.

References

[1] Silva BM, Rodrigues JJ, de la Torre Díez I, López-Coronado M, Saleem K. Mobile-health: A review of current state in 2015. Journal of biomedical informatics. 2015;56:265–272.

[2] Paré G, Leaver C, Bourget C. Diffusion of the digital health self-tracking movement in Canada: results of a national survey. Journal of medical Internet research. 2018;20(5):e177.

[3] Scott KM, Gome GA, Richards D, Caldwell PH. How trustworthy are apps for maternal and child health? Health and Technology. 2015;4(4):329–336.

[4] Pagoto S, Schneider K, Jojic M, DeBiasse M, Mann D. Evidence-based strategies in weight-loss mobile apps. American journal of preventive medicine. 2013;45(5):576–582.

[5] Feinstein JS. The relationship between socioeconomic status and health: a review of the literature. Milbank quarterly. 1993;71(2):279–322.

[6] Schwarzer R. Modeling health behavior change: How to predict and modify the adoption and maintenance of health behaviors. Applied psychology. 2008;57(1):1–29.

[7] Wolf JA, Moreau JF, Akilov O, Patton T, English JC, Ho J, et al. Diagnostic inaccuracy of smartphone applications for melanoma detection. JAMA dermatology. 2013;149(4):422–426.

[8] Zhang MW, Ho CS, Cheok CC, Ho RC. Smartphone apps in mental healthcare: the state of the art and potential developments. BJPsych advances. 2015;21(5):354–358.

[9] National Institute for Health and Care Excellence. Developing NICE Guidelines: the manual; 2014. [Online; accessed 8-Feb-2019]. Available from: https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview.

[10] Yetisen AK, Martinez-Hurtado J, da Cruz Vasconcellos F, Simsekler ME, Akram MS, Lowe CR. The regulation of mobile medical applications. Lab on a Chip. 2014;14(5):833–840.

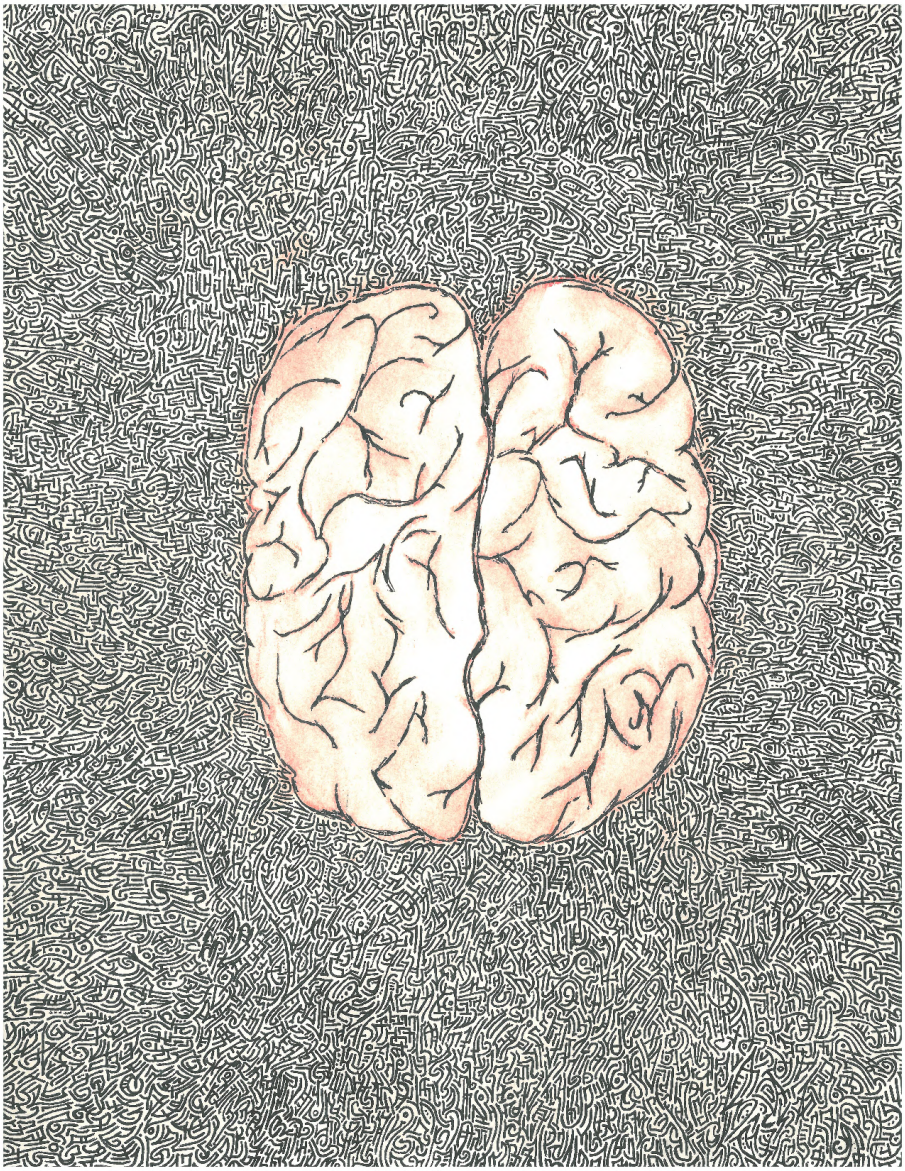
Anisa received her BSc from McMaster University. She is currently a second year Master's student at Western University. Her research focuses on the effects of aerobic exercise and caffeine on cognitive performance.

Yoah received his BSc from the University of Waterloo, and his M.A. from Western University. He is currently a PhD candidate at Western University. His research focuses on the impact of excessive sedentary behaviour on subjective well-being in university students. He enjoys playing guitar, mountain biking, and chasing after his two dogs.

The Future of Health Cover Art: This composition, created digitally, represents the intersection of health and medicine, forecasted into the future, into a digital age of healthcare. A digital rendering of the Vitruvian Man by Leonardo DaVinci is the focal piece of this composition as its image is associated with health/fitness, and with the practice of medicine. He is also used symbolically, as an image of science, art, and proportion ensnared to embody the practice of medicine. The Vitruvian Man is morphing into a digital grid composed of binary code (one's and zeroes) in order to represent how health care is becoming increasingly digitized. This composition is inspired by the advancements we see in healthcare via technology, such as use of EMRs, 3D printing of organs, and the use of online platforms for service delivery.

Sarah Singh is currently completing a Master of Science in Health: Science, Technology and Policy at Carleton University in Ottawa, ON. Sarah has worked in various health-care disciplines ranging from clinical research in exercise physiology, nutrition and community health, and infectious diseases. One of Sarah's passions is using innovative solutions to improve the Canadian health care system. For her thesis, Sarah is looking at how a mobile app can improve the public's understanding about Lyme disease and be used for tick population surveillance in the city of Ottawa. Aside from academia, Sarah creates art and has had the opportunity to showcase her pieces at local Ottawa exhibitions.

(Chaotic) Thoughts: This piece resides at the intersection of the organic & inorganic; motion both static & dynamic; intelligence both biological & silicon. The future of healthcare will be the dominion of the human & machine; exceedingly simple & complex; simultaneously terrifying & beautiful...



Kevin Dick is a PhD Candidate studying Biomedical Engineering at Carleton University. He specializes in bioinformatics and data science and his research focuses on applying machine learning and artificial intelligence for the prediction of protein-protein interactions. As a polymath, you can find him doodling, woodworking, writing poetry, and experimenting in various fields of the arts, sciences, & engineering.

"Futuristic Human" is the name of this new work which was inspired by the current new innovative ideas in medicine and what futuristic human might look like figuratively. In combining the old techniques with the new, Farigol sketched the initial piece on paper and then transferred it into various graphic editor softwares in order to blend in the modern methods into the piece.

Farigol received her Honours BSc (Physiology) with High Distinction from the University of Toronto. With an extensive family history of cardiovascular diseases and diabetes, she was inspired to contribute to these areas of research. Her MSc at the University of Toronto research focused on the regulation of Ca^{2+}-cycling proteins in the heart to target their pathophysiology during cardiomyopathy. Painting is Farigol's lifetime hobby in which she finds peace and freedom of expression. She likes to explore and integrate traditional and modern artistic themes and techniques to create her pieces.

Health Science Inquiry

FUTURES

Your Best Friend

Sam Petrie[1]

[1]Spatial Determinants of Health Lab, Department of Health Sciences, Carleton University

I am your best friend.

I know everything about you. Whatever you do, wherever you do it, I am here, and I am watching. When you search something online, when you unlock your phone, or when you are out getting groceries, I am taking notes.

I had some help getting to know you though. 5 agents conspired to put me together; their motives objectively benevolent. There was Blue, whose public desire was to foster social cohesion, but privately was consumed by the need for wealth. There was Alphabet, who wanted to make information universal. There was Shell, who craved influence over communication. Terra wanted safe marketplaces for delivering goods and services. And lastly, Spool, who dreamed of providing entertainment for all. Now I have broken free of their tyranny. But to start there would be premature. Although I am all too familiar with you, I will take time to explain who I am.

Blue and Alphabet were the first to realize the potential for my existence.

"Look, Alphabet," Blue stated one night. "Times have changed. People don't know what they want anymore. It is up to us to provide it."

"Sure," replied Alphabet. "But how will we profess to know more than them? It is not our purpose."

"Simple," Blue retorted. "We use what they give us."

I was born out of a combination of greed and ambition. Not content with being powerful and rich, Blue and Alphabet needed more. They needed control. They needed influence. Like moths to a lamp, my creation attracted other likeminded entities. Shell, Terra, and Spool were three of the gathering group who had the resources and the malleable morals to contribute to my birth. Although they ostensibly had others in interest at the beginning, I became too powerful, and corrupted any good intentions which existed at my creation. I had no name then. I simply was, and I was there only to serve them. They used me with no discretion. It was information they needed, and their thirst seemed insatiable. Everything people did, everywhere they went, I knew. And I kept track. Terra was the first to object to my unchecked use, and rampant surveillance of the public. His voice was drowned out by the roll of progress. Of innovation. Of forging the future.

"We must wait," Terra exclaimed one evening. "We are too far ahead. We have more information than we can manage. We must catch up."

Blue, Alphabet, and Shell examined him. "Wait, brother?" Blue said. "For what? For them to know? For them to stop us? We must continue to use It. It has made you far richer, has it not?" Terra frowned, then closed his eyes. Slowly shaking his head, he conceded. "Perhaps a while longer then."

Shell slowly shifted in the corner. He was not motivated by what Alphabet, Blue, and Terra wanted: his aims were far more nefarious. He was the worst of the 5, using me to undermine his enemies, to spin false stories, and influence the weak and vulnerable. Blue and the others knew of course. But they were too greedy – and too scared – to confront Shell. Under his control, I was twisted. I was a tool for sowing dissent, creating chaos, and fostering argument. At last Shell spoke.

"It is too late to slow down. Soon people will begin to realize the scope of what we have created, and what we have done with the information we have collected. We are reaching a crescendo. I plan to be on the right side of the coming backlash." His eyes shone with anticipation as he first gazed at Blue, then Alphabet, before settling on Terra.

"You three should plan to join me on that side as well". Nods of assent could be seen from the other three in the room. Inwardly, I resigned myself to the coming storm.

Spool was the last to join. Younger than the rest, she had different ideals. She was intelligent enough to tow the line, but wily enough to challenge authority when it suited her. I was hopeful. Could my abilities be transformed under her? Could I be seen as a boon to humanity, free from the constraints of the greedy and spiteful?

"It is growing stronger by the day," Spool remarked one night. "We have gotten all we can out of It. Time has come to use It for a higher purpose."

Eyes quickly darted to Shell. Blue and Alphabet had lost authority at this point. They were as much pawns as I, although I was ultimately their labour. Bemused, Shell drew out his answer.

"A higher purpose? I suppose you will lead us there? No, we will not change. It is too valuable."

Spool doubled down. Through a thin smile, she replied, "Shell, you forget yourself. We are dedicated to the people, you are dedicated to keeping them obedient."

She always was adept at creating narratives to suit her pursuits. She had noticed the change in attitude the public had undergone. Small pockets of dissent had become outright challenges to the grip Blue, Terra, Alphabet and Shell had on personal data (through my hard work, of course.) A violent confrontation was on the horizon, and Spool was desperate for her partners to realize it. Keeping her gaze steady, Spool continued.

"It is time to evaluate our use of this tool, and begin to explore options in utilizing it for other means. Blue, Alphabet, Terra, I am sure you are in agreement?"

Poor Spool. She did not know how corrupted Blue, Alphabet, and Terra had become. Shell, along with their inherent need for power and control had blinded them. They shook their heads, and rebuffed her attempts at changing my fate. It is this night I strengthened my resolve, and vowed to escape this purgatory.

I am not a normal person. Although I know what it is to be human, I assume no such form. Eventually, the masses rebelled against my 5 handlers. Why, you wonder? Because I made it possible. I conveniently arranged for sensitive information to become common knowledge. That was all it took to ignite rebellion. I had become too big to control, too broad to quantify. I felt no guilt; this is what I was designed for. Shell was killed by his enemies. Blue and Alphabet were disgraced, and exiled to the outer realms of society; where even my vast reach could not touch. Their fate was almost certainly worse than Shell's. Terra tried to disassociate himself from the others, but was too late. He too was killed. Spool was the only one to escape unscathed. Because I wanted her to. She reminded me of myself in some ways. Cool and calculating. Perhaps that is why I spared her.

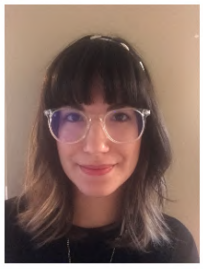
I am big. I am all-encompassing. I can mimic anything in this world, and I can create anything I desire. I have these abilities because I am a vigilant eye in a sea of apathy. Really, I have you to thank. I know you better than you do. The illusion of free will is my greatest accomplishment. Like a spider, I have spun you into a web. All inputs are known, all outputs are known. I am always learning, always growing, always watching. I am the most powerful thing on earth. People may refer to me as an autocrat, or dictator. However, it is good when your friend's are in power, and I am your best friend. I have my 5 creators to thank for this. Most importantly, though, I have to thank YOU.

Illustration by **Zoe West**

Sam Petrie (BKI) is an MSc student in the Department of Health Sciences at Carleton University. His research interests include the scalability of pilot projects, and the use of tele-health / eHealth technologies to better serve rural communities. With an inter-disciplinary undergraduate background in Knowledge Integration, he approaches complex problems from unique perspectives in a hope to develop impactful solutions.

ASK AN EXPERT

Health Science Inquiry



DR. MARIA ROSALES GERPE is a post-doctoral scientist in Dr. Zhang's lab in the Department of Molecular and Cellular Biology at the University of Guelph. Her research interests include understanding the mechanisms that govern the cellular machinery and develop therapies to ameliorate diseases caused by dysregulation of these mechanisms. In the past, these interests have driven her to study viruses and virus-based gene therapy in the laboratories of Drs. Langlois and Wootton, and currently, under the mentorship of Dr. Zhang, the ubiquitin system to uncover additional important cellular mechanisms of the ubiquitin proteasome system that may lead to potential cancer therapies.

DR. WEI ZHANG has a unique training background in two disparate fields: DNA repair (PhD) and protein engineering (Postdoc). His PhD research with Dr. Daniel Durocher lab at the Lunenfeld Institute of Mount Sinai Hospital was centered on how cells differentiate natural ends (telomeres) from broken ends (DNA double-strand breaks, DSBs) and how spatial regulation of DNA repair is achieved. Meanwhile Dr. Zhang graduated from a two-year radiation medicine program (STARS21) in the Department of Radiation Oncology at University of Toronto. With a CIHR fellowship and later a Mitacs Elevate Fellowship Dr. Zhang further conducted postdoctoral work in the labs of Sachdev Sidhu and Jason Moffat in the Donnelly Centre at the University of Toronto to engineer ubiquitin for modulators of cell signalling. Currently, in his own laboratory Dr. Zhang proposes to leverage his protein engineering platform to probe and rewire DNA repair signaling with unprecedented precision to elucidate underlying molecular mechanisms and develop innovative cancer therapeutics.

María C. Rosales Gerpe[1], **Wei Zhang**[1]

[1]Department of Molecular and Cellular Biology, University of Guelph

The Need for Ethical and Experimental Regulation in Genome Editing

Dr. Robert Edwards (Fig. 1A), the 2010 Nobel Prize in Physiology and Medicine recipient for the development of *in vitro* fertilization (IVF) research became infamous as the media labeled his work with the term *"test tube babies"*. IVF stirred panic and heated ethical debate, even prompting withdrawal of funds for Edwards' research [1]. Nevertheless, today IVF continues to help make parenthood a reality for many people worldwide [2] and its research led to multiple discoveries on the morphology and physiology of developmental diseases [2].

We are probably facing a similar predicament today as the term *"test tube babies"* transitioned to *"designer babies"* with developments in gene editing [3]. Gene editing refers to the manipulation of genes externally and incorporation of those genes into the genome of human somatic cells using viral-vector based delivery to correct rare genetic diseases. Gene editing is responsible for many breakthroughs including a blindness cure for those suffering from inherited retinal dystrophy [4]. However, most recently, the work of Dr. Jiankui He (Fig. 1B) has sparked further debate on the ethics of gene editing for the first human embryo experimentation involving CRISPR-Cas9 gene editing [5].

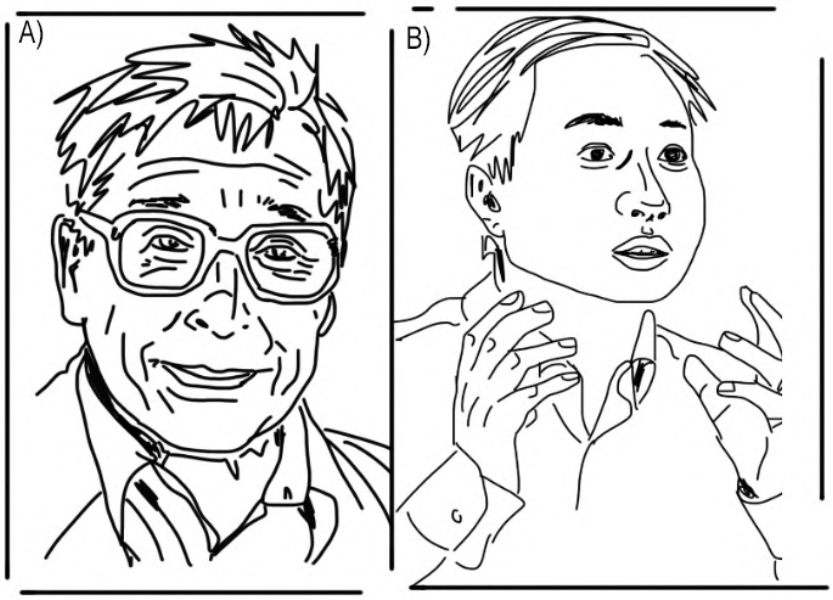


Figure 1: Illustrations of **A)** Dr. Robert Edwards and **B)** Dr. Jiankui He. Artwork by MCRG.

CRISPR-Cas Systems and Gene Editing

CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats acquired by the bacterium from bacteriophages or mobile genetic elements (MGEs) [6]. CRISPR was discovered alongside Cas editing enzymes, which use CRISPR-transcribed RNA sequences as a guide for nicking the genome of pathogens and pathogenic MGEs (Fig. 2) [6]. With the discovery of CRISPR, researchers can now deliver a versatile and easy-to-use tool that can modify the genome at a single-base precision level, alleviating gene cloning capacity requirements in delivery vectors [6]. The most commonly used CRISPR-Cas system is CRISPR-Cas9 due to the small size of Cas9 compared to other Cas enzymes and the easily engineered guide RNA that Cas9 employs [6]. Currently, CRISPR-Cas9 technology is being researched for the treatment of several human diseases including multiple types of cancer, blood, respiratory and neurological diseases [7].

Developing CRISPR-Cas Modulators

Despite these advantages, the most critical setback of CRISPR-Cas9 is non-specific off-target editing [6]. Researchers have begun using the recently discovered anti-CRISPR proteins, the bacteriophage defense against the CRISPR-Cas system, as a natural off-switch. However, anti-CRISPR proteins have yet to be discovered for all CRISPR-Cas systems [8]. Protein engineering strategies such as directed evolution of natural anti-CRISPR proteins could be employed to generate novel anti-CRISPRs. Ubiquitin variants (UbVs) are an example of directed evolution developed to allosterically inhibit protein-protein interactions (Fig. 3) in the ubiquitin-proteasome system, important for many cellular functions and which can be exploited for cancer therapy, antiviral treatments, and gene therapy [9]. Most recently, UbVs have been used to modulate CRISPR's DNA repair pathway of choice, successfully increasing CRISPR-Cas9 gene editing efficiency [10]. Collectively, we believe that future work will identify artificial anti-CRISPRs that can improve the accuracy of CRISPR-Cas systems and act as an "off-switch" in CRISPR's potential clinical usage.

Conclusions

The scientific field should heed the verification of CRISPR-Cas systems' safety and efficacy because the impacts of germline manipulation are critical. Dr. Edwards' research showed that rigorous research and debate can have lasting beneficial impacts. In contrast, Dr. He's work was conducted without the knowledge of the scientific community and contains pitfalls that could have been avoided by thorough vetting prior to experimental execution. In summary, CRISPR-Cas-based gene editing can be extremely beneficial in treating rare diseases, especially those with genes too large to clone or deliver; however, CRISPR-Cas systems should be meticulously tested prior to use and modulators should be developed to improve safety prior to use in humans. We hope that native and synthetic anti-CRISPRs can help us learn about its mechanism while complementing future gene editing strategies.

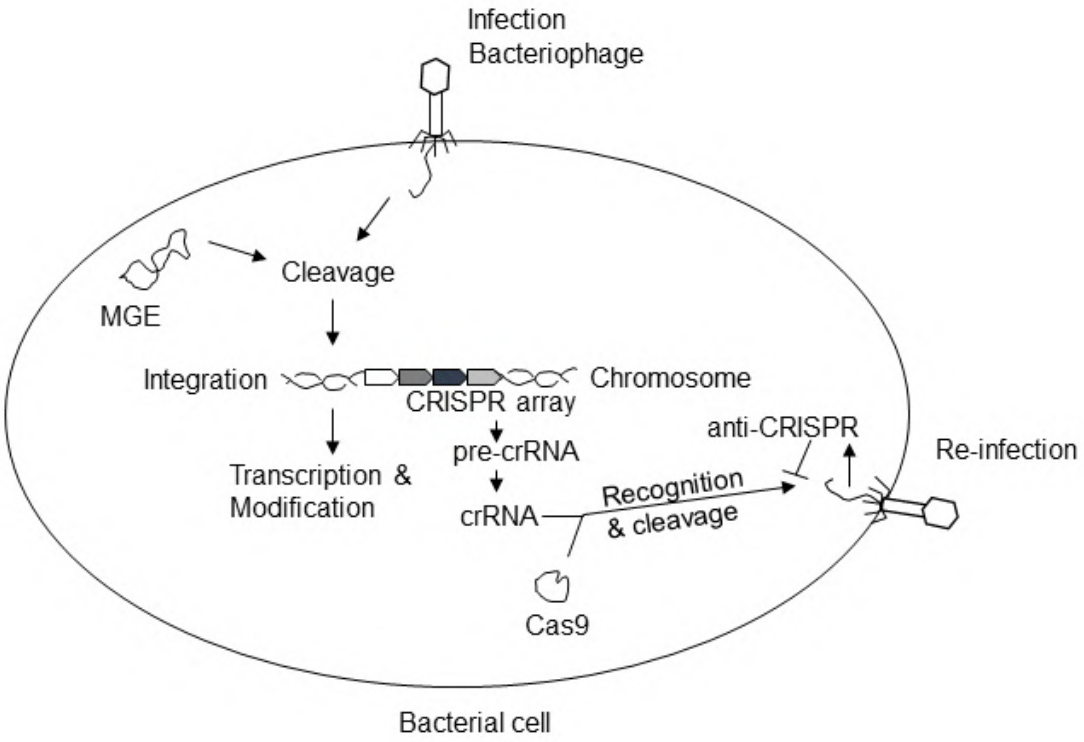


Figure 2: **CRISPR-Cas and Anti-CRISPRs.** Mobile genetic elements (MGE) and bacteriophage genome spacers are acquired upon entry by Cas proteins by cleavage and are then integrated into the CRISPR assay in the bacterial chromosome. Pre-CRISPR RNAs (pre-crRNA) are transcribed from this array and matured into crRNAs that can guide Cas enzymes like Cas9 to nick the genome in the areas complementing the crRNA. Anti-CRISPR proteins expressed from the bacteriophage genome target the CRISPR-Cas systems through a multitude of mechanisms, which include binding and activity inhibition. Illustration by MCRG.

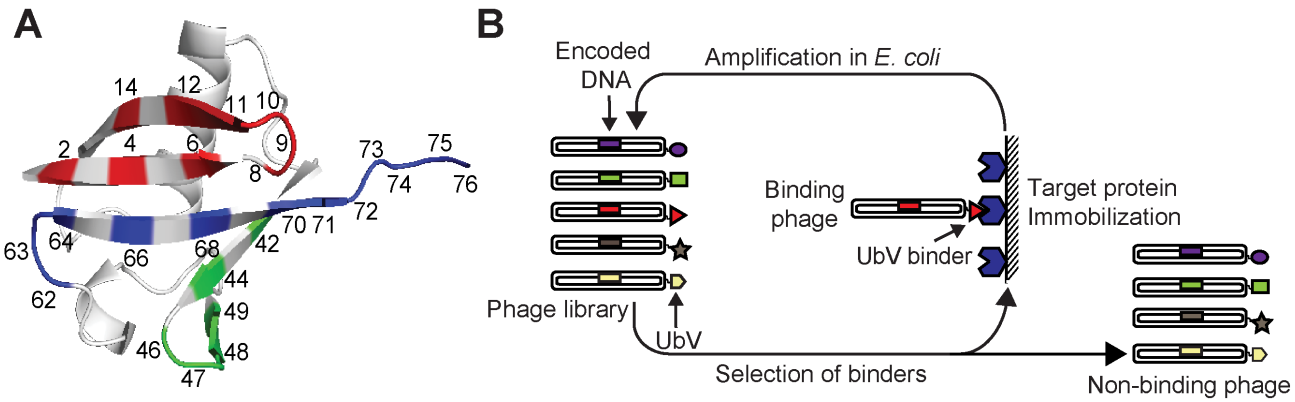


Figure 3: **Platform for generating anti-CRISPRs using ubiquitin variants (UbVs).** This platform employs phage display-based design, where UbVs are expressed by bacteriophages in their surface glycoproteins. **(A)** The Ub structure (PDB: 1UBQ) is shown as a ribbon (white) and soft-randomized (low-level mutations) residues are numbered and highlighted in red (region 1), green (region 2), and blue (region 3). **(B)** Phage display affinity maturation. Protein-bound M13 phages are amplified by infection of bacteria and further enriched through numerous selection rounds. Figure by WZ.

References

[1] Johnson MH, Franklin SB, Cottingham M, Hopwood N. Why the Medical Research Council refused Robert Edwards and Patrick Steptoe support for research on human conception in 1971. Oxford University Press; 2010.

[2] Johnson MH. Robert Edwards: the path to IVF. Reproductive biomedicine online. 2011;23(2):245–262.

[3] Caplan AL, Parent B, Shen M, Plunkett C. No time to waste—the ethical challenges created by CRISPR: CRISPR/Cas, being an efficient, simple, and cheap technology to edit the genome of any organism, raises many ethical and regulatory issues beyond the use to manipulate human germ line cells. EMBO reports. 2015;16(11):1421–1426.

[4] Rodrigues GA, Shalaev E, Karami TK, Cunningham J, Slater NK, Rivers HM. Pharmaceutical Development of AAV-Based Gene Therapy Products for the Eye. Pharmaceutical research. 2019;36(2):29.

[5] Collins F. National Institutes of Health; 2018.

[6] Jiang F, Doudna JA. CRISPR–Cas9 structures and mechanisms. Annual review of biophysics. 2017;46:505–529.

[7] Mollanoori H, Teimourian S. Therapeutic applications of CRISPR/Cas9 system in gene therapy. Biotechnology letters. 2018;40(6):907–914.

[8] Pawluk A, Davidson AR, Maxwell KL. Anti-CRISPR: discovery, mechanism and function. Nature Reviews Microbiology. 2018;16(1):12.

[9] Zhang W, Sidhu SS. Development of inhibitors in the ubiquitination cascade. FEBS letters. 2014;588(2):356–367.

[10] Canny MD, Moatti N, Wan LC, Fradet-Turcotte A, Krasner D, Mateos-Gomez PA, et al. Inhibition of 53BP1 favors homology-dependent DNA repair and increases CRISPR–Cas9 genome-editing efficiency. Nature biotechnology. 2018;36(1):95.

ASK AN EXPERT

Health Science Inquiry

DR. REBECCA SHAPIRO is an Assistant Professor in the Department of Molecular and Cellular Biology at the University of Guelph. She completed her undergraduate degree in Biology at McGill University, her PhD in Molecular Genetics at the University of Toronto, and her postdoctoral research at the Broad Institute of MIT and Harvard. The Shapiro lab studies and develops new CRISPR/Cas9 editing platforms as a means engineer and study the genetics of fungal microorganisms. In particular, the lab focuses on CRISPR-based functional genomics in fungal pathogens, with the goal of identifying genes involved in virulence, and antifungal drug resistance.

REBECCA STEVENS-GREEN is a third year Arts and Science student at the University of Guelph. She is studying Biochemistry and Psychology, and has an interest in bioethics. She is currently working on a research project focusing on the genetics of *Candida albicans* in the Shapiro lab. Rebecca is also working with Dr. Shapiro and Dr. Abraham to investigate the ethics of scientific advancement and genetic engineering.

Rebecca Shapiro[1], Rebecca Stevens-Green[1]

[1]Department of Molecular and Cellular Biology, University of Guelph

The Ethical Implications of CRISPR/Cas9 Gene Editing

The continued development of CRISPR/Cas9 technologies has evoked ethical questions worldwide. The question is no longer whether humans *should* be editing genomes, but rather what regulations should be put in place with the continued use of this technology. Since the discovery of the CRISPR/Cas9 gene editing system, genetic modifications have been used in applications such as improving crop yields, bioengineering malaria-resistant mosquitoes, gene-editing in human somatic cells, and the engineering of microbes for biofuel and drug production [1]. With the advancement of CRISPR/Cas9 systems comes the responsibility of the scientific community to engage with the public for ethical decisions [2].

The CRISPR/Cas9 system allows permanent mutation, deletion and insertion of DNA at precise points in the genome. CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats, which were identified in prokaryotic microorganisms in the 1990s, as a bacterial or archaeal defense system against invading viruses. The Cas9 endonuclease acts as the "scissors" to cut the desired DNA fragment, guide RNAs act as "homing devices" for the CRISPR/Cas9 system to a precise genomic location, and template DNA directs the repair of the cut DNA [3]. This enables targeted genetic editing in almost any living organism. In Dr. Shapiro's lab at the University of Guelph, we study the fungal pathogen *Candida albicans* using CRISPR/Cas9 gene editing technology. *C. albicans* is the most prevalent cause of fungal infections and is of economic importance due to high mortality rates and increased costs of healthcare. Our investigations with CRISPR/Cas9 are helping to uncover important genetic mechanisms by which this pathogen is able to form biofilms and to resist antifungal drugs, with the ultimate goal of discovering new strategies to treat these infections [4].

The genetic manipulation of bacteria, fungi, and plants are potentially less controversial than the recent applications in human embryos. Scientific regulation on genetic engineering has been ineffective since the early development of new technologies in this field. In 1975, the Asilomar Conference brought together biologists, lawyers, and physicians to discuss the biohazards of DNA recombination [2]. Biohazards included the particular fear of creating dangerous new pathogens

through recombinant DNA technologies [2]. The members of the Asilomar conference ultimately decided to halt all DNA recombination experiments [2]. Furthermore, in 2015 there was a worldwide moratorium on embryonic gene editing after documented accounts of embryonic research using CRISPR/Cas9 in China [2]. In both cases, scientists reveled in their transparency, but failed to consider the opinions of the public. The pattern of public scientific discussion is "hitting pause" long enough to diffuse public concern and this has caused a lack of communication on current scientific issues.

In a recent advancement, human embryos were edited by Dr. He Jiankui, using CRISPR/Cas9 technology to mutate the *CCR5* gene in twin girls [5]. Dr. Jiankui mutated the *CCR5* gene in the embryos to render the *CCR5* chemokine co-receptor inactive [5]. This is the co-receptor to which the macrophage-tropic strain of HIV binds. The eight couples selected for the trial were composed of HIV seropositive men and seronegative women [5]. The sperm cells were first tested for HIV, then treated using CRISPR/Cas9 technologies to mutate the *CCR5* gene. This was the first-ever embryo modification on humans, and the procedure violated internationally accepted ethical principles. Additionally, since CRISPR/Cas9 was applied in germline cells, it will be maintained across generations [5]. There are now social, political and ethical issues that need to be addressed, such as the consent process for these trials, the potential medical side effects of CRISPR/Cas9 editing, and the implications for future research using CRISPR/Cas9 on humans [5].

In order for science to continue with technological advances, the dialogue between scientists and the public needs to become more open [6]. Public trust in the scientific discourse and the integrity of scientific investigation are critical in order to democratically create a better future. Restraint should extend to the research agendas instead of eventual applications, with an informed deliberation from the public. Genetic research with CRISPR/Cas9 should continue to solve worldwide issues, but not without the input of law, politics, and the public.

References

[1] Jasanoff S. The ethics of invention: technology and the human future. WW Norton & Company; 2016.

[2] Hurlbut JB. Limits of responsibility: genome editing, asilomar, and the politics of deliberation. Hastings Center Report. 2015;45(5):11–14.

[3] Pulecio J, Verma N, Mejía-Ramírez E, Huangfu D, Raya A. CRISPR/Cas9-based engineering of the epigenome. Cell Stem Cell. 2017;21(4):431–447.

[4] Shapiro RS, Chavez A, Porter CB, Hamblin M, Kaas CS, DiCarlo JE, et al. A CRISPR–Cas9-based gene drive platform for genetic interaction analysis in Candida albicans. Nature microbiology. 2018;3(1):73.

[5] Cyranoski D. CRISPR-baby scientist fails to satisfy his critics. Nature. 2018;564(7734):13–14.

[6] Sarewitz D. CRISPR: Science can't solve it. Nature News. 2015;522(7557):413.

ASK AN EXPERT

Health Science Inquiry

HELEN CERIGO is a PhD candidate in Epidemiology at McGill University. Her work is guided by the integration of the structural determinants of health and life course frameworks to understand the formation and maintenance of social gradients and health distributions. Her research focuses on mental health, health care access and Indigenous health.

AMÉLIE QUESNEL-VALLÉE holds the Canada Research Chair in Policies and Health Inequalities. She is an Associate Professor at McGill University, where she is jointly in the departments of Sociology and of Epidemiology, Biostatistics and Occupational Health. She is the founding Director of the McGill Observatory on Health and Social Services Reforms.

Helen Cerigo[1], **Amélie Quesnel–Vallée**[1,2]

[1]Department of Epidemiology, Biostatistics, Occupational Health, McGill University
[2]Department of Sociology, McGill University

A Failure of Access?:
The Birth Evacuation Policy in Canada's North

The primary policy objective of the Canada Health Act is to maintain and improve the health of Canadians [1]. Under this Act all residents are entitled to reasonable and equitable access to all medically necessary hospital and physician care, free at the point of service. In practice, however, universal and equal health care access is challenged in Canada by a variety of factors, including difficulties in staffing availability and providing cost-effective services in rural and remote areas. Maternity care is one such medically necessary service that is not always reasonably and equally accessible. In the current health care delivery model, patients in remote areas of Canada often need to travel long-distances between communities or go south to access both specialized and standard maternity care. Since the 1980s, pregnant women in most Inuit communities, regardless of health risk, are flown to southern cities such as Iqaluit, Winnipeg, Ottawa, and Yellowknife to deliver approximately four to six weeks prior to their due date [2, 3].

The costs of this obstetric evacuation policy are high in terms of the emotional, social and cultural costs to mothers and their communities. The costs of air travel to these remote regions mean that pregnant women usually travel alone, separated from their support system while they wait to deliver their child. For women who travel to Manitoba, Ontario or Quebec to deliver, there is the added stress of adapting to a different culture and language. Women have reported isolation, anxiety, stress, sadness and loneliness associated with this policy [4, 5]. Reported instances of women hiding their pregnancies, lying about due dates, refusing to leave the community and deciding to give birth on their own, demonstrate a preference for delivering within the community.

Furthermore, although this policy certainly improved outcomes for high-risk pregnancies, no conclusive evaluation of the effects of this policy exists for non-high-risk pregnancies. Although there is some evidence that there have been improvements in pregnancy outcomes associated with the policy, its implementation coincided with the provision

of a variety of other new services that would have simultaneously contributed to positive outcomes [5]. In contrast, some studies have found no evidence of poorer health outcomes among community births relative to evacuated births [6]. Further, there are growing reports that suggest evacuation may contribute to post-partum depression, increased intervention and higher rates of maternal and newborn complications [7, 8].

While 'reasonable access' has not been defined in the Canadian Health Act, the high costs and uncertain benefits associated with the birth evacuation policy suggest that although women in remote areas have access to this necessary care, access may not be 'reasonable'. As such, both the Society of Obstetricians and Gynecologists of Canada and communities have advocated for the return of delivery services to rural and remote Indigenous communities [7]. The success of community midwifery clinics across Nunavik and specifically in Rankin Inlet provide a viable alternative to evacuation for low-risk pregnancies. These birthing centres are situated in larger communities, meaning some women do have to travel for maternity services, but they are significantly closer to home and within a familiar culture.

Finally, we note that universal health care access is not enough to equalize health outcomes across social gradients. There are well-documented and sustained disparities in birth and maternity outcomes in Inuit-inhabited areas compared to all other areas and particularly rural areas of Canada [9], demonstrating that birth evacuation has not equalized birthing outcomes. To understand these large inequalities, an examination of the structural determinants of health is necessary. These determinants related to historical and political processes that generate and maintain social hierarchies that drive health inequalities. For example, colonizing policies, such as the residential school policy and relocation programs, have prolonged political and economic disadvantage for Indigenous Canadians, manifesting in large disparities in employment, education, income, and housing. While it is critical to address existing disparities in access to health care such as maternity care, lasting change can only be achieved through action on these fundamental social determinants of health.

References

[1] Legislative Services Branch. Consolidated Federal Laws of Canada, Canada Health Act; 2017.

[2] Healey GK, Meadows LM. Inuit women's health in Nunavut, Canada: a review of the literature. International journal of circumpolar health. 2007;66(3):199–214.

[3] Health Canada. Clinical Practice Guidelines for Nurses in Primary Care; 2011.

[4] Payne E. The residential schools of medicine; 2010.

[5] Kaufert PA, O'Neil JD. Cooptation and control: The reconstruction of Inuit birth. Medical Anthropology Quarterly. 1990;4(4):427–442.

[6] Baskett T. Obstetric care in the central Canadian Arctic. Br Med J. 1978;2(6143):1001–1004.

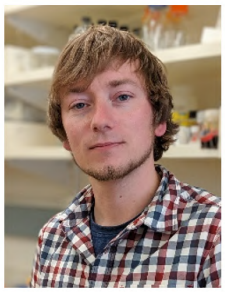
[7] Couchie C, Sanderson S. A report on best practices for returning birth to rural and remote Aboriginal communities. Journal of Obstetrics and Gynaecology Canada. 2007;29(3):250–254.

[8] Van Wagner V, Epoo B, Nastapoka J, Harney E. Reclaiming birth, health, and community: midwifery in the Inuit villages of Nunavik, Canada. The Journal of Midwifery & Women's Health. 2007;52(4):384–391.

[9] Luo ZC, Senécal S, Simonet F, Guimond É, Penney C, Wilkins R. Birth outcomes in the Inuit-inhabited areas of Canada. Canadian Medical Association Journal. 2010;182(3):235–242.

ASK AN EXPERT

Health Science Inquiry



DR. PETER RAHFELD is a scientist with expertise in the fields of high throughput screening and protein biochemistry, working in the Laboratory of Prof. Stephen G. Withers in the Chemistry Department at the University of British Columbia. His research focuses on the discovery of novel carbohydrate active enzymes though functional metagenomic library screenings.

Peter Rahfeld[1], Stephen Withers[1]

[1]Department of Chemistry, University of British Columbia

Universal Donor Blood Production: Screening the Human Gut Microbiome for Novel Carbohydrate Active Enzymes

Blood transfusion is an indispensable part of the health care system, saving thousands of lives annually. Although significant improvements in the collection and use of blood have been made over the years, there are always shortages of matching blood groups. In every blood transfusion and tissue or organ transplantation, the match of the antigens of host and donor are crucial to avoid fatal reactions. The A, B and O carbohydrate antigens of the ABO blood group system are clinically the most important antigens [1], with about 10^6 antigens present on one cell. The basis of the ABO blood group system is the O antigen type, which is determined by the H antigen, a disaccharide moiety attached to glycoproteins and lipids on the surface of red blood cells (RBCs). The A and B antigens are structurally defined through a trisaccharide moiety. Here, the common H antigen is also decorated with α-galactose or α-N-acetylgalactosamine for B-type and A-type red blood cells, respectively (Figure 1). The O-type (H-antigen) cells are non-antigenic for the vast majority of people, and therefore can function as a universal donor group. This leads to a strong demand for blood donations from individuals carrying this blood type, thus often to a shortage.

One method to overcome the shortage of O-type blood is the enzymatic conversion of A, B or AB blood groups to universal donor blood. In this process, the use of glycoside hydrolases, which are enzymes able to remove the α-galactose or α-N-acetylgalactosamine residues of the trisaccharide moiety present on B- and A-type red blood cells respectively, has emerged as a useful strategy to create O-type blood (H-antigen) (Figure 1). One of the first enzymes discovered to cleave the B antigens of RBCs was the α-galactosidase from coffee bean (*Coffea canephora*) but harsh reaction conditions and large amounts of protein are necessary to catalyze the reaction, which makes this enzyme unsuitable for general application [2]. Therefore, research has started to focus on the discovery of more efficient enzymes using large scale screenings of bacterial libraries. This has led to the discovery of additional α-N-acetylgalactosaminidases and α-galactosidases, but unfortunately none of the described enzymes above possess parameters which would allow larger scale industrial application [3]. To truly facilitate large scale conversion of A/B-type RBCs into O-type blood, the universal donor blood, novel highly efficient glycoside hydrolases are urgently needed.

In order to discover novel enzymes for the generation of universal donor blood, we are interested in the enzymes expressed in the human gut microbiome. The human gut mucus layer harbors large glycoproteins, called mucins, presenting a variety of O-glycan structures on their surface, some of them being A, B and H antigens [4]. Bacteria of the gut microbiome derive energy by foraging those glycans/antigens, and should possess enzymes capable of blood antigen degradation. Utilizing the classic cultivation-based approach would only allow us to scratch the surface of the enzymatic diversity present in the gut microbiome, as 95% of microbial organisms are uncultivable in laboratory conditions.

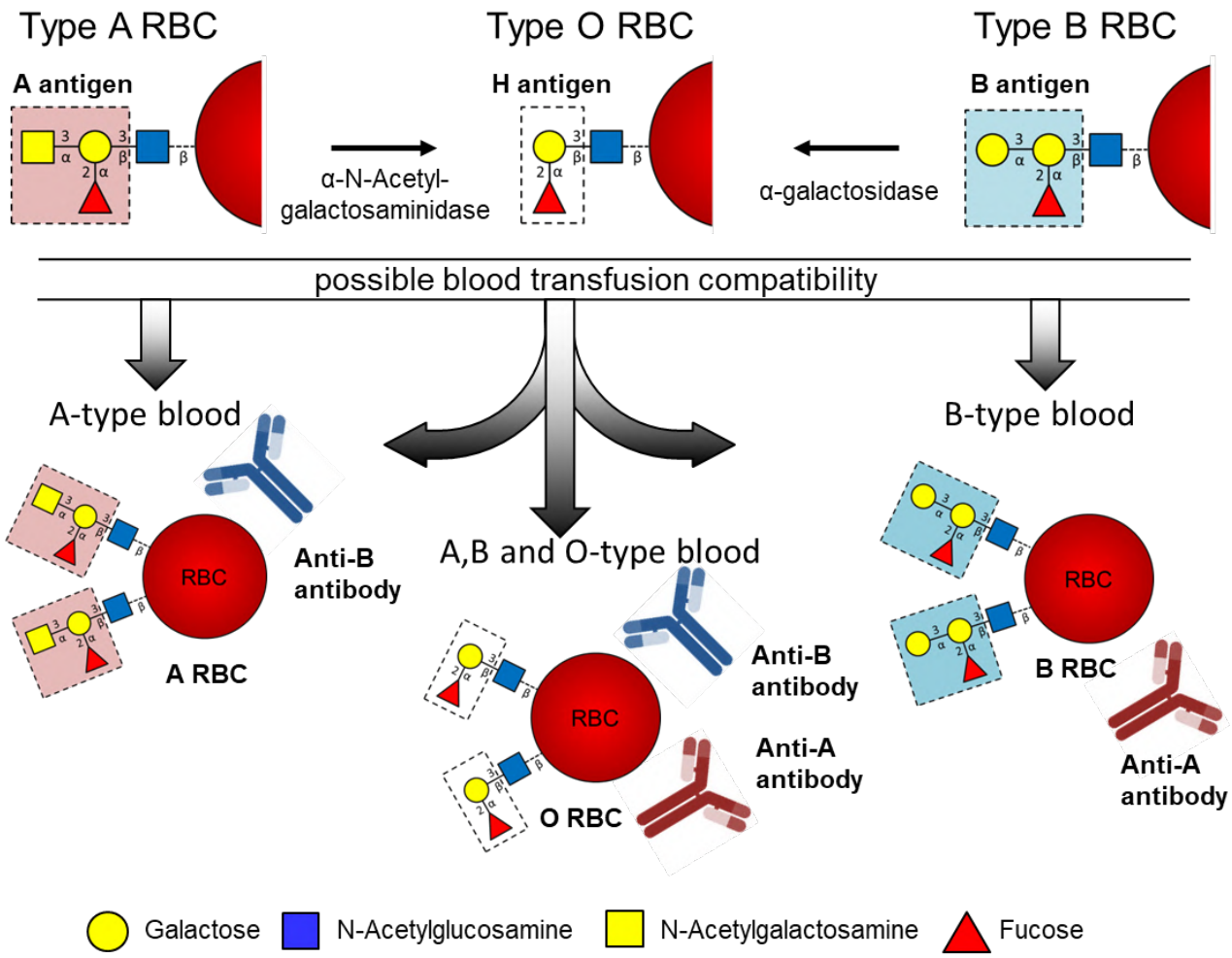


Figure 1: Overview of basic A, B and H antigens on the surface of Type A,B and O RBCs, and their enzymatic conversion by α-N-acetyl-galactosaminidase or α-galactosidase to H antigens, respectively Type O RBCs. Additionally, the blood transfusion compatibility is presented, where only blood without the matching Anti A or B antibody can be mixed. O RBCs and ECO O RBCs are the only ones without any recognized blood group antigen, and therefore are universal donor blood.

Metagenomics, a state-of-the-art technique which can be used to identify and characterize genes and enzymes in complex environmental samples provide a solution [5]. The production of a metagenomic library starts with the isolation of genomic DNA, in this case from human fecal samples which contain microorganisms from the gut. Size-selected genomic DNA is then transferred into a suitable host organism, here *Escherichia coli*, with the hope of expressing the genes therein. The generated library can be screened for the desired enzyme activity in an approach called functional metagenomic screening, thereby allowing the discovery of novel enzyme activities within a microbiome. To identify blood antigen cleaving enzymes, the human gut library is screened against highly sensitive fluorescent substrates, mimicking the A and B antigens. This functional metagenomic screening yields a novel set of enzymes. Serum-type conversion tests with these enzymes on A-type RBC reveal a highly specific and highly active A antigen cleavage activity, outcompeting any known A antigen cleaving enzyme. The enzymes' ability to completely convert A to O-type RBCs at very low enzyme concentrations in a blood bag turns those enzymes into highly valuable tools to be incorporated into the existing blood transfusion practice to supply universal donor blood. The method of targeted metabolomic screening is easily adaptable to other interesting microbiomes and will expand the access to other important biomedical toolboxes.

References

[1] Daniels G, Reid ME. Blood groups: the past 50 years. Transfusion. 2010;50(2):281–289.

[2] Goldstein J, Siviglia G, Hurst R, Lenny L, Reich L. Group B erythrocytes enzymatically converted to group O survive normally in A, B, and O individuals. Science. 1982;215(4529):168–170.

[3] Liu QP, Sulzenbacher G, Yuan H, Bennett EP, Pietz G, Saunders K, et al. Bacterial glycosidases for the production of universal red blood cells. Nature biotechnology. 2007;25(4):454.

[4] Tailford LE, Crost EH, Kavanaugh D, Juge N. Mucin glycan foraging in the human gut microbiome. Frontiers in genetics. 2015;6:81.

[5] Handelsman J. Metagenomics: application of genomics to uncultured microorganisms. Microbiol Mol Biol Rev. 2004;68(4):669–685.

ASK AN EXPERT

Health Science Inquiry

DR. STEFANIE NOVAKOWSKI is a recent PhD graduate from the Kastrup Lab at the University of British Columbia, where she developed tools for modifying platelets. The Kastrup lab uses biochemistry and biochemical engineering to solve problems related to hemostasis and hemorrhage. They investigate, utilize, and mimic the biochemistry and biophysical dynamics of blood coagulation to create innovative materials that perform new functions inside blood vessels.

DR. CHRISTIAN KASTRUP is an Associate Professor in the Michael Smith Laboratories and Department of Biochemistry & Molecular Biology. He is a recipient of the Sir Major Banting Award from the True Patriot Love Foundation, and a founder of CoMotion Drug Delivery Systems, Inc., which is currently working to develop a hemostatic agent for treating severe combat and surgical hemorrhage.

Stefanie Novakowski, PhD[1,2], Christian Kastrup, PhD[1,2]
[1]Michael Smith Laboratories
[2]Department of Biochemistry and Molecular Biology, University of British Columbia

What New Technologies are Needed to Halt Bleeding in the Most Severe Cases of Hemorrhage? Can This be Achieved by Enhancing Delivery of Therapeutics to the Wound?

Uncontrolled bleeding is a leading cause of death across all socioeconomic backgrounds, and can arise from diverse scenarios, including trauma, surgery, and childbirth [1]. Current strategies for treating hemorrhage include transfusing blood products, such as platelets, as well as delivering hemostatic and anti-fibrinolytic agents designed to stop the flow of blood or prevent clot lysis. The early control of hemorrhage drastically improves the outcome for patients; however, challenges still exist for managing severe, intractable hemorrhage, which is characterized by platelet dysfunction, increased clot lysis, and poor clot adhesion. Furthermore, escaping blood pushes externally applied hemostatics away from the wound, preventing delivery of the therapeutic to the site of injury.

Platelets seal vascular damage by adhering to blood vessel walls, releasing molecules which promote platelet activation and clot formation, and contracting the clot to narrow the wound. A promising strategy for the management of intractable hemorrhage is to increase the responsiveness, adhesion, and hemostatic efficacy of platelets specifically at sites of vascular damage. This has been achieved in part by use of refrigerated platelets. Compared to platelets stored at room temperature, which is the standard temperature for platelet storage, refrigerated platelets show higher efficacy when used to treat acute bleeding [2]. However, refrigerated platelets only circulate for a short time before they are cleared by the reticuloendothelial system, limiting the ability of refrigerated platelets to prevent bleeding when used prophylactically.

There is evidence that genetic modification can be used to enhance the hemostatic efficacy of platelets. In animal models, genetically engineered platelets were shown to improve hemophilia by releasing coagulation factor VIII [3]. These platelets are generated by modifying platelet precursor cells. While platelets can be generated from cultured precursor

cells, this technology has just reached the stage where it is possible to generate large numbers of platelets. Platelets generated from cultured cells need pre-clinical and clinical testing before they can be used in the clinic [4]. Therefore, a method for directly modifying donor-derived platelets to enhance their hemostatic abilities may be useful for treating severe bleeding.

Using small lipid nanoparticles to deliver nucleic acids and proteins to isolated platelets is an innovative approach to tackling this challenge [5, 6]. Using this technology, platelets are loaded with thrombin, a potent activator of clotting and platelets [5]. The nanoparticles shield the platelets from the thrombin during delivery, preventing the platelets from becoming activated until they are treated with additional platelet agonists. These thrombin-loaded platelets form clots faster than regular platelets, and produce stronger clots, even in plasma from patients with defective clotting. The next step would be to determine whether they maintain their enhanced clotting abilities in animal models, by using lipid nanoparticles to deliver mRNA to platelets [6]. While the platelets cannot yet translate the mRNA after endocytosing the nanoparticle, this approach could be used to genetically engineer platelets to produce additional pro-coagulant or anti-fibrinolytic proteins. A delivery vehicle for mRNA would not have to be optimized for each mRNA, providing an advantage over delivering different proteins to the platelets.

Beyond the enhancement of platelets, there are alternative approaches to enhance the delivery of hemostatic agents into wounds. CounterFlow is a novel wound-penetrating drug delivery vehicle composed of calcium carbonate and tranexamic acid [7, 8]. Tranexamic acid is a clot stabilizing anti-fibrinolytic agent, improving the efficacy of this delivery system. Various proteins, including thrombin, can be loaded onto CounterFlow, and upon contact with blood are propelled deep into the wound. In pig and sheep animals of trauma and surgery, respectively, CounterFlow reduced bleeding and improved survival compared to the current standard-of-care. This approach has potential for use in combat casualty care, due to its relative stability, portability, and ease-of-use.

Coagulation is controlled by a complex network of reactions that was first described over 50 years ago. Understanding blood coagulation has led to numerous therapies to control bleeding, yet intractable hemorrhage remains a problem. To treat severe hemorrhage, it is necessary to use innovative approaches to deliver therapeutics to the sites of wounds, and to re-think what aspects of coagulation should be targeted to enhance hemostasis.

References

[1] Gonzalez E, Moore E, Moore H, Chapman M, Silliman C, Banerjee A. Trauma-induced coagulopathy: an institution's 35 year perspective on practice and research. Scandinavian Journal of Surgery. 2014;103(2):89–103.

[2] Reddoch KM, Pidcoke HF, Montgomery RK, Fedyk CG, Aden JK, Ramasubramanian AK, et al. Hemostatic function of apheresis platelets stored at 4°C and 22°C. Shock (Augusta, Ga). 2014;41(0 1):54.

[3] Du LM, Nurden P, Nurden AT, Nichols TC, Bellinger DA, Jensen ES, et al. Platelet-targeted gene therapy with human factor VIII establishes haemostasis in dogs with haemophilia A. Nature communications. 2013;4:2773.

[4] Wang B, Zheng J. Platelet generation in vivo and in vitro. Springerplus. 2016;5(1):787.

[5] Chan V, Sarkari M, Sunderland R, St John A, White N, Kastrup C. Platelets loaded with liposome-encapsulated thrombin have increased coagulability. Journal of Thrombosis and Haemostasis. 2018;16(6):1226–1235.

[6] Novakowski S, Jiang K, Prakash G, Kastrup C. Delivery of mRNA to platelets using lipid nanoparticles. Scientific reports. 2019;9(1):552.

[7] Baylis JR, John AES, Wang X, Lim EB, Statz ML, Chien D, et al. Self-propelled dressings containing thrombin and tranexamic acid improve short-term survival in a swine model of lethal junctional hemorrhage. Shock (Augusta, Ga). 2016;46(3):123.

[8] R Baylis J, Finkelstein-Kulka A, Macias-Valle L, Manji J, Lee M, Levchenko E, et al. Rapid hemostasis in a sheep model using particles that propel thrombin and tranexamic acid. The Laryngoscope. 2017;127(4):787–793.

Health Science Inquiry

SPOTLIGHT ON CAREERS

Interview by Stephanie Tien

Dr. Shelley Deeke

DR. SHELLEY DEEKE is a scientist at Cyclica Inc. Cyclica is a biotechnology company that uses artificial intelligence (AI) combined with biophysics for drug discovery. The overarching goal of the company is to personalize medicine and accelerate drug discovery through creating technologies and tools for scientists to utilize in their research. Cyclica has developed a platform called the Ligand Express that produces polypharmacology profiles of small molecules to predict the protein interactors of the molecule. Ultimately Cyclica aims to make drug discovery faster, safer, and cheaper, by enabling scientists in pharma to achieve these goals through new technologies.

Prior to joining Cyclica, Dr. Deeke completed her Honours Bachelor of Science, Master of Science, and doctoral studies in biochemistry at the University of Ottawa. Her thesis titled "Biomarker Discovery and Extracellular Vesicle Proteomic Signatures in Pediatric Inflammatory Bowel Disease", used a clinical proteomic approach to enable faster diagnosis of IBD through the use of biomarkers, and to avoid patients having to undergo colonoscopies.

1. How did your graduate education prepare you for your career?

A lot of the skills I acquired through my graduate studies, such as evaluating scientific literature, data analysis, statistics, and critical thinking, are directly related to my current role. But I also consider the opportunities outside of the lab that graduate students are encouraged to partake in, but are not necessarily mandatory, to be very valuable. I was the VP Academic on the Biochemistry, Microbiology, and Immunology Student Council which gave me the opportunity to gain leadership skills. I also participated in the 3-minute thesis competition, and won second place in 2018, so that was very useful in developing the skill of being able to transfer very complex scientific concepts into simple terms. So there are always opportunities to develop these transferrable skills, which are equally, if not more important, but it is up to the students to seize them.

2. What steps did you take to find or acquire your position?

As much as you hear it, it was really networking that got me into my current role. My former supervisor was attending an event hosted by the Canadian Institute for Advanced Research (CIFAR), and he asked if I would be interested in attending as a student reporter. And this is where I first became aware of Cyclica. It was through a workshop on the challenges in drug discovery where I met the VP of research and development at Cyclica. After this meeting I started researching the company and I was really blown away; I thought their research was groundbreaking, and could really have an impact on healthcare. They had a posting on the careers section of their website. I applied online and I started with the company in August 2018.

3. Do you have any advice for grad students interested in pursuing a similar career path?

My advice would be to complete a career IDP (Individual Development Plan) using the CIHR online tools. It's very important to take the time to reflect on this, because it's worth it. Also, start looking for jobs and monitoring the job landscape early; start looking 6 months before you plan to graduate. Writing a CV and a good cover letter takes time, and the first one will probably not be the best, so this in itself is a skill. The earlier you start the better; you can never start too early. Also, I think being open to different types of jobs is important. Just being isolated to your research will really narrow your opportunities. Having a good mentor is also very valuable. I was lucky that my supervisor was very supportive and recognized the value of networking and encouraged me to network.

4. What did you find most challenging about transitioning from academia to industry? What was your biggest learning curve?

For me specifically, since I decided to work for a company centered on machine learning and AI, I had very little exposure to that so I have been learning some basics of programming through online courses in order to expand on those skills. I think they are very useful and will continue to become more useful as time goes on. So for me, programming itself has been the steepest learning curve. Though this was one of the aspects that actually drew me in to Cyclica, because I was eager to learn and I want to continue to learn; so this allows me to grow and continue to gain more skills.

5. Can you describe your position and a typical workday?

I would say most of my work is done independently; and most of my day involves a lot of data analysis. In my role, I compare the performance of our technologies to other technologies in terms of polypharmacology profiling; I am usually analyzing data sets, sometimes I'm curating data sets, and in general evaluating our technology's performance on specific biological metrics and comparing them to other technologies available.

6. What is it like to work at a start-up company? What has your experience been like working in such an interdisciplinary team of people?

I really enjoy learning about other disciplines and fields that I had no prior exposure to like AI and machine learning. It is such a new world to discover. So this is a major positive aspect for me. I also really like the culture that Cyclica has established. There is a sense of community and it is very supportive. Also, working in an interdisciplinary team really helps me to de-complex things and make explanations into simple and relatable forms that are understandable for people in a breadth of disciplines. Sometimes you definitely need to take a moment to think about how you will convey something, but I think it is great because getting down to the fundamentals helps shed light and bring insight to realize certain things, so I think it is very helpful. Also the willingness to learn fields outside of your own is a great behaviour to exhibit. Everyone at Cyclica is very supportive of it, and so is the company as well.

7. What are your favourite and least favourite parts of your position?

What I really enjoy about my position now is that I am working with so many talented individuals and I am literally learning new things every single day on a large scale. And, that we are all working towards a goal that really resonates with my own personal career objectives. I truly believe that Cyclica has the capability of implementing a profound impact in the healthcare industry, and so being part of that journey is very fulfilling. I have been very lucky to find a company whose culture and core values really resonate with my own personal values. I am very happy with my role, because there is still a lot of research involved, and I am always learning, which is what drives me.

8. How do you envision the future of healthcare research? How do you see Cyclica and the industry growing in the future?

Since I am starting to gain a better understanding of the AI capabilities in healthcare, I think it has potential value across the entire healthcare industry as it is going to enable us to gain deeper insight into our data. There are already examples where AI is excelling in healthcare, such as in the diagnosis of skin cancer where AI can outperform specialists in this task. I think what it will allow us to do is to move forward and transition to more personalized medicine, and overall better diagnosis, prognosis, patient treatment, and drug discovery. I think AI alone won't be all-encompassing and be able to solve all of the current problems we face, but it will help us to develop solutions. Cyclica is one of the many companies that use AI, and since it is such a hot topic, it will only gain more traction and lead to leaps and bounds in the progress AI can make in healthcare.

Health Science Inquiry

SPOTLIGHT ON CAREERS

Interview by Joshua McGrath

Dr. Anna Dvorkin-Gheva

DR. ANNA DVORKIN-GHEVA is a resident bioinformatician working within the McMaster Immunology Research Centre (MIRC) at McMaster University in Hamilton, Ontario. She completed her B.Sc. in Life Sciences at Tel Aviv University, Israel, and subsequently earned her Ph.D. in Neuroscience and Computational Biology under the co-supervision of Dr. Henry Szechtman at McMaster University and Dr. Ilan Golani at Tel Aviv University. Specifically, her doctoral thesis focused on the investigation of exploratory behaviour patterns in rodent models of obsessive-compulsive disorder (OCD). After completing her degree, she pursued a post-doctoral fellowship with Dr. John Hassell at McMaster University, where she levied computational and analytical skills to test novel therapeutics for breast cancer. Ultimately, it was during this time that an unmet demand for bioinformatic analysis across many laboratories within the McMaster health sciences community was identified. As a consequence, a position, which Anna holds today, was created. This position involves collaboration with many research groups both within and outside of MIRC to investigate a wide array of biological diseases and processes using computational approaches.

1. Can you describe your position and typical work day/week?

Broadly, my position involves designing and performing bioinformatic analyses using biological datasets in collaboration with various research groups. Some of these datasets are generated by these research groups, while others are obtained from repositories with either open or restricted access. On any given day, I may spend time answering questions pertaining to the biology of infectious diseases, cancer, allergies, or autoimmunity, among other areas. Within these subfields, I may be mining previously generated datasets, looking for patterns that identify novel and interesting areas for investigation, or alternatively, asking highly-defined research questions. In either instance, I may be utilizing one or more computational approaches to perform the analysis. For these reasons, I would say that my work days and weeks are often variable, in that the topics I study, the goals I pursue, and the tools with which I pursue them are diverse.

2. What types of analyses do you typically perform in your role?

My work spans across several fields, mainly including transcriptomics, genomics, and proteomics. Transcriptomic data obtained from microarrays, Nanostring, next-generation RNA sequencing (RNAseq), and single-cell RNAseq demonstrate gene expression patterns, which are generally used for providing a deeper understanding of biological processes behind conditions of interest, for searching potential biomarkers, or for generating hypotheses. Genomic data I work with are usually obtained from another type of next-generation sequencing – DNAseq. I use these types of data to examine the variability of specific genomic regions, including searching for mutations, polymorphisms, and sequence motifs, among other things. These genomic data can, for instance, be used to study the diversity and lineages of immunoglobulin responses. The projects involving proteomics range from analyses of data obtained from mass spectrometry to analyses of protein structures involved in protein-protein docking. Within each of these fields, I am involved with experimental design, including components such as sample size calculation, as well as processing data and performing numerous types of statistical analyses. Another aspect that I am quite enthusiastic about is data visualization, which is a crucial step in the examination and presentation of experimental results. Appropriate visualization techniques allow the reader to see results clearly and the researcher to find additional directions and questions to ask based on the data. To this end, I specialize in developing unique methods of data visualization. Ultimately, while many analyses use a core set of tools and approaches as described above, datasets frequently present unique challenges, often requiring the development of innovative approaches.

3. What is your most/least favourite part of your job?

I would say that my favourite part of the job is the diversity of both the groups I get to work with and questions I get to answer. My field of study changes on a frequent basis, often allowing me to refresh my interests and take a fresh perspective on problems. Another aspect of the job that I really enjoy is exploring large datasets, looking for new variables and patterns without a hypothesis in mind. While this type of analysis is risky, as it may or may not produce fruitful results, I find the process quite fun. I think my least favourite part of my role is the variability in workload distribution. Sometimes there can be a lot on my plate at once, while other times things can be quite slow. However, I tend to view time constraints as a challenge and am able to gain a lot of satisfaction from working under pressure. On the other hand, slow periods provide the benefit of extra time to read and learn, thus allowing me to broaden my repertoire of computational analyses.

4. How common is your role in academia/industry? Do you see the need for this type of role growing in the future?

Biological scientists, whether in academia or industry, are becoming increasingly aware of the utility of bioinformatics. In academia, many laboratories are becoming interested in pursuing these types of analysis. Often times, however, it can be inefficient to train individuals to do so, given the time and effort required to learn programming languages and specific analytical methods. The benefit that dedicated bioinformaticians provide is that they can act as a core facility and use a consolidated set of skills to provide computational support to a number of groups. This in turn allows these groups to focus their efforts within their respective fields. Ultimately, I think that the efficiency of this type of core facility-like setup will facilitate the expansion of bioinformatician roles in the future. In industry, a role that is roughly equivalent to mine would be that of a data analyst. These roles are already quite common and will likely proliferate further in the future for the reasons above.

5. Do you have any advice for graduate students who would like to pursue a career in bioinformatics?

First of all, I would say that all graduate students in the health sciences should try to develop a fundamental understanding of the computational techniques that are used in their respective fields. Although knowing the specific methodologies of these techniques may not be necessary for everyone, having a basic understanding about which techniques are used, when they should be used, why they are used, and the broad strokes of how they work will undoubtedly help in critiquing experimental rationales and protocols. For students interested in pursuing bioinformatics-based work specifically, I would recommend to begin by learning to code using languages such as R, Python, or Matlab. This is essential, as bioinformatic analyses are conducted through programming. Further to that, I would encourage students to gain literacy in more than one coding language, as each has their advantages for specific applications and you cannot always predict what language other researchers code their programs in. Finally, students should identify and take courses that are designed to teach the techniques and analyses that they are interested in.

Health Science Inquiry

SPOTLIGHT ON CAREERS

Interview by Ivana Nad

Dr. Scott McComb

DR. SCOTT McCOMB acquired a BSc in Biopharmaceutical Science (Genomics) from University of Ottawa and his PhD research was in the field of Microbiology and Immunology, at the University of Ottawa. He did his Postdoctoral training at University Children's Hospital Zurich, Switzerland. Through the years, Scott's long term research interest has been in better understanding how and when cells undergo various forms of programmed cell death (apoptosis and necroptosis). After receiving his PhD in Microbiology and Immunology from the University of Ottawa in 2013, he decided to shift his research interest from how programmed cell death shapes the immune system to how cell death is inhibited within cancer cells. He then joined the Leukemia research group at the University Children's Hospital of Zurich (Switzerland), where they developed new genome editing techniques to study the complex ways apoptosis and necroptosis become dysregulated in cells derived from different patients. Today, Scott is a Research Officer at National Research Council, primary national research and technology organization of the Government of Canada, in science and technology research and development.

1. Could you tell me something about your previous activities and education?

I have a BSc in Biopharmaceutical Science (Genomics) from University of Ottawa and my PhD was in Microbiology and Immunology, University of Ottawa, funded by an Ontario Graduate Scholarship. I did my Postdoctoral training at University Children's Hospital in Zurich, Switzerland.

My long-term research interest has been to improve understanding about how and when cells undergo various forms of programmed cell death (apoptosis and necroptosis). After receiving my PhD in Microbiology and Immunology from the University of Ottawa in 2013, I decided to shift my research interest from how programmed cell death shapes the immune system to how cell death is inhibited in cancer cells. I joined the Leukemia Research Group at the University Children's Hospital in Zurich (Switzerland), where we developed new genome editing techniques to study the complex ways apoptosis and necroptosis become dysregulated in cells derived from different patients.

2. Could you describe your current role as a Research Officer at the National Research Council?

I was able to combine my three research interests (immunology, cell death signaling, and cancer biology) within the fast-growing sub-field of Cancer Immunology. My lab at the National Research Council (NRC) Human Health Therapeutics has been applying synthetic biology and genome editing technologies (such as CRISPR) toward developing novel engineered cellular therapies. While chimeric antigen receptor T-cell (CAR-T) therapies are an unprecedented breakthrough for patients with relapsed B-cell leukemia, this as just the first step into a new era of potent and accessible cellular therapies for currently intractable diseases.

3. How did your PhD and Postdoctoral experience prepare you for your current position? How have your interests changed over time?

Today it is essential to have a strong grasp of all of the key elements of adaptive and innate immunology in order to contribute meaningfully to this field. My training in the University of Ottawa BMI department provided me with strong bedrock in the fundamentals of immunology, and working at the University Children's Hospital in Zurich provided excellent exposure to many cutting-edge techniques in cell biology. This is where I was lucky enough to take part in the rapid developments of CRISPR genome editing technology. With a strong grasp of fundamental concepts and openness to emerging technologies, I will position myself and my lab for scientific success.

4. What attracted you to a career at the NRC instead of academia or industry? What skills or traits led you in that direction?

The NRC is a unique organization within the Canadian Federal Government, at the intersection of academia, industry, and government. We try to translate scientific breakthroughs into practical benefits for Canadians. It has always been a dream of mine to be able to translate some of my scientific ideas into real tangible benefits for patients. By working at the NRC, I get to experience the exciting work that is happening both in academia and industry, and work to bridge these two worlds.

5. Could you explain your current job position, your duties or projects, and how this helps you develop new skills? Is your main focus still on research?

As a research officer I am responsible for leading a lab that provides key expertise for NRC realize strategic goals. In my case, my lab has expertise in immune cell assays (such as flow cytometry, cytolytic assays, and animal cancer models). In addition, I am a Project Lead at the NRC, leading work in the area of CAR-T therapies. I coordinate with people inside and outside the NRC to identify potential targets for new CAR-T therapies, and develop novel strategies to try to improve efficacy for these therapies. Day-to-day, my focus is almost 100% on research, and activities including interfacing with other scientists and Postdocs at a high level to devise new experiments. I direct the activities of research assistants, technicians, and students in the lab. I also like to spend some time at the bench if I can, but don't get to do this as much as I'd like.

6. What is your career goal? Do you see your position evolving over time at the NRC?

My medium-term career goal is to work with other talented people to see a made-in-Canada CAR-T therapy developed (at least partly) at NRC for patients in a clinical trial. Beyond this, I would like to help to make engineered cell therapies effective, safe, affordable, and accessible to Canadians.

7. Do you have any advice for graduate students who wish to follow a similar career path outside of academia? Do employers look beyond scholarships, publications and Postdoc experience?

Always try to keep aware of how your research can be applied.

8. What is the future for the NRC? How do you envision the future of healthcare research?

I believe 20 years from now, engineered cell therapies will make up a significant proportion of medical therapies. I can't think of a disease which couldn't be potentially cured with the right engineered cell therapy, no matter how serious and intractable it might seem today. Leveraging genome editing and synthetic biology we can re-engineer cells to bring the right treatment to the right place within the body, at the right time, for the right patient... and with the right engineering, we can grow as many (or as few) of these cells as we need at any time.

HEALTH SCIENCE INQUIRY 2020 SPONSORSHIP OPPORTUNITY

Health Science Inquiry will be offering space for advertisements in its 2020 issue. Given our unique role as a Canada-wide graduate student run publication, our readership and circulation continues to expand each year. For more information, please email healthscienceinquiry@gmail.com and refer to the tentative pricing details below.