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Medical Innovations

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ABOUT US

UOJM is an international peer-reviewed journal led and published by the students of the Faculty of Medicine. We welcome submissions in a variety of areas in biomedical research and feature original research, review articles, news and commentaries, case reports and opinion pieces. Our articles are written in both English and French, and represent the only bilingual medical journal in Canada run by students.

Le JMUO est un journal revu, édité et publié par les étudiants de la Faculté de médecine. Nous encourageons les soumissions d'une variété de différents domaines en recherche biomédicale et publions des articles de recherche originale, des articles de revue, des nouvelles et commentaires, des rapports de cas et des pièces d'opinion. Nos articles sont écrits en français et en anglais et représentent le seul journal médical bilingue géré par les étudiants au Canada.

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CHEO

Announcing
UOJM Reviewer Award

The publication of high-quality manuscripts cannot be achieved without the contribution of dedicated peer reviewers. High-quality peer reviews are critical to the publication process, as they provide constructive feedback to authors to help improve their manuscripts. The UOJM editorial team is enormously thankful to all of our reviewers who have volunteered to participate in the peer review process for UOJM. Their time and efforts have been integral to the editorial process, helping to ensure that the quality and standards that define UOJM are upheld for the current issue.

Starting this issue, we are honouring two outstanding reviewers with the UOJM Reviewer Award. Key criteria for selection of award recipients included being readily available for peer review when invited and submitting constructive reviews that were demonstrative of critical appraisal in a timely manner. Upon careful review of all peer reviewers, we are pleased to announce **Lubina Nayak** and **Hao Wang** as the recipients of the inaugural UOJM Reviewer Award.

Congratulations and well done, Lubina and Hao!

Managing Editor
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Linda Yi Ning Fei
Phillip Staibano

La publication de manuscrits de haute qualité ne pourra pas être achevée sans la contribution d'évaluateurs de pairs dédiés. Des évaluations par les pairs de haute qualité sont critiques pour le processus de publication, afin de fournir de la rétroaction critique aux auteurs pour aider à améliorer leurs manuscrits. L'équipe éditoriale du JMUO est énormément reconnaissante de tous nos évaluateurs qui se sont présentés comme bénévoles pour participer dans le processus d'évaluation par les pairs du JMUO. Leurs temps et leurs efforts ont été intégrants au processus éditorial, en aidant à assurer que la qualité et les standards qui définissent le JMUO sont soutenus dans le présent numéro.

Commençant par ce numéro, nous honorons deux évaluateurs exceptionnels avec le prix Évaluateur du JMUO. Les critères pour la sélection des récipiendaires comprennent être disponibles régulièrement pour l'évaluation par les pairs quand inviter, et soumettre des évaluations constructives qui démontrent une estimation critique dans un délai raisonnable. Après une considération prudente de tous nos évaluateurs, nous sommes fiers d'annoncer comme récipiendaires **Lubina Nayak** et **Hao Wang** pour le premier prix Évaluateur du JMUO.

Félicitations et bravo, Lubina et Hao!

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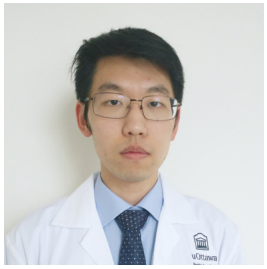

Hao Wang, B.Math
University of Ottawa, MD Candidate 2022
Hao is a first year medical student at the University of Ottawa. Prior to studying medicine, Hao studied mathematics and worked briefly as a statistician. Research has always been one of his passions, whether it be conducting his own research or reading that of others. In particular, Hao has an interest in interdisclinary research, stating, "I am amazed at how seemingly different fields can merge seamlessly to produce something valuable". His research interests lie at the junction between mathematics and healthcare. Hao is currently working on using directed acyclic graphs to demonstrate the interconnected nature of factors leading to poverty in disadvantaged populations in Ottawa.

Ameeta Lubina Nayak, BScH.
University of Ottawa, MD Candidate 2022
Lubina is a first year medical student at the University of Ottawa. Outside of reviewing for the UOJM, she also enjoys doing her own research. She is currently involved in research in urologic oncology at the Ottawa Hospital Research Institute. Lubina used to be a competitive diver and gymnast, and in her spare time now she coaches both sports. Lubina also loves to travel and has visited over 20 countries and hopes to continue to see more in the future.

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UOJM: Preface

With the arrival of spring comes the start of the ninth cycle of UOJM, and the release of **UOJM issue 9.1: Medical Innovations**. In the midst of this season of rebirth and transformation, we are proud to present an issue that highlights the wonders of scientific discovery and medical breakthrough, all while showcasing the achievements of future clinical and scientific leaders.

Over the past ten months, we have had the privilege of overseeing the scientific, educational, and advocacy roles that comprise the University of Ottawa Journal of Medicine. As Canada's only bilingual academic medical journal, UOJM has been a stage for graduate and medical students, both within Canada and around the world, to present their research findings and publish their perspectives and commentaries about topical issues in medicine. We are also proud to announce that the **UOJM is now officially indexed in the *Directory of Open Access Journals (DOAJ)***: this is an important step in continuing to build UOJM readership and in attracting high-quality research and writing from around the world.

Since the start of the academic year, we have been present at the 2018 Ontario Medical Students' Weekend in Ottawa, Ontario and the second-annual Interdisciplinary Student Research Conference on Healthcare, which have allowed us to garner interest amongst budding clinicians and medical researchers, while building professional relationships with students in various faculties, including law and nursing. Our current UOJM executive team has also been working persistently throughout the year to host seminars and workshops focused on topics including peer-review and bench-to-bedside research.

UOJM 9.1: Medical Innovations reverently explores the awe-inspiring, yet enigmatic, nature of scientific revolution. We begin this issue with an interview of one of the leading clinician-scientists at the University of Ottawa Heart Institute for a discussion of innovations in clinical cardiology and the importance of training future clinician-scientists. We then weave empirical articles pertaining to practical innovations that are being championed at the University of Ottawa, including 3D printing for clinical practice and medical education. Finally, we highlight the engrossing experiences of medical students who have witnessed medicine outside of Canada, and have drawn conclusions that could transform one's understanding of medicine and egalitarianism in medical practice. Thus, this issue focuses on the multitude of ways that innovation can be cultivated in medicine: from the laboratory, to the classroom—to a giant tanker traversing the Arctic Circle; but, as you will come to see, the requirements for becoming a true medical innovator are consistent—an unfettered curiosity and passion, a dogged work ethic, and a grounded sense of humility and self-awareness that is free of confirmation bias and personal ego.

As we move into the next academic year, we are excited to announce our **Fall 2019 issue**, which will delve into the complexities of **Inner-City and Rural Medicine**. Medical practice is impacted by a multitude of physiological, personal, and social factors—not limited to where a patient lives. Where we live influences how we grow, where we go to school, what we eat, where we work, what we value, and ultimately, how healthy we are. Understanding the nuances that contribute to rural and inner-city healthcare needs, including access to medical resources, social assistance programs, patient education initiatives, and mental health support, will help to ensure that healthcare is customized to the needs of patients living in urban and rural environments. UOJM issue 9.2 will review the overlapping and distinct features that contribute to inner-city and rural medical practice with the hope of inspiring young researchers and clinicians to always be mindful of how societal and environmental differences are important factors in personalized and patient-specific healthcare.

The submission deadline for our **Fall 2019 issue is September 1st, 2019**. High-quality writing will be recognized with an honorarium award. Submissions can be made online, and details regarding article formatting and the submission process can be found on our website at *www.uojm.ca.*

We hope you enjoy and are inspired by UOJM issue 9.1: **a showcase of medical innovations!**

Editors-in-Chief
Linda Yi Ning Fei
Phillip Staibano

JMUO: Préface

Avec l'arrivée du printemps viennent le début du neuvième cycle du JMUO, et la sortie du **JMUO numéro 9.1 : Les Innovations Médicales.** Dans le milieu de cette saison de renaissance et transformation, nous sommes fiers de présenter un numéro qui surligne les merveilles de la découverte scientifique, tout en démontrant les réussites des futurs cliniciens et scientifiques-chefs.

Pendant les dix derniers mois, nous avons eu le privilège de surveiller les rôles scientifiques, éducationnels et promotionnels qui comprennent le Journal médical de l'Université d'Ottawa. Comme le seul journal médical scolaire bilingue au Canada, le JMUO sert comme une estrade pour les étudiants de troisième cycle et du programme de médecine, au Canada et mondialement, de présenter leurs résultats de recherche et de publier leurs perspectives et commentaires sur des problèmes actuels en médecine. Nous sommes également fiers d'annoncer que **le JMUO se retrouve officiellement dans le « *Directory of Open Access Journals (DOAJ)* »** : une étape importante pour continuer d'agrandir le lectorat du JMUO et pour attirer de la recherche et de l'écriture de haute qualité du monde entier.

Depuis le début de l'année scolaire, nous avons été présents à la Fin de semaine des étudiants en médecine de l'Ontario à Ottawa, Ontario pour 2018, et la deuxième Conférence de recherche étudiante interdisciplinaire de la santé annuelle, qui nous ont permis d'engendrer un intérêt entre les cliniciens et chercheurs médicaux en herbe, tout en construisant des relations professionnelles avec des étudiants dans les différentes facultés, y inclut le droit et les sciences infirmières. Notre équipe exécutive actuelle du JMUO a également travaillé à travers de l'année avec persistance pour héberger des séminaires et des ateliers centrés sur des sujets incluant de la recherche révisée par les paires et de la recherche du laboratoire au chevet.

Le JMUO 9.1 : Les Innovations Médicales explorent respectueusement la nature imposante, mais énigmatique, de la révolution scientifique. Nous commençons ce numéro avec une entrevue avec un des cliniciens-chercheurs principaux à l'Institut de cardiologie de l'Université d'Ottawa pour une discussion sur les innovations de la cardiologie clinique et l'importance de l'entrainement des cliniciens-chercheurs futurs. Nous explorons ensuite des articles empiriques sur les innovations pratiques qui sont soutenues par l'Université d'Ottawa, y inclut l'imprimerie 3D pour les pratiques cliniques et l'éducation médicale. Finalement, nous surlignons les expériences palpitantes des étudiants en médecine qui ont constaté la médecine hors Canada, et sont arrivés à des conclusions qui peuvent transformer la compréhension de la médecine et de l'égalitarisme dans les pratiques médicales. Ainsi, ce numéro centre sur les différentes façons que l'innovation peut se faire cultiver dans la médecine : du laboratoire, à la salle de classe – à un navire-citerne géant traversant le cercle arctique; mais, comme vous verriez, les demandes pour devenir un véritable innovateur médical sont consistantes – une curiosité et une passion sans entraves, une éthique de travail tenace, et un sens d'humilité et de conscience en soi qui est libre de biais de confirmation et d'égo personnel.

Pendant que nous faisons transition à la prochaine année scolaire, nous sommes impatients d'annoncer notre **numéro d'automne 2019**, qui plongera dans les complexités de **La Médecine Urbaine et Rurale**. La pratique médicale est impactée par plusieurs facteurs physiologiques, personnels et sociaux – sans se limité sur où vit un patient. Où on vit influence comment on grandit, où on va à l'école, où on travaille, ce qu'on tient en valeur, et, ultimement, comment on est en santé. Comprendre les nuances qui contribuent aux besoins en santé rurale et urbaine, y incluent l'accès aux ressources médicales, les programmes d'assistances sociales, les initiatives d'éducation pour les patients et le support pour la santé mentale ; aideront à assurer que les soins de santé sont propres aux besoins des patients vivant dans des environnements urbains et ruraux. **Le numéro 9.2 du JMUO** révisera les caractéristiques chevauchantes et distinctes qui contribuent à la pratique médicale urbaine et rurale avec l'espoir d'inspirer les jeunes chercheurs et cliniciens qui seront toujours conscients des différences sociétales et environnementales sont des facteurs importants pour les soins personnalisés et centrés sur les patients.

La date limite pour la soumission pour notre **numéro d'automne 2019 est le 1er septembre 2019.** L'écriture de haute qualité sera récompensée avec un prix d'honneur. Les soumissions peuvent être faites en ligne, et les détails sur le format des articles et le processus de soumission peuvent se trouver sur notre site web *www.uojm.ca.*

Nous espérons que vous aimez et soyez inspirés par le numéro 9.1 du JMUO : **une vitrine d'innovations médicales!**

Rédacteurs en chef
Linda Yi Ning Fei
Phillip Staibano

Cutting-edge Innovations in Cardiac Health: Galvanic Insights from a Clinician-Scientist, Dr. Benjamin Hibbert

Faizan Khan[1], Phillip Staibano[2], Mimi Xiaoming Deng[2] , Linda Yi Ning Fei[2]

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ABSTRACT

Dr. Benjamin Hibbert, MD, PhD, FRCPC is an interventional cardiologist, an assistant professor, as well as the director of the Vascular Biology and Experimental Medicine Laboratory at the University of Ottawa Heart Institute. With a focus on performing revolutionary bench-to-bedside research, Dr. Hibbert's research interests include the development of novel cardiac biomarkers, elucidating the mechanisms that underlie pathological arterial remodeling in transplant vasculopathy, and the pharmacodynamics of adjuvant antiplatelet and antithrombotic agents in cardiac disease. We had the privilege of speaking with Dr. Hibbert about his career path, research experiences, and perspectives on the importance of the clinician-investigator program in training the oncoming generation of clinician-scientists. We also discuss the burgeoning field of meta-research and the role that methodological scrutiny has on the development of clinical guidelines and evidence-based medicine. We hope that this interview inspires the next generation of clinicians to pursue clinical investigator programs (CIP) and incorporate academia into their medical practice.

RÉSUMÉ

Dr Benjamin Hibbert, MD, PhD, FRCPC, est un cardiologue interventionniste, un professeur adjoint, ainsi que le directeur du Laboratoire de biologie vasculaire et de médecine expérimentale à l'Institut de cardiologie de l'Université d'Ottawa (ICUO). En se concentrant sur la recherche du laboratoire-au-chevet révolutionnaire, les intérêts de recherche clinique et de sciences de base de Dr Hibbert incluent le développement de biomarqueurs cardiaques nouveaux, l'élucidation des mécanismes sous-jacents le remodelage artériel pathologique lors de la vasculopathie de transplantation, et les pharmacodynamiques d'agents antiplaquettaires et antithrombotiques adjuvants dans les maladies cardiaques. On a eu le privilège de discuter avec Dr Hibbert sur son parcours professionnel, ses expériences de recherche, et les perspectives sur l'importance du programme du clinicien-chercheur pour l'entrainement de la génération future de cliniciens-scientifiques. On a aussi discuté du champ naissant de meta-recherche et le rôle que l'examen minutieux a sur le développement de lignes directrices et la médecine factuelle. On espère que cette entrevue inspire la prochaine génération de cliniciens à poursuivre des programmes de clinicien-chercheur (PCC) et incorporer le milieu universitaire dans leur pratique médicale.

Tell us a bit about your academic background and your current professional roles.

I completed all my education and training at the University of Ottawa: undergraduate degree in Biology/Biotechnology, medical school, as well as my internal medicine and cardiology residency training. During my internal medicine training, I started my PhD in biochemistry as part of the clinician-investigator program (CIP), which I completed alongside my cardiology training. I then completed a two-year fellowship in interventional cardiology at the University of Ottawa Heart Institute (UOHI). So, now I am a clinician-scientist. My clinical responsibilities include critical care cardiology, percutaneous coronary intervention, and treating valvular and congenital heart diseases with transcatheter technology. My research focus is on vascular biology, specifically working on translational projects—trying to take basic science insights and move them into *early* clinical practice.

How did you choose a clinician-scientist career in cardiology?

I am from a small town, and so, when I got into medical school, I thought I was going to go into family medicine because

Keywords: Interview; Cardiology; Translational Research; Meta-research; Biochemistry

that was the kind of doctor that I knew. I think this is true of anything—there is a tremendous amount of role modelling in life. In medical school, I loved the study of cardiovascular medicine. I had the opportunity to work with excellent interventional cardiologists, such as Drs. Christopher Glover, Michael Froeschl, Ed O'Brien, and Marino Labinaz, and I have taken little bits of all of them that I admired and have incorporated them into my current clinical and academic work. I benefited from being at the right place at the right time, which helped me find something that I was really passionate about. During my undergraduate degree, I got an opportunity through the NSERC scholarship to work in the laboratory of professor Vance Trudeau, doing research on goldfish endocrinology. I had a phenomenal experience and that is when I got the bug for research. When I started medical school, I realized that I missed doing research, and wanted to continue it. So, in first year of medical school, I started working in the laboratory of Dr. Ed O'Brien, an interventional cardiologist at the UOHI who does vascular biology research. He was a rare hybrid in terms of a clinician who did basic science research. During my medical training, as I spent more time doing research, I realized that I really wanted to have this as part of my career—and that is when I learned about the CIP.

What factors do you think students should take into account as they contemplate pursuing a clinician-investigator program (CIP) alongside their medical residency training?

I think the clinician-investigator program (CIP) is the only way to train a clinician-scientist, *period*. I think training medical students in research methodologies so early on in their training does them a disservice, not because the skill set that you learn is not applicable, but I genuinely worry about picking a topic and researching it *without* actually knowing what the clinical practice is like in that particular field. If you train people too early, there will be more attrition and they will likely change fields. Additionally, clinical training is getting so long now that building CIP training longitudinally throughout enables people to obtain their graduate degrees without spending too many additional years, which may otherwise discourage people from pursuing academia. The advantage of CIP is that when you enter the program, you have chosen the speciality of medicine (e.g., general surgery, cardiology, etc.) that you want and your research training and development is focused around your own clinical practice. I would love to know what percentage of students completing the combined MD/PhD program actually end up working in the clinical field in which they did their research training. I think there is a huge advantage, both in terms of career development and applied research when you study the field that you are going to work in as a clinician.

As I mentioned earlier, during my undergraduate degree, my research focused on goldfish endocrinology. While I learned the research skills at that time, my manuscripts on the complexities of the goldfish pituitary gland are not necessarily helping to develop my current career. I think the CIP is perfect in that it provides protected time for longitudinal research during your clinical training—that is exactly how my current professional life is structured. I think the CIP program does mimic what your life is going to look like if you become a clinician- scientist. You will be doing research while you are doing clinical work—that is a beautiful way to prepare residents to transition from trainee to assistant professor, which is exactly the goal of training clinician scientists: to do applicable translational research. I credit Dr. Jonathan Angel for leading the CIP at the University of Ottawa at that time, and I hope the university continues to support this training program because I think that is the only way you will get people that genuinely end up doing the kind of work required to become a proficient and productive clinician-scientist.

Did you gain experience with clinical research methodologies during your CIP, and do you find yourself using both sets of skills as a clinician-scientist?

I do both clinical and basic science research as a practicing clinician-scientist. I got a lot of exposure to clinical research methodologies during my residency training, as I collaborated in clinical trials and observational studies. Although I didn't get any formal training in clinical research methodologies, which would be nice to have, I did get a lot formal training in biochemistry. So when I was making the decision to pursue the CIP, I thought it was more important to get trained in bench-top research because that is not something you can pick up on the fly, whereas I thought the clinical research methodology is much more learnable. Also, at that time, I was interested in basic science research—it takes a lot more time and so I wanted to spend a lot of my protected time on that. And I'm glad I did.

You have done work in endothelial progenitor cells and their role in arterial repair. This is a medical innovation that has the ability to revolutionize cardiology practice. Would you be able to speak to the process in seeing these revolutionary laboratory findings turn into clinical trials and how they will eventually find their way into clinical practice?

I think you are going to be disappointed with this answer. I don't think any of the stem cell or progenitor cell research (in cardiology) is going to reach prime time. This speaks to difference between the left and the right hands not talking to each other. Something I realized very early in the cardiology field is that a lot of these stem cell innovations work very well in healthy volunteers, but the reality is that when we look at stem cells from older patient populations, they are not as functional. The engraftment is poor, therapeutic benefit is less, and you get fewer of the cells. This is a major limitation to therapy and researchers are trying to find a work-around to this. This field has been going on for a long time and I think lot of the luster has been worn off. As part of my training, I did a lot of preclinical work and I realized very early that it's very difficult to get enough cells to treat a patient and it's difficult to enroll patients in clinical trials. We have very good therapies for these patient populations that don't necessarily require stem cell-based therapies. I'll go out on a limb and say ten years from now, we are still not going to be treating patients with progenitor stem cells for cardiovascular disease. I've actually moved away from that line of work and I think it's important that as scientists we are realistic about evaluating the evidence and the data. When we realize a therapy is not working, we move on. I see it too often that people marry their careers to ideas that are clearly not going to translate but they hammer on it without making significant progress. I have started collaborating with industry on new technologies in structural heart disease. And I have been impressed working with these companies and engineers and I actually think there's a lot that academic research can learn from industry: *the willingness to abandon ideas that aren't working and the willingness to explore ideas that might seem infeasible or improbable.* That's how you truly make innovations and discoveries and impact in medicine. All too often I see in academia people married to hypotheses and concepts, unwilling to be flexible and truly evaluate the evidence. So, one of the things that I have started doing in my career is working with industry to really try to do these early procedures and early innovations—we'll be publishing some interesting first in-human work looking at novel therapies for heart failure soon. I think I'll be working a lot more with industry to try and leverage the knowledge base and the engineering expertise and really move the needle in terms of translational work.

How would you define *medical innovations*?

I think some of the most fascinating innovations are the use of technology or reapplying technology or insights that we already have to different problems. Recently, for example, Dr. Pietro di Santo (cardiology and a PhD Epidemiology trainee) and I ran a clinical trial to assess blood flow in the hand. This is commonly done in clinical practice to make sure arteries are good in the hand before we either put tubes in them or we take them for bypass grafts for surgery. We realized that we could use something as easy as photoplethysmography with an iPhone to do what we try to clinically in looking at the hand much more accurately. We published this randomized-control trial in the *Canadian Medical Association Journal* (1) demonstrating this concept and now we are moving this to the next level. Our goal is to use this iPhone technology to select patients for use of arterial conduits and bypass. This is an example of applying a readily available technology to a clinical problem that we encounter in practice on a regular basis.

I alluded to earlier we have been working a lot with industry. We understand that differences in the pressures of the chambers of the heart can be important for patients' symptoms. Therefore, we have been working with Edward Lifesciences to look at new forms of shunting technology to decompress the left atrium for patients with heart failure. We are working to develop a new type of shunting procedure to help these patients. There is nothing novel about the concept of intra-cardiac shunts, but the innovation is in how they are delivered, what devices are used, what occurs in terms of the healing of these devices, and how it impacts patient care. I do see, even in the research that we do here, really innovative and novel approaches to problems by simply applying the technology and knowledge that we already have and leveraging that to treat patients that we see everyday. From a bench-to-bedside approach, we need to do a lot more of that. *There are lots of interesting basic science insights that occur, but the reality is, the people who are doing that basic science research don't really understand the clinical problem and clinical context, so they are unable to see that through to translation.* And that's where clinician scientists come by providing that clinical insight and context. What I see in the future for this kind of work, if we want to be successful and capitalize on the investment

that we make, is a lot more collaborative teamwork between basic scientists, engineers, clinician-scientists, and clinicians to move this forward. We still work too often in silos; I think you'll see a lot more collaborations moving forward especially if we want to be successful in advancing medical technologies.

Meta-research, or research on research, is revolutionizing research practices and how we evaluate scientific methodologies. Can you tell us about some of your current work in meta-research?

One of the things that I am particularly proud of is the work of Dr. Dan Ramirez, who did his Masters in epidemiology. One of the things that often gets overlooked is that *science is not perfect, science is dirty.* We like to think that papers in high-impact journals are high quality and we like to think that conclusion from our scientific work are immutable. One of the things we have learned is that there is a lot of really poorly done science published in excellent journals. We may either reject therapies because of poorly done work, or we embrace therapy because of poorly done work. In our work published in *Circulation Research* (2), we found that the methodological rigour in basic science research is shockingly bad, and this is likely reflected in the reproducibility crisis that we have. Probably about 85% of the work is completely irreproducible largely due to methodological problems. We spend large proportions of our research budgets on fundamental sciences and, to be frank, the work is simply not good. There is, and has to be a lot of room for improvement. We owe a debt to society when the public provides funds for academic fundamental research that those funds get used appropriately. We have a lot of work coming out on this, highlighting how even in top journals of science, there's low quality research being done. *If there's one thing we can do on the basic science front, it is this: there needs to be a revolution in terms of methodologies and how we do science.* Because I think the flip side of that is, the public will wake up to it and you'll have trouble lobbying the government for funding for research if that money is not being well spent. So, that's one area that I am particularly proud of Dan and our group:we have been able to highlight some of these things and make significant contributions to the field, and I hope moving forward all of that will improve.

As students undergoing graduate and clinical studies, we are often told of the importance of maintaining a work-life balance. As a leading clinician-scientist at UOHI, how do you manage your work-life balance?

Yeah, I don't. This is very different from my colleagues so don't take this as gospel—I worry when people strive to find "work-life balance". You *always* trade them off. And that's an unfortunate and hard truth to hear. On one hand, people who spend a ton of time on their personal life probably are not as productive professionally. And that's life—you have only twenty-four hours in a day. On the other hand, people who bury themselves in their professional life obviously make sacrifices at home. So, when I'm with my family, I try to focus and spend quality time with my family. When I'm working professionally, I try to be as efficient as possible. And the reality is that I sacrifice things in both realms: I don't accomplish all the professional things that I want to accomplish and I don't spend nearly as much time with my family as I want to spend. I think the concept of work-life balance is a myth. I think work and life are competing interests because they both require time. I very much doubt that there are people in the world who are super-successful both professionally as well as at meeting all the demands of their personal life. I have made sacrifices in terms of my hobbies, and the time I spend going out with my friends. I have really compartmentalized my life into my personal work and my family—I prioritize those two things and the reality is when my professional life gets busy, my personal life suffers and if I spend more on my personal life, then my professional productivity suffers. That balance between the two is different for everyone and people have to find what is an acceptable balance to them, but there is no true balance. There is no way to be super-successful at both—at least I've never met anyone who is.

Would you be able to provide any advice for students who are interested in pursuing a career in general or interventional cardiology?

If you want to be a community interventional cardiologist and put stents in from morning to afternoon, call it a day and occasionally do a STEMI call, I don't think it's that different than any other clinical job that's out there. There are lot of hard-working doctors out there putting in a lot hours,work hard to do really good for their patients. However, if you want to be an academic interventional cardiologist, general surgeon, thoracic surgeon, or pediatrician for example, I think you have to recognize that that is a commitment, and *that* commitment is paid in time. You may get through your training, but if you're not willing to put the hours in, you're simply not going to be successful at what you do. Even putting in the hours, you are

not necessarily guaranteed to be successful. So, if you're going to commit to this career path, you want to make sure you are willing to put in the work and the hours. I see often, people who train to become an academic fail: not because they are not capable and not because they don't have enough support, but because life happens. Again, to go back to that work-life balance: they are unable to put in the time to get the work done. I would just warn people to be honest with themselves, about what lifestyle they want, how many hours they want to work, how much they enjoy it, and how much they're willing to sacrifice for it, because you have to love it if you're going to put in huge amounts of hours doing something.

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Book Review: *Bad Blood—Secrets and Lies in a Silicon Valley Startup*

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ABSTRACT

This book review appraises John Carreyrou's non-fiction book *Bad Blood*. The text provides penetrating insights on Theranos, an American laboratory diagnostics company that promised to revolutionize laboratory medicine. The author's award-winning prose relays the events leading to the eventual discovery of fraud at Theranos as well as the subsequent collapse of the company. The book can be faulted for being unripe. Publication prior to a full resolution to the Theranos affair precludes analysis of the longer-term impacts of this fraud. Notwithstanding, *Bad Blood*'s imperfect timing, the book remains a seminal text amidst journalistic chronicles of medical innovation gone wrong.

RÉSUMÉ

Cette critique littéraire évalue le livre non-fiction de John Carreyrou « Bad Blood ». Le texte donne un aperçu pénétrant sur Theranos, une compagnie américaine de diagnostics de laboratoire, qui promet de révolutionner la médecine laboratoire. La prose primée de l'auteur raconte les évènements menant à la découverte éventuelle de la fraude à Theranos, ainsi que le collapse subséquent de la compagnie. Ce livre peut être critiqué pour être inachevé. Sa publication avant la résolution complète de l'affaire Theranos empêche l'analyse des impacts à longue durée de cette fraude. Néanmoins le choix de moment imparfait de « Bad Blood », le livre reste un texte séminal entre les chroniques journalistiques d'innovations médicales mal tournées.

The seductive allure of medical innovation has been used successfully throughout time by people seeking to conceal unethical or even criminal acts. John Carreyrou's non-fiction book *Bad Blood - Secrets and Lies in a Silicon Valley Startup* (1) offers readers a comprehensive journalistic exposé of Theranos, a now-defunct laboratory diagnostics company formerly based in Palo Alto, California. This company, established in 2003 by former Stanford University student Elizabeth Holmes at age 19, purported to offer a broad range of clinical diagnostic tests performed on a futuristic device using capillary blood from the fingertip. In a radical departure from conventional tests requiring full tubes of drawn blood, Elizabeth Holmes rose to fame by claiming her fear of needles drove her and her team to pioneer several advances in robotics and clinical chemistry. These alleged developments allowed Theranos to offer revolutionary tests on only microlitres of blood using next-generation assays. Theranos affirmed this was all possible without sacrificing any diagnostic accuracy but never adduced this claim in the medical literature, citing a need to protect proprietary secrets. An effective storyteller, Carreyrou begins by providing the reader with insight into company founder Elizabeth Holmes' early life. In a relatively brief 299 pages, the author then details how Holmes' alleged innovations would eventually be revealed, over a decade later, to be consummate fantasy. Theranos' fingertip tests are presently thought to have been an elaborate fabrication crafted primarily in service of Holmes' pursuit of wealth and recognition. Media reports suggest certain Theranos tests were ultimately generated using traditional assays performed on equipment procured from conventional device vendors. Less fortunate patients had their results derived using unreliable prototypes of Theranos' own technology. Written in an easy-reading popular style, *Bad Blood* concludes by detailing the early stages of Theranos' spectacular collapse following methodological scrutiny from experts in pathology and clinical laboratory medicine, as well as regulatory enforcement from the United States Department of Health and Human Services.

Drawing mainly from interviews of former Theranos staff, collaborators and other closely-related primary sources, John Carreyrou emphasizes the day-to-day interactions that underpinned Holmes' deception of investors, media, physicians, regulators and vulnerable patients alike. Against

Keywords: Health Technology Fraud; Laboratory Regulation; Diagnostic Accuracy; Assay Development

the backdrop of a scientific community intent on minimizing the role of individual personality traits or interpersonal dynamics on the trajectory of scientific discovery, Carreyrou expertly holds the scientific reader's attention to a specific true account of a young and charismatic charlatan who leveraged personal qualities to circumvent, if briefly, our esteemed process of vetted medical discovery. In several passages, Carreyrou vividly recounts Holmes' hypnotic voice, entrancing gaze, and self-assured demeanor as she misled scientifically-illiterate Silicon Valley investors seeking to profit from Theranos' meteoric rise. The author effectively relays how the superficial charm, aura of success and particularized bravado of Holmes and her associates kept inquisitive scientists, physicians and regulators away from Theranos headquarters for several years. Major pharmacy chains in the United States agreed to distribute Theranos tests based entirely on Holmes' outstanding salesmanship and without any published validation studies. Inescapable for the medical audience is the sub-textual implication that Holmes' seemingly-innocuous idiosyncrasies sufficed to pervert the regular course of peer-reviewed medical innovation and facilitated patient harm from faulty laboratory tests. Reading between the lines, *Bad Blood* also places a heavy burden on the shoulders of the physician or medical scientist: if a teen Stanford dropout can execute a complex fraud under the guise of medical innovation, what role will legitimate medical innovators have to play in ensuring that scientific discovery is not subverted in a manner that causes people harm?

Carreyrou's strict adherence to fact-based reporting will permit readers to form their own answer to this question as well as arrive at their own conclusions when determining what exactly went wrong within Theranos. From strikingly detailed reconstructions of the contorted sequence of events leading to Theranos' downfall, the reader will emerge with several possible loci on which to plausibly rest blame. It is possible that Silicon Valley itself is culpable; an innovation-driven culture that wantonly prioritizes technological innovation over patient safety is a clear path to disaster. Perhaps the media played a role. Carreyrou holds a magnifying glass to Holmes' depictions in popular outlets, whose content creators eagerly heralded Holmes as the archetypal manifestation of women's success in Silicon Valley's predominantly male environment. Holmes' ascent to renown fit neatly within prevailing social movements promoting women's achievements in Science, Technology, Engineering and Medicine and those fostering overdue gender equality within these same fields of endeavour.

Lastly, it would also be possible to conclude that there is a fundamental flaw with the overall conduct and regulation of medical innovation. Although eventually subject to scientific scrutiny and regulatory control, North American medical scientists and regulators spared Theranos from rigorous methodological assessment for more than ten years as the numbers of harmed patients continued to grow at alarming rates.

Bad Blood's cardinal limitation is prematurity. The book was concluded too soon, and any sensations of incomplete resolution felt by readers as the book draws to a close are entirely justified. The book's early publication precluded a complete understanding of the criminal outcomes of Elizabeth Homes' wire fraud trial, which remains underway. A complete account of the harms attributable to Theranos' defective tests is similarly unavailable. There is reason to believe these harms may be significant and numerous; Theranos' battery of offerings included tests used to dose drugs with narrow therapeutic indices, such as prothrombin time. Theranos patients have also reported receiving inaccurate results of endocrine function, including one patient whose severely elevated estrogen led her physician to believe her breast cancer may have returned. Finally, the book's swift publication prevented a complete analysis of Theranos' long-term impacts on the broader field of laboratory diagnostic medicine. Prior to collapse, Theranos had successfully lobbied legislators in Arizona to legalize patient-direct ordering of any diagnostic test offered by any clinical laboratory in the state without the involvement of a licensed primary healthcare provider. Ominously, this law remains in effect today despite the revelation that for many Theranos patients who received erroneous results, it was primary providers who ordered retests and in doing so stymied the cascade of patient harms that might otherwise have followed.

Above all else, the story of Theranos and Elizabeth Holmes forces the medico-scientific community to confront a difficult reality: In our new millennium, which presumably symbolizes the cumulative pinnacle of human achievement, it remains possible to perpetrate health-technological fraud while entirely concealed under the lustrous guise of innovative medicine.

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Why I Write Academic Blogs

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ABSTRACT

Peer-reviewed academic publications are considered a gold standard for sharing scholarly work. However, this traditional method is not without challenges; peer-reviewed journals take several months to publish articles and often limit accessibility through scientific rhetoric and restricting full-texts to those with paid memberships. Based on the literature and my personal experiences, I explain how academic blogging can help overcome these barriers, while introducing other challenges: smaller word counts, feedback from less reviewers, and potential for misinterpretation. Overall, I urge others in academia to consider including blogs in their repertoire for disseminating knowledge rather than aiming solely for peer-reviewed articles.

RÉSUMÉ

Les publications scolaires révisées par les pairs sont considérées comme l'étalon d'or pour le partage d'œuvres universitaires. Par contre, cette méthode traditionnelle n'est pas sans défis ; les journaux révisés par les pairs prennent plusieurs mois pour publier des articles et limitent souvent l'accessibilité en exigeant une rhétorique scientifique et une adhésion payée pour les articles complets. Basé sur la littérature et sur mes expériences personnelles, j'explique comment tenir un blogue scolaire peut aider à surmonter ces barrières en introduisant d'autres défis : un nombre de mots plus petit, la rétroaction venant de peu de critiques, et le potentiel pour l'interprétation erronée. Dans l'ensemble, j'encourage les autres dans les domain es scolaires à considérer d'inclure les blogues dans leur répertoire de partage de connaissances, au lieu de viser seulement pour des articles révisés par les pairs.

During my post-secondary academic career, I have become familiar with the high regard held for peer-reviewed publications. Not only are they a valuable tool for scholars in all disciplines to share their work with peers and colleagues, but they also serve as a testament to one's scholarly endeavours. As a student, I am always impressed when I encounter individuals who have published many articles throughout their academic careers. Admittedly, I have also experienced imposter syndrome from witnessing these achievements, feeling as though I have fallen short for not meeting this implicit expectation to publish. As a result, publishing peer-reviewed articles has been a goal of mine for many years. However, I quickly learned that publishing in scholarly journals is not without issues, namely slow turnaround times between submission and publication, as well as limitations to accessibility with respect to physically accessing full-text articles and engaging diverse groups of readers. Consequently, I turned to academic blogging as an alternative medium through which I could disseminate my work in addition to the traditional peer-reviewed route. By supplementing my personal experiences with evidence from the literature, I hope to discuss turnaround time and accessibility as they pertain to both peer-reviewed journals and academic blogs. The aim of this commentary is to explain why I view the latter as essential, while also presenting benefits and drawbacks of both mediums so that readers are empowered to decide what they prefer.

TURNAROUND TIME

One issue I have encountered in the world of peer-review is the slow turnaround time. For example, some papers I have submitted have taken several months to be published—this is not uncommon. In an analysis of papers published in the PubMed database between 1980 (in 4,353 journals) and 2015 (in 9,045 journals), a median turnaround time of about 100 days between submission and decision was found (1). However, this can sometimes take even longer; one manuscript I have previously submitted has been under review for almost a year. One reason for these long turnaround times is the high volume of submissions (1). For instance, the number of yearly submissions to PLoS ONE was about 30,000 in 2014; Academic Medicine, a prominent medical education journal, receives about 1,500 submissions each year (1,2). Naturally, finding multiple reviewers for this many articles is particularly difficult, resulting in further increases to submission-decision turnaround time (1). Furthermore, receiving this decision

Keywords: Publication; Blogging; Peer-review; Scholarship; Knowledge; Research

is not the end of the process; acceptances typically include major and minor revisions for authors to incorporate in a resubmission that must be reviewed once again. From a revisions perspective, increased turnaround time can be beneficial because it enables multiple reviewers with relevant knowledge and experience to appraise the submission and offer constructive feedback, ultimately improving the quality of the work. However, such delays in disseminating research and scholarship can also serve as a rate-limiting step for advancing the field and educating others about our work. For time-sensitive publications, like systematic reviews, slow turnaround times can even increase the risk of findings becoming outdated by the time they are published. In fact, the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0) states that literature searches should be updated every six months (3).

Contrary to scholarly journals, academic blogs publish articles a lot more quickly. One reason for their faster turnaround times are that blogs typically publish shorter articles as compared to traditional journal articles. For instance, KevinMD.com, a prominent healthcare blog, has a maximum word count of 1,000 words; articles of this length can be read more quickly, allowing for a submission-decision turnaround time of about 10 days, with subsequent publication occurring in 1-3 weeks (4). From my personal experience, these timelines were even shorter. Additionally, the Canadian Medical Association Journal (CMAJ) also has a 1000-word maximum and a quick submission-decision turnaround time, accepting one of my pieces within 5 days of submission and publishing it 11 days later (5). However, while smaller word counts allow articles to be more efficiently reviewed, authors must sometimes sacrifice depth of content in order to remain within these limits. Another reason that blogs have quicker turnaround times is that they do not undergo a thorough peer-review process. Though this allows blog submissions to be appraised more quickly, it also limits authors to feedback from one reviewer instead of receiving comments from multiple reviewers. Nonetheless, submissions to KevinMD.com, CMAJ Blogs, and many other blogs available online are still appraised by individuals with relevant knowledge and experience while also publishing articles promptly. This allows for more content to be produced in a shorter period of time, making academic blogging more efficient than the traditional route of publication (6).

ACCESSIBILITY

Another issue I have encountered with peer-reviewed publication is regarding accessibility. While some journals are openly accessible, many require paid subscriptions to access full-text articles. As a result, those without such memberships cannot read these journals, which hinders individuals from engaging with the research detailed within them. Seeing the value in such engagement, I aimed for my peer-reviewed articles to be publicly accessible; however, the 3,000 USD fee for open access publishing in many journals severely limited my ability to do so (6). Even when I was able to publish articles that were accessible in full, they were written in scientific language—as per the journals' specifications—that caters to scholars already in the field. On the one hand, this is helpful because these scholars are most directly immersed in the field, making them well-positioned to create meaningful change based on the contents of these publications. However, tailoring peer-reviewed articles exclusively to researchers in the field also limited my ability to engage individuals from diverse academic backgrounds who may have had useful insights to offer but were unable to navigate my discipline-specific terminology and phrasing. Moreover, such scientific rhetoric hinders knowledge translation for the general public, unfairly excluding them from consuming certain knowledge simply because they are not from the field wherein that knowledge was produced. This is especially concerning when the content has potential to affect members of the public, such as research about cutting-edge treatments or how the next generation of health professionals are being trained. While reducing or eliminating open access fees may not be feasible for journals not receiving subsidies to cover publication costs, accessibility to journal articles can be partially improved by encouraging authors to simplify their rhetoric.

Authors can also improve accessibility to their content by disseminating it in academic blogs in addition to peer-reviewed journals (6). Most academic blogs are freely accessed by the general public and do not ask contributing authors to pay open access fees. This not only enables those with an interest in the blog to engage with its content, but also encourages authors to submit articles—myself included. Moreover, academic blogs typically publish articles written in casual language that is more engaging than the scientific rhetoric in many traditional journals, thereby improving readability for consumers of diverse backgrounds and levels of education (6). Wanting to engage the general public and individuals from other fields, this was appealing to me. Through my submissions to KevinMD.com and CMAJ, for instance, I was able to generate rich discussion amongst individuals outside

of the medical education field about physician empathy and medical school admissions. Another benefit of open access and conversational tone is that they allow blogs to grow their following substantially, giving their articles a larger reach than journals requiring paid subscriptions and scientific rhetoric. For example, KevinMD.com receives about 3 million views per month, and the Harvard Macy Institute blog receives an average of about 1500 hits on each post (4,7). One potential drawback of academic blogs being openly accessible is that, given their greater diversity in readership as compared to peer-reviewed journals articles, they may be more susceptible to misinterpretation if not written clearly. Nevertheless, the ability for academic blogs to disseminate information to such large audiences is a powerful tool; in addition to writing for peer-reviewed journals, scholars should leverage academic blogs to increase their readership and discussion about their work. These conversations are valuable for generating awareness, perspectives, and even solutions about the topic covered in the articles, which ultimately help to advance the field.

CONCLUSION

Overall, peer-reviewed publications are undoubtedly an integral part of academia, and I am not suggesting that we devalue them. Instead, I hope that others may consider academic blogging as a complementary—not mutually exclusive—option to their traditional peer-reviewed journal publications. In this article, I explained my reasons for including academic blogging to my repertoire, while also providing benefits and limitations for both mediums with respect to issues of turnaround time and accessibility, with literature and personal experiences supporting my claims. With this information, readers can weigh these considerations and arrive at their own conclusions regarding academic blogs. Nonetheless, whether it be through peer-reviewed journals, academic blogging, or a combination of both mediums, we have a social responsibility as researchers, scholars, and aspiring physicians, to progress our respective fields, and society as a whole, through education and knowledge translation.

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Medical Innovation Taking Form: 3D Printing at The Ottawa Hospital

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ABSTRACT

Three-dimensional (3D) printing is an emerging medical technology with capacity to revolutionize multitude aspects of clinical care and medical education. This commentary highlights The Ottawa Hospital Medical 3D Printing Program, a leading Canadian site for the manufacturing of 3D-printed clinical solutions. In Ottawa, 3D printing has already been employed to optimize pre-operative surgical planning, facilitate communication with patients, and enhance medical learning and outreach efforts. Rapid advances in manufacturing technology are poised to further expand current medical applications of 3D printing nationwide.

RÉSUMÉ

L'impression tridimensionnelle (3D) est une technologie médicale émergente avec la capacité de révolutionner plusieurs aspects des soins cliniques et de l'éducation médicale. Ce commentaire surligne le programme d'impression médicale 3D de l'Hôpital d'Ottawa, un site canadien éminent pour la fabrication de solutions cliniques imprimées en 3D. À Ottawa, l'impression 3D a déjà été employée pour optimiser la planification chirurgicale préopératoire, pour faciliter la communication avec les patients, et pour améliorer l'apprentissage médical et la portée. Des avances rapides en des technologies de fabrication sont prêtes à développer de plus les applications médicales actuelles d'impression 3D à l'échelle nationale.

Three-dimensional (3D) printing describes a group of manufacturing techniques permitting digital blueprints to be translated into the synthesis of 3D objects. The first form of 3D printing, originally coined stereolithography, was patented in 1986 (1). Since that time, rapid advances in manufacturing instrumentation and materials technology has led to 3D printers with capabilities approaching or surpassing those of traditional manufacturing techniques. Indeed, modern 3D printing enables custom objects, composed of a wide variety of materials, to be synthesized with acute accuracy and precision, often with significant time- and cost-savings (2). These features of 3D printing lend themselves well to applicability in medicine, where vast patient diversity and rapid technological advancement demand flexible and expedient material solutions.

3D-printed objects have demonstrated utility in a widening variety of clinical applications over the last two decades (3,4), often with significant cost and/or time savings compared to traditional approaches (5). In clinical settings, 3D printing technology has been employed to facilitate surgical planning, fabrication of surgical tools, medical and patient education, as well as bioprinting of synthetic tissues, amongst other applications (6). The continual widening of these applications is expected to push the 3D printing medical devices market value to upwards of $1.88 billion USD by 2022 (7).

Consequent to an evolving interest in the clinical value of 3D printing, specialized manufacturing teams and facilities are increasingly incorporated into the hospital and medical education milieu. One such example of this collaboration between engineering and medicine is The Ottawa Hospital (TOH) Medical 3D Printing Program. Formally established in 2017, TOH's 3D Printing Program acts as a central hub, integrating contributions from a dynamic group of teams at TOH and the University of Ottawa Faculty of Medicine. Under the leadership of radiologists Dr. Frank Rybicki and Dr. Adnan Sheikh, the TOH Medical 3D Printing Program aims to explore means by which advances in 3D printing can be harnessed to tailor novel clinical solutions and innovations in medical education. TOH's 3D Printing Program is Canada's first hospital-integrated 3D medical printing institution and serves an increasingly important component of medical care

Keywords: 3D Print; Medical Innovation; Anatomical Model; Medical Education

for patients at TOH (8).

In this commentary, we focus on the current practices and future directions of the TOH Medical 3D Printing Program. Through description of specific applications and pilot educational programs, we aim to convey how 3D manufacturing is currently revolutionizing clinical care and medical education at TOH, as well as provide a prelude for notable innovations on the horizon.

SURGICAL APPLICATIONS OF 3D ANATOMICAL MODELING

High-acuity radiological imaging permits the physical recapitulation of patient-specific 3D-printed anatomical models. Through this process, radiologists and surgeons are able to visualize and physically engage with anatomical structures in situ, just as they would encounter them during surgery. Patient-specific 3D anatomical models may therefore permit a degree of surgical planning and preparedness not otherwise attainable with traditional radiological imaging. For this reason, preoperative anatomical models are one of the more prevalent clinical applications of the TOH 3D Printing Program. Customized 3D-printed structures have been used preoperatively at TOH to model complex fractures of the pelvis, reproduce neoplastic masses of varying origin, and to instruct the dimensions of physical implants so as to ensure optimization with biological structures during reconstructive surgery. In each case, 3D models may have facilitated a greater awareness of patient anatomy prior to surgery, potentially benefitting patient care by improving surgical precision, mitigating the risk of surgical error, and decreasing the duration of surgery. Indeed, in a recent systematic review, a majority of studies described a significant reduction in operating time, improved anatomical representation, and enhanced surgical outcomes when similar anatomical models have been employed at other centers (9).

According to physicians involved in previous surgical applications of 3D printing, the technology offers a tangible clinical benefit. Dr. Joel Werier, an Orthopaedic Surgeon and Oncologist at TOH has employed 3D-printed models to plan complex oncology surgeries since the TOH 3D Printing Program was initiated. He recently remarked that "3D printing is revolutionizing the way we look at anatomy" (10). He added, "it adds another perspective to how we view tumours, how we plan our surgery techniques, and our ability to offer precision surgery" (10).

In addition to their use in preoperative planning, 3D-printed models can allow TOH patients an opportunity to gain unique insight into their illness. For example, Dr. Sukhbir (Sony) Singh, of the TOH Surgical Gynecology Department, sought the aid of the 3D printing program for assistance with a complex uterine abdominal myomectomy surgical case requiring the excision of forty-eight subserosal and two submucosal fibroids (11). The goal of the procedure was to preserve the patient's uterus, permitting a chance of future pregnancy that would not have been possible following an invasive hysterectomy. Prior to the surgery, Dr. Singh presented the 3D model to his patient so as to explain her upcoming procedure in the context of her own anatomy. Patient understanding of their health status and of proposed surgical procedures is important to ensure the integrity of patient's surgical decision-making (12). We postulate that incorporating anatomy or procedure-specific 3D models in the patient-physician interaction, such as in this case, may help to better inform patients and to promote accurate expectations of their postoperative course.

APPLICATIONS IN MEDICAL EDUCATION

With few exceptions, anatomical knowledge forms the groundwork from which all clinical decisions are based. Traditional teaching in medical anatomy has emphasized the conjunctive use of two-dimensional (2D) images and cadaveric-based learning. However, there are limitations associated with each of these educational models. For instance, 2D images fall short in engendering an understanding of depth, dimension, or scale amongst learners. While considered a valuable learning resource, cadaveric simulation is limited by high cost, lack of availability, and ethical issues (13). Adjunctive use of 3D-printed educational models in medical education can help address these limitations and optimize anatomical learning. 3D models allow learners to appreciate those details of anatomical structures that would otherwise be obscured by 2D images. By providing both normal and pathology-specific anatomical models, 3D printing also promotes an awareness of anatomical variants and abnormalities less amenable to cadaveric simulation (14).

In collaboration with the TOH 3D Printing Program, researchers at the University of Ottawa are actively exploring the utility of 3D-printed anatomical models in anatomical education. The tracheobronchial tree, housed within the lungs, is a complex biological structure that is difficult to appreciate in 2D images or visualize in the cadaveric laboratory. 3D-printed bronchial structures, however, provide healthcare practitioners and

trainees an opportunity to physically interact with respiratory anatomy, potentially allowing for a greater understanding of normal and pathologic respiratory physiology. Radiologist Dr. Carolina Souza is currently leading an investigation aiming to examine the utility of a 3D-printed tracheobronchial medical education model in promoting accurate interpretation of pulmonary computed tomography (CT) scans amongst medical students and residents. Their group hypothesizes that the 3D model will provide an opportunity for superior learning as compared to traditional 2D textbook images (unpublished). Innovation in clinical teaching, however, is but one example of the power of 3D printing to inspire a fascination of medicine and science. 3D-printed biological structures also provide members of the public an opportunity to interact and engage with medical concepts that would otherwise be limited to healthcare trainees. The TOH 3D Printing Program recently launched a permanent exhibit showcasing 3D-printed anatomical models at the Canada Science & Technology Museum. The exhibit consists of two parts: a display of mounted 3D-printed anatomical structures including models of the heart, lungs, pelvis, and liver as well as a hands-on exploration area where 3D-printed anatomical models are visually concealed but identified through touch & feel. This has become one of the most popular exhibits at the Canada Science & Technology Museum, which welcomes 650,000 visitors annually (15).

3D-printed models have also been integral in another outreach initiative recently launched at the Canada Science & Technology Museum. Medical Curiosity on Stage, a series of interactive and captivating presentations hosted by University of Ottawa medical students, seeks to immerse young children and adolescents in science, technology, engineering, mathematics, and medicine (STEMM) topics. The program is the first of its kind in Canada, and to our knowledge, internationally. Each session aims to foster health promotion and preventative medicine by providing interactive and fun presentations centering on science and technology. Concepts presented in previous shows include the signs and symptoms of common medical conditions (i.e. myocardial infarction, stroke, fractures), medical equipment (i.e. heart valves, catheters, and stents), basic cardiopulmonary resuscitation (CPR) skills, simulated medical procedures (i.e. bone internal fixation and intubation), and the biology of microscopic zebrafish larvae, amongst many other topics. Since its inception in May 2018, the series has relied on 3D-printed anatomical models that allow attendees to have hands-on exploration of structures related to the given presentation. The low-cost nature of these items permits some members of the audience to be gifted the models to take home with them. Those involved in Medical Curiosity on Stage hope that these outreach efforts provide young children with positive early experiences and foster enthusiasm to pursue future experiences in STEMM.

FUTURE DEVELOPMENTS

At the intersection of medicine and academia, the TOH 3D Printing Program is at the natural crossroads for the development and deployment of research innovations within the healthcare sector. Several innovations are currently in development and being assessed for translation to clinical patient care. Here we highlight a number of innovations being actively studied at the TOH 3D Printing Program.

Arterial Phantoms

3D-printed blood vessels are increasingly being used to visualize patient- and pathology-specific states in the field of cardiovascular surgery. Preoperatively, 3D-printed blood vessels can facilitate the selection and intended location of endovascular stents in complex aortic aneurysms and coarctations (16–18). Likewise, in other settings, 3D-printed blood vessels have been employed to aid surgical practice amongst medical trainees and to evaluate the utility of imaging technologies in endovascular interventions (19,20). However, the degree to which these 3D-printed models recapitulate physiological characteristics of blood vessels has been limited thus far. At the TOH 3D Printing Program, research is underway to improve the fidelity and the utility of these so-called "arterial phantom" models for surgical planning and training.

Surgical Guides

In prosthodontics, 3D printing technology has been used to create patient-specific surgical guides. These structures, unlike patient-specific anatomical models, are designed to precisely overlay a patient's teeth and incorporate intentional gaps in material to indicate the desired location for needle passes or surgical drills. By this means, surgical procedures may be "templated", allowing the placement of dental implants with superior precision compared to conventional techniques (i.e., gypsum stone and denture models) (21). It is conceivable that this application of custom 3D printing be extended to the guidance of anesthetic injections or biopsy procedures in other medical fields. The feasibility of related applications is currently under investigation at the TOH 3D Printing Program.

Implantable Scaffolds for Bone Growth

In Australia, a novel 3D-printed solution was devised for treatment of osteomyelitis-mediated tibial bone destruction (22). In such cases, traditional management would favor an above-knee amputation. This outcome was obviated by the transplantation of 3D-printed scaffold containing fibular bone tissue and blood supply grafted from the contralateral leg (22). While long-term growth and functional outcomes are not yet known in this patient case, the TOH 3D Printing Program is making very preliminary assessments regarding the viability of generating similar tissue-based scaffolds.

CONCLUSION

There is no doubt that 3D printing technology is revolutionizing healthcare. In this article, we have reviewed select major projects pioneered at the TOH 3D Printing Program, including those relating to surgical and medical education. We have also highlighted a number of putative future applications that could harness 3D printing technology to improve patient care in Ottawa. There are, however, limitations of 3D printing that must be acknowledged. Foremost of these limitations is the up-front cost of 3D printing materials and equipment, the attainment of personnel familiar with the technology, as well as the paucity of evidence demonstrating clinical efficacy of 3D printed devices in certain applications (9,23). With ongoing research at the TOH 3D Printing Program, amongst other centers, we expect these limitations to be gradually minimized while clinically efficacious applications of 3D technology become progressively more prevalent.

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Wikimedica: une Plateforme Collaborative de Transfert des Connaissances Médicales en Libre Accès

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RÉSUMÉ

La médecine moderne ne peut plus se pratiquer sans l'aide de bases de connaissances cliniques. Or, toutes celles disponibles sont payantes et fermées et s'il est un domaine qui pourrait bénéficier d'un accès libre à de l'information fiable, de qualité et à jour, c'est celui de la santé. Wikimedica (http://wikimedi.ca) est une plateforme libre accès conçue à cette fin qui permet tant aux cliniciens de terrain qu'aux étudiants de collaborer dans la création et l'amélioration des connaissances essentielles à leur professions.

ABSTRACT

Modern medicine cannot be practiced without the help of basic clinical knowledge. However, all that is available is payment based and restricted, and if ever there was a field in which one could benefit from free-access to trustworthy, high quality and up to date information, it would be healthcare. Wikimedica (http://wikimedi.ca) is a free-access platform created for this purpose which allows working clinicians and students to collaborate on the creation and the improvement of the knowledge essential to their professions.

Voilà bien longtemps que l'étendue de la connaissance médicale a outrepassé les limites d'un seul cerveau et il est désormais impossible de pratiquer la médecine sans s'aider de bases de connaissances cliniques. Que ce soit pour confirmer un diagnostic ou choisir un traitement, elles sont devenues indispensables lorsque vient le temps d'orienter nos décisions de soins. Dans le domaine, les options se limitent essentiellement à UpToDate ou Dynamed; tous deux demandant le gros prix pour l'accès à leur service, surtout pour les institutions. À cet effet, plusieurs d'entre elles ont été contraintes, devant une augmentation des frais d'accès dépassant le 600% en 8 ans, à délaisser UpToDate pour son seul compétiteur (1).

Pourtant, s'il est un domaine où l'accès à la connaissance devrait être libre (consultation et réutilisation sans barrière légale, monétaire ou technique), c'est bien celui de la santé : nos systèmes publics en sont tributaires, sa production a largement été financée par nos impôts et la qualité des soins est somme toute garante d'une information de qualité et à jour. C'est un impératif moral. Alors pourquoi n'existe-t-il pas de base de connaissances cliniques complète, fiable et en libre accès? Le célèbre Wikipédia est largement utilisé à ces fins mais tant son mandat encyclopédique que son manque de complétude sur certains sujets de pointe rendent son utilité limitée (2). Citons aussi WikEM, une très bonne ressource elle aussi en libre accès, mais limitée à la médecine d'urgence. Le Dr. James Heilman (urgentologue britano-colombien et ardent défenseur du libre accès), dans un article intitulé *Open Access to a High-Quality, Impartial, Point-of-Care Medical Summary Would Save Lives: Why Does It Not Exist?* (3), explore les raisons pour lesquelles le libre accès n'a pas percé en clinique. Quelques initiatives se sont attaquées à ce défi de taille dans le passé, comme Medpedia ou Wikemerg.ca, mais quasiment toutes ont échoué, n'ayant pu trouver d'adéquation pour ses éditeurs entre compensation monétaire, prestige et avancement de carrière (3). À ceci j'ajouterai que l'échec de ces projets est également attribuable à leur utilisation d'un modèle éditorial classique par comité exclusif d'experts. Il est également possible que la communauté médicale n'était tout simplement par mûre pour opérer une transition vers le libre accès. La seule initiative ayant eu un semblant de succès est le contenu médical sur Wikipédia (qui ironiquement ne cible pas les professionnels) ce qui s'explique principalement de par son processus éditorial collaboratif, informel et révisé par les pairs. Dr. Heilman suggère ensuite que si les créateurs de ce contenu sur Wikipédia, au nombre de 2500, choisissaient d'écrire quelques articles de niveau clinique, d'adapter ceux existants ou d'en réviser d'autres, en peu de temps nous aurions bâti cette base de connaissance impartiale, de qualité et surtout, en libre accès. Bref, la force du nombre…Et en santé, cette

Keywords: Wiki; Collaboration; Knowledge Transfer; Inter-professionnal; Open-access

force existe, il suffit seulement de la canaliser. Chaque jour, il se produit dans nos programmes une somme faramineuse d'informations cliniques qui aussitôt dispensée tombe aux oubliettes. Pensez à toutes les présentations que vous avez dû donner... Et si ces producteurs de contenu se fédéraient afin de ne plus travailler en isolation et unissaient leurs efforts. Et si tout ce travail à titre d'étudiant ou de clinicien pouvait bénéficier d'un deuxième souffle et servir de fondation ou d'amélioration d'une base de connaissances médicales de qualité, impartiale, à jour, collaborative et en libre accès. Voilà justement le principal objectif que Wikimedica s'est donné (http://wikimedi.ca) (**Figure 1**, **Figure 2**). Ça, mais aussi de rassembler sur une plateforme tous les professionnels de la santé afin de briser les cloisons historiques qui séparent chaque spécialité : la collaboration interprofessionnelle est, après tout, plus que jamais actuelle. Et qui de mieux pour enseigner l'examen de l'épaule qu'un physiothérapeute?

Wikimedica

Figure 1. Le logo de Wikimedica (http://wikimedi.ca)

Figure 2. La page d'accueil intègre des liens vers les portails de chaque profession, des nouvelles et une barre de recherche permettant de naviguer tout le contenu de la plateforme.

Pour ce faire, le format du wiki s'est imposé comme le plus adapté: une plateforme où les utilisateurs sont aussi éditeurs et appelés à bonifier le contenu dans le cadre d'un processus éditorial révisé par les pairs. Peuvent se retrouver sur Wikimedica une multitude d'outils: résumés cliniques, algorithmes, protocoles, médicaments, outils pédagogiques (cours, flashcards, cas cliniques, etc.), calculateurs médicaux, etc. En fait, il n'y a pas de limite à ce qui peut être intégré à Wikimedica et dans ce cadre, le projet vise à contrer la multiplication des sources d'informations cliniques (applications, PDF, documents papiers...) en offrant une consultation efficace et efficiente, que ce soit dans le cadre d'un travail scolaire ou au chevet d'un patient. À cet effet, une ontologie a été développée afin de standardiser la conception des pages. Plusieurs mécanismes ont également été mis en place pour éviter la péremption de l'information par sa duplication. Différentes pages partageant un même contenu peuvent donc se parler pour mutuellement se tenir à jour lorsque l'une est modifiée. Par ailleurs, la connaissance sur Wikimedica est structurée de deux façons simultanées : une page définit du texte lisible par l'humain, mais aussi des données sémantiques navigables par un programme informatique. Par exemple, il vous est possible de demander au système de vous indiquer toutes les maladies dont la dyspnée est un symptôme. En étoffant un peu votre requête avec d'autres symptômes et des signes, vous obtiendrez un diagnostic différentiel pour une présentation clinique donnée. Les possibilités sont donc infinies, surtout lorsque l'on met ces données en relation avec d'autres. En association avec un dossier médical électronique, la révision de la qualité de l'acte pourrait devenir automatisée. À plus grande échelle et avec le concours de l'intelligence artificielle, Wikimedica pourrait s'intégrer à un assistant de prise en charge clinique, personnalisant ses recommandations selon le patient. Les intelligences artificielles (IA), qui ont déjà fait leur entrée en santé, méritent que l'on s'y attarde. La preuve sera bientôt faite qu'en les associant à un clinicien, elles amélioreront l'issue des soins à un patient, les rendant ainsi indispensables (4). Imaginez donc le préjudice que subiraient nos systèmes de santé publics s'il fallait que ces IA soient contrôlées par des intérêts mercantiles et alimentées par de la donnée fermée. Et contrairement au scénario UpToDate discuté en début de texte, passer au compétiteur sera loin d'être une mince affaire. Maintenant, imaginez l'ampleur du problème éthique si nous n'avions aucun moyen de savoir

si les recommandations d'un tel outil sont motivées par un partenariat entre le fournisseur et un tiers ou le cheminement logique ayant mené un algorithme à proposer un traitement s'étant avéré préjudiciable (5). Ici, Wikimedica se positionnerait comme source de données libre et ouvertes, s'alliant au privé pour fournir des systèmes d'IA transparents et non-exclusifs.

Wikimedica partage les mêmes idéaux fondateurs que Wikipédia : la libération de la connaissance, la collaboration wiki comme mode éditorial et la même plateforme technique (MediaWiki). Cependant, il existe trois différences clés sur Wikimedica:

1. Il est destiné aux professionnels de la santé;
2. Seuls les professionnels de la santé peuvent le modifier;
3. L'anonymat n'y est pas permis.

Ces contraintes vont de soi. Wikipédia est avant tout grand public, alors que Wikimedica contient de l'information technique. Conséquemment, Wikimedica ne peut être modifié que par des professionnels (ou étudiants de ces professions) et ces derniers ne peuvent être anonymes, car ils doivent engager leur responsabilité déontologique, garantissant ainsi la qualité de leurs contribution stout en permettant la reconnaissance de leurs apports. Le processus éditorial n'appartient donc plus à un petit noyau, mais à la communauté entière et est mis en place par tout un système de suivis des modifications, d'alertes, de discussion et de suggestions. Il ne se change pas une virgule sur Wikimedica sans que l'on sache qui l'a fait, où et à quel moment. La connaissance sensible, par exemple un dosage, y est protégée, la fluidité du processus éditorial fait en sorte qu'une information erronée peut être corrigée instantanément et les dernières avancées sont intégrées sans délai.

Avec Wikimedica, le transfert des connaissances devient dynamique et collaboratif. Il reste que cette manière de faire constitue un changement de paradigme et beaucoup voient d'un mauvais œil la possibilité que leur travail puisse être modifié par d'autres. Pourtant, l'expérience nous démontre que les contributions sur des systèmes collaboratifs vont dans le sens de l'amélioration (6). Pour une plateforme sans anonymat telle que Wikimedica, le risque de vandalisme est virtuellement nul, surtout lorsqu'on le compare aux bénéfices d'un cycle d'améliorations raccourci et collaboratif. Également, d'autres ont tendance à être suspicieux du fait que l'accès en lecture soit public. Wikimedica n'a cependant pas inventé Dr. Google et ne croit pas non plus que l'information devrait être censurée dans la seule crainte qu'elle soit mal utilisée: faisons confiance au jugement citoyen. Nos sociétés fourmillent d'esprits créatifs, nul besoin d'être médecin pour innover en médecine. Il y a donc fort à parier qu'un individu inventif trouvera des façons de repenser la connaissance diffusée par un système en libre accès pour solutionner d'autres défis. C'est dans ce contexte que le libre accès prend toute son importance et vient agir comme catalyseur de l'innovation. Pourtant, lorsque présenté aux décideurs, le concept accroche, possiblement puisque les licences libre accès sont perçues à tort comme une cession de droits et une perte de contrôle. En fait, en plus d'encourager le progrès, le libre accès donne une portée bien plus grande aux œuvres et s'impose comme un impératif éthique, comme l'a formulé l'UNESCO en 1999 (7):

« L'égalité d'accès à la science ne répond pas seulement à un impératif social et éthique du développement humain, elle est aussi indispensable si l'on veut exploiter pleinement le potentiel des communautés scientifiques dans le monde entier et faire tendre le progrès scientifique vers la satisfaction des besoins de l'humanité (8). »

Disons que le libre accès a le vent dans les voiles. Le journal même dans lequel vous lisez ces lignes en est la preuve, mais aussi le fait que ce mode de publication ait été adopté pas des grands noms de l'éducation comme le MIT ou Johns Hopkins, sans oublier qu'à partir de 2020, toute recherche financée par l'Union Européenne devra être publiée en libre accès (9, 10).

Au moment de la rédaction de ce texte et après deux ans d'existence portée par ses bénévoles, Wikimedica compte 1 068 utilisateurs (plus de 95% des étudiants en médecine de l'Université Laval), 1 172 pages, une bonne partie des notes de cours du préclinique et 18 954 modifications. La plateforme vient de s'ouvrir aux autres universités et autres programmes de la santé. Dans un futur proche, en plus de l'expansion du contenu général, Wikimedica se donne comme objectif de créer un corpus de pages couvrant les sujets du EACMC partie 1, de poursuivre le développement de ses partenariats, de permettre la reconnaissance de l'édition comme formation continue, de se déployer dans des pays en voie de développement... et bien d'autres.

Dans l'immédiat, Wikimedica n'est disponible qu'en français mais ce n'est pas parce que le concept ne s'appliquerait pas au monde anglo-saxon, bien au contraire. Le choix initial de langue provient du fait que l'université dans laquelle le projet a pris forme est francophone et qu'une initiative de ce type a plus de chances de prendre racine dans cette communauté relativement homogène du monde médical nord-américain.

L'avènement d'une version anglaise de Wikimedica n'est donc qu'une question de temps. Autrement, Wikimedica est ouvert aux contributeurs de tous horizons, tant ceux intéressés à améliorer la qualité de l'information, à rédiger du contenu ou encore à porter le projet ainsi que ses principes dans leur communauté respective, qu'elle soit étudiante ou professionnelle. Le projet n'a pas comme ambition de convaincre les professionnels en pratique de changer leurs habitudes, mais tentera de prendre racine dans la relève médicale issue de la génération du web et le monde de l'éducation, milieux chez qui les idéaux de libre accès et de responsabilité sociale portés par Wikimedica résonneront tout particulièrement. Sur ce, je vous laisse avec notre énoncé de mission :

« Fournir aux professionnels de la santé une plateforme libre, fiable, innovante et collaborative, afin de faciliter le transfert des connaissances essentielles dans un système de santé au service de tous (11). »

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A Call-to-Action Against Rising Medical Student Tuition

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ABSTRACT

There is growing concern among medical students regarding the unprecedented increases in medical school tuition fees, which have been far exceeding inflation. One consideration is how these increasing fees and resulting debt may be impacting student demographic—particularly with respect to socioeconomic status—as well the types of clinical careers that medical students are pursuing, given the lower average salaries earned by primary caregivers. This second point is especially concerning given the shortage of primary care physicians in Canada.

RÉSUMÉ

Il existe une inquiétude croissante entre étudiants de médecine par rapport aux augmentations sans précédent dans les frais de scolarité des écoles de médecine, qui dépassent de loin l'inflation. Une considération est que ces frais augmentant, et les dettes résultante, pourraient y impacter les segments démographiques des étudiants—surtout par rapport au statut socioéconomique—ainsi que les choix de carrières cliniques que les étudiants en médecine poursuivent, étant donné que les salaires sont plus bas en moyen pour les fournisseurs de soins primaires. Le deuxième point est encore plus préoccupant, étant donné le manque de médecines de soins primaires au Canada.

Medical education is known to be a particularly stressful time for aspiring physicians. Students undergo three to four years of intensive formal education, the goal of which is to prepare them for the ultimate responsibility of caring for patients. Although the pressures of matching to residency, acquiring a breadth of knowledge, and managing holistic personal health are well-documented and expected, financial constraints to medical education are becoming an increasing concern. The financial toll of medical training is predominantly driven by an unprecedented increase in medical tuition fees. Medical students in Ontario cite increasing debt levels upon graduation as a major source of stress (1), yet the government has failed to take action. An urgent call is being put forward to implement a freeze on medical tuition rates and to restructure the Ontario Student Assistance Program (OSAP) and line of credit (LOC) debt repayment schedules. This article assesses the financial and societal impact of three proposals to change the tuition structure. The financial impact of student debt was determined by creating a proprietary financial model of the projected student tuition and living costs throughout their years of medical school; all projections are based on publicly available information.

Proposal #1 | Place an indefinite freeze on medical school tuition in response to the disproportionate historical rise in tuition above the national inflation rate. This will result in savings of $8 009.

HISTORY OF TUITION INCREASE

Ontario set a precedent for drastic increases in tuition in May 1998, when the Conservative government deregulated increases in tuition for professional programs such as Medicine and Dentistry (2). Over a three-year period, from 1997 to 2000, tuition rates for Ontario medical schools went up by an astounding 116% compared to just 13% at other Canadian medical schools. Since then, tuition rates at Ontario medical schools have steadily risen at a rate of about 5% per year (3), compared to an inflation rate of 1.87% over the same period (4). Tuition for Ontario medical school students currently sits at an average of $26 221 and is expected to surpass $30 000 by 2020 (5) (**Figure 1**). If tuition increases were frozen for the next four years, this would result in average savings of $8 009 per student based on current tuition rates (5).

Proposal #2 | Postpone both OSAP and LOC interest repayment until after residency, when students have the financial flexibility to afford these payments. This would result in savings between $7 617 (OSAP component) and $24 213 (both OSAP and LOC).

Keywords: Policy; Tuition; Perspective

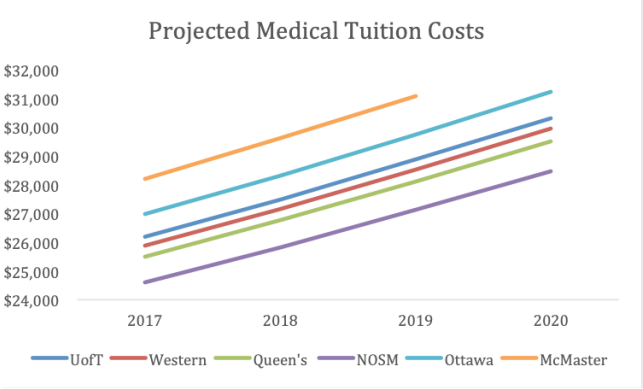

Figure 1. Projected of anticipated increases in annual tuition for Ontario medical schools

DEBT ACCUMULATION

In addition to the rising cost of tuition, students in Ontario incur an average annual cost of living of $25 552; this covers basic needs such as transportation, food, and housing (5). Furthermore, third- and fourth-year medical students incur annual living costs of $29 992 and $33 052, respectively, with the marked increase being attributable to unavoidable non-tuition-related fees such as those for the Canadian Resident Matching Service (CaRMs) and elective applications (**Figure 2**). Taking tuition into account, medical students are expected to incur annual expenses of $51 743 after one year, and $229 628 after four years (at an annual inflation rate of 2%).

Cost of Living ($)	
Books and supplies	400
Housing	9,600
Food	4,800
Cell Phone	720
Clothing/Laundry	1,605
Utilities and Internet	1,020
Transportation	1,800
Personal Expenses	1,020
Insurance	84
Medical association fees	22
Entertainment	1,050
Travel	1,401
Miscellaneous	2,000
Total for Year 1/2	25,522
Non-Tuition Unavoidable Fees	
Year 3	
Electives applications	2,400
Electives accommodations	2,000
Electives travel	2,000
Total for Year 3	29,922
Year 4	
CaRMS application	500
CaRMs travel/accommodations	6,000
LMCC fee	1,030
Total for Year 4	33,052

Figure 2. Annual cost of living for Ontario medical students

The primary cause for financial strain is the inherent mismatch between medical school costs and the cash inflow with which students cover these costs. Medical students generate an average $16 046 in cash inflow, most of which is through OSAP grants and a final year medical student stipend (**Figure 3**). This means that the rest of their medical school costs must be covered through their OSAP loans and a LOC, both of which accrue interest. Students are granted up to $8 400 in OSAP loans per year (5). This loan, coupled with their expected cash inflow, leads to a difference of $28 276 in first year expenses that students must cover with their LOC. After four years, the average medical student is expected to graduate with $34 622 in OSAP debt and $129 658 in LOC debt (**Figure 4**).

Income Sources Year 1/2 ($)	
*Scholarships and bursaries	-
*Grants	-
*Family contribution	-
Summer Income	5,000
OSAP Grant	10,900
Total	15,900
Income Sources Year 3 ($)	
Scholarships and bursaries	-
Grants	-
Family contribution	-
OSAP Grant	10,900
Total	10,900
Income Sources Year 4 ($)	
Scholarships and bursaries	-
Grants	-
Family contribution	-
Health Force Ontario Grant	1,500
Final Year Stipend	9,000
OSAP Grant	10,900
Total	21,400

*Although some students receive funding through family support and entrance scholarships, these projections assume that students are entirely self-funded

Figure 3. Annual sources of income for independent Ontario medical students

Accumulated Debt After Medical School ($)		
School	OSAP	Line of Credit
UofT	34,622	131,229
Western	34,622	129,880
Queen's	34,622	128,208
NOSM	34,622	124,880
Ottawa	34,622	134,595
McMaster*	25,707	110,212
Average	34,622	129,658

*McMaster's medical program is 3 years long

Figure 4. Projected OSAP and Line of Credit debt accumulation following medical school

Of major concern for medical students is that their residency salary is primarily used to cover their annual cost of living and is often not enough to cover annual interest repayments. The average first year resident in Ontario earns $57 967 (6); this comes at a point in their life where major investments such as buying a home may contribute to even further debt. The average amounts of interest that have to be paid on accumulated OSAP and LOC debts after graduation are $1 904 and $4 149 per year, respectively (**Figure 5**). Assuming that residents are unable to pay down their interest, they would accumulate $24 213 in interest alone after four years of residency (**Figure 6**). Thus, postponing interest repayments until after residency—when students have the financial flexibility to pay it—would result in dramatic savings.

Interest Payment Calculations

OSAP		
Federal Loan Interest Rate	prime +	2.50%
Prov. Loan Interest Rate	prime +	1%
Fraction of federal OSAP		70%
Fraction of provincial OSAP		30%
**OSAP Interest Rate		5.5%
**LOC Interest Rate		3.2%
Annual LoC Interest		$4,149.06
Annual OSAP Interest		$1,904.18
Annual LoC and OSAP Interest		6053.25

*OSAP loans are comprised of 70% federal loan and 30% provincial
**Interest rates have risen since publication of this paper due to an increase in the variable prime rate

Figure 5. Calculation of annual interest payments following medical school completion

Impact of Postponing Debt Repayment ($)

Scenario Analysis	Savings
OSAP Interest Postponement	7,617
LOC Interest Postponement	16,596
OSAP Postponement at LOC Rate	4,432
Total Savings (OSAP + LOC)	24,213
Total Savings (with OSAP at LOC Rate)	21,028

Figure 6. Savings incurred if interest repayment is postponed until after residency

Proposal #3 | Allow students to fund their medical school years entirely through OSAP loans. This would offer savings of $10 056 in LOC interest payments while students are in medical school. The government would simultaneously benefit in the form of increased interest payments coming from a low-risk investment.

GOVERNMENT RESPONSE

In acknowledgment of high student debt levels, the Ontario government offers a Resident Loan Interest Relief Program through which medical residents are not required to pay principal or interest on their OSAP debt throughout the duration of their residency (7). In return, the resident must promise to provide physician services in Ontario for five years following their medical residency. If the resident breaches their Return of Service (RoS) agreement, they incur a financial penalty and are required to pay any interest that would have otherwise accumulated. Although this program provides relief to some students, it comes with many limitations. Many Ontario medical students complete their residency outside of the province; it places a strict geographical limitation on physicians who may be hoping to settle elsewhere; there is no promise that these residents will find employment in Ontario; and it runs the risk of an even greater increase in debt if they breach their agreement. Additionally, with respect to residency prospects, Ontario has the largest number of unmatched medical graduates in the country. Since 2014, there has been a disproportionate increase in the number of unmatched Ontario graduates relative to the rest of Canada (**Figure 7**) (8). This trend further compounds the trouble medical students may have with debt repayment and lessens the desired effect of the Resident Loan Interest Relief Program.

Unmatched Ontario Medical Students

Year	Number Unmatched
2016	19
2017	35
2018	53

Figure 7. Annual number of unmatched Ontario medical students

Several years ago, the Ontario Medical Student Association (OMSA) approached members of the provincial government at Queen's Park and asked for an increase in OSAP loans to match the rising tuition costs (9). This would drastically benefit students who are reliant on lines of credit, as they are required to pay interest on their LOC while they are in medical school as described above. For the average medical student graduating with $129 658 owed on their LOC, they are required to pay $9 992 in interest throughout their four years spent in school (**Figure 8**). Unfortunately, at that time the provincial government was reluctant to make changes to OSAP loan limits for medical students. While the government does offer a 30% off tuition student grant, the maximum OSAP loan allotment per year is capped at $8 400; this creates a dramatic

compounding effect of unaffordable LOC interest payments while students are still enrolled in school (10). Increasing the OSAP loan threshold for medical students also provides a financial incentive for the government, as they would be able to receive more in interest payments after student graduation at a very low risk of default.

	LOC Interest Payments ($)
Year 1	905
Year 2	1,863
Year 3	3,140
Year 4	4,149
Total	10,056

Figure 8. Projected annual line of credit interest payments by medical school year

In recent years, the government had made notable changes in OSAP to make education more accessible for students in a breadth of disciplines: undergraduate students whose families earn less than $50 000 annually were eligible for free tuition, and doctoral students were granted a lifetime limit of up to 400 weeks (or 7.7 years) of OSAP payments (10). However, with a shift in provincial leadership, the new government announced in January 2019 that it would make several changes to OSAP, including overall reductions in OSAP grants and loans, elimination of interest-free status during the 6-month grace period after graduation, and elimination of full tuition support for students from low-income families (11). While some of the government's precedence of adjusting OSAP shows their receptiveness to the voice of medical students, the more recent changes in the OSAP structure further highlight the negligence of the government in addressing mounting student debt.

SOCIETAL IMPACT

Rising tuition levels not only have significant financial impacts at the individual student level, but also have broader systemic impacts that are negatively shaping the national healthcare landscape. At the forefront of these concerns is the drastic shift seen in medical student demographics. Following the deregulation of tuition in 2000, it was found that the proportion of Ontario medical students coming from families earning less than $40 000 dropped from 22.6% to 15% compared to just a 0.2% decrease in other provinces that had not experienced tuition deregulation (1). In the same period, a study at Western University found that their average medical student's family income was $140 000 compared to $80 000 just three years prior (12). These findings are in alignment with historical U.S. data which showed that as tuition fees rose in the 1970s and 1980s, the socioeconomic status of enrolling medical students increased (13). Finally, the 2007 National Physicians' Survey has found that increasing tuition levels have resulted in a lack of diversity of student backgrounds (14).

Another implication of increased debt load revolves around the primary care crisis. As it stands, primary care is in high need but low supply (15). A potent factor contributing to this deficit is the relatively lower average salary primary caregivers receive compared to other specialties. While there is limited data in Canada, researchers from the U.S. have begun to draw a relationship between medical school debt and deterrence from the primary care specialty (16). In a 2014 retrospective analysis of 136 232 physicians who graduated from U.S. medical schools between 1988 and 2000, physicians that graduated with higher debt had lower odds of practicing in primary care (17). The influence of financial drivers such as increasing debt levels will negatively impact physician services being offered in primary care, thereby worsening the quality of care that the population receives.

Rising medical school debt has also been thought to contribute to rural physician shortage. Research shows that students from rural and peripheralized communities have a larger likelihood of returning to these communities after their training (16). This premise is largely why medical schools such as the Northern Ontario School of Medicine (NOSM) and Western favor incoming applicants from rural Ontario. However, students from rural parts of Canada have significantly larger education debt at entry compared to students from urban centers and are more likely to come from families of lower socioeconomic status and parental income. These factors make it less likely for such students to pursue a medical education in the face of rising tuition fees and a greater financial burden on their families (18). Overall, unregulated increases in tuition may result in a deterrence that disproportionately affects perfectly qualified candidates who would most likely serve areas of Ontario and Canada in need.

Irrespective of the impact that tuition has on the socioeconomic status of medical students, several studies have shown that medical students come from more affluent families. These families tend to be more educated, wealthy, and underrepresent Canadian minority groups such as Blacks, Aboriginals, and rural Canadians (19). By financially

decreasing access to medical education, physicians are becoming distanced from the Canadian population, making it more difficult to supply Canadians with relatable and compassionate caregivers. Current efforts to address the lack of diversity within the medical profession fail to address root causes such as financial barriers. Although there are specific programs which have been established within Ontario to serve as a patchwork repair system to deal with diversity issues—such as the University of Toronto's Black Student Application Program (20)—more of these admissions/financial assistance programs may become warranted as tuition continues to grow at an unprecedented rate, which would further complicate the admissions process rather than address the actual cause.

PROPOSAL SUMMARY

This paper addresses the overwhelming financial burden that Ontario's future physicians are facing, and the negative downstream systemic consequences that have resulted. While the rising tuition has thus far damaged Ontario's health care system, this paper proposes three distinct strategies to reduce and reverse physician debt. In the long run, this will ensure that there is less of a socioeconomic gap between physicians and their patients and will place less of a financial hinderance on those medical students considering a career in primary care.

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Rituximab and Immune Molecule Modulation in Burkitt's Lymphoma Cell Lines

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ABSTRACT

Objective: Burkitt's lymphoma is an aggressive B cell malignancy that is associated with Epstein-Barr virus (EBV) infection. The monoclonal antibody rituximab is used to treat many B cell malignancies, including Burkitt's lymphoma. Studying immune molecule modulation in Burkitt's lymphoma allows insight on developing new or refining existing immunotherapy agents for refractory or chemotherapy-resistant patients. The main purpose of this study was to explore rituximab's impact on the expression of immune molecules associated with immune activation or immune inhibition by comparing the expression of rituximab-treated cells to IgG-treated cells using flow cytometry.

Methods: Burkitt's lymphoma cell lines Raji, Ramos, Bjab, and an EBV-transformed B cell line, COX, were cultured and treated with an optimally-determined concentration of rituximab or human IgG for 24 hours. Immune modulation was determined by flow cytometric analysis of the immune molecules HLA-I, HLA-DR, PD-L1, and CD40.

Results: Treatment of cells with rituximab, 10 µg/ml, completely downregulated CD20 expression and modulated expression of immune molecules. Compared to human IgG control, rituximab treatment decreased HLA-1, HLA-DR and CD40 expression on all cell lines, but significantly only for HLA-I on Bjab. Interestingly, the immune inhibitor PD-L1 was decreased on EBV-positive COX and Raji but increased on EBV-negative Ramos and Bjab.

Conclusion: Since HLA-I expression is critical for CD8 T-cell mediated tumor cell destruction, the downregulation of HLA-I could contribute to an immune escape mechanism. As this was a small study, there is limited transferability of the results to the clinical setting and further experiments comprising larger cell panels are needed.

RÉSUMÉ

Objective: Le lymphome de Burkitt est une malignité agressive de cellules B qui est associée avec l'infection par le virus d'Ebstein-Barr (EBV). L'anticorps monoclonal rituximab est utilisé pour traiter plusieurs malignités de cellules B, y inclut le lymphome de Burkitt. Étudiant la modulation de molécules immunitaires dans le lymphome de Burkitt donne un aperçu sur le développement de nouveaux agents d'immunothérapie et le raffinement d'agents existants pour les patients réfractaires ou chimiorésistants. Le but principal de cette étude était d'explorer l'impact de rituximab sur l'expression de molécules immunitaires associées à l'activation ou l'inhibition immunitaire, en comparant l'expression de cellules traitées par rituximab aux cellules traitées par IgG, en utilisant la cytométrie en flux.

Méthodes: Les lignées de cellules du lymphome de Burkitt : Raji, Ramos, Bjab et une lignée de cellules B transformées par le EBV, COX ; ont été cultivées et traitées avec une concentration optimale de rituximab ou d'IgG humain pendant 24 heures. La modulation immunitaire a été déterminée par analyse de cytométrie en flux des modulateurs immunitaires HLA-I, HLA-DR, PD-L1, et CD40.

Résultats: Le traitement de cellules avec le rituximab, 10 µg/ml, a complètement réprimé l'expression de CD20 et l'expression modulée des molécules immunitaires. Comparé au contrôle d'IgG humain, le traitement par rituximab a diminué l'expression de HLA-1, HLA-DR et CD40, mais seulement de façon significative pour l'HLA-I de la lignée Biab. Curieusement, l'inhibiteur immunitaire PD-L1 a diminué pour les lignées EBV-positive COX et Raji, mais a augmenté pour les lignées EBV-négatives Ramos et Bjab.

Conclusion: Comme l'expression de HLA-I est critique pour la destruction de cellules tumeurs par les cellules T CD8, réprimer le HLA-I peut contribuer à un mécanisme d'évasion immunitaire. Comme cette étude était très petite, la transférabilité de ces résultats est limitée dans le contexte clinique et donc, plus d'expériences comprenant plusieurs types de cellules sont nécessaires.

Keywords: Immunotherapy; Immune Molecules; Rituximab; Burkitt's Lymphoma

Burkitt's lymphoma is a rare aggressive mature B cell malignancy (1). It accounts for 40% of all childhood non-Hodgkin lymphomas but only less than 5% of adult lymphomas (2). Burkitt's lymphoma is found in three epidemiologically distinct forms that are prevalent in different populations: the endemic form, the sporadic form, and the immunodeficiency-associated form (3). The endemic form is most prevalent in Africa and the Middle East and is the form that is associated with EBV. It is diagnosed at a median age of 4-7 years. The sporadic form can be detected all over the world and at any age and represents less than 3% of all non-Hodgkin lymphomas (3). The final form is associated with the human immunodeficiency virus (HIV), is not linked with EBV, and its development does not correlate with CD4 T cell levels. All three subtypes have the same morphology and involve the overexpression of the MYC oncogene expressed on chromosome 8 (4). The activation of the MYC oncogene and resultant uncontrolled cell proliferation is triggered by a translocation with one of three immunoglobulin genes on chromosomes 2, 14, or 22. The translocation between chromosomes 8 and 14 is the most common, triggering 80% of cases of Burkitt's lymphoma.

Over the past few decades, therapeutic techniques boosting the immune system's ability to fight cancer, or immunotherapy, have become a mainstay in cancer treatment (5). For example, "checkpoint" molecules involved in immune activation that subdue the immune response and prevent autoimmunity have been identified and have been engineered as an additional avenue to prevent cancer growth (6). T cell activation occurs with two main stimulatory steps. The first step is triggered by the binding of the T cell receptor on naïve CD4+ or CD8+ T-cells to the human leukocyte antigen (HLA) on an antigen presenting cell (APC). The HLA is antigen-bound and this first step allows specificity of the T cell's effector function. The second signal entails the co-stimulatory signals that are also required for appropriate immune activation. The main co-stimulatory signal includes the interaction between CD28 on the T cell and B7 on the APC, but the binding of CD40L on the T cell and CD40 on the APC is also important in certain T cell functioning (7). The absence of these co-stimulatory signals would result in anergy of the T cell (6). This intricate activation process is further sophisticated by its regulation, both centrally and peripherally. Occurring in the lymph nodes, central regulation arises through the binding of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) on the surface of T cells to B7 on the APC. As this interaction induces anergy of the T cell, CTLA-4 is typically only upregulated when there is strong antigen stimulation, and its upregulation out-competes the CD28:B7 interaction. Peripheral regulation occurs at a later stage of the immune response and involves the interaction between programmed cell death protein 1 (PD-1) on T cells and its ligand programmed cell death ligand 1 (PD-L1) on its target cells, including cancer cells. This interaction also results in decreased T cell proliferation and signalling, thus preventing immune-mediated damage towards targeted tissues.

As cancer develops, there is a dynamic interplay between the immune system and cancer called immunoediting, whereby tumours can escape immune system defenses. Although there are many mechanisms by which tumour cells can escape the host immune system, interfering with antigen presentation is an important theme. Tumour cells can down-regulate the expression of HLA Class I on the surface to prevent recognition and attack by CD8+ cytotoxic T cells (8). Tumour cells can also interfere with CD4+ T cell-mediated signalling through the down-regulation of HLA Class II (9). Checkpoint pathways are also not exempt from tumour cell interference, and significant evidence exists of the manipulation of PD-L1 and CTLA-4 pathways by cancer cells to evade immune defenses (6).

Rituximab, a monoclonal antibody targeting the CD20 receptor, has been shown to be an effective biologic agent against other types of non-Hodgkin lymphomas such as diffuse large B cell lymphoma (DLBCL) (10). The use of rituximab has also been extended to other B cell lymphomas and there have been several studies that have shown its safety and effectiveness in treating Burkitt's lymphoma (11,12). Most importantly, a recent randomized control clinical trial was conducted to see if the addition of rituximab to a short chemotherapy protocol improves event-free survival in Burkitt's lymphoma patients (2). This study included 260 HIV-negative Burkitt's lymphoma adult patients. These patients were first stratified into two groups based on the presence or absence of central nervous system or bone marrow involvement, and then randomly assigned to the rituximab or no rituximab treatment groups. The rituximab group achieved a better prognosis with an event-free survival of 75% compared to 62% in the no rituximab group. This study solidified the evidence to support rituximab as a treatment for Burkitt's lymphoma in adult patients.

The implementation of rituximab in chemotherapy protocols has also been studied in pediatric Burkitt's lymphoma populations and a recent randomized controlled trial showed favourable results (13). This international study randomized 600 patients with high-risk B cell non-Hodgkin's lymphoma to

standard Lymphome Malins de Burkitt (LMB) chemotherapy with or without the addition of rituximab. A planned interim analysis including 310 randomized patients, of which 85% had Burkitt's lymphoma, showed a 1-year event-free survival rate of 94% in the rituximab group, compared to 81% in the standard chemotherapy group. This finding led to an early closure of the study as the rituximab arm had significantly improved outcomes, confirming that this drug's efficacy also extends to the pediatric population.

Despite the improved outcome with chemotherapy in Burkitt's lymphoma, poor outcomes continue to be observed in patients with relapsed disease or who are chemotherapy-resistant (3). A retrospective study conducted by the European Group for Blood and Marrow Transplantation described a 3-year overall survival rate of only 7% in chemo-resistant adult patients (14). For pediatric patients with relapsed or refractory mature B cell non-Hodgkin lymphoma, the 5-year overall survival rate was noted to be less than 30% (15). As well, even with the addition of rituximab as salvage therapy in relapsed mature B cell lymphoma pediatric patients, poor survival rates were observed (16). The survival rates of the 37 pediatric and adolescent patients at 1 and 3 years were 40.5% and 37.6%, respectively.

The purpose of this study is to gain further insight into the mechanistic actions of rituximab in the treatment of Burkitt's lymphoma and to delineate an explanation for the poor outcomes in refractory or relapsed diseased states. The study comprised investigating the cell surface expression of antigen-presenting molecules (HLA-1 and HLA-DR), and two paradoxical immune molecules: PD-L1, an immunosuppressive checkpoint regulator, and CD40, a costimulatory molecule involved in T cell activation. Rituximab treatment of the cell lines may uncover an altered modulation of immune molecules playing an important role in tumor immune escape mechanisms. These changes could help explain potential resistance to rituximab treatment.

This is a pre-clinical study to determine whether rituximab treatment modulates HLA Class I, HLA DR (HLA Class II), CD40 or PD-L1 expression in a panel of Burkitt's lymphoma cell lines. The first objective of this study was to determine the optimal concentration of rituximab to deplete CD20 on the surface of lymphoma cells. The second objective was to determine if rituximab treatment of Burkitt's cells alters the expression of HLA Class I, HLA-DR, CD40, or PD-L1.

MATERIALS AND METHODS

Cells

Cell lines included three well-characterized Burkitt's lymphoma cell lines Bjab (Dr. Jacques Thibodeau, Université de Montréal), Ramos (Dr. Mani Larijani, Memorial University), and Raji (Dr. Gerald T Nepom, Benaroya Research Institute), and one EBV-transformed B cell line COX (11th International Histocompatibility Workshop). Cells were grown in complete medium (CM) consisting of RPMI-1640 (Invitrogen) containing 10% complement-inactivated fetal bovine serum (Invitrogen), 2mM L-glutamine (Invitrogen), 2mM antibiotic antimycotic (Invitrogen), and 1mM sodium pyruvate (Invitrogen) at 37 °C in a CO_2 incubator. The medium was replenished when the cells reached a density of 5-8 x 10^5/ml and all experiments were completed on healthy and viable cells as determined by Trypan blue exclusion.

Rituximab Treatment

Rituximab (Health Sciences Centre Pharmacy, St. John's, NL), a humanized anti-CD20 monoclonal antibody, was tested on COX to determine the optimal concentration of rituximab. Cells were harvested, counted, and cultured at 2.5 x 10^5 cells/ml in CM. Cell cultures were treated with rituximab or human IgG (hIgG) (Sigma), ranging from 5 µg/ml to 100 µg/ml, for 24 hours, after which CD20 expression was determined by flow cytometry. The assay was conducted to determine the rituximab concentration that most effectively down-regulated CD20 expression.

To determine if rituximab treatment altered the expression of HLA Class I, HLA DR, CD40 or PD-L1 in Burkitt's cells, cell lines were treated at time 0 with the appropriate concentration of rituximab or the control antibody, hIgG, at the same concentration. The cells were incubated for the same time period as the previous experiment (24 hours), followed by flow cytometry to determine expression of immune molecules.

Antibodies and Flow Cytometry

Flow cytometry was conducted to measure surface expression of CD20, irrelevant antibody IgG1/2a (ebioscience/local source), HLA Class I (antibody W6/32, in house), HLA-DR (antibody L243, in house), CD40 (antibody B-B20, Abcam), and PD-L1 (antibody MIH2, Abcam). Briefly, 2.5 x 10^5 cells/assay tube was removed and centrifuged at 1400 rpm for 7 mins. The cells were washed twice with FACS (Fluorescence Activated Cell Sorting) buffer and after resuspending the cells, 100 µL was added to each 5 mL tube. 25 µL of primary mouse antibody

(IgG1/2a, W6/32, L243, B-B20, or MIH2) was then added to each tube and the tubes incubated on ice for 30 minutes. After incubation, they were washed twice with FACS buffer and then 25 µL of secondary antibody (phycoerythrin (PE)-labelled goat anti-mouse IgG, Jackson ImmunoResearch) was added to each tube. The cells were then incubated in the dark on ice for 30 minutes. After incubation, the cells were washed twice and resuspended in 150 µL of paraformaldehyde to fix the cells. Samples were then analyzed on a BD FACSCalibur flow cytometer. Each cell line was tested three times, aside from COX for which only two experiments were conducted. Only two experiments were conducted for COX due to technical difficulties in the experimental protocol.

Interpretation and Statistics

The expression of the immune molecules was determined by the mean fluorescence intensities (MFI) quantified by Kaluza software (**Figure 1**). The MFI for each marker was adjusted by subtracting the background MFI, accounting for the irrelevant IgG1/2a binding. The MFIs from the three experiments were averaged for use in statistical calculations. Statistical analysis was carried out using Microsoft Excel software. The significance of differences between hIgG and rituximab treatments was calculated using a two-tailed, paired students t-test. A p-value of less than 0.05 was considered to be significant.

RESULTS

The first objective was to establish a concentration of rituximab that downregulated cell surface CD20 expression but did not have a huge impact on cell viability. COX cells, which have high levels of CD20, were treated with various concentrations for 24 hours, after which flow cytometry and viability assays were performed. As shown in **Figure 1** (**A, B**), all concentrations of rituximab blocked CD20 expression. Compared to untreated cells, the number of viable cells was reduced in a dose-dependent manner (**Figure 1C**), as compared to untreated with only a small impact at the lower concentrations. Based on these results and literature reports (17, 18), 10 µg/mL was selected as the concentration of rituximab for subsequent experiments.

Three sets of experiments were performed on rituximab or hIgG-treated Burkitt's lymphoma cells, Raji, Ramos and Bjab, and two sets on EBV-transformed COX cell line, followed by flow cytometric analysis. Representative histograms comparing expression of HLA-I, HLA-DR, CD40, and PD-L1 on rituximab and hIgG treated Bjab cells is shown in **Figure 2**. Compared to the control hIgG-treated cells, rituximab treatment somewhat reduced expression of HLA-I, HLA-DR, and CD40 on all cells whereas the effect on PD-L1 was variable and cell-dependent (**Figure 3**).

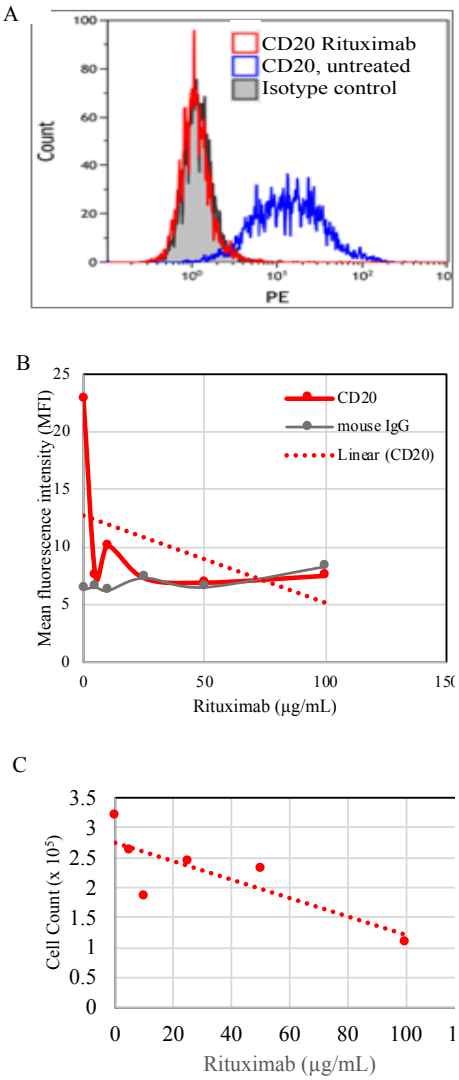

Figure 1. Determination of the optimal concentration of rituximab concentration to downregulate cell surface expression of CD20 on COX cells. Cells were treated or not with indicated concentrations of rituximab for 24 hours and then assayed for CD20 expression by flow cytometry and viable cells. **A:** Representative flow histogram illustrating loss of CD20 using rituximab (10µg/ml) to treat COX cells. **B:** CD20 downregulation by rituximab is dose dependent, as indicated by decreased mean fluorescence intensities for all concentrations of rituximab compared to untreated cells. **C:** The number of viable cells was inversely correlated with increasing concentrations of rituximab.

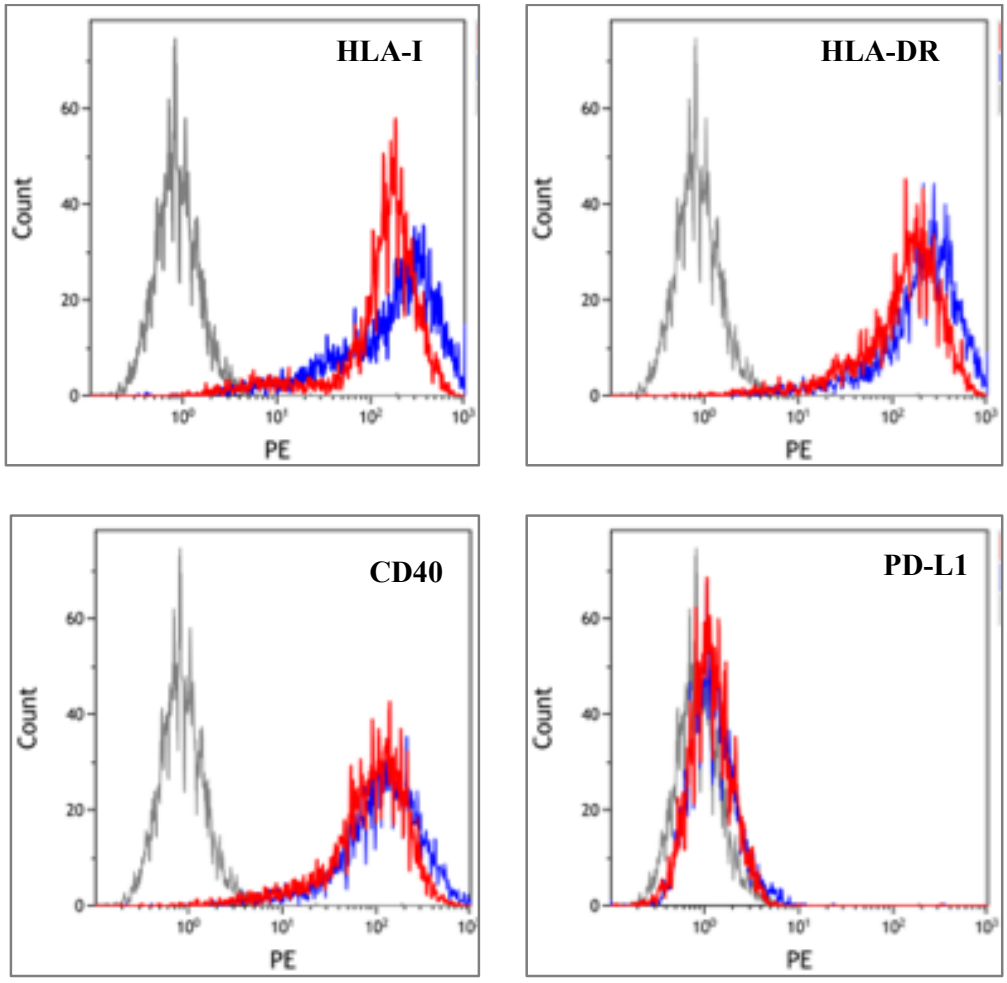

Figure 2. Flow histograms of a representative experiment on cell line Bjab showing expression of HLA-I, HLA-DR, PD-L1 and CD40 following rituximab treatment (red lines) or hIgG treatment (blue lines).correlated with increasing concentrations of rituximab.

HLA-class I was significantly ($p = 0.013$) reduced on rituximab treated Bjab cells and although reduced on other cells, the effect was not statistically significant (**Figure 3A**). Similarly, the downward trend for expression of HLA DR, a class II MHC molecule, and CD40 on all treated cells is apparent (**Figure 3B** and **3B**), but not significant. None of the cell lines expressed much constitutive PD-L1 and rituximab treatment had variable effects (**Figure 3C**). As shown, Raji and COX cells displayed decreased expression after rituximab treatment, whereas Ramos and Bjab showed increased and variable PD-L1 expression after rituximab. None of the rituximab-mediated changes in PD-L1 were statistically significant.

DISCUSSION

While rituximab treatment of Burkitt's lymphoma cell lines did show a trend to downregulate surface expression of the immune molecules HLA DR, CD40 and PD-L1, in the majority of cases this was not statistically significant. There was a significant downregulation of HLA Class I expression in the Bjab cell line.

The downregulation in HLA Class I expression could potentially have negative implications in the use of rituximab to treat Burkitt's lymphoma. As mentioned earlier, a mechanism through which tumour cells evade immune surveillance is by downregulating HLA Class I on their surface to limit the attack of cytotoxic T cells (8). These CD8+ T cells typically recognize tumor-associated antigens on cancer cells through binding to the antigen on HLA Class I on the cancer cell, an interaction that is limited when this HLA molecule is downregulated (19). This result suggests that rituximab treatment could potentially contribute to an immune escape mechanism in Burkitt's

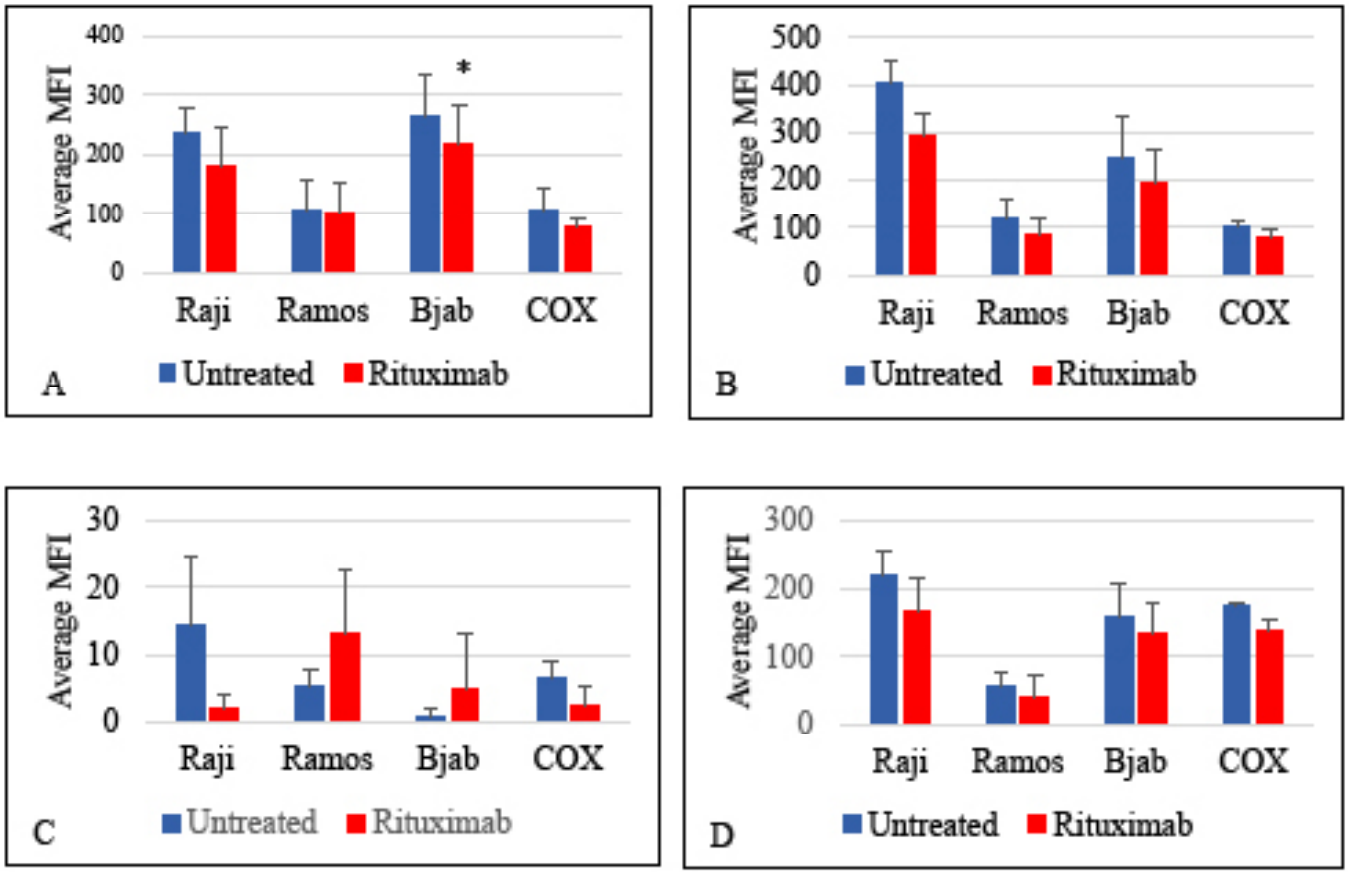

Figure 3. The expression of immune molecules HLA Class I (**3A**), HLA-DR (**3B**), PD-L1 (**3C**), and CD40 (**3D**), measured by mean fluorescence intensity (MFI), on the cell surface of Burkitt's lymphoma cell lines and an EBV-positive B cell line after rituximab treatment. The figures show the averages of three independent experiments, with the exception of two independent experiments for COX line. The error bars represent standard error with * signifying $p < 0.05$.

lymphoma, which could negatively impact prognosis.

Despite the immune mechanism illustrated above, the repercussions of the loss of HLA Class I expression in the setting of B cell lymphomas are not well-defined. Interestingly, our results showed a downward trend for HLA-DR expression, which is supported by previous reports showing downregulation of HLA Class II in patients receiving standard chemotherapy with rituximab. This was found to be a negative prognostic factor in B cell lymphomas, but the same has not been shown for HLA Class I expression (19,20). In a retrospective analysis of 144 patients with diffuse large B cell lymphoma and that were treated with standard chemotherapy, the loss of HLA Class I expression did not correlate with a worsened prognosis (19). The authors suggest the work of natural killer cells and rituximab in conducting antibody-dependent cellular cytotoxicity or direct cell killing has compensated for the decreased activity of cytotoxic T cells through HLA Class I interactions.

CONCLUSION

Based on these results, rituximab treatment tends to result in a decreased cell surface expression of the immune molecules HLA Class I, HLA Class II, PD-L1, and CD40 on Burkitt's lymphoma cell lines. However, aside from HLA Class I expression on the Bjab cell line, the results were not statistically significant. With these limited results, it is difficult to extrapolate them to the clinical setting to determine whether rituximab therapy will improve treatment outcomes in refractory or relapsing cases of Burkitt's lymphoma. More data should be collected through further experiments including a wider variety of Burkitt's lymphoma and B cell lines. If subsequent experiments confirmed these results, exploring the mechanism by which rituximab downregulated HLA-I expression is the next avenue to pursue.

This could be significant as one of the central anti-tumour immune mechanisms is cytolytic CD8+ T cell destruction of tumour cells, which require ample HLA expression.

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Development of a 3D Printed Neuroanatomy Teaching Model, University of Ottawa

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ABSTRACT

Gross anatomy is seen as one of the basic bodies of medical knowledge. Likewise, neuroanatomy is foundational to clinical neurosciences. However, neuroanatomy is different from gross anatomy due to the complexity of the central nervous system, and the fact that some of its structures cannot be dissected or demonstrated in anatomy cadaveric lab. The use of anatomical models in medical curricula has been reported as an effective tool in anatomy learning. They have been used to replace cadaveric material when the latter is difficult to acquire, or when the anatomical structures cannot be dissected (for instance the brain ventricles). Moreover, anatomic models allow leaners to visualize the structures in a 3-dimensional modality. The goal of this study was to create a 3D printed neuroanatomy model in order to complement the University of Ottawa anatomy models' library, and help medical students visualize the pathway of different nervous tracts on a 3D simulation model. To assist with this, 2D images of slices of the cerebrum, brainstem, and spinal cord sections were downloaded online to be imported to Adobe Photoshop CC 2015. The images were manually converted to black and white, and separated into different layers to export each component separately into Tinker CAD (online software). The different components were then assembled on Tinker CAD to create 3D printer compatible files. The files were printed using white ABS on a Replicator 2X MakerBot printer. Two survey questions (Likert style) were sent to students via Google docs to evaluate their satisfaction with the model.

RÉSUMÉ

L'anatomie macroscopique est connue comme une base de la connaissance médicale. De même, la neuroanatomie est la fondation aux neurosciences cliniques. Pourtant, la neuroanatomie est différente de l'anatomie macroscopique due à la complexité du système nerveux central, et le fait que quelques structures ne puissent pas être disséquées ou démontrées dans un laboratoire d'anatomie. L'usage de modèles anatomiques dans les programmes médicaux a été rapporté comme un outil efficace pour l'apprentissage de l'anatomie. Ils ont été utilisés pour remplacer le matériel cadavérique qu'on ne peut pas facilement acquérir, ou si la structure anatomique ne peut pas se faire disséquer (par exemple, les ventricules du cerveau). De plus, les modèles anatomiques permettent aux apprenants à visualiser les structures dans une modalité tridimensionnelle. Le but de cette étude comprenait de créer un modèle de la neuroanatomie imprimé en 3D, pour ajouter à la bibliothèque de modèles anatomiques de l'Université d'Ottawa, et assister aux étudiants de médecine à visualiser les différentes voies nerveuses dans un modèle de simulation 3D. Pour assister à cette tâche, des sections de lames 2D du télencéphale, du tronc cérébral, et de la moelle épinière ont été téléchargées en ligne pour être importés dans Adobe Photoshop CC 2015. Les images ont été converties à noir et blanc, et séparées dans des différentes couches pour exporter chaque composant séparément dans Tinker CAD (logiciel en ligne). Les différents composants ont ensuite été assemblés dans Tinker CAD pour créer des fichiers compatibles avec l'imprimant 3D. Les fichiers ont été imprimés en utilisant un ABS blanc dans l'imprimant Replicator 2X MakerBot. Deux questions de sondages (en style Likert) ont été envoyées aux étudiants par Google docs pour évaluer leur satisfaction avec le modèle.

Unlike many components of the contemporary medical school curriculum, the study of anatomy has a history that extends back through the centuries to Aristotle and Galen. In medicine, gross anatomy has been seen as foundational, one of the basic bodies of knowledge that must be mastered as part of medical training in order to apply the diagnostic and treatment skills required for clinical competence (1). "Likewise, neuroanatomy has been seen as foundational to clinical neurosciences, and it is included in every North American medical curriculum," according to Mauteen & D'Eon (2). "Neuroanatomy is the cornerstone upon which is built an understanding of the nervous system and its disorders," according to Crossman (3).

Keywords: 3D Printing; Neuroanatomy; Innovation in Medical Education

However, neuroanatomy is quite different from gross anatomy, and this is attributable to the complexity of the central nervous system (CNS), as well as the many structures that are difficult to dissect and demonstrate in the anatomy cadaveric lab (for example, the brain ventricles, the nervous tracts, etc.). Moreover, CNS lesions do not manifest with local signs and symptoms. Although this is also true of other organ systems, such as the cardiovascular system, the difference is the inaccessibility of the CNS to direct physical examination. For instance, a lesion in the dorsal column-media lemniscus pathway will manifest as loss of touch sensation below the level of the lesion and it will present in a different side of the body based on the location of the lesion along the tract (e.g. above or below the medulla). Therefore, for lesions of the nervous system there is the need for a certain level of mastery of neuroanatomy to associate a lesion with the exact structure in the nervous system that induced it.

Anatomical models have long been used in anatomy education to supplement or replace cadaveric material when the latter is difficult to acquire. From the 14th until 18th century in France, Germany and Italy, anatomy was studied with the help of ivory figurines made by artists. After the invention of plastic, new opportunities in the study of anatomy were developed. At the beginning of 20th century, anatomy lessons were taught using plastic models of organs (4). Gültiken stated that the subjects introduced by plastic models are easier to learn and comprehend, as formaldehyde may mask the finer details of the anatomical complex (5). Therefore, the use of three-dimensional (3D) anatomical models is ubiquitous in medical education. They allow the user to move away from the clutter, discomfort, and complexity of a cadaveric dissection and further clarify characteristics or functions of an anatomical structure that are not readily apparent in situ (6).

One of the neuroanatomy objectives at the University of Ottawa is for the students to locate the different nervous pathways and identify the outcome of a lesion in any part along the different tracts. The nervous pathways are very fine structures that cannot be dissected or demonstrated in anatomy cadaveric lab, and they are not purchasable from the market as 3D models. To address this issue and allow students to better identify the tracts, clarify the interconnectedness of the nervous system and facilitate the "locate the lesion" diagnostic approach, a 3D printed neuroanatomy model exclusive to the University of Ottawa was created to complement its anatomy library.

METHODS

2D images of slices of the cerebrum, brainstem, cervical, thoracic, and lumbar spinal cord were downloaded online and imported to Adobe Photoshop CC 2015. The images were manually converted to black and white, which were then separated into different layers and exported separately into Tinker CAD (online software). The different components were then assembled on Tinker CAD to create 3D printer compatible files (stereo lithography STL format). The files were printed using white ABS on a Replicator 2X MakerBot printer in the Faculty of Medicine' Health Sciences library at the University of Ottawa (7). The printed pieces measured 5x4x0.5 cm, 8x4x0.5 cm and 10x8x1 cm for the spinal cord, the brain stem, and the cerebrum slices, respectively. The pieces were then mounted on metal rods, and wires were passed through to demarcate the spinothalamic tract, corticospinal tract, and dorsal column-medial lemniscus pathway (**Figure 1**). The 3D model was introduced to students in neuroanatomy sessions and was kept in the lab allowing student access at any time. After approval by the Ottawa Health Research Institute-Research Ethics Board (OHRI-REB), two survey questions (Likert style) with a consent letter were sent to students via a Google

Figure 1. 3D printed neuroanatomy model showing the corticospinal, spinothalamic and dorsal column-medial lemniscus tracts

docs to evaluate their satisfaction with the model. The overall response rate to the survey was 43.8% (70 out of 160 possible students). Students responding to the survey were those who regularly attend the labs. 79% (n = 55) of the students stated that the 3D model helped them better memorize the pathway of the tracts at different levels of the CNS and 80% (n = 56) stated that it enhanced their understanding of difficult neuroanatomy concepts (**Figure 2**).

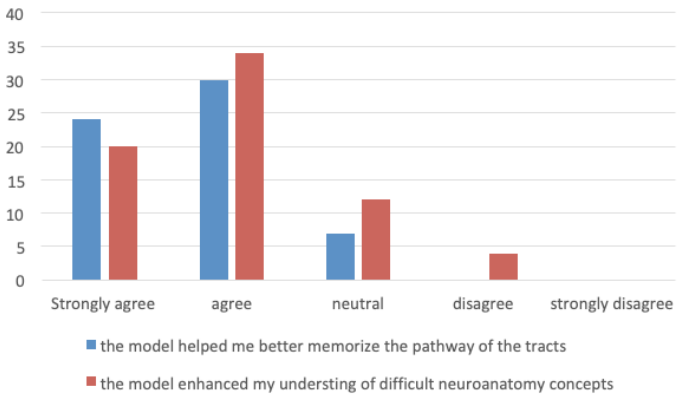

Figure 2. Students' perception of the neuroanatomy model as an educational tool (Second year medical students at the University of Ottawa, n=70).

DISCUSSION

The best model for investigating human anatomy has always been the human cadaver itself, because, in most cases, all the parts are present in the correct arrangement, the fine membranous and facial elements are intact, and the presentation of structures (soft, hard, smooth, rough, dry, moist) is accurate. It is safe to say that, from the beginning of curiosity, early man investigated wounds and organs of their dead brethren (6). However, in today's regulated and socially conscious institutions, access to a cadaver may be limited through budgetary or social issues, or, even if a cadaver is available, presentation of the desired cadaveric anatomy may be confusing, such as that of the pelvic spaces and fascia. Further, sometimes the structures cannot be demonstrated in cadaveric labs such as the nervous pathways. These issues can be addressed with fabricated anatomical models. Recent technological advances in 3D printing have resulted in increased use of this technology in the medical field (1,8). At the University of Ottawa, anatomy is taught to pre-clerkship students on a system base (musculoskeletal, vascular, respiratory, renal, gastrointestinal, endocrine, reproductive and nervous systems). The labs start with 30 minute PowerPoint presentation followed by a quiz of two multiple-choice questions. The students then spend an hour with their assigned tutors exploring the cadavers; the sessions are supplemented by the 3D plastic models. Neuroanatomy is taught to medical students in their second year of studies. It is a complex subject and it even has the reputation of the subject that students fear the most. Some of the neuroanatomical structures cannot be demonstrated in the anatomy cadaveric lab. This issue was addressed by creating a 3D printed model of the nervous pathways. A survey of two Likert style questions was then sent to students. The majority of students responding to the survey were satisfied with the model as they stated that it enhanced their learning and helped them better understand difficult neuroanatomy concepts. 3D printing is one technological advancement that may reduce the need for purchasing a large library of physical 3D anatomical models. These models provide versatility; they can be tailored to the desired learning objectives and to conform to learner characteristics. They offer a great advantage over static 2D images in terms of orientation and exploration of internal structures. Moreover, the advantage of printing the models using different colors allow better visualization of anatomical structures. The only limitation of this technique is that it can be time consuming depending on the size of the printed object.

CONCLUSION

Neuroanatomy is perceived as a complex subject and educators are encouraged to deliver it in a simplified, easy to understand fashion. The use of different instructional approaches allows students to successfully retain information. 3D printing has advanced tremendously over the past two decades, becoming fundamental in the development and construction of physical 3D anatomical models. Advantages of these models over cadaveric specimens include their application in many educational formats (lectures, online material, and print) in addition to being portable, non-perishable and cost effective. These models can be altered to enhance desired learning objectives or to conform to learner characteristics. They offer a great advantage over static 2D images in terms of orientation and exploration of internal structures. 3D printing as an educational tool is uniquely flexible in responding to the evolving environment, leading to improved student learning outcomes and more retention of information. Therefore, it is recommended to continue developing opportunities where 3D printing can supplement traditional learning approaches. One future directive would be the assessment of the use of 3D teaching tools on students' examination performance.

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From Zero to Neuro-Reprogramming: Innovations in Translational Neuroregenerative Medicine

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ABSTRACT

The acquisition of live human nervous tissue for research presents ethical and technical constraints. As a result, clinicians and scientists resort to using animal models to investigate human neuronal development and degeneration. However, innate differences in neurobiology between species impede the translation of disease pathologies and development of therapeutic strategies. The discovery and examination of endogenous neural stem cells (NSCs) have been critical for our understanding of neuronal development, degeneration, and regeneration. NSCs can exist in different developmental stages, embryonic through adult, and possess the capacity to generate the various cells that make up the nervous system. Human somatic cells can be obtained non-invasively and genetically reprogrammed into NSCs, serving as an alternative and ethical means to acquire stem cells for translational study and potential therapy. Novel methods to generate NSCs of various developmental origins and regional identities are evolving rapidly to provide safer, quicker, and more efficient genetic reprogramming strategies. Reprogrammed NSCs share many molecular and functional attributes with their endogenous counterparts and can be used for in vitro modeling at a large scale. The accessibility to study patient-specific NSCs allows for causal inferences of human disease mechanisms that may be unfeasible to model in animals. Given the novelty of this burgeoning field, the opportunity for translational discoveries in neuroregenerative medicine is unprecedented. This review will highlight the advances in manufacturing NSCs and their translational implications for disease modeling and potential treatment in the human nervous system.

RÉSUMÉ

Obtenir de tissu nerveux humain vivant pour la recherche présente des contraintes éthiques et techniques. Ainsi, les cliniciens et les scientifiques finissent par utiliser des modèles animaux pour étudier le développement et la dégénération neuronaux humains. Par contre, des différences innées entre les espèces en neurobiologie entravent la traduction de pathologies médicales et le développement de stratégies thérapeutiques. La découverte des cellules souches neurales (CSN) endogènes et leur étude ont été critique pour notre compréhension du développement, de la dégénération et de la régénération neuronaux. Les CSNs peuvent exister en différents stades de développement, embryonnaire à adulte, et possèdent la capacité de générer les différentes cellules qui froment le système nerveux. De plus important, les cellules somatiques humaines peuvent être obtenues de manière non invasive et reprogrammées génétiquement en CSNs, et ainsi peuvent se servir comme un moyen alternatif et éthique d'acquérir des cellules souches pour l'étude translationelle et des thérapies potentielles. De nouvelles méthodes pour générer des CSNs de plusieurs origines développementales et d'identités régionales évoluent rapidement pour fournir des stratégies génétiques de reprogrammation sécuritaire, rapides et efficaces. Les CSNs reprogrammées partagent plusieurs attributs moléculaires et fonctionnels avec leurs équivalents endogènes et peuvent être utilisées comme modélisation in vitro sur une grande échelle. L'accessibilité à étudier des CSNs propres aux patients permet l'ingérence causale de mécanismes de maladies humaines qui seront peut-être impossibles avec des modèles animaux. Malgré la nouveauté de ce champ naissant, il y a une opportunité sans précédent pour des découvertes translationelles en la médecine neuro-génératrice. Cette revue surlignera les avancements en la fabrication de CSNs et leur implication translationelles pour la modélisation de maladies et les traitements potentiels du système nerveux.

The acquisition of live human nervous tissue for research presents ethical and technical constraints. As a result, clinicians and scientists resort to using animal models to investigate human neuronal development and degeneration. However, innate differences in neurobiology between species impede the translation of disease pathologies and development of therapeutic strategies. The discovery and examination of

Keywords: Genetic Reprogramming; Neural Stem Cells; Translation; Neurodevelopment; Neurodegeneration

endogenous neural stem cells (NSCs) have been critical for our understanding of neuronal development, degeneration, and regeneration. NSCs can exist in different developmental stages, embryonic through adult, and possess the capacity to generate the various cells that make up the nervous system. Human somatic cells can be obtained non-invasively and genetically reprogrammed into NSCs, serving as an alternative and ethical means to acquire stem cells for translational study and potential therapy. Novel methods to generate NSCs of various developmental origins and regional identities are evolving rapidly to provide safer, quicker, and more efficient genetic reprogramming strategies. Reprogrammed NSCs share many molecular and functional attributes with their endogenous counterparts and can be used for in vitro modeling at a large scale. The accessibility to study patient-specific NSCs allows for causal inferences of human disease mechanisms that may be unfeasible to model in animals. Given the novelty of this burgeoning field, the opportunity for translational discoveries in neuroregenerative medicine is unprecedented. This review will highlight the advances in manufacturing NSCs and their translational implications for disease modeling and potential treatment in the human nervous system.

DISCOVERY OF ENDOGENOUS NSCS AND DEATH OF A DOGMA

Throughout much of the 20th century, it was believed that the adult mammalian central nervous system had very little capacity to regenerate and fix itself. This dogma was set forth by the "father of neuroscience", Santiago Ramón y Cajal, famous for his intricate drawings of neuronal networks that established the neuron doctrine (1). Through his observations of severed neuronal axons, he stated, "In adult centres the nerve paths are something fixed, ended, immutable. Everything may die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree" (2). However, nearing the end of the 20th century, the discovery of endogenous neural stem cells (NSCs) in the brain and spinal cord shattered this long-held belief (2–4). Today, human NSCs are being manufactured "from scratch" and used for modeling human neuronal developmental and degeneration as well as personalized drug screening. They are also being tested as therapeutic agents for treatment (5–8).

Both the brain and spinal cord host NSCs within specialized compartments in the ventricular regions as well as the dentate gyrus of the hippocampus. NSCs are defined by their ability to generate specialized cell types of the nervous system including neurons, oligodendrocytes, and astrocytes and thus pose as prime candidates for cellular replacement of damaged, diseased, or dead cells in a variety of neurodegenerative contexts (10). As such, endogenous NSCs have been subject to targeted manipulation in animal models to promote regeneration (8,11–13). However, endogenous NSCs do not play a significant role in physiological central nervous system repair which partly contributed to the scientific community's dismissal of them throughout the 20th century. Moreover, their numbers in vivo are limited and spatially restricted, which may be a concern when the generation of enough cells in the right location is a requirement for effective repair (15–17).

A NEW ERA: GENETICALLY REPROGRAMMED NSCS

To circumvent issues with targeting endogenous NSCs, methods have been developed to manufacture NSCs that resemble endogenous NSCs at various developmental stages and from different regions in the nervous system (1–4). These revolutionary advancements have provided researchers with unprecedented access to study human neural cells with few ethical and technical constraints. Notably, reprogrammed NSCs have been used to treat neurological disorders in pre-clinical animal models and have entered clinical testing in the treatment of Parkinson's disease, spinal cord injuries, and macular degeneration of the eye (5–7). Since its inception in 2006, the field of NSC reprogramming has rapidly expanded without any signs of slowing down (1,9–11). The remainder of this review will highlight the technological advancements in NSC reprogramming methods as well as their value in translational research and clinical use.

IN VITRO REPROGRAMMING: GENOMIC, PROTEOMIC OR CHEMICAL INTERVENTIONS

The most common means for genetically reprogramming NSCs involves an *in vitro* intervention. First, a small patient sample of skin, urine, hair, or blood is obtained and cultured to generate enough cells (e.g. fibroblasts, keratinocytes, mesenchymal cells) as starting material. Subsequently, the global gene expression profile of the starting population must be altered to match that of NSCs which can be achieved via the induction of gene regulatory networks (GRNs) characteristic of NSCs (12–15). Put simply, expression of certain transcription factors dubbed "pioneering factors" are sufficient to orchestrate a change in the gene expression landscape of the whole cell by activating such GRNs. For example, induced overexpression of Sox2 alone is capable of converting somatic cells into NSCs both *in vitro* and *in vivo* (next section) (16,17). In this case, Sox2 binds to DNA in regions of heterochromatin that are normally

inaccessible, resulting in the upregulation of NSC-specific genes and downregulation of the original cell identity. The induced NSCs (iNSCs) produced are capable of extensive self-renewal and multi-potential differentiation; they also exhibit gene expression profiles characteristic to NSCs (18). Therefore, at the fundamental level, iNSCs possess similar molecular and functional properties as endogenous NSCs.

To induce expression of pioneering factors, several strategies have been used including genomic, proteomic, and chemical interventions (1,12). The most effective and commonly used strategy is the integration and forced overexpression of pioneering factor genes using viruses (19). This strategy permits the stable expression of transduced genes in dividing daughter cells but comes with the risk of DNA instability due to random gene insertion. As such, iNSCs generated using this method are not clinically translatable. However, non-transducing strategies have been developed to minimize the risks associated with permanent genomic modifications. These strategies include non-transducing viruses (e.g. adenovirus, Sendai virus), transient overexpression of pioneering factor genes using non-viral methods (e.g. electroporation and transfection of plasmids or RNA), transfection with transcription factor proteins, and/or using small chemical molecules to modulate endogenous transcriptional machinery (e.g. histone modifying proteins) (1,12,13). The latter strategy, when using only small chemical molecules, is dubbed the safest method for clinical translation because it avoids the introduction of foreign genetic material. Therefore, more protocols utilizing this strategy are being developed (15,20).

Despite low reprogramming efficiencies of most methods, once iNSCs are formed, they can be expanded long-term in culture to scale production for downstream applications (12,19,21). iNSCs can also be cryo-preserved to be shipped and used for later applications with no decline in regenerative potential. This allows enough iNSCs to be generated for autologous transplant or creation of a cell bank for allogenic transplantation (8). However, given the various methods of generating iNSCs, it is unclear if iNSCs can reliably give rise to all major cell types of the nervous system as similarly as their endogenous counterparts. Hence, there is continued interest in the field for generating iNSCs that bear the utmost homology to endogenous NSCs. Furthermore, it has been demonstrated that endogenous NSCs and iNSCs of spinal cord identity are superior for the repair of spinal cord injury compared to their brain counterparts (22,23). Therefore, it is expected that iNSCs will be most therapeutically effective when placed in their "natural" environment which they can recognize and support.

IN VIVO REPROGRAMMING OF ASTROCYTES

In 2013, in vivo reprogramming of rodent spinal cord astrocytes into iNSCs was first reported which was replicated in the rodent brain (17,24,25). Astrocytes are abundant in the nervous system making them an attractive target for cellular reprogramming (26). It must be noted that other cell types can be reprogrammed into NSCs *in vivo*, however, given their relative abundance, astrocytes may be the best candidate. Furthermore, relative to the cells commonly used in *in vitro* reprogramming, the gene expression profile of astrocytes more closely resembles NSCs which facilitates genetic reprogramming. In vivo reprogrammed iNSCs display characteristic self-renewal, multi-potential differentiation, and can differentiate into neurons which integrate and form synaptic connections with neighbouring neurons. Importantly, iNSCs can be reprogrammed in neurodegenerative disease and injury models including Alzheimer's, brain stab injury, and spinal cord injury and can survive long-term (up to 8 months) indicating the therapeutic potential of this strategy (17,24,27). However, an impediment to effective regeneration lies in the ability to faithfully direct iNSC fate in vivo and generate enough cells with a desired specialized phenotype.

To selectively reprogram astrocytes *in vivo*, a viral-based intervention is commonly used to induce overexpression of pioneering factor Sox2 (**Figure 1**) (17,27,28). Some main advantages of directly converting cells *in vivo* include that it avoids the time constraints imposed by *in vitro* reprogramming and is potentially less invasive. However, a safe and efficient means for the viral delivery of genetic material will be important for realization of this strategy in humans. Such a strategy must also meet the need for targeting regional populations of astrocytes, thereby allowing for a mechanistic approach for directing regeneration in a spatial manner while minimizing off-target effects (**Figure 1**) (27).

MODELING NEURONAL DEVELOPMENT AND DEGENERATIVE DISEASES

Reprogrammed NSCs have provided unprecedented access to study live human brain and spinal cord neuronal cells, which were previously only attainable through biopsies, post-mortem tissue, or embryonic derived tissue. Since iNSCs can be directed to a specific developmental lineage from embryonic to adult, appropriate models for neurodevelopment and neurogenesis can be generated (**Figure 2**) (2,29,30). Furthermore, patient-derived iNSCs can be generated which

recapitulate characteristic hallmarks of the associated disease including amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's, Parkinson's, and Huntington's disease (30–36). For example, iNSC-derived neurons from Alzheimer's patients display the typical pathological features in vitro including elevated amyloid beta plaques and phosphorylated tau proteins (2,32). Similarly, neurons derived from Parkinson's patients posses higher than normal levels of both oxidative stress and alpha-synuclein impairing neuronal survival and function (37,38). Subsequent interventions using molecular or genetic techniques can then be applied to rescue pathological phenotypes in patient cells or induced in control cells which do not bear the original disease phenotype (2,30,31,39,40). Therefore, iNSCs represent a new platform for which studies can be designed to better understand human specific disease mechanisms and facilitate the development of therapeutic targets.

In addition to drug development, iNSCs can be used for drug screening to predict whether a patient will be drug-resistant as is the case with many neuropsychiatric conditions (4,33,39,41). An interesting study involving iNSC-derived hippocampal granule neurons from patients with bipolar disorder demonstrated hyperexcitability, irregular mitochondrial function and altered gene expression compared to healthy controls. The impaired phenotypes in patient derived neurons were rescued with lithium treatment but only in the subset of patients who responded to treatment. Gene expression analysis revealed that lithium significantly altered gene expression in neurons derived from lithium-responsive patients (560 genes) compared to lithium-nonresponsive patients (40 genes) (42). This presents an opportunity for personalized drug screening, as patient specific responses to drugs can be observed *in vitro* while also determining the genetic predispositions of drug resistance. As such, efforts to model cellular mechanisms of disease have increased and represent important tools for personalized medicine and potential development of therapeutic treatments in non-responsive patients.

An emerging strategy to model human brain development and dysfunction involves the formation of "brain organoids" from iNSCs (4,30,39–41,43–45). These in vitro miniature brains are developed in 3D and can consist of distinct human brain regions including ventricles, cerebral cortex, hippocampus, hypothalamus, forebrain, midbrain, choroid plexus, and more. Brain organoids can be generated either by the autonomous self-regulating activity of iNSCs to form random brain structures or by directing the development of iNSCs with signaling cues to form distinct structures. Furthermore, different regionalized brain organoids can be fused ("assembloids") to model brain regional connectivity and interactions. For example, inhibitory GABAergic interneurons migrate from the ventral forebrain into the dorsal cortex during normal brain development which can be recapitulated in assembloids consisting of ventralized and dorsalized regions (46).

The main advantage of 3D organoid modeling is that it permits cell-to-cell communication among the different specialized cells in the organoid, thereby mimicking in vivo brain interactions more accurately than 2D *in vitro* systems. The intrinsic complexity of this model is useful to study the interactions amongst different human brain cells, immune cells, and pathogens, which is necessary for a wholesome understanding of pathophysiology. Moreover, these brain structures are reminiscent of human-specific neurodevelopment (e.g. outer radial glial cells in cerebral

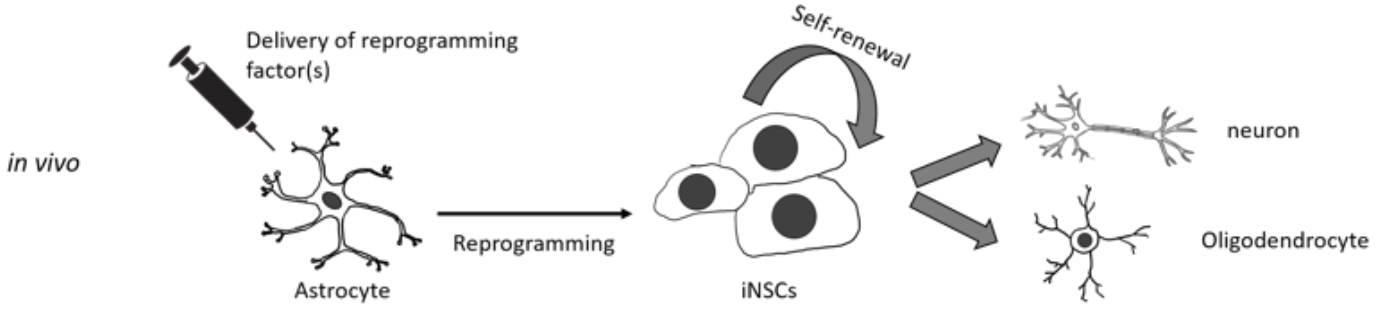

Figure 1. Method and rationale for astrocyte reprogramming into iNSCs *in vivo*. Astrocytes are selectively targeted using viral vectors and induced to overexpress reprogramming factors. Resulting iNSCs can self-renew and differentiate into neurons and oligodendrocytes which functionally integrate with the existing neuroanatomy. Challenges remains to safely and selectively target regional astrocyte populations as well as to direct fate of iNSCs towards specific neuronal and oligodendrocyte lineages.

cortex development) which is not possible to study in animal models (47). Therefore, human brain organoids are better suited than animal models for the study of human-specific neurodevelopmental disorders such as micro/macrocephaly (48,49).

Neuropsychiatric disorders, such as schizophrenia and autism spectrum disorder, have also been difficult to model in animals given their polygenic basis and complex pathophysiology involving dysregulation in cell-to-cell communication and brain circuitry (33,39,41,50,51). The nature of brain organoids is such that neural circuitry is integrated within the system. Therefore, neural transmission among regionalized brain organoids can be causally dissected using molecular and genetic manipulations in conjunction with electrophysiological analysis. Another major advantage is that organoids from patients and family-matched controls can be studied in comparison to one another to reveal significant genetic contributors to disease pathology (**Figure 2**) (52,53). (Poly)genetic mutations present as defects in organoid development, cell differentiation and maturation, neuronal synapse function, and circuit transmission. A major limitation of this model, however, is the furthest size and developmental stage that organoids can attain before becoming necrotic. Engineering organoids to contain vasculature will permit further development and maturation *in vitro* for modeling post-natal brain development and degeneration (45,54). Finally, it is crucial to integrate the information derived from organoid research with *in vivo* neurophysiology for reliable and accurate inference. This should be addressed by complementing *in vitro* modeling with live human and animal studies.

CLINICAL APPLICATION

The human central nervous system is ineffective at functional recovery over the course of degeneration or injury and thus may benefit from an exogenous source of regeneration (55–57). iNSCs are a promising tool for the treatment of neurodegenerative disorders, given they are inherently programmed to regenerate the different specialized cells of the nervous system (18). As such, iNSCs might be able to replace degenerating and/or dead cells to combat the progression of neurodegeneration and restore homeostatic neuronal functioning (18,23,58). Pre-clinical testing involving implantation of NSC grafts in animals has proven to be beneficial for multiple conditions (59,60). Some of the successful animal trials progressed towards clinical trials for Parkinson's disease, spinal cord injury, and macular degeneration of the eye (5–7). However, these trials are still in their infancy and their effectiveness has yet to be determined. Major challenges for these strategies include promoting cell graft survival, controlling iNSC fate *in vivo*, and promoting structural and functional integration of iNSCs with host cells.

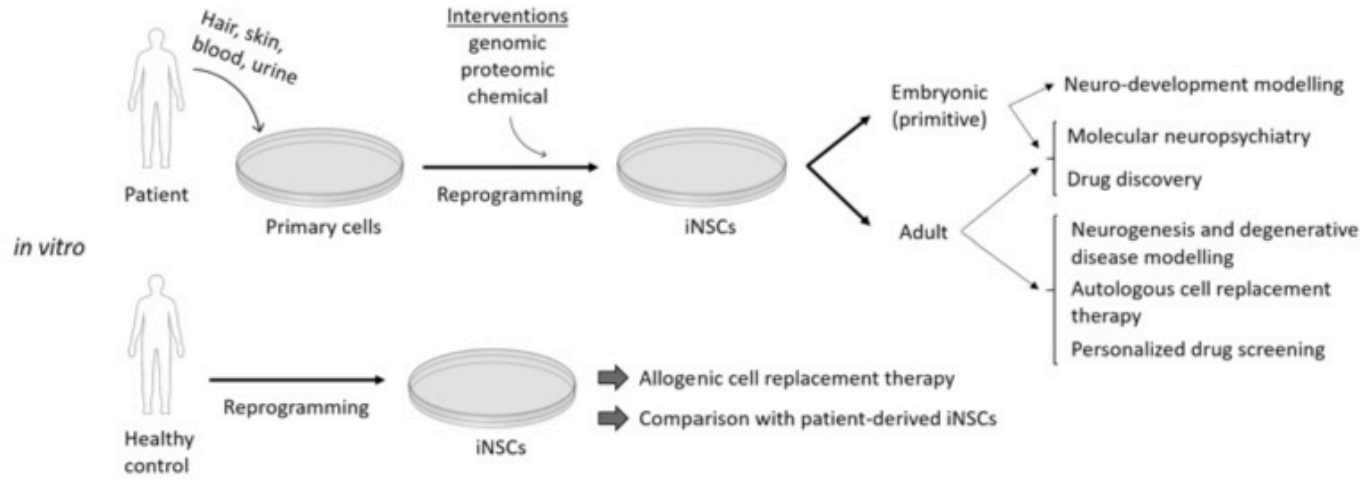

Figure 2. Overview of genetic reprogramming procedure *in vitro*. and translational implications of iNSCs.
(A) First, patient somatic cells are obtained and **(B)** cultured to yield enough primary cells for reprogramming. **(C)** Many methods including genomic, proteomic or chemical interventions are available for reprogramming iNSCs with specified developmental and regional identities. iNSCs have multiple translational purposes including cell replacement therapy and discovery of human specific neurodevelopment and disease mechanisms. **(D)** iNSCs can be generated from control patients and used for allogenic transplants or comparative analysis with patient-derived iNSCs. and oligodendrocyte lineages.

Nonetheless, the development of iNSCs from adult human tissue has mitigated the ethical constraints that accompany embryonic and fetal-derived tissue use while also providing an autologous source of cells for transplant which minimizes immunogenicity (61). Therefore, iNSCs can be patient-specific and scaled up in production for later transplant. The obvious drawback is the time frame during which iNSCs need to be cultured *in vitro*, thereby representing a possible limitation for patients that require an urgent intervention. A solution could be to use an isogenic cell bank for all patients, which would permit immediate access to cells and minimize the variability between different iNSC lines. This, however, would replace the benefits of autologous treatment with the risks of allogenic transplantation (8,61).

CONCLUSION

Insult to the human central nervous system was presumed to be permanent, but today's scientific advances in genetic reprogramming have revolutionized the way we study and treat neurological disorders. The advancements in genetic reprogramming strategies to create iNSCs has provided scientists with human neuronal cells and organoids that mimic patient-specific conditions and can be used to identify the molecular underpinnings of human disease. This strategy can be used to develop therapeutic targets and test drug efficacy in a patient-specific manner. Given their endogenous regenerative capacity and demonstrated effectiveness in pre-clinical models, iNSCs hold the potential for treating a variety of neurodegenerative disorders. The major challenges moving forward include creating more developed *in vitro* models of human neurobiology, integrating the information from *in vitro* models with our understanding of *in vivo* neurophysiology, and translating the pre-clinical effectiveness of iNSC transplantation into successful human trials.

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Efficacy and Toxicity of Treatments for Primary Central System Lymphoma: Review of the Recent Literature

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ABSTRACT

Primary central nervous system lymphoma (PCNSL) is an uncommon type of central nervous system lymphoma, most commonly presenting as hemiparesis and headache. Currently, there is a wide range of treatments for PCNSL, consisting of various permutations between chemotherapy, radiation and autologous stem cell transplant (ASCT). Although the backbone of PCNSL treatment consists of high-dose methotrexate (HD-MTX), the role of combination versus single agent chemotherapy, combined modality (chemotherapy + radiation) versus chemotherapy or radiation alone, and the use of consolidative ASCT are contested. Surgery does not have a role in the treatment of PCNSL although stereotactic biopsies tend to help with symptomatic relief. Radiation monotherapy is generally reserved for patients with contraindications to chemotherapy or as a palliative measure. Combined chemotherapy and radiation treatment has been shown to have a great efficacy, although its increased neurotoxicity compared to chemotherapy alone is a major drawback. A growing body of research is focused on comparing the efficacy of various chemotherapeutic regimens. Currently, the MATRix regimen comprising of HD-MTX (3.5g/m^2)-cytarabine/rituximab/thiotepa is widely used. The additional survival benefit of ASCT is contested although its role in the treatment of refractory or relapsed PCNSL is generally agreed upon. Finally, intrathecal HD-MTX has been shown to have added survival benefit when added to the standard therapies. Further retrospective and prospective studies are required to compare the efficacy and toxicity of various treatment options, with a focus on different chemotherapeutic agents and ASCT.

RÉSUMÉ

Le lymphome primitif du système nerveux central (LPSNC) est un type peu commun de lymphome du système nerveux central, qui se présente souvent avec une hémiparésie et une céphalée. Actuellement, il y a une grande variété de traitements pour le LPSNC, consistant en plusieurs permutations de la chimiothérapie, la radiation et l'autogreffe de cellules souches. Bien que le pilier du traitement du LPSNC consiste en méthotrexate à haute dose (MTX-HD), le rôle de multiple versus un seul agent chimiothérapeutique, d'un modèle combiné (chimiothérapie + radiation) versus la chimiothérapie ou la radiation seule, et de l'usage d'autogreffe de cellules souches consolidatrice, sont contestés. La chirurgie n'a pas un rôle dans le traitement du LPSNC malgré que des biopsies stéréotaxiques ont tendance à aider avec un soulagement symptomatique. La radiation comme monothérapie est surtout réservée pour les patients ayant des contrindications à la chimiothérapie ou comme mesure palliative. Le traitement par combinaison de chimiothérapie et de radiation a démontré beaucoup d'efficacité, par contre sa neurotoxicité augmentée comparée à la chimiothérapie seule est un important désavantage. Un montant augmentant de recherche cible la comparaison de l'efficacité d'une variété de régimes chimiothérapeutique. Actuellement, le régime MATRix composé de MTX-HD (3.5 g/m^2)/ cytarabine/rituximab/thiotepa est utilisé largement. Les chances de survie augmentée par autogreffe de cellules souches sont contestées, mais son rôle dans le traitement du LPSNC réfractaire ou récurrent est généralement convenu. Finalement, le MTX-HD intrathécal a démontré des avantages pour la survie, quand ajouter aux thérapies standards. Des études rétrospectives et prospectives sont requises pour comparer l'efficacité et la toxicité de la variété d'options de traitement, avec une cible sur les différents agents chimiothérapeutiques et l'autogreffe de cellules souches.

Primary central system lymphoma (PCNSL) is an uncommon type of non-Hodgkin lymphoma, comprising 3-4% of brain tumours and 4-6% of extranodal lymphomas (1, 2). Its incidence is decreasing in the general population, but is increasing in those above the age of 65 (3).

Acquired or genetic immunodeficiency are the established

Keywords: Primary Central Nervous System Lymphoma; Chemotherapy; Radiation Therapy

risk factors for developing PCNSL. Specifically, patients with human immunodeficiency virus (HIV) and congenital immunodeficiency disorders (e.g. Wiskott-Aldrich syndrome) carry a risk of 2-6% and 4% compared to the general population for developing PCNSL, respectively. Other diseases inducing immunosuppression (e.g. systemic lupus erythematosus) and post-transplant status have also been associated with increased risk of PCNSL (3, 4).

The international Extranodal Lymphoma Group suggest using age (more or less than 60), Eastern Cooperative Oncology Group(ECOG) performance status (0-1 versus 2-4), serum lactase dehydrogenase level (normal versus elevated), cerebrospinal fluid (CSS) protein concentration (normal versus elevated), and involvement of deep brain structures (no versus yes) as prognostic indicators for PCNSL (5). Unfortunately, the prognosis of PCNSL remains poor despite the emergence of new therapies in the field (6).

The clinical signs and symptoms vary depending on the site of involvement in the central nervous system. PCNSL most commonly involves the periventricular white matter (51%) and basal ganglia (48.9%). The most frequent presenting symptoms were shown to be hemiparesis (56.2%) and headache (51.7%) in a retrospective study of 176 patients with PCNSL (7). Other common symptoms include neuropsychiatric symptoms and other signs of raised intracranial pressure (i.e. nausea and vomiting). Seizure and visual symptoms occur less frequently in 14% and 4% of patients, respectively (8).

Suspicion of PCNSL should prompt imaging of the central nervous system, with MRI as the preferred modality. Subsequent investigations include lumbar puncture for CSF analysis, slit lamp examination of both eyes for potential ocular pathology and stereotactic needle biopsy of the involved tissue (9). The definitive diagnosis of PCNSL is made by histopathological analysis. Therefore, brain biopsy should not be delayed after the suspicion of PCNSL (9). Once the diagnosis of PCNSL is made, a whole-body PET scan and bone marrow biopsy should be performed to rule out secondary diseases with CNS involvement (10).

Here, we review the existing literature on studies comparing the effectiveness and toxicity of various modalities in the treatment of PCNSL. We also attempt to appraise and identify the existing gaps in the literature.

TREATMENT OVERVIEW

Treatment of PCNSL consists of an induction and a consolidation phase. The induction phase aims at achieving a complete radiographic response (CR), while the goal of consolidation phase is to maintain remission. It is commonly accepted that high-dose (3-8g/m^2) methotrexate (HD-MTX) is the backbone of PCNSL induction therapy. The roles of whole brain radiation, combined versus single agent chemotherapy and autologous stem cell transplant in both phases are debated. As such, there is no agreed upon algorithm in the treatment of PCNSL (11). Such lack of consensus stems from the rarity of the disease and lack of sufficient large scale randomized clinical trials (9). Generally, PCNSL is managed by a multidisciplinary team including hematologists, radiation oncologists, neuroradiologic, neurosurgeons, ophthalmologists, and allied health care professionals (12, 13).

SURGERY

Currently, there is no role for surgery in the treatment of PCNSL. The tumour is usually deeply located in the brain, making surgical access difficult. Also, the multifocal and diffuse nature of the disease allows for microscopic infiltration across the visible margins of the tumour (14). The data from a retrospective study of 33 patients suggested that while surgery does not improve survival outcomes, it does not play a negative role in survival (15). The authors argued that microsurgical excision of tumours with a single focus and progressive neurological deterioration can improve survival (15). Further studies involving larger groups of patients are required to further explore the exact role of surgery in the treatment of PCNSL.

RADIATION MONOTHERAPY

Due to its diffuse nature, radiotherapy of PCNSL should involve the whole brain. Up until 1980, whole brain radiotherapy (WBRT) monotherapy was the mainstay of therapy for PCNSL (9). Unfortunately, the outcomes of this treatment were shown to be poor with 5 year-survival of less than 10% (16). One of the most promising results of WBRT monotherapy was demonstrated in a study led by the Radiation Therapy Oncology Group, where 62% of patients achieved CR. Unfortunately, the response was not durable with only 48% and 28% survival after 1 year and 2 years, respectively (17). Currently, the use of WBRT is recommended in patients with contraindications to chemotherapy and those failing to achieve CR following systemic chemotherapy (18).

COMBINED RADIOTHERAPY AND CHEMOTHERAPY

To increase the response duration, different chemotherapeutic agents were added to WBRT. The RTOG conducted a trial in which 54 patients received two or three cycles of cyclophosphamide, doxorubicin, vincristine and dexamethasone (CHOD), followed by high-dose WBRT (total dose of 59.4 Gy). The 2-year survival was 42% and the median survival for the entire group was 16.1 months. Compared to the study above by Nelson et al. (1992), which investigated radiation monotherapy, addition of CHOD to WBRT did not lead to a significant improvement in overall survival (OS) (19). This lack of efficacy is attributed to poor permeability of blood brain barrier (BBB) to vincristine and doxorubicin (13).

Addition of HD-MTX to WBRT in subsequent studies was shown to be effective. Namely, upfront treatment of 52 patients with HD-MTX (3.5g/m^2), procarbazine, vincristine and intrathecal methotrexate (MTX), followed by a consolidation therapy with high-dose WBRT (45 Gy) and high dose-cytarabine led to a remarkable improvement in OS compared to previous studies. The mean OS was 60 months with relapse occurring in 18 patients after 3-35 months. Interestingly, the OS of the elderly population was the same with or without WBRT, although addition of WBRT led to higher rates of late neurotoxicity in this population (20). Subsequent studies produced similar results, confirming that the combination of HD-MTX plus WBRT, is superior to WBRT alone (21-23).

So far, there is only one prospective phase 3 randomized clinical trial which investigated the difference between first line HD-MTX (4g/m^2) combined with WBRT (45 Gy) as compared to chemotherapy alone. The objective of the study was to demonstrate that HD-MTX treatment is non-inferior to HD-MTX and WBRT, with a margin of 0.9. Although the OS was not significantly different between the two arms (32.4 months in HD-MTX/WBRT, confidence interval: 25.8–39.0; versus 37.1 months in HD-MTX alone, confidence interval: 27.5–46.7), the progression free survival (PFS) was higher in the arm receiving WBRT (18.3 months in HD-MTX/WBRT; 11.9 months in HD-MTX alone). The non-inferiority hypothesis of the study was not met as the confidence interval crossed the 0.9 margin set initially. Finally, the patients receiving WBRT experienced greater rates of neurotoxicity (24). Despite its interesting findings, a variety of methodological issues existed in the study, calling the validity of its conclusions into question. Specifically, from the 551 patients enrolled, 411 met the eligibility criteria for the intention to treat group and only 318 patients were treated per protocol due to 93 protocol violations. Once the 93 patients, in whom the protocol violations were committed, were excluded from the denominator, a source of bias was introduced as many of those excluded failed to achieve CR and therefore had a lower PFS (25).

Nowadays, WBRT is mainly used as consolidation treatments. Its major downside is the side effect of neurotoxicity, which is more pronounced when WBRT is used in high doses or in combination with chemotherapy. As a result of this toxicity, many centres avoid using WBRT (13). To account for the issue of neurotoxicity, a few recent studies have investigated the effect of dose-reduced WBRT (dR-WBRT). In a single centred study, the induction therapy consisted of rituximab, MTX, procarbazine, and vincristine. The patients attaining CR (2/3 of the study population in this case) were then treated with dR-WBRT (23.4 Gy), followed by a consolidation treatment with cytarabine. The results were unparalleled with a median PFS of 7.7 years, 3-year OS of 87%, and stable neuropsychological testing scores 48 months following treatment in those completing the regimen. This study was also unique for using immunotherapy in the treatment of PCNSL (26). An ongoing trial is exploring the role of immunotherapy alone by comparing PFS in a group treated with immunotherapy and WBRT, versus immunotherapy alone (NCT01399372).

SYSTEMIC CHEMOTHERAPY

Intravenous HD-MTX administered as rapid infusion is the most effective agent in the treatment of PCNSL. Depending on the centre, HD-MTX is administered alone or in combination with other medications. A retrospective study of 288 immunocompetent patients demonstrated that doses of MTX above 3g/m^2 led to improved survival (27). The best therapeutic dose of HD-MTX is currently not agreed upon, however. To compare the effectiveness and toxicity of HD-MTX monotherapy versus HD-MTX combined with other chemotherapeutic agents, a phase II randomized trial was conducted. The authors concluded that HD-MTX combination with cytarabine led to an increase in PFS and a better CR rate compared to HD-MTX monotherapy. Finally, treatment-related toxicity was higher in the polychemotherapy group (28).

Prospective studies exploring HD-MTX monotherapy (usually 8g/m^2) demonstrated a 2-year OS of 61-63%, while those investigating the role of HD-MTX combination therapy revealed a greater 2-year OS of 65-78% (13, 29, 30). In terms of combination therapy, rituximab is most commonly combined with HD-MTX. The superiority of HD-MTX-rituximab (HD-MTX/R) combination over HD-MTX

monotherapy was demonstrated in a retrospective study. The results demonstrated an overall improvement in OS and PFS. Remarkably, the median PFS improved from 4.5 months in patients treated with HD-MTX alone to 26.7 in those treated with HD-MTX/R (31). Subsequently, a phase II study of patients aged 18–70 years demonstrated that the MATRix regimen was superior to HD-MTX-cytarabine, and HD-MTX-cytarabine/thiotepa (32). The CRs after 30 months in the HD-MTX-cytarabine/rituximab/thiotepa, HD-MTX-cytarabine/rituximab, and MTX-cytarabine were 49%, 30%, and 23%, respectively. The authors of this study concluded that the MATRix regimen can be used as a new chemoimmunotherapeutic regimen in the treatment of PCNSL in patients under the age of 70. Unfortunately, grade 4 hematological toxicity (i.e. neutropenia and thrombocytopenia) were higher in patients treated with the MATRix regimen as compared with the other two groups (32).

HIGH-DOSE CHEMOTHERAPY/AUTOLOGOUS STEM CELL TRANSPLANTATION (HDC/ASCT)

HDC/ASCT seems to be a reasonable option for relapsed/refractory PCNSL. A single-arm multicentre study used an induction regimen of rituximab, high-dose cytarabine and thiotepa, followed by HDC/ASCT conditioning of rituximab, carmustine and thiotepa to test the effectiveness of HDC/ASCT on immunocompetent patients (< 66 years) who were refractory to HD-MTX-based regimens. Patients received HDC/ASCT regardless of their response to induction therapy. Those not achieving CR following HDC/ASCT were treated with WBRT. The results following HDC/ASCT were remarkable for CR of 56.4%, 2-year PFS of 46.0% and OS rates of 56.4%. Unfortunately, 4 treatment-related deaths were reported (33). This study confirmed similar conclusions by earlier studies regarding the effectiveness of HDC/ASCT in the treatment of refractory/relapsed PCNSL. Despite the promising responses, the restrictive age criteria introduced a selection bias.

Another study expanded the inclusion criteria of the previous study, looking at relapsed and refractory diseases as well as those with partial response to first-line therapy. Patients were treated with high-dose cytarabine and etoposide as salvage treatment, followed by intensive combined thiotepa, busulfan, cyclophosphamide and ASCT. The 2-year OS was 45% in all patients and 69% amongst those who completed the treatment. Also, the 2-year PFS was 43% in the entire population and 58% in the HDC/ASCT subpopulation (34). The promising results of these studies allowed certain guidelines to recommend HDC/ASCT as an option for chemotherapy-sensitive patients with relapsed or refractory PCNSL (35).

The role of HDC/ASCT as first line therapy for PCNSL has also been investigated. A study used HD-MTX (8g/m^2), cytarabine and thiotepa as induction therapy, followed by carmustine and thiotepa as conditioning therapy. The patients were subsequently treated by ASCT. Promising results were found with a 5-year OS of 69% for all patients and 87% for patients completing the entire regimen. All of the patients receiving HDC experienced WHO grade 3/4 neutropenia and thrombocytopenia. Also, 16.7% of the patients experienced leukoencephalopathy after a median follow-up of 63 months. Regardless of the neurotoxicity, the authors considered the treatment effective and this amount of toxicity minimal (36).

A centre in Canada reproduced similar results with a different combination of upfront thiotepa, busulfan, cyclophosphamide, and ASCT. Although the 5-year OS was lower (44%) than that reported by Illerhaus et al. (2006), no neurotoxicity was observed. The choice of medications in this study is remarkable as both busulfan and thiotepa penetrate the BBB at levels greater than 90%, while other common agents, such as carmustine, cyclophosphamide and etoposide have much lower penetration levels (15-70%, 20% and 5%, respectively). Moreover, both busulfan and thiotepa have steep dose-response curves, further allowing high concentration in the CNS. The unique pharmacokinetics suggests that busulfan and thiotepa have greater potency compared to other medications, while resulting in a lower side effect profile. Furthermore, the treatment-related-mortality (TRM) was relatively high (14%). Notably, all of the mortalities were observed in patients who were over the age of 60 and had poor performance status (37).

To summarize, HDC/ASCT presents a promising treatment for patients with refractory and relapsed PCNSL. Although various studies have demonstrated the effectiveness of HDC/ASCT as first-line therapy, no study to date has compared HDC/ASCT, HD-MTX-based chemotherapies or combination chemoradiotherapy as first line therapies. Two ongoing clinical trials attempt to compare the efficacy and toxicity of HDC/ASCT versus chemotherapy or WBRT (NCT01011920 and NCT00863460). In general, HDC/ASCT seems to have a greater benefit to harm ratio in immunocompetent patients who are under the age of 60 and have good performance status (KPS>60% at the time of transplant). As such, this population should be the primary target of HDC/ASCT until further data on the use of HDC/ASCT in PCNSL emerges (13, 37).

CEREBROSPINAL FLUID THERAPIES

The exact role of intrathecal (IT) chemotherapy is controversial, partly due to the paucity of evidence in the literature around its effectiveness. Three retrospective studies demonstrated no benefit in terms of disease control, survival and neurotoxicity with IT therapies comprised mainly of HD-MTX in the treatment of PCNSL (38-40). One out of the three studies specifically explored the role of prophylactic HD-MTX-based IT therapies (38).

On the other hand, a prospective phase II study in 2009 demonstrated promising results with the use of IT therapies (41). Prior to this study, Pels et al. (2003) conducted another phase II study where they used chemotherapeutic regimens based on HD-MTX and HD-cytarabine, in combination with intraventricular MTX, prednisone and cytarabine. The results were promising with a CR rate of 61%, median OS of 50 months, and median time to treatment failure (TTF) of 15 months (42). The study in 2009 aimed to explore the role of IT therapy by using the same regimen without IT therapy. While the CR rate was comparable (53%) to the previous study, the rate of early relapse was much higher with a TTF of only 8 months (41). Put together, the two studies demonstrated a clear benefit in using direct chemotherapy injection into the CSF, which is in contradiction to the conclusion by previous retrospective studies. No significant neurotoxicity was observed in either study.

ELDERLY PATIENTS

Although the role of HD-MTX in the treatment of PCNSL in the elderly is well established, there is insufficient evidence comparing the effectiveness and toxicity of other agents combined with HD-MTX. The only randomized control study comparing MTX-based chemotherapies in the elderly (>60 years) was a phase II trial comparing MTX and temozolomide combination (MT arm) versus MTX, procarbazine, vincristine, followed by consolidation with cytarabine (MPV-A arm). Treatment in the MPV-A arm was associated with enhanced OS, PFS and CR compared to the MT arm. Toxicity was similar between the two arms, with abnormalities in liver function tests as the most common manifestations of toxicity (43). Neuropsychological testing did not detect any neurotoxicity in either group and EORTC QLQ-BN20/QLQ-C30 questioners demonstrated the quality of life was enhanced in both groups. Further details about dosing, efficacy, and toxicity of MTX/temozolomide and MTX/procarbazine/vincristine/cytarabine regimens are being investigated in an ongoing clinical trial (NCT00503594) (20).

WBRT does not seem to be a reasonable choice in the elderly population due to its disproportionately higher risk to benefit ratio. A systematic review exploring the effects of various first line therapies in the treatment of PCNSL in elderly patients (≥60) reported that although WBRT leads to a slight increase in PFS and OS, it is associated with unacceptable increase in neurotoxicity (1). Two retrospective studies demonstrated similar results in terms of neurotoxicity with no change in OS as a result of treatment with WBRT (20, 44).

In general, treatments based on HD-MTX are well tolerated and enhance the quality of life in elderly patients. No difference seems to exist between treatment with HD-MTX plus an oral agent, versus HD-MTX plus more aggressive IV therapies. As such, combination of HD-MTX and oral agents (e.g. procarbazine) is preferred (1).

CONCLUSION

Over the past years, a growing amount of literature has described the characteristics and novel treatments for PCNSL. HD-MTX is the backbone of therapy in the treatment of PCNSL, with HD-MTX-based combination therapies producing better survival outcomes than HD-MTX alone. Similarly, combination of WBRT and HD-MTX-based chemotherapies has been shown to lead to greater survival outcomes than chemotherapy alone. Unfortunately, HD-MTX-based combination chemotherapy and combined chemoradiation are associated with greater toxicity compared to HD-MTX alone and chemotherapy alone, respectively. Therefore, the risks and benefits of various therapies (including the ongoing clinical trials) should be clearly discussed with patients and the choice of therapy should be considered in relation to the patient's goal of care and available resources. Finally, HDC/ASCT seems to be an appropriate option for refractory/relapsing PCNSL. Despite the advances in the treatment of PCNSL, the prognosis of this disease remains poor and many questions regarding the best approaches to its therapy, particularly in the elderly population, remain unanswered.

FUTURE DIRECTIONS

Further retrospective and prospective studies are required to explore the ideal therapies for various patient populations. Given the promising results of the study showing the superiority

of the combination of immunotherapy and dR-WBRT, further studies should investigate the role of immunotherapy in PCNSL. Finally, the upfront use of ASCT in combination with chemotherapy and/or radiation should be further elucidated. Retrospective studies can also determine clinicians' tendency for using ASCT in elderly versus younger patients

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A Circumpolar Experience: How Social Determinants of Health, Climate Change, Grapes, and Medical Innovation are Related

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ABSTRACT

This report shares my experience on an Arctic expedition with the *Students on Ice Foundation*. Social determinants of health (SDHs), including climate change, are considerably worse in Indigenous populations than in non-Indigenous populations and carry profoundly negative implications for Indigenous healthcare. Climate change has a more significant effect at the poles than anywhere else, compounding the effects of other SDHs and worsening Indigenous health outcomes. There are innovative ways in which SDHs and the effects of climate change can be mitigated and ways in which Indigenous healthcare can be improved, particularly with programs such as *Students on Ice*.

RÉSUMÉ

Ce rapport de stage donne un survol sur l'expérience d'un étudiant en médecine de première année complétant un stage en rhumatologie pédiatrique par l'entremise de la Société canadienne de rhumatologie (SCR). Les étudiants peuvent faire demande pour travailler avec un rhumatologiste afin d'avoir une opportunité de vivre un horaire alternant entre des soins externes et des soins hospitaliers, au cours de l'été. Ce stage est unique : il expose aux étudiants de médecine au préexternat des expériences d'apprentissage qui leur préparent pour l'externat et l'avenir. Il offre des opportunités pratiques ainsi qu'un aperçu de la recherche dans cette spécialité ; tout dans un établissement scolaire canadien mondialement connut.

Last summer, I was awarded a once-in-a-lifetime opportunity to embark on a polar expedition through Greenland and Nunavut. For two weeks, I lived on a ship with 127 youth from 20 countries and learned from over 90 world-renowned researchers, authors, artists, educators, and Elders. While this expedition was not one of a medical nature, it has revolutionized the way in which I will practise medicine. My expectations of this program run by *Students on Ice Foundation* were, at first glance, straightforward: foster meaningful relationships with Canada's Indigenous population; learn about the impact of climate change on the world; become more empowered to inspire positive environmental change; and develop professional international relationships with globally-minded individuals. Not only did this expedition exceed my expectations, it provided me with the resources to combine my passion for environmental preservation with my desire to advocate for Indigenous populations in healthcare settings. Reflecting on this expedition, I realize now that my expectations were not simple in the slightest. To understand the vibrant, beautiful, and complicated life that exists in our northern regions, one must be prepared, educated, and willing to ask difficult questions.

Keywords: Publication; Blogging; Peer-review; Scholarship; Knowledge; Research

Eight nations rest, in part, above the 66° latitude of the Arctic Circle: Canada, The United States of America, Denmark (including Greenland and the Faroe Islands), Iceland, Finland, Norway, Sweden, and Russia (1). Together, these nations comprise the Circumpolar North and are unique in that they face challenges distinct to each other and not experienced by countries outside this region. Climate, extreme landmass distances, and high costs of living have transformed communities such as Pond Inlet, Nunavut, Canada (72.7° Latitude) and Resolute Bay, Nunavut, Canada (74.7° Latitude) into entirely different places from Ottawa, Ontario, Canada (45.4° Latitude). In fact, aside from sharing a national anthem and prime minister, they are probably more different than they are alike. As a medical student, I focused primarily on the healthcare practices and distribution of healthcare resources amongst these regions. For instance, during one of my community visits, I searched for the differences in the social determinants of health (SDH) between the relatively "large" community of 1,600 people in Pond Inlet, and the "large" community of 935,000 people in Ottawa. Every morning, as I sat at the ship's breakfast table with my eggs, toast, and fruit salad, I tried to predict what I would see each day and how I might feel. I was shocked every night with how wrong I was in my prediction.

The social determinants of health (SDH) are well-known in the medical profession as the personal, social, economic, and environmental factors that play a large role in both individual and population health (2). They include factors such as income, culture, education, and access to healthcare. It has been repeatedly proven that Indigenous populations have more detrimental SDHs than non-Indigenous populations in Canada (2-7). For example, in 2016, the median annual income of a Nunavut resident was $5,000 lower than that of a non-Nunavut resident (3). The rates of tuberculosis in any of the four Inuit regions in Canada is 300 times that in the rest of the country, and the life expectancy in the same regions is ten years lower than the national average (4-5). Only 29% of Inuit children earn a high school diploma, compared to 85% nationally (6). Compound these SDHs with years of cultural oppression and abuse during the colonization era, as well as Residential Schools, it is unfortunately no surprise that suicide rates amongst Indigenous people are six times the national average (7). Indigenous people have SDH differences that form more of an equality chasm than a gap. Living for two weeks immersed in Northern culture with Elders and Inuit students was the first time I experienced first-hand the human impact of these unsettling statistics. Food costs were astoundingly high (one bell pepper was $17.59); I met 14-year-old students who have smoked cigarettes for years and teenagers who were pregnant; many Inuit knew someone who committed suicide; and every Inuit student and Elder had a scar from the BCG vaccine that is still required because tuberculosis is so rampant. These SDHs are present and visible and have a much greater impact than mere words and statistics can express. Don't be fooled–not every Northerner smokes and not every teenage female in Nunavut becomes pregnant. But if the saying is that "one is too many," then what should be said about the thousands of disadvantaged Indigenous people?

Interestingly, one of the SDHs is physical environment. Iqaluit, Nunavut's capital, is a more southernly community in the territory, meaning many are much farther north and significantly colder. No trees grow north of the Arctic Circle because of its tundra ecosystem, and there is a thick layer of permafrost, making it impossible for fruits and vegetables to grow. Additionally, climate change is taking its toll at the poles more than anywhere else (8). As sea ice melts, more water becomes exposed to the sun, absorbing more heat, thus melting more ice, and exposing more water. It is a vicious cycle. Many global climate models have even predicted that, for the first time, the Arctic will be ice-free for at least part of the year by the end of the 21st century (8). Indigenous communities have relied on hunting as a main food source for centuries; caribou, seal, whale, polar bear, and goose, to name a few, are staples in the Indigenous diet. Northern animals have evolved to survive icy and snowy habitats, but they, too, are seeing the effects of global warming. Polar bears have less time to hunt on sea ice and expend more energy trying to swim to and from sources of food than ever before; walruses, which usually scrounge the ocean floor for food, have had to retreat to shore because the ice is beyond their reach; caribou are changing their migration patterns as seasonal patterns shift (9). Animal behaviour change means that the Indigenous people must either adapt their age-old hunting practices to match the new requirements of their prey or face worsening food insecurity.

Aboard the ship, Nancy Etok, a teacher from Kuujjuaq, Quebec, stated in a workshop, "Our traditional food is becoming harder to come by. Hunters are away for longer times, in more unfamiliar places, and bringing back less food than ever before, if they do come back at all. When we can't eat our traditional food, we lose not only physical satiety, but a sense of cultural fullness. So much of our self-worth is rooted in foods that we grew up on that climate change is terrifying for all of us" (10). The dire climate situation has resulted in a rapid increase in research proving its negative effects on Indigenous health. A recent exploratory study determined that climate change has negatively affected the fresh water quality and quantity in Nunatsiavut, the Inuit region of Labrador (11). Another study proves that climate change is affecting Inuit access to harvest grounds, which impacts food supply and downstream health effects (12). Several other studies have demonstrated that changes in weather, ice stability, and wildlife and vegetation patterns are adversely impacting Indigenous mental health because of a loss of cultural identity (13-15). For a population that already has a stark suicide risk, the added stress of climate change only compounds a worsening problem (7). On my trip's final day, I remember eating my toast, eggs, and fruit salad, now conscious of the fact that the grapes alone would cost someone living at the same latitude $15. I felt inspired to amalgamate everything I had learned in political workshops, small group discussions, and cultural group activities to educate my peers on established initiatives that help mitigate these dire circumstances, while also brainstorming new solutions.

After disembarking the ship for the last time on the shores of Greenland–which should have been Resolute Bay, Nunavut,

but we were, ironically, diverted because of changing sea ice patterns–I took one final breath of cool summer air, far fresher than the city air to which I am accustomed, and began the next step of my journey: bringing my knowledge home. I thought back to one workshop, where an Indigenous rights activist speaking about climate change had tears in her eyes after stating she has not been able to find caribou in over two years, and knew I would dedicate my efforts to people like her. While the solutions to Indigenous health equality are far from simple, there are still countless opportunities for innovation in a multitude of disciplines. A recent study published by Lancet suggested that trying to mitigate climate change will be the single best thing governments can do for healthcare (16). Perhaps solutions lie again in education: school curricula, from primary to post-secondary, can start including climate change in their learning objectives, with projects dedicated to improving carbon footprints and school recycling programs. The United Nations established a list of 17 sustainable development goals (SDGs) in 2015 that aim to address gaps in poverty, literacy, finances, climate, and inequality worldwide (17); what is required to help reach these goals is inspired, creative people willing to advocate for change. On my trip, for example, I had the opportunity to meet Dominique Souris of Waterloo, Ontario, during an on-shore small-group discussion about the SDGs. Dominique felt so passionate about these SDGs that she founded an environmental advocacy company that empowers young adults to become leaders for the environment in their community. Dominique's organization, Youth Climate Lab, has earned her a place as one of Canada's Top 30 Under 30 Sustainability Leaders. From another perspective, the University of Ottawa Medical School integrates Indigenous health lectures into part of its curriculum (18); other programs should implement this, or even invite Indigenous guest speakers to their classes to describe their daily challenges first-hand. Additionally, while some hospital programs fly doctors to remote Northern regions as part of their residency training, medical students may benefit from having this opportunity earlier in their training, as I had, to be exposed to medicine in the North. On an individual level, mitigating climate change starts with diligent recycling or taking public transportation to run errands instead of driving. Personally, I now have more motivation to invest in medical software that will allow a paperless practice. Each exceptionally vast domain of innovative expertise provides the opportunity for public engagement, youth involvement, and consultation with Indigenous populations to collaborate innovatively to better the health of our nation.

Perhaps the beginning lies (or floats) in programs such as *Students on Ice*. Without this program, I would not have been inspired to investigate and think about all that I have, and my perspectives on how profound the SDHs are, including climate change, would be entirely different. It is *Students on Ice* where I could achieve my goals of fostering meaningful discussions, and meeting and learning from International youth and world-renowned staff. It is also where I learned that, despite every ounce of adversity, the Arctic remains incredibly beautiful, founded on thousands of years of culture and traditions. I made a dogsled harness from scratch with a Colorado researcher who is a self-taught Inuktitut speaker; I studied Arctic flowers with Elders and the Curator of Botany at the Canadian Museum of Nature; I stitched a ball from caribou skin with Nunavut's top stitcher; I paddled a traditional sealskin kayak with a Canadian gold-medal Olympian; and I whale-watched with the Canadian Commissioner of the Environment and Sustainable Development. The best part is we were united by the dream of making a difference. My greatest fear is that one day these lands will no longer exist as they do today, preventing others from sharing similar experiences. I remain optimistic in believing that all healthcare professionals (and all people, for that matter) will seek opportunities to advocate for equality and justice for all and will view every $4 kilogram of grapes at the grocery store with new humility and gratitude. If one should get lost along the way, he or she simply needs to seek the northern lights to illuminate the path.

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Coupling Culture and Medicine in Chile

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ABSTRACT

This elective report provides an overview of a month-long Internal Medicine elective in Coronel, Chile, completed by a first-year medical student from Ottawa and a second-year medical student from Western in July 2018. As a couple, we had the opportunity to apply to the International Federation of Medical Students Association (IFMSA) together in order to complete our international exchange in the same city. While in Chile, we had the opportunity to shadow many subspecialties, learn how one becomes a physician in South America, and gain exposure to Chilean culture and traditions from our host family. Our experience was unique in that it allowed us to learn about medicine and Chilean patient populations within our assigned hospital, but also from the family members we visited who work as Chilean physicians.

RÉSUMÉ

Ce rapport de stage donne un survol d'un stage en médecine interne pendant un mois à Coronel, Chili, complété par un étudiant de médecine en première année d'Ottawa et par un étudiant en deuxième année de Western, en juillet 2018. Comme couple, on a eu la chance de faire demande ensemble à travers de la Fédération internationale des associations d'étudiants en médecine (IFMSA) afin de compléter notre échange international dans la même ville. Au Chili, on a eu l'occasion de suivre plusieurs sous-spécialités, d'apprendre comment devenir médecin à l'Amérique du Sud, et de gagner une expérience unique aux cultures et traditions chiliennes de notre famille hôte. Notre expérience a été unique, car elle nous a permis d'apprendre à propos de la médecine et la population de patients chiliens à notre hôpital assigné, ainsi qu'avec les membres de famille qu'on a visitée qui travaillent comme médecins au Chili.

This past summer, we travelled to Chile for a one-month elective in Internal Medicine (IM). Each of us had particular reasons for selecting Chile as an elective choice. For Kaitlin, she was interested in understanding more about Mitch's background and the country his family was from. For Mitch, he was interested in experiencing medicine in a country he had visited often since his childhood. We were placed in Coronel, a small mining town near Concepcion. There were lots of ups and downs, difficult situations, and new experiences over our four weeks, and now that we are back in Canada, we have had time to think about our experiences. These are some of our thoughts, tips, and reflections in hopes that they may provide some insight into our elective experiences and stimulate questions to further investigate for those contemplating participation in an international elective.

Doing an elective in a country where you do not speak the language always leads to some unease (1). While Chile is a Spanish speaking country, we were assured that our instruction would be in English. We arrived on our first day to our host family, who spoke only Spanish. We were out of our element from the beginning and had to improvise in order to communicate. Simple things, like how the shower worked, when dinner was or what areas of town were safe to explore became difficult conversations due to the language barrier. A good translator app certainly went a long way.

Our first day in the hospital proved to be even more difficult due to communication issues. We had been given some orientation materials via email from the student coordinators for the exchange, but nothing more. We had the name of the doctor but no directions or a place to meet. We arrived at the hospital to discover there were not room numbers, a directory, or clear areas for different departments. After locating our attending physician, he gave an impassioned speech to us (along with two other exchange students) and set off to the wards to show us how things were done. At least that is what we believe happened, as everything was in Spanish.

We completed our elective alongside a cohort of Chilean medical students from nearby Concepcion. Days on which

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Chilean medical students were present were straightforward and educational. They made sure we were understanding various patient presentations, showed us unique findings on patients' physicals and translated the doctors' instructions into English. One thing we overlooked was that it was Chilean winter and the students had their break in the middle of our time there. More than half of our time in the hospital was completed without these medical students to guide us. Many days, we would show up to the IM ward only for the doctor to ask why we "had not gone home yet?" or "oh, you are back?". When we think about the situation now, it makes a lot more sense. It would be like seeing exchange students in the hospital on Christmas break, when all the local medical students had gone home. While at first discouraging, the days where there was little work to be done on the IM wards ultimately provided us with the opportunity to shadow other areas of the hospital including the Emergency Department and Surgical Operating Room (OR).

Observing surgeries in Chile was quite similar to our previous experiences in Canadian ORs. The sterile procedure was identical, as was the role of the scrub nurses and medical students in the OR. Often, there was also an anesthesiology nurse to support the anesthesiologist which was unique. It was quite rare during our time in Chile for us to see a patient under general anesthetic, as most patients were instead placed under spinal anesthesia. Surgeries moved much faster in Chile than in Canada with few breaks in-between patients, often coming at the expense of patient privacy. For example, doors to ORs were open at all times, allowing healthcare professionals not involved in the patient's direct care to see the patient being draped and sterilized. In Canada, patient autonomy is placed at the forefront of care, and the breaks between each OR case allow time to prevent these breaches in patient confidentiality. Further, with no central heating in Chile, ORs were kept at the necessary temperature through electric heaters. If you were worried about fainting in a Canadian OR, you had better hope you were not stuck beside the heater in a Chilean OR, scrubbed in and hoping for the compression socks to keep you upright long enough for the surgery to end.

In the 1970s, the small town of Coronel where our hospital was located was a booming city with a rich mining industry. The mines have since closed, and Coronel is now one of the poorest cities in Chile (2). Our hospital faced extremely high rates of respiratory disease, and Coronel is referred to anecdotally by physicians in South America as the "tuberculosis capital" of Chile. According to our preceptor, every internist at our hospital had been treated for tuberculosis at least once throughout their career. As a whole, Chile does not have a tuberculosis epidemic, but the Coronel region does (3). When planning an elective, remember that research on the whole country will not necessarily identify localized health crises. We arrived without our own N95 masks only to realize that in Coronel, this piece of equipment would be key in protecting ourselves from respiratory illnesses like tuberculosis. If a patient in Coronel was given a mask to prevent the spread of their tuberculosis, the mask was often re-used for many days until it was no longer tight on the patient's face. Infection control measures were ignored in Coronel, not due to ignorance, but rather due to cost.

The hospital in Coronel also operated "Poly-Clinics" which functioned similar to a walk-in where patients could come in and see whichever doctor was on-call for clinic that day. Within these clinics, there were often many learners, plus a doctor seeing the patient. It definitely came as a shock to see patients so open to the high number of learners in the room. For the first little while, we would always ask the other medical students and/or doctors to introduce us to the patient and obtain consent. We quickly learned that Chilean patients were more than used to being examined by multiple different learners without introduction. We were often sent off to complete physicals without any means of translating our intentions to the patients, yet patients would lift their gown so we could check their legs for peripheral edema after listening to their heart sounds, even without prompting. It seemed strange and unfair for the patient to be examined so many times in a row, but no patient seemed to mind. They actually seemed very appreciative of the multiple opinions a medical team could provide in just one short visit.

Finally, we had the opportunity to visit Mitch's family in Chile. His dad was born in Chile, and many of his cousins still live there. His grandfather worked for the Chilean government in the Ministry of Health. When General Pinochet overthrew the government in 1973 and began to persecute government workers and their families, many feared for their lives and fled the country (4). This trip served as an opportunity for both of us to learn more about this history and to spend time with these family members. Many of them still work in healthcare and we were able to discuss the differences between our healthcare systems. Although many of our experiences in Coronel led us to believe that Chilean healthcare was quite different from

Canadian healthcare, our conversations with Mitch's family made us realize things were really quite comparable. In larger centers, like Santiago, where Mitch's family is from, healthcare is extraordinarily similar. Hospitals function identically, with many departments, consulting services, and state of the art equipment. What this highlighted more than anything was the disparity in healthcare quality depending on location. This made us think of the similar issues Canada faces. In our nation's Indigenous communities, we lack in many aspects of healthcare including access to specialists or gold standard diagnostic testing, much like Coronel (5). Our experiences reminded us that the issues we face here in Canada are universal.

Overall, our elective in Chile was an eye-opening experience, but not in the ways one might expect. In the Chilean healthcare system, paternalistic practice remains common in stark contrast to the beneficence principles we strive to uphold here in Canada. There are clear disparities in the quality of healthcare based on location. However, Chile also practices modern, evidence-based medicine with state-of-the-art technology. It is a medical system in flux, and it highlights many of the issues we see in our own medical system as well. Moreover, it left us both interested to return to see how the healthcare system continues to develop and to see more of the beautiful landscape the country is famous for.

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The University of Ottawa Journal of Medicine (UOJM) is a peer-reviewed journal published by graduate and medical students of the Faculty of Medicine. The UOJM is the only bilingual institutional medical journal in Canada, welcoming high-quality submissions in English or French. Accepted articles include original research, reviews and clinical practice, news and commentaries, case and elective reports, and interviews. The UOJM is currently accepting submissions for our upcoming **Fall 2019 Issue 9.2: Inner-City and Rural Medicine.**

Medical practice is impacted by a multitude of physiological, personal, and social factors—not limited to where a patient lives. Where we live influences how we grow, where we go to school, what we eat, where we work, what we value, and ultimately, how healthy we are. Understanding the nuances that contribute to rural and inner-city healthcare needs, including access to medical resources, social assistance programs, patient education initiatives, and mental health support, will help to ensure that healthcare is customized to the needs of patients living in urban and rural environments. **UOJM issue 9.2** will review the overlapping and distinct features that contribute to inner-city and rural medical practice with the hope of inspiring young researchers and clinicians to always be mindful of how societal and environmental differences are important factors in personalized and patient-specific healthcare.

The submission deadline for our Fall issue is **September 1, 2019 at 11:59PM**. High-quality writing will be recognized with an honorarium award. Submissions can be made online and questions can be directed to *contact@uojm.ca.*

Call for Artwork

With the upcoming release of UOJM 9.2, we are looking for creative artwork to be featured on the cover of our issue! Submissions must fit with the theme of **Inner-City and Rural Medicine** and may be drawn by hand or digitally. PDF files are preferred but not required. Artwork submissions can be emailed to contact@uojm.ca by September 1, 2019 at 11:59PM!

Linda Yi Ning Fei & Phillip Staibano

Co-Editors-In-Chief

University of Ottawa Journal of Medicine

Appel de Soumissions

Le Journal médical de l'Université d'Ottawa (JMUO) est une revue évaluée par les pairs publiée par les étudiants de troisième cycle et les étudiants de médecine de la Faculté de médecine. Le JMUO est la seule revue médicale institutionnelle bilingue au Canada, accueillant des soumissions de haute qualité en anglais ou en français. Les articles acceptés comprennent la recherche originale, les revues et la pratique clinique, les nouvelles et les commentaires, les rapports de cas et de stage, et les entrevues. Le JMUO accepte actuellement des soumissions pour notre prochain **numéro 9.2 d'automne 2019 : La médicine urbaine et rurale.**

La pratique médicale est impactée par plusieurs facteurs physiologiques, personnels et sociaux – sans se limité sur où vit un patient. Où on vit influence comment on grandit, où on va à l'école, où on travaille, ce qu'on tient en valeur, et, ultimement, comment on est en santé. Comprendre les nuances qui contribuent aux besoins en santé rurale et urbaine, y incluent l'accès aux ressources médicales, les programmes d'assistances sociales, les initiatives d'éducation pour les patients et le support pour la santé mentale ; aideront à assurer que les soins de santé sont propres aux besoins des patients vivant dans des environnements urbains et ruraux. **Le numéro 9.2 du JMUO** révisera les caractéristiques chevauchantes et distinctes qui contribuent à la pratique médicale urbaine et rurale avec l'espoir d'inspirer les jeunes chercheurs et cliniciens qui seront toujours conscients des différences sociétales et environnementales sont des facteurs importants pour les soins personnalisés et centrés sur les patients.

La date limite de soumission pour notre numéro d'automne est **le 1er septembre 2019 à 23 h 59**. L'écriture de haute qualité sera récompensée avec un prix d'honneur. Les soumissions peuvent être faites en ligne et les questions peuvent être dirigées à *contact@uojm.ca*.

Appel d'œuvres

Avec la publication imminente du JMUO 9.2, nous cherchons des œuvres créatives pour être mises en exergue sur la couverture de notre numéro ! Les soumissions doivent s'aligner sur le thème **La Médicine Urbaine et Rurale** et pourront être dessinées à la main ou numériquement. Les fichiers PDF sont préférés, mais ne sont pas obligés. Les soumissions d'œuvre peuvent être envoyées par courriel à contact@uojm.ca par le 1er septembre 2019 à 23 h 59!

Linda Yi Ning Fei & Phillip Staibano

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