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All articles are externally peer-reviewed with the exception of poetry, short stories and book reviews. All manuscripts are internally reviewed. Informed consent practices and any conflicts of interest are specified in the articles if applicable.

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Preface

Dear UTMJ Reader,

We are thrilled to present Volume 97, Issue 3 of the University of Toronto Medical Journal, which focuses on the important and evolving topic of the Human Microbiome. The Spring 2015 Issue of the University of Toronto Medical Journal first considered the Human Microbiome, exploring this burgeoning field and its potential applications in clinical medicine. Since this issue, our understanding of the microbiome, and the field of microbiology more broadly, has exploded. The microbiome, understood as the genetic material of the microbes living on and within our bodies, contributes to essential processes such as food digestion, immune regulation, and the production of vitamins. Further, many pathological processes, such as autoimmune diseases, are associated with dysbiotic states. While past research has largely focused on understanding the microbiome and performing clinical procedures to restore healthy microbiota, newer studies have begun to uncover and explore the novel roles for the microbiota in diagnosing and treating medical conditions, such as cancer, depression, and type 2 diabetes mellitus. With this dramatic increase in microbiome research, researchers and clinicians must navigate an onslaught of new information and determine how to meaningfully translate these new discoveries into clinical practice.

In the Spring Issue of the University of Toronto Medical Journal, we will address the important topic of the Microbiome. We believe that this issue will bring forth many areas that are worth exploring, including but not limited to the known understanding of how the microbiome affects immunity and contributes to disease, novel associations between dysbiotic states and disease, how antibiotics affect the microbiome, the ethical issues around sample collection and privacy in mapping the human microbiome, as well as mediating how the public will understand discoveries about the microbiome. We hope that this issue will inform our international readership about the current understanding of the microbiome and identify priorities for future research.

This is the third and final issue of the University of Toronto Medical Journal’s 97th volume. We would like to sincerely thank our dedicated editorial team for all the hard work that went into preparing this issue, and their continued efforts throughout the year. We are grateful for the patrons and faculty that continue to support the University of Toronto Medical Journal and the authors that have allowed us to showcase their important work. We hope that you find this issue informative and thought-provoking.

Sincerely,

Tatiana Yeuchyk and Kathleen Simms
Editors-in-Chief
2019-2020 UTMJ Editorial Team

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Award Winning Manuscripts

The University of Toronto Medical Journal (UTMJ) was established in 1923 and is Canada’s oldest student-run medical journal. We strive to uphold the UTMJ’s legacy of excellence by publishing interesting and timely research articles for our esteemed readers. Medical trainees continue to be important contributors to many of the research articles published by the UTMJ. We recognize the value in student research and are proud to serve as an outlet for this work. The UTMJ has established three awards to acknowledge outstanding submissions from medical trainees in each of our issues. We would like to congratulate the following award winners for the current issue on Microbiome:

First Prize
First episode psychosis: the commensal gut microbiota perspective
Sylvie Bowden, Kenya A. Costa-Dookhan, Dallas Leavitt, Sri Mahavir Agarwal, Margaret Hahn

Second Prize
The journey to Ancient Ithaca: addressing the diagnostic odyssey of rare disease through systems-level interventions
Connor Brenna

These awards would not be possible without the continued support of the University of Toronto Medical Society and our readers. Please consider supporting the UTMJ so that we can further our efforts to promote student research, publish impactful articles and grow our readership. Donations can be made online through our website, www.utmj.org, or sent to the following address:

University of Toronto Medical Journal, 1 King's College Circle, Room 2260, Toronto, ON, Canada, M5S 1A8.
Recent months have been marked by unprecedented change as the world has responded to the novel COVID-19 pandemic. The medical community and the general public have joined in monitoring the development of COVID-19, with fears and concerns propagating alongside media coverage of the increasing spread, morbidity, and mortality of the virus. Healthcare professionals have been on the front lines from the start, showing incredible dedication amid challenging circumstances in caring for patients affected by COVID-19 together with their other duties. However, treating these patients with limited available knowledge about the virus’ properties including transmission, mechanism of action, vulnerabilities, and best management, works out in practice like placing a bandage over a gushing wound. In the short term, it is the best that is available, but an effective long-term solution is indispensable. This brings us to another type of front line: that of basic science and clinical research. Scientists and investigators have been conducting experiments and reporting on clinical outcomes incessantly, sharing the most up-to-date information at seemingly breakneck speed. High-impact academic journals have accommodated the need for scientific progress by expediting their review processes and publishing data on a rolling basis. In a message on their website, PLOS writes that they are “fast-tracking all relevant research related to the coronavirus and resulting pandemic,” while they implore their reviewers to “carefully consider the need for additional experiments or analyses in revision requests, especially if the conclusions are adequately supported by the data.” On January 31, 2020, 94 journals and institutions signed an agreement to give open access to cutting-edge COVID-19 publications, including Springer Nature, the New England Journal of Medicine, and The Lancet. This is a critical step in facilitating an international, coordinated response during the current crisis. This is accompanied by a rise and increased acceptance of preprint publishing, making data accessible before it even completes the peer-review process. The past several months have witnessed discoveries in the realms of viral structure, infectious processes, potential mechanisms of action of new drugs and treatments, as well as vaccine development. Clinicians all over the world have shared clinical characteristics and outcomes of COVID-19 patients to help colleagues thousands of miles away better treat their patients, as well as ingenious strategies to mitigate shortages of protective equipment. The progress we have seen already is inspiring to say the least, and is the result of cross-border collaborative efforts.

The experience of the global community during the COVID-19 pandemic has irrefutably demonstrated the significance of scientific literature in the dissemination of knowledge and in informing care. There is an invaluable relationship of trust between research consumers and providers in a worldwide setting that can too often be wrought with misinformation. As always, of course, scientific literature must be read through a critical lens; history has shown that errors do make their way through even a complete review process. To be sure, this risk is perpetuated while the latter is expedited, but this is a price that must be paid to avoid months of delay in accessing and applying vital new data. The reputations of journals and the overall reliability of their review processes help experts to assess and implement newly-published information to practice. Research is undoubtedly instrumental to achieving change from every direction during this pandemic, targeting prevention, protection, and treatment.

The role of the researcher is clear: to conduct studies in their research domain, analyze data, make conclusions, and communicate them effectively. However, the journey does not end there. The value of research findings depends entirely on how they are received, interpreted, and applied in the real world. The next steps are largely in the hands of the consumers of this medical literature. Individuals who are trained in science and medicine have a unique part to play in informing the information revolution that is unfolding with COVID-19. This role carries in itself significant responsibility, beginning with committing to reading and staying up-to-date in a field that is developing every day. Further, the information must be integrated and brought together to make broader conclusions that are helpful to society, be it in clinical practice, public health, or elsewhere. Moreover, these individuals have a valuable role to play in interpreting and sharing new information with their communities, acting as translators for complex scientific language and processes. One who is able to...
Acknowledging another healthcare hero: the importance of scientific research during the COVID-19 pandemic

As we end our tenure as co-Editors-in-Chief of the University of Toronto Medical Journal, the important role scientific journals play in mediating life-saving or life-sustaining information from the bench to the bedside is once more impressed upon us. When considering the significance of such journals throughout the evolution of the COVID-19 pandemic, we appreciate the privilege we have had in sharing novel research with the broader scientific community and our admiration for the seemingly tireless dedication of researchers, reviewers, and editors throughout these unprecedented times. In a milieu of uncertainty, communicating accurate and relevant information is essential, and we would be amiss to not recognize these important actors as healthcare heroes.

References

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Background

On January 30, 2020, the World Health Organization declared the 2019 novel coronavirus (COVID-19) outbreak a Public Health Emergency of International Concern. By April 24, 2020, nearly 3 million cases of COVID-19 with nearly 200 thousand deaths have been confirmed globally. Shortages are being experienced around the world and due to these inefficiencies, physicians are being forced to decide who is more deserving of resources. In response, the world is making the effort to “flatten the curve” so that health care resources and facilities are able to accommodate. As such, the world has employed social distancing measures and encouraged people to stay home. COVID-19 has undoubtedly impacted the world in numerous ways and continues to do so. One such way is its impact on medical education. Medical schools across Canada have cancelled all in-person teaching, including classes and clinical placements. As clerkship rotations are purely clinical in nature, this kind of learning cannot be replicated online, effectively leaving clerkship medical students with their education on hold. Despite no organized placement of medical students into roles, many have organized roles and initiatives for themselves. Medical students across Canada have volunteered in a variety of means, as well as joined together to develop and lead extraordinary initiatives. However, with an uncertainty in establishing an “end” to the pandemic and in determining whether Canada will face a physician shortage, is it worth looking forward and further planning how best to utilize Canadian senior medical students? Medical education prepares students to not only care for the sick, but to function as part of a team and support a larger goal. With the unique skills to be able to assist and the national possibility of needing increased physician support, it may be worth considering how senior medical students can be transitioned into helpful roles in the hospital.

Abstract

On January 30, 2020, the World Health Organization declared the 2019 novel coronavirus (COVID-19) outbreak a Public Health Emergency of International Concern. By April 24, 2020, nearly 3 million cases of COVID-19 with nearly 200 thousand deaths have been confirmed globally. Shortages are being experienced around the world and due to these inefficiencies, physicians are being forced to decide who is more deserving of resources. In response, the world is making the effort to “flatten the curve”, a term used repeatedly to describe slowing the rate of increase of new cases so that health care resources and facilities are able to accommodate. As such, the world has employed social distancing measures and encouraged people to stay home. COVID-19 has undoubtedly impacted the world in numerous ways and continues to do so. Non-essential travel has been cancelled, large gatherings such as conferences and festivals have been cancelled, and employees are being encouraged to work from home.

Furthermore, COVID-19 is impacting education across Canada. Since late February, we have heard on the news that elementary schools, high schools, and universities have closed and content changed to online delivery to complete the semester’s material and examinations. Initially, medical schools sought to limit transmission and therefore protect both medical students and the greater public by prohibiting medical students from being involved in the care of patients with suspected or confirmed COVID-19. However, by mid-March, medical schools across Canada came to similar decisions and cancelled all in-person teaching, including classes and clinical placements. First- and second-year pre-clerkship classes have been changed to a purely online format and third- and fourth-year clerkship rotations have been cancelled. As clerkship rotations are purely clinical in a hospital or clinic environment, this kind of learning cannot be replicated in an online format, effectively leaving clerkship medical students with their education on hold.

This has caused a myriad of emotions. Some have experienced initial disappointment over a change in routine or removal from clinical duties and opportunities for learning. Others have experienced anxiety over cancellation of planned elective experiences, uncertainties in learning opportunities prior to graduation – or for fourth-year students – postponement of medical licensing board examinations. But medical students have rallied and risen to the challenge, finding ways to support each other,

Corresponding Author:
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sylvie.bowden@mail.utoronto.ca
 frontline workers, their families, and local communities. However, with an uncertainty in establishing an “end” to the pandemic and in determining whether Canada will face a physician shortage, is it worth looking forward and further planning how best to utilize Canadian senior medical students?

COVID-19 has called into focus the real reason for going into medicine

As the news brings us daily updates on the growing pandemic, there is increasing recognition of the deadlines and severity of this virus. With the numbers of infected and dying across the world reaching new record highs daily, shortages on medical equipment and staff, and public lockdowns to decrease transmission, many are living with a certain degree of fear. There is an unprecedented appreciation for health care workers as we recognize the risks they are taking to care for the sick. As a third-year medical student, just over one year shy of entering the profession myself, this presents the question of commitment and courage: How prepared am I to stand on the frontlines? In times of uncertainty, fear, and resource shortages, am I still as eager to show up and care for the sick as on a “routine” day? In reflecting on this, I acknowledge I had an initial moment of fear and hesitancy, but overwhelmingly I feel that I want to be on the frontlines with the staff and residents I have worked with over the past several years.

It is this desire to help – strengthened at a time when help is needed most – that drove many of us into the field of medicine in the first place. We wanted to prevent adverse health outcomes, to heal others, and support the physical, mental, and emotional health of the people in our local and broader global communities.

Despite pre-clerkship classes being changed to a purely online format and clerkship rotations being cancelled, medical students across Canada have risen to the challenge. Initial disappointment over changes in routine, removal from clinical duties and opportunities for learning, cancellation of medical licensing board exams have been set aside. Medical students across Canada have volunteered in a variety of ways, as well as joined together to develop and lead extraordinary initiatives. Examples of such roles for University of Toronto medical students, gathered from both public postings as well as platforms dedicated to medical students, are listed in Tables 1 and 2.

Table 1. Volunteer positions for University of Toronto medical students

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screeners or clinical assessors</td>
<td>Volunteer at hospital entrances to address concerns of patients and families standing in line and identify patients in line who should be fast-tracked through screening, given their respiratory and/or other symptoms.</td>
</tr>
<tr>
<td>Contact tracing and public health counselling</td>
<td>Volunteer with Toronto Public Health and the Ministry of Health to serve as contact tracers and public health counsellors.</td>
</tr>
<tr>
<td>Kids Help Phone hotline</td>
<td>Volunteer with a crisis text line to support concerned children and adolescents.</td>
</tr>
<tr>
<td>Friendly Neighbour hotline</td>
<td>Volunteer with University Health Network’s OpenLab to help deliver essential items – including food, pet supplies, diabetes supplies, and others – to isolated seniors living in the Toronto area.</td>
</tr>
</tbody>
</table>

Table 2. Initiatives led by University of Toronto medical students

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Care Providers (HCPs) Support Initiative</td>
<td>Support HCPs with life tasks outside the wards, including childcare or babysitting, pet care, grocery and pharmacy runs, and general errands.</td>
</tr>
<tr>
<td>Student-Senior Isolation Prevention Partnership during COVID (SSIPP: COVID Edition)</td>
<td>Partner with the Home-Based Care Program run by family physicians at Toronto Western Hospital to match medical students with elderly patients in the community. Assignments are determined by a Toronto-based Family Health Team and seek to provide regular phone check-ins with elderly patients for patient education on COVID-19 and social comfort.</td>
</tr>
<tr>
<td>“Skype a Scientist”</td>
<td>Teach a classroom of students, of any grade, about a field of study online.</td>
</tr>
<tr>
<td>COVID-19 Startup</td>
<td>Develop an app or tool to support contact tracing through dynamic risk assessment and targeted outreach.</td>
</tr>
<tr>
<td>Mask Building Initiative</td>
<td>Produce mock masks for training health care providers in proper donning and doffing, so as not to waste real N95 masks, given the context of national resource shortages.</td>
</tr>
<tr>
<td>COVID-19 Web Resource Centre</td>
<td>Develop a webpage that gathers and summarizes all credible information for the public. Create a social media profile that the public can follow, linking them to new updates on the webpage.</td>
</tr>
<tr>
<td>COVID-19 Communications App</td>
<td>Create an app to address the communication between public health agencies (municipal, provincial, and federal) and the general public.</td>
</tr>
<tr>
<td>Sourcing personal protective equipment (PPE)</td>
<td>Source PPE to support frontline workers by searching for unused PPE such as masks, gloves, and gowns, asking for donations, and picking up and dropping off PPE at designated locations.</td>
</tr>
<tr>
<td>Ontario-wide coordinated 3D printing of Personal Protective Equipment (PPE) for HCPs</td>
<td>Collaborate with teams from McMaster and Queen's Universities on an initiative to 3D print PPE (face shields and masks) for HCPs.</td>
</tr>
<tr>
<td>National Blood Drive</td>
<td>Coordinate a national blood drive competition in partnership with the Canadian Federation of Medical Students to support the current blood donation shortage.</td>
</tr>
<tr>
<td>Frontlines’ Positive Encouragement</td>
<td>Organize a letter-writing campaign to send notes of personal support to Toronto physicians.</td>
</tr>
<tr>
<td>COVID Women’s Initiative</td>
<td>Partner with women’s shelters in the Greater Toronto Area to raise awareness of how COVID-19 may impact women’s health and to further assist them.</td>
</tr>
<tr>
<td>Ethics Resource for COVID-19</td>
<td>Create a guide providing information regarding ethical considerations in the COVID-19 pandemic.</td>
</tr>
<tr>
<td>UofT Med Music</td>
<td>Create student-produced and personalized music content for patients who cannot be visited by family, volunteers, or other visitors. (Currently partnered with Mount Sinai Hospital, Toronto Rehab Institute, Baycrest, and Holland Bloorview).</td>
</tr>
</tbody>
</table>

These initiatives demonstrate that we as medical students are wholly invested in the health and well-being of our community. Medical students have led by example, choosing to self-isolate and educate those around them on the importance of doing so. They have initiated prevention initiatives and initiatives to maintain the health of our peers, families, and local communities. In addition to caring for our immediate social circles, initiatives are much broader to reach even the most vulnerable in our community.
Filling the gap: student initiatives

The cessation of clerkship and other clinical activities raises the following question: How significant is the practical value of medical education? The government and Faculty of Medicine should have been able to plug every class into some support role during this crisis. While we may not be able to learn from “normal” clinical encounters, we are armed with knowledge and practical experience from our pre-clerkship courses, undergraduate degrees, and numerous extra-curricular involvements that we can apply to helping the medical community during this time.

It can be reasoned that medical students are “unnecessary” in the hospital milieu, and thus their removal aligns with social distancing measures and protects students from the risk of acquiring COVID-19. However, as the situation continues to evolve and health care systems become increasingly strained across the globe, it is not only physical resources that are lacking, but also healthcare professionals.

To mitigate impending or actual shortages in health care staff and to alleviate the strain and burden on those that have been working since the beginning of the epidemic, we have seen numerous professional schools graduate their students early to facilitate their transition into the workforce.  

In light of severe interruptions to medical education programs due to the COVID-19 pandemic, medical schools in the UK have been granted the power to graduate their students early to allow them to work for the NHS in an effort to help staffing levels. On March 25, the UK’s regulatory and training bodies released a joint statement offering final year medical students early provisional registration and foundation year 1 (FY1) doctors early registration. As fully registered doctors, FY1 trainees are able to practice with less supervision, have a wider range of prescribing responsibilities, and are thus able to work more independently and reduce strain on staff physicians whose focus is better preserved for the acutely ill. However, as a physician’s duty is first to do no harm, there exists a balance. Medical students and junior doctors still require comprehensive training and clinical and educational supervision, particularly given the difficult circumstances under which they are joining the health care workforce. Thus, it is imperative that safeguards are put in place to ensure sufficient training to support safe medical practice and care of patients. To this end, the UK’s General Medical Council has listed such training and supervision requirements in delineating these new roles. Other professional schools have done the same. The College of Respiratory Therapists of Ontario has asked programs to fast-track respiratory therapist students’ graduation so they can start work early. Fanshawe College will enable their students to finish courses virtually while beginning to work on the front line.

While it can be hoped that social distancing measures will be sufficient to flatten the curve and prevent overwhelming the Canadian health care system, there remains the possibility that physician shortages could soon add to the existing medical equipment shortages. Over 3,300 health care workers have been infected in China as of March, with over 22 deaths. In Italy, 20% of health care workers have been infected and the number of deaths continues to rise. Physician acquisition of COVID-19 is significant in numerous regards. While the majority will be asymptomatic or only experience mild symptoms, they will still be required to quarantine for two weeks due to the risk of viral shedding leading to transmission, thereby pulling them out of practice. More significantly, those who experience more severe symptoms – including pneumonia, acute respiratory distress syndrome (ARDS) and multi-organ dysfunction – will not only be removed from the workforce, but will require intensive treatment and further burden a health care system already experiencing strain. Furthermore, studies have observed that elderly patients, aged 60 years and older, make up a larger proportion of severe to critical cases and have higher fatality rates. In 2019, out of 86,092 actively practicing Canadian physicians, the Canadian Medical Association listed 19,957 (23.2%) as aged 55-64 years old and 13,956 (16.2%) as aged 65 years old and greater. As almost 40% of Canadian physicians are over the age of 55, they are at high risk and may unfortunately succumb to the illness. With uncertainty in establishing an “end” to the pandemic and in determining whether Canada will face a physician shortage, is it worth looking forward and planning how best to utilize senior medical students?

At present, there is a national focus on prioritizing the health and safety of our patients, providers, and greater community, and limiting the spread of COVID-19. This has rightly taken precedence over continuing medical student learning. However, medical students are in a place where they are able to be more than learners. Equipped with past experiences and several years of medical teaching, they are able to provide some assistance in the health care milieu. Fourth-year medical students are most notably in this position, as they have at present finished their core clinical and elective rotations, and the majority of their selective clinical placements. The decision to end fourth-year clinical placements prematurely will not negatively impact the completion of their MD program requirements or graduation eligibility. Furthermore, over 2,000 Canadian medical students matched to a residency program on March 3, 2020. Aside from having to write the Medical Council of Canada licensing exam, fourth-year medical students are in a unique position of being as ready to practice now as they will be on the arbitrary start date traditionally set as July 1.

Senior medical students possess unique skills after having spent countless hours in the clinical environment. They are familiar with the roles of and able to liaise with the interprofessional health care team, able to respect confidentiality and privacy concerns, and are trained to have difficult conversations with patients and families. Most importantly, they are familiar with the daily tasks that physicians and residents need help with and as such are in a position to be able to lighten their loads so that they can focus their attention on the patients who are sickest. In addition to the increased volume of patients, with increasing patient acuity, more mental effort and time is required to care for patients safely. There is increased cognitive effort in diagnosing and managing using the latest evidence-based medical recommendations. Providers must also dedicate a sufficient amount of time to donning (putting on) and doffing (taking off) PPE using the correct technique to prevent lapses that could prompt transmission. These factors have been noted in numerous studies to be not only challenging but demanding of time. Thus, medical students in a unique position to assist in non-COVID patient duties, opening time and cognitive space for physicians to be better able to treat the acutely ill.
Conclusion

While there was no organized placement of medical students into roles, many have organized roles and initiatives for themselves. This makes me proud to be a medical student during this time. My faith is renewed by peers who I am proud to work alongside presently, and I am heartened that our community will continue to be well cared for in the years to come.

Medical education prepares students to not only care for the sick, but to function as part of a team and support a larger goal. With the unique skills to be able to assist and the national possibility of needing increased physician support, it is worth considering how senior medical students can be transitioned into helpful roles in the hospital. Future directions include a virtual curriculum on COVID-19 transmission, diagnosis, and management, as well as general disaster preparedness. As future pandemics are likely, becoming involved in the response now is valuable experience that can be drawn on in the future as students move on to staff positions.

Acknowledgments

No sources of funding were used to support this research.

References


Dr. Barry J. Marshall was awarded the 2005 Nobel Prize in Physiology/Medicine for the discovery of Helicobacter pylori as well as its role in peptic ulcers. His work overturned the canonical wisdom that bacteria cannot survive in the stomach as well as establishing a definitive, microbiological treatment for ulcers – estimated to have saved over a million lives.

Currently Dr. Marshall is a Clinical Professor at the University of Western Australia, where he leads the Marshall Centre for Infectious Diseases Research and Training (founded in his honour). Dr. Marshall further serves as a Consultant Gastroenterologist at the Sir Charles Gairdner Hospital. His present research interests expand on his ground-breaking work and is seeking novel strategies to manage immunity via the microbiome as well as devise early diagnostic methods for bowel syndromes.

**UTMJ:** Dr. Marshall, you have previously likened the gut microbiome to an extra organ, could you clarify how you see the role of the microbiota, as we understand it today?

**BJM:** The microbiome is largely controlled by your diet, plus a genetic factor like your blood group and a component you inherit or catch from your mother. After you develop it, it's going to influence how you absorb or metabolize food; it may produce certain hormones and chemicals which maybe there in smaller or larger amounts. So you can see that the gut microbiome could potentially be like another organ, almost like an endocrine organ in some respects. Understanding it and ultimately figuring out how to use it in beneficial ways for patients is going to be a big advance.

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**Interview with Dr. Barry J. Marshall, Nobel Laureate**

Interviewers: Imindu Liyanage, Kathleen Simms

Dr. Barry J. Marshall
Image Source: University of Western Australia
(https://www.uwa.edu.au/profile/barry-marshall)
That was about July 1981, and for the next 6 months, I was immediately interested, because it was a great project to start off with. So, it had gastritis. We thought you get it when you get older, anybody that believed gastritis was a disease. That inflammation, which was called gastritis, was a histological phenomenon we knew [then], we were looking at whether these bacteria could only survive but thrive in the stomach and beyond?

It’s hard to say how I developed the idea. I was always interested in microbiology, it’s just something that came naturally to me. But I guess the idea started when I met Dr. [Robin] Warren, who’s a pathologist. On tissue sections taken from biopsies of the stomach, he could see these curved bacteria. He showed them to me and said, “I’ve been seeing this for a couple of years, nobody else is interested, everybody says it’s contamination; but how could it possibly be if they’re all identical and I’m seeing them in a number of patients.”

At that point I was immediately interested, because I knew that the medical books said that bacteria don’t exist in the stomach – it’s too acidic. So, I said, “wow, this could be a good paper.” I’d never written a paper before, and wouldn’t it be good if my first paper would be helping Dr. Warren with the discovery of this new bacteria. Just any kind of publication would have been fun for me, and so we went off on this quest, if you like. That was about July 1981, and for the next 6 months, we played around with them in different ways. We were trying to figure out how could these bacteria live in the stomach, and could they be cultured, and where did they come from, and what were they?

We didn’t start off focusing on ulcers. With the pathology we knew [then], we were looking at whether these bacteria made some inflammation in the stomach and then one thing could lead to another, and inflammation could lead to some disease. That inflammation, which was called gastritis, was a histological phenomenon you could see in biopsies, but there was hardly anybody that believed gastritis was a disease, because we knew that in most countries, a majority of people had gastritis. We thought you get it when you get older, so practically nobody was doing any work on it. So, it was a great project to start off with.

So how did you eventually identify helicobacter?

At that time, there was some excitement about other enteric bacteria, particularly Campylobacter. It had been one of those bacteria that we could culture for many years, and we were starting to see epidemics of it from time to time from people drinking contaminated milk. [...] So, we had a few clues about how to grow these bacteria, but we had to spend a lot of time studying ulcers and stomach bacteria. Really we were like babes in a wood, we didn’t realize how difficult it was going to be. Fortunately, if you don’t understand something is a difficult task, you may tackle it in a new way.

One thing we struggled with was where and how to sample these bacteria. It was actually Dr. Warren who said to me, “when you take these biopsies Barry, don’t take them near ulcers because the anatomy is so screwed up [...]. Take your biopsies away from the ulcer, because we’re just trying to find where these bacteria live and what they’re doing there.” Lo and behold, that was the key that unlocked the linkage between helicobacter in the stomach and the ulcers.

Along the way, we studied lots of people, and looked closely at their biopsies and the wall of their stomach with normal histological sections. We could see that really there was no other bacteria in the stomach except ones you swallowed from time to time. These would be just passing through, and be sitting on the top of the stomach, and so that gave us a pretty good concept that led onto how we think about the microbiome now [...].

It’s not everyday that one overturns a fundamental paradigm. How did you contend with the inevitable controversy and pushback?

Having seen Helicobacter under the microscope, and having cultured it, there is just no doubt about it. It’s proven as far as you’re concerned. It’s not one of those things that you have any doubt about yourself. The controversy was if so many people have the bacteria, and all these people turned out perfectly fine and don’t have symptoms, how could it be a pathogen. So many times in the past people have found bacteria on the skin, bacteria on the mouth, and obviously in the colon. So to then come along and say, oh by the way, thousands of researchers have been working for fifty or one hundred years on the cause of ulcers, and have not noticed these bacteria, is understandably controversial. I have to say that were I to switch roles, and someone from Australia published a letter in the Lancet about bacteria causing ulcers – I would have probably [had my doubts].

It did take quite a few resources to check out a new discovery. Really the people doing ulcer research and stomach research were interested in acid as the cause of ulcers. They weren’t focused on the microbiome or microbiology, and so it wasn’t really possible for someone who was not in that area to check it out. The best I could say was I’m neutral, and I’m going to wait to see what happens.
A lot of gastroenterologists were willing to stick their neck out and give it a go. A good friend of mine actually, a top researcher from the United States, Dr. David Graham (he was Professor and Chief of Medicine at Baylor College of Medicine in Texas) said, “the great thing about the bacteria theory of ulcers is that it’s going to be so easy to disprove”. You can take that in the good scientific way, which is that if it’s a good hypothesis, you can test it.

So if I said to you that bacteria caused some disease, well then that’s easy to test: give me some antibiotics, give them to somebody with the disease and they should get better. We were in the throws of doing that kind of research, and within a couple of years, everybody was trying that out […].

BJM: Speaking of proving your hypothesis, perhaps one of your most famous experiments was ingesting H. pylori on purpose to prove its virulence. Can you tell us how that experiment came about?

UTMJ: Well the good scientific way of studying a new bacterium is to develop an animal model, put the bacterium in the animal model and look at what diseases come about. Hopefully you fulfill Koch’s Postulates, which means that putting a pure-culture bacterium on an animal model is going to cause to the disease to arise. But if the bacterium is well adapted to humans, like Helicobacter pylori, which has been specific to humans for maybe a million years, going as far back as we can tell, it didn’t necessarily have the correct proteins on its surface to attach to the stomach of different animals. I mentioned to you that your blood group determines a little bit about what kind of microbiome you’re going to have. So, it can be very challenging to grow a bacterium specific to humans in another organism.

I was getting stuck trying to prove [Helicobacter] is a human pathogen. After a couple of years, there was an argument that […] the ulcers come first and then after a while they effect the ecology in the stomach and the microbiome changes in these ulcers. It was very difficult to get past that. At that stage, we had tried many animals, including pigs, and they all turned out to be immune. The crucial question is does it effect humans, not does it effect animals. So, I needed to get this experiment done.

It was July 1984, we got some cultures from a patient of mine and I scraped a couple of petri dishes with bacteria, and around 2 o’clock in the morning, I drank it, and thought let’s see what happens. Of course, I was doing a busy clinical job, so it wasn’t a very good experiment. I was also trying to be objective. After a few days, I developed dyspepsia, then after a few more days, nausea, vomiting, bad breath, and my stomach was gurgling in different ways. Finally, I had the endoscopy and showed the biopsies to my colleagues and sent a few down to Dr. Warren in his pathology department and they all said: you’ve been infected with bacteria and you have gastritis – which is the main thing which we think leads on to everything else.

So that was it, we fulfilled Koch’s postulates for gastritis. I didn’t actually develop an ulcer and after two weeks, we got rid of the bacteria. The reason people with ulcers can’t remember when the caught the bacteria is that they probably caught it years ago. At that point we pretty much worked out the whole sequence of events, which explained a lot. But again, people didn’t have to believe it. It was only one case, I was also slightly embarrassed to admit that I was experimenting on myself, which was not scientific. You can imagine that if every medical discovery was based on self-experiment on one person, we’d be believing all kinds of crazy things. So one thing led to another, but it did mean that I changed my career and that this was going to be the most important thing I could do at that stage. After a couple more years, we got some funding and started doing some real research.

By this point, nobody still believed me. But I started to get a couple of early publications and some interest from the Lancet in the UK, and then from some colleagues in the United States, like George Buck in Houston, and a lot of good Campylobacter bacteriologists in Canada. I went to a meeting on Campylobacter in Ottawa, and really everyone was very excited by then.

I could tell you that after our first publication, Dr. Warren and I took our wives out to a nice restaurant, and Dr. Warren’s wife said, “you know, if you’re right about this, you could win the Nobel Prize, it’s pretty important”. Then Robin [Dr. Warren] said, “Barry when do you think we’ll win it”, and I said, “next year”. Of course, it was 23 years before we got to that stage, so it was quite the journey.

UTMJ: Where do you see your research and the field of the microbiota progressing in the coming years?

BJM: Talking about the microbiota, I think we were correct that the gastric content (the stomach) doesn’t really have very much of a microbiota. One of the things that acid does is sterilize your food. You can imagine that for stone age man, anything with protein would have been edible – things like dead animals and out of season fruit. Also, humans were pretty unhygienic in those days, so it was useful to sterilize your food in the stomach. It can then come in intimate contact with the intestine, and be absorbed, then finally […] it goes into the colon where the grassy bits and cellulose and various other things like carbohydrates get broken down further and you can extract more nutrition out of then. So it’s adds quite a bit of extra value to have a microbiome, depending on what you were eating.

I’m interested in [the microbiome] and we’re doing research on it here. It’s quite a difficult thing to study because realistically you’re measuring something in feces, and healthy people don’t go around collecting fecal samples. So you have to be well organized to do stud-
It's a great thing. Maybe 10% of what you read in the new journals, like such and such observed in such and such disease, in small numbers – that kind of thing; probably 10% of that will pay off and turn into something that will be useful for everybody. [...] But that's a great thing.

**UTMJ:** Is there anything else you would like to add?

**BJM:** People need to be critical of the literature because there's a lot of smoke and not much fire there at the moment. If you sift through the literature, anybody can get some fecal samples and run it through a machine and they're not necessarily experienced in microbiology and gastroenterology. It's got to be the other way now, because it's now very easy to do microbiology experiments without thinking too much about what this means in real world patients. Just follow the scientific process, be sceptical, try and prove everyone else wrong – which is a bit annoying for them at times. If you can prove them wrong, this could be the next big thing.

**UTMJ:** Duly noted Dr. Marshall. On behalf of the University of Toronto Medical Journal, we are immensely grateful for your time. It's certainly not every day we converse with a Nobel Laureate, or the founder of a major scientific discipline. We do sincerely appreciate your time.

**BJM:** Thanks very much, and certainly anything to do with microbiology and the gut, Canada [has] a terrific track record for that kind of research. I'm looking forward to a lot of success.
Internal Medicine Enrichment & Development (IMED): early exposure to medicine subspecialties and its influence on students’ perceptions of a career in internal medicine

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Abstract

Introduction: There are limited opportunities for pre-clerkship medical students to experience the breadth of internal medicine (IM) subspecialties. Previous studies suggest specialty choices are made as early as prior to clerkship. Due to limited exposure, factors influencing students’ career decisions may be rooted in bias. Internal Medicine Enrichment & Development (IMED) is a 2-week program of clinical observerships, career talks, and workshops in 9 IM subspecialties. This study aimed to investigate whether IMED would influence students’ interest, understanding, and perceptions toward IM.

Methods: 16 pre-clerkship students at the University of Ottawa participating in IMED were surveyed at baseline and at program completion on their interest and self-perceived understanding of IM, as well as on negative perceptions about a career in IM. Likert scale survey responses were compared using Wilcoxon signed-rank testing.

Results: Comparison of pre-program and post-program surveys revealed an overall significant improvement in student interest in IM and self-perceived understanding of IM physician lifestyle, differences between subspecialties, and between academic and community-based practice. After participating in IMED, 81% of students stated they were more likely to pursue a career in IM. Participants reported changes in perceptions of the work hours, paperwork, and procedural skill required in IM. Career talks were the component of IMED most attributed as being responsible for changes in perception. Despite the self-reported changes in perception, there were no significant differences in the number of negative perceptions about IM held by participants at baseline and program completion.

Conclusion: This study demonstrates how a structured, early-exposure program can influence pre-clerkship students’ perceptions of a career in IM. Participation in IMED increased students’ self-perceived understanding of the career along with interest in IM. Implementing programs such as IMED across Canada can provide increased clinical exposure to IM subspecialties for pre-clerkship students and help inform early career decision making.

Introduction

Medical students in Canada often have difficulty selecting a residency program as the application deadline predates exposure to all specialties. At many medical schools, including the University of Ottawa, exposure to internal medicine (IM) is limited to the clinical teaching unit (CTU) during the 6-week core rotation in third year. Students therefore do not gain structured clinical exposure to the variety of subspecialties IM has to offer. Surgical programs across the country also experience a lack of exposure in the medical school curriculum and as a result, many medical schools across Canada have adopted the Surgical Exploration & Discovery (SEAD) summer program first established by the University of Toronto to provide pre-clerkship medical students with early exposure to a variety of surgical subspecialties.1 However, there is a current and regrettable absence of an equivalent IM summer program. Evidence from studies assessing medical students’ decision-making regarding specialties of interest suggest that specialty choices are often made as early as prior to the start of clerkship, and that the majority of students are able to predict their ultimate residency by the end of their second year of medical school.2,3 These studies highlight the importance of early clinical exposure for students to make an informed decision regarding their specialty of choice.
Internal Medicine Enrichment & Development (IMED) is an initiative established at the University of Ottawa that offers an early introduction to IM and its subspecialties for pre-clerkship medical students. IMED is a 2-week summer immersion program involving morning clinical observerships, lunchtime career talks delivered by staff, and afternoon hands-on workshops led by staff and residents. As such, IMED provides a comprehensive overview of IM subspecialties, allowing pre-clerkship medical students to gain an appreciation for the breadth of the discipline, explore their interests within the specialty, and network with IM staff and residents.

As a result of limited exposure to IM subspecialties in the undergraduate medical curriculum, many factors negatively influencing students’ decisions to pursue a specialty may be rooted in bias. Therefore, the aim of this study was to investigate whether early exposure to IM and its subspecialties through the IMED program would affect students’ interest in and understanding of the specialty. This study also aimed to identify whether students’ perceptions of IM – particularly negative perceptions about the career – would be altered through the first-hand, early exposure offered by the IMED program.

Methods

Internal Medicine Enrichment & Development (IMED) Program

IMED is a 2-week summer program developed by 2 medical students at the University of Ottawa with a keen interest in IM. It is currently organized annually by the Internal Medicine Interest Group, a medical student-run initiative at the University of Ottawa. The IMED program consists of 3 main components: (1) morning observerships, (2) lunchtime career talks, and (3) afternoon hands-on workshops. For each day of the program, participants spend the morning in a clinical setting observing a different IM subspecialty at 1 of 3 sites of The Ottawa Hospital with 1-on-1 assignment to a staff physician. All participants convene at lunchtime for a career talk delivered by a staff physician from a different subspecialty each day. The career talk involves discussions around scope of practice, decision to pursue the specialty, lifestyle and work-life balance, along with addressing any questions students may have about the specialty. Students then participate in hands-on workshops pertinent to the specialty involving case-based learning, interactive discussions, and procedural skills/simulation-based training such as central line insertion, code blue/ACLS simulation, bedside echocardiography, and ultrasound workshops.

In 2019, IMED provided 16 pre-clerkship medical students at the University of Ottawa with the opportunity to gain exposure to 9 IM subspecialties – general internal medicine, endocrinology, rheumatology, hematology, medical oncology, nephrology, cardiology, infectious diseases, and critical care medicine.

Participants & Study Design

Pre-clerkship medical students at the University of Ottawa were invited to apply to the IMED program for the summer of 2019. The program was advertised by email via class presidents’ listserv announcement received by all pre-clerkship medical students, by email to members of the Internal Medicine Interest Group, and by live announcement at Internal Medicine Interest Group events. A total of 70 applications were received, from which 16 program participants were selected via a randomized lottery of applicants. Student interest in IM was not a prerequisite for application and had no bearing on the selection process.

IMED program participants were asked to complete a survey prior to the start of the program and at program completion. This prospective cohort study aimed to investigate whether structured, early exposure to IM and its subspecialties through the IMED program would affect pre-clerkship medical students’ interest in and understanding of the specialty. This study also aimed to identify whether students’ perceptions of IM – particularly negative perceptions about the career – would be altered through such exposure, as well as evaluate what specific components of the 2-week program were most responsible for changing students’ perceptions.

Survey Design

A survey addressing students’ understanding of the career of an IM physician, interest in the specialty, and specific negative perceptions about a career in IM was developed (Appendix). The survey was reviewed by an IM faculty physician prior to administration.

Three questions in the survey were designed to assess students’ exposure and interest in IM. Students were asked if they had previous opportunities to connect with IM staff and residents, if they knew how to conduct research in IM, and if they would rank IM as their first-choice residency. An additional 3 questions were designed to assess students’ self-perceived understanding of the specialty. Students were asked if they felt they understood what the career of an IM physician looks like, which specialties were more procedural-based, and the differences between community and academic practice. Students were also asked in the post-program survey if they were more likely to pursue a career in IM following the completion of IMED.

To assess students’ negative perceptions towards a career in IM, students were asked for their level of agreement towards 5 negatively biased statements about the work hours, the work-life balance, the work brought home, the amount of paperwork, and the requirement of working in an academic hospital, the job prospects of the specialty, and the level of procedural skill required in the specialty. Students were subsequently asked to identify which component of IMED they felt was most responsible for the change in their perception, if applicable, in each of the 6 areas.

Responses were rated on a 5-point Likert scale with 1 being “Strongly Disagree” and 5 being “Strongly Agree”. Surveys were administered online and responses were collected anonymously for analysis.

Data Analysis

Differences between pre-program and post-program survey data from students who participated in IMED were analyzed.
using the one-tailed Wilcoxon signed-rank test, a non-parametric test comparing paired data. An alpha of 0.05 was considered statistically significant.

Ethics Approval

Ethics exemption for this study was obtained from the Ottawa Health Science Network Research Ethics Board. This quality improvement study is registered with the IQ@TOH Project Registry.

Results

A total of 16 pre-clerkship medical students at the University of Ottawa participated in the IMED program in 2019 and completed both pre-program and post-program surveys (Table 1).

Table 1. Demographics of IMED 2019 program participants at the University of Ottawa

<table>
<thead>
<tr>
<th>Program Participants</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of participants</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Female</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Pre-clerkship year</td>
<td></td>
</tr>
<tr>
<td>MS1</td>
<td>15 (94)</td>
</tr>
<tr>
<td>MS2</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Language stream</td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>9 (56)</td>
</tr>
<tr>
<td>French</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Internal medicine as preferred residency</td>
<td></td>
</tr>
<tr>
<td>Disagree/strongly disagree</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Neutral</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Agree/strongly agree</td>
<td>6 (38)</td>
</tr>
</tbody>
</table>

Exposure and Interest in Internal Medicine

At baseline, prior to the start of the IMED program, 57% of participants reported not having had opportunities to develop connections with IM residents and staff (indicating either “Disagree” or “Strongly Disagree” with the statement) while a minority of 6% of participants responded with “Agree” or “Strongly Agree” (Figure 1). At program completion, the number of students who reported having had opportunities to connect with IM residents and staff increased to 44%. The percentage of participants who reported having a strong idea of how to conduct research in IM also increased from 13% at baseline to 60% at program completion.

With respect to baseline interest in IM, 38% of participants were considering IM as their residency program of choice (indicating either “Agree” or “Strongly Agree” in agreement to this statement) while 31% reported the opposite (indicating either “Disagree” or “Strongly Disagree”). At program completion, the number of students considering IM as their residency of choice increased to 56% while the number of students in disagreement decreased to 13%. When asked specifically if participation in IMED influenced their interest in IM, 81% of participants responded that they were more likely to pursue a career in IM following the completion of IMED.

Understanding of Internal Medicine

Wilcoxon signed-rank testing revealed that students’ level of agreement with statements surrounding their understanding of IM was greater after participation in IMED compared to baseline (Figure 2). More students responded “Agree” or “Strongly Agree” to understanding what the career of an IM physician looks like (p≤0.001), understanding which subspecialties of IM are more “procedure-heavy” compared to those that are more “medicine-heavy” (p≤0.001), and understanding the differences between academic vs. community IM (p≤0.001) upon completion of the program.

Negative Perceptions About Internal Medicine

Participants in the IMED program self-reported changes in their perceptions of IM upon completion of the IMED program (Figure 3). At the end of the 2-week program, 56% of participants reported perceiving the work hours of an IM staff to be more than they had previously believed and 44% reported perceiving IM staff spending more time on paperwork compared to patient contact than previously believed. In addition, 44% of participants acknowledged that IM required more procedural skill than previously believed.

IMED participants attributed lunchtime talks as most responsible for all changes in their perceptions of IM, with the exception of perception changes regarding the amount of...
paperwork staff complete, for which 100% of students attributed morning observerships as most responsible. Of the students who reported a change in their perceived level of procedural skill required in IM, 30% stated the afternoon workshops were most responsible for this change.

However, despite these self-reported changes in perceptions, there were no significant differences in the number of negative perceptions about IM held by students at baseline and at program completion (Table 2). The most prevalent negative perception held by 88% of participants at the start of the program was that IM physicians spend more time on paperwork than communicating with patients, and this remained the most prevalent perception held by 75% of participants in the post-program survey.

Table 2. IMED program participants’ perceptions about internal medicine at the start of the IMED program and upon completion of the program. * indicates a negative perception about internal medicine

<table>
<thead>
<tr>
<th>Perception</th>
<th>Pre-Program n (%)</th>
<th>Post-Program n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More balanced</td>
<td>7 (44)</td>
<td>10 (63)</td>
</tr>
<tr>
<td>Less balanced</td>
<td>5 (31)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Neutral</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Requirement of mainly working in an academic hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More</td>
<td>5 (31)</td>
<td>10 (63)</td>
</tr>
<tr>
<td>Less</td>
<td>5 (31)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Neutral</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Level of procedural skill required</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More</td>
<td>7 (44)</td>
<td>10 (63)</td>
</tr>
<tr>
<td>Less</td>
<td>5 (31)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Neutral</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Number of patients seen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More</td>
<td>7 (44)</td>
<td>10 (63)</td>
</tr>
<tr>
<td>Less</td>
<td>5 (31)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Neutral</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Time spent on paperwork vs. communicating with patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somewhat more/more</td>
<td>14 (88)</td>
<td>12 (76)</td>
</tr>
<tr>
<td>Equal</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Somewhat less/less</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Work brought home each night vs. other specialties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More work/significantly more work</td>
<td>7 (44)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Less work/significantly less work</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Average</td>
<td>9 (56)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Job prospects in the majority of IM subspecialties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More</td>
<td>5 (31)</td>
<td>8 (50)</td>
</tr>
<tr>
<td>Less</td>
<td>6 (38)</td>
<td>3 (19)</td>
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<tr>
<td>Neutral</td>
<td>5 (31)</td>
<td>5 (31)</td>
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<tr>
<td>Disagree/strongly disagree</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agree/strongly agree</td>
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</tr>
<tr>
<td>Somewhat more/more</td>
<td>14 (88)</td>
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<td>Equal</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Somewhat less/less</td>
<td>1 (6)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>No change from previous belief</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than previously believed</td>
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<td>Morning observerships</td>
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<td>More balanced</td>
<td>10 (63)</td>
<td>2 (13)</td>
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Figure 3. IMED program participants’ self-reported changes in their perception of internal medicine (IM) upon completion of the program. Students were asked “Did your perception about the _______ for an internal medicine staff change?” Pie charts indicate specific component of IMED which students attributed to being the most responsible for the change. The influence of IMED workshops came into play in changing students’ perceptions of IM physicians to be more than they had initially believed prior to the program. Lunchtime talks were the component of IMED most often responsible for changes in students’ perceptions with the exception of student perception of the amount of paperwork completed by IM staff, for which morning observerships were arranged in academic hospital settings, students still reported a significant improvement in their agreement with understanding the differences between community and academic practice. This could perhaps be explained by the program providing students with a greater understanding of the demands of an academic career relative to any prior exposure to community-based practice students may have had. As students were surveyed for their level of agreement with statements describing their understanding of IM as a specialty, this study is limited in its ability to evaluate students’ knowledge. Future studies making use of pre-program and post-program testing may be useful to assess the utility of IMED in improving students’ medical content knowledge and/or knowledge of IM as a specialty.

Studies have demonstrated that when making career decisions, medical students are influenced by the expected work hours, lifestyle, and work-life balance of a specialty.10 Many participants of IMED reported the work hours and amount of paperwork completed by IM physicians to be more than they had initially believed prior to the program. Lunchtime talks were the component of IMED most often responsible for changes in students’ perceptions with the exception of student perception of the amount of paperwork completed by IM staff, for which morning observerships were arranged in academic hospital settings, students still reported a significant improvement in their agreement with understanding the differences between community and academic practice. This influence of IMED workshops came into play in changing students’ perceptions of the level of procedural skill required of an IM staff.

When students were asked to rate their level of agreement with negatively biased statements about IM, no significant differences between baseline and post-program responses were revealed. The most prevalent negative perception amongst participants was that IM physicians spend more time on paperwork than communicating with patients, and this remained the most prevalent perception at program completion. While not included in this study, it would be interesting to therefore explore whether participants in this program viewed these perceptions as a deterrent to the specialty, which would offer a possible explanation for the discrepancy between the increase in interest in IM despite the unchanged prevalence of negative perceptions. Further studies on IMED...
participants in future iterations of the program could employ qualitative grounded-theory methodology to capture the impact of students’ perceptions on individualized career decision making. The negative perceptions about IM that were examined in this study have been studied in previous surveys of medical students, where workload, paperwork demands, and lifestyle were common deterrents from IM. In one study of graduating medical students, IM and its subspecialties was listed as one of the top specialties in which students changed their career plans due to “badmouthing” (negative comments students hear about potential career choices). What is more interesting is that students were a common source of badmouthing, and that the majority of badmouthing took place in the first 2 pre-clinical years of medical school. Moreover, multiple studies assessing medical students’ decision-making regarding specialties of interest suggest that specialty choices are often made as early as prior to the start of clerkship, and that the majority of students are able to predict their ultimate residency by the end of their second year of medical school. These studies highlight the importance of early clinical exposure for students to make an informed decision in deciding on their specialties of choice. As the IMED program takes place in the summer after students’ first or second year of medical school, it is ideally situated to provide students with first-hand exposure to explore their own biases and perceptions of a career in IM.

This study is not the first to demonstrate that early exposure for pre-clerkship students can influence career interest and understanding of specialties. Rather this study contributes to the existing body of knowledge surrounding the value of pre-clerkship exposure to IM through structured programs. The IMED program is also not unique as a student-run initiative, with programs such as the SEAD program developed at the University of Toronto and the Pre-Clerkship Residency Exploration Program (PREP) at Dalhousie University accomplishing similar results. The unique advantage of IMED over informal observerships available to all University of Ottawa pre-clerkship students is its structured 2-week curriculum. While students may pursue observerships for a number of reasons, students may be drawn to arrange observerships with specific specialties that pique their interest. Rotating through each of the 9 subspecialties of IM is mandatory in the IMED program, which provides students with exposure to subspecialties they might not have otherwise explored. While the number of IM subspecialties included in the IMED program was constrained due to financial and scheduling barriers, the IMED program could be expanded in future iterations to encompass more subspecialties – including those which pre-clerkship medical students are not often exposed to such as medical biochemistry, pain medicine, and clinical pharmacology. This expansion is facilitated by the growing interest from divisions within The Ottawa Hospital Department of Medicine to get involved in showcasing their specialty. Subspecialty-specific exposure and interest was not captured in this study and may have contributed to the increase in student interest in IM as a whole despite the persistence of negative perceptions about the specialty. This is an area for potential further research into whether medical students who participate in IMED have changed perceptions of specific subspecialties within IM, particularly for those subspecialties which are not as accessible or visible within the undergraduate medical curriculum.

Limitations of this study included the potential variability of experiences between students who participate in the program. As morning observerships were designed to be 1-on-1 with a preceptor, participants completed their clinical observerships at different hospital campuses with different preceptors. While the 2-week IMED program exposed students to a wide number of IM physicians overall, the number of physician interactions within each subspecialty of IM remained limited. It is known that individual physician personality traits influence student experiences in clinical settings. This is further emphasized by the fact that less than half of all participants reported having had an opportunity to connect with an IM resident or staff upon completion of the program. In addition, despite the fact that an interest in IM was not a prerequisite for participating in the IMED program, this study may have been affected by sample bias, as students who applied to participate in the program likely had a greater baseline interest in IM than the general medical student population. The lack of long-term follow up of participants in the IMED program also prevents any conclusions from being made about whether involvement in the program ultimately influences residency selection and career decisions. These limitations highlight future directions of research surrounding the IMED program which may be studied in subsequent iterations of the program. Further studies employing a longitudinal approach may aid in the exploration of the impact of IMED on career decision making and the choices students make during the CaRMS process. Moreover, although this present study did not explore the role of preceptor attitudes, or gender representation within subspecialties, the systematic exposure to a variety of physicians and subspecialties within IM offered by the IMED program provides valuable opportunities for future research in these areas.

Conclusion

This study demonstrates how a structured, early-exposure IM summer program can influence pre-clerkship medical students’ perceptions of a career in IM. Overall, participation in IMED increased students’ self-perceived understanding of IM as well as interest in the career. Students also self-reported changes in previously held beliefs about a career in IM upon completion of the program. However, despite these self-reported changes in perceptions, there were no significant differences in the number of negative perceptions about IM held by students at baseline and at program completion. Implementing programs such as IMED across Canada can increase clinical exposure to IM subspecialties for pre-clerkship medical students and help inform early career decision making.

Acknowledgments

The authors would like to thank the Department of Medicine at The Ottawa Hospital, the Canadian Federation of Medical Students’ Student Initiative Grant, and the University of Ottawa’s Aesculapian Society Conference Fund for their generous donations in support of this program.

References

APPENDIX

Pre-Program Survey Questions
1. I have had the opportunity to develop strong connections with residents and staff within the field of IM.
2. I have a strong idea of how to conduct research in the field of IM as a medical student.
3. If I had to decide my residency choice today, I would rank internal medicine first.
4. I understand what a career in IM looks like (in terms of hours, pay, research opportunities, job prospects, lifestyle).
5. I understand which subspecialties of IM are more “procedure heavy” compared to those which are more “medicine heavy”.
6. I understand what community vs. academic practice in IM can look like.
7. To what extent do you feel that the hours of an internal medicine staff are longer than other physicians?
8. How do you think internists across all sub-specialties would describe their work-life balance?
9. To what extent do you think internists bring home work in terms of patient duties/administrative work with them each night compared to the average physician?
10. To what extent do you think internists spend time writing paperwork for patients compared to communicating with patients face-to-face?
11. To what extent do you think there are limited jobs in internal medicine?
12. Did your perception about the work hours for an internal medicine staff change?
   a. If your perception changed, were the work hours shorter or longer than you had previously believed?
   b. Which activity was most responsible for changing your perception?
13. Did your perception about the amount of work brought home as an internal medicine staff change?
   a. If your perception changed, was the amount of work brought home less or more than you had previously believed?
   b. Which activity was most responsible for changing your perception?
14. Did your perception about the amount of paperwork compared to patient contact for an internal medicine staff change?
   a. If your perception changed, was the amount of paperwork compared to patient contact less or more than you had previously believed?
   b. Which activity was most responsible for changing your perception?
15. Did your perception about the requirements for mainly working in an academic hospital for an internal medicine staff change?
   a. If your perception changed, do you now think it’s less or more of a requirement to mainly work in an academic hospital as an intern compared to what you previously believed?
   b. Which activity was most responsible for changing your perception?
16. Did your perception about the job prospects in the majority of internal subspecialties for an internal medicine staff change?
   a. If your perception changed, do you now think the job prospects in the majority of internal subspecialties are more or less favourable compared to what you previously believed?
   b. Which activity was most responsible for changing your perception?
17. Did your perception about the level of procedural skill required for an internal medicine staff change?
   a. If your perception changed, do you now think the level of procedural skill required to be an internist is more or less compared to what you previously believed?
   b. Which activity was most responsible for changing your perception?
18. Following IMED, are you more or less likely to pursue internal medicine as a career?

Post-Program Survey Questions
1. I have had the opportunity to develop strong connections with residents and staff within the field of IM.
2. I have a strong idea of how to conduct research in the field of IM as a medical student.
3. If I had to decide my residency choice today, I would rank internal medicine first.

Primary Research

Internal Medicine Enrichment & Development (IMED): early exposure to medicine subspecialties and its influence on students’ perceptions of a career in internal medicine


[18]
First episode psychosis: the commensal gut microbiota perspective

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Abstract

Background: The rates of type 2 diabetes (T2D) in patients with schizophrenia (SCZ) are 3-5-fold higher than in the general population, contributing to a 2-fold higher risk of cardiovascular disease mortality. Antipsychotics, namely second-generation antipsychotics (SGAs), the cornerstone of treatment for this illness, induce weight gain and increase risk for diabetes. Accumulating research has demonstrated that the gut microbiome (GMB) plays a primary function in energy metabolism and could be a central factor in the pathophysiology of obesity and metabolic dysfunction. Antipsychotics are well known to contribute to metabolic dysregulation in patients with SCZ, possibly through their impact on the GMB. This effect may be mediated by changes in dietary pattern induced by antipsychotics. Alterations in the GMB therefore may be contributing to both the etiology and concurrent metabolic dysregulation observed in schizophrenia spectrum disorders.

Objective: In this review, we aim to explore how GMB affects the pathophysiology and treatment in this difficult-to-treat condition.

Methods: This paper is a narrative review. MEDLINE, Google Scholar, and PsychINFO databases were searched for articles containing the following MESH terms: first episode psychosis [AND] schizophrenia [AND] gut microbiome [AND] gut microbiota [AND] metabolic syndrome [OR] metabolic dysfunction [OR] metabolic side effects [AND] second generation antipsychotics [OR] atypical antipsychotics. Inclusion criteria for studies are full-text, English journal articles, published/in press before February 2020, and reporting changes in the gut microbiome among patients with psychosis who are receiving atypical antipsychotic treatments.

Discussion: Through this review, the GMB has been discussed in relation to patients with first episode psychosis and the changes that occur within the microbiota when antipsychotic medication is introduced. SGAs have a high propensity to cause metabolic dysfunction as well as gut dysbiosis. While mechanisms are still to be elucidated, the interactions between the GMB and SGAs largely involve neurotransmitter modulations, gastrointestinal barrier functionality, and dietary changes.

Conclusion: This commentary highlights the need for more large scale, clinical studies investigating antipsychotic-induced changes to the gut microbiome and the importance of making changes to a patient’s care pathway with the GMB in mind.

Introduction

Research has demonstrated that the gut microbiome (GMB) plays a greater role than simply aiding digestion and nutrient absorption. Given its primary function in energy metabolism, the GMB is a central factor in the pathophysiology of obesity and metabolic dysfunction. Close relationships exist between GMB shifts and obesogenic profile, both in terms of diversity, which is reduced among individuals with obesity, and composition, in which the relative abundance of certain phyla change with weight gain.1 In addition to metabolic dysfunction, the GMB has been implicated in brain structure, function, and development, ultimately influencing cognition. Pre-clinical studies have shown that changes in the GMB in mice influence cognition and brain structure.2 There is evidence that dietary changes and inflammation contribute to this, but mechanisms have yet to be established and clinical studies assessing cognition are far and few between.3

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The GMB is becoming increasingly relevant to psychiatry in the prognosis and treatment of severe mental illnesses. Over the past decade, there have been numerous studies pointing to the role of the GMB in psychological processes and neuropsychiatric disorders.

An additional influence on the GMB unique to those with severe mental illness is antipsychotic medication. Antipsychotics—alongside psychosocial interventions—are the cornerstone of treatment in psychiatric illness, and influence both psychopathology and the GMB. There are two classes of antipsychotics: first generation antipsychotics and second-generation antipsychotics (SGAs). While the GMB is at the intersection of metabolic and cognitive dysfunction, there is further possibility that there may be influence of shared sites and actions between SGAs and the GMB. This perspective paper will seek to explore the GMB and metabolic changes mainly seen in patients who are considered antipsychotic-naive first episode psychosis (FEP) patients but will also include studies relating to those who have been exposed to longer term treatment with SGAs. The focus of this narrative review is to evaluate the literature on the topic of GMB dysbiosis and metabolic dysfunction among patients with psychosis receiving SGA treatment.

Methods

This paper is a narrative review. MEDLINE, Google Scholar, and PsychINFO databases were searched for articles containing the following MESH terms: first episode psychosis [AND] schizophrenia [AND] gut microbiome [AND] gut microbiota [AND] metabolic syndrome [OR] metabolic dysfunction [OR] metabolic side effects [AND] second generation antipsychotics [OR] atypical antipsychotics. Inclusion criteria for studies are full-text, English journal articles, published/in press before February 2020, and reporting changes in the gut microbiome among patients with psychosis who are receiving atypical antipsychotic treatments.

Results

Severe Mental Illness: The Patient Population

Psychosis is defined as a loss of contact with reality, manifesting with hallucinations, delusions, and disorganized thinking/behaviours. Psychotic symptoms can present in a range of psychiatric disorders, such as schizophrenia, bipolar disorder, and major depression with psychotic features. The global prevalence of psychotic disorders has been reported as 4.6 per 1000 people. Prior to their first episode of psychosis, patients commonly experience a prodromal period involving subsyndromal psychotic symptoms, negative symptoms, and functional decline ranging from weeks to years. In patients eventually diagnosed with schizophrenia or bipolar disorder, the first episode of psychosis typically occurs between 15 to 30 years of age. Substance use disorder commonly precedes, coincides, or follows FEP and is associated with worse outcomes, including decreased treatment adherence and increased relapse, hospitalization, and suicide attempts.

As the duration of untreated psychosis has been associated with negative long-term outcomes, it is imperative that intervention not be delayed. Management largely centers around pharmacologic measures, with current guidelines recommending antipsychotics, specifically SGAs, as first-line treatment of FEP patients.

Overview of second-generation antipsychotics

SGAs are commonly used for the treatment of schizophrenia, bipolar disorder, depression, and a host of additional indications under drug-specific circumstances. While the literature has not found a significant difference in efficacy of reducing positive symptoms between agents, with the exception of clozapine, systematic reviews and meta-analyses have demonstrated the superiority of SGAs over first generation antipsychotics in reducing negative symptoms and treatment discontinuation, with little difference in efficacy between SGAs. In Canada, the prescription of antipsychotic medications was noted to have doubled, exceeding 7 million prescriptions annually between 2005 and 2012. Worldwide, the number has continued to increase for both adults as well as for youths, secondary to the increase in prescription of SGAs and longer duration of use. This has important health implications when considering the nature of treatment for these disorders is often lifelong. Thus, it is imperative to consider the adverse effects these medications have. SGAs are commonly favoured over their “first generation” counterparts as they have been argued to have a lower propensity for causing extrapyramidal side effects (EPS). However, SGAs are indisputably associated with significant metabolic sequelae, including weight gain, glucose dysregulation, and dyslipidemia. The illnesses associated with these metabolic disturbances negatively impact cognition, thus highlighting the complex interplay between the metabolic and cognitive adverse effects of SGAs. Beyond this, the metabolic side effects of SGAs may also contribute to lack of drug compliance, with patients who experience weight gain being more than 13 times more likely to discontinue medication than those who do not experience weight gain.

Adverse metabolic effects of SGAs

Patients with mental illness suffer from high rates of cardiometabolic comorbidity, including obesity, type 2 diabetes, dyslipidemia, and hypertension, which have been associated with risk factors including the use of multiple antipsychotic medications, adjunctive use of antidepressants and/o mood stabilizers, the presence of affective symptoms, younger age at FEP onset, and male gender. The weight gain caused by SGAs is primarily centrally distributed, leading to an increase in waist circumference which itself has been associated with adverse outcomes, including the subsequent development of insulin resistance and metabolic syndrome. A high risk of weight gain has most consistently been attributed to clozapine and olanzapine, with quetiapine and risperidone having moderate risk, and aripiprazole and ziprasidone having low risk. In a systematic review by Hirsch et al., the majority of studies of olanzapine and clozapine found a significant association with type 2 diabetes mellitus. While the exact mechanism for these comorbidities has not yet been elucidated, several contributory pathways have been put forth, including increased appetite and poor diet, suppression of basal metabolic rate, and dysregulation of glucose metabolism through blockade of the muscarinic M3 receptor. Finally, recent literature has implicated the GMB in the progression of SGAs metabolic side effects, which will be the focus of the rest of this review.
GMB changes associated with SGAs

The literature has linked specific changes in GMB to weight gain and metabolic disturbances. These same changes are seen with SGA treatment. GMB diversity appears to decrease with longer SGA use, as illustrated in both pre-clinical and clinical studies. Diversity also appears to decrease during the early stages of SGA treatment. In connection to obesity, decreased diversity is a characteristic of an obesogenic profile (i.e. greater adiposity, dyslipidemia, impaired glucose homeostasis, and low-grade inflammation).

A systematic review by Zydecka et al. of 10 articles, including 15 experiments of SGAs in both humans and animals, found that in studies examining bacterial content of stool, dysbiosis was demonstrated in all but one study. More specifically, an increase in the Firmicutes/Bacteroidetes (F/B) ratio was not only the most common abnormality, but was also demonstrated in all of the studies that examined for that parameter. This is significant as animal studies have largely demonstrated that an increase in the F/B ratio is strongly associated with an increase in body fat, obesity, and metabolic syndrome. In humans, this relationship has been more difficult to demonstrate, with some studies finding no such association, while others have found a similar increase in the F/B ratio in obese individuals, and still some have not reported bacterial phyla. Some of the other known taxonomic alterations that are influenced by SGAs in humans include Actinobacteria, Proteobacteria, and Verrucomicrobia phyla, as well as bacteria that are members of the Bifidobacterium genus. Increases in Proteobacteria and Actinobacteria abundance coupled with decreases in Verrucomicrobia have been illustrated with risperidone use among adolescents. Decreases in Akkermansia have been reported in non-obese adults with SGAs and increases in Bifidobacterium seen in adults with first episode psychosis treated with risperidone.

While the mechanism by which SGAs alter the GMB remains uncertain, several have been proposed (see Figure 1).

Figure 1. A summary of putative mechanisms by which SGAs cause adverse metabolic effects via disruption of the GMB. SGA: second generation antipsychotic, NT: Neurotransmitter, SCFA: short chain fatty acid, FIAF: fasting-induced adipocyte factor.

SGAs compromise the gastrointestinal barrier

SGAs may be antimicrobial. Prebiotic treatment has previously been shown to decrease intestinal permeability through increased integrity of tight junction proteins. Because the GMB plays a part in maintaining the gastrointestinal barrier, SGAs could cause an increase in intestinal permeability. Increased intestinal permeability in turn allows movement of pathogens and antigens beyond the gut, inducing inflammation and culminating in metabolic side effects.

SGAs alter diet, and diet modifies the GMB

Independent of SGAs, diet has been implicated in determining the structure and function of the GMB. Changes in GMB composition due to diet can happen as quickly as within 24 hours of an alteration in diet. Looking at specific diets, those which are high in fat have been linked to changes in the GMB, namely an increase of Firmicutes to Bacteroidetes, which has also been correlated with obesity. In pre-clinical studies, high fat and high sugar diets (modeling the human “western diet”) increased Roseburia spp. and Ruminococcus glycolicus, which have been positively correlated with insulin levels and a homeostatic model of insulin resistance, two key markers of metabolic dysfunction. Plant-based versus animal-based diets also impact the GMB. Animal-based diets have illustrated increases in Akkermasia spp., Bilophila spp. and Bacteroidetes spp., and decreases in Roseburia spp., Eubacterium rectale and Ruminococcus bromii, the latter group all sharing a common feature of being fermenters of dietary plant polysaccharides. Alterations in the GMB strongly associated with the “western diet” have been proposed to occur through lower consumption of microbiota-accessible carbohydrates (MACs). One food which has been discussed frequently in conjunction with the GMB is yogurt. Consumption of yogurt modifies GMB composition depending on the strain of bacteria. For instance, yogurt with Bifidobacterium lactis has been shown to have immunomodulatory effects.

SGAs modify diet, so it follows that changes in diet may account for SGA-mediated changes in the GMB. Additionally, clozapine and olanzapine have been shown to induce food craving and binge eating in patients. Looking to “hunger hormones”, SGAs also affect serum ghrelin and leptin levels. In a study assessing five SGAs (clozapine, olanzapine, risperidone, quetiapine, and amisulpride), elevated serum ghrelin levels were associated with all but quetiapine. With regards to leptin, the consensus is that SGAs such as olanzapine and clozapine increase serum levels. Taken together, dietary choices greatly influence the composition of the GMB independently of SGAs, and the introduction of an SGA potentially causes GMB-altering dietary changes.

SGAs disrupt the GMB through neurotransmitter antagonism

Gut bacteria produce and are receptive to the neurotransmitters gamma aminobutyric acid (GABA), serotonin, dopamine, and norepinephrine. As examples, Lactobacillus are capable of producing GABA, Streptococcus has been shown to produce serotonin, and Proteus vulgaris can produce dopamine and norepinephrine. A recent review by Strandwitz has identified several studies showing species of bacteria beyond those mentioned that are able to produce neurotransmitters. Along with neurotransmitter production, both gram positive and negative bacteria have been shown to respond to norepinephrine and dopamine with increased growth (in culture) and virulence.

SGAs function as antagonists at serotonin (mainly the 5-HT2A receptor subtype), norepinephrine (alpha and beta),...
and dopamine D2 receptors, thereby inhibiting reuptake of these neurotransmitters. While this improves psychopathology, it also changes the structure and function of the GMB, and may be a pathway by which weight gain and other forms of metabolic dysfunction occur.42

**Metabolic consequences of GMB disruption**

SGAs have been shown to cause gut dysbiosis resembling illness, antibiotic treatment, or dietary changes.35,44 While several mechanisms of action have been suggested by which GMB dysbiosis deleteriously affects metabolism, a precise mechanism of action has yet to be determined. The following putative mechanisms will be discussed in detail given the literature supporting them: increases in lipogenesis, absorption of short chain fatty acids (SCFA), inflammation, and fasting-induced adipocyte factor (FIAF) (see Figure 1).

**Lipogenesis**

Dysbiotic changes in GMB composition and function strongly affect major organ systems. Colonized mice show upregulated absorption of monosaccharides compared to germ-free mice.45 When these monosaccharides reach the liver, it responds with an increase in carbohydrate response element binding protein (chREBP) and sterol regulatory element binding protein-1c (sREBP), which is followed by increased lipogenesis and lipoprotein lipase.23,25,36,45

SCFAs are produced by the GMB and gut and absorbed into the blood, making available an otherwise inaccessible source of nutrients like butyrate, acetate, and propionic acid. The extent to which this occurs depends in part upon the abundance of phyla that ferment MACs into SCFAs.23,32

The downstream effects of SCFAs on metabolic outcomes are variable. Colonizing germ-free adult mice with the microbiota of an obese mouse led to weight gain, without an associated increase in food or calorie consumption compared to mice colonized with the microbiota of a lean mouse.46 Furthermore, caecal gross energy content was smaller, while butyrate levels, and acetate levels were larger in genetically obese mice, suggesting that perhaps production and absorption of SCFAs is more efficient in an ‘obese’ GMB.46 In contrast, addition of butyrate and propionate to a high-fat diet prevented weight gain in mice.47 Similarly adding MACs (which the GMB converts to SCFAs) to a high-fat diet prevented weight gain in mice.48

SCFAs might also lead to decreased activity of AMP-activated protein kinase (AMPK) in skeletal muscles and liver tissue, resulting in upregulated deposition of SCFAs in adipose tissue.23,49,50 Some evidence indicates SCFAs may be anti-inflammatory in nature, which would be metabolically beneficial.20

**Inflammation**

A compromised GMB can lead to antigens crossing the gastrointestinal area into the blood, where inflammation follows. Neuroinflammation relates the brain and the gut in a gut-brain axis, causally linking gut microbiota to stress in the central and enteric nervous system enhancing sensitivity to stress and caloric intake.31

The resulting psychological stress, proinflammatory cytokines, and hypoglycemia can activate the hypothalamus-pituitary-adrenal axis,32 and overactivation may, in turn, deleteriously affect the GMB in a loop.33 While the GMB influences endocrine pathways and behavior, endocrine disease and behavioural states also influence the GMB.32,54

Additionally, proinflammatory cytokines activate the JNK/IKK pathway, which promote the activity of genes involved in lipid metabolism.32

**FIAF**

FIAF is secreted by adipose tissue, the liver, and the intestine. It inhibits lipoprotein lipase (LPL), which promotes the deposition of lipids in adipose tissue.32,45 Bäckhed et al., found that conventionalized mice gained weight while germ-free mice did not, and that this effect was abolished in fiaf knockdown mice.45 Consistent with a role as a LPL inhibitor, colonized mice displayed greater LPL activity.45 Taken together, this suggests that GMB dysbiosis might cause weight gain by upregulating FIAF.

**Impact of research involving SGAs and the GMB**

Studies have suggested that the degree of weight gain attributable to SGAs may be greater in antipsychotic-naive patients than in chronically treated adult patient populations, with the greatest increases in weight and metabolic parameters occurring during the first year of treatment.51 This is significant as many FEP patients are antipsychotic-naive and rushed by their treating team to be started on an SGA immediately, as early intervention has been associated with improved treatment outcomes.50 However, as the majority of FEP patients are relatively young in age, they not only have to cope with the lifetime impact of the metabolic sequelae of their treatment, but are also forced to cope with weight gain at a time in their life where their appearances may be of greater personal importance. This may negatively impact their self-esteem, further taxing their mental health at a time when it is already being challenged by their primary disease state. These negative influences on quality of life may further impede medication compliance. Patients may attribute their weight gain and other adverse effects to starting their medication (often a correct association), and thus may choose to discontinue their medications in the hopes of stopping these adverse effects without appreciating the consequences on symptom control. There is significant literature, however, to suggest that antipsychotic discontinuation, even if for a brief period before being restarted, has adverse effects on long term outcomes, including time to remission and risk of relapse.57,58 Indeed, a retrospective cohort study by Winton-Brown et al.48 found that treatment discontinuation was associated with a five times greater risk of relapse.48 Furthermore, a systematic review by Zipursky et al. found that patients who continued treatment with antipsychotics had one year relapse rates of 3%, while those who discontinued had relapse rates of 77% at one year and 90% at two years.57 Relapses may then lead to increased difficulty in controlling symptoms, requiring larger antipsychotic doses or the use of clozapine, both associated with increases in negative metabolic effects. A study by Hickling et al. examining antipsychotic medication non-adherence to in FEP patients found that 34% of patients reported non-adherence, with contributory factors including younger age and less satisfaction with medication information.59 Others have reported that up to half of patients...
are non-adherent in the first year following initiation of treatment with antipsychotics. The impact of research on the interplay between SGAs and the GMB therefore extends beyond attenuating metabolic side effects, and into addressing issues of medication compliancy, self-esteem, risk of psychiatric relapse, and time to remission.

**Clinical importance of understanding the GMB in SGA treatment**

FEP patients typically respond well to treatment initiation with APs, having relatively rapid resolution of psychotic symptoms, as antipsychotic sensitivity is increased in the early stages of psychosis as compared to later. Given the evidence in the literature demonstrating the metabolic adverse effects of SGAs, physicians should be cognizant of the weight gain and cardiometabolic risks associated with starting patients on such medications, particularly FEP patients who are most commonly antipsychotic-naïve and thus in the position to experience the greatest metabolic insult. Monitoring metabolism is important in the initial stages of treatment, but must be continued throughout. Since treatment regimens for this patient population are often long term, if not lifelong, it is imperative that physicians make efforts to reduce untoward metabolic effects. Strategies to reduce weight gain and cardiometabolic risk include choosing SGAs with better cardiometabolic risk profiles whenever possible (i.e. aripiprazole or ziprasidone). Although behavioural modifications are often recommended as first line interventions to combat metabolic comorbidities, they may be challenging to adopt in a patient population that is often limited in motivation and by the inherent nature of their disorder and the medications used to treat it. However, physicians should not be deterred and should continue to work with their patients to incorporate various health-risk behavioural modifications, such as involving caloric intake, choosing healthier food options, and increasing physical activity. Lastly, in light of the metabolic sequelae described above, including increases in fasting plasma glucose, cholesterol levels, triglyceride levels, blood pressure, and weight, physicians should routinely screen their patients according to current guidelines and begin treatment of abnormal values and subsequent disease states appropriately.

As described above, factors associated with antipsychotic non-adherence include younger age and less satisfaction with medication information. To promote adherence, physicians should endeavour to provide better information about antipsychotics to their patients, especially those who are younger and at greater risk for non-adherence.

Current commonly employed methods of reducing SGA-induced weight gain include metformin and topiramate. Omega-3 fatty acids have also been proven to be protective against metabolic syndrome in schizophrenia patients. The facility with which the GMB changes in response to diet, probiotics, and prebiotics, as well as the role it plays in metabolic symptom progression, make the GMB an attractive target for the future development of SGA-adjuvant treatments.

**Discussion**

**Summary: Present understandings and future directions**

A limitation of this study is that it is a narrative review rather than a systematic one. It is also worth bearing in mind that the GMB and metabolism both seem to be disrupted in psychiatric patients prior to beginning SGAs. This means that the extent to which observed changes in the GMB are uniquely attributable to SGAs rather than the progression of the disease itself is difficult to assess in human subjects, where ethical implications of withholding treatment preclude a placebo-controlled patient group in many instances. However, in studies where first-generation antipsychotics or other pharmacological treatments are compared to SGAs, the GMB and weight were adversely affected by SGAs.

Pre-clinical studies have been able to illustrate clearer relationships between SGAs, obesity, metabolic dysfunction, and the GMB. Currently, four studies (see Table 1) have been conducted in humans reporting on SGAs in relation to microbiome diversity and metabolic changes. From pre-clinical and clinical studies, it is understood that SGAs have their effects on the GMB by blocking neurotransmitter receptors, altering diet, and increasing intestinal permeability. While we are slowly beginning to recognize pathways for the GMB’s involvement in SGA-induced metabolic dysfunction, there is more to be understood, namely through exploration with larger sample sizes and longer follow up among FEP patients and those who have been chronically treated.

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</tr>
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<tbody>
<tr>
<td>Bahr et al., 2015</td>
<td>9-15 year old males with and without psychosis</td>
<td>Risperidone (in the psychosis group)</td>
<td>↓ Bacteroidetes/Firmicutes</td>
<td>↑ BMI</td>
</tr>
<tr>
<td>Yuan et al., 2018</td>
<td>FEP patients</td>
<td>Risperidone</td>
<td>↑ Bifidobacterium spp. and Escherichia coli, ↓ Lactobacillus spp. and Clostridium cocoides</td>
<td>↑ BMI, fasting glucose, triglycerides, LDL, hs-CRP, SOD, and HOMA-IR in Risperidone group</td>
</tr>
<tr>
<td>Flowers et al., 2017</td>
<td>Bipolar disorder</td>
<td>Any SGA or no SGA</td>
<td>↓ diversity among females, ↓ Akkermansia, ↑ Butyrella, ↑ Lachnospiraceae</td>
<td>↑ relative abundance of Akkermansia in SGA group was only found among non-obese patients. Obese patients had ↑ Lachnospiraceae abundance, ↑ BMI in SGA group</td>
</tr>
<tr>
<td>Flowers et al., 2019</td>
<td>Bipolar disorder or schizophrenia</td>
<td>Raw unmodified potato starch, SGA, or lithium or lamotrigine</td>
<td>↓ Alitripitae abundance among SGA users, diversity among females, ↑ Actinobacteria with starch</td>
<td>Not examined</td>
</tr>
</tbody>
</table>

BMI: body mass index, FEP: first episode psychosis, LDL: low density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, HOMA-IR: homeostatic model assessment of insulin resistance
Interpretation of literature

In summary, the literature to date illustrates the potential importance of targeting the GMB for the treatment of metabolic costs of SGAs. The literature also highlights the potential mechanistic role played by the GMB in mediating SGA-induced weight gain. Finally, further research into the interplay between the GMB, SGAs, and metabolism may allow earlier diagnosis and better monitoring and treatment of schizophrenia, other psychiatric disorders, co-morbid obesity, and obesity-related conditions (i.e. type 2 diabetes, metabolic syndrome). As has been reviewed, there appear to be baseline differences in metabolic as well as GMB parameters that differentiate FEP from healthy individuals. This separation becomes even more apparent as a psychotic illness progresses and with the introduction of SGAs. Common characteristics which occur among FEPs when starting SGAs include decreases in GMB diversity, transition of the GMB towards that of an obesogenic profile, and an increase in Firmicutes with a corresponding decrease in Bacteroidetes at the phyla level. It should be noted, however, that although many studies illustrate these findings, there are several that do not or that show conflicting results, therefore drawing the importance of continuing research.

In addition to exploring differences between FEP and healthy individuals, as well as changes in the GMB while FEP individuals progress through their treatment, the literature points to the importance of increasing clinical trials which focus on interventions for metabolic adversities among this population, be them pharmacotherapy or diet-based. Clinical trials should also explore how GMB-based interventions may complement SGA treatment and potentially improve SGA efficacy. Furthermore, the literature surrounding this topic also points to the importance of research in patients who are most vulnerable to metabolic dysfunction (i.e. youth and those who have never been exposed to SGAs), especially because they are at the greatest risk for long-term changes and therefore long-term metabolic complications.

Finally, while this review as well as the literature surrounding this topic focus on the interplay between the GMB, SGAs, and metabolic dysfunction among FEP patients, these investigations also present an opportunity to understand host-microbial interactions, psychotic illness, and metabolic dysfunction in general.

Future directions

We suggest that future research initiatives explore metabolic, proteomic, and lipidomic assessments. Going further than metabolic side effects, we suggest that future research initiatives explore how GMB alterations correlate with changes in cognition (both structural and functional) and psychopathology, as this relationship has yet to be reported in this patient population. Collectively, an understanding of the interplay between SGAs and the GMB which includes metabolic, psychopathological, and cognitive changes, is the ultimate goal. In addition, discussion of GMB changes when starting chronic treatment with an SGA was limited to studies assessing GMB composition due to the limited available literature. Future research directions should thus focus on other ways to analyze the GMB. Future research directions could explore novel options for co-therapy to prevent or reduce metabolic adverse effects. For example, clinical trials could explore if benefit could be derived from the simultaneous treatment of SGAs with probiotic, prebiotic or symbiotic therapy. Further research is also needed to better understand co-therapy options that can mitigate SGA-induced metabolic dysfunction, such as the oral hypoglycemic agent Metformin, in a patient population with severe mental illness.

References


Lactobacillus reuteri’s role in the prevention of colorectal cancer: a review of literature

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Medical University of the Americas, 27 Jackson Road, Suite 302, Devens, Massachusetts 01434, United States

Abstract

Background: Probiotics have many health benefits, which include decreasing intestinal inflammation and down-regulating metabolites and inflammatory mediators that can lead to the progression of tumors. Lactobacillus reuteri (L. reuteri) is a crucial bacterium that colonizes many mammals. Through analysis and evaluation of peer-reviewed articles relevant to the topic of interest, the findings in this review suggest that L. reuteri can slow tumor progression.

Hypothesis: Lactobacillus reuteri facilitates the prevention of colorectal cancer through inhibition of tumor progression.

Methodology: A database search through MEDLINE with exclusion criteria narrowed down material to the most relevant searches. The similarities that existed between various articles are highlighted in summary findings to help strengthen the argument for L. reuteri.

Conclusion: The findings of this review support the hypothesis that states, "Lactobacillus reuteri facilitates probiotics in the prevention of colorectal cancer through inhibition of tumor progression." L. reuteri was able to prevent colorectal cancer in animal models through the inhibition of tumor progression. Findings showed that this bacterium was critical in the inhibition of tumor progression, the reduction in inflammation, and thus the prevention of tumor progression into carcinogenesis or further metastasis.

Background

Colorectal cancer (CRC) is the third leading cause of cancer deaths worldwide, with 1.65 million new cases and almost 835,000 deaths in 2015. Every year, approximately 8% of cancer deaths are a result of colorectal cancer, with the highest incidence rates being in Australia, New Zealand, Europe, and North America. The rise in the cases of CRC is due to sporadic environmental factors and genetic risk factors, which lead to random mutations in DNA; however, as advancements in screening techniques for CRC have continued to improve, mortality rates from CRC have progressively declined.

CRC affects both the colon and the rectum and has malignancy potential, which, if not caught early, can lead to metastasis. The survival rate of CRC is dependent on the stage at the time of diagnosis, with a 5-year survival rate of 90% for local metastasis, 70% for regional metastasis, and 10% for those with distant metastasis. CRC has multiple risk factors, which include diets high in processed meat or low in fiber, as well as chronic inflammatory diseases such as ulcerative colitis and Crohn's disease. Non-modifiable risk factors include age and genetics; however, most of the risk factors for CRC, such as lifestyle, diet, alcohol use, and exercise, are modifiable. Routine medical tests like fecal occult blood test, colonoscopy, and sigmoidoscopy can help with early detection of CRC. Furthermore, due to the high incidence and mortality rates of CRC, further research and studies on promising cures or prevention methods are of great essence.

CRC Tumor Genesis

Fearon and Vogelstein, describe the developmental process of CRC as one that follows several concise and consecutive steps. Cells that contain β-catenin end up developing into tumors even though initial mutations and growth from epithelial or stem cells occur at random. The adenomatous polyposis coli (APC) gene has 15 exons with a molecular weight of over 300 kDa. The protein formed by the APC gene is responsible for inhibiting the activation of β-catenin and keeping it contained just within the cytoplasm. Once the APC gene is mutated, it can no longer act as a tumor suppressor.

Studies show that the loss of function of the APC gene leads to activation of β-catenin and its eventual translocation to the nucleus, causing subsequent KRAS activation that finally leads to the development of adenomas. Other studies suggest that just β-catenin itself and mutations in glycogen synthase kinase-β are responsible for a subset of some CRC cases. Others also suggest that H. pylori, mainly accountable for gastric tumors, may also have a role in some cases of CRC. The proinflammatory signaling tumor necrosis factor-α (TNF-α) that is produced by gastric tumors induces the translocation of β-catenin to the nucleus even without the mutation of the APC gene.

Probiotics

There has been a growing focus on the use of probiotics in treating many gastrointestinal diseases, including cancer.
studies link intestinal microbiota and lack of dietary fiber intake to the rise in number of CRC cases. These studies have suggested that microbial imbalance in the colon leads to increased growth of bacteria, some of which are carcinogenic. Because of their ability to restore microbial balance in the gastrointestinal tract, probiotics show a promising future role in the prevention and control of CRC. Evidence shows that there is an inverse correlation between the amount of healthy colon flora and the degree of the mucosal immune response. It is because of these findings that Kechara in 2013 suggested that the administration of live probiotics can help restore healthy intestinal flora, improve intestinal health, enhance immune response, and prevent cancer.

*Lactobacillus reuteri* (L. *reuteri*) is specifically examined amongst the various other probiotics because of its ability to limit the degree of inflammation in patients with ulcerative colitis (especially among children), a known risk factor for the development of CRC. It is also one of the probiotics that have been of great interest to researchers. *L. reuteri* is known to colonize the gastrointestinal tracts, urinary tracts, skin, and mammary glands of many mammals. It has antimicrobial activity with an ability to inhibit the aggregation and growth of other microbes. Some particular strains of this bacterium have reduced the production of pro-inflammatory cytokines like TNF-α, while also promoting T cell development.

Probiotics modulate immune system response, induce apoptosis of cancer cells, decrease the degree of inflammation caused by chronic inflammatory diseases, and reduce a patient’s chances of developing CRC. The overall objective of this study is to demonstrate the benefits of specifically administering L. *reuteri* to help prevent the development or progression of CRC.

### Methodology

The authors had free access to MEDLINE through PubMed, and searched the database using the following key terms: “colorectal cancer” and “*Lactobacillus reuteri*.” The search included these terms with and without quotation tags and together with publication types. Google Scholar was also used with the terms “*Lactobacillus reuteri* and colorectal cancer,” “Probiotics and colon cancer,” and “Colon cancer probiotic prevention.” Articles were narrowed down by selecting those that were most recently published. Abstracts of articles were then examined by the authors and filtered based on whether or not they were in English, were available in full text, and had open-access. The methodologies (cohort, randomized control trials, or systematic reviews) used in the studies were also taken into account.

### Inclusion and exclusion criteria

The publication year was refined to the custom range of 2010–2018. Articles that were older than ten years and were not in English were excluded. In search criteria, keywords like “*Lactobacillus reuteri*,” “probiotics,” and “colorectal cancer” were used in combination or alone to help find relevant articles for this review. The study populations included mammalian cell lines, mice, and rats. The information was gathered and tabulated by author name, year of publication, study design, study population, outcome, and results. The quality of articles was analyzed based on their “impact factor,” which is a measure of importance or rank of the journal calculated by the average number of times its articles are cited in other peer-reviewed research papers. The summary of the research articles used for this review is shown in the evidence table below.

### Table 1. Evidence Table

<table>
<thead>
<tr>
<th>Study details</th>
<th>Population and setting</th>
<th>Method of allocation</th>
<th>Outcome and methods of analysis</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authors: Blasingame, Camara A.; Billups, Leonard H.; Graham, omas; Henre, JaNell; Carter, Brianna; readgill, David W.; and Alexander, A. Deloris</td>
<td>University of North Carolina, Chapel Hill, Texas A&amp;M University</td>
<td>Mice were randomly assigned to controls, pre-treatment or post-treatment groups. Mice were examined after a 26-week latency period.</td>
<td>The bacterium L. <em>reuteri</em> was unable to prevent tumor formation in animals and this was an objective finding</td>
<td>Mice treated with bacterium alone did not show an increase in tumor formation. This was in comparison to animals that were in other treatment groups. The study determined that the bacterium did not alter morbidity in animals treated with AOM and this was quantified through tumor number, mortality, and penetrance.</td>
</tr>
<tr>
<td>Year: 2016</td>
<td>Eligible populations:</td>
<td></td>
<td>Method of analysis:</td>
<td>Limitations: There was a significant effect on gender with females having a higher tumor burden. There also were fewer females in the experiment, which could have skewed the results.</td>
</tr>
<tr>
<td>Citation: Blasingame, Camara A.; Billups, Leonard H.; Graham, omas; Henre, JaNell; Carter, Brianna; readgill, David W.; and Alexander, A. Deloris (2016) “Modulation of Colorectal Cancer by the Probiotic Organism <em>Lactobacillus Reuteri</em>,” Professional Agricultural Workers Journal: Vol. 3: No. 2, 3.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country of study: United States</td>
<td>Excluded population:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aim of the study: To determine if L. <em>reuteri</em> could protect mice from carcinogen-induced colorectal cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study design: Random trial</td>
<td>Human subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lactobacillus reuteri's role in the prevention of colorectal cancer: a review of literature

Authors: Chien-Chang Chen, Wei-Chuan Lin, Man-Shan Kong, Hai Ning Shi, W. Allan Walker, Chun-Yen Lin, Ching-Tai Huang, Yung-Chang Lin, Shih-Ming Jung and Tzu-Yen Lin

Year: 2012

Country of study: China

Aim of the study: To determine if tumor growth could be suppressed in colon cancer

Study design: Randomized control trial

Methods of analysis: The imaging revealed that there was a restriction of growth for L. reuteri. The histamine created by the bacterium slows gene expression and decreases inflammation. Cytokines in plasma can be reduced by L. reuteri. The findings of the study concluded that there was an increase in cell death and a down-regulation of mRNA and inflammatory molecules such as MHC class I.

Limitations: The study did not analyze different strains of La, which could limit their suggestions.

Citation: Authors. Year. Title. Journal of Pathology. Volume 187, Issue 1, pages 1623–1634.

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Authors: Chunxu Gao, Bhanu Priya Ganesh, Zhongcheng Shi, Rajesh Rasik Shah, Robert Fultz, Angela Major, Susan Venable, Monica Lugo, Kathleen Hoch, Xiaowei Chen, Anthony Haag, Timothy C. Wang, James Versalovic

Year: 2017

Country of study: United States

Aim of the study: To determine if histamine plays an important role in the suppression of inflammation-associated colon cancer.

Study design: Preclinical studies

Methods of analysis: The hdc gene produces histamine, which is important for the bacterium to reduce tumors when compared to the control. The histamine created by the bacterium slows gene expression and decreases inflammation.

Limitations: Histamine is only one of many microbial metabolites that can have a profound effect on human anatomy.

Citation: Authors. Year. Title. Journal of Pathology. Volume 187, Issue 1, pages 1623–1634.

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Authors: Melinda Anne Engevik, Berkley Luk, Anne Hall, Bhanu Priya Ganesh, and James Versalovic

Year: 2016

Country of study: United States

Aim of the study: To determine if L. reuteri decreases adherent tumor mucins and enhances chemotherapeutic susceptibilities via ERK/JNK pathways.

Study design: Experimental

Methods of analysis: The hdc gene produces histamine, which is important for the bacterium to reduce tumors when compared to the control. The histamine created by the bacterium slows gene expression and decreases inflammation.

Limitations: Histamine is only one of many microbial metabolites that can have a profound effect on human anatomy.

Citation: Authors. Year. Title. Journal of Pathology. Volume 187, Issue 1, pages 1623–1634.
Lactobacillus reuteri’s role in the prevention of colorectal cancer: a review of literature

**Authors:** Gao, C., Major, A., Rendon, D., Lupu, M., Jackson, V., Shi, Z., Mori-Akiyama, Y., Versalovic, J.

**Year:** 2015

**Citation:** Gao, C., Major, A., Rendon, D., Lupu, M., Jackson, V., Shi, Z., Mori-Akiyama, Y., Versalovic, J. 2015. Histamine H2 receptor-mediated suppression of intestinal inflammation by probiotic Lactobacillus reuteri. MBio. 2015;e01398-15.

**Country of study:** United States

**Aim of the study:** To determine if histamine could suppress intestinal inflammation with the administration of probiotics.

**Study design:** Experimental


**Year:** 2015

**Citation:** Kahouli I, Mahotra M, Tomaro-Duchesneau C, Saha S, Marinescu D, et al. (2015) Screening and In-Vitro Analysis of Lactobacillus reuteri Strains for Short Chain Fatty Acids Production, Stability and Therapeutic Potentials in Colorectal Cancer. J Bioequiv Availab 7:039-050. DOI: 10.4172/jbb.1000212

**Country of study:** Canada

**Aim of the study:** L. reuteri analysis of different strains for short-chain fatty acid production and the possible therapeutic benefits.

**Study design:** Research article

**Authors:** Liu, Y., Fatheree, N.Y., Manganese, N., Rhoads, J.M.

**Year:** 2010

**Citation:** Liu, Y., Fatheree, N.Y., Manganese, N., Rhoads, J.M. 2010. Human-derived probiotic Lactobacillus reuteri strains differentially reduce intestinal inflammation. Am J Physiol Gastrointest Liver Physiol. 2010;299:G1087-G1096.

**Country of study:** United States

**Aim of the study:** To determine if L. reuteri strains were able to suppress intestinal inflammation.

**Study design:** Experimental

**Authors:** Liu, Y., Fatheree, N.Y., Manganese, N., Rhoads, J.M.

**Year:** 2010

**Citation:** Liu, Y., Fatheree, N.Y., Manganese, N., Rhoads, J.M. 2010. Human-derived probiotic Lactobacillus reuteri strains differentially reduce intestinal inflammation. Am J Physiol Gastrointest Liver Physiol. 2010;299:G1087-G1096.

**Country of study:** United States

**Aim of the study:** To determine if L. reuteri strains were able to suppress intestinal inflammation.

**Study design:** Experimental

**Department of Pathology, Texas Children’s Hospital, Houston, Texas, USA**

**Eligible populations:** Human subjects

**Excluded population:** Human subjects

**All L. reuteri mice were prepared freshly before administration. Each mouse received diluted water with an equal volume of absolute ethanol. Adult female mice were fed L. reuteri, daily by oro gastric gavage following acclimatization and at least 5 days prior to TNBS installation.**

**Statistics:** Experimental results were expressed as means +/- standard errors and correlations were determined using the Pearson correlation method. Analysis of variance was used. Other data were presented as box-and-whisker plots showing the median, 10th and 90th percentile. Objective findings.

**Authors:** Mangalat, N., Rhoads, J.M. 2010. Human-derived probiotic Lactobacillus reuteri and Sprague-Dawley rat pups. The bacterium produced lactic acid and the production of SCFAs was strain-dependent. These fatty acids may actually be the reason this probiotic has inhibitory effects.

**Country of study:** United States

**Aim of the study:** To determine if L. reuteri strains were able to suppress intestinal inflammation.

**Study design:** Experimental

**University of Texas (UT) Medical School at Houston, TX**

**Eligible populations:** Human derived L. reuteri and Sprague-Dawley rat pups.

**Excluded population:** Human subjects

**Specific strains of the bacterium showed the ability to stunt growth of tumors. Short-chain fatty acids produced by the bacterium were viewed while the bacteria grew. The expansion of colon cancer cells with the administration of probiotics was evaluated using an assay.**

**Statistics:** SCFAs were calculated using linear regression equations from corresponding standard curves. Data were presented as means +/- standard errors and correlations were determined using the Pearson correlation method. Analysis of variance with Tukey’s comparison test and Student’s T-Test.

**Objective findings.**


**Country of study:** United States

**Aim of the study:** To determine if histamine could suppress intestinal inflammation with the administration of probiotics.

**Study design:** Experimental

**Faculty of Medicine, McGill University**

**Eligible populations:** Human epithelial CRC adenocarcinoma cell line Caco-2.

**Excluded population:** Human and mice subjects

**Cells were maintained in medium and supplemented with 20% fetal bovine serum. All cells were left to attach for 24-48 h in 96 well plates.**

**Statistics:** Experimental results were expressed as means +/- SE and one-way analysis of variance was used. A P value of <0.05 was considered statistically significant.

**Objective findings.**


**Country of study:** United States

**Aim of the study:** To determine if histamine could suppress intestinal inflammation with the administration of probiotics.

**Study design:** Experimental

**Department of Pathology, Texas Children’s Hospital, Houston, Texas, USA**

**Eligible populations:** Female mice (45 days old).

**Excluded population:** Female mice (45 days old).

**L. reuteri strains were able to control inflammation that was induced by the endotoxin LPS.**

**Statistics:** Experimental results were expressed as means +/- SE and one-way analysis of variance was used. A P value of <0.05 was considered statistically significant.

**Objective findings.**
Results

A 2012 cohort study by Chen was examined in which mice were orally pretreated with a Lactobacilli strain. This study sought to determine if probiotics can prevent CRC. They did the research using L. acidophilus, a strain of lactobacillus, to find out if it can increase cell death and halt cancer growth. The researchers used female mice aged 4 to 6 weeks old that were then divided into four groups. One group of BALB/c mice were inoculated with a colon cancer cell line CT-26 only; the next BALB/c group was pretreated with 1 x 10⁸ CFU and L. acidophilus for 14 days, before the administration of CT-26; the third BALB/c group was pretreated with 1 x 10⁸ CFU and E. Coli for 14 days, before administration of CT-26; finally, the fourth BALB/c group was not pretreated. 

Chen’s findings demonstrated that there was a 36% reduction in tumor volume in the mice that received the bacterium three weeks post-CT-26 inoculation, and a 42% reduction in tumor volume 24 days post-CT-26 inoculation. The researcher then used an analysis of variance to assess the findings. H&E staining of dorsal-lateral flank tumors suggested that oral administration of lactobacilli enhanced apoptosis of tumor cells due to the down-regulation of MHC class molecules, hence decreasing the extent of metastasis. Chen concluded based on these findings that probiotics play a pivotal role in modern healthcare and hold a promising future in treatment, prevention, and management of CRC.

In a comparative study, Kahouli used human epithelial colorec-
L. reuteri's role in the prevention of colorectal cancer: a review of literature

An experiment by Blasingame was conducted to determine if the bacterium L. reuteri could offer protection to mice that were exposed to a carcinogen from developing colorectal cancer. This randomized control study used mice models that were assigned to either treated or non-treated groups. The mice were injected with 10mg/kg bodyweight of Azoxymethane (AOM), which is a carcinogenic compound known to induce colorectal cancer in mice. The groups of mice were either given AOM alone or AOM and L. reuteri, L. reuteri alone, or neither. After a 26-week latency period, a total of 34 mice were euthanized and examined.15

Using analysis of variance on collected data, findings showed that while there was reduced tumor size with mice treated with L. reuteri, there was no change in mortality.16 Of note in this study, there were increased tumor numbers in female mice compared to males. For those treated with L. reuteri, in addition to the reduction of tumor size, it was noted that angiogenesis in these cells was also reduced, affecting cancer tissue establishment.16

Research done in 2012 combined the study of metabolites and bacterial genetics to investigate TNF-α inhibitory factors produced by the bacterium L. reuteri.17 The study found that histamine blocked TNF-α production by 80% when compared to the control.17 It was found that L. reuteri produces the biogenic amine histamine, which was identified and quantified in TNF-α inhibitory fractions using nuclear magnetic resonance (NMR) and mass spectrometry.17 The findings showed that histamine was able to suppress TNF-α production through the activation of a histamine receptor. This study demonstrated that lactobacilli were able to convert L-histidine into an immunoregulatory signal, histamine, which in turn suppressed the production of pro-inflammatory TNF-α production.17 While many previous studies used animal models, findings by Thomas were strengthened by the fact that the study was performed on human monoclonal cell lines.

Gao's research, concluded in 2017, investigated and analyzed results from histidine deficient mice. Histidine is a common amino acid that makes up histamine. Histidine deficient mice have a predisposition to carcinogenesis. To investigate whether histidine deficiency was linked to the increased cancer rates, Gao examined the relationship between survival rates, mortality rates, and genetic names.18 In the study, groups were divided based on their expression of histidine, and the data was then plotted and compared among 2113 patient samples of 15 data sets. Histidine deficient mouse-tail clippings were used for DNA extractions. L. reuteri was then cultured, and cells were centrifuged with this bacterium before the introduction of AOM. Fifteen weeks later, the mice were euthanized and cells from their ilea, ceca, and colons retrieved to determine mRNA expression of histidine. The findings indicated that L. reuteri administration increased the abundance of histamine in the HDC deficient mice.18 Elevated levels of the gene responsible for histamine production inferred a higher rate of survival in the case of CRC (P = 0.02).

Gao in 2015 investigated whether L. reuteri had any effects on intestinal inflammation in trinitrobenzene sulfonic acid (TNBS) induced mice models.19 L. reuteri collected from the breast milk of women was used to colonize the mice. Colitis caused by TNBS produced different cytokines in the colon of mice that were then quantified based on their mRNA expression. Data was collected, measured, and then analyzed using a T-test and analysis of variance. This study further supported that histamine was shown to play an essential role in suppressing colonic inflammation. The histidine-posi
tive strains contained human TNF-α production by myeloid cells.19 Adjunctively, PET scan imaging was also used to offer visuals on the ability of L. reuteri to suppress intestinal inflammation.

It was determined that when the bacterium was suppressed, it was unable to decrease intestinal inflammation as determined by weight loss and Wallace scores for colitis, and demonstrated a significant decrease (p<0.05) in both categories.19 A cohort study was done in 2010 by Liu which demonstrated similar findings, showing that different strains of L. reuteri can differentially control LPS-induced inflammation.20 These researchers explored the effects of the bacterium on the rats. Further supporting previous studies, the L. reuteri used were also gathered from the breast milk of Finnish women. Newborn rats were separated from their mothers and given either a unique rodent formula, a formula containing L. reuteri, a formula containing LPS from E. coli, or LPS in combination with one of the four designated strains of the bacterium.20 After this, the rats were euthanized, and their terminal ilea were excised and examined.

In addition, the study by Liu et al. demonstrated and further supported the findings of Gao that multiple strains of L. reuteri can inhibit LPS induced IL-8 secretion.20 The mRNA expression of IL-13 (expressed by CD4 helper T cells) was also significantly decreased in the intestines of rats that were fed with a formula containing the bacterium. The findings demonstrated that histamine was produced by L. reuteri strain 6475, and that histamine inhibits TNF-α production, a cytokine.20 Histamine further increased the intracellular cAMP and histamine signaling through histamine receptors that blocked the activation of downstream signal cascades that ultimately decreased TNF-α production.

The random trial completed by Engevik suggested that probiotics increased tumor cell susceptibility to 5-Fluorouracil (5-FU) treatment, a chemotherapeutic drug. The results showed a significant decrease in cancer cells.21 Engevik also showed that after inoculating a mucus-producing adenocarcinoma cell line with probiotics, those that had been pre-treated with L. reuteri and Bifidobacterium species were able to reduce the level of inflammation by decreasing the ability of adherent and secreted mucus expressed.
More specifically, in this particular case, *L. reuteri* ATCC 6475 was found to be capable of altering the amount of mucin (this was determined by immunofluorescence).\textsuperscript{21} 

Verma in 2013 explored the importance of lactobacilli as a prophylactic agent against colon cancer.\textsuperscript{22} This study used Dawley rats to illustrate how one's diet can be a contributing risk factor for CRC. In the study, different probiotics were used for their protective potential against 1, 2 dimethyldihydrazine (DMH) induced colon carcinogenesis.\textsuperscript{22} The animals, which were placed in groups, were fed the probiotic for one week and then were injected with DMH. Results showed a significant decrease in tumor counts in the rats that were pretreated with the bacterium.\textsuperscript{22} 

Also similar to previous studies used in this review, Verma used Sprague Dawley rats that were orally fed with 1 x 10\textsuperscript{8} lactobacilli daily for one week and then injected with dimethyldihydrazine (DMH), a carcinogen used to induce cancer.\textsuperscript{22} For the rats pretreated with lactobacilli and DMH, a significant decrease in tumor counts was noted when compared to the DMH treated rats.\textsuperscript{22} The findings of this research and others used in this review are summarized in table 1 above. Notwithstanding the different methods and approaches used in said studies, they demonstrate typical results supporting the hypothesis of this review.

**Discussion**

While examining the relevant literature, it was evident that the results strongly supported the argument that the administration of the bacterium *L. reuteri* can prevent colorectal cancer in certain cell lines and animal models by inhibiting tumor progression. This finding needs to be further explored in human trials. The only study that contradicted the findings was Blasingame, which showed that the bacterium did not significantly alter morbidity in AOM treated animals, as measured by tumor number, mortality, penetrance, or multiplicity.\textsuperscript{16} However, the findings also showed that there was a significant effect along gender lines, with females experiencing a higher tumor burden compared to males. That said, there also was a smaller number of females used in the study, which could have skewed the results.

The other studies in this review suggest that the bacterium *L. reuteri* can decrease inflammation by inhibiting mediators such as IL-8 and TNF. Inflammation plays a crucial role in the pathogenesis of cancer. As the study by Engevik demonstrated, histamine from *L. reuteri*, specifically strain 6475, stimulated increased levels of cAMP, a well known second messenger that plays a role in signal cascade (MEK/ERK MAPK signaling via protein kinase A. Inhibition of this pathway resulted in the suppression of TNF-α production, an important cytokine secreted by macrophages and responsible for activating endothelium.\textsuperscript{21} Furthermore, increased cAMP causes leukocyte extravasation and vascular leakage. Thus, when TNF-α is inhibited, there is a reduction in inflammation, thereby decreasing the progression of carcinogenesis responsible for CRC.

The study by Chen et al. in 2012 demonstrated that oral administration of lactobacillus reduced tumor growth and the extent of tumor invasion into local tissues. The study also showed that *L. reuteri* enhanced the apoptosis of cancer cells by down-regulating MHC class 1. Apoptosis is the phenomenon of programmed cell death, which can be activated by two pathways: either the intrinsic or the extrinsic pathway. Both pathways utilize caspases, functioning on eliminating cells. These pathways are essential in getting rid of cells that are no longer functional, thereby decreasing the risk that they could become cancerous. BAX and BAK are pro-apoptotic proteins that encourage the apoptosis of cells, whereas Bel-2 prevents apoptosis. MHC class 1 molecule is found on the surface of most nucleated cells and presents antigens to CD8+ cytotoxic T cells, which are cells that directly kill virus-infected cells. Reduction in tumor growth and enhanced apoptosis strengthened the researchers’ resolve that the administration of the bacterium can prevent CRC. However, this study showed two limitations; only female mice were used, which may introduce a selection bias into the study, and the researchers did not analyze the different strains of lactobacilli.

According to Gao, histamine is one of the many microbial metabolites that can have a profound effect on humans and showed that *L. reuteri* increased hdc gene expression and histamine production in the intestines of the histidine deficient mice.\textsuperscript{15} The hdc gene is crucial as it reduced the number and size of colonic tumors in mice that were treated with specific strains of *L. reuteri*.\textsuperscript{15} The histamine generated by the probiotic caused suppressed cytokine gene expression, which down-regulated inflammatory mediators and therefore decreased colonic inflammation.

Gao and colleagues’ study findings further strengthened Gao’s argument by showing that hdc+ *L. reuteri* did indeed suppress inflammation in the colon by decreasing cytokine gene expression.\textsuperscript{19} They also noted that H2 histamine receptors are found predominately in the mammalian gastrointestinal tract, which further strengthens this argument. A drawback to this finding is that the mechanism behind the phenomenon displayed here is not well understood, as there is limited information on probiotic-mediated immunomodulation in vivo.\textsuperscript{19}

Further support of histamine production by *L. reuteri* and decreasing carcinogenesis by inhibiting TNF-α production via H2 receptor activation downstream and cAMP was demonstrated by Liu in 2010. As mentioned in the above sections, TNF-α contributes to acute inflammation through the recruitment of white blood cells. Thomas’ research in 2017 complimented Liu’s study findings as they also found that histamine was responsible for the decrease in inflammation in CRC cells.

The study by Gao in 2015 showed that *L. reuteri* reduced inflammation by inhibiting LPS induced IL-8 production in cultured intestinal epithelial cell lines in rats. LPS is a pathogen-associated molecular pattern (PAMP) found on gram-negative bacteria, which helps in eliciting an immune response when detected in the human body. LPS is an endotoxin comprised of a polysaccharide and Lipid-A. LPS induces multiple effects in the body, including edema, neutrophil chemotaxis, shock, and macrophage activation. Reducing LPS expression would reduce the inflammatory response in the body. Gene expression of Interleukins 1 and 6, mediators of acute inflammation, was measured in the colons of healthy mice, and suggested a significant decrease (p<0.05) after pretreatment with *L. reuteri*.\textsuperscript{19}

Engevik’s study showed how adherent mucins play a role in the pathogenesis of cancer. The study then demonstrated that Lactobacillus species were capable of altering total adherent mucin by stimulating the release of stored mucin.\textsuperscript{21} It was found that these adherent mucins caused an increase in Sialyl-Lewis X expression. Sialyl-Lewis X is a trisaccharide antigen that serves as a ligand for Lipid-A. LPS and the bacterium did indeed suppress cAMP, which in turn reduced inflammation in CRC cells. The study by Chen et al. in 2012 demonstrated that oral administration of lactobacilli reduced tumor growth and the extent of tumor invasion into local tissues. The study also showed that *L. reuteri* enhanced the apoptosis of cancer cells by down-regulating MHC class 1. Apoptosis is the phenomenon of programmed cell death, which can be activated by two pathways: either the intrinsic or the extrinsic pathway. Both pathways utilize caspases, functioning on eliminating cells. These pathways are essential in getting rid of cells that are no longer functional, thereby decreasing the risk that they could become cancerous. BAX and BAK are pro-apoptotic proteins that encourage the apoptosis of cells, whereas Bel-2 prevents apoptosis. MHC class 1 molecule is found on the surface of most nucleated cells and presents antigens to CD8+ cytotoxic T cells, which are cells that directly kill virus-infected cells. Reduction in tumor growth and enhanced apoptosis strengthened the researchers’ resolve that the administration of the bacterium can prevent CRC. However, this study showed two limitations; only female mice were used, which may introduce a selection bias into the study, and the researchers did not analyze the different strains of lactobacilli.

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selectins. Increased numbers of these ligands lead to an increase in metastatic capacity of colon cancer cells. L. reuteri Engevik found that mice colonized with L. reuteri had decreased mucin levels.

Limitations

The limitations of each study have been detailed, where applicable in the results section above. For example, in Gao et al.’s 2015 study, even though it concluded that L. reuteri reduced the number and size of colonic tumors, it is important to note that they examined only certain strains of the bacterium and this could limit its applicability to only the specific strains that were used. As for Gao et al. 2017, the study only used four separate mouse pups, two males and two females, which is not a sufficient sample size.

For this review, considering that studies in languages other than English were excluded and that studies included in the review ought to have been published recently narrowed down the amount of data and pool of resources available to help support or disprove the hypothesis of this study. Also, the use of only free-access publications available on the MEDLINE database further reduced the pool of data that the researchers could have access to in order to strengthen the case for L. reuteri’s use as a critical probiotic. These researchers are of the view that more research is needed to further investigate L. reuteri in the treatment of CRC in humans. More funding should be made available, and the body of knowledge about this promising probiotic further explored.

Conclusion

In closing, the findings of this review support the hypothesis that states, "Lactobacillus reuteri facilitates in the prevention of colorectal cancer through inhibition of tumor progression in animal models." Results in various studies above show that L. reuteri is critical in the inhibition of tumor progression through its ability to halt the progression of tumors and to decrease inflammation, which would otherwise progress to uncontrolled growth and metastasis.

This research helps expand the body of knowledge on a topic that is heavily underresearched considering the encouraging outcomes thus far. Probiotics are a promising healthcare resource. In this case, we recommend that further research be pursued to investigate L. reuteri’s capacity to decrease susceptibility to tumors and to decrease immune response and inflammatory mediators like TNF-α in the human form of CRC. For instance, we recommend that studies in the future focus on how L. reuteri interferes with the binding of selectins to mucin. This finding shows a promising breakthrough in CRC management, especially when it comes to therapeutic and prophylactic treatments. Probiotics could eventually play a significant role in cancer treatment, possibly as adjuvant therapeutic and prophylactic treatments.

References

The Journey to Ancient Ithaca: addressing the diagnostic odyssey of rare disease through systems-level interventions

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Abstract
The “Diagnostic Odyssey” is a common pathway of misdiagnosis and diagnostic delay that many patients with rare diseases find themselves forced to negotiate, just as Homer’s character Odysseus struggled for an entire decade after the Trojan War to return home to Ithaca. Rare diseases are to some extent, by virtue of their rarity, always going to resist diagnosis. Nonetheless, there are several interventions that we can implement in the healthcare system to limit the delays and frustrations that patients with rare diseases experience between the onset of their symptoms and the initiation of treatment for a correctly diagnosed condition. These include adaptation of medical education to better reflect the integration required in the environment of modern healthcare, the uptake of new technologies and in-practice resources directed at diagnosing rare disease, and the utilization of patient navigators to accompany patients and advocate for them on their journeys to diagnosis. The “Diagnostic Odyssey” therefore represents an actionable target for all healthcare providers – and students – to work towards eliminating.

The case of JS is not unusual, except that her diagnosis of EGPA was made relatively rapidly: a 2016 study by Cottin et al. quotes the mean length of time from the onset of asthmatic symptoms to diagnosis as 11.8 years with a standard deviation of 18.2 years. EGPA is not unique in this regard. The path to diagnosis for rare diseases is commonly long, and it is weathered by ailing patients who spend years seeking a cause for their symptoms. For example, the average delay from symptom onset to diagnosis of CHC cobalamin metabolism defects is reported to range from 3 to 240+ months, and this same delay for early-onset dementia averages 4.4 years. Rare diseases are typically defined by a population frequency of 1/2000 persons or less, but these conditions affect more than 3 million Canadians. The diagnostic odyssey – a common pathway of misdiagnosis and diagnostic delay that many patients with rare diseases find themselves forced to negotiate – is a widespread, frustrating, and harmful misadventure.

The etiology of the diagnostic odyssey is multi-factorial and, unfortunately, many of these factors resist elimination. Intuitively, physicians are better prepared to recognize common diseases; both because their training likely focuses on those afflictions which they can expect to see more frequently, and because once in practice their clinical experience statistically affords them less exposure to rare diseases. Consequently, physicians are inherently not as well-equipped to diagnose and treat uncommon diseases.

Despite this barrier, the diagnostic odyssey is in many ways actionable from a systems perspective. Even if some amount of delay in the diagnosis of rare disease cannot be altogether extinguished, there are several levels at which carefully designed interventions can contribute to reducing the time patients with rare diseases spend struggling to find validation and treatment for their symptoms. Some of the interventions for which effectiveness has already been demonstrated include: the incorporation of probabilistic diagnostic decision support systems – such as IBM’s artificially-
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intelligent supercomputer, Watson9 – in clinic settings, which suggest the possibility of rare diseases on the basis of consistency with case presentations;10,11 the use of specialized search engines such as FindZebra, which have been demonstrated as more effective tools for diagnosing rare diseases than non-specific search engines such as Google or PubMed;12 the creation of centers specifically focused on the diagnosis and treatment of rare diseases, like in China, have been credited with enabling a faster escape from the diagnostic odyssey;13 and new technologies such as next-generation DNA sequencing have demonstrated efficacy for making diagnoses of rare diseases with high sensitivity and high specificity, presenting – especially as costs decrease – a possible future for panel testing in uncertain cases.14 In parallel with these advances, there appears to be a role for education: an international survey performed in 2013 indicated that a majority of physicians felt that additional training around rare diseases would support faster diagnosis.14

The perpetual diagnostic odyssey warrants continued development and adoption of new ideas to reduce the time-to-diagnosis for patients with rare diseases. The demonstrated utility of these previously-tried interventions does, however, illuminate several of the core causes of delayed diagnosis: a lack of integrative provider education, limited resources that proffer easy access to information on uncommon conditions, and a medical system structure in which patients can “fall through the cracks”. This present article aims to highlight and provide perspective on the future of this task, through the suggestion of several novel interventions which have not been previously proposed or studied. For physicians, these interventions include updates in medical education with a greater focus on integration, as well as the utilization of new-in-practice diagnostic tools (not unlike those which have previously been successful) designed to help address rare diseases. Beyond physicians, there is also a unique role in rare disease medicine for patient navigators, in aiding patients during their journey to diagnosis.

Medical education can perpetuate the diagnostic odyssey by presenting medicine in silos. In traditional block curricula such as that described by Li et al (2018) with reference to Chinese undergraduate medical education (representative of many countries’ training programs), students learn topics related to one body system or one specialty before moving on to the next.15 In the United States, this same format has been demonstrated to effectively teach the information within each block, but discourage integration across these blocks.16 Our training appears to divide us into experts of disparate fields, with a more limited understanding of the interfaces between them.16,17 Consequently, it is my experience that students graduate into a practice in which they struggle to form cohesive teams with specialists of other areas. This is compounded by the bureaucracy that underpins the healthcare system and preserves the division between the silos in which we find ourselves. In a hospital setting, I have observed specialists in one field argue with those in another about who ought to be responsible for a patient’s care. We fax referrals and seldom follow up to make sure they were received – a large proportion of referred patients do not even appear to ultimately see the provider they were referred to.18,19 At times, it is possible that the tension between resource stewardship (which includes limiting unnecessary referrals) and quality patient care can contribute to diagnostic delays.20 It is inevitable that no one provider can know everything, and therefore be in a position where they can easily diagnose rare diseases with multi-system presentations, but it is reasonable to expect that through improved connectedness, we will be able to limit those spaces between specialists where patients on the diagnostic odyssey are temporarily or permanently lost to follow-up. At the level of medical education, this means a greater focus on healthcare systems integration. This may involve a departure from block-based curricula to an alternative such as a “spiral curriculum – a method characterized by repetitive exposure to topics on a longitudinal basis, which has been evidenced in some settings but not yet studied in the context of rare disease education16,21 – as well as increased training around what circumstances would warrant casting a wide diagnostic net to appropriately bring in specialists from many fields in order to make the diagnosis of a rare disease.

For those already in practice, several novel tools now exist to aid physicians in recognizing and diagnosing rare disease. Orphanet, for example, is a resource dedicated to mapping out rare diseases in ways which are accessible to health providers, patients and families, and researchers.22,23 By leveraging technological innovations like intelligent search algorithms and mass information storage, these types of databases can put a wealth of information about rare disease at the fingertips of all stakeholders who participate in the diagnostic odyssey.23 These resources yet experts to contribute information on rare diseases, and make it available to everyone through search engines specific to uncommon diseases.23 For physicians in practice, utilizing resources like Orphanet when the possibility of a rare disease arises can shorten the time from symptom onset to diagnosis for patients with unexplained presentations (and who have already, unfruitfully, seen several specialists).

Finally, a third intervention which can alleviate the diagnostic odyssey is the implementation of patient navigators, particularly those with specialized training in the context of rare diseases. These professionals can help patients to negotiate the labyrinthian medical system, in which it is easy to get lost between providers, guiding them through their diagnostic journey and advocating for those patients who are temporarily forgotten within the system.24 Patient navigators comprise a relatively new profession within the medical system, but one already evidenced to bolster the continuity of patient care and help to connect patients with the right resources – whether that is the appropriate doctors or reliable sources of information.25 It is known that patients with undiagnosed rare diseases tend to have many physicians involved in their care, which can make for a confusing medical record and increasing diagnostic uncertainty.26 In these circumstances, there is a unique role for patient navigators to forge therapeutic relationships with patients so that they do not have to navigate the diagnostic odyssey alone.

The diagnostic odyssey associated with rare disease is a consuming journey that begins surreptitiously, for many patients, beginning with the onset of a first symptom. It is a major contributor to dissatisfaction with the healthcare system, and also to morbidity and mortality in the context of diseases for which treatment delays can be of great consequence.28 Describing the intuitive nature of delayed diagnoses for diseases which are unfamiliar to physicians, we can – by embracing integrative medical education, creating and utilizing high-quality resources geared towards rare disease diagnosis, and accepting help from other professionals such as patient navigators – develop our environment into one which more effectively serves the patients who are negotiating the twists and turns of elusive diagnoses. In the Odyssey of each patient, these inter-
ventions represent opportunities for us to help an individual reach their diagnostic Ithaca.

References
Dr. Susan Poutanen is a pioneering microbiome researcher, microbiologist, and infectious disease physician. She is the co-principal investigator of the Microbiota Therapeutics Outcome Program – an interdisciplinary initiative which fosters multiple clinical and academic projects around the use of microbiota transplants. Her own diverse research encompasses gastrointestinal dysbiosis, antibiotic resistance, rapid diagnosis, and application of artificial intelligence.

Dr. Poutanen is graduate of the University of Toronto’s Medical School, where she also completed her residencies in Internal Medicine and Medical Microbiology. She went on to complete an infectious disease fellowship at Stanford University and a Masters of Public Health, with an emphasis on Epidemiology, at the University of California at Berkley.

UTMJ: Thank you for sitting down with the university of Toronto Medical Journal. Before we get started, would you mind introducing yourself?

SP: I'm Susan Poutanen, medical microbiologist and an infectious disease physician here at the University Health Network, Sinai Health, Department of Microbiology; also affiliated with the University of Toronto, in the Laboratory Medicine and Pathobiology Department, and the Department of Medicine.

UTMJ: You’re one of the co-principal investigators with the Microbiota Therapeutic Outcomes Program. Could you explain what this program is?

SP: We call it MTOP for short. It’s a program that we initially developed with Dr. Susy Hota and myself as co-leads, initially for the care of patients with recurrent C. difficile infections. It was basically a program that we would be able to have both donors being able to provide samples of fresh fecal materials that we could then use to make fecal transplants for our patients with recurrent C. diff. We also recognized that there was a need and a research interest at the University of Toronto to also provide FMT for other indications that were being investigated. So, we initially built it for our clinical needs, and then realized that expanding it to offer researchers other non-clinical needs would be helpful – so we went ahead and did that, and we ourselves are also pursuing other indications for FMT in our own research.

UTMJ: How does the research model of the Microbiota Therapeutics Outcome Program unique and, in your experience, why is this structure beneficial?

SP: For one, the infrastructure to set up a fecal matter transplant program is actually quite substantial, involving a number of different logistical elements. Just from an efficiency perspective, once there’s a system set-up, it makes sense to make it a regional system to address multiple needs. But, the program that we have here at U of T is unique in that it really facilitates cross departmental interest in being able to utilize FMT as a potential resource. It’s not just with regard to humans, we also create FMT for mice, for example. We are collaborating with a number of different investigators at U of T, some of which are immunologists looking at mice models of FMT benefits, others of which are looking at benefits of FMT for different clinical indications in humans, like bipolar disorder, obesity and metabolic syndrome and then our own interest, looking at potential using it to eradicate carriage of antibiotic resistance organisms. So, it allows for that cross-fertilization across a lot of different disciplines, in different areas.

For our own interests, certainly as an infectious disease microbiologist – I haven’t usually delved into psychiatry or endocrinology or hepatology, so it’s very informative to work with other colleagues who are of a different primary interest. […] And we’re at a point now where we could argue that infectious disease spans into many disciplines, beyond the classic ID/microbiology.

UTMJ: Other researchers, and really the public at large, have increasingly demonstrated an interest in fecal microbiota transplant. Have you experienced any challenges in communicating with the public about this therapy, and if so, what misconceptions have you found you’ve come up against?

SP: It’s interesting when you think about fecal transplants,
Interview with Dr. Susan Poutanen

because we thought that our patients, being the first public that we interact with, would have been the first to have that ‘ick factor’; and yet, because of how sick our recurrent C. difficile patients are, we actually didn’t see that. We had patients asking for this before we could even provide it, and there was not an ‘ick factor’ whatsoever in their minds. They simply recognized the challenges of what they were living with in terms of recurrent symptoms, and so we didn’t see that so much.

In communicating to the public at large, it’s interesting because we had a volunteer with us who was a non-medical professional and she was just incredibly impressed with the use of something that she normally flushed down the drain […] as a clinically useful therapeutic. She actually reached out to us, and her roommate happened to be someone in the public relations area and she was so interested that she ultimately uses us as a case for classes to really share with non-medical people. So again, there’s no ‘ick factor’ whatsoever. If anything, there’s an interest to help and promote the knowledge of MTOP, and to help get more donors to help support the program.

I think when folks initially think about it, there may be an early thought that this should be something that’s not looked upon very highly, but in fact there seems to be a real acceptance. I think that part of it maybe that with social media - there’s a whole lot more dialog and interplay between the medical community and the public. There’s a large interest, as well, looking at natural therapeutics, and this certainly falls into that, so I think there’s a different acceptance nowadays than perhaps 20 - 25 years ago.

UTMJ: The World Health Organization highlights that Antibiotic Resistance is a growing health concern. How do treatment strategies, such as those provided by MTOP, provide an alternative to antimicrobials?

SP: It’s definitely an ongoing concern and looking for alternate therapeutics is where a lot of folks are going to, because of this ongoing battle of creating a new drug, and having resistance, and this whole chicken-egg challenge. What’s certainly beneficial about fecal transplant is that there’s the potential that it can be utilized to eradicate resistance and carriage of resistant organisms. We haven’t necessarily had definite studies, but if that were to be shown that it’s beneficial, then you have a non-therapeutic means of essentially replacing one’s microbiota with a resistant form. So, you have the potential to avoid antimicrobials. […] It’s a potential game changer all together, in terms of really changing one’s microbiota, so we don’t have the same concerns of resistance, or resistant infections – but, we’re not quite there yet. I think there’s a lot more work that needs to be done, but it’s certainly promising.

UTMJ: Interest in research in the microbiome has been growing exponentially, so in what directions do you foresee this field heading in?

SP: You’re completely right, it’s really going into all different disciplines. At this point, I think we’re still exploring all the different areas where there are purported associations, and I, right now, see it continuing to expand into different fields. I don’t see it limiting just yet. Certainly, we’re just getting data from some of the original mouse and human studies that are ongoing. We’ll have a better understanding if this is more hype and hope than reality. I don’t think we have the definite data just yet to really say that this is all hype, and there isn’t really data about which way to go just yet, so I suspect that it will continue to expand. We’re seeing it now in GI, hepatology, we’re seeing it in endocrinology, in psychiatry, in infectious diseases and there’s a lot of discussion with regard to cardiovascular disease as well as autoimmune disease - it can go on and on and on. At this point, I think it’s still very much open to all disciplines to explore.

UTMJ: That concludes our questions. We wanted to say thank you for sitting down with us. As medical students, we’re excited about the field of the microbiome and learning from an expert such as yourself.

SP: It’s my pleasure.
Interview with Dr. Rob Kozak

Dr. Rob Kozak is a Clinical Microbiologist at the Sunnybrook Health Sciences Centre and the University of Toronto. He received his Doctor of Philosophy (PhD) in Microbiology and Immunology from McGill University in 2010. Since then, he has worked across the nation studying viruses such as Ebola, Crimean-Congo Hemorrhagic Fever Virus, Zika, and now SARS-CoV-2. Alongside Dr. Samira Mubareka and Dr. Arinjay Banerjee, Dr. Rob Kozak managed to isolate SARS-CoV-2 and is now at the forefront of studying the virus to hopefully develop a vaccine.

UTMJ: How did you get involved with the project to work on isolating the virus?
RK: Sunnybrook cared for Canada’s first patient with SARS-CoV-2. From that first case to now, we have been fortunate to have excellent leadership, where we have had opportunities and been given resources to merge the clinical findings and the science. Dr. Mubareka (a clinician-scientist with a track record in coronavirus research) and I decided after that first case that isolating the virus was our top priority. We knew if this were possible, then we could share it with other labs for research as well as for use in diagnostic assays. Dr. Banerjee, a top-notch post-doctoral fellow from McMaster who also has done work on MERS-CoV, joined our team and we got to work on it.

UTMJ: What was the hardest part of isolating the virus?
RK: Although I have isolated novel viruses in the past, for me it is always the waiting. Cells are infected and then you have to wait a few days to see if there is cytopathic effect, indicating the virus is growing. Then you confirm the virus is there with PCR and eventually whole genome sequencing, all of which takes time. You wonder if it is going to be successful, or if you’re going to have to start again from scratch. We really felt this pressure, since all the time you know that there are a lot of people who need to start working with this virus to start understanding pathogenesis and testing therapies. Our team was really lucky to have an expert like Dr. Banerjee with us, his experience really helped get things done faster.

UTMJ: How is research coordinated and expedited during pandemics?
RK: It is certainly a bit of a balancing act. Clinical duties take priority – which in a microbiology lab means we needed to continue with our day-to-day responsibilities, while working with our hospital colleagues to coordinate SARS-CoV-2 testing. Research is mostly done in your spare time, which means a lot of evenings and weekends (and luckily, I have a very supportive partner). I’m grateful to work with a team of clinicians and scientists and this has really helped spread the work around and get it done quicker.

UTMJ: When do you suspect we will be able to develop a vaccine to SARS-CoV-2?
RK: Most vaccine candidates are currently in preclinical development, but a few have progressed to Phase I (safety stud-
It’s been really exciting to see how quickly the global scientific community has come together to put forward multiple approaches and platforms. I’m working with Dr. Gary Kobinger, who developed a vaccine against Ebola virus, as well as other scientists in Quebec to develop and test promising candidates. I know how experienced the team is, and how hard everyone is working, so this gives me great hope. I would like to be optimistic and say that there will be vaccine candidates in Phase III trials in the next 8-12 months.

**UTMJ:** What is the process of development like and what are some of the main barriers?

**RK:** There are multiple strategies for vaccine development, including using different parts of the virus so the body can “recognize” it later, as well as different delivery systems to generate an immune response. One of the major challenges is predicting which combination is going to be successful for a given pathogen. For example, there are a few chronic viruses that to date, and not for lack of trying, scientists have not been successful in generating a protective vaccine (namely HIV and hepatitis C). Nonetheless, one strategy is to select an antigen from the virus (a protein) and put that antigen into a vaccine platform for delivery. This can be a viral vector (like adenoviruses) or DNA (like a plasmid) or a protein (like what is done with the influenza vaccine). Our group has completed this first stage, and now we are moving on to evaluate whether the vaccines induce a strong immune response in animals, and whether it is protective when animals are challenged with SARS-CoV-2. We are using titred virus stock for this – another reason why isolating and growing the virus from patients was so important. Following safety and efficacy studies in animals, it will then be studied for safety among healthy human volunteers. Phase III studies in humans is where it is determined whether the vaccine is actually protective. Each phase of the development and testing in animals and humans takes time. You have to vaccinate and then wait. Timing, dosing (whether additional doses are needed, time to protection), and production are the next steps. The good news is that there are many groups working on this all over the world, so I’m optimistic we are going to have 3 or 4 really great vaccines against SARS-CoV-2.

**UTMJ:** What current therapeutics are being tested to treat COVID-19?

**RK:** Some clinical trials for therapies among very sick patients have already been published. Many more are underway both for outpatients (patients who are positive, but well enough to be sent home to isolate) and for patients who require hospitalization. The clinical trials thus far are looking at a range of different drugs and approaches. Some are experimental, like the antiviral Remdesivir; and some are drugs that are being repurposed, such as chloroquine. There are also currently several trials using convalescent sera from patients who have recovered from COVID-19.

All of this is very exciting since Sunnybrook is involved in several of these trials, so I am working with many motivated healthcare providers all of whom are working to find treatment options. As a microbiologist it is great to play a small role in these studies by supporting testing during the trials.

**UTMJ:** Can you speak to the collaboration between different nations and groups across the world that led to isolating the virus?

**RK:** Since the first cases in Canada, we have really seen collaboration and knowledge sharing between with both Canadian and international groups. As an example, when we started working to isolate the virus, I reached out to scientists Dr. Julian Druce and Dr. Ian Macaky in Australia. These groups had recently isolated the virus from patient samples there. They were extremely collaborative and shared protocols and recommendations. It saved us a tremendous amount of time to not have to start from scratch and optimize protocols to be successful. I also received support and suggestions from colleagues in China.

Now we are working to characterize the virus in different cell lines, and have been fortunate to have colleagues in Toronto, Guelph, and Quebec who have shared cell lines without hesitation.

It’s truly inspiring to see many groups sharing knowledge and resources. That’s how we are going to beat this thing!

**UTMJ:** What advice do you have for Canadians during this uncertain time?

**RK:** Be hopeful and work together, these are characteristics that make Canadians great. There are many people working hard on the front lines, including, but not just, healthcare providers. Individuals in these settings are giving 110%. We’ve seen some truly inspiring efforts by Canadians to help support each other in any way they can and helping those in need to the best of their ability. From a research perspective, scientists in Canada and all over the world are learning more about the virus everyday—so staying positive that there will be vaccines and therapeutics in the near future is important. Lastly, we need to continue to follow the advice of public health experts (even if it changes over time), to ensure we keep working together to end COVID-19.
**Interview with Dr. Vinod Chandran**

*UTMJ Interview Team (Happy Inibhunu and Jeff Park)*

Dr. Vinod Chandran, MBBS MD DM PhD, a rheumatologist and clinician-scientist, is an Associate Professor of Medicine & Laboratory Medicine and Pathobiology at the University of Toronto, an Adjunct Professor at the Memorial University of Newfoundland, an affiliate scientist at the Krembil Research Institute, a member of the graduate faculty at the Institute of Medical Science, University of Toronto, a scientist with the Creative Destruction Lab, Rotman School of Management, University of Toronto and a staff physician at the University Health Network and Mount Sinai Hospitals. He co-directs the Psoriatic Disease Program at the University Health Network, Toronto, Canada.

Dr. Chandran’s research interests lie in the genetic and molecular epidemiology of psoriasis and psoriatic arthritis (PsA), especially with regard to prognosis. His translational research program is focused on developing proteomics and metabolomics-based screening and prognostic tools for psoriatic arthritis. His bench research aims to identify mechanisms underlying inflammation and joint damage in psoriatic arthritis and develop novel topical and systemic anti-psoriatic therapies. He is also investigating the cutaneous microbiome in psoriasis and PsA and its relationship to psoriatic disease phenotype and genotype. He is a member of the executive committee of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis. He is an active collaborator in multi-centre research consortia such as the International Psoriasis and Arthritis Research Team and the Spondyloarthritis Research Consortium of Canada and aims to conduct validation studies of discoveries made at his program through these collaborations.

**UTMJ:** Can you tell us a little bit about yourself as a physician and clinician-scientist?

**VC:** I am a rheumatologist, who takes care of patients who have arthritis and other related diseases. I came to Canada many years ago to do my fellowship on psoriatic arthritis. In my field, you are always looking for reasons why some patients get arthritis. With psoriatic arthritis, people get skin disease first and then usually within 10 years, they develop inflammatory arthritis that affects the joints in their hands, feet and spine. So, I thought psoriatic arthritis would be a good model to study the early pathogenesis of arthritis. Most of my work during my PhD and fellowship involved studying immunity-related genes, especially the human leukocyte antigen (HLA) genes. I have since continued to work on identifying genes as well as proteins and metabolites associated with development and progression of psoriatic arthritis.

**UTMJ:** What is the current state of your research on the topic of HLA and its relationship with the onset of psoriasis?

**VC:** We have shifted our focus from not just looking at HLA, but genes outside the HLA region as well in an unbiased manner. We have conducted genome-wide association studies by developing a large research network, including our research team here at the University of Toronto, University of Michigan, Memorial University of Newfoundland, as well as University of Rochester, New York. We have a large cohort here in Toronto where patients have been carefully and systematically evaluated. We use their data to find genes and other markers that are the most relevant to psoriatic arthritis.

Subsequent to that, we started investigating other factors that may cause the disease. Psoriatic arthritis is a complex disease, which means there are multiple factors at play, genetic factors being just one. Early studies done by one of our colleagues showed that infections, especially the ones that require treatment with antibiotics, are more likely to result in psoriatic arthritis. The question was whether the infection or the antibiotic treatment (that may have altered the microbiome) triggers psoriatic arthritis. We still don’t have a definite answer to this question.

The question is whether gut dysbiosis occurs before or after the development of psoriatic arthritis. A colleague of ours in New York is working on this at a large gut microbiome centre. We have not begun such a study here yet, but will do so soon, in collaboration with a large research team investigating inflammatory bowel disease (IBD) here in Toronto. The link between IBD and psoriatic arthritis is interesting. Psoriatic arthritis and psoriasis have been shown to be linked with Crohn’s disease in familial studies. So, if you have psoriasis, you are also more likely to get Crohn’s disease as well. Many of the genes are similar in these conditions, and treatments are also quite similar. Gut dysbiosis is another link between obesity and metabolic syndrome and psoriatic disease. So how these environmental factors cause inflammation in joints is a good question, and that is what we are trying to understand.

**UTMJ:** Can you shed some light on the current research you are working on related to the microbiome?
VC: There has been a lot of attention given to the gut microbiome. The other aspect of the microbiome is of course the skin, which is the largest organ in the body. My PhD student characterized the skin microbiome of healthy people, patients with psoriasis without arthritis, patients with psoriasis and arthritis in the hands and feet, and patients with psoriasis and arthritis in the hands, feet, and the spine. In addition, different HLA alleles have been associated with different manifestations of the disease; HLA-C*06 is primarily associated with skin diseases and -B*27 is with joint disease. Our hypothesis was that there would be differences in the microbiome based on the psoriatic disease phenotype as well as based on HLA genotype. Our results show that there were no differences in the microbiome of the patients with psoriasis and psoriatic arthritis, or different types of psoriatic arthritis. However, there were small, but statistically significant differences based on the type of HLA alleles. These findings are novel and will soon be published. We believe that there is a potential interaction between the skin microbiome and the susceptible genes in patients with psoriasis.

UTMJ: What happens when patients have both genetic risk and dysbiosis or metabolic syndrome?

VC: Most diseases happen due to interactions between genetic and environmental factors. Even AIDS develops due to the interaction between HIV and a genetically susceptible host; there are subjects who never develop HIV disease despite being repeatedly exposed. In autoimmune diseases, such as Crohn’s disease or psoriasis, genetic factors alone may not be sufficient to cause the disease. Environmental triggers, such as smoking, infection, injury, or obesity are also important. At this moment, all we can say is that the individuals with both genetic and environmental risk factors are at a greater risk of developing psoriasis and psoriatic arthritis.

UTMJ: Are there any particular challenges that you have faced in your work?

VC: The challenge in skin microbiome studies is the amount of DNA that you get. The yield for microbial DNA from skin is quite low. Stool samples are easier to work with because you get a lot of DNA from them. Another consideration is which part of the skin are we going to extract samples from. When you are working with the gut microbiome, one usually obtains stool samples, but one can acquire samples, for example, from the colon or small intestine, via scopes. We are trying to do a similar approach with the skin, by taking samples from the extensor aspect and/or flexor aspect of the skin or the scalp. It has been shown that in healthy individuals, the microbiome is different in all these areas. We chose to sample the skin from the extensor aspects of the extremities because that is the most common site of psoriasis. We take samples from lesions using swabs, put it into solution, extract DNA and then sequence it. We also take control samples from the same patient from the opposite side, and also from healthy controls. Each step of the study has challenges that we have overcome.

UTMJ: What are the clinical implications of the work in psoriatic arthritis and the microbiome you have done so far?

VC: Nowadays, the treatment for psoriatic arthritis is trial and error, because we don’t fully understand how each patient develops the disease. You try one drug and it often does not work, so you try something else. By identifying the disease factors that I already mentioned, we will hopefully know which drug will work for the patient and what treatment would be the most effective. For instance, it is possible that combining drug treatment with dietary interventions to alter the microbiome could be beneficial for some patients, especially with treatment resistant disease. Sometimes we see psoriatic patients, who after receiving bariatric surgery, need no treatment for psoriatic disease anymore. This may be due to a change in the gut microbiome. In the case of skin psoriasis, if certain bacteria metabolites drive psoriasis, we may be able to ameliorate it with novel topical medications.

UTMJ: Based on your tremendous experience in this field and collaboration with various experts, what advice do you have for medical students, who are trying to embark on a similar path as yourself, a rheumatologist and clinician-scientist?

VC: As a medical student, it is important to get as much exposure to clinical practice and research as you can. First off, become passionate about something and explore it. In the first year of medical school, as you are learning about different diseases and systems, see what piques your interest. There are some fundamental methods and approaches in medicine that will not change, but the understanding of certain diseases might. So find an area that you really care about and then explore and learn. Second, try to engage in positive interactions with physicians and clinician-scientists to understand how your chosen area of interest are handled in both clinical and research settings. Summer studentships and other opportunities throughout the year, here in Toronto, are excellent opportunities to figure out what you want to do while learning from world leaders. By second or third year, you start to get a fair idea of what you want to do or what areas interest you. Then, of course, if you are keen on becoming a clinician-scientist, it is strongly recommended that you do a PhD. This can be done in MD/PhD programs or even after residency. Take note, the journey is long. Therefore, try to get the exposure and opportunities to explore your passion early with different research programs, especially during the summer. You can also shadow physicians and scientists to see what actually goes on in a typical day. There is quite a lot of work to do in this journey, but it is ultimately a satisfying one.
Interview with Dr. Jen Gommerman

UTHMJ Interview Team (Kathleen O’Brien and Alexandra Florescu)

Dr. Jen Gommerman

Dr. Jen Gommerman received her Ph.D. (Immunology) at the University of Toronto in 1998. She went on to do a post-doctoral fellowship at Harvard Medical School studying the complement pathway and then joined Biogen Inc. as a Staff Scientist in 2000. During her tenure at Biogen, she became interested in B cells, multiple sclerosis, and the TNF superfamily of molecules. After 3 years in Industry, she returned to Academia as an Assistant Professor (Immunology) at the University of Toronto in 2003, and in 2015 was promoted to full Professor. Dr. Gommerman’s basic research continues to focus on how members of the TNF superfamily of molecules regulate immunity and autoimmunity. Her team has uncovered a novel gut-brain axis that regulates neuroinflammation. With respect to translational work, Dr. Gommerman has been examining the role of B lymphocytes in multiple sclerosis patients, and she is the lead investigator on a study examining the effect of global migration on susceptibility to autoimmune disease.

UTHMJ: You have a lot of exciting research going on and we are wondering if you can expand on your findings related to the microbiome.

JG: So I want to qualify I'm not a 'microbiome researcher' (although I'm not sure what that means), but what we don’t do is we don’t go in and look at microbial communities and attempt to understand how those communities are formed, how they’re maintained, the metabolites they produce and so on. We get help to do that because that is not our core expertise. However, we have the ability to change microbiomes in our mouse models, or even introduce microbiomes from human subjects into our mouse models and then ask how that impacts the immune system. Probably our best paper on looking at that was our recent publication looking at these mucosal B cells – these are called plasma cells, they're B cells that make lots of antibodies and they can live for a very, very long time, up to decades in humans. What we found was that unexpectedly these cells that like to live in the gut and make IgA can get recruited to extraintestinal tissues. In particular we looked at the brain during EAE (the multiple sclerosis model) and sure enough they can be recruited to the brain where they actually dampen inflammation. In the context of the microbiome we did an experiment where we altered the microbiome by introducing a single microbe (a protist) into a pre-existing microbiome and that did reduce the disease that we were looking at! We postulated, although we didn’t prove it directly, that this could be because of more migration of these intestinal plasma cells to the Central Nervous System (CNS) and they might have more potent anti-inflammatory activity. Because the gut microbiome years have also taken on a major administrative role as the graduate coordinator.

At first my lab was dedicated to further understanding some of the things I’ve worked on in industry around this pathway called the lymphotixin pathway, and I ended up going more and more into gut immunology because we know that this pathway is quite important in gut inflammation and more specifically in generating immunoglobulin A responses which is the humoral immune response of the gut. And so that brought me into the trajectory of gut immunology, at the same time we’d been looking at this pathway in an animal model of multiple sclerosis (MS) called ‘Experimental Autoimmune Encephalomyelitis’ or ‘EAE’, and somehow these two fields ended up sort of converging in my lab – now we are very interested in the gut-brain axis and how this can affect diseases such as MS but also other broader ranging health issues.

UTHMJ: To start off, could you tell us a bit about your career trajectory and how you got to where you are now?

JG: Okay, so I’m kind of home-grown because I did both my BSc and PhD here in immunology. I had studied signal transduction in mast cells doing my PhD but I wanted to move into a lab where I could really try to understand immunological questions in the intact animal. And so, I went to Harvard and worked with a guy named Michael Carroll on the complement pathway. He had just made complement knockout mice and was discovering that complement proteins are not just important in acute inflammation but also play more subtle roles in the adaptive immune response. So I worked with him for a couple of years and collaborated at the same time with some folks in industry at Biogen, a major company in Cambridge, Massachusetts. Then the opportunity came up for me to cross the river and go work there and it was a good time to do that so that’s what I did, and I was a scientist in Biogen for three and a half years. And then a posting came up for an assistant professorship here and I applied, came and interviewed here the day before SARS broke in Toronto...and then had to wait quite a while for an answer because everyone was quarantined. Anyways, it all worked out and I started my lab here in September 2003 and have been promoted up to professor now and in the last eight
can promote different types of immune responses, it can be a bad guy or it can be your friend in terms of tuning less inflammatory-type immune responses, or, and there’s not many examples of this, but there are some that show that there can be outgrowth of microbes that either favour a more inflammatory immune response or fail to develop these anti-inflammatory feedback mechanisms.

UTMJ: Just following up on that, you have a lot of findings about IgA plasma cells that can prevent against the development of multiple sclerosis or help to dampen the disease, and that these cells come from the gut and then go to the brain. What’s the future directions of the research that you’re doing as it pertains to how the microbiome impacts the immune system?

JG: I mean we’re not at a stage in microbiome research I think where we can say ‘take this microbe and you are going to feel better’. I think what we do need to understand is whether some microbial communities will promote wellness maybe in the context of some of the already established therapies. For example, in MS, one of our best therapeutic tools is Rituximab, or Ocrelizumab, which is anti-CD20. This is an agent that gets rid of B cells but it spares plasma cells, and one thing we’re interested in looking at is whether the mechanism we described in the paper you’re talking about, whether it is operational in the context of Rituximab treatment. Rituximab treatment, for example, doesn’t work very well in the progressive form of MS, so maybe one thing we can do is augment its efficacy by promoting an anti-inflammatory microbiome at the same time. In the future, I think we’ll hopefully be looking at therapies that involve replacing microbiomes with healthy microbiomes, for example, what we already do in the case of C. difficile infection. Or maybe even more practical is to look at the metabolites that come from those microbial communities and using those as treatments in disease because it can be hard to change an established microbiome.

UTMJ: And specifically, for the lab that you’re running, do you see a future for incorporating further microbiome research?

JG: For sure, thanks to Dr. Dana Philpott we have a germ-free vivarium at the University of Toronto. So what that means is you can house mice in this facility that lack a microbiome, and when you do that it provides a blank slate for introducing new microbial communities. One thing we’re really interested in doing is looking at patient microbiota in these mice and starting to ask; what are the aspects of patient or healthy microbiota from healthy controls? Something I am really interested in is how microbiota change with age, or if you’re chronologically aged, how you can somehow make lifestyle choices that keep your microbiota healthier. I think those are big questions and the best way to answer those questions are in these germ-free mice. Now it’s not a perfect system, and in fact a paper just came out in Cell, a commentary, that was sort of a little more negative about this approach. However, it still remains our best tool for looking at causality in changes in microbial communities, and in particular clinical phenotype. That’s research that is going on at UofT and that is definitely where my lab’s going.

UTMJ: Can I just ask a more technical question...In terms of getting mice that don’t have a microbiota, how do you ensure that? How do you actually go about doing that?

JG: So you have to do a sterile C-section. And then to propagate strains you would implant an early stage embryo into a germ-free foster mother, because you inherit the microbiome of the vaginal canal as you’re born. It’s later replaced with more complex microbiota, but if the mom is germ-free and in a germ-free environment then the offspring will be germ-free as well. But it requires a lot of rigour to maintain a germ-free facility. The facility is a vacuum but all it takes is a few little bugs and now you are not germ free anymore – you have a flourishing community.

UTMJ: You have spoken a lot about animal research, but your lab has also seen findings in humans. What are these?

JG: In our paper, we collaborated with a group at UCSF and they were able to show that in MS patients, there was a change in the level of IgA in the gut during an MS flare or relapse. Although we didn’t have direct evidence for this, we wondered if it was similar to what we were seeing in the mice – that the IgA producing cells were leaving the gut in order to put out a fire somewhere else, in this case in the brain. I know that this UCSF group has followed up on that and they will have some work forthcoming in not too long.

UTMJ: The microbiome has been getting a lot of ‘hype’ recently... What do you think about all of this hype and about the future of the microbiome research in general?

JG: Every field struggles with this – every time there’s new excitement around a scientific advance you start thinking ‘silver bullet’, that this is going to be it, this is going to solve all of our problems. When you think about it, one of the best therapies we have for a lot of different chronic diseases is good diet and exercise. In fact, let’s use that as an example: good diet and exercise. Okay, that makes your disease better. But what’s the molecular mechanism for why that works, because for example not all MS patients are able to exercise or having a good diet can be expensive or out of reach if you live in a food desert. So, we really need to understand what those molecular mechanisms are so that we can hone in on what exactly is beneficial about those approaches. The microbiome is the same way, so right now we’re just grappling with the fact that the microbiome is so complex that of course there is going to be a lot of discoveries in the field that we’ll have to think about and ruminate on before we can really put them into...
practice. I think that while us scientists are usually very careful about communicating these things to the public, the media is not so good at conveying what we get excited about. We have a long way to go. Because people don’t want to hear that, they want to know that they’ve got their silver bullet and they have it right now. But it’s going to take time to really understand the molecular mechanisms behind why microbiome A is disease prone and microbiome B is disease resistant. But that’s essential if you’re going to make movements forward.

JG: Well, both. We’ve been rightly focused on the intestinal microbiome because it is the richest source. It’s an incredibly diverse ecological community. I think for sure, there is more and more research on different microbiomes – here at U of T, I know that Rupert Khaul has been looking a lot at the microbiome of the reproductive tract. Skin microbiome is clearly very important in diseases like psoriasis and acne, for example. All of these things are super important. It is just that the gut has the richest source of microbes, so that has been a major source of study. And, I think intuitively and as clinicians, you have probably heard this a lot too, if your gut is not well your body is not well – and there has to be some reason for that. Anatomically, I think there are some interesting connections between the gut and the brain that we are curious about.

JG: Our journal is often read by people involved in clinical work – how well melded do you find basic science to be with translation into clinical practice?

JG: Well, it is way better than it used to be. I would say I have just as many clinical colleagues as I have basic research colleagues, and I think we do a pretty good job at working together. But this has taken time. There used to be a time even as little as ten years ago, where the basic scientist was supposed to really focus on animal models and in-vitro models and not go beyond. We were somehow almost discouraged from doing translational work. It is totally different now. To get funded, you don’t have to show that your work has translational evidence, because there is an important place for purely discovery research, but a lot of people do. For me, it has always been a part of my approach, perhaps because I worked for a drug company and I saw all stages of clinical development from earliest bench research all the way to the design of drug trials and seeing the results of trials come in — that is a super exciting part I really like. Overall, I think it has gotten a lot better, but it takes a team. The old model of ‘one researcher, one grant and one lab’ still happens and it can be effective but there is a lot more team research now.

JG: There is my research job and there is my administrative job. I have had moments in both, so I can give you an example of each.

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JG: [Laughs.] We can be less busy. Honestly, I think the will is there, it is just finding the time to work together, to do meaningful science together. The will is there. And I know for clinician-scientists, protected time is really important. I can’t comment on that because I am not in that world, but that would make sense to me. You just need the time and the bandwidth to be able to meet and work together. And the funds. [Laughs]

JG: What have been some top moments that have made you go “wow, I really am happy to have the job I do”?

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JG: There is my research job and there is my administrative job. I have had moments in both, so I can give you an example of each.

We did some work back in 2011 where we had this Lupus animal. But we were already thinking in terms of the gut. When we looked in the kidneys of these mice, which were nephritic, we noticed that the classical antibody deposition you would normally see in a nephritic kidney which are IgG complexes, weren’t IgG, they were IgA. We took this beginning observation and we worked it all the way to the end. It turned out that these mice which overexpressed this cytokine called BAFF developed a disease that is very similar to IgA nephropathy, a disease that is actually the most common form of glomerulonephritis and has no treatment. So that was cool, and the other thing we noticed in these mice is that if you took these mice and made them germ free, so got rid of their microbiota, their kidney disease went away. The overexpression of the BAFF cytokine was not sufficient to drive the kidney disease, the microbiome was an important cofactor. The third big thing in this paper, is we thought, if BAFF drives this disease in mice, then maybe there is a similar pathway going on in humans. We found two cohorts of IgA nephropathy patients and we measured in the serum of these patients the level of BAFF and the level of the related cytokine APRIL, which shares the same receptors as BAFF. BAFF levels weren’t elevated in the patients, but APRIL levels were. So we published both the mouse and human data in this JACI paper. And the paper got completely ignored. We were very happy with the paper and it was actually a collaboration between myself and Biogen, so it was nice to continue to work with Biogen on that, but it pretty much got ignored by the IgA nephropathy community at least — actually pretty much by everyone. [Laughs]

A couple of years later, fast forward one or two years, two big Genome Wide Association Studies (GWAS) papers came out (where you look at all the genetics of a patient group compared to controls). In the IgA nephropathy group, one of the top hits was APRIL. Still our paper was ignored, in fact I don’t think our paper was even cited by either of those studies. Fast forward a few more years, and someone had the bright idea of testing the drug Budesonide in IgA nephropathy patients – maybe they
Interview with Dr. Jen Gommerman

work will get ignored, for sure, but if it really has a clinical impact, hopefully it will emerge in time. To see that it is part of that clinical picture is really rewarding. I don't want to imply that our paper was the only paper that has directed the field like this, but it's a piece and that feels good.

Is that a good story? [Laughs and smiles.]

Just from being a graduate coordinator, watching people graduate – going to their thesis presentation and seeing where they go afterwards. I have this nice picture that I tweeted in the fall when I was giving a talk at Harvard, and there were seven or eight U of T students that were all at different stages of their careers in Boston and they had come to see my talk. I knew them as students so that was a really big moment.

UTMJ: Those were all our questions, unless there was something else you wanted to share with our readers.

JG: Just to underscore that I am not a microbiome researcher. I am an immunologist that has recognized the microbiome is a major influence on the immune system, and that is my perspective. So, I wouldn't describe myself as an expert microbiologist, because I think all immunologists have to understand the microbiome. That should be your top statement. [Laughs]
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