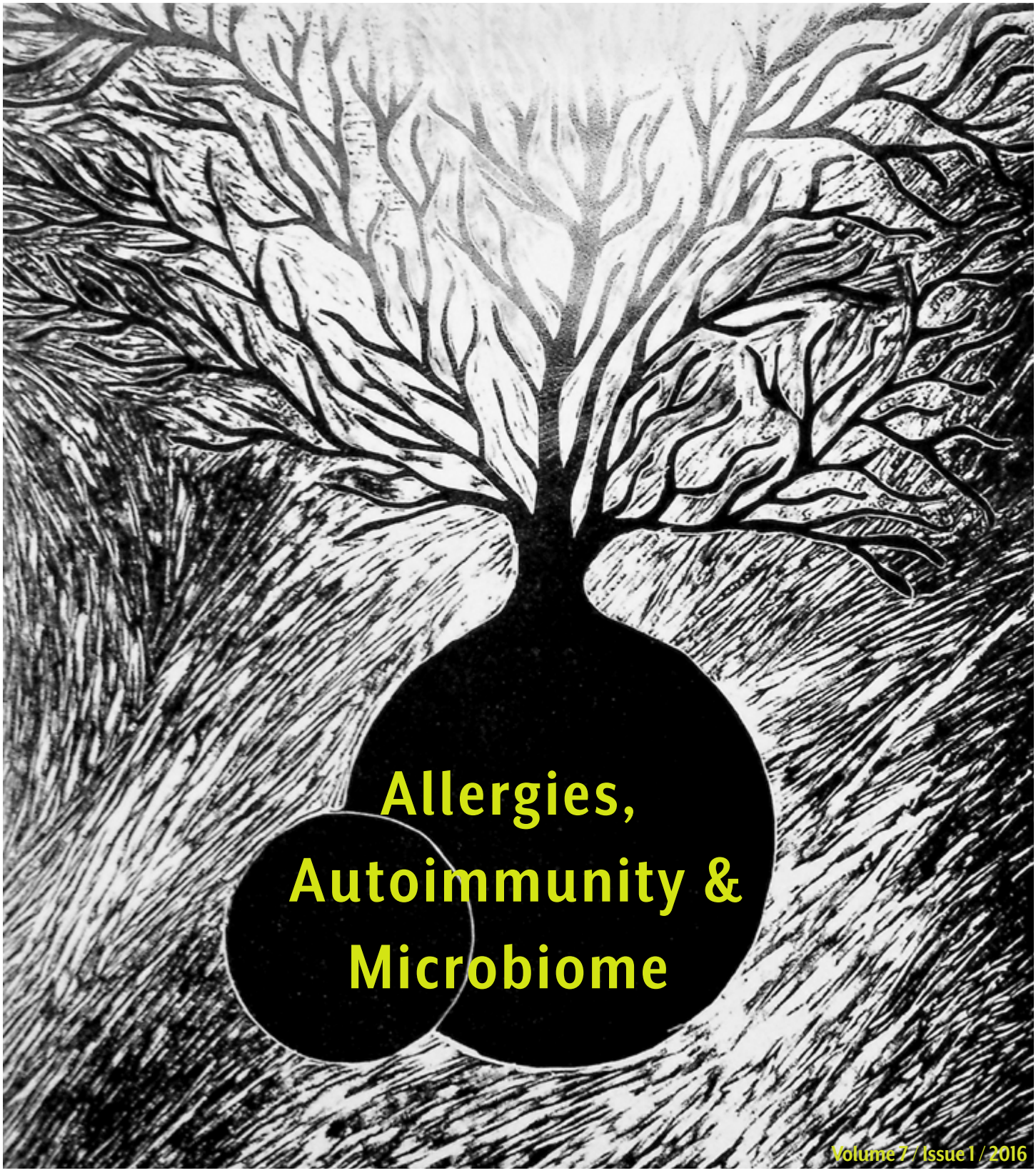
HEALTH SCIENCE INQUIRY

A publication platform for graduate students to discuss, discover, and inquire…



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MAIN SUBMISSIONS

Cover Design

Contagions *David Longpre*

Description of Cover Design: "Contagions." This artist proof of a larger wood block relief print, presents a metaphor for humanity as Earth's contagion. Similar with this year's theme of allergy, autoimmunity and microbiome, it is equally imperative to understand how humanity reacts with the biome of the planet, just as small viruses and particles reacts to our own bodies. With a desire for infinite growth, humanity will eventually deplete the remaining resources from our host; we, as a species, must realize this paradox. The print is a small excerpt from a series held in the University of British Columbia Print Resource Collection.

About the Artist: David Longpre is an artist, currently completing his Masters of Architecture at the University of Calgary. He received his Bachelor of Fine Arts, Major in Visual Arts, from the University of British Columbia. David's work has a prominent focus on themes on humanity, history, nature, and urban/infrastructural environments. His practice primarily involves print media photography, and more recently, the digital arts. More of his work can be found on his website at davidlongpre.ca

Allergy, Autoimmunity, and Microbiome

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ASK AN EXPERT

SPOTLIGHT ON CAREERS

SPONSORSHIP

HEALTH SCIENCE INQUIRY TEAM

Special Thanks to Our 2016 Partnering Journal

LETTER FROM THE CO-EDITORS-IN-CHIEF

Dear Readers,

It is with great pleasure that we present the 7th annual issue of the Health Science Inquiry on Allergies and Autoimmunity.

Allergic reactions and autoimmune diseases are growing problems in our society. Continuing changes of our environment and globalization that led to movement of populations around the world promoted emergence of new immune-related disorders.

While many immune diseases are still not treatable, the success in recent studies led to a greater understanding of the underlying causes of human immune-related disease, enabled early diagnosis, and allowed patients to make decisions regarding disease management. In our 7th publication of HSI, we explore these advances and considerations focusing on the themes: Allergy, Autoimmunity and Microbiome.

With submissions from across the country, HSI continues to serve as a national platform for student involvement and discussion. We continue to be impressed by and grateful for the excellent submissions we receive from Canadian graduate and medical students. We are equally thankful to this year's partnering journal, Innate Immunity, for their commitment to student development.

In addition to our Main Submissions, HSI also features News Articles and expert testimony on topics related to Immunity and Microbiome. We additionally publish career information and blog on all topics related to science, discovery and student life which you can find on our website (www.healthscienceinquiry.ca).

We would like to thank our dedicated 2015-2016 HSI team consisting of over 30 Canadian graduate and medical students from across the country for their valuable contributions to provide a forum and a voice for Canadian graduate and medical students. We hope that this publication incites discussion among readers, peers and colleagues.

Sincerely,

WooJin Kim and Suzanne Osborne
Co-Editor-in-Chief

NEWS ARTICLES

News Reporters from HSI's Editorial Team investigated various issues in Allergies, Autoimmunity and Microbiome.

The Tangled Relationship Between Autoimmunity, Alzheimer's Disease, and Exercise

By Logan Townsend

Normally the immune system protects the body from potentially harmful substances by producing antibodies that destroy these substances. However, sometimes our immune system malfunctions and the body detects its own tissue as harmful substances and ultimately destroys healthy bodily tissues – this is known as autoimmunity. (1)

Alzheimer's disease (AD) is the most common form of dementia in the elderly and the fourth leading cause of death in Western countries. (2) It will be exceedingly difficult to pinpoint one thing responsible for the pathology of AD (Rebecca MacPherson. Conversation with: Logan Townsend. 2015 Nov 11*), but evidence is beginning to emerge that autoimmunity may play a role. Autoimmunity in the pathogenesis of AD has previously been ignored because antibodies capable of attacking neuronal cells circulate in healthy populations. However, the blood-brain barrier that was thought to protect the brain from systemic antibodies is dysfunctional in AD, conceivably making the brain susceptible to these circulating antibodies and thus contributing to the pathological features of AD. (1-3)

One of the neurological hallmarks of AD is the accumulation of amyloid plaque that is detrimental to neuronal health. (4) Beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) is important for the production of these plaques and can be used in early AD detection (4). The mechanisms behind the amyloid plaque formation and elevated BACE1 activity seen during AD are complex, but increased and dysfunctional cellular stresses appear to be important precursors. (4) For instance, 5' AMP activated protein kinase (AMPK), the cellular energy and fuel gauge, is hyperactive in the brains of AD afflicted individuals and is thought to be at least partially responsible for the accumulation of amyloid plaques and BACE1 activity in AD.

It is well known that exercise can prevent and treat obesity and glucose intolerance, both of which are significant risk factors for developing AD, and it now seems that exercise can also directly affect the neurological mechanisms of AD. Dr. Rebecca MacPherson, a post-doctoral fellow at the University of Guelph, investigated the effects of a single bout of exercise on markers of neurodegeneration in obese glucose intolerant mice. (4) This study demonstrated for the first time that a single bout of exercise (2 hours) reduced neuronal AMPK activity which could have neuroprotective effects since AMPK contributes to BACE1 activity and amyloid plaque formation. Indeed, "the most important finding from this study", according to Dr. MacPherson, "is that one bout of exercise can reduce BACE1 protein content and activity in the frontal cortex of obese glucose and insulin intolerant mice". These results highlight the therapeutic potential of a single bout of exercise to ameliorate changes in early AD-associated neuropathology.

At the same time, consistent exercise appears to rescue the cognitive declines and neuropathology of AD, regardless of disease progression or symptom severity. Cho and colleagues (5) introduced an exercise program of only 30 minutes of running 5 times a week for 12 weeks into a mouse model that demonstrates the cognitive deterioration and brain pathology of AD. Regardless of disease progression, the exercise intervention reversed cognitive declines and improved learning and memory. Moreover, extending on Dr. MacPherson's results, this study shows that prolonged exercise training (of 12 weeks) can significantly reduce

BACE1 proteins and reverse amyloid plaque accumulation. (5)

As Dr. MacPherson notes, "BACE1 inhibition has become a key therapeutic target for Alzheimer's disease and there are currently several BACE1 inhibitors undergoing human clinical trials". Therefore, it is very promising that a single exercise session can reduce BACE1 content while consistent exercise training can similarly reduce BACE1 content in addition to plaque formation. (4,5) Considering Canada's aging population, these studies are the first of many that will provide valuable information in terms of designing evidence-based preventative or therapeutic lifestyle interventions for AD. ■

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Logan Townsend

Logan received his BA from the University of Lethbridge in Alberta where he began researching sexual differentiation in the metabolic response to high-intensity interval exercise. He is currently finishing his MSc researching how the hormones associated with the menstrual cycle may influence the hormonal regulation of appetite and satiety. After this he is pursuing a PhD in hepatic interleukin-6 signalling at the University of Guelph.

BIO-FLASH® Providing Early Diagnosis of Autoimmune Diseases

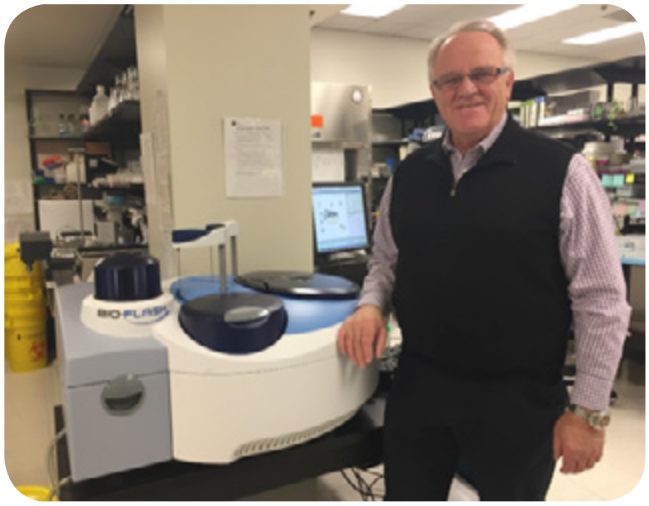
By Christine Foran

In 2012, Dr. Marvin Fritzler, MD, Professor at the Cumming School of Medicine and Director of Mitogen International acquired for the University of Calgary, the BIO-FLASH®—a new machine for diagnosing autoimmune diseases. Not only new to Calgary, the BIO-FLASH® was the first of its kind in North America. Currently there are still only 60 machines worldwide, with the University of Calgary now owning two.

There are over 80 types of autoimmune diseases (1) affecting approximately 5-8% of the population (USA) (2). Examples of these diseases are: type 1 diabetes, rheumatoid arthritis, and systemic lupus (3), with symptoms ranging in severity from fatigue, joint pain, seizures, skin rashes and others that might be related to vital organ damage (2). For those affected, rather than protecting them from disease, their immune system works against them. Their best chance of preventing irrecoverable organ damage is early detection and treatment.

The BIO-FLASH® was first released in 2009, with revisions prompting the 2012 BIO-FLASH® 2.4.0 (4). Dr. Fritzler explained that the BIO-FLASH® system uses chemiluminescence to detect the self-destructing immune molecules such as autoantibodies in the blood. More importantly, BIO-FLASH® identifies the precise products of the cell (specific proteins, nucleic acids, phospholipids) that the immune system is attacking, enabling the physician to make an accurate diagnosis—promoting early and accurate treatment. Hence, the BIO-FLASH® expedites the most appropriate and effective treatment, eliminating a manual trial and error (5) and subjective approach (6).

Dr. Fritzler stated, "The BIO-FLASH® detects certain abnormalities in blood when other systems fail." He also explained that the turn-around time to complete a BIO-FLASH® test and generate a report has dramatically improved. Many tests can be completed in an hour, compared to past systems, which took up to a week. In addition, test reliability



has improved substantially.

The BIO-FLASH® can process as many as 1,000 blood samples in a day (7). Recently, the University of Calgary adopted a second BIO-FLASH® system. Dr. Fritzler explained that one system is dedicated for patient services and tested approximately 50,000 blood samples last year. Of those samples, approximately 70% were from Albertans, 20% from other provinces, and 10% from other parts of the world such as Europe, Japan, Australia, and the USA.

Dr. Fritzler applauds the benefits of BIO-FLASH® stating the machine provides superior speed and reliability. "Faster results means the patient can be diagnosed and treated sooner. It has improved the work flow in our lab because it is fully automated and the results are incorporated in our Laboratory Information Systems and uploaded digitally to the patient's electronic health record on NetCare." And while new technology will encounter glitches, Dr. Fritzler stated that BIO-FLASH® has provided "excellent hands on technical support."

The second BIO-FLASH® system is being used to develop new tests. Dr. Fritzler spoke passionately about his almost 40 years working at the University of Calgary, with a focus to improve the diagnosis of complex autoimmune diseases. Dr. Fritzler emphasized the necessity of early diagnosis, treatment, and disease prevention providing two examples.

The first example is that of an undiagnosed client with lupus, presenting for the first time to a physician and already showing signs of kidney disease. The second example pertains to a child, brought to the emergency room due to progressive seizures, reason unknown. Dr. Fritzler explained that if the cause is autoimmune encephalitis, an immediate life saving diagnosis can now be made with antibody testing. These two examples also illustrate Dr. Fritzler's ongoing research, to provide 'point of care' diagnostics that could be used in emergency rooms or at the patients' bedside to make diagnoses even faster. His lab is constantly evaluating leading edge technologies that can be used for personalized and preventative medicine.

For the University of Calgary, BIO-FLASH® epitomizes its desire and commitment to lead in research, detection, and prevention. For those who suffer from autoimmune diseases, such commitment to early detection and personalized medicine is highly welcomed. ■

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Demystifying Systemic Lupus Erythematosis

By Michelle Le

When Angelina Pitt-Jolie received a preventative double mastectomy upon finding out she had the BRC-A2, a gene known to increase the risk of acquiring breast cancer, the world had a peak interest in breast cancer and prevention measures. Equally, when Selena Gomez announced her Lupus diagnosis this past year, there was an overwhelming interest in the media. To jump on the bandwagon of popular media, HSI presents an article on the mysterious Systemic Lupus Erythematousus (SLE) and its ongoing research.

Systemic Lupus Erythematousus: the nuts and bolts

Systemic Lupus Erythematousus is an autoimmune disease affecting close to 1 in 1000 people worldwide with the incidence rate increasing yearly. Although the mortality rate of lupus has significantly decreased over the past 10 years, there is no real cure for SLE. A lupus diagnosis is mostly determined through clinical presentation rather than a specific serum biomarker. As a result, overlapping and evolving symptoms can make SLE difficult to recognize and diagnose. The most common clinical presentations of SLE include skin rash and photosensitivity, which enables a quick lupus diagnosis. Arthritis, nephritis, pleuritis, pericarditis, anemia and leukopenia are also symptoms commonly seen in lupus patients. While the severity of clinical symptoms is variable, the most severely affected organs are the central nervous system, the kidneys, and the lungs. Disability consequences including work loss, activity limitations, perceived mental and physical exhaustion and reduced quality of life are commonly found in SLE patients with targeted organ damage (1).

Lupus frequently affects women of child-bearing age and is more commonly diagnosed in women than in men. Lupus is significant during childbearing years as the disease will increase the risk for miscarriages by 12.4% (2,3) and the development of neonatal lupus (4) and autism (5). However, it is possible for women with lupus to have a successful pregnancy provided that pregnancy planning is discussed alongside the care of a rheumatologist. Also common in 30 to 40-year-old women with lupus is a five- to six-fold increased risk of coronary artery disease (CAD) (6).

Clinicians and patients alike are excited for the medications that are currently being developed for lupus. In the past 50 years, belimumad (Benlysta ®) has been described as the most exciting break through in lupus research. Belimumad Is a monocloncal antibody that targets BLyS, an upregulated mediator that prevents autoreactive B cells from being activated in lupus. Apart from Benlysta, off label medications such as cortisone and chemotherapy are the most commonly used for lupus management.

Research: an ongoing hope for SLE patients

While the mechanism of lupus has yet to be discovered, many researches are currently being conducted to have a greater understanding of the disease and its manifestations. Founded in 1970, McGill University Health Centre (MUHC) Lupus Clinic in Montreal, Canada is the second largest lupus clinic in North America. Notably, the McGill Lupus Clinic, known for its research in the field of lupus epidemiology, has one of the largest cohort lupus studies in the world with over 700 participants.

Currently, several McGill clinic doctors are involved with lupus research. Dr. Christian Pineau is the co-director of the lupus and vasculitis clinic at the McGill University Health Centre. He describes the research done at McGill as crucial to learning more about lupus. Dr. Pineau himself is interested in defining and limiting the burden of cardiovascular disease and non-vascular cardiac diseases in SLE. Notably, Dr. Pineau has actively pursued strategies aimed at preventing cardiac disease in the systemic lupus patients by focusing more attention on potentially reversible cardiac risk factors such as hypertension, cholesterol, antiphospholipid antibodies, and homocysteine. Lupus may also affect child bearing and

cause miscarriages due to the effect of increasing blood clotting. Dr. Evelyne Vinet, a clinician and scientist at MUHC, studies the reproductive issues in women with lupus. In preliminary studies, Dr. Vinet and her colleagues have found that women with lupus are more likely to have a child with autism compared to women without lupus. Research on the association of lupus with malignancy is spearheaded by Dr. Sasha Bernatski and involves over 40 lupus centres. Additionally, Dr. Louis-Pierre Grenier investigates the role of increased risk of recurrent thrombosis in lupus while Dr. Joyce Rausch studies the role of anti phospholipid syndrome commonly present in lupus. Elucidating the mechanism of lupus manifestation is equally important as studying clinical presentations. In the basic science department, Dr. Emil Nashi is studying the B cell activation pathway involved in lupus. Specifically, Dr. Nashi is investigating how B cells respond to their environment and comparing this between lupus patients and people without autoimmune disease.

What's next for lupus research?

Though research is promising, there is still much to be learned in this field of autoimmune diseases. Going forward, Dr. Pineau of the McGill Lupus Clinic believes that there needs to be an increased focus placed on lupus epigenetics and associated microbiome to have a better understanding of lupus development and to predict lupus severity in individuals. Medication development for lupus management is also on the radar. There is no doubt that many questions about SLE have yet to be answered. Research in SLE presents as a promising field for rising young scientists. ■

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Interview with Dr. Azad: Understanding the interactions between prenatal environments and allergies.

By Thilina Bandara

Allergies and asthma affect one in three people, and cause over 200 deaths a year in Canada (1). It is now understood that asthma and allergies may be the result of interactions between genetics, lifestyle and environmental triggers early in life (2), which leads to the hope that effective early childhood interventions can improve the lives of millions worldwide.

A group of researchers across Canada are working to assess exactly which risk factors underlie the complex nature of allergies and asthma.

Started in 2007, The Canadian Healthy Infant Longitudinal Development (CHILD) Study is a longitudinal birth cohort study that tackles many specific research questions to help assess the larger picture surrounding allergy and asthma. Life stress, nutrition, genetics and environmental exposures are among the risk factors researchers are assessing in the CHILD study across Canada (3): To accomplish this over 3,629 pregnant mothers were recruited, representing over 10,000 Canadians overall (4).

Many types of data are being collected from the participants, and their homes, to account for the complexity of allergies and asthma. The children are clinically assessed at three months, and ages one, three and five, where parental and child blood, breastmilk, meconium, viral swabs, urine, stool samples, and infant peripheral blood are collected.

Repeated questionnaires over five years, pre- and postnatal nutrition, health status and medication data will allow researchers to assess biological environmental factors, while allergen, endotoxin and beta-glucan levels in household dust provide information on built environmental factors. Together these data give researchers an understanding of the conditions under which these children develop.

Follow-up data regarding pulmonary health status, genetics, and allergy testing will then give insights into the causal links between possible risk factors and poor health outcomes.

“The study is really a national treasure and a gold mine for students,“ says Dr. Azad on the value of the CHILD study. “We now have 5 years of data on these over-3500 families, which is an amazing resource and there are endless questions you could ask.”

Dr. Azad’s research focuses on how the maternal environment affects child health outcomes, specifically obesity and allergies. Utilizing the breast milk samples that were collected, Dr. Azad’s team is conducting both molecular and epidemiological analyses to investigate the hunch many researchers have that breastfeeding is protective for children’s health.

“CHILD is now a platform for all sorts of longitudinal data and questions”

The findings from the CHILD study have widespread implications on policy in Canada and around the world. Dr. Azad’s work specifically applies to breastfeeding regulation and policies. She hopes that her findings regarding the possible added benefits of breastfeeding on childhood immunity informs best practices for future mothers and improves industry regulations of baby formula.

Going forward, researchers anticipate continuing the analysis to assess all the possible links between the many dimensions of the study. Dr. Azad looks forward to the new generations of research that will emerge from the data, and hopes student take advantage of the CHILD study’s large dataset.

For more information, students can access to any of the 40+ investigators involved in the CHILD study by visiting the contact us page on the CHILD website (http://www.canadianchildstudy.ca/ask.html). ■

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Thilina Bandara

Thilina Bandara is a PhD student and a Natural Sciences and Engineering Research Council of Canada Doctoral Fellow in the Department of Community Health and Epidemiology at the University of Saskatchewan. He is also currently involved in built environment and health equity research at the Saskatchewan Population Health and Evaluation Research Unit. His research interests include health equity, knowledge translation and One Health.

MAIN SUBMISSIONS

Call for Submissions

In October 2015, graduate students across Canadian Institutions were asked to submit commentaries on various aspects of **Allergy, Autoimmunity and Microbiome**. The commentaries were 700-800 words in length and focused on one of three specified topics:

- Understanding Allergies and Autoimmunity: Current Research and Advances
- Our Dynamic Microbiome: Its Role in Shaping and Regulating The Immune System in Health and Disease
- Environmental Influence on Allergies and Autoimmune Disorders

Review / Judging Process

Starting in March 2016, each submission was reviewed by blinded Reviewers from HSI. Reviewers provided feedback to the authors by critically assessing the content and writing of each commentary. After receiving feedback from Reviewers, authors were given three weeks to revise their submission and resubmit their manuscript to the journal. Our team of Senior Editors went through each commentary, providing a decision on publication and any final comments.

2016 Winner

The author of the highest scoring paper for each category was granted expedited review for possible publication in our partner journal, ***Innate Immunity***. All the submissions were outstanding, and the editorial team highly commend the authors for their achievement. After tabulating the results, we are pleased to announce the winning submissions for the 2016 issue of ***Health Science Inquiry***:

"Early Introduction of Peanut: New Horizons in Preventing Food Allergy"
Elizabeth Simms

Past Winners

- Chelsea Himsworth's paper was published as a 'Reflection and Reaction' piece in a 2010 issue of ***The Lancet***: **http://www.thelancet.com/journals/laninf/article/PIIS1473-3099%2810%2970148-1/fulltext**
- Timothy W. Buckland's paper was published as a 'Salon' piece in a 2011 issue of ***The Canadian Medical Association Journal***: **http://www.cmaj.ca/content/early/2011/10/11/cmaj.111419.long**
- Marc Bomhof, Jane Polsky, and Denise Darmawikarta's paper was showcased on the 'News' section in 2012 of the ***International Journal of Obesity*** website: **http://www.nature.com/ijo/index.html**
- Leigh M. Vanderloo and Gillian Mandich's paper was published in a 2013 issue of the ***Canadian Journal of Community Mental Health***: **http://www.cjcmh.com/doi/abs/10.7870/cjcmh-2013-032**

Main Submission

A Brief Overview of Non-Celiac Gluten Sensitivity

Hieu Ly[1*] & Kevin Singh[2]

1. Corresponding author. Department of Health and Rehabilitation Science, Faculty of Health Sciences, Health Promotion Research Laboratory, Western University, London, Ontario. 2. Kevin Singh, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario. Email: kevin.singh@medportal.ca

The adoption of a gluten-free diet (GFD) has become an increasingly popular trend, despite the fact that most individuals do not have a diagnosis of wheat allergy (WA) or celiac disease (CD) (1). Although WA and CD are defined as immune and autoimmune conditions, respectively, certain aspects of non-celiac gluten sensitivity (NCGS) are still scrutinized by experts (1, 2). It is also still unclear whether NCGS is indeed an immune-mediated condition (1), especially since there is contradictory evidence on this topic (3-6). Furthermore, a lack of diagnostic tools may contribute to misdiagnoses and misunderstandings of this condition. However, many individuals with NCGS have described overall symptomatic improvements after adopting a GFD (5-7). The aim of this paper is to further explore this complex condition to better stratify patient populations.

Definition, Symptoms, and Rates of NCGS

NCGS describes individuals without WA or CD who have adverse reactions when ingesting products containing gluten, but may experience alleviation in symptoms by adopting a GFD (1). Common symptoms associated with NCGS are abdominal pain, distension, nausea, and diarrhea. Individuals may also report nonspecific extraintestinal symptoms such as headache, fatigue, rashes, and general malaise (2, 8). In a prospective multicenter study that included 28 centers (12,255 participants), 391 individuals were identified with suspected NCGS (3.19%) and 340 individuals received new CD diagnoses (2.77%), which is a ratio of 1.15 to 1 (8). Additionally, researchers found that adult women are more likely to report NCGS-related symptoms than men (female to male ratio of 5.4:1), and some individuals with NCGS may also experience irritable bowel syndrome (IBS; 47%), food intolerance (35%), allergy (22%), and other autoimmune disorders (14%) (8).

Diagnostic Protocol for NCGS

Some researchers have found that NCGS is not characterized by specific antibody markers (3) or an accentuated inflammatory response to gliadin (4). In contrast, others have reported that there are detectable differences for certain biomarkers (e.g., eosinophils and immunoglobin G) (5, 6). The mixed findings on this topic have made it difficult for clinicians to diagnose individuals with NCGS (1). However, a two-step process for diagnosing NCGS was suggested by experts, which included guidelines that previous diagnostic procedures lacked (2). Initially, a clinician can examine patients' responsiveness to a GFD through a self-administered instrument known as the Gastrointestinal Symptom Rating Scale (2). Subsequently, patients can be introduced to a double-blind placebo-controlled gluten challenge, which includes the elimination and reintroduction of gluten in patients' diets (2). This diagnostic protocol is critical for clinicians to be able to separate NCGS from other conditions, such as IBS (2, 6, 9), and to better understand its underlying etiologies. This is exemplified in a randomized control trial of 72 participants who were suspected of IBS, in which 31 (83.8%) individuals on a GFD experienced fewer symptoms compared to 9 (25.7%) individuals on the gluten-containing diet (9).

The Effects of a GFD in the Treatment of NCGS

The standard treatment for NCGS is to restrict the intake of dietary gluten (2). For example, there was a reduction in anti-gliadin antibodies and improvement in symptoms for 41 NCGS patients (93.2%) who followed a strict compliance to a GFD for six months (5). Generally, individuals expressed an alleviation of symptoms after eliminating gluten from their diet (6), and some have reported an increase in the overall severity of their symptoms after ingesting small amounts of gluten (7). However, researchers have also reported that there were no effects of ingesting gluten among those with

suspected NCGS, and other dietary triggers could potentially be responsible for their symptoms (3). Although there has been an expanding market for gluten-free products (1), there is a financial barrier associated with the adoption and adherence to a GFD because gluten-free products are on average 242% more expensive than regular food items (10). Therefore, it is crucial to have standardized procedures to correctly diagnose those with NCGS, before clinicians provide recommendations for individuals to adopt a GFD.

Future Directions

The increased number of cases of NCGS worldwide signals a need for standardized diagnostic procedures to determine the extent to which this condition affects the global population (1). The newly developed NCGS diagnostic protocol is a step forward to further our understanding of this complex condition. Individuals with suspected NCGS should receive a proper diagnosis from clinicians who are familiar with the diagnostic protocol prior to receiving any treatment. More evidence is needed to establish sound reasoning for advising individuals to adopt a GFD, which could potentially be a lifetime commitment. It is necessary to provide the resources (e.g., nutrition counselling from dietitians) for those who require support adopting a GFD, especially for individuals in low-income areas (10). Thus, further research on NCGS should aim to evaluate and further develop diagnostic procedures to optimize clinical decision making, and develop public health strategies to support those afflicted by NCGS worldwide. ■

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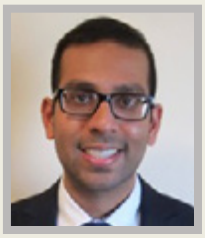

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Early Introduction of Peanut: New Horizons in Preventing Food Allergy

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Food allergy is a serious healthcare concern, with over 7% of Canadians self-reporting at least one food allergy (1). Common food allergies include egg (affecting 1% of Canadian children), milk (< 1%), fish (1%), wheat (< 1%), and tree nuts (1.6%) (1). Peanut allergy in particular affects 1-2% of children in westernized countries, and its prevalence has doubled in the past 10 years (2). Peanut allergy is unique in that it is unlikely to be outgrown, persisting in 80% of allergic children into adulthood (3), and it accounts for the majority of fatal reactions to foods (4).

Food allergy impacts the daily habits of food-allergic individuals and their families, as well as the community at large. Bans on allergenic foods, such as peanut, are becoming more common in schools and community locales. The prevention of food allergy is an important medical priority, particularly since there is a marked lack of disease-modifying therapies available for food-allergic individuals. This commentary will discuss the findings from a recent study that may significantly impact the clinical approach to preventing severe food allergies.

Older clinical guidelines recommended the avoidance of common allergenic foods in infancy and early childhood as a means of preventing food allergy. These guidelines were in place in Canada until as recently as 2013 and were largely based on consensus rather than direct evidence (5).

Over the past decade, evidence began to emerge that cast doubt on the protective benefit of delayed introduction of allergenic foods. One such study observed that the prevalence of peanut allergy in Jewish children in the United Kingdom was 10-fold higher when compared to Israeli Jewish children of similar ancestry. This discordance in peanut allergy prevalence correlated with differences in timing of peanut introduction into the diet: children in the U.K. generally did not consume peanuts in the first year of life, while Israeli children were routinely eating peanuts starting at 7 months of age (6).

The Learning Early About Peanut Allergy (LEAP) Study, lead by Dr. Gideon Lack, was established in 2006 to investigate whether early dietary introduction of peanut could prevent peanut allergy. The results of this landmark study were published in the February 2015 edition of the New England Journal of Medicine (7).

The LEAP Study enrolled 640 infants aged 4 – 11 months who were considered at risk for peanut allergy due to the presence of severe eczema, egg allergy, or both. Participants were randomized to either avoid or regularly consume peanuts until 60 months of age. They were also stratified into separate cohorts according to the presence or absence of a preexisting sensitivity to peanut as defined by skin prick test: sensitized children had a wheal size of 1-4 mm and unsensitized children had no measurable wheal size. The primary outcome of the study was the proportion of participants with clinical peanut allergy at 60 months of age, as defined by oral food challenge.

The results of the LEAP Study were remarkable. In the unsensitized cohort, 13.7% of children who had been randomized to avoid peanut had clinical peanut allergy at 60 months compared with 1.9% of unsensitized children who had been randomized to consume peanut ($p < 0.001$). This represented an 86.1% relative reduction in the prevalence of peanut allergy. In the peanut-sensitized cohort, 35.3% of children in the avoidance group and 10.6% of children in the consumption group had peanut allergy at 60 months ($p = 0.004$). This represented a 70% relative reduction in the prevalence of peanut allergy. Peanut-specific serum antibodies were also measured over the course of the study. Children who consumed peanut had increased peanut-specific IgG4, while children who avoided peanut had elevated titers of peanut-specific IgE and a lower ratio of peanut-specific IgG4:IgE. IgE antibodies coat

the surface of allergic effector cells and activate these cells upon allergen binding, while IgG4 antibodies are thought to be protective in allergy due to their ability to bind allergen in circulation and block its IgE-binding capacity (8). The LEAP Study authors concluded that in infants at high risk of developing peanut allergy, peanut consumption in the first year of life significantly reduced the prevalence of peanut allergy by five years of age.

The concept of oral tolerance has been known since 1946, when Merill Chase demonstrated that feeding guinea pigs the contact sensitizing agent 2:dinitrochlorobenzene rendered them hyporesponsive to subsequent intracutaneous exposures to the drug (9). The LEAP Study is the first randomized control trial to directly demonstrate the ability of early oral expose to prevent clinical food allergy in both sensitized and unsensitized children. Subsequent clinical studies are evaluating the feasibility of extending this early exposure regimen to other food allergens and cohorts of low risk children (10). A recent study led by McMaster University investigator Maxwell Tran has found that early introduction of eggs and milk is protective against the development of allergies to these foods (11). These findings may help shape future clinical guidelines and food allergy prevention strategies

Beyond these clinical implications, the LEAP Study findings lend credence to the theory that route of initial antigen exposure can dictate the nature of the antigen-specific immune response, be it tolerance or allergy. There is mounting evidence that early exposure to peanut through the skin may lead to allergic sensitization (12, 13), and the LEAP study has demonstrated that early oral exposure can lead to tolerance. Further research in this area will lead to a greater understanding of the biological mechanisms driving allergic sensitization and immune tolerance. ■

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Promoting a healthy gut microbiome in preterm infants

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Introduction

Establishing a healthy gut microbiome early in life is deemed essential for lifelong health, and recent research has begun to explore how profoundly important this is for preterm infants (1). Gut microbiome growth occurs in utero, during, and after birth, and is influenced by several factors such as mode of delivery, gestational age, type of feeding, environment of care, and antibiotic use (2,3). In healthy newborns, gut microbiome development begins with facultative anaerobes such as Lactobacillus, followed by the colonization of anaerobic genera including Bifidobacterium and Clostridium (2). Preterm infants demonstrate distinct imbalances of these microbiota, termed dysbiosis, putting them at risk for several adverse health outcomes (2). Specifically, the gut microbiome of preterm infants shows markedly decreased bacterial diversity, a lack of Bifidobacterium and Lactobacillus, and an increased colonization of potentially pathogenic microorganisms called Proteobacteria (2,4). Preterm infants born via caesarean section are at an even further disadvantage than those born vaginally, as the lack of maternal vaginal and epithelial flora exposure results in further abnormal alterations during gut microbiome development (5).

Consequences of Dysbiosis

Dysbiosis largely impacts the immune system, as the immune system and gut microbiome interact to establish normal digestive capabilities, build immune tolerance to foods and select antigens, and protect against pathogens (6). Thus, the low diversity of gut microbiota and resulting dysfunctional immune system are associated with a compromised gastric mucosal integrity. This perturbation and ensuing biochemical cascade may contribute to the development of life-threatening infections including sepsis and necrotizing enterocolitis (NEC) (1,4,6). Researchers have used stool sample analysis to confirm this, finding that preterm infants who develop NEC demonstrate significantly less bacterial diversity in their gut microbiome than controls (3). In addition to these imminent risks, asthma, obesity, diabetes, autism, depression, and inflammatory bowel disease are among the many long-term health conditions associated with abnormal gut microbial colonization in early life (2,5,7). Evidently, resolving this dysbiosis to promote healthy gut bacteria is essential for the survival and health of these vulnerable infants.

Probiotics

Probiotic use has been under study in the preterm neonatal population to rectify such microbial imbalances. Favourable outcomes have been observed in select clinical trials, including an increase in gut colonization and reduction in the incidence of NEC following probiotic administration (6,8). However, some concerns about the quality and scope of probiotic research to date as well as the regulation of these products seem to persist. Probiotics must survive in the gastrointestinal tract at high levels, however the minimum effective dose at which this occurs has yet to be elucidated (6). Reviews examining the safety and efficacy of probiotic use have concluded that there is a lack of systematic adverse events reporting in probiotic intervention studies coupled with poor intervention documentation (6). There is a need for the use of head-to-head studies in addition to improved and standardized detail reporting (i.e., type, duration, and amount of probiotic) to strengthen this knowledge base further (6). Outside of controlled research, probiotic supplementation has not been widely adopted in North American neonatal intensive care units (NICUs). This is partially due to concerns about the lack of a rigorous regulatory framework for these products, as well as difficulties associated with developing a domestically available formulation with evidence-based efficacy and safety (4). Probiotic administration to preterm infants likely requires additional research and practitioner uptake before

it will be fully integrated into practice.

Breastfeeding and Skin-to-Skin Contact

While the research and adoption of probiotic use is still in progress, lower risk avenues have been identified as promising interventions to develop the gut microbiome. Skin-to-skin contact is becoming widely encouraged in NICUs and consists of placing the infant between their mother's breasts on her bare chest (9). This practice has numerous health benefits including the promotion of microbial transfer and maintenance of lactogenesis (i.e., the production of breast milk) (5). Although minimal studies have directly examined skin-to-skin contact and microbiome development (9), researchers consistently cite this practice as having a positive influence on gut microbiome acquisition and diversity (2,5,10). Breastfeeding already has an extensive portfolio of health advantages, and is now regarded as an important mechanism for promoting gut microbiome health (4). Breast milk contains several bioactive compounds, such as immunoglobulins, cytokines, and oligosaccharides, which orchestrate the development of gut microbial communities (3). For example, feeding infants with breast milk in the NICU has significantly reduced the incidence of sepsis and NEC, and this reduction has been linked in part to the beneficial microbial species introduced into the infant gut by breast milk (1).

Conclusion

While evidence continues to accumulate, it can be concluded that addressing the microbiome in preterm infants and encouraging its diversity should be a priority for healthcare providers and researchers. Probiotics have demonstrated effectiveness in various clinical trials and are presently endorsed for use among preterm infants by the Canadian Pediatric Society (4). However, continued studies with improved designs and documentation will help to inform practice guidelines and persuade providers. More research is needed to solidify the benefits of skin-to-skin contact and breastfeeding in promoting healthful gut microbiome development, specifically in preterm infants. Nonetheless, these two practices represent low-cost and low-risk means to develop the preterm infant gut microbiome and can be championed by NICU staff for optimizing the acute and long-term health of these infants. ■

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Main Submission

Regulatory B cells: The new cells on the block to modulate allergic inflammation.

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Despite its heterogeneity, common clinical manifestations of allergic disease include redness, itchiness and swelling of the affected areas. In those with allergic disease, the exposure to allergens (e.g. antigens that healthy individuals normally have no reaction to, such as pollen and animal dander) can induce IgE-mediated inflammatory processes. The allergic response is canonically mediated by IgE antibodies against allergens, whereby cross-linking of IgE bound on the surface of effector cells propagate the allergic pathways. This can result in the maturation of cluster of differentiation 4^+ ($CD4^+$) T cells into T helper type-2 (Th2) cells and an increase in eosinophilia (1). Eosinophilia, a hallmark of allergic disease manifestation, is the infiltration of the granulocytic cell known as eosinophils, mediated by an increase in Interleukin (IL)-5. Overall, the allergic inflammatory response is facilitated by the release of type 2 cytokines, such as IL-4 and IL-13, which further induce the maturation of IgE-producing B cells (2; Figure 1).

It is thought that the induction of immunological tolerance can mitigate allergic inflammation through the desensitization of the immune system to allergens. Establishing tolerance involves the interplay of regulatory T cells (Tregs), the immunosuppressive IL-10 cytokine, and the process of T cell anergy where pro-inflammatory responses towards allergic substances are weakened (2).

Currently, there is a renewed interest in B cells as an integral component of both tolerance and the allergic disease framework. While B cells are normally associated with allergy pathogenesis through the production of IgE and other Th2 cytokines, evidence suggests that a subset of B cells (known as regulatory B cells or Bregs) have a regulatory role in suppressing allergen-induced inflammation (2). This review will discuss the inhibitory capacity of Bregs in allergic disease, their mechanism of inhibitory action, and their identification and role in allergen tolerance in human allergies.

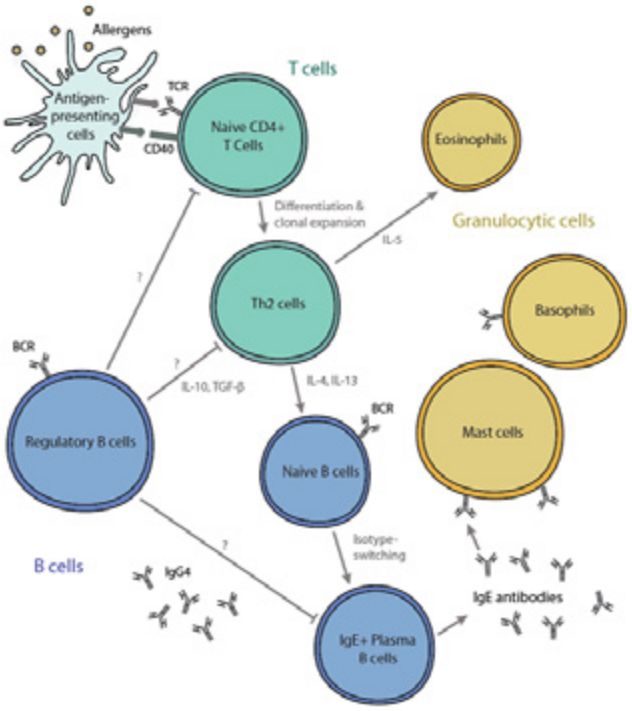

Figure 1. Pathogenesis of the allergic inflammatory cascade in asthma.

The Role of Regulatory B Cells in Allergic Disease

After the initial characterization of B cells with inhibitory properties by Katz et al. (3), several studies directly showed that the transfer of B cells induced tolerance and attenuated inflammation in mouse models of allergic airway disease, anaphylaxis, and contact hypersensitivity through IL-10 (4–7). Furthermore, IL-10-producing Bregs have been shown in humans at similar frequencies compared to Bregs in mice (5).

The Mechanistic Function of Regulatory B cells

Bregs are capable of attenuating inflammation at sites

of immune activation through the secretion of IL-10 (Br1) and TGF-β (Br3). IL-10 has been shown to have an immunosuppressive effect through the suppression of Th2 inflammatory processes by binding to T cell receptors and blocking co-stimulatory signaling. Meanwhile, TGF-β binds T cell receptors to encourage the maturation of Tregs, which have the capacity to inhibit the activation of effector T cells. The disruption of TGF-β receptor signaling has been shown to increase an individual's susceptibility to develop allergic asthma. While TGF-β has been implicated in mouse allergen tolerance, IL-10 has been implicated in that of humans; however further research needs to be done to determine whether B cell production of TGF-β also has allergen tolerance effects in humans. In addition, the inhibitory immunoglobulin, IgG4, is secreted by Bregs to induce a protective effect against IgE by interfering with allergen-IgE interactions and binding to excess allergen (2).

Currently there is interest in the application of Bregs in the field of allergy immunotherapy to achieve an induced state of tolerance and higher levels of IL-10, TGF-β, and IgG4-specific antibodies, thus modulating allergic inflammation (2).

Characterization of Regulatory B cell Phenotypes

CD19 is considered to be a pan B cell surface marker in both mouse and human models. However, Breg identification is difficult in humans due to a lack of a universal phenotypic characterization. Fortunately, there have been parallels between human and mouse phenotypic characterization of Bregs (5). Common phenotypes in literature used to identify Bregs include: $CD1d^{+}CD5^{+}$, $CD5^{+}FoxP3^{+}$, $CD24^{+}CD38^{+}$ and $CD24^{+}CD27^{+}$ (5, 10-11), which have been shown to exert their modulatory role through IL-10 production. Furthermore, it has been shown that these Breg phenotypes express forkhead box 3 (FoxP3), a transcription factor important for regulating the development and function of regulatory T cells. Although the current understanding of Breg development and differentiation into Br1 and Br3 is limited due to a lack of mouse and human studies of allergic inflammation (8), several studies are being conducted to elucidate the complexities of Bregs.

In humans it has been shown that levels of $CD5^{+}FoxP3^{+}$ Bregs were lower in the blood but higher in the airways of allergic asthmatics compared to healthy controls (9–11). These findings were supported by a higher proportion of $IL\text{-}10^{+}$ Bregs present in the airways of allergic asthmatics compared to healthy controls (10). Taken together, these findings suggest the possibility that Bregs may be trafficking to sites of inflammation to elicit immunomodulatory processes, however their suppressive roles may not be enough to overcome the chronic allergic inflammation experienced in allergic asthmatics.

Conclusion

While evidence shows that the primary mode of action of Bregs may occur at local sites of allergic inflammation in an IL-10-dependent manner, TGF-β and IgG4 antibodies may also play crucial immunosuppressive roles. Overall, further investigation into the functions and phenotypic identification of regulatory B cells will help build on the complex framework of the pathobiology of allergic disease with the goal of identifying novel drug targets for future therapeutic strategies. ■

List of abbreviations

Ag- Antigen, Br1 - IL-10-producing regulatory B cell, Br3 - TGF-β- producing regulatory B cell, Breg - Regulatory B cell, CD - Cluster of differentiation, FoxP3- forkhead box P3, Ig - Immunoglobulin, IL– Interleukin, TGF-β - Transforming Growth Factor β, Th2 - T helper type-2, Treg - Regulatory T cell

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John-Paul Oliveria

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Main Submission

IgE+ B cells in the pathogenesis of allergic asthma: fundamental but often forgotten.

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Introduction

As of 2012 the World Health Organization had declared asthma as the most common, non-infectious disease among children (1). In addition to debilitating health concerns clinically manifested as recurrent episodes of breathlessness and wheezing, asthma also poses significant financial burdens and is estimated to cost Canadians $4.2 billion by 2030 (1). As such, asthma research is warranted not only by the clinical symptoms patients face but also by the economic consequences of the condition. Allergic asthma (AA) is a chronic inflammatory disorder hallmarked by airway eosinophilia, airway hyperresponsiveness, and reversible airflow obstruction (2). AA is further characterized as an IgE-mediated disease whereby inhaled allergens trigger type 2 inflammation by binding to membrane-bound IgE on the surfaces of mast cells and basophils. This induces the activation and release of inflammatory mediators and promotes clinical symptoms such as wheezing, coughing and shortness of breath (2; Figure 1). Consequently, this allergen-induced, IgE-mediated inflammatory response has also been shown to incite increased allergen-specific IgE in the airways of allergic asthmatics (3). Since B cells solely produce IgE it is evident that these cells play a crucial role in initiating asthma-related inflammatory processes. The aim of this article is to provide a brief overview of the B cell and allergic asthma literature. The role of B cells in the pathogenesis of allergic asthma will be highlighted and therapeutic implications for targeting IgE and IgE+ B cells will be explored.

Role of IgE and B cells in allergic asthma

Limited studies have documented the role of IgE and IgE+ B cells in the pathogenesis of AA. Here we summarize the current literature available reporting on the levels of IgE and relative frequencies of IgE+ memory B cell subsets in individuals with AA. Wilson et al. (4) observed significant increases in allergen-specific IgE in the bronchoalveolar lavage fluid of allergic asthmatics 24 hours after segmental allergen challenge. This trend was observed in the airways, suggesting localized accumulation of allergen-specific IgE (4). Similarly, Van de Pol et al. (3) observed an increase in allergen-specific IgE that persisted for at least 5 weeks after whole-lung allergen challenge. This increase in allergen-specific IgE levels was supplemented by findings of significantly increased production of type 2 cytokines (e.g., IL-4, IL-5, IL-13) pivotal to AA pathogenesis (3).

IgE has been established as an effective therapeutic target for the treatment of AA given its role in the pathogenesis of the disease; however the trafficking and relative frequencies of memory B cell subsets that produce IgE have been sparsely explored. Kidney et al. (5) initially reported on the importance of B cells within the airways of asthmatics when they found that asthmatic sputum had a larger proportion of B cells within the lymphocyte population when compared with non-asthmatics. More importantly, Kidney et al. (5) reported that sputum B cells positively correlated with sputum eosinophils, further highlighting the potential role of B cells in AA pathogenesis. This paper was published approximately 20 years ago, and since then, very limited research has been done to determine the role of B cells in allergic asthma. However, if there is a strong relationship between the frequencies of B cells and eosinophils, determining a functional relationship between these two cells would shed light on whether B cells play a role in asthma disease severity. More recently, Oliveria et al. (6) demonstrated that higher levels of IgE+ B cells were present in the sputum of allergic asthmatics (12.2% of airway lymphocytes) compared to healthy controls (5.6% of airway lymphocytes), suggesting localization of IgE+ B cells in the airways of asthmatics. The proportion of B cells between allergic asthmatics and healthy controls were comparable between Kidney et al. (5) and Oliveria et al.'s

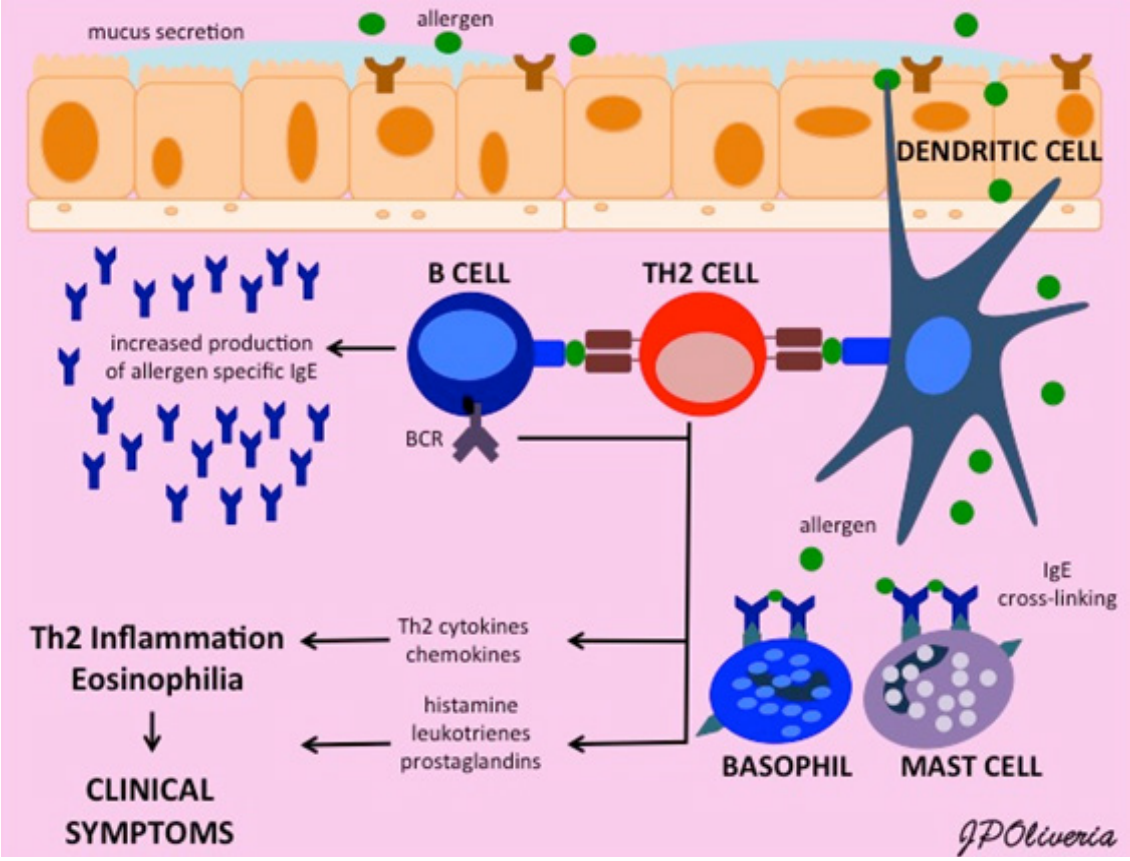

Figure 1: Pathogenesis of the allergic inflammatory cascade in asthma.

(6) studies. Oliveria et al. (6, 7) also showed that there were no changes in the frequency of IgE+ B cells in peripheral blood or bone marrow of allergic asthmatics following allergen inhalation challenge.

Wilson et al. (4) and Van de Pol et al. (3) both showed increases in allergen-specific IgE in the airways after allergen-induced exacerbations, implicating their relevance in disease manifestation and presence of clinical symptoms. Since B cells are the sole producers of IgE, further studies need to be done on characterization of B cells to determine their function in allergic asthma disease. Particularly, it is imperative to study the kinetics of IgE+ B cells following a whole-lung allergen challenge to determine whether changes to the IgE+ B cell population occur mainly in the airways. Considering currently published data, more studies also need to be conducted on the frequencies and function of IgE+ B cells and IgE in the airways of allergic asthmatics to delineate their role in AA pathogenesis. Specifically, characterizing the contribution B cells may add to local inflammation in the airways would further implicate their role in asthma pathogenesis.

Anti-IgE therapy - omalizumab and beyond

Having established the relative importance of B cells and IgE in the pathobiology of asthma, there is currently a focus on investigating treatments that specifically target IgE. Anti-IgE therapies have been efficacious in the treatment of moderate to severe AA, particularly in cases where inhaled corticosteroid therapy is ineffective. Omalizumab (Xolair®) is a humanized monoclonal antibody that binds to free, circulating IgE. This prevents IgE binding to high (FcεRI) and low affinity (FcεRII) IgE receptors on mast cells and basophils, thereby inhibiting the degranulation and release of inflammatory mediators (8). A systematic review by Rodrigo et al. (9) found that omalizumab therapy was able to reduce the rate of asthma exacerbations by up to 50% and significantly improve quality of life scores of allergic asthmatics (9). As an alternative to omalizumab, a new anti-IgE therapy being developed, ligelizumab, demonstrated an almost 50-fold increase in affinity to human IgE compared to omalizumab (10). Another alternative, quilizumab, which targets M1-prime (a protein specific to membrane bound IgE+ B cells), has been shown to reduce the production of IgE after allergen inhalation challenge (11). Despite the therapeutic potential of anti-IgE, major drawbacks of antibody therapies are their cost and that they must be

taken regularly for long-term treatment as their effects are known to wane following the termination of treatment (8). Additionally, anti-IgE therapies are prescribed to a small proportion of patients with moderate-severe allergic asthma. Thus ongoing research is being undertaken to explore the therapeutic effects of anti-IgE therapy in other diseases, including atopic dermatitis (itchy, sensitive skin) and chronic urticaria (rash, hives). It is important to explore the therapeutic effects of anti-IgE therapies due to the efficacy this therapy has shown in improving the quality of life of allergic asthma patients.

Conclusion

To date, limited research has alluded to IgE and B cells as integral components of the pathogenesis of AA, since targeting their depletion dampens disease manifestations. Although there are several anti-IgE treatments currently being developed in the treatment of asthma, including one already approved by Health Canada, there is still a long way to go before the development of a long-term therapy that can manage the diverse range of patients diagnosed with AA. In addition, further research on the function of B cells, particularly B cells located in the airways, needs to be conducted in order to gain a better grasp on the role of B cells in AA pathogenesis. This much-needed research will aid in anti-IgE and anti-B cell therapy development. However, beyond the search for new therapies, asthma-related research has vast potential to be translated into other domains of allergy and immunology, as well as the treatment of other IgE-mediated disorders. ■

List of Abbreviations

AA – Allergic asthma, FcεRI - high affinity IgE receptor, FcεRII - low affinity IgE receptor, IgE - Immunoglobulin E, IL - Interleukin

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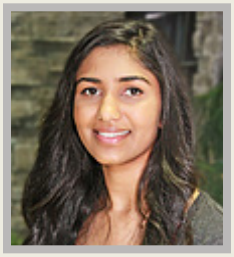

Spandana Amarthaluru

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John-Paul Oliveria

John-Paul Oliveria is a 3rd-year Doctor of Philosophy Candidate in the Department of Medical Sciences at McMaster University. He began his MSc in the McMaster Cardio-Respiratory Lab in 2011 and transferred to his PhD in 2013. His research focuses on the biology of B cells (IgE+ B cells and regulatory B cells) and the pathogenesis of allergic asthma.

Main Submission

Hair loss vs. emotion: How negative emotions could be increasing your hair loss

Rebecca Lewinson

Introduction

Alopecia Areata (AA) is a chronic inflammatory skin disease that affects hair follicles, causing marked hair loss on the scalp and body (1, 2). Globally, it affects 0.2% of individuals (3, 4), has a lifetime prevalence of 2% (4), and accounts for up to 2% of dermatology patients (1). The disease occurs equally within both sexes and affects individuals of all ages (2, 4). Although the etiology of AA is not known, there are various factors that may play a role in its occurrence and severity, including immune system dysfunction, genetic, and psychological factors (1). Some research has shown that AA may be exacerbated and precipitated by stressful life events (5), but it is generally accepted that AA has several psychosocial consequences including lowered self-esteem, depression, and less frequent social outings (3). Depression and anxiety are commonly diagnosed alongside of AA and researchers have found that there is a clear link between the severity of AA and depression and anxiety symptoms (4). As such it is vital that AA patients be screened and subsequently treated for any anxiety and depression symptoms that may be present both at the onset of their AA as well as throughout their illness.

Link between depression, anxiety, and Alopecia Areata

Individuals diagnosed with AA have been found to have a higher prevalence of both depression and anxiety, with incidence rates as high as 93% and 40% respectively in the United States of America (3). Since AA is a condition which can be quite traumatizing and psychologically damaging due to the social repercussions that are associated with baldness or thinning hair, researchers have explored this relationship to discover contributing factors to both anxiety and depression within the AA spectrum of severity. Several studies have found that although the incidence rate of AA is equal among males and females, females are particularly susceptible to anxiety, depression and other

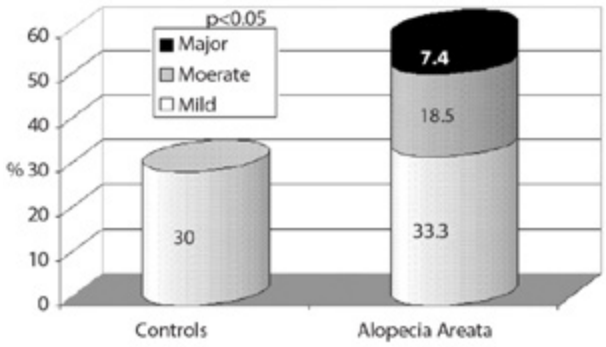

Figure 1. Depression Assessment of Healthy Controls and AA Patients over the age of 16 years (1).

psychological disorders (2). The reasoning for this is likely the social value that women place on their hair and the societal pressure placed on women to have hair, causing them more stress and trauma when their hair falls out (3). Additionally, women are less likely to accept changes in appearance, leading to lower self-esteem and therefore higher rates of depression (3). Figure 1 demonstrates the relationship between the severity of AA and the occurrence of depression when compared to controls (1).

Despite this link between AA and depression and anxiety it is still unclear whether AA is causing anxiety and/or depression or whether those who have anxiety and depression are more likely to go on to develop AA (2 - 4). There has been evidence that depression could be a precursor to AA, including one study which showed that the use of the antidepressant Citalopram during treatment of AA on patients with major depressive disorder significantly decreased their hair loss symptoms when used in conjunction with a dermatological treatment (5). Additionally, it has been shown that when depressed patients with AA underwent hypnotic therapy

alongside the use of the antidepressant Imipramine, their psychological well-being improved significantly, and their hair regrowth increased as well. This indicates that there may be some underlying relationship between depression and the severity of AA (5).

Links between life stressors and Alopecia Areata

In approximately 25% of AA patients in a 10-year study based in Boston, Massachusetts, a significant stressful life event such as a death in the family, family or work stress, or marital problems occurred prior to the onset of the disease (5). Additionally, it has been found in numerous studies that due to the stressful nature of AA, those who have a more severe form of AA (indicated by more persistent and diffuse hair loss throughout the body) are also found to have a higher prevalence of both depression and anxiety, indicating that stressful life events may accelerate the onset of AA (2, 4). Similarly, AA patients seem to have experienced more stressful life events when compared to their healthy siblings, indicating a link between stress level and symptoms relating to AA (5). Interestingly enough, the duration of the disease does not seem to be an accelerating factor to hair loss; instead, it has been found that the patient's anxiety and stress levels towards their disease are related to the severity of hair loss that they experience (2, 4).

Conclusion

Overall, AA patients experience a higher prevalence of both anxiety and depression when compared to the general population. Future research is needed to better understand the nature of this relationship and to determine effective treatment methods that combat AA as well as depression and anxiety symptoms. Based on the available evidence, one might speculate that the severity of AA may be related to the severity of which the patient experiences depression and anxiety symptoms. Stress appears to be implicated with the disease and exacerbates the symptoms of AA, which in turn seems to elevate symptoms of both anxiety and depression (1). Consequently, it has been suggested that psychological testing or screening should be completed in conjunction with a diagnosis of AA for all patients (1, 3). By properly managing and alleviating the symptoms for both anxiety and depression in AA patients, it becomes likely that the AA symptoms will also significantly decrease (5). This in turn may lower their overall stress and anxiety levels, which could lessen their symptoms even further. ■

List of Abbreviations

AA- Alopecia Areata

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Rebecca Lewinson

Rebecca Lewinson graduated from the University of Ottawa in 2014 with a B.Sc. specialization in Psychology. She has worked since 2013 as a research assistant, during which time her primary focus has been spent creating a reliable age-friendly checklist which hopes to improve the lives of senior citizens and disabled individuals through manipulating the built environment and social support structures that they experience, as well as aiding in developing an online wellness program for youth. Her main research interest lies in mental illnesses and the preventative applications associated with them. Rebecca has worked in the public health sector for over six years in various roles, including delivering programs to youth regarding mental health, and working as a senior medical scribe in an emergency department.

Main Submission

Does the weather play a role in psoriatic disease?

Ryan T. Lewinson[1]

1. Leaders in Medicine MD/PhD Program, University of Calgary, Calgary, Alberta, Canada

Introduction

Nearly one million Canadians live with psoriatic disease (1), the foundation of which is psoriasis. Psoriasis is an autoimmune disease characterized by regulatory T-cell defects leading to migration of immune cells to the epidermis, keratinocyte proliferation, and local release of inflammatory cytokines (2). This results in the classic psoriasis lesion, a sharply demarcated erythematous plaque with scale. Nearly 30% of individuals with psoriasis will progress to developing the associated condition of psoriatic arthritis (1). In this case not only does the individual experience skin lesions but also irreversible inflammatory joint damage. While genetic, lifestyle, and drug-related factors are believed to have a role in psoriatic disease (2), the contribution of environmental factors is less understood. We probably all recognize that our skin feels different from winter to summer, and similarly we may notice a particular 'sense' in our joints when a change in weather, such as rain, is imminent. Subjectively, we know the weather can affect our skin and joints, but what role does it have in the context of psoriatic disease?

Ultraviolet Radiation

One theory regarding climate and psoriatic disease has been that differing levels of ultraviolet (UV) radiation exposure alters immunologic signals related to psoriasis (3). This concept is central to treatment practices for psoriatic disease in which UV phototherapy can effectively improve psoriatic skin lesions (4). Given the benefit of UV light for psoriasis, one could then pose the question of whether healthy individuals who live in climates with higher UV exposure would be at reduced risk of developing psoriatic disease. In general, UV levels are increased towards the equator and decreased at the poles, as UV levels are directly related to proximity to the sun. Thus it might be hypothesized that national psoriatic disease prevalence would be inversely proportional to the proximity of a given country to the equator. However, Jacobson et al. (5) found that psoriasis prevalence was not correlated with a country's absolute latitude relative to the equator. This study, however, did not account for factors such as genetics, socioeconomic status, lifestyle, and comorbid disease, which are also associated with psoriasis.

From a joint pain perspective, few studies have been performed on the effects of UV radiation on psoriatic arthritis. For other inflammatory arthropathies conflicting evidence exists. For example, in the case of Cutaneous Lupus Erythematosus (CLE), UV exposure seems to be related to arthralgia for a subset of patients (6). Conversely, for Rheumatoid Arthritis (RA), it was proposed that UV exposure may reduce the risk of disease development (7). It is important to recognize that both CLE and RA are classically seropositive arthropathies, while psoriatic arthritis is seronegative. It is not yet known if this would influence biological response to UV exposure.

Humidity

Humidity is a measure of the relative amount of moisture in the air. Laboratory studies have found that when skin is exposed to low levels of humidity, the tissue responds by increasing keratinocyte proliferation and degranulation of Mast cells, resulting in epidermal hypertrophy and inflammation (8). These findings are similar to the pathologic changes associated with psoriasis plaques (2). However, an epidemiological study from Spain found that psoriasis prevalence was similar in the dry, central-regions of the country compared to other more humid regions (9). Thus the role of humidity in psoriasis remains unclear.

Regarding pain in psoriatic arthritis, no study has specifically investigated the role of humidity in day-to-day pain variability. A case was previously reported where 47%

of workers in a moisture-damaged health facility developed rheumatic arthralgia of which one case was psoriatic arthritis (10). This was believed to be associated with abnormally high relative humidity indoors, although fungal exposure could also be a possibility. Conversely to this, a "climate therapy" study conducted on Norwegians with psoriasis found that psoriatic symptoms including perceptions of joint pain seemed to improve when individuals were relocated to a tropical island (11). It is possible that UV exposure also contributed to these changes, but it seems evident that the precise role of humidity in joint symptoms in psoriatic disease remains unclear.

Conclusion

There appears to be preliminary evidence that weather plays a role in psoriatic disease, but its specific relationship to disease development, progression, and management have yet to be determined. Likely, weather-related factors interact with a combination of genetic and lifestyle susceptibilities inherent to the individual patient. These relationships may be further elucidated through prospective studies in which these baseline traits can be accounted for. This may provide insight as to how weather can impact psoriatic disease, improve our understanding of disease physiology, and how weather-related benefits and risks can be optimized for individual patients. ■

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ASK AN EXPERT

Canadian experts in the field of allergies, autoimmunity and microbiome were asked to give their opinion about breakthroughs with considerable importance in healthcare management and medicine. This section presents the thoughts and opinions of those specialists who spend their lives studying these issues from different perspectives.

Immune system over-reactivity – are allergens the real aggressors? Who is to blame?

Christine McCusker, MSc, MD, FRCP[1] & Adam Byrne, MSc, MD, FRCPC

1. Clinical Director, Clinical Immunology Laboratory (MCH), Head of Immunology, Special Interest Section-CSACI and Research Director, Meakins-Christie Laboratories MUHC-Research Institute

The immune system is a dynamic and versatile defence system capable of differentiating pathological molecules (or antigens) from harmless ones and forming appropriate responses. This system evolves in response to environmental changes and adapts to counter perceived threats. However the recent and rapidly changing profiles of these environmental exposures in the Western world may have led to the maladaptive responses seen in allergic (atopic) diseases. These increasing diseases include asthma, allergic rhinitis, food allergies and eczema which result from inappropriate responses to otherwise benign proteins or allergens. All allergens stimulate immune activation; non-allergic individuals form active immune tolerance, the appropriate adaptive response. In those with allergies, however, allergens induce proliferation and differentiation of CD4 T-cells into the TH2 phenotype which produces cytokines IL-4, IL-5, IL-9 and IL-13(1). These cytokines, in turn, can induce reactive airways and stimulate a B-cell switch to produce allergen-specific antibodies of the IgE class. IgE then binds to receptors on effector cells, including mast cells. (2). Allergen contact subsequently leads to IgE cross-linking, activation of the effector cells and the release of mediators such as histamine and tryptase (2). The rapid release of these mediators results in symptoms including hives, eczema, rhinitis, asthma, and anaphylaxis (2).

Activation of TH2 immunity appropriately occurs in response to threats such as parasitic infections. In the absence of these and other immune stimulators, genetically susceptible individuals may respond to allergen exposure with skewed activation of TH2 cells (3). Environmental influences such as increased hygiene and a reduction in exposure to complex antigenic environments and infection which collectively reduce overall immune stimulation may be causatively linked to the disproportionately increased frequency of allergic disease in the western world. This hygiene hypothesis, first proposed as an explanation for this burgeoning frequency of atopy, was based on observations that farm children experienced less atopy than their urban raised peers (4) and children of lower birth order also developed fewer allergies compared with elder siblings.

The microbiome hypothesis, a refinement of this concept, suggests that exposure to complex microbial flora, both pathogenic and commensal, results in the development of appropriate immune-regulation to allergens (3). The microbiome is the sum of symbiotic microbial species present in an individual, estimated to be over 100 billion in the GI tract alone (5). Evidence suggests that balanced immune regulation depends upon a healthy microbiome. In germ-free mice with no microbiome, T-cell dysregulation toward TH2 (6) and higher susceptibility atopic disease (7) is shown. Colonization of the germ-free mice with Bacteroides fragilis restored appropriate T cell balance (8).

In humans, alterations in the microbiome have been associated with increased atopy. One study showed lower numbers of total commensal microorganisms, including notable decreases in Bacteroides species, in food sensitive children compared with a control group (9). In asthmatic adults alterations in the pulmonary microbiome, including increased Proteobacteria and decreased Bacteroides

species, has been demonstrated (10). Events linked to altered gut microbiota including Caesarean section delivery, perinatal antibiotic use, and bottle feeding are also associated increased atopy (9). As such reducing infectious disease spread and external modulation of the microbiome through increased hygiene, antibacterial wipe use, and antibiotic use may be promoting the development of atopy in at risk individuals.

The practice of recommending food avoidance for pregnant and breastfeeding mothers, coupled with delayed introduction of "allergenic" food in infants, may also be contributing to the increase in food allergies. One study examining peanut allergy prevalence in genetically similar populations in Israel and England found a marked increase in peanut allergy in English children. They identified the key major lifestyle difference in peanut allergic versus non allergic children as delayed age at first introduction to peanuts (11). In the subsequent, randomized control trial there was a significant decrease in peanut allergies in children encouraged to consume peanuts early (between the ages of 4-11 months) as compared to those avoiding until 2 years of age (12). These results suggest that the development of tolerance to foods may be achieved with early introduction in the diet although the optimal timing and form of these introductions remain to be confirmed.

In summary current evidence suggests that promoting the formation of appropriate immune responses to allergens depends on the development of complex microbiota and introduction of complex antigens early in infant development. Allergens are otherwise harmless proteins. Promoting the formation of immunotolerance and targeting TH2 pathways will be the keys to reduction and prevention of atopic diseases. ■

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Christine McCusker

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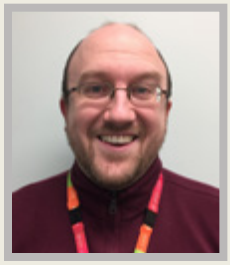

Adam Byrne

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Ask an Expert

How can we work our microbiome to improve our overall health and immunity – the good, the bad, and the ugly?

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Some see the microbiome as the new Wild West, a biological frontier to explore, populated with bacteria competing for ecological space. Studying the microbial populations within our bodies should lead to a better understanding of the role of microbes in our lives and, notably, the discovery of new ways to maintain and even improve our health. However, as in all good westerns, there is the good, the bad and the ugly. Now, let us explore the gut microbiome.

Most of the bacteria in our intestine benefit our organism and, as a whole, can even be considered as an organ. They are commensals and symbionts; we provide them with food and shelter while they perform essential functions like digestion and protection from pathogens. Due to its plasticity, our microbiome can evolve faster than our genome and therefore allow adaptation to external factors such as changes in food sources. For example, transfer of genes from marine bacteria to the gut microbiome of Japanese individuals could have allowed a better digestion of the seaweeds used in sushi (1).

Then there are the bad; pathogens or, more precisely, what some call the pathobionts (2). These are opportunistic pathogens that, in the right conditions, can cause infections. One of these turncoats is *Clostridium difficile*. This bacteria is present in 2-17% of healthy adults and lives a seemingly peaceful life inside a healthy intestine (3). However, when elderly people are exposed to antibiotics, the disturbance in their gut microbiome leads to an increase in *C. difficile*, which in turn can increase toxin production (4). These toxins are correlated with the severity of infection.

Finally, there's the ugly - not a specific microorganism but rather our lack of knowledge on the impact of external factors on the gut microbiome. We have known for years that antibiotics can alter the bacterial population within our gut, still very few studies have thoroughly evaluated the impact of antibiotic use on individuals. This is what we set out to do in our 2015 study which evaluated the impact of an antibiotic, Cefprozil, on the gut microbiome of healthy individuals (5). Previous research using this antibiotic suggested that it had a limited effect on the microbiome and few side effects (6). What we observed was somewhat different; indeed, the bacteria that comprised the majority of the gut microbiome were not affected by Cefprozil. Any impact was primarily observed in low abundance bacteria, whose precise functions are still not properly characterized. Only two bacteria were consistently increased after antibiotic treatment; one of them was *Lachnoclostridium bolteae*, a cousin of *C. difficile*. In addition, we observed a bloom of the opportunistic pathogen *Enterobacter cloacae* within a subset of individuals. These individuals also had lower initial microbiome diversity. This shows that antibiotics are not only modifying the gut microbiome, but that these modifications depend on the individual's initial microbiota.

This implies that medication and other medical interventions affect our microbiome in ways that we have yet to understand and predict. In the coming years we need to evaluate the effects of drugs on the microbiome in order to understand their hidden impact on their host. Only then will we be able to tame the ugly and guarantee that our microbiome remains beneficial to human health. ■

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Jacques Corbeil

Dr. Jacques Corbeil, Canada Research Chair in Medical Genomics, focuses on deciphering the interactions between agents such as HIV-1, respiratory viruses, other microorganisms, and the human host. Professor Corbeil's research generates large amounts of data, so his team is applying new algorithmic and bioinformatics approaches to sort out these complex host-pathogen systems.

Frédéric Raymond

Frédéric Raymond is a post-doctoral fellow at Laval University in Quebec City. His research interests converge around using bioinformatics and genomics to better understand infectious diseases and improve health. He loves working on large and complex datasets.

Ask an Expert

Immune system over-reactivity – Are allergens the real aggressors? Who is to blame?

Christopher J. Olesovsky, BHSc[1], Maxwell Tran, BHSc[1], & John-Paul Oliveria, BSc, PhD(c)[1*]

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The majority of allergic disease pathologies are caused by immunoglobulin E (IgE)-mediated mechanisms that are initiated by allergens. Although a number of different allergic diseases exist, we will focus on allergic asthma (AA), allergic rhinitis (AR), and food allergies, given their increasing global prevalence over the last 50 years (1). Worldwide, approximately 40-50% of children are sensitized to one or more common food or aeroallergens (1). Table 1 provides prevalence statistics in North America for common allergic diseases in both adults and children (1-4). One possible theory to explain the rising trend of allergic pathologies is the hygiene hypothesis. This theory was originally proposed by Strachan in 1989 and suggests that the increase in allergic conditions throughout the 20th century may be attributed to lower rates of infection and allergen exposure among children (5). Strachan believed that infections and unhygienic contact could promote protection against allergic diseases. Although his theory oversimplifies the observed phenomena and does not consider the importance of the timing of allergen exposure, disease phenotypes, the environment, and the individual's genotype, the hygiene hypothesis holds some truth in explaining the upswing in allergic diseases (5). This theory has still not gained widespread acceptance, largely due to contradicting evidence over the years. For example, one study indicated that low socioeconomic status in children was a strong predictor of the development of asthma, which indirectly demonstrates that unhygienic exposure may not be protective (6). More recent evidence has supported the hygiene hypothesis, suggesting that avoidance of common allergens in early childhood can predispose children to the development of allergies (7,8).

In 2000 the American Academy of Pediatrics (AAP) encouraged parents to delay the introduction of common food allergens, particularly peanuts, to infants considered at high risk of developing atopy (9). However, in 2015, the Learning Early about Peanut Allergy (LEAP) study found that children who regularly consumed a peanut snack had a lower risk of developing peanut allergy than children who avoided all peanut products (7). The study randomly assigned 640 infants between the ages of 4-11 months with risk factors for developing food allergies (severe eczema, egg allergy, or both) to either consume or avoid peanuts until 60 months of age. Prior to randomization, all participants underwent a skin prick test against peanut allergen to stratify participants based on their initial peanut allergy status. Infants that developed wheals greater than 4mm in diameter were excluded on the basis of having preexisting peanut allergy. Those with wheals less than 4mm in diameter were stratified into either a negative cohort (wheals <1mm) or a positive cohort (wheal 1-4mm) and then randomized to peanut consumption or avoidance. Infants in the consumption group were given at least 6 grams of peanut protein per week in the form of Bamba, a peanut butter and puffed maize snack (7). Among those in the negative cohort (n=530), the ratio of peanut allergy at 60 months in the avoidance group compared to the consumption group was over 7:1 ($p<0.001$). The ratio was lower in the positive cohort (n=98), but still over 3:1 ($p=0.004$), which further highlights the benefits of early peanut consumption (7). This groundbreaking LEAP study

Table 1. Current prevalence of common allergic diseases in North America

Type of Allergy	Prevalence in Children	Prevalence in Adults	Reference
Allergic rhinitis	40%	20%	1
Food Allergy	6%	4%	2
Allergic asthma	13.5%	8.5%	3,4

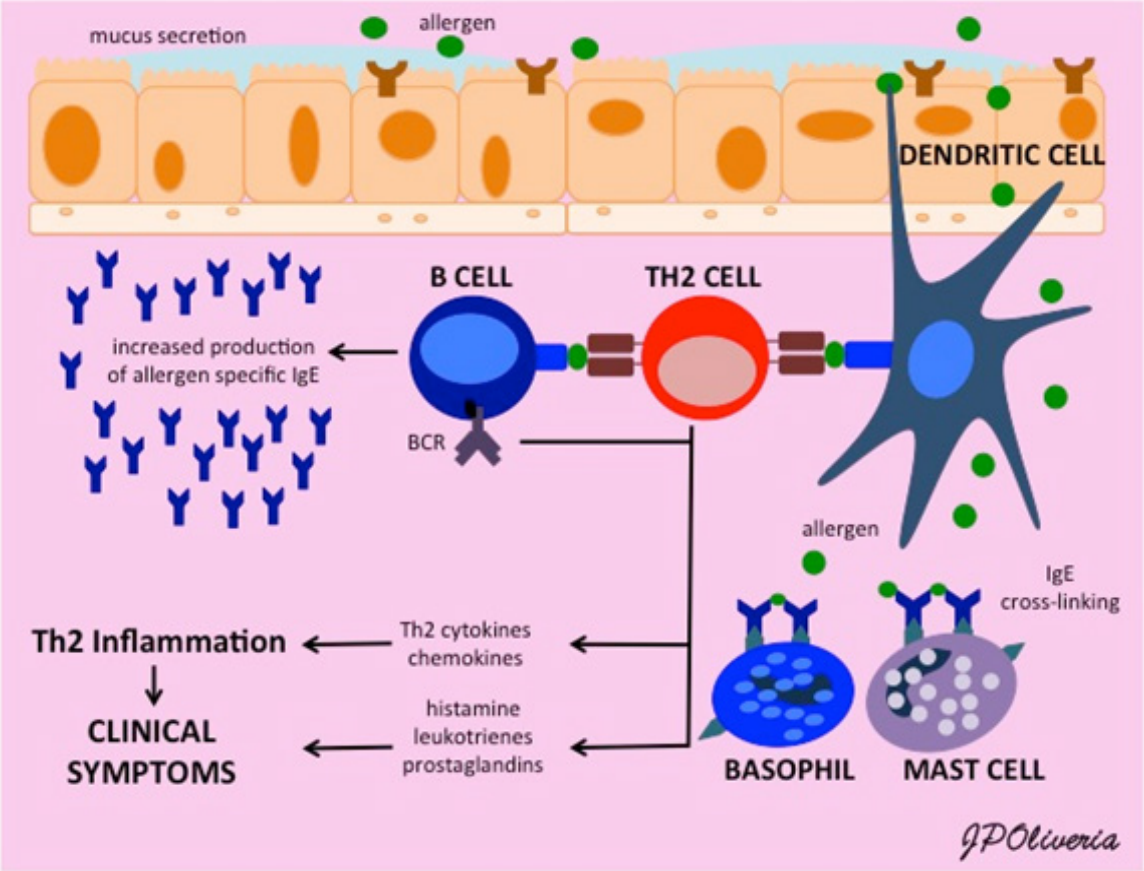

Figure 1. Pathogenesis of the allergic inflammatory cascade in asthma.

has a variety of implications, most significantly, starting a shift towards early exposure of potentially allergenic foods among children considered high risk for allergy (10).

In addition to the LEAP study, which specifically focused on peanut allergy, other studies have investigated the effects of early life exposure to other allergens. One such study investigated an inner-city birth cohort considered at high risk of developing asthma (n=560) (8). Within this cohort, a nested case-controlled study of 104 infants was completed to determine associations between environmental factors, aeroallergen sensitization, and recurrent wheezing at age three. In this study, children with the highest exposure to cockroach, mouse, and cat allergens during their first year of life were the least likely to have recurrent wheeze and allergic sensitization (odds ratios of 0.60, 0.65, and 0.75, respectively; $p \leq 0.01$) (8). This study suggests that early exposure to aeroallergens among children may also act as a protective factor against the development of early wheeze, a frequent precursor to asthma. Congruent with Strachan's hygiene hypothesis, the findings in this study strengthen his initial notion that exposure to allergens is critical for building tolerance at a young age to prevent the onset of allergic diseases (5).

Early exposure to common allergens seems to reduce the risk for developing allergies, but once an allergy does develop, allergen avoidance is highly suggested (yet sometimes unfeasible). The inability to avoid environmental allergens has resulted in vast research in drug development for the treatment of allergies. At the forefront of this exciting field is allergy immunotherapy, whereby increasing doses of allergen are administered to a patient to develop immune tolerance (11). Allergen-specific immunotherapy (AIT) is a desensitizing therapy that has the potential to decrease allergic symptoms if tolerated by the individual. The therapy modulates important cells in IgE-mediated inflammation, including T-cells, B-cells, basophils, eosinophils, and mast cells (11). In the pathogenesis of allergic diseases, T-helper type 2 cells are important cells in propagating allergic responses and inflammatory processes driven by type 2 cytokines (e.g., IL-4, IL-5, IL-13); however, by inducing a tolerant state in these peripheral T-cells, allergic inflammation can be dampened (refer to Figure 1 for an outline of the pathogenesis of the allergic inflammatory cascade). AIT promotes the generation

of allergen-specific regulatory T-cells, which effectively suppresses T-cell proliferation and the accompanying type 2 cytokine release (11). Several types of AIT exist, varying in routes of allergen administration, including oral immunotherapy (OIT), subcutaneous immunotherapy (SCIT), and sublingual immunotherapy (SLIT) (12). OIT has shown promising results among individuals with peanut, egg, and milk allergies, yet it remains unclear whether a permanent state of tolerance can be achieved using OIT (12). SLIT and SCIT are considered more effective than OIT because the allergen is directly absorbed into the blood stream with avoidance of first-pass metabolism in the liver (12). However, in order to achieve the desired clinical effects of these treatments, compliance is of critical importance. A recent retrospective analysis found that only 23% of SCIT users and 7% of SLIT users complete the recommended 3-year treatment duration, which may prevent the desired clinical effects of immunotherapy (13). Fortunately, alternative therapeutics are being developed to attenuate allergen-induced responses. Although these therapies are not curative, they are effective in reducing allergic symptoms. Two of the most promising therapies include omalizumab, a humanized antibody that selectively binds to the heavy chain of free IgE in the serum, and mepolizumab, a humanized monoclonal antibody against IL-5 (14). One study found that targeting thymic stromal lymphopoietin (TSLP), an upstream cytokine that promotes allergic inflammation, with an anti-TSLP antibody could also effectively attenuate allergen-induced airway responses in patients with mild AA (15). Another potential therapy is an antibody against the alarmin cytokine IL-33, another upstream cytokine in the allergic cascade (15,16).

Although allergens are the aggressors when it comes to initiating an allergic response, early life exposure may confer protection against their development. Furthermore, after allergic sensitization, AIT can be used to desensitize an individual to certain allergens. Thus, allergens cannot always be perceived as the enemy; in some cases, they serve as valuable assets in protecting against and treating allergies. Due to the increasing prevalence of allergic diseases continued investigation into novel therapies for allergy treatment is imperative. ■

List of Abbreviations

AA - allergic asthma, AR - allergic rhinitis, AIT - allergen specific immunotherapy, IgE – immunoglobulin E, LEAP - Learning Early about Peanut Allergy, OIT - oral immunotherapy, SCIT - subcutaneous immunotherapy, SLIT - sublingual immunotherapy, TSLP - thymic stromal lymphopoietin

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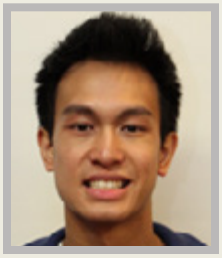
John-Paul Oliveria

John-Paul Oliveria is a 3rd-year Doctor of Philosophy Candidate in the Department of Medical Sciences at McMaster University. He began his MSc in McMaster Cardio-Respiratory Lab in 2011 and transferred to his PhD in 2013. His research focuses on the biology of B cells (IgE+ B cells and regulatory B cells) and the pathogenesis of allergic asthma.



Maxwell Tran

Maxwell Tran is a 3rd year Bachelor of Health Sciences (Honours) Candidate in the Faculty of Health Sciences at McMaster University. He is a research student at the Firestone Institute for Respiratory Health and the McMaster Cardio-Respiratory Lab. His research focuses on uncovering the early life determinants and prognostic factors for food allergies and allergic asthma.

Christopher J. Olesovsky

Christopher J. Olesovsky is a 4th-year Bachelor of Health Sciences (Honours) student at McMaster University, and he is set to graduate this coming May 2016. He has been working at the McMaster Cardio-Respiratory Lab for the past two years as a research student. He completed his 3rd year project in 2014-2015 and he is currently completing a 4th year thesis project.

SPOTLIGHT ON CAREERS

Interview with Dr. Claudia Hui - an Analyst at Bloom Burton & Co.

By Rebecca Liu

"Dr. Claudia Hui completed her PhD in Immunology at McMaster University investigating how genetic and environmental factors influence the development of allergic diseases and asthma, with particular emphasis on the role of epithelial-derived mediators in linking epithelial injury, tissue responses, and the recruitment and differentiation of progenitors into effector cells of allergic disease. Prior to this, Dr. Hui received her MSc in Physiology and Pharmacology from McMaster University and a BSc. in Physiology from McGill University. Dr. Hui is currently working as an Analyst at Bloom Burton & Co., a healthcare-specialized investment bank in Toronto, where she conducts technical and commercial due diligence and strategy consulting in biotechnology and healthcare. Dr. Hui's expertise helps the Bloom Burton & Co. team with monetization planning and determining the fundamental value of companies across all healthcare sectors."

1) What steps did you take to find or acquire this position? In particular, what educational background and extracurricular involvement helped prepare you for this position?

I stumbled across this position serendipitously, but I would say discipline, hard work and sheer tenacity landed me this job. I had initially considered going into Management Consulting (in September 2013). To prepare myself for a change in career path from academia to that, I did a lot of research and spoke with several Management Consultants. I joined McMaster's Graduate Management Consulting Association (GMCA) and signed up for the various courses they offered, including Mini MBA Lecture Series and Practice Case Interview Series.

In April 2014, Bloom Burton & Co. advertised their exclusive networking event for those interested in employment opportunities through GMCA. I submitted my resume and was selected to attend. During the event, I met everyone at the firm and gained valuable insight on Bloom Burton & Co., the people and culture, and its values.

Following the event, I reached out expressing my interest for a job as a contract consultant; however, nothing panned out (immediately) – I was told that I would be contacted when the Bloom Burton & Co. team has the need for my assistance. I was disappointed and a little deflated. However, in May 2014, the opportunity presented itself: Bloom Burton & Co. contacted me for an opportunity to work on an ad-hoc project as a contract consultant. Although I was wrapping up my experiments, writing up my thesis and preparing for my defense, I knew this was an opportunity I had to take. One project led to another, and before I knew it, I contracted on various projects while finishing my PhD.

In September 2014, Bloom Burton & Co. was hiring for an Analyst. Given that my previous experience had all been limited to jobs in research and academia, I reached out

to a few of my contacts to gain insight on what industry would be looking for. I was invited to do a case study, and subsequently, an in-person interview. Again, I turned to my contacts to familiarize myself with industry interviewing processes. I even did three to four mock interviews with them. I was offered the position in late November 2014! And officially made my jump into industry and started my career as an Analyst in January 2015.

2) What unique non-academic skills do you believe are most valuable in your current position?

Curiosity and skepticism. It is important to be curious, and also to have the desire to learn more and seek evidence to support the information and data companies present to you. I think in science especially, people always try to showcase their best results, and so it is important to be critical of data and conclusions companies present to you and not blindly believe everything they tell you.

3) Can you briefly describe one of the projects you are currently working on?

One of my current projects involves advisory and support work that covers a broad range of tasks, mainly indication, product and company assessments, and prioritizing new opportunities that align with our client's business model. I explain each of these briefly below:

Indication Assessment: Involves providing the client a general overview of the specific indication of interest, standard of care, unmet need, clinical path, market dynamics (i.e., market size, pricing, reimbursements, etc.) and competitive landscape. Our deliverable informs the client whether the indication of interest provides a sound business case.

Product/Company Assessment: Includes both the assessment of companies, as well as individual assets (a program within a company that our client may be interested in acquiring or in-licensing). Our work covers early-stage all the way to commercial-stage companies. This also includes review of data room material (i.e., experimental data, intellectual property, regulatory filings and correspondences, balance sheets, etc.). Our deliverable includes an assessment on the merit of the science, indication, market potential, timelines and inflection points, competitive landscape, etc. We also suggest potential deal structures and possible next steps our client could take.

Company Triaging: Over the span of several months, we assessed numerous companies and products and provided an individual assessment on each opportunity. Our interim deliverable included a product/company review matrix that prioritized the opportunities based on a list of criteria we assessed, and this in turn allowed our client to pursue specific opportunities and to start the negotiation process.

4) What are some of the benefits and drawbacks of your current position and how does it relate to your training in allergy and autoimmunity (if applicable)?

My firm is quite unique in the sense that it is an investment bank, but we also have other services we provide, such as consulting and company incubation.

With that said, there are many benefits of my current position. First and foremost, I get to wear many different hats depending on whom our clients are. I get to interact with senior management, as well as leading scientists who discovered the technologies.

Furthermore, I love learning and this job allows me to learn on the job, every day! I learn about different technologies and indications, which allows me to develop detailed knowledge about the various technologies and sectors. I learn to analyze companies and science from the perspective of investors, which is something that does not come naturally to a scientist. I also get to put my education to use. My PhD comes in handy since immunology tends to play a big role in drug development.

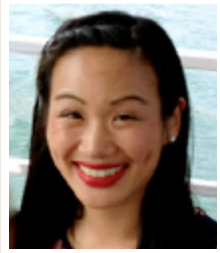
Finally, as a scientist by trade, we all hope to see (our) research go from bench side to bedside. My current position gives me the opportunity to do exactly that – I get to partake and witness great science and technologies go from the labs to the clinics.

A drawback is that the field moves very quickly. While that can be very exciting, it also means that I constantly have to keep up with the latest advances in the field, all of which can and will have a direct impact on my work, whether assessing new technologies and companies, or providing advisory work for companies. However, this is no different than when I was in graduate school, where I constantly had to keep up with the latest publications and discoveries in my field. What is different now is that I no longer just follow the allergy and immunology space, but I have to follow the full spectrum, from oncology to schizophrenia, to rare orphan diseases. Consequently, the hours can get pretty long and I find myself sitting in front of the computer a lot.

5) Can you give any advice to graduate students looking to pursue a career within your field?

I will pass on an advice that I received from a professor and mentor of mine before I started my job at Bloom Burton & Co:"Always be skeptical of the science/data. Most of what you will see will be cherry-picked and "spun". Never take anything at face value."

Through my own experience, another piece of advice would be to NETWORK! People and companies are always looking for talent, and many times, it is just a matter of meeting the right people at the right time. ■



Rebecca Liu

Rebecca H. Liu is a second-year PhD candidate in Health & Rehabilitation Sciences (Health Promotion) at the University of Western Ontario. Her research focuses on using health coaching as a behavioural intervention among specialized populations to reduce cardiometabolic health risk.

Interview with Dr. Steven Smith - a Scientific Advisor at GSK

By Rebecca Liu

"Steve Smith completed his PhD at McMaster University and Post-doctoral training at St. Joseph's Hospital in the Firestone Institute for Respiratory Health. Mr. Smith currently works as a Scientific Advisor in the respiratory division of GlaxoSmithKline. This experience has allowed him to work as a member of an interdisciplinary team, and participate in grant and pharmaceutical sponsored trials, which have had varying degrees of complexity and challenges."

1) What unique non-academic skills do you believe are most valuable in your current position?

The great thing about academics is that you develop a range of skills that are not all about techniques and the ability to reference a paper from memory. For example, I developed the skills to manage people while I was a graduate student. I developed the skill of communicating complex ideas in an understandable manner. And last but not least, I developed the skill to know how to challenge myself and reflect on how to improve.

2) Can you briefly describe one of the projects you are currently working on?

In the Medical Affairs department, we engage with the scientific community to better understand the needs of patients through sharing ideas with health care professionals.

3) What are some of the major benefits and drawbacks of your current position and how does it relate to your training in allergy and autoimmunity (if applicable)?

The major benefit of my position is that I am able to utilize the knowledge I gained as a graduate student in the Department of Allergy and Immunology to engage with the scientific community. As mentioned above, academics provides you with the skills you need to achieve at a high level in any career path.

4) Can you describe the landscape and scope of opportunity within your field for Master's and PhD-trained students?

My department is comprised of PhDs and MDs. There are very few MSc's in Medical Affairs.

5) Can you give any advice to graduate students looking to pursue a career within your field?

Get clinical experience. The reason I believe I was selected for the position is that I had direct clinical experience. My PhD was in a lab that performed clinical trials, so I was familiar with the pharma industry and how they interact with academics. Also, be open to any position available. You never know. You might like a pharma position that you weren't thinking of initially when deciding on potential career paths.

6) What are some resources (websites, readings, listings) that you can recommend for graduate students interested in this field?

Unfortunately, the pharma industry is very closed off. I am still learning of new positions, and still don't know of all of the positions available. The best thing to do is to discuss your ideal position with someone that is already in that position, and they might be best able to help you navigate the complex system. ■

Interview with Dr. Bhargavi Duvvuri - a Postdoctoral Fellow working on Rheumatoid Arthritis and Peptide-based immunotherapy at McMaster University

By Effie Viguiliouk

"Dr. Duvvuri is a Michael G. DeGroote Postdoctoral Fellow (basic biomedical sciences) at Dr. Larché's laboratory, Department of Medicine, McMaster University, Hamilton, Canada. Dr. Duvvuri works in the field of peptide-based immunotherapeutics for the treatment of autoimmune (rheumatoid arthritis) and allergic diseases including the investigation of underlying molecular mechanisms. Dr. Duvvuri has also been responsible for designing in-silico pipelines, immunological protocols and executing clinical trials related to allergen-related immune products. In addition, Dr. Duvvuri is a project management liaison between a laboratory at McMaster University and the industrial sponsor Adiga Life Sciences.

Previously, Dr. Duvvuri worked as the Arthritis Society and the Canadian Arthritis Network Postdoctoral fellow at the Hospital for Sick Children Research Institute, Toronto, Canada. Her research studies on childhood Arthritis were focused on the development of molecular screening methods for the categorization of patients based on their clinical, phenotypic and epidemiological data. Dr. Duvvuri did an MSc in Biotechnology from Osmania University, India and a PhD in Health Sciences from York University, Canada. Her PhD research demonstrated molecular basis for different aspects of immune diversity that have broader implications in understanding immune surveillance, autoimmunity and antibody related cancers. She also conducted collaborative research on infectious diseases to investigate the interplay of host cellular immunity and pathogen evolution – particularly on avian and human influenza viruses. For her PhD studies, along with various fellowships and awards, Dr. Duvvuri was honoured with The Canada's Governor General Academic Gold Medal (2013), the most prestigious award that students in Canadian schools can receive for outstanding academic excellence at the graduate level. In addition to research, she is passionate about teaching and mentoring students."

More info: https://ca.linkedin.com/in/dr-bhargavi-duvvuri-0079b24b

1) Can you briefly describe one of the projects you are currently working on?

My current and long-term research focus is to explore mechanisms underlying pathophysiology of autoimmune diseases (ADs) and apply that knowledge towards the development of disease-modifying and possibly preventive therapies for ADs.

In continuation of my research experience in autoimmunity and arthritis, I came to McMaster University to work on Rheumatoid arthritis (RA). RA is an autoimmune disorder in which the immune system mistakenly attacks its own body's tissues. It is not clear how the disease starts. Existing research suggests that, on top of genetic factors, one of the triggers for RA may be a change in one amino acid called arginine. An enzyme in the body called Peptidylarginine Deiminase (PAD) can change arginine amino acids into an unnatural amino acid called citrulline. As a consequence, natural proteins in the body that contain the amino acid arginine are changed into proteins with citrulline in them. Because the immune system has never seen these novel proteins before, it attacks them, causing inflammation, especially in the joints. A type of white blood cell called "CD4+ T cells" can detect the changed amino acids in small fragments of the new proteins. The fragments are called "peptides" or "epitopes". These peptides trigger the T cells to make and release signals (called "cytokines") that drive inflammation in the joints. My proposed study aims to identify the citrullinated epitopes responsible for driving RA. These identified epitopes can potentially be used to

develop a therapeutic vaccine for RA in a form of peptide-immunotherapy.

2) What steps did you take to find or acquire this position? In particular, what educational background and extracurricular involvement helped prepare you for this position?

My current post-doc position is mainly focused on RA. Hence, having a PhD in immunology with experience in in silico epitope discovery, along with laboratory research experience in arthritis that included a prestigious fellowship from the Arthritis Society of Canada helped me to acquire this position. Interdisciplinary research skills were also very important. I worked on various projects that required bioinformatics, as well as basic and clinical immunology skills. I have utilized every opportunity to continue in a research and academic career such as lab experience, delivering research talks and lectures, presenting my research findings in conferences, supervising students, serving as a judge in science fairs, etc.

3) What unique non-academic skills do you believe are most valuable in your current position?

Perseverance, good work ethic, ability to work in a team, being able to quickly adapt to projects, emotional stability, openness to challenges, and being goal-oriented.

4) What are some of the benefits and drawbacks of your current position investigating allergy and autoimmunity?

My current position is unique in the way that I work in an academic setting, but in the scope of an industrial background. Hence, apart from working on basic research questions, my project has a huge translational potential to bring our research findings from clinical development to the clinic.

Benefits: Availability of resources, access to cutting-edge technologies and real-time knowledge/experience on how a research finding is brought to the level of a clinical product.

Drawbacks: There are not many, if a person has the non-academic skills as mentioned above.

5) Can you describe the landscape and scope of opportunity within your field for Master's and PhD-trained students?

There is a great scope of opportunity for students in the field of ADs. Tremendous progress has been made over the years in the understanding of pathophysiological mechanisms underlying ADs. Hence, numerous opportunities at both the theoretical and technical levels exist to further our understanding of ADs in the areas of biomarkers development, etiology, immunology, epidemiology, and clinical therapeutics with the ultimate goal to develop novel approaches for the prevention and treatment of ADs.

6) Can you give any advice to graduate students looking to pursue a career within your field?

As I said before, there is huge potential in this area of research. The key is to start early and gain experience in research at basic and clinical levels. Maybe work as a volunteer, or as a summer, thesis or co-op student. It is very important to gain as much experience as you can. Do not limit yourself to just wet lab research. With a wealth of genetic data accumulating from research, there is also a greater need for computational approaches to analyse data. Having basic knowledge on programing skills and computational tools will help in the long run. Hence, starting early will allow you to explore opportunities in as many areas as possible. Contact supervisors and apply for independent funding where ever possible; having your own fellowship bolsters your research career and your chances of getting into prestigious laboratories. Make a routine habit of reading scientific literature of interest that will expand your perspective on your field of interest.

7) What are some resources (websites, readings, listings) that you can recommend for graduated students interested in this field?

I update myself on ADs by reading peer-reviewed journals related to immunology and medicine, and by attending research talks and seminars/webinars in hospitals and universities. I also sign up for e-alert services of leading journals, and organizations/societies in this field. ■

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