

Innovation from cell to society



Success Stories



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Making a Difference From cell to society

AllerGen NCE Inc. (AllerGen), the Allergy, Genes and Environment Network—one of Canada's Networks of Centres of Excellence (NCE)—is pleased to present its eighth issue of *Success Stories*, featuring the research accomplishments of allergy, asthma, anaphylaxis, genetics and environment researchers, their students and partner organizations.

The Fall 2014 issue of *Success Stories* shares results from AllerGen-supported projects exploring new and emerging topics in health research. Feature stories highlight:

- the ethical implications of biobanking;
- an international partnership to improve asthma care in El Salvador;
- the workplace productivity loss associated with uncontrolled asthma;
- a new clinical trials group studying allergic rhinitis; and
- an AllerGen trainee at the forefront of Canada's microbiome research.

Since its inception, AllerGen has supported innovative research and development, capacity building activities, stakeholder engagement and partnerships that foster research commercialization, social innovation and knowledge mobilization, enabling Canadians to better prevent, manage and treat allergy, asthma, anaphylaxis and related immune diseases.

Now nearly ten years into its mandate, the Network pursues its goals with mature and globally-connected research teams; a balanced portfolio across investments in discovery, development, commercialization and knowledge mobilization; and an integrated research strategy spanning three Legacy Projects and three Enabling Platforms that build upon core research investments established in 2005.

Legacy Projects:

- **Canadian Healthy Infant Longitudinal Development (CHILD) Study**

This national birth cohort study collects immunological, physiological and genetic data from over 3,300 Canadian children from pre-birth to age five in order to explore the root causes of asthma, allergies and other chronic immune and inflammatory diseases.

- **Clinical Investigator Collaborative (CIC)**

This multi-centre, Canadian-based Phase II clinical trials group fast-tracks early-stage potential drug candidates for allergic asthma, severe asthma and allergic rhinitis to accelerate the development of new therapies for allergic disease.



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- **Canadian Food Allergy Strategic Team (CanFAST)**

This highly innovative, nationally networked research team contributes to our understanding of the origins, causes, prevalence and treatment of food allergy and anaphylaxis, and informs the development of improved clinical management strategies and public health measures.

Enabling Platforms:

- **Gene-Environment Interactions**
- **Biomarkers and Bioinformatics**
- **Patients, Policy and Public Health**

Written for Canadian families and healthcare providers, *Success Stories* offers those living and dealing with allergic conditions and related immune diseases practical information about the latest leading-edge research results. We hope you enjoy reading this issue of *Success Stories*. [A](#)

Judah A. Denburg
Judah Denburg, MD, FRCP(C), Scientific Director and CEO

Diana Royce
Diana Royce, EdD, Managing Director and COO

What obligation do researchers have to return samples—and report any unexpected findings from them—to patients and their families? Should patients have access to the results of experiments that use their specimens? What happens to the personal information that is shared?



The Ethics of Biobanking: Is the Public On Board?

There is a good chance you have either decided to become an organ donor or at least entertained the idea. But have you ever considered donating your DNA, blood or urine—even a tumour—to science? The collection of biological samples for future research is called biobanking, and in 2009 *Time Magazine* flagged it as one of the top-ten ideas that is changing the world.

The practice began decades ago with small, university-based biobanks set up for specific research needs. It was not long before governments and other institutions established their own biobank repositories, storing increasingly sophisticated specimens and information about the people who provided them. Today, several countries, Canada among them, have set up population-wide biobanks.



**Timothy Caulfield, Professor,
University of Alberta**

Biobanks can make substantial contributions to medicine, allowing researchers to link genetic material and other biological data to various aspects of health and disease. This is precisely the goal of the landmark Canadian Healthy Infant Longitudinal Development (CHILD) Study—funded by Allergan and the Canadian Health Institutes of Research (CIHR)—which is following 3,300 babies from birth to age five, collecting biological samples such as breast milk, blood, urine, feces and nasal secretions. Along with detailed dietary and socio-economic information from parents, samples of outdoor and indoor air quality, and dust particles from homes, these biobanked samples will provide vital data to help scientists understand how the complex interplay between genes and the environment contributes to the development of asthma, allergies, Type 2 diabetes and cardiovascular disease, among other conditions.

Modern research: an ethical dilemma

While most Canadians agree that biobanking moves research several steps forward, complex ethical issues surround the practice. The ethical implications raise questions such as: What obligation do researchers have to return samples—and report any unexpected findings from them—to patients and their families? Should patients have access to the results of experiments that use their specimens? What happens to the personal information that is shared?

Professor Timothy Caulfield, a University of Alberta law professor and Canada Research Chair in Health Law, finds the

topic so “endlessly fascinating” that he has devoted significant energy to studying it.

“I consider biobanking one of the greatest challenges in research ethics, not just nationally but throughout the world,” says Professor Caulfield, who is also an Allergan Principal Investigator and the author of *The Cure for Everything: Untangling the Twisted Messages about Health, Fitness and Happiness* (Viking Canada).

With funding provided by Allergan, Professor Caulfield’s recent study of biobanking ethics is one component of his broader analysis of the legal and ethical issues surrounding allergy and asthma research. Through this work, he hopes to establish ethically sound, evidence-based health research policies applicable to the study of allergy, asthma and anaphylaxis.

In research we trust?

To get a sense of Canadians’ attitudes toward biobanking, Professor Caulfield asked them directly. His 2012 telephone survey polled over 1,200 Albertans to ask a series of questions about trust, consent, withdrawal of consent, access to data, and ownership of material. They were also asked about a relatively new aspect of biobanking: commercialization.

When the results were analyzed, it came as no great surprise to Professor Caulfield to learn that “people have a lot of trust in university researchers, but their level of trust declines when industry is involved.”

This poses a practical problem: “It’s expensive to maintain a

PUBLIC TRUST IN BIOBANKING RESEARCH			
Individual or group involved in the research	Trust a great deal	Trust somewhat	Do not trust at all
Insurance industry	7.1%	46.4%	46.5%
Provincial governments	18.7%	60.4%	20.8%
For-profit industry	6.0%	31.4%	62.6%
Data collection organizations	33.6%	54.4%	12.0%
Disease-based foundations	40.0%	50.2%	9.8%
Government-funded university researchers	45.1%	48.7%	6.2%
Industry-funded university researchers	19.5%	53.6%	29.6%
Hospitals	46.9%	46.6%	6.5%
Doctors	60.7%	34.8%	4.5%

Source: Caulfield et al. Biobanking, Consent, and Control: A Survey of Albertans on Key Research Ethics Issues. *Biopreservation and Biobanking*, 2012; 10, (5): 433-8.

biobank and institutions don’t always have the funds to sustain the initiative, so they increasingly turn to industry to help share the costs,” he explains. While people understand the need for commercialization, “They’re not happy about it and are less inclined to give industry *carte blanche* with their samples.” An Australian study reached a similar conclusion. “It’s an issue that the medical community will have to address going forward,” says Professor Caulfield.

To consent or not to consent

By their very nature, biobanks bring up consent issues that don’t arise in traditional “one-off” research projects: When providing a specimen for future research, does the donor give unlimited consent? Should the donor be able to provide or decline consent separately for each potential research application? Should a donor be permitted to withdraw consent if, for example, a private company becomes involved with the biobank handling their specimens?

Professor Caulfield’s survey sheds light on some of these questions. As it turns out, a slim majority of Albertans (51.8%) are willing to provide “broad consent,” meaning unconditional permission for researchers to repeatedly use their samples. At the other end of the spectrum, close to one in five (18%) would prefer to be asked every time a sample is used. The remainder (30.8%) would like to have a say in *how* their samples can be used. For example, they may allow their tissues to be used for developing cancer treatments, but not cosmetics. Or they may give their blessing to the use of their samples in certain commercial enterprises, but not others.

According to Professor Caulfield, many biobanks function on the presumption of broad or general consent: “Give us your samples and we’ll do a variety of studies on it.” The Alberta study results underscore the need for more debate on the issue, he says. Even if those who prefer to have control over every use

of their samples represent a minority, Caulfield says, “It’s a big challenge on a population level.” The legality of broad consent is also at issue. “Current laws don’t make it clear whether the practice is legitimate,” he adds.

As part of this AllerGen-supported study, Professor Caulfield’s research team undertook a comprehensive analysis of the international literature on broad *versus* informed consent for biobanking projects. From an analysis of 593 articles on the subject, they learned that, just like Canadians, people in other countries do not agree on questions of consent. In a U.S. analysis, for example, 48% of respondents were comfortable giving broad consent, 42% favoured specific consent, and 10% said they would opt for something in between.

Although some experts see nothing ethically or legally suspect with broad consent, Professor Caulfield maintains there is clearly more work to do in this area. “It’s not that we need public consensus to develop sound research policies,” he says. We do, however, “need to understand how the public feels so we can prepare for future controversies.” Indeed, individuals have already filed a number of lawsuits concerning consent, privacy and data protection. “These cases remind us that not all biobank donors are willing to waive their right to informed consent.”

In Texas, for example, the Department of State Health Services (DSHS) provided over 8,000 samples of newborn “bloodspots” (tiny spots of dried blood left over from mandatory newborn screening tests) to researchers between 2002 and 2009. As the DSHS did not obtain parental consent to distribute these samples, the Texas Civil Rights Project brought a class action suit against the state in March 2009. As a result, over five million bloodspot samples were destroyed.

Like the requirement to obtain consent, a donor’s right to withdraw previously given consent constitutes a foundational principle in research ethics, says Professor Caulfield. “It’s a way

to put boundaries on the increasingly common use of broad consent.” In practice, however, the rapid spread of biobank data within the international research community makes it difficult to manage requests for withdrawal. “The rock band The Eagles may have said it best,” Caulfield suggests: “You can check out any time you like, but you can never leave.”

Updates on personal health

Many biobank donors also wish to be informed about the results of studies involving their samples. At the very least, they want to know if analysis of the samples uncovered new information about their personal health. In 2013, Professor Caulfield was one of several researchers who polled leukemia patients at the Princess Margaret Hospital in Toronto for their views on the topic. Of the 100 survey participants, 78 had already consented to have their samples deposited in the hospital’s Hematologic Malignancy Tissue Bank. Survey results showed a clear consensus: 98% of respondents wanted access to any new personal health information that came to light from their biospecimens. “It’s one of the few areas of near-universal agreement across different studies,” says Professor Caulfield. Here, the law supports the wishes of patients: “Canadians have a common-law right to access their health information.”

When asked about who owns donated samples, most patients (62.2%) perceived the samples to be the property of the research institutions, while only 19.4% claimed ownership of the material themselves. An additional 16.3% viewed the samples as the researchers’ property, and the remaining 2% ascribed ownership to the research funder.

In the Alberta survey, 44% of respondents felt specimens donated for research purposes belonged to the research institution, 26% of respondents thought the specimens belonged to the individual donor, 23% thought the researcher retained ownership and seven percent thought the research funder did.

Although many courts have not yet settled the issue of ownership, Professor Caulfield notes that a June 2014 Ontario court decision is the first Canadian legal decision on tissue ownership—and it will be influential, if only in a symbolic sense. The case established that human tissue provided by a patient is personal property. Not only that, once it is removed from a patient, it is owned by the hospital. “It seems to say that, in Canada, once tissue is removed from your body you lose control over it,” says Professor Caulfield.

The question becomes still thornier when a biobank changes hands. This happened when Genizon Biosciences Inc., a Quebec biotechnology company that specialized in identifying genes for complex disorders, filed for bankruptcy in 2011. The company liquidated all its assets except its biobank, which held samples from 50,000 donors. Later that year, the Superior Court of Quebec ordered Genome Quebec to act as the biobank’s trustee. Following an attempt to find another organization to take charge of the biobank’s data and samples, Genome Quebec turned down two bids and decided that it would continue managing the biobank.


In such cases, “It’s not clear what should happen to the samples and data,” says Professor Caulfield. Can they be sold like material goods? Can they be transferred to another country? Alternatively, should they be destroyed? “The choice could have far-reaching implications for participants’ privacy, autonomy and dignity,” he says.

Paddling through murky waters

As Professor Caulfield notes, biobanks still operate in murky ethical and legal territory. Hoping to further advance his research, he organized a virtual workshop on these issues with the participation of the international experts best equipped to address them. The venture, which yielded “an unbelievable response,” received support from Allergan for which Professor Caulfield is grateful: “It was my interactions with the Allergan team that inspired this unique project.”

An academic paper resulting from the workshop was published in the *Journal of Law and the Biosciences*. Titled “A review of the key issues associated with the commercialization of biobanks,” the 2014 paper looks at the ethical minefields surrounding biobanking—from public trust, ownership and consent, to conflict of interest and management of samples following a bankruptcy.

In the coming months and years, Professor Caulfield intends to continue exploring the ethics of biobanking from multiple perspectives. Another Allergan-funded initiative will see him “looking at how the scientific community views these issues, especially the pressure to commercialize.”

With a handle on both the scientific and public views of biobanking, Professor Caulfield hopes to contribute to the creation of ethical and enforceable guidelines, and health policies that “rest on a base of evidence—just like good science.” 

“Education and health promotion have a particularly strong impact on asthma outcomes. By providing a concentration of expertise and resources in one place, I felt we could interrupt the vicious cycle of asthma...”



Asthma patients breathe easier in El Salvador

Bordering Guatemala and Honduras, El Salvador is the smallest and most densely populated country in Central America. Covering a mere 8,000 square miles, the country can be crossed in about half the time it takes to get from Toronto to Montreal.

As it happens, this tiny country has a big health problem—asthma. In 2008, asthma accounted for 45% of the emergency department visits at the Dr. José Antonio Saldaña National Hospital in the country's capital, San Salvador. In that same year, the hospital admitted about 70 asthma patients every month, of which two-thirds were women. Perhaps most alarmingly, the death rate from asthma is about seven times higher in El Salvador than in Canada.



**Dr. Dean Befus, Professor,
University of Alberta**

AllerGen investigator Dr. Dean Befus, a professor of pulmonary medicine at the University of Alberta, is well aware of the country's asthma problem. "It's a poor country by world health standards, and lung disease is especially prevalent there," says Dr. Befus, who is Director of the Alberta Asthma Centre (AAC) in Edmonton, Alberta. "Some of the major issues are burning wood and other biofuels for cooking, and smoke in the kitchen. When you add limited access to asthma medications, it's hardly surprising that so many of the country's inhabitants suffer from uncontrolled asthma."

A vision to end a vicious cycle

When Dr. Gustavo Zayas, a colleague originally from El Salvador, approached Dr. Befus with the idea of setting up an asthma program in his homeland, Dr. Befus enthusiastically embraced the project. Long concerned with issues of global development, Dr. Befus previously had worked in West Africa and Thailand studying diseases endemic to those locations, and he believed that with Shawna McGhan, Director of Health Innovations at the AAC, and the AAC's 20 years of experience in asthma education, they could help improve the standard of asthma care in El Salvador.

As far as Dr. Zayas was concerned, the project could not start soon enough. "I'll never forget the laboured movements of one asthma patient I treated in El Salvador," he recalls. "His anguish showed on his face and such images have motivated me to do my part to alleviate the suffering." Establishing an asthma clinic was a critically important starting point. In Dr. Zayas's experience,

"Education and health promotion have a particularly strong impact on asthma outcomes. By providing a concentration of expertise and resources in one place, I felt we could interrupt the vicious cycle of asthma, which includes missing school or work, lost income and strain on the family budget."

Not that the researchers expected any quick fixes. At just 3.9% of its gross national product, El Salvador's healthcare spending falls far below that of nearby Costa Rica (10.5%) and Panama (8.3%). Given that 39% of Salvadorans live in rural areas and may have to walk up to three hours to reach a physician, access to healthcare ranks as a major national concern. "We knew it could take quite a while to see an impact from the changes we had in mind," says Dr. Zayas.

Preparing the ground

As a team, they set about making the asthma clinic a reality: they knew just where to start—the International Partnership Initiative (IPI) program developed by the Networks of Centres of Excellence (NCE) in 2006. The NCE's IPI program supports the partnering of Canadian NCEs with foreign organizations to tackle pressing scientific, economic and cultural issues.

In 2007, AllerGen received \$828,000 from the IPI program. As one of five AllerGen projects selected to receive IPI support, Dr. Befus's proposal and the associated partnership with the International Union Against Tuberculosis and Lung Disease (the Union)—an aid organization known for its programs and for bringing medications to low-income populations—was a centrepiece of the program.

To further support the ability of healthcare providers to educate patients and their families about asthma in El Salvador, Dr. Befus and his team developed a set of Spanish-language teaching tools, including flipcharts and an action plan. A well-known Salvadoran artist, Mauricio Mejía, created many of the illustrations used in the tools, enhancing their cultural relevance.



Spanish-language asthma teaching tool.

With NCE seed money in place, Dr. Befus, together with Dr. Anne Fanning of the University of Alberta, and the Union, organized an international respiratory conference in Edmonton, bringing together a “Who’s Who” of people interested in asthma and lung disease. “We wanted to understand what asthma initiatives were underway around the world and to forge strategic partnerships with international organizations,” he says. The guest list at the 2008 conference included representatives from the World Health Organization, the Union, Canada’s International Development Research Centre (IDRC), First Nations leaders, and health professionals from El Salvador, including leaders from the Dr. José Antonio Saldaña National Hospital.

Dr. Befus lost no time securing the necessary partnerships and, with the help of Dr. Zayas and other AAC colleagues, he brokered a Memorandum of Understanding between the University of Alberta and the Salvadoran Ministry of Health.

Training the trainer

The AAC team then trained local health providers to diagnose and treat asthma in line with best international practices. “Our model was to train the trainer,” says Dr. Befus. A Salvadoran physician and nurse were invited to Canada for three months of intensive education in asthma diagnosis, drug therapies and

patient management, including educational programs. “We took them to lung health clinics in Edmonton, Calgary and Winnipeg where they had the opportunity to observe health providers interacting with patients,” he says.

To further support the ability of these healthcare providers to educate patients and their families about asthma in El Salvador, Dr. Befus and his team developed a set of Spanish-language teaching tools, including flipcharts and an action plan. A well-known Salvadoran artist, Mauricio Mejía, created many of the illustrations used in the tools, enhancing their cultural relevance.

Alberta Health Services donated refurbished equipment to the clinic, including a plethysmograph or “body box”—a sealed chamber the size of a small telephone booth, used to measure lung capacity—facilitating more accurate diagnoses of asthma and other lung diseases.

Shawna McGhan was instrumental to the training effort, taking her cue from their Salvadoran collaborators. “We asked asthma care providers and patients in El Salvador about their needs and listened to their suggestions,” she says. As a result, “We were able to sketch out a model of how to organize asthma education and management in El Salvador.”



Staff at Clínica del Asma Dr. Dean Befus.

Overcoming hurdles

As often happens with long-running projects in foreign climes, the team encountered its share of hurdles. Given the high frequency of earthquakes in San Salvador, members of the AAC team found it to be both challenging and exciting to work in the “valley of the hammock,” as the region is known due to the intense earthquake activity at the foot of the San Salvador volcano.

“We faced earthquakes, hurricanes and epidemics,” says Dr. Zayas. When the H1N1 influenza pandemic hit the region in 2009, El Salvador prohibited visitors to enter the country, delaying some phases of the project by several months. Later, a triple-whammy of mud slides, falling trees and a dengue fever outbreak put construction of the clinic on hold again. “My role was that of facilitator,” says Dr. Zayas. “I helped to overcome these issues to allow a dream-maker like Dr. Befus to see his vision through to completion.”

Glitches also arose in the drug procurement process. While the Union proved critical in supplying inexpensive, high-quality medications for primary care, “We still heard about situations in which brand-name drugs were on back-order for months,” says McGhan. In the meantime, “the hospital would run out of asthma medication and the funds to purchase more.”

None of these obstacles prevented the project from reaching its pivotal milestone. In November 2013, the “Clínica del Asma Dr. Dean Befus” opened adjacent to the Saldaña

National Hospital. Although only 250 square feet in size, “the clinic’s impact is big because of the expertise it houses,” says Dr. Befus.

An optimistic future


Healthcare providers in the new clinic show patients how to use the tools developed by the project team. “We modelled the asthma action plan on the one we developed in Alberta with the help of AllerGen colleagues in Quebec, which uses traffic lights to give patients feedback on their level of asthma control and what to do about it,” explains Dr. Befus.

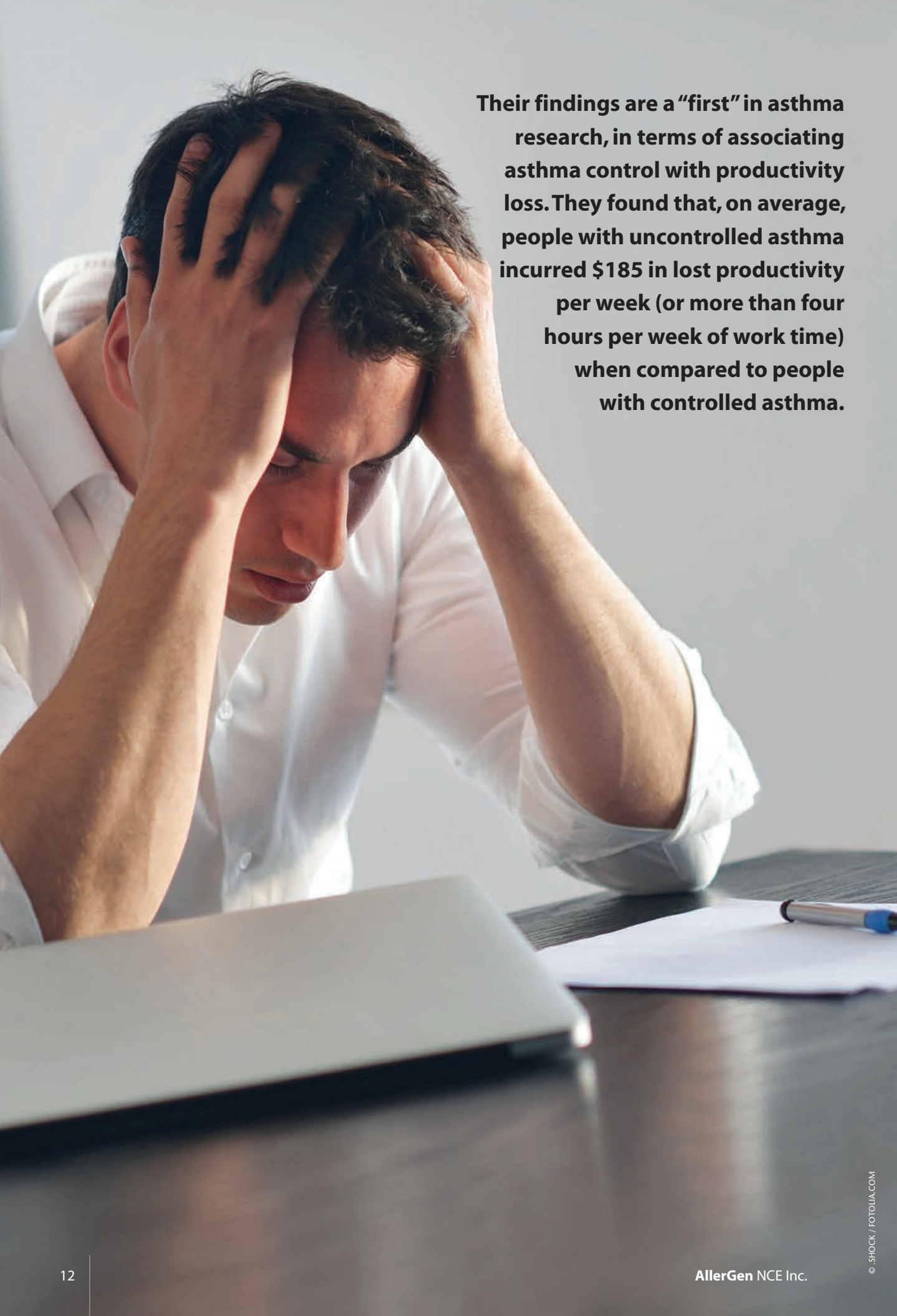
The project is also expanding beyond the clinic’s walls, with local Salvadoran “health promoters,” typically elders in indigenous communities, sharing what they learn about asthma prevention and care with the wider community. “The plan is to disseminate this knowledge throughout society, from community hospitals to public health centres, schools and sports teams,” Dr. Befus says. “Health promoters may have limited medical training, but they have the respect and connections to reach the public. We see them as very important for raising awareness.”

Indeed, Dr. Befus believes in empowering people to manage their own care. “You’re not going to get anywhere by having a bunch of foreign academics walk in and tell people what to do,” he says, noting that for people to embrace and benefit from an educational program, “they have to actively participate.”

New challenges continue to crop up. For example, the Union is re-evaluating its Asthma Drug Facility, a mechanism for providing affordable access to asthma drugs. “It’s unfortunate,” says Dr. Befus. “Obviously, we may have gaps to fill.”

The AAC team is optimistic about the clinic’s future and its potential to improve the quality of life for Salvadoran families with asthma. “This project has the support of the country’s Minister of Health, who understands the role of community and family in asthma management,” Dr. Befus says. “I am confident that the high quality of the clinic will add value to the society,” an ongoing mission in which Dr. Befus hopes to play a continuing role.

“I find the Latin American culture warm and wonderful,” he says. “There’s something uniquely gratifying about pitching in to help solve some of the health challenges faced by people in this region.” 



Their findings are a “first” in asthma research, in terms of associating asthma control with productivity loss. They found that, on average, people with uncontrolled asthma incurred \$185 in lost productivity per week (or more than four hours per week of work time) when compared to people with controlled asthma.

The Economics of Asthma: The Cost of Being at Work, but Not Being “All There”

New research has highlighted that workplace absenteeism, and a related problem called “presenteeism,” is high among people with uncontrolled asthma, diminishing employee productivity and negatively affecting the bottom line of Canadian businesses.

In contrast to absenteeism, when workers take sick days because they are unwell, presenteeism occurs when employees turn up for work but their productivity and effectiveness are reduced because of illness or a medical condition—resulting in a job that is not done as well as it could be.

Add the two together and overall productivity loss due to uncontrolled asthma can amount to more than 10% of an affected employee’s hours per week at work.



**Dr. Mohsen Sadatsafavi, Assistant Professor,
The University of British Columbia**

Asthma is a chronic lung disorder in which the airways become inflamed, narrowed and lined with mucous, making it difficult to breathe. Environmental factors, ranging from pollen, dust mites, animal dander and even cold air, can trigger symptoms. Typically, asthma develops in childhood and persists into middle age and beyond, which means its impact on workplace productivity can be substantial over an employee’s career, according to Dr. Mohsen Sadatsafavi, a health economist and an assistant professor of respiratory medicine at The University of British Columbia (UBC).

“Most research on the economics of asthma focuses on direct costs, such as the cost of medications and of visits to the doctor’s office or to the emergency department,” says Dr. Sadatsafavi. “While some studies have looked at the indirect costs, relatively little has been done to specifically measure presenteeism—the ‘on-the-job’ productivity loss due to asthma—and few studies have attempted to associate this productivity loss with asthma control.”

Working under the weather

Dr. Sadatsafavi believes that presenteeism is an underappreciated yet critical component in calculating the true burden of asthma. Underappreciated, because presenteeism is not always apparent: it is obvious when someone *does not* show up for work, but it is difficult to tell when, or how much, a medical condition hinders productivity when a person is on the job. Critical,

because presenteeism is a reflection of poor asthma control, causing a productivity decline that may be preventable.

“The burning question is: If a person with uncontrolled asthma achieved clinical control, how much productivity loss could be avoided?” says Dr. Sadatsafavi.

To find the answer, Dr. Sadatsafavi joined a multidisciplinary team of health researchers from UBC to study the extent of productivity loss in people with asthma and the association of this loss with clinical control. The study was funded through the Collaborative Innovative Research Fund (CIRF), sponsored by GlaxoSmithKline Canada. Dr. Mark FitzGerald, a professor in the Department of Medicine and co-Director of the UBC Institute for Heart and Lung Health, was the study’s Principal Investigator.

Dr. FitzGerald’s research team surveyed 300 employed adults with asthma from Vancouver and Kelowna, British Columbia. The subjects were evaluated using the Global Initiative for Asthma (GINA) Control Classification—an international guideline for determining whether a person’s asthma is “under control” or otherwise. The guideline categorizes asthma as “controlled,” “partly controlled,” or “uncontrolled,” based on five characteristics: daytime symptoms of asthma, including wheezing, coughing and chest tightness; limitations on activity; nighttime symptoms and awakening; the need for reliever medication; and lung function.

Once their level of control had been assessed, study subjects completed two questionnaires to help measure the



effect of their asthma on their workplace productivity. The Work Productivity and Activity Impairment (WPAI) questionnaire posed questions designed to measure the number of work hours lost due to absenteeism, presenteeism and impairment in daily activities. The second questionnaire, called the Valuation of Lost Productivity (VOLP), captured other aspects of the work environment, including team productivity, the availability of a suitable replacement worker and the time sensitivity of the job.

Using the VOLP, the researchers asked the subjects about the nature of their work, how critical their roles were to team productivity, whether a suitable replacement would be available to cover an absence and whether or not their co-workers would be “idling” if they were not at work. “Think of a teacher that doesn’t show up to school on Monday morning,” suggests Dr. Sadatsafavi, lead author of the study. “If there is no qualified replacement immediately available, then time is wasted, productivity is lost and there is an impact on students, other teachers and so on.”

Hidden costs of asthma

The team then calculated in dollars and cents the productivity loss due to uncontrolled asthma using information captured by the WPAI and VOLP questionnaires and standard wage rate tables.

Their findings are a “first” in asthma research, in terms of associating asthma control with productivity loss. They found that, on average, people with uncontrolled asthma incurred \$185 in lost productivity per week (or more than four hours per week of work time) when compared to people with controlled asthma. Assuming 50 work weeks per year, the total productivity loss among those with uncontrolled asthma reaches an annual average of \$9,240 per employee, compared with those whose asthma is well controlled.

The study also revealed that the greatest proportion of productivity loss was due to presenteeism—in fact, 90% of reduced workplace productivity stemmed from on-the-job losses, while only 10% was due to actual work days missed.

"Presenteeism was also more strongly associated with asthma control, which means it is more preventable than absenteeism," points out Dr. Sadatsafavi.

Even people with controlled asthma, or those with no asthma at all, experience lost productivity due to absenteeism and presenteeism from time to time. By using individuals with controlled asthma as the reference group, the study removed the impact of non-asthma-related productivity loss, and also productivity loss due to residual asthma impairment that even patients with controlled asthma experience. With these factors taken into account, the reported levels of additional productivity loss can be considered "preventable" through achieving asthma control.

Listening to patients

Dr. FitzGerald believes that estimating the burden of asthma in association with asthma control should be emphasized in future studies. "The concept of clinical control plays a central role in the current management of asthma," he says. "With proper management, asthma can be controlled in the majority of patients. Traditionally, asthma control has only been looked at in terms of clinical endpoints and quality of life scores. This novel study has provided additional insights into the indirect costs associated with poor asthma control."

Dr. Larry Lynd, one of the study's co-authors and Director of the Collaboration of Outcomes Research and Evaluation (CORE) group at UBC, believes that understanding preventable productivity loss will help policymakers identify where best to allocate scarce healthcare resources. "We know that the majority of Canadians can achieve asthma control with proper treatment," says Dr. Lynd, "but the reality is that control is actually quite poor."

With funding and support from AllerGen, Dr. Lynd has established the Platform for Outcomes Research and Translation in Asthma and Allergy (PORTAL)—a collection of research projects that explore the economic burden and health outcomes associated with asthma and allergies.

A key feature of PORTAL research involves asking Canadians about their personal experiences, values and preferences for health interventions. "Evidence shows that inhaled corticosteroids are the best asthma controller medication available, but if people don't adhere to the treatment, then we need to



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"We know that the majority of Canadians can achieve asthma control with proper treatment," says Dr. Lynd, "but the reality is that control is actually quite poor."

know why and what drug therapies they prefer instead," says Dr. Lynd.

As new treatments and technologies compete with existing ones for increasingly limited resources, incorporating patient preferences into healthcare policy decisions may ultimately help patients stay on their therapies longer, improve clinical outcomes and maximize the use of healthcare dollars over the long term.

Dr. Sadatsafavi agrees that improved clinical outcomes should be a priority for policymakers. "In our study, the big message is that asthma remains uncontrolled in a large percentage of the population and much of the related workplace productivity loss is preventable. As an asthma researcher, this strikes me as a significant care gap that we need to address." **A**

Traditional allergic rhinitis studies place participants outdoors to do battle with the very substances in their day-to-day life that cause them to wheeze, sneeze and suffer.



Nothing to Sneeze at: A Better Way to Study Allergic Rhinitis

Cat dander, dust mites and ragweed. Tree pollen, wood shavings and mould. These allergens are among the “usual suspects” that cause the sneezing, sniffing and scratchy, watery eyes of allergic rhinitis, which affects up to 50% of Canadians at some point in their lives.

Although common, allergic rhinitis, also known as hayfever, is hardly trivial. According to AllerGen investigator Dr. Anne K. Ellis, an associate professor at Queen’s University in Kingston, Ontario, the condition “puts a serious dent in our quality of life, especially when it persists for days and weeks on end.”



**Dr. Anne Ellis, Associate Professor,
Queen's University**

The economic impact is equally concerning: when the cost of physician visits and medications is added to workplace productivity losses, allergic rhinitis exacts a toll of \$1 billion per year in Canada.

Research holds the key to overcoming these challenges, according to Dr. Ellis. But not just any research: “We should be focusing our efforts on controlling the disease process, not just the symptoms,” she says. However, conducting research to discover the causes of and treatments for allergic rhinitis “can be a challenging process,” Dr. Ellis concedes. The reasons? She believes that there are several.

Bringing the outdoors in

First, traditional allergic rhinitis studies place participants outdoors to do battle with the very substances in their day-to-day life that cause them to wheeze, sneeze and suffer. Each participant’s exposure level is not only influenced by geography and other place-specific variables, such as weather patterns and pollen counts in their city or neighbourhood, but also by their personal lifestyle, including time spent outdoors. “There is no use testing treatments for outdoor allergens if someone spends most of their time inside,” Dr. Ellis points out.

Second, participants have “a hard time doing the ‘home-work’ required in these studies, which means dutifully recording their symptoms,” says Dr. Ellis. A string of sneezes? The details must be entered into a log book. Itchy, burning, teary eyes? The day, time, and triggering activity must be carefully recorded. In plain language, it’s time-consuming and burdensome. A

further complication, Dr. Ellis points out, is that “study participants don’t always take their study medications as directed.”

The Environmental Exposure Unit (EEU) at the Kingston General Hospital was designed to provide a controlled testing environment that avoids these pitfalls. Established in the 1980s, the EEU has a dispersal system that circulates airborne allergens through the testing room, ensuring that study participants—up to 140 people at a time—receive equal, controlled doses of any given allergen, regardless of the weather or time of year.

During the exposure period, participants are free to engage in real-life activities, such as watching movies, reading, eating or walking around inside the EEU. “It’s like bringing real life into the lab,” says Dr. Ellis, who has served as the EEU’s director since 2009. Since all participants are immersed in the same setting, “We don’t have to adjust our results to account for differences in lifestyle.”

As a further advantage, the EEU allows researchers to ensure that study participants take their study medications and complete their record-keeping logs. “The EEU is the ideal environment to deliver a controlled allergen exposure to large groups of people and to test the effectiveness of various medications,” says Dr. Ellis.

Taking hold of the reins of research

Third, while the EEU solves one problem in allergy research, there are still other obstacles to overcome, Dr. Ellis points out. While antihistamines and other treatments may offer short-term, temporary relief from allergic rhinitis, the symptoms usually come back. “We also need research that allows us to

study the underlying immune dysfunction at play in allergic rhinitis,” she says.

In Dr. Ellis’s opinion, to achieve this shift in focus the academic community must assume a larger role in allergic rhinitis research. Dr. Ellis and her colleagues noticed that, in recent years, research trials have been undertaken primarily by primary care physicians, rather than allergists. “I saw a need to bring allergy research back into the academic fold,” she says.

In 2009, with funding from AllerGen, Dr. Ellis invited the country’s leading academic allergic rhinitis clinician-scientists to a think tank-styled workshop. The objective: to determine the best model for studying the root causes of allergic rhinitis in Canada.

The group identified AllerGen’s Clinical Investigator Collaborative (CIC)—a unique clinical trials consortium—as the model to emulate. Established in 2005 and led by AllerGen Principal Investigator Dr. Paul O’Byrne of McMaster University, the CIC has developed standardized procedures and protocols to study allergic asthma.

Within the CIC framework, top asthma and allergy scientists from six Canadian research institutions use these protocols to collaborate on clinical trials that evaluate potential new asthma drugs. The CIC trials give pharmaceutical and biotechnology companies a quick, cost-efficient way to test promising new products in their pipelines. Given the cost of bringing new drugs to market, “It makes economic sense to test candidate drugs early on to know whether they’re worth pursuing,” notes Dr. Ellis.

Following the CIC’s winning formula

Dr. Ellis’s workshop served its purpose: researchers from five Canadian universities and hospitals agreed to join forces to create standardized procedures and protocols to guide allergic rhinitis trials, much as the CIC does for studies in allergic asthma.

Dr. Ellis brought to the team a strong expertise in nasal allergen challenge (NAC)—a technique that delivers a controlled dose of allergen spray into a participant’s nasal passages and measures the immune system’s response before and after treatment with a medication. With co-lead Dr. Helen Neighbour, an assistant professor at McMaster University who was trained at Imperial College in London, UK, the duo tackled

a question that had been nagging at them for some time: Among the different protocols for NAC, which one is the most reliable? “Different investigators use different methods and different doses, which makes it hard to compare one study to another,” says Dr. Ellis. “We wanted to set some standards.”

After a review of NAC protocols described in the scientific literature, Dr. Ellis and her collaborators selected a relatively complex protocol as their gold standard. As Dr. Ellis explains it, rather than exposing participants to a fixed dose of allergen, the protocol involves a screening procedure to determine the most suitable dose for each individual. “Two people may be allergic to the same substance, but vary in their sensitivity to it,” she says. For example, some may feel a tiny throat tickle in the presence of a cat, while others wheeze. “We thought it made sense to tailor the dose of allergen to each participant in order to induce a consistent allergic response.”

In 2012, additional AllerGen funding enabled Dr. Ellis’s team to launch a pilot study and put the selected protocol through its paces. They ran the study at four sites: Université Laval, Queen’s University, McMaster University and the University of Alberta.

A total of 23 participants underwent tests to confirm what they were allergic to, and then had the allergen sprayed into their noses during two separate visits: the first time to gauge their sensitivity to the allergen and establish the right dose for them; and the second time to document their response to this dose. At various intervals following exposure, the researchers recorded symptoms and collected blood samples to measure how the immune system was reacting. This pilot study allowed the participating sites to gain expertise in the new NAC protocol, paving the way for future refinements.

At the study’s completion in early 2013, Dr. Ellis’s team officially became the Allergic Rhinitis Clinical Investigator Collaborative (AR-CIC)—a new arm of the CIC specializing in allergic rhinitis trials.

The AR-CIC immediately set out to improve the NAC protocol they had tested in the pilot study. “We noticed some inconsistencies in the severity of symptoms a given patient would achieve from challenge to challenge,” Dr. Ellis explains. “We were able to modify the dosing criteria to achieve more consistent responses and we are now sure we are offering industry the best there is.”

AR-CIC COLLABORATORS		
Academic site	Investigator	Specialty
Queen's University/Kingston General Hospital	Anne Ellis, MD (lead)	Allergy & Immunology
McMaster University/St. Joseph's Healthcare	Helen Neighbour, MB, PhD (co-lead)	Respirology
Université Laval	Louis-Philippe Boulet, MD	Respirology
University of Alberta	Harissios Vliagoftis, MD	Allergy & Immunology
McMaster University	Paul Keith, MD	Allergy & Immunology
	Susan Wasserman, MD	Allergy & Immunology

A partnership poised for progress

When Hamilton-based Adiga Life Sciences came knocking on the AR-CIC's door, the timing was perfect. "We had a refined NAC protocol to validate and Adiga wanted us to run trials on their new cat allergy peptide-based immunotherapy," says Dr. Ellis. "I was eager to get going."

Dr. Ellis has always held high hopes for allergen immunotherapy. An increasingly popular treatment option for allergy sufferers, immunotherapy can "retrain" the immune system by exposing it to controlled doses of allergen. "The idea is that people develop a tolerance for the allergen over time," Dr. Ellis explains. In fact, immunotherapy allergy shots have a good track record, with about 80% of patients reporting significant improvement in symptoms.

Traditional immunotherapy for allergic rhinitis calls for a long series of injections. Not only do many patients balk at the thought of needles, but the shots come with a risk of anaphylaxis. "The risk is low, but not insignificant," says Dr. Ellis. "Those of us who have been practicing allergists for some time have seen at least one anaphylactic reaction to an allergy shot, so we take it very seriously."

Adiga's peptide-based immunotherapy breaks new ground. The underlying research behind the treatment, led by Dr. Mark Larché, a McMaster University professor and an AllerGen investigator, identifies the short peptide sequences, called "epitopes," within an allergen molecule that drive the allergic response. Those data are being used to design a new pharmaceutical product, comprised of synthetic peptides, that induces tolerance to the allergen when administered through the skin.

As Dr. Ellis sees it, the Adiga product, dubbed Synthetic Peptide ImmunoRegulatory Epitopes (SPIRE), represents a safer

and more convenient allergy treatment. "The epitopes elicit the same allergic response as the full allergen without activating the immune pathways that can lead to anaphylaxis," she says. What's more, the treatment regimen may only require four shots over four months—a substantial improvement over weekly shots given over a number of years, often required in traditional immunotherapy.

Adiga wanted to look for biomarkers (measurable substances in the body that signal disease or other processes) to gain insight into the workings of their peptide immunotherapy, while Dr. Ellis wanted to validate the AR-CIC's NAC protocol and study how allergen challenges impact gene expression. "We figured we could help each other," she says. Following a "great meeting of minds," AR-CIC and Adiga formed a partnership to make their combined vision a reality. "We're testing SPIRE in our NAC trials and collecting samples of urine, blood and DNA, so Adiga can evaluate the full effect of their immunotherapy treatment," she says. "It shows what you can accomplish through collaboration."

In 2014, Dr. Ellis was appointed to the Board of Directors of Clinical Trials Ontario. In this role, she takes another step towards achieving her goal of elevating allergic rhinitis research standards in Canada. As for the AR-CIC's future, Dr. Ellis believes that the partnership with Adiga Life Sciences shows the value of this clinical trials consortium in advancing allergy research. "We're now poised to conduct multi-centre studies of allergic rhinitis and to evaluate promising new drugs for its potential treatment," she says. [A](#)

“We are also studying the effect of living with pets and siblings on an infant’s microbiome,” says Dr. Azad. “The million dollar question is: What happens next in terms of health and disease outcomes?”



HQP Profile—Meghan Azad: Minding the Microbiome

Most people do not think about the nearly four pounds of microbes living in and on their bodies.

But AllerGen trainee Dr. Meghan Azad does and she is fascinated by the trillions of bacteria, viruses, fungi and other microorganisms that inhabit our gut, lungs, mouth and skin—even our belly buttons. Weighing as much as the human brain, these communities of microbes, known collectively as the microbiome, outnumber our human cells by 10 to one.



**Dr. Meghan Azad, Post-doctoral fellow,
University of Alberta**

From human genome to microbiome

"When I was a graduate student, scientists succeeded in mapping the human genome—all of the genes in the human body—thinking it would solve many pressing health problems," says Dr. Azad, a post-doctoral fellow at the University of Alberta. "When the genome didn't provide all the answers, researchers honed in on the microbiome to help us understand what goes wrong when we are sick, and how and why some people develop certain medical conditions—from asthma and allergies to cancers, infections and inflammatory bowel disease—while others do not."

Dr. Azad and other microbiome researchers are quickly realizing that the interactions between these complex communities of bacteria and their human hosts are far more extensive, and may be far more important for our health, than anyone could have imagined.

"It makes sense," says Dr. Azad. "We are born with one human genome each but we have thousands of microbial genomes. The microbiome has a huge impact on our health."

Dr. Azad is a member of one of only seven research teams funded by the Canadian Institutes of Health Research (CIHR) to study the microbiome. Led by AllerGen investigators Dr. Anita Kozyrskyj (Professor, University of Alberta) and Dr. James Scott (Associate Professor, University of Toronto), the \$2.5 million project, titled Synergy in Microbiota Research (SyMBIOTA), is looking at the makeup of the infant microbiome and how variations in this internal ecosystem affect health and disease later in life.

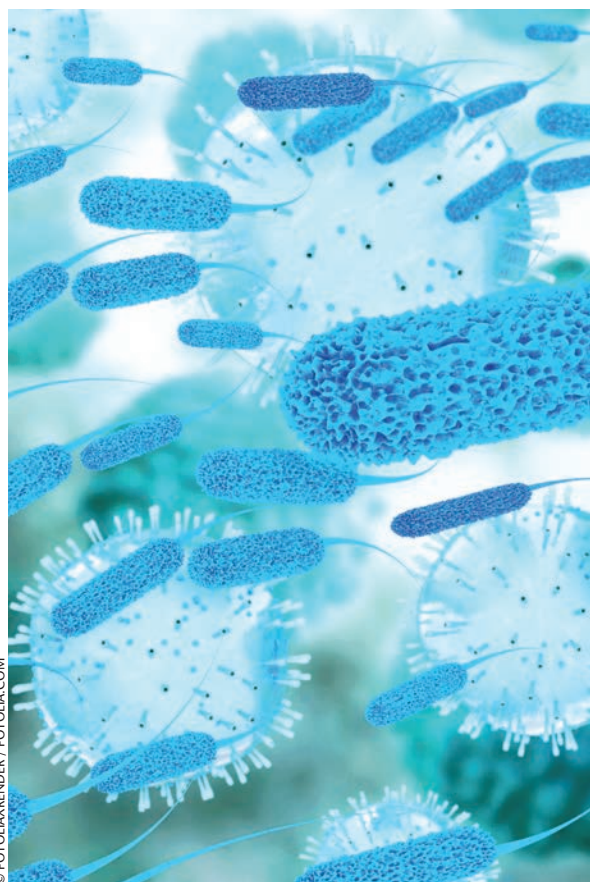
"I am so fortunate to be part of the SyMBIOTA team," says Dr. Azad. "This is an incredibly exciting area of research that traces the processes by which your gut becomes colonized with bacteria and how it is affected by your environment—what you eat, where you live and so on."

Finding her way

Dr. Azad has always been interested in genetics, research and health. In 2010, she graduated from the University of Manitoba with a PhD in Biochemistry and Medical Genetics focusing on cell signalling pathways in cancer. But after a chance visit to the University's career counselling centre, her research took a sharp turn.

"The career centre gave me a test that indicated I was ideally suited for a career in taxes or accounting, rather than laboratory-based research," says Dr. Azad. "I wasn't prepared to leave research, but since I love working with graphs, charts and data, the counsellor suggested I pursue epidemiology—a field that uses mathematical models to help determine the causes of disease in specific populations. It was a perfect fit for me."

In 2011, shortly after she joined the SyMBIOTA team, Dr. Azad applied to become part of the AllerGen Students and New Professionals Network (ASNPN)—a national network of student trainees and early-career professionals involved in allergic disease research. Founded in 2005, the ASNPN offers training, education and professional development opportunities to support, educate and mentor trainees. "My supervisor, Dr. Kozyrskyj, encouraged me to join," notes Dr. Azad. "She



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has been a wonderful mentor—from providing guidance on my research to career tips and connecting me with AllerGen. It was a great piece of advice.”

Through AllerGen’s trainee network, Dr. Azad has received numerous research and travel awards, participated in poster competitions highlighting her research, acquired new research skills through laboratory exchanges, and gained networking and skills training at annual trainee symposia. She also gained leadership and management skills serving as a member of the ASNPN Leadership team from 2012 to 2014.

This support, training and experience, Dr. Azad believes, were factors in her being selected as a Banting Postdoctoral Fellow in 2013.

The Banting Fellowship, valued at \$70,000 per year for two years, is Canada’s most prestigious award for post-doctoral research. While most fellowships are awarded based upon the candidate’s personal and research accomplishments, the Banting Fellowship additionally evaluates the applicant’s research team, training environment and supporting network. “I believe I was successful in receiving a Banting Fellowship

because I had SyMBIOTA and AllerGen behind me,” concludes Dr. Azad. “It’s incredible to have a whole network of people that are rooting for you.”

Connecting to CHILD

Dr. Azad’s connection with AllerGen runs deeper than her participation as a Network trainee. Her SyMBIOTA research uses data and biological samples from AllerGen’s Canadian Healthy Infant Longitudinal Development (CHILD) Study—a nation-wide birth cohort study involving over 3,300 infants and their families.

Launched in 2004 with \$12 million from AllerGen and the CIHR, CHILD looks at how the environment to which a child is exposed during pregnancy and in the first few years of life can interact with genetics to cause allergies, asthma and other chronic diseases. The CHILD Study recruited pregnant mothers and is carefully monitoring each child and its home environment from before birth until age five.

Dr. Azad’s research uses fecal samples collected from babies’ diapers, information provided by parents on questionnaires, measurements from clinic visits, and environmental assessments of the families’ homes to understand how early exposures shape the gut microbiome and eventually affect the development of chronic diseases.

The analysis is complex, incorporating several steps and SyMBIOTA collaborators. Dr. James Scott’s laboratory at the University of Toronto (U of T) extracts bacterial DNA from CHILD Study fecal samples. The DNA is sent to Dr. David Guttman, Director for the Centre for the Analysis of Genome Evolution & Function at U of T, where his research team uses high-throughput gene sequencing technology to tease out the unique genetic signatures of each microbe.

“Until recently, bacteria were studied by culture-based methods,” says Dr. Azad. “However, up to 80% of gut bacteria cannot be grown in a culture dish, so researchers never really knew which bacteria were present. It is only with the new gene sequencing methods that we are able to see a complete snapshot of the bacteria carried by each infant.”

Dr. Azad then compares each infant’s gut microbiome against the environmental exposure data collected by the CHILD Study. “It’s like a giant, exciting jigsaw puzzle,” she says. “We are constantly looking back and forth between the babies’

gut bacteria and environmental factors—like mode of delivery, infant diet, antibiotic use, household dust and mould, and the presence of siblings or pets—to try to find patterns and pieces that fit together.”

Breakthrough findings

In March 2013, Dr. Azad, Dr. Kozyrskyj and the SyMBIOTA team made international headlines when they published findings in the *Canadian Medical Association Journal* (CMAJ) showing that babies born by cesarean section lacked a type of bacteria found in babies born vaginally. They also found that formula-fed babies had differences in their gut bacteria compared to those who were strictly or partially breastfed.

“Those early results were based on data from 24 infants at the age of three months,” Dr. Azad points out. “Think of how much more we will discover by tracking the microbiome of thousands of children as they grow and develop.”

Now that all children in the CHILD Study have celebrated their first birthday, Dr. Azad has the largest pool of infant microbiome data in the world with which to work. In early 2014, she analyzed data from this larger group to see if the microbiome of the cesarean section babies had “caught up” to the babies born vaginally. “We saw a huge shift in the microbiome of babies between three and 12 months,” she says. “Interestingly, babies born by cesarean section still had a deficiency in the gut bacteria called *Bacteroides* at one year of age compared to babies born vaginally, but the deficiency was reduced if they were breast fed.”

Another analysis of the one-year-olds found evidence that partial and extended breastfeeding influences the microbiome to protect against early childhood overweight.

More to come

Skilled at finding patterns in the flood of new data being generated by the CHILD Study, Dr. Azad is also investigating the impact of antibiotics—even in tiny doses—on an infant’s microbiome. While other studies have looked at whether antibiotics in general affect gut bacteria, the SyMBIOTA research aims to pinpoint the dosages, and the types of antibiotics, that have the biggest impact.

“We are also studying the effect of living with pets and siblings on an infant’s microbiome,” says Dr. Azad. “The million

dollar question is: What happens next in terms of health and disease outcomes?”

To tackle this question, the SyMBIOTA team is looking to see if any of the one-year-olds in the CHILD Study are wheezing—an early indicator of asthma—or developing food allergies. What they discover may influence everything from building codes and household purchasing behaviours to decisions about childbirth and delivery, diet, breastfeeding, and whether or not to own a family pet.


A career on the rise

Through her work with SyMBIOTA and the CHILD Study, and as first author on several related publications in high-impact journals, Dr. Azad is gaining international recognition as one of the world’s brightest young scientists. In July 2014, she was chosen through a multi-stage international selection process to participate in a prestigious week-long Nobel Laureate Meeting in Lindau, Germany. The annual event—the only one of its kind—unites more than 30 Nobel Prize winners with an elite group of young researchers from around the globe to discuss advances in medicine and physiology.

“It was truly inspiring to meet and interact with the Nobel Laureates—their unwavering passion for science was contagious,” says Dr. Azad. “The meeting offered a tremendous opportunity to connect with other young scientists—I now have an international network of potential collaborators at the top of their respective fields.”

Although microbiome research is still new and much remains unknown, it has become a worldwide priority: in 2012, *Time Magazine* dubbed it “one of the fastest rising fields of medical research.”

Dr. Azad hopes to remain at the forefront of this emerging field, perhaps as head of her own laboratory and research program. “I would love to be an independent investigator working with the CHILD Study,” she says. “There is so much valuable data in CHILD and we are beginning to understand what an ‘unhealthy’ microbiome looks like. I see this relationship with CHILD as an ongoing collaboration upon which to build my career.”

Having recently accepted a faculty position as Assistant Professor at the University of Manitoba and the affiliated George & Fay Yee Centre for Healthcare Innovation, Dr. Azad is well on her way. 



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AllerGen NCE Inc.

McMaster University

Michael G. DeGroote Centre for Learning & Discovery

1280 Main Street West, Room 3120

Hamilton, ON L8S 4K1

Networks of Centres of Excellence

Telephone: (905) 525-9140 ext. 26502

Fax: (905) 524-0611

E-mail: info@allergen-nce.ca

www.allergen-nce.ca

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