Winter 2014

AllerGen

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 the seventh issue of *Success Stories*, showcasing the research accomplishments of leading Canadian researchers, students, and stakeholder organizations specializing in allergy, asthma, anaphylaxis, genetics and the environment.

This issue of *Success Stories* shares the achievements of five new AllerGen-supported research projects. Its feature stories explore:

- developing an asthma vaccine for newborns;
- the connections between children's genetic profiles and their risk of developing asthma after exposure to traffic-related air pollution
- allergy/asthma support and education programs designed with and for Aboriginal communities ;
- a quest to provide higher quality asthma care for Canadians; and
- an emerging researcher's initiative to create a national anaphylaxis registry.

Since its inception, AllerGen has supported excellence in research and fostered commercialization, social innovation and knowledge mobilization to enable Canadians to better prevent, treat and manage allergic diseases and asthma. Our national network mobilizes globally recognized Canadian researchers with expertise across a wide range of the biomedical, social and natural sciences. Our researchers work in trans-disciplinary and multi-sectoral teams with national and international collaborators and partner organizations to address gaps in knowledge and seize new opportunities in diagnostics, therapeutics, health care, public health, ethics, policy, clinical care and patient education.

Now almost nine 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.
- **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.

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Enabling Platforms:

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

By sharing our stories of research success, we aim to keep Canadians up-to-date on advancements in the science of allergy and asthma. We hope you find this issue of *Success Stories* to be informative and inspiring!

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

Diana Royce, EdD, Managing Director and COO

It's during the initial months after birth, however — a period Dr. Kollmann calls the "window of vulnerability and of opportunity" — that the environment assumes greatest importance.

Developing a Vaccine for Asthma and Allergies

Asthma, allergies and related immune disorders are becoming more common. While speculation about the biological and environmental causes of this increase abound — heredity, diet, traffic-related air pollution, an overly sanitized environment and more accurate diagnoses have all been implicated — scientists have yet to find a way to prevent these conditions from developing in early life.

Dr. Tobias Kollmann, an immunology researcher and associate professor at The University of British Columbia (UBC), seeks to change that. His champion in the battle is the *Listeria monocytogenes* (Listeria) bacterium. His weapon of choice: a vaccine. The best time to administer this vaccine, he believes, is at birth.

Dr. Tobias Kollmann, Associate Professor, The University of British Columbia

As researchers of complex diseases often say, "genetics loads the gun, environment pulls the trigger." Animal research has shown that the pulling of the trigger for asthma and allergies begins even before a newborn emerges from the womb. "Depending on how allergens are introduced into the fetal environment, there may be more or less risk of developing allergies after birth and in early childhood," says Dr. Kollmann.

It's during the initial months after birth, however — a period Dr. Kollmann calls the "window of vulnerability and of opportunity" — that the environment assumes greatest importance. While infants are born with a sophisticated immune system capable of distinguishing between harmless and dangerous foreign substances, they also experience a dramatic postnatal surge in exposure: within 24 hours of birth, babies have been colonized by more bacteria than the number of people living on earth. "Babies go from a sheltered environment to a virtual cesspool, and their immune systems have to distinguish between microbes that can harm them and microbes they will need to help them build amino acids, vitamins and the like," Dr. Kollmann explains. "All this happens within minutes to hours after birth — there's no transition in the human body that's so profound, so rapid, and yet so successful."

Successful, but not perfect: with such an onslaught of foreign matter flooding the organism, it is not surprising that the immune system occasionally mistakes a friendly substance for a foe and mounts a misguided attack.

For some newborns, molecules such as dust, pollen and even animal dander are perceived as dangerous invaders, triggering an immune response that can give rise to asthma and its symptoms — wheezing, chest tightness and difficulty breathing. It is this overactive response that Dr. Kollmann's vaccine aims to prevent.

Like all vaccines, the Listeria vaccine tricks the immune system into action by pretending it is an actual infection. In designing the vaccine, "you can knock out the disease-inducing parts of the microorganism used and retain those parts that generate the desired immune response," says Dr. Kollmann, who likens the process of weakening a microbe for use in a vaccine to "molecular surgery." In response to the vaccine, the immune system produces weapons to fight off the microorganism, which remain in the body (a process called "immune memory") on the lookout for the return of the same invader.

Lessons from Listeria

Developing a vaccine to stimulate the immune system and suppress the allergic response that triggers asthma has long been a priority for Dr. Kollmann.

Past research has shown that Listeria can decrease susceptibility to asthma and allergies in adult mice by re-directing their allergic response. Human studies have established that this bacterium can also activate a newborn's immune system. In one study, Listeria played a starring role in a rural region in Germany. After discovering that children in a particular farming community had a lower risk of developing some allergies — particularly asthma — than the average German child,

In an ideal world, Dr. Kollmann would also like to see the vaccine used to treat pre-existing asthma, though he notes that just about all vaccines tend to perform better as preventive therapy than as treatment. "Perhaps the vaccine could be used as part of a desensitization protocol, much as we currently use to treat allergic reactions like hay fever," he suggests. "The idea is that the allergic response would subside over time."

researchers tested the children for the presence of various bacteria. As it happened, a high proportion of them had been exposed to Listeria. This finding supported the so-called "hygiene hypothesis," which suggests that an overly sanitary environment can prime children to develop allergies, and helped to earmark Listeria as an anti-allergy molecule worthy of further study.

These and other findings paved the way for the development of a Listeria vaccine, which, in experimental models, has successfully prevented infections in adult mice and primates for over 20 years.

Connecting the dots

Dr. Kollmann's inspired step was to put together ideas about the crucial influence of the postnatal environment on the immune system, the preventive clout of the Listeria vaccine in mice, and the lower rates of asthma in children who have been exposed to the bacterium.

To move this idea from "brain to bench," Dr. Kollmann enlisted the help of four AllerGen co-investigators: Drs John Gordon, Professor of Immunology at the University of Saskatchewan; Mark Larché, Canada Research Chair in Allergy & Immune Tolerance at McMaster University; Bruce Mazer, Professor of Allergy & Immunology at McGill University; and Kelly McNagny, Professor of Medical Genetics at UBC.

The research team used newborn mice to test a Listeria vaccine that had been designed to stimulate and modify the immune system. These were not typical mice, though: they had been primed to develop asthma. Because mice do not spontaneously develop asthma, the researchers used antigens — molecules that trigger an immune response — to induce an artificial asthma-like process in their airways.

The immunization proved an unqualified success: a single dose of the Listeria vaccine successfully prevented the development of asthma in these mice. To see how this effect played out in the lungs and airways, Dr. Kollmann and his team analyzed the respiratory systems of the immunized mice. They found a reduced level of airway inflammation and constriction, and less fluid build-up than they would have expected to see in asthmatic mice, confirming that the vaccine successfully protected them against asthma at the molecular level.

With these promising findings in hand, the team repeated

the experiment with a different Listeria strain. Once again, the mice did not develop asthma and showed low "twitchiness" and few cellular signs of asthma in their lungs and airways. These consistent results confirmed for Dr. Kollmann that "Listeria may be particularly well suited for protecting against asthma."

The second prong of the project tested whether a single dose of the Listeria vaccine was sufficient to treat established asthma in mice. In this case, the vaccine significantly reduced one component of the asthmatic response — infiltration of a particular type of immune cell into the lungs — but did not affect other aspects of asthma. Dr. Kollmann views this result as "promising, though obviously not as robust as the vaccine's preventive effect," and speculates that higher or repeated vaccine doses may be required to produce a therapeutic effect on cases of pre-existing asthma.

Thinking ahead, Dr. Kollmann's group has developed several Listeria vaccine strains suitable for oral administration. If they become commercially available, oral vaccines would eliminate the 'ouch' factor of traditional needle vaccines. The team is now conducting tests to find out how these oral strains perform in mice. They also plan to test the Listeria vaccine for its protective effects against peanut and cat allergy with the help of their AllerGen collaborators.

Towards a human vaccine

The big leap forward, of course, will be to test these vaccines in larger animals, and finally in humans. However, even if all continues to go according to Dr. Kollmann's best-case scenario, it will still take years before an asthma vaccine will be available for newborns. And then, not all babies will be candidates: according to Dr. Kollmann, the cost-benefit balance would not justify administering the vaccine as a standard procedure. Instead, he envisions a scenario in which only higher-risk newborns — perhaps those with a family history of asthma — receive the vaccine.

In an ideal world, Dr. Kollmann would also like to see the vaccine used to treat pre-existing asthma, though he notes that just about all vaccines tend to perform better as preventive therapy than as treatment. "Perhaps the vaccine could be used as part of a desensitization protocol, much as we currently use to treat allergic reactions like hay fever," he suggests. "The idea is that the allergic response would subside over time."

Noting the considerable economic burden caused by asthma — from the direct costs of medications, doctor visits and hospitalizations to the costs associated with missed days at work — Dr. Kollmann says a human asthma vaccine could offer much-needed savings to the healthcare system and overall economy. From a commercial standpoint, it helps that "vaccines are really inexpensive to produce," he adds. "You can just keep growing the altered form of Listeria in a petri dish." A further bonus: the vaccine has none of the side effects of asthma-controlling steroids upon which many people with asthma currently rely.

Dr. Kollmann views vaccination as the most promising approach to preventing or treating allergy and asthma. The benefit, he says, lies in the fact that they address the problem at its source rather than temporarily alleviating symptoms. He hopes that the medical research community will continue to broaden its view of the role of vaccines in medicine and envisions a future in which newborn children are vaccinated against a variety of disease-inducing pathogens — perhaps even the environmental agents behind allergies and asthma.

It takes a village

Dr. Kollmann credits AllerGen for much of his project's success. He says the Network provided support every step of the way, from review of the initial proposal and financial support to feedback and discussions about future product development and intellectual property rights. Through AllerGen, Dr. Kollmann's research group has also collaborated with other laboratories in Canada and the U.S., and with the Karolinska Institute in Stockholm, Sweden.

While insisting that he has "stood on the shoulders of giants" to conduct his vaccine research, Dr. Kollmann concedes that he has, in fact, also broken new ground. When asked to describe the key insights gleaned from his work, he zeroes in on two: First, that allergy and asthma can be conquered through vaccines, and second, that vaccinating early in life gives the biggest benefit or 'bang-for-the-buck.' In choosing to make early life the focus of his future immunology research, Dr. Kollmann says he knows he is on the right track. "The payoff won't be immediate," he says, "but, in the long-run, it will be huge."

"The key variable is how close you live to a major road and how many cars and trucks go past the road you live on."

From Traffic Lanes to Twitchy Lungs

What do traffic fumes have to do with asthma? Quite a bit, it turns out. Pollution from cars, trucks and other vehicles can lead to the development of asthma in children who are already genetically susceptible to the disease, according to research from Canada and Europe.

AllerGen investigator Dr. Michael Brauer, a professor in the School of Population and Public Health at The University of British Columbia (UBC), along with his colleague Dr. Chris Carlsten, Chair in Occupational and Environmental Lung Disease at UBC, took this line of research to a new level: by analyzing gene-environment interactions in a large database of children, they have drawn more precise connections between children's genetic profiles and their risk of developing asthma after exposure to traffic-related air pollution (TrAP).

Dr. Michael Brauer, Professor, The University of British Columbia

Perhaps surprisingly, just living in a highly polluted city, such as Beijing or Jakarta, does not appear to cause asthma, although it clearly worsens symptoms in those who already have the disease. The reason, according to Dr. Brauer, is that for development of asthma there seems to be something specific about traffic pollution as a trigger, in contrast to the overall level of urban air pollution, which contributes to many other diseases. As he explains, "The key variable is how close you live to a major road and how many cars and trucks go past the road you live on."

Not all children who grow up near high-traffic areas will develop asthma, though. Studies have found the risk to be higher in children born with specific genetic variants. Drs Brauer and Carlsten used the results of these prior studies as a springboard for their own work. They asked the central question: Does TrAP cause the asthma, or does it simply serve as window dressing that conceals the true cause? "We figured that if we could determine whether children with specific genetic mutations were at higher or lower risk of developing asthma in traffic-polluted environments, it would strengthen our hypothesis that the pollution actually causes asthma," Dr. Brauer explains.

The researchers were also curious as to whether or not the risk of allergic rhinitis — the condition behind the dripping nose, itchy throat and streaming eyes typically associated with airborne allergens such as pollen, dust mites or pet dander — might also have a connection to high TrAP exposure. Why this interest in allergic rhinitis? For one thing, the condition is common in children. By recent estimates, about 8% of children aged six to seven and 14% of young teenagers suffer from it, and its prevalence is on the rise in many countries. What's more, allergic rhinitis is strongly associated with asthma. Finally, population research has linked exposure to certain environmental irritants, including TrAP, to the onset of allergic rhinitis.

To explore these questions, Drs Brauer and Carlsten collaborated with a team of AllerGen investigators from across the country, as well as national and international partner organizations, including the Centre for Allergy Research (CfA) at Sweden's Karolinska Institute. With funding from AllerGen, this team conducted the Traffic pollution, Asthma, Genetics (TAG) Study.

Prime suspects

Human DNA contains more than 20,000 genes, and most of these come in different forms, or variants. Faced with this overwhelming array of genetic candidates to consider as they set out to identify a genetic factor in TrAP-induced asthma, the researchers eventually honed in on just 10 variants of four genes to investigate in the TAG Study.

The first, a gene called gluathione S-transferase P1, or GSTP1, plays a role in cellular signaling and inflammation control. Previous research has linked a relatively common variant of GSTP1 to the development of asthma and allergies. The second, known as the tumour necrosis factor or TNF gene, regulates inflammation and cell death. A particular TNF variant increases vulnerability to asthma from exposure to second-hand smoke.

The researchers' painstaking efforts paid off: the results of the pooled analysis showed that children with specific genetic profiles had a significantly greater risk of developing asthma in high-TrAP environments. Most dramatically, TrAP-exposed children with one variant of the GSTP1 gene had double the expected risk.

The third and fourth genes that the team chose to study produce a class of proteins called toll-like receptors (TLR). Two of these receptors, TLR2 and TLR4, appear to play crucial roles in mobilizing the immune system against invading bacteria, and Dr. Brauer had reason to suspect that abnormalities in these receptors might serve as biochemical 'bridges' linking TrAP to an allergic response. In all, the team identified 10 variants of the four candidate genes that they believed might underpin the link between asthma, allergic rhinitis and TrAP.

Playing TAG

With their prime suspects identified, the TAG Study combined data from over 15,000 children enrolled in six (two Canadian and four European) birth cohorts. For each child, the researchers collected and catalogued the distance of the child's residential address from busy roads, the degree of exposure to TrAP, the presence of any of the 10 targeted genetic variants, the presence of other common risk factors for asthma and allergy, and whether or not the child had developed asthma or allergies by age seven or eight. In total, the researchers obtained complete data sets for over 5,000 subjects.

Their next step was to weave the disparate threads of information into a set of common variables, which Dr. Brauer admits was no small task. Then came the crux of the analysis: assessing the influence of the GSTP1, TNF, TLR2 and TLR4 gene variants on the development of asthma and allergic rhinitis as a function of TrAP exposure.

Key culprits

The researchers' painstaking efforts paid off: the results of the pooled analysis showed that children with specific genetic profiles had a significantly greater risk of developing asthma in high-TrAP environments. Most dramatically, TrAP-exposed children with one variant of the GSTP1 gene had double the expected risk. "This supports the plausibility of a causal relationship and brings us closer to understanding the mechanism of action of traffic pollution in vulnerable people," Dr. Brauer says. A variant of the TNF gene also bumped up the risk of TrAP-

mediated asthma, though not to the same extent as the GSTP1 variant.

With allergic rhinitis, the results were not as revealing. The analysis did tease out a link between one variant of the TNF gene and the development of allergic rhinitis at age seven to eight — the first study to document such a link — but it did not uncover an overall tie between TrAP and childhood allergic rhinitis.

While previous studies have touched on the role of some of the 10 gene variants targeted by the TAG investigation, this study was by far the largest of its kind, involving thousands of children from Canada, the Netherlands, Germany and Sweden. "Earlier studies were limited to one geographic area and smaller numbers of participants," Dr. Brauer says. "We collaborated with several international centres and put together a harmonized database." One of the chief limitations of gene-environment studies is that the number of subjects is often too small to yield statistically meaningful results. The TAG study answered the pressing need for analysis of pooled study populations drawn from the cohorts of smaller studies. "You need to cast a wide net to capture the subtle interplay between genes, environment, and disease," he notes. Results of the study for children with asthma were recently published in *Environmental Health Perspectives* and the findings for allergic rhinitis were featured in the *Journal of Allergy and Clinical Immunology* last year.

Dr. Brauer says that these results illustrate how a person's genes and living conditions work in tandem to increase the risk of asthma. "Population studies of asthma that don't take subjects' genetic vulnerabilities into account may dilute our ability to identify impacts of pollution and to subsequently create suitable prevention strategies," he says. "When we know that we are protecting the most vulnerable people, then we can be sure that we are protecting the full population."

Better breathing

The TAG Study offers a rich data source that can be mined for future analyses. "With approval from the participating cohorts, the data can be used by other researchers," Dr. Brauer says. Indeed, a student in Germany plans to use the TAG database to delve into the gene-environment interactions that may precipitate eczema, and a U.S. group has asked to use the data as part of another study.

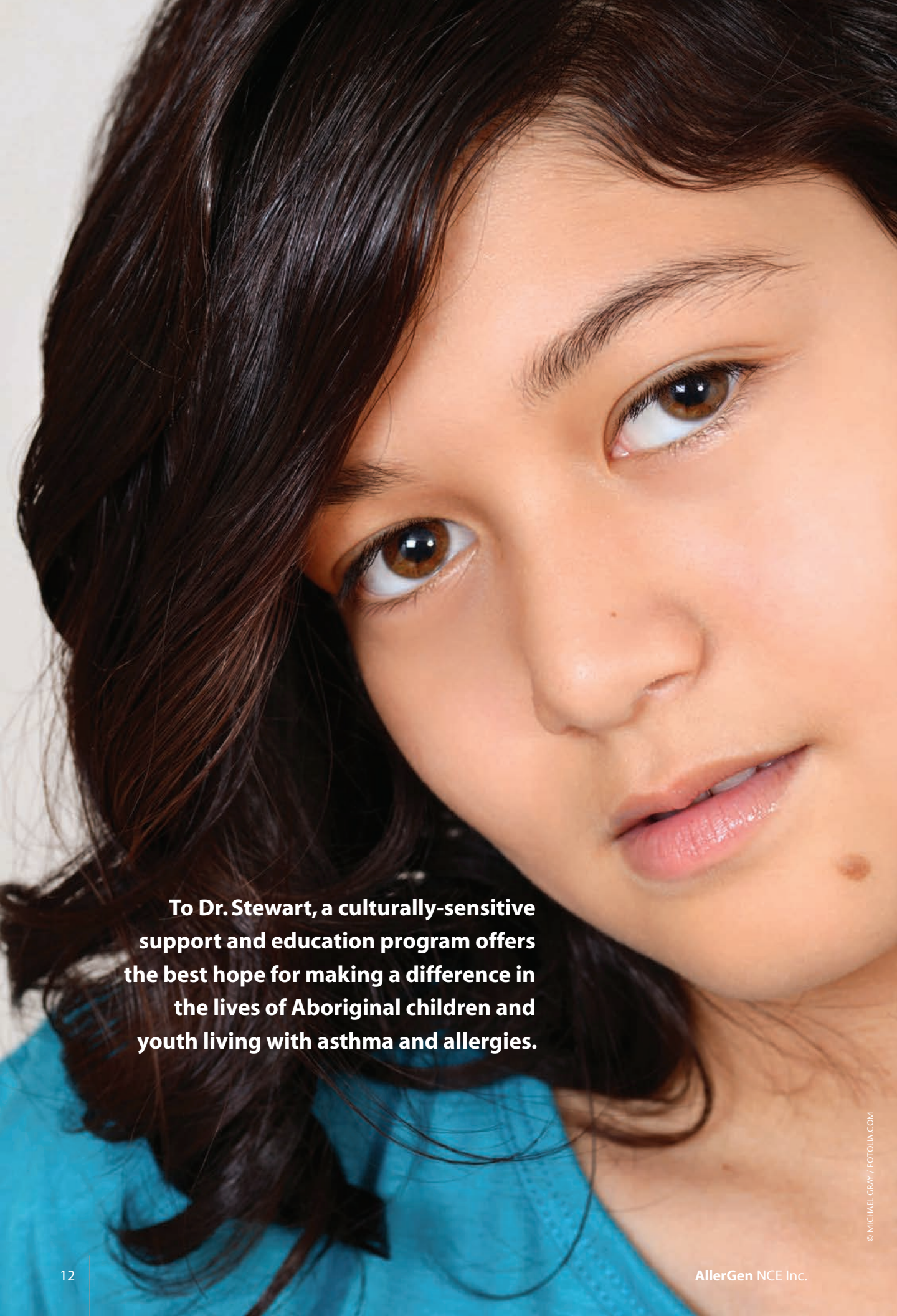
In the meantime, Dr. Brauer has set his sights on changing social policy rather than medical practice. And what policies might the TAG research promote? Those aimed at creating less congested living areas, for one. "Studies have shown that when people move away from high-traffic areas, their risk of heart disease decreases," Dr. Brauer says. "The same may very well be true for asthma."

Dr. Brauer favours urban planning strategies that separate roads and vehicles from people. Existing transportation networks were designed to help cars get around easily, he maintains. He would like to see human health, rather than convenience, inform roadway design policies. "We could have buffer zones between residential areas and roadways," he suggests, "or we could dedicate every other road to bicycle or foot transportation." Not one to stop at conducting research, Dr. Brauer has been appealing to governments to develop health-oriented guidelines for municipal transportation planners. To help make his case, he recently co-authored a Commentary for the *Canadian Medical Association Journal* and a report for Health Canada documenting the adverse impacts of traffic pollution on the health of Canadians.

The power of partnership

Dr. Brauer says that he would not have undertaken the TAG analysis without AllerGen's support. "This project came out of an AllerGen workshop on gene-environment interactions that I attended a few years ago," he recalls. "One of the Europeans in the group mentioned the need for this kind of study and suggested that Canada take the lead. With AllerGen' support we were well-suited to do so." AllerGen also proved instrumental in connecting Dr. Brauer with international experts in the genetics of asthma, who "gave me the background information I needed to get started."

Dr. Brauer counts the nurturing of student talent as one of the most rewarding aspects of this research experience. "The students on the TAG project have gotten to know each other and some are planning further collaborations," he says. As a case in point, Elaine Fuertes, an AllerGen trainee and PhD candidate at UBC, collaborated with Sweden's renowned Karolinska Institute on the project, and as a result, is currently working there. "It's a good feeling to know that we've helped launch young people in new career directions."



To Dr. Stewart, a culturally-sensitive support and education program offers the best hope for making a difference in the lives of Aboriginal children and youth living with asthma and allergies.

'Home-Grown' Asthma Support for Aboriginal Children and Youth

Poor living conditions and unreliable access to health services significantly affect health outcomes among Aboriginal Canadians. Dr. Miriam Stewart, a professor in the Faculty of Nursing and School of Public Health at the University of Alberta, has made a career out of trying to improve access to services and supports for vulnerable people in Canada. Concerned about the gaps in social support for First Nations and Métis children and youth with asthma and allergies, she asked young Aboriginal people and their parents from three provinces exactly what support they wanted and needed — and then delivered interventions tailored to those needs. Perhaps that's why the interventions proved so successful.

Dr. Miriam Stewart, Professor, University of Alberta

Asthma and allergies are the most common chronic conditions affecting Aboriginal children and adolescents. Young Aboriginal people are far more likely to end up in the hospital for asthma, both as emergency outpatients and as inpatients, than are their non-Aboriginal counterparts. High first- and second-hand exposure to cigarette smoke, poor housing conditions, and inadequate access to health services combine to increase the vulnerability of this population.

To Dr. Stewart, a culturally-sensitive support and education program offers the best hope for making a difference in the lives of Aboriginal children and youth living with asthma and allergies. Having worked with Aboriginal populations for many years, Dr. Stewart has an intimate understanding of the systemic barriers facing young people in these communities. She also knows first-hand about the personal suffering asthma and allergies can cause: her own severe asthma and allergies have landed her in the hospital more than once, and now that commercial airlines allow pets on board, she no longer flies.

In response to the dearth of studies assessing the support needs of Aboriginal children and youth with asthma and allergies and their parents, Dr. Stewart assembled a research team including investigators Drs Malcolm King, Heather Castleden, Jeff Masuda and Nicole Letourneau, and research staff Roxanne Blood, Sharon Anderson, Lisa Bourque Bearskin and Rob Watson.

This multidisciplinary, multi-site team designed, implemented and evaluated pilot support-education interventions in a study called "Engaging Aboriginal families affected by allergies and asthma in support-education program development." The study, funded in part by AllerGen and conducted in several communities in Alberta, Manitoba and Nova Scotia, involved partnerships with various health providers and not-for-profit organizations. In forging these alliances, Dr. Stewart drew upon the professional network she had established over the years as an AllerGen investigator. "I already had a long list of partners I could tap into," she says.

To help recruit participants for the study, the researchers assembled advisory committees that included Aboriginal community leaders and community service providers. These committees held several meetings to discuss the proposed interventions and seek consensus. "This took time, but was crucial to the recruitment process," Dr. Stewart says. She also enlisted the help of 31 research assistants hailing from three universities partnering on the project — University of Manitoba, University of Alberta, and Dalhousie University — and from local high schools. Many of these research staff were Aboriginal and/or had experience working with Aboriginal communities.

The art of listening

In the first phase of the study, Dr. Stewart and her collaborators assessed the support needs of this population and the resources available to them. Her team held pre-intervention focus groups and individual interviews with the children, young people and

The peer mentors, all from Aboriginal communities, provided the empathy and support that the study participants had not previously experienced when dealing with their illnesses. Tapping into resources developed by Aboriginal culture-based health experts, AllerGen research assistants working in Dr. Stewart's research program trained the peer mentors in the delivery of play-based instruction.

parents in the participating sites. The interventions differed from site-to-site according to the preferences identified. "We listened to what they wanted and proceeded accordingly," she says. What they didn't want, it soon became clear, was "teaching and lecturing."

In the focus groups, youth spoke of being left out of activities, having trouble breathing during exercise, missing school, and feeling different. They reported receiving little support from sources outside their immediate families. Parents, in turn, reported being challenged by poverty, living conditions containing allergy triggers such as dust or mould, under-diagnosis of health issues, lack of knowledge and support, and perceived discrimination when seeking health care for their children.

Immersive and culturally meaningful activities were requested by many participants, so that is what Dr. Stewart's team delivered — in six separate interventions. Each intervention used a unique combination of games, traditional dances, artistic expression, and culturally appropriate home-cooked meals as a context for the delivery of health education and social support. While chasing balls or drawing pictures of their homes, children had the opportunity to discuss the challenge of maintaining their lungs in good working order and managing the stress associated with asthma attacks and allergic reactions. "Let's face it," Dr. Stewart says, "if you don't make it fun, people won't engage and won't get anything out of it."

Peer power

The team engaged a mix of health service providers and peer mentors with experiential knowledge to deliver the programs. "Research has demonstrated the value of peer support across a variety of populations and health conditions," Dr. Stewart observes, adding: "This shouldn't come as a surprise. People are more inclined to listen to and learn from other people who've lived in their shoes." Community elders and traditional healers also participated in some of the programs.

Most interventions ran for six to eight weeks with each weekly session lasting about two hours. Participants pre-selected the discussion topics, which included keeping homes allergen free, avoiding asthma triggers, the culturally relevant and safe use of traditional medicine, and how to manage peer pressure and seek support. Through the oneHealth Internet portal used in one Alberta-based intervention, parents in remote communities were able to interact with other affected parents, as well as with asthma and allergy experts, in Alberta, British Columbia and Ontario.

Some Alberta and Nova Scotia communities requested asthma camps for children and adolescents, so that is what was provided to them. Designed to increase knowledge about asthma and allergies, to build problem-solving skills and to exchange support with peers, the camps delivered their messages through music, art, and creative games such as "tag the asthma triggers" and "asthma Pictionary." Trained health professionals and peer mentors facilitated group discussions.

Discussions on the use of tobacco required particular sensitivity, Dr. Stewart noted. "It was a balancing act between recognizing the uses of tobacco considered culturally appropriate, and sharing information about the impact of tobacco on asthma," she says. "Rather than make people feel guilty about smoking, we put the focus on steps they could take to help their children feel better and get healthier, such as restricting smoking to certain times and places."

The peer mentors, all from Aboriginal communities, provided the empathy and support that the study participants had not previously experienced when dealing with their illnesses. Tapping into resources developed by Aboriginal culture-based health experts, AllerGen research assistants working in Dr. Stewart's research program trained the peer mentors in the delivery of play-based instruction.

Following the support-education interventions, participants reported decreased loneliness, greater ease speaking to friends about their condition, increased awareness of their disease, appreciation of the support provided by their parents, and enhanced knowledge of asthma triggers and how to avoid them. They also gave the interventions a collective rating of 4.5 out of 5 on the "fun" scale. In the words of one participant: "It ended too soon. When are we going to get to do this again?"

Parents also benefited, and came away from the interventions more prepared to seek support in the future. "They came to appreciate the value of professional and peer support, not just for their children's health problems, but for other challenges in their lives, as well," according to Dr. Stewart.

Peer mentors, meanwhile, had the satisfaction of witnessing participants' growth over the course of the programs. One peer mentor's observation about an initially resistant camper exemplifies this change: "At the beginning, he was a lot more introverted and he didn't see the value in it. By the end of camp, he really liked the camp environment and grew from the gatherings."

Opening Doors

In the study's final phase, meetings were held with Aboriginal community representatives and health stakeholders to discuss the findings and their implications for future programming. Several recommendations emerged, including asthma training programs for community health providers, educational sessions for students and school staff, and accessible support interventions using technology. A dissemination grant, recently awarded by the Canadian Institutes of Health Research (CIHR), will allow Drs Stewart, Castleden and Masuda to share the results of this study, which they hope will ultimately help to increase the relevance, uptake and efficacy of health programs in Aboriginal communities.

Even as she wraps up this project, Dr. Stewart is already hard at work on several follow-up studies, also funded by CIHR. "Right now, we're conducting a study in which we offer telephone and online support to supplement face-to-face interactions," she explains. "We are finding that people prefer face-to-face contact, so we are planning a future intervention that blends remote support with in-person support."

Dr. Stewart hopes that this work will spur the creation of sustainable programs and inform the development of government policies to support them. It stands to reason that interventions tailored to the self-reported needs of local communities make the most effective and efficient use of health care dollars: "When people are consulted, they buy into the intervention, which means that they take the learning to heart, which means they become healthier."

In Dr. Stewart's experience, the success of such programs depends on building relationships with the people involved. "You can't swoop into a community and offer support from 'on high' as an expert," she says. "People will shut down. But, if you gain people's trust, the door swings wide open."

To address the issues of inconsistent and suboptimal asthma care across the country, Dr. To focused on bridging the gap between the established guidelines and the real-life practice of asthma management in the offices of primary care physicians.

A Canadian Quest for Higher Quality Asthma Care

Evidence-based asthma guidelines? **Check.**
Effective asthma medications? **Check.**
Educational patient tools available in print and online? **Check.**

On the face of it, the foundation for uniform, high-quality asthma care already exists in Canada, yet variations in care persist. One person may undergo a lung function test in her doctor's office to help diagnose asthma, while another experiencing the same symptoms does not. One individual may receive a prescription for an inhaled corticosteroid — the first-line controller therapy — along with a written asthma action plan, while another in the same condition goes home empty-handed.

Dr. Teresa To
Senior Scientist, The Hospital for Sick Children; Professor, University of Toronto

Although mortality from asthma has steadily declined in recent years, emergency room visits, hospitalizations and limitations on daily life activities are still all too common among those with asthma — often as a result of significant differences in the way patients are diagnosed and treated.

"This should not be happening in our era," says AllerGen investigator Dr. Teresa To, a senior scientist at Toronto's Hospital for Sick Children and professor at the University of Toronto. Dr. To has devoted over a decade of her career to identifying inconsistencies in asthma care and systematically testing solutions to this problem.

The 2010 Canadian Thoracic Society (CTS) guidelines give step-by-step instructions for effective asthma care, she says, "though it's clear the recommendations are not being consistently followed." It seems that this gap has existed for some time. In 2006, *The Reality of Asthma Control* (TRAC) study, conducted at the Centre for Clinical Epidemiology and Evaluation at The University of British Columbia, determined that only 47% of some 1,000 surveyed patients had their asthma controlled according to guideline criteria. The U.K.-based *International Asthma Patient Insight Research* (INSPIRE) study, which recruited roughly 3,400 patients from 11 countries including Canada, yielded similar findings, with control eluding 57% of surveyed patients.

Facts *versus* feelings

Curiously enough, virtually all patients in the TRAC study *felt* they had their asthma under control. This does not surprise Dr. To. In her experience, patients "get used to living with asthma and come to see their symptoms as normal."

Dr. To saw this 'disconnect' first-hand when she was part of a team developing a new smartphone application to help asthma patients monitor their symptoms. An asthma educator who has asthma herself gave the app a trial run. As a health professional, she firmly believed that she had her own asthma in check. "After using the app for a week, she was blown away," Dr. To reports. "She was in the yellow zone, which meant her control was shaky." Dr. To says this example supports her observation that "asthma patients routinely overestimate how well they're doing."

Physicians are also vulnerable to such misperceptions. Among the family doctors polled in the TRAC study, 88% maintained that they had their patients' asthma under control. Specialists were even more optimistic, with 90% making the same claim.

Although some people with uncontrolled asthma may truly fail to respond to treatment, experts believe that most could achieve control if they received proper diagnosis and care. "Of course, patients also need to follow the treatment plan, which doesn't always happen," Dr. To admits. For some patients, cost may stand in the way of filling a prescription. Others may be wary of the steroids in asthma controller medications. "The inhaled steroids used to treat asthma do not have the same serious side effects as oral steroids, such as permanent stunting of growth in children," says Dr. To, "but some patients lump all steroids together." Dr. To also notes that people with asthma

living in remote areas and Aboriginal communities may face barriers to accessing care, affecting their asthma control.

The API advantage

To address the issues of inconsistent and suboptimal asthma care across the country, Dr. To focused on bridging the gap between the established guidelines and the real-life practice of asthma management in the offices of primary care physicians.

Encouraged by the development and application of evidence-based performance indicators in diseases such as diabetes and stroke, Dr. To developed a set of 15 asthma performance indicators (APIs) to reduce the misdiagnosis and mismanagement of asthma in primary care settings. Then, with support from the Canadian Institutes of Health Research (CIHR), the Government of Ontario, and the Public Health Agency of Canada, she spent five years validating the indicators and testing their usefulness in two community health centres and three family health teams in Southern Ontario.

To help the five participating sites collect patient information using the APIs, Dr. To developed a useful data collection tool — now copyrighted as the Primary Care Asthma Performance Indicators Form (PC-API) — which grouped the 15 APIs into nine categories: pulmonary function tests; medication use; asthma control; exacerbations; health care use; action plan; asthma education; smoking cessation; and quality of life. Participating sites used the PC-API form in 20 asthma patient visits: 10 randomly selected prospective visits; and 10 randomly selected retrospective visits, evaluated by a chart review.

The results, which analyzed API information for 100 patients across the five practices, revealed that most participating family doctors viewed the PC-API form as "feasible" and "practical" to use. Equally encouraging, the physicians used spirometry (a lung function test) to confirm an asthma diagnosis in about 75% of cases — a significant improvement over typical practice, in which fewer than 50% of asthma diagnoses involve the use of this technology. Part of this difference may stem from the PC-API form serving as a 'reminder.' Use of the PC-API form may have generated other improvements as well, including greater use of inhaled steroids, better inhaler technique, and reduced use of 'rescue' medications to combat asthma flare-ups.

In tandem with her work on APIs, Dr. To spent several years developing the Primary Care Asthma Pilot Program (PCAPP), a multipronged educational initiative that features patient self-management training, symptom monitoring, home visits, and community presentations. "Patients don't take their asthma seriously enough," says Dr. To. "When they recover from a flare-up, they think they're 'good to go' and stop managing themselves," risking reduced asthma control, and possibly a visit to the emergency department or hospitalization.

The PCAPP initiative worked so well in the eight Ontario communities where it was tested from 2003 to 2006 that to date the provincial government has provided funding to roll it out at over 150 sites across the province. Now called the Primary Care Asthma Program (PCAP), the program "is no longer a pilot or an experiment, but part of the fabric of care," says Dr. To.

An indicator short-list

Recognized as a positive force for change in the asthma community, Dr. To would like to see both the PCAP and API programs implemented from coast to coast. To help make her vision a reality, AllerGen made funding available to Dr. To for a one-day national workshop to solicit advice from 27 asthma care experts.

15 validated Asthma Performance Indicators (APIs)

- Education from certified asthma educator
- Pulmonary function monitoring
- Asthma control monitoring
- Controller medication
- Asthma control
- Acute health services use
- Pulmonary function test
- Use of action plan
- Quality of life
- Use of reliever medication
- Smoking cessation
- Asthma exacerbations
- Inhaler technique
- Primary care visits
- Routine care provider

To *et al.* Evidence-based performance indicators of primary care for asthma: a modified RAND Appropriateness Method. *International Journal for Quality in Health Care 2010;* 22, (6): 476-485.

The workshop, held in Toronto in April 2013, aimed to develop a national strategy for monitoring asthma care based on Dr. To's previously developed APIs. One recommendation to emerge from the workshop was to pare down the 15 APIs to a short list of five — and to reach national consensus on these indicators. "In practice, family doctors may not have the time to review 15 different parameters at every visit," Dr. To points out. "If we give them five indicators they must go through, it could streamline their care."

While the top-five list is still being developed, Dr. To views a pulmonary function test, such as spirometry, as a leading candidate. "Spirometry not only helps to diagnose asthma that would otherwise get missed, it also helps avoid overdiagnosis," she notes. "Research has shown that when a spirometry test is given to people taking asthma medications, about a third of them turn out not to have asthma."

She predicts smoking cessation could also make the top-five: "There's still a debate about whether smoking causes asthma, but we know that it can trigger a flare-up and possibly reduce the effectiveness of treatment," says Dr. To, adding that family doctors greatly influence a patient's motivation to quit. "We want to have an indicator in place to remind doctors to discuss quitting with their asthma patients who smoke."

Finally, Dr. To hopes to see the use of an Asthma Action Plan on the short list, noting that the 2010 CTS guidelines recommend a written action plan for all patients. Many preformatted plans use traffic light colours to give patients feedback on their level of control: green, yellow or red. "Red means you need to change your treatment plan or you may need to go to the emergency department, while yellow means you have to be on the alert and probably tweak your regimen," she says. Despite the guidelines, Dr. To believes many patients may not actually receive an action plan.

Workshop participants also proposed a pan-Canadian agreement to set objectives and standards for asthma treatment, along with a system for collecting, storing and monitoring data. Given that Ontario doctors currently use 13 different electronic medical record (EMR) systems, uniform data collection could present a challenge. "We need to agree on a system, which could include EMR, portals, surveys, or some combination of these methods," Dr. To says. "We also need to determine what data to collect."

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Going national

In November 2013, with endorsement from AllerGen, Dr. To applied for a new CIHR grant to kick-start a nationwide API implementation and evaluation study. AllerGen will provide partnered funding to support the venture. In the meantime, Dr. To says she values AllerGen's support, which has helped her to move beyond local, regional and provincial initiatives towards establishing a national set of evidence-based performance indicators for the effective treatment and management of asthma.

Along with Ontario, the provinces of B.C., Alberta, Saskatchewan, Manitoba and Quebec have shown interest in deploying Dr. To's API program, and she hopes to bring the rest of the country on board. Her CIHR proposal includes the use of a tablet or similar device to help family doctors use the APIs and send their data to a central repository. "We would give the doctors feedback on how well they're performing," she says. "After a month, we might let a doctor know that he only gave smoking cessation counselling to five out of 10 smokers with asthma who visited his office."

Dr. To says a national project could achieve lift-off as early as 2014. "It could have an impact at the individual patient and policy levels, so I'm eager to get going."

Anything from bee stings to medications can trigger anaphylaxis — a life-threatening allergic condition that involves several organ systems. But it is food allergies, particularly allergies to peanuts, tree nuts, fish, milk or eggs, that appear to be the most common triggers.

C-CARE Registry Tracks Anaphylaxis Across Canada

Dr. Moshe Ben-Shoshan, a pediatric allergist and immunologist at Montreal Children's Hospital, remembers well the day in 2013 when a teenage girl walked into the emergency department and went into anaphylactic shock. The 14-year-old had taken a bite of a cookie purchased elsewhere in the hospital, but spat it out when something did not seem right. Moments later, her throat tightened and she ran towards the emergency department. Although the teenager was previously prescribed an auto-injector for her peanut allergy, she did not carry it.

Dr. Moshe Ben-Shoshan, Pediatric allergist, Montreal Children's Hospital

"We were shocked by how quickly she deteriorated," says Dr. Ben-Shoshan, a former AllerGen trainee. "She stumbled through the emergency doors and collapsed. We almost lost her. While she survived, there are other deaths that are completely preventable. Her story is an example of the importance of medication in a case of anaphylaxis."

Now, Dr. Ben-Shoshan is an AllerGen Principal Investigator and one of the driving forces behind the Cross-Canada Anaphylaxis Registry, also known as C-CARE — a registry of anaphylaxis cases across the country. C-CARE is the first registry in the world to track episodes of anaphylaxis as they are reported. The database is helping Dr. Ben-Shoshan and a multidisciplinary research team assess Canada's rate of anaphylaxis, and monitor the triggers and management of the condition in emergency medical services, emergency departments and allergy clinics across the country.

Anything from bee stings to medications can trigger anaphylaxis — a life-threatening allergic condition that involves several organ systems. But it is food allergies, particularly allergies to peanuts, tree nuts, fish, milk or eggs, that appear to be the most common triggers. In 2010, a nationwide study found that about 2.5 million Canadians, or one in 13, suffer from a significant food allergy.

Gaps in knowledge about the prevalence, causes, and proper management of allergies and anaphylaxis make it difficult to treat these conditions effectively, according to Dr. Ben-Shoshan. Previous efforts to estimate the number of anaphylaxis cases in Canada have relied upon retrospective reviews of medical charts or analyses of epinephrine auto-injector prescriptions — offering an "incomplete picture" of the condition. "It is crucial to have data that accurately represent the rate of anaphylaxis and its causes," says Dr. Ben-Shoshan, "and Canada is the first country to develop a prospective nationwide registry that will do just that."

Emerging clinician-scientist

A pediatrician by training, Dr. Ben-Shoshan moved from Tel Aviv, Israel, to Canada in 2006 to pursue a post-doctoral fellowship in pediatric allergy and immunology at McGill University. "I wanted to pursue a fellowship to enrich my understanding of a specific area of pediatrics," explains Dr. Ben-Shoshan, "and the area that interested me most was the immune system, because it relates to everything in the body."

At McGill, Dr. Ben-Shoshan worked under the mentorship of leading allergy experts Drs Bruce Mazer, the Division Head for Pediatric Allergy and Immunology, and Ann Clarke, an allergist and a professor in the Department of Medicine. Within days of his arrival in Canada, Dr. Clarke introduced Dr. Ben-Shoshan to the AllerGen Network. He was immediately impressed by the Network's trans-disciplinary approach to supporting asthma, allergy and related immune disease research across sectors and medical and academic specialties. "Prior to my experience with AllerGen, I was primarily involved in clinical work, which is highly competitive," says Dr. Ben-Shoshan. "There is a big difference at AllerGen, which encourages research partnership, not competition."

C-CARE identifies cases of anaphylaxis through reports from 'first responders,' including ambulance paramedics, emergency department staff and allergists.

As an AllerGen trainee, Dr. Ben-Shoshan collaborated on several AllerGen-funded research projects. Working with Dr. Clarke and a Canadian research team, he contributed to a major breakthrough in understanding peanut allergy by identifying a gene that triples the risk of a child developing the allergy. The findings, published in *The Journal of Allergy and Clinical Immunology* in March 2011, represented an important step forward in understanding the genetic risk factors for this disease.

Also in 2011, Dr. Ben-Shoshan received AllerGen's inaugural *Emerging Clinician-Scientist Fellowship Award*. Valued at $250,000, this award allowed Dr. Ben-Shoshan — a physician with a passion for research — to share time between treating patients in the clinic and honing his skills as a researcher. "The *Emerging Clinician-Scientist Fellowship Award* allowed me to develop my skills as an epidemiologist, establish collaborations with other investigators and research sites, and dedicate my focus and research time to the C-CARE study," says Dr. Ben-Shoshan.

Moving beyond rescue

C-CARE was launched in 2010 to tackle the gaps in knowledge about anaphylaxis in Canada. With funding from AllerGen and in-kind support from Health Canada and other partners, Dr. Ben-Shoshan assembled a multi-institutional research team with cross-disciplinary expertise. The team includes: Dr. Ann Clarke (allergist and epidemiologist, McGill University); Dr. Sebastien La Vieille (Health Canada); Dr. Lawrence Joseph (biostatistician, McGill University); and Dr. Susan Waserman (allergist and immunologist, McMaster University).

C-CARE identifies cases of anaphylaxis through reports from 'first responders,' including ambulance paramedics, emergency department staff and allergists. If a patient is willing to be

included in C-CARE, information about the episode, including symptoms, possible triggers for the reaction and how the anaphylaxis was managed, is entered into the registry's database. C-CARE participants — or in the case of children, their parents — complete an annual questionnaire about ongoing anaphylactic symptoms, potential triggers, allergy testing, trigger avoidance measures, medication use, medical and family histories, and personal demographics.

By following participants over the long term, Dr. Ben-Shoshan believes C-CARE will provide the first reliable estimate of anaphylaxis rates in Canada and open the door to new ways of preventing and treating the condition. He also believes the registry will reveal why some people with allergies develop anaphylaxis while others do not.

Health Canada and other partner organizations, such as Anaphylaxis Canada, Association Québécoise des Allergies Alimentaires, and the Allergy/Asthma Information Association have assisted with the design of C-CARE recruitment and enrollment procedures and with the selection of data for analysis, and will eventually provide a conduit to policy makers to share findings and promote effective strategies for the prevention and management of food allergies and anaphylaxis.

Early findings from C-CARE were published in the September 2013 issue of *The Journal of Allergy and Clinical Immunology*. Among 168 children with anaphylaxis admitted to the Montreal Children's Hospital between April 2011 and April 2012, food was the most common anaphylactic trigger. The study revealed that in 84.5% of the anaphylaxis cases, peanut or tree nut was the major culprit, and 50% of milk- and peanut-induced anaphylaxis episodes were caused by accidental exposure to the known allergen. As well, although treatment guidelines recommend prompt administration of epinephrine regardless of severity, 23.6% of patients in the study were treated with steroids or antihistamines alone. "Our results highlight that anaphylaxis is a substantial health problem, inadvertent exposures to known food allergens are common culprits, and epinephrine is underused," the authors wrote.

Recent C-CARE data collected across participating Montreal hospitals — the Montreal Children's Hospital, Montreal General Hospital, Royal Victoria Hospital and Sacré-Coeur Hospital — suggest that the rate of anaphylaxis in Montreal emergency departments is higher than those reported in the United States and in countries in Europe and Asia. "These differences may be due to differences in methodologies or hospital catchment populations," Dr. Ben-Shoshan explains. "Alternatively, they may be due to truly different rates of anaphylaxis among countries or due to cohort effects."

Connecting C-CARE coast to coast

C-CARE is now in its third year of operation and the number of participating centres is set to expand across the country. New sites will include the Janeway Pediatric Research Institute in Newfoundland (Dr. Robert Porter); Sainte-Justine Hospital in Montreal (Drs Jocelyn Gravel and Anne Des Roches); Emergency Medical Services Outaouais in Quebec (Dr. Jocelyn Moisan); and the British Columbia Children's Hospital (Drs Paul Enarson and Edmond Chan). This expansion will allow Dr. Ben-Shoshan's team to compare anaphylaxis rates and management across provinces.

Health Canada has donated $50,000 to support the expanded registry and will use C-CARE results to evaluate the role of health policies, particularly those related to food labelling, in the prevention of anaphylaxis in Canada. Dr. Ben-Shoshan believes that Canada's unique anaphylaxis registry may eventually attract international collaborators. "As more and more results become available, physicians across the globe will be able to see that the registry provides important data," he says. "Likely, they will want to examine what is happening in their own centres and compare their results to Canada."

Dr. Ben-Shoshan's work in the field of allergies and anaphylaxis continues to garner recognition. In 2013, AllerGen, in partnership with the Fonds de recherche santé Québec (FRSQ), awarded Dr. Ben-Shoshan a *Clinical Research Scholar, Junior 1 Career Award*. The award, which recognizes outstanding young clinical investigators who wish to pursue research on allergic and related immune diseases, will further Dr. Ben-Shoshan's work with the C-CARE registry and allow him to study the environmental, genetic and socio-demographic factors associated with food allergies.

"AllerGen has supported me in so many ways since I arrived in Canada," says Dr. Ben-Shoshan. "Networking, collaboration and partnership are essential to scientific discovery and development. This is the foundation that AllerGen provides across sectors and within the Network. I think that is priceless."

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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

Telephone: (905) 525-9140 ext. 26502
Fax: (905) 524-0611
E-mail: info@allergen-nce.ca

www.allergen-nce.ca

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