



# AllerGen

Spring 2016

*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)—proudly presents its tenth issue of *Success Stories*, showcasing the research and knowledge mobilization achievements of its researchers, students and partner organizations.

This issue of *Success Stories* shares groundbreaking new research about the origins of allergic disease, highlights a new pollution monitoring technology, provides insight into Canadian anaphylaxis patterns, and profiles the rising career path of a Network trainee. Featured stories highlight:

- the discovery that four types of gut bacteria play a role in protecting children against asthma;
- the link between a baby's exposure to air pollution and the development of allergies;
- a personal, portable air quality monitor;
- new statistics about anaphylaxis rates, triggers and treatment; and
- an AllerGen trainee's trajectory to success in research and publication.

For the past decade, AllerGen investments have enabled significant scientific discoveries about the origins of allergic disease, advanced drug development, forged a strong national research community in allergy and asthma, and expanded research and clinical training opportunities to prepare the next generation of leaders in the field.

Over the next several years, working closely with partners and stakeholders, AllerGen will focus on translating and commercializing key research findings from its 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 biological samples and immunological, physiological and genetic data from over 3,500 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 offers biotechnology and pharmaceutical companies an opportunity to evaluate promising new



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drug molecules for the treatment of allergic diseases in both the upper and lower airways.

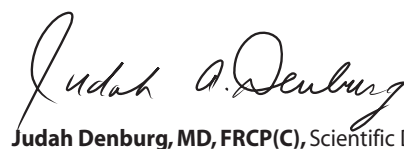
- **Canadian Food Allergy Strategic Team (CanFAST)**

This innovative, nationally-networked research team provides new knowledge about 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**

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 is not yet clear why some infants have low levels of FLVR bacteria, but finding out could prove crucial for predicting which children are at risk for asthma, and perhaps even for preventing the condition from developing in the first place.**



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# Anti-Asthma Squad: Four Gut Bacteria Help Protect Kids from Developing Asthma

If you were holding a baby in your arms and wondered if an asthma diagnosis could lay in its future, the baby's diaper would likely be the last place you would think to look for an answer. But think again: researchers at The University of British Columbia (UBC) have traced a solid line between specific bacteria in an infant's gut and the risk of developing asthma.



**Dr. Brett Finlay, Professor**  
The University of British Columbia



**Dr. Stuart Turvey, Professor**  
The University of British Columbia

Dr. Brett Finlay, a microbiologist and a Peter Wall Distinguished Professor at UBC, and Dr. Stuart Turvey, a pediatric immunologist at BC Children's Hospital who holds the Aubrey J. Tingle Professorship in pediatric immunology, led the research that discovered four types of gut bacteria play a critical role in protecting children against asthma. More specifically, infants with low levels of these bacteria at the age of three months had a significantly higher risk of asthma, even if their bacteria levels normalized later. "It points to a window in the first 100 days or so of life, when disruptions in the normal composition of bacteria in the gut can derail the immune system and lead to asthma down the road," says Dr. Finlay.

## The importance of "flavour"

The bacteria are called *Faecalibacterium*, *Lachnospira*, *Veillonella* and *Rothia*—tongue-twisting names that Drs Finlay and Turvey have collapsed into the acronym FLVR, pronounced "flavour." It is not yet clear why some infants have low levels of FLVR bacteria, but finding out could prove crucial to predicting which children are at risk for asthma, and perhaps even for preventing the condition from developing in the first place. "My guess is that certain factors known to disrupt normal gut bacterial colonization, such as caesarean-section delivery and exposure to antibiotics, might play a role," says Dr. Finlay.

Their research, which was funded by the Canadian Institutes of Health Research (CIHR) and published in the journal *Science Translational Medicine* in September 2015, quickly grabbed worldwide attention, generating over 400 headline stories within 24 hours. The research team, including co-first authors Dr. Marie-Claire Arrieta and Leah Stiemsma, juggled 90 interviews from international media outlets in countries as far-flung as

Korea and Brazil. Dr. Turvey's mother saw a report of the Canadian scientific discovery on the local 6 p.m. news—at her home in Sydney, Australia.

"This is the first study to identify some of the specific microbes that influence asthma," says Dr. Turvey. "We received emails from families affected by asthma thanking us for our work." The outpouring of gratitude attests to the burden asthma places on families. "I think we sometimes underestimate this," he admits. "People are eager for anything that might help—even bacteria."

## The smoking gun

We used to think of bacteria as our enemies, and early antibiotic researchers waged war against them. It's only in recent years that scientists have recognized the importance of "friendly germs"—bacteria that keep our digestive system in working order and may keep a host of ailments at bay. The idea that we can happily coexist with germs has kindled researchers' interest in the makeup of our microbiome—the trillions of bacteria, viruses, fungi and other microorganisms that inhabit our body.

The more scientists delve into the microbiome, the more they find: we now know that imbalances in the microbiome can predispose people to obesity, metabolic disorders, urinary tract infections, and eczema, among other conditions.

The digestive system may seem like an unusual place to search for asthma clues, but the UBC team had good reason to look there. Many of the factors linked to asthma—like caesarean-section delivery, formula feeding or early life exposure to antibiotics—have to do with bacteria, according to Dr. Turvey. For example: "A caesarean section is a sterile procedure and the baby misses out on being exposed to the invisible, and possibly helpful, microbes in the mom's birth canal."



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**The digestive system may seem like an unusual place to search for asthma clues, but the UBC team had good reason to look there. Many of the factors linked to asthma—like caesarean-section delivery, formula feeding or early life exposure to antibiotics—have to do with bacteria, according to Dr. Turvey. For example: “A caesarean section is a sterile procedure and the baby misses out on being exposed to the invisible, and possibly helpful, microbes in the mom’s birth canal.”**

“We also know that the microbiome has a bearing on immune system function, and asthma involves immune disruption,” adds Dr. Finlay. “There have been a number of ‘smoking guns’ to suggest that microbes might be involved in asthma development, but no experiments to prove it. That’s the gap we were able to fill.”

### Tracking down the right bugs

In their research, Drs Finlay and Turvey, both AllerGen investigators, used data from 319 children enrolled in the Canadian Healthy Infant Longitudinal Development (CHILD) Study, a unique birth cohort study that is tracking 3,500 Canadian children and their families from pregnancy to the age of five in an attempt to unearth the root causes of allergy, asthma and other chronic diseases. Dr. Turvey leads the Vancouver arm of

the CHILD Study, which is funded by AllerGen and CIHR. Other CHILD Study sites are located in Winnipeg, Edmonton and Toronto.

Using stool samples collected from the children at three months and again at one year of age, the research team pieced together a picture of the babies’ gut environments and the bacteria living there. They also assessed the children for early signs of allergies and asthma during clinical check-ups at ages one and three years.

The connection between gut bacteria and asthma risk did not leap out immediately; it was only when the researchers dug down to the level of specific bacterial genres that the link became evident. Children with low levels of FLVR at three months of age were more likely to wheeze and to have positive allergy skin tests (both are telltale signs of future asthma) at the age of one





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year, even if their FLVR levels had become normal by then. On the flip side, children with no signs of asthma at one year of age had high levels of FLVR bacteria in their three-month stool.

And there was more. The babies who went on to develop asthma had higher or lower levels of certain bacterial by-products in their urine, suggesting that these chemicals might induce the immune system to either trigger or ward off asthma.

To confirm the significance of the FLVR bacteria, the researchers conducted a separate study in mice. They bred “germ-free” mice without any gut bacteria and transferred stool from three-month old babies who were FLVR-deficient into the mice. They found that the animals developed inflamed lungs—an early signal of asthma. However, if the researchers deliberately supplemented the mice with the missing FLVR bacteria, inflammation decreased and the risk for asthma disappeared.

Although Dr. Finlay calls the study’s findings “preliminary,” the research seems to support the idea that we are making our environment too clean, a theory known as the “hygiene hypothesis.” “We have done a great job getting rid of microbes that cause infectious diseases, which were the leading cause of death a century ago, but we may have gone too far,” he warns. In other words, “we may be living too cleanly, which could be contributing to the rise in asthma and allergies. We need to push the pendulum back toward a middle ground to achieve a balance between hygiene and helpful environmental exposures.”

## Opening the door

The FLVR discovery could profoundly impact medical practice. It opens up the possibility of flagging children most at risk for developing asthma by testing their microbiome in the first three months of life. Those children could be monitored closely and treated quickly if they showed signs of asthma. It also opens the door to developing FLVR probiotic treatments to prevent asthma in the first place.

Before probiotic therapies for infants become a reality, however, researchers will need to spend more time at the lab bench. “We need to confirm our results in larger groups of children and in different parts of the world,” says Dr. Turvey. “We also need to make sure that any new probiotic supplements or treatments are safe for babies,” he notes. All this could take several years, but “at least we’ve opened the door.”

In the meantime, the Finlay and Turvey labs are forging ahead in their quest to fill in the remaining knowledge gaps. Dr. Finlay’s team is planning follow-up studies in Ecuador to find out whether or not the FLVR phenomenon extends to children who grow up in a very different environment, and UBC has filed a patent for the FLVR discovery that could lead to a new therapy down the road.

For the time being, parents intent on keeping their infants away from germs might want to reconsider their position, says Dr. Finlay. “There’s such a thing as good dirt, and we shouldn’t fear it so much.” **A**

**A landmark study, published in *Environmental Health Perspectives* in May 2015, suggests that exposure to traffic-related air pollution (TrAP) in a baby's first year of life may lead to the development of allergies to foods, mould, pets, and pests. It is the first study to identify such an early link.**





Traffic pollution. Nobody likes it. We know that breathing in traffic exhaust is bad for us, yet most of us simply put up with it. But what if you found out that these fumes could make your toddler more prone to becoming allergic to cats or dogs? Or to household mould? Or even to milk or peanuts?

New Canadian research by Dr. Michael Brauer, an AllerGen investigator and a professor in the School of Population and Public Health at The University of British Columbia (UBC), is pointing in that direction. Together with Dr. Hind Sbihi, an AllerGen trainee and postdoctoral fellow in his laboratory, Dr. Brauer published a landmark study in *Environmental Health Perspectives* in May 2015, that suggests that exposure to traffic-related air pollution (TrAP) in a baby's first year of life may lead to the development of allergies to foods, mould, pets, and pests. It is the first study to identify such an early link.



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



**Dr. Hind Sbihi, Postdoctoral Fellow**  
The University of British Columbia

Dr. Brauer, a Harvard-educated air pollution specialist, previously investigated whether genes influence the effect of air pollution on asthma risk, discovering that children with specific genetic profiles had a significantly greater risk of developing asthma in high-TrAP environments.

Studies by other researchers had shown that pollution exposure increases allergic flare-ups in older children and adults. However, given the importance of the early years of life in shaping the immune system, Dr. Brauer wondered whether TrAP might set the very youngest among us—babies in *utero* and infants—on a course toward allergy. “Most studies to date have looked at older children,” says Dr. Brauer. “Our focus on pregnancy and the first year of life is what makes this research unique.”

### 2,500 kids—2,500 environments

To gather information for his study, Drs Brauer and Sbihi used data from the Canadian Healthy Infant Longitudinal Development (CHILD) Study, an AllerGen legacy project. Launched in 2008 and led by a consortium of over 40 internationally renowned Canadian researchers and physicians, this massive project is following over 3,500 children in four cities (Toronto, Vancouver, Winnipeg, and Edmonton) from pre-birth until they turn five years old. Data is collected from questionnaires, home inspections, and various biological samples including blood and stool. Most pertinent to Dr. Brauer's investigation: at age one, the

children underwent allergy tests for sensitivity to 10 common allergens, ranging from cat hair and fungus to peanut and egg.

Dr. Brauer's analysis focused on about 2,500 of the CHILD Study subjects, using estimates of nitrogen dioxide (NO<sub>2</sub>), a common pollutant, in the children's environment to assess their exposure to TrAP in the first year of life. “We didn't just rely on air pollution levels at a child's home address—we examined the child's schedule of activities to unearth other possible TrAP sources,” he says. For instance, a child might live on a quiet street near a park, but attend daycare near a freeway, or spend time at parent and baby programs in a community centre downwind from a bus depot. The model also considered the microenvironment of each home. Were the windows mostly open or mostly shut? Did the ventilation system move fresh air through the house or recirculate stale air? Did the heating and air conditioning work as they should? All of this data rolled up into the final estimate of total TrAP exposure.

As expected, children living in the two larger cities, Toronto and Vancouver, had more TrAP exposure than those living in Winnipeg and Edmonton, though within each city, TrAP exposure varied significantly from child to child. Depending on where they lived and how they spent their days, “some children had five or even 10 times more pollution exposure than others,” says Dr. Brauer.

Dr. Sbihi did most of the number crunching. “She collected all the information about where these thousands of children



lived, whether they relocated, and where they moved throughout the day, and fed this data into our TrAP-estimation model,” says Dr. Brauer. “It was painstaking work and Hind did it expertly.”

### Car fumes and allergies

Next, the researchers crossed TrAP estimates with results from each child’s allergy tests. The findings left no doubt: TrAP exposure in the first year of life did increase the risk of allergy. Specifically, every 10% increase in NO<sub>2</sub> exposure raised the risk of allergy by 16%. “That may not sound like a lot, but when you consider that some infants had 10 times more TrAP exposure than others, the difference in allergy risk can be substantial,” says Dr. Brauer. On the other hand, increased TrAP exposure during pregnancy did not affect the children’s allergy risk after birth. Allergy rates also differed across the four study cities:

the proportion of allergic children was highest in Vancouver (23.5%), followed by Toronto and Edmonton (both 17%), and lowest in Winnipeg (9%).

So how might breathing in car fumes in infancy trigger an allergy later on? While the precise mechanisms are not yet known, Dr. Brauer says researchers have at least three theories to investigate: that the exhaust modifies the expression of newborns’ genes, leading to allergic sensitivity; that the fumes react chemically with the allergens; and that the pollutants alter the connections between cells, making it easier for allergens to get through.

### Germs welcome!

The study also teased out some protective factors that the researchers had not expected. Daycare, for one. “Children who attended daycare were less vulnerable to the effects of TrAP on



allergy risk,” Dr. Brauer explains. “We’re not sure why, but we suspect that the increased exposure to everyday germs in day-care settings directs the immune system to develop normally to combat pathogens, rather than veering towards an allergic response.” The researchers also found that babies with older siblings, cats or dogs in the house were less likely to show allergy at age one. Here again, increased germ exposure may help to explain the difference—or it could be that only the parents who were less likely to have allergies themselves owned pets, and that they transmitted their protective genes to their kids.”

Taken together, these findings support the “hygiene hypothesis” of allergy development, which says that shielding infants from dirt and bacteria may derail the normal development of the immune system during the critical first few months of life. According to the hygiene hypothesis, squeaky-clean environments don’t provide enough exposure to germs to “educate” the immune system to defend itself against microbes or other invaders. “It seems that there is such a thing as too clean,” says Dr. Brauer. Not that continuous exposure to germs would solve the problem, though. “As with many things in life, balance is key.”

The study also lent support to the notion that the immune system has a “window of opportunity” vital to its development. According to Dr. Brauer, this window—likely open during the first few months of life—“may steer the immune system toward an allergic path or a non-allergic path.”

## More to learn

News of Dr. Brauer’s study reverberated rapidly through the mass media, leading to interviews with the *CBC*, the *UK Telegraph*, and *Global News*, among others. Dr. Brauer attributes this media buzz to an abiding interest in allergy. “Allergies affect everyone,” he says. “Chances are, you either have an allergy yourself or you have an affected family member.”

The media latched onto the idea that “pollution causes allergy,” which Dr. Brauer views as a vast oversimplification. “We never claimed it’s a cause,” he says. “At best it’s one of many contributing factors.” Journalists were also curious to know why the Vancouver children had such high allergy rates. Was the city too polluted? Should city planners be doing something differently? Dr. Brauer says there are many possible reasons related to the environment and differences in the populations

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between cities: “Among other possible factors, Vancouver has a relatively affluent population, and we know that wealthier urban populations tend to have higher allergy rates.”

It’s also far from clear whether or not the link between early exposure to TrAP and allergic susceptibility persists over time. “It is possible that the children will lose the added vulnerability as they get older,” says Dr. Brauer, who plans to follow the same group of children up to school age to find out. He will also revisit the genetic link uncovered in his previous research to determine whether early TrAP exposure increases the risk of allergy in everyone or just in people with a particular genetic profile.

Also on the drawing board: “We’ll look at which of these kids develop asthma and find out if it corresponds to early TrAP exposure.” Finally, Dr. Brauer plans to find out whether allergy-prone children have a different assortment of gut bacteria from non-allergic children, to further probe the hygiene hypothesis.

In the meantime, how might this particular study help new parents to protect their children from developing allergies? In this regard, Dr. Brauer cautiously recommends “taking reasonable steps to avoid polluted areas.” When choosing where to live, for example, “even a block away from a major roadway may be better than right on it.” What parents don’t need to worry about: everyday germs, dust and dirt. “Don’t try to protect kids too much,” he advises. “Let them play in the sandbox and get dirty—it’s good for the immune system!” 



**Between 2016 and 2019, the researchers plan to test current and future enhanced AirSENCE prototypes at the University of Peking and other selected sites. Why Beijing? For one thing, “the University is a top research institution,” says Dr. Evans. Also, the megacity has high levels of air pollution, and “there’s a growing interest in measuring pollution levels in China. It will be interesting to see how the Beijing results compare to the Canadian data.”**



# AirSENCE: Getting Personal with Air Pollution

If you're planning to buy a new home, you may want to talk to Jeffrey Brook. Dr. Brook is not a real-estate agent or a lawyer, so he won't have much to say about easements or local amenities, but he can give you insight into something that's at least as important: the quality of the air in the neighbourhood you have your eye on.

Dr. Brook, a senior scientist with Environment Canada, Assistant Professor at the University of Toronto (U of T) and Research Leader within AllerGen, is a national authority on air quality. With U of T colleague, Dr. Greg Evans, a professor of chemical engineering, and their crackerjack research team, they are working to develop a portable air quality monitor that tells you where—and when—air pollution levels go up and down.



**Dr. Jeffrey Brook**  
Assistant Professor  
University of Toronto



**Dr. Greg Evans, Professor**  
University of Toronto

Named AirSENCE (Air SENSor for Chemicals in the Environment), the device uses a panel of sensors to gauge the levels of five common air pollutants: nitrogen oxides, ozone, carbon monoxide, carbon dioxide, and particulate matter. You can mount the sensor just about anywhere, including inside your home, and have instant access to the data it generates through your smart phone.

If air pollution levels on your block spike during rush hour, AirSENCE would let you know. If polluted air wafts over from the highway to a nearby park, AirSENCE would let you know that, too. It could even generate data on the air quality in your back yard or living room. "You might call it the personal computer of air quality monitoring," says Dr. Brook. This "smart" device can also translate these values into an overall estimate of your personal environment's air quality health index (AQHI), a scale designed to inform people about the impact of air quality on human health.

## Origins of AirSENCE

The Canadian Healthy Infant Longitudinal Development (CHILD) Study—a unique birth cohort study funded by AllerGen and the Canadian Institutes of Health Research (CIHR)—sparked the development of AirSENCE. Since 2008, the CHILD Study has been tracking more than 3,500 Canadian children and their families from pre-birth to age five to root out the causes of

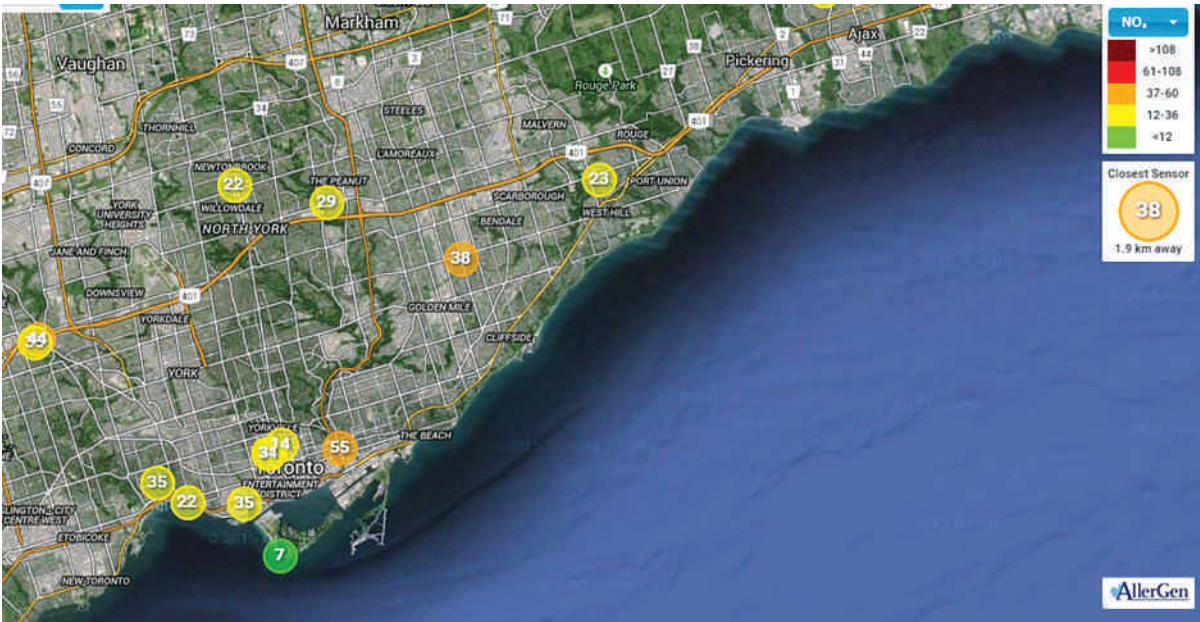
allergies, asthma and other chronic diseases. Along the way, CHILD Study researchers have been collecting questionnaires, biological samples, and detailed data on air pollutants, house dust and chemicals in the home.

As one of the CHILD Study's environmental experts, Dr. Brook was hoping to better understand the impact of early life exposure to traffic pollution on the development of allergies and asthma, but he had a nagging feeling that he needed to do more than "guesstimate" pollution levels obtained from questionnaires and refined with computerized models. In 2012, with AllerGen funding, Dr. Brook launched *Better Exposure Avoidance Measures* (BEAM), a research project focused on developing improved methods for directly assessing air quality.

"We envisioned a technology that could provide immediate, accurate results that CHILD researchers or anyone else could easily interpret, without a lot of lab costs," says Dr. Brook. "We called this the 'plug-and-play' idea." Also on the agenda: a device that could measure multiple pollutants at the same time. The reason? "Research suggests that it's the sum total of pollutants that causes health problems, rather than a single culprit."

## A better widget

A compact, portable sensor emerged as the most logical device to build. "Think of it as a souped-up smoke detector or carbon



Nitrogen oxide concentrations estimated with AirSENCE during 2015 Pan Am Games.

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monoxide sensor configured to measure several pollutants at once,” says Dr. Evans, who is Director of the Southern Ontario Centre for Atmospheric Aerosol Research (SOCAAR). His engineering doctoral student Natalia Mykhaylova, an AllerGen trainee with a background in pharmaceutical chemistry, built the first AirSENCE prototype. The design was deceptively simple: housed in a Tupperware container, the model combined commercially available sensors with customized circuitry. “We found out early on that sensors have widely varying levels of performance,” says Mykhaylova. “Some sensors will not respond until pollution levels get quite high, while others are not specific enough—they respond to the wrong chemicals — so we had our work cut out for us.”

Within a few years, Mykhaylova churned out three more prototypes, each one more sensitive and accurate than the last. “We tested them in several ‘microenvironments’—near a highway, by a smaller road, at a public transportation stop, and in

an indoor location,” she says. These next-generation sensors proved reliable enough to measure key pollutants and track small changes over time. The third prototype even had wireless connectivity, which meant that several devices could be networked together and the collective data accessed online.

Before the device could become a commercial product, however, it needed a name. “We considered some ‘sexy’ names, but in the end our team decided to go for some *gravitas*,” says Dr. Evans. “AirSENCE, which Jeff [Brook] came up with, seemed to capture the essence of the technology.”

From Pan Am to Beijing

When the government agencies working on Toronto’s 2015 Pan Am and Parapan Am Games learned about AirSENCE, they “saw how this technology could let athletes and visitors to the city appreciate Toronto’s generally clean air, while helping more vulnerable visitors—especially those with allergies, asthma or



other respiratory conditions—make decisions about when to train, sightsee and schedule their activities,” says Dr. Brook.

Seizing the opportunity, the BEAM team placed AirSENCE monitors near athletic venues and around Toronto as part of the Games’ infrastructure. Interested parties could view the monitors’ output on an interactive online map. “You could click on locations to see hourly AQHI readings and the concentrations of key air pollutants over the previous three days,” he says. Several news sources, including the *CBC*, gave a shout-out to the sensor and its online mapping tool.

On the tailwind of the pilot project’s success during the Pan Am Games, the researchers are gearing up for a larger-scale evaluation in Beijing, China. In addition to continued support from AllerGen, the team has financial backing from the Ontario-China Research and Innovation Fund, a program created by both governments to strengthen business ties between the two regions. They are collaborating with a Canadian company called AUG Signals and graduate student Kris Herod on the design of a brand new, breadbox-sized AirSENCE prototype. This prototype will address many of the limitations of earlier versions identified through extensive research, development and field testing.

Between 2016 and 2019, the researchers plan to test current and future enhanced AirSENCE prototypes at the University of Peking and other selected sites. Why Beijing? For one thing, “the University is a top research institution,” says Dr. Evans. Also, the megacity has high levels of air pollution, and “there’s a growing interest in measuring pollution levels in China. It will be interesting to see how the Beijing results compare to the Canadian data.”

Dr. Brook credits AllerGen for getting AirSENCE to this point. “AllerGen has supported us since the beginning,” he says. “The Network quickly recognized the value of a technology that gives real-time, location-specific air quality readings to people with allergic disease and respiratory disorders.” If all goes as planned, the device will find its way to retail stores within a few years.

## Citizen sense

All this is happening at a good time: a growing public interest in environmental health has brought the issue of air quality into greater focus. “We used to view air pollution exposures as


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something we didn’t have much choice about, but the Internet has helped people become more aware of the dangers,” says Dr. Brook. Governments too are keen to help people make informed choices about their exposure to air pollution. “Policy-makers have been talking about empowering citizens to make decisions about the environments they spend time in,” he says.

What kinds of decisions? For one thing, accurate information about air pollution could influence the zoning of new schools, daycare centres and retirement homes. On a more personal level, air quality data may help people choose which route to take to work, which bike path to use, or even where to buy a new home. Indeed, Dr. Evans says he gets weekly calls from people asking for guidance on such matters. For example: “The other day, I got a call from a mom with young children who was looking to move to an area very close to a major highway. I told her that many factors go into a decision to purchase a home, but in terms of air quality, I would have concerns about sending a child to a daycare that close to a highway, especially if that child has asthma or allergies.”

For their part, Drs Evans and Brook envision a future in which all of us can get moment-to-moment feedback on the air we are breathing, no matter where we are. Their team has worked on a prototype that attaches to a bicycle. They also have plans for a battery-operated version. “Some people have suggested that personal air sensors will be the next GPS,” Dr. Brook says. There is no doubt that the AirSENCE team is helping to make that happen. 



**“There is no logic to anaphylaxis, at least none that we understand. One person may progress to an anaphylactic response within two or three exposures to an allergen, while another may experience hives with each exposure and never progress to the anaphylactic level.”**

# Investigating Anaphylaxis: Finally, Some Numbers

How could a healthy young girl—one with no known serious food allergies—die from eating an ice cream cone? The tragic incident happened in March 2013, when a 12-year-old girl collapsed after eating ice cream at an Ontario shopping mall. She died in hospital a short time later. While no specific cause of death was confirmed, doctors believe a food allergy may have triggered a fatal anaphylactic reaction.

In the case of Andrea Mariano, a first-year student at Queen's University in Kingston, Ontario, there was no doubt: she died from anaphylaxis (a severe allergic reaction) after consuming a smoothie on campus in September 2015. Contrary to her usual habit, Mariano was not carrying her epinephrine auto-injector for her allergies to dairy and peanut.



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

Few things strike as much fear in people's hearts as the thought of a loved one experiencing a life-threatening anaphylactic reaction. What makes anaphylaxis so frightening is its seeming randomness: nobody with allergies can be assured it won't happen to him or her.

"There is no logic to anaphylaxis; at least none that we understand," says Dr. Moshe Ben-Shoshan, a pediatric allergist and immunologist at Montreal Children's Hospital. "One person may progress to an anaphylactic response within two or three exposures to an allergen, while another may experience hives with each exposure and never progress to the anaphylactic level."

## An urgent need to know

Given the dramatic symptoms of anaphylaxis, one might think that researchers and physicians know a lot about it—what causes it, how often it occurs and whom it affects—but Dr. Ben-Shoshan maintains that this is not the case. "Data on anaphylaxis are sparse and imprecise," he says. "We can't be sure they reflect the actual number of cases that occur every year across the country." What's more, not all cases are straightforward to diagnose. For example, "if a young person comes to the emergency room with breathing problems and hives, the physician may think it's from a virus or stress."

In the hope of gaining greater insight into anaphylaxis rates, triggers and treatment, Dr. Ben-Shoshan established the Cross-

Canada Anaphylaxis REgistry (C-CARE). Funded by Allergan, the registry was launched in 2010 and has since been collecting data from thousands of adults and children who have had anaphylactic reactions. Hospitals in British Columbia, Ontario and Quebec contribute data to the registry, and expansion to other parts of the country is underway. Dr. Ben-Shoshan and his collaborators believe the registry, which has partnership and support from Health Canada and other organizations—is a powerful tool that will improve the management of severe allergic reactions from both a medical and a public health perspective.

## Big reveal: anaphylaxis rates on the rise

C-CARE has already answered a critical question Dr. Ben-Shoshan had been wondering about for some time: are anaphylaxis rates rising in Canada? The unfortunate answer is yes. An analysis of C-CARE data from his own pediatric hospital revealed that the percentage of emergency department (ED) visits for anaphylaxis doubled between 2011 and 2015. The analysis also identified a serious underuse of epinephrine auto-injectors: just slightly more than 50% of those who had an auto-injector used it before they got to the ED, which increased the risk that multiple epinephrine doses would be administered in hospital. When asked about their reasons for holding off, people often cite "panic" or "fear of the needle," says Dr. Ben-Shoshan. "There's clearly a huge need for education, both for health professionals



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**Patients are invited to become part of the registry, and if they agree, C-CARE personnel populate the database with information on symptoms leading up to the anaphylactic event, triggers (if known), timing of epinephrine administration, other treatment strategies, and outcomes.**

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and for the public, to make sure epinephrine is given immediately when a reaction occurs.”

A case Dr. Ben-Shoshan encountered a few years ago at the Montreal Children’s Hospital highlights that need: a 14-year-old girl had purchased a cookie elsewhere in the hospital, taken a bite, and then spat it out when she started feeling ill. Even that half-chewed bite took an extreme toll: her throat closed up almost instantly and she had to run to the ED, where she collapsed. “If we hadn’t administered epinephrine on the spot, we would probably have lost her,” he says, adding that “epinephrine is the only medication capable of stopping an anaphylactic reaction in progress.” Such cases are what drive Dr. Ben-Shoshan in his quest for more and better data.

## Mysteries of the immune system

After receiving his medical degree and pediatric training in Israel, Dr. Ben-Shoshan moved to Canada in 2006 to pursue a postdoctoral fellowship in pediatric allergy and immunology at McGill University. In 2011, Dr. Ben-Shoshan received AllerGen’s inaugural *Emerging Clinician-Scientist Fellowship Award*. Valued at \$250,000, this award allowed him to share time between treating patients in the clinic and honing his skills as a researcher.

“What interested me most was the immune system, because it relates to everything in the body,” he says. “Most of the time, the immune system does exactly the job it is meant to do, but when things go wrong, they can go very wrong—very fast.”

The rate of food allergies in Canada came as a surprise to Dr. Ben-Shoshan, especially compared to the much lower rates in his native country. Although scientists can’t fully explain the discrepancy, the fact that “parents tend to introduce peanut to their children much earlier in Israel” may have a bearing, he says. A more communal living style, as exemplified in the kibbutz, probably doesn’t hurt, either. Even in Canada, “new immigrants have a relatively low risk of allergies, but their children have a higher risk, so there’s clearly something in the environment or lifestyle that makes people born here more vulnerable.”

The need to understand that “something” is what spurred Dr. Ben-Shoshan to launch C-CARE.

It is the first registry in the world to track episodes of anaphylaxis prospectively, at the time they occur. The C-CARE research team has forged ties with emergency department staff, ambulance paramedics and allergists, who provide reports of anaphylaxis cases as soon as they happen. Whenever possible, the initial diagnosis is double-checked with lab tests.

Patients are invited to become part of the registry, and if they agree, C-CARE personnel populate the database with information on symptoms leading up to the anaphylactic event, triggers (if known), timing of epinephrine administration, other treatment strategies, and outcomes. C-CARE staff keep in contact with registry participants to ask about any follow-up allergy tests or if the anaphylaxis trigger was confirmed. To complete the data set, participants (or their parents) fill out annual questionnaires about allergy status and symptoms, use of medications, and their living environment.

Since emergency physicians don’t always have a chance to gather anaphylaxis information on the spot, the registry also collects data retrospectively. “We look through old charts from the ED every day and extract whatever information we can from previous anaphylactic events,” says Dr. Ben-Shoshan.

## Numbers talk

A growing slate of publications attests to the registry’s vitality: the researchers have already published two dozen papers and abstracts that are quickly filling in the gaps of anaphylaxis knowledge.

For starters, the database helped link close to 80% of anaphylactic reactions in hospital emergency departments



to food allergens. "It's always food, wherever you look," says Dr. Ben-Shoshan. Among the various food triggers, peanut is the most common in children, shellfish in adults.

While peanut tops the list of triggers for a child's first anaphylactic reaction, it is less likely to be a trigger in children with recurring events. Could it be that families become extra cautious after that first incident and thus avoid another exposure? Dr. Ben-Shoshan hopes that the registry will help to answer this question too. What he already knows, thanks to C-CARE, is that accidental exposure to a known allergen accounts for only one in four anaphylactic events in children. In the remaining 75% of cases, the families didn't know about the child's allergy before the event.

Data mined from the registry may even help to diagnose anaphylaxis: Dr. Ben-Shoshan and his collaborators have discovered that children with severe and milk-induced anaphylaxis have elevated levels of tryptase, an enzyme released by

immune cells, during and for up to 24 hours after the event. Further, they established that the difference in tryptase levels during and following a reaction is a sensitive diagnostic tool regardless of the triggering factor. "Tryptase can be measured in the blood, so a lab test could be used to help diagnose anaphylaxis," he says. Once aware of the diagnosis, people could better protect themselves against future events.

Looking ahead, Dr. Ben-Shoshan plans to use C-CARE to study the effect of food labelling on the behaviour of people at risk of anaphylaxis. "We ask all the participants in our database if they think their allergic reaction had to do with poor food labelling," he says. If the numbers skew toward a link, "it would suggest that governments need to change their policies around labelling."

Whatever the numbers reveal, they can only help. Forewarned, as the saying goes, is forearmed. [A](#)



**Dr. McNagny introduced Dr. Gold to the AllerGen network and encouraged him to take advantage of AllerGen’s programs and awards for students and new professionals.**

**Dr. Gold didn’t know it at the time, but he would work with Dr. McNagny right up to the completion of his doctoral degree in 2015. With Dr. McNagny’s guidance and AllerGen’s behind-the-scenes support, Dr. Gold began studying what makes the immune system tick.**



## HQP Profile—Matthew Gold: Paragon of Productivity

Many people take a long time to figure out who they are and what they want to do in life. Matthew Gold, an AllerGen trainee, is not one of those people. A career as a research scientist has always felt right to him, and now that he's actually a career scientist, the feeling just keeps getting better. And while he rarely speaks of his own accomplishments, Dr. Gold has a CV that would make a seasoned researcher envious, and he's only 30. His publishing record alone—he is an author in no fewer than 23 peer-reviewed journal articles—speaks volumes about his work ethic and dedication to his calling.



**Dr. Matthew Gold, Postdoctoral Fellow  
Princess Margaret Cancer Centre**

Not that it all came quickly to him. A physiology undergraduate degree from McGill University left Dr. Gold with a wide open research slate, and he took his time looking for a focus, doing what he calls “a long and winding PhD” from 2007 to 2015, at The University of British Columbia (UBC). Eventually, he settled on the study of immune responses as a subject rich enough to occupy him for—well, the rest of his life.

Dr. Gold also changed academic supervisors before finding a mentor with whom he really “clicked”: Kelly McNagny, a professor of medical genetics at UBC and Scientific Director for the Centre for Drug Research and Development (CDRD) in Vancouver. Straight away, Dr. McNagny introduced Dr. Gold to the AllerGen network and encouraged him to take advantage of AllerGen's programs and awards for students and new professionals. Dr. Gold didn't know it at the time, but he would work with Dr. McNagny right up to the completion of his doctoral degree in 2015. With Dr. McNagny's guidance and AllerGen's behind-the-scenes support, Dr. Gold began studying what makes the immune system tick.

### From CD34 to asthma

Dr. Gold had his introduction to allergy research working with AllerGen trainees Dr. Steven Maltby, now a postdoctoral fellow at the University of Newcastle, Australia, and Dr. Marie-Renée Blanchet, now a faculty member at Laval University. Their work centred on CD34, a protein that functions as an immune

system traffic cop, either ferrying immune cells to different parts of the body or blocking their passage. In a series of experiments, the research team showed that CD34 is an important player in diseases that involve the immune system: it allows eosinophils (a type of immune cell) to infiltrate the colon and trigger ulcerative colitis; and it helps dendritic cells (specialized immune messenger cells) to migrate to the lungs, where they promote inflammation. These discoveries set the foundation for what would be Dr. Gold's future research, primarily focusing on how modulation of the innate immune system can influence the development of allergic disease.

### Working hard, working smart

One of Dr. McNagny's key areas of research is how genes and the environment play off each other to raise or lower the risk of allergy, and Dr. Gold wanted to get involved. Previous research had suggested that disruptions in the gut microbiome (the collection of bacteria living in the digestive system) might increase vulnerability to asthma. Intrigued by this hypothesis, Dr. Gold joined Dr. McNagny's multidisciplinary research team, which was digging into the matter.

In one experiment, the researchers treated newborn mice with two widely used antibiotics, streptomycin and vancomycin, to find out if the medications would affect the microbiome. Streptomycin did not, but early life administration of vancomycin “reduced microbial diversity and shifted the composition of the



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**Working together, the researchers showed that exposing mice to particulate matter made them more reactive to ovalbumin, an allergen found in eggs. Specifically, the pollutants prompted the lungs to release uric acid, which triggered a cascade of immune changes that, in turn, heightened the mice’s allergic sensitivity. “It was like a giant puzzle that we assembled together,” Dr. Gold says.**

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microbiome, which made the mice more vulnerable to allergic asthma as adults,” says Dr. Gold. “This told us that the timing of antibiotic exposure is crucial—an early dose could raise the risk of asthma, while the same dose later on might have no effect.”

Following a meeting with Dr. Jeremy Hirota, now a UBC faculty member who was, at the time, an AllerGen trainee working in a different UBC lab, Dr. Gold also felt himself pulled toward air pollution research. The hypothesis under consideration: whether tiny amounts of particulate matter in outdoor air might increase sensitivity to allergens. “The AllerGen network helped bring our two labs together for the collaboration,” Dr. Gold recalls. “Dr. Hirota’s lab had human lung and pharmacology experience, while our lab brought immunology expertise to the table to help push his research over the edge.”

Working together, the researchers showed that exposing mice to particulate matter made them more reactive to oval-

bumin, an allergen found in eggs. Specifically, the pollutants prompted the lungs to release uric acid, which triggered a cascade of immune changes that, in turn, heightened the mice's allergic sensitivity. "It was like a giant puzzle that we assembled together," Dr. Gold says. "Jeremy's lab would do an experiment, our lab would go off and work on another piece, and then we'd put our heads together and figure out what it all meant." For Dr. Gold, this was the best way to work. "It was a very creative process," he says.

This open-ended, exploratory approach is what made Dr. McNagny's research lab such a good fit for Dr. Gold. "It was a wonderful environment for following your nose," he says. For his part, Dr. McNagny views Dr. Gold with the pride reminiscent of a parent whose child may one day surpass him. "I took a chance on Matt—he didn't have much experience with allergy models when he started at my lab—and it was like watching a kid in a candy store," he says. "I sensed Matt would thrive if given free rein as a researcher, and I was proven more than right. He didn't just work hard: he worked smart."

### The "Gold" standard for publishing

According to Dr. McNagny, one of the things that makes Dr. Gold unique, particularly for such a young scientist, is his uncanny instinct for "sniffing out the experiments that answer a research question elegantly and conclusively"—that, and his ability to get published. Although Dr. Gold has only begun his postdoctoral work, it's already clear that the "publish or perish" imperative will never hang heavily over his head. He has co-authored 23 published research articles and published several review articles on topics ranging from mouse models of allergic asthma to the role of mast cells in human health and disease.

Two of his recent articles resulted from a group project that initially sputtered. During his undergraduate studies, Dr. Gold had become interested in SHIP-1, a multipurpose protein that plays a role in cancer and inflammation. It was speculated that knocking out the SHIP-1 gene from immune cells close to the gut might throw the microbiome off balance, and thus increase the severity of asthma in mice. While the microbiome studies weren't entirely informative, he did identify some interesting roles of SHIP-1 in regulating the immune response.

Dr. Gold went on to show that removing SHIP-1 from

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**"The AllerGen trainee program was one of my only funding sources during my PhD, and without the connections I made through AllerGen, I would not be where I am now—a post-doctoral fellow in a prestigious lab," he says.**

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dendritic cells protected mice not only from asthma, but from several other immune diseases, including parasitic infections. This discovery led to Dr. Gold's most recent publication, a 2016 article in the *European Journal of Immunology*.

### In constant motion

Despite his whirlwind research and publishing schedule, Dr. Gold has made time to help build community among his peers. When he learned of a vacancy for regional director for the AllerGen Students and New Professional Network (ASNP) in 2010, he jumped at the chance to fill the volunteer position—not only for the personal experience, but as a way to "give back" to AllerGen.

"The AllerGen trainee program was one of my only funding sources during my PhD, and without the connections I made through AllerGen, I would not be where I am now—a post-doctoral fellow in a prestigious lab," he says.

After completing his PhD in 2015, Dr. Gold had the luxury of receiving multiple offers for postdoctoral appointments. He opted for the Princess Margaret Cancer Centre in Toronto, where he has been studying the mechanisms that keep dendritic cells in balance. Now, with the potential to develop a tumour vaccine based on dendritic cells on the horizon, this work may enable the development of new and promising immunotherapies for cancer.

As for the future, Dr. Gold wants nothing more than to continue his lab work. Far from being daunted by the long, slow march to scientific discovery, he says he enjoys the challenge. "You're in constant motion," he says. "No project is ever complete, and one small finding leads to another and then another. It might make some people go a little bit crazy, but it works for me." 





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# Success Stories

## 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](mailto:info@allergen-nce.ca)

[allergen-nce.ca](http://allergen-nce.ca)

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