Winter 2019

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)—proudly presents its twelfth issue of *Success Stories*.

Success Stories is written for Canadian families, healthcare providers, policymakers and community organizations. Each issue provides up-to-date information on new research into asthma, allergies and anaphylaxis, and explores what causes these illnesses, how better to manage, treat and prevent them, and steps towards finding cures.

The Winter 2019 issue of *Success Stories* shares a few of the recent research and knowledge mobilization achievements of AllerGen researchers, students and partner organizations. This issue's feature stories include information about:

- the best time to introduce allergenic foods to babies;
- a salivary protein that may help to predict and manage stress;
- a new genetic clue to peanut allergy;
- the link between a mom's psychological wellbeing and her baby's risk of developing allergies; and
- an oral immunotherapy food allergy clinic led by a former AllerGen trainee.

Now in its 14th year, AllerGen has invested in over 200 research and knowledge translation projects across the country to discover and implement novel diagnostics, therapies and disease management strategies for Canadians living with allergy and asthma.

AllerGen's integrated research strategy, spanning three Legacy Projects and two Enabling Platforms, builds upon core research investments made since 2005.

Legacy Projects:

- **Canadian Healthy Infant Longitudinal Development (CHILD) Study**
  This world-leading birth cohort study follows the health and development of nearly 3,500 Canadian children to uncover ways to predict, prevent and treat asthma, allergies, obesity and other chronic diseases.

- **Clinical Investigator Collaborative (CIC)**
  This multi-centre, Canadian-based Phase II clinical trials group evaluates promising new drug molecules for biotechnology and pharmaceutical companies to enhance the treatment of allergic diseases in both the upper and lower airways.

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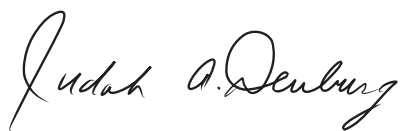
- **National Food Allergy Strategy / Canadian Food Allergy Strategic Team (NFAST-CanFAST)**
  This innovative, nationally-networked research team provides new knowledge about the origins, causes, prevalence and treatment of food allergy and anaphylaxis, and informs the development of improved clinical management strategies and public health risk management measures.

Enabling Platforms:

- **Gene-Environment Interactions**
- **Biomarkers and Bioinformatics**

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 interesting and informative.



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

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"Infants who avoided cow's milk products in the first year of life were nearly *four times* as likely to be sensitized to cow's milk at age one," says Dr. Sears. "That's huge!"

All in Good Time

Amid ever-changing advice about when to introduce allergenic foods to babies, CHILD Study research sends a clear signal

Wait a year before introducing peanuts to your allergy-prone baby. Better yet, wait three years. Avoid eating eggs while you're breastfeeding. No, eggs are fine. But definitely keep your baby away from dairy. Introduce some foods early yet breastfeed exclusively for six months. Confused yet? Imagine the turmoil for new parents trying to protect their babies from developing food allergies.

Dr. Malcolm Sears, Professor
McMaster University

Until recently, parents were instructed to hold off on feeding certain foods to babies at risk of food allergies: peanuts, tree nuts, milk, eggs and soy were all on the list of foods to avoid until well after baby's first birthday. Today, parents are told the opposite: get babies eating these foods ASAP. What happened? Why such a dramatic shift in thinking?

In a nutshell: better research. After years of study, scientists now have a clearer understanding about the best time to introduce potentially allergenic foods to infants—and waiting is not the answer.

A 2017 study led by Dr. Malcolm Sears, a respirologist and professor of medicine at McMaster University in Hamilton, Ontario, is one of several large studies to reach this conclusion. The research involved a national team of investigators participating in AllerGen's CHILD Study—a major Canadian research effort involving nearly 3,500 Canadian children and their families across four provinces. Concerned about the rise in allergies to peanuts and other common foods, Dr. Sears and his team set out to gain insight into "which pattern of food exposure in early childhood was the least likely to lead to allergy."

Using data from more than 2,100 CHILD Study infants and their parents, the team analyzed information about the babies' diets at three, six, 12, 18 and 24 months of age. They paid particular attention to the age at which parents introduced peanut, egg white, and cow's milk products such as yogurt, cheese and ice cream.

The researchers then grouped the children into three categories based on the baby's age of first exposure to these test foods: early (before six months of age), usual (between seven and 12 months of age), and delayed (after 12 months of age).

When the babies were seen at age one year, they were tested for sensitization to cow's milk, egg white, and peanut. "Sensitization means you react to a skin allergy test, which isn't the same as having symptoms of allergy," notes Dr. Sears. "However, sensitization can be an early sign of a future problem and a substantial number of sensitized children do go on to develop an allergic disorder."

The researchers looked for connections between the timing of the exposure to these foods and the babies' skin test results. The analyses left little doubt: delaying the introduction of any one of these foods beyond the first year of life significantly raised the odds of sensitization to that food. How significantly? "Infants who avoided cow's milk products in the first year of life were nearly *four times* as likely to be sensitized to cow's milk at age one," says Dr. Sears. "That's huge!" Delaying the introduction of eggs and peanuts until after the baby's first year *nearly doubled* the risk of sensitization to those foods at age one.

After controlling for other factors that could also affect allergy risk, such as ethnicity, breastfeeding status or whether a mother had allergies herself, the findings remained conclusive. "We were pleased that the results were so clear—it wasn't just a case of maybe, possibly, or could be," says Dr. Sears, though he is quick to add: "However, this was an observational study, not a clinical trial, so we cannot claim 'cause and effect.' Nonetheless, we believe our results strongly indicate that when

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In the CHILD Study, 76% of parents introduced egg to their infants at seven to 12 months of age, while only 3% did so before six months. With peanut, only 1% of parents ventured an exposure before six months and 63% avoided feeding peanut entirely during their babies' first year.

it comes to timing the introduction of these foods, earlier is better."

The early introduction of eggs—before one year—seemed to be especially beneficial: exposure to eggs significantly reduced the odds of developing sensitization to any of the three foods tested, according to Dr. Sears.

Dr. Sears notes that the majority of food allergies are related to the immune protein immunoglobulin E (IgE). When a food allergy occurs, the body's immune system triggers cells to release IgE to neutralize the food allergen, resulting in allergic symptoms. "We think that early exposure to allergenic foods may help babies become tolerant to these foods, so that they do not produce excess IgE, which in turn reduces sensitization," he says.

Taking a LEAP forward

The CHILD Study's results bolster the growing body of research that has reached similar conclusions. In 2015, the United Kingdom's landmark LEAP (Learning Early About Peanut Allergy) study found that introducing peanuts early in life to allergy-prone infants decreased their likelihood of having a peanut allergy at age five by more than 80%.

Studies of farm animals and dust mites have further challenged the misperception that exposing young children to allergens promotes allergic reactions. If anything, "these studies showed that introducing children early to these allergens protects them, rather than increasing their risk," says Dr. Sears.

Such discoveries have led researchers to speculate that peanut avoidance is actually fuelling the spike in peanut

allergy. "It's possible that the more we avoid it, the worse the epidemic," says Dr. Sears. "Introducing peanuts earlier could give us a chance of turning things around. In Israel, babies start eating peanut-containing foods very early, and peanut allergy is virtually unknown there."

Which raises the question: why did it take so long to discover the advantage of early exposure? As Dr. Sears sees it, the avoidance strategy made intuitive sense to both doctors and parents. "Previously, it was thought that waiting to introduce peanut allowed the gut and immune systems to mature and would help prevent allergies, so it's understandable that parents might be anxious about introducing foods to an infant when there's a risk that the child might be allergic."

Previous recommendations calling for delayed food introduction rested on limited evidence and targeted at-risk infants only. Nonetheless, the practice of avoidance took hold in the general population over time. In the CHILD Study, 76% of parents introduced egg to their infants at seven to 12 months of age, while only 3% did so before six months. With peanut, only 1% of parents ventured an exposure before six months and 63% avoided feeding peanut entirely during their babies' first year.

This is why Dr. Sears views the scientific method as paramount. "You challenge ideas and accepted practice by rigorously studying them until you can either confirm or refute them," he says. "Our results and other recent studies have demonstrated, with little remaining doubt, that introducing potentially allergenic foods early is the way to go."

The bigger picture

The study's findings were published in *Pediatric Allergy and Immunology (PAI)* in 2017, though Dr. Sears began thinking about this line of investigation as early as 2002. Then in 2008, AllerGen and the Canadian Institutes for Health Research (CIHR) awarded a $12 million grant to launch the CHILD Study, with Dr. Sears as its Founding Director.

"CHILD is a longitudinal study, meaning health data are gathered regularly on the same infants as they grow and develop over many years," he explains. "This means we can examine a wide range of health problems, see what factors are associated with them, and better understand how these problems develop over time. We already knew that food allergy was a driver of asthma, so it made sense to use CHILD data to look at factors that could affect the risk of food allergy, such as the timing of first exposure."

In step with the collaborative mindset championed by AllerGen, the *PAI* article lists 11 researchers as co-authors, including the CHILD Study's current Director and co-Director, Dr. Padmaja Subbarao (The Hospital for Sick Children) and Dr. Stuart Turvey (The University of British Columbia), respectively.

The paper's lead author, Maxwell Tran, is an AllerGen trainee and medical student who worked in Dr. Sears' lab while still an undergraduate student in McMaster University's Bachelor of Health Sciences program. Tran spotted Dr. Sears' study in a research directory. "I reached out to his lab, one thing led to another, and before long I was his summer student," an opportunity made possible by AllerGen's *Undergraduate Summer Studentship* program.

Tran also had a very personal interest in Dr. Sears' work. "Growing up, I had pretty severe asthma and food allergies," he says. As background work for the research leading to the *PAI* findings, Tran did a thorough review of the existing research literature, where he found "a lot of controversy about when to introduce potentially allergenic foods to children. This confirmed that there was a clear need for studies like this one."

More work to be done

As often happens with research discoveries, these CHILD findings have raised many new questions related to the optimal timing of first exposure: Is five months of age better than six months to introduce allergenic foods? Is four months even better? How does early introduction fit with recommendations to breastfeed exclusively for six months? Is early introduction recommended for children who have a parent or sibling with a food allergy? Dr. Sears and the CHILD researchers intend to explore such questions in new analyses using an even larger subset of the CHILD Study participants.

There's also work to do on the public education front. To this end, Dr. Sears, Maxwell Tran, and their team are working to get the word out to the wider clinical community—and to parents directly. In 2017, Tran wrote a short AllerGen Research*SKETCH* lay summary to make the team's findings accessible to a broad Canadian audience.

In line with the evidence supporting early introduction of foods, newer feeding guidelines recommend "breastfeeding exclusively for four months, then continuing to breastfeed while starting to introduce allergenic substances at four to five months," says Dr. Sears. But while the message is clear—early is better—Dr. Sears understands that parents and caregivers may take time to adopt the new guidelines. "That's why it will be important for family doctors, pediatricians and allergists to speak in a unified and reassuring voice. We hope our study will help them do that."

Not only did levels of CABS1 increase with a "bad mood," but "our analysis also connected higher CABS1 with a depressive and anxious mood in the week preceding the saliva test," says Dr. Befus.

The Stress Molecule

A University of Alberta researcher and his team have identified a molecule that increases during acute stress—and that may offer clues to our ability to handle stressful situations

Stress is a popular topic these days. Rarely a week passes without a news item telling us about stress and its negative effects on health. As most of us know from personal experience, stress can cause symptoms such as stomach pain or diarrhea—a testament to the strong link between the nervous and digestive systems. Stress also plays a role in heart and lung diseases and has been shown to weaken the body's immune system, which means it could have a bearing on allergies and asthma as well.

Despite the physical symptoms stress produces, it can be notoriously hard to detect and predict. But that could be changing—thanks to a clue found in saliva.

Dr. Dean Befus, Professor
The University of Alberta

AllerGen Research Leader Dr. Dean Befus, a professor of pulmonary medicine at the University of Alberta, led an international research team that studied the effects of stress on a protein they identified in human saliva. In earlier research, the protein, known as CABS1, had only been identified in the male reproductive system.

"CABS1 is influenced by the nervous system and it exhibits anti-inflammatory activity," explains Dr. Befus. "Typically, the hormone cortisol has been used as a measure of stress, but we wondered if CABS1 could also be used as a stress marker."

Why look at CABS1, among the countless molecules one might study?

In previous research, Dr. Befus and his team studied a similar protein in rats, called SMR1, which responds to signals from the nervous system to reduce inflammation and allergic symptoms. With research support from AllerGen, Dr. Befus even collaborated with a Canadian company to develop an asthma drug based on SMR1, though the drug was unsuccessful in a clinical trial in human asthma conducted in collaboration with the AllerGen Clinical Investigator Collaborative (CIC). "Some human immune cells responded to the rat-based drug, but humans don't make SMR1," says Dr. Befus. "We looked for it and couldn't find it."

Instead, they found that humans possess salivary CABS1. "The molecule had so many similarities to SMR1, including its chromosomal location, that we began to suspect CABS1 might similarly fall under the brain's control and, therefore, offer a new way to measure and predict stress, negative mood and emotional distress," he says.

Three faces of stress

To study CABS1, Dr. Befus teamed up with psychologist Dr. Thomas Ritz from Southern Methodist University in Dallas, Texas. A psychobiologist who studies how personal experience affects physiology and expression of disease, Dr. Ritz had previously researched the effect of stress on asthma, making him a natural collaborator for the CABS1 project.

Together, the researchers conducted a trio of experiments on university student volunteers to analyze CABS1 levels in people subjected to different types of stressful situations.

In the first study, participants filled out questionnaires about their mood, anxiety and stress levels over a four-week period. The researchers measured the level of CABS1 in their saliva at multiple points over the four weeks to see how stable CABS1 was, and how its levels responded to changes in emotional status.

The results supported Dr. Befus' theory: CABS1 levels were significantly related to self-reported acute stress—in fact, the higher the stress level, the greater the amount of CABS1 in saliva. The study also picked up on a subtle connection between CABS1 levels and the participants' feelings and emotions. Not only did levels of CABS1 increase with a "bad mood," but "our analysis also connected higher CABS1 with a depressive and anxious mood in the week preceding the saliva test," says Dr. Befus.

"All three studies reported in our paper showed a connection between stress and the levels of CABS1," says Eduardo Reyes-Serratos, an AllerGen trainee and University of Alberta graduate student who was an author of the scientific publication. "Given that the majority of patient visits to doctors' offices are related in some way to stress, this finding could lead to improvements in healthcare down the road."

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In a second study, designed to evoke feelings of acute stress, participants had a short time to prepare a presentation, which they delivered in a mock job interview for a senior position at a major corporation. The presentation was followed by a surprise mental arithmetic test, again designed to cause stress. This well-known "Trier Social Stress Test (TSST)" mimics real-life acute stress because "it puts subjects under 'evaluative threat,' which is a fancy way to say that they are being observed and judged," says Dr. Befus. Again, the researchers collected saliva from participants at several points during the experiment.

This study's results showed that CABS1 levels rose significantly after the stressful situation, then fell within 45 minutes, adding further evidence that the molecule reacts to acute stress.

The third study honed in on long-term stress as experienced during the university final exam period. In this experiment, the research team collected saliva from participants at both a low-stress point—during the middle of an academic term, well before finals—and a high-stress point: in the midst of the final exam period.

Interestingly, the results showed that exam-induced stress, a longer-lasting form of stress than in the first two experiments, did *not* have an effect on participants' CABS1 levels. However, consistent with Dr. Befus' earlier findings on the role of the SMR1 protein in reducing inflammation in rats, the participants' levels of CABS1 tracked with specific molecules involved in the body's inflammatory response.

While CABS1's mode of action remains a mystery, Dr. Befus speculates that the central nervous system signals the body to release CABS1 to "lift" the physiologic burden of stress and possibly to fight infection. "Different parts of the molecule may carry out different functions," he says.

"All three studies reported in our paper showed a connection between stress and the levels of CABS1," says Eduardo Reyes-Serratos, an AllerGen trainee and University of Alberta graduate student who was an author of the scientific publication. "Given that the majority of patient visits to doctors' offices are related in some way to stress, this finding could lead to improvements in healthcare down the road."

The *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* published the team's findings in April 2017.

What is stress, anyway?

In everyday conversation, stress is a catch-all word. We use it to describe our anxiety about a deadline, our dismay at the evening news, and our irritation with difficult people. In science, however, the word has a somewhat narrower meaning. As Reyes-Serratos explains it, "stress is a complex physiologic response to a perceived threat, which involves many components of the nervous system and mobilizes various pathways in the body." Also known as "fight-or-flight," the stress response readies the body to face an outside threat.

Whatever the stimulus, the stress response prompts the body to release a surge of hormones. This hormonal cocktail, in turn, triggers physiologic effects such as a pounding heart, rapid breathing, and tense muscles under sweat-drenched skin.

While the stress response has its uses—think of a mother lifting a car to rescue her child—it may also kick in during much milder threats, such as running late for an appointment or during a minor disagreement. Close to seven million Canadians reported experiencing most days as stressful in 2014, suggesting that stress is a commonplace experience for many. Over time, stress's physiological wear-and-tear on the body may contribute to conditions such as cancer, stroke, respiratory ailments and heart disease—and the physical and economic costs can be enormous.

That's where molecules like CABS1 may help. "Being able to accurately measure stress levels may improve the prevention and management of stress-associated mental and physiological disorders," Dr. Befus maintains.

As it turns out, CABS1 serves not only as a barometer of stress, but also as a clue to an individual's ability to handle stressful situations. Among the participants in Dr. Befus's trio of 2017 studies, about 15% carried a smaller form of CABS1. On average, this group perceived life as less stressful.

"As far as we can tell right now, CABS1 seems to behave a lot like the SMR1 protein, which breaks down into different pieces," says Dr. Befus. "It appears that certain smaller forms of the protein are common among people who are resilient to stress."

Despite their exciting findings, Dr. Befus speaks cautiously as CABS1 research is still in its early stages and no other studies have confirmed his findings—yet. "Reproducibility is one of the basic tenets of science," he says. "If you don't get the same results the next time around, you must revisit your hypothesis." To this end, he is repeating the exam stress experiment with a larger sample size. Dr. Befus also plans to take a closer look at whether chronic stress induces changes in CABS1.

Promising applications

If future studies support their findings to date, the team believes CABS1 could become a recognized biologic marker of both stress and resistance to stress, with many promising applications. For example, employers could develop a CABS1-based screening tool to identify candidates suited to high-stress occupations. Along similar lines, a CABS1 molecular analysis could complement psychological tests to predict an individual's susceptibility to stress.

CABS1 could also find uses in the military. To this end, Dr. Befus has teamed up with a colleague at the University of Alberta who has studied stress in Canadian troops before their deployment to Afghanistan and after their return to Canada. Through this collaboration, Dr. Befus has collected saliva samples from 317 military personnel taken at various points in their journeys to and from Afghanistan. "We also have a wealth of data on these individuals, including the presence of post-traumatic stress disorder (PTSD) during or after deployment," he says. Over the next few months, his research team will measure CABS1 in the samples to see how levels of the molecule relate to the soldiers' psychological states.

Of course, the experience of military personnel with stress does not represent the experience of the average Canadian, but Dr. Befus maintains this makes the investigation all the more powerful. "Soldiers are trained to deal with stress so their CABS1 response could give us even more information about resilience," he says. Questions his future research will address include: What types of training reduce the impact of stress? Might CABS1 levels predict performance on the front lines? Do interventions designed to reduce the impact of PTSD also reduce CABS1 levels?

In the meantime, Dr. Befus has been contacted by scientists hoping to study CABS1 in skin disorders and inflammatory bowel disease. Private companies have also shown interest in the molecule—including a group keen on developing a medical device that could prompt the nervous system to boost CABS1 in saliva. But isn't the idea to reduce CABS1 levels? "Not necessarily," says Dr. Befus. "In the case of inflammatory bowel conditions, such as Crohn's disease or ulcerative colitis, we may want to increase the component of CABS1 with anti-inflammatory activity."

Encouraged by such strong interest in the molecule, AllerGen, together with the University of Alberta and its industrial liaison office, TEC Edmonton, have helped Dr. Befus' team file a patent to develop a non-invasive CABS1-based saliva test. They hope that the test could eventually help diagnose acute and chronic stress, as well as conditions such as PTSD.

"As we learn more about CABS1's anti-inflammatory properties, there may even be the potential to commercialize parts of the molecule as a treatment for some of the negative aspects of stress itself," adds Dr. Befus.

It looks like big things may be in store for this powerful little molecule.

"When you conduct a GWAS, you don't have any biases going in," says Dr. Asai. "You end up finding mutations that you wouldn't expect to have an influence on whatever condition you are investigating—in this case, peanut allergy."

New Genes on the Scene

New research by AllerGen investigators identifies a group of genes that contribute to food allergy and peanut allergy —and point to a possible strategy for predicting the risk

This much we know: the propensity for peanut allergy lurks in our DNA. According to studies of families, individuals with an affected sibling have much greater odds of becoming allergic to peanuts than the general population. As with all science, however, the devil lies in the details: Which genes are involved, and what do they do? Can we identify people with higher-risk genes and help them beat the odds?

Dr. Denise Daley, Associate Professor
The University of British Columbia

Dr. Yuka Asai, Assistant Professor
Queen's University

The search for genes associated with any particular disease is difficult and often takes years to accomplish. But, in the case of peanut allergy, a group of Canadian researchers and their international collaborators have proven themselves equal to the task. In a marathon study that spanned more than five years, they tracked down several gene variants associated with a higher risk of peanut allergy and with food allergy in general. In particular, they found that a gene called *c11orf30/EMSY*, or *EMSY* for short, may help to explain why some people have a greater disposition to allergy in general.

"There's a surprising lack of research on the genetic basis of peanut allergy," says Dr. Denise Daley, a Tier II Canada Research Chair at Vancouver's St. Paul's Hospital involved with the study. "The genes we identified in our study give us a fuller picture of the genetic influences on food allergy, which could eventually help doctors identify children at risk."

Filaggrin on the frontlines

The idea for the study followed the discovery of a defective gene found in up to half of all people with eczema. The filaggrin gene plays an important role in the skin's barrier function, according to Dr. Yuka Asai, a dermatologist and an assistant professor at Queen's University, who had previously played a key role in unearthing the filaggrin mutation. "Besides eczema, filaggrin mutations have been linked to asthma, allergic rhinitis, and other allergic conditions, so it seemed a logical next step to see if the gene might also play a role in peanut allergy," says Dr. Asai.

For the first part of the study, the team conducted a genome-wide association study (GWAS), which involves scanning millions of genetic markers across the DNA. "When you conduct a GWAS, you don't have any biases going in," says Dr. Asai. "You end up finding mutations that you wouldn't expect to have an influence on whatever condition you are investigating—in this case, peanut allergy."

What led the group to focus on peanut allergy in the first place? For one thing, it tends to last a lifetime. "Just 20% of affected people outgrow a peanut allergy, as compared to 80 to 95% of those with egg or milk allergies," says Dr. Asai. Concerns about the apparent rise in the prevalence of peanut allergy gave their research quest added urgency. While defective genes alone cannot fully explain the phenomenon—DNA changes very slowly in a population—the team speculated that "susceptibility genes might be interacting with environmental changes to potentially cause an increase in prevalence." Their study sought to uncover such genes.

Having put *EMSY* on the map for peanut allergy, the researchers have several more investigative threads to follow. "We've identified *EMSY* as a risk factor for food allergy overall, but we'd like to know: does it raise the risk of some food allergies more than others?" asks Dr. Clarke. "Could it have an effect on non-food allergies, such as eczema or rhinitis?"

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Labour of years

As a first step, the group obtained salivary DNA from 850 peanut-allergic individuals in the Canadian Peanut Allergy Registry (CanPAR) housed at McGill University. Founded in partnership with Food Allergy Canada, the Allergy/Asthma Information Association, and Allergies Québec, CanPAR collects data on people with peanut allergy across the country. The researchers also acquired samples from close to 1,000 people with no history of asthma, eczema, allergic rhinitis, or food allergy.

Next, they scanned the entire genome of each saliva sample for single nucleotide polymorphisms (SNPs, pronounced "snips"). SNPs, the most common type of genetic variation, represent a change in a single DNA building block. Such minuscule genetic changes act as markers to help locate genes associated with diseases. In some cases, SNPs may even alter a protein manufactured by the gene or affect how the protein is regulated, in turn leading to changes in health and even producing disease.

"We looked at about 1.4 million SNPs and extrapolated another 6.4 million using statistical algorithms— that's close to 8 million bits of data for each subject," says Dr. Aida Eslami, the postdoctoral fellow who led the analysis. Complicating the math was the fact that "SNPs often 'travel together' in specific DNA sequences," Dr. Eslami explains. "This means that individual results are not independent from each other, and we had to correct for this in our analysis."

Having made the necessary tweaks, Dr. Eslami fed the data into a high-performance computer for a day-long number-crunching session. "That was the fast part," says Dr. Daley. "What is not always apparent in research is the tremendous amount of work that comes before this step"—from designing the study to writing the research proposal to AllerGen that made the study possible to collecting the samples. "It took us over five years to get to the point of analyzing the data," she says, adding that "you can't be a scientist without having patience."

For the second part of the study, the researchers conducted a meta-analysis combining their GWAS results with the findings of six other genetic studies of American, Australian, German and Dutch populations. In this case, they sought to uncover genes associated with both peanut allergy and overall food allergy.

New genetic suspects

The complex protocol paid off. Not only did the Canadian GWAS portion of the study identify numerous SNPs associated with peanut allergy, but 85 of those SNPs surfaced in at least one of the other populations included in the meta-analysis.

The meta-analysis also turned up new genetic suspects for peanut allergy not singled out in the GWAS analysis on the Canadians alone. Among these, the *EMSY* gene emerged as a significant contributor to food allergy and a suspected contributor to peanut allergy, occurring twice as often in peanut-allergic individuals. "The association between *EMSY* and peanut allergy didn't quite reach statistical significance in the CanPAR study alone, likely because the sample size of subjects wasn't large enough," says Dr. Eslami.

The *EMSY* story goes well beyond numbers, however. Implicated from previous research in the atopic march—a progression of allergy-related symptoms that often culminates in asthma—*EMSY* is known as a histone-modifying gene. Histones are proteins that spool around DNA and regulate whether genes get turned on or off. Histone modification plays a central role in epigenetics—the effect of environmental factors on gene expression. In theory then, *EMSY* could be involved in triggering expression of an allergy, which would help to explain how known environmental factors such as diet, method of food preparation and other environmental factors could connect with genetic susceptibility.

As it turns out, some of the other genetic suspects identified in the analysis modify the exact same histone as *EMSY* does. "This doesn't happen very often in genome-wide studies and it suggests a clear biological connection between these genes," says Dr. Daley.

Could the result be a fluke? Dr. Daley maintains it's unlikely because of the replication of the finding by collaborators and co-authors. "Our group had the expertise to minimize experimental errors and maximize the impact of the CanPAR study." Study co-lead Dr. Clarke, a physician and professor at the University of Calgary, concurs. "Thanks to the interdisciplinary network in AllerGen, we had all the right people at the table," she says. "Denise and I connected at an AllerGen meeting, and that's how the collaboration got started." Drs Asai and Eslami, both emerging researchers in AllerGen's Highly Qualified Personnel (HQP) program, blended easily into the team.

The paper reporting the GWAS and meta-analysis findings was published in *The Journal of Allergy and Clinical Immunology (JACI)* and lists 31 authors. "It's indicative of how science is conducted today," says Dr. Daley. "We don't work alone in basement labs anymore. It's all about national and international collaboration."

Examining *EMSY*

Having put *EMSY* on the map for peanut allergy, the researchers have several more investigative threads to follow. "We've identified *EMSY* as a risk factor for food allergy overall, but we'd like to know: does it raise the risk of some food allergies more than others?" asks Dr. Clarke. "Could it have an effect on non-food allergies, such as eczema or rhinitis?" The list of areas to explore doesn't stop there: some of the "suggestive genes" identified in the study play a role in creating endothelial cells (cells lining the interior surface of blood vessels), and the group plans to dig further to find out if endothelial cells behave differently in people with food allergies.

In theory, *EMSY* could also shed light on one of the fundamental mysteries of food allergy: why an allergy persists for a lifetime in one individual, yet is outgrown in another. According to Dr. Clarke, "it's entirely possible that these 'decisions' are made by genes turning on and off during an individual's development."

Finally, Dr. Daley plans to use the *JACI* study as a springboard to create a peanut allergy risk score. "Risk factors would be weighted according to how much they raise the risk for peanut allergy," she says. "*EMSY* would be one factor among many." Ideally, a high risk score would warn physicians and parents that an allergy may be lurking down the road and allow them to take preventative action. "For example, if a baby were to have an elevated risk score, parents could expose the baby to a potentially allergenic food sooner rather than later, as we know that early exposure has a protective effect."

According to Dr. Kozyrskyj, this is the first study to identify a plausible explanation for the link between maternal distress and childhood allergy. "Earlier studies were not able to explain the 'why,'" says Dr. Kozyrskyj.

Anxious Mom, Allergic Kid?

A mother's distress not only affects her interactions with her baby —it can also throw the baby's immune system off-kilter

As anyone who has been around children knows, babies instantly pick up on their mothers' moods. Mom smiles, baby smiles. Mom's upset, baby fusses. Mom is stressed out ... baby gets an allergy? Is that even possible, and how might it work?

AllerGen investigator Dr. Anita Kozyrskyj, a professor in the Department of Pediatrics at the University of Alberta, is looking for answers to these questions.

Dr. Anita Kozyrskyj, Professor
University of Alberta

Studies have linked a mother's distress during and after pregnancy to her child developing an allergy, but exactly how one leads to the other has been unclear. A separate line of research has connected childhood allergies with disruptions in a baby's developing immune system.

Dr. Kozyrskyj and her team are weaving these two threads together to better understand how a mom's distress could lead to immune changes in her newborn, and how this link may translate into allergies down the road.

In 2017, Dr. Kozyrskyj's team conducted a study with 403 mothers and their babies participating in the CHILD Study—AllerGen's national birth cohort project collecting a vast range of health, lifestyle, genetic and environmental exposure information from thousands of Canadian families.

Mothers completed a questionnaire consisting of 20 questions about depression experienced during their pregnancies and after their babies were born. The questions, which covered a range of symptoms—from feeling lonely or sad to experiencing restless sleep—were designed to assess a mother's overall level of distress. The research team then categorized the participants based on the timing of the symptoms they reported: while pregnant, after birth, during both these time periods, or not at all.

Mothers also provided information about their breastfeeding and other infant feeding practices, as well as medication use and details about the home environment.

Antibodies on guard

When the infants were three months old, the researchers collected their stool samples to measure levels of secretory IgA (sIgA), an immune antibody, secreted in the gut. A critical marker of immune maturation in infants, sIgA "prevents harmful bacteria from penetrating the lining of the gut but allows harmless environmental molecules to pass through, thereby teaching the immune system to distinguish between good and bad foreign substances," explains Dr. Kozyrskyj.

Because sIgA does not pass from mom to baby through the placenta, newborns have negligible amounts of this antibody at birth. During their first few months of life, infants receive sIgA primarily from their mothers' breastmilk, after which their guts begin to independently produce the molecule.

Why zero in on sIgA as the marker of a strong immune system? Dr. Kozyrskyj says that previous studies have found respiratory infections and allergic disorders tend to occur more frequently in people with sIgA deficiency, suggesting that sIgA may help to prevent these conditions.

And why explore the link between sIgA and stress? An animal study in which sIgA levels fell in mice exposed to stress caught Dr. Kozyrskyj's attention. "This finding made me wonder whether stress during pregnancy and after birth could affect the developing immune system in humans as well," she says.

Of note, sIgA levels were not lowered in infants of mothers who were distressed only during pregnancy or only after their baby's birth. It would seem that "a continuous stretch of maternal distress has a greater influence on infant gut immunity than pre- or post-natal distress in isolation," says Dr. Kozyrskyj, adding that "this study highlights the importance of maternal wellbeing throughout the pregnancy and birth journey."

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Mother's stress, baby's immune system

Examining the questionnaire responses, Dr. Kozyrskyj's team found that 12% of women experienced significant distress symptoms only during pregnancy (prenatal period); 8.7% of women had symptoms only after they gave birth (postnatal period); and 9.2% of women had symptoms both before and after the birth (pre- and post-natal periods). It was in this last group that the findings were most compelling: infants born to mothers who experienced distress both during and after pregnancy had the lowest levels of sIgA among all infants in the study. Specifically, infants born to these women were "three times as likely to have reduced sIgA levels compared to infants whose mothers were not depressed, which is highly significant," Dr. Kozyrskyj says.

Of note, sIgA levels were not lowered in infants of mothers who were distressed only during pregnancy or only after their baby's birth. It would seem that "a continuous stretch of maternal distress has a greater influence on infant gut immunity than pre- or post-natal distress in isolation," says Dr. Kozyrskyj, adding that "this study highlights the importance of maternal wellbeing throughout the pregnancy and birth journey."

According to Dr. Kozyrskyj, this is the first study to identify a plausible explanation for the link between maternal distress and childhood allergy. "Earlier studies were not able to explain the 'why,'" says Dr. Kozyrskyj. "One of the hypotheses floating around was that distressed mothers were more likely to smoke and less likely to breastfeed—behaviours that could theoretically lower sIgA levels and weaken the child's immune system."

But that's not what the Kozyrskyj study found. Using information from health questionnaires, the researchers classified the infants into three categories: exclusively breastfed, partially breastfed, and not breastfed. They found that while the formula-fed infants had lower sIgA levels than the breastfed infants overall, "formula-fed infants with more severely depressed mothers had lower sIgA than other formula-fed babies," says Dr. Kozyrskyj. "The connection between depression and lower sIgA levels held true, even when breastfeeding status was considered in our analysis."

Their analysis also examined the impact of a mother's allergies or antidepressant use and found no connection to lower sIgA in the infants.

So what's next for this research team? There are several more "intriguing threads to follow," says Dr. Kozyrskyj. Having established a connection between a mother's psychological wellbeing and her newborn's immune health, Dr. Kozyrskyj would like to dig deeper into how exactly the one impacts the other. "The B cells which secrete sIgA into the intestine start to be produced by the fetus. Stress during pregnancy elevates maternal cortisol levels which could lower fetal production of B cells and subsequently sIgA levels after birth," says Dr. Kozyrskyj, though she admits this is just conjecture. "In truth, we don't yet know what physiological mechanisms could account for our results. Stay tuned for follow-up studies."

She also plans to investigate whether the severity of maternal depression tracks with the magnitude of sIgA reduction in the infant in what is known as a "dose-response effect."

Longer term, Dr. Kozyrskyj hopes to find out if the low-sIgA children in her study grow up to have higher rates of asthma and allergy. "The CHILD Study is unique in that it has been following families and their babies since before birth—and the children are now eight years old. This incredibly rich trove of health data and samples will allow us to finally answer the question of whether or not maternal depression ultimately raises the risk of childhood allergy."

The microbial connection

Dr. Kozyrskyj has one more lead she plans to follow: the possibility that maternal stress perturbs the infant's gut microbiome—a known contributor to immune health.

An expert in the gut microbiome—the community of micro-organisms or bacteria that live in the digestive tracts of humans —Dr. Kozyrskyj leads the $2.5 million SyMBIOTA (Synergy in Microbiota Research) project funded by the Canadian Institutes of Health Research (CIHR).

The idea that maternal depression affects bacteria in the child's gut has some support: animal studies have shown that stressing pregnant mothers affects the composition of bacteria in their gut and vagina, which in turn alters their offspring's gut microbiome. In humans, an early report has found reduced levels of lactic acid bacteria in infants born to stressed pregnant mothers.

According to Dr. Kozyrskyj, the infant gut microbiome goes through a series of predictable changes in the first year of life. When the maturation process unfolds normally, the infant develops a protective bacterial barrier as part of a healthy immune system. Disturbances in the microbiome, however, can steer the immune system toward dysfunction. As an example, "lactic acid bacteria appear to stimulate IgA production, so having fewer of these bacteria in early infancy could cause IgA to drop," she says. By the same token, "IgA plays a key role in establishing the gut microbial composition—so it seems that the influence goes in both directions."

Getting the word out

Dr. Kozyrskyj also has an immediate task at hand: sharing the current study's results with the media, the public and the scientific community. "I'm fortunate to have Liane Kang, a graduate student at the University of Alberta, on the case," she says. "Liane has run with the study from beginning to end and she was the lead author of the *Brain, Behavior & Immunity* journal article published in November 2017."

Kang created an explanatory video to help readers interpret these research results. She also received an AllerGen Research *SKETCHES* grant, which facilitated her translation of the academic paper into a clear-language summary for a general audience.

Dr. Kozyrskyj, for her part, was "surprised and pleased" when the children's charity UNICEF noted her team's paper in one of its blog posts, praising the study for "generating breakthrough insights about child health," and asking the provocative question: *Will decision-makers listen and act on the new insights through improved policies and programs?*

Dr. Kozyrskyj sees several ways this could happen. For instance, "our findings encourage the development of community programs and policies to assist mothers in distress, and highlight the need for family and healthcare professionals to support the psychosocial wellbeing of women during pregnancy and in the months after birth."

Given that depression affects between seven to 12% of women during pregnancy and seven to 19% of women after giving birth, Dr. Kozyrskyj hopes that this research will prompt pregnant and new mothers to "speak out, seek treatment, and ask for social support."

"The idea is to mix all the allergens together and treat the mix as a single allergen," Dr. Bégin explains. "If the patient reacts with symptoms, you dial back the dose and frequency of exposure, then slowly increase them again until the patient tolerates the whole mix."

Taking a Bite out of Food Allergies

Philippe Bégin, a former AllerGen trainee, won't rest easy until oral immunotherapy becomes accessible to all who need it

When allergist Philippe Bégin isn't in his research lab testing out a new procedure, he may be meeting with government officials to advocate for better allergy treatment in his province, giving a media interview, or meeting with parent groups. Most likely, though, he's hard at work taking care of patients in a new food-allergy treatment clinic he established at Sainte-Justine Hospital in Montreal, Quebec.

Dr. Philippe Bégin, Allergist
Sainte-Justine Hospital

What drives Dr. Bégin—both an MD and a PhD—through his jam-packed days is an unwavering vision of "effective, accessible treatment for people with severe food allergies." The treatment he campaigns for is oral immunotherapy (OIT), a procedure that exposes allergic patients to minute doses of an allergenic food, such as peanut, in a supervised medical setting. The dose is slowly increased, with the goal of desensitizing patients' immune systems so that they can safely eat the food without experiencing an allergic reaction.

A relatively new approach to treating food allergies, OIT has shown success in protecting people with peanut, egg or milk allergy against accidental reactions, so long as they remain on the treatment. In some cases, the effect can be maintained over a prolonged period. "About half of the people treated with OIT for five years retain their tolerance even after the treatment ends," notes Dr. Bégin.

Currently, there are two primary roadblocks to accessing OIT therapy: distance and time. But Dr. Bégin hopes that both hurdles will eventually be overcome, possibly with a new approach that he helped to develop.

Confronting the challenges

Here's the scenario: a child with severe food allergies in Baie Comeau, Quebec, is accepted for OIT treatment. She and her mother take the bus 680 kilometres to Montreal—the closest medical centre that offers the procedure. The treatments continue twice per month for a year and a half until the therapy is complete and the child can safely tolerate her food allergen. "See the problem?" asks Dr. Bégin. "This treatment regimen could work in some European countries where most small communities are located close to major cities. But it isn't practical in countries like Canada where rural or small-town patients may live an eight-hour drive away from a treatment centre. Riding a bus or hopping on a plane every two weeks for 18 months is not realistic."

That is the challenge of distance.

The second challenge confronting OIT is that most treatments are designed as a "single-allergen therapy," meaning that the 18-month treatment desensitizes a patient to just one allergen at a time. For people with allergies to multiple foods, gaining freedom from allergies requires sequential treatment protocols—a process that could take years: one year for milk, another year for egg protein, and so on. In cases where patients struggle with the up-dosing regimen, it can take even longer.

Hence, the problem of time.

That's where "enabled" OIT comes in. The innovative protocol involves supplementing the exposures to food allergens with a drug currently approved for allergic asthma to suppress the overactive immune response. This protocol radically reduces the time required to achieve tolerance, addressing one of OIT's key challenges.

How did Dr. Bégin become involved with OIT and this therapeutic approach in the first place?

OIT "champion"

The journey began 15 years earlier, during Dr. Bégin's training as a physician and researcher. While studying medicine at the University of Montreal, he returned to his hometown of Chicoutimi each summer to work on a Master's degree specializing in the genetics of asthma. During this period, he joined the AllerGen trainee network and began actively participating in AllerGen's Highly Qualified Personnel (HQP) program. "People say you should look for wise mentors to help guide your career, but I found it beneficial to interact with students and researchers at my own academic level," he says. "You tend to find each other again years later, when you're more established and experienced, and these initial relationships provide the basis for collaborating on interesting projects. The AllerGen network was an ideal place for me to connect and interact with other trainees in the field of allergy and asthma, and it helped to guide me in the direction of food allergy, in particular."

After completing his medical degree, Dr. Bégin set his sights on becoming an allergist, though he wanted to also continue as a researcher in addition to becoming a practicing physician. During his allergy subspecialty training at the Centre Hospitalier de l'Université de Montréal (CHUM) and Sainte-Justine hospital, he worked with two AllerGen-funded investigator, both in the lab and the clinic.

In 2013, Dr. Bégin received AllerGen's *Emerging Clinician-Scientist Research Fellowship* award, valued at $250,000. Created to bridge the gap in allergy and clinical immunology expertise in Canada, the award—one of the most prestigious in the country—gives promising young immunologists and allergists the opportunity to pursue a combined career as a clinician and academic researcher. "That award was a turning point in my career," says Dr. Bégin. "The Fellowship was the springboard to an international research opportunity that gave me a chance to work with the 'best of the best.'"

During his Fellowship, Dr. Bégin worked with Dr. Kari Nadeau, one of North America's foremost allergy experts at the Sean N. Parker Center for Allergy and Asthma Research located at Stanford University in California. Dr. Nadeau had been exploring a way to shorten and simplify the OIT protocol for patients with multiple food allergies, and Dr. Bégin "jumped right in."

Dr. Nadeau's pioneering technique exposed patients to allergenic foods simultaneously, rather than sequentially. "The idea is to mix all the allergens together and treat the mix as a single allergen," Dr. Bégin explains. "If the patient reacts with symptoms, you dial back the dose and frequency of exposure, then slowly increase them again until the patient tolerates the whole mix."

The unique protocol, which Dr. Bégin evaluated in a proof-of-concept trial, significantly shortened the time required to desensitize patients to multiple foods, so that "it takes just four to five weeks longer than the time required to treat for a single food," says Dr. Bégin. Even so, "the whole regimen took an average of 85 weeks, which is still unacceptably long."

New treatment directions

Enter omalizumab, a biologic drug indicated for the treatment of asthma. Because the drug targets immunoglobulin E (IgE), an antibody that is implicated in both asthma and food allergies, the researchers speculated that by suppressing the allergic response with omalizumab they could expose food-allergic patients to larger doses of the allergen "mix" and further accelerate the desensitization process.

They tested this theory in a second proof-of-concept study and discovered that the addition of omalizumab allowed them to increase the first dose of the allergen mix from 6-12 mg to 1,200 mg without increasing the rate of allergic response. By doubling the dose every subsequent visit, Drs Nadeau and Bégin succeeded in increasing the speed of sensitization while limiting the risk of a serious allergic reaction.

At the trial's conclusion, the omalizumab-enabled protocol reduced the average time to desensitization from nearly two years (85 weeks) to just over four months (17 weeks). "We were incredibly excited with this improvement," says Dr. Bégin. "OIT patients and their families have to miss school and work every two weeks to come to appointments, so anything that can shorten the up-dosing phase and increase the treatment's safety makes an enormous difference for them."

While it could take some time before omalizumab is approved by the US Food and Drug Administration or Health Canada for use in OIT, Dr. Bégin says it is nonetheless gaining recognition for enabling simultaneous treatment of severe multiple food allergies.

Beyond the benefit for patients, the technique "costs less

and requires fewer staff than standard OIT," he says. Given the shortage of human resources in the healthcare system, "we should always be asking ourselves: how can we do more with the resources we have?"

Quebec leads the way

Dr. Bégin's experience at Stanford built up his resume—an essential step in the career of a successful scientist. "I came back to Canada with expertise in my field, which put me in an excellent position to compete for research grants to continue studying OIT," he says.

Returning to Montreal in 2014, Dr. Bégin accepted a position as an Adjunct Clinical Professor at the CHUM, where he quickly established a research lab and a busy clinical practice. But that wasn't enough. Deeply committed to making OIT available to those in Quebec who need it, he approached the provincial government with a proposal to open a public OIT clinic at Montreal's Sainte-Justine Hospital. A local not-for-profit group, ByeByeAllergies, raised $780,000 to support the clinic, and in the summer of 2017, Quebec's health minister announced that the province would match these funds. The clinic opened a few months later with sufficient funding to operate as a three-year pilot project.

Now one year on, Sainte-Justine's OIT clinic is serving nearly 200 patients, with the capacity to ramp up to 250 and the goal of treating 750 patients over the three-year pilot period. "After one year, we have received over 1,100 eligible applications for OIT treatment, and those are only severe cases, so there's clearly a need," says Dr. Bégin. The clinic's mandate also includes establishing provincial clinical standards and evaluating treatment costs. If all goes well, "we hope to extend the model to the rest of the province."

So far so good: the clinic is getting the hoped-for clinical results and patients are tolerating the regimen. But does OIT help patients achieve a lasting tolerance to their allergenic food?

"At the end of treatment, around 85% of kids will be able to tolerate a full portion of their allergen, as long as they eat their maintenance dose every day," says Dr. Bégin. "A proportion of these kids will achieve clinical remission, meaning they remain tolerant despite stopping their daily dose, but we cannot predict when and to whom this will happen."

While allergic reactions, most of them mild, to the OIT doses occur in virtually all cases, "it's something patients are prepared to deal with it," says Dr. Bégin. "You can't compare those reactions to worrying all day about the possibility of an accidental exposure to a food allergen." With OIT, "patients gain control and peace of mind. Many of them tell us the therapy has changed their lives—but they need to have discipline and understand the risks."

For Dr. Bégin, the clinic also represents a unique research opportunity because it serves a real-life population. "Rather than the patient being the research subject, the clinic itself becomes the subject, with the goal of determining the best way to dispense care at a macroscopic level," he says. He describes it as a "'living laboratory' for studying and adjusting OIT procedures and processes—one that can generate insights not available from previous clinical trials and that will inform the design of future trials."

All this costs money, of course. While confident that OIT's benefits outweigh its costs, Dr. Bégin notes that "governments are used to spending very little on allergy. Typically, an allergist prescribes an epinephrine autoinjector to a patient with a food allergy and says, 'see you in two years.'" To justify the costs of deploying OIT on a provincial level, Dr. Bégin is working with Dr. Thomas Poder, an expert in health economics at the University of Sherbrooke. Together, they are developing an algorithm that will translate the psychosocial burden of food allergies into a "loss of quality-adjusted-life-years". "This will allow us to consider an individual's quality-of-life in the economic equation," he says.

In 2017, Dr. Bégin became a full AllerGen investigator and the Canadian Society of Allergy and Clinical Immunology (CSACI) recognized him with its *Early-Career Award* for demonstrating outstanding dedication to his specialty. As much as he values this recognition, he knows that making an impact with clinical research is "a long game."

"You have to deal with disappointment on a regular basis, like when an experiment doesn't work out or a grant application is rejected," says Dr. Bégin. But he wouldn't have it any other way. "Just last week, I got hugs from two dads whose kids graduated from our OIT program. Before OIT, they had endured terrifying visits to the hospital emergency room and lived with the constant fear of repeating those episodes. When you hear that kids and their families feel safe for the first time, all the irritants of research become worth it."

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