



Spring 2013

Innovation from cell to society

Success Stories



NCE RCE

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Making a Difference From cell to society

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

In this issue, we share the highlights of five AllerGen-supported research projects. Feature stories include:

- a possible connection between a rise in premature births and childhood asthma in Canada;
- how protein research in mice sheds light on the development of asthma, colitis and colon cancer in humans;
- the impact of out-of-pocket medication expenses on asthma control in children;
- how probiotics may ease asthma symptoms, and;
- a unique Canadian workshop exploring occupational allergies.

Asthma and allergic diseases are global public health concerns and the prevalence of these diseases continues to increase worldwide. In Canada, one in three people now live with allergic disease and the economic and healthcare burden of these conditions reaches billions of dollars annually.

Since 2005, AllerGen NCE has united Canada's leading experts in allergic diseases and asthma. Working in partnership with organizations and stakeholders across sectors, AllerGen addresses gaps in knowledge and seizes opportunities to generate new preventive strategies, diagnostic tests, therapeutic approaches, medications, public policies and regulations. Through its Success Stories and other initiatives, AllerGen supports knowledge mobilization and delivers publicly accessible information and educational tools to diverse audiences.

AllerGen invests in research in three Legacy Projects supported by three Enabling Platforms:

Legacy Projects:

1. Canadian Healthy Infant Longitudinal Development (CHILD) Study

The CHILD Study is the largest multidisciplinary, longitudinal, population-based birth cohort study looking at maternal and infant health in Canada, and is designed to be one of the most informative studies of its kind in the world.

2. Clinical Investigator Collaborative (CIC)

This multi-centre, Canadian-based Phase II clinical trials group fast-tracks early-stage potential drug candidates for allergic asthma, allergic rhinitis and severe asthma.



3. Canadian Food Allergy Strategic Team (CanFAST)

This highly innovative, cross-Network approach to food allergy and anaphylaxis research incorporates biomedical, clinical, population and psychosocial information in order to translate an understanding of food allergy into disease management and public health measures.

Enabling Platforms:

1. Gene-Environment Interactions

Strategic Focus: Genetics, environmental exposures and gene-environment interactions in allergy and asthma.

2. Biomarkers and Bioinformatics


Strategic Focus: Biomarkers, immune monitoring and drug development/discovery.

3. Patients, Policy and Public Health

Strategic Focus: Knowledge mobilization, social science, psychology, sociology, medical geography, ethics and health economics.

AllerGen research results benefit Canadians across generations — from infants, children and teens to their parents, grandparents and extended families.

In sharing these stories, AllerGen aims to decrease the burden that allergy and asthma impose on Canadian productivity and economic growth, contribute to Canadian innovation and commercialization, and improve the quality of life for Canadians living with allergic diseases, asthma, and anaphylaxis.

We hope you enjoy this latest issue! 

A handwritten signature in black ink that reads "Judah A. Denburg".

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

A handwritten signature in black ink that reads "Diana Royce".

Diana Royce, EdD, Managing Director and COO



**Between 2006 and 2007,
more than 54,000 Canadian
babies, or more than one
in 12 births, were preterm;
a jump of 25% over the past
decade, according to data
from the Canadian
Institute for Health
Information (CIHI).**

Can Helping 'Preemies' Breathe Easier Lead to Childhood Asthma?

To promote lung maturation in babies born prematurely, doctors typically prescribe powerful corticosteroid drugs to a mother before she delivers. But is this practice safe or could it contribute to the development of childhood asthma? Intrigued by a possible connection between the rise in premature births and a surge in the number of asthmatic children in Canada, AllerGen NCE investigators, Drs Cameron Mustard and Jason Pole from the University of Toronto, set out to determine if these two trends could be related.



Dr. Cameron Mustard,
Professor, University of
Toronto and President,
Institute for Work &
Health



Dr. Jason Pole, Scientist,
Pediatric Oncology
Group of Ontario
(POGO) and Assistant
Professor, Dalla Lana
School of Public Health,
University of Toronto

Exploring the connection between premature babies and asthma through traditional research methods might have taken years of study and millions of dollars in funding. But with support from AllerGen NCE, these researchers tapped into a one-of-a-kind Canadian database and found an answer in less than two years and with a cost-effective budget.

Premature Births and Childhood Asthma — Are They Related?

A preterm or 'preemie' baby is born before 37 weeks of pregnancy. Between 2006 and 2007, more than 54,000 Canadian babies, or more than one in 12 births, were preterm; a jump of 25% over the past decade, according to data from the Canadian Institute for Health Information (CIHI). Babies born prematurely can face lifelong health hurdles, including learning and behavioural problems, cerebral palsy, vision and hearing loss, and in particular, lung problems.

At full term, a baby's lungs produce surfactant, a foamy liquid that moistens the lining of the lungs' air sacs and allows the inner surfaces of the sacs to remain open during breathing. Premature babies lack surfactant in their lungs, and without it, they struggle to breathe.

A mother at risk of delivering her baby between 24 and 34 weeks of pregnancy is typically prescribed corticosteroid drugs to speed up the development of her unborn baby's lungs. Corticosteroids, such as betamethasone or dexamethasone, stimulate the baby's immature lungs to produce surfactant, resulting in an improved ability to breathe and fewer respiratory treatments after birth.

Drs Pole and Mustard suspected that if premature births and childhood asthma were related, corticosteroid drugs may be the culprit. In Canada, 20% of children are diagnosed with asthma before the age of 12, and asthma is the leading cause of school absences and pediatric admissions to hospital emergency departments.

When a child has asthma, the lungs' airways are constantly inflamed. The body's immune system responds to the inflammation by constricting the airways even further, making breathing difficult and causing symptoms such as wheezing, coughing, chest tightness or shortness of breath. Asthma sufferers often describe a full-blown asthma attack as "trying to breathe through a straw."

Medical Practice Re-evaluated

Re-evaluating the benefits of a drug treatment protocol, even for well accepted therapies, can challenge or confirm what is often considered to be "best medical practice." In the case of hormone replacement therapy (HRT), which was commonly prescribed to alleviate the symptoms of menopause, follow-up research eventually showed that HRT placed women at a higher risk of developing other diseases, such as cancer. As a result, the use of HRT has been greatly restricted and is no longer commonly prescribed.

To determine whether or not administering corticosteroid therapy to premature babies contributes to the development of asthma, AllerGen researchers needed a longitudinal study—a study where a group of people who have experienced the same event in a selected time period (called the 'cohort') are



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followed at regular intervals over many years. Longitudinal studies use statistical computer models to analyze repeated individual observations and search for trends across the cohort. Information is collected from participants through biological samples, questionnaires and interviews—all of which require time, manpower and money to complete.

Fortunately, Dr. Pole found a way to gather and evaluate cohort data in a way that was fast, inexpensive and produced results that were “just as good,” according to Dr. Mustard, as those gained through traditional longitudinal study methods.

Mining Unusual Databases in Nova Scotia

The AllerGen team discovered that valuable information on pregnancies and child health, previously collected by doctors and academics in Nova Scotia, could be harvested and used for their research.

The ‘Nova Scotia Atlee Perinatal Database’ (NSAPD) uses hospital records to document the details of every labour and delivery in the province. The ‘Maternal-Child Health Database’ (MCHD) tracks the long-term health of all mothers and

children who live in Nova Scotia by linking together other databases: Atlee Perinatal Database; Hospital Admissions (CIHI); Physicians’ Office Visits (MSI); Vital Statistics; Perinatal Follow-Up; Maternal Serum Screening; Fetal Anomaly; Pediatric Cardiology; Childhood Epilepsy; Family Benefits; and the Cancer Registry data.

Access to these population-based databases was facilitated by Dr. Alexander Allen, Director of the Perinatal Epidemiology Research Unit at Dalhousie University in Halifax, Nova Scotia. As the driving force behind the establishment of these comprehensive databases, Dr. Allen provided AllerGen researchers with insights and knowledge on how to effectively use and analyze the information.

To investigate a possible link between premature birth and childhood asthma, Dr. Pole used the databases to examine a cohort of 113,000 babies born in Nova Scotia between 1989 and 1998. Twins and other multiple births, babies whose mothers experienced a thyroid problem or asthma during pregnancy, and babies who moved out of the province were excluded from the study. Dr. Pole was able to identify babies that were born

After extensive data analysis, the AllerGen team found that corticosteroid therapy administered to premature infants had a small, yet significant, elevated risk for the development of childhood asthma between the ages of three and six years. The risk appears to be time-dependent, with the greatest risk appearing early in childhood and diminishing as the child ages.



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prematurely, babies who had received corticosteroid drugs to promote lung development, as well as babies who eventually received doctor-prescribed asthma treatments between three and six years of age.

Dr. Pole's analysis considered several confounding factors: the baby's birth weight and prematurity, the type of delivery (caesarean section or vaginal delivery), the mother's age, whether or not the mother was diabetic or smoked during her pregnancy, the type of corticosteroid used (betamethasone or dexamethasone) and how often the corticosteroid was administered and when.

Painstakingly, the AllerGen research team studied the effects of each of these variables and entered the data into a complex computer model to establish whether a premature baby who received corticosteroid therapy was likely to develop asthma in early childhood.


An Answer Comes to Light


After extensive data analysis, the AllerGen team found that corticosteroid therapy administered to premature infants had a small, yet significant, elevated risk for the development of childhood asthma between the ages of three and six years. The

risk appears to be time-dependent, with the greatest risk appearing early in childhood and diminishing as the child ages.

The strength of this research, which became Dr. Pole's PhD thesis, was rooted in the large size of the population group he examined and the fact that he was able to track each individual's health over a long period of time. Ultimately, Dr. Pole's work earned several prestigious awards from the Canadian Society for Epidemiology and Biostatistics (CSEB) and the Society for Pediatric and Perinatal Epidemiologic Research.

Dr. Mustard believes that Dr. Pole used the Nova Scotia databases and AllerGen NCE's funding dollars "exceptionally well" and adds that the work demonstrates the importance of being "appropriately vigilant about the possible adverse effects of drugs."

Dr. Pole is intrigued by additional research underway to investigate the risk of unintended health consequences of corticosteroid exposure before birth. "There is mounting evidence for a host of outcomes — asthma is just one of them," Dr. Pole says. "Further research is needed to examine the smallest possible steroid dose required to be effective, which could, in turn, reduce the risk of developing asthma during childhood." 

A close-up photograph of a male scientist with glasses and a white lab coat. He is holding a small, dark-colored mouse in his gloved hand. The background is a blurred laboratory setting with blue equipment.

Dr. McNagny explored how his findings in mice could shed light on the development of asthma, colitis and colon cancer in humans. He found that when the gene responsible for making CD34 in humans is inserted into the protein-free mice, the mice will regain their susceptibility to these diseases.

Piecing Together a Protein Puzzle

What do asthma, colitis and colon cancer have in common? A protein called CD34, according to Dr. Kelly McNagny, a stem cell biologist and professor at the University of British Columbia (UBC). Found on specialized body cells such as stem cells, mast cells, dendritic cells and eosinophils (a type of white blood cell), this protein contributes to the development of all three of these chronic, inflammatory illnesses.



**Dr. Kelly McNagny, Professor,
Department of Medical Genetics,
University of British Columbia**

According to Dr. McNagny, CD34 is present in both mice and humans. With his research team at UBC, Dr. McNagny discovered that when CD34 is removed from the cells of laboratory mice, the mice become highly resistant to developing asthma, colitis, colon cancer and other inflammatory diseases. Surprisingly, the mice do not seem to experience any negative side effects associated with losing the protein.

Dr. McNagny explored how his findings in mice could shed light on the development of asthma, colitis and colon cancer in humans. He found that when the gene responsible for making CD34 in humans is inserted into the protein-free mice, the mice regain their susceptibility to these diseases.

Exciting implications of Dr. McNagny's research suggest that one day, medications could be developed to remove or deactivate this protein in humans, offering hope that people living with asthma, colitis or colon cancer could enjoy a newfound resistance to these inflammatory diseases.

Breakthrough Discoveries Supported by Allergan

Despite widespread study and over 25,000 academic publications devoted to the subject of CD34, researchers have not yet been able to determine exactly what this cellular protein does. A long time puzzle-lover, Dr. McNagny became determined to find out.

With grants from Allergan NCE and the Canadian Institutes of Health Research (CIHR), Dr. McNagny partnered with Drs Paul Kubes and Chris Mody, professors at the University of Calgary. Dr. Kubes is an expert on immune responses and how cells move around the body, while Dr. Mody is a clinical researcher with expertise in human infectious diseases. According to the

researchers, support provided by Allergan NCE was invaluable to the success of the project. The Allergan Network "really facilitates collaboration" and "puts you in contact with the right people, which helps things to move along," Dr. McNagny says.

For their research, the team adopted a 'genetic' approach to study how CD34 functions. They removed the genes responsible for producing the protein from laboratory mice and watched for any health effects to help determine what role the protein plays. However, when the protein was eliminated from the mice, the team did not detect any physiological or behavioural changes. In fact, the mice continued to exhibit the three natural behaviours commonly referred to in the laboratory environment as 'the three f's' — feeding, fighting and fornicating — and did not exhibit any abnormalities in blood tests, stem cell defects or any other health problems.



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**CD34 is not isolated to stem cells;
it is also found on mast cells,
eosinophils and dendritic cells
scattered throughout the body.
However, on these cells, only one
member of the protein family is
expressed, and when CD34
is removed, the other protein
‘family members’ are unable to
compensate for its loss.**

Puzzled, Dr. McNagny and his team persevered with their research. Eventually, they made two breakthrough discoveries. First, CD34 does not act alone but is part of a ‘family’ of proteins that can compensate for each other’s functions. When CD34 was removed from the mouse stem cells, other proteins in the family took over its function, which explained why no negative health effects of the missing protein were seen.

Second, CD34 is not unique to stem cells; it is also found on mast cells, eosinophils and dendritic cells scattered throughout the body. However, on these cells, only one member of the protein family is expressed, and when CD34 is removed, the other protein ‘family members’ are unable to compensate for its loss.

With these important findings, the AllerGen researchers realized that if they tested mice lacking this protein in diseases

“I feel confident that we will come up with new therapies to be used in clinical settings,” Dr. McNagny says. He adds that the opportunity to network with other leading Canadian allergy and inflammation experts at AllerGen NCE meetings has “opened my eyes to other research I could be doing.”



involving mast cells, eosinophils and dendritic cells, they would obtain a clearer picture of how CD34 functions in the body.

Molecular Teflon

Although the initial research focus of Dr. McNagny's team was to study the protein on stem cells, their molecular discoveries led them in the direction of mast cells and eosinophils — cells known for their role in allergy and asthma and producing unpleasant symptoms of a runny nose and a wheezy chest.

When the team examined CD34-deficient mice in models of allergy and asthma, they found the mice were highly resistant to the diseases and were even able to ward off colitis (an inflammation of the large intestine) and colon cancer. When the team replaced the mouse genes with human genes for encoding the protein, the mice once again became prone to developing allergies and asthma.

“I am amazed at how similar the mouse and human proteins are and how easy it was to put the human protein in and regain sensitivity to asthma,” Dr. McNagny says. “It is clear that the protein is doing the same thing in both species.”


But how does the protein located on mast cells and eosinophils actually work? Dr. McNagny describes the CD34 protein as “molecular Teflon,” which acts as an anti-adhesion molecule and helps the mast cells and eosinophils to penetrate


into tissues and do their job. “In the case of allergy and asthma, eosinophils and mast cells leave the blood and get into the lungs much more efficiently if they have this protein,” Dr. McNagny explains. “Without it, they can't crawl into tissues, so by removing the protein, we are blocking the traffic of these inflammatory cells into the tissues.”

Looking to the Horizon

Dr. McNagny points out that for the past 50 years, there have been roughly five classes of drugs available to treat allergy and asthma — and they are all remarkably similar. Now, with the results of their AllerGen-funded research, Dr. McNagny and his team are certain that a new, safe and more effective drug for allergy and asthma is on the horizon.

“I feel confident that we will come up with new therapies to be used in clinical settings,” Dr. McNagny says. He adds that the opportunity to network with other leading Canadian allergy and inflammation experts at AllerGen NCE meetings has “opened my eyes to other research I could be doing.”

AllerGen NCE shares in Dr. McNagny's enthusiasm and continues to support this research in the quest for a novel and life-improving treatment for asthma and allergy. 



Intrigued by the role that financial burden plays in asthma management, Dr. Ungar designed a research study to examine how a family's out-of-pocket medication expenses may affect asthma control, and ultimately, a child's health.

Drug Plans Can Impact Kids with Asthma

Every year, acute asthma exacerbations cause more Canadian children to visit emergency departments and hospital wards than any other medical condition. Despite available treatments, fewer than 25% of children with asthma have their disease under optimal control.

Dr. Wendy Ungar, an AllerGen NCE investigator and a senior scientist at The Hospital for Sick Children in Toronto, is passionate about understanding the socioeconomic factors that contribute to asthma attacks in children. In particular, Dr. Ungar investigates the impact that public and private drug plan policies have on the management of pediatric asthma.



Dr. Wendy Ungar, Associate Professor, Health Policy, Management and Evaluation, University of Toronto and Senior Scientist, Child Health Evaluative Sciences, The Hospital for Sick Children

Prescription medications are routinely prescribed to manage pediatric asthma. Often, the cost of these medications is not subsidized by provincial drug programs and families are required to pay part, or all, of the treatment costs. Intrigued by the role that this financial burden plays in asthma management, Dr. Ungar designed a research study to examine how a family's out-of-pocket medication expenses may affect asthma control, and ultimately, a child's health.

Parents and Kids Speak Out

Although the relationship between household income and access to asthma health services and medications has been studied before, Dr. Ungar's study was the first to examine the impact of medication cost-sharing as a percent of household income and associate that with the number of times a child was admitted to an emergency room or hospital for acute asthma exacerbation.

Dr. Ungar assembled a research team and recruited families to participate in the study through The Hospital for Sick Children, Brampton Memorial Hospital, and family physician and specialist offices located in the Greater Toronto Area.

The researchers conducted extensive interviews with parents or children old enough to respond independently, usually 13 years or older. They collected detailed information on the child's asthma history, prescribed medications, the

family drug plan, total household income and the previous use of respiratory-related health care services.

Following interviews with families of 490 children with asthma, Dr. Ungar used funding from AllerGen NCE and in-kind support from the Institute for Clinical Evaluative Sciences (ICES) to link the information with several health care databases, including Ontario Health Insurance Plan (OHIP) records. They tracked whether the child was admitted to an emergency room or was hospitalized due to an asthma attack during the year following the interview. "When you study asthma, looking at when a child has an emergency room visit is important information because it indicates their asthma is worsening," Dr. Ungar explained.

Dr. Ungar and her team were interested in understanding the effects that cost-sharing mechanisms such as premiums, deductibles, fixed co-payments, percentage co-payments and annual maximums had on medication-purchasing behaviour. They examined these factors in a subgroup of the families (87% of the sample) with medication insurance. Although it was challenging to distinguish the effects of these different mechanisms, Dr. Ungar's team's findings generated valuable insights.

Paying Out-of-pocket Affects Asthma Control

The study revealed that for each 1% increase in the amount of household income that a family needed to spend out-of-pocket



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[Researchers] collected detailed information on the child’s asthma history, prescribed medications, the family drug plan, total household income and the previous use of respiratory-related health care services.

for asthma medications, there was a 14% related increase in the rate of severe asthma attacks resulting in an emergency room visit or a hospital admission. Children from high-income families had 28% fewer severe attacks than children from low-income families.

“There is a highly significant relationship between cost sharing and asthma exacerbation,” Dr. Ungar said. “Cost sharing acts as a financial barrier to families obtaining the optimal

medication regimen required for their child with asthma.”

Children with asthma are typically prescribed two or three medications to properly manage the disease. When paying out-of-pocket, some families could face a prescription bill of over \$100 per month. According to Dr. Ungar, even in cases where a drug plan may cover 20% to 50% of the costs, the financial burden for some families can be overwhelming, considering the other health care costs that families face.

Families with a low household income may choose not to purchase all the medications that have been prescribed or they may use the medications sparingly to make them last longer. Sometimes, families will opt to purchase the least expensive medication, known as the ‘reliever’ drug, that opens up the airway, rather than the more expensive drug, known as the ‘controller.’ “The unfortunate paradox is that the expensive drug is the one that is most needed to control airway inflammation and prevent future exacerbations,” Dr. Ungar said.

A Surprising Finding

During the study, the researchers made a surprising finding: children from families that had a drug plan with an annual deductible greater than \$90 experienced 95% fewer exacerbations of their asthma. A deductible is the fixed dollar amount that a family pays out-of-pocket before health insurance begins to cover some, or all, of the cost of the drug. Once the deductible threshold is reached, the co-payment drops drastically, usually to nothing. Dr. Ungar and her team were puzzled by this finding. They had expected to find that a deductible resulted in fewer medication purchases, and therefore more asthma exacerbations. What they observed was exactly the opposite.



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One explanation for their findings is that low-to-moderate deductibles actually encourage consumers to be conscientious about filling their prescriptions immediately. Consumers want to meet the deductible's threshold because on the other side it is perceived as a 'free' benefit. "What this says to me is that we have to take a really close look at our drug plans and truly understand how the different combinations of characteristics related to co-payments and deductibles affect health outcomes," Dr. Ungar said.

Dr. Ungar's team found that an inadequate medication regimen is not the only factor contributing to asthma flare ups. Boys, children under the age of four, children with pets in the home, and children with multiple allergies to food, drugs or insects are also prone to more asthma exacerbations, according to the study results. As well, children without an asthma action plan to help them manage their disease experience significantly more asthma exacerbations.

"This is why Canadian doctors are trying to promote asthma education," Dr. Ungar said. She added that licensed asthma educators are available in Canada to provide education and support for children with asthma and their families.


Policy Makers Eyeing Data

Dr. Ungar says her team's research would not have been possible without AllerGen NCE's funding support, which was "absolutely instrumental" to the project. The study's findings have been published in a series of seven papers from 2008 to 2012 and have attracted considerable attention from the media and people in the health policy-making community.

Sometimes, families will opt to purchase the least expensive medication, known as the 'reliever' drug, that opens up the airway, rather than the more expensive drug, known as the 'controller.'

"Policy makers are very interested in questions around pharmaceutical costs and access," Dr. Ungar said. "We are making sure that decision makers at local, provincial and national levels are getting this information, not just academics."

Dr. Ungar calls for even more research into the effects of public and private drug plan policies on children's health. Specifically, studies into the barrier effects of private drug plans are needed, as well as consultation on how changes to health care delivery would affect access to necessary medications and impact the health outcomes of Canadian children.

When families are burdened by out-of-pocket medication expenses, there can be unintended, negative consequences — not only for families, but for the health care system itself. Although provincial health plans may not routinely pay for asthma medications, they do pay for emergency room visits and hospitalizations when asthma exacerbations occur. "This is the most expensive way to deliver care," Dr. Ungar said. 



Funded by AllerGen NCE and the Canadian Institutes of Health Research (CIHR), this research has identified a specific, live probiotic strain that has therapeutic potential in the treatment of allergic airway disease and asthma.

Probiotics—Helpful or hoopla?

From television commercials to supermarket signs, claims that certain bacteria — known as probiotics — are good for your health, are everywhere. A growing number of yogurt companies, beverage manufacturers, and even some cereal products, are promoting the benefits of probiotics to treat and prevent a variety of illnesses.

But what are probiotics? And are they really good for your health?



Dr. John Bienenstock,
Distinguished University Professor,
Pathology and Molecular Medicine,
McMaster University



Dr. Paul Forsythe, Assistant Professor,
Division of Respiriology, Department of
Medicine, McMaster University

Probiotics are live micro-organisms that, when taken in adequate amounts over sufficient time, may help with digestion and offer protection from harmful bacteria in the intestine. Although the field of bacterial health is still new and emerging, some studies have shown that certain bacterial strains may be helpful for people with irritable bowel syndrome and pouchitis (a type of inflammatory bowel disease).

Researchers at McMaster University have now discovered that probiotics may also have an anti-inflammatory effect *outside* the gut. Funded by AllerGen NCE and the Canadian Institutes of Health Research (CIHR), this research has identified a specific, live probiotic strain that has therapeutic potential in the treatment of allergic airway disease and asthma.

But before asthmatics throw out their inhalers and stock up on probiotic yogurt, the McMaster researchers emphasize that the type and amount of probiotic contained in commercial products and fortified foods is likely well below the level needed to ultimately impact health.

Why Research Bacteria?

AllerGen Investigators Drs Paul Forsythe, Mark Inman and John Bienenstock are interested in researching new therapies to treat asthma and became intrigued by clinical studies that found allergic children to have diminished amounts of good bacteria in their gut in comparison to non-allergic children.

Probiotic manufacturers were quick to suggest that their products could successfully treat allergies and asthma by increasing the levels of good bacteria in the body. However, Dr. Bienenstock noted that, “most of these claims were not backed by satisfactory scientific evidence.” With a surge in public interest in the area, and more probiotic products flooding the market, the McMaster team felt that there was a need for rigorous scientific investigation into the benefits of probiotics. So, the team set out to investigate whether probiotic therapies could potentially treat allergies and asthma.

A Nine-Day Diet

The most common symptoms of asthma are inflammation (swelling) and hyper-responsiveness (“twitchiness”) of the airways. In their research, Drs Forsythe, Inman and Bienenstock

Oral treatment with the live strain of *Lactobacillus rhamnosus* significantly decreased the mice’s allergic response to the egg white protein and reduced the level of airway inflammation and “twitchiness” by 75%.



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This research has the potential to yield substantial economic benefits for Canada. A new therapy that decreases asthma rates could result in improved workplace productivity and reduced healthcare costs.

studied laboratory mice that were allergic to the protein found in egg whites. When the mice breathed in egg protein allergen, they experienced inflamed and “twitchy” airways — two major characteristics of human asthma.

The researchers fed the asthmatic mice a probiotic diet for nine days. They used two strains of bacteria commonly found in the human intestine, *Lactobacillus rhamnosus* (JB-1) and *Lactobacillus salivarius*, which have previously been shown to demonstrate anti-inflammatory effects in animals with inflamed colons. Both live and dead strains of the bacteria were used and compared.

After nine days of treatment with these probiotics, the allergic mice were re-exposed to egg white protein. The results were astonishing. Neither the dead strain of *Lactobacillus rhamnosus*, nor *Lactobacillus salivarius* live or dead, produced any significant effect in the asthmatic mice. However, oral treatment with the live strain of *Lactobacillus rhamnosus* significantly decreased the mice’s allergic response to the egg white protein and reduced the level of airway inflammation and “twitchiness” by 75%.

How a bacterium works

At the time, the team’s discovery was the first demonstration that oral treatment with a bacterium could improve the symptoms of allergic airway disease in allergen-sensitized animals. The results were “surprising,” according to Dr. Forsythe.

Once they observed such a remarkable improvement in asthma symptoms, the researchers were eager to explore how the bacterium *Lactobacillus rhamnosus* (JB1) works in the lung at a molecular level. Dr. Khalil Karimi, a McMaster University colleague, joined the team in this endeavour.

The researchers suspected that live *Lactobacillus rhamnosus*



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worked by enhancing the regulatory immune response of allergic mice through the production of regulatory T cells which help to suppress airway inflammation and reduce asthma symptoms.


To test their hypothesis, the researchers fed asthmatic mice live *Lactobacillus rhamnosus* for nine days to boost their immune response. They extracted regulatory T cells from the mice and transferred the cells into a second group of mice that were also allergic to egg white protein but had not been fed the probiotic. The second group of mice was subsequently exposed to egg white protein and their allergic response analyzed. After receiving the transferred T cells, the second group of mice also showed a 75% improvement in their allergic response to egg white protein, even though they had not consumed the probiotic. “The effect of the probiotic seems to be mediated, at least in part, by these regulatory cells,” Dr. Forsythe said.

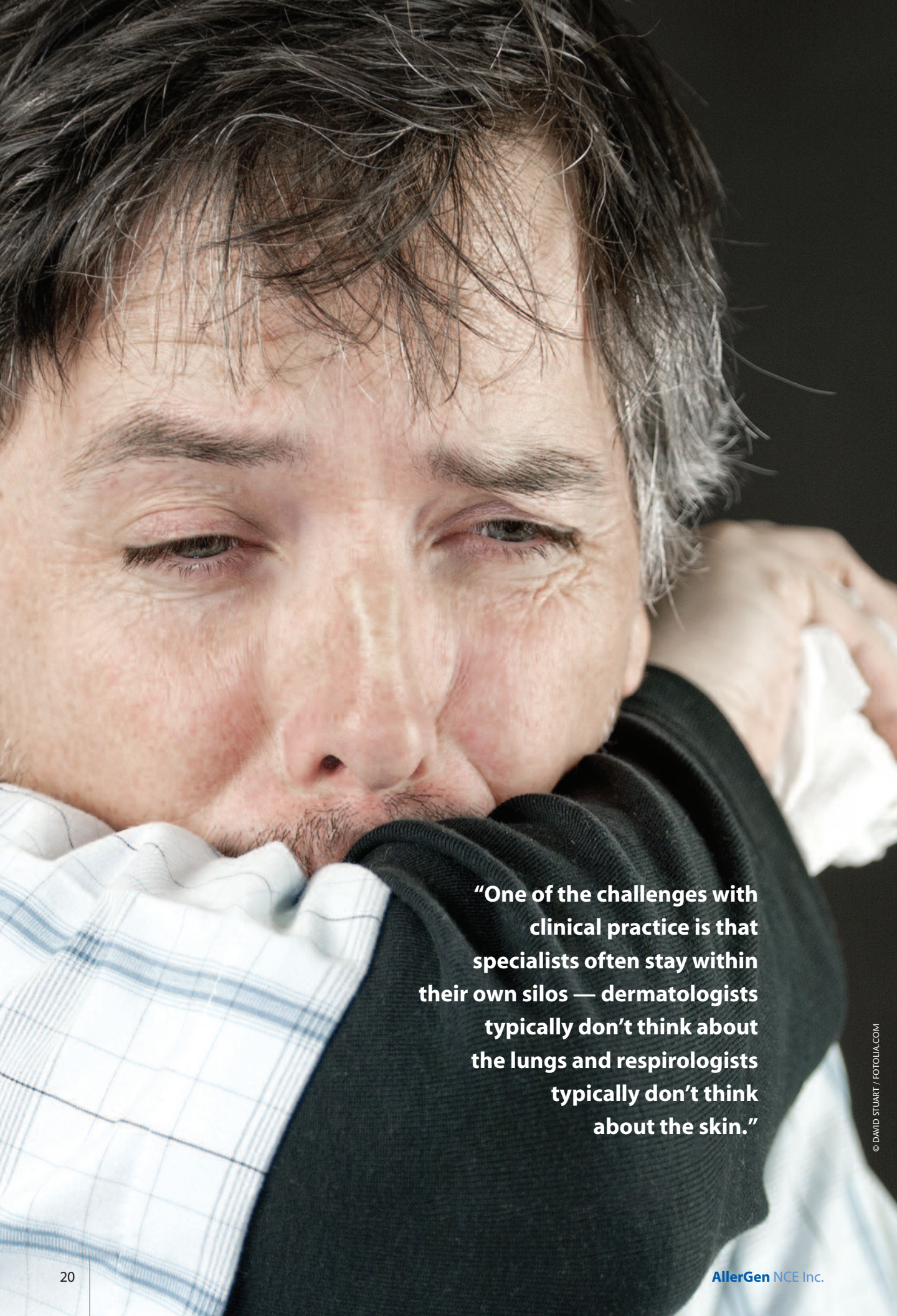
Probiotics for allergy and asthma

In additional studies, Drs Forsythe, Inman, Bienenstock and Karimi found that when the bacterium was introduced into cell

cultures made from specific human cells, an anti-allergic response — similar to the response seen in mice — occurred. This finding further solidified their commitment to develop an effective probiotic treatment for human allergy and asthma.

Their ongoing research focuses on mapping the specific mechanisms behind the anti-allergic action of *Lactobacillus rhamnosus* and exploring whether or not probiotics can be used to prevent the initial development of allergic disease. In an ongoing study, the McMaster investigators are feeding probiotics to pregnant mice to determine if their pups will be protected from developing allergies and asthma.

This research has the potential to yield substantial economic benefits for Canada. A new therapy that decreases asthma rates could result in improved workplace productivity and reduced healthcare costs. “Our studies were very important for attracting industry and maintaining their interest,” Dr. Bienenstock said. “We believe that our research into this bacterium will lead to treatment, and possibly even prevention, of allergic disease.” 



“One of the challenges with clinical practice is that specialists often stay within their own silos — dermatologists typically don’t think about the lungs and respirologists typically don’t think about the skin.”

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Joining Forces to Explore Occupational Allergies

Dr. Linn Holness, an AllerGen NCE investigator and professor at the University of Toronto, has a long-standing interest in understanding how exposure to workplace chemicals can cause employees to develop allergic skin reactions or allergic asthma.

Repeated exposure to a chemical allergen can cause a hypersensitivity which causes the body's immune system response to overreact, even when exposed to a tiny amount of the chemical. For some workplace allergens, it is still unclear how people become hypersensitive at the cellular and molecular levels. Interestingly, evidence from some animal studies and a few patient case reports suggest that repeated chemical contact with the skin may play a role in the development of respiratory symptoms.



Dr. Linn Holness, Professor, Department of Medicine, University of Toronto and Director, Centre for Research Expertise in Occupational Disease, St. Michael's Hospital

Breaking down Silos

Dr. Holness has conducted a number of workplace-based studies, assessing people with both lung and skin problems. During her work, Dr. Holness recognized that in order to more fully understand the interaction between the lungs and the skin, both as a route of exposure and as a response organ system, skin and lung experts needed to collaborate. "One of the challenges with clinical practice is that specialists often stay within their own silos — dermatologists typically don't think about the lungs and respirologists typically don't think about the skin," Dr. Holness said.

Dr. Holness believes that one of the primary reasons why clinical specialists are prone to "one-system thinking," is that they rarely have a forum to talk to one another. Similarly, laboratory researchers who study the connections between the skin and the lungs don't often have the opportunity to interact with workers who suffer from occupational allergies or with workplace safety professionals who deal with exposures in the workplace.

To bridge these gaps, Dr. Holness envisioned a forum where Canadians with different expertise in occupational allergies could meet to share their knowledge, build consensus on research gaps, and brainstorm new opportunities for future collaboration.

AllerGen NCE helped Dr. Holness turn her vision into a reality. With AllerGen's support, Dr. Holness organized a multi-

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disciplinary workshop that brought together clinical specialists, research scientists, workplace safety professionals and students interested in pursuing allergy-related post-graduate work. According to Dr. Holness, AllerGen's role in promoting the workshop within the Network was instrumental to the workshop's success. "It would have been hard to sell our idea for a workshop to a more traditional agency, since this area of research is in its infancy," Dr. Holness said.

Collaborating on a Research Road Map

During the workshop, specialists from different areas collaborated to define the most pressing issues in the field of occupational allergies. They reached a consensus on how to move the most



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promising research forward and outlined a research agenda that combined basic research questions about disease mechanisms with practical and clinical questions that are top-of-mind for physicians dealing with patients with work-related allergies.

Participants agreed that an important area for future research is a deeper exploration into the interaction between the skin and the lungs. “This is important from a prevention perspective,” Dr. Holness said. “Traditionally, when we think people are exposed to an allergen that might cause lung problems, we provide them with respiratory masks. Similarly, if we think an allergen is a skin sensitizer, we recommend they wear gloves. But, if it is proven you can sensitize through either system, then we actually need to be providing protective equipment for both systems.”

Inspiring Young Minds and Gaining International Recognition

AllerGen NCE funding and support has contributed to important gains in moving research on occupational allergies forward. Victoria Arrandale was inspired by the workshop to pursue her PhD studies with Dr. Holness. During her doctoral studies, Dr. Arrandale studied several of the questions raised in the workshop’s research agenda and was invited to present her findings at Yale University. This talented young researcher continues to be a member of AllerGen’s Student and New Professionals Network, taking advantage of the many capacity building and professional development opportunities offered to AllerGen trainees.

In addition, the workshop was instrumental in fostering international recognition of Canadian research efforts.



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Dr. Holness also noted that the identification of biomarkers to differentiate between different routes of exposure “may be potentially useful in the diagnosis and treatment of disease.” In other words, understanding exactly how allergic disease works at a cellular level may help scientists devise objective diagnostic tests and offer better treatments for employees who suffer from work-related allergies.

Dr. Holness was invited to host the Occupational and Environmental Exposure of Skin to Chemicals (OEESC) conference in 2011 — an international meeting that brings together experts in skin diseases and chemical exposure. “The workshop was pivotal to us having this valuable opportunity to host OEESC 2011,” Dr. Holness said. “It brought together a diverse group of people that are needed around the table in order to develop an integrated, multi-disciplinary research agenda. None of these successes could have been possible without AllerGen NCE.”

According to Dr. Holness, the understanding of work-related allergic skin diseases and asthma is still in its infancy and researchers are just beginning to unravel the complex connection between the skin and the lungs in terms of chemical exposures. Further research into occupational allergies is needed to reduce chemical exposures and improve safety equipment guidelines.

As well, more research means health professionals will be better equipped to assess skin and lung problems and help employees who have already developed occupational allergies speed up their return to work. “It is plausible that a better understanding of the exposures and routes of exposure relevant to allergic respiratory disease will lead to improved compensation for workers who may have a non-traditional route of exposure and sensitization,” Dr. Holness added.

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AllerGen NCE Inc.
McMaster University
Michael G. DeGroote Centre for Learning & Discovery
1280 Main Street West, Room 3120
Hamilton, ON L8S 4K1

Networks of Centres of Excellence

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

www.allergen-nce.ca

