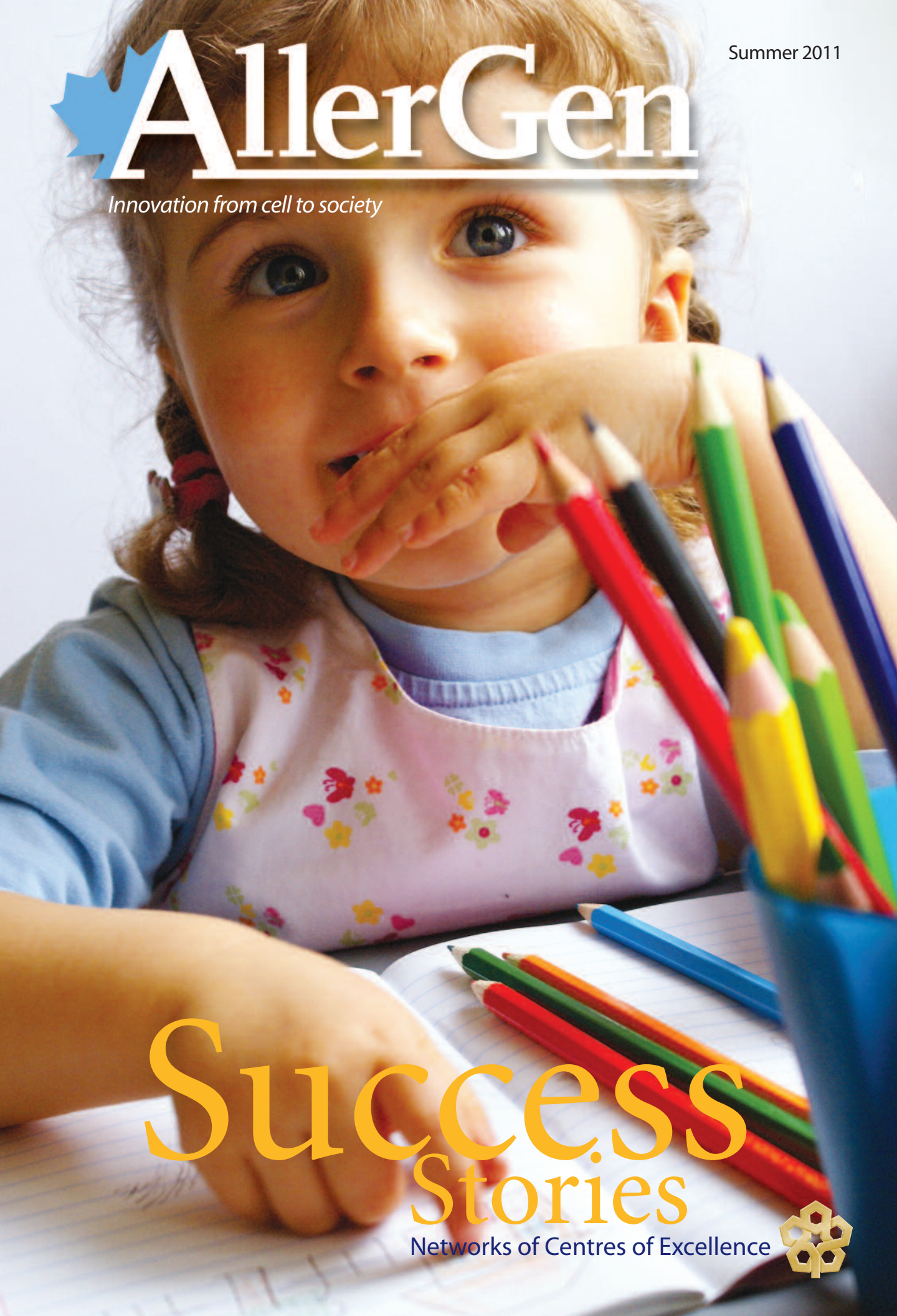
AllerGen
Innovation from cell to society
Summer 2011
Success
Stories
Networks of Centres of Excellence

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Making a Difference
from cell to society

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

In this issue, the results of five AllerGen-supported projects are presented. These projects were undertaken in collaboration with partner organizations including The Hospital for Sick Children, TEC Edmonton, Asthma Society of Canada, National Asthma Patient Alliance, McMaster University, National Lung Health Framework, Public Health Agency of Canada, GABRIEL European Consortium and international research collaborators from the United States, Belgium and South Africa. Beneficiaries of this research include industry, clinicians and their patients, public policy makers, other researchers and ultimately Canadian families living with asthma and allergic diseases.

The stories showcase findings that will benefit future generations of Canadians and those living with allergies, asthma and anaphylaxis around the world. Results include new diagnostic tools, new treatment therapies, online-education tools for asthma educators and sufferers, and outcomes relevant to policy makers responsible for early childhood development and chronic disease management.

Stories featured in this issue include:

- Urine Samples Advance Asthma Diagnosis and Help Patients 'Breathe Easy'
- A New Generation of e-Learning Tools for Asthma Education
- The Global Search for Allergy and Asthma Genes: Genetic Testing, Counselling and Novel Therapies on the Horizon
- The Front Lines: Studying Asthma During Early Childhood Development
- Adults Raised in Poor Socioeconomic Circumstances Show Increased Susceptibility to Chronic Disease.

Since 2005, AllerGen NCE has worked to catalyze and support innovative research and discovery of causes, prevention and treatments of allergic and related immune diseases. AllerGen NCE also contributes to the development, translation, mobilization, commercialization and policy use of research for the benefit of Canadians impacted by allergic disease, asthma and anaphylaxis nationally and globally.

AllerGen invests in research in the following broad programmatic areas:

1. Gene-Environment Interactions

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

2. Diagnostics and Therapeutics

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

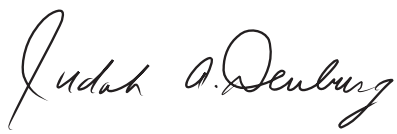
3. Public Health, Ethics, Policy and Society

Strategic Focus: Allergic disease management and surveillance.

In addition, AllerGen NCE supports four cross-programmatic, multi-disciplinary research teams:

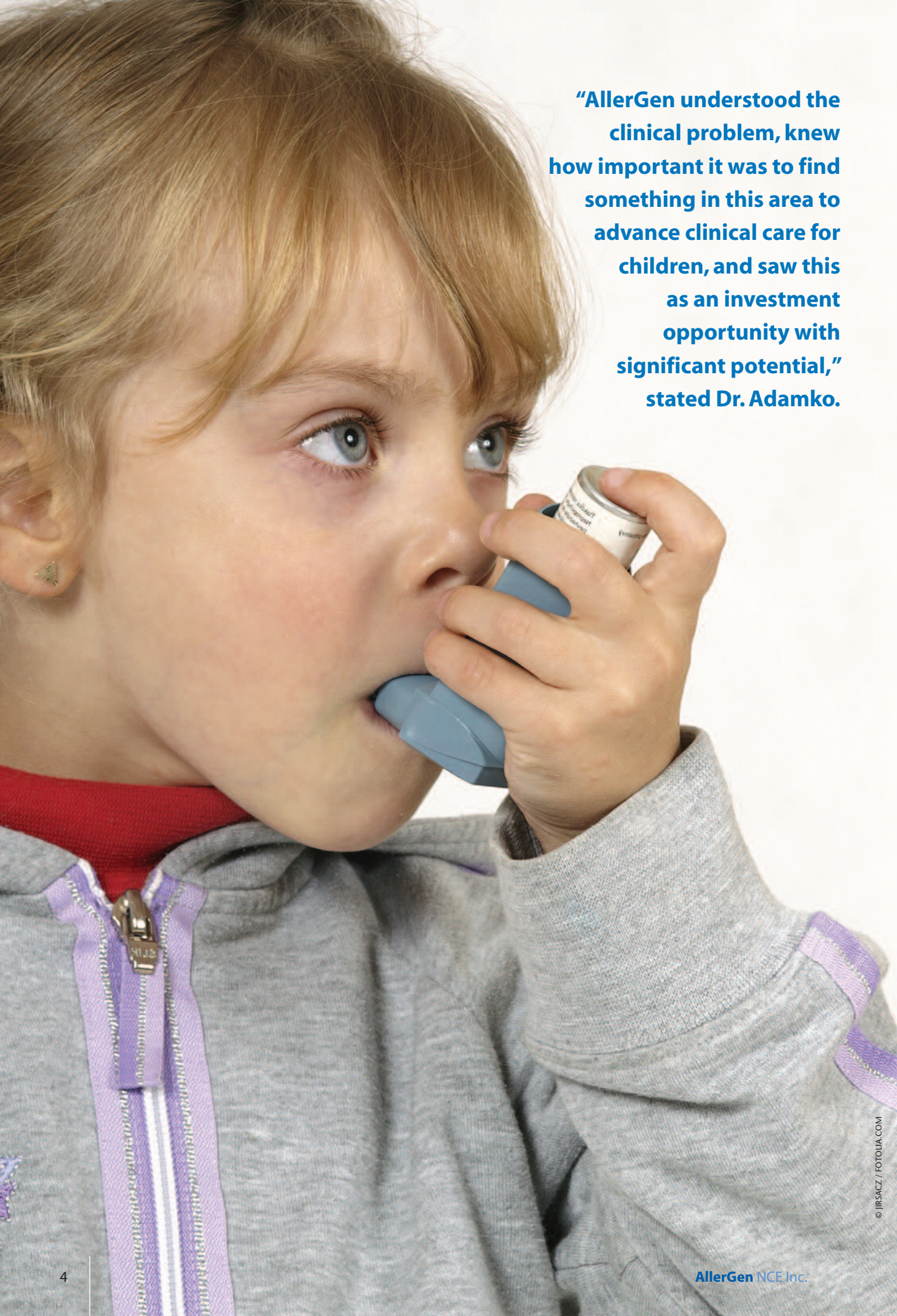
i. The Canadian Healthy Infant Longitudinal Development (CHILD) Study
ii. Food Allergy and Anaphylaxis – the Canadian Group on Food Allergy Research or CanGoFAR team
iii. Mind-Body Interactions and Allergic Disease
iv. Occupational and Work-related Allergy and Asthma.

The number of Canadians directly or indirectly affected by asthma and allergic diseases surpasses 50%. Over one third of Canadians are likely to develop asthma over their lifetime. AllerGen NCE aims to accelerate research that exposes the root causes of asthma and allergy and offer new and improved management solutions to those living with these chronic conditions. AllerGen NCE hopes that, through its network of allergic and immune disease research experts and industry, healthcare and patient partner organizations, these stories will accelerate dissemination, discussion and translation of AllerGen-supported research results.



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

Diana Royce, EdD, Managing Director and COO



"AllerGen understood the clinical problem, knew how important it was to find something in this area to advance clinical care for children, and saw this as an investment opportunity with significant potential," stated Dr. Adamko.

Urine Samples Advance Asthma Diagnosis and Help Patients 'Breathe Easy'

For many years, asthma experts have tried to unlock the secrets of accurately diagnosing asthma, as well as predicting asthma attacks before an individual ends up in the emergency room. They have looked for answers in the air asthma sufferers exhale; in cell scrapings from their lungs; in the mixture of saliva and mucus they cough up (referred to as *sputum*); and in their blood. No one thought that the key to diagnosing and effectively managing asthma lay in the uniqueness of an asthma patient's urine sample — until now.

Dr. Darryl Adamko, MD, Associate Professor, University of Alberta

Dr. Darryl Adamko, an Associate Professor at the University of Alberta, has dedicated himself to research that improves the lives of children with breathing disorders. As an expert in pediatric respirology, Dr. Adamko knew firsthand the difficulty doctors faced when diagnosing asthma in young children and prescribing appropriate drug treatment plans. So, Dr. Adamko committed himself to developing a test to be used by family physicians that offered an accurate asthma diagnosis and facilitated appropriate treatment decisions. AllerGen NCE supported this commitment, and as stated by Dr. Adamko, "AllerGen understood the clinical problem, knew how important it was to find something in this area to advance clinical care for children, and saw this as an investment opportunity with significant potential."

The Challenges of Asthma

Asthma is a chronic, lifelong disease of the airways in the lungs. The airways are always inflamed, even when symptoms are not present. When an inflamed airway constricts because of immune system distress, the airway is further narrowed, which can result in symptoms such as wheezing, coughing, chest tightness or shortness of breath. Adult asthma sufferers often compare a full-blown asthma attack to "trying to breathe through a straw." It doesn't take much imagination to know that an asthma attack is a very frightening experience, especially for children and their parents.

One in five Canadian children under the age of 19 are living with asthma and it is the leading reason for missing school, visiting the emergency department or being admitted to a hospital. One in ten Canadian adults also suffer from asthma and it is the third leading reason for work absenteeism. There is also evidence that the number of people suffering from this disease is steadily rising in Canada, as well as in other first world nations. Asthma has detrimental impacts upon the health and lifestyle of many Canadians, as well as enormous economic impacts on Canadian healthcare costs and productivity.

Asthma experts, like Dr. Adamko, say that asthma can be difficult to diagnose, especially in children. The accuracy of the diagnosis usually rests with the patient's or the care-giver's ability to explain the symptoms to the doctor, as well as with the doctor's experience in detecting this disease. As a disease, it is both *under-diagnosed* and *over-diagnosed*. In other words, asthma could be incorrectly diagnosed as some other type of condition, or symptoms could be diagnosed as asthma when, in fact, it is not. The other problem for doctors and patients is knowing when to increase or decrease medications. Often, by

the time a patient is having worsening of symptoms, the airways are quite inflamed. Better measures of asthma control and severity would be helpful.

While diagnostic tests exist, they are limited in their usefulness in a typical doctor's office. For example, the best test is a biopsy of the airways. This involves inserting a tube down the throat of a patient while he or she is under general anesthetic, in order to remove lung tissue samples that can be examined under a microscope. This is an invasive, painful and potentially dangerous procedure and it is not suitable for use in community medicine clinics. Non-invasive diagnostic tests are also available, such as spirometry. Spirometry objectively measures the amount of air inhaled and exhaled in order to determine the level of airway obstruction. The difficulty with this test lies in the inability of young children and some elderly patients to blow into the spirometer tube. Further, most clinicians do not have access to such a machine on a regular basis. A third diagnostic, the 'sputum' test, requires the patient to cough deeply and spit up saliva and mucus from the lungs, which are then examined under a microscope. This is also a challenge, in that many people, especially young children, have difficulty providing an adequate sample. Typical clinical settings also lack trained laboratory technicians who can routinely analyze these test samples. Blood tests conducted on individuals with asthma may show abnormal cell counts or antibodies, which indicate allergic reactions and inflammation in the airways. This test is useful in diagnosing *allergic* asthma; however, for many people with asthma, allergies are not the main problem. Tests for exhaled gases like nitric oxide are also useful, but their accuracy is not as good as the sputum test. Likely, the problem with many of the non-invasive tests is that they only measure one variable. We are learning that asthma is a complex disease and not every patient has the same markers of the disease. Overall, the tests available are not typically used by family physicians, who are the primary healthcare providers for Canadians. Thus, most patients are simply treated based on symptoms.

The starting point for this research was the belief that people with asthma produce chemicals in their bodies due to inflammation associated with the disease. These chemicals should, therefore, eventually end up in the patient's urine. The first phase of the project was to study the chemicals produced by the body's various metabolic processes....

© ADAMKO

AllerGen investigator Dr. Darryl Adamko, MD, treating a patient.

Using Urine to Diagnose Asthma

Dr. Adamko was not satisfied with the available asthma tests, particularly because of their unsuitability for young children. He was convinced that he could develop a urine test that was easy to analyze and would produce better results. This endeavour was greatly encouraged by The Hospital for Sick Children in Toronto (SickKids), which funded the initial research using animal models, and by AllerGen NCE, which funded the human study.

The starting point for this research was the belief that people with asthma produce chemicals in their bodies due to inflammation associated with the disease. These chemicals

should, therefore, eventually end up in the patient's urine. The first phase of the project was to study the chemicals produced by the body's various metabolic processes, called metabolites, using guinea pig urine to develop a profile for asthma. Dr. Adamko explained that the reason for studying guinea pigs first was that there are significantly fewer differences between individual guinea pigs than there are between humans. This helps researchers rapidly sort out the methodological *kinks*. For example, in developing the animal model, Dr. Adamko discovered that, "asthma inflammation of the airways affects the metabolism of cells from all over the body, not just the lungs."

The second phase of the project was to develop a profile for asthma as it appears in human urine. Dr. Adamko collected urine samples from children with the assistance of Dr. Brian Rowe, a clinician scientist and emergency room physician at the University of Alberta. He also relied on Kim Cook, a nurse who volunteered her time because she believed in the importance of this research. The samples were gathered from a cross-section of healthy children; non-symptomatic asthmatic children; and, asthmatic children when they were having an asthma attack. Using technology known as nuclear magnetic resonance (NMR) spectroscopy, Dr. Adamko believes that they have identified asthma's chemical *fingerprint*.

The beauty of NMR is that it is able to simultaneously track metabolites from different pathways in the body. Dr. Adamko believes that he will be able to predict when an asthma attack is imminent, based on the chemical profile of a patient's urine. This new diagnostic method of using urine and NMR to detect asthma has a provisional, worldwide patent, which was funded by AllerGen NCE in partnership with TEC Edmonton. TEC Edmonton is a joint venture between the University of Alberta and the Edmonton Economic Development Corporation that helps transform new technologies into business opportunities. "AllerGen is making sure that ownership of this idea stays in Canada," says Dr. Adamko.

The next and final step in this research is to show that asthma's chemical *fingerprint* can be found in a large number of asthmatic children, and to further refine the chemical *fingerprint's* definition. To complete this phase of the research, Dr. Adamko will be working with Dr. Adnan Custovic, a pediatric allergy specialist in the United Kingdom, who will provide 500 urine samples from asthmatic children of different ages for testing. Dr. Adamko expects to successfully use his method to predict asthmatic children in the United Kingdom cohort. He anticipates completing this next phase of research by the end of 2011, and then publishing a major scientific paper on his results.

The Future Looks Brighter for Asthma Diagnosis and Management

This new approach, using urine and NMR technology to diagnose and manage asthma, has the potential to revolutionize medical practice. An objective test, which is non-invasive and safe, would be enthusiastically welcomed by asthma sufferers and parents around the world. Doctors and patients could finally *breathe easy*, knowing that they have the right diagnosis and therapy for their respiratory symptoms. This new diagnostic technology could also be used to formulate highly individualized treatment plans for patients, which translates into better health outcomes and more effective patient care. Tailor-made plans could increase patient compliance with recommended treatments — compliance is currently a major challenge to optimal asthma control because patients are often hesitant to regularly take powerful medications such as corticosteroids. Furthermore, this method could be used to predict an imminent asthma attack, which would save lives and reduce the demand on already strained emergency healthcare services.

AllerGen NCE's continued collaboration with TEC Edmonton to further develop this diagnostic technology has resulted in the establishment of a new Canadian start-up company called *Respirylite*, which protects the intellectual property on which this new diagnostic approach is based and supports its translation and commercialization. Due to the foresight of AllerGen NCE and TEC Edmonton, this method of asthma diagnosis is also available for global licensing, and has the potential to generate impressive revenues given the global impact of this chronic disease.

However, for Dr. Adamko, improving the everyday lives of Canadians, especially children, is what continues to motivate him to conduct this research and pursue its commercial development. "If this technology leads to a widely available test for asthma that helps to not only convince people that they have asthma, but helps them to adjust their medications — if any of these things occur as a result of this research, then that's success."

"There is tremendous value in on-line education for different audiences," states Dr. Levinson. "We have developed very high quality educational materials for different audiences, which, through on-line technology, have the potential to reach more people than ever before."

A New Generation of e-Learning Tools for Asthma Education

Research clearly shows that patient and professional education is one of the best defenses against asthma attacks. An ounce of prevention really is worth a pound, or two, of cure.

After meeting during one of AllerGen NCE's networking events, Dr. Scott Tebbutt, a molecular biologist and geneticist, and Dr. Anthony Levinson, a neuropsychiatrist and neuropsychology and medical education expert, decided to combine forces to create high quality, web-based educational tools for asthma patients, health care professionals and medical students.

This successful collaboration has resulted in innovative web-based animations that offer step-by-step explanations of how asthma occurs, as well as novel e-learning courses on asthma management.

Dr. Scott Tebbutt, Assistant Professor in the Department of Medicine at the University of British Columbia, and Principal Investigator at the Providence Heart + Lung Institute at St. Paul's Hospital

Dr. Anthony Levinson, Associate Professor and Director of the Division of e-Learning Innovation at the Michael G. DeGroote School of Medicine, McMaster University

The Art of Reinvention

Creating animations about asthma was not a new experience for Dr. Tebbutt, an Assistant Professor in the Department of Medicine at the University of British Columbia, and Principal Investigator at the Providence Heart + Lung Institute at St. Paul's Hospital. By all accounts, the asthma animations that he had already created were amazing. If the Oscars had a "scientific animations" category, he could very well have had a golden statuette sitting on his desk, no doubt flanked by countless piles of academic papers and unwashed coffee mugs.

Dr. Tebbutt wondered, however, if his animations had maximum educational value. The original animations he had developed were not designed in consultation with patients, patient advocacy groups or experts from other fields. When Dr. Tebbutt met Dr. Levinson through AllerGen NCE, he realized that together they could create animations and other e-learning tools that were more educationally effective. Dr. Levinson is an Associate Professor and Director of the Division of e-Learning Innovation at the Michael G. DeGroote School of Medicine, McMaster University. Also recruited to the team through AllerGen NCE's networking efforts, were Dr. Wendy Ungar from the University of Toronto and The Hospital for Sick Children, a specialist in evaluating the effectiveness of health care initiatives,

and Beth Anderson, co-founder and current CEO of Arkitek Studios, Inc., an animation studio based in Seattle, Washington.

Recognizing the vital importance of asthma education and the need for better educational tools, AllerGen NCE provided $60,000 to the team, enabling their e-learning project to proceed.

Understanding Your Target Audience

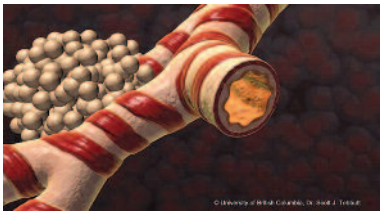
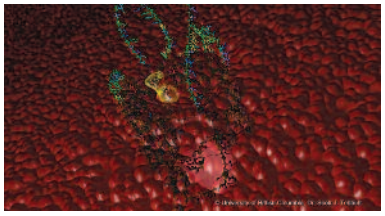
A challenge inherent in creating animations that explain how asthma works on a molecular level is determining how much information is appropriate for each target audience. Animations intended for the general public, asthma patients and their families need to have a narrative that is easy to follow, while animations for professionals with a strong science background, like healthcare professionals and medical students, require a narrative that takes into account that audience's prior knowledge of genetic concepts.

Drs Tebbutt and Levinson set up four focus groups to determine the effectiveness of their animations for different audiences. The focus groups, held at different centres across Canada, were made up of people with a variety of backgrounds and interests, including teenagers, parents, teachers, physicians, patient associations and policy makers.

The groups developed application-specific recommendations. Drs Tebbutt and Levinson incorporated these recommendations into their animations' final design, which were completed by talented graphic arts and animation student trainee, Mr. Kick Chen, with help from Ms. Angela Hussainkhel, a molecular biology student.

In addition to creating audience-specific animations, Dr. Levinson and his team, including Ms. Lisa Colizza and Mr. Ed Mallon at the Division of e-Learning Innovation at McMaster University, set out to create a web-based education course for patients and their families on asthma management. For this endeavour, they partnered with the Asthma Society of Canada. This was a strategic partnership, given that the Asthma Society of Canada had already developed a great deal of content in consultation with asthma patients and had a large network of clinical experts and asthma educators that could be utilized. "This partnership enabled us to take a few shortcuts and focus on further refining the content that the Asthma Society had already developed," says Dr. Levinson.

The on-line education course that Dr. Levinson's team developed was subsequently reviewed by members of the National Asthma Patient Alliance. Seeking feedback from *end-users* during the development phase ensured that the final product did, in fact, deliver high quality education tailored to each target audience.

Original animation stills.

The Global Impact of Web-Based Asthma Education

The e-learning course for the public called *Taking Control of Your Asthma* was launched by McMaster University in partnership with the Asthma Society of Canada on World Asthma Day, May 5, 2009 and has been widely promoted by the Asthma Society of Canada through its newsletters and website. During the first two years following its launch, *Taking Control of Your Asthma* has been viewed 3,500 times by 2,500 individuals from 66 countries.

Analysis reveals that visitors to the website are spending a lot of time on the course, and that there are numerous visitors returning to the site on multiple occasions, suggesting that viewers are finding it very useful and accessible. Dr. Levinson reports that people from all over the world have been accessing and incorporating their animations into local education programs.

The *Taking Control of Your Asthma* course is freely available at www.machealthpublic.ca and at the direct link www.takingcontrolofyourasthma.ca. The team's animations are available at http://genapha.icapture.ubc.ca.

What's Next?

The next phase of dissemination of these materials is to use the animations in on-line programs offered by medical schools, starting with McMaster University's Michael G. DeGroote School of Medicine. The plan is that eventually, medical students from around the world will improve their understanding of asthma, and increase their skills in asthma diagnosis and treatment using these animated learning modules.

Dr. Levinson is also working with his team and the Asthma Society of Canada to *repurpose* their asthma education course so that it can be used to train lay people responsible for offering asthma education programs in their local communities. This variation of the program will be used to *Train-the-Trainers*. An adapted version of the program has proven to be a useful resource for peer educators, both teen and adult, new immigrants and Aboriginal community leaders. It has been used as the foundation for an *Asthma Ambassadors* peer educator program sponsored by the National Asthma Patient Alliance of the Asthma Society of Canada, as well as to develop a *Train-the-Trainer* version for use by First Nations, Inuit and Métis community leaders in partnership with the Asthma Society of Canada.

While Drs Tebbutt and Levinson will continue to freely offer the content on-line, they are also looking for opportunities to produce spin-off products that have revenue-generating potential. As examples, they are exploring opportunities for their content to be repackaged for use on mobile devices and incorporated into electronic platforms used in the healthcare system.

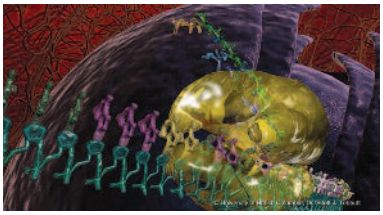
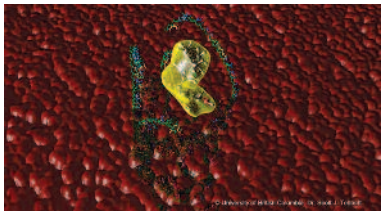
"If we came up with a formula for educating patients that contributed to improved health outcomes, there would be other audiences that would be interested in incorporating that kind of education into point-of-care learning modules," says Dr. Levinson. He adds that, "the key is to come up with something that can be integrated into the usual systems of care, and that may require either customization or syndication into other electronic health platforms."

AllerGen NCE Supports High-Impact Educational Initiatives

Dr. Levinson praises Dr. Tebbutt for his dedication to developing the animations. "He had the sense that people need some visuals to understand complex concepts," says Dr. Levinson, "and he took the bull by the horns."

"Animations can make science exciting," adds Dr. Tebbutt. "They also have high impact and help people better remember what is being taught." Dr. Tebbutt also gives his collaborator, Dr. Levinson, a lot of credit: "He took the animations to a level that I could never have imagined."

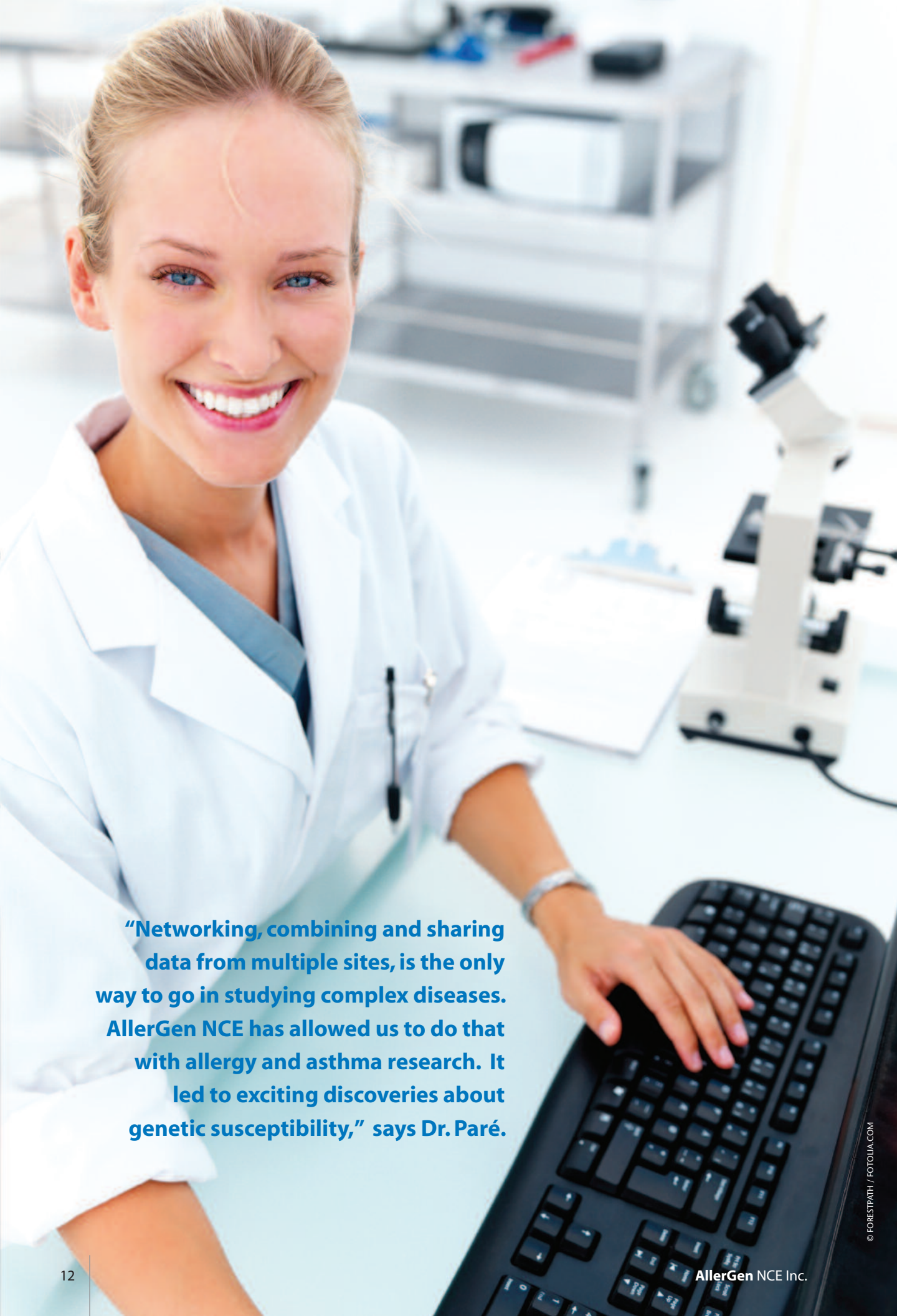
Dr. Levinson explains that there are few high quality animations that explain the core concepts of asthma. And the fact that their team's materials were developed in consultation with a wide range of experts and lay audiences makes them *extremely valuable*. It is expensive to develop animations, and almost impossible to get funding to create animations geared towards healthcare education, that is, without support from AllerGen NCE.

Original animation stills.

However, "there is tremendous value in on-line education for different audiences," states Dr. Levinson. "A lot of people invest a great deal of time and energy in developing materials that get locked into a local presentation or a face-to-face session. We have developed very high quality educational materials for different audiences, which, through on-line technology, have the potential to reach more people than ever before. AllerGen NCE has been very supportive of that and recognizes that if it's done well, this endeavour brings together the best of many disciplines and has the potential for wide-spread dissemination, unlike many other media or technologies."

AllerGen NCE, through its networking efforts, also effectively united key players and stakeholders and promoted a valuable partnership with the Asthma Society of Canada and the National Asthma Patient Alliance. "It really is a case of the whole being greater than the sum of its parts," says Dr. Levinson. "Without AllerGen," adds Dr. Tebbutt, "that networking would never have happened."



"Networking, combining and sharing data from multiple sites, is the only way to go in studying complex diseases. AllerGen NCE has allowed us to do that with allergy and asthma research. It led to exciting discoveries about genetic susceptibility," says Dr. Paré.

The Global Search for Allergy and Asthma Genes: Genetic Testing, Counselling and Novel Therapies on the Horizon

For the past 15 years, genetic research teams have been searching for the genes associated with allergies and asthma. Yet, no sooner did one team confidently identify a gene as one of many involved in allergic disease, another team would report that they were unable to replicate the results.

Researchers around the world soon realised that small sample sizes resulting in *false-positive* data, and a failure to incorporate environmental factors contributed to the discrepancies in the research results of different teams. Additionally, environmental factors played a larger role than originally anticipated in influencing whether or not a person born with a genetic susceptibility eventually develops allergic disease.

Dr. Peter Paré, MD and Professor, Department of Medicine and Pathology, University of British Columbia

Learning from the Past

Dr. Tom Hudson, MD, President and Scientific Director of the Ontario Institute of Cancer Research, and Dr. Peter Paré, MD and Professor, Department of Medicine and Pathology, University of British Columbia, recognized the need for allergy and asthma genetic studies that use data from large sample sizes, and which included individuals from different environments. With the support of AllerGen NCE, they brought together other Canadian researchers working in the area of allergy and asthma genetics and a Canada-wide collaboration was born. This group of researchers combined forces to undertake a series of studies that pooled biological samples and data collected in Vancouver (Drs Andrew Sandford, Denise Daley and Moira Yeung), Winnipeg (Drs Allan Becker and Anita Kozyrskyj), Chicoutimi (Dr. Catherine Laprise) and Quebec City (Dr. Yohan Bossé). This national team also established an important collaboration with a team in Perth, Australia. In total, genetic testing conducted on approximately 5,000 people was incorporated into the final analysis.

In one study, the team tested 100 genes that were previously reported in the scientific literature as being involved in the development of allergies and asthma. The team then attempted to replicate previous results by using a large sample size to avoid random errors and, in addition, took into account environmental factors. Would a gene considered as a candidate for allergies and asthma vary significantly when asthma patients and non-asthmatic individuals were compared? The team could only replicate 14 of the 100 previous *candidate genes* that they studied. "This was an important study because it confirmed some genes as true asthma genes and many of the others as false-positives," stated Dr. Paré.

Moving Forward in Genetics Research by Leaps and Bounds

In addition to testing 100 genes gathered from the scientific literature on allergy and asthma genetics, the team added 50 genes that had never before been tested. As a result, the team identified seven new genes that are likely involved in allergic diseases. "We added to the world's knowledge by not only showing which ones were likely true genes, we also came up with some novel ones," says Dr. Paré.

One of the new genes, referred to as TSLP, is particularly exciting because other researchers in the AllerGen Network came up with this gene independently, and did so based on its function. In Dr. Paré's opinion, "This is networking at its best. The genetic studies confirmed the functional studies."

The team is also excited about TSLP because it makes a protein that is found in airway lining cells called epithelium. The

implication of this is that new medications could potentially be given *via* inhaler to influence that gene.

Due to major technological advances over the last five years, genetic research teams looking for the genes involved in a certain disease can now look at all of the genes that make up the human genome, instead of confining their search to a small number of potential candidates. However, testing every single gene creates the potential for false-positive results, which must be counteracted by using large sample sizes.

As a result, AllerGen NCE's Canadian team joined forces with a major European research group to collect samples and data on more than 10,000 asthma cases and 16,000 controls. The group is called GABRIEL (http://www.gabriel-fp6.org/) and the cases and controls were pooled from 23 studies in 10 countries. This unprecedented collaboration of asthma genetics researchers is driven by the need to get very large sample sizes. "Bringing the Canadian and European samples together allowed this research group to become a major world player in the scientific community," states Dr. Paré.

This international research effort, supported by AllerGen NCE, has culminated in the publication of a ground-breaking paper in *The New England Journal of Medicine*, which is the most prestigious medical journal in the world. Excitingly, this study confirmed the importance of TSLP and other genes expressed in the airway epithelium, suggesting a whole new paradigm for the origin of asthma as a primary airway epithelial disease.

One potential benefit of this research includes the identification of new mechanisms of disease, which in turn suggests new therapies. A second outcome will be the eventual use of genetic profiling to assess risk for disease. Dr. Paré and his colleagues hope that in the future, genetic testing and counselling can be routinely done in cases where a person has a parent who suffers from asthma or allergies. "Genetic testing

could be used to tell people what their risk of developing asthma or allergy is, and maybe to also tell them what environmental factors they need to change in their life," says Dr. Paré.

Besides the potential that new therapies will be developed based on knowledge of the genes involved in asthma and allergic disease, it is likely that genetic analyses will predict who will respond best to specific therapies and who is most likely to develop an adverse response. The therapeutic and commercial potential of this type of research is significant.

result of the intense networking supported and promoted by AllerGen NCE. Specifically, AllerGen NCE contributed to bringing together 21 individuals from four Canadian Universities and three provinces, thereby making the project a truly national undertaking." This partnering success paved the way for a partnership with Australia and the collaboration of the European research group, GABRIEL, which provided $1.2 million in funding to have the Canadian samples genotyped."

Dr. Paré added: "Networking, combining and sharing data

According to the team's final report, "The unprecedented scope and scale of this project and the speed with which it progressed, is a direct result of the intense networking supported and promoted by AllerGen NCE. Specifically, AllerGen NCE contributed to bringing together 21 individuals from four Canadian Universities and three provinces, thereby making the project a truly national undertaking." This partnering success paved the way for a partnership with Australia and the collaboration of the European research group, GABRIEL, which provided $1.2 million in funding to have the Canadian samples genotyped."

The Power of Research Networks

Dr. Paré and his research team can attest to the many benefits of being part of a research network like AllerGen NCE. First, even the best research ideas cannot be explored without funding. AllerGen NCE provided the bulk of the research funding to the tune of almost $1 million. This money enabled Drs Hudson and Paré to leverage further funding from the Canadian Institutes of Health Research ($160,000); Burroughs Wellcome Fund ($45,495); and Australia's Busselton Population Medical Research Foundation ($29,000).

Secondly, AllerGen NCE facilitated collaboration of researchers from across Canada and around the world to work together to combine their expertise, research samples and data. According to the team's final report, "The unprecedented scope and scale of this project and the speed with which it progressed, is a direct result of the intense networking supported and promoted by AllerGen NCE. Specifically, AllerGen NCE contributed to bringing together 21 individuals from four Canadian Universities and three provinces, thereby making the project a truly national undertaking." This partnering success paved the way for a partnership with Australia and the collaboration of the European research group, GABRIEL, which provided $1.2 million in funding to have the Canadian samples genotyped."

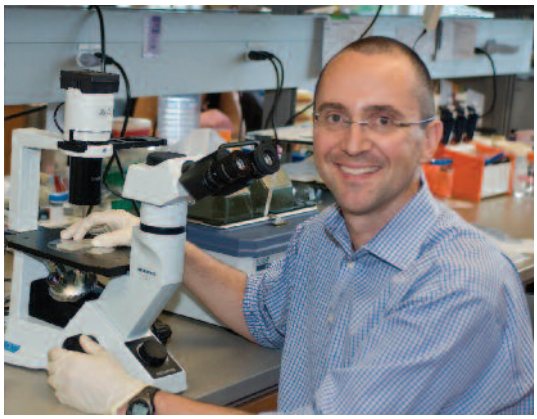
Dr. Paré added: "Networking, combining and sharing data from multiple sites, is the only way to go in studying complex diseases. AllerGen NCE has allowed us to do that with allergy and asthma research. It led to exciting discoveries about genetic susceptibility." It also led to this Canadian group becoming a global player in genetics research.

Last, but not least, this project, in partnership with AllerGen NCE, has supported the training of 14 highly qualified personnel. Being part of the Network has helped trainees broaden their research skills, establish national contacts and develop their careers. Two of the 14 trainees, Drs Daley (University of British Columbia) and Bossé (McGill University) are now university faculty members and hold their own peer-reviewed grants. "This project was a springboard for the careers of a number of young investigators," said Dr. Paré. Dr. Paré concludes: "AllerGen NCE trainees are success stories in themselves."

The team believes that the process by which the immune system "learns" from the environment can be exploited to develop novel therapies. For example, a child may be treated with a vaccination in the early years to train the immune system and prevent or mitigate immune diseases, like asthma and allergies, later in life.

The Front Lines: Studying Asthma During Early Childhood Development

According to the 2010 survey *Asthma Insight and Management in Europe and Canada (EUCAN AIM)*, asthma has a significant impact on the Canadian healthcare system, with one in every six households across Canada having at least one family member diagnosed with this disease. This is a major concern among healthcare professionals and parents alike. Typically, our bodies do not react to everyday external stimuli like pollen or peanuts, but in the case of allergies and asthma our immune system mounts an over-enthusiastic response that can even be fatal. Researchers believe that understanding how the immune system develops in childhood and how it forms a response to different external stresses is the key to curbing this worrying trend.

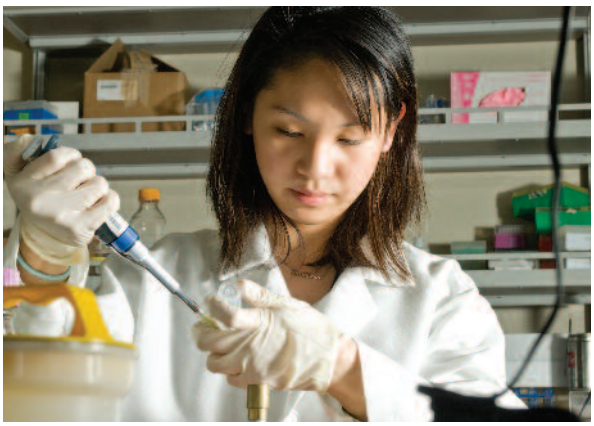


Dr. Stuart Turvey, PhD, Associate Professor, University of British Columbia, Pediatric Immunologist, BC Children's Hospital, and Co-Director of the Immunity in Health & Disease research cluster, Child & Family Research Institute

The early stages of a child's life play a vital role in their social, emotional and physical development. The role of the immune system in development, however, has yet to be defined and still remains a mystery. Through the advancement of technology and the networking approach of Allergen NCE Inc., a team led by Drs Tobias Kollmann and Stuart Turvey have been able to shed new light on how the immune system develops and reacts to stresses such as asthma and allergies during the early years of life. The team leaders believe that by studying the immune system as it develops, they can help ease the strain allergies and asthma cause later in life. That the early life immune system is not mature is a misconception, states Dr. Kollmann. He says "The early life immune system is not immature. It's just different." Kollmann goes on to explain that while there are some changes in the first month of a newborn's life, the innate immune system doesn't undergo major changes over a lifetime. Before birth, the immune system is geared to preventing an immune response while in the womb. At the time of birth, the immune system shifts focus to become more adept at fighting off threats from the external environment, such as bacterial and viral infections. By the time a child reaches five years of age, the immune system is very robust.

Working Together

The team, led by Drs Kollmann and Turvey, examined the immune system of newborn infants to determine how, and at what times, different genes are expressed during infancy. Drs Kollmann and Turvey want to figure out the extent to which changes in our immune system are pre-programmed and how genetic variation affects the process of change. They are also interested in determining how our immune system is influenced by the environment. To gather the necessary data, the team followed a cohort of babies from birth to two years of life, as part of the mini-CHILD Study, which was the pilot phase of AllerGen's national birth cohort *The Canadian Healthy Infant Longitudinal Development* (CHILD) *Study*. Newborns are much more susceptible to infectious diseases than older children and adults. Many immune factors leading to allergy and asthma seem to be set in stone, or at least in motion, in early life. However, most work on vaccines and asthma is done at the adult level and as a result, very little is known about this crucial



Kathleen Wee, PhD student, supervised by Dr. Stuart Turvey.

Research conducted in Dr. Stuart Turvey's laboratory at the Child & Family Research Institute.

developmental stage in a child's life. Specifically, there is limited research on how the immune system changes throughout infancy. Dr. Kollmann feels that filling this knowledge gap is imperative for developing new medicines. He notes that, "the only way we are going to get better vaccines or change the way we treat asthma and allergy is by studying the early-life time period."

One of the long-term goals of this project is to develop better medicines that can prevent or treat asthma and allergy related illness. One of the discoveries made is that the early immune system may potentially be driven by environmental exposures. The team believes that the process by which the immune system "learns" from the environment can be exploited to develop novel therapies. For example, a child may be treated with a vaccination in the early years to train the immune system and prevent or mitigate immune diseases, like asthma and allergies, later in life. This project has far reaching potential and through AllerGen's networked approach, international collaborations have been formed to help study environmental exposures towards realizing the long-term goal of developing vaccines and other new treatment options for allergy and asthma.

Many of the tools necessary for this project required refining and adapting to meet researchers' needs. Drs Kollmann and Turvey developed and standardized a new technique for high-throughput immune phenotyping essential to completing this project. This new technique, called Polychromatic Flow Cytometry, is quick and can be used to analyze a large number of targets using small amounts of blood. This screening process generates tremendous amounts of data that need to be analyzed in order to find the key pieces of information. By partnering with a team of global data analysis experts based in Vancouver called Visual Analytics, Drs Kollmann and Turvey hope to develop and use complex computer algorithms to detect patterns of gene expression and analyze them. Dr. Kollmann is convinced that this approach represents a groundbreaking platform that could change how data analysis is conducted in future studies.

AllerGen NCE: Developing Relationships and Translating Knowledge

Dr. Turvey believes that this project provided a strong foundation for the CHILD Study, which has commenced and has the potential to fundamentally change the way we think about asthma and allergies." Dr. Turvey notes, "we've also begun training the next generation of investigators. People coming through my lab are enthusiastic about studying asthma and allergy." Four students helped develop this project, all of which started as Masters students and have since continued their studies in a PhD program or medical school. Another four new students have since joined the project and are developing the skills to become robust researchers. Internationally, four students from South Africa have also participated in the project.

Both Drs Kollmann and Turvey believe that, with the help of AllerGen NCE, the correct steps are being taken to ensure future success. "The AllerGen NCE network has positioned our project to achieve very tangible goals for commercialization of our research results." He is confident that AllerGen NCE has contributed to the success of this project, which has brought together a wealth of expertise from all over the world. Grants from the National Institutes of Health (NIH), the Canadian Institutes of Health Research (CIHR), and AllerGen NCE have enabled collaborations with scientists from leading Canadian research universities such as the University of British Columbia, McGill and McMaster Universities, as well as other institutions in the United States, Belgium and South Africa. These relationships have been beneficial to all involved and have enabled the teams to compare the immune systems of children and adults in different environments.

Drs Kollmann and Turvey both feel that the main goal of this study is the advancement of knowledge and research that addresses needs that have not been met anywhere else in the world. They are optimistic that, over the long-term, their results can be used to develop novel methods for asthma and allergy treatments and want to ensure that the knowledge gained from their research is disseminated as quickly as possible. Dr. Turvey believes that the long-term prospects of this study are immense. The genetics have been completed and Drs Kollmann and Turvey have helped find targets for modulators of the immune system. While this work is complete, more work will be needed in the future to have an impact on policy makers and to develop a commercially viable product.

Dr. Turvey believes in the value of a multidisciplinary approach to solving the complex challenges posed by allergic disease and feels that the AllerGen network has enabled researchers from across the country and around world to collaborate. He stated that, "bringing people together is the ultimate success story." AllerGen NCE has also enabled him to work in fields that he may not have had access to in the past. "I've learned that bringing together people with different skill sets allows them to do a much better job and allows us to ask questions that I wouldn't even have thought existed because I didn't know about them. We understand little about how the body works, but with new computer models, the workings of the immune system are becoming clearer." He emphasizes that, "the more you can invest in research, the better the outcome for everybody, even if not immediate. In the long-term, research can result in new products, tools and services as well as generate improvements to health, qualify of life and productivity that benefit the entire society."

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They found that people from families with a lower level of income and education had a hyperactive immune system. This hyperactivity can lead to an increase in vulnerability to chronic respiratory diseases later in life.

Adults Raised in Poor Socioeconomic Circumstances Show Increased Susceptibility to Chronic Disease

Children raised in unfavourable social and economic environments have been shown to have increased susceptibility to chronic disease later in life. Recent findings have uncovered a link between factors such as family income, education and occupation, and susceptibility to chronic disease. This includes allergenic responses and susceptibility to respiratory and cardiovascular disease. The early part of a child's life is, therefore, considered critical in terms of optimal physical and social development.

Dr. Michael Kobor, Assistant Professor, University of British Columbia

Dr. Edith Chen, Co-Director, Psychobiology of Health Laboratory, University of British Columbia

An AllerGen NCE-funded interdisciplinary team, led by Drs Michael Kobor, Greg Miller and Edith Chen, used a combination of molecular diagnostic tools and psychological assessments to examine how a child's environment can program their immune system in a way that persists into adulthood.

Combining their expertise in molecular biology and psychology, Drs Kobor, Miller and Chen asked: how does early-life socio-economic status (SES) impact vulnerability to allergies and respiratory diseases in adulthood? The study involved examining adults that came from families that had either high- or low-SES during early-life development and comparing responses to inflammatory factors that are known to be involved in an allergic response.

Using Novel Approaches to Explain Real World Phenomena

Dr. Kobor believes that an innovative approach, combining the distinct disciplines of molecular biology and psychology, was needed in order to create this study, and that this approach was able to accomplish something that could not have been possible without the variety of expertise found within the team. "An important aspect of our study was that it was done in the human population rather than in a model organism," says Dr. Kobor.

To accomplish their goals, the research team divided 103 participants into two groups:

i) Adults that had a low-SES family during childhood, and
ii) Adults that had a high-SES family during childhood.

Early-life SES was defined by parental occupation during the first five years of life. This information was obtained through interviews with the parents of enrolled subjects.

From this data, the team examined the genes that control the immune response involved in the development of respiratory disease. They found that people from families with a lower level of income and education had a hyperactive immune system. This hyperactivity can lead to an increase in vulnerability to chronic respiratory diseases later in life. Interestingly, the team found that adult SES was not a factor in their results, suggesting that these patterns only develop during early-life and can persist into adulthood.

The major accomplishment of this team is the discovery that gene expression patterns associated with early-life SES persist in the genetic "fingerprint" of an individual for decades. Dr. Kobor says, "The interesting thing is that we have confirmed that this is something that we can measure in adults that originates in early childhood."

The Impact: Future Research and Society

During the course of this research, important and mutually beneficial partnerships were established. First, the pairing of researchers from different disciplines created an interdisciplinary team with expertise in psychology as well as molecular biology. Prior to this, the team of Drs Kobor, Miller and Chen had never collaborated together. The opportunity to ask questions that covered the molecular biology implications of the psychological impact of SES arose from this unique partnership. In addition to the multi-disciplinary networking within the team, AllerGen's investment of $231,670 in this project helped leverage support from the Human Early Learning Partnership, which provided an additional $95,000 to this initiative from the British Columbia Ministry of Children and Families.

Dr. Kobor notes that this research is innovative in many important respects, including the collaborations between researchers from different disciplines and the synergy that was created by the interdisciplinary approach. "This was truly a team effort," says Dr. Kobor, who notes that," AllerGen has made a difference in enabling interdisciplinary studies exploring the mind-body connection."

Another innovative aspect of this study was the research approach. Comparing the psychological and physiological effects of past life circumstances, using molecular biology analyses is novel. Dr. Kobor suggests that the ability to examine the SES of participants 30 to 40 years ago and compare their present day genetic *fingerprints* is something that could not have been easily accomplished by researchers within a single discipline.

The major accomplishment of this team is the discovery that gene expression patterns associated with early-life SES persist in the genetic "fingerprint" of an individual for decades. Dr. Kobor says, "The interesting thing is that we have confirmed that this is something that we can measure in adults that originates in early childhood." In addition to connecting early-life SES and health in adulthood, this research also enabled the team to leverage a substantial grant from the National Institutes of Health (NIH) for a follow-up project. The new project is designed to be larger and involve more sophisticated ways of analyzing the outcomes. A publication in the *Proceedings of the National Academy of Sciences* (PNAS), (2009), a leading global multi-disciplinary journal, also resulted from this work.

On a broader scale, this study has helped to pave the way for new scientific directions in interdisciplinary research, and develop targeted tools and new methodologies for use by other researchers.

This project has sparked interest in everyone from the academic to the non-scientific community. Through publications, presentations and lectures, the knowledge gained from this study has been widely disseminated to a variety of audiences and has garnered interest from the Canadian Institute for Advanced Research (CIFAR), which incubates ideas that aim to revolutionize the international research community and change the lives of people the world over. Dr. Kobor believes that, "perhaps people will refer to this paper as one of the first to inspire a new wave of research about the mind-body connection."

The Next Step: Translating this Knowledge to Benefit Society

The short-term goal of this team of researchers was to demonstrate a molecular link between early-life SES and vulnerability for acquiring chronic diseases later in life. Now that this link is established, the next step in this process will be exploring the connection between early life-stress and adult health with policy-makers in health care and industry. In the long-term, the discovery that molecular mechanisms programmed in early-life development persist well into adulthood can potentially lead to reduced demands on the healthcare system through the implementation of social and economic policy frameworks that address low SES for families with children.

Overall, the identification of a genetic *fingerprint* that persists from early-life into adulthood and the discovery that the immune system can be affected by early-life SES development is, perhaps, the most important tangible finding to come out of Drs Kobor, Miller and Chen's work. However, Dr. Kobor points out that there is a lot more to this study than academic findings. While the results are the most tangible achievement from this research, Dr. Kobor believes that the new relationships that arose from this collaboration are as important as any of the results achieved in the lab, and that AllerGen NCE has given him the opportunity to make these significant connections.

Success Stories

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