SPECIAL REPORT

NEW KIDS ON THE BLOCK

BY JOEL SCHLESINGER

Some of the most intriguing research currently underway in Winnipeg focuses on the hunt for better treatments for lung-related illness, such as influenza and asthma. And much of this work is being done by a new wave of scientists who are just starting their careers.

TAKE A DEEP BREATH. NOW BREATHE OUT.

It's a simple, conscious act of a bodily function that normally happens unconsciously all day, every day.

As a result, we often take breathing for granted. Our respiratory system works automatically. It provides a steady supply of oxygen to our body, and it removes carbon dioxide waste, too. We don't think about it, it just happens.

But without the ability to breathe, we can't live. Indeed, every year, more than 10,000 Canadians die from chronic respiratory illness. It is the third leading cause of death in Canada behind cardiovascular disease and cancer.

It is for that reason that the Manitoba Health Research Council has partnered with various groups, including the Manitoba Institute of Child Health, on a number of research projects related to respiratory illness. Some of these research projects aim to better understand the causes of diseases such as asthma. Others look to better treatments or possible cures. But all are designed to improve the lives of the approximately 75,000 Manitobans who suffer from chronic lung disease.

The project teams are headed by some of Manitoba's leading researchers, people who have earned a reputation for their work, at home and abroad. But these teams also include students, young researchers who are just starting to make their mark in the field of medical science.

This special report, sponsored by the Manitoba Health Research Council, highlights the some of the work being done in this province, and shines a light on some of the young researchers who are doing it.

BABY'S BREATH

New treatment guidelines may save lives

Dr. Man Yi examines smooth cells from a lung as part of her research.

IT'S EVERY PARENT'S NIGHTMARE.

A baby is born with persistent pulmonary hypertension, a condition that makes it difficult for the infant to breathe properly. Every year, as many as three per cent of babies in Canada are born with this condition. About a third of these infants will die.

"It's not common, but when it happens it is severe," says Dr. Man Yi, a researcher at the Department of Pediatrics and Child Health at the University of Manitoba's Faculty of Medicine.

Persistent pulmonary hypertension, or PPHN, usually occurs when a newborn's lungs remain full of fluid, making it difficult for them to breathe.

As Yi explains, when babies are still in the womb, their lungs are filled with fluid, and the blood pressure on the right side of the heart, which pumps blood to the lungs, is very high. In the hours right before birth and immediately afterward, the fluid is absorbed by the baby's body and the blood pressure on the right side of the heart normally drops.

But due to infection or reasons still unknown, some babies are born with fluid still in the lungs. As a result, the heart struggles to push the blood into the lungs, where it is oxygenated before flowing to the rest of the body. It's not unlike trying to pump air into an already inflated ball.

When this happens, the baby's skin turns blue because not enough blood is able to get into the lungs to be oxygenated and then returned to the heart to be pumped out to feed the rest of the body. "If the condition lasts a long time, it can have an effect not only on the lungs and the heart, but also on other organs like the brain."

The most common treatment for babies with this condition is to provide oxygen, but no guidelines exist on how much oxygen should be given. Too little can starve the baby's organs of oxygen, but too much can be equally damaging.

"There are really no guidelines for how much oxygen we should supply to the baby and how fast we should increase oxygen requirements," she says. "If we're using too much, it may…worsen the baby's condition."

Yi's goal is to establish guidelines to ensure babies receive the best treatment.

Currently, she is focusing on the role played by smooth muscle cells in the pulmonary artery. When these cells are stressed and constrict, they reduce the blood supply to the lungs. As part of her research, Yi has been working with smooth muscle cells from the lungs of piglets, treating them with different levels of oxygen and measuring the effects.

One of the concerns of doctors has been that too much oxygen might actually harm the cells, but her research so far has found that doesn't happen. She has found, however, that high levels of oxygen cause the smooth muscle cells to proliferate – a condition unique to newborns because their bodies are already growing rapidly at a cellular level. This is a normal condition for growth in early life as long as cells proliferate in the right areas.

When smooth muscle cells proliferate along the arterial walls, it can lead to potential long-term problems for babies who survive PPHN because the build-up creates an unnatural condition called "remodelling," in which the pulmonary artery's smooth muscle lining thickens and become less elastic. As a result, the child's main artery feeding the lungs is narrowed permanently. Blood flow to the lungs is reduced, increasing blood pressure and potentially leading to lifelong heart problems, she says.

If Yi's research can find the right balance of oxygen – not too much or too little – she says they can develop enhanced treatment guidelines that will improve outcomes for the babies who survive PPHN. The guidelines might also help save the lives of the one-third of newborns with the PPHN for whom the condition would have otherwise proven fatal.

FLU FIGHT

Researcher hopes to deliver the knock-out punch to influenza

Andrea Kroeker uses a microscope to examine proteins involved in virus replication.

Influenza poses a serious health risk.

Every year, the flu virus is responsible for infecting as much as 15 per cent of the Canadian population. Over the course of a typical flu season, the virus will be responsible for as many as 20,000 hospitalizations and cause between 2,000 and 8,000 deaths.

And while influenza can attack anyone, the people most vulnerable to infection tend to be the estimated three million Canadians who suffer from asthma and other chronic lung diseases. These individuals experience more inflammation in their lungs, more difficulty breathing, and they are more likely to end up in hospital.

It is with these facts in mind, that a team of researchers at the University of Manitoba is looking for ways to combat the virus. A key member of the team is Andrea Kroeker, a doctoral student in the Department of Physiology at the U of M's Faculty of Medicine.

As Kroeker explains, once the flu virus infects the body, it triggers a response from the immune system, which tries to destroy the virus before it can cause lung damage and lead to difficulty breathing.

But the flu virus doesn't play fair. Once a viral particle infects a cell, it uses the cell's proteins and energy to reproduce. New viral particles are then released from the cell, and spread to other cells to do the process all over again.

Kroeker's job is to identify cell proteins that are involved in the virus replication process. Once that is done, the question will be whether these proteins can be blocked, thereby stopping the influenza infection in its tracks. "A virus evolves to use its host," says Kroeker. "It can adapt to your immune response and can sometimes replicate despite this response."

If Kroeker and her team can isolate the proteins necessary for viral replication, it opens the door to better, targeted treatment, says Kroeker. "If you can prevent the virus from manipulating the host cell, essentially it can't replicate, and then you prevent infection."

Developing new ways to battle infections often involves creating a new drug. But that won't necessarily happen in this case. Instead, the research team is investigating a drug already on the market that can do the job.

"If we wanted to start from scratch along the lines of 'I want to block this specific protein that no one's ever done before,' it would probably take a long time," explains Kroeker. "But if you could find a drug on the market that's already being used to block that protein, but you've never thought of using it for influenza and never tested it for that purpose, it's a quicker route."

One of the best known examples of this pharmaceutical treatment crossover is Viagra – also known as sildenafil citrate. It was used to treat high blood pressure and angina before it was prescribed to help men with erectile dysfunction.

"Finding new uses for drugs already on the market is not common but can be extremely useful," says Kroeker.

UNDERSTANDING ASTHMA

Researcher aims to help teens outgrow lung condition

Jennifer Protudjer surveyed a group of children as part of her asthma research project.

Is there a link between screen time and asthma in children and teens?

Jennifer Protudjer believes there is, and her research on the subject may help young people learn how to better manage their conditions as they get older.

Asthma today affects about 12 per cent of Canadian children, which is nearly twice the rate of a few decades ago, says Protudjer, a doctoral candidate in the Department of Applied Health Sciences at the University of Manitoba.

The causes of asthma are many and varied. But what puzzles scientists is why some children will "grow out of" their condition, while others don't.

One leading suspect is obesity. Today, it is estimated that one in three Canadian children are obese or overweight. Moreover, the numbers of overweight children and children with asthma appear to be rising at roughly the same rates over time.

Another factor in the equation is how asthma affects children as they grow up. "With asthma, there's something called the gender shift, where it switches from having a higher prevalence in boys before puberty to a higher prevalence in girls from puberty onward," says Protudjer. "This has been attributed to a number of things, not the least of which is that when girls go through puberty they gain more adipose tissue (body fat) than boys. Boys become leaner and more muscular, whereas girls – for biological reasons – will develop a higher proportion of body fat relative to their total body mass." This is where Protudjer's study comes into play.

She surveyed a group of children with asthma between eight and 10 years of age. The children were evaluated again at 12 to 13 years of age to see if their condition persisted during early puberty, if any youth "grew out" of their asthma, or if any new cases of asthma developed.

Many studies have found an association between obesity and persistent asthma in teen girls and not teen boys, as did Protudjer's. "It tells us that girls who are overweight are more likely to keep their asthma through life as compared to girls who are within a normal weight range."

She says it's likely there is more than one reason for this association. For example, diets rich in saturated fatty foods and low in fruits and vegetables may promote inflammation, whereas diets rich in fresh vegetables and fruit are thought to reduce inflammation. Asthma attacks are triggered by inflammation.

Researchers also suspect that a lack of exercise could play a role. Protudjer's study didn't find that association, but she did find another possible factor. "What we were able to show is children with higher rates of screen time – be it television, computers or cell phones – were nearly twice as likely to have asthma at eight to 10 or to have asthma between 12 to 13."

The research, says Protudjer, is observational and was not designed to explain the reasons behind this association. But some scientists speculate that children take shallower breaths while doing sedentary activities like watching TV. And they suspect that long, repeated periods of shallow breathing may cause changes in the airway.

Protudjer's work did not stop there. She also spent time talking with teens about how they spent their time. They talked about school, the trials and tribulations of being a teen and how they like to spend their free time – often in front of a computer or television.

"We didn't just want to report on how children with higher rates of screen time are more likely to develop asthma," she explains. "We wanted a better sense of how youth with asthma perceive screen time, and, naturally, we found they view screen time as being very important."

Protudjer hopes this nuanced understanding of teens will lead to more effective guidelines that could reduce asthma rates in at-risk children as they enter their teenage years.

"Rather than telling them to not engage in that at all, we can tell them that we understand screen time is important to them, but for the reasons that we talked about, they are encouraged not to have high levels of screen time," she says.

"We're hoping that it will inform health care in a modest way and improve care for children and teens."

QUEST FOR A CURE

Researcher aims to redefine asthma therapy

Dr. Kanami Orihara is focusing on the causes of airway remodelling as part of her research.

When we think of treatments for asthma, the puffer often comes to mind.

It's the device asthma sufferers use to inhale medications, which reduce airway inflammation that narrows the bronchial tubes. This allows the individual to breathe normally following an asthma attack.

While effective, inhalers have never been useful in treating the underlying condition for those with persistent asthma because of structural changes within the airway, called airway remodelling.

Dr. Kanami Orihara, a researcher in the Department of Immunology at the University of Manitoba's Faculty of Medicine, wants to change that.

"When airway remodelling occurs, these structural changes often lead to reduced lung function or decreased air movement into and out of the lungs," explains Orihara, who moved from Japan to Winnipeg to carry out post-doctoral research with Dr. Redwan Moqbel, who is head of the Immunology Department.

So while inhalers can be used to treat inflammation, a person's asthma condition can continue to worsen because of the structural remodelling taking place in the the cells lining the airways.

Over time, the remodelled airway becomes increasingly narrow and inelastic. Breathing becomes more difficult and attacks, brought on by irritants or illnesses that trigger inflammation, are more severe. In fact, most asthma experts believe that airway remodelling leads to persistent asthma, making it a lifelong condition.

Orihara's research is concerned with the causes of airway remodelling at the molecular level. Her work focuses on two molecules: glutamate, a well-known neurotransmitter with an uncertain role within the immune system, and amphiregulin, a protein molecule secreted from cells that line the airways.

"We believe this molecule (amphiregulin) is a key factor in airway remodelling," she says. "We know that amphiregulin does not respond to corticosteroid treatment; that's why we're targeting this molecule as a possible new therapeutic option for asthma sufferers."

But it's not just amphiregulin itself that Orihara and other researchers suspect to be the root cause of the remodelling. She is exploring whether a high level of glutamate in the immune system is responsible for triggering an increase in amphiregulin, which in turn spurs the remodelling of the cells.

"Our lab believes that glutamate may contribute to the severity of asthma symptoms and may be responsible for an earlier onset," she says.

So far, she has found that treating cells with glutamate in conditions that mimic asthma increases the level of amphiregulin. The next step of the study, now underway, will focus on comparing samples from mild and severe asthma patients.

If Orihara can demonstrate the relationship between these molecules, she says it could lead to more effective treatments and possibly something even more helpful down the road.

"The goal is to treat or prevent the remodelling," she says, "but it could also be used to develop medication to prevent asthma."

THE POWER OF 'D'

Elusive vitamin may help ease lung infections

Natascha Clark treats blood cells with bacteria as part of her research.

While the value of taking vitamin supplements has often been a subject of debate among those in the medical community, few would argue against the benefits of Vitamin D pills.

Of all the minerals and vitamins the body needs, Vitamin D is the hardest to get into our diets because it is only found in significant amounts in some types of fish.

Indeed, the easiest way to get a dose of Vitamin D is through exposure to the sun. But even in sun-drenched places such as Florida, Vitamin D deficiencies are commonplace.

This poses a serious problem because a lack of Vitamin D has been linked to a number of health problems, including cancer, diabetes, heart disease and asthma.

Now, Natascha Clark, a master's student in the Department of Immunology at the University of Manitoba's Faculty of Medicine, is trying to better understand if Vitamin D can play a role in helping to prevent asthma exacerbations or the infections that sometimes cause them to occur.

Clark says Vitamin D is important because it plays a role in helping to regulate the body's immune system. Basically, it eases inflammation, one of the most damaging effects of infection to the body. "Vitamin D is already used as a therapy for people with Crohn's disease, and it has the potential for use to treat diabetes, cancer and a whole bunch of different conditions," she says.

Most medical experts recommend people get their Vitamin D from supplements rather than exposure to the sun because too much of the latter has been linked to skin cancer. But supplements contain inactive Vitamin D. And it's believed that people with certain inflammatory diseases, like asthma or Crohn's, might not have enough of the enzymes needed to break down the inactive form of the vitamin so it can be used by the body.

As part of her research, Clark has been working with the active form of Vitamin D to determine whether it's effective in regulating the immune system's response to a condition associated with childhood asthma known as respiratory syncytial virus (RSV).

Vitamin D is known to down-regulate the immune system's overly exuberant response to bacterial infections and to promote production of certain responses that are of benefit, she says. This reduces the symptoms of inflammation and the severity of the infection. But it's yet to be proven to have the same effect on viral infections.

The work involves treating white blood cells, called peripheral blood mononuclear cells, with either bacteria or the RSV virus and then treating them with Vitamin D.

"I'm comparing how Vitamin D responds to bacterial and viral infections," says Clark, who, along with her colleagues Drs. Allan Becker and Kent Hayglass, is part of a national consortium studying the development of immunity in babies, specifically factors that may contribute to the development of allergies and asthma. "The reason I am looking at viruses is because people with lung diseases like asthma tend to get a lot more, and more serious, viral infections."

So far, results have shown Vitamin D does indeed reduce the inflammatory response in cells infected with bacteria, but she found it had no detectable effect in regulating responses to viral infections. How Vitamin D helps one major family of responses and not another is a key question for her future research. Now her study will compare responses of non-allergic people with those of severe and mild asthmatics to determine whether the effects of Vitamin D are different among the three groups.