SPECIAL REPORT

Quest for

Manitoba is an important centre for cancer research, thanks in part to projects funded by the Manitoba Health Research Council and CancerCare Manitoba Foundation under a program that supports world-class graduate, doctoral and post-doctoral students

By Joel Schlesinger

The fight against cancer is a never-ending series of battles on a global scale. And although recent studies suggest more people are winning their personal battles against this disease, it remains the No. 1 cause of death among Canadians, claiming the lives of 75,000 people last year alone.

As a result, researchers around the world are working to crack cancer's secrets in a bid to enhance treatments and perhaps come up with a cure.

Some of this important work is taking place right here in Manitoba, according to Dr. Spencer Gibson, Director of Research for CancerCare Manitoba and Manitoba Research Chair at the Department of Biochemistry and Medical Genetics at the University of Manitoba's Faculty of Medicine.

"It's research that will help us understand why cancer is a killer, why it keeps coming back, how we can develop better therapies to target cancer and not healthy cells, and how we can make existing therapies better," Gibson says of the work taking place in this province.

Four graduate and post-doctoral students at the University of Manitoba are playing an integral role in the ongoing effort to eradicate cancer.

Funded jointly by the Manitoba Health Research Council (MHRC) and CancerCare Manitoba Foundation through the MHRC Co-ordinated Trainee Competition, they are able to carry out research that may someday lead to new treatments and maybe even a cure.

Since 2008, the MHRC Co-ordinated Trainee Competition has provided essential funding to world-class graduate, doctoral and post-doctoral students to pursue groundbreaking research on cancer.

"The funding that we give here is to support the trainee in recognizing their expertise, allowing them to succeed," says Gibson. "It focuses on the trainees' success so that they can go on and have an impact on the understanding and treatment of cancer and then be future leaders in cancer research to the various areas that they go on to in the future."

This special report, sponsored by the Manitoba Health Research Council, highlights some of their work.

MHRC-CCMB team, from left: Dr. Spencer Gibson, Dr. Shannon Healy, Dr. Sandrine Lafarge, Dilshad Khan, and Heather Champion.

the cure

UNLOCKING CANCER'S SECRETS

The genesis of any cancer starts in the heart of a cell, or its nucleus. For decades, scientists have known cancer is caused when a cell divides uncontrollably, invading new cells, attaching to organs, entering the bloodstream and spreading to the rest of the body. This is what makes cancer so deadly.

But the biochemical mechanisms that drive this process have largely remained a mystery. For a long time, researchers thought cancer got its start from a genetic mutation within a cell. But increasingly, scientists are focused on a new field of science that marries the fields of biochemistry and genetics.

Called epigenetics, this scientific discipline looks at how genes within a cell can be expressed, altered and even muted in a way that changes the way that cell divides, builds new tissue, and carries out other activities to sustain itself.

Dr. Shannon Healy, a post-doctoral fellow and MHRC/CancerCare Manitoba Foundation partnership trainee, is currently conducting research in this area. Specifically, she is looking into how certain molecules affect proteins known as histones.

Essentially, histones are involved in packaging the DNA very tightly in the nucleus."The most basic way to look at a histone is as a spool of thread," explains Healy. "So, DNA – the blueprint for life – is the thread and histones are the spool."

Previously, it was believed that histones were limited to the role of packaging. But research has revealed that they have a much larger role to play in directing how DNA will determine whether a particular genetic trait is expressed – or not.

Like DNA, histones can by modified, and a number of complex molecules – methyl, acetyl and phosphoryl groups – can affect how histones carry out their role in helping DNA direct the chemistry of life.

"Each of these compounds – methyl, acetyl and phosphoryl groups – can bind to a specific location on the histone, which leads to different outcomes," she says. "That might be turning a DNA expression up very strongly or it could silence it."

With cancer, genetic expressions are turned on or off in a cell when they aren't supposed to be activated or silenced.

"What we know is it's not necessarily a mutation in the DNA sequence that is causing the cancer, but instead it's an alteration in the expression of genes within a cell."

Healy has been studying one modification in particular: phosphorylation of histones. She has been looking at how the phosphoryl molecule attaches to a site on a histone and then potentially turns the once-normal cell into a cancerous one.

This process is believed to be caused by an enzyme called MSK. Like all enzymes, MSK is a product of the body's chemistry set. "It's a protein that resides in the cell's nucleus, and catalyzes the attachment of phosphates on many different proteins, including histones," Healy says. "That's its job in life."

MSK allows for a histone to be phosphorylated. In other words, that phosphoryl molecule binds to a part of histone, which then turns on expression of various genes.

"MSK should be intermittently active, but in cancer, it's on all the time," says Healy. "MSK will phosphorylate the system more than it should, and this will turn on a large number of genes, and these genes are involved in telling a cell to divide or even to become invasive." And those are the two properties ubiquitous to all cancer. "The cells are able to move around by squeezing through other cells, entering the bloodstream and metastasizing or attaching to other organs," she says. "These are the programs that are set into place."

Healy and others are trying to understand this mechanism and determine how new therapies might be developed to block histone phosphorylation. "Our main objective is to describe what's going on as a consequence of this phosphorylation event," she says.

What Healy and her colleagues uncover here in Winnipeg may not directly lead to a new treatment. But it is a stepping stone. "We are working with other groups that are interested in this mechanism, and they are in turn developing new drugs," she says. "We are just one cog in the wheel toward prevention and/or treatment."

KILLING CANCER

Can cancer be tricked into killing itself, or at least making itself more vulnerable to treatments such as chemotherapy?

That's the question that many scientists around the world are asking as they attempt to unravel the mysteries surrounding how this disease functions.

Here in Winnipeg, researcher Dilshad Khan believes the answer may be related to the intricate machinations that take place within the nucleus of a cell, which contains all the materials needed to create or maintain life.

Specifically, Khan is looking into how changes in ribonucleic acid (RNA), through a process called splicing, affects the development of MCL1, a protein linked to cancer.

First some background.

DNA is the blueprint for life and essentially contains all the instructions needed for the cells to divide and grow.

RNA, meanwhile, acts as a kind of biochemical contractor for DNA. So, for example, if the DNA within a cell contains instructions for a particular protein, the RNA will retrieve the information and use it to create the protein.

But things don't always go as planned.

Each strand of RNA is made of components known as exons and introns. Exons contain information that influences RNA behaviour. The introns do not and must be removed before RNA can carry out its function. This process of re-organization is known as splicing, and it can change the way RNA interprets the information gleaned from DNA. And that can alter the makeup of the protein the RNA is creating.

"Through splicing, the non-coding information is cut and the protein-coding information is pasted together to produce functional proteins," explains Khan, a doctoral candidate in the Department of Biochemistry and Medical Genetics at the University of Manitoba. Through various combinations of cutting and pasting, a large variety of proteins can be created." This is where MCL1 comes into play.

Depending on how RNA behaves, it will create either a long-form variant of the MCL1 protein (known as a long isoform) or a short-form version (known as a short isoform). In a cancer cell, the long isoform of MCL1 helps the cell to thrive. But the short isoform actually weakens the cancer cell. In theory, a large amount of short isoform MCL1 could cause the cancer cell to "kill itself." But the reality is the RNA will only produce enough short isoform to weaken the cell and make it more vulnerable to cancer treatments, such as chemotherapy.

Part of Khan's research also involves investigating how drugs that inhibit HDAC proteins can be enlisted in the effort to weaken cancer cells. The HDAC protein is part of a complex that instructs the cell on RNA splicing. So, for example, it may influence the RNA to create a long isoform of MCL1, which would have the effect of supporting the cancer cell. But by using certain inhibitors, the RNA could be instructed to create a short isoform version of MCL1, thereby helping to weaken the cancer cell, leading to death.

Scientists have long known that HDAC inhibitors can cause an increase in production of short isoform MCL1. But the exact mechanism – the biochemistry – is poorly understood. Khan's work aims to shed light on these processes. "We are trying to figure out what are the biochemical mechanisms that produce the short isoform rather than the long one in response to HDAC inhibitors," explains Khan, adding, "We have some interesting results."

Needless to say, Khan's work has tremendous implications.

"If the cancer cell's own machinery can be tricked to produce its own lethal protein though splicing, this would provide a means for specific targeting of the cancer cell without affecting the normal cells of the body," she says.

Dr. Spencer Gibson, Director of Research for CancerCare Manitoba, agrees. Current chemotherapies are proven to be effective in treating cancer, but they can also cause serious damage to the body. By altering the mechanisms of survival, such as through splicing of MCL1, cancer cells can be killed and perhaps allow less toxic doses of chemotherapy to be effective at killing cancer.

"The potential benefit (of Khan's research) is this type of treatment would not have the toxic side-effects that you would see with typical chemotherapy," says Gibson.

TARGETING THE TUMOUR

Radiation therapy is one of three most common treatments for cancer, along with chemotherapy and surgery. At its most basic, radiotherapy involves killing cancer cells using a high-energy beam of radiation. If all the malignant cells are killed, the patient is cancer-free.

There is only one main drawback with radiation: using it to destroy cancer cells can often kill or damage other healthy cells. In some cases healthy cells damaged by radiation can become cancerous decades later as a result of the exposure.

"The ideal situation in radiotherapy is you deliver a uniform dose to the target and absolutely no dose anywhere else, but that's not physically possible because the radiation has to enter the patient in order to get to the tumour," says Heather Champion, a master's student in medical physics, part of the Division of Medical Physics at CancerCare Manitoba and the Department of Physics & Astronomy at the University of Manitoba.

Advances in diagnostics have made radiotherapy increasingly effective. CT scans of patients provide cancer specialists and other clinicians with a precise map of the size, shape and location of a cancerous tumour. Treatment planning specialists are adept in selecting the best beam orientations and some other parameters that must be put into a treatment planning algorithm that determines how to deliver a dose of radiation while doing as little damage as possible to healthy tissue.

In an optimization problem like this, a mathematically superior solution is referred to as a "Pareto" optimal solution.

But finding an optimal solution is time-consuming. It can take anywhere from two hours to five days. And, more often than not, there are many good solutions. "There are many different options available with different trade-offs involved in treating with radiotherapy," Champion says.

For instance, in order to provide adequate tumour coverage, some critical structures may receive a dose of radiation. Every organ has a different radiation tolerance, and different associated complications (which have differing implications for the patient's quality of life in the future).

To overcome those kinds of dilemmas, Champion has been working with an interdisciplinary team, which includes astrophysicist Dr. Jason Fiege and radiotherapy physicist Dr. Boyd McCurdy, to develop treatment planning software that will generate Pareto optimal solutions, automatically providing clinicians with the best trade-off options available.

Aptly named PARETO – short for 'Pareto-Aware Radiotherapy Evolutionary Treatment Optimization' – the software crunches the data and variables, like beam directions and intensities, to provide clinicians with a well-rounded set of viable options for radiation treatment.

"The clinician says, 'I need to deliver this dose to the tumour without affecting normal organ function. How do I do that?'" Champion says. "Then our program will give them many options of how to do that while minimizing the dose to the critical structures below tolerance." This is in contrast to the current standard approach where a human technician develops a treatment plan option one solution at a time.

The software's magic is a genetic algorithm that finds the best treatment options. "It's a computer algorithm that is based on the principles of biological evolution," she says. "Each solution will have a measure of its success in the different objectives." These are called the "fitness values," which, taken together, measure a solution's benefits versus its negative effects. "These are basically mathematical functions that describe how well each solution achieves the different objectives."

So far, tests using data from patients who have already undergone treatment have been successful. The software has produced treatment plans of superior quality to ones generated by other more limited software that provides only one plan for a given set of inputs. Further testing is planned, including providing treatment options for patients who have yet to receive radiation therapy.

If successful, Champion says the software will likely increase the efficiency of treatment while reducing waiting times because clinicians will no longer have to spend a lot of "hands-on" time with treatment-planning software.

"Currently, it takes a few hours to generate a database of solutions for a patient using the software, and that's time where the clinicians don't have to be monitoring the system," she says. "Otherwise, they would be using a manual approach where a human technician would change the beam angles and other parameters, and they would keep going until they finally find a solution, which can take days for difficult cases."

KICKING CANCER OUT OF ITS HOME

Smoking, drinking and eating poorly are well-known risk factors for cancer. But not everyone who smokes gets the disease. Nor does being a heavy drinker or a lover of fast food seal one's fate to the disease.

Why one person gets cancer, while another who lives the same lifestyle doesn't, has long been a focus of researchers.

The genes we inherit from family members play their role, but researchers are also increasingly interested in how our individual biochemical makeup can create an environment in which the disease thrives or dies, explains Dr. Sandrine Lafarge, a post-doctoral fellow with ties to the Department of Immunology and the Manitoba Institute of Cell Biology.

Lafarge's area of study has focused on one type of cancer in particular: chronic lymphocytic leukemia (CLL). "This cancer mostly affects adults around age 70; it is rarely seen in patients under age 50," she says.

The prognosis for the disease falls into two categories. Some people can live relatively normal lives and do not receive treatment. For others, the disease is more aggressive. "They require a lot of chemotherapy," she says. "They tend to have really poor outcomes."

Lafarge has zeroed in on a molecule called ZAP70 (zeta-chain-associated protein kinase 70). It is not normally found in the healthy counterpart of this type of cancer cell. She says it is found in higher concentrations in patients with the more aggressive form of the disease, and it is suspected to play a role in allowing cancer to adapt to the environments where it can grow.

With CLL, this cancer of the white blood cells grows in the bone marrow where normal blood cells – red and white – are produced, and in the lymph nodes and spleen. In order to survive and multiply, the cancer cells need an accommodating micro-environment in these areas.

In patients with the aggressive disease, it is theorized that ZAP70 provides cancer cells with the ability to find "home sweet home" in their body.

"These cells find a supporting micro-environment where they are protected from the chemotherapy drugs and they can proliferate more easily," she says. "When someone has CLL, they accumulate leukemic cells in the blood, the lymph nodes, the spleen and the bone marrow, and they can survive a long time in these structures."

The cancer cells grow in the marrow, spleen and lymph nodes unimpeded until they take up all the room to the point where these structures can no longer carry out their normal functions. "The disease progresses to the point where the cancer cells take over all the bone marrow, for example, so there's no room left for the marrow to produce normal red and white blood cells." And without red blood cells, which deliver oxygen, and white blood cells, which fight infections, the patient will die.

Lafarge's research is premised on the theory that cancer cells with high amounts of ZAP70 have the ability to attach themselves within these structures more easily than those cancer cells with lower levels.

It has been known for some time that CLL patients that express a lot of ZAP70 have a worse prognosis. According to Lafarge's research, this seems to be because their cancer cells are more apt at finding and staying in supportive niches in the body; adhering to structures in the bone marrow, spleen and lymph nodes.

But that is just half of the research battle. The main goal is to map ZAP70's precise role in promoting cancer growth in these micro-environments. Once completed, this research could form the basis for developing targeted treatments that exploit the differences in the two subtypes of the disease and interfere with the specific mechanisms that ZAP70-expressing cancer cells use to stay stuck in their niche. "We hope to use the information to develop new therapies that could be used to treat the more aggressive type of disease."

Although Lafarge's work focuses on a specific type of leukemia, it may serve as a foundation for research into treatment of other aggressive cancers too. "This is a very new and exciting area," she says. "If you can alter the environment of a cancer cell, you can alter its ability to survive."