Ottawa Health Research Institute
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Research Triumphs

Winter / Spring 2007

OHRI discoveries in the fight against:

- **Blood clots**
- **Kidney disease**
- **Cancer**
- **Diabetes**
- **Muscular dystrophy**

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About the cover: Dr. Marc Rodger (left) and Dr. Alejandro Lazo-Langner (right) with a blood vessel angiogram in the background (see page 2 for full story). Angiogram obtained from Wikipedia (http://en.wikipedia.org/wiki/Image:Cerebral_angiography%2C_arteria_vertebralis_sinister_injection.JPG) and reproduced in accordance with Image Use Policy.

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A personal reflection on 11 years at the OHRI

A message from retiring CEO Dr. Ronald Worton

In January 1996, just 11 years ago, I was offered the position of Director of Research at the (then) Ottawa General Hospital. The details were finalized on a Tuesday, the written offer received on Thursday and my acceptance faxed on Friday. We flew to Ottawa on Saturday, put in an offer on a house, had it accepted Sunday, and on Monday I announced to the Hospital for Sick Children in Toronto that I would be leaving at the end of June. That is how certain I was that the move to Ottawa was the right move at the right time. After 25 great years at "SickKids" I was excited at the prospect of creating a new research institute at "the General" in Ottawa.

I began my new position on the fourth floor of the cancer centre at the General on August 1, 1996. There were two of us – Rose Moore, my new executive assistant, and me. Next to arrive was Catherine Duff who had worked with me at SickKids for several years and who was instrumental in the identification of the gene responsible for Duchenne muscular dystrophy 10 years earlier (see page 6 story). She came as Lab Manager and helped to set up all the labs, order equipment, and coordinate the move of my own lab from Toronto. In the meantime I poured over an enormous stack of CVs, among them Drs. Rudnicki, Kothary, Bulman, Megeney, Wallace and Picketts.

That fall I had a visit from Dr. David Grimes, Director of the Loeb Health Research Institute at "the Civic", who welcomed me to Ottawa and invited me to attend a meeting with "The Loeb" Scientific Advisory Committee chaired by Dr. Lou Siminovitch, who incidentally, had recruited me to SickKids 25 years earlier. At that meeting I met Robert Hanlon and several scientists from The Loeb for the first time. At the time there were clear signs that the General and the Civic were heading for merger and I began to think about the day when the institutes would inevitably become one.

In 1998 the hospitals merged and the Ottawa General Hospital Research Institute was left without an Ottawa General Hospital. Notionally we became The Ottawa Hospital Research Institute but this was unsatisfactory for all since we were just one of two institutes in The Ottawa Hospital. As The Loeb continued to grow and mature under the direction of Dr. Michel Chrétien, who had arrived in January 1998, the "Institute at the General" began to take shape with scientists in the Neuroscience Research Institute, the University of Ottawa Eye Institute and the Cancer Research group all becoming full or associate members. In early 2000, planning for the full institute merger began, strongly supported by The Ottawa Hospital CEO, David Levine and uOttawa Dean of Medicine, Dr. Peter Walker. An interim Board chaired by uOttawa VP Research, Dr. Howard Alper guided the merger, with Robert Hanlon leading the administrative integration. I was appointed CEO and Scientific Director of the new Institute and VP Research of The Ottawa Hospital starting April 1, 2001, the day we became "the OHRI" and the day before my 59th birthday.

> ***"And now, 20 years after Dr. Grimes took the first steps to create a research institute at the Civic and 11 years after I moved onto an empty floor at the General, here we are with 105 scientists, close to 300 clinical investigators, over 275 graduate students and research fellows and a total staff of over 1,200 people who call the OHRI home."***

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Blood clots pose a great risk to people on dialysis, but new research is providing hope

Every day, your kidneys filter about 150 litres of blood. When kidneys fail and a transplant is not possible, the only option is dialysis, a procedure in which blood is artificially filtered with a machine several times a week. Dialysis has saved millions of lives, but the procedure has complications, and more than half of patients will be hospitalized each year. One of the most common causes of hospitalization is a blood clot blocking the vein used for dialysis (called dialysis access failure or thrombosis).

It has been known for some time that certain people have a greater risk of developing dialysis access failure, but new research in Ottawa has revealed what may be the most potent genetic risk factor yet.

Drs. Alejandro Lazo-Langner, Marc Rodger, Phil Wells, Nancy Carson, and Greg Knoll collaborated in a project that examined the DNA of 416 dialysis patients. They found that those who had a particular combination of mutations in two genes (TGF-1 and PAI-1) were nearly twenty fold more likely to suffer dialysis access failure. This gene combination occurred in 2-4 per cent of the patients.

Thrombosis Research Group members

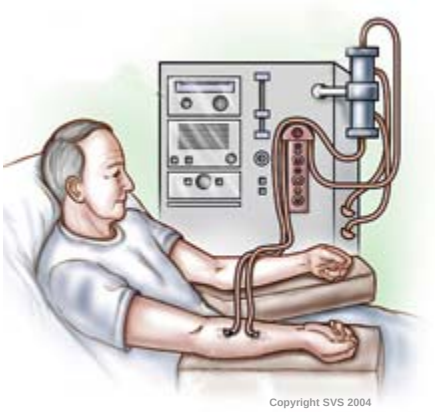
Studies in cell cultures had previously indicated that the protein products of these two genes interacted, with TGF-1 increasing the amount of PAI-1. But this was the first study to test the result of this interaction in patients. The discovery was published in the prestigious scientific journal *Blood.*

"If this result holds up in further studies, it would be the most potent risk factor ever discovered for dialysis access failure," said Dr. Lazo-Langner. "It is particularly exciting because if this gene combination is involved in blood clotting in dialysis patients, it might also be involved in blood clotting in stroke, heart attack, and other conditions, so the potential is enormous."

In theory, drugs might be designed that could prevent the interaction of these two proteins and thus prevent the formation of dangerous blood clots. The discovery could also be used to develop a diagnostic test to identify those at greatest risk.

This is just one of a number of influential studies done by the Thrombosis Research Group, affiliated with the Ottawa Health Research Institute, The Ottawa Hospital, and the University of Ottawa.

"I came to Canada and to Ottawa because the work here is highly regarded, the people are very welcoming, and the environment is very supportive of research," said Dr. Lazo-Langner, who came from Mexico in 2004 to do his Master's degree in Epidemiology as well as a clinical and research fellowship in thrombosis. "As a whole, I'd say the most influential work in the diagnosis and treatment of thrombosis comes from Canada and I wanted to learn from the best," he adds.



A dialysis machine filters blood.
Image reproduced with permission from the Society for Vascular Surgery (www.VascularWeb.org).

> ***"If this result holds up in further studies, it would be the most potent risk factor ever discovered for dialysis access failure."***
>
> Dr. Alejandro Lazo-Langner

His mentor, Dr. Marc Rodger, is the leader of the thrombosis program.

"Over the last 15 years, our understanding of blood clotting has dramatically improved, and so has medical care for clotting conditions," he said. "This study opens up a whole new avenue of research, and although not all avenues lead to advancements in care, some of them will, so we have to keep at it."

Evading the immune system could improve experimental cancer therapy

Viruses are the ultimate parasites, invading our cells and hijacking our molecular machinery to make thousands of copies of themselves while making us sick. But in a strange way, viruses have also turned out to be extremely useful to humans. One of most powerful examples of this may turn out to be "oncolytic" viruses that are particularly good at replicating in and destroying cancer cells. While the theory of oncolytic viruses has been around for some time, there has been a resurgence of interest in recent years as scientists have discovered new oncolytic viruses and engineered them to be better and safer.

Over the last six years, Dr. John Bell and his team at the Centre for Cancer Therapeutics have identified a number of oncolytic viruses and pioneered their development. They have been involved in promising clinical studies in cancer patients, but they are also continuing their work in mice to try to understand how oncolytic therapy works and how it could be improved. Their latest research, published in the journal *Molecular Therapy*, addresses one of the biggest challenges in the field: how to deliver a virus to tumours in the face of an immune response that has evolved to recognize and destroy foreign invaders.

Anthony Power, a PhD student in Dr. Bell's lab, spearheaded this project.

> ***"These results are exciting because we think this strategy could be adapted for use in patients quite easily."***
>
> Anthony Power, PhD student

"The body begins to produce antibodies to a virus within days of exposure, and within a few weeks there are enough antibodies in the blood to completely neutralize further doses of that virus," says Power. "Our research suggests that we need multiple doses of virus to get rid of most tumours, so this is a problem we're trying to get around."

One way to get around the problem is to avoid antibodies in the blood stream by injecting virus directly into tumours. This approach poses its own problems though, because many tumours are difficult to reach, and small undetected tumours would be missed.

In the current study, Power and his colleagues developed and tested an approach they call the "Trojan horse". It involves infecting "carrier cells" with virus in the test tube and treating mice with these virus-carrying cells instead of naked virus. The idea is that the carrier cells would shield the virus from antibodies in the blood and thus allow it to reach tumours. Within hours, carrier cells that lodge in or near a tumour would produce hundreds of virus particles that could go on to infect and destroy the cancer.

Dr. John Bell (left) and PhD student Anthony Power (right)
Photo by Wayne Cuddington, The Ottawa Citizen (reproduced with permission).

Using a variety of techniques, including sophisticated imaging, Power found that the Trojan horse approach could indeed help the virus evade antibodies, reach tumours, and replicate in them. When comparing the Trojan horse and the naked virus head to head, he also found that the Trojan horse virus was much better at eliminating lung tumours from mice.

"We've thought of a number of strategies to help oncolytic viruses evade the antibody response, but this one is probably the simplest and the furthest along," says Power. "These results are exciting because we think this strategy could be adapted for use in patients quite easily."

Dr. Bell and his team are part of the Ottawa Health Research Institute, an affiliated institute of the University of Ottawa and the research arm of The Ottawa Hospital. They recently partnered with oncolytic virus researchers in San Francisco to create a company to bring their discoveries through the clinical testing phase in patients. The company, called Jennerex Biotherapeutics (www.jennerex.com), was just named one of Canada's top 10 life science companies by the Ottawa Life Sciences Council.

Practice makes perfect

Mistakes happen in every line of work, but conventional wisdom tells us that practice makes perfect. The problem is, how do you "practice" a life or death emergency situation? In medicine, you can work with cadavers, animals, and mannequins, but this only recreates part of the experience and evidence suggests that the part we're missing may be the most important.

"When researchers looked at errors that were made in emergency situations in the operating room, they found that most of those errors were not caused by a lack of knowledge or technical skills," says Dr. John Kim, a critical care physician, professor, and researcher. "Rather, errors are usually caused by a set of non-medical skills we refer to as crisis resource management, or CRM. This would include, for example, a physician becoming fixated on one particular problem and missing others. It also includes delays in response time, or failure to act due to uncertainty."

Residents practice their crisis resource management skills at the Skills and Simulation Centre.

The University of Ottawa was one of the first centres in Canada to try to teach these skills to residents using what's called full-theatre high fidelity human patient simulation. At the Skills and Simulation Centre at The Ottawa Hospital's Civic Campus, residents in critical care, emergency medicine, and anesthesiology are thrown into emergency situations that seem all too real, with dummy patients that can scream and vomit, and nurses and respiratory therapist actors who have been trained to respond to each situation consistently. Vital signs, including heart beat, blood pressure, and oxygen level, change depending on actions taken by the resident. When blood work is ordered it doesn't necessarily arrive on time, and clinical signs do not always lead to the correct diagnosis.

Dr. Kim videotapes each session and reviews them with residents afterwards. At a recent screening, first-year residents cringed when watching themselves on tape. One commented that he knew what to do, but he hesitated because there were so many distractions. In a session in which two residents did the simulation together, they noted that it was difficult because they never established who would be in charge. These are properties of real-world situations that cannot be learned by reading books, and cannot be evaluated through multiple-choice exams.

"We've come a long way in making these simulations seem real and medical schools across the world are adopting this technology," says Dr. Kim. "But there is still a big gap in our knowledge about how to evaluate performance in these scenarios consistently. This is important because we need to be able to evaluate residents to tell them how to improve, and to tell if we're actually making a difference."

To address this issue, Dr. Kim and his colleagues developed a scale to rate crisis resource management skills, with categories for leadership, problem solving, situational awareness, resource utilization, and communication. They conducted a research study to attempt to validate the scale, and the results were recently published in the journal *Critical Care Medicine*. They found that when three different experts independently evaluated more than 110 videotaped sessions, there was a fairly good correlation between the scores that they gave to each resident. Using this scoring system, they also found that third-year residents had significantly better crisis resource management skills than first-year residents, a result which they believe can be attributed to their increased clinical experience.

> ***"High fidelity simulation has the potential to greatly reduce medical errors and increase patient safety, if we can learn how best to use it."***
>
> Dr. John Kim

"We believe this is the first successful attempt to systematically evaluate this technology to evaluate performance in a generic medical emergency," says Dr. Kim. "Although the results are preliminary, they represent an important first step. High fidelity simulation has the potential to greatly reduce medical errors and increase patient safety, if we can learn how best to use it."

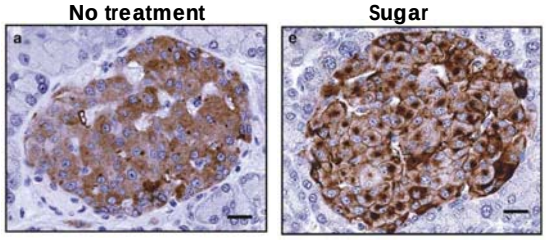
What do the brain and the pancreas have in common?

An unexpected link may shed light on diabetes and neurodegenerative disease

The brain is a three pound sac of nerves that makes all of our movements, sensations, and thoughts possible. The pancreas is a tongue-shaped organ located behind the stomach that produces proteins involved in digestion and metabolism. What could they possibly have in common? According to a novel theory, certain diseases of the brain and the pancreas might be triggered by a very similar mechanism.

Type 1 diabetes occurs when the pancreas doesn't produce enough of a hormone called insulin, which regulates the body's ability to use sugar from the blood. Without frequent insulin injections, people with type 1 diabetes would go into a diabetic coma and die. While it is known that this disease is caused by the body's immune system attacking the beta cells in the pancreas that produce insulin, the cause of this misguided attack remains the subject of much research. Dr. Fraser Scott's lab has traditionally focused their research on the role of diet, the gut immune system, and the target beta cells in the development of this disease, but when a young postdoctoral fellow from Germany joined the team, he brought some intriguing new ideas with him.

Dr. Alexander Strom had spent several years studying PrP, the protein that is famously associated with brain wasting diseases such as Creutzfeld Jakob Disease in humans and Bovine Spongiform Encephalopathy in cattle. In these diseases, PrP adopts an infectious misfolded form that accumulates in spongy plaques in the brain. The normal non-infectious form of this protein can be found in tissues throughout the body, including the pancreas, but its role there has remained a mystery.



PrP (stained brown) forms clumps in the pancreas after animals are given a high dose of sugar.
Reproduced from *Laboratory Investigation (doi:10.1038/labinvest.3700500)*

Dr. Strom and research associate Dr. Gen-Sheng Wang decided to look at normal PrP in the pancreas more closely, and their results, publshed in the journal *Laboratory Investigation*, turned out to be very interesting.

"We looked at PrP in normal rats, and we found that it was forming unique clump-like structures called aggregates in the beta cells that produce insulin," said Dr. Wang. "Similar clumps have been observed in cell cultures before, but never in animals, so this is a very novel finding."

Drs. Alexander Strom (left), Fraser Scott (middle), and Gen-Sheng Wang (right)

They also looked at PrP in a rat strain prone to develop type 1 diabetes and they found that the clumps were much more common. Finally, they found that when they gave normal rats a large dose of sugar directly into the blood stream, the number and size of PrP clumps increased greatly. These clumps were never observed in cells other than the beta cells.

"It's definitely speculation at this point, but our evidence suggests that these PrP clumps may have a role in blood sugar regulation, and perhaps even in diabetes," said Dr. Strom.

Protein clumping, or aggregation is a relatively common phenomenon in neurodegenerative disease. For example, Huntington's diseases is caused by the aggregation of the Huntington protein in the brain, and Alzheimer's is thought to be caused by the aggregation of a protein called beta-amyloid. These aggregates seem to attract the attention of the immune system, triggering inflammation and tissue destruction.

"It is intriguing to wonder if perhaps the inflammation we see in type 1 diabetes could be triggered in some people by an immune response against these PrP aggregates," said Dr. Scott. "It also suggests the exciting possibility that insulin-producing cells could be defective before they are attacked by immune cells, and we are currently doing experiments to test this theory."

The inside sto

World's first ge

and how it turned Ottawa into a leading

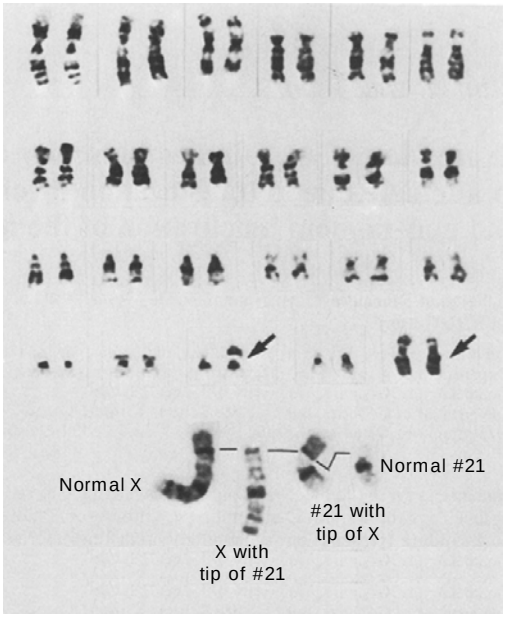
When asked how and why he embarked on what turned out to be one of the most significant medical research projects ever, Dr. Ronald Worton answers with one word: serendipity. Then he starts drawing the X chromosomes of a young girl from Belgium. The first time he saw those chromosomes was in 1977, but he still remembers exactly how they looked and the precise pattern of light and dark bands.

Eventually, these chromosomes would lead to the discovery of the gene responsible for Duchenne muscular dystrophy (DMD), the first disease-causing gene ever to be identified without already knowing the protein encoded by the gene. It would also turn out to be the largest human gene ever discovered, more than 100 times the average size. The knowledge gained along the way opened the gates for a flood of gene discoveries in the late 1980s and early 90s, and paved the way for the Human Genome Project itself.

"At the time, we knew that what we were doing was incredibly important for people with Duchenne Muscular Dystrophy, but I don't think we appreciated just how important it was for science," says Dr. Worton today, 20 years after the discovery of the gene.

> ***"At the time, we knew that what we were doing was incredibly important for people with Duchenne Muscular Dystrophy, but I don't think we appreciated just how important it was for science."***
>
> Dr. Ronald Worton

Although he made the discovery in Toronto, Dr. Worton has been a health research leader in Ottawa for the last 11 years, as CEO and Scientific Director of the Ottawa Health Research Institute, the research arm of The Ottawa Hospital and an affiliated institute of the University of Ottawa. By recruiting and supporting top scientists from across Canada and around the world, he has helped turn Ottawa into a major centre for neuromuscular disease research and stem cell research (the field that many believe will finally enable treatment of these diseases).



Top four rows show the chromosomes (in pairs) of the girl in whom the Duchenne muscular dystrophy gene was discovered. Pairs are supposed to be identical, but in the case of this girl, the tip of one X (magnified in bottom row) was switched with the tip of a chromosome #21.

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The story of the discovery of the DMD gene includes many twists and turns. One of these is the fact that Dr. Worton's team identified the gene in a girl, while DMD almost always affects boys. The reason for this has to do with our chromosomes – the structures that contain all our genes, arranged in a defined order. Humans have two copies of each chromosome, except for the "X" which is present in only one copy in males. DMD, like a number of other genetic disorders, primarily affects males because it is caused by a problem on the X chro-

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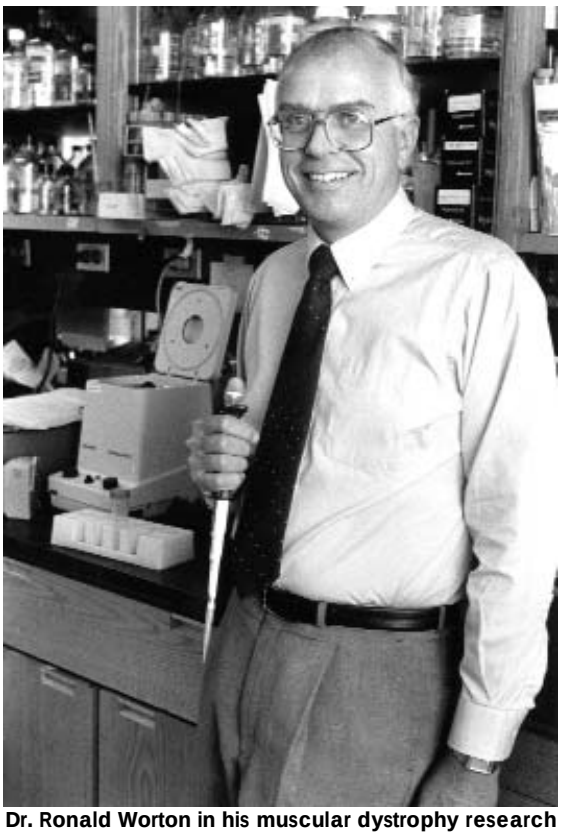
mosome. With only one copy of the X, males cannot compensate for these problems the way females can.

In the 1970s and 80s, Dr. Worton led the cellular genetics lab at the Hospital for Sick Children in Toronto and he was particularly interested in disorders involving chromosomes. In 1977, a pediatrician from Belgium named Dr. Christine Verellen joined Dr. Worton's research group, and she brought with her the famous chromosomes that would lead to the identification of the DMD gene.

"In Belgium, Dr. Verellen had treated a young girl with DMD, and when we looked at that girl's chromosomes, we could tell immediately that something was wrong," said Dr. Worton. "Every chromosome has a unique pattern of light and dark bands, but in this girl, the patterns on some of the chromosomes were different. It looked like the top end of one X chromosome had been exchanged with the top end of chromosome 21 – a rearrangement called a 'translocation'."



Dr. Ronald Worton in his muscular dystrophy research laboratory in Toronto

They published this finding and by 1982, research groups around the world had identified five more cases of females with muscular dystrophy with similar X chromosome rearrangements.

"The simplest interpretation was that in each of these young girls, the gene for DMD was disrupted by the break in the X chromosome," said Dr. Worton. "There is a genetic reason why these girls showed symptoms of DMD, even though they still had one normal X chromosome, but the more important part of the story is that this obvious visible break suggested a method by which we, and others, could identify the gene."

Two main groups led the global race to identify the gene: Dr. Worton's team in Toronto and Dr. Lou Kunkel's team in Boston. They would take very different approaches and encounter unique difficulties. Dr. Worton's group purified chromosomes from the Belgian girl by fusing her cells with mouse cells, and then using a special genetic trick to select only those cells with a single human chromosome – the one with the disrupted DMD gene. That turned out to be the easy part. It took nearly a year of tedious molecular work – doing experiments with exotic names like "zoo blotting" and "chromosome walking" to find the translocation breakpoint, subsequently confirmed to be within the DMD gene.

Although the Worton and Kunkel labs were in steep competition, they also worked together and shared results and they agreed to publish part of their work together in 1986. A media frenzy followed, but in yet another twist, it turns out that one of the most meaningful stories, which happened just weeks after the discovery, was never told.

"Dr. Margaret Thompson at SickKids was providing genetic counseling for a woman from a family with a history of DMD," said Dr. Worton. "Her brother and nephew were both affected, and she was a carrier. She desperately wanted another child, but she knew that any boy that she had would have a 50 per cent chance of developing the disease. When Dr. Thompson saw her she was already pregnant and we decided to offer prenatal diagnosis. We tested her brother and identified the mutation in the DMD gene. We then tested the woman, and confirmed that she carried a copy of the

defective gene. Finally, we tested cells from her unborn baby, and determined that it was male, but did not have the mutant gene. Four months later she had a perfectly healthy boy. She sent me pictures, and she was so thankful. This was the world's first pre-natal diagnosis for muscular dystrophy – a memorable highlight in my career."

Research over the next few years revealed that the DMD gene encodes a protein, named "dystrophin" by Dr. Kunkel, that helps strengthen muscle fibres and protect them from injury. Dystrophin was shown to be part of a multi-protein complex that resides at the muscle fibre membrane, and in people with DMD, this whole complex is disrupted. This leads to muscle weakness so severe that by age 9-12, most patients will be confined to a wheel chair. Research on dystrophin opened the door to further research on this multi-protein complex, with several of the proteins involved now shown to be defective in other forms of muscular dystrophy. In a broader context, the techniques learned in identifying the DMD gene led to a golden age of disease gene discovery, which included identification of the Cystic Fibrosis gene by Dr. Worton's colleague at SickKids, Dr. Lap-Chee Tsui.

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In May 2007, the 20th anniversary of the discovery of the DMD gene will be celebrated in Ottawa at an international symposium (www.ohri.ca/dmdsymposium). Keynote speeches will be given by both Dr. Worton and Dr. Kunkel. DMD researchers from around the world will discuss the state of their research and how best to move forward.

> ***"This was the world's first pre-natal diagnosis for muscular dystrophy – a memorable highlight in my career."***
>
> Dr. Ronald Worton

Although there is no cure yet, there has been great progress, especially in stem cell research. Just this year, a team from Italy showed that dogs with DMD could be treated quite effectively by a transplant of normal muscle stem cells. At the OHRI, Dr. Rashmi Kothary's group recently revealed a new approach to improve DMD gene therapy in mice, and Dr. Michael Rudnicki and Dr. Jeff Dilworth have made great strides in understanding how stem cells give rise to muscle tissue, and how best to harness this process for disease treatment. A number of researchers at the neighbouring CHEO Research Institute are also making important progress on related neuromuscular diseases – myotonic dystrophy and spinal muscular atrophy.

"I'm really looking forward to this meeting," said Dr. Worton. "Not only will it will be an opportunity to see many of my old friends from around the world – many who played a significant role in the discovery of the DMD gene – but it will also be a poignant reminder of how a simple idea led to a whole new field of research, and to new approaches to therapy for this devastating disease."

A personal reflection on 11 years at the OHRI

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fellows and a total staff of over 1,200 people who call the OHRI home. The research budget has increased from zero in 1986 to about $17 million in 1996 to over $75 million in 2006-07. Over the last six years we have had exemplary support from The Ottawa Hospital, the University of Ottawa and from the OHRI Board of Directors. In particular, I would like to acknowledge the phenomenal support of Hospital President, Dr. Jack Kitts, University President, Dr. Gilles Patry and Board Chair, Jacquelin Holzman.

Now we are about to begin the third decade with a solid base of outstanding researchers and a new leader, Dr. Duncan Stewart, a cardiologist and stem cell researcher. He will bring a new perspective – that of the physician-scientist – to the Institute and will undoubtedly bring a greater integration with the scientific staff at the University of Ottawa Heart Institute. He will lead the development of the next scientific and business plan of the Institute and will spearhead a proposal to the Research Hospital Fund of the Canada Foundation for Innovation for new facilities that will propel the Institute to a new level of excellence.

And what will I be doing? As Chair of Research Canada I will continue to advocate for stronger and better planned federal government support. As Vice-Chair of the Board of the Ontario Research Fund I will be working with the provincial government to maximize the opportunities for health research in the province. Thus, I am not leaving the field, but am only changing my role to a more global one; one that I hope will benefit the OHRI along with all health research institutes in Canada.