Kidney Research Centre Captures Canada Research Chair

Distinguished Investigator, Dr. Rhian Touyz, Brings Research Magic to KRC with Prestigious 7-Year Award

With the new KRC structure being built outside her small office at the University of Ottawa Health Sciences Building, Dr. Rhian Touyz talks enthusiastically about her internationally recognized work on high blood pressure. To her left, on the wall, are framed covers of three of the most prestigious cardiovascular journals in the world, showing her research pictures of coloured cells from tiny blood vessels from human patients. Within these cells, the glowing labelled proteins shed light on how smooth muscle cells can cause the tiny arteries to constrict and remodel, and thereby increase resistance to the blood flowing through them, leading to high blood pressure.

Dr. Touyz is precise and beautifully spoken. When asked what got her interested in high blood pressure, she says, “In South Africa, where I grew up, there is a large proportion of the population who have severe high blood pressure, the cause of which is largely unknown, and this touched me. Together with my interest in cardiovascular physiology when I was an undergraduate student, I was intrigued. I was also struck by the terrible damage that hypertension does to a large number of patients.” She notes that about 30% of the adult western population has high blood pressure, usually without a known etiology. And it is searching for this cause, at the molecular and cellular levels in vascular smooth muscle cells, that drives Dr. Touyz. Whatever does go wrong, she notes, also is associated with injury and inflammation to these vessels, so hypertension is also a disease, which, at its origin, damages the vasculature. In fact, her laboratory has shown that Src tyrosine kinase, which belongs to a large family of proteins, alters the response of angiotensin II, a well-known hormone, which tends to raise blood pressure.

Another main emphasis of her research involves small molecules, called reactive oxygen species, which can also damage cells of these small vessels, and again, contribute to increased vascular resistance and elevated blood pressure. Her third focus fits right in line with the long history of the Kidney Research Centre in studying the transport of ions across cell membranes. “We identified in hypertensive patients alterations in calcium and magnesium transport in vascular smooth muscle and kidney cells. We wondered what the underlying mechanism was for this and found that a specific, recently identified protein controls magnesium transport and showed that regulation of this transporter is altered in hypertension. Understanding more about the protein causing this abnormal transport again will lead to an understanding of the cause of hypertension.”

As Dr. Touyz explains her research interests, one keeps wondering how she has accomplished so much to date. Now, only after being in Ottawa for two months, she has eight colleagues working with her, with another three to join her group in the Kidney Research Centre in the near future. But her scope is broader than this dynamic dozen in Ottawa. “At the same time, we are very fortunate to continue our collaboration with the CIHR Multidisciplinary Hypertension Group of the Clinical Research Institute of Montreal directed by Dr. Ernesto Schiffrin. Indeed, some of my group and research projects are continuing in Montreal. This is important and establishes essential links between the KRC and other internationally renowned laboratories. Indeed, this networking of teams between Ottawa and Montreal, and even across Canada, will allow for better outcomes and identification of the causes of hypertension.”

(Continued on page 3)
Since our last KRC newsletter, there has been a wealth of good news. First, construction of the new KRC laboratory facility is proceeding at an excellent pace. The shell of the new facility structure at the University of Ottawa Medical School (depicted below) is already completed, and we expect to move into the 15,000 square foot space on the 2nd floor in the summer of 2006. With this move, the KRC will acquire new state of the art research equipment and expand its efforts into the prevention of kidney disease progression.

The KRC has also developed a Clinical Research Unit, with the support of the Ottawa Health Research Institute (OHRI) and the Department of Medicine at The Ottawa Hospital. This unit, located in the Professional Building next to the Riverside Campus, is the centre for patient-focused research studies in the KRC, and houses all research nurse coordinators and assistants. The development of this unit will allow us to expand our research studies that directly impact on patient care, such as those described in the current newsletter.

Under the leadership of Dr. Marcel Ruzicka, a KRC clinical investigator, a Renal Hypertension Unit has been developed at the Riverside Campus of The Ottawa Hospital. The unit will be a focus for patient care, education and clinical research studies in hypertension, a major cause of chronic kidney disease. Indeed, Dr. Ruzicka has recently received a Research Grant from the Department of Medicine of The Ottawa Hospital to study the effect of sleep disorders in hemodialysis patients on the development of hypertension.

I am also pleased to report several significant achievements of our KRC students and post doctoral fellows since our last newsletter.

Monika Sklepowicz received her Masters degree and Rania Nasrallah her PhD degree under the supervision of KRC scientist, Dr. Richard Hebert. Dr. Wissam Faour, a post doctoral fellow in Dr. Kennedy’s laboratory, received a prestigious salary award from the Kidney Research Scientist Core Education and National Training (KRESCENT) program. This award will allow Dr. Faour to continue his research on “Identification of the role of the prostaglandin E4 receptor subtype in the molecular physiology of the kidney and its implication in proteinuria.” Mr. Jean-Louis Michaud, a graduate student in Dr. Kennedy’s laboratory, is the recipient of a prestigious Canadian Institutes of Health Research (CIHR) fellowship award. In Dr. R. Touyz laboratory, Glacia Callera received a prestigious Heart and Stroke Foundation (HSFC) Research Fellowship salary award and Fatiha Tabet received a Canada Graduate Scholarships – Doctoral Award from the CIHR.

Every year, nephrology trainees involved in KRC studies attend the major international and national meetings where the latest kidney research is presented. These trainees also present their work at our weekly rounds in Ottawa, at the Centre for Kidney Disease. At the 2004 meeting of the American Society of Nephrology, and at the annual meeting of the Canadian Society of Nephrology in 2005, an unprecedented number of research presentations was delivered by our trainees (including awards to Drs. C. White and A. Mulay, both supervised by Dr. G. Knoll), and these led to several important research publications on which they were co-authors.

Congratulations are due to all of our research trainees! Indeed, these achievements highlight the impact of the local presence of research expertise and infrastructure on training and ultimately enhanced patient care.

As you will find in this newsletter, there is other big news. Dr. G. Knoll, the Medical Director of Renal Transplantation has received a major $3 M grant from the CIHR to conduct a clinical trial on the effects of a blocker of the renin-angiotensin system, ramipril, on clinical outcomes in renal transplant patients.

Finally, we are delighted that Dr. Rhian Touyz, The Canada Research Chair in Hypertension has arrived to the KRC with her talented research team, to study mechanisms in which high blood pressure can damage blood vessels, ultimately affecting the kidneys, heart, brain and other organs. Read more about her exciting research in this issue.

Dr. Kevin Burns

A message for the Kidney Research Centre

Happy 5th Anniversary

The KRC is no toddler, despite being only 5 years old. There is now a remarkably solid foundation for great achievements in the years to come. As outlined in this Newsletter, our principle investigators have achieved great things, and a new KRC structure is well underway. Dr. Kevin Burns, the Director of the KRC, is not only a Director with limitless vision and stamina, but he has also just been awarded another major grant for $700,000 from the Canadian Institutes of Health Research. He will continue his pioneering work on the renin angiotensin system within the kidney. He is now focusing in on one enzyme, ACE2, which may play a fascinating role in the progression of kidney disease in adult onset diabetes.
Ottawa Kidney Patient Learns His Disease Is the Subject of Key Research

“I was shocked, I thought this was a dead issue,” said John whose disease started in childhood.

You might want to try to put yourself in John’s shoes eight years ago. But even with small feet you’d have a problem. John couldn’t get them on because of the huge swelling of his ankles. He felt terrible with his abdomen full of fluid and his face swollen. He was also losing massive amounts of protein in his urine.

His doctor at CHEO and his family were saddened by the clear biopsy diagnosis of a disease of his kidney filters: focal segmental glomerulosclerosis (FSGS). Moreover another family member had the same disease.

And John? This twelve year old was only sad because he couldn’t continue to play hockey.

Today at age twenty, as he looks back, not only is the seriousness of his disease apparent, but he understands too clearly the struggle he and his doctors are in to slow the deterioration of his kidney function.

What can be done? Whatever it is, Dr. Chris Kennedy of the Kidney Research Centre is in a key position to help. He is a leading investigator into the fundamental changes in glomerular filter cells – podocytes – which cause John’s disease – FSGS.

Perhaps it’s his football background, but Dr. Kennedy is so passionately goal oriented, he doesn’t hesitate to touch on a sensitive issue – basic versus applied research.

Studying kidney cells without a clear end point in mind won’t satisfy him. “Of course,” he says, “there is a place for curiosity based medical research, but for me there has to be a natural progression to understanding disease mechanisms.”

Dr. Kennedy has clearly progressed. John’s case provides even further direction to Dr. Kennedy’s research, which is funded by the Kidney Foundation of Canada and the Canadian Institutes of Health Research.

“Familial FSGS stimulated us to look at mouse models of the disease – a disease we can induce by targeting the mouse’s genetic structure.” In fact, more than 5 years ago, Dr. Kennedy was acutely aware that modifying podocytes by gene manipulation could change the architecture of the glomerular filter.

“We believe a podocyte’s health rests upon its elaborate internal scaffolding that gives rise to a highly developed appearance. When we introduce the defect, the architecture of the cells changes dramatically: they form fewer of the finger-like extensions required for filtration. We want to be in a position to change the genetic defect, or at least modify the effects on the podocyte scaffolding, and thereby prevent the protein loss, scarring, and ultimate kidney failure.”

No doubt John and his family depend on this. “Indeed,” John says, “I’m afraid my children will get it.” And learning about Dr. Kennedy’s work in the course of this interview has encouraged him greatly. “I was shocked,” he said, “I thought this was a dead issue.”

John, who was part of a previous clinical study with Dr. Filler at CHEO, also notes, “Patients should be involved, if for no other reason it is in their own interest.”

(Continued from page 1)

What attracted an international star like Dr. Touyz to Canada’s Kidney Research Centre in Ottawa? “I should say first that I am very grateful to KRC Director Dr. Burns for his efforts in recruiting me, and to the University of Ottawa for supporting my nomination for the Canada Research Chair, and I am so pleased to be part of the OHRI. Why Ottawa? I was impressed by the strong integrated basic science and high quality of clinical research thrust of the KRC, which makes possible real translational research. By that I mean being able to apply basic laboratory findings to clinical problems: in this case, better treatment and/or prevention of hypertension in patients. It should be stressed that high blood pressure and the kidney are closely related. Not only do the kidneys play a major role in the development of hypertension, but the kidneys themselves are a major target of the adverse effects of high blood pressure. Improved management of patients with hypertension, through the better understanding of what causes hypertension, will prevent many patients from the devastations of end stage renal disease. Dr. Touyz adds that the opening of the Hypertension Clinic within the Division of Nephrology in July 2005, combined with an emphasis on fundamental research in the KRC is “the perfect opportunity to study patients with both renal disease and hypertension, and promote translational research.”

What really gives Dr. Touyz a rush? “The fascinating dynamics of cells, which after all are the basic building blocks of all tissues and organs. It is really exciting to see live cells with labelled proteins within them – in different colors – and watch these proteins like lit-up neon signs travel within the cells, glowing and fluorescing in different colors.” Now she lights up herself. “That’s how we get to grips on how genes, proteins and molecules regulate cell changes and what these changes do to the vessels and to kidneys.”

“So you are like a fashion couturier dressing devious proteins in different colours and then watching them do their subcellular dance in kidney and vascular cells. Is that it?” Dr Touyz smiles, “Making successful research magic is something very much like that”.

KIDNEY RESEARCH CENTRE • OCTOBER 2005
Transplant Doctor and Patient Share a Commitment to Help Others through New Drug Trials

“I’m big on research,” says Mitzi, “on anything that will benefit other patients.”

Mitzi’s transplanted kidney showed excellent function when she was asked if she would participate in a research study. The purpose of the study was to determine if switching to a new type of anti-rejection drug might help patients like her.

“I was very willing to experiment because I was doing well.”

But if she was doing well, why not leave things as they were? It’s simple: she wanted to help.

“I had complete trust in my doctors — I was in a protective, safe environment, and if there were any adverse effects, I was sure they would be promptly identified.”

Mitzi was part of a study to determine if a modification of one of her anti-rejection drugs, mycophenolate mofetil (MMF), would improve outcomes. Since MMF can cause stomach irritation, Dr. Greg Knoll, Medical Director of Kidney Transplantation, and a key investigator in Mitzi’s clinical trial, wanted to know if enteric coated pills of MMF are of benefit in reducing stomach distress in transplant patients. Just as enteric coated aspirin reduces stomach symptoms, the study showed this was also true for enteric coated MMF, while still preserving function in the transplanted kidney.

Dr. Knoll says, “I couldn’t do these research projects without seeing patients. Their kidney transplants need constant monitoring, with careful attention to the drugs which prevent rejection.”

In fact, Dr. Knoll is part of a splendid research environment: his patients stimulate his research ideas, and his research helps his patients directly. And Mitzi’s passion to help is a big part of the splendor.

Because of these projects, there is better understanding of what the best drugs are, how to measure the recipient’s graft function, and how to assess the function of living donors. The group’s clinical research — how to track rejection, how to measure kidney function, how to predict outcomes — gives him, and his colleagues, tools to better treat patients such as Mitzi.

There is something special about Mitzi’s situation: she has several siblings with kidney disease who have received transplants as well. In fact, one is a nurse who now works in a clinical research unit at another University Hospital. This means Mitzi has access to all kinds of information, as well as a family who watches over her.

Still, she never hesitated to enroll in the study. “My family and husband have always been behind me, always supportive.”

Why did Dr. Knoll start off in transplantation research? “I saw that transplantation is the real treatment of choice — it provides a dramatic change.” This year alone he has had three publications in one of the foremost kidney journals.

The transplant group cares for about 500 transplant recipients, and does about 50 transplants each year, with results as impressive as anywhere else. This quality of care and outcome persist despite the transplantation of patients over 75 years old, and other patients with past histories of major diseases. Undoubtedly, the outcomes are enhanced by successful research trials and the partnership of patients like Mitzi and Dr. Knoll.

“I’m big on research,” says Mitzi, “on anything that will benefit other patients.”

Flash!

Dr. Knoll has received 3 million dollars from the Canadian Institutes of Health Research to undertake a study involving 12 Canadian transplant centres. The will determine if an angiotensin converting enzyme blocker will slow down the rate of loss of kidney graft function, and lower mortality from all causes, as shown in non-transplanted kidney patients. The answers will emerge from this multi-centered trial involving more than 500 patients.