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HEALTH PERSPECTIVES

MUHC
MCGILL UNIVERSITY HEALTH CENTRE

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Signalling Progress

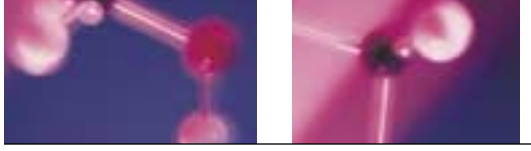
A large hibiscus perches happily on the windowsill of Dr. Morag Park's busy office. "It grows quickly," Park says, "and has to be clipped back a couple of times a year." But she doesn't mind. The plant's robustness is a lot like Park's own hearty determination to find answers that she hopes will lead to patient-tailored treatments for breast cancer.

"First we have to learn why two women with breast cancer can have very different prognoses," the Scottish-born Park explains. She is well on her way to finding out. In 2000, together with Dr. Sarkis Meterissian, Park established the McGill University Health Centre (MUHC) Research Institute's Breast Cancer Functional Genomics Group with a $1.5 million grant from the Montreal Breast Cancer Foundation. In April of this year, the group was part of a team of researchers across Canada who study genetics and women's health to receive a multi-million dollar grant from Genome Canada, the largest non-profit funding agency in the country for genetic research.

An important part of Park's research is a long-term project to collect and analyze samples that may help explain how normal breast tissue cells become cancerous. To this end, she joined forces two years ago with clinicians, pathologists and other MUHC and McGill University investigators, who would later become involved in the Breast Cancer Functional Genomics Group, to establish

(continued on page 2)

Thirteen years of collaboration have solidified the relationship between Dr. Morag Park (left) and senior technician Monica Naujokis. Today, they are part of the MUHC's Breast Cancer Functional Genomics Group, which is searching for answers that may lead to patient-specific treatments for breast cancer.

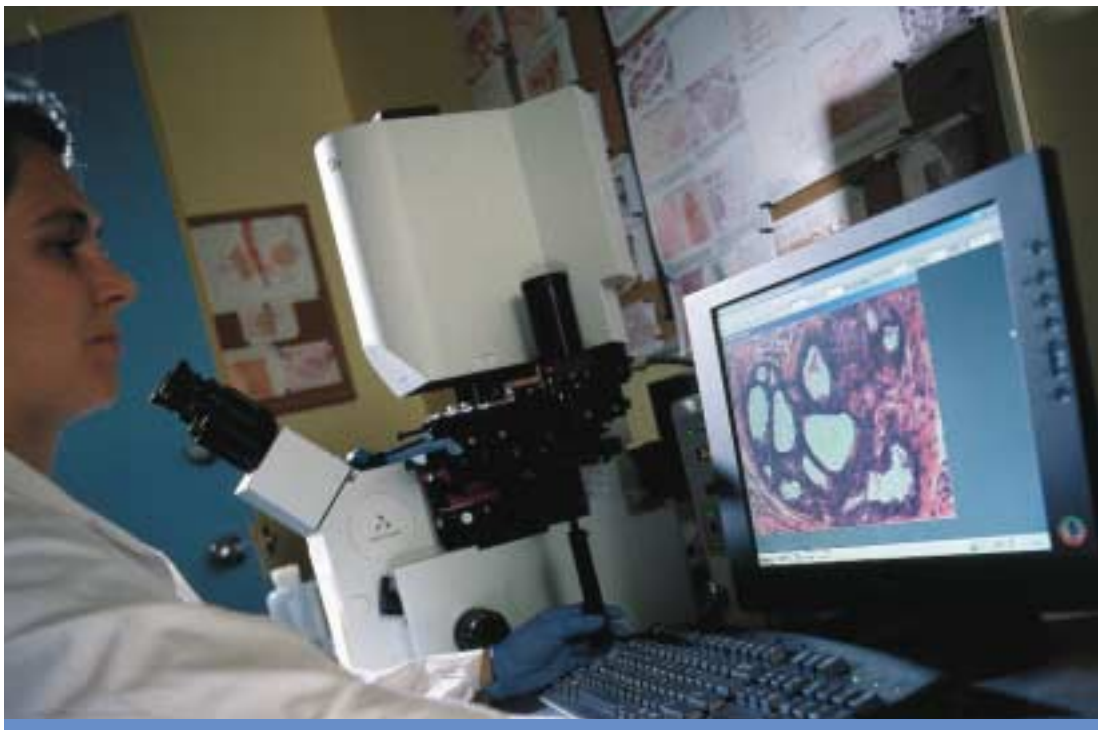


(**Signalling Progress** *continued from page 1)*
a world-class breast cancer tumour bank. Although achieving their goal wasn't easy, they now collaborate with researchers and clinicians throughout the province through tissue-banking activities funded by Fonds de la recherche en santé Québec (FRSQ).

But Park's passion for collaborative research extends back even further, to 1983, when she and a fellow post-doctoral student at the National Health Institute in Washington, D.C. made a groundbreaking discovery in the field of oncogenes. They identified an important receptor for one of the molecular signals that instruct cells how to migrate and invade. Since then, she and her colleagues have gained a deeper understanding of the very complex process of molecular signalling and how it can go astray to result in cancer.

"In normal tissue, the process by which cells multiply, organize themselves and eventually self-destruct is tightly regulated. Healthy cells stay where they're supposed to. With cancer, this process becomes deregulated and the cells are more likely to detach from one another," she says. "Essentially, when we die from cancer, it's because these cells become motile and migrate to other sites around the body. This is called metastasis."

As tumours progress, the signals their cells send and receive change. "By teasing out the molecular mechanics behind this deregulation and studying the differences in tumour behaviour, we can make discoveries that will help drive therapeutic strategies, or at least identify therapeutic targets, for individual patients," she says. In other words, by understanding how particular tumours signal their cells to detach, travel and invade, researchers and clinicians may one day be able to identify a patient's tumour signal type and target it specifically. This could eventually replace administering general treatments of chemotherapy or radiotherapy, which are very hard on the body as a whole. "If we know what the signals are that tell a cell to express a certain genetic expression profile, which is a map of the genes in the cell's DNA that shows which ones are switched on and which ones are dormant, we'll understand how normal cell behaviour becomes deregulated and how it can lead to metastasis. When that happens, treatments will improve dramatically."



Working with the manufacturer, Arcturus, Dr. Park and her colleague Dr. Tanya Fournier (shown here) developed this laser capture microdissection machine to overcome the problem of having a mix of normal and cancerous cells in breast tumour samples. Researchers view the magnified image on screen then shoot a laser at targeted cells, fusing them to a special membrane. When the membrane is pulled away, the selected cells stick to it and can be analyzed separately.

Funding for basic research has provided the groundwork to begin to understand this process. Her basic research lab in the Molecular Oncology Group at the MUHC's Royal Victoria Hospital site, which is a training environment for students and post-doctoral fellows, has been funded upwards of $500,000 a year in grant money from the Canadian Institutes of Health Research, the National Cancer Institute of Canada, and the Canadian Cancer Society through the Canadian Breast Cancer Research Initiative.

To investigate how changes in molecular signalling occur, researchers need a global perspective of a tumour at a particular point in time to compare it to other tumours and to the tumour itself at other stages. It's only by comparing these profiles that they can begin to identify how sets of genes and signals interact. But until recently, getting a global perspective was close to impossible. "Traditional research methods proceed slowly," Park explains, "isolating one gene at a time." This process doesn't show the thousands of simultaneous gene interactions that occur in any given moment. Fortunately, the last few years have seen technological advances in genomics and proteomics, such as the development of DNA microarrays, which have allowed researchers worldwide to investigate a large number of gene interactions at a time. This greatly reduces the amount of time needed to get a clearer picture of how genes interact and of the thousands of possible gene interactions that may lead to cancer. Not surprisingly, these technological advances have spawned a leap forward in molecular and genetic research.

Park credits the unique synergy that is characteristic of the MUHC as a research and teaching hospital, as well as the hospital's close relationship with McGill University, for allowing the Breast Cancer Functional Genomics Group to be at the forefront of this movement. "This work is hugely collaborative. I would never have been able to come this far, to set up the tumour bank, on my own," she says. "The fact that the MUHC reorganized to focus on tumour types indicated there was a group of clinicians and oncologists whose primary interest was breast cancer. Also, the creation of the new breast cancer clinic at the Royal Victoria Hospital site, which is now the breast cancer centre for the MUHC, meant there was already a large team of professionals on the clinical side with an interest in this disease.

"Through interactions with all these people, we learned about the DNA microarray methodology that Dr. Tom Hudson was instrumental in developing, and we realized it could be used to look at breast cancer genetic expression profiles. Hudson works at the Montreal Genome Centre, which is currently housed at the MUHC. When it became clear that clinicians, surgeons, oncologists and other scientists were all interested in using his methodology, we joined together to write a grant proposal to the Montreal Breast Cancer Foundation, which ended up awarding us the funds to form the Breast Cancer Functional Genomics Group at the MUHC. It was really quite serendipitous."

It hasn't all been smooth sailing for Park and her teammates. "Once we had the methodology, one of the limiting factors was the small size of the tissue samples." Breast cancer tumours tend to provide tissue samples that are a fraction of the size required by microarray analysis protocols. Furthermore, the tumours are heterogeneous, meaning that samples are usually composed of a mix of normal and cancerous cells. As a result, sample analysis produced aggregate results rather than specific information about the different cells.

MUHC HEALTH PERSPECTIVES

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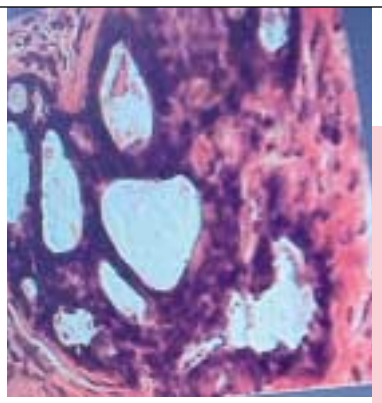

> **"Through our relationship** with the Montreal Breast Cancer Foundation, we've been able to interact with the women who raised the money for our first machine and who helped establish the MUHC Breast Cancer Functional Genomics Group. And many of these women, of course, have breast cancer. So when we're banking the tissue and doing the experiments, we're constantly thinking of them and remembering our commitment to them. It gives us momentum to at least try to ask the right questions."

Hot on the trail of solutions, Park and her teammate, Dr. Svetlana Sadekova, who directs the Breast Cancer Functional Genomics Group, devised a technique that allowed them to amplify tumour samples to a usable size. Park's team also found a way to isolate the cancerous cells in samples to avoid getting aggregate results, allowing them to compare a patient's cancerous cells with healthy ones. These discoveries were made in collaboration with Arcturus, an instrument manufacturer in California that makes laser capture microdissection machines.

"Essentially, these machines are large microscopes that emit a laser that targets whatever cells you're after in a tumour sample," she says. The laser fuses the targeted cells to a special membrane, which is then pulled away from the sample, taking the cells with it. "Our goal is to be able to apply this technology to biopsy material, which is a really non-invasive diagnostic strategy. We're not there yet, but that's the direction we're going in."

After Park and her team overcame the hurdles of samples that were both heterogeneous and too small, they tackled the problem of how to store the samples in a tumour bank while preserving their integrity. The next task was to come up with a system to make the data available to all members of their team across the MUHC. She couldn't be more pleased with the results. "Our tumour bank is considered to be a Canadian gem, not only because we've shown proof of principle — that we can effectively handle our tissue samples and create an interactive database — but also because of our unique placement within the MUHC and the FRSQ. We're able to rapidly collect samples and we can manage quality control at every step."

The Montreal Breast Cancer Foundation and the MUHC Research Institute provided Park with the funds to buy the first laser capture microdissection machine in Quebec. Money for the second one came, in part, through a grant from the Canadian Foundation for Innovation, awarded to members of the FRSQ who are investigating breast and ovarian cancer. Similar machines will be installed at centres throughout the province, with Park's lab becoming the training ground for FRSQ members who are focusing on these cancers. In addition, the Montreal Breast Cancer Foundation recently awarded the Breast Cancer Functional Genomics Group a second grant of $1.5 million to help integrate its team with researchers and clinicians at l'Université de Montréal and l'Université Laval, bringing together expertise from across the province.

"We're now able to start analyzing, in a meaningful way, the differences in tumours, and hopefully we'll have results soon," she says. "This is all part of a worldwide initiative. We're already collaborating with several large research groups, where we do the analysis on our tissue samples, and then interact with them to look at the data and integrate it into the huge data sets that are being deposited around the world. My hope is that this information will remain available to researchers internationally so that collaboration can continue.

"You know, there will never be a single silver bullet for cancer, but I think that as one big team, with everyone working together, we can come up with combinations of strategies that will benefit the patient. That's really the goal." ❊

Equipping Excellence

As most people know, a Pap test, or smear, checks the cervix for changes to cells that may lead to cancer. Roughly one test in ten returns abnormal results. Because cervical cancer is most treatable in its early stage, and because it has few other symptoms at this stage to raise the alarm, it's imperative to follow up on abnormal Pap results.

Follow-up begins with a visit to a medical centre. There, a health-care provider will try to determine the extent of the abnormality, probably by using a **colposcope**. This is a close-focusing electric telescope with a bright light at one end. The colposcope is positioned outside the patient's body so that the light shines on the surface of the cervix, which earlier in the exam will have been painted with a staining solution, usually an acetic acid such as table vinegar. The solution causes the cells to better reflect light. Because abnormal cells reflect more light than healthy ones, they appear as white areas. The whiter the area, the worse the abnormality, or displasia.

Image courtesy of ACMI Corporation

After locating the displasia, the physician will take a sample of the tissue and send it to a laboratory for analysis. A representative price for a colposcope is approximately $15,500, although prices may vary depending on the manufacturer and product features.

If you want to learn more about the equipment used by MUHC professionals, or if you just want to test your knowledge in this area, visit the MUHC Foundation's web site at **www.muhcfoundation.com** and take the "How Much Does It Cost?" challenge. ❊

This series is intended to be informative; the McGill University Health Centre Foundation does not endorse any particular manufacturer or model of equipment shown and described here.

Racing to the finish line

"No marathon gets easier later. The half way point only marks the end of the beginning."

JOE HENDERSON, RUNNING GURU.

Petr Kavan is a long-distance runner, a triathlete who knows all about training, pacing and the importance of running through the wall. Ask him what it takes to break the tape after 42.2 foot-pounding, grueling kilometres and he'll tell you it's mostly the ability to stay focused on the finish line. Ask him what it takes to complete the marathon rebuilding of the McGill University Health Centre's Division of Pediatric Hematology-Oncology and he'll say exactly the same thing.

The 40-year-old Kavan arrived in Montreal in September 2000, having travelled 6,219 kilometres from Prague to take up his position as head of the pediatric hematology-oncology division at the MUHC's Montreal Children's Hospital site. As expected, the transatlantic flight was the first step in a long journey to overhaul a department that was very close to disappearing, a loss that would have had tragic consequences. Without pediatric hematology-oncology, the hospital would have been forced to stop treating children with cancer.

When Kavan arrived the situation was dire: the program was being held together by a single physician, a number of patients were being referred to Sainte-Justine Hospital, and teaching and research activities were minimal. Although pediatric hematology-oncology is a relatively new discipline, recognized for just over 30 years in North America and Europe, it has become a critical component of medical education. The lack of full teaching and research activities in this area meant that comprehensive oncology training was unavailable at the MUHC for McGill University's medical students, an unacceptable state of affairs for a university teaching hospital known for its expertise in oncology.

The program needed rescuing and Kavan was the man for the job. Known for his unwavering commitment to pediatric cancer patients, he had also proven he understood what it took to create a viable institution. In 1989, Kavan's native Czechoslovakia was without a single pediatric bone marrow transplant program, so he and a colleague set one up at Charles University Hospital Motol. By the time he left, close to 50 children a year were receiving transplants. During the same time he collaborated with Czech health-care professionals and researchers throughout Europe to establish a solid pediatric hematology-oncology program with strong research initiatives. "The Czech government even constructed a new building to house our program. When I considered the opportunity in Montreal, I believed I had the knowledge and experience to rebuild the MUHC's program because I had already done it once and because I work quite hard," he explains.

Since his arrival two years ago, he has effectively put the MUHC on the map with regards to treating pediatric cancers. "The immediate task was to stabilize the program by building a strong and multi-talented team," he says. "If you look at a sport such as hockey, you can bring the best players to the rink, but it will be one or two years before they really start to play well together." Keeping to a realistic timeline, Kavan pulled together pediatric experts from other MUHC departments, including Dr. Blair Whittemore from the MUHC's Montreal General Hospital site. Three new physicians were hired, two from France and one from the Czech Republic. Their collective expertise allows them to treat children suffering from many hematology-oncology problems, ranging from malignant disorders such as solid tumours, brain tumours, retinoblastoma (a rare childhood eye cancer) and leukemia, to benign hematological disorders such as sickle cell anemia, thrombocytopenia (a disease involving a deficiency of platelets in the blood), neutropenia (a blood disorder that increases a person's susceptibility to bacterial infections), and others.

Kavan believes the Glen hospital will facilitate collaboration. "Take my proposal to set up a new program for young adults (under 25) with cancer, for example. They most likely have a pediatric type of the disease and it's well documented that the outcomes for them are better if they're treated according to pediatric protocols by people who understand pediatric specifics. This is a great challenge and an excellent opportunity for the MUHC to lead the way."

Kavan's team reorganized patient management so that waiting times are rarely longer than 30 minutes. They also created disease-oriented clinics where children suffering from the same or similar disorders are treated on the same morning or afternoon. This makes a more efficient use of resources and also increases professional collaboration

because experts from like areas are in close proximity. The resulting environment is much more relaxed for patients, families and caregivers.

Under Kavan's direction, the team set up several new programs, including a retinoblastoma program, headed by Dr. Anne-Sophie Carret and Dr. Rosanne Superstein, that collaborates with other hospitals throughout the province. They also introduced new treatment protocols at the MUHC for histiocytosis, a little seen but deadly disorder with similarities to cancer, and joined an international society for health-care professionals treating this disease. "This year we'll be able to do 15 bone marrow transplants, which is the most this hospital will have ever done," he says.

Kavan's pride in his department's accomplishments runs parallel to his belief in teaming up with other experts at the MUHC. "Our brain tumour program is very strong, mainly due to our collaboration with radiation oncologist Dr. Carolyn Freeman at the General and with Dr. Jean-Pierre Farmer and Dr. Jose Luis Montes, both neurosurgeons at the Children's. In fact, 65 percent of all Quebec pediatric brain tumour cases — 40 to 45 a year — are referred to the MUHC, so we're achieving our goal of treating more patients."

Like any competitive triathlete, once Kavan establishes a benchmark of excellence in one area, he moves on to master the next. "After the department was stabilized and we were assured that patients were getting the treatment they needed, we had to make the program much more academic," he explains. "Only by having strong teaching and research components will its future be guaranteed." Kavan is excited about both. "In coming here, to McGill and its medical school, I was being given the chance to belong to an institution that had a great tradition behind it and was renowned around the world," says Kavan. "I felt I was being awarded an opportunity to make a difference.

"In Canada, if you want to teach oncology to the men and women who will be tomorrow's medical pioneers, you have to include pediatrics, and you must have a clinical base to draw on," he explains. Happily for Kavan, his clinical base has grown steadily. "For the first time we're training undergraduate McGill medical students. We instruct 120 students every day for four months, which is a very intensive schedule. But we've received very good evaluations from the students, so we're quite encouraged. We've improved our residency programs, and next summer we're reactivating our fellowship program. I already have four very good candidates. I'm also quite proud of the fact that we're teaching PhD students."

When it comes to lab research, Kavan feels his program still has a long way to go. He wants to apply the current international focus on molecular biology to pediatric cancers. "We know that genetics and predisposition play an important role in pediatric cancers. The average age of children with cancer is between three and five, so environmental factors play a smaller part," he says. "When we uncover which genes are involved, we can then better predict cancer behaviour, patient prognoses and treatment outcomes."

To find answers to his questions, Kavan is eager to link with current research efforts at the MUHC. "There is great research being done by my predecessor, Dr. Michael Whitehead, and by Dr. Rima Rozen and her team," he says (Rozen is Scientific Director of Pediatric Research). "I want to collaborate with her pharmacogenetics program so that we can try to get a better understanding of the relationship between drugs and tumour biology. This will help us improve how we target specific tumour cells. But we're not there yet. First, we need two years to develop our lab research and to establish closer ties with the research initiatives at the adult sites.

"You know, we have a huge advantage over other pediatric hospitals because we have many hematology-oncology experts on the adult side who understand our needs. They're extremely supportive and they want to help, and this can only benefit our patients," he says. "I gave up pretty much everything to come here and do something good for patients, for this community, and for the MUHC and McGill. We have everything we need here. By pulling together, we can establish our program as a player at the international level." ❊

Portraits in Time

Thousands of individuals have helped advance the development of the McGill University Health Centre, and in every issue of *MUHC Health Perspectives*, we feature some of these significant contributors.

SIR THOMAS GEORGE RODDICK (1846-1923)

The wide stone gates at the Sherbrooke Street entrance to McGill University stand as a tribute to Dr. Thomas George Roddick, whose distinguished career began in 1868 when he received his medical degree from McGill and was one of the first graduates to receive the prestigious Holmes Medal.

Other firsts were to follow: Roddick was the first chief surgeon of the Royal Victoria Hospital and the first Canadian director of medical services in a military campaign (the Northwest Rebellion of 1885). A few years later, he introduced Joseph Lister's antiseptic system of surgery to the city when he brought it to the Montreal General Hospital, drastically reducing post-surgical mortality rates. In 1890, he became professor of surgery at McGill while working out of the General. Roddick also served as a member of Parliament for eight years and as dean of McGill's medical faculty from 1901 to 1908.

Roddick's crowning accomplishment came in 1912, when after nearly two decades of campaigning he succeeded in establishing the Medical Council of Canada, which provided a common system of examination for medical students throughout Canada. For his efforts, the council elected Roddick as its first president. He was further recognized two years later when he was knighted. His widow, Lady Roddick, donated the gates to McGill in 1925 in loving memory of her husband.

DR. HAROLD CUSHING (1873-1947)

At the turn of the nineteenth century in Montreal, Dr. Harold Cushing was a quiet but effective crusader in the field of pediatrics. One of the driving forces behind the creation in 1904 of the city's first pediatric hospital, called the Children's Memorial Hospital, he remained a key player there until his death more than four decades later.

Cushing spent 30 years trying to convince the faculty of medicine of his alma mater, McGill University, to establish an autonomous department of pediatrics. When it was finally created in 1937, one year before Cushing retired, the university rewarded his efforts by naming him the department's first head. Today, the McGill University Health Centre continues to recognize Cushing's remarkable contributions, honouring his memory with a bronze bust that graces the Forbes-Cushing Amphitheatre at the Montreal Children's Hospital. ❊


Everything's Coming Up Roses

Healing Gardens Dinner Auction raises $130,000

The magic of Expo '67 returned to Île Sainte-Hélène's Biosphere for one special evening on September 19. The occasion was the MUHC Foundation's first annual Healing Gardens Auction, an opportunity for over 200 guests to relive the exuberance and optimism of the time while generating a new set of memories that will be cherished for years into the future.

The brainchild of the event's chairman Stuart Webster, the Healing Gardens Auction set out to create six gardens across the McGill University Health Centre's five sites and at the same time to raise much-needed funds to purchase patient monitoring equipment for the nurses of the MUHC.

Taking their cue from their chairman, the members of the Healing Gardens committee — Bim Bushell, Donna Carroll, Tracy Cochran, Bob Giguère, Jackie Gilchrist, Raymond Girard, Charlie D. McKee Jr., Rachel Renaud, Stephen Sheunert, Leslie C. Thompson and Claire Webster — worked for months to identify locations where the gardens would be landscaped and to organize an event that would have guests dig just a little deeper on behalf of the MUHC's nurses. The results couldn't have been better.

Under the guidance of patrons Dr. Sylvia and Dr. Dick Cruess and Joanie and Alex Paterson, the guest list quickly filled up and the scene was set for auctioneer David Crack to cajole and encourage bidders to outdo one another for the honour of naming the gardens.

With sponsors covering the hard costs of landscaping the gardens and Daccord Webster Design donating the actual garden designs, all the money raised through the auction and silent auction will go to the purchase of equipment. Thank you to each of the table captains for contributing to a truly successful and inspiring event and to all the bidders and donors. The MUHC, its patients and its staff will reap countless rewards for years to come from your generosity.

To get a taste of what the evening was like, please visit the photo gallery on the Foundation's web site at www.muhcfoundation.com. ❇







Planting the seeds for the future; a few of the over 200 guests at this year's Healing Gardens Auction.

The MUHC Foundation is extremely grateful to the following individuals who agreed to captain a table for the evening:

Peter & Pippa Abraham
Gregor Angus
Mary & David Culver
Susan Curry
The Honourable James A. Grant & Nancy Grant
Sandra & David Hannaford
Sarah Ivory & Guthrie Stewart
Gail & Peter R. Johnson
Linda & Peter Leus
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