Dr. Mohit Kapoor’s mission to cure a painful disease

Arthritis research team believes two biomarkers hold the key to changing lives
Krembil unwaivering in the search for a cure for arthritis

Many Canadians take for granted the ability to perform simple tasks such as grocery shopping, taking a walk or mowing the lawn. For many others, however, these everyday tasks are anything but routine. That’s because one in six Canadians lives with arthritis, a painful, incurable disease that affects the bones and joints, and limits a person’s mobility and overall quality of life.

Arthritis patients are our parents and grandparents, our brothers and sisters, our friends and co-workers. And some day soon, many more Canadians will find themselves fighting this disease, which costs our economy an estimated $33 billion each year.

The joint pain and swelling associated with arthritis affects the well-being of patients in myriad ways. It robs them of basic function, it puts a strain on family and work relationships and its economic impact is far-reaching.

It’s for these reasons that the Arthritis Program at the Krembil Research Institute and the Campaign to Cure Arthritis exist. We see the effects performing day-to-day activities – but complications from the disease. It’s painful or difficult to leave the house, so they choose not to. Research surrounding OA has traditionally focused on the physical manifestations of the disease, severe joint pain and limited range of joint movement leading to difficulties performing day-to-day activities – but experts are realizing the need to investigate the disease’s impact on one’s quality of life within the broader social context.

Dr. Anthony Perruccio, an epidemiologist and scientist at the Krembil Research Institute, and Dr. Rajiv Gandhi, a Krembil clinician investigator and orthopaedic surgeon at Toronto Western Hospital, are currently looking at how OA can impact engagement in social activities, starting with examining the concept of healthy aging.

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Not participating in usual social activities and you can become depressed. And depression itself can increase the physiological sensation of pain, so you can see a downward spiral.”

On the flip side, the society of convenience in which we currently live is contributing to a less active population. Everything from library books to groceries can be delivered to one’s door, making it increasingly unnecessary for a person to leave home.

“There’s just less reason to be physically active,” says Dr. Gandhi, adding that this lack of activity may lead to obesity and in turn to increased risk of OA.

So why focus the research on the social impact of OA? Declines in social participation can contribute to worse individual health and greater societal and economic burdens.

“It’s costing an extraordinary amount of money to deal with this disease,” Dr. Perruccio says.

It’s a disease that affects millions, and almost two-thirds of the costs associated with the disease are indirect to healthcare costs such as short- and long-term disability and lost work productivity. And it’s only going to get more expensive, as people are now living longer.

“There are [extensive efforts] both in Canada and internationally to really understand healthy aging,” adds Dr. Perruccio.

“We’ve done quite well in the past century in limiting the fatal diseases and, as a consequence, longevity has gone up.”

Indeed, at the turn of the 20th century, an individual in Canada who lived past the age of 65 in 1901 would live no longer than 66 years. By 2009, according to the World Health Organization, this increased to 80 years. “So, the assumption, however, is that these extra years are ‘good years,'” Dr. Perruccio says. “But the longer you live, the longer you can assume a decline in quality of life.”

In parallel research, Drs. Perruccio and Gandhi are endeavouring to identify subgroups of the disease, with a goal of achieving more personalized approaches to medicine to better the treatment of OA.

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Measuring the social impact of osteoarthritis

Joint pain often robs people of the ability to enjoy life and can lead to depression

Daina Lawrence

Btween 4.8 and 5.3 million Canadians live with osteoarthritis (OA), and many begin to pull away from their social circles and neighbourhood networks as a result of complications from the disease. It’s painful or difficult to leave the house, so they choose not to.

The research will focus on how pain in OA leads to daily activity limitations and, in turn, to social participation issues, and what factors may exacerbate or dampen these effects. These studies will gather information from national and provincial health studies currently underway, while others will rely on patient surveys detailing the social limitations experienced as a result of living with OA.

Not surprisingly, the researchers expect to find not only that joint pain leads to missed life activities, but also how often this can lead to depression.

“There’s a pretty big overlap,” explains Dr. Gandhi. “As quality of life goes down, you’re

not participating in usual social activities and you can become depressed. And depression itself can increase the physiological sensation of pain, so you can see a downward spiral.”

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The mission to cure osteoarthritis

Dr. Mohit Kapoor and his team believe their discovery of two biomarkers could lead to better tracking and treatments.

Marjo Johne

“Osteoarthritis (OA) is a debilitating disease that affects more than one in 10 Canadian adults – a number expected to rise to one in four by 2040 as the country’s population ages. In this chronic condition, cartilage between bones is destroyed, and the fluid that cushions and lubricates joints breaks down and loses viscosity.

By the time OA shows up on X-rays or even through magnetic resonance imaging (MRI), there isn’t much for doctors to do except manage its symptoms, which include stiffness and pain in the joints. In many cases, the symptoms of OA – which are often complicated by significant weight gain as patients become less active – get worse over time to the point where the affected joint must be operated on and replaced.

“There’s no cure for osteoarthritis,” explains Dr. Mohit Kapoor, senior scientist and Research Director of the Arthritis Research Group at the Krembil Research Institute. “As of today, there are no approved drugs in the world that can stop this disease from progressing.”

This could soon change, thanks to a discovery at Krembil of a pair of biological markers for OA in the spine. About three years ago, Dr. Kapoor and his research team at the Buchan Arthritis Research Centre – comprising postdoctoral fellow Dr. Akihiro Nakamura along with Dr. Raja Rampersaud, a spine surgeon at Toronto Western Hospital and one of Dr. Kapoor’s research partners – began studying tissue biopsies taken from 55 patients with various stages of spine OA.

Using a tool developed at Krembil, the study looked at 2,100 microRNAs – small ribonucleic acid (RNA) molecules throughout the body that control almost 60 per cent of our genes – and spotted two particular microRNAs that increased significantly as destruction of the cartilage got worse.

“These two biomarkers – known as microRNA-181a-5p and microRNA-4454 – contribute directly to cartilage destruction and increased inflammation,” says Dr. Kapoor. “What we also found was that they depleted collagen – the most important component of cartilage – and..."
promoted the death of cartilage cells,” he says. “When you look at the relationship between the levels of these two [bio]markers and compare this to the clinical imaging using MRI, the MRI and the levels of the [bio]markers show a significant correlation.”

“So what does this all mean for patients with OA? “We’re on the cusp of developing a blood test to diagnose OA, along with injectable treatments to repair damaged cartilage,” Dr. Kapoor says. “Can we track arthritis, can we monitor the OA keeps getting worse. So what we’re working on now is a way of refining the progression.”

Dr. Rampersaud says the Krembil team has developed two new tools: one to detect OA biomarkers in patients’ blood and another to block the microRNAs that contribute to OA.

“The blockers, to turn off these destructive microRNAs, are designed to be injected into the joint,” says Dr. Kapoor. “Once they show promise, we will then move forward into the clinical phases.”

With a biomarker panel for blood testing and blockers to stop the culprit microRNAs, doctors will find it easier to diagnose OA in its early stages and halt the progression of the disease, says Dr. Kapoor.

“This test is not meant to replace clinical imaging, but rather to be a complementary tool for diagnosing the nature of the arthritis and to tell if your disease is early stage or advanced, so your doctor can decide on the most appropriate intervention,” says Dr. Kapoor. Dr. Rampersaud says the biomarker panel will also allow for a more effective and tailored approach to treatment. For instance, doctors who might normally recommend exercise could instead send a patient for surgery consideration more quickly because of biomarker panel results.

“If somebody has a really high level of biomarkers and is not likely to respond to conservative treatment such as exercise, then the doctor could say, ‘Let’s consider surgery sooner, rather than later,’” says Dr. Rampersaud. “Otherwise, a doctor could be prescribing exercise for years, while the OA keeps getting worse. So what we’re working on now is a way of refining the progression.”

Dr. Rampersaud says the Krembil team is also looking at how the biomarker panel can be used to assess patients’ progress after surgery or drug therapy. This would open the door to truly personalized medicine where treatment is fine-tuned based on each patient’s biological response to therapy.

“So the next step is researching how we can better track patients’ response to treatment,” says Dr. Rampersaud. “It’s a very exciting project – one that I think is going to change the life of OA patients, hopefully in the near future.”

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Finding the clues to diseases such as lupus and kidney disease is one of the most complicated research puzzles for modern medicine. But Dr. Joan Wither and her research team intend to meet that challenge head-on.

It can be a mouthful simply to explain the groundwork research that Dr. Wither, a senior scientist at the Krembil Research Institute and a rheumatologist in the Arthritis Program at Toronto Western Hospital, is conducting.

Her research program focuses on identifying the genetic and immune system abnormalities that lead to systemic autoimmune rheumatic diseases (SARD), including systemic lupus erythematosus (SLE), Sjögren’s syndrome and scleroderma.

Dr. Wither is hunting for biomarkers for these diseases, which are related. A biomarker is exactly what it sounds like – a measurable substance in a person, or any organism, that indicates some sort of change such as an infection or a disease.

Her SARD research has four goals, the first of which is to identify biomarkers for the early identification of patients at risk of developing SARD. Dr. Wither is also looking to evaluate therapies for prevention and to map and understand the immune mechanisms that lead to “flares” in autoimmune diseases and their progression, so there can be better diagnosis and treatment for every patient’s disease. Finally, she says, it’s important to develop diagnostic tests using biomarkers to monitor how SARD progresses and anticipate when it leads to more severe problems, such as renal (“kidney”) disease.

Dr. Wither is looking at people with autoimmune disease and tailoring treatment to the nucleus of cells.

Dr. Wither says there can be better diagnosis and treatment for future treatment programs. Dr. Wither has co-written a paper on her work that has been recently published and other papers are being prepared for publication soon that will share her findings with her peers around the world.

Having a positive ANA test doesn’t necessarily mean that these patients have illness. Sometimes antibodies develop that are found in SARD. The amount and pattern of these antibodies can be tested through an antinuclear antibody (ANA) test.

Some people have abnormal levels of these antibodies. “We focus on the patients who have positive ANA tests,” Dr. Wither explains. The project, one of several in which Dr. Wither is involved, is just starting to produce results that can be analyzed for future treatment programs. Dr. Wither has co-written a paper on her work that has been recently published and other papers are being prepared for publication soon that will share her findings with her peers around the world.

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LUPUS & KIDNEY DISEASE

Exploring the link between lupus and kidney disease

Lupus is known as the disease with a thousand faces. There are many types, and the severity, symptoms, and frequency of flare-ups can vary. Women of child-bearing age (15 to 45 years old) are most affected, and in Canada, the estimates of the number of patients vary widely, ranging from 15,000 to 50,000.

What is known about lupus is that about 70 per cent of lupus patients develop kidney disease. “Of those, probably 10 to 15 per cent [of patients] will have significant renal involvement – ultimately leading to renal failure and requiring dialysis or a transplant,” says Dr. Joan Wither. The problem with kidney disease is that once it appears, it’s easy to diagnose, but we actually don’t have any really good [bio] markers that tell whether the kidney disease is responding to therapy. We only detect kidney disease by the damage that occurs,” Dr. Wither says. She is conducting research to change this. The research, published in Arthritis Research & Therapy last year, is incredibly complicated in its science, but deceptively simple in its premise. Dr. Wither and her team are looking for biomarkers for kidney disease, using urine samples.

“We became interested a number of years ago, so we gathered a large cohort of patients who had flare-ups of kidney disease,” she explains. “They were treated and followed over time, so we knew exactly what was going on in their kidneys, and at the same time, we obtained urine samples. The kidney produces the urine and [that] tells us whatever is going on in the kidney,” says Dr. Wither.

“We also obtained urine from patients with recent kidney biopsies and samples from lupus patients who had flare-ups that led to the development of their kidneys. Finally, we obtained samples from people who had kidney disease and had already been treated, and it had settled down. “We found seven [bio]markers that could give us insight into the kidneys’ involvement in lupus and may replace the need for repeat biopsies in the future,” she says.

This research is important because it may also enable doctors to predict a flare-up before the damage occurs and adjust their therapy to get the best response to treatment.

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Using stem cells to fight osteoarthritis at the source

Determined to find a cure, arthritis team digs into their own pockets to fund the fight against the disease

A clinical trial involving patients with osteoarthritis (OA) taking place at the Krembil Research Institute is using stem cells to better understand and help find a cure for one of the most debilitating health problems of our day.

Supported by the Campaign to Cure Arthritis – which includes $8 million personally donated by all of the physicians and surgeons in the Arthritis Program at Toronto Western Hospital – the vision-ary study focuses on the evolving field of regenerative medicine to help reduce inflammation and replace lost cartilage.

The study at Krembil, the first North American mesenchymal stem cell trial for treating knee OA, could allow clinicians to repair damage biologically – at the source – rather than having to perform surgery to replace disease-ravaged joints in patients’ hips, knees, spines and shoulders.

Mesenchymal cells are found in various tissues and fluids, are able to modulate the immune response and can support tissue regeneration.

“We want to put ourselves out of business as joint-replacement surgeons,” says Dr. Nizar Mahomed, a senior scientist at Krembil, who is also medical director of the Arthritis Program and a leading orthopaedic surgeon at Toronto Western Hospital. “We want to change the trajectory of this disease.”

The philosophy focuses on improving the knowledge of OA – which accounts for 80 per cent of arthritis cases and affects patients’ functioning, quality of life and productivity – and finding a mechanism to cure it from within. Regenerative medicine may indeed hold the key to changing the environment in which degenerative joint diseases develop and worsens. Fundraising efforts to back arthritis research were kick-started in 2011 by 10 orthopaedic surgeons, the campaign founders.

They felt strongly about the need to improve care for patients with arthritis, each personally donating $125,000 over five years to bring forward this project. The vision is to see a world where patients do not suffer from degenerative joint disease and are able to manage their arthritis as a chronic condition.

The study takes patients with osteoarthritis of the knee and rotates them into one of two treatment groups: stem cells or placebo (saline). Researchers are monitoring patients for four years to see if stem cells produce better results than a placebo.

OA is a chronic disease that affects millions of people across the country and the world. Arthritis affects up to 20 million people in Canada, and more than 350 million people worldwide. It is the second leading cause of disability in the country. The cost to the Canadian society is estimated to be $56 billion annually, and the cost of lost productivity is estimated to be $2.6 billion annually.

It is a degenerative disease, affecting the movement of a joint and leading to loss of function and pain. In the knee, for example, it can lead to a person losing their ability to walk or performing daily activities and can affect quality of life. The current treatment is to manage symptoms, and stem cells could help stop and reverse the degeneration.

The clinical trial is being conducted at Krembil, and the goal is to enrol 24 patients by mid-2019 for the OA treatment group and to enrol five patients in the control group.

“We hope to show that the trial is feasible and that we can enroll patients at a rate that is not too difficult, and that the treatments can be safely and effectively given,” says Dr. Mary Gooderham, director of the Arthritis Program and scientist leading the study.

It is also the first OA clinical trial in the world to assess the role of mesenchymal cells in producing new cartilage and bone tissue, and the first to examine the potential of both autologous and allogeneic mesenchymal stem cells for the treatment of OA.

Mesenchymal cells are derived from bone marrow and are known to have the ability to differentiate into bone, cartilage, muscle, fat, and other cells. They can also promote the growth of new blood vessels, inhibit the growth of inflammation, and protect bone and cartilage.

The patients enrolled in the study are divided into two groups. The first group will receive autologous mesenchymal stem cells taken directly from their bone marrow, while the control group will receive placebo.

The patients in both groups will receive a single injection of stem cells into the knee joint and will have biopsies taken directly from the knee joint (28 days and 12 months after treatment) to measure the bone and cartilage production.

“We will be looking at the markers of bone and cartilage, and those will allow us to see if there’s any difference between the two groups,” says Dr. Gooderham.

If the results are positive, the study will move forward, with the goal of showing the mechanism by which stem cells work.

“The goal is to prove that stem cells can be used to regenerate cartilage,” says Dr. Gooderham. "We don't want to just show improved function, we want to show improved structure."
years, for a collective gift of $1.25 million. And last year the surgeons – now 12 of them – renewed their commitment with new gifts totalling $1.5 million. To date, the Campaign to Cure Arthritis has raised $50 million – double the original target.

Dr. Mahomed, who is among the donors, performs some 300 hip and knee replacements annually, surgery he says is considered “the gold standard” for treating OA. Yet as many as one-quarter of patients continue to experience pain after the procedure. All patients experience a loss of mobility, and the devices have a finite lifespan, so they must be replaced when worn out.

Advances to date in OA research, such as developing new biomaterials and techniques for the artificial implants to alleviate pain and restore function, have focused on treating the symptoms of the disease. But this frustrates clinicians, says Dr. Mahomed, who is also the Nicki and Breyce Douglas Chair of Orthopaedic Surgery and the Smith & Nephew Chair in Orthopaedic Surgery Research. “There is no treatment that prevents, halts the progression or reverses the stage of the disease.”

Using the body’s own stem cells to reduce inflammation and regenerate the damaged osteoarthritic joint tissue, essentially restoring it back to its original healthy state, is a viable option, says Dr. Armand Keating, a Krembil scientist internationally recognized for his work in stem cell transplantation.

The research involves mesenchymal stromal cells (MSCs), which are present in the bone marrow and other tissues. These “nurturing” cells can have anti-inflammatory properties and can stimulate the regeneration of cells in damaged tissue. Dr. Keating’s research focuses on understanding more about how MSCs function to identify a cell population that can help alleviate pain and restore function.

Researchers will isolate and grow those cells that have been identified, Krembil says, with the most promising capacity to have effective therapeutic properties. Once these cells have been identified, Krembil researchers will isolate and grow those with the most promising capacity to have restorative and anti-inflammatory properties, optimizing their impact.

“We need to tweak and modify these cells to improve that response,” says Dr. Keating, who is optimistic about the results of the research and advances in the field of cell therapy. “We hope to achieve some fairly significant milestones in the next five years.”

Krembil has the potential to become the global leader of regenerative medicine in orthopaedics, he predicts. “Funding is critical to move these studies forward. Medical science has proven that when the right resources are applied, we can make progress on ways to prevent, treat and cure these types of chronic diseases.”

Dr. Keating says that UHN’s orthopaedic surgeons “need to be commended” for undertaking, moving forward and even financing research that could make artificial joint replacements obsolete. “It’s extraordinary - almost unprecedented. They’re really interested in finding out the best way to deal with this disease, and it might not be surgical, although that would still be quite some time in the future,” he comments, noting that even if this happened, orthopaedic specialists would still be required to deal with cases of trauma and to administer injections in joints.

Dr. Mahomed says that breakthroughs in stem cell treatments for OA would alleviate a major source of disability among Canadians, ease its impact on individuals and their families, provide clinicians with better strategies for managing degenerative joint disease and reduce the enormous cost of its management in the healthcare budget.

“We’re going to bankrupt our system if we don’t find better ways of dealing with this problem,” he says.

Understanding the different mechanisms associated with the disease, and genetic profiles associated with the disease, including why patients respond differently to therapies, can help to tailor treatments to the individual, leading to so-called personalized medicine. This would turn standardized, one-size-fits-all treatments for osteoarthritis into a system of predictive, preventive and precise care, with the ultimate goal of being more cost-effective.

“The whole world of science in this area is evolving in a good way,” Dr. Mahomed adds. “We’ve got a problem that we need to solve, and we’re solving it.”

“We want to put ourselves out of business as joint-replacement surgeons. We want to change the trajectory of this disease.”

– Dr. Nizar Mahomed

“Personally invested in finding a cure.”

Physicians and surgeons in the Arthritis Program at Toronto Western Hospital have pledged $3 million of their own money to help find a cure.

“When you get that sort of commitment, it’s hard to say no [to supporting that].”

– Tony Fell, founding co-chair of the Campaign to Cure Arthritis
Discovering new ways to improve the quality of life for Canadians with ankylosing spondylitis

AS is a severe, painful form of arthritis that affects more than 400,000 Canadians. Chris Atchison

Gerald Major was about 12 years old when his body began to change. And not solely in the typical way that a teenager’s body transforms and grows, somewhat awkwardly, before settling into adulthood. This was different.

Gerald, a hockey player and top-performing track and field athlete, began to feel that his knees were “loose” after competitions and training. He put it down to an active lifestyle and rigorous athletic training. Soon, recovery times began to lengthen, and his ankles also began showing signs of stress.

“My older brother had knee issues, so I wrote it off,” the Oakville, Ont., resident recalls. “Medicine was different then.”

It wasn’t until he was about 21 years old that Gerald was diagnosed with ankylosing spondylitis (AS), a severe form of arthritis that affects more than 400,000 Canadians.

The disease causes the immune system to become overactive, attacking the joints of the spine and pelvis, and causing the formation of bone spurs. It can also eventually lead to spinal fusion and back curvature, and in severe cases, paralysis—usually from injury.

Common symptoms include pain and fatigue, as well as inflation of the eyes. A recent study by researchers at University Health Network (UHN) also found that there is a higher rate of cardiac- and stroke-related mortality among AS patients than those without the disease.

And AS is about three times more prevalent in men than in women.

Now in his mid-40s, Gerald, a former hedge fund executive, has been on long-term disability for five years and has undergone seven surgeries to address joint damage from his AS. Another operation is on the horizon.

He says that the stress and discomfort of living with the disease eventually began to take a psychological toll.

“When anything physical hurts you like that, it’ll eventually affect your mind,” he says. “I think eventually my mind took me out of the game. My body was just a mess. I was crumbling.”

But there is increasing hope for patients such as Gerald, thanks in large part to rapid advancements in the understanding, detection and treatment of the disease.

While there is no known cure for AS, advanced biologic drug treatments—genetically engineered medicines using molecular biology—are producing rapid improvements in quality of life for those living with AS. In some cases, the medicines are delaying the progression of the condition.

“These drugs can often be life-changing in terms of quality of life,” explains Dr. Robert Inman, a rheumatologist and co-director of the UHN Spondylitis Program.

“Patients will sleep poorly, they’ll wake up with morning stiffness and during the day, the pain and stiffness take a major toll on their functioning. If you look at biologic trials, significant improvements in back pain, which is the primary outcome, is achieved in about 65 per cent of patients.”

These same patients are also displaying significantly better outcomes when treatment is begun early.

But Dr. Nigil Haroon, also a rheumatologist and co-director of the UHN Spondylitis Program, notes that despite major improvements, detection and diagnosis of the disease remain a challenge.

That’s because AS symptoms often mimic those displayed by people with chronic back pain, and the symptoms can be easily missed by physicians, sometimes resulting in diagnosis delays of five years or more.

“Imagine a busy family physician or orthopaedic surgeon seeing hundreds of back pain patients. How do you make that diagnosis when there is no dependable distinguishing feature?” he asks.

“Not everyone can be referred for AS. We can talk about young age, morning stiffness and similar AS-like features, but in practice, they do not help much. Even MRI [magnetic resonance imaging] has its limitations, and early back pain, with its very subtle changes, is very difficult to see in an X-ray.”

Then there’s the lack of a specific test for AS, leaving the diagnosis up to a clinician’s professional judgment and expertise.

“AS-related conditions affect about [up to] 11 per cent of individuals in Canada, compared to the more than 40 per cent of individuals who have chronic back pain some point in their life,” Dr. Haroon points out, underscoring the potential for misdiagnosis.

In addition, many young patients will initially seek assistance from physiotherapists or chiropractors—clinicians who may not be as experienced in AS detection and diagnosis—for what they believe to be simple back pain.

“It’s a healthcare system challenge,” Dr. Inman comments.

“That’s why Drs. Inman and Haroon are working with physiotherapists, chiropractors and family practitioners to track a better model for patient referral, with the focus on referring the right patient at the right time to a rheumatologist, while also producing educational materials to boost understanding of the disease among healthcare professionals. Developing personalized biologic treatment regimens is another priority.

“To do that,” Dr. Inman says, “we use several different modalities, including the clinical profile of the patient, but increasingly genetic and immune profiling.”

We look at which aspect of the patient’s immune system is turned on at that time that would allow us to target treatment to that particular patient. The hope is that by doing so we can develop drugs which not only control the disease but cure it.”

Their team is also working diligently to advance diagnosis and treatment of AS, with a focus on creating change through their research.

The UHN Spondylitis Program is taking a lead role in studying the gene HLA-B27 (a gene present in the majority of AS patients), for example, with a focus on what activates the gene in some patients but not others. Other researchers are looking at what role, if any, Macrophage Migration Inhibitory Factor (MIF)—which is involved in bone formation and is found in much higher levels in AS patients—might play in the progression of the disease.

A better understanding of MIF could also improve AS detection and diagnosis. For Gerald, the biologic drug Infliximab, which he’s been taking for nearly 10 years, has offered relief from AS symptoms and a far greater quality of life. He goes as far as to call its effects “game-changing.”

But he feels that the key to managing and living a productive life with a disease such as AS—along with drugs and other therapies—is for patients to educate themselves and become active in the management of their illness. He now volunteers his time to teach a pain-management class for arthritis patients.

“My message is, ‘Get engaged and take care of your health,’” he says. ■

KREMBIL
Osteoarthritis (OA) often strikes feet, knees, spines, hips and hands. When this cartilage-destroying condition targets hands, many times the hitchhiker’s tool bears the brunt of the damage. Exceptionally common and painful, OA of the thumb can become debilitating. This often-overlooked digit comprises 40 to 50 per cent of hand function. Yet, research into hand and thumb OA, as well as what can be done to improve the condition, has not been wide-ranging or abundant.

Scientists at the Krembil Research Institute are now conducting a clinical trial in which biomarkers are being collected from surgery patients for analysis. Biomarkers are measurable, organic substances whose presence can indicate disease, infection or environmental exposure. Learning more about biomarkers could help scientists find a control or a cure for OA.

Dr. Heather Baltzer, the Krembil clinician investigator leading the trial, says the research is needed because previous studies of hand OA have produced disparate conclusions.

That’s known is that hand OA is more common in women, which could be attributed to changes in estrogen levels, and in those aged 65 and older, she says.

In other parts of the body, obesity is a known risk factor for OA because of extra strain on weight-bearing joints such as the hips and knees. But with the hands, there isn’t the same impact from strain. So studying OA in the small joints of the hand may provide insight into other causes.

“This is really a good first step,” says Dr. Baltzer, also a plastic surgeon who specializes in hand surgery at Toronto Western Hospital’s Hand Program. She is specifically focusing on chronic conditions such as arthritis of small joints of the hand and wrist, acute trauma reconstruction (reattaching severed fingers) and reconstructions from cancer damage within the hand.

A cure for OA is not imminent and treatment is limited. “When we see patients early, we use steroid injections or use splinting,” says Dr. Baltzer. A Nova Scotia native who did her undergraduate medical training and residency training in plastic surgery at the University of Toronto. She also completed one year of subspecialty fellowship training at the Mayo Clinic in Rochester, Minn.

Some people, says Dr. Baltzer, respond to steroid treatment, then stabilize and are able to function well. However, others receive no relief from anti-inflammatory drugs, so their hand or thumb OA becomes unbearable. Also, she points out, some hands or thumbs will display terrible OA damage in X-rays, but patients report no pain. She acknowledges that pain is subjective, and people tolerate it differently.

“But at a certain stage, there is pain all of the time. People wake up at night in pain,” she says. That is when surgery is suggested.

For Michael Widdifield that was just the case. In October 2016, Michael, 59, was the recipient of Dr. Baltzer’s expertise, when she and her team operated on his right hand. “I’m just so happy and very pleased with how the surgery went. I don’t have chronic pain any more,” says Michael, a retired Newmarket, Ont., resident.

Starting at age 17, Michael held construction jobs, wielding sledgehammers and manoeuvring small equipment, eventually becoming a tower crane operator. “I’ve had problems, like carpal tunnel syndrome, with my wrists since I was in my 20s,” he says. “I’ve always had pain.”

One day, about three years ago, he suddenly packed it in after the OA pain overwhelmed him. “I couldn’t work any more. I climbed down from the crane, and that was my last day.” Soon after, tests showed that not only were his hands and wrists full of OA, but also his whole body was plagued.

Taking up to seven heavy-duty painkillers per day, he asked his family physician to arrange wrist-replacement surgery. His doctor referred him to Dr. Baltzer, and their meeting was promising.

“She’s been fantastic from day one,” he says. “She was very confident. She knew what was wrong with me and told me she could fix it. And she treated me with a lot of respect and understanding.”

Michael says his surgery involved the removal of bone at the base of the thumb, shaving another nearby bone, splitting tendons and then weaving the tendons between bones. Following the three-hour procedure, he wore a cast for six weeks. Michael is taking fewer painkillers and appreciating a life with diminished pain.

“I can’t thank her enough for doing what she did,” he says.

While Michael’s OA could be attributed to his past occupations, Dr. Baltzer wants to better understand OA. “In end-stage OA patients, they’re in so much pain,” she says.

Her hope is that the biomarker study and her team started in 2016 will lead to remedies that eliminate pain and restore function.

Expected to finish the study by the end of the year, the clinical trial team plans to collect biomarkers from 10 to 15 patients who will undergo hand surgery for their thumb OA after steroids or splints failed to reduce pain. To date, the male and female patients have all been aged 50 and over, Dr. Baltzer says.

Biomarker material being collected includes synovial tissue, synovial fluid, blood, urine, cartilage and bone. The samples are frozen and stored in an arthrosis biobank at Krembil.

Working with world-leading experts, including cartilage biologists and stem cell researchers, Dr. Baltzer says Krembil is “a really ideal venue to come up with answers.”

While hundreds of biomarkers exist, approximately 20 that are more common in those with OA will be studied. They are also the elevated biomarkers in those with OA.

As the trial progresses, Dr. Baltzer wants to develop and refine the techniques used to acquire biomarker samples from patients. She will also be looking for patterns in those biomarkers that differ from the norm. The results will then be applied to develop the next level of research.

“I want to understand what could be a future target for treatment, and the difference between patients with pain and those without,” she says.
Researchers have dedicated their careers to helping lupus patients

Autoimmune disease affects one in 1,000 Canadians and primarily strikes women of child-bearing age

David Israelson

Christina Girgenti was 21 years old when she got the diagnosis that would change her life. She had been experiencing painfully inflamed joints and extreme fatigue, and blood tests revealed the cause: lupus. It was a disease she knew little about.

“When I was diagnosed, I had no idea of the severity of the illness,” says Christina, now 35. “It was very painful. It was debilitating. I was very limited in what I could do.”

Lupus is an autoimmune disease that affects one in 1,000 Canadians and primarily strikes women of child-bearing age. Because lupus can attack any tissue in the body, the symptoms can vary from easy to see, and may include headaches, painful joints, skin rashes, mouth ulcers, fatigue, fever and many others. In addition, the inflammation caused by lupus can attack organs such as the brain, the lungs and the heart. In Christina’s case, her lupus flare-ups affected her kidneys.

“Over time, the inflammation caused my kidneys to slowly get worse, until I lost kidney function,” she says. “I was on dialysis for a year.”

Because of the severity of her symptoms, Christina didn’t know whether she would ever be able to pursue a career or have children.

Now, 14 years after being diagnosed with lupus, Christina is symptom-free, with a flourishing career as a registered nurse, a husband and a two-and-a-half-year-old son, Charlie. She attributes her current health to a 2012 kidney transplant and the ongoing, diligent care of Dr. Murray Urowitz and his team at the Lupus Clinic at the Toronto Western Hospital.

“I truly believe that if I hadn’t met Dr. Urowitz, I wouldn’t be here today,” says Christina.

Dr. Urowitz is a researcher at the Krembil Research Institute, a rheumatologist and clinical director of the Centre for Prognosis Studies in the Rheumatic Diseases at UHN. He has dedicated his career to helping lupus patients like Christina lead happier, healthier lives, while also working to unravel the mysteries of a very complex disease.

“In lupus, something goes wrong with the immune system, so that rather than being protective and warding off outside invaders, the immune system actually [attacks] the body itself,” he explains.

“But the questions are: Why do some people get kidney inflammation, while some people get inflammation in the brain or the lungs? And, ‘Are there subsets of [lupus] that are going to respond to treatment differently than others?’”

At the heart of Dr. Urowitz’s quest to answer these kinds of questions is a treasure trove of data. For more than 30 years, he has been developing a lupus database of patient information, from physician assessments to lab tests to patient-reported outcomes. Currently, the computerized database contains information about 1,900 patients and 48,000-plus visits, making it one of the richest and most expansive lupus data collections in the world.

As Dr. Urowitz puts it, he’s a scientist with a data lab. Instead of test tubes and chemists, there are computer programmers and biostatisticians. “The basis of the research is to use the data lab to try and understand this disease better, by dissection and breaking it down,” he says.

Over the years, insight gleaned from the lupus database has led to important discoveries that have had an impact on the diagnosis, prognosis and treatment of the disease. Dr. Urowitz and his team have been able to map the course of their patients’ disease, allowing them to group together, or phenotype, patients into clinical subsets. Lupus has traditionally been identified as a “relapsing-remitting illness – in other words, it comes and goes. But the team found that some patients are “monophasic,” meaning they somehow kick the illness for good.

Some patients have flare-ups for one to three years, then it goes away, and for the next 20 years, nothing. They’ve reset their immune system,” says Dr. Urowitz.

“But right in the centre is the patient. If you pay attention, you can learn how to deal with it better,” says Dr. Touma.

Another example of the power of data is in understanding the impact of pregnancy on lupus. Researchers have found that women with active lupus have a higher risk of flare-ups or pregnancy loss.

“Now we tell our patients with lupus who want to be pregnant, ‘All you have to do is work with us to get your disease inactive for a year or two and then you can go for it,’” says Dr. Urowitz. “We learned that by going back to the data and asking, ‘Who had the complications and who didn’t?’ changed [our] practice. And now I have about 300 godchildren.”

One of Dr. Urowitz’s current passions is identifying lupus comorbidities — complications that are not from the disease itself, but are a consequence of the disease or its treatment. One such example is premature atherosclerosis, where young women whose lupus is now controlled develop heart attacks and strokes at a younger age than ordinarily expected. This has alerted physicians to screen patients earlier for evidence of atherosclerosis and to initiate appropriate therapy. It has also stimulated research into the role of inflammation in the development of atherosclerosis in the general population. Dr. Urowitz and his team have also been able to identify osteoporosis (decreased bone strength) and osteonecrosis (bone death) as important comorbidities in patients with lupus, likely due to long-term corticosteroid treatment. Another comorbidity they are working on is decoding is cognitive impairment in lupus patients. That investigation was prompted when Dr. Urowitz noticed more and more patients telling him they were having difficulty finding words or remembering names.

“When you hear that once or twice, you don’t pay much attention. But when you start hearing it over and over again, you start paying attention,” he says.

Through initial testing, Dr. Urowitz and his team determined that people with lupus do have more cognitive abnormalities than normal, age-matched people.

Now, Dr. Zahi Touma, a rheumatologist, clinician-scientist at Krembil and another researcher at Toronto Western Hospital’s Lupus Clinic, is working on developing a standardized test to help lupus patients understand their cognitive decline in lupus patients. By monitoring patients with a standardized test, says Dr. Touma, researchers could identify which patients are experiencing cognitive decline, and ultimately determine why it’s happening.

“Cognitive impairment could be related to the inflammation within the brain. But it could also be related to blood clotting, which we often see in lupus patients. And there are thoughts, as well, that maybe it’s a consequence of the lupus and the corticosteroids [used to treat the inflammation],” says Dr. Touma. “The better we can measure it, the better we can understand it. And maybe, down the road, we will be able to develop a preventive measure or a treatment for that.”

Dr. Urowitz says patient input is essential to his research, and he has brought patients a valuable part of his team. “When I describe my team, I say, ‘There’s the principal investigator, a full-time program and a full-time biostatistician and a team of physicians, including Drs. Dafaia Gladman and Jorge Sanchez-Guerrero and many fellows from here and around the world,’” he says.

“I think in the centre is the patient. If she’s not there, all of this is gone. So it’s a very special relationship.”

Though Dr. Urowitz’s research is in remission, Christina still gets a checkup with Dr. Urowitz every three months. And she says she’s always going to take part in the study at the clinic.

“I had two family members who died from lupus who died from complications of this, and back then they didn’t know as much as they do now. So I think going to help them gain more knowledge and discover new things about lupus, I am more than willing to do it.”
PSORIATIC ARTHRITIS

Can biomarkers pinpoint the triggers behind psoriatic arthritis?

One-third of Canadians with psoriasis also develop inflammatory arthritis in the affected joints

There is no cure for psoriatic arthritis, but Drs. Dafna Gladman and Vinod Chandran of the Krembil Research Institute are part of an international group looking for the cause, improved diagnostics and more effective treatments.

What exactly is psoriatic arthritis?

Dr. Gladman, a Krembil senior scientist, rheumatologist and co-director of the Psoriatic Arthritis Clinic at Toronto Western Hospital, explains it is a form of arthritis that occurs in people with psoriasis. Psoriasis is a chronic inflammatory skin condition that occurs in up to 3 per cent of the general population. Psoriatic arthritis is an inflammatory arthritis which presents with pain and swelling in the affected joints and affects about one-third of people with psoriasis.

“In about 10 to 15 per cent of patients, the psoriasis either comes first or at the same time as the arthritis,” says Dr. Gladman. “That’s a major question for which we don’t have a definitive answer, but we have a number of ideas,” says Dr. Gladman. “We’ve done some studies, and we’ve demonstrated that environmental factors such as infection and injury are risk factors for the development of psoriatic arthritis and even psoriasis.”

Other risk factors include obesity and genetic history.

Can biomarkers pinpoint inflammatory arthritis in the affected joints and even psoriasis? Dr. Vinod Chandran’s goal is to shorten the time between when patients with psoriatic arthritis visit their primary doctor and when they receive a diagnosis.

Dr. Vinod Chandran’s goal is to shorten the time between when patients with psoriatic arthritis visit their primary doctor and when they receive a diagnosis. What triggers psoriatic arthritis is still unknown, but there are some intriguing avenues of research.

“Commonly, people go to a doctor, and they’re reporting having arthritis – complaining of pain – and receiving a diagnosis,” says Dr. Gladman. “Then we’re also looking for biomarkers for the development of comorbidities [the presence of more than one disorder or disease – such as heart disease] because we know that psoriasis and psoriatic arthritis are not just about skin and joints.

Dr. Chandran says that they’ve looked at blood, skin and joint fluid, and they are looking at 10 biomarkers. The hope is to have a test within the next few years, depending on funding, that can be used by primary physicians and dermatologists.

“The goal is to shorten the time between when patients visit their primary doctors – complaining of pain – and receiving a diagnosis.”

“In fact, we want to get it to less than six months, because our research partners in Ireland have demonstrated that even a six-month delay in diagnosis is detrimental,” says Dr. Gladman.

The impact of arthritis on the Canadian economy is approximately $33 billion each year. By 2031, this is expected to double.

Dr. Dafna Gladman is pursuing intriguing avenues of research into psoriatic arthritis, though the trigger for the condition remains unknown.

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“In fact, we want to get it to less than six months, because our research partners in Ireland have demonstrated that even a six-month delay in diagnosis is detrimental,” says Dr. Gladman.
In 2013, Taube Zeitman started experiencing mild back pain. She didn’t think it was too serious — maybe a herniated disc. But it was uncomfortable enough that she went to her doctor. Not much was done during the visit, other than a referral to a physiotherapist, who gave her several exercises to do. But over the next six months, the pain got worse. “There was pain down my leg. I couldn’t stand, and I could only walk slowly,” she says. Taube figured it would take a year to see a back specialist and even longer to get an MRI (magnetic resonance imaging) scan, but her physiotherapist said she’d only have to wait a few weeks. She was right. Two weeks later, Taube met with Dr. Andrew Bidos (chiropractor) in Dr. Raja Rampersaud’s interprofessional pain clinic at Toronto Western Hospital, who determined that an MRI was indeed necessary in her case. Unfortunately, Taube’s diagnosis was more than a herniated disc: arthritis, spinal stenosis and spondylolisthesis — all painful back ailments.

Fortunately, Taube was able to see a back specialist quickly and get more information about her ailments. But how was she able to get her appointment so fast when others have to wait months? Her physiotherapist is part of a new program called the Inter-professional Spine Assessment and Education Clinic (ISAEC). Launched in 2013 by Dr. Rampersaud, a Krembil clinician investigator and orthopaedic surgeon at Toronto Western Hospital, ISAEC is an innovative shared-care model that gives patients and other non-specialist medical professionals a better understanding of what they’re dealing with. As part of the shared-care commitment between family doctors, physiotherapists, chiropractors and spine specialists, it also gets patients in to see specialists faster than they would otherwise if deemed necessary.

The program, which was seed-funded by philanthropy, was born out of five years of research conducted by Dr. Rampersaud and his team. As a spine specialist within six weeks.

One of the problems he found was that people would often get passed around from one provider to the next, until they landed in the right place. A process of elimination is not only poor care, but costly in both time and money for patients and the healthcare system. Many would be given an MRI as a default procedure, which is not only expensive, but other things often show up in those scans that end up being investigated further, even if they don’t need to be. “We all have some degree of wear and tear but that spine pain means it is the cause of the pain,” he says.

Other issues weren’t identified early enough because family doctors often don’t have adequate back or musculoskeletal (joints, bones and muscles) training. “It’s a vicious cycle for patients of not getting better, and I’m not getting further tests or treatment,” he says.

Dr. Rampersaud’s research led to the creation of ISAEC. The doctors get information on how to better identify and manage a back problem, and for patients who are not responding to initial management, timely access to a network of providers who specialize in back and arthritis conditions. And the patient is seen quickly. The program mandates that they see an advanced-practice clinician, such as a physiotherapist or chiropractor, within two weeks and a surgical or medical specialist within six weeks.

It also gives people like Taube a clearer picture of what’s going on. Her physiotherapist had an idea that Taube might have spinal arthritis, so she was able to give her relevant exercises to ease the pain. Taube was happy to do them because she understood how they could help, and Dr. Rampersaud benefited because now, by seeing the patient, he can help. “We can give patients a more comprehensive assessment,” he says.

The program, which has been in a pilot phase, was recently given the green light to expand across the province by the Ontario government. Dr. Rampersaud also wants to start looking at patient-care issues such as access to other musculoskeletal conditions. He thinks the ISAEC program can be extended to people experiencing pain in other joints such as the shoulder.

His colleague Dr. Christian Veillette, an orthopaedic surgeon and shoulder specialist at Toronto Western Hospital and a Krembil clinician investigator, started looking at the role of advance-practice clinicians or extended-scope practitioners in his work. Examining shoulder referrals in a more formal fashion, he quickly realized that the same problems existed. “We found that almost 60 per cent of referrals for shoulder conditions have the incorrect diagnosis at the time of referral and a large majority have undergone inappropriate diagnostic imaging,” he says. As a result, they have modelled the Extended Scope Practitioner (ESP) Clinics on the core elements of ISAEC.

In the meantime, the Arthritis Program at Toronto Western Hospital continues to innovate. It’s testing a mobile app that providers in the program can use to create and manage personalized patient-care plans and, with consent, track a patient’s progress. The app, developed by Drs. Veillette and Rampersaud, asks both the provider and the patient to fill out a brief questionnaire with key information. The app then automatically develops a care plan the patient can use.

The app is also a part of the Arthritis Centre for Health Transformation, another program started by Drs. Rampersaud and Veillette. The Centre is working to further advance innovative models of care — looking at how technology, through computer-based learning systems, can be used to provide greater insights about individual patients. The more information they can get before a patient comes in to the hospital (for example, through submitting data from home), the more productive the hospital appointments will be.

“We spend more than 70 per cent of the time collecting information and only the last few minutes of a visit on what we’ll do,” says Dr. Rampersaud. “With technology, we can spend more time on the things that really matter.”

As for Taube, she may need surgery. She’s not yet sure whether she wants it, but now, thankfully, she has access to a team of medical professionals. Taube believes that if it wasn’t for ISAEC, she’d still be waiting to be seen. “I’d still need to be examined, and it could have been another two years before I’d be able to have surgery,” she says.

Innovative spine assessment clinic fast-tracks information for patients in pain

Frustration and empathy led to the creation of a new shared-care model

Bryan Bortykowski

Dr. Christian Veillette holds a tablet featuring Dr. Raja Rampersaud. They have created a mobile app that providers in their program can use to create and manage personalized patient-care programs and track progress.
Dynamic donors play a key role in advancing arthritis research

Tony Fell and Bryce Douglas are instrumental in campaign progress and results

David Israelson

No one will ever accuse Tony Fell and Bryce Douglas of not thinking big. They are a dynamic duo – founding co-chairs of the Campaign to Cure Arthritis in support of the Arthritis Program at Toronto Western Hospital and keenly supportive of the leading-edge research being done at the Krembil Research Institute. “One thing we like about the arthritis scientists at Krembil is that they are in the vanguard of a lot of this research,” Mr. Fell says.

In addition to co-chairstng the Campaign to Cure Arthritis, Mr. Douglas and his wife Nicki have provided a significant gift to establish the Nicki and Bryce Douglas Chair of Orthopaedic Surgery. Mr. Fell and his wife Shari have also donated a significant amount to support research aimed at curing arthritis, so people will no longer require hip, joint and knee replacements.

It is a personal connection to arthritis that has motivated both Mr. Fell and Mr. Douglas to actively support arthritis research and care. “Arthritis in its different forms handicaps millions of Canadians, including my family,” says Mr. Douglas, the former deputy chairman and managing director of RBC Dominion Securities Inc. “When I heard that there was a group of innovative research scientists trying to find ways to cure this problem, it was something I wanted to get involved in,” he says.

More than 4.6 million Canadians are affected by arthritis, osteoarthritis is the third-leading cause of disability in the country. Canada spends more than $21 billion annually on arthritis care every year (including 100,000 joint replacements).

“Arthritis has an impact on peoples’ lives. It impacts the economy in terms of lost jobs and it has been costing the health-care system huge amounts of money,” says Mr. Douglas, who enjoyed a 41-year career with RBC Capital Markets and its predecessor, Dominion Securities.

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Mr. Fell notes that “7 per cent of all hospital costs in Canada come from joint replacements. How many people do we all know who have had them?”

Mr. Fell says. “There are big ideas. Our goal is to cure this debilitating disease or stop it before it starts,” Mr. Fell says.

Mr. Douglas is well aware how monumental it would be to find a cure. “It impacts on your whole lifestyle, whether it’s going for a walk, playing tennis, playing with your kids and your grandchildren. I can tell you. It really hurts,” he says.

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The clinicians and researchers of the Arthritis Program have personally pledged $3 million of their own money toward the program.

“When you get that sort of commitment, it’s hard to say no [to supporting that],” Mr. Fell says.

The Krembil Research Institute is one of the principal research institutes of University Health Network, Canada’s largest research hospital. Scientists at Krembil are relentlessly pursuing cures for debilitating, chronic diseases in three main areas:

1. BRAIN & SPINE DISORDERS
   such as epilepsy, stroke, dementia, depression, pain, spinal cord injury, concussion, Alzheimer’s disease and Parkinson’s disease.

2. BONE & JOINT DISORDERS
   such as osteoarthritis, psoriatic arthritis, rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis.

3. EYE DISORDERS
   such as glaucoma, macular degeneration and retinopathy.

Support the relentless pursuit of cures:
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Scientists at the Krembil Research Institute are relentlessly pursuing cures for diseases of the bones and joints.

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