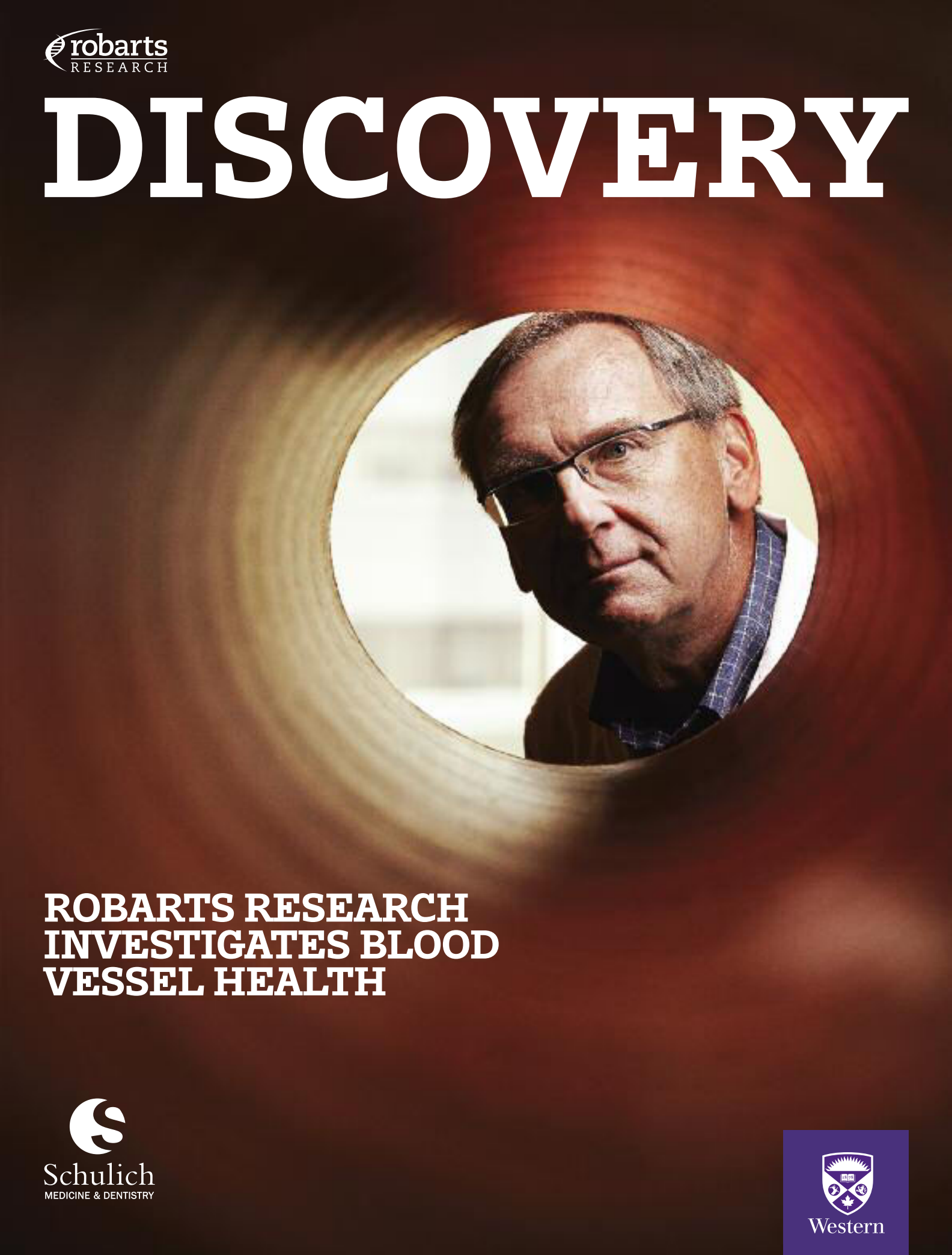
robarts RESEARCH

DISCOVERY



ROBARTS RESEARCH INVESTIGATES BLOOD VESSEL HEALTH

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YOU'RE SO VEIN: UNRAVELING THE MYSTERIES OF BLOOD VESSEL HEALTH

THE VASCULAR BIOLOGY GROUP AT ROBARTS RESEARCH INSTITUTE IS FINDING ANSWERS TO SOLVE SOME OF CANADA'S LEADING CAUSES OF DEATH AND DISABILITY

BY WENDY HAAF

From heart attacks and strokes, to peripheral artery disease, heart failure, kidney disease and diabetes, Canada's leading causes of death and disability all share a common theme: unhealthy, dysfunctional blood vessels growing old before their time. This is also the thread connecting the scientists in the Vascular Biology Group at Robarts Research Institute. They are unravelling how the major risk factors for these conditions wreak their havoc on blood vessels, from the aorta to the tiniest capillary, and how to short-circuit or repair the resulting damage.

"There's high blood pressure, lipids, diabetes, and a network of genetic findings, and there's the fundamental process of getting old," noted cardiologist and co-director Dr. Geoff Pickering, who is one of the group's three clinician-scientists. "We dissect these at the molecular level, at the potential therapy level, and at the population level."

Dr. Pickering's clinical connection planted the seeds of one of his most significant discoveries. He realized tissue otherwise discarded by his cardiac surgery colleagues might hold valuable clues to blood vessel health. After taking the tissue down to a single smooth muscle cell, Dr. Pickering generated such a pure preparation they were able to observe the cell behave in a healthy manner, contracting normally, and an unhealthy one, non-contracting.

When the scientists looked at the difference between the two behaviours, a growth factor dubbed FGF9 popped up as something that might play a role in healthy behaviour. The body is capable of growing new vessels as we age, but they're often leaky, imperfect, and cause more harm than good—for instance, feeding tumours, or causing buckling or separation of the retina in the eye.

Dr. Pickering demonstrated that FGF9 is a critical factor in forming cohesive, stable vessels with well-differentiated linings. Its job happens to be working on the supporting actors, that give blood vessels structure, Dr. Pickering explained, including precursors to pericytes, the smooth muscle cells that give blood vessels the ability to contract and relax. The hypothesis is that FGF9 recruits key stem cells, and coordinates the construction of new vessels.

Dr. Geoff Pickering in his lab

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Stem cell biologist David Hess, PhD, another of the vascular biology scientists, calls pericytes the 'conductors of the orchestra' in healthy blood vessel formation.

Hess is exploring angiogenesis from another angle, using stem cells from bone marrow and umbilical cord blood to study how haematopoietic precursor cells instruct epithelial progenitor cells to form a new vessel. "We're working on learning how to make more of these specialized stem cells and studying the communication between the haematopoietic cells, which are sending, and the endothelial cells, which are signal-receiving," he explained. Using genomic analysis, Hess has identified the mRNAs these haematopoietic cells produce to stimulate angiogenesis, and is now trying to pinpoint the proteins involved in this messaging.

In the meantime, the group has already successfully restored roughly 80 per cent of blood flow in a model of limb ischemia, by transplanting human stem cells into immunodeficient mice. Working closely with Hess and his colleagues, an American company has used this work as proof of concept for a clinical trial in humans, which is now underway. By decrypting the intercellular communication, Hess is hoping to identify proteins that might be used in place of stem cells. Currently, 100,000 North Americans per year lose a lower limb due to diabetes-related complications, and such an advance could have the potential to virtually eliminate the need for such amputations.

Another Vascular Biology Group researcher, co-director Murray Huff, PhD, has made a discovery that could one day preclude the need for people with diabetes to regenerate new vessels, and indeed might even prevent the disease from occurring in the first place. →

In Type 2 diabetes and pre-diabetes (insulin resistance), the liver pumps out an overabundance of very low density lipoprotein (VLDL) particles, which are thought to be one of the culprits behind the abnormally accelerated atherosclerosis that strikes such individuals. VLDL carry triglycerides and cholesterol. "We're fairly sure these particles are toxic to the blood vessel wall," noted Huff.

Several years ago, while examining the anti-cancer properties of molecules derived from citrus fruits, one of Huff's colleagues discovered that, when incubated with a grapefruit flavonoid, human liver cells secreted less fat than usual. Huff's lab built on this work, eventually revealing that the original flavonoid, and another (nobiletin), purified from tangerine pith, inhibited the synthesis and secretion of VLDL from liver cells. The group also elucidated the molecular mechanisms behind the effect.

Could nobiletin prevent atherosclerosis in mice bred to become obese and pre-diabetic on a high-fat diet, mirroring that of the average North American? The results of Huff's next experiments were even more spectacular than he could have imagined. Compared to their cousins who ate the same diet with no therapy, nobiletin-fed mice not only developed 60 to 70 per cent less atherosclerotic plaque; they were much slimmer, and their blood levels of glucose, insulin, triglyceride, and cholesterol were much lower. The results were also impressive in mice that were already obese and insulin-resistant. "Within three weeks of the addition of nobiletin, the obesity is rectified by 25 per cent and by 12 weeks, it's reduced by 50 per cent," Huff said. "The blood fats have dropped by half, and levels of glucose and insulin are completely normal." Preliminary results from further studies suggest the compound actually blocks the inflammatory response directly within the blood vessel wall.

Diabetes and metabolic syndrome doesn't just damage blood vessels by promoting atherosclerosis; these conditions also impair normal, insulin-mediated relaxation of the vessels, an effect that's partially allayed by some antihypertensive medications—discoveries that were made by another Vascular Biology clinician-researcher, pharmacologist Ross Feldman, PhD, starting more than 20 years ago.

More recently, Feldman and Rob Gros, PhD, have made fascinating findings about how other hormones—estrogen and aldosterone—act on blood vessels. The pair also demonstrated that these steroid hormones act on a receptor called GPR30 (G-protein coupled receptor 30), the function of which had been previously unknown (then misidentified as an estrogen-only receptor, dubbed GPER), thus accounting for their formerly unexplained, fast-acting effects. Traditional steroid receptors do their work relatively slow. "Ross Feldman and I debunked the theory that GPR30 was an estrogen-only receptor," said Gros, "and have shown that it can, more importantly, signal for aldosterone. While the underlying mechanisms aren't yet clear, drugs that interfere with the aldosterone pathway reduce blood pressure and cardiovascular disease risk."

What's more, Feldman's team has made a finding that helps explain estrogen's sometimes contradictory cardiovascular effects: protecting against cell death under some circumstances, and promoting it in others. "It turns out if you change the balance between the traditional estrogen receptor and GPR30, you can turn estrogen into a bad actor," Feldman said. "Same cells, same hormone—opposite effects." One factor that seems to change the balance

TOP: Murray Huff, PhD
BOTTOM RIGHT: Rob Gros, PhD

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—Murray Huff, PhD

is blood vessel injury, which appears to cause estrogen to promote blood vessel re-growth. "Additionally, there is a genetic basis and in work with Dr. Rob Hegele, we've identified a pretty common variant of this receptor which has implications in terms of blood pressure and metabolic effects."

As director of the Martha G. Blackburn Cardiovascular Genetics Laboratory and an endocrinologist, Dr. Hegele is renowned for uncovering the genetic basis for various lipid abnormalities and other atherosclerosis risk factors using DNA sequencing. In collaboration with Feldman and Gros, Dr. Hegele also revealed a common variant of andenylyl cyclase (the master regulator of cardiovascular function) isoform IV, which is linked dramatic elevations in blood pressure.

Such findings, and countless others, have the potential to point drug developers toward promising new treatments like those Dr. Hegele is testing in phase II and III clinical trials involving patients with genetically induced, sky-high LDL cholesterol levels that don't respond to statin drugs. The medications, which are injected once a month, are monoclonal antibodies which essentially mimic the effects of a genetic variant that confers unusually low LDL levels. "We're at the point where these patients come in with cholesterol that's off the charts, and we find the misprint in a gene that explains why. By virtue of them coming here, we can offer them the opportunity to participate in a clinical trial of this new class of drugs. It's all part of a continuum." ■

Rob Gros, PhD is investigating cellular and molecular mechanisms involved in the regulation of vascular and cardiac function

1/5
Canadians has hypertension; another 1/5 has pre-hypertension

1/5
Canadian adults has metabolic syndrome

NEARLY 7 IN 10
Canadians 20 years and older have diabetes

500,000
Canadians are currently living with heart failure; 50,000 new patients are diagnosed each year

800,000
Canadians have peripheral artery disease

EVERY 7 MINUTES
Someone in Canada dies of heart attack or stroke-related illness

80%
of people with diabetes die of heart attack or stroke

$12.2 MILLION
Cost on Diabetes in Canada each year

$20.9 BILLION
Cost on heart attack and stroke in Canada each year

Canadians with diabetes are 23 times more likely to be hospitalized for a limb amputation than those without the disease

In the next half hour, four Canadians will die of heart attacks and strokes, and another three will be diagnosed with heart failure.