Nova Scotia Health Authority

Research focus

Over the past 20 years, the Division of Hematology* has established Dalhousie Medical School and the QEII Health Sciences Centre in Halifax, Nova Scotia, as a leading centre for clinical research. Even though division members carry heavy clinical loads, they've put research front and centre, with a focus on evaluating new protocols and medications for diagnosing and treating clotting disorders, bleeding disorders and cancers of the blood. Together, division members have built a research team and infrastructure that enables them to run 80 to 90 studies at any given time and manage roughly $2.5 million in research funding per year.

By making research a top priority, the division has vastly improved patients' access to promising new treatments and the best possible care. The division has gained an international reputation as a top patient recruiter and provider of high-quality data, making it a reliable partner for academic research groups and pharmaceutical companies looking to test new agents, combinations and doses in clinical trials. Division members also pursue many investigator-driven studies, including local collaborations with colleagues in obstetrics and gynaecology, orthopedics, oncology, and emergency medicine. At the same time, they're involved in national and international research groups seeking to improve the understanding and treatment of diseases and disorders of the blood.

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hematology

Trial treatment a miracle for woman with multiple myeloma

Just 20 years ago, patients with multiple myeloma rarely survived more than three years. Yet Linda Kenney of Blockhouse, Nova Scotia, is going strong 11 years after she was diagnosed with the disease. "I've been in complete remission for six years," says Linda. "It's a miracle, really."

The miracle medication for Linda has been elotuzumab, a targeted therapy for multiple myeloma introduced in large-scale clinical trials in 2009. For Linda, the trial's timing couldn't have been better. She had just relapsed after nine months on an earlier trial medication, following two previous relapses after standard chemotherapy and a bone marrow transplant. Now, after 66 cycles of elotuzumab and counting, she is disease-free and enjoying life.

"We've seen great advances in the past few years with targeted therapies for multiple myeloma," says Dr. Darrell White, staff hematologist at the QEII and senior associate dean at Dalhousie Medical School. "Our goal is to turn what was once a terminal illness into a chronic disease that can be managed with ongoing treatment. Linda is a perfect example of how this can be possible."

The second most-common blood cancer, multiple myeloma results when plasma cells proliferate out of control. Fortunately, there are numerous new drugs in development for the disease. "We focus on phase-three trials, which compare the new drug against the gold standard, so patients have access to either the best-proven or the experimental treatment," notes Dr. White. "Through clinical trials, we're extending patients' periods of remission by years and working towards an eventual cure."

Hematology: research operations

Efficiency is job one in hematology research

The Division of Hematology's research unit takes a unique approach to providing as many patients as possible with access to leading-edge treatments through clinical trials. Although all hematologists are clinical generalists and see patients with every kind of blood disorder and disease, they do specialize when it comes to research. At the same time, every hematologist is a sub-investigator on all of his or her colleagues' studies, allowing them to enroll patients in each other's trials.

"Our approach ensures all hematologists are aware of all studies underway and see the opportunities to enroll patients into relevant trials," explains Susan Pleasance, associate director of hematology research for the Nova Scotia Health Authority (NSHA). A registered nurse with management and research training, Sue has worked in research with the division for more than 20 years.

As Sue notes, clinicians in the Division of Hematology have 24-hour access to pertinent study material for all studies, via a shared drive. "This allows them to assess if there's a diagnostic or treatment trial that should be offered to the patient they're caring for, " she says, "so we avoid missing opportunities for our patients."

Sue has worked closely with division members to develop systems and efficiencies that enable them to successfully manage a high volume of studies. "Consistent funding is paramount in running a large research operation," she says. "Diversity of studies and pooling of funds has led to a stable funding base to support long-term, full-time research staff positions."

A big part of the division's research success has been its approach to staffing. "We've streamlined the workload to make optimal use of people's skills," Sue explains. "Our research coordinators are all nurses who come to this position with a rich background in either hematology or research. This enables them to provide highly proficient clinical care to patients in studies, in addition to their research role. Our coordinators are supported by research assistants, so they can stay focused on nursing roles while the assistants look after other important tasks such as study administration, preparation and data entry. The addition of research assistants eight years ago has really increased the quality of data collection and research operations in general."

Meanwhile, an administrative coordinator handles all matters pertaining to research ethics and regulations—bringing expertise and efficiency to this highly specialized role. A team lead oversees day-to-day operations, allowing Sue and a data management coordinator to run a large clinical trial involving 15 sites across Canada.

With so many new medications in development and such a strong reputation for excellence, the division receives more requests to join studies than it can realistically entertain. "We carefully assess the scientific merits of all studies that come our way, and choose those that will best serve our patients' needs," Sue explains. "We want a diverse array of high-quality studies, so ideally all patients have the option to take part in a study."

Sue Pleasance (left) works closely with Claudia Harding (centre) in the Pharmacy Department and Donna Gamble (right) in the Medical Day Unit to oversee and coordinate the logistics of delivering medications to patients in clinical trials.

Hematopathologist Dr. Allam Shawwa (left) and hematologist Dr. David Macdonald (right) examine patient samples to identify sub-types of lymphoma.

Research coordinator Trisha Hudson with Drs. Allam Shawwa and David Macdonald in the QEII Health Sciences Centre's new automated clinical pathology lab.

Blood cancer breakthroughs

Scientific discoveries have triggered an explosion of new medications for blood cancers, with transformational results. "Improvements in cure rates for hematological cancers have been astounding," says Dr. Drew Bethune, head of the NSHA Cancer Care Program. "Our hematology group is very dedicated to clinical trials—they've played a key role in advancing cancer care's biggest success story so far."

Proper ID crucial for lymphoma success

There are three main types of lymphoma, each of which follows a dramatically different course. Hodgkin's lymphoma is now highly curable, for example, while the two types of non-Hodgkins's lymphoma (aggressive and indolent) continue to pose challenges. Fortunately, there are numerous promising drugs in development. The key to successful treatment is to correctly identify the sub-type of lymphoma.

"We work with three hematopathologists, who analyze proteins on the surface of the lymphoma cells to distinguish the sub-type," explains hematologist Dr. David Macdonald. "This is critical to ensuring patients receive the right treatment."

In Hodgkin's lymphoma, researchers are looking for less toxic treatments. "For decades, we pushed the cure rates in Hodgkin's to over 70 per cent for advanced disease and 90 per cent in limited disease, but those advances have come with the cost of toxicity—including some secondary cancers or damage to the heart or lungs," Dr. Macdonald says. "We're testing agents we hope will be safer." Indolent non-Hodgkin's lymphoma cannot be cured, because the cells divide so slowly, they evade chemotherapies designed to kill rapidly dividing cells. Even so, new targeted therapies have extended survival to as long as 15 to 20 years, compared to previous survival rates of 7 to 10 years. "Our goal is to balance survival with quality of life, so we avoid long-term side effects," Dr. Macdonald says.

The search continues for drugs that will gain a lasting remission from aggressive non-Hodgkin's lymphoma. "This is a fast-moving cancer that's resistant to second-line treatments if the first line fails," he says. "We hope to have access to that next transformational drug."

Hematology research staff

Research coordinators: Angie MacNeil (team lead), Rebekah Conlon, Valerie Dorcas, Blaine Gallant, Trisha Hudson, Judith James, Heather Lynch, Donna Mann, Judy Richard

Research assistants: Jenna Drew, Nova Lee Horne, Flynn Regan, Rebecca Robichaud

Administrative coordinator: Brittany Scott

Data management coordinator: Abongnwen Abianui

Hematology research: leukemia

Toward a new era in leukemia treatment

While some types of leukemia are now curable, others remain difficult to destroy. The good news is, new agents are being introduced at a rapid rate and many patients are achieving long-term remission.

"The drug-development pipeline has been quite rich over the past five years," says Dr. Stephen Couban, head of the Division of Hematology. "As scientists gain a better understanding of the molecular pathogenesis of the different types of leukemia, we're seeing more targeted therapies that eliminate cancer with fewer side effects."

Dr. Couban is a leading force in building national and international research collaborations and currently co-chairs the National Cancer Institute of Canada's Hematology Disease Site. As he notes, some forms of leukemia are relatively rare, so many centres must band together to enroll enough patients in clinical trials to be able to tell if a new drug is working or not.

Important pockets of success

One of the most outstanding leukemia success stories of recent years has been the arrival of an oral therapy for chronic myeloid leukemia (CML). "CML used to be the most common reason we would have to perform a stem cell transplant," says Dr. Andrea Kew, a hematologist who works closely with Dr. Couban. "Now we have a 'magic pill,' imatinib, which keeps the disease in remission."

New agents are also improving survival in myelodysplastic syndrome (MDS), a disorder that can lead to bone marrow failure or leukemia. "We're moving to a new standard of care in MDS, with new intravenous and oral treatments," remarks Dr. Kew. "One trial at a time."

New protocols can be just as important as new drugs. One international study led by Dr. Couban found that using stem cells collected from peripheral blood, rather than the bone marrow, produced better results in stem cell transplants. Another recent study, conducted with the Dana Farber Institute, revealed that aggressive drug regimens used to eradicate childhood acute lymphoblastic leukemia (ALL) can also be used to improve survival in adults with ALL—as long as the patients are young to middle-aged. Yet, he admits, "Survival rates are still not what we want them to be in many blood cancers."

Dr. Stephen Couban and Dr. Andrea Kew concentrate their research efforts on testing new treatments and approaches to curing leukemia.

The challenge of AML

AML (acute myeloid leukemia) strikes like lightning. Left untreated, it progresses rapidly and can be deadly in months. First-line treatment is chemotherapy to induce remission. "We've been using the same induction chemo for the past 40 years, because nothing has yet proven better," says Dr. Kew. "Up to 60 to 80 per cent of patients go into remission—the challenge is to keep them there."

Stem cell transplant can consolidate remission, but it's a risky procedure. "There's a chance that the stem cell transplant will cure the leukemia, but there's also a chance of very serious problems," explains Dr. Kew. "It's a really tough choice to make, as up to 20 to 30 per cent of patients die from transplant-related complications."

New targeted agents are coming along all the time, with mixed results in clinical trials. "There are so many genetic mutations in AML, it's hard to know which ones to target," says Dr. Kew. "But some treatments are working for some patients, which is great progress. We're moving toward an era of personalized medicine, where patients' drug regimens will be tailored to their specific pattern of mutations—so we don't have to make them sick to make them better."

Living with chronic leukemia

Patients with chronic leukemia can live for decades, but may be plagued by the side effects—and high costs—of years on drugs. Fortunately, there are many exciting new drugs in development for the most common form of chronic leukemia, known as CLL (chronic lymphocytic leukemia), which studies show can prolong progression-free survival, with fewer troublesome side effects.

"We're seeing higher rates of remission with these new medications, which are generally very well tolerated by patients," says Dr. Sue Robinson, who leads several large trials in CLL. As she notes, "These trials give us access to drugs our patients would not otherwise have the opportunity to receive."

Meanwhile, Dr. Couban and Dr. Wanda Hasegawa are running a study to see if CML patients in remission on imatinib can safely stop the drug altogether. "A lot of younger people, especially, want to know if there's a chance to enjoy a drug-free remission, away from the fatigue, muscle and joint pain, and heightened risk of heart attack and stroke that comes with being on the medication," says Dr. Hasegawa. "We are monitoring their blood very closely for any early signs of recurrence, in which case they receive another drug to put them back in remission."

Hematology research coordinator/nurse Heather Lynch is caring for Susan Greek as she goes through treatment for acute myeloid leukemia (AML). Susan is in remission from low-risk AML after completing four rounds of intense chemotherapy through a clinical trial. The hematology division researchers will follow Susan for five years through the study.

Hematology research: clotting disorders

Dr. David Anderson (left) is collaborating with orthopedic surgeon Dr. Michael Dunbar (right), to lead a nationwide Canadian Institutes of Health Research-funded study involving nearly 3,500 patients from coast to coast. The researchers want to know if aspirin can be used instead of far more costly prescription blood thinners to prevent blood clots in patients following hip and knee replacement surgeries.

Blood clots: improving diagnosis and management of a potentially dangerous event

Blood clots are a common and potentially fatal disorder. One in every thousand people will develop a blood clot in his or her lifetime—often following surgery, but also during or after pregnancy, while battling cancer, or for no apparent reason at all.

Dr. David Anderson, head of the Division of Hematology for many years, started studying the prevention, diagnosis and treatment of clotting disorders with Dr. Sue Robinson after joining the division in the early 1990s. "There was a long history of research in the division that we continued to build upon," recalls Dr. Anderson, Dalhousie Medical School's Dean of Medicine as of July 1, 2015. "We've seen many advances over the past 20 years that have changed the face of how we manage people with clotting disorders."

Deep vein thrombosis is the most common clotting disorder. It usually occurs in the legs, leading to local pain and swelling. If the clot should travel to the lungs, however, it results in pulmonary embolism. Initially this causes shortness of breath but it can also be fatal, as the clot can obstruct blood flow to the lungs. Prompt diagnosis and appropriate treatment is critical.

Clinical decision tools transform care

Dr. Anderson and Dr. Phil Wells from the University of Ottawa revolutionized the frontline diagnosis and management of blood clots. They and their colleagues developed and validated clinical judgment tools—now known and used around the world as Wells' Criteria—that enable far more rapid, accurate and non-invasive assessment.

"Diagnostic testing was often invasive and painful," explains Dr. Anderson. "Patients with suspected clots were frequently injected with contrast dyes to reveal clots in x-rays, but it was hard to identify who should be sent for these investigations. We developed criteria based on patient history, risk-factor profile and clinical findings. Over many studies, we proved our decision tool could be used by clinicians in emergency settings to correctly identify who should be investigated, using what sorts of tests, for blood clots."

Their work also showed that providing clinicians with decision tools led to more efficient use of limited health care resources, while ensuring more accurate diagnoses, less unnecessary testing, fewer adverse events and better health outcomes for patients. Dr. Anderson and other members of the division continue to work with Dr. Wells, as part of VECTOR (VEnous thromboembolic Clinical Trials and Outcomes Research), a national research group that has secured $50 million in research funding over the past 15 years to improve diagnosis and treatment of clotting disorders.

A pilot study with the Department of Emergency Medicine is testing a new way to assess patients who may have a blood clot. Rather than sending blood samples to the lab for analysis, the study involves performing a blood test on the spot, in the emergency setting, in addition to a clinical exam. Principal investigator Dr. Sudeep Shivakumar (left) and research coordinator/nurse Blaine Gallant (centre) predict this approach will dramatically speed time to diagnosis—sparing patients from hours of waiting in emergency, while ensuring potentially lifesaving treatment is promptly given.

Advancing a new generation of treatments

From the 1950s to 2009, there was just one oral drug for treating blood clots—Warfarin. While effective at dissolving clots, patients on Warfarin require close monitoring. "Warfarin is a bit unpredictable," says hematologist Dr. Sudeep Shivakumar. "It lasts a long time in the body and it interacts with vitamin K, clotting factors and other medications, so the dosage needs to be constantly adjusted based on the results of regular blood tests."

Researchers in the Division of Hematology were involved in clinical trials that led to the approval of three new anti-clotting drugs in Canada since 2009. "The new medications are creating a big shift in how we use blood thinners," notes Dr. Shivakumar. "They are targeted to just one specific clotting factor, they don't interact with foods or other medications, and they are cleared from the body quickly, so we can give a consistent dose with no need for constant bloodwork."

Dr. Shivakumar and his colleagues are involved in about ten clinical trials a year, to learn more about the best ways to use the new blood thinners. "There's still a lot we need to know," he says. "For example, how soon do we stop these drugs before surgery? How long can we keep people on them? What are the risks of extended use? And, what do we do if a patient is bleeding? Unlike Warfarin, which has an antidote in vitamin K and clotting factors, there are no antidotes to the new medications."

The cancer connection

Cancer makes the blood sticky and prone to clotting, which is why Dr. Shivakumar is particularly interested in cancer-related blood clots. He's building collaborations with cancer doctors across the Maritimes to explore how best to manage blood clots in cancer patients. For example, patients with central lines are vulnerable to developing clots—Dr. Shivakumar wants to know if these patients should be treated with blood thinners, proactively. "There are lots of questions about using blood thinners in cancer patients as a preventative measure," he says. "At the moment, there is no clear evidence if they are beneficial or not, so we need to look further."

Hematology research: bleeding disorders

Carol Anne Rogers (left) has mild VWD, while her sister, Jean Gillis (centre), has a severe form of the disease. Both are long-time patients of Dr. Sue Robinson (right), who has involved them in research she's doing with colleagues in Ontario to understand how different genetic mutations influence the severity of symptoms. Jean also took part in the first clinical trial of Von Willebrand factor concentrate manufactured using recombinant DNA technology, rather than concentrated from donor plasma.

Stemming the flow of bleeding disorders

Bleeding disorders—caused by low levels of clotting factors in the blood—are passed down through the generations. The most common is Von Willebrand disease, named after the man who identified the disease in the 1920s.

"Most cases are mild, but one in a million people has the severe form of the disease, known as Type 3 VWD," says Dr. Sue Robinson, hematologist and director of the Nova Scotia Bleeding Disorders Clinic. "Here in Nova Scotia, we have the highest rates of severe VWD in Canada, so we've become involved in various studies over the years."

Dr. Robinson monitors 17 Nova Scotians with severe VWD, tracking their levels of the Von Willebrand clotting factor, treating them with oral medications or a condensed plasma product called concentrate, and giving them intravenous iron treatments as needed.

"VWD has a greater effect on women, who experience heavy periods and postpartum bleeding, and face a high risk of anemia," notes Dr. Robinson. She recently completed a study with colleagues in Dalhousie's Department of Obstetrics & Gynaecology, to see if women with bleeding disorders could alleviate their heavy periods with a lower dose of a non-hormonal drug called cyklokapron. "The recommended dose is high and leads to side effects like nausea, abdominal pain and headaches, so many women don't take it," she says. "We found we could cut the dose by as much as two-thirds and still control bleeding, with virtually no side effects. Now more women are able to control their heavy periods."

Dr. Robinson and her gynaecology colleagues have since established a virtual clinic for women with bleeding disorders. "Now gynaecologists and hematologists can confer on cases that require our combined expertise," she notes. "We've also developed guidelines for women who are carriers of hemophilia, and are working on guidelines for women with VWD, to help them manage issues they face during menstruation, pregnancy and childbirth."

The genetics of VWD is of great interest to Dr. Robinson, who has involved VWD patients in genetic studies with collaborators at Queen's University and the University of Toronto. "We want to understand the nature of the disease and how various genetic mutations influence the severity of symptoms," she says, adding that she's grateful for patients' willingness to travel to Ontario and to take part in clinical trials.

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