

The Microenvironment



THE CANADIAN
HEMATOLOGY
SOCIETY

SOCIÉTÉ
CANADIENNE
D'HÉMATOLOGIE

December 2019

NEWSLETTER

Inside this Issue...

President's Message	1
2018 CHS Abstract Award Winners	3
Rare Blood Disorders Organization	4
Remembering Dr. Stephen Couban	5
Successful ISLH Vancouver Congress	6
Farwell to Dr. Peter Galbraith	7
Review: by Dr. Danielle Hammond	8
Review: Sirolimus for acute GVHD	10
RK Smiley Project Updates	11
Upcoming Events	12
CHS @ ASH 2019—in pictures	13
Call for Applications: Chief Resident	14
RK Smiley Grant—next round, 2020	14
Job Postings	15
Membership Matters	16

2019 CHS Executive Board

President	Dr. Nicole Laferriere
Past-President	Dr. Lynn Savoie
Vice-President	Dr. Jason Berman
Treasurer	Dr. Hassan Sibai
Secretary	Dr. Christopher Hillis
Executive Vice-Pres.	Dr. Gail Rock
Chief Resident	Dr. Caroline Malcolmsen

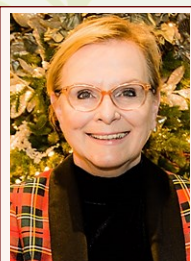
MICROENVIRONMENT

Editor	Dr. Danielle Hammond
--------	----------------------

CANADIAN HEMATOLOGY SOCIETY
199—435 St. Laurent Blvd.
Ottawa, ON K1K 2Z8 CANADA
Phone: 613-748-9613
Fax: 613-748-6392
Website: canadianhematologysociety.org
Email: chs@uniserve.com

MESSAGE FROM THE PRESIDENT

Canadian hematology community's rich professional leadership advances field: promotes education, research and patient care



Dr. Nicole Laferriere
President, CHS

Dear Colleagues,

I have been reflecting on the richness of professional leadership in the Canadian Hematology community. Within Hospitals, Universities and sub-specialty organizations and across communities of need, our members give their time and expertise to advance the care of patients. This begins as medical students and continues throughout our professional practice. The Canadian Hematology Society was formed to advance our profession and promote a high standard of Hematologic education, research and patient care across the country.

Our community is deeply saddened by the loss of two esteemed CHS colleagues.

Dr. Stephen Couban, a former CHS president inspired us with his exemplary dedication to our profession. To acknowledge his legacy the CHS has named an annual resident research award in his memory.

*h t t p s : / /
www.dignitymemorial.com/
obituaries/halifax-ns/stephen-
couban-8221490.*



Stephen Couban
CHS Awards Gala
Dec. 9, 2012, Omni CNN
Centre, Atlanta, Ga.

Dr. Peter Galbraith was perhaps the last living founding member of the CHS. Dr. John Matthews wrote a thoughtful obituary for the *ASH Hematologist*; March -April 2019, Volume 16, Issue 2:

[http://
www.yourlifemoments.ca/
sitepages/obituary.asp?](http://www.yourlifemoments.ca/sitepages/obituary.asp?oid=1095093)

[oid=1095093.](http://www.yourlifemoments.ca/sitepages/obituary.asp?oid=1095093)

On the right, from our CHS files: a lovely photo of Dr. Galbraith cutting the CHS 40th Anniversary cake at the CHS ASH Gala, Dec. 11, 2011, Andaz Hotel, San Diego, Ca.



The Canadian Hematology Society was a co-sponsor for the International Society of Laboratory Hematology (ISLH) held in Vancouver May 2019. **Dr. Catherine Heyward** and **Dr. Ruth Padmore** were the Canadian organizers for this outstanding meeting. The leadership of our peers is essential for our professional growth as we meet and learn from one another.

We have developed our CHS website this year to include information regarding Hematology Conferences, sub-specialty professional group links and incorporated the Educational Portal content. You can now complete your membership application on line. We have much to be proud of and invite you to visit the

new CHS website. If you have ideas regarding further content/improvements, please consider joining our Website Advisory Committee. **We want to hear from you!**

Dr. Tom Nevill has stepped down as editor of The Microenvironment after many years of service. We thank him for this invaluable work. This issue is the first for our new editor **Dr. Danielle Hammond** (MDACC Leukemia Fellowship). We welcome her and we are grateful for her talent and commitment to the Microenvironment.

I look forward to seeing you **Sunday December 8th at the CHS ASH Gala at the Rosen Plaza**. This year we have changed the format of the evening to enable more casual mingling throughout. Please join us as we honour the recipients of the Abstract Awards and Paper of the Year. The Lifetime Achievement Award will be presented for the 3rd year to another outstanding Hematology leader, **Dr. Victor Blanchette**.

See you at ASH.

Nicole

Le message du Présidente

Le leadership professionnel de la communauté canadienne de l'hématologie favorise l'éducation, la recherche et les soins aux patients

Chers collègues

J'ai réfléchi au sujet de la richesse du leadership professionnel dans la communauté canadienne de l'hématologie. Au sein des hôpitaux, des universités et des organisations de spécialités et des communautés qui en ont besoin, nos membres donnent leur temps et leur expertise pour faire progresser les soins des patients. Cela débute pendant nos années d'étudiants en médecine et se poursuit tout au long de notre pratique professionnelle. La Société canadienne d'hématologie a été créée pour faire progresser notre profession et promouvoir des normes élevées en matière d'éducation, de recherche et de soins des patients en hématologie partout dans le pays.

Notre communauté est profondément attristée par la perte de deux collègues, hautement estimés au sein de la société canadienne d'hématologie (SCH). Le **Dr Stephen Couban**, ancien président de la SCH, nous a inspirés par son dévouement exemplaire qu'il a dédié à notre profession. Pour reconnaître son héritage, la SCH a nommé un prix de recherche annuel pour les résidents en sa mémoire. (<https://www.dignitymemorial.com/obituaries/halifax-ns/stephen-couban-8221490>).

Le **Dr Peter Galbraith** était peut-être le dernier membre fondateur vivant de la

SCH. **Dr John Matthews** a écrit une nécrologie touchante pour l'hématologue de la SCH dans le volume 16, numéro 2 de mars-avril 2019. Nos dossiers contiennent une jolie photo de lui coupant un gâteau du 40e anniversaire de la SCH pour le bulletin Microenvironment. (<http://www.yourlifemoments.ca/sitepages/obituary.asp?oid=1095093>).

La Société canadienne d'Hématologie a coparrainé L'International Society of Laboratory Hematology qui s'est tenue à Vancouver en mai 2019. La **Dre Catherine Heyward** et la **Dre Ruth Padmore** étaient les organisatrices canadiennes de cette réunion exceptionnelle. Le leadership de nos pairs est essentiel à notre croissance professionnelle alors que nous nous rencontrons et que nous apprenons les uns des autres.

Cette année, nous avons créé notre site web de la SCH afin d'y inclure de l'information sur les conférences en Hématologie, des liens vers des groupes de professionnels spécialisés et le contenu du portail éducatif. Vous pouvez maintenant remplir votre demande d'adhésion en ligne.

Nous avons de quoi être fiers et nous vous invitons à visiter le nouveau site web de la SCH. Si vous avez des idées pour améliorer le contenu, veuillez

envisager de vous joindre à notre comité consultatif du site web. Nous voulons avoir votre opinion!

Le **Dr Tom Nevill** a démissionné de son poste de rédacteur en chef du microenvironnement après de nombreuses années de service. Nous le remercions pour son précieux travail. Ce numéro est le premier ouvrage de notre nouvelle rédactrice en chef, la **Dre Danielle Hammond** (Bourse de recherche sur la leucémie du MDACC). Nous lui souhaitons la bienvenue et lui sommes reconnaissants de son talent et de son engagement envers le microenvironnement.

J'ai hâte de vous voir le dimanche 8 décembre au Gala de la SHS au Rosen Plaza. Cette année, nous avons modifié le format de la soirée pour permettre plus de rencontre décontractée tout au long. Rejoignez- nous pour rendre hommage aux lauréats des prix pour les meilleurs résumés et les meilleurs articles scientifiques de l'année. Le prix d'excellence pour l'ensemble des réalisations sera remis pour la troisième année à un autre leader exceptionnel en Hématologie, **Dr Victor Blanchette**.

À bientôt à la ASH.

Nicole

2018 CHS Abstract Award Winners

CHS President, Dr Nicole Laferriere, presented the CHS Abstract Awards at the CHS Members' Annual Meeting and Awards Gala, on December 2, 2018, at the Westin Gaslamp Quarter in San Diego, California. Photos of the 2018 Abstract Winners at the awards gala evening are below with descriptions of their winning categories and abstracts.

Residents & Fellows—CROOKSTON Award

Robert Puckrin, MD

PGY3 Internal Medicine Resident, University of Toronto



Winning Abstract:
Molecular Residual Disease Monitoring Provides Insufficient Lead-Time to Prevent Morphologic Relapse in the Majority of Patients with Core-Binding Factor AML

Residents & Fellows Category — 2018

Tracy Murphy, MD

Fellow, Princess Margaret Cancer Centre



Winning Abstract:
Delayed hematologic recovery in AML patients after induction chemotherapy is associated with inferior relapse-free survival and persistence of preleukemic mutations

PhD & Post-Doctoral Category—2018

Qiang (Wayne) Liu, PhD

Post-doctoral Fellow, Princess Margaret, UHN



Winning Abstract:
Identification of compounds that target acute myeloid leukemia stem cells using a scalable next-generation screening platform

Residents & Fellows Category — 2018

William Silverstein, MD

Resident Physician, Faculty of Medicine, University of Toronto



Winning Abstract:
Appropriateness of B12 Administration in a Real-World Population

2020 Canadian Hematology Society EXECUTIVE BOARD



President
Dr. Nicole
LAFERRIERE
Thunder Bay



Past—President
Dr. Lynn
SAVOIE
Calgary



Vice—President
Dr. Jason
BERMAN
Ottawa



Treasurer
Dr. Hassan
SIBAI
Toronto



Secretary
Dr. Chris
HILLIS
Toronto



**Executive V—P
Vice—President**
Dr. Gail ROCK
Ottawa



Chief Resident
Dr. Caroline
MALCOLMSON
Toronto

The Network of Rare Blood Disorder Organizations (NRBDO): "supporting you in your advocacy"

Contributed by
Jennifer van Gennip
NRBDO

The **Network of Rare Blood Disorder Organizations** (NRBDO) is thrilled to be invited to share more about our coalition and its member patient organizations with the Canadian hematology community through this publication.



The NRBDO is a pan-Canadian coalition of not-for-profit organizations representing people with rare blood disorders and/or people with a chronic condition who are recipients of blood or blood products or their alternatives. We were founded in 2004.

Our Members

Current member patient groups of the NRBDO are:

1. Answering TTP (Thrombotic Thrombocytopenic Purpura)
2. Aplastic Anemia and Myelodysplasia Association of Canada (AAMAC)
3. Canadian Association for Porphyria (CAP)
4. Canadian Hemophilia Society (CHS)
5. Canadian Immunodeficiencies Patient Organization (CIPO)
6. Canadian Organization for Rare Disorders (CORD)
7. Fanconi Canada
8. GBS/CIDP Foundation of Canada
9. HHT Canada THH (Hereditary Hemorrhagic Telangiectasia)
10. Sickle Cell Disease Association of Canada (SCDAC)
11. Thalassemia Foundation of Canada (TCF)

Supporting You in Your Advocacy

We are a coalition of national patient groups who advocate together on matters of blood supply and safety, and provide the patient advocate voice for physicians who are facing policy challenges in providing the best care for their patients with rare blood disorders.

Core Values

Our core initiatives fall into three categories:

1. Comprehensive Care

We envision high quality, effective, accessible, interdisciplinary care for all Canadians affected by rare blood disorders. We are pleased to work closely with the stakeholders, including the

medical community, to advocate to this end. We work to identify and create opportunities for our member patient groups in the development of comprehensive care standards, documents, and support materials.

Recently this has involved helping to build a case for support for a version of the Canadian Bleeding Disorder Registry (used for hemophilia) for Immune Globulin recipients.

2. Treatment Safety, Supply, and Access

We advocate as the need arises on issues related to blood supply and safety, and access to treatment.

Currently this involves advocating to Canadian Blood Services (CBS) and the provinces and territories for robust patient engagement in the review process for new blood products, and advocating for new therapies that replace blood products to be distributed through CBS and Hema-Quebec rather than placed on the provincial/territorial formularies.

Recently we have also worked with the Canadian Apheresis Group to improve access to solvent detergent plasma (SDP) and successfully fought Bill S-252 which would have greatly impeded efforts in Canada to increase self-sufficiency in plasma supply.

3. Knowledge Transfer and Exchange

The NRBDO hosts semi-annual fora where speakers and discussions aim to build the capacity of our member groups. For example, our 2019 Fall Forum focused on the development of Emergency Room Guidelines, with assistance from the Canadian Association of Emergency Physicians (CAEP); and our Spring Forum featured presentations on new and curative therapies that are in the pipeline for rare anemias.

We have also held workshops on effective CADTH patient input submissions, how to gather patient data, and information sessions on pharmacare for rare disease.

Looking for Champions

Rare blood disorder patient groups are always eager to connect with physicians willing to learn about their disorder and champion their cause.

If that's you, we'd love to talk to you!

You can learn more about the NRBDO or connect with any of our member patient groups at www.nrbdo.ca, or via email at info@nrbdo.ca.

Remembering Dr. Stephen Couban

An accomplished, knowledgeable physician, renowned for professional leadership, accomplishment and unfailing courtesy and respect

By John Kelton MD

Stephen Couban was born in Athens Greece in 1961 and then moved to England with his family and spent his formative years in Surrey and Kent.

During this time, he acquired a love of all things English as well as a gentle accent, which is characteristic of a refined and educated English gentleman. This was an accent that he assiduously maintained through his entire life.

When Stephen was 14, the family moved to Nova Scotia, initially Prospect Bay and then to Halifax. Stephen learned to love the East Coast and he was determined that he would live out his life in that most beautiful part of Canada.

His undergraduate training was at McGill, and then he completed an MD degree (cum laude) from Dalhousie University. A brief stint in general practice in Nova Scotia led to additional training first in internal medicine at Dalhousie, followed by hematology training at McMaster University.

It was at McMaster when I first met Dr. Stephen Couban. His persona was as striking as was his intellect. He always wore perfectly pressed white shirts, thin dark ties, and then there was that accent. Perhaps even more curious were his manners. Stephen Couban displayed the exquisite, impeccable manners and grace of a 19th century English gentleman.

My memories of him are precise. Always, a twinkle in his eyes, his mouth slightly pursed as he held back a laugh. We quickly became comfortable enough with each other, that one day, I felt bold enough to ask if in fact he was a time traveler from Victorian England. He paused, met my gaze, looked a bit puzzled and said, "let me think about that comment". I was to learn that if I had held his gaze, he would have only been able to maintain his serious look for a minute before he would have burst into laughter.

Dr. Stephen Couban was truly an "old-school physician". A man who believed in courtesy and respect, no matter the situation.

Steve Couban was one of those rare individuals who could bring a smile to your face simply by appearing in your thoughts. He was a great physician, knowledgeable, and more importantly, he was a caring and kind man. His love and

kindness extended to his partner Jim, his family, and his many friends. And perhaps most importantly, to his patients.

I knew him as a superb doctor, but my most intense memories relate to the mischievous imp living just below the surface of this dignified man.

A l m o s t
i m m e d i a t e l y
during his time in Hamilton, Steve fell into lockstep with another resident, Parveen Wasi. Theirs was a near perfect friendship, full of

pranks, laughter, gossip and above all, kindness and mutual caring. A friendship that would expand and include Jim, and of course, Lily the dog. For Steve, there was no such thing as a prank that shouldn't happen.

I recall, after he had returned to the East Coast, Parveen had one of those serious birthdays, one divisible by 10. Such a sentinel event could not be forgotten by Steve. Happy Birthday messages to Parveen were sent to all of the medical wards, the physicians' offices, the laboratories, and throughout the hospital announcing the special day. To the end, Steve persisted in claiming that it was an innocent error on his part that the birthday best wishes declared her to be a decade older than she was.

Dr. Stephen Couban had both ambition and aspirations to continue his growth, both personally and intellectually. His McMaster hematology training was followed by a National Cancer Institute of Canada Terry Fox Fellowship in bone marrow transplantation at the Princess Margaret Hospital. There he further honed his clinical skills as he prepared to turn to Dalhousie.

At Dalhousie he worked with Dr. Louis Fernandez, Dr. David Anderson, Dr. Sue Robinson, among other distinguished



Stephen Couban (1961—2019)

Continued, next page

physicians. Dr. Stephen Couban became the Director of the Dalhousie Blood and Bone Marrow Transplant Program, and also rose to the Division Head of Hematology. Rising to national and international prominence, he led numerous clinical trials to advance the science.

His many contributions nationally and internationally included co-chair of the hematology site group for NCIC, President of the Canadian Bone Marrow Transplant Group, and President of the Canadian Hematology Society, among others.

Despite his remarkable level of scholarship, he had a life outside of work, and with his life partner, Jim Matthews, he travelled the world from Crete, to Mexico, and bicycled in Greece, India, and of course throughout Canada.



His level of self-discipline in work and vigorous exercise was balanced by his joyous ability to periodically give up control. In my experience, that loss of control, often happened at our dinners.

After Steve left Hamilton, we began a tradition of dinners at the annual hematology

meetings. Dinner guests included Steve, (the organizer), Nancy Heddle, sometimes Ronan Foley, always Parveen

Wasi, and me. A week or two ahead of the meeting, Steve would send us a serious "topic" for conversation at the dinner. Perhaps a discussion of the design of a clinical trial he was about to start, or the use of antibiotics in neutropenia.

But all this planning was for naught. Invariably, and after more than adequate wine was consumed, serious conversation would degenerate into laughter and fun. "Oh, dear", he would exclaim, then furiously rub his eyes with the back of his closed fists, "I seem to have lost control". It was true. For that evening, his self-discipline was lost. The meal ended, the "topic of the dinner" never visited.

For me, the sweetest part of these dinners was the ritual that followed. Steve and Parveen would excuse themselves to get some fresh air. We would give them 15 minutes before we would leave. There they would be, sitting on a bench, laughing and enjoying each other's company.

Reading Dr. Stephen Couban's obituary and comments from the guestbook, I know that Steve would have modestly acknowledged the many awards he received during his career. He would have been pleased to be appreciated by the many students he taught.

But most of all, he would have been proud to know that the patients he cared for, cared so much about him.



Successful ISLH 2019 Congress in Vancouver draws over 700 delegates from 71 countries



Dr. Catherine Hayward
PRESIDENT, ISLH

Vancouver Convention Center. It was preceded by a one-day educational workshop.

Over 700 people representing 71 countries, were in attendance. The scientific planning for the conference, which was a great success, was collaborative effort involving ISLH, the

The XXXII International Symposium on Technical Innovations in Laboratory Hematology (ISLH 2019) was held from May 9 to 11, 2019 at the

Canadian Hematology Society (CHS), the Canadian Association of Pathologists-Association Canadienne des Pathologistes (CAP-ACP) and the North American Specialized Coagulation Laboratory Association (NASCOLA).

Highlighting the educational program were the society's two named awardees:



Dr. Marie Christine Bene was awarded the Berend Houwen Memorial Lecture and presented on the "**Wonderful Adventure of Monoclonal Antibodies**".



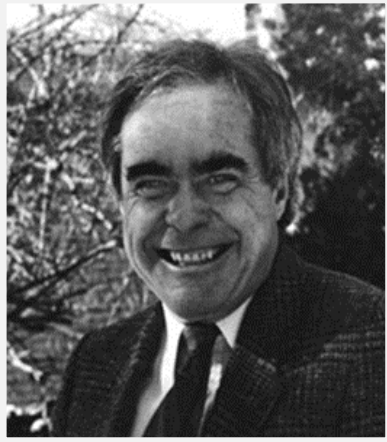
Dr. Kari Stefansson was awarded the Wallace H. Coulter Distinguished Lecture and presented on the "**Genetics of Common Diseases**".

In addition to the named lectures, and simultaneous sessions, the educational program included over 40 additional oral presentations and hundreds of poster presentations focusing on the latest topics in the field of Laboratory Hematology.

The abstract proceedings of the symposium were published in the official journal of the society, *The International Journal of Laboratory Hematology*

Dr. Peter Galbraith: farewell to a CHS co-founder

A full life, well-lived! A legacy of outstanding accomplishment, leadership and friendship - an inspiration to many



Dr. Peter Galbraith (1931—2018)

Husband, father, grandfather, great-grandfather, physician, researcher, teacher, skier, tennis player, golfer, exuberant undeterred guitar strummer and unaccomplished singer, inimitable reader of "The Night Before Christmas", aficionado of fine food and wine, true friend (aka Rotten

Pierre), lover of life, inspiration to many, and a grateful beneficiary of a charmed life. He was an honourable and deeply loved man. Peter drank lustily from the cup of life until, after the death of his beloved wife Ruth, he determined that he was now full.

After graduating from Queens (Meds 56) and two years of postgraduate training, Peter completed subspecialty training in Boston. He returned to Kingston as a clinical assistant, found a permanent position at Queen's and rose to the rank of Full Professor, with cross-appointments in the Departments of Paediatrics and Oncology.

He was the founding Head of the Division of Hematology/Oncology and directed the Hematology training program for over 25 years. He ran a division renowned for its compassion both for patients, and for the interns and residents who rotated through.

Peter was also instrumental in establishing the chemotherapy unit at Kingston General Hospital and was a founder of the

Palliative Care Service. He was one of the founding members of the Canadian Hematology Society and became its president in 1984. Peter was elected by his Canadian colleagues as a councillor of the American Society of Hematology (1987-1991) and appointed to two ASH sub-committees.

When Peter suddenly became ill his children honoured his fervent and oft-repeated wish to prioritize quality of life over quantity, and to forgo treatments that realistically would only extend the dying. Peter had a say in the ending of his life's story and he chose comfort care. So, amidst the laughter and tears of his loving family he achieved what he set out to achieve a good and gentle death. Peter's family found peace, knowing they had kept him safe along his journey.

There are three people who deserve special mention for the safe and loving space they ensured for Peter in his later years. Helene Reis was a beacon of hope, his trusted confidante and the most loyal of friends. David Freedman welcomed Peter into his home unconditionally, became the de facto guardian of Peter's dignity and agency, and a stalwart source of empathy when Peter needed respite from the machinations of his bossy daughters. Amey Brooks provided a charming haven at Brooks Landing, and the care that she poured on dad and his family goes so far beyond expectations that words defy us.

Peter would welcome a donation directed for the establishment of The Peter R Galbraith MD Award for Palliative Education to promote and support advanced training in palliative care medicine within Hematology and Oncology. <https://givetoqueens.ca/project/view/1047/1577>

Acknowledgement:

*In deep appreciation to **Meredith Galbraith** for contributing this article.*

ISLH 2019 Congress: continued from previous page

(IJLH), which is published by Wiley and the Wiley Online Library. They can be accessed at <https://onlinelibrary.wiley.com/toc/1751553x/2019/41/S2>. The IJLH 2019 Education Issue, containing freely accessible article by ISLH2019 speakers, can be accessed at <https://onlinelibrary.wiley.com/toc/1751553x/2019/41/S1>.

In addition to the educational program, the corporate program was anchored by a vibrant exhibit floor of the leading companies in the field of laboratory hematology and a corporate symposium workshop series. Overall, ISLH 2019

was a huge success and we thank CHS for their valued partnership. We look forward to ISLH 2020 in Melbourne, Australia, May 21-23, 2020 with a pre-meeting workshop on May 20th. ISLH 2021 will be back in North America, in the city of New Orleans.

Luspatercept - TRAPpings of Success for Ineffective Erythropoiesis

By Dr. Danielle Hammond

Fellow, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX (Formerly Department of Medicine, Division of Hematology, Queen's University, Kingston, ON)

The pathogenic hallmark of both lower risk myelodysplastic syndromes (MDS) and β -thalassemia is ineffective erythropoiesis. The death of late-stage erythroid precursors leads to chronic anemia and tissue hypoxia, prompting an erythropoietin (EPO) driven expansion of the early erythroid precursor pool, resulting in the paradox of erythroid marrow hyperplasia and peripheral anemia. To add insult to the injury, the expansion of early erythroid precursors upregulates factors that downregulate hepcidin expression, resulting in secondary iron overload.

Current frontline therapies are suboptimal. Responses to erythropoiesis stimulating agents (ESAs) are limited in those with supratherapeutic endogenous EPO levels¹ and by the fact that late-stage erythroid differentiation is EPO independent.² Chronic red cell transfusions, in turn, impose a significant quality of life burden on the patient and further exacerbate secondary iron overload, even with concurrent iron chelation.

Dussiot et al.³ and Suragani et al.^{4,5} converged on a strategy to ameliorate such ineffective erythropoiesis, using activin receptor type IIA and IIB ligand traps, respectively, in mouse models of β -thalassemia and MDS. Ligand traps are molecules that inhibit signaling pathways by sequestering ligands from their cognate receptors. TGF- β superfamily ligands which include TGF- β 1-3, activins, growth differentiation factors, and bone morphogenetic proteins increase Smad2/3 protein phosphorylation via cell-surface serine/threonine kinase receptors.

Activated Smad 2/3, in turn, suppresses terminal erythroid differentiation by decreasing the availability of critical transcription factors like GATA-1.6 To that effect, TGF- β is one of the hematopoietic suppressive cytokines secreted by myeloid-derived suppressor cells (MDSC) implicated in the development of cytopenias in lower risk MDS.⁷

Sotatercept (ACE-011) and luspatercept (ACE-536) are fusion proteins containing the extracellular domain of an activin type II receptor and human IgG1 antibody. As is often the case in medicine, their utility in boosting erythropoiesis was a serendipitous discovery. As inhibition of activin signaling also prevents osteoclast-dependent bone resorption, sotatercept was initially studied as a treatment for osteoporosis in menopausal women.⁸ Surprisingly, treated women showed rapid increases in hematocrit.

Both Dussiot et al. and Suragani et al. demonstrated that mouse orthologs of sotatercept (RAP-011) and luspatercept (RAP-536),

respectively, could alleviate the anemia of ineffective erythropoiesis in an EPO independent manner of their mouse models. Dussiot's group also showed a reduction in hepcidin expression and iron indices. Both groups identified growth differentiation factor 11 (GDF11) as the most likely target by which the ligand trap exerted its effects. However, this has since been countered given that RAP-536 still exerted its beneficial effect on erythropoiesis in a thalassemic mouse model with knockout of hemopoietic GDF11.⁹

On this basis, luspatercept (REBLOZYL, Celgene Corp.) was moved to the clinical trial arena for both lower risk MDS and β -thalassemia. With the phase 2 experience in lower risk MDS, endogenous EPO levels <500 U/L and a lower transfusion burden predictably correlated with better erythroid responses. Curiously, the presence of ring sideroblasts and/or the SF3B1 mutation also were associated with better erythroid responses. Although SRSF2 mutations were less frequent than SF3B1 mutations in the studied population, this preferential response was not similarly noted in patients with alternative splicing mutations (which are mutually exclusive).

The phase 3 MEDALIST trial of luspatercept versus placebo in lower risk (R-IPSS very low/low/intermediate) MDS refractory, intolerant, or ineligible (on the basis of an endogenous serum EPO >200 U/L) to ESAs was therefore limited to transfusion dependent patients with either $\geq 15\%$ ring sideroblasts or $\geq 5\%$ ring sideroblasts and an SF3B1 mutation.¹⁰ The trial, which includes Canadian patients, was initially presented at the 2018 American Society of Hematology (ASH) meeting. Updated results, including responses with respect to SF3B1 allelic burden and other baseline mutations, will be presented at the upcoming 2019 ASH meeting.^{11,12}

The primary endpoint of RBC-transfusion independence for at least 8 weeks was reached in 38% (58/153) of patients who received luspatercept, compared with 13% (10/76) patients who received placebo (OR 5.1, $P < 0.0001$). Moreover, 40% of responders remained transfusion-free at 1 year. 53% of luspatercept-treated patients, compared to 12% of placebo-treated patients, achieved a modified erythroid response defined as a 4 unit or greater reduction in transfusion over 8 weeks or a mean rise of 15 g/L in hemoglobin over 8 weeks without red cell transfusions ($P < 0.0001$). The median peak hemoglobin increase in patients who responded to luspatercept was 26 g/L. There were no concerning safety or tolerability signals. A phase 3 trial of frontline luspatercept versus ESAs in red blood cell (RBC) transfusion dependent lower risk MDS is ongoing (NCT03682536). However, the inclusion criteria are agnostic to the presence of ring sideroblasts or SF3B1 mutation status. A phase 2 study is also ongoing in non-RBC transfusion dependent patients, similarly with no restriction regarding ring sideroblasts or SF3B1 mutation status (NCT03900715).

The phase 3 BELIEVE trial comparing luspatercept to placebo in RBC-transfusion dependent adults with beta-thalassemia or hemoglobin E/beta-thalassemia also included Canadian patients and was presented in parallel at the 2018 ASH meeting.¹³ Crossover was permitted after 48 weeks at which point treatment status was unblinded. Patients in both treatment arms continued to receive iron chelation therapy and RBC transfusions to maintain their usual target hemoglobin level.

The primary endpoint was a $\geq 33\%$ reduction in RBC transfusion burden, with a reduction of ≥ 2 RBC units from baseline, during weeks 13-24 of treatment. After a median follow-up of three years, 48 of 224 patients (21%) in the luspatercept arm compared to 5 of 112 patients (5%) in the placebo arm experienced this endpoint (OR 5.8; $P < 0.001$). Moreover, 158 of 224 (71%) of luspatercept-treated patients experienced a $\geq 33\%$ -percent reduction in RBC transfusion requirements during any consecutive 12 weeks period of treatment, compared to 33 of 112 (30%) placebo-treated patients ($P < 0.001$).

The durability of these erythroid responses has yet to be determined. There was a statistically significant ($P < 0.0001$) reduction in serum ferritin levels (mean difference of $-240 \mu\text{g/L}$ between the groups) after 48 weeks of therapy, possibly due to reduced red cell transfusion requirements. However, this was accompanied by only a modest improvement in myocardial iron estimated by T2* MRI (mean difference -2.39 ms between groups, $P = 0.0391$) and no statistically significant ($P = 0.8685$) difference in liver iron concentration.

Luspatercept had limited side effects in this population as well, with the most common adverse events being headache (26% with luspatercept vs. 24% with placebo), bone pain (20% vs. 8%), arthralgia (19% vs. 12%), and fatigue (14% vs. 13%). Only 1% of luspatercept-treated patients had a cerebrovascular accident or deep vein thrombosis. A randomized, placebo-controlled trial is ongoing in B-thalassemia patients who are not RBC-transfusion dependent (NCT03342404), with an analogous primary endpoint. Iron chelator use and quality of life measures are secondary endpoints.

Future Directions

On November 8, 2019, luspatercept was FDA approved for RBC-transfusion dependent adult patients with beta-thalassemia. April 4, 2020 is the FDA review deadline for its use in lower risk MDS. It remains unclear why luspatercept is especially effective in lower risk MDS with ring sideroblasts and/or SF3B1 mutation. Akin to the story of lenalidomide in MDS with isolated del(5q), evidence of clinical efficacy precedes the mechanistic understanding.

While only one such trial is currently listed (NCT01464164), a rationale next line of investigation would be in the much rarer congenital anemias marked by ineffective erythropoiesis, including Diamond Blackfan anemia and Congenital dyserythropoietic anemia. Cost effectiveness will be a particular

concern for use in α -thalassemia and other congenital hemoglobinopathies marked by ineffective erythropoiesis, as such patients are concentrated in lower-income countries. Moreover, as gene therapy becomes a viable treatment modality for α -thalassemia, the demand for non-curative therapies may wane.

References

1. Buckstein R, Balleari E, Wells R, et al. ITACA: A new validated international erythropoietic stimulating agent-response score that further refines the predictive power of previous scoring systems. *Am J Hematol*. 2017;92(10):1037-1046.
2. Hattangadi SM, Wong P, Zhang L, Flygare J, Lodish HF. From stem cell to red cell: regulation of erythropoiesis at multiple levels by multiple proteins, RNAs, and chromatin modifications. *Blood*. 2011;118(24):6258-6268.
3. Dussiot M, Maciel TT, Fricot A, et al. An activin receptor IIA ligand trap corrects ineffective erythropoiesis in β -thalassemia. *Nat Med*. 2014;20(4):398-407.
4. Suragani RN, Cawley SM, Li R, et al. Modified activin receptor IIB ligand trap mitigates ineffective erythropoiesis and disease complications in murine β -thalassemia. *Blood*. 2014;123(25):3864-3872.
5. Suragani RN, Cadena SM, Cawley SM, et al. Transforming growth factor- β superfamily ligand trap ACE-536 corrects anemia by promoting late-stage erythropoiesis. *Nat Med*. 2014;20(4):408-414.
6. Martinez PA, Suragani RN, Bhasin M, Li R, Pearsall RS, Kumar R. Rap-536 (Murine ACE-536/Luspatercept) Inhibits Smad2/3 Signaling and Promotes Erythroid Differentiation By Restoring GATA-1 Function in Murine β -Thalassemia. *Blood*. 2015;126(23):751-751.
7. Chen X, Eksioglu EA, Zhou J, et al. Induction of myelodysplasia by myeloid-derived suppressor cells. *J Clin Invest*. 2013;123(11):4595-4611.
8. Ruckle J, Jacobs M, Kramer W, et al. Single-dose, randomized, double-blind, placebo-controlled study of ACE-011 (ActRIIA-IgG1) in postmenopausal women. *J Bone Miner Res*. 2009;24(4):744-752.
9. Guerra A, Oikonomidou PR, Sinha S, et al. Lack of Gdf11 does not improve anemia or prevent the activity of RAP-536 in a mouse model of β -thalassemia. *Blood*. 2019;134(6):568-572.
10. Fenaux P, Platzbecker U, Mufti GJ, et al. The Medalist Trial: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept to Treat Anemia in Patients with Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes (MDS) with Ring Sideroblasts (RS) Who Require Red Blood Cell (RBC) Transfusions. *Blood*. 2018;132(Supplement 1):1-1.
11. Fenaux P, Mufti GJ, Buckstein R, et al. Assessment of Longer-Term Efficacy and Safety in the Phase 3, Randomized, Double-Blind, Placebo-Controlled MEDALIST Trial of Luspatercept to Treat Anemia in Patients (Pts) with Revised International Prognostic Scoring System (IPSS-R) Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes (MDS) with Ring Sideroblasts (RS) Who Require Red Blood Cell (RBC) Transfusions. *Blood*. 2019;134(Supplement 1):841-841.
12. Platzbecker U, Dunshee D, Komrokji RS, et al. Luspatercept Significantly Reduces Red Blood Cell (RBC) Transfusion Burden, Regardless of Gene Mutation Frequency, Spectrum, and Prognostic Significance, Among Patients (Pts) with LR-MDS Enrolled in the MEDALIST Trial. *Blood*. 2019;134(Supplement 1):2999-2999.
13. Cappellini MD, Viprakasit V, Taher A, et al. The Believe Trial: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept in Adult Beta-Thalassemia Patients Who Require Regular Red Blood Cell (RBC) Transfusions. *Blood*. 2018;132 (Supplement 1):163-163.

YOUR CHS NEWSLETTER

The MICROENVIRONMENT



Member submissions welcome!

Contact: office@canadianhematologysociety.org

Sirolimus for acute graft vs host disease: the prophylaxis becomes the treatment

Roman Shapiro¹, MD and
Dennis Dong Hwan Kim², MD, PhD

¹Fellow, Dana-Farber Cancer Institute, Boston, MA (Formerly Adult Hematology Program, University of Toronto, Toronto, Canada)

²Allogeneic Blood and Marrow Transplant Program, Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada

Acute graft vs host disease (aGVHD) in the context of an allogeneic stem cell transplantation develops at the cross-road of both HLA-dependent factors and immune effects stemming from an interplay between a non-native graft being exposed to an inflammatory milieu. This inflammatory milieu develops in a host whose native immune regulation is disturbed by existing comorbidities, by preceding disease and its chemo-immunotherapy, and by a pre-transplant conditioning regimen [1].

The decision regarding the type of front-line therapy of aGVHD is in large part dependent on the severity of the presentation with respect to organ damage, as is encompassed with clinically accepted grading scores used in practice [2,3]. Systemic immunosuppression is the mainstay of current therapy in higher grades of aGVHD, with most patients receiving methylprednisolone 2mg/kg/day as the preferred first-line treatment. The expected effectiveness of systemic therapy with methylprednisolone may be predicted with the use of clinically validated biomarkers of aGVHD as was shown with the Ann Arbor score and MAGIC consortium [4,5].

The Ann Arbor score, for example, was based on the expression of the TFNR1, ST2, and REG3a biomarkers, with Ann Arbor scores 1 (AA1) representative of non-relapse mortality (NRM) less than 10% in the training and validation sets, AA2 representative of NRM of approximately 25%, and AA3 representative of NRM > 40% [4]. Based on retrospective validation sets of patients used to develop the Ann Arbor score, patients who develop AA 1-2 aGVHD are more likely to respond to systemic therapy with steroids, while those with AA 3 are more likely to develop gut GVHD and may benefit from alternative intervention in the context of a clinical trial [4]. Evaluation of the Ann Arbor biomarker profile of aGVHD in clinical practice is occurring prospectively in the context of several ongoing clinical trials.

Once systemic therapy with methylprednisolone is started in patients developing aGVHD, the goal is to minimize long-term steroid-related side effects by initiating a taper as soon as sustained treatment response is achieved. However, the attainment of a response to methylprednisolone is variable and the time taken to achieve this

response may necessitate long courses of steroid [6]. Furthermore, some patients with aGVHD will be unable to have their steroid dose tapered without necessitating secondary immunosuppression therapy [7]. In a significant proportion of patients, therefore, a long exposure to steroid treatment will be accompanied by the anticipated side effects of such therapy: hypertension, osteoporosis, mood and sleep disturbance, hyperglycemia, an increased risk of infection, among many other effects.

Alternative steroid-sparing aGVHD therapies are therefore being studied in an effort to reduce the burden of steroid side effects resulting from treatment. One of the more promising options is with sirolimus, an mTOR inhibitor with multiple effects on the immune system [8]. Initially shown to be effective in the prophylaxis against aGVHD [9], sirolimus has the advantage of promoting the activity of regulatory T-cells while blocking the proliferation of activated T-cells thereby leading to their apoptosis [8]. When combined with tacrolimus, sirolimus was shown to effectively reduce the rate of aGVHD while having the added benefit of reduced rates of mucositis and delayed engraftment seen with other effective aGVHD prophylaxis regimens [9]. However, this came at the expense of a higher rate of sinusoidal obstruction syndrome, infections, and cytopenia [1,9].

Pidala et. al. report the preliminary results of a trial evaluating the efficacy of sirolimus in comparison with prednisone in Minnesota (MN) standard risk aGVHD with AA score 1-2 [10]. The primary end-point of the trial, day 28 CR/PR, is an accepted surrogate for long-term response to treatment [11]. Secondary endpoints include day 56 CR/PR, and prednisone taper efficacy.

According to the preliminary results, there was no difference in the primary endpoint between the prednisone and sirolimus arms. The sirolimus arm also had a greater steroid-sparing effect, with up to 67% of standard risk MN patients who have AA 1-2 not requiring any steroid treatment at all (secondary outcome). In addition, it appeared that upfront treatment with sirolimus did not impact the efficacy of aGVHD treatment with prednisone if it was required as subsequent salvage therapy [10].

Although a relatively small study, this phase II trial demonstrated the potential therapeutic efficacy of sirolimus as a steroid-sparing agent among MN standard risk aGVHD patients with AA 1-2 biomarker prediction score. However, questions remain regarding which patients would most benefit from sirolimus instead of steroids alone. In particular, were the treatment groups in the trial balanced in terms of risk factors for treatment-refractory GVHD, including the development of hyperacute GVHD and sex-mismatched transplants [12]? What was the time in

therapeutic range for sirolimus? How was response assessed in patients who died from competing phenomena such as infection prior to the day 28 assessment time?

Furthermore, since patients who received sirolimus prior to day 14 post transplant were excluded from the study, the effect of sirolimus treatment in patients who received sirolimus for GVHD prophylaxis is not addressed in this study. These questions are important to consider in the final analysis of the clinical trial, and if not addressed, merit additional study in a future phase III trial.

Should this change practice?

The results of this trial may be practice-changing for the MN standard risk group of patients with aGVHD who have AA 1-2 risk score. However, the trial specifically randomized patients based on the Ann Arbor biomarker profile, which is not yet routinely used in practice in Canada. The results of this trial argue for a stronger push for the incorporation of aGVHD biomarker profiles into clinical practice because without appropriate patient selection the premature incorporation of sirolimus as an acute GVHD treatment may lead to a suboptimal institutional experience. This may especially be the case if sirolimus is used to treat a significant proportion of patients who would have been otherwise identified as AA 3, a group in whom the effectiveness of sirolimus for the treatment of aGVHD still requires investigation in the context of a clinical trial.

References

1. Nasserredine S, Rafei H, Elbahesh E, Tabbara I. Acute graft versus host disease: a comprehensive review. *Anticancer Research* 2017; 37: 1547 – 1555.
2. MacMillan ML, Robin M, Harris AC, DeFor TE, et al. A refined risk score for acute GVHD that predicts response to initial therapy, survival and transplant-related mortality. *Biol Blood Marrow Transplant* 2015; 21(4): 761 – 767.
3. Schoemans HM, Lee SJ, Ferrara JL, Wolff D, et al. EBMT-NIH-CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. *Bone Marrow Transplantation* 2018; 53: 1401 – 1415.
4. Levine JE, Braun TM, Harris AC, Holler E, et al. A prognostic score for acute graft-versus-host disease based on biomarkers: a multicenter study. *Lancet Haematol* 2015; 2(1): e21 – e29.
5. Major-Monfried H, Renteria AS, Pawarode A, Reddy P, et al. MAGIC biomarkers predict long-term outcomes for steroid-resistant acute GVHD. *Blood* 2018; 131(25): 2846 – 2855.
6. Salmasian H, Rohanizadegan M, Banhosseini S, Rahimi Darabad R, et al. Corticosteroid regimens for treatment of acute and chronic graft versus host disease (GVHD) after allogeneic stem cell transplantation. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD005565. DOI: 10.1002/14651858.CD005565.pub2.
7. Mielcarek M, Furlong T, Storer BE, Green ML, et al. Effectiveness and safety of lower dose prednisone for initial treatment of acute graft-versus-host disease: a randomized controlled trial. *Haematologica* 2015; 100(6): 842 – 848.
8. Abouelnasr A, Roy J, Cohen S, Kiss T, Lachance S. Defining the role of sirolimus in the management of graft-versus-host disease: from prophylaxis to treatment. *Biol Blood Marrow Transplant* 2013; 19: 12 – 21.
9. Cutler C, Li S, Ho VT, Koreth J, et al. Extended follow-up of methotrexate-free immunosuppression using sirolimus and

Continued, bottom of next page

The Monocyte Monolayer Assay: Enhancing Care for the “Untransfusables”

Principal Investigator: Christine Cserti-Gazdewich (2018 Winner)
Toronto General Hospital

The limits of traditional red blood cell (RBC) unit crossmatching lie in “overcall” (for those with high frequency alloantibodies (HFA) that are not necessarily hemolytic), and in “undercall” (for those vulnerable to hyperhemolysis syndrome (HHS) despite seemingly compatible crossmatches).¹

HFAs can doom patients to undertransfusion (or rare donor inventories to depletion) if their significance is over-estimated. In contrast, and no matter how well selected RBCs may be, HHS can occur (and recur), especially in those who already endure sickle disease (SCD). HHS occurs in 1 in 102 to 103 of SCD transfusion encounters, with frequently uninformative investigations on culpable triggers, and serious case fatality rates (up to 1 in 5). The monocyte monolayer assay (MMA),² a “living crossmatch,” quantifies phagocytic indices for monocytes facing any number of donor red blood cell (RBC) options paired with a patient’s serum proteins.

In the Toronto laboratory of Don Branch, this technique has been pioneered and optimized,³ and applied in various populations.⁴⁻⁸ Being labour-intensive, its adoption remains limited,⁹ and more evidence is required before its Canadian expansion. In our 2-year cohort of 20 patients, we aim to show that the MMA can enhance care by absolving falsely positive RBC in HFA, or interdicting falsely negative RBC crossmatches in HHS.

We are tracking post-transfusion freedom from hemolysis as a primary outcome, as well as avoided undertransfusions and unnecessary rare unit consumptions. We have also developed patient-centered information on the procedure for test-specific informed consent.

This cohort may ultimately strengthen the case for scaling up the MMA in patients otherwise deemed “untransfusable,” and overturn some previously entrenched disadvantages.

Participating Sites: UHN, Sunnybrook Hospital, St Michael’s Hospital, Mount Sinai Hospital, CBS

References

1. Danaee A, Inusa B, Howard J, Robinson S. Hyperhemolysis in Patients With Hemoglobinopathies: A Single-Center Experience and Review of the Literature. *Transfus Med Rev* 2015;29:220-30.
2. Zupanska B. Assays to predict the clinical significance of blood group antibodies. *Curr Opin Hematol* 1998;5:412-6.
3. Tong TN, Burke-Murphy E, Sakac D, et al. Optimal conditions for the performance of a monocyte monolayer assay. *Transfusion* 2016;56:2680-90.
4. Michelis FV, Branch DR, Scovell I, et al. Acute hemolysis after intravenous immunoglobulin amid host factors of ABO-mismatched bone marrow transplantation, inflammation, and activated mononuclear phagocytes. *Transfusion* 2014;54:681-90.
5. Tong TN, Cserti-Gazdewich CM, Branch DR. Value of MMA crossmatch? *Transfus Med* 2016;26:301-2.
6. Lau W, Sumner C, Oldfield L, Branch DR, LeMay A-S. Anti-Sc2 of the Scianna Blood Group System can cause hemolytic transfusion reactions: Serendipity and Monocyte Monolayer Assay confirm clinical significance. *Canadian Society for Transfusion Medicine Annual Meeting*; 2017 April 20-23, 2017; Ottawa, Ontario. p. 124.
7. Pendergrast J, Binington B, Tong TN, et al. Incidence and Risk Factors for IVIG-Mediated Hemolysis. *American Society of Hematology*; 2017 Sunday, December 10, 2017 Atlanta, GA. p. 2398.
8. Pendergrast J, Willie-Ramharack K, Sampson L, Laroche V, Branch DR. The role of inflammation in intravenous immune globulin-mediated hemolysis. *Transfusion* 2015;55 Suppl 2:S65-73.
9. Nounsi GT, Billingsley KL, Moulds JM. Successful transfusion of antigen positive blood to alloimmunised patients using a monocyte monolayer assay. *Transfus Med* 2015;25:92-100.

Predictors of the Rowland Universal Dementia Assessment Scale Performance in Adults with Sickle Cell Disease

Principal Investigator: Kevin H. M. Kuo (2019 Winner)
University Health Network and University of Toronto

Background: Sickle cell disease (SCD) patients are at significant risk for stroke and silent cerebral infarcts. At least 33% of adults have cognitive dysfunction. However, access to specialized assessments is limited, and there is currently an unmet need for a fast, easy to administer, screening tool for cognitive impairment in SCD. The Rowland Universal Dementia Assessment Scale (RUDAS) is a 6-item task-based questionnaire that evaluates executive function, memory, language, visual-spatial function, praxis and judgment. It has been validated in many cultures and neurocognitive diseases other than SCD.

Hypothesis: Poor RUDAS performance is associated with the presence of SCD complications independent of age, socioeconomic and education factors.

Methods: Study design: cross-sectional, two adult sickle cell comprehensive care centers in Canada. Inclusion criteria: out-patients ≥18 years-old; all SCD phenotypes. Exclusion criteria: inability to obtain informed consent and/or follow study instructions. Intervention: RUDAS was administered twice, 2-4 months apart, in French or English, based on the patient’s preference. Survey

on demographics and patient-reported outcomes (PROMIS® tools for Depression and Anxiety) were completed. Baseline characteristics, SCD complications, and laboratory results were collected. Statistical plan: t-tests, Fisher exact and chi-squared tests, for continuous and discrete variables respectively, were performed to identify possible association between RUDAS and biologic, socioeconomic, and cultural factors, SCD related complications, comorbid conditions, laboratory parameters, and use of disease-modifying therapy (Table). Associations with univariate $P < 0.05$ were included in the multiple linear regression model. Multicollinearity was assessed.

Results: Of the 252 participants, 92 were from Centre Hospitalier de l’Université de Montréal in Montréal, 160 were from University Health Network in Toronto. Median age at time of survey was 31.5 years (IQR 25-44). Female to male ratio was 1.15. Sickle genotype was distributed as follows: SS 55% (N=138), SC 32% (N=80), other sickle genotypes 13% (N=34). Median RUDAS score was 26 (IQR 24-28), mean score \pm standard deviation was 26.0 ± 2.9 . Suspected cognitive impairment (defined as RUDAS score $< 23/30$) was found in 12% (N=29) of the participants. On univariate analysis, RUDAS score declined significantly with age ($P < 0.001$), lower eGFR ($P < 0.001$), lower systolic blood pressure ($P = 0.022$), and lower reticulocyte count ($P = 0.007$), while higher level of education ($P = 0.012$), employment and/or active

enrolment in a study program ($P < 0.001$), and diagnosis of depression ($P = 0.009$) were predictive of higher RUDAS scores (Table). Reticulocyte count, eGFR, and highest level of education remained independent predictors of RUDAS score on multiple linear regression ($P = 0.003$, < 0.001 , and 0.001 respectively; see Table for effect size). Center, language of administration, age and diagnosis of depression were not associated with RUDAS score on multiple regression. R^2 of the model was 0.323. All variance inflation factors in the model were < 2.0 .

Conclusions: Reticulocyte count and eGFR, but not SCD genotype, being independent predictors of RUDAS suggests disease phenotype may contribute to neurocognitive decline and deserves further exploration. RUDAS does not appear to be influenced by age, language of administration, socioeconomic status, and depression, on multiple regression with mild collinearity. Interestingly, education was independently associated with RUDAS score, despite previous studies showing RUDAS was not biased by education. Recruitment is ongoing at two additional sites to further delineate these relationships and to explore the role of silent cerebral infarct in neurocognitive decline in SCD patients. RUDAS may be a promising tool to identify the patients at higher risk for cognitive impairment who may benefit from access to specialized neurocognitive, educational and social interventions.

References continued from previous page

tacrolimus in related and unrelated donor peripheral blood stem cell transplantation. *Blood* 2007; 109: 3108 – 3114.

10. Pidala JA, Hamadani M, Dawson P, Alousi AM, et al. Sirolimus vs prednisone as initial systemic therapy for Minnesota standard risk (MN-SR). *Ann Arbor 1/2 acute graft-vs-host disease*

(GVHD): primary results of the multi-center randomized phase II BMT CTN 1501 trial. *Biol Blood Marrow Transplant* 2019; 25(3): S50 – S51.

11. MacMillan ML, DeFor TE, Weisdorf DJ. The best endpoint for acute GVHD treatment trials. *Blood* 2010; 115(26): 5412 – 5417.

12. Westin JR, Saliba RM, De Lima M, Alousi A, et al. Steroid-refractory acute GVHD: predictors and outcomes. *Advances in Hematology*, vol. 2011, Article ID 601953, 8 pages, 2011. <https://doi.org/10.1155/2011/601953>.



Canadian Hematology Society (CHS)
Annual Reception, Dinner & Awards Evening
Sunday, December 6, 2020
 San Diego, California, USA
 Contact: office@canadianhematologysociety.org

INTERNATIONAL SOCIETY FOR LABORATORY HEMATOLOGY (ISLH)
XXIV International Symposium on Technical Innovations in Laboratory Hematology
May 21—23, 2020
 Melbourne, Australia
 Contact: <https://www.islh.org/2020/>

American Society for Apheresis (ASFA)
2019 Annual Meeting
May 6—9, 2019
 Austin, TX, USA
 Contact: <https://www.apheresis.org/page/ASFA2020>

Welcome to Cell Therapy Transplant Canada (CTTC—formerly CBMTG)
2019 Annual Meeting & Conference
June 22—25, 2020
 Quebec City, QC
 Contact: <https://www.cttcanada.org/>



European Hematology Association (EHA) Annual Congress
June 11-14, 2020
 Frankfurt, Germany
 Scientific program: annual.congress@ehaweb.org
 Logistics: eha@mci-group.com



38th World Congress of the International Society of Hematology (ISH)
September 13—16, 2020
 Bangkok, Thailand

Canadian Hematology Training Programs

<https://www.canadianhematologytraining.ca/program/>

Saturday, July 18, 2020 - Transfusion Medicine Workshop & Jerry Scott Educational Half-Day

TRANSFUSION MEDICINE WORKSHOP

- **Location** - Chestnut Residence & Conference Centre, 89 Chestnut Street
- **Time** - 7:45 am - 12:00 pm

JERRY SCOTT EDUCATIONAL HALF-DAY

- **Location** - Chestnut Residence & Conference Centre, 89 Chestnut Street
- **Time** - 12:00 - 5:00 pm

Registration for the national 2020 Hematology Retreat is now open. The deadline is May 25, 2020.
 For complete details & registration form, please visit: <https://www.canadianhematologytraining.ca/program/>

CHS @ ASH, Orlando, 2019 - IN PICTURES



Dr. Victor Blanchette
CHS 2019 Lifetime Achievement Award



Dr. Blanchette & colleagues, 1980



**Address to CHS members at
Awards Gala, Dec. 8, 2019, Orlando**



**Aaron Schimmer, University of Toronto,
accepts the 2019 Paper of the Year Award**



**CHS Executive, from LEFT, Nicole Laferriere, President, Gail Rock, Exec. Vice-President, Chris Hillis, Secretary, Caroline Malcolmson, Chief Resident, Lynn Savoie, Past-President.
(Missing, Hassan Sibai, Treasurer, and Jason Berman, Vice-President)**



**Hope to see you next year at
ASH Dec 5—8, 2020, in San Diego!**



Call for Applications: CHS Chief Resident

The CHS is inviting applications for the position of:

Chief Hematology Resident, 2020 – 2021

We are seeking a physician currently enrolled or accepted into a Canadian hematology training program to represent trainees at the CHS executive and serve as the Chief Canadian Hematology Resident.

Term: one-year; from July 1, 2020 to June 30, 2021

Expectations

- The successful candidate will sit on the CHS executive committee and attend the twice annual CHS executive retreat meetings (usually in Toronto or Ottawa, spring & fall) and will attend the CHS executive lunch-meeting at ASH.
- The Chief Canadian Hematology Resident will work with the CHS executive to develop novel educational material for residents and CHS members. These activities may include developing hematology cases for posting on the CHS web portal, writing 1-2 articles for the Microenvironment newsletter on a relevant hematology topic.
- The Chief Resident will be encouraged to develop and implement new educational initiatives, and will assist in the selection of the annual "Best in Canadian Hematology" paper and the annual *RK Smiley research grants*.

- The Chief Resident will also help raise awareness of the CHS among hematology trainees.

Suitability

- This position would be well-suited for a trainee with an interest in an academic career focused on education and/or leadership.
- The position requires a time commitment of approximately four hours per month.

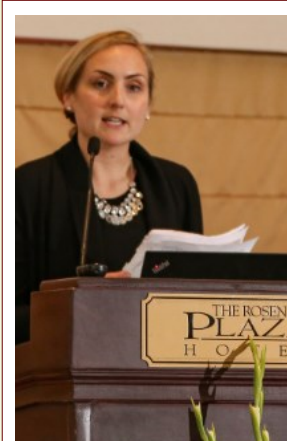
To apply please send

1. A one-page letter that includes a statement on your career interests.
2. A letter of support from your program director (1 page maximum).
3. A copy of your CV. (Maximum, 10 pages.)

Please send application (and queries) by EMAIL to:
CHS@CanadianHematologySociety.org

Deadline:

1800 hrs (Eastern) Friday, January 31, 2020



Caroline Malcolmson,
current Chief Resident, at
the CHS Awards Gala at
ASH 2019, Orlando.

The RK Smiley Research Grant — 2020

The CHS is inviting applications for the:

2020 RK Smiley Research Grant

- This Research Grant offers start up grants of \$20,000 aimed at pilot projects which are expected to lead to larger follow-up studies funded by CIHR or other grant funding agencies.
- It is expected that funds will be used within one year of the award being granted.
- Eligible applicants may be clinicians or scientists with a project relevant to the field of hematology.
- Preference will be given to groups who will benefit maximally from the limited start up funds.
- Only one application per applicant will be accepted.

Application Details:

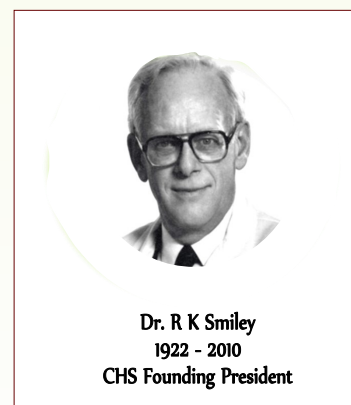
- Title of project
- PI and Co-investigators
- Maximum length: one page
- Additional page: budget
- Double-spaced, font size 12
- Relevance to hematology
- CV of PI

Details:

canadianhematologysociety.org

Deadline

Friday, February 28, 2020



Dr. R K Smiley
1922 - 2010
CHS Founding President

The Canadian Hematology Society established this new research award in honour of our founding President, Dr. R. Kennedy Smiley, to mark our 40th Anniversary in 2011.

JOB POSTINGS

⇒ HEMATOLOGIST

The Saskatchewan Cancer Agency

- **Permanent**, Full Time (1 Vacancy)
- **Location:** Regina, Saskatchewan

Duties

- The diagnosis and treatment of patients with both benign and malignant hematological conditions, including full provision of autologous and allogeneic stem cell transplant services.
- Responsibilities in both benign and malignant patients, proportions to be determined collaboratively based on interests of the candidate.

Required

- MD with subspecialty training in internal medicine & hematology.
- Eligible for licensure with the College of Physicians and Surgeons of Saskatchewan; and membership with the Sask. Health Authority, Regina.
- Eligible for CMPA coverage or equivalent
- Criminal record check
- Language: written and verbal English fluency
- Asset: experience in benign and malignant hematology

For information

Contact Dr. Abdulhakim Eswedi, Regina Team Lead – Hematology:
Abdulhakim.Eswedi@saskcancer.ca

To Submit a CV

Cassandra Ash, Recruitment Coordinator; **Cassandra.Ash@saskcancer.ca**, OR
Danielle Schultz, Recruitment Coordinator; **Danielle.Schultz@saskcancer.ca**

Complete details online

https://canadianhematologysociety.org/wp-content/uploads/Regina_Hematologist_Updated.pdf



⇒ PHYSICIAN

Canadian Blood Services



Join Canada's Lifeline!

CBS is seeking a Physician to help further our mission and join our dynamic team committed to saving & improving the lives of Canadians.

Duties

- A member of a multidisciplinary team that maintains the medically-relevant, biological and technical standards established for blood collection, processing, testing, storage and distribution processes.
- Support and further develop the scientific and medical aspects of donor and patient-related CBS services.
- Support transfusion & transplantation education and public awareness; and share our knowledge with partners, donors, patients and others.
- Direction on medical/technical policies & procedures in support of best manufacturing practices, and safety/adequacy of products and services.

Required

- Medical degree and license to practice in the province of residence
- Meet all relevant provincial requirements for province of residence
- Specialty certification in Hematology, Hematopathology, Transfusion Medicine or a related field is preferred
- Eligible for University appointment in the province of residence

Location

- Any Canadian Blood Services location.

This is a full-time position; but part-time applications will be considered.

Inquiries and questions

Dr. Isra Levy, Vice President, Medical Affairs & Innovation;

Isra.Levy@blood.ca

To apply; Please submit a cover letter and CV to **Tracy.OTOole@blood.ca**

Complete details online

<https://canadianhematologysociety.org/wp-content/uploads/CanadianBloodServices-Physician.pdf>



⇒ ACADEMIC HEMATOLOGIST

University of Alberta

- **Department of Medicine**
- **Competition No.** A100640184 Will remain open until filled.

Duties

- The University of Alberta, Division of Hematology, in partnership with Alberta Health Services, seeks a Hematologist with expertise in myeloid malignancies and post-allogeneic hematopoietic stem cell transplant care, to be based at the University of Alberta and Cross Cancer Institute.

Required

- An MD (or equivalent) with certification in Hematology with the Royal College of Physicians & Surgeons of Canada
- Eligible for licensure: College of Physicians and Surgeons of Alberta
- Specialized training and expertise in the management of adult patients with acute leukemia and other myeloid neoplasms.
- Candidates should have experience in the management of patients who have undergone allogeneic hematopoietic stem cell transplantation.

Interested candidates

- Please submit *online* a letter of intent and CV outlining education, qualifications, experience, research interests, and three letters of reference.
- To: <https://www.careers.ualberta.ca/Competition/A100640184/>

For information

Dr. Joseph Brandwein, Director, Division of Hematology

E-mail: **jbrandwe@ualberta.ca**

https://canadianhematologysociety.org/wp-content/uploads/UofA-SEP19-003_1.pdf

niagarahealth

Extraordinary Caring. Every Person. Every Time.

⇒ BENIGN HEMATOLOGY & THROMBOSIS

Niagara Health & Walker Family Cancer Centre

Niagara Health seeks a highly motivated physician to join the Department of Oncology, Service of Hematology and Thrombosis. Practice includes community based benign hematology.

- A thrombosis service to support our peri-operative program, Heart Investigation Unit, Interventional Radiology, Emergency Department and Oncology program/Walker Family Cancer Centre.
- Includes in-Patient consultations and ambulatory clinics with appropriate nursing support in Niagara Health. (No requirement for provision of inpatient general internal medicine services.)
- Overhead expenses in the shared offices are significantly subsidized.

Required

- Independent license or eligible for independent license with the College of Physicians & Surgeons of Ontario (CPSO)
- FRCP(C) in Hematology
- Eligible to work in Canada without restrictions

Closing Date - Until Filled

Contact Medical Affairs, Niagara Health;

MedicalAffairs@niagarahealth.on.ca

Phone: 905-378-4647 ext. 44224

<https://canadianhematologysociety.org/wp-content/uploads/Profile-Benign-Hematology-Thrombosis-2019-1.pdf>

Your



Canadian Hematology Society

Société Canadienne d'Hématologie

Newsletter

Membership Matters



The Canadian Hematology Society has represented all physicians and scientists with an interest in the discipline in Canada since it was founded in 1971, and currently has over 500 members.

1. Active Members

- Physicians and researchers in the practice of clinical or laboratory hematology in Canada, or
- Canadian physicians engaged in such practice, or
- Persons with university degrees making continuing contributions to research in hematology physiology or pathology in Canada

Active members only shall:

- vote
- hold office
- receive CHS grants, and
- pay dues.

2. Allied Health Members

- Health care workers engaged in the practice of clinical or laboratory hematology in Canada

3. Members-in-Training (Associate Members)

- Residents and fellows engaged in hematology training
- Masters and PhD graduate students
- Post-doctoral fellows engaged in hematology research
- The Program Director shall sponsor membership
- Shall hold all privileges of the Corporation except payment of dues or voting at the AGM
- Expected to become Active Members upon completion of training

4. Emeritus Members

- All individuals who have retired from full time hematology practice or research, or those who were active members and request a transfer of status with adequate reason.

5. Honourary Members

- Non-members may be invited to become Honorary Members of the corporation by virtue of their outstanding contributions to any discipline which is of importance to hematology.

CHS members are reminded ... if you have not sent your \$100 dues payment for 2019, it is now past due.

The CHS Annual Dues for 2020 is \$100.

Payable on January 1, 2020; due on March 1, 2020.

Annual dues payments may be made online at the CHS website: www.canadianhematologysociety.org

Or by mail to: Canadian Hematology Society, 199-435 St. Laurent Blvd., Ottawa, Ontario K1K 2Z8

Please provide the following information with your payment:

2020 Membership Renewal / Address Change: Canadian Hematology Society

Membership Status

Active ☐

Associate ☐

Allied ☐

Emeritus ☐

Name: _____

Title: _____

Email: _____

Work Address: _____

Has your status changed?

Yes ☐

No ☐

Work Phone: _____

Work Fax: _____