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.

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?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 sous-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 mémoire quir. (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 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
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

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

**Residents & Fellows Category — 2018**

**Residents & Fellows Category — 2018**

Qiang (Wayne) Liu, PhD  
Post-doctoral Fellow, Princess Margaret, UHN  
Winning Abstract:  
Identifcation of compounds that target acute myeloid leukemia stem cells using a scalable next-generation screening platform

William Silverstein, MD  
Resident Physician, Faculty of Medicine, University of Toronto  
Winning Abstract:  
Appropriateness of B12 Administration in a Real-World Population

**PhD & Post-Doctoral Category—2018**

**2020 Canadian Hematology Society EXECUTIVE BOARD**

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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

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 throughout 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.

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

Husband, father, grandfather, great-grandfather, physician, researcher, teacher, skier, tennis player, golfer, exuberant underdeterred guitarist 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 subcommittees.

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

(ISLH), which is published by Wiley and the Wiley Online Library. They 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 ß-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 Surgani 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 ß-thalassemia and MDS. Ligand traps are molecules that inhibit signaling pathways by sequestering ligands from their cognate receptors. TGF-ß superfamily ligands which include TGF-ß1-3, 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-ß 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 Surgani 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 ß-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 ≥ 15% ring sideroblasts or ≥ 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. 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 ≥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 ≥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 stastically significant (P<0.0001) reduction in serum ferritin levels (mean difference of -240 μg/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 β-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 β-thalassemia, the demand for non-cure therapies may wane.

**References**


Contact: office@canadianhematologyociety.org
Sirolimus for acute graft vs host disease: the prophylaxis becomes the treatment

Roman Shapiro, MD and Dennis Dong Hwan Kim, MD, PhD

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 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 obstruction syndrome, infections, and cytopenia [1,9].

Pidal 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

9. Cutler C, L, Ho VT, Koreth J, et al. Extended follow-up of metotrexate-free immunosuppression using sirolimus and...
In the Toronto laboratory of Don Branch, this technique has been pioneered and optimized, and applied in various populations. Being labor-intensive, its adoption remains limited, 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 avoiding falsely positive RBC in HFA, or indiscriminating 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 “untransfusables,” and overturn some previously entrenched disadvantages.

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

References
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 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

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/

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
CHS @ ASH, Orlando, 2019 - IN PICTURES

Dr. Victor Blanchette
CHS 2019 Lifetime Achievement Award

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

Dr. Blanchette & colleagues, 1980

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!

December 2019, the Microenvironment - Page 13
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 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**

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**The RK Smiley Research Grant — 2020**

**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**

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.
 пу органические и ткани. Некоторые из них: 
1. Хематология
   - Специализация в диагностики и лечения кроветворных и малигнизирующихся состояний.
   - Включает полное использование аутологических стволовых клеток.
   - Роль в обеих доброкачественных и злокачественных состояниях.
2. Отделение гематологии Университета Альберты
   - Программа подготовки в гематологии.
   - Взаимодействие с Канадским агентством по гематологии.
   - Сотрудничество с Обществом по гематологии.

Для информации
Контакт: Доктор Абдулхаким Имети, Группа Regina – Гематология: Abdulhakim.Eswedi@saskcancer.ca
Следующие CV: Cassandra.Ash@saskcancer.ca, Danielle.Schultz@saskcancer.ca

 пу органические и ткани. Некоторые из них: 
1. Бензиновая гематология
   - Специализация в диагностике и лечении бензиновых состояний.
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Для информации
Контакт: Доктор Иса Леви, Вице-президент, Офис медицинских вопросов и инноваций: Isra.Levy@blood.ca
Следующие CV: Dr. Isra Levy, Vice President, Medical Affairs & Innovation; Isra.Levy@blood.ca

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Следующие CV: Dr. Isra Levy, Vice President, Medical Affairs & Innovation; Isra.Levy@blood.ca


**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. **Honorary 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.

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**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:

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**2020 Membership Renewal / Address Change: Canadian Hematology Society**

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