The Microenvironment

April 2017

THE CANADIAN HEMATOLOGY SOCIETY

SOCIÉTÉ CANADIENNE D'HÉMATOLOGIE

C H S C H

NEWSLETTER

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2017 CHS Executive Committee

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MESSAGE FROM THE PRESIDENT

Dr. Lynn Savoie
President, CHS

Dear Colleagues,

I wish I could wish you a happy spring but at least in Alberta it feels like this winter is never-ending! I must say this has me feeling somewhat down and I'm hoping my general mood will be better by the time you read this.

Congratulations to our winners!

Once again I congratulate all our award winners at ASH and hope you enjoyed our annual general meeting and Gala event, at least this thought makes me smile :).

Microenvironment newsletter

I hope you enjoy this issue of the microenvironment as put together by Dr Nevill. It never ceases to amaze me how he and our office staff come up with such a great read time after time.

Having said that we would love for any of you to get involved whether it be by submitting article, ideas for articles or any other content you might wish to see. In particular we would love to find someone to partner with Dr Nevill and perhaps take over going forward.

Many ways to become involved

This brings me to the topic of your involvement in our society. We strive to represent the hematology community in Canada as best we can and can only do so with your input and involvement.

As I write this we have put out a call for the **next chief resident** to start at the beginning of the next academic year and thus encourage you to apply, or remind any of your interested trainees to do so.

Later this year other members of our **executive** will also need replacing – please consider joining us or nominating a well deserving colleague for a role.

Also, please continue to let us know of the great academic work being done in this country by applying for our **awards and grants**.

We are currently in the process of reviewing the always-inspiring applications for the R K Smiley Award and as per usual will be rewarding research at all levels at ASH 2017.

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Interactive portal activity

It pleases me that our portal continues to gain traction. There is now a wealth of great CME content archived for your perusal at any time with new cases and image challenges posted every month thanks to our chief residents over the years. ***A huge thanks goes out to them!***

Don't forget to check out our product reimbursement library if you have any drug coverage questions around the country.

Coming up in **2018** is the CHS is co-hosting the ISH **Hematology World Congress** in Vancouver from Sept 13-16. Mark your calendars now and watch this space for further details.

As always let me know your thoughts and don't forget to pay your dues!

Dr. Lynn Savoie,
President, CHS

Le message du Président

Chers collègues

J'aimerais pouvoir vous souhaiter un bon printemps, mais au moins en Alberta, on a l'impression que cet hiver ne finit jamais! Je dois dire que cela me fait sentir un peu triste et j'espère que mon humeur générale sera meilleure au moment où vous lisez ceci.

Félicitations à nos gagnants

Encore une fois, je félicite tous nos lauréats à ASH et j'espère que vous avez apprécié notre assemblée générale annuelle et notre gala, au moins cette pensée me fait sourire :).

Bulletin (Microenvironment)

J'espère que vous apprécierez ce numéro du microenvironnement tel que mis en place par le Dr Nevill. Il ne cesse de m'étonner de voir comment il et notre personnel de bureau arrivent avec une lecture impressionante journal après journal.

Cela dit, nous aimerions que vous vous impliquiez, que ce soit en soumettant des articles, des idées d'articles ou tout autre contenu que vous souhaiteriez voir. En particulier, nous aimerions trouver quelqu'un pour collaborer avec le Dr Nevill et peut-être continuer son travail dans l'avenir.

De nombreuses façons de s'impliquer

Cela m'amène au sujet de votre participation dans notre société. Nous nous efforçons de représenter la communauté de l'hématologie au Canada de la meilleure façon possible et nous ne pouvons le faire qu'avec vos commentaires et votre participation.

En écrivant ceci, nous avons lancé un appel pour que le prochain résident en chef commence au début de la prochaine année scolaire et vous encourage donc à présenter une demande ou à rappeler à vos stagiaires intéressés de le faire.

Plus tard cette année, d'autres membres de notre exécutif auront également besoin d'être remplacés - s'il vous plaît envisager de vous joindre à nous ou de nommer un collègue bien mérité pour un rôle. Laissez-nous Poursuivez également avoir à propos de l'excellent travail universitaire accompli dans ce pays en postulant pour nos bourses et subventions. Nous sommes actuellement en train d'examiner les demandes toujours inspirantes pour le Prix R K Smiley et comme d'habitude récompensera la recherche à tous les niveaux à ASH 2017.

Un portail Web interactif

Il me plaît que notre portail continue à gagner de la traction. Il ya maintenant une richesse de contenu archivé pour votre lecture à tout moment avec de nouveaux cas et des défis d'image affichés chaque mois grâce à nos résidents en chef qui y ont c ontribué au fil des ans. ***Un grand merci à eux!***

N'oubliez pas de consulter notre bibliothèque de remboursement des produits si vous avez des questions sur la couverture des médicaments dans tout le pays.

En **2018**, la SCH accueillera le Congrès mondial de l'hématologie à Vancouver du 13 au 16 septembre. Marquer vos calendriers maintenant et regarder cet espace pour plus de détails.

Comme toujours, merci me faire connaître vos pensées et n'oubliez pas de payer vos cotisations!

Dr. Lynn Savoie,
President, CHS

UPDATE: ISH-CHS 2018 VANCOUVER

The ISH 2018 congress will begin with an opening plenary session on Thursday, September 13, 2018. The closing session will be on Sunday, September 16.

PROMOTIONAL ACTIVITIES AND PLANS

The CHS will have a booth at EHA in May, 2017 in Madrid, Spain and at ASH in December, 2017, to promote attendance at the Vancouver 2018 meeting. We will also be sending promotional materials to other international meetings.

We have developed some flyers and banners and are developing a more detailed information pamphlet about ISH 2018 to augment the current material.

THE SCIENTIFIC PROGRAM

The Scientific Program will be packed with a broad selection of current and controversial topics of interest in benign and malignant hematology.

We hope to see all of the CHS members there!

Vancouver Convention Centre
ISH 2018 Congress venue

Dr. Tom Nevill,
Scientific Committee Chair
Dr. Gail Rock,
Organizing Committee Chair

Congress website:
http://www.ish2018.com/

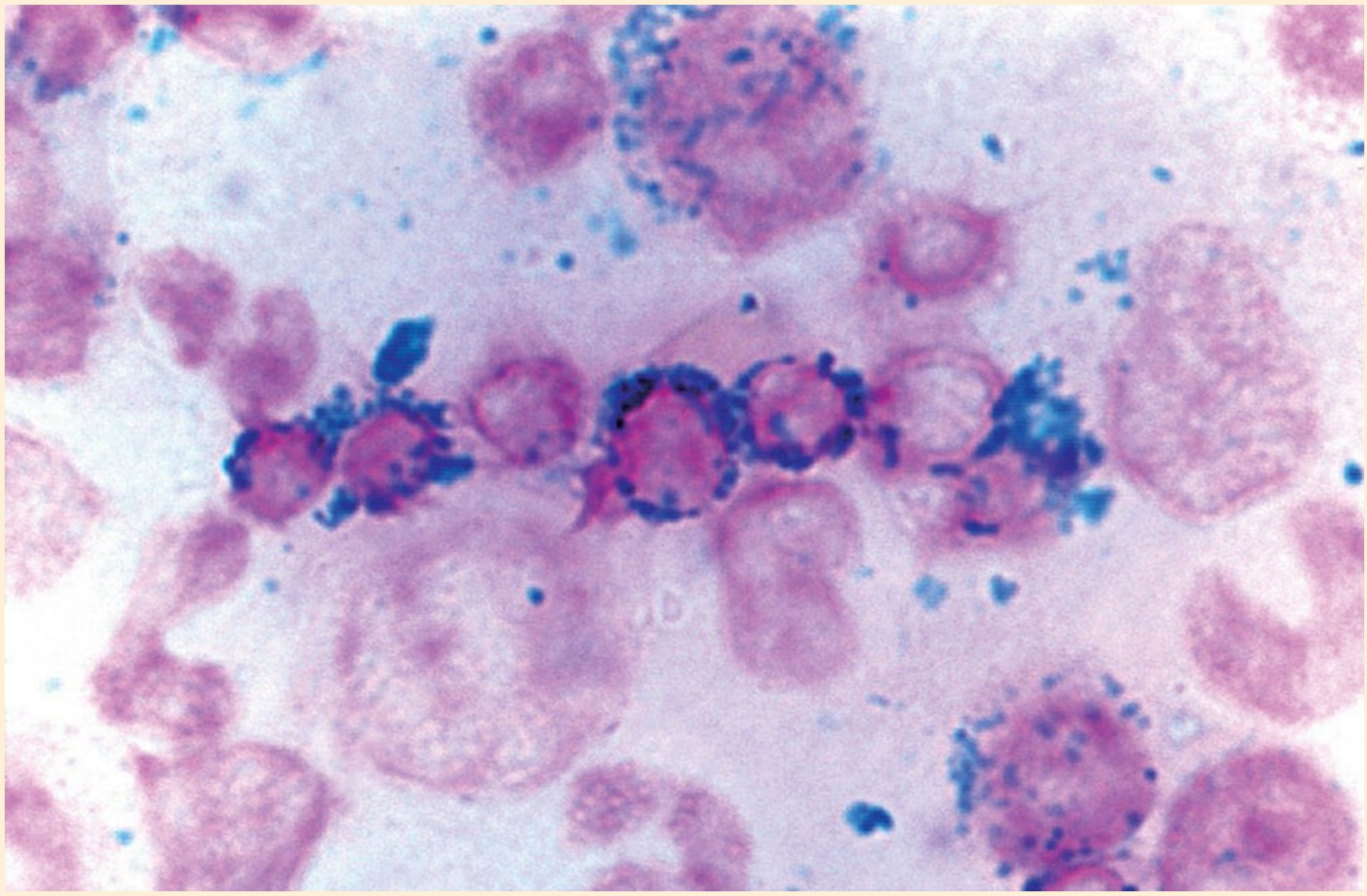
Do you know the diagnosis?

Danielle Hammond, MD, Department of Medicine, University of Toronto, Toronto, Canada

The most likely associated mutation is:

A. SF3B1
B. TP53
C. TET2
D. DNMT3A

Answer: See Page 6



2016 CHS Abstract Award Winners

John H. Crookston Award

Impact of wait times for autologous stem cell transplantation in patients with aggressive non-Hodgkin lymphoma, a subset analysis of the Canadian Cancer Trials Group LY.12 clinical trial

Tanya Skamene, M.D.
(Supervisor—Annette Hay, M D)
CCTG
Queen's University
Kingston, Ontario

High dose chemotherapy followed by autologous stem cell transplant (ASCT) is the standard curative option for patients with relapsed or refractory aggressive non-Hodgkin lymphoma (NHL). Cancer Care Ontario (CCO) treatment guidelines recommend that no more than 91 days should elapse from the first day of salvage chemotherapy to ASCT. The investigators set out to evaluate the impact of wait times on outcomes in the context of the international CCTG LY.12 phase 3 clinical trial. In this trial, patients with relapsed/refractory NHL were randomly assigned to salvage with Cisplatin and Dexamethasone and either Gemcitabine (GDP) or Cytarabine (DHAP) -- with or without rituximab. Patients proceeded to ASCT only if they were felt be chemosensitive.

In their analysis, Skamene and colleagues calculated three wait times -- Total Wait Time (TWT; day 1 of salvage to day of ASCT), Apheresis Wait Time (AWT; day 1 of salvage to first day of stem cell collection), and SCT Wait Time (SWT; last day of stem cell collection to day of ASCT). Patients were considered to have experienced "delay" in TWT, AWT or SWT if the time intervals exceeded 91, 70 and 21 days respectively.

Overall survival (OAS) and event-free survival (EFS) were compared between patients who met and exceeded TWT targets using a Cox proportional hazards model. Univariate and multivariate analyses were performed to estimate the adjusted hazard ratio (HR) for TWT with the following co-variables: age, ECOG, disease stage, presence of extranodal sites, and response after salvage cycle 2.

Of 619 patients enrolled on LY.12, 307 (47%) had sufficient response to salvage (and had adequate stem cell collections) to go on to ASCT. The majority of patients had poor-risk disease at study entry -- 58% had stable disease (SD) or progressive disease (PD) to primary therapy or had an initial CR < 1 year. Following 2 cycles of salvage chemotherapy, 24% achieved CR/CRu, 46% achieved PR and 29% had SD.

The median TWT for the transplanted population was 91 days (range 50-217) – i.e. 50% of patients exceeded the CCO guideline. Median AWT was only 63 days (range 0-151) but 32% of patients exceeded the 70 day target. The median SWT was 26 days (range 6-146) -- 57% of patients exceeded the 21 day target. However, there was no difference in median OAS (HR 0.96, p=0.81) or EFS (HR 1.13, p=0.46) between those patients who met and those who exceeded TWT targets. The 4-year OAS/EFS for patients who met and exceeded TWT were 62%/43% and 64%/50%, respectively. When analyzed as a continuous variable, TWT did not affect OS (HR 0.99) or EFS (HR 0.99). In univariate and multivariate analysis, only the presence of ≤1 extranodal sites of disease was found to be predictive of OAS in the transplanted population (HR 0.51, p=0.005).

Tanya Skamene, M.D., winner of the 2016 CHS Crookston Award at the CHS Gala at ASH in San Diego. The award is named for the late John Hamill Crookston (1922-1987) Laboratory Hematologist-in-Chief at Toronto General Hospital and Professor of Medicine and Pathology at the University of Toronto .

This important analysis has two interesting conclusions. Firstly, the total wait time for ASCT for patients with relapsed/refractory lymphoma is longer than CCO guidelines in one-half of patients who actually were transplanted (which may be an underestimate of TWT as patients that progressed while waiting might never have gone to ASCT). More importantly, patients with longer than the median TWT did not have inferior outcomes. The influence of wait times on ASCT outcome may be a difficult question to answer in a more definitive fashion but it is possible that outcomes depend more on tumour biology than how long it takes to deliver the therapy.

2016 CHS Abstract Award Winners

Residents and Fellows Award

Characterization of Bleeding in Hemophilia Carriers and Comparison to Women with Type 1 von Willebrand Disease, Type 3 von Willebrand Disease Obligate Carriers and Controls

Natasha Satkunam, M.D.
(Supervisor—Paula James, M D)
Queen's University
Kingston, Ontario

Hemophilia carriers report abnormal bleeding even when Factor VIII and Factor IX levels are normal. This study sought to characterize bleeding in this population using the International Society on Thrombosis and Hemostasis Bleeding Assessment Tool (ISTH-BAT). For comparison, the investigators utilized normal healthy controls, women with Type I von Willebrand disease (vWD) and obligate carriers of Type III vWD. This was a prospective, observational study involving the Global Emerging Hemostasis Panel (GEHEP). Clinics in North America, Europe and South Africa identified hemophilia carriers (n=168) and existing ISTH-BAT data was used for the vWD cohorts along with 46 age-matched female controls.

Mean ISTH-BAT bleeding score (BS) was higher in hemophilia carriers (5.7 vs. 2.48, $p<0.001$), than normal controls with more mucocutaneous, post-surgical and menstrual bleeding. When compared to Type I vWD patients, ISTH-BAT BS was lower in hemophilia carriers (5.7 vs. 8.7, $p<0.001$) with vWD patients having more mucocutaneous bleeding and menorrhagia.

Of interest, hemophilia carriers had higher scores than Type I vWD patients with respect to muscle hematomas and hemarthroses. When compared to Type III vWD obligate carriers, hemophilia carriers had higher ISTH-BAT BS (5.7 vs. 3.0, $p=0.009$), with regards to both mucocutaneous bleeding and muscle hematomas/hemarthroses.

Hemophilia carriers have more mucocutaneous and MSK bleeding than age-matched female controls and obligate carriers of Type III vWD although the latter also had higher ISTH-BAT BS than healthy controls. Although hemophilia carriers do not have as much mucocutaneous bleeding as Type I vWD, musculoskeletal bleeding is more frequent in hemophilia carriers. The pathophysiology of increased bleeding in the hemophilia carriers is not well defined and further study of this unique patient population will be required to determine appropriate management.

2016 CHS Abstract Award winners enjoy the CHS Gala evening, December 4, 2016 in San Diego. From LEFT, Vincent-Phillippe Lavallée M.D., Tanya Skamene, M.D., Dr Lynn Savoie, Canadian Hematology Society President, Natasha Satkunam, M.D. and Jesse D. Lai, B. Sc.

2016 CHS Abstract Award Winners

PhD and Postdoctoral Award

Differential glycosylation between recombinant factor VIII produced in baby hamster kidney and Chinese hamster ovary cells confers differences in immunogenicity in hemophilia A mice

Jesse D. Lai, B. Sc.
(Supervisor—David Lillicrap, M D)
Queen's University
Kingston, Ontario

Development of factor VIII antibodies are a major clinical problem in hemophilia A. Different recombinant factor VIII products may have differing immunogenicity, possibly due to differences in protein glycosylation that affects the removal of factor VIII from the circulation and antigen presentation. In this study, the investigators examined differences in 25 N-linked glycans between baby hamster kidney recombinant factor VIII (BHK-FVIII) and Chinese hamster ovary recombinant factor VIII (CHO-FVIII) using a lectin binding ELISA technique.

Lai and colleagues found that BHK cell lines exhibit a lower proportion of high-mannose glycans and higher levels of fucosylated glycans and sialic acid capping ($p < 0.01$ for all three findings). The BHK-FVIII had a significantly shorter circulating half-life than CHO-FVIII (6.06 hours vs. 10.01 hours, $p < 0.0001$). Immunogenicity of the two recombinant factor VIII products was studied in a murine model by subcutaneous and adjuvant -coupled IV infusions. BHK-FVIII was associated with a higher percentage of factor VIII-specific IFN-γ-secreting splenocytes on ELISPOT done seven days after subcutaneous injection. Factor VIII-specific IgG, measured by ELISA, developed in all BHK-exposed mice, but only 47% of CH0-treated mice ($p < 0.01$). Factor VIII inhibitors were measured by one-stage clotting assay and were present in 100% vs. 37% of mice ($p < 0.01$).

The investigators rightfully conclude that BHK-FVIII has more rapid clearance and is more immunogenic than CHO-FVIII. They suggest that these properties relate to its high mannose and sialic acid-containing glycans. Clearly, these findings have potential clinical relevance with regards to the challenges faced when patients with hemophilia A develop factor VIII antibodies.

The DIAGNOSIS? Answer: *(from Page 3)*

Ringed sideroblasts are beautifully demonstrated with Prussian blue staining. Refractory anemia with ring sideroblasts (RARS) is a myelodysplastic syndrome (MDS) characterized by isolated erythroid dysplasia and 15% or more bone marrow ring sideroblasts. This condition is now called "MDS with ring sideroblasts and single lineage dysplasia" (WHO 2016).

There is a high prevalence of associated somatic mutations of SF3B1, which encodes a spliceosome protein. The SF3B1 mutation has prognostic value in RARS and other MDS subtypes -- it identifies a distinct MDS subset with ring sideroblasts that is unlikely to develop detrimental subclonal mutations and is characterized by indolent clinical course and favourable outcome (Malcovati, L. et al. Blood 2015;126: 233–241).

The other mutations listed are also common in MDS, but are not associated with RARS. TP53 has tumour suppressor activity regulating downstream target genes involved in cell cycle arrest, apoptosis, senescence, DNA repair and metabolism -- somatic mutations of it portend a poor prognosis. TET2 and DNMT3A products are both involved in methylation of CpG islands.

2016 CHS Abstract Award Winners

PhD and Postdoctoral Award

Transcriptional Landscape of APL Identifies Aberrant Podoplanin Expression as a Defining Feature and Missing Link for the Bleeding Disorder of This Disease

Vincent-Phillippe Lavallée M.D.
(Supervisor—Guy Sauvageau, M D, PhD)
Hôpital Maisonneuve-Rosemont
Montréal, Quebec

Acute promyelocytic leukemia (APL) is a favourable-risk subgroup of AML characterized by t (15;17) and early bleeding complications -- the leading cause of death in APL. The bleeding propensity is thought to be due to aberrant expression on leukemic promyelocytes of (1) tissue factor (F3) resulting in disseminated intravascular coagulation and (2) annexin A2 (ANXA2) leading to hyperfibrinolysis. Early intervention is critical in minimizing early death in APL. Podoplanin (PDPN) is a surface glycoprotein expressed in most cell types, but not in blood cells. CLEC-2 -- the PDPN receptor -- is expressed on normal platelets and is thought to be necessary for the separation of blood and lymphatic vessels during embryogenesis. PDPN expression (whether endogenous or ectopic) in cell lines induces platelet aggregation, which can be inhibited by either chemical compounds or monoclonal antibodies.

In this study, the investigators analyzed the transcriptome of 30 APL patients, aiming to identify clinically useful markers and to better understand the hemostasis-related transcriptomic landscape of this subgroup. Analysis of gene expression and mutations was performed and compared to 400 non-APL AML patients and sorted normal hematopoietic cell populations (n=63) previously reported (Lavallée *et al*, Nature Genetics, 2015 and Lavallée *et al*, Blood, 2016). PDPN was the single most differentially overexpressed gene in APL; *PDPN* is not expressed in whole blood, bone marrow or in any sorted cell subpopulations from these normal tissues -- including promyelocytes. This indicates that platelets are never exposed to PDPN in the adult vasculature and reveals that this gene is ectopically expressed in APL promyelocytes. Lavallée and colleagues hypothesize that aberrant PDPN expression on leukemic promyelocytes contributes to the abnormal platelet aggregation seen in APL.

They were able to demonstrate that high *PDPN* expression is associated with lower platelet counts at presentation and that there was a strong inverse correlation between the number of circulating $PDPN^+$ promyelocytes and platelet counts. Furthermore, incorporating anti-PDPN antibody (clone NC-08, Biolegend) in the EuroFlow protocol, revealed PDPN expression was 90% sensitive and 100% specific for APL. In fact, PDPN was the most discriminatory transcript of all of the coagulation and fibrinolysis genes examined – including F3 and ANXA2, which largely overlap in APL and other human AML.

PDPN expression is a new biomarker for APL that can be detected by flow cytometry in newly diagnosed AML leading to prompt management. PDPN expression may contribute to defective primary hemostasis and could provide a new target for inhibitors in this setting.

Members of the CHS Executive Committee at ASH 2016 in San Diego. From LEFT: Aaron **Schimmer, Past-President**, Zach **Liederman, Chief Resident**, Lynn **Savoie, CHS President**, Vikas **Gupta, Secretary**, Nicole **Laferriere, Vice-President**, Hassan **Sibai, Treasurer.**

Canadian Contribution to the Development of Heparin and Warfarin

By Dr Tom Nevill, Editor
The *Microenvironment*

Charles Best was born February 27, 1899 in West Pembroke, Maine although his parents, Herbert and Luella were Nova Scotians. An exceedingly bright young man, he enrolled in a Bachelor of Arts Program at University College, University of Toronto in 1915 at the age of 16.

His formal education was interrupted by WW I and in 1918 he served with the 2nd Canadian Tank Battalion during The Great War. After the Armistice, he returned to finish his degree in physiology and biochemistry and then enrolled in Medicine.

Charles H. Best and Banting, ca. 1924

In 1921, he began to work as an assistant to Dr. Frederick Banting, a surgeon, after winning a coin flip for the position with Clark Noble (see Microenvironment History Corner, March 2014). Banting and Best began work in the laboratory of J.J.R. MacLeod who supplied them with ten dogs from which they planned to isolate pancreatic extracts. The two researchers initially had difficulties refining the extract and a biochemist, Dr. James Collip, was assigned by MacLeod in January 1922 to purify insulin; Banting, Best and Collip subsequently shared the patent for insulin.

Connaught Laboratories on the University of Toronto campus began producing large-scale quantities of insulin later in 1922. Frederick Banting and J.J.R. MacLeod were awarded the Nobel Prize in Medicine in 1923 for their ground breaking discovery and Banting split his prize money with Charles Best (MacLeod did the same with Collip). Following his work with insulin, Best went on to a position at the National Institute of Medical Research in London, England.

In 1916, Jay McLean, a 2nd year medical student was working on "cephalins" – substances isolated from canine brain that had procoagulant activity -- with physiologist William Henry Howell at Johns Hopkins Medical School in Baltimore, MD. McLean completed his project early and unexpectedly isolated fat soluble phosphatides from canine liver that had anticoagulant activity. His work was picked up by another medical student, L. Emmett Holt Jr. and an apparently distinct fat soluble anticoagulant was isolated from canine liver which Howell and Holt named "heparin" after the Greek word for liver ("hepar").

In 1922, Howell proposed an aqueous extraction protocol for isolating heparin although this substance was ultimately shown to be different to the substances previously isolated by both McLean and Holt. This water-soluble heparin was moved into commercial production but human studies performed at the Mayo Clinic in Rochester, MN in 1923-24 revealed significant side effects – fever, nausea and headaches – that prevented its widespread use.

In 1928, Charles Best returned from the UK to replace J.J.R. MacLeod as Professor and Head of Physiology at the University of Toronto. He assembled a team of biochemists, physiologists and clinicians with his initial research focus being the purification of heparin to allow for its clinical use in the prevention of thrombosis. Arthur Charles and David Scott began this work with Best at the Connaught Laboratories and in 1933 published a series of papers on their progress isolating insulin from bovine liver, intestine and lung tissue.

Connaught Laboratories, University of Toronto

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One unfortunate side note is worthy of mention. To increase the yield of heparin, the bovine tissue had to be autolyzed producing a smell of decaying tissue so vile that production had to be moved from the city laboratory to the Connaught Dufferin Farm! Production was initially hampered by inconsistent potency from batch to batch, leading to angry complaints from other researchers. Best was not deterred and two teams worked in unison at Toronto General Hospital and the Department of Physiology and School of Hygiene to refine their product.

This led to a key publication on the use of heparin to prevent thrombus formation in traumatized canine veins and the first human trials spearheaded by Toronto General Hospital's Dr. Gordon Murray, began in May 1935. By the late 1940s, other researchers had developed new techniques for producing higher yields of heparin at lower cost and Connaught Laboratories ultimately bowed out of commercial heparin production in the early 1950s. Nevertheless, James Marcum, a noted medical historian recognized "the key person for heparin (development) was Charles Best as he had the novel combined role of top academician and director of production of biologic products".

Charles Best was made a Companion of the Order of Canada in 1967, Commander of the Order of the British Empire in 1971 and received the Queen Elizabeth II Silver Jubilee Medal in 1977. He received 18 honorary degrees (including degrees from Oxford University, Cambridge University, Université Sorbonne and University of Chicago) and was inducted into the Canadian Medical Hall of Fame in 1994. He died in Toronto on March 31, 1978.

Frank Schofield was born in Rugby, Warwickshire, England on March 15, 1889. His father was a mathematics teacher at a college that specialized in missionary work and young Frank, at age 8, spent a great deal of time talking with a Korean student at the college about his homeland. Although Frank Schofield graduated from high school in 1905, he had a substandard academic record, a reputation for misbehaving and could not find the financial support to attend college.

With his father's permission, he set sail for Canada in January 1907 at the age of 17. After working to raise tuition money, he enrolled in the Ontario Veterinary College in Toronto where he was much more diligent with his studies, graduating at the top of his class in 1910. He received a PhD in Veterinary Science from the University of Toronto in 1911.

Dr. Frank Schofield

In 1914, Dr. Schofield became a lecturer in microbiology at the OVC but took on a Presbyterian missionary position in Korea in 1916. His work there was intended to provide education and social organization to Koreans who were suffering under occupation by the Japanese Empire that had begun in August 1910.

What he accomplished there would earn him a special place in the hearts of Koreans -- Frank Schofield was not one to keep his distance from the oppressed. He was determined to learn Korean and by 1918, he had taken on a Korean name – "Suk Ho Pill" – and was teaching classes in Korean. He was also a fierce advocate of the Korean people, speaking out against the attempts by the Japanese to assimilate them into Japanese culture and force them into poverty – as did a number of the missionaries in Korea at the time.

He spoke to his students about an independence movement and before this movement went public on March 1, 1919, the organizers informed him of their plans so that Dr. Schofield could photograph the uprising.

These photographs stand as a stark reminder of the brutal response of the Japanese occupational force. Many of the protesters were beaten, jailed and tortured as were a number of the missionaries although Frank Schofield was specifically spared.

He responded by caring for the injured at the Severance Hospital and housing members of the

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independence movement at his house, before launching a foreign publicity campaign (initially supported by the Presbyterian Church) against the Japanese occupation. Dr. Schofield was not specifically against the Japanese occupation; he was simply anti-colonialism, even being critical of his native Britain's colonial activity.

He was invited to meet with the Korean President but eventually government officials declared the missionaries troublemakers and Frank Schofield the "most pronounced agitator". However, the Japanese did not expel Dr. Schofield from Korea -- it was actually the Presbyterian Church of Canada that became concerned about his outspoken behaviour and recalled him to Canada in 1920.

Frank Schofield returned to teach at the Ontario Veterinary College in Toronto and then in Guelph, Ontario (after the OVC moved there in 1922), until his retirement in 1955. The fact that he survived his time in Korea unscathed is of great hematologic importance!

In the early 1920s in the Canadian Prairies and the Northern Plains of the United States, healthy cattle and sheep began to die of internal hemorrhage of uncertain etiology. This became a major threat to this important industry – and would become even more so when the Great Depression of the 1930s set in a decade later.

Sweet clover

When the extent of the problem was identified and the animals were examined, no nutritional deficiency or offending organism could be found. This led investigators to focus on the livestock's diet – the sweet clover hay that they grazed on. It soon became apparent that the hemorrhagic problems peaked when the climate was damp.

In 1924, Dr. Schofield discovered that the damp hay was infected with *Penicillum nigrans* and *Penicillum jensi* moulds. This mouldy hay would have been discarded were it not for the financial hardship that the farmers were facing at the time. "Sweet clover disease" produced bleeding manifestations within 15 days of consumption and the animals died after 30-50 days. Frank Schofield showed the disease was reversible if the mouldy hay was replaced with fresh fodder or if the cattle were given blood transfusions. Despite Schofield's clear description of the cause of fatal hemorrhagic disease in livestock, farmers remained skeptical and failed to heed his warnings about the risk of livestock consuming mouldy hay. In the early 1930s, a desperate Wisconsin farmer provided Karl Link with a milk can full of unclotted blood from his cattle.

Link spent six years performing a series of experiments to help identify the actual compound that led to the hemorrhagic diathesis. In 1940, he identified this substance as dicoumarol that was formed by the oxidation of natural coumarin by mouldy hay. Through his work, funded by the Wisconsin Alumni Research Foundation ("WARF"), Link developed 150 variants of coumarin with "#42" being the most potent – he named this "WARFarin". In 1948, Link helped market Warfarin as a rodenticide and thereafter helped prepare the application for its use for the prevention and treatment of thromboembolism in humans as "Coumadin".

The development of lab monitoring of anticoagulation in humans took some time but it was ultimately used in President Dwight Eisenhower in 1955 after he suffered a myocardial infarction.

President Dwight Eisenhower

After his retirement from teaching in Guelph, Frank Schofield was invited by Korean President Rhee to teach pathology at Seoul National University. Korea had been liberated from Japanese rule in 1945 by the United States and Russian Armies and in 1958, Dr. Schofield returned to a grateful Korea where he was awarded both the Republic of Korea Medal of Culture and a key to the city of Seoul.

He returned to Canada in the early 1960s and was awarded an honorary Doctorate of Law by the University of Toronto in 1962. In 1969, Schofield again returned to Korea where he died on April 12, 1970. He was the first foreigner to be buried in the Patriots Section of the Korean National Cemetery.

Eltrombopag for Nontransplant Therapy of Acquired Aplastic Anemia

Danielle Hammond, MD
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Successful allogeneic stem cell transplantation is the only curative treatment for aplastic anemia (AA). However, performance status or lack of a timely and suitable suitable donor may preclude its use. The standard nontransplant option for severe AA is intensive immunosuppressive therapy (IST) with horse antithymocyte globulin (hATG) and cyclosporine (CSA). Although 60-70% of patients historically achieve hematological response with this regimen,[1,2,3,4] one third of patients will relapse, often as CSA is tapered or discontinued. Other challenges include a 5% risk of clinical hemolysis due to expansion of a paroxysmal nocturnal hemoglobinuria clone, and a 10-15% risk of clonal evolution which predispose the development of MDS or AML.

Attempts to boost IST response rates by adding high -dose corticosteroids, sirolimus, or mycophenolate mofetil to the the hATG + CSA backbone have been disappointing. Similarly, offering more potent IST upfront in the form of rabbit ATG (rATG),[5] cyclophosamide, and alemtuzumab, have failed to improve long term response rates while increasing toxicity. In the event of nonresponse or relapse, however, these more toxic agents continue to serve as salvage IST options.

Similarly, the addition of hematopoietic growth factors -- including erythropoietin stimulating agents (ESAs) and G-CSF -- to standard IST have shown no clinical benefit in AA. One explanation is that these cytokines act on committed progenitors whereas autoimmune attack of the hematopoietic stem cell (HSC) and early progenitor pool is the purported mechanism for AA-associated cytopenias. The second is that these growth factors are often markedly elevated to begin with in severe AA.[1] However, there are multiple lines of evidence which suggest that thrombopoietin (TPO) has a pleiotropic role in hematopoiesis, beyond its obvious action as the primary endogenous factor driving platelet production. First, TPO receptors, known as c-Mpl receptors, are present on a fraction of HSCs. Second, the c-Mpl knockout mouse model demonstrates reduced HSC and early progenitor numbers. Similarly, patients with congenital amegakaryocytic thrombocytopenia (CAMT), in which there are bi-allelic mutations in the c-Mpl gene, have an extremely high risk of developing aplastic anemia. Eltrombopag (Revolade) is an oral, nonpeptide TPO mimetic. It uniquely provides an additive effect to endogenous TPO by virtue of selective binding to the transmembrane as opposed to extracellular domain of the thrombopoietin receptor. It was initially approved in Canada for splenectomized adult patients with chronic ITP refractory to first-line treatments and patients with hepatitis C-associated thrombocytopenia. Similar to other TPO mimetics, potential toxicities include thrombocytosis, thrombosis, reversible bone marrow fibrosis and hepatotoxicity.[24]

The seminal study of eltrombopag in aplastic anemia came out of the National Institute of Health (NIH) in 2012 with an additional cohort reported in 2014. This phase 2 study used a dose escalation protocol of eltrombopag monotherapy (maximum dose 150mg daily) in patients with severe AA refractory to IST. It elicited a hematologic response in 17/43 patients (40%) by 12 weeks, 7 of which ultimately were trilineage. Responding patients were kept on drug until there was either sustained robust counts or a clinical plateau. Most strikingly, when eltrombopag was discontinued in 9 patients with robust responses, all but one remained in hematologic remission, supporting the hypothesis that it was expanding the effective HSC pool. On serial bone marrow assessment, 8 out of 43 patients had clonal evolution while on drug, 5 of which involved chromosome 7 abnormalities.

However, there was no appreciable increase in bone marrow fibrosis with a median follow up of 13 months. This study was the basis of approval by the FDA and Health Canada for eltrombopag in severe AA refractory to IST.[24] The same group subsequently performed a single centre prospective study looking at the addition of eltrombopag to standard IST in 92 treatment naïve patients with severe AA, which was presented at the 2015 American Society of Hematology Meeting. It was theorized that by

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administering eltrombopag earlier in the disease course, prior to profound depletion of the HSC pool, the likelihood of hematologic recovery could be maximized while limiting the risk of clonal evolution to MDS/AML by preserving clonal diversity. Eltrombopag was administered starting at day 14 (due to potential concerns for hepatotoxicity) for six months (first cohort) or three months (second cohort), or concurrently from day 1 for six months (third cohort). In all cohorts combined, eltrombopag with hATG + CSA demonstrated overall response rates at three and six months of 80 percent and 85 percent, respectively; complete response rates were 28 percent and 34 percent at these time points. These were 20-30 percent higher than historical rates with standard IST alone ($p < 0.001$).

The best response rates were achieved in the cohort receiving eltrombopag on day 1, with 94% of these patients achieving a hematologic response at 6 months, 60% which were complete. Again, there was no appreciable increase in marrow fibrosis on serial bone marrow assessment. 7 out of 92 patients (8%) had clonal evolution with 5 of the 7 patients showing chromosome 7 abnormalities after a median follow up of 19 months. Bolstered by these results, The European Group for Blood and Marrow Transplantation is currently enrolling for their multi-centre, open label, randomized control study (RCT) of standard IST with or without eltrombopag as first line nontransplant therapy in severe AA (RACE trial). The primary outcome will be rate of (early) complete response by 3 months, but an important secondary outcome will be cumulative incidence of clonal evolution at the 2-year mark. The is also a concurrent European multi-centre RCT looking at eltrombopag in in combination with CSA in moderate AA (EMAA trial).

Such success has not been as clearly replicated with the use of eltrombopag for thrombocytopenia in higher risk myelodysplastic syndromes (MDS). The ASPIRE trial randomly assigned patients with higher risk MDS and acute myeloid leukaemia to eltrombopag monotherapy versus placebo. Although there were fewer clinically relevant bleeding events in the eltrombopag group, no difference in platelet transfusion independence or haematological improvement was seen. Reassuringly, no difference in disease progression or overall survival was observed either. Similarly, the SUPPPORT trial was terminated early when interim analysis found eltrombopag with azacitidine to be inferior to placebo + azacitadine in establishing platelet transfusion independence in intermediate int-1, int-2 or high-risk MDS patients. A complete assessment of disease progression at time of study termination, including AML progression, is pending. Pharmacodynamic antagonism between azacitidine and eltrombopag was one proposed explanation for this surprising result. In contrast, eltrombopag was recently shown to significantly improve platelet counts and reduce bleeding events among patients with low risk and int -1 MDS who had severe (platelet count <30) thrombocytopenia. Collection of long-term data, including survival, is ongoing.

Bottom line: There is early optimism that eltrombopag represents a major breakthrough in the nontransplant treatment of aplastic anemia. This optimism should be tempered, however, until long-term data addressing the theoretical risks of spurring clonal evolution and marrow fibrosis is available.

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Contact: http://www.transfusion.ca/Events/

American Society for Apheresis (ASFA)
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May 3—6, 2017
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Contact: http://www.apheresis.org/page/ASFA2017

Canadian Blood and Marrow Transplant Group (CBMTG)
Theme: *Engagement and Resilience Of The Blood and Marrow Transplant Team*
May 5—6, 2017
Winnipeg, Manitoba
Contact: http://www.cbmtg.org/page/2017ThemedMeetings

Canadian Blood and Marrow Transplant Group (CBMTG)
Theme: *Innovation in Blood and Marrow Transplant*
June 9—10, 2017
Calgary, Alberta
Contact: http://www.cbmtg.org/page/2017ThemedMeetings

European Hematology Association (EHA)
22nd Congress
June 22—25, 2017
Madrid, Spain
Contact: https://www.ehaweb.org/

Canadian Blood and Marrow Transplant Group (CBMTG)
Theme: *Pre & Post-Transplant Issues in Blood and Marrow Transplant*
September 8—9, 2017
St. John's, Newfoundland and Labrador
Contact: http://www.cbmtg.org/page/2017ThemedMeetings

Canadian Apheresis Group Annual Meeting
September 22—24, 2017
Montreal, Quebec
Contact: http://cagcanada.ca/annual-general-meeting/

Canadian Hematology Society (CHS)
Annual Reception, Dinner & Awards Evening
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Atlanta, Georgia, USA
Contact: chs@uniserve.com

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Sept 13-17, 2018
Vancouver Convention Centre
Contact: http://www.ish2018.com/

Job Postings

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The Department of Medicine at Oakville Trafalgar Memorial Hospital is recruiting a full-time Hematologist. The scope of this position will be predominantly benign hematology with cross-coverage of malignant hematology inpatients. They must have fellowship standing in the Royal College of Physicians & Surgeons of Canada (FRCPC) in Internal Medicine and have completed additional training in Hematology. Contact: Dr. John McPhaden at jmcphaden@haltonhealthcare.com

MEDICAL ONCONOLOGIST—BELLEVILLE, ONTARIO

Quinte Health Care – The Dr Douglas A MacIntosh Cancer Clinic in partnership with The Cancer Centre of Southeastern Ontario (CCSEO) are searching for a Medical Oncologist. To apply forward a letter of intent and a copy of curriculum vitae to: Dr Roger Lévesque, Head Medial Oncology, Quinte Health Care, 265 Dundas Street East, Belleville , Ontario, K8N 5A9. Tel: 613- 969-7400 ext 2371; Fax 613-969-0486; email : rlevesque@qhc.on.ca

BENIGN HEMATOLOGIST—RICHMOND HILL, ONTARIO

Mackenzie Health is pleased to announce a new full-time position for a benign hematologist. Interested applicants should send a curriculum vitae and letter of intent to: Dr. Matilda Ng MD, FRCPC; Head, Division of Medical Oncology/Hematology; Mackenzie Richmond Hill Hospital; 10 Trench Street, Richmond Hill, ON L4C 4Z3; Phone: (905)883-2153; Email: matilda.ng@mackenziehealth.ca

HEMATOLOGIST—TORONTO, ONTARIO

Humber River Hospital is seeking applications for a hematologist with an interest in benign hematology. Contact: Chief of Medicine, Dr. D. Fishbein at sfishbein@hrh.ca; Humber River Hospital, 1st floor, 1235 Wilson Ave., Toronto, ON

STAFF HEMATOPATHOLOGIST—TORONTO, ONTARIO

Department of Clinical Pathology Sunnybrook Health Sciences Centre, a fully affiliated academic Health Sciences facility of the University of Toronto, invites applications for the position of Staff Hematopathologist. Applicants may direct enquiries and submit their CV in confidence to: Dr. Jeannie Callum, Chair, Search Committee, C/O Dawn Dawkins, B204, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario, M4N 3M5. Please send applications to dawn.dawkins@sunnybrook.ca For more information about Sunnybrook, visit the website at www.sunnybrook.ca

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To obtain more information please contact

Dr. Susan Kahn, Director, Thrombosis Fellowship, c/o Maureen Morganstein 514-340-7587.

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For more information: leukemiabmtprogram.org

Interested candidates should submit a CV and names of three references to:

Dr. Sujaath Narayanan, Fellowship Director Leukemia/ BMT Program, BC Cancer Agency
& Vancouver General Hospital
Phone: (604) 875-4089
FAX: (604) 875-4763
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Auro Viswabandya
Fellowship Director, Allotransplant
Telephone: +1-416-946-4501 x 3256
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Mailing Address:
Princess Margaret Cancer Center
Division of Medical Oncology and Hematology
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Your Canadian Hematology Society
Société Canadienne d' Hématologie Newsletter

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- Physicians in the practice of clinical or laboratory hematology in Canada
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Only active members shall:

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- Residents and fellows engaged in hematology training
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Associate members will not be required to pay dues until completion of their training.

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