The Microenvironment

April 2015

THE CANADIAN HEMATOLOGY SOCIETY

SOCIÉTÉ CANADIENNE D'HÉMATOLOGIE

CHS SCH

NEWSLETTER

Inside this Issue...

2014 CHS Executive Committee

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MESSAGE FROM THE PRESIDENT

Dr. Aaron Schimmer
President, CHS

Dear Colleagues,

The Canadian Hematology Society (CHS) strives to offer meaningful educational programs for our members.

New Interactive Web Portal

In that regard, I am delighted to announce the launched a new interactive web portal that will deliver innovative and useful educational material.

Monthly case studies will be posted on this portal along with a series of multiple choice questions to test your knowledge on the diagnosis and management of important hematologic diseases. The following month a discussion on aspects of the case will be posted and there will be an opportunity for dialogue through the portal.

We hope you will find these cases and questions helpful as you review for Royal College exams and keep up to date with the rapidly changing landscape in hematology. A special thank you to **Dr. Hassan Sibai** who is spearheading this new initiative on behalf of the CHS. Please visit the portal at www.chsportal.ca and check out the most recent case. Don't forget, if you are among the first 5 people to answer the questions correctly, you can win great CHS prizes.

CHS Awards

It was great seeing so many colleagues at the CHS gala at ASH in San Francisco this past December. Congratulations to our trainees (**Drs. Hubert Tsui**, **Joanna Graczyk**, **Danielle Oh**, and **Daisuke Ennishi**) for winning merit awards for their ASH abstracts.

New this year: we awarded the "***Best in Canadian Hematology***" for the paper of the year. Awards were made in the clinical category and basic/translational category.

Dr. Marc Rodger and his team received the clinical award for their paper "Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial" *(The Lancet, Volume 384, Issue 9955, Pages 1673 - 1683 (8 November 2014))*.

Dr. Liran Shlush and colleagues were recognized in the basic/translational category for their paper "Identification of pre-leukaemic Haematopoietic stem cells in acute leukaemia" *(Nature, 506, 328–333 (20 February 2014))*. We received many applications for the paper of the year and it was amazing to see such tremendous and practice- changing work being done by our members. We will offer this competition again next year, so please watch for the call for nominations.

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CHS Executive Board

In closing, I would like to thank **Dr. Julie Stakiw** who has joined the CHS executive as Treasurer and **Dr. Margaret Warner** who will serve an additional term as Secretary. We are fortunate that **Dr. Lynn Savoie** will continue as Vice-President, **Dr. Stephen Couban** as Past-President and Dr. **Gail Rock** as Executive Vice President. Finally, I would like to thank all of the CHS members for their continued support of the Society. We welcome your feedback and involvement in the CHS.

Dr. Aaron Schimmer
President, CHS

President
Dr. Aaron
Schimmer

Past-President
Dr. Stephen
Couban

Vice-President
Dr. Lynn
Savoie

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Dr. Julie
Stakiw

Secretary
Dr. Margaret
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Vice-President
Dr. Gail Rock

Le message du Président

La Société canadienne d'hématologie (SCH) s'efforce d'offrir des programmes éducatifs sérieux à ses membres.

Nouveau portail Web interactif

À cet égard, je suis ravi d'annoncer le lancement d'un nouveau portail Web interactif qui fournira du matériel éducatif innovant et utile.

Des études de cas mensuels seront affichées sur ce portail avec une série de questions à choix multiples pour tester vos connaissances sur le diagnostic et la gestion des maladies hématologiques importantes. Le mois suivant, une discussion sur les aspects du cas sera affichée et un échange via le portail sera possible. Nous espérons que vous trouverez ces cas et ces questions utiles pour la révision de votre examen du Collège Royal et pour rester à jour sur les changements rapides dans le domaine de l'hématologie.

Un remerciement spécial va au **Dr Hassan Sibai** qui est le fer de lance de cette nouvelle initiative au nom de la SCH. Veuillez visiter le portail au www.chsportal.ca et consulter le cas le plus récent. N'oubliez pas, si vous êtes parmi les cinq premières personnes à répondre correctement aux questions, vous pouvez gagner de superbes prix offerts par la SCH.

Prix de la SHC

Nous avons été ravis de voir autant de collègues lors du gala de la SCH à la Société américaine de l'hématologie (ASH) à San Francisco en décembre dernier. Nous tenons à féliciter nos stagiaires (les **Drs. Hubert Tsui, Joanna Graczyk, Danielle Oh,** et **Daisuke Ennishi**) d'avoir gagné les prix du mérite pour leurs résumés à l'ASH.

Nouveauté cette année : nous avons obtenu le « Best in Canadian Hematology » pour l'article de l'année. Des prix ont été offerts dans la catégorie de recherche clinique et la catégorie de recherche de base ou translationnelle.

Le **Dr Marc Rodger** et son équipe ont reçu le prix clinique pour leur article « La daltéparine en période antepartum versus sans daltéparine en période antepartum pour la prévention des complications de la grossesse chez les femmes enceintes atteintes de thrombophilie (TIPPS) : un essai randomisé ouvert multinational » (*The Lancet, Volume 384 , numéro 9955, pages 1673 à 1683 (8 novembre 2014*).

Le **Dr Liran Shlush** et ses collègues ont été reconnus dans la catégorie de la recherche de base ou translationnelle pour leur article intitulé « Identification des cellules souches hématopoïétiques pré-leucémiques dans la leucémie aiguë » (*Nature, 506, 328-333 (20 février 2014*)). Nous avons reçu de nombreuses applications pour l'article de l'année et nous avons été agréablement surpris de voir l'évolution remarquable des pratiques de travail réalisée par nos membres. Nous offrirons cette compétition l'année prochaine à nouveau, par conséquent, veuillez prêter attention à l'appel des candidatures.

Conseil d'administration de la SCH

Pour terminer, j'aimerais remercier le **Dr Julie Stakiw** qui a rejoint le conseil d'administration de la SHC à titre de trésorière et le **Dr Margaret Warner** qui servira un mandat supplémentaire en tant que secrétaire. Nous sommes heureux que le **Dr Lynn Savoie** continuera en tant que vice-présidente, le **Dr Stephen Couban** comme président sortant et le **Dr Gail Rock** en tant que vice-présidente exécutive.

Enfin, je tiens à remercier tous les membres de la SHC pour leur soutien continu à la société. Nous apprécions vos commentaires et votre participation au sein de la SHC.

Dr. Aaron Schimmer
Président, SHC

2014 CHS RESEARCH ABSTRACT AWARD WINNERS

Sensory Neuropeptides Prime the Splenic Marginal Zone for Humoral Immunity

JOHN H. CROOKSTON AWARD WINNER

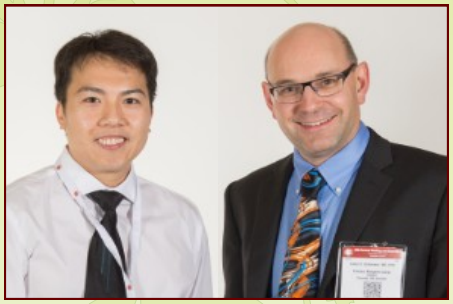
Dr. Hubert Tsui, University of Toronto, Toronto, ON

The spleen is a key component of the immune system in humans and its functions include a central role in the mononuclear phagocyte system and the production of antibodies from lymphatic nodules within its white pulp.

The splenic marginal zone divides the filtering red pulp and the immune white pulp and contains B lymphocytes that detect incoming antigen and produce antibodies in response to this challenge. This research study focused on the presence of sensory nerve synapses in the splenic marginal zone and the immune response of mice deficient in the neurotransmitter, substance P.

Mice deficient in substance P, Tac-1$^{-/-}$ mice, were observed to have splenomegaly with an expanded marginal zone that demonstrated a high Ki-67 proliferative index. These mice displayed a persistent polyclonal pan-B cell lymphocytosis with a significant decrease in total basal IgG ($p < 0.001$) but not IgM. This finding was felt to be consistent with a defect in immune transition between T-independent polyspecific and T-dependent (germinal centre) antibody response. The investigators postulate that marginal zone B-cell mobilization relies upon sensory neuropeptide (substance P) release in response to inflammatory stimuli.

This interesting paper has great potential to enhance our knowledge of humoral immune response. The investigators are attempting to build on their hypothesis with T-cell antigen challenge, cell tracing and electrode experiments as modulation of the substance P axis may have important therapeutic implications.



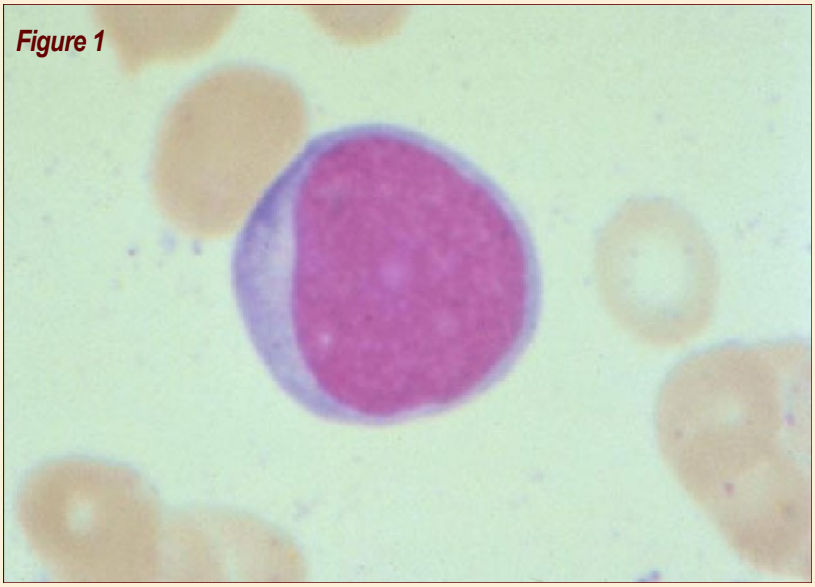
Dr. Hubert Tsui, LEFT, University of Toronto, - who **received the 2014 John H. Crookston Award** for the best paper in the Residents & Fellows category of the CHS Annual Abstract Awards, at the CHS 2014 Awards were presented during the Annual Meeting and Awards Gala, December 7, 2014 in San Francisco—chats with Dr. **Aaron Shimmer, CHS President**, during the annual reception prior to the event.

Do you know the diagnosis?

A 24-year-old man presented with a 1-week history of exertional dyspnea and central pleuritic-type chest pain. He was afebrile, had no other constitutional symptoms and had no significant past medical history.

- Blood work showed a hemoglobin of 154 g/L, a WBC count of 6.7 x 10^9/L (with a normal differential) and a platelet count of 194 x 10^9/L.
- Creatinine, liver function and LDH were all normal.
- Chest X-ray revealed an enlarged cardiac silhouette and a right pleural effusion.
- A CT scan of the chest showed an 8 x 8 cm upper mediastinal mass that was compressing the superior vena cava and the innominate vein as well as a large pericardial effusion and a small right pleural effusion.
- Pericardiocentesis was performed and yielded cloudy yellow fluid with a nucleated cell count of 1560 x 10^6/L, a protein of 47 g/L and a LDH of 121 U/L.
- Differential revealed 62% lymphocytes, 10% macrophages, 2% neutrophils and 26% atypical cells (Figure 1).
- Flow cytometry and molecular analysis on the pericardial fluid did not show any evidence of either a clonal B-cell or T-cell population.
- Blood tumour marker testing revealed normal levels of B-hCG, alpha fetoprotein, CEA and CA 19-9.
- Bone marrow examination was done which was entirely normal.

Figure 1



The patient underwent anterior mediastinotomy, creation of a pericardial window and biopsy of the mass and the pericardium which showed only fibrous tissue with crushed inflammatory cells and edema.

Do you know the diagnosis?

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2014 CHS RESEARCH ABSTRACT AWARD WINNERS

RESIDENTS & FELLOWS CATEGORY

Autologous Stem Cell Transplantation Improves Survival for Patients with Follicular Lymphoma in First or Second Relapse: Results of a Comparative Effectiveness Instrumental Variable Analysis

Dr. Daniel Oh, Tom Baker Cancer Centre, Calgary, AB

High-dose therapy with either autologous (ASCT) or allogeneic (AlloSCT) stem cell support has been proposed to be a curative strategy in follicular lymphoma (FL).

This research study involved an analysis of patients with relapsed FL being treated with ASCT at two Alberta transplantation centres over a 10-year period (2001-2010).

There were 568 patients, aged 18-60 years, diagnosed with FL over this time frame and 108 patients underwent ASCT – 96 patients at Centre A and 84 patients at Centre B (61.5% and 16.7% of their FL patients, respectively; p<0.001).

The two centres differed in a number of ways;

- Centre A employed ASCT earlier in the disease course (in 1st or 2nd relapse, REL 1/2) than Centre B (58.3% vs. 7.1% of ASCT patients, p <0.001) and also utilized AlloSCT more frequently (16.7% vs. 3.6% of all SCTs, p=0.004).
- Centre B more commonly enrolled patients on clinical trials than Centre A (39.3% versus 12.5% of FL patients, p<0.01).

Outcome analysis revealed an overall survival from time of REL 1 (OAS) of 89% for Centre A and 59.5% for Centre B (Figure 1; p <0.001).

Factors predictive of OAS in multivariate analysis were, in addition to treatment centre, FLIPI score 0-2, absence of disease transformation and the use of Rituximab in treatment/ maintenance.

Patients that underwent ASCT at REL 1/2 had a superior 5-year OAS (92.4%; Figure 2) to those that underwent ASCT beyond REL 1/2 (62.5%) or no ASCT (66.5%) (P=0.0006). For the small number of patients that underwent AlloSCT, 5-year OAS was not shown to be superior to the latter two groups.

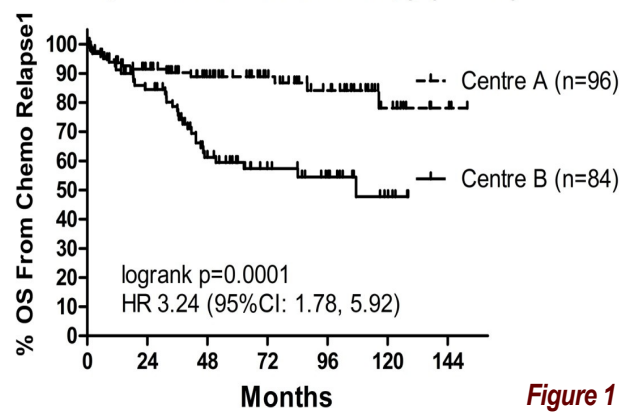


Figure 1

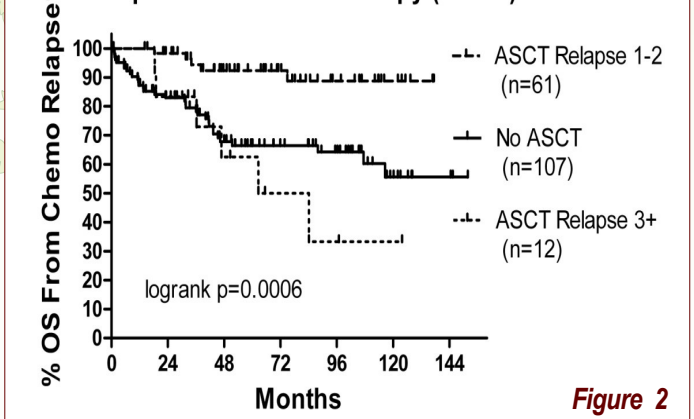


Figure 2

This study suggests that high-dose therapy (HDT) with ASCT has a role in the treatment of FL and the results are superior when it is utilized earlier in the course of disease. However, the debate will continue as the introduction of newer treatments for FL will likely delay the decision to proceed to HDT in this indolent disease. Poor outcomes in patients subsequently undergoing HDT for advanced disease will likely only serve to fuel those opposed to ASCT.

2014 CHS RESEARCH ABSTRACT AWARD WINNERS

RESIDENTS & FELLOWS CATEGORY

Population Based Analysis of Outcomes of Primary Central Nervous System Lymphoma Suggests a Treatment Strategy Including Intensive Chemotherapy with ASCT Provides a Survival Advantage for Patients

Dr. Joanna Graczyk, Tom Baker Cancer Centre, Calgary, AB

Primary CNS lymphoma (PCNSL) has a poor prognosis and management has varied widely.

This study summarized the results of treatment of 107 patients with HIV-negative PCNSL in Alberta over a 16-year period ending in December 2013.

Initial therapy included high-dose chemotherapy [Methotrexate (MTX) or Cytosine arabinoside] with (n=8) or without (n=56) whole brain irradiation (WBRT), WBRT alone (n=28) or palliation only (n=14).

High-dose Thiotepa, Busulfan ± Cyclophosphamide with autologous stem cell transplantation (ASCT) was incorporated into primary therapy in 29 patients in first partial remission and a further 9 patients at the time of relapse.

With a median follow-up of 60.7 months, 5-year overall survival (OAS) was 57.8% for all patients that underwent ASCT, 36.7% for high-dose MTX ± WBRT and 15.5% for WBRT alone (Figure 1).

In patients ≥65 years, OAS was 60% for high-dose MTX-based therapy and 11.8% for WBRT; ASCT did not result in 5-year OAS in any of the 3 patients that were treated in this age group.

The investigators performed a multivariate analysis in patients age <65 years and the only factor found to be predictive of event-free survival (EFS) was the use of ASCT.

With this in mind, a uniform Alberta treatment protocol was instituted in November 2011 that included chemotherapy induction without WBRT followed by high-dose Thiotepa and Busulfan conditioning.

Patients treated in this fashion had 2-year EFS of 64.6% compared to 45.1% in the other 93 historical patients treated prior to this date. For PCNSL patients treated in first partial remission, ASCT was associated with grade 3-4 non-hematologic toxicity and a 9.7% treatment-related mortality.

It was noted that the use of WBRT in association with either high-dose MTX or ASCT was associated with an increased risk (OR 3.8) of neurotoxicity.

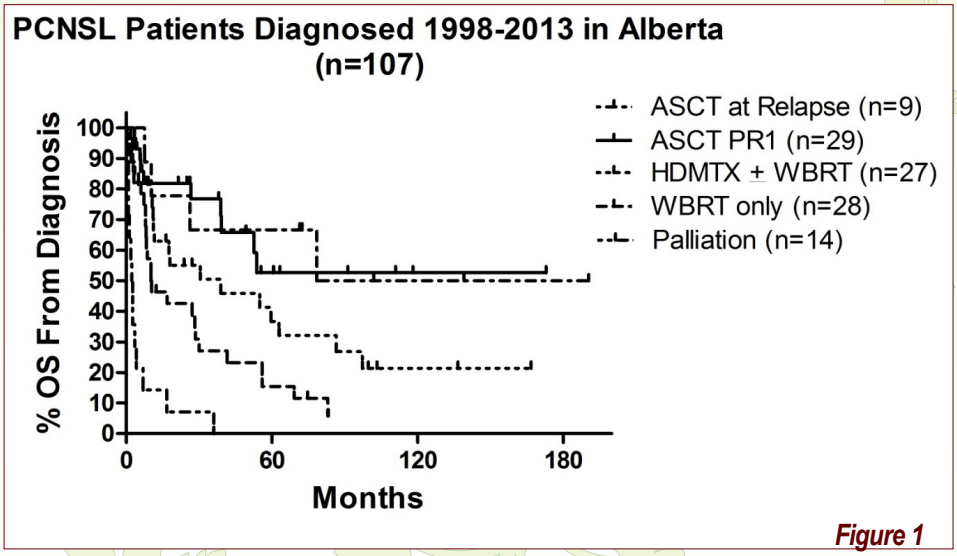


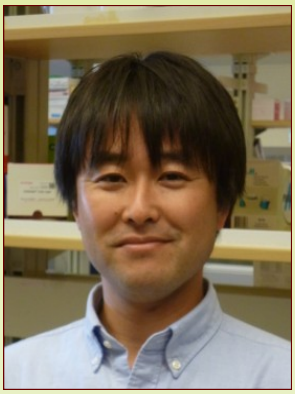
Figure 1

This study demonstrates that a uniform, population-based approach incorporating chemotherapy induction and ASCT may cure a majority of patients with PCNSL <65 years of age. The use of WBRT results in significant toxicity in this patient group and, except in exceptional circumstances, is best avoided. The use of ASCT is associated with substantial morbidity and a 10% treatment-related mortality and appears to be inferior to non-transplant strategies in older patients with PCNSL The Alberta results do require confirmation in a larger, multi-institutional study before it can supplant high-dose MTX as the standard of care in PCNSL.

2014 CHS RESEARCH ABSTRACT AWARD WINNERS

PHD AND POST-DOCTORAL CATEGORY

Clinical Significance of Genetic Aberrations in Diffuse Large B Cell Lymphoma



Dr. Daisuke Ennishi
Centre for Lymphoid Cancer, BC Cancer Agency, Vancouver

Although diffuse large B cell lymphoma (DLBCL) can be cured in the majority of patients, a significant proportion of those affected are refractory to (or relapse after) standard therapy.

The genetic abnormalities that correlate with outcome in DLBCL still need to be determined in order to refine and develop new therapies. This study examined genetic aberrations in a large group of newly diagnosed DLBCL patients (n=348) who received uniform therapy in the province of British Columbia.

Based upon previously described mutations in DLBCL, targeted re-sequencing of 56 genes (with concurrent copy number analysis) was performed on fresh frozen biopsy material in all subjects. Cell-of-origin classification was established by Nanostring technology previously published by this group of investigators.

A total of 194 study participants were found to have a germinal centre B (GCB) subtype of DLBCL, 107 patients had an activated B cell (ABC) subtype and 47 patients were unclassifiable or unknown. The five-year disease specific survival (DSS), with a median follow-up of 6.5 years, was 72% for the entire cohort; the ABC subtype had an inferior DSS compared to the GCB subtype.

Mean mutation frequency was 8.25 per case (range 0-58) with 10 mutated genes being statistically more significant in the GCB subtype, including BCL2, STAT3, EZH2, CREBBP and TNFRSF14. Four mutated genes were seen more frequently in the ABC subtype – MYD88, CD79B, PRDM1 and PIM1.

Copy number analysis revealed 78 amplification peaks and 96 deletion peaks with deletion of 1p36.32 (the site of TNFRSF14) found more frequently in the GCB subtype and deletion of 9p21.3 (the site of CDKN2A) found more frequently in the ABC subtype. DSS was inferior in the ABC subtype with MYD88 mutations and in the GCB subtype with a TP53 mutation. Prognosis was also found to be correlated with mutations in CREBBP, PIM1, TNEM30A and BTG1 in all DLBCL patients.

This work shows that genetic aberrations clearly correlate with prognosis in DLBCL and that these mutations may be specific to the cell-of-origin. These findings should allow for the development of targeted and tailored therapy in DL BCL, increasing the likelihood of improved patient outcomes.

Invitation to submit ...

The Microenvironment **will be happy to consider for publication, articles submitted by members who have sponsored student summer projects.**

Queries should be directed to:

- **Dr. Tom Nevill, The Editor, *The Microenvironment***
- **Email: chs@uniserve.com**

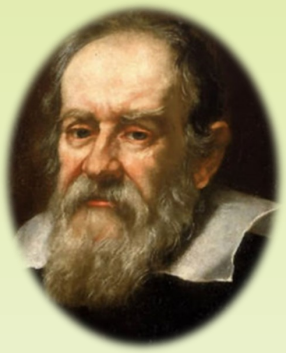
STUDENT RESEARCH ARTICLES

HISTORY CORNER

A Brief History of Chemotherapy

By Dr. Tom NEVILL

The development of chemotherapy as a key component in the management of hematologic malignancies was not a straightforward process.



Galileo Galilei
1564–1642

A number of pioneers in the field were subject to ridicule (or punishment) with these trailblazers having to engage in pitched battles with highly esteemed colleagues whose beliefs were contrary to theirs (and ultimately proven to be incorrect).

In fact, one can see similarities with **Galileo's** efforts in the 17th century to convince other astronomers and the Catholic Church that the geocentric model was wrong.

"Leukemia" first described in 1845

In 1845, a 24-year-old German pathologist, **Rudolf Virchow**, described the entity "**leukemia**" – an accumulation of white blood cells in the blood – which he felt was a disease that arose from the blood-forming organs.

Rudolph Virchow
1821—1902

Over the next 70 years, leukemia became known as a family of diseases, with the "acute" form being universally considered as fatal.

Thus, it was not well received by the medical community in 1930 when a Swiss physician, **Dr. W. Gloor** published a report on successfully inducing a complete remission in a 42-year-old American businessman, **Eugene Metzger**, with hyperleukocytotic AML. Dr. Gloor's treatment regimen consisted of a combination of radiation, Arsenic and another radioactive compound, Thorium-X.

His employers considered him either a liar or a fool and he was fired and banished to a remote community for the remainder of his medical career. Mr. Metzger fared better – he became a well-known philanthropist in New York, lived to the age of 102 and has a building named after him at Mount Sinai Medical School.

Arsenic trioxide had actually been reported by physicians at Boston City Hospital to reduce white blood cell counts in both healthy and leukocytotic patients in 1878.

While Gloor's publication generated little interest (outside of his Swiss employers), the world community did take notice of a report from **Forkner** published in JAMA in 1931 showing that As_2O_3 had considerable efficacy in patients with CML.

"Chemotherapy" coined in early 1900s

It is interesting that the word "***chemotherapy***" was originally coined in the early 1900s by a German chemist, **Paul Ehrlich**, and was simply intended to refer to a chemical used to treat a disease. While interested in drugs to treat cancer, Ehrlich himself was not particularly optimistic of his chances of success.

Not surprisingly, there was much greater interest at the time in finding drugs to treat infections (antibiotics) and his work spawned, in 1907, the first modern antibiotic used to treat syphilis, an arsenic compound named *Arsphenamine*. Today, the term "chemotherapy" is considered synonymous with "cancer chemotherapy"– drugs that are used to treat malignancies.

War gases byproduct leads to cancer chemotherapy

Most physicians are at least peripherally aware that the development of the first cancer chemotherapy was a byproduct of research done on vesicant war gases (which were actually used on WWI battlefields) during WWII.

From previous experience, it had become clear that exposure to mustard gas led to the depletion of both bone marrow and lymph nodes in humans. During WWII, Yale University obtained a contract from the US Office of Scientific Research and Development to study the chemistry of mustard compounds.

Two prominent (and now famous) pharmacologists, **Louis Goodman** and **Alfred Gilman Sr**. were asked to examine these compounds for potential therapeutic effects. After observing marked regression of murine lymphoid tumors with a mustard compound, Nitrogen mustard, they convinced a thoracic surgeon (**Dr. Gustaf Lindskog**) to administer this compound to a patient with airway obstruction from non-Hodgkin lymphoma.

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A Brief History of Chemotherapy (continued)

This clinical experiment took place in 1943 and a marked regression in the lymphoma was observed (although the results had to be shrouded in secrecy until the end of WWII).

Louis S. Goodman
1906—2000

Alfred Z. Gilman
1908—1984

Once Goodman and Gilman were able to publish their data in JAMA and Science in 1946, Nitrogen mustard was used widely in the United States in the treatment of lymphoma. Beginning in the early 1950s, a series of experiments led to the synthesis and testing of two related alkylating agents, *Cyclophosphamide* and *Chlorambucil*.

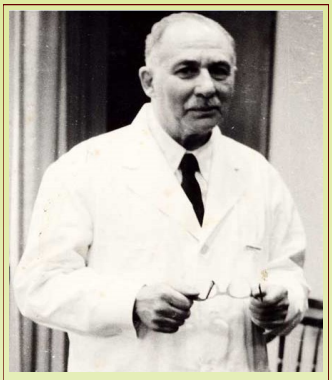
With the discovery of Nitrogen mustard, one would have thought that chemotherapy treatments would become an accepted part of the management strategy in lymphomas.

Vehement opposition to chemotherapy for cancer

Unfortunately, after the initial excitement, an "air of pessimism" pervaded the literature and the hematologic community when it was observed that responses to Nitrogen mustard were either partial or brief. **Dr. William Dameshek**, a Harvard-trained hematologist, who had founded the journal *Blood* in 1946 and had described both CLL and chronic MPDs, was intimately involved in the initial Nitrogen mustard trials.

He went on to serve as President of ASH (who named a prize in his honour) but was deeply affected by his personal experience with these trials and "could never again be persuaded that cancer was curable by drugs".

Dr. Damashek became the leader of a group of academic physicians that became harsh critics of cancer drug development. By all accounts, this was a bitter battle that raged for years, pitting hematologic colleagues, government, academic institutions and the pharmaceutical industry against each other, likely holding up cancer chemotherapy development for a number of years.



Sydney Farber

In 1948, **Sidney Farber** began his developmental contributions on a different track – childhood leukemia. He observed that there was anecdotal evidence of children with acute leukemia getting worse with folic acid supplementation.

This led him to propose that using a folate inhibitor might be beneficial in the treatment of ALL. The first drug trialed, *Aminopterin*, produced promising results and Farber collaborated with Lederle Laboratories to develop another folate antagonist, *Amethopterin* – better known as *Methotrexate*. That same year, **Hitchings and Elion** isolated a substance that inhibited adenine metabolism and by 1951 they had developed two such drugs that remain mainstays of ALL therapy to this day, *6-Thioguanine* and *6-Mercaptopurine*; for this work, they received the **1988 Nobel Prize in Medicine**.

Once again, it was the search for effective antibiotics and antimalarial drugs that led to the formation of programs that screened and synthesized compounds for clinical testing. These programs occasionally yielded, as a byproduct, an effective chemotherapy agent – for example, *Actinomycin D*. However, the more important contribution of these programs to cancer chemotherapy was the experience that it provided to a group of individuals who subsequently used that experience for the purpose of cancer drug development.

Following WWII, it was **Sloan-Kettering Institute**, led by **Dusty Rhoads** and including much of the staff from the Chemical **Warfare Service**, that led the charge in chemotherapy development. Using a murine model to screen compounds for activity, it was at SKI that corticosteroids were shown to have efficacy, albeit transient, in lymphoid tumours.

While a number of the aforementioned chemotherapy agents were being used in childhood ALL in the 1950s, it was a Canadian contribution from the Noble brothers that finally moved cancer chemotherapy forward in the 1960s.

As described in a previous edition of *The* ***Microenvironment*** **(March 2014 History Corner)**, the delivery of leaves from the Madagascar periwinkle plant to **Dr. Clark Noble** for study as a

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diabetes therapy led to **Dr. Robert Noble** isolating *Vinblastine*; in turn, further investigations revealed a second vinca alkaloid with therapeutic potential in lymphoid malignancy, *Vincristine*.

In the mid-1960s, **Brunner and Young** developed a new alkylating agent, Ibenzmethyzin, subsequently renamed *Procarbazine*, which had significant activity in Hodgkin lymphoma. With the final two pieces in place, modern combination chemotherapy was soon to be born. Important concurrent developments in blood product support and antimicrobial therapies contributed to a number of outspoken chemotherapists beginning to talk about a "cure" for leukemia and lymphomas.

Dr. James Holland led a large cooperative group in the study of sequential chemotherapy in childhood ALL. Prior to 1960, 255 children were treated by this group with no 5-year survivors reported.

Dr. James Holland

This cooperative group developed the cyclically administered "VAMP" protocol (*Vincristine*, *Amethopterin* (MTX), *Mercaptopurine* and *Prednisone*) in the late 1960s and by 1970, most investigators felt "a fraction" of childhood ALL could actually be cured. Not everyone agreed; a letter to the Editor of *Pediatrics* in late 1969 from four prominent physicians questioned Dr. Holland's results – "…what good can come of exaggerating the effectiveness of current therapy…".

In the early 1960s, Hodgkin lymphoma was typically treated with single-agent alkylators and was uniformly fatal. In the mid-1960s, **Dr. Vincent DeVita** and colleagues developed the MOMP protocol and then, replacing *Methotrexate* with the newly developed *Procarbazine*, MOPP.

Today, it is hard to imagine the fierce resistance that these treatments faced within the NIH and the hematology community, but after intense bickering, they were only put into clinical trial after the Head of the NIH Clinical Centre, **Dr. Tom Frei**, made an executive decision to proceed.

This was prescient as the complete remission rate in Hodgkin lymphoma went from 0 to 80% with almost 50% of advanced stage patients in the original trial, never experiencing a relapse. It is telling that the article in *Annals of Internal Medicine* in 1970 that detailed the first results with MOPP remains, to this day, the most cited article in the journal's history.

1. Beutler, E. *Leukemia* 15:658, 2001.
2. DeVita V.T. & Chu E. *Cancer Res* 68:8643, 2008.

CHS Translational/Basic Science 2014 Paper of the Year

IDENTIFICATION OF PRE-LEUKEMIC HEMATOPOIETIC STEM CELLS IN ACUTE LEUKEMIA

Nature 506:328-333, 2014

Dr. Liran I. Shlush accepts the CHS 2014 Paper of the Year Award in the Translational/Basic Science category, at the CHS Annual Meeting and Awards Gala, in San Francisco, Dec 7, 2014.

Dr. Liran I. Shlush
Clinical Fellow
Leukemia Service
Ontario Cancer Institute, PMH
Toronto, ON

Acute myelogenous leukemia (AML) is a clonal disorder that evolves from a single ancestral cell although the sequence of genetic changes has not been well-defined. It has been shown that many malignancies have a complex clonal architecture with genetically distinct subclones co-existing with the dominant clone. Furthermore, when neoplastic cells from relapse are compared with those at diagnosis, the former are frequently found to have developed from a minor subclone, not the dominant clone. In such situations, the delivery of curative therapy may depend upon eliminating both the dominant and minor AML clones with the initial treatment strategy. In fact, the ideal goal would be to target and eliminate the pre-leukemic hematopoietic stem cell clone.

In attempting to understand the biology of AML, it is intriguing that leukemia-associated genes have been found in a small number of healthy elderly individuals.[1] Related to this finding is the question of whether leukemic clones can be traced back to non-tumourigenic ancestral clones and, if so, whether these ancestral clones persist in AML patients thought to be in complete remission. In this study, Dr. Liran Slush and colleagues initially performed deep sequencing targeting 103 commonly mutated leukemia genes on peripheral blood samples from 12 AML patients at diagnosis. Normal T-cells from these patients were also analyzed as "non-leukemic" comparisons. DNMT3A mutations (typically seen in ~25% of AML patients) were found in 4/12 AML samples; to their surprise, 3/4 of these patients also had the same mutation found in their T-cells. This finding was confirmed in analyzing a further 71 AML patients; 17/71 had DNMT3A mutations in their CD33+ blasts with 12/17 having the same mutation in their T-cell samples. In addition, 15/17 had NPM!c mutations in the DNMT3A^{mut} CD33+ blasts but none of the T-cell samples had this mutation. Taken together, these findings clearly demonstrate that DNMT3A mutations occur in ancestral cells and supported previous suggestions that NPM1c (and FLT3) mutations are late events in the evolution of AML.[2]

The investigators subsequently utilized high-resolution cell sorting techniques to isolate non-leukemic hematopoietic stem/progenitor cell populations in 11 AML patients. They were able to demonstrate an overall median DNMT3A^{mut} allele frequency of 24.6% for hematopoietic stem cells (HSCs), multilymphoid progenitors and common myeloid progenitors. As it has previously been estimated that single HSCs provide only ~0.5% of clonal contribution during steady-state hematopoiesis,[3] the observed allele frequency was consistent with growth-advantaged expansion of DNMT3A^{mut} clones. Xenograft repopulation assays were then undertaken to confirm this finding. HSCs were obtained at diagnosis on two AML patients with a DNMT3A mutant frequency of 20-30% and transplanted into 35 immunodeficient mice. Multilineage engraftment was demonstrated in 24 of the mice. In a subgroup analysis of 12 of these mice, the DNMT3A^{mut} allele frequency had increased (to a median of 57%) with kinetic studies indicating an increase in allele frequency over time. These results led the researchers to conclude that the DNMT3A^{mut} HSCs do seem to have a competitive growth advantage over non-mutated HSCs.

Dr. Shlush and colleagues went on to examine DNMT3A^{mut} and NPM!c^{mut} allele frequency in mature and progenitor cells from 5 patients at diagnosis and in early (3 months) and late (3 years) remission. Compared to diagnostic CD33+ blasts, CD33+ myeloid cells in early remission samples still had a similar (or higher) DNMT3A^{mut} allele frequency but no evidence of the previously seen NPM!c^{mut} allele. Analysis of patients in late remission showed both a rise in DNMT3A^{mut} allele frequency and, in some samples, a re-emergence of the NPM1c^{mut} allele. In a limited analysis of 6 other AML patients, IDH2 mutations (without NPM1 mutations) were also demonstrated in mature and progenitor cell populations in 2 samples suggesting IDH2 mutations may also occur as a pre-leukemic event.

This truly elegant research paper identifies pre-leukemic hematopoietic stem cells that may occur in healthy individuals and certainly could pre-date AML diagnosis for months or years in a significant proportion of patients. The mutation-bearing HSC, or a down-stream progenitor, may then develop another mutation (e.g. NPM1c) which drives progression to clinically detectable AML. The persistence of pre-leukemic HSCs may act as a reservoir for disease relapse and should be a target for future treatments.

1. Busque et al. *Nature Genet* 44:1179, 2012.
2. Shlush et al. *Blood* 120 :603, 2012.
3. Kim et al. *Blood* 96 :1, 2000.

CHS Clinical 2014 Paper of the Year

ANTEPARTUM DALTEPARIN VERSUS NO ANTEPARTUM DALTEPARIN FOR THE PREVENTION OF PREGNANCY COMPLICATIONS IN PREGNANT WOMEN WITH THROMBOPHILIA (TIPPS): A MULTINATIONAL OPEN-LABEL RANDOMISED TRIAL

Dr. Marc Rodger,
Thrombosis Program
Ottawa Research Institute
Ottawa, ON

Dr. Marc Rodger accepts the CHS 2014 Paper of the Year Award in the Clinical category, at the CHS Annual Meeting and Awards Gala, in San Francisco, Dec 7, 2014. Presenting the award is **Dr. Molly Warner,** Secretary on the Canadian Hematology Society Executive Board.

Lancet 384:1673-1683, 2014

Thrombophilias are common acquired or genetic predispositions to develop deep venous thrombosis and/or pulmonary embolism (VTE) and include Factor V Leiden, Prothrombin gene mutation, Antithrombin deficiency, Protein C or S deficiency and antiphopholipid antibody. Women are more prone to VTE during pregnancy and women with thrombophilia are especially at risk.[1,2] It has also been shown that women with thrombophilias or a history of VTE are at risk for placenta-mediated pregnancy complications (PMPCs) including pre-eclampsia, placental abruption, birth of small-for-gestational age (SFGA) infants and pregnancy loss.[3,4] However, clinicians have struggled with the question of whether antepartum thromboprophylaxis is warranted in this high-risk patient population.[5]

The Thrombophilia in Pregnancy Prophylaxis Study (TIPPS) investigators sought to address this important issue by randomizing pregnant women with thrombophilia to no antepartum prophylaxis versus prophylaxis with low-molecular weight heparin. Over a 12 ½ year period, 3022 women were screened for eligibility in 36 tertiary care centres in Canada, Australia, USA, UK and France. Participants had to be (1) <21 weeks gestation; (2) have a confirmed thrombophlia and (3) be at increased risk for PMPCs, have a prior history of VTE or be at increased risk for VTE. A total of 292 women were randomly assigned to no antepartum prophylaxis (No DALT) or Dalteparin 5000 IU once daily until 20 weeks then 5000 IU twice daily until 37 weeks (DALT). The study was initially blinded and placebo-controlled but after 26 months of low accrual, the placebo component was eliminated. Ultimately, for on-treatment analysis, 141 subjects were in the No DALT arm and 143 patients were in the DALT arm. Patient characteristics were well-balanced between the two groups with an overall mean age of 31.8 years and a gestational age of 11.9 weeks. The most common thrombophilia was Factor V Leiden (60% of patients), Prothrombin gene mutation (22%) and Protein S deficiency or antiphospholipid antibody (8% each).

The primary study endpoint was a composite outcome that included symptomatic major VTE, severe or early pre-eclampsia, birth of a SFGA infant or pregnancy loss. The DALT cohort had 25 patients (17.1%) that met one or more components of the primary outcome (VTE 1, pre-eclampsia 7, SFGA infant 9 and pregnancy loss 12). The No DALT group had 27 patients (18.9%) that met the primary endpoint (VTE 2, pre-eclampsia 4, SFGA infant 12 and pregnancy loss 10) with a p value of 0.70. In planned subgroup analyses directed at each form of thrombophilia and each type of prior PMPC, there remained no statistical benefit to receiving Dalteparin with regards to the composite primary outcome in any subgroup.

Major bleeding events were infrequent in both study arms (DALT, n=3; No DALT, n=2) but non-major bleeding was seen in 19.6% of the DALT cohort and 9.6% of the No DALT arm (p=0.01). Allergic skin reactions (15 versus 11 patients) and raised hepatic transaminases (4 versus 0 patients) were more common in the DALT compared to the No DALT arm. Congenital anomalies were seen in 6 children born to Dalteparin-treated participants and 2 children from the No DALT cohort. None of the patients in the study developed heparin-induced thrombocytopenia.

Two additional observations from this study are worth mentioning. Firstly, patients receiving ASA and Dalteparin showed an interesting trend toward fewer primary outcomes (3/43) compared with ASA patients in the No DALT arm (12/57) suggesting combination therapy may be worthy of study. Secondly, in the No DALT group, none of the women without a prior history of provoked VTE experienced major VTE during the study period. This supports consensus guidelines that women with thrombophilia lacking a prior history of VTE do not require antepartum anticoagulant prophylaxis. However, all three women that developed major VTE while on study had a history of prior VTE and all were receiving Dalteparin,

continued, page 12 ⟶

suggesting that pregnancy prophylaxis in this subgroup may need to be intensified. Importantly, contrary to previously published single-centre trials,[6] low-molecular weight heparin does not improve live birth rates in women with thrombophilia and a history of pregnancy loss.

This trial provides valuable guidance for the management of thromboprophylaxis in pregnancy. Its completion is a testimony to the determination of the group of TIPPS investigators and we congratulate Dr. Marc Rodger for this achievement.

1. Heit et al. *Ann Intern Med* 143:697, 2005.
2. Gerhardt et al. *N Engl J Med* 342:374, 2000.
3. Pabinger et al. *Arterioscler Thromb Vasc Biol* 21:874, 2001.
4. Rodger et al. *PLoS Med* 7:e1000292, 2010.
5. Bates et al. *Chest* 141(suppl 2):e691S, 2012.
6. Gris et al. *Blood* 103:3695, 2004.

CHS @ ASH...

Guest Speakers

Dr. Christine Chen
National Residents Retreat

Dr. Chris Hillis
Choosing Wisely Canada

CHS Paper of the Year 2014 Winners

Dr. Liran I. Shlush
Translational/Basic Science category

Dr. Marc Rodger
Clinical category

Upcoming Events — Mark your calendar - Save the date!

Canadian Hematology Society (CHS)
Annual Reception, Dinner & Awards Evening
Sunday, December 6, 2015
Orlando, Florida
Contact: chs@uniserve.com

International Society of Thrombosis and Haemostasis (ISTH)
25th World Congress
July 11—17, 2015, Toronto, Ontario
Contact: https://www.isth.org

Canadian Blood and Marrow Transplant Group (CBMTG)
Annual Conference
May 13-16, 2015, Montreal, Quebec
http://www.cbmtg.org

International Society for Laboratory Hematology (ISLH)
28th International Symposium
Chicago, Il, May 19-21, 2015
Contact: http://www.islh.org/

...in pictures

CHS 2014 Abstract Award Winners

The **CHS 2014 Research Abstract Awards** were presented by Dr**. Molly Warner,** LEFT, CHS Board Secretary. In the photo with Dr. Warner, is **Dr. Joanna Graczyk,** Tom Baker Cancer Centre, Calgary, Alberta. Photo on the right, FROM LEFT are, Dr. **Daisuke Ennishi** Centre for Lymphoid Cancer, BC Cancer Agency, Vancouver; Dr. **Daniel Oh,** Tom Baker Cancer Centre, Calgary; and Dr. **Hubert Tsui,** University of Toronto, recipient of the 2014 John H. Crookston Award.

Opportunity to network and socialize with peers

Fellowships

LEUKEMIA/BONE MARROW TRANSPLANTATION FELLOWSHIP VANCOUVER

The Leukemia/Bone Marrow Transplantation Program of British Columbia offers 1 or 2 Year fellowships to provide advanced training in the management of adults with hematological malignancies including all aspects of allogeneic and autologous hematopoietic stem cell transplantation (HSCT).

Candidates should be registered in, or completed a recognized hematology or oncology training program.

For more information: leukemiabmtprogram.org

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

BC Cancer Agency
CARE + RESEARCH
An agency of the Provincial Health Services Authority

Dr. Donna Forrest, Fellowship Director Leukemia/BMT Program, BC Cancer Agency & Vancouver General Hospital
Phone: (604) 875-4089
FAX: (604) 875-4763
Email: dforrest@bccancer.bc.ca

Clinical or translational research fellowship in Myeloproliferative Neoplasms (MPN) Princess Margaret Cancer Center, Toronto

The Elizabeth and Tony Comper MPN program at Princess Margaret Cancer Center offers a unique opportunity for a one or two-year clinical or translational fellowship in MPN. The MPN program works closely with a team of leukemia and transplant physicians, and there will be opportunity to train in other aspects of myeloid malignancies and allogeneic transplantation depending on candidate's interest and career goals.

We are actively involved in clinical, laboratory, and translational research, and have a large portfolio of clinical trials. In addition to gaining clinical experience, fellows will have the opportunity to participate in clinical and translational research projects, the design of clinical trials, to learn the principles of conducting research, and to participate in the academic activities of the program.

UHN Princess Margaret Cancer Centre

The expected start date is July 2015 or January 2016, but is negotiable. Candidates must have completed training in internal medicine, and sub-specialty training in hematology or medical oncology. Overseas candidates should have Canadian equivalent training in the above disciplines.

For additional information or an informal discussion, please contact: Dr. Vikas Gupta, MD, FRCP, FRCPath Princess Margaret Cancer Centre 610 University Avenue, 5-303C Toronto, ON CANADA M5G 2M9 tel: (416) 946-4521; fax: (416) 946-6546 email: vikas.gupta@uhn.ca

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

ANSWER:

This patient was diagnosed with fibrosing mediastinitis and was reviewed by an expert consultant in a U.S. institution who agreed with this diagnosis.

- He was started on corticosteroids and Rituximab but within one month developed progressive dyspnea due to worsening pleural effusions.
- He underwent thoracentesis and reimaging showed an increase in the size of his mediastinal mass.
- PET scan revealed FDG-avid supraclavicular, hilar, mediastinal and upper abdominal lymph nodes and it was decided to re-biopsy the disease in his chest.
- However, a repeat CBC showed a new thrombocytopenia (101 x 10^9/L) and circulating immature cells.
- A bone marrow examination (done 5 months after his original marrow exam) revealed 85% blasts that were positive for CD33, CD36, CD56 and CD64 but negative for all lymphoid markers.
- Cytogenetics revealed a highly complex hyperdiploid karyotype that also included t(2;5)(p23;q35), the sites of the ALK and NPM1 genes, respectively.
- He was diagnosed with acute monoblastic leukemia and went into complete remission with induction chemotherapy.
- Allogeneic stem cell transplantation was planned but he unfortunately relapsed within 2 months.

Opportunities

Chief, Division of Hematology-Oncology

The Chief of the Division of Hematology-Oncology will have a strong background in academic Pediatrics and be responsible for the supervision and development of clinical service, educational, and research activities for the members of the Division. Individuals with a strong academic programme and track record of accomplishment are encouraged to apply.

The successful candidate should be eligible for an academic appointment at the University of Toronto. Rank and salary ($400,000 - $600,000) per annum commensurate with qualifications and experience.

All candidates must be certified or eligible for certification in Pediatrics by the Royal College of Physicians and Surgeons of Canada.

Interested individuals should submit:

- a letter of application,
- curriculum vitae, and
- the names and addresses of three referees
- by May 15, 2015 to:

Dr. Denis Daneman, Chair of Pediatrics
University of Toronto and Pediatrician-in-Chief,
Department of Pediatrics,
Hospital for Sick Children, 555 University Ave. ,
Toronto, Ontario M5G 1X8 Canada.

Telephone: (416)813-6122,
Fax: (416) 813-7479.

Visit our Web site, or for additional information regarding the Department of Pediatrics, see

www.utoronto.ca/paedadm/paedadm2htm.

Transfusion Medicine Specialist

Posting Date: November 19, 2014
Position profile – The Transfusion Medicine Specialist will provide medical expertise to the transfusion medicine services, Saskatoon Health Region and across the northern part of the Saskatchewan. Annual salary $301,179.99 -$346,356.00; located in Saskatoon, SK.

Applicants must have or be eligible for certification with the Royal College of Physicians and Surgeons of Canada (Hematology or Hematopathology) with specific training in Transfusion Medicine or a suitable combination of training and experience, and must be eligible for licensure with the College of Physicians and Surgeons of Saskatchewan. All qualified candidates are encouraged to apply; however, Canadian citizens and permanent residents will be given priority.

Interested candidates should submit their curriculum vitae in confidence to:
Dr. Joseph Blondeau, Interim Head
Department of Pathology and Laboratory Medicine; Saskatoon Health Region/ University of Saskatchewan
Royal University Hospital 103 Hospital Drive Saskatoon, SK S7N 0W8
Tel: 306 655-2167
Fax: 306 655-0235
Email:
joseph.blondeau@saskatoonhealthregion.ca

Bone Marrow Transplant Physician

The University of Alberta, Faculty of Medicine & Dentistry, Department of Medicine, Division of *Hematology,* in partnership with Alberta Health Services, invites applications for a bone marrow transplant physician to be based at the University of Alberta Hospital and Cross Cancer Institute.

Located in Edmonton, Alberta, Canada, the Faculty has been internationally recognized as among the world's top 50 medical schools and as one of Canada's premier health-education institutions.

The successful candidate will be an MD with certification in Hematology with the Royal College of Physicians & Surgeons of Canada, and be eligible for licensure with the College of Physicians and Surgeons of Alberta (CPSA).

In addition, the candidate will have prior specialized training and clinical experience in the field of allogeneic bone marrow transplantation. Prior administrative and organizational experience would be an asset.

The position will be accountable to the Director, Division of Hematology and Edmonton Zone Hematology Lead, as well as the Director of the Alberta Blood and Marrow Transplant Program.

Interested candidates are asked to submit online:

- a letter of intent and curriculum vitae outlining their qualifications, experience and academic interests,
- along with three letters of reference to:

Dr. Joseph Brandwein
Director, Division of Hematology
University of Alberta
4-112 Clinical Sciences Building
11350 - 83 Avenue
Edmonton, AB, Canada T6G 2G3

Applications will begin being reviewed on November 5, 2014; however, the competition will remain open until the position is filled.

Department of Medicine can be found on the Faculty's Home Page at www.med.ualberta.ca. Details about Alberta Health Services can be found at www.albertahealthservices.ca

The Microenvironment

April 2015

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 400 members.

Active Membership

- Physicians in the practice of clinical or laboratory hematology in Canada
- Scientists with PhD degrees making continuing contributions to research related to hematology in Canada
- Allied Health Professionals with university degrees making sustained contributions to clinical or laboratory hematology practice or hematology research in Canada.

Only active members shall:

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

Associate Members

- Residents and fellows engaged in hematology training
- Masters and PhD graduate students
- Post-doctoral fellows engaged in hematology research

Associate members will not be required to pay dues until completion of their training.

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.

Honorary Membership

- 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 … that dues for the year 2015, were due on January 1, 2015.

Your $75. annual dues payment 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:

2014 Membership Renewal: Canadian Hematology Society

Membership Status

Active ☐
Associate ☐
Emeritus ☐

Has your status changed?

Yes ☐
No ☐

Name: _____

Title: _____

Email: _____

Work Address: _____

_____

Work Phone: _____

Work Fax: _____