

The Microenvironment



The Canadian
Hematology Society

NEWSLETTER

November, 2011

IN THIS ISSUE

President's Report	1
CHS at ASH	3
Do You Know the Diagnosis?	3
History Corner <i>Dr. Ernest A. McCulloch</i>	4
CHS Marks 40 Years! <i>R. K. Smiley Grant Competition Announced</i>	5
Ask the Expert <i>by Dr. Joseph M. Connors</i>	5
The "Other" CHS <i>Hemochromatosis Society Recruiting Interested Physicians</i>	7
AYA Cancer Patients <i>Task Force Recommendations On Health Care in Canada</i>	7
Focus Canadian Research	8
Q & A <i>with Dr. Richard Wells</i>	10
Mini Review <i>Molecular Diagnostics in AML Dr. Mona Hassanein & Dr. Joseph Brandwein</i>	12
Opportunities <i>Postings & Fellowships</i>	15
Membership Matters <i>2011 Renewal information</i>	16

San Diego, 2011



(More details, Page 3)

CHS at ASH

Plan to attend the
Canadian Hematology Society
Annual Reception, Awards Presentations and Dinner

Sunday, December 11th, 2011, beginning at 6:30 pm

At The Andaz San Diego Hotel
600 F Street, San Diego, California

RSVP by November 22nd
to chsatah@gmail.com

THE PRESIDENT'S REPORT

CAN WE CALL THIS A CHEMOTHERAPY DRUG CRISIS YET?



Dr. Tom Nevill
President, CHS

Last year, Pharmaceutical Services at my hospital circulated a brief memo indicating that the Daunorubicin supply was critically low world-wide and we quickly had to

switch our standard induction chemotherapy in acute myelogenous leukemia to Cytosine arabinoside and Idarubicin.

At the time, there was a flurry of e-mails that circulated amongst the physicians and pharmacists with one stating rather humorously: "What are we going to run out of next—Ara-C"?

...continued on Page 2

CHS 2011 Executive

President:

Tom Nevill

Past-President:

Jerry Teitel

Secretary-Treasurer:

Molly Warner

Vice-President:

Stephen Couban

Executive Vice-President:

Gail Rock

**CHS celebrates
40 YEARS in 2011!**

PRESIDENT'S MESSAGE: Can we call this a chemotherapy drug crisis yet?

...continued from Page 1

Sure enough, a few months ago, a world-wide shortage of Cytosine arabinoside was announced and disaster was only averted (for the time being) at the eleventh hour. These developments should not have come as a surprise to me.

A few years ago, after another “new generation” antibiotic was put on backorder forcing us to change our standard febrile neutropenia management, I recall thinking—“What are they going to run out of next—Penicillin?”

Last year, I began to get phone calls from various pharmacies in British Columbia asking me to provide an alternative to Pencillin V that I had been prescribing for encapsulated organism prophylaxis in chronic graft-versus-host disease patients. Yes, they had run out of Pencillin!



The shortage of key chemotherapeutic agents is much more alarming and strikes at the heart of hematologic oncology practice.

Over the past year, in short order, we have been asked to deal with supply shortages of Vincristine, Etoposide, Bleomycin, Leucovorin, Busulfan and Melpha-

lan. All of these backorders were announced with little or no lead time and required considerable scrambling to deal with the needs

“The shortage of key chemotherapeutic agents is much more alarming and strikes at the heart of hematologic oncology practice.”

of patients scheduled for treatment with one of these drugs. Last week, as the acute leukemia referral centre for the entire province, we were notified of a shortage of 6-Mercaptopurine with VGH’s current supply consisting of 6 tablets.

Physicians and patients are left asking why are these drug shortages happening? Having read a considerable amount about this shortage, it is fair to say that either no one is certain or no one is willing to explicitly say why. There has been mention of a “scarcity of raw ingredients” and “manufacturing glitches” (i.e. failure to meet regulatory standards).

Perhaps the most concerning possibility is that the reason may lie within changes that have occurred within the pharmaceutical industry. There is a body of opinion that company mergers have led to financial restructuring that has

reduced manufacturing capacity, especially of older generic drugs with “small profit margins”.

Regardless of the cause of the drug shortages, physician and pharmacist organizations have initiated a dialogue with government regulators and the pharmaceutical industry to find ways to address this crisis.

In 2010, there was a shortage of over 200 prescription drugs identified by a U.S.-based watchdog organization, more than twice the number of shortages reported only five years earlier.



The same organization has indicated that the number of drugs in short supply in the first quarter of 2011 was, once again, double that reported in the same time period in 2010.

It is fair to say that this drug shortage crisis now threatens the basic care of hematology patients in Canada and a solution must be found.

***Dr. Tom Nevill,
President,
Canadian Hematology Society***

CHS at ASH

RSVP by November 22
chsataash@gmail.com

The Canadian Hematology Society invites you to attend our **Annual Reception, Business Meeting, Awards Presentation Ceremony and Dinner** at the 53rd American Society of Hematology (ASH) Annual Meeting and Exposition. It will be held at the Andaz San Diego Hotel, 600 F Street, on Sunday, December 11, 2011, San Diego, California.



We look forward to having you join us for an elegant, casual evening, beginning with a reception at 6:30 PM at the **Andaz San Diego Roof Top Lounge**. The reception will be followed by the business meeting, the awards ceremony, and then a dinner featuring a choice of a three-course, plated meal.

A total of **five CHS Research Awards** will be presented in the following categories:

- PhD and Post doctoral Category:
Two awards, of \$3,000. each
- Residents and Fellows Category:
Two awards:
- 1 award of \$3,000.
- 1 award of \$5,000.*
- Junior Faculty Category (within 5 years of appointment): One award of \$3,000.

*The \$5,000. award in the Residents & Fellows Category, the Crookston Award, is presented to the Resident with the best paper.

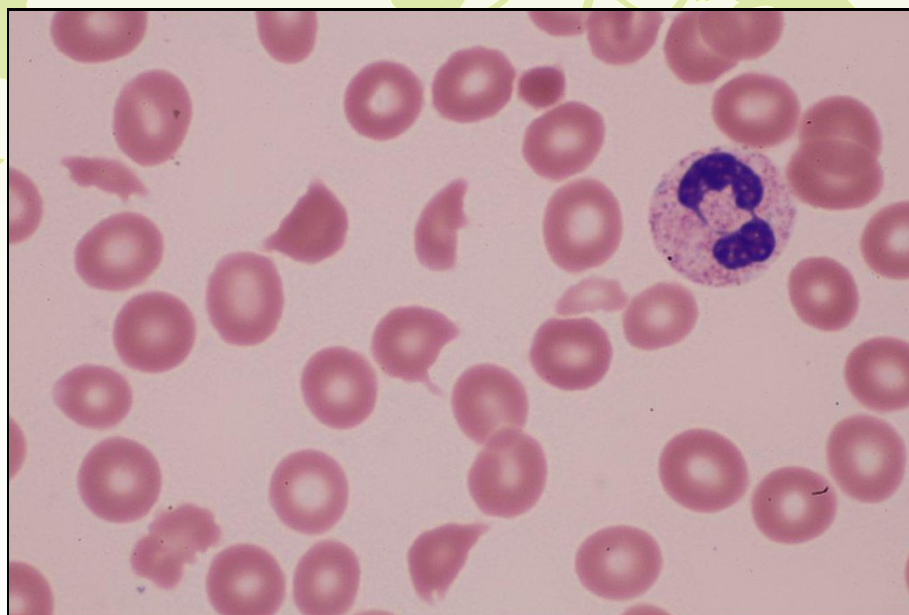
DO YOU KNOW THE DIAGNOSIS ?



Considering the information below, do you know the diagnosis?

- A 50-year-old man with a 3-year history of IgG kappa multiple myeloma for which he is on Lenalidomide 25 mg p.o. daily and Dexamethasone 40 mg p.o. weekly presents with sudden onset of right visual field defect.
- A CT scan of the brain confirms a small, subacute left occipital lobe infarct.
- CBC showed a hemoglobin of 95 g/L, WBC $6.5 \times 10^9/L$ and a platelet count of $4 \times 10^9/L$.
- Peripheral smear is shown on the RIGHT.

What is the diagnosis?



(For the answer, see bottom of page 14.)

HISTORY CORNER

Canadian stem cell pioneer mourned world-wide

Ernest Armstrong McCulloch was born in Toronto on April 21, 1926. He received his M.D. from the University of Toronto in 1948 and traveled to London, England to do post graduate research at the Lister Institute.

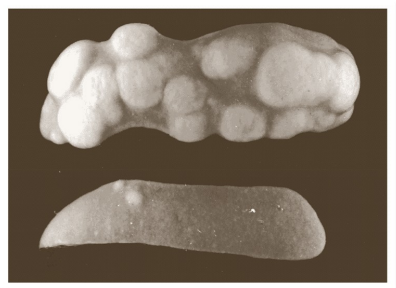
In 1957 he joined the newly formed Ontario Cancer Institute and began working closely with **Dr. James E. Till**, a biophysicist.

In the early 1960s, McCulloch and Till performed a series of pioneering experiments that led to the creation of the first quantitative clonal method for identifying stem cells.

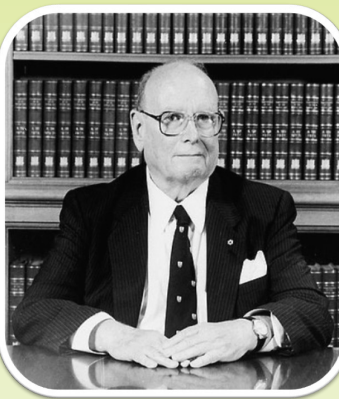
Great Discovery "Accidental"

In a discovery that McCulloch always described as "accidental", the pair began injecting bone marrow into irradiated mice.

They noted the formation of visible nodules in the spleen in proportion to the number of bone marrow cells injected and postulated that each of these "spleen colonies" may have arisen from a single "stem" cell.



This was subsequently confirmed and, in a further collaboration with Lou Siminovitch, a molecular biologist, the group were able to



Dr. Ernest A. McCulloch

1926 - 2011

demonstrate that these single cells were capable of self renewal, a turn that became a key component of the stem cell definition.

Their work was first published in a "largely ignored" paper in *Radiation Research* but followed up with a landmark publication in *Nature* in 1963 that firmly established Toronto as the city where stem cell signs was born.

From the beginning of their partnership, McCulloch and Till agreed to alternate partnership of the results, a "plan that insured them against arguments about priority that could well sour their relationship".

McCulloch went on to focus his research efforts on cellular and molecular mechanisms affecting the growth of malignant stem cells in acute myelogenous leukemia.



Dr. James Till

Several Prestigious Awards

In 1988, he became an Officer of the **Order of Canada** and in 1999 he was made a **Fellow of the Royal Society of London**.



In 2004 he was inducted into the **Canadian Medical Hall Fame** along with his long-time colleague, James Till. In 2005, the pair were awarded the **Albert Lasker Award for Basic Medical Research**, the most prestigious medical science award in the United States and widely regarded as a **precursor to the Nobel Prize**.

Ernest McCulloch died at the age of 84 on January 20, 2011 — the year that marks the 50th anniversary of the stem cell discovery that led to extraordinary advances in the field of medicine.



After the funeral, James Till simply remarked "I've lost a supportive and steadfast friend".

Dr. McCulloch is survived by his wife, Ona, and their five children.

Canadian Hematology Society marks 40 Years! Establishes R. K. Smiley Research Grant Competition

Dr. R. K. Smiley was the first president of the Canadian Hematology Society when it was formed in 1971.

Marking the 40th Anniversary of its inception the Executive of the Canadian Hematology Society has initiated an annual research grant competition to be awarded in Dr. Smiley's honour: the **R.K. Smiley Research Grant Competition**.



Dr. Tom Nevill
Current
CHS President

Program to provide \$10,000

"This program will provide start up grants of **\$10,000** that will be aimed at pilot projects expected to lead to larger follow-up studies funded by CIHR or other grant funding agencies," stated CHS President, Dr. Tom Nevill.

Applicants may be clinicians or scientists with a project that is relevant to the field of hematology.

Details:

Applications should be:

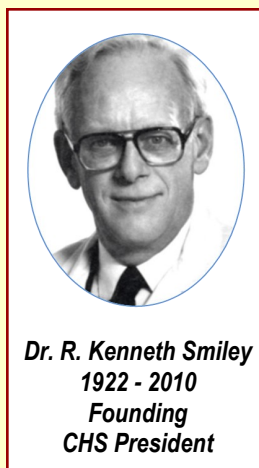
- maximum one page length
- double-spaced
- font size 12

Applications will contain:

1. Title of project
2. Principle investigator and Co-investigators
3. Background
4. Relevance to hematology
5. Research proposal
6. Budget

Important notes:

- Applications should be sent electronically to **chs@uniserve.com**
- Application **deadline** is 1800 hrs EDT on **January 31, 2012**
- Successful applicants will be notified in April 2012



Dr. R. Kenneth Smiley
1922 - 2010
Founding
CHS President

ASK THE EXPERT

Follicular lymphoma - North America's most common non-Hodgkin lymphoma

In this "Ask The Expert" column, **Dr. Joseph M. Connors, Clinical Professor and Director at the BCCA Centre for Lymphoid Cancer in Vancouver**, British Columbia discusses the case of:

a 52-year-old woman who presents with a 6-month history of bilateral, non-tender cervical lymphadenopathy. She reports a 2-month history of fatigue and drenching night sweats. Physical examination confirms multiple 2 cm nodes palpable in the anterior and posterior cervical chains on both sides of the neck as well as bilateral axillary and inguinal lymphadenopathy. The spleen was palpable 4 cm below the left costal margin. Blood testing showed a hemoglobin of 120 g/L, WBC count of $15.8 \times 10^9/L$ with 10.2 abnormal lymphoid cells and a platelet count of $175 \times 10^9/L$.

Flow cytometry on the lymphoid population showed that the cells were CD19, 20 and 22 as well as BCL2 positive

but CD5 negative. Cervical lymph node biopsy revealed follicular lymphoma, grade 2 with a t(14:18 translocation).

Commentary: About 25% of patients with non-Hodgkin lymphomas have follicular lymphoma making it the single most common non-Hodgkin lymphoma in North America now that gene expression profiling has divided diffuse large B cell lymphoma (DLBCL) into at least three diseases.

Follicular lymphoma, as seen in this case, is usually (~85%) associated with a t(14;18), which transposes intact *BCL2* near to the IgH promoter and leads to constitutive rather than episodic expression of the anti-apoptotic *BCL2* protein blocking cell death that should have occurred as increasing numbers of additional genetic errors accumulate in the malignant cells.

.... continued on Page 6

Although this patient presents with typically widespread disease (~90% have advanced stage disease at diagnosis), she has several atypical findings. Prominent B symptoms only occur in a minority (~15%) of patients and peripheral blood involvement is distinctly unusual. Especially given these unusual features we need to ask what other data are required.

This patient is constitutionally ill with B symptoms and advanced stage follicular lymphoma (stage IV B, peripheral blood positive). But does she have more than that? Additional data will be helpful. A markedly increased LDH level (>150% of normal), hypercalcemia or clearly defined nodules in the spleen on CT scanning would convince me she also harbors transformed DLBCL.(1)

Either close inspection of the abnormal peripheral blood cells to see if they are large and pleomorphic or blastic or a bone marrow biopsy may reveal transformed lymphoma. Some authorities consider a high SUV (standardized uptake value) by PET scan to indicate transformed disease but appropriately sized biopsy based studies have shown that the ranges of SUVs in follicular and transformed lymphoma overlap widely, rendering this an insensitive measure for identification of transformed lymphoma.(2)

How should this patient be treated? If transformed lymphoma is found (so-called discordant or composite lymphoma with both follicular and DLBC lymphoma at diagnosis), as hinted by the leukemic phase and prominent B symptoms, treatment with CHOPR (cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab) should be initiated because it is as effective for treatment of discordant lymphoma as for ordinary DLBCL.(3) The underlying follicular lymphoma will also respond but will not be cured leaving the patient at risk of subsequent progression of the follicular component or possibly a second episode of transformed disease.

Through 10 years the survival of patients with ordinary DLBCL and those with discordant lymphoma are the same but after that those who started with transformed lymphoma do worse with more recurrences and more deaths due to lymphoma.(3) If no evidence of transformed DLBCL can be found the patient should be offered CVPR (cyclophosphamide, vincristine, prednisone and rituximab) or similar. After either CHOPR or CVPR



Joseph M. Connors, MD

**Clinical Professor & Director
BCCA Centre for Lymphoid
Cancer**

responding patients should be offered maintenance rituximab because it will prolong the remission of the follicular component of the disease.(4-6)

What can we learn from this case?

First, when unusual findings are present (leukemic lymphoma cells; B symptoms) one should search for evidence that more than the initially documented disease is present. Second, remember that what we label as one disease, follicular lymphoma, covers a variety of natural histories from an excellent survival with minimal treatment to crescendo disease taking the patient's life in short time. A large part of this variation is driven by development of transformed lymphoma, the pivotal event determining

survival in most patients with follicular lymphoma. Finally, even widespread, symptomatic lymphoma can be effectively treated offering a patient an extended survival even without cure of the underlying disease.

References

1. Al-Tourah AJ, Gill KK, Chhanabhai M, Hoskins PJ, Klasa RJ, Savage KJ, Sehn LH, Shenkier TN, Gascoyne RD, Connors JM. Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. *J Clin Oncol* 2008;26:5165-9.
2. Noy A, Schoder H, Gonen M, Weissler M, Ertelt K, Cohler C, Portlock C, Hamlin P, Yeung HW. The majority of transformed lymphomas have high standardized uptake values (SUVs) on positron emission tomography (PET) scanning similar to diffuse large B-cell lymphoma (DLBCL). *Ann Oncol* 2009;20:508-12.
3. Sehn LH, Scott DW, Chhanabhai M, Berry B, Ruskova A, Berkahn L, Connors JM, Gascoyne RD. Impact of concordant and discordant bone marrow involvement on outcome in diffuse large B-cell lymphoma treated with R-CHOP. *J Clin Oncol* 2011;29:1452-7.
4. Salles G, Seymour JF, Offner F, Lopez-Guillermo A, Belada D, Xerri L, Feugier P, Bouabdallah R, Catalano JV, Brice P, Caballero D, Haioun C, Pedersen LM, Delmer A, Simpson D, Leppa S, Soubeyran P, Hagenbeek A, Casasnovas O, Intragumtornchai T, Ferme C, da Silva MG, Sebban C, Lister A, Estell JA, Milone G, Sonet A, Mendila M, Coiffier B, Tilly H. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet* 2011;377:42-51.
5. Marcus R, Imrie K, Solal-Celigny P, Catalano JV, Dmoszynska A, Raposo JC, Offner FC, Gomez-Codina J, Belch A, Cunningham D, Wassner-Fritsch E, Stein G. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J Clin Oncol* 2008;26:4579-86.
6. Hochster H, Weller E, Gascoyne RD, Habermann TM, Gordon LI, Ryan T, Zhang L, Colucci N, Frankel S, Horning SJ. Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: results of the randomized phase III ECOG1496 Study. *J Clin Oncol* 2009;27:1607-14.

THE OTHER CHS! - CANADIAN HEMOCHROMATOSIS SOCIETY

Hemochromatosis, known to be the most common genetic disorder in Canada, is carried by 1 in 9 Canadians. Crippling and potentially fatal complications of iron overload are preventable by early diagnosis and treatment.

The Canadian Hemochromatosis Society is a registered non-profit charitable society, founded in Victoria, BC by Marie Warder in 1980 and incorporated in 1982. Goals and activities of the Society to increase awareness of the Canadian public and the medical community regarding the importance of early screening, while supporting those affected by it. The Society does not receive any direct government funding, and is supported solely through fundraising activities, donations and membership fees. Headquartered in Richmond, BC, the CHS maintains a central registry and publishes and distributes newsletters and research questionnaires.

The Society is interested in recruiting physicians with an interest in hemochromatosis:

The CHS Board seeks at least two representatives from each province to assist in vetting publications, directing patients and physicians to hemochromatosis experts in their geographical region and to help answer queries from the public and medical practitioners.

If you are interested in hemochromatosis, please contact:
Dr. Samuel Krikler, Surrey Memorial Hospital
 Program of Laboratory Medicine & Pathology
 1376096th Ave., Surrey, BC V3V 1Z2
 (604) 585-5666

Sam.Krikler@fraserhealth.ca

PROVISION OF HEALTH CARE IN CANADA FOR ADOLESCENT AND YOUNG ADULT-AGED (AYA) CANCER PATIENTS

While cancer is relatively uncommon among AYAs, its personal, societal and socioeconomic impact is disproportionately high when compared to older adults. Somewhat surprisingly (and in contradistinction to children and older adults), survival of AYA patients has changed little over the past 30 years.

The *Canadian Task Force on Adolescent and Young Adults with Cancer* was established in 2008 by C17 (directors of Canadian pediatric oncology centres in Canada) and the Canadian Partnership Against Cancer. The mission of the task force was to insure prompt, equitable access to the best care and to support research in AYAs in order to optimize their quality of life and treatment outcomes. A survey of existing services was undertaken and survivors, healthcare professionals and policy makers were consulted.

The following six themes were identified and formed the basis of the task force's recommendations:

1. Active therapy and supportive care

Services must be provided to address the unique needs of AYAs with cancer and AYA survivors of cancer in order to redress inequities in the care provided to them relative to children and older adults.

2. Psychosocial needs

AYAs with cancer have unique psychosocial needs that

must be met to enable each one to reach their full potential as productive, functioning members of society.

3. Palliation and symptom management

The challenge of providing palliative care to AYA patients who have unique needs related to the developmental stage must be addressed.

4. Survivorship

Implementation of life-long monitoring and follow-up of survivors of cancer in childhood, adolescence and young adulthood will provide economic and other societal benefits and help mitigate late or long-term treatment effects.

5. Research and metrics

Research and the establishment of outcome metrics are required to investigate issues critical to AYAs with cancer and AYA survivors of cancer in order to target interventions and healthcare policy to improve all phases of cancer management.

6. Awareness and advocacy

Awareness of issues specific to AYAs with cancer must be improved and advocacy efforts to increase awareness and advocate for change must be nurtured.

For a more detailed outline of the findings and recommendations of the Canadian Task Force on Adolescent and Young Adults with Cancer, see the May 2011 edition of the *Journal of Adolescent and Young Adult Oncology* (Fernandez et al).



Dalteparin versus Unfractionated Heparin in Critically Ill Patients

Deborah Cook et al

on behalf of the PROTECT Investigators

McMaster University Health Sciences Centre, Hamilton, ON

N Engl J Med 2011;364:1305-1314

Venous thromboembolic disease (VTE) is an important complication seen in critically ill patients in the Intensive Care Unit (ICU).

While a number of prior randomized trials support the benefits of prophylactic anticoagulation in ICU patients, the value of low molecular weight heparin when compared to unfractionated heparin (UFH) is less certain.

In this multicentre, randomized, placebo-controlled study performed in North/South America, Saudi Arabia, Australia, New Zealand and the United Kingdom, 3746 critically ill patients were given either Dalteparin or UFH.

The primary study outcome was proximal leg deep venous thrombosis as assessed by twice weekly compression ultrasonography testing.

The DVT rates were no different in the two groups (Dalteparin 5.1%; UFH 5.8%, $p=0.57$) but there were significant differences

in a number of secondary outcomes. Pulmonary embolism was more common in the UFH cohort (2.3% vs. 1.3% in the Dalteparin group, $p=0.01$) as was the development of heparin-induced thrombocytopenia as assessed by a standard platelet serotonin release assay (0.6% vs. 0.3%, $p=0.046$).

Major bleeding, death in hospital and serious adverse events did not differ between the two cohorts although pulmonary embolism patients spent longer periods on ventilation, were in hospital longer and had higher death rates.

This study highlights the importance of prophylactic anticoagulation in critically ill patients. The use of low molecular weight heparin does not reduce the risk of proximal leg DVT in this population over what can be achieved with unfractionated heparin and the risk of major bleeding and the probability of survival until discharge is also no different. There may be some advantage to LMW heparin in terms of reducing the risk of heparin-induced thrombocytopenia and pulmonary embolism although these were uncommon even with UFH.

Whether this justifies the routine use of the more expensive LMW heparins as prophylaxis in critically ill patients remains to be determined.



Incidence and Prognostic Value of Eosinophilia in Chronic Graft-versus-Host disease after Nonmyeloablative Hematopoietic Cell Transplantation

Imran Ahmad et al

Hôpital Maisonneuve-Rosemont, Université de Montréal, Quebec

Biol Blood Marrow Transplant 2011 May 3 (Epub)

Chronic graft-versus-host disease (GVHD) is a major determinant of quality of life as the major source of morbidity after allogeneic stem cell transplantation and it remains the most common cause of treatment-related mortality in this patient population. Eosinophilia is not infrequently observed in patients with chronic GVHD and has been linked with better post-transplantation outcomes in a number of studies, primarily by being associated with less severe forms of chronic GVHD.

However, chronic GVHD may also play a role in reducing the risk of relapse of the underlying malignancy. This anti-tumour activity may be especially important in patients receiving reduced-intensity or non-myeloablative (NMA) transplant conditioning where the preparative regimen is primarily selected for its immunosuppressive (rather than cytotoxic) activity. In this regard, the relevance of eosinophilia in NMA SCT has not yet been determined and the investigators sought to evaluate this in a homogenous NMA SCT cohort. In this study, 170 adult



patients underwent NMA SCT from a matched sibling after Fludarabine and Cyclophosphamide conditioning, 52% for multiple myeloma and 34% for non-Hodgkin lymphoma. Only 8.2% of the patients developed acute GVHD but 81.2% developed chronic GVHD at a median of 142 days post-SCT.

In the latter group, 44% of patients were noted to have an eosinophil count $> 0.5 \times 10^9/L$ at a median of 4.5 days before the diagnosis of chronic GVHD was made. Eosinophilia resolved with steroid therapy in all but 6 patients.

The investigators found that eosinophilia was less common in the subset of patients with poor prognosis chronic GVHD characterized by a platelet count $< 100 \times 10^9/L$ ($p=0.023$) but no other chronic GVHD features could be linked to the presence of eosinophilia. Furthermore, with a median follow-up of 58 months, chronic GVHD with eosinophilia was not associated with a difference in overall survival, relapse or non-relapse mortality.

This paper confirms that eosinophilia is a common feature of chronic GVHD and has a potential role as a biomarker for the condition with a positive predictive value of 88%.

While eosinophilia was rarely observed in the severe form of chronic GVHD associated with thrombocytopenia, it could not be correlated with any other out-

come measures in this cohort of NMA transplant patients.

However, this may not have been possible to demonstrate in a study population that was predominantly multiple myeloma patients undergoing a procedure in which the development of chronic GVHD is thought to be a prerequisite for a successful outcome.

Constitutive Activation of Metalloproteinase ADAM10 in Mantle Cell Lymphoma Promotes Cell Growth and Activates the TNF α /NF κ B Pathway

Hanan Armanious et al

Cross Cancer Institute and University of Alberta, Edmonton, AB Blood 2011;117:6237-6246

ADAM10 is a member of a family of metalloproteinases that play a key role in regulating the bioavailability of adhesion molecules and ligands to various cellular-signaling receptors. Activation of ADAM10 has been implicated in the pathogenesis of several solid tumours including colorectal and pancreatic carcinomas. While it is known that ADAM10 has effects on the development of marginal B cells, its role in hematologic malignancies has not yet been determined.

However, ADAM10 cleaves TNF α releasing its active form that, in turn, activates NF κ B, a pathway that has been reported to be activated in mantle cell lymphoma (MCL). The investigators

used this knowledge to hypothesize that ADAM10 may be important in the pathogenesis of MCL. In this study, 3 MCL cell lines, 9 frozen MCL tumour samples and 3 fresh leukemic MCL samples were all shown by Western blot analysis to express the active/mature form of ADAM10.

None of the peripheral blood mononuclear cells from five healthy controls showed expression of ADAM10. Immunohistochemistry staining for ADAM10 was then performed on fixed/paraffin-embedded MCL tumours and demonstrated positivity in 20 of 23 samples.

Finally, ADAM10 knockdown experiments using short interfering RNAs (siRNA) in MCL cells showed growth inhibition and cell-cycle arrest with corresponding reductions in TNF α production and NF κ B transcription. In addition, growth inhibition of MCL cells induced by the proteasome inhibitor Bortezomib was enhanced by siRNA knock-down of ADAM10.

This paper has provided new insight into the pathogenesis of mantle cell lymphoma in which ADAM10 clearly plays a central role. This finding may have therapeutic potential in that the inhibition of ADAM10 appears to enhance the anti-tumour activity of Bortezomib. The authors do note that ADAM10 inhibitors have already been developed and are being used in clinical trials in breast cancer.





Dr. Richard Wells

Presenting a view of the wide breadth of hematology practice— this column explores the day-to-day life of a hematology practitioner and the factors that influenced choosing this career path.

You did your medical school in St. John's, NL— what was it like to be a medical student on "The Rock"?

Since I am a Newfoundlander, being a medical student on the Rock seemed quite normal to me at the time. At M.U.N. the minimum prerequisite for admission to med school was two years of undergraduate studies.

I was seventeen years old when I started medical school, and lived at home with my parents and two younger sisters – so for me it was a bit like an extension of high school.

There were only 56 students in our class, so we all knew one another by the end of the first month. I had steeled myself for a ruthlessly competitive, cutthroat academic milieu, and so I was quite disappointed when it turned out to be relaxed, friendly, and conducive to group learning.

The small class size and friendly atmosphere led to a certain amount of high jinks. I remember on one occasion deciding with a small group of Key Opinion Leaders that the morning of a lecture from an eminent visiting neuroscientist from NIH would be the best time to celebrate a newly invented "Possum Queen" festival. Eight of us, dressed as hillbillies, interrupted the lecture to sing a paean to Libby, our favoured candidate for this honour. Then we retired to our seats in the theatre and made barnyard noises. Good times!

It may not be known to most CHS members that there is no such thing as a "Newfoundland accent". The province is made up of isolated, sociologically divergent communities that were for centuries connected only by boat.

This was brought home to me when I started my fourth year clerkship in Medicine at St. Clare's Mercy Hospital in downtown St. John's. One of my patients was a 70-year-old gentleman from Fermeuse, an outpost a little way down the Southern Shore.



Dr. Richard A. Wells
Sunnybrook Health
Sciences Centre

He and I quickly discovered that, although we had lived our entire lives only 50 km apart and although we both spoke what we thought of as English, we could not communicate – I could not understand what he said, and he could not understand me. It was a frustrating and wonderful experience!

What led to your decision to do Hematology and then further studies in the U.K.?

My first engagement with Haematology was in the first section of second year at M.U.N. The section was taught by two Englishmen: Dr. Richard Huntsman, a Cambridge-educated British officer type, and Mr.

Griffiths, an edentulous and erudite Cockney. Both taught with great charisma and showed fabulous and beautiful 35mm slides -- I was hooked!

During my third year of medical school I realized I wasn't quite ready to be a doctor and I began to search for a way to experience more of the academic life. I had the incredible good luck to win an opportunity to study at Oxford.

There I had the even greater good luck to meet Sir David Weatherall, who took me under his wing at the MRC Molecular Haematology Unit (which later became the Weatherall Institute of Molecular Medicine). My four years in Oxford were incredibly exciting and enriching, and put me irrevocably on track to be a clinician scientist.

Q & A with Dr. Richard Wells

.... continued from Page 10

After Oxford I was comfortably pursuing postdoctoral work in molecular evolution at Yale when my father was diagnosed with acute leukaemia and died of leukostasis. This pulled me back into clinical medicine and haematology; I abandoned my fellowship and returned to St. John's for my PGY1 year. Later I entered the U of T.

Did you always have an interest in laboratory research?

My dad was a marine biologist, so I was exposed to experimental science from a young age. I got my first chance to participate in research at age 17 as a summer student after my second year at MUN, working with a highly creative and charismatic Chemistry Prof named Paris Georgiou.

We found that the residues left behind when crude oil is burnt are far more genotoxic than crude oil itself – a good reason not to clean up oil spills by setting them on fire. I loved the experience and have been hooked ever since – until recently, when the pain of getting research funding has finally come to outweigh the pleasure of doing research.

What is a typical work week like for you?

My working week has changed substantially over the past few years. In the past I'd spend a little while each day at clinical paperwork and have one outpatient clinic, and the rest of my time would be

spent on my lab – discussing projects with my team and colleagues, troubleshooting at the bench, and other fun things. Now, I spend all of my non-clinic time in my office. I have hours of paperwork every day. Much of this involves advocacy in various forms -- writing to the Ontario Ministry of Health on behalf of patients, requesting access to medications, appealing MOH decisions, and responding to the Ministry's vexatious requests for further information. However, the great majority of my time is spent in a desperate search for research money.

In recent years it has become more difficult to obtain peer-reviewed funding for research, and for me this has drained most of the pleasure from being a clinician scientist. Much of my life is now spent fretting about how to support my lab. I usually schedule some time in the middle of the day during which I lie on the floor of my office in the foetal position; this seems to ameliorate somewhat the psychic distress caused by having so many consecutive unsuccessful grant applications.

What are your retirement plans?

If I won the lottery I would retire tomorrow. My spouse Anne, who is also a haematologist, and I would like to volunteer in health care overseas. Owing to the poor performance of my RRSPs, I will likely need to work until I die.



- The **Canadian Hematology Society Annual Reception, Awards Presentation & Dinner**, will be held **Sunday December 11, 2011**, beginning at 6:30 pm, at the Andaz San Diego Hotel, 600 F Street, San Diego, Ca. For more information: chs@uniserve.com
- The **American Society of Hematology (ASH) 53rd Annual Meeting and Exposition**, will be held **December 10 – 13, 2011**, at the San Diego Convention Centre, San Diego, California. For more information: <http://www.hematology.org/Meetings/Annual-Meeting>
- The **Canadian Apheresis Group (CAG) 2012 Annual General Meeting**, will be held **Saturday, April 14, 2012**, at the Westin Harbour Castle in Toronto. For more information: <http://www.apheresis.ca>
- The **Canadian Bone Marrow Transplant Group (CBMTG) 17th Biennial Conference**, will be held **April 11 – 14, 2012** in Toronto, Ontario. For information: <http://www.cbmtg.org/biennialconference>

MINI REVIEW

Molecular Diagnostics in AML

Mona Hassanein, MD
and

Joseph Brandwein, MD, FRCPC

Acute myeloid leukemia (AML) is a heterogeneous disorder composed of various genetically defined subtypes. In recent years, advances in molecular diagnostics have heralded an explosion of new markers which have provided important diagnostic and prognostic information, and identified potential new therapeutic targets.

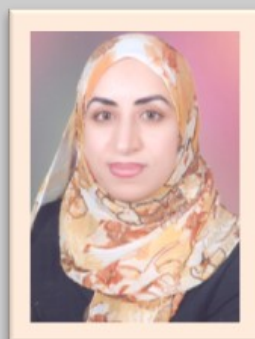
Reverse-transcription polymerase chain reaction (RT-PCR) is the most widely used approach for the detection of recurrent gene fusions or other mutations, where amplification of c-DNA is performed after previous reverse-transcription of RNA sequences. Many of these are associated with specific chromosomal translocations and inversions, often in association with an AML subtype with distinctive morphology and treatment response.

The balanced translocation t(15;17) (q22;q21.1) in acute promyelocytic leukemia (APL, AML-M3), results in a PML/RARA fusion gene which can be readily detected by PCR. This rearrangement is highly specific for APL and is currently the gold standard for rapid diagnosis of this disorder, permitting the rapid institution of appropriate therapy. Several variant chromosome translocation involving RARA, but not PML have been identified in APL, such as the t(5;17), and t(11;17).

When the PML/RARA fusion is not confirmed by PCR in a patient with suspected APL, fluorescent in-situ hybridization (FISH) analysis can determine whether one of these rare

translocations is present¹.

The balanced translocation t(8;21) (q22;q22), juxtaposes the RUNX1 (AML1) gene on chromosome 21 with the RUNX1T1 (ETO) gene on chromosome 8 to form a RUNX1/RUNX1T1 chimeric product.



**Mona Hassanein,
MD**

*Department of Medical
Oncology and Hematology
Princess Margaret Hospital,
University of Toronto*

RUNX1-RUNX1T1 is seen in approximately 7 % of adults with newly diagnosed AML. It is one of the three cytogenetic abnormalities in AML which, if found, result in the diagnosis of AML regardless of the bone marrow blast count. In patients with unavailable or failed cytogenetics, molecular testing for the RUNX1-RUNX1T1 fusion transcript by PCR can confirm this subtype.

The CBFB gene is located at 16q22, which is the breakpoint in the inv(16) and t(16;16) rearrangements. These results in the formation of a novel fusions gene, CBFB-MYH11, most commonly associated with

AML, FAB M4Eo. This form of AML is also seen in about 7 % of adults with AML. The identification of the inv(16)(p13.1q22) or t(16;16) (p13.1;q22) is diagnostic of AML without regard to the bone marrow blast count. The detection of CBFB-MYH11 transcripts by PCR can confirm this AML subtype.

The name Core Binding Factor (CBF) leukemia is used to refer to AML with either t(8;21)/RUNX1-RUNX1T1 or inv(16)/CBFB-MYH11 rearrangements. CBF AML has a favorable prognosis with intensive chemotherapy alone, and is generally not transplanted in first complete remission (CR1)².

However, the presence of a concurrent c-KIT-D816 gene mutation in these patients is associated with a high relapse rate³. Therefore, patients with CBF AML should be screened for a co-existing c-KIT mutation, and patients with this mutation should be considered for allogeneic stem cell transplant (alloSCT) in CR1.

Rearrangements of 11q23 are seen in approximately 6 % of young adults with de novo AML, and in a higher proportion of patients with therapy related leukemia after exposure to topoisomerase II inhibitors. Translocations of 11q23 involve the MLL gene and can be detected by FISH or PCR. These generally have had a poor outcome when treated with conventional chemotherapy⁴. Approximately 40-50 % of AML will have a normal karyotype by conventional cytogenetic analysis. This is a very heterogeneous group of patients with variable age, morphological features, and clinical

.... continued on Page 13

MINI REVIEW

.... continued from Page 12

course. Using molecular techniques, a number of gene mutations have been identified in these patients, and many of these have been recently demonstrated to have important prognostic value.

FMS-like tyrosine kinase 3 (FLT3) is a transmembrane tyrosine kinase receptor that stimulates cell proliferation. The most common mutation is an internal tandem duplication (FLT3-ITD), producing constitutive activation of the FLT3 receptor. This mutation occurs in about 30% of AML cases with normal karyotype, and has been associated with high initial leukocyte counts, a high relapse rate and inferior survival⁵.

Consequently, such patients are often referred for alloSCT in CR1, and data are emerging that such patients may benefit from this treatment. A less common mutation, involving a point mutations in the activating loop of the kinase domain of FLT3 (FLT3-TKD), occurs in about 5% of cases and does not appear to be associated with an inferior outcome. A number of oral FLT3 inhibitors have been developed and are currently in clinical trials, both alone and in combination with standard chemotherapy, in patients with FLT3 mutations.

Abnormalities in the nucleophosmin (NPM1) gene are found in 40-50 % of patients with de novo AML with normal karyotype. NPM1 mutations have been associated with more favourable outcomes, particularly in the absence of a FLT3-ITD mutation, compared to those without this mutation.

In patients under age 60, 5 year overall survival is in 60% range with chemotherapy, and studies suggest that there is no additional

benefit of alloSCT for these patients in first CR⁶. Patients with a normal karyotype AML and co-existing FLT3-ITD and NPM1 mutations, or neither mutation, have an intermediate prognosis⁷.



**Joseph Brandwein,
MD, FRCPC**
*Department of Medical
Oncology and Hematology
Princess Margaret Hospital,
University of Toronto*

The CEBPA (CCAAT/enhancer binding protein alpha) gene encodes a transcription factor essential for myeloid differentiation. About 7-13% of patients with cytogenetically normal AML will have CEBPA mutations. Such patients have a superior overall survival that is independent of other high-risk molecular features. However, the favorable effect of CEBPA mutations may be limited to patients who carry two copies of the mutant allele and are negative for FLT3-ITD mutations⁸.

Minimal Residual Disease (MRD) monitoring in AML

For the detection of leukemia cells below the microscopic level, PCR-based techniques provide the highest sensitivity. RT-PCR allows the identification of one abnormal cell out of 10⁴ -10⁶. In patients with

APL, sequential monitoring for PML-RARA by RT-PCR has been widely utilized. The presence or reappearance of residual transcripts in either marrow or peripheral blood is indicative of impending relapse, and should prompt the institution of further therapy.

In CBF AML, many centers have incorporated molecular monitoring for RUNX1-RUNX1T1 and CBFB-MYH11 by RT-PCR post-chemotherapy; increasing levels of transcripts, particularly to levels > 10⁻², is highly predictive of impending relapse, and may inform of the need for further chemotherapy and/or transplant. MRD monitoring can be utilized as well for NPM1 mutations; outcomes appear to be significantly improved when patients have a greater reduction in the number of NPM1 mutant copies (<0.01NPM1/ABL1 ratio)⁹.

The interval from the increase or reappearance in transcripts to the hematological manifestation of relapse is reported to be in the range of 3-6 months. Therefore, molecular monitoring is usually performed every 3 months, at least during the first two years when the relapse risk is highest.

Novel molecular targets and techniques

A number of new mutations have recently been identified and reported to be of prognostic value. Mutations of the TET2 gene have been found in 12-23% of AML patients, and one study found this to be associated with inferior survival in patients with NPM1 mutations¹⁰.

Other mutations, involving IDH (isocitrate dehydrogenase)¹¹, RUNX1¹² and WT1 (Wilms tumour 1)¹³ have also recently been reported to have adverse prognostic

...continued on Page 14

MINI REVIEW

value in normal karyotype AML. However, the precise role of these novel mutations in guiding therapeutic decisions remains to be defined.

With the advent of newly available genetic technologies, such as high throughput sequencing and microarrays, the detection of molecular markers and their characterization has been facilitated.

In the coming years, these techniques will result in more rapid and cost effective evaluation of mutational status in patients, thereby providing more precise prognostic information. It will also likely accelerate the development and evaluation of novel therapeutic approaches in AML which selectively target these mutations.

References

1. Melnick A, Licht JD. Deconstructing a disease: RAR α , its fusion partners, and their roles in the pathogenesis of acute promyelocytic leukemia. *Blood* 1999; 93:3167.
2. Marcuzzi GM, Mrozek K, Ruppert AS, et al: prognostic factors and outcome of core binding factor acute myeloid leukemia patients with a t(8;21) differ from those of patient with inv(16): a Cancer and Leukemia Group B study. *J Clin Oncol* 2005; 23: 5705-5717.
3. Schnittger S, Kohl TM, Haferlach T, et al : KIT-D816 mutations in AML-ETO-positive AML are associated with impaired event-free and overall survival. *Blood* 2006; 107: 1791-1799.
4. Krauter J, Wagner K, Schäfer I, et al. Prognostic factors in adult patients up to 60 years old with acute myeloid leukemia and translocations of chromosome band 11q23: individual patient data-based meta-analysis of the German Acute Myeloid Leukemia Intergroup. *J Clin Oncol* 2009; 27:3000.
5. Santamaría CM, Chillón MC, García-Sanz R, et al. Molecular stratification model for prognosis in cytogenetically normal acute myeloid leukemia. *Blood* 2009; 114:148.
6. Dohner K, Schlenk RF, Habdank M, et al: mutant nucleophosmin (NPM1) predicts favorable prognosis in younger adults with acute myeloid leukemia and normal cytogenetics: interaction with other gene mutations. *Blood* 2005; 106:3740-3746.
7. Gale RE, Green C, Allen C, Mead AJ, Burnett AK, Hills RK *et al.* the impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. *Blood* 2008; 111: 2776- 2784.
8. Taskesen E, Bullinger L, Corbacioglu A, et al. Prognostic impact, concurrent genetic mutations, and gene expression features of AML with CEBPA mutations in a cohort of 1182 cytogenetically normal AML patients: further evidence for CEBPA double mutant AML as a distinctive disease entity. *Blood* 2011; 117:2469.
9. Schnittger S, Kern W, Tschulik C, et al. Minimal residual disease levels assessed by NPM1 mutation specific RQ-PCR provide important prognostic information in AML. *Blood* 2009; 114:2220–2231.
10. Metzeler KH, Maharry K, Radmacher MD, et al. TET2 Mutations Improve the New European LeukemiaNet Risk Classification of Acute Myeloid Leukemia: A Cancer and Leukemia Group B Study. *J Clin Oncol* 2011; 29:1373.
11. Paschka P, Schlenk RF, Gaidzik VI, et al. IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. *J Clin Oncol* 2010; 28:3636.
12. Schnittger S, Dicker F, Kern W, et al. RUNX1 mutations are frequent in de novo AML with noncomplex karyotype and confer an unfavorable prognosis. *Blood* 2011; 117:2348.
13. Becker H, Marcucci G, Maharry K, et al. Mutations of the Wilms tumor 1 gene (WT1) in older patients with primary cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. *Blood* 2010; 116:788.

.... continued from Page 13

...from Page 3:

DO YOU KNOW THE DIAGNOSIS ?

THE ANSWER:

The peripheral smear shows a profound thrombocytopenia and numerous red cell fragments. The serum creatinine was 105 μ mol/L (normal <115), the LDH was 713 U/L (normal <241) and serum protein electrophoresis showed an IgG M-protein of 18 g/L. Of note, he had undergone high-dose Melphalan with autologous stem cell transplantation shortly after his diagnosis of multiple myeloma.

On this occasion, the patient was diagnosed with thrombotic thrombocytopenic purpura and his Lenalidomide was stopped. He was treated with daily plasma exchange and his platelet count and serum LDH normalized within 5 days. He was discharged on 81 mg of ECASA and has remained off of anti-myeloma therapy with a normal platelet count for the past two years.

Career Opportunities



The Ottawa Hospital
L'Hôpital d'Ottawa



uOttawa
L'Université canadienne
Canada's university

HEMATOPATHOLOGIST

The Dept. of Pathology and Laboratory Medicine, Division of Hematopathology & Transfusion Medicine, at the Ottawa Hospital seeks a full-time staff Hematopathologist.

Asset: developed subspecialty interest in the fields of hematopathological pathology of malignant hematology, tissue typing, laboratory quality management, and medical administration. The selected candidate will receive an academic appointment in the Department of Pathology and Laboratory Medicine, at the University of Ottawa. Candidates must hold a MD degree, appropriate specialty certification and must be licensed or eligible for licensure in the province of Ontario.

For more information and application procedure contact:

Dr. Antonio Giulivi

Division Head, Hematology and Transfusion Medicine

The Ottawa Hospital, General Campus

E-mail: agiulivi@ottawahospital.on.ca

The Division of Hematology, Departments of Oncology and Medicine, University of Calgary, Tom Baker Cancer Centre, and the Calgary Zone of Alberta Health Services, invite applications for a

DIRECTOR of the Calgary-based Alberta BLOOD AND BONE MARROW TRANSPLANT PROGRAM

Qualifications: MD or equivalent, certification in Internal Medicine & Hematology or Medical Oncology, eligibility for licensure in Alberta, at least 7 years clinical experience in BMT, academic rank of Associate Professor or Professor, proven track record in clinical or translational BMT research, and demonstrated leadership and administrative skills.

Please submit a curriculum vitae, a statement of career goals and the names of three referees by **November 30, 2011** to:

Douglas Stewart, MD, FRCPC

Chief, Division of Hematology and Hematological Malignancies

Departments of Medicine and Oncology, University of Calgary

Tom Baker Cancer Centre, 1331 – 29 Street N.W.

Calgary, AB, Canada T2N 4N2 Tel: 403-521-3347

E-mail: douglas.stewart@albertahealthservices.ca



Fellowships

Thrombosis Fellowship 2012-2013 **Jewish General Hospital, McGill** **University, Montreal, Quebec**

The JGH Thrombosis Program is currently accepting applications for a one year fellowship (July 1, 2012 - June 30, 2013) to acquire and consolidate expertise in Thrombosis. Specific areas of clinical activity include the Thrombosis Clinic, Anticoagulation Clinic and In-patient Thrombosis Consultation Service.



Jewish General Hospital

Our Thrombosis Program also encompasses a broad range of research activities that relate to diagnosis, risk factors and treatment of venous and arterial thromboembolic disease.

For information contact Dr. Susan Kahn,
susan.kahn@mcgill.ca

Thrombosis Clinical & Research **Fellowships - Up to 3 positions**

Applications are encouraged from MDs who have completed or who will complete General Internal Medicine, Respiriology and/or Hematology training. Foreign medical graduates with equivalent qualifications are eligible.

Applicants may apply to one of three training streams:

- 1.) **Clinical Fellowship**, one-year—To consolidate expertise in thrombosis.
- 2.) **Clinical and Research Fellowship**, 2-3 years (to become a clinician investigator in thrombosis (Fellows enroll in the Master's of Clinical Epidemiology Program at the University of Ottawa).
- 3.) **Clinical and Education Fellowship**, 2-3 years (to become a clinician educator in Thrombosis. (Fellows enroll in a Master's in Education).

To apply, please contact:

nlanglois@ohri.ca

Details are also available on the CHS website.



The Microenvironment

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 its founding 40 years ago in 1971. Our society now has over 300 members.

Active Membership is open to physicians engaged in the practice of clinical or laboratory hematology in Canada and to any persons doing scholarly research in hematology in Canada.

In appropriate cases, the requirement for a university degree or other qualifications may be waived if in the opinion of the Executive Committee the candidate is making significant continuing contributions to science.

We welcome residents and fellows in approved university training programs in hematology or hematological pathology as **Associate Members**. Associate members will not be required to pay dues until the completion of training.

Emeritus Membership is open to individuals at the age of 65 or those who were active members and request a transfer of status with adequate reason. Emeritus members will not be required to pay a membership fee.

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 ...

to please remit your 2011 Annual Dues. **Your \$75. annual dues payment** may be made online at the CHS website: www.canadianhematologysociety.org

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

Please provide the following information with your payment:

2011 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: _____