The Microenvironment

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THE CANADIAN HEMATOLOGY SOCIETY

SOCIÉTÉ CANADIENNE D'HÉMATOLOGIE

C H S C H

NEWSLETTER

Inside this Issue...

Annual CHS Members Gala at ASH

MESSAGE FROM THE PRESIDENT

Dr. Lynn Savoie
President, CHS

Happy Fall to all our CHS members!

Those who know me well know that I travel a lot for work and this week is no exception. I find myself writing this in a hotel room in Ottawa where I have come to torture – I mean examine - candidates.

Yes, that event that has stayed with each and every one of us for the rest of our lives is upon us – The Royal College Exams. By the time you are reading this we will have a new class of freshly minted Hematology Fellows of the Royal College of Physicians and Surgeons of Canada. Let us congratulate them and encourage them to become dues paying members!

Yesterday I was in Toronto for our semi-annual meeting of the CHS executive. These meetings are always full of great discussions about our achievements at the executive level and of our members at large. This is always most evident at our fall meeting where we select the annual paper of the year and the trainee awards for abstracts presented at ASH.

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2016 CHS Executive Committee

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As usual I was truly impressed by the quality of the work we reviewed and excited by the depth of the field of budding researchers in hematology in Canada. This bodes well for the upcoming call for submissions for the RK Smiley grant awards.

Another topic we spent much time on is the web portal, with which I hope more of you are becoming familiar. Although I believe this is a great learning resource for all of us I would love to hear any feedback you might have (chs@uniserve.ca). We also touched on membership and I would like to take this opportunity to ask you to promote the CHS among your pediatric, hematopathology and allied health colleagues as we value their membership but find them under-represented in our numbers. Also, if you enjoy reading the Microenvironment we welcome any suggestions you might have and would love for you to get involved – after all Tom Nevill cannot be editor for ever.

Finally, ASH is rapidly approaching. We hope to see you at our Gala Dinner on Sunday night where you can mingle with colleagues from around the country, have your say at our annual general meeting, and applaud our young investigators.

See you in San Diego!

Dr. Lynn Savoie

President, CHS

Le message du Président

Dr. Lynn Savoie
Président

Joyeuse automne à tous nos membres du SCH! Ceux qui me connaissent bien savent que je voyage beaucoup pour le travail et cette semaine ne fait pas exception. Je me retrouve en train d'écrire ceci dans une chambre d'hôtel à Ottawa où je suis venu torturer - j'entends examiner - les candidats. Oui, cet événement qui reste avec chacun d'entre nous pour le reste de nos vies est arrivé - Les examens du Collège royal. Au moment où vous lisez ceci, nous aurons une nouvelle classe de chercheurs en hématologie fraîchement sortis du Collège royal des médecins et chirurgiens du Canada. Félicitons-les et encourageons-les à devenir des membres payants!

Hier, j'étais à Toronto pour notre réunion semestrielle de l'exécutif du SCH. Ces réunions sont toujours pleines de grandes discussions au sujet de nos réalisations au niveau exécutif et des membres en général. Ceci est toujours plus évident lors de notre réunion d'automne où nous sélectionnons le papier annuel de l'année et les prix des stagiaires pour les résumésqui seront présentés à ASH. Comme d'habitude, je suis vraiment impressionnée par la qualité du travail que nous avons examiné et excité par la profondeur du domaine des chercheurs en herbe en hématologie au Canada. Cela augure bien pour l'appel à venir pour les soumissions pour les prix RK Smiley.

Un autre sujet sur lequel nous avons passé beaucoup de temps est le portail Web, avec lequel j'espère que vous vous familiarisez de plus en plus. Bien que je pense que c'est une excellente ressource d'apprentissage pour nous tous, j'aimerais recevoir vos commentaires (chs@uniserve.ca). Nous avons également abordé l'adhésion et j'aimerais profiter de l'occasion pour vous demander de promouvoir la SCH parmi vos collègues en pédiatrie, en hématopathologie et en santé apparentée, dont nous apprécions leur adhésion, mais nous les trouvons sous-représentés dans nos nombres. En outre, si vous aimez lire le Microenvironment, nous vous invitons à nous faire part de vos suggestions et aimerions votre implication - après tout, Tom Nevill ne peut pas être éditeur pour toujours.

Enfin, ASH s'approche rapidement. Nous espérons vous voir lors de notre dîner gala, dimanche soir, où vous pourrez vous mêler à des collègues de partout au pays, avoir votre mot à dire lors de notre assemblée générale annuelle et applaudir nos jeunes enquêteurs.

Rendez-vous à San Diego!

Dr. Lynn Savoie
Président, SHC

Invitation to submit ...

The Microenvironment

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

STUDENT RESEARCH ARTICLES

Queries should be directed to:
Dr. Tom Nevill, Editor
The Microenvironment
chs@uniserve.com

UPDATE: ISH-CHS 2018 VANCOUVER

The ISH 2018 congress will begin with an opening plenary session on Thursday, September 13, 2018. The closing session will be on Sunday, September 16. Various corporate-sponsored sessions will be held each day at noon as well as at the end of some days throughout the congress. Financial considerations, including the registration fee, budget and the venue contract are currently being finalized.

PROMOTIONAL ACTIVITIES AND PLANS

The CHS will have a booth at the ASH 2016 Exhibition to promote ISH 2018, and we are looking into the feasibility and benefits of having an exhibit booth at EHA in May, 2017.

We have developed a "Save the Date" flyer and a large pop-up banner for use at these and other meetings in our exhibition booths. We also include information about the city of Vancouver and the myriad interesting activities, tours, fine dining, etc., in the Vancouver area.

As more program details become finalized, we intend to develop another, more detailed information pamphlet about ISH 2018 to augment the current material.

We are working with our professional conference organizing company, International Conference Services (ICS), to develop a list of other meetings in 2017 and early 2018 where we would either have a physical presence or arrange for appropriate material to be distributed to advertise our meeting.

ASSOCIATED GROUPS

- **Patient groups**: Collectively, the various related patient groups that we have contacted, have expressed an interest in participating in the meeting and possibly holding a session for representatives of each of the individual groups. This activity would run in parallel to the scientific sessions.
- **Medical organizations**: Various other medical organizations were contacted by the CHS President in 2015 shortly after the CHS was awarded the ISH meeting. Several have indicated that they have already scheduled their own activities; and we are currently following up with the others to offer them the opportunity of holding their own sessions within the timeframe of the ISH meeting.

THE SCIENTIFIC PROGRAM

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

Canada has a rich history in the field of hematology and the CHS plans to focus attendees' attention on our country's special role in translational research in the following areas:

- Stem cell biology
- Telomeres in health and disease
- Transfusion medicine
- Venous thromboembolic disease
- Immune thrombocytopenia, Heparin-induced thrombocytopenia and Thrombotic thrombocytopenic purpura
- Von Willebrand disease
- Anti-platelet agent therapy
- Vinca alkaloid development
- Lymphomas: Basic science and treatment regimens
- Hodgkin lymphoma: Radiotherapy and autologous stem cell transplantation
- Novel myeloma therapies

This should be an exciting program and both the meeting and the venue will be a showcase for Canada.

The ISH 2018 venue—the Vancouver Convention Centre—is located in one of the world's most beautiful settings on Vancouver's downtown waterfront with a dramatic mountain background. For pre and post congress, the Vancouver area offers exciting activities and adventures, spectacular tours, fine dining, theatre and more.

We hope to see all of the CHS members there!

Dr. Gail Rock
Organizing Committee Chair

Dr. Tom Nevill
Scientific Committee Chair

Chief Resident Report: Dr. Zach Liederman

Dr. Zachary Liederman
University of Toronto

CHS CHIEF RESIDENT

Dear Colleagues,

It has been a great year at the Canadian Hematology Society and I look forward to continuing to represent residents in 2017.

I have recently had the opportunity to review the ASH abstracts submitted to CHS and can confidently say that Canadian residents and fellows have made incredible contributions to hematology over the past year.

In our role at the CHS, we continue to strive to provide ongoing support to residents and fellows as they progress through training. Building on Eric Tseng's efforts from last year we have published multiple new image and academic cases on the CHS webportal and have exciting ideas in development. If you haven't had the chance to participate, now is the perfect time to explore the innovative educational resources available. For those that are regular contributors, there is a tight race for "*CHS Points*" and the winner will be announced at the CHS Annual Meeting at ASH San Diego in December.

Finally, we are looking to expand our case selection for 2017 and are inviting residents from programs across Canada to submit cases. This is an exciting opportunity to share an interesting case you have participated in and showcase local expertise at your institution. Cases will be published on the CHS webportal and authors will be recognized as Guest Editors. This will be accompanied by a certificate of recognition and cash prize.

Email me at Zachary.Liederman@one-mail.on.ca for updates on educational content or if you would like to get involved. I look forward to seeing everyone at the annual meeting in San Diego.

Zach Liederman

Do you know the diagnosis?

A 33-year-old man, originally from Taiwan, presented with a 6-month history of progressive fatigue, night sweats, weight loss and early satiety.

- Physical examination revealed conjunctival pallor, a grade II/VI systolic ejection murmur and a spleen that was palpable 4 cm below the left costal margin.
- A CBC revealed a hemoglobin of 78 g/L, a WBC count of 27.2 x 10^9/L and a platelet count of 86 x 10^9/L.
- Differential revealed neutrophils of 10.8 x 10^9/L, monocytes of 11.2 x 10^9/L and a spectrum of granulocytic precursors including 1.5 x 10^9/L blasts.
- Creatinine, electrolytes and liver function tests were all normal except for a LDH of 385 U/L (upper normal of 220).
- Bone marrow examination revealed chronic myelomonocytic leukemia with 9% blasts and a normal karyotype.

Blood grouping results are shown below:

Forward Grouping

Anti-A antisera	Negative
Anti-B antisera	Negative
Anti-AB antisera	Negative
Anti-D antisera	4+

Reverse Grouping

A cells	4+
B cells	4+
O cells	Weak +

Red cell phenotyping revealed the patient to be Lewis Ag a-b+

Do you know the diagnosis? (Answer: Page 14)

Great professional success and enduring popularity mark the outstanding legacy of an inspiring clinician

By Dr Tom Nevill

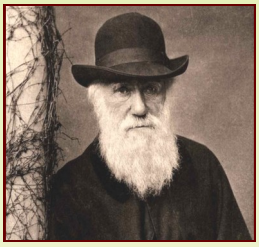
William Osler was born in Bond Head, north of Vaughn, Ontario, in what was then *Canada West*, on July 12, 1849.

Featherstone Lake Osler

His father, **Featherstone Lake Osler**, was a former Lieutenant in the British Royal Navy who was asked to be the science officer on the **HMS Beagle** for **Charles Darwin**'s classic voyage to the Galapagos Islands. Unfortunately, he had to turn the position down to stay in England with his dying father. When Featherstone retired from the Royal Navy, he became a minister and moved to Canada in 1837 where he and his wife settled in Bond Head. William was the eighth of nine children born to the Oslers and the family moved to Dundas, Ontario when William was 8 years old.

William was a bright and "high-spirited" child who was expelled from grammar school for abusive language. He was ultimately educated at Trinity College School in Weston, Ontario and it was there that he was introduced to the microscope – a touchstone for his life. He enrolled at Trinity College at the University of Toronto with the initial intention of following his father into the ministry. However, his microscopy work drew him into medicine and after two years at the University of Toronto Medical School, he switched to McGill University in Montreal from which he graduated with his MD in 1872. Not surprisingly, his first clinical paper in medical school was on the gross and microscopic findings in breast cancer and his graduation thesis was on histopathology.

William Osler pursued post-graduate training in John Burdon Sanderson's physiology laboratory in London, England and then spent a short time in Germany where he met Rudolph Virchow. In 1874, he was invited to join the faculty of McGill University and returned to Montreal where he had a general practice, taught medical students and quickly rose to the position of Professor over the next decade. In 1884, he was recruited by Dr. Samuel Gross, a preeminent surgeon, to become Professor of Clinical Medicine at the University of Pennsylvania in Philadelphia. Osler left U Penn in 1889 to become the Physician-in-Chief and one of four founding members of the new Johns Hopkins Hospital in Baltimore, Maryland. **He established the Johns Hopkins University School of Medicine** and was instrumental in establishing Johns Hopkins as the outstanding medical institution in the United States.



Charles Darwin

He remained in Baltimore for 16 years but in 1905 he was invited to replace his former mentor, John Burdon Sanderson, as **Regius Professor of Medicine at Oxford University** in England. He accepted and, while there, **founded the Quarterly Journal of Medicine, was curator of the Bodlein Library** and was an **outspoken supporter of public health** and sanitary measures. He had a baronetcy conferred on him in 1911 for his many contributions to medicine and died December 29, 1919 at age 70 of pneumonia during the Spanish Flu Pandemic.

William Osler conducting clinic at Royal Vic

HISTORY CORNER, Continued: Sir William Osler (1849-1919)

It is truly a challenge to summarize William Osler's contributions to medicine in a concise fashion. It has rightfully been said: "*he put the art and science of medicine together as well as anyone ever has*". Osler stressed hard work (he did almost 1000 autopsies to hone his microscopic skills), direct patient interaction, history-taking and observation, compassion, bedside teaching and lifelong learning.

He was admired and respected and was a role model for students and physicians alike. He was charming, generous and humourous and developed strong relationships with many of his colleagues. **Many would say his greatest innovation was the introduction of the microscope to the clinic to assist in the diagnosis of blood disorders** – he introduced the microscope to U Penn and established the Clinical Microscopy Laboratory at Johns Hopkins.

Osler also had a tremendous influence on the medical school curriculum; he introduced patient-based teaching, created the first clinical clerkship and recognized the importance of "graded learning" – a concept that gave rise to residency training programs. He had a lifelong interest in the history of medicine and the humanities and was an avid reader of the classics. His personal library, bequeathed to McGill University upon his death, contained 7000 books!

William Osler was a prolific writer and had **over 1600 publications;** although he wrote extensively on hematology, oncology and the microscope, 1/3 of his papers dealt with cardiovascular disease. However, his contributions to the understanding of hematology should not be minimized.

The development of lens combinations in 1830 improved microscopic resolution and in 1865, Max Schultze first described "granule masses" on blood smears.

Osler began studying this "third component" of blood in 1873 while working on samples taken from rats. He reported that these masses were composed of agglutination of small "pale round discs" that occurred as single units in blood and were 1/8-1/2 the size of red blood cells. He enumerated these "plaques" (later named "plates" and then, platelets by James Wright in 1910) as ~250,000/ mm^3 although he recognized that the numbers varied greatly in health and disease**.** He was also the first to contend that "white thrombi" were composed "chiefly of plaques", establishing their importance in blood clotting.

Chronic fatal idiopathic anemia was first described in 1849 by Thomas Addison and became known as "Addisonian anemia". In 1870, work by Flint and Fenwick linked this form of anemia to gastric atrophy and one year later Michael Biemer coined the term "progressive pernicious anemia". Although William Osler's contribution is often minimized (or completely overlooked), he and William Gardner reported the first detailed clinical, hematologic and pathological features of PA in 1877.

Their important observations included the characteristic lemon tint of the skin, the peripheral sensory loss (worse in the feet than the hands), macroovalocytes in the blood, intense bone marrow hyperplasia with large nucleated cells containing fine nuclear chromatin (the first description of a megaloblast although this terminology was later applied by Ehrlich in 1880), thinning of the gastric membrane and posterolateral sclerosis of the spinal cord. Although he was a proponent of Arsenic treatment for PA until his death, Osler did recognize that, while the average survival was 12 months, some patients improved "with a better diet". It was in 1920 (the year following Osler's death) that George Whipple (a 1905 Johns Hopkins graduate!) proposed raw liver as a treatment for anemia and the effectiveness of ingested or injected "raw liver juice" in PA led to Whipple receiving the Nobel Prize in Medicine in 1934.

Bloodletting was first employed in Egypt in 1000 BCE but Hippocrates was perhaps the first to describe its value in "plethora" in ~400 BCE. However, a proper scientific description of "cyanotic polycythemia" did not come until Louis Henri Vasquez reported a 40-year-old man with cyanosis, dilated veins, facial plethora and hepatosplenomegaly in 1892. Although he hypothesized that the patient had heart disease as the root cause, no cardiac abnormalities were found at the time of the patient's death the following year.

Osler Library of History of Medicine

HISTORY CORNER, Continued: Sir William Osler (1849-1919)

In 1903, William Osler delivered a lecture to the American Association of Physicians on four of his patients with chronic cyanosis, polycythemia and an enlarged spleen – a condition he called "Vasquez's disease". He reported this as a new clinical entity with a number of recurrent features – headaches, lightheadedness, eyrthromelalgia, hypertension, vascular disease and intense bone marrow hyperplasia. He likened the disease to a red cell counterpart of leukemia – oversupply without corresponding demand – and advocated treatment with phlebotomy, oxygen supplementation and splenic irradiation. The condition became popularly known as "Osler-Vasquez's disease". He also expanded knowledge of the conditions associated with secondary polycythemia including congenital heart disease, high altitude and emphysema although he noted that the elevation in red cell count was not as marked as in Osler-Vasquez's disease.

William and Grace Osler with son, Revere

In 1901, Osler described 3 patients with recurrent epistaxis and telangiectasiae of the lips, tongue, gingiva, oral mucosa and skin which he connected to a case report by Rendu in 1896. Two of his three patients were brothers and he carried out a thorough evaluation of their extended family. He found that five other family members were affected involving 3 generations, clearly establishing it as a hereditary condition. By 1907, he had completely studied a second family and had identified six other kindreds in the literature. The condition became known as Osler-Weber-Rendu disease which had recurrent epistaxis as it hallmark presentation. Osler also contributed to the first descriptions of malarial parasites within red cells and hypersplenism-related anemia and leukopenia.

In 1892, while at Johns Hopkins, William Osler published the first edition of the textbook, *The Principles and Practice of Medicine*, the most popular reference of its time, emphasized by the fact that it was translated into 6 languages. Osler personally oversaw the first seven editions of the text and it became the standard medical text around the world for over 40 years. The 1st edition of *The Principles and Practice of Medicine* contained 25 pages on anemia, leukemia and Hodgkin disease but by the 7th edition published in 1909, Osler had 41 pages on hematology/oncology and now included sections on purpura, hemophilia, scurvy, the spleen, myeloma, amyloidosis and hemochromatosis.

Paul Revere

Sir William Osler had an interesting, unusual and ultimately tragic personal life. He married Grace Revere, who was the great granddaughter of **Paul Revere** and whom he had met in Philadelphia. At the time, she was the wife of Dr. Samuel Gross – who had recruited him to U Penn – although she was 50 years younger than her first husband.

Eight years after Gross' death in 1884, Osler married Grace Revere and they had two boys – Paul (who died in infancy) and Revere, whose death in 1917 in Flanders field during WWI was a crushing emotional blow to his father. Upon William Osler's death in 1919, he donated his brain to science and it currently resides at the Mutter Museum in Philadelphia. Grace Osler died in 1928 and Sir William and Lady Osler's ashes rest in the Osler Library of the History of Medicine at McGill University in Montreal.

William Osler was an **inspiring clinician** and his **enduring popularity** was borne out by the founding of the Osler Society of McGill University in 1921, the Osler Club in London in 1928, the American Osler Society in 1970 and the Japanese Osler Society in 1983. The famous American neurosurgeon, Dr. Harvey Cushing, wrote a treatise on William Osler's life for which he received the Pulitzer Prize in 1925. William Osler has a building named in his honour at Johns Hopkins University Medical School and has elementary and high schools named after him in three Canadian provinces. He was elected to the Canadian Medical Hall of Fame in 1994.

Sir William Osler had **great professional success** and gave a name to a number of clinically important findings – Osler's sign, Osler's nodes, Osler's syndrome and Osler's triad -- but he was not always correct in his initial evaluation. He first thought that platelets were bacterial "organisms", he did not believe that the erythrocyte inclusions seen in malaria were the actual parasite and he was considered a therapeutic nihilist (although there were few treatments available for medical conditions in the late 1800s!). Osler was, first and foremost, committed to lifelong learning as is clearly expressed in one of his most memorable quotes:

"*Start out with the conviction that absolute truth is hard to reach in matters related to our fellow creatures…slips in observation are inevitable…errors in judgement must occur in an art which consists largely of balancing probabilities*"

Reference

Stone, *Br J Haematol*, 2003.

Mini Review

Somatic Gene Mutations in Health and Benign Hematologic Disease

Dr. Thomas Nevill, Clinical Professor,
University of British Columbia, Vancouver, BC

Dr. Thomas Nevill

Somatic gene mutations – mutations occurring in the non-reproductive cells in the human body – have taken on increasing importance in hematologic malignancies.

In a 2011 publication, Rafael Bejar reported finding a mutation in one of 18 key genes associated with myeloid malignancies in one-half of a cohort of 439 patients with myelodysplastic syndrome (MDS).[1]

Of great clinical relevance was the fact that five of these genes (EZH2, TP53, RUNX1, ASXL1 and ETV6) were of independent prognostic importance. In fact, the presence of any one of these mutations upgraded the IPSS score by one level, thereby having the potential to alter the therapy recommended to an individual with MDS. Bejar recently expanded on these initial observations by examining a larger cohort of MDS patients and demonstrated that the spectrum of prognostically significant genes was broader than initially suspected (**Table** 1) and that the total number of mutated genes in a given patient also influenced survival (**Figure** 1).

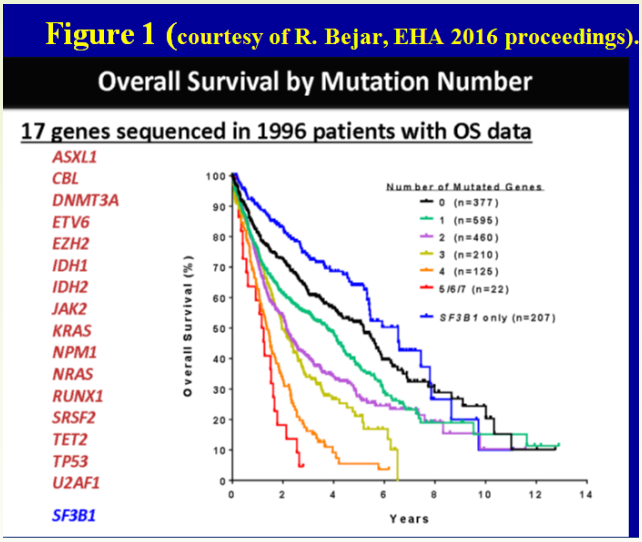
Table 1: Prognostically significant mutations in MDS.
(courtesy R. Bejar, EHA 2016 proceedings)

Favourable	(HR)	Unfavourable	(HR)
• SF3B1	0.8	• PRPF8	3.2
		• TP53, FLT3	2.0
		• EZH2	1.6
		• RUNX1, CBL	1.4
		• IDH2	1.3
		• ASXL1, U2AF1	1.2

HR = Hazard ratio

With the literal explosion of molecular genetics in malignant disease over the past decade, Bejar's findings were not unexpected. However, the subsequent report of the presence of myeloid gene mutations (and their clinical relevance) in benign hematologic disease has been met by a degree of surprise amongst clinicians and scientists alike. While clonal hematopoiesis in aplastic anemia (AA) has been suspected for decades and paroxysmal nocturnal hemoglobinuria (PNH) is clonal by nature, would the presence of myeloid gene mutations be anticipated in either disorder? Some knowledgeable scientists suggested – rightfully so, it appears -- that somatic mutations might well be detectable in healthy individuals.

Figure 1 (courtesy of R. Bejar, EHA 2016 proceedings).

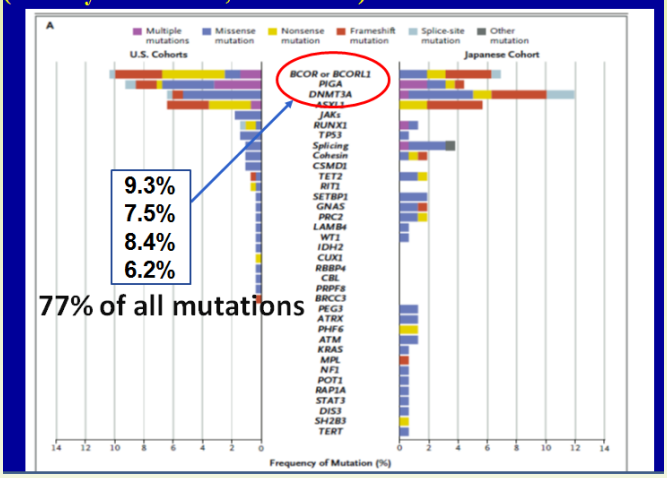


Modern sequencing techniques – "next generation" (NGS), "massively parallel" or "deep" sequencing – were used to analyze 439 patients with AA for evidence of clonal mutations in a collaboration between the NIH, the Cleveland Clinic and Kanazawa University.[2] The investigators studied 106 genes recurrently mutated in myeloid malignancies as well as the PIG-A gene that is mutated in PNH. At least one gene mutation was found in 36% of AA patients and 13% had more than one (and up to 7) mutations in the same or a different gene. Of interest, identified mutations are biased towards cytosine→ thymine transition mutations at CPG sites – a well-described age-related phenomenon relating to the relative instability of the cytosine nucleotide.

The spectrum of mutations in AA are broad but the four most common constituted 77% of all mutations – BCOR/BCORL1, PIG-A, DNMT3A and ASXL1 (**Figure** 2).

Conversely, mutations in TET2, TP53, RUNX1, JAK2 and the splicing factor genes (e.g. SF3B1) are distinctly underrepresented in AA patients. This study also showed that the variant allele frequency (VAF) in AA (median of 9.3%) is much lower than the VAF typically seen with somatic mutations in MDS (median of 30%).

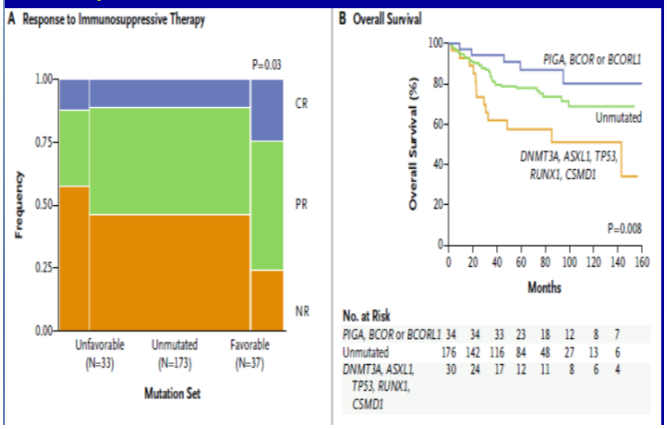
Figure 2. Mutations seen in AA patients.
(courtesy of Yoshizato, NEJM 2015)



It is noteworthy that the frequency of mutations did, in general, increase with age. The exceptions to this rule were BCOR/BCORL1 and PIG-A, which usually remained stable over time. The investigators were able to correlate these three mutations with a favourable response to IST and a better OAS. On the other hand, DNMT3A, ASXL1, RUNX1, TP53 and CSMD1 mutations predicted for a poor response to IST and an inferior overall survival (OAS; **Figure** 3), particularly in those patients younger than age 60 years.

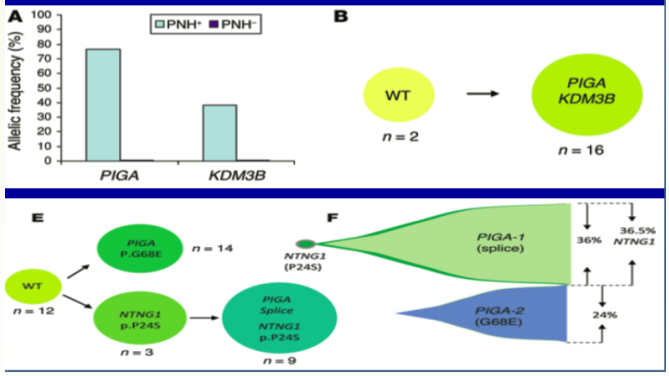
Recently, NGS has also been used to evaluate PNH patients for somatic gene mutations.[3] Genetic analysis for mutations in the PIG-A gene revealed the majority of PNH patients do indeed have either a point mutation in this gene or a microdeletion (Xp22.2) that spans the PIG-A locus. Most interesting was the fact that six patients had two – or in one case, three – different PIG-A mutations present in completely separate clones (i.e. biclonal or triclonal disease). However, even modern sequencing could not detect a PIG-A gene mutation in all PNH patients although targeted sequencing (90% sensitivity) was considerably more accurate than the now outdated Sanger sequencing (42% sensitivity). In this study, additional sequencing for 61 myeloid malignancy-related genes was performed and one-half of the patients had a detectable abnormality with an average of two mutations per patient (range 0-6). The most common myeloid mutations seen were TET2 (3 patients) and JAK2, MECOM and RIT1 (2 patients each). From a clinical standpoint it was noteworthy that those patients with a somatic mutation had a higher granulocyte PNH clone size than those lacking a mutation (69% versus 50%, respectively; p=0.04).

Figure 3. Influence of gene mutations on response to IST and OAS.
(courtesy of Yoshizato, NEJM 2015)



What was truly remarkable in this study from Shen et al was the sequence of acquisition of the PIG-A and myeloid gene mutations in PNH patients. It was first noted by the researchers that the VAF of a myeloid gene mutation in one patient exceeded the VAF for the PIG-A mutation. This led to further investigation of the clonal architecture in the cohort using single clone sequencing and bacterial subcloning.

Figure 4. Varying clonal architecture in PNH. PIG-A as the ancestral event (top) with secondary KDM3B mutation. A biclonal PNH patient (bottom) with PIGA (P.G68E) as the only mutation in one clone and NTNG1 ancestral mutation followed by a secondary, different PIG-A mutation (splice) in the other clone.



Different patterns of mutation acquisition from the initial wild type (WT) clone were observed in a number of patients. The PIG-A mutation was the only mutation in 50% of patients; however, in others, it proved to be the initial (ancestral) event – based upon its higher VAF – before a later myeloid gene mutation (10% of cases; **Figure** 4, top). Intriguingly, the PIG-A mutation was also found to be a secondary event, following on an initial myeloid gene mutation (30% of cases; Figure 4, bottom). These two observations suggest PNH patients

demonstrate strikingly similar patterns of clonal selection and evolution to that seen in MDS patients.

Figure 5. Incidence of Age-Related Clonal Hematopoiesis ("ARCH")
(courtesy of Jaiswal, NEJM 2014)

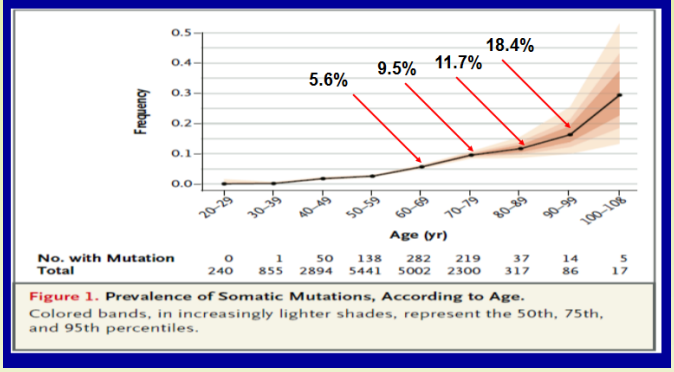
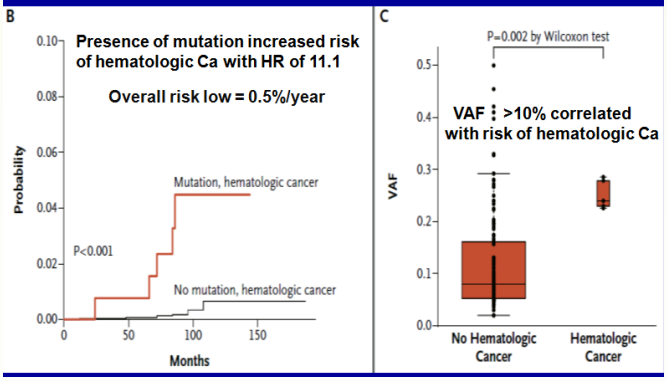


Figure 1. Prevalence of Somatic Mutations, According to Age.
Colored bands, in increasingly lighter shades, represent the 50th, 75th, and 95th percentiles.

One of the most influential next-generation sequencing myeloid mutation studies was recently reported by Jaiswal and colleagues.[4] This paper described the results of sequencing for 160 mutations in a cohort of 17,182 healthy subjects with normal hematologic parameters. Mutations were detected in 746 individuals (4.3%) although 93% of these had only one mutation and the VAF was typically low (median of 9%). More importantly, the acquisition of mutations was clearly correlated with the age of the individual – exceedingly rare up to the fourth decade of life, rising to ~5% in middle age and reaching almost 20% when subjects reached their 90s (**Figure** 5).

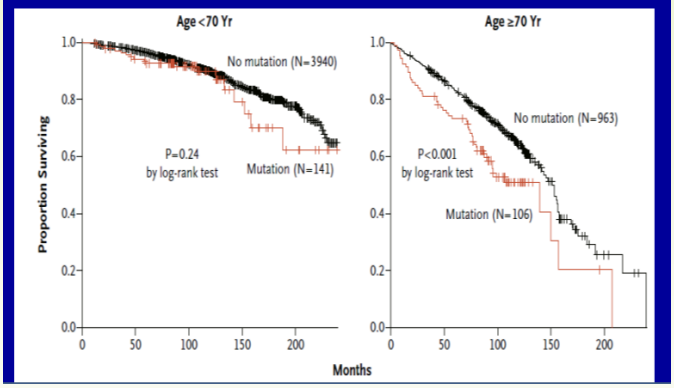
Figure 6. ARCH is associated with increased risk of hematologic malignancies. (courtesy of Jaiswal, NEJM 2014)



At a nucleotide level it was significant that over 50% of the mutations involved age-related cytosine→ thymine transitions. These findings led to the use of the term "age-related clonal hematopoiesis" ("ARCH"), a subgroup of individuals with clonal hematopoiesis of indeterminate potential ("CHIP") which also encompasses patients with clonality and cytopenias (but lacking the dysplasia needed for a MDS diagnosis; "CCUS").

However, one should not assume that ARCH is a "benign" condition as the five most common mutations seen in this condition are the "usual suspects" – DNMT3A, TET2, ASXL1, TP53 and JAK2. Furthermore, the presence of a mutation carried with it a hazard ratio of 11.1 for developing a hematologic malignancy in follow-up. The overall risk of this occurrence remained low (~0.5% per year), but the incidence was much higher if the VAF of one of the aforementioned mutations was >10% (**Figure** 6). What was truly fascinating was the fact that the presence of a myeloid mutation increased a subject's risk of all-cause mortality in follow-up – particularly those ≥70 years of age – with the primary cause of death being vascular disease (ischemic heart disease and stroke) (**Figure** 7).

Figure 7. All-cause mortality according to age and presence of mutation. (courtesy of Jaiswal, NEJM 2014)



It is hard to minimize the important role that genomics play in modern society. It has increased our understanding of normal human physiology and both inherited and acquired diseases. It has become a critical starting point for the development of targeted pharmacotherapies in hematologic (and other) malignancies. The recent studies discussed above have shown it may assist us in deciding treatments in benign diseases and, with the discovery of "silent" mutations in healthy subjects, it may soon play a role in preventative medicine.

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1. *Bejar et al, N Engl J Med 364:2496, 2014.*
2. *Yoshizato et al, N Engl J Med 373:1673, 2015.*
3. *Shen et al, J Clin Invest 124:4529, 2014.*
4. *Jaiswal et al, N Engl J Med 371:2488, 2014*

Five Things to Know About: Acute Promyelocytic Leukemia

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1. **Acute promyelocytic leukemia (APL), a distinct subtype of acute myeloid leukemia (AML), is both highly curable and lethal.** Early recognition of APL is critical to prevent early death. Early death is the leading cause of treatment failure in APL and occurs in 20% of cases. [1] Early death occurs in part to APL's characteristic coagulopath, disseminated intravascular coagulation and fibrinogenopenia. APL is highly curable with long term overall survival rates of 80% and remission rates of up to 95%. [2]

2. **APL has a characteristic morphologic appearance on peripheral blood smear.** There are 2 morphologic variants of APL: hypergranular and microgranular. APL is characterized by t(15;17)(q22;q21), generating a *PML-RAR*µ fusion transcript. The PML-RARµ oncoprotein prevents differentiation, apoptosis and enhances self-renewal of promyelocytes.

3. **When APL is suspected, all-trans retinoic acid (ATRA) must be initiated urgently with aggressive transfusion support in the absence of a confirmed diagnosis.** ATRA promotes differentiation of APL blasts through degradation of the PML-RARµ oncoprotein. [3]

4. **Patients with low to intermediate risk APL can be treated with arsenic trioxide (ATO) and ATRA.** The Sanz score stratifies patients into three risk groups: low (WBC ≤10×10^9/L and platelets >40×10^9/L), intermediate (WBC ≤10×10^9/L and platelets ≤40×10^9/L), and high (WBC >10×10^9/L). [4] A phase III multicenter study compared ATRA plus chemotherapy to ATRA plus ATO and demonstrated that ATRA plus ATO was not inferior and may be superior. [2]

5. **Differentiation syndrome (DS) is a life-threatening complication that may occur when APL is treated with either ATRA and/or ATO.** DS consists of unexplained fever, weight gain, pulmonary infiltrates, pleuropericardial effusion, renal failure and hypotension. [5] Preventative corticosteroids should be considered in patients presenting with a high WBC. Corticosteroids should be initiated when DS is suspected. ATRA and/or ATO should be continued despite DS unless severe organ dysfunction develops.

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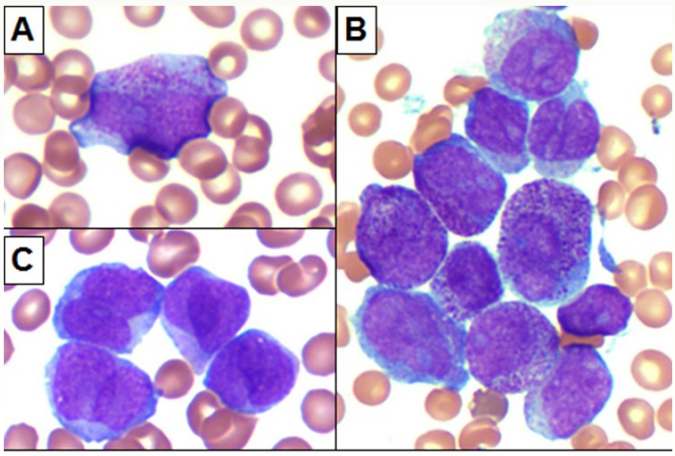
1.McClellan JS, Kohrt HE, Coutre S, *et al*. Treatment advances have not improved the early death rate of acute promyelocytic leukemia. *Haematologica* 2012; 97(1): 133-136.
2.Lo-Coco F, Avvisati G, Vignetti M, *et al*. Retinoic Acid and Arsenic Trioxide for Acute Promyelocytic Leukemia. *NEJM* 2013; 369:111-121.
3.Zhou GB, Zhao WL, Wang ZY, *et al.* Retinoic Acid and Arsenic for Treating Acute Promyelocytic Leukemia. *PLoS Medicine* 2005 Jan; 2(1): e12.
4.Sanz MA, Lo Coco F, Martin G, *et al*. Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups. *Blood* 2000;96(4):1247–53.
5. Sanz MA & Montesinos P. How we prevent and treat differentiation syndrome in patients with acute promyelocytic leukemia. *Blood* 2014 May; 123 (18): 2777-2782.

Figure 1



Acute promyelocytic leukemia (APL), peripheral blood **(A)**, bone marrow **(B)**. **(C)** Microgranular variant of APL, peripheral blood. Original magnifications, 600 X

Canadian Hematology Society / Société Canadienne d'Hématologie

2017 RK Smiley Research Grant

Established in 2011 to mark the Fortieth Anniversary of the Canadian Hematology Society's service and to support hematology practitioners in Canada, this award is named in honour of the CHS Founding President, Dr. R. Kennedy Smiley. Many impressive submissions from across Canada were received in response to the previous invitations to submit applications to this new research grant program.

The CHS Executive Committee is very pleased to announce that the next deadline for submissions to the R K Smiley Award is Friday, February 24, 2017.

The R K Smiley Research Grant will provide start up grants of $10,000 aimed at pilot projects expected to lead to larger follow-up studies funded by CIHR or other grant funding agencies.

It is expected that funds will be used within one year of the award being granted.

- Applicants may be clinicians or scientists with a project relevant to the field of hematology.
- The Principal Investigator must be a member-in-good-standing of the Canadian Hematology Society.
- Preference will be given to groups who will benefit maximally from the limited start up funds.

ELIGIBILITY CRITERIA:

APPLICATIONS MUST CONTAIN

- ☐ **1. Title of project**
- ☐ **2. Name of Principal Investigator**
- ☐ **3. Names of Co-investigators**
- ☐ **4. Proposal: 1 page, maximum length**
- ☐ **5. Project Background**
- ☐ **6. Relevance to hematology**
- ☐ **7. Budget: 1 additional page, maximum**
- ☐ **8. CV of Principal Investigator**

FORMAT REQUIREMENTS

☐ **MS Word format** ☐ **Double-spaced** ☐ **Font size 12**

N.B.

- Applications should be emailed to the CHS at **chs@uniserve.com**
- **by the deadline: 1800 hrs EDT, Friday, February 24, 2017.**
- Your application will be complete only when you have received a **confirmation email.**
- Successful applicants will be notified in May 2017.

Dr. R. Kennedy Smiley
1922 - 2010

Founding President

of the

Canadian Hematology Society

Sponsored in part by the pharmaceutical industry.

BENEFITS OF CHS MEMBERSHIP

- **Attend reception and awards dinner** at American Society of Hematology (ASH)
- **Compete** for (best abstracts presented at ASH) **CHS Education Awards**
- **Compete** for **RK Smiley Research Grant**
- **Compete for CHS Paper of the Year Award**
- **Access the members-only interactive Web Portal**
- **Keep up to date on CHS news, events, opportunities, and much more by receiving the CHS Newsletter, *The Microenvironment*.**

The mission of the Canadian Hematology Society (CHS) is to lead and influence hematology clinical practice and research in Canada through being a recognized and valued voice of the Canadian hematology community.

MEMBERSHIP APPLICATION FORMS

are available through the office or on the website
http://www.canadianhematologysociety.org

CONTACT INFORMATION

Canadian Hematology Society
199-435 St. Laurent BLVD
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Fax: 613-748-6392
http://canadianhematologysociety.org/
Email: chs@uniserve.com

CHSCH

Upcoming Events

Canadian Hematology Society (CHS)
Annual Reception, Dinner & Awards Evening
Sunday, December 6, 2015
Rosen Plaza Hotel, 9700 International Drive
Orlando, Florida
Contact: chs@uniserve.com

36th World Congress of the International Society of Hematology (ISH)
Apr 18 - 21, 2016
Glasgow, Scotland, UK
Contact: http://www.ish2016.com/

Conference of the Canadian Society for Transfusion Medicine (CSTM)
April 20—23, 2017
Ottawa, Ontario, Canada
Contact: http://www.transfusion.ca/Events

American Society for Apheresis (ASFA)
May 3 - 6, 2016
Annual Meeting: Ft Lauderdale, Florida, USA
Contact: http://www.apheresis.org/page/ASFA2017

Canadian Blood and Marrow Transplant Group (CBMTG)
1st of 3 Themed Meetings
Focus: *"empowerment and resilience in the BMT team"*
May 5-6, 2017
Winnipeg, Manitoba
Contact: http://www.cbmtg.org/page/2017ThemedMeetings

Canadian Blood and Marrow Transplant Group (CBMTG)
2nd of 3 Themed Meetings
Focus: *"exploring innovation within the BMT field"*
June 9—10, 2017
Calgary, Alberta
Contact: http://www.cbmtg.org/page/2017ThemedMeetings

21st European Hematology Association (EHA)
Jun 22 - 25, 2017
Madrid, Spain
Contact: http://www.ehaweb.org/congress-and-events/22nd-congress

Canadian Blood and Marrow Transplant Group (CBMTG)
3rd of 3 Themed Meetings
Focus: *"pre and post-transplant issues"*
September 8—9, 2017
St. John's, Newfoundland & Labrador
Contact: http://www.cbmtg.org/page/2017ThemedMeetings

ISH & Canadian Hematology Society (CHS) Joint Congress:
37th World Congress of the International Society of Hematology (ISH)
Sept 13-17, 2018
Vancouver Convention Centre
Contact: http://www.ish2018.com/

WANTED: Editor for The Microenvironment

The Canadian Hematology Society is looking for a new Editor for its newsletter, *The Microenvironment*.

Under the guidance of the CHS Executive, the Editor is responsible for soliciting and providing content for the newsletter that is published three times yearly – Spring, Summer and Fall. The newsletter focuses on Canadian research and educational issues of interest to CHS members. It continues to be a primary mode of communication for Canadian hematologists, hematopathologists and scientists with an interest in the discipline.

Anyone interested in fulfilling this important role for the hematology community in Canada can contact the Canadian Hematology Society offices in Ottawa (cag@cagcanada.ca) or the current editor of *The Microenvironment*, Dr. Thomas Nevill (tnevill@bccancer.bc.ca) .

The DIAGNOSIS? Answer: (from Page 4)

The patient had a forward grouping consistent with blood group O+ but his sera reacted with O cells on reverse grouping. Further testing revealed a weakly positive reaction with anti-H antisera and, as he was Lewis b+, he was diagnosed with a ParaBombay phenotype.

The Bombay phenotype was first described in Bombay, now Mumbai, India in the early 1950s after a number of patients were noted to type as blood group O whose sera reacted strongly with O cells. It is most common in Taiwan (1 in 8000) and India (1 in 10,000) with an unusual variant of high frequency on Reunion Island. However, it does occur in Europeans, albeit at a rate of 1 in one million.

This disorder is a result of a mutation in the FUT1 gene (on chromosome 19q13.3) which is responsible for production of the fucosyltransferase enzyme that catalyzes the final step of synthesis of the H antigen – the mandatory building block for ABO blood group antigens (whose genes are encoded on chromosome 9).

An individual who does not form H antigen will have naturally occurring anti-H antibodies but there will be no adverse effect from this (and it will probably go undiagnosed) unless a red cell transfusion is necessary. Those with a Bombay phenotype (genotypically h/h or "Oh" – normals are either HH or Hh) who receive O red cells (which contain on their surface an abundance of H antigen) will have a severe hemolytic transfusion reaction. They must only receive red cells from another patient with a Bombay phenotype.

The FUT2 gene, which lies within 35 kb of the FUT1 gene encodes for an enzyme that results in a soluble form of H antigen in saliva and other body fluids (except CSF). Of great relevance (see below), the FUT2 gene, also plays an important role in the synthesis of the Lewis blood group antigens. The FUT2 gene determines your status as an H antigen secretor (Se or se); all Bombay phenotype patients are non-secretors (se/se) and do not have H antigen in their body fluids. If a patient has a FUT1 gene mutation but has a secretor phenotype (Se/Se or Se/se genotype), they will produce H antigen in their body fluids and are referred to as having a ParaBombay phenotype.

Individuals with this phenotype may have enough H antigen in their plasma to produce reactions on forward grouping (corresponding to their actual ABO group) and may have weak or no detectable anti-H in their serum – making transfusion of O cells possible. While testing of saliva for H antigen can be done, the involvement of FUT2 in Lewis antigen formation is such that all Lewis b+ individuals will have a secretor phenotype (and thereby be ParaBombay if they have a FUT1 gene mutation).

Detection of the Bombay/ParaBombay phenotype in an individual generally requires a high index of suspicion amongst hematologists and even for those in transfusion medicine. Strongly and widely-reactive O red cell crossmatching would make one consider an alloreactive antibody against a high-incidence antigen but anti-H would be far down the list of likely possibilities.

The even less likely way in which the Bombay phenotype can present is a result of the H antigen's role in leukocyte adhesion to the vascular endothelium for migration to sites of inflammation. Patients with leukocyte adhesion deficiency Type II have a fucosylation deficiency that makes them unable to form H antigen needed for endothelial adhesion. They usually present in childhood with recurrent infections, growth retardation and cognitive abnormalities and all have a Bombay phenotype.

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:

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

Clinical Research Fellowship in Mature B-cell Lymphoproliferative Disorders (including Multiple Myeloma, Chronic Lymphocytic Leukemia, Waldenstrom's macroglobulinemia, and Amyloidosis)

Princess Margaret Cancer Centre/Ontario Cancer Institute, Toronto, ON

We are currently offering a clinical research fellowship in the treatment of multiple myeloma and associated mature B-cell lymphoproliferative disorders.

Fellows will have the opportunity to gain clinical experience in the care of patients with myeloma and related disorders, including application of the principles of intensive therapy and stem cell transplantation as well as the use of novel agents in drug development. Fellows will have the opportunity to participate in clinical investigation (writing/directing study protocols, participation with the NCIC, applying for grant support, etc). Depending upon candidate interest, opportunities in laboratory research and/or patient/faculty education and supportive care in mature B cell disorders are available.

Candidates must be eligible for registration with the College of Physicians and Surgeons of Ontario and hold subspecialty certification in Hematology or Medical Oncology from the Royal College of Physicians and Surgeons of Canada.

Fellowships are for 1 year with an option to extend to 2 years. Start dates negotiable.

Interested candidates should forward their curriculum vitae to:

Dr. Christine Chen
Department of Medical Oncology and Hematology
Princess Margaret Cancer Centre
tel: (416) 946-2827, fax: (416) 946-4563, email: christine.chen@uhn.ca

Fellowship in Maternal/Fetal Hematology

Mount Sinai Hospital, Toronto

This fellowship in Maternal/Fetal Hematology is intended for physicians who have completed basic Hematology training and wish to pursue clinical and academic excellence in the approach and management of hematological disorders in pregnancy.

The Medical Disorders in Pregnancy Program at the University of Toronto provides a wide breadth of exposure to clinical hematological disorders peripartum including immune disorders, hemoglobinopathies, thromboembolism, myeloproliferative disorders, malignancies, and hemostasis as well as laboratory based exposure including the investigation and management of hemolytic disease of the fetus and newborn and fetal/neonatal alloimmune thrombocytopenia.

The successful candidate will have at least 50% time dedicated to their postgraduate program.

It is the intent of the fellowship that the successful candidate will develop clinical and academic expertise.
Duration: 2 years
Start date: from July 1, 2017

Please submit curriculum vitae, including the names of three referees, with a covering personal letter to:

Ms. Laurel Davis, Fellowship Coordinator for the Division of Hematology and Oncology, University of Toronto at laurel.davis@uhn.ca.

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.

Active members only 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 Membership

- 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.

Allied Health Membership

Individuals who have post-secondary graduation, and who make sustained contributions to clinical or laboratory hematology practice or hematology research in Canada. *Regular membership fees apply.*

CHS members are reminded ... that dues for the year 2016, are now due.
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:

2016 Membership Renewal / Address Change: Canadian Hematology Society

Membership Status

Active ☐
Associate ☐
Emeritus ☐
Allied Health ☐

Has your status changed?

Yes ☐
No ☐

Name: _____
Title: _____
Email: _____
Work Address: _____
_____
Work Phone: _____
Work Fax: _____