The Microenvironment

The Canadian Hematology Society

NEWSLETTER

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THE PRESIDENT'S REPORT

Physicians and the pharmaceutical industry: *An important relationship*

Dr. Tom Nevill
President, CHS

After a successful Annual General Meeting and Research Awards Dinner at ASH in Orlando in December, I decided to write about an important but sometimes controversial topic. By this I am referring to the increasingly important relationship between physicians and the pharmaceutical industry.

There is, at times, an appropriate concern about this relationship being driven by monetary gain for both parties or the creation of a conflict of interest in the area of research or drug prescription. However, the interactionbetween physicians and industry is also an important component of the practice of medicine in the 21st century and can be incredibly rewarding for both sides. Evaluation of new (and established) drugs in clinical research trials is critical in the licensing of new therapeutic agents and the scientific determination of their value.

The pharmaceutical industry is often responsible for the initial development of a new agent and then must engage clinical researchers to evaluate it in an actual patient population.

Some drugs are found to be of little or no benefit but others appear efficacious and, after phase III testing, can become groundbreaking in the

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President's Message

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treatment of hematologic disease. Certainly the best example in my practice was the development of tyrosine kinase inhibitors for the management of chronic myeloid leukemia.

As a stem cell transplantation (SCT) physician, CML was always put forward as the disease that best exemplified the power of allogeneic SCT. Then along came the targeted agent, Imatinib mesylate, and a decade later, it is clear that SCT in chronic phase CML is virtually obsolete. The main issue that surfaced with the development of targeted agents in hematology (and many such drugs have followed Imatinib in the years since it was licensed) is the acquisition cost of these drugs.

Many have focused their frustration at the pharmaceutical industry for what they consider their exorbitant pricing of these agents. No doubt there are two sides to this argument and I do not have the desire or space to summarize this debate. However, I can say that I have seen a tremendous willingness on the part of drug companies to engage and work with physicians to complete pivotal clinical trials and develop evidence-based guidelines for the use of new drug therapies.

There is no question that this is in the financial best interest of the company licensing the drug, but I have been swayed by a genuine desire on the part of these companies to see more patients receive their drug, honestly believing that it will improve their quality of life.

I have been somewhat less impressed by the funding agencies in their approach to new drugs in hematology and their, at times, nonsensical decisions. I do understand that there are only so many dollars that can be put into drug costs in any one province (since drug funding currently is a provincial decision). However, the process for getting drugs approved for funding is considerably more difficult and less dependent upon input from practitioners.

Targeted agents are revolutionizing hematology and physicians are working with the pharmaceutical industry to gain access to these important drugs for their patients. Targeted agents are expensive but also, in many cases, far more effective than the previous standard treatments. The funding agencies need to step forward and join the discussion with an open mind; there must be a compromise position that can be arrived at.

In closing, I can unequivocally say that the CHS has received unrestricted support from a wide range of pharmaceutical companies in its efforts to promote communication, education and research amongst hematologists in Canada and that these companies appear committed to this support over the long run.

On the left side of this page we have listed our industry sponsors for 2010 and, on behalf of the Canadian Hematology Society, thank them all for their support.

CHS 2010 RESEARCH AWARDS

The CHS 2010 Research Awards were presented in December at the Annual Reception and Awards Gala. The awards evening is held each year in conjunction with the annual business meeting. **Brent A. Williams**, a resident at St. Michael's Hospital in Toronto, was the winner of the most prestigious of the five awards presented at the 2010 event in Orlando, Florida—***the John H. Crookston Award,*** for the best paper given by a resident.

Winners in the category of *Residents & Fellows,* were **Alina S. Gerrie** and **Christopher P. Venner.** In the category of *PhD & Postdoctoral*, were **Lorri D. Martin** and **Mahadeo A. Sukhai**. Read more about these five winning entries over the next three pages; and on Page 6, a feature about Dr. John H. Crookston, for whom our top award is named.

Brent A. Williams - 2010 John H. Crookston Award Winner

NK-92 preferentially targets acute myeloid leukemia stem cells

Despite advancements in therapy, the majority of patients with acute myeloid leukemia (AML) ultimately succumb to the disease. Novel therapies are required in AML and natural killer cell lines have been developed to target a variety of malignant cells, including leukemia stem cells (LSCs), the CD34+,CD38- fraction of AML blasts. The investigator and colleagues developed a human permanent natural killer cell line (NK-92) that preferentially targets LSCs and evaluated its action and that of another NK cell line, KHYG-1, against both AML cell lines and primary AML samples.

Brent Williams, Princess Margaret Hospital, Toronto, Ontario, accepts the 2010 John H. Crookston Award, for best paper given by a resident, from CHS President, Dr. Tom Nevill.

NK-92 was shown to result in 33.8-99.0% cell lysis when tested by chromium release assay in five different AML cell lines. KHYG-1 produced 33.0-82.2% cell lysis in the same five cell lines. Lysis was completely inhibited by calcium chelation with EGTA, supporting granule exocytosis as the primary killing mechanism. When the activity of NK-92 and KHYG-1 was then tested against five primary AML samples, cytotoxicity was much more modest – 15.6-43.9% and 1.3-17.7%, respectively. However, when CD34+,CD38- AML LSCs were separated out, they were more sensitive to NK-92-induced lysis at three different effector:target ratios (58.9%, 78.3% and 72.9%) than were CD34+,CD38+ blasts (20.3%, 43.5% and 38.5%, respectively). Furthermore, when killing of clonogenic primary AML blasts from five patients was testing using their own methylcellulose cytoxicity assay, lysis was much higher (three samples showed 100% lysis, one sample 98.4% and the other 86.3%). The investigators concluded that NK-92 may be a useful treatment in AML in light of its ability to preferentially kill LSCs.

Brent A. Williams
(Supervisor: Armand Keating) Princess Margaret Hospital, Toronto, Ontario

CANADIAN HEMATOLOGY SOCIETY

Impact of immunoglobulin heavy chain translocations in chronic lymphocytic leukemia: negative impact on patients with isolated del(13q) abnormality

Alina S. Gerrie receives a CHS *Residents and Fellows* Research Award, Dec. 5, 2010, in Orlando, Florida.

Flourescence in situ hybridization cytogenetic analysis (FISH) has shown that certain abnormalities are both common and prognostically relevant in CLL. Patients with del (17p) and del (11q) consistently have a poor treatment-free and overall survival while +12 and normal FISH patients are considered intermediate-risk and a del(13q) abnormality is thought to confer a favourable prognosis. Recently, immunoglobulin heavy chain translocations [t(IGH)] have been reported to convey a poor prognosis in CLL and the author and colleagues sought to confirm this and to determine its influence on other known FISH abnormalities.

Between 2006 and 2009, 142 CLL patients were studied using a FISH panel and an IGH break apart probe; 55% had del(13q), 29% had +12, 26% had t(IGH), 14% had del(11q) and 9% had del(17p). Patients with t(IGH) had a similar survival to all those without this translocation. Similarly, t(IGH) had no influence on the prognosis for patients with poor- or intermediate-risk FISH results. However, for patients with del(13q), the presence of t(IGH) led to a significant reduction in treatment-free survival and a trend toward worse overall survival. In fact, the t(IGH) brought the prognosis for the del(13q) cohort down to a level between poor- and intermediate-risk CLL conclude that the presence of t(IGH) is highly prognostically relevant in the large cohort of CLL patients with a del(13q) abnormality on FISH.

Alina S. Gerrie
(Supervisor: Cynthia Toze)
Vancouver General Hospital, Leukemia/BMT Program
Vancouver, British Columbia

The anti-malarial mefloquine demonstrates pre-clinical activity in leukemia and myeloma and is dependent upon toll-like receptor signalling for its cytotoxicity

Known drugs, with established safety and toxicity profiles, may have previously unrecognized anti-cancer activity allowing them to be rapidly repurposed for animal and human testing. The author and colleagues have compiled an in-house library of such drugs and have screened for cytotoxic activity against hematologic malignancies. From this screening process, the investigators have identified an anti-malarial agent, Mefloquine, as having promising activity against leukemia and myeloma cell lines.

In this study, leukemia and myeloma cell lines were treated with Mefloquine for 72 hours in pharmacologically achievable concentrations. Decrease in cell viability was shown in all 10 leukemia cell lines, all 9 myeloma cell lines and, in addition, all 6 primary AML samples tested. The authors also showed that Mefloquine was much less toxic to normal hematopoietic cells and murine dendritic cells. They went on to test the effects of Mefloquine in mouse xenograft models and demonstrated that oral Mefloquine delayed leukemia and myeloma cell growth by up to 60%. To determine the mechanism by which Mefloquine induces cell death, gene expression oligonucleotide array analysis was performed on Mefloquine-treated malignant cells. This revealed that Mefloquine altered the expression of genes involved in toll-like receptor (TLR) signalling including STAT1, OAS1, IRF1 and IL-8 in malignant cells but not in normal dendritic cells. In subsequent knockdown experiments, the investigators were able to show that STAT1 activity and TLR adapter proteins MyD88 and TRIF1 were required for Mefloquine to induce malignant cell death and furthermore that the cytotoxicity appeared to be mediated, in part, by TLR-related generation of reactive oxygen species.

Mahadeo A. Sukhai receives a 2010 CHS Research Award in the PhD and Postdoctoral category.

Mahadeo A. Sukhai
(Supervisor: Aaron Schimmer)
University Health Network and Princess Margaret Hospital,
Toronto, Ontario

2010 RESEARCH AWARD WINNERS

Induction of microRNA-143 and 145 in pre-treatment CD34+ cells from patients with myelodysplastic syndrome after *in vitro* exposure to lenalidomide correlates with clinical response in patients harbouring the del(5q) abnormality

Christopher P. Venner receives a CHS *Residents and Fellows* Research Award, Dec. 5, 2010.

Myelodysplastic syndrome (MDS) is a heterogeneous clonal bone marrow disorder characterized by hematologic cytopenias and frequent chromosomal abberations. The most common cytogenetic abnormality seen alone or with other abnormalities in MDS is deletion of the long arm of chromosome 5 [del(5q)]. The use of the oral immunomodulatory drug Lenalidomide (Revlimid) in low-risk MDS with del(5q) is associated with a 75% major erythroid response rate, although its mechanism of action remains unknown. The author and colleagues attempted to unravel this mystery by focusing on short RNA molecules, called microRNAs (miRNA), that play a key role in gene regulation and can be aberrantly expressed in various disease states. Preliminary data from the investigator's laboratory suggested that miRNA-143, 145 and 146 may be upregulated in patients with del(5q) MDS and that this may be key to their responsiveness to Lenalidomide.

In this study, pre-Lenalidomide-treated CD34+ marrow cells from 31 patients [(11 with del(5q), 20 without del(5q)] were exposed to Lenalidomide *in vitro* and then examined for miRNA expression. For the entire cohort, a 1.6 fold increase in miRNA-143 and a 1.7 fold increase in miRNA 145 were observed. Both the del(5q) and the non-del(5q) patients demonstrated a similar increase in these two miRNAs. When correlated with reported clinical responses of the patient to Lenalidomide, the del(5q) cohort that responded to Lenalidomide showed a significant increase in miRNA-143 and 145. Conversely, there was no demonstrable relationship between miRNA expression and clinical responses in the non-del(5q) patients. The investigators concluded that miRNA-143 and 145 were therefore unlikely to play a role in the disease phenotype or the Lenalidomide response in non-del(5q) MDS.

Christopher P. Venner
(Supervisor: Aly Karsan)
British Columbia Cancer Agency, Vancouver, BC

Cancer-specific nuclear positioning of translocation prone gene loci in non-malignant B-cells from patient with multiple myeloma

Many hematologic malignancies are associated with recurrent unbalanced chromosomal translocations that are integral to the progression of the disease. In multiple myeloma (MM), the immunoglobulin heavy chain locus (IGH) is frequently involved in translocations with the CCND1 [t(11;14)] and the FGFR [t(4;14)] gene. These recombination events recur at specific breakpoints and spatial proximity to translocation-prone gene loci (TPGL) is thought to play a key role. The author and colleagues utilized 3D-FISH and other analysis techniques to measure the spatial and radial positioning of TPGL in non-malignant progenitor and B-cell populations to determine their propensity to translocate.

In this study, 900 cells from multiple myeloma patients with IGH translocations and 300 cells from healthy donors underwent 3D analysis. The investigators were able to demonstrate that IGH, CCND1 and FGFR3 were positioned in close proximity to each other in normal CD34+ progenitors and CD19+ B-cells from MM patients and that the clinical Non-malignant CD19+ B-cells from MM patients also displayed radial positioning of TPGL in the nucleus consistent with a predisposition to translocate. Furthermore, the authors were able to show that positioning of key genes at the boundary of the chromosomal territory (CT) appeared to allow for intermingling with adjacent CTs and utilization of adjacent transcription enzymes to produce the translocation. To further support this hypothesis, the investigators were able to show that at least one CCND1 and FGFR3 allele are positioned outside of its own CT in 59% of CD19+ B-cells from MM patients.

Lorri D. Martin, receives a 2010 CHS Research Award in the category of PhD & Postdoctoral.

Lorri D. Martin (Supervisor: Linda Pilarski) Cross Cancer Institute, Edmonton, AB and Manitoba Institute of Cell Biology, Cancer Care Manitoba, Winnipeg, Manitoba

A LANDMARK LEGACY

John Hamill Crookston (1922—1987)

John Hamill Crookston (1922-1987) was the Laboratory Hematologist-in-Chief at Toronto General Hospital and a Professor of Medicine and Pathology at the University of Toronto from 1957 until his death in 1987. He had left Toronto in 1951 after being elected to an Elmore Research Studentship at the University of Cambridge.

He worked closely in London with Sir John V. Dacie, one of the preeminent haematologists of the 20th century, and together they wrote three seminal papers on cold antibody-induced hemolytic anemia.

It was in London that he met Marie Cutbush Crookston (1920-2009), a graduate of the University of Melbourne in Australia, who had come to London in 1947. She worked for a decade with Dr. P.L. Morrison at the MRC Blood Transfusion Unit, had discovered and described the Duffy blood group system and had co-authored many articles on hemolytic disease of the newborn, exchange transfusion, red cell survival and long-term preservation of blood.

However, when she married John Crookston in 1957, she abandoned her PhD and the two moved to Toronto where they both ultimately assumed key roles in organizing the first Blood Transfusion Laboratory at Toronto General Hospital in the mid-1960s. The Crookstons had an intense interest in immunohematology and formed the Ontario Antibody Club which was active for the next quarter of a century.

Marie Crookston became an assistant professor in the Department of Pathology at the University of Toronto. She published data on the conversion of incomplete antibodies to direct agglutinins by chemical modification which directly led to the commercial development of modified Rh antisera. In 1984, she coauthored with Dr. Peter Issitt, the landmark paper "Blood Group Terminology: Current Conventions".

It was John and Marie Crookston who coined the term "HEMPAS" and described the features of this condition, a hereditary dyserythropoietic anemia associated with a positive acidified-serum test. John Crookston also authored numerous papers relating to hemoglobinopathies and developed a large collection of hematopathology slides that can now be accessed through the Internet: www.thecrookstoncollection.com

Following his untimely death in 1987, the Canadian Hematology Society established an award for the best paper, given by a resident, at ASH in honor of John H. Crookston.

In 2002 the Canadian Blood Services presented Marie Cutbush Crookston with a CBS Lifetime Achievement Award.

Dr. Tom Nevill
President, Canadian Hematology Society

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For registration and other details:
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In Memoriam

Remembering Dr. Julye C. Lavoie

Julye Lavoie was born in Montréal, Québec, an unexpected addition for her mother, Louiselle, and father, Camille-André. From an early age, Julye was a cheerful, intelligent and, above all, determined individual who would have all of these traits tested when she was diagnosed with Hodgkin lymphoma at the age of ten.

Dr. Julye C. Lavoie (1971 - 2008)

After successful treatment of this condition with radiation, she drew on her healthcare experience as motivation to pursue a career in medicine.

She attended medical school in Sherbrooke, Québec and graduated in 1994. Following graduation, she did internal medicine training in Montréal followed by subspecialization in hematology, successfully obtaining her Royal College Fellowship in 1999.

Julye decided to obtain further training in stem cell transplantation and moved to Vancouver, British Columbia to do a Leukemia/BMT Fellowship with the BC Cancer Agency. Her successful two-year fellowship was highlighted by a first author paper in *Blood* detailing long-term follow-up of patients that had undergone autologous stem cell transplantation in Vancouver for relapsed/refractory Hodgkin lymphoma.

At the completion of her fellowship in September 2001, Julye accepted an Attending Staff position with the Leukemia/BMT Program of BC and quickly put her enthusiasm to work. She developed protocols for CMV and fungal infection monitoring and management as well as outpatient leukemia chemotherapy and autologous BMT schedules for the Leukemia/BMT Daycare Unit.

She excelled in mentoring students and BMT Fellows on research projects leading to a number of successful publications in these areas of expertise. Just as her academic career was truly blossoming, Julye's health began to fail and she was diagnosed with Cushing's disease for which she required a bilateral adrenalectomy. Not to be deterred, she persevered and returned to work six months after major surgery, rolled up her sleeves and began reorganizing the Leukemia/BMT Daycare and once again took on a summer student.

Julye's private life also began to flourish and she married her life-long partner, Fred Boucher, in 2006, the same year that they were expecting twin girls. After the devastating loss of the girls, Elisabeth and Viviane, in her second trimester, Julye demonstrated her great determination by giving birth to a daughter, Clara-Nabella, in December 2007.

Julye & daughter, Clara-Nabella

Tragically, she was diagnosed at the same time with an unresectable malignant thymoma, and after a 9-month battle, died on September 26, 2008, with family, friends and colleagues at her bedside.

In recognition of her remarkable life and her outstanding efforts in mentoring students, the Leukemia/BMT Program of BC established the Julye Lavoie Student Scholarship that is awarded annually to the student with the most worthy summer research project.

ASK THE EXPERT

Myeloma treatment:

CASE:
A 68-year-old woman with a 10-year history of hypertension and diabetes mellitus and a history of an anterior myocardial infarction requiring balloon angioplasty and insertion of an LAD stent presents with a 6 month history of increasing mid-thoracic back pain.

Investigations reveal that she has multiple lytic lesions in her vertebrae with throracic compression fractures at T 5, T8 and T10. She has an anemia of 85 g/L with a serum creatinine of 165 umol/L. Serum calcium is normal although serum beta-2 microglobulin is 6.5 mg/L. Serum protein electrophoresis reveals an IgA lambda M-protein of 76 g/L, an albumin of 24 g/L and a 24-hour urine protein of 5.4 g (90% of which are lambda light chains). Bone marrow aspirate and biopsy show extensive infiltration with pleomorphic plasma cells; FISH analysis confirms deletion of 13q and t(4;14).

DISCUSSION:
This woman has Durie-Salmon stage 3A, ISS 3 IgA multiple myeloma. Not surprisingly she has the poor prognosis chromosome translocation t(4;14) which is more commonly found in association with IgA myeloma. The height of her monoclonal protein in her serum and the degree of proteinuria is also concerning. It is uncertain if her mildly elevated creatinine is from her myeloma or diabetes.

Kevin Song MD, FRCPC

LEUKEMIA/BONE MARROW TRANSPLANT PROGRAM OF BRITISH COLUMBIA
Division of Hematology

Her co morbidities of diabetes and recent myocardial infarction as well as her advancing age leads me to be concerned about the tolerability of high-dose chemotherapy followed by autologous stem cell rescue (ASCT). Furthermore, the benefit of high-dose chemotherapy is debatable for patients known to have t(4;14), particularly if they also present with anemia[1].

I would offer non-ASCT options. I would favor a combination of melphalan, prednisone and bortezomib. The VISTA study has demonstrated that patients receiving this regimen achieve high-remission rates similar to what can be achieved with ASCT[2].

Importantly, response can be achieved rapidly. Progression Free and Overall Survival is also significantly improved compared to melphalan and prednisone.

This regimen has also been shown to be effective for patients with renal dysfunction. This bortezomib containing regimen is known to be particularly effective for patients with high-risk karyotype. I would also modify the regimen to the weekly dosing of bortezomib.

Bringhen et al has demonstrated that such a strategy can reduce side-effect and particularly the incidence of neuropathy and improve the delivery of bortezomib[3]. This can be accomplished without affecting the level of response and survival significantly. This weekly delivery is also more convenient for the patient and will improve compliance.

As a part of her supportive care she should also be treated with bisphosphonates. At initial presentation, a consultation with a dentist is appropriate prior to initiation of bisphosphonate therapy to avoid the

Rapid pace of change

risk of osteonecrosis of the jaw. I would then give her pamidronate 30mg IV monthly. A recently published trial by the Nordic Myeloma Study Group demonstrated that 30 mg monthly is as effective as 90 mg monthly but with less side-effects[4].

In assessing her back pain, consideration should be made for CT or MRI of the spine to rule-out a mass near the spinal cord. If such as mass is found, radiation should be given. With the initiation of chemotherapy and supportive measures, there should be improvement in her pain. If the pain does not improve in spite of a good response to treatment, vertebroplasty should be considered.

After initial treatment, I would follow her closely for relapse. At the time of biochemical relapse (prior to progression of symptoms), lenalidomide with dexamethasone would be the most appropriate treatment[5]. Data is supportive of the benefit of lenalidomide for patients with t(4;14)[6].

When she progresses from treatment with lenalidomide, I would consider retreatment with bortezomib. Retreatment with bortezomib can be beneficial if there was prolonged benefit with the first treatment[7]. To improve response, I would also add in cyclophos phamide and prednisone[8].

This patient should also be considered for research studies if available as there is a rapid pace of change in the treatment of myeloma and availability of newer molecules continues to expand.

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Q & A In conversation . . .

In an attempt to capture the wide breadth of hematology practice, this new column is being introduced to provide a more detailed description of the day-to-day life of a hematology practitioner and the reasons for his/her chosen career path.

Interview with community hematologist, Dr. Michael Delorme, Hematologist, Kelowna, BC

Q. What attracted you to the hematology subspecialty?

A. I went into medical school wanting to be a cardiac surgeon. That all changed in second year when we were doing the Hematology section of the big pre-clinical course of that year. I was in small group sessions with Dr. Bruce Barton, an elder statesman of Hematology at the University of Western Ontario. Somehow, he made everything interesting and understandable. It was literally a life-changing contact and I never looked back. I continue to be attracted by the patients, whose variety of clinical problems keeps things interesting.

Dr. Michael Delorme

Q. What do you see as the most significant changes in hematology since you finished training?

A. The explosion in molecular technology and the understanding of molecular pathology that this has allowed is revolutionizing the field. There is still much to be made sense of but therapeutics are changing and will inevitably become more individualized. There is little doubt this rapid expansion in knowledge will continue to make hematology a vibrant subspecialty.

Q. When did you decide to pursue community-based hematology rather than an academic/ University Hospital-based practice and why?

A. After my hematology training, I did a two year basic science research fellowship then started my own lab. However, I was a bit slow to realize that a research career is as much or more about trying to find money as coming up with ideas. I eventually gave up on research and became involved in residency education, which I thoroughly enjoyed. However, manpower shortages in the hematology division at that time meant I was not really supported in doing this. I had visited Kelowna previously and fell in love with the place. When an opportunity to practice here became available, I investigated and the rest is history.

Q. You are working in Kelowna, BC – how big is Kelowna and why did you choose it as a place to live and work?

A. The Kelowna area has a population of about 180,000. However, there are twice that many people again within a two hour drive. I have people come to see me from even 4 to 5 hours away, a total catchment area of about 750,000, as I am the only hematologist doing "general hematology" in the interior of BC.

As a place to work, it was very attractive because the hospital provided tertiary level care in most areas. A new Cancer Centre had recently been built and was in a phase of active growth. I soon discov-

with Dr. Michael Delorme

ered that the hospital and medical services were much more efficient and responsive than what I had been used to in a large teaching centre. Alas, budget cuts and health administration restructuring have taken some of the shine off, as they have everywhere, but it remains a good place to work.

As a place to live, there are probably few places better for outdoor lifestyle. There are 2 great ski hills within an hour drive and 3 more in under 3 hours. You can be in wilderness in about 30 minutes for camping. The terrain of the area is challenging and beautiful for cycling. The lake provides for swimming and sailing and the world class ocean kayaking of the west coast is easily accessible.

Q. How much of your practice is benign hematology and how much is malignant hematology? Is general medicine a significant component of your work day?

A. Most of my practice is benign hematology though there is a sizable portion of patients with myelodysplasia and myeloproliferative disorders. Lymphoma and myeloma are treated at the regional Cancer Centre, where I worked part-time until things became too busy at the office. Resource and manpower issues mean that patients with acute leukemia are transferred to Vancouver for treatment. I am not involved in general medicine care or coverage at this time.

Q. Do you do any laboratory work and, if not, do you miss it?

A. Unfortunately, I am not directly involved in lab work. The lab is run by excellent general pathologists, some of whom have at least some hematopathology training. Samples are routinely sent to Vancouver for more specialized testing (flow, cytogenetics, special hemostasis). I still look at marrows on my patients when I get the chance but miss being in the hemostasis lab.

Q. Are there times that you wish that you had stayed at a teaching hospital and more involved in clinical research?

A. I don't have the patience for clinical research but still have an interest in teaching and evaluation. I do miss interaction with trainees.

Q. What would you tell a hematology trainee who was considering pursuing a community-based hematology practice?

A. Overall, I consider community practice very rewarding and would encourage them. They would need to select their community carefully. The catchment area needs to be large enough. Ideally, there should be a regional Cancer centre since care of malignant hematology patients is becoming too specialized and resource intensive to be run out of most community hospital ambulatory care departments. They would also need to ensure adequate lab resources. If they were happy providing patient care and having a measure of control and flexibility running a private office, they would likely enjoy community practice.

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MINI REVIEW

Exploring some examples of what we have

Sara J. Israels
Department of Pediatrics and Child Health and the Manitoba Institute of Cell Biology, University of Manitoba

Introduction

The study of patients with inherited platelet disorders has taught us much about the hemostatic function of platelets. Astute clinicians identified Glanzmann thrombasthenia and Bernard-Soulier syndrome early in the last century, and the development of the platelet aggregometer in the early 1960s facilitated the identification of additional disorders of platelet function. Molecular technology and informative animal models have defined the basis for many of the classic inherited platelet disorders, and have enhanced our understanding of platelet function.

Platelets play a central role in the hemostatic process at sites of vascular injury. They function as circulating monitors of the integrity of the blood vessel wall; the dynamics of blood flow dictate that platelets are found primarily along the vessel wall, well positioned for rapid response to endothelial damage. Fundamental to their "first responder" role is their ability to be captured by exposed collagen fibrils and von Willebrand Factor (VWF) in the subendothelial matrix, followed by transformation from inactive to activated cells that adhere tightly to the injured site and to each other. Activated platelets undergo rapid cytoskeletal rearrangement, allowing them to spread on the subendothelial matrix and maximize surface contact.

The adherent platelets provide a base upon which additional platelets accumulate, releasing soluble mediators such as ADP and thromboxane A_2 that recruit additional platelets to the primary plug. This is facilitated by a conformational change in the αIIbβ3 integrin increasing its affinity for adhesive ligands, most importantly fibrinogen, which cross-links adjacent platelets to form a stable aggregate. Activation also results in release of storage granule contents, and the expression of negatively charged phospholipids promoting assembly of coagulation factor complexes. Inherited defects in platelet receptors, granules and cytoskeleton impair adhesion or activation events, and lead to mucocutaneous bleeding. Comprehensive reviews of platelet function and inherited platelet disorders have been published recently (1-3). This mini-review will provide only a few examples of what we have learned from inherited platelet disorders.

Defects in adhesive receptors

Bernard-Soulier Syndrome: Deficiency of functional Glycoprotein Ib-IX-V

Bernard-Soulier Syndrome (BSS) is an autosomal recessive disorder that results from quantitative or qualitative defects in a component of the major platelet VWF receptor, the GPIb-IX-V complex, which is abundant on normal platelets. These defects impair platelet adhesion to VWF at sites of vascular injury, particularly under conditions of high shear. BSS is typically associated with macrothrombocytopenia, and absent platelet agglutination responses to ristocetin *in vitro* (3). The receptor complex consists of four polypeptides: GPIb α, GPIbβ, GPIX and GPV. Mutations that result in abnormalities or deficiency of GPIbα, GPIbβ, or GPIX impair the intracellular assembly of the complex and its expression on the platelet surface. The adhesive defect is primarily due to the loss of VWF binding by the GPIbα subunit; the macrothrombocytopenia and cytoskeletal defects result from loss of interaction of GPIbα with the platelet membrane skeleton. *Platelet-type von Willebrand Disease: Gain-of-function of Glycoprotein Ib-IX-V*

learned from inherited platelet disorders

Gain-of-function mutations in GPIb promote spontaneous interaction between VWF and GPIbα, resulting in accelerated clearance of the high molecular forms of VWF and platelets from the circulation, an abnormal increased agglutination response to ristocetin *in vitro*, loss of the high molecular weight multimers of VWF from plasma, and thrombocytopenia. Similar clinical and laboratory features are seen in von Willebrand Disease (VWD) type 2B, but the defect in 2B VWD is in the domain of the VWF molecule that binds GPIbα, while in platelet -type VWD the mutations are in the complementary VWF-binding domain of GPIbα (4).

Storage granule disorders

There are three primary types of platelet granules: lysosomes, and two types of platelet specific storage granules (electron dense δ-granules and α-granules). Dense granules contain serotonin, a non-metabolic pool of adenine nucleotides and calcium, which is responsible for the density of these granules viewed by electron microscopy. Alpha-granules contain numerous proteins including adhesive proteins, coagulation factors, anticoagulant factors, chemokines, and growth factors. Many storage granule disorders are linked to defects in intracellular trafficking that regulates movement of newly synthesized proteins from the endoplasmic reticulum and the Golgi complex to intracellular organelles and the plasma membrane.

Delta granule disorders

δ-granule disorders (also called storage pool deficiencies (SPDs)) cause mild-to-moderate bleeding diatheses, and are associated with impaired secondary aggregation responses to some agonists. Decreased or absent δ-granules may occur in isolation, or more rarely, as part of a syndrome associated with defects in other organelles such as melanosomes and lysosomes, or α-granules. δ-SPD syndromes associated with oculocutaneous albinism, recurrent infections and defects in vesicular trafficking include Chediak-Higashi syndrome (mutations in the lysosomal trafficking regulatory gene, *LYST*) and Hermansky-Pudlak syndrome (mutations in at least eight different genes, each involved with organelle biogenesis or cargo protein trafficking) (5).

Alpha granule disorders

Gray platelet syndrome is associated with macrothrombocytopenia, absence of platelet granules visible using light microscopy, and variably impaired aggregation responses to thrombin and collagen (6). Proteins destined for α-granules are not appropriately stored, resulting in the release of adhesive proteins and growth factors from megakaryocytes into the bone marrow leading to myelofibrosis. The molecular defect is unknown although the trafficking defect may involve proteins that mediate vesicle membrane fusion. Quebec platelet disorder (named for the home province of the original family) is characterized by α-granule protein degradation due to aberrant expression and storage of urokinase plasminogen activator (uPA) in the α-granules. Recently, a tandem duplication of the uPA gene, *PLAU*, has been identified (7). The unique clinical feature of this disorder is delayed-onset bleeding that responds to anti-fibrinolytic drug therapy.

Diagnosis of platelet disorders

As there are no population-based data, the prevalence of inherited platelet disorders is unknown. In clinical studies of patients presenting with mucocutaneous bleeding, platelet function abnormalities are at least as common as VWD (9). A Canadian registry of platelet disorders has collected 577 cases since 2004 (available at: http://www.fhs.mcmaster.ca/chr/data.html). Many of these patients have incompletely characterized platelet abnormalities, but the numbers support the observation that platelet disorders are not rare. Investigation of patients with platelet disorders can be challenging because the possible causes of mucocutaneous bleeding are many, and specialized testing can sometimes be difficult to access or interpret (10). Tools to aid in the diagnosis of platelet disorders have been developed by members of the Association of Hemophilia Clinic Directors of Canada and are available on the AHCDC

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website http://www.ahcdc.ca/. These include a diagnostic algorithm, descriptions of platelet disorders and standardized bleeding questionnaires.

Studies of inherited platelet disorders have taught us much about normal platelet production and function. These small, anucleate cells continue to amaze us with their complexity, and there is still more to learn.

Cytoskeletal defects

Cytoskeletal components support the plasma membrane and maintain the shape of resting platelets. Reorganization of the cytoskeleton following platelet activation results in the extension of filipodia and platelet spreading. The cytoskeleton also plays an essential role in proplatelet formation by megakaryocytes.

MYH9 disorders: defects in myosin heavy chain

The MYH9-related disorders (May-Hegglin anomaly, Fechtner, Epstein and Sebastian syndromes) typically present with macrothrombocytopenia and mild-to-moderate bleeding symptoms. These disorders, though identified as separate entities (thus the eponyms), are all associated with mutations in the *MYH9* gene that encodes non-muscle myosin-heavy chain IIA (NMMHC-IIA). A variety of mutations have been detected in the *MYH9* gene but most affect dimerization of the protein and its assembly into filaments. Phenotypic variation among the syndromes includes combinations of Döhle body-like inclusions in granulocytes, nephritis, sensorineural hearing loss and cataracts (8).

The mechanism by which abnormal myosin assembly produces these phenotypes is not yet clear, although myosins are involved in functions such as cytokinesis and cell motility. In platelets, this is reflected in defective activation-induced shape change and poor clot retraction.

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OPPORTUNITIES

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DEPARTMENT OF MEDICINE

Hematologists

Division of Hematology, Department of Medicine,
The Ottawa Hospital and the
Faculty of Medicine, University of Ottawa

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For more information please contact Dr. Susan Kahn at 514-340-7587; susan.kahn@mcgill.ca.

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The Microenvironment

Canadian Hematology Society
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