Editorials and Perspectives

447 Regulation of LMO2 mRNA and protein expression in erythroid differentiation
Stephen J. Brandt and Mark J. Koury

Proliferation, differentiation, and survival of erythroid progenitors are ultimately controlled through activation and repression of specific genetic programs. In this perspective article, Drs. Brandt and Koury examine the role of LIM domain-only protein 2 (LMO2) as an important transcriptional regulator in erythropoiesis. See related article on page 479.

449 Autoimmune mechanisms in the pathophysiology of myelodysplastic syndromes and their clinical relevance
A. John Barrett and Elaine Sloand

Accumulating evidence has shown that marrow failure in some patients with myelodysplastic syndrome is associated with autoimmunity, T-cell mediated myelosuppression and cytokine-induced cytopenias. In this perspective article, Drs. Barrett and Sloand expound on auto-immunity in myelodysplastic syndromes, in particular focusing on what has been learned from study of patients with trisomy 8. See related article on page 496.

451 Cord blood transplantation: state of the art
Eliane Gluckman and Vanderson Rocha

Cord blood is an unlimited source of hematopoietic stem cells for allogeneic hematopoietic stem cell transplant. In this perspective article, Drs. Gluckman and Rocha examine the current status and the new challenges of cord blood transplant. See related article on page 536.

454 Therapy-related myeloid neoplasms
Richard A. Larson

Therapy-related myeloid neoplasm is the term recently proposed by the World Health Organization to cover the spectrum of malignant disorders previously described as therapy-related myelodysplastic syndrome or therapy-related acute myeloid leukemia. In this perspective article, Dr. Larson explores the important question of whether the poor prognosis of these conditions reflects t-MN per se or, rather, associated findings such as complex cytogenetics that are also seen, although less frequently, in de novo myeloid neoplasms. See related article on page 542.

459 Autoimmune hemophilia at rescue
Pier Mannuccio Mannucci and Flora Peyvandi

Acquired hemophilia is much more clinically severe than congenital hemophilia, and is more difficult to diagnose, also because cases are seen in an array of clinical settings that are not usually equipped to tackle them. In this perspective article Drs. Mannucci and Peyvandi examine the management of this condition. See related article on page 566.

Original Articles

462 Interleukin-1 regulates hematopoietic progenitor and stem cells in the midgestation mouse fetal liver
Claudia Orelio, Marian Peeters, Esther Haak, Karin van der Horn, and Elaine Dzierzak

Interleukin-1 is known to play a role in mediating the hematopoietic stem cell activity in the aorta-gonad-mesonephros region of the developing embryo. This study extends this notion, showing that IL-1 and its receptor are also involved in the physiological regulation of the proliferation and differentiation of the hematopoietic stem/progenitor cells of murine fetal liver.

470 Proteasome inhibition induces apoptosis in primary human natural killer cells and suppresses NKp46-mediated cytotoxicity
Xiangling Wang, Astrid Ottosson, Chunyan Ji, Xiaoli Feng, Magnus Nordenskjöld, Jan-Inge Henter, Bengt Fadeel, and Chengyun Zheng

Bortezomib is a synthetic small molecule inhibitor of the chymotryptic activity of the 26S proteasome. Effects of bortezomib on normal immune cells have also been previously reported. This study adds to observations on the effects of bortezomib on natural killer (NK) cells. Effects include induction of apoptosis in resting NK cells, together with suppression of NK-mediated cytotoxicity via the NKp46 pathway. The concern is raised that treatment with bortezomib could interfere with NK cell-mediated attack on tumor cells, or on infected cells.

479 MicroRNA 223-dependent expression of LMO2 regulates normal erythropoiesis
Nadia Felli, Francesca Pedini, Paolo Romani, Mauro Biffoni, Ornellia Morsilli, Germana Castelli, Simona Santoro, Simona Chicarella, Antonio Sorrentino, Cesare Peschle, and Giovanni M.arziali

Erythropoiesis is tightly controlled by transcription factors, one of which is the LIM domain-only protein LMO2, but little is still known of the involvement of microRNAs (miRs) in erythroid cell development. This article shows that miR-223 downregulates the expression of LMO2.
and thereby blocks erythroid differentiation. See related perspective article on page 447.

**Bone Marrow Failure**

Diagnosis of Fanconi anemia in a cohort of 87 patients with bone marrow failure
Fernando F. Pinto, Thierry Léblanc, Delphine Chamassiotis, Gwenaelle Le Roux, Benoit Breton, Bruno Cassinat, Jérôme Larghero, Jean-Pierre de Villartay, Dominique Stoppa-Lyonnet, André Baruchel, Gérard Socié, Éliane Glückman, and Jean Soulier

Fanconi anemia is a genetically heterogeneous disease characterized by chromosomal instability, congenital malformations and bone marrow failure. Its diagnosis currently relies on history, physical examination and positive chromosome breakage tests. This study proposes a diagnostic strategy based on a combination of molecular and functional assays on peripheral blood and fibroblasts that allows early and accurate confirmation or rejection of Fanconi anemia diagnosis in patients with bone marrow failure.

**Myelodysplastic Syndromes**

Immune mediated autologous cytotoxicity against hematopoietic precursor cells in patients with myelodysplastic syndrome
Martine E.D. Chamuleau, Therésia M. Westers, Linda van Dreunen, Judith Groenland, Gert J. Ossenkoppele, and Arjan A. van de Loosdrecht

Adaptive immune system combined with autologous killer cells in patients with myelodysplastic syndrome following treatment with antithymocyte globulin suggests that the immune system plays a role in at least some of these cases. This paper describes an activated adaptive immune system with high density single nucleotide polymorphism arrays identifies novel common genomic lesions and acquired uniparental disomy.

**Chronic Lymphocytic Leukemia**

Caspase-independent type III programmed cell death in chronic lymphocytic leukemia: the key role of the F-actin cytoskeleton
Sandrine Barbier, Laurent Chatre, Marline Bras, Patricia Sancho, Gaël Roué, Clémence Virely, Victor J. Yuste, Sylvie Baudet, Manuel Rubio, Josép E. Esquerra, Marska Sarfati, Hélène Merle-Béral, and Santos A. Susin

Stimulation of the CD47 membrane receptor activates an original mechanism of cell death in chronic lymphocytic leukemia (CLL) cells that is caspase-independent. This study provides an exhaustive characterization of the CD47 anti-tumor signaling in CLL that may help to define new targets for further therapeutic strategies.

**Stem Cell Transplantation**

Cord blood stem cells for hematopoietic stem cell transplantation in the UK: how big should the bank be?
John M. Goldman, and J. Alejandro Madrigal

The need for umbilical cord blood units as an alternative source of hematopoietic stem cells for transplantation is increasing. This study defines the optimal size of a cord blood bank for a population of various ethnic background. See related perspective article on page 451.
After successful treatment of malignant diseases, therapy-related myelodysplastic syndrome and acute myeloid leukemia have emerged as significant problems. This study shows that allogeneic stem cell transplantation can cure a significant portion of these patients. See related perspective article on page 542.

Hodgkin’s Lymphoma

Classical Hodgkin’s lymphoma in adults: Guidelines of the Italian Society of Hematology, the Italian Society of Experimental Haematology, and the Italian Group for Bone Marrow Transplantation on initial work-up, management, and follow-up

During the last decades, survival of patients treated for classical Hodgkin’s lymphoma (HL) has improved substantially, and the overall cure rate for this neoplasm is about 80-85% at present. This article provides practice guidelines for the initial workup, therapy and follow-up of classical Hodgkin’s lymphoma. Extensive recommendations are given to prospectively limit the risk of therapy-related gonadic damage and to preserve fertility.

Disorders of Hemostasis

Deletion of five residues from the coiled coil of fibrinogen (Bβ Asn167_Glu171del) associated with bleeding and hypodysfibrinogenemia

Genotype:phenotype correlation in dysfibrinogenemia remains unpredictable, and so additions to clinical data are valuable. In this report, the authors identify a novel mutation resulting in loss of 5 amino acids from the fibrinogen B’ chain and causing hypodysfibrinogenemia. The mutation is associated with bleeding in this family but caution is counselled in attributing this directly or entirely to the abnormal fibrinogen.

Thrombosis

Functional consequences of the prothrombotic SERPINC1 rs2227589 polymorphism on antithrombin levels

This study examines the functional consequences of a SNP in the antithrombin SERPINC1 gene. The results suggest a biological explanation for the relationship between the SNP and venous thrombosis.
Letters to the Editor

Thalassemia Syndrome
593 A novel εδβ0-thalassemia deletion associated with an α globin gene triplication leading to a severe transfusion dependant fetal thalassemic syndrome
Christian Rose, Julien Rossignol, Anne Lambilliotte, Sandrine Depret, Nathalie Le Metayer, Serge Pissard

Myeloproliferative Disorders
594 Successful unrelated donor stem cell transplantation for advanced myelofibrosis in an adult patient with history of orthotopic liver transplantation
Jolanta B. Perz, Ute Hegenbart, Nicolaus Kroeger, Gerd Otto, Anthony D. Ho, Peter Dreger

Malignant Lymphomas
596 CIITA or RFX coding region loss of function mutations occur rarely in diffuse large B cell lymphoma cases and cell lines with low levels of major histocompatibility complex class II expression
Lisa M. Rimsza, Wing C. Chan, Randy D. Gascoyne, Elias Campo, Elaine S. Jaffe, Louis M. Staudt, Jan Delabie, Andreas Rosenwald, Shawn P. Murphy

Errata Corrige

Continuing Medical Education

Therapy-related myelodysplastic syndrome and acute myeloid leukemia

Classic Hodgkin’s lymphoma

Diagnosis of Fanconi anemia in patients with bone marrow failure

Immune-mediated autologous cytotoxicity against hematopoietic precursor cells in myelodysplastic syndrome