Editorials and Perspectives

745 A role for the renin-angiotensin system in hematopoiesis
Tea Soon Park and Elias T. Zambidis

In this perspective article, Drs. Park and Zambidis give a comprehensive overview of the role of the renin-angiotensin system. They highlight that its broad function goes beyond the well-characterized activities in maintaining cardiovascular homeostasis. See related article on page 857.

748 Bridging the gap between the north and south of the world: the case of treatment response in childhood acute lymphoblastic leukemia
Martin Stanulla and André Schrauder

Minimal residual disease (MRD) analyses provide strong prognostic information and can be used to identify a majority of patients with childhood acute lymphoblastic leukemia at a high risk of relapse. In this perspective article, Drs. Stanulla and Schrauder comprehensively summarize the current knowledge in the field and how simplified MRD analyses can be successfully implemented also in countries with limited economic resources. See related articles on page 781 and 870.

752 Chronic lymphocytic leukemia microenvironment: shifting the balance from apoptosis to proliferation
Silvia Deaglio and Fabio Malavasi

Most information on chronic lymphocytic leukemia has been derived from circulating cells, but, proliferation occurs in tissue sites. Drs. Deaglio and Malavasi examine critical receptor/ligand interactions likely to influence growth or apoptosis in the tissue microenvironment. See related paper on page 790.

756 The regulation of proplatelet production
Amy E. Geddis

The process by which megakaryocytes break down into platelets is slowly becoming clearer. It is now clear that these processes also determine the morphology of the platelets that are formed. Dr Geddis here summarizes recent work using in vitro and in vivo models, which demonstrate how factors within the megakaryocyte and their interactions with the marrow environment give rise to normal and abnormal platelets. See related article on page 800.

759 Definition, diagnosis and treatment of immune thrombocytopenic purpura
James N. George

Novel drugs have recently been approved for the treatment of immune thrombocytopenic purpura. In this perspective article, Dr. George examines definition, diagnosis and treatment of this condition. See related article on page 850.

762 α1-antitrypsin and the maintenance of hemostatic balance
Joseph Emmerich

Although antitrypsin usually plays only minor role in hemostasis, a single point mutation can convert it into a potent inhibitor of thrombin and produce an associated bleeding tendency. In this perspective article, Dr. Emmerich compares the phenotype and laboratory findings in the three available reports of this rare phenomenon. See related article on page 881.

764 Paying for open access

Haematologica is owned by a non-profit organization, the Ferrata Storti Foundation, and serves the scientific community with strict adherence to the principles of open access publishing. A number of recent initiatives aimed at improving the journal further have had a significant impact on production costs. To continue to provide open access, the journal now needs to share these high costs of publication with authors. Therefore, authors are now required to pay page charges.

Iron Metabolism

765 Cross-talk between the mitogen activated protein kinase and bone morphogenetic protein/hemojuvelin pathways is required for the induction of hepcidin by holotransferrin in primary mouse hepatocytes
Guillemette Ramey, Jean-Christophe Deschêmin, and Sophie Vaïlont

The circulating hormone hepcidin plays a central role in iron homeostasis. The findings of this study show that transcriptional activation of hepcidin by holotransferrin occurs in primary mouse hepatocytes through both BMP/HJV and TFR2/ERK pathways.
Iron Metabolism
Activated macrophages induce hepcidin expression in HuH7 hepatoma cells
Pavle Matan, Timothy B. Chaston, Bomee Chung, Sunit Kaila Sra, Andrew T. McKie, and Paul A. Sharp

Macrophage-released cytokines are relevant in modulating hepcidin expression. The findings of this study suggest that the interleukin-1β and bone morphogenetic protein signaling pathways are central to the regulation of hepcidin expression by macrophages.

Acute Lymphoblastic Leukemia
A simplified minimal residual disease polymerase chain reaction method at early treatment points can stratify children with acute lymphoblastic leukemia into good and poor outcome groups
Carlos A. Scrideli, Juliana G. Assumpção, Mônica A. Ganazza, Marcela Araújo, Silvia R. Toledo, Maria Lúcia M. Lee, Elisabete Delbuono, Antonio S. Petrilli, Rosane P. Queiroz, Andrea Biondi, Marcos B. Viana, José A. Yunes, Silvia R. Brandalise, and Luiz G. Tone

This paper describes a simplified PCR strategy for minimal residual disease (MRD) monitoring in children with acute lymphoblastic leukemia. Since this method is cheaper and simpler than standard methods, it may be particularly suitable for countries with limited economic resources. See related perspective article on page 748.

Chronic Lymphocytic Leukemia
Gene expression profiling reveals differences in microenvironment interaction between patients with chronic lymphocytic leukemia expressing high versus low ZAP70 mRNA
Basile Stamatopoulos, Benjamin Hadre-Kains, Carole Eguether, Nathalie Meuleman, Anne Soreé, Cécile de Bruyn, Delphine Hanosset, Dominique Bron, Philippe Martiat, and Laurence Lagneaux

ZAP70 is a strong indicator of poor prognosis in chronic lymphocytic leukemia. In this study, using gene expression profiles associated with ZAP70 expression, the importance of microenvironmental interaction for tumor behavior is revealed. See related perspective article on page 752.

Platelet Disorders
Intrinsic impaired proplatelet formation and microtubule coil assembly of megakaryocytes in a mouse model of Bernard-Soulier syndrome
Catherine Strassel, Anita Eckly, Catherine Léon, Claire Petitjean, Monique Freund, Jean-Pierre Cazenave, Christian Gachet, and François Lanza

Bernard-Soulier syndrome is caused by a deficiency of the platelet surface glycoprotein Ib-IX-V complex resulting in a severe platelet function defect. However, this is compounded by a reduction in platelet numbers and the platelets in the circulation are abnormally large. As for many other platelet disorders, recent evidence and findings of this study suggest that the defective morphology has its origins in megakaryocyte function. See related perspective article on page 756.

Thrombosis
Low TAFI activity levels are associated with an increased risk of a first myocardial infarction in men

Case control studies can be useful ways of investigating mechanisms of disease but demonstrate associations rather than proving causes. Thus it should not be surprising that the results are sometimes not intuitively obvious or run counter to what is expected. In this report from a large case-control study this is exactly what has occurred. Corresponding genetic analyses are unable to resolve the problem, but the complexity of the coagulation system and its relationship with inflammation is able to provide alternative explanations.

Hemostasis
Tissue factor-expressing monocytes inhibit fibrinolysis through a TAFI-mediated mechanism, and make clots resistant to heparins
Fabrizio Semeraro, Concetta T. Ammollo, Nicola Semeraro, and Mario Colucci

It is often noted that the activation of the fibrinolytic system begins as the clot is formed, but it is also true that antifibrinolytic mechanisms are activated at the same time and both depend on the generation of thrombin. In this paper, the authors show that the increased thrombin generation driven by monocyte-associated tissue factor activates TAFI and thus make the clot more resistant to fibrinolysis.

Stem Cell Transplantation
Impact of hematopoietic chimerism at day +14 on engraftment after unrelated donor umbilical cord blood transplantation for hematologic malignancies
Federico Moscardó, Jaime Sanz, Leonor Senent, Susana Cantero, Javier de la Rubia, Pau Montesinos, Dolores Planells, Ignacio Lorenzo, José Cervera, Javier Palau, Miguel A. Sanz, and Guillermo F. Sanz

Primary graft failure remains a substantial setback of umbilical cord blood transplantation (CBT). The results of this study emphasize that the extent of donor chimerism very early post-transplant is predictive of hematopoietic engraftment following single-unit CBT in adult patients suffering from malignant hematologic disease.
Infectious Disorders

Multicluster nosocomial outbreak of parainfluenza virus type 3 infection in a pediatric Oncohematology Unit: a phylogenetic study

Antonio Piralla, Elena Percivalle, Alessandra Di Cesare-Merlone, Franco Locatelli, and Giuseppe Gerna

Human parainfluenza virus type 3 (hPIV-3) has been reported to cause nosocomial outbreaks of respiratory infection, in particular among hematopoietic stem cell transplant patients. The results of the present study indicate that a nosocomial outbreak of hPIV-3 infection occurred among patients followed in an Oncohematology Unit over a period of about 15 weeks during the fall season.

Review Article

Iron Metabolism

Matriptase-2 (TMPRSS6): a proteolytic regulator of iron homeostasis

Andrew J. Ramsay, John D. Hooper, Alicia R. Folgueras, Gloria Velasco, and Carlos López-Otín

The family of membrane anchored serine proteases is increasingly being acknowledged as having critical physiological functions, exemplified recently by the discovery of the iron regulatory role of matriptase-2. This protease, encoded by TMPRSS6, has a specific role in hepcidin inhibition and iron absorption. In this review article, the authors discuss our current knowledge on this new and exciting issue.

Decision Making and Problem Solving

Platelet Disorders

Platelet count response to H. pylori treatment in patients with immune thrombocytopenic purpura with and without H. pylori infection: a systematic review

Donald M. Arnold, Ashley Bernotas, Ishac Nazi, Roberto Stasi, Masataka Kuwana, Yang Liu, John G. Kelton, and Mark Crowther

Eradication of H. pylori improves thrombocytopenia in some patients with immune thrombocytopenic purpura by mechanisms that remain obscure. To determine the independent effect of H. pylori eradication therapy on platelet count response, the authors performed a systematic review of all studies reporting treatment responses compared to H. pylori-negative controls. The findings strengthen the causal association between H. pylori infection and immune thrombocytopenia in some patients. See related perspective article on page 759.

Hematopoiesis

Angiotensin-(1-7) stimulates hematopoietic progenitor cells in vitro and in vivo

Silvia Heringer-Walther, Klaus Eckert, Sarah-Mai Schumacher, Lutz Uharek, Anna-Kaja Wolf-Goldenberg, Florian Gemba, Iduna Pichtner, Heinz-Peter Schultheiss, Kathy Rodgers, and Thomas Walther

This study demonstrates that the angiotensin II metabolite Ang-(1-7) stimulates the proliferation of hematopoietic progenitor cells and promotes their engraftment in a xenograft model, suggesting that the renin-angiotensin system is a regulator of blood cell formation. See related perspective article on page 745.

Chronic Myeloid Leukemia

The level of BCR-ABL1 kinase activity before treatment does not identify chronic myeloid leukemia patients who fail to achieve a complete cytogenetic response on imatinib

Jamshid Soroushi Khorashad, Simon Wagner, Liat Greener, David Marin, Alistair Reid, Dragana Milejkovic, Hetal Patel, Shaun Willimott, Katy Rezvani, Gareth Gerrard, Sandra Loaiza, John Davis, John Goldman, Junia Melo, Jane Apperley, and Letizia Foroni

This study investigated the in vitro inhibition of Crkl phosphorylation by imatinib in CD34+ cells from patients with chronic myeloid leukemia, and showed that it does not correlate with the cytogenetic response, possibly indicating that BCR-ABL1-independent resistance mechanisms exist.

Myeloproliferative Neoplasms

Significant increase in the apparent incidence of essential thrombocythemia related to new WHO diagnostic criteria: a population-based study

François Girardon, Gilles Bonicelli, Céline Schaeffer, Morgane Mounier, Serge Carillo, Ingrid Lafon, Pauline Marie Carril, Inès Janoray, Emmanuelle Ferrant, and Marc Maynadie

The findings of this study confirm the relevance of the new WHO diagnostic criteria in allowing earlier diagnosis of essential thrombocythemia.

Acute Lymphoblastic Leukemia

Establishment and validation of a standard protocol for the detection of minimal residual disease in B lineage childhood acute lymphoblastic leukemia by flow cytometry in a multi-center setting

Julie Irving, Jenny Jesson, Paul Virgo, Marian Case, Lynne Minto, Lisa Eyre, Nigel Noël, Ulrika Johansson,
Marion Macey, Linda Knotts, Margaret Helliwell, Paul Davies, Liam Whitty, David Barnett, Jeremy Hancock, Nick Goulden, and Sarah Lawson on behalf of the UKALL Flow MRD group and UK MRD steering group

Flow cytometry to detect minimal residual disease is a sensitive and specific means to detect impending relapse in B lineage acute lymphoblastic leukemia (ALL). However as with all relatively sophisticated procedures assurance is needed that the methodology is widely applicable, and reproducible in different laboratories. In this paper, the UK ALL Flow MRD Group and the UK MRD steering group describe a four color flow protocol that was applicable to most patients and showed similarly high levels of concordance both between different laboratories and with MRD as detected molecularly. See related perspective article on page 748.

Malignant Lymphomas

CD4 counts and the risk of systemic non-Hodgkin’s lymphoma in individuals with HIV in the UK
Mark Bower, Martin Fischer, Teresa Hill, Iain Reeves, John Walsh, Chloe Orkin, Andrew N. Phillips, Loveleen Bansi, Richard Gilson, Philippa Easterbrook, Margaret Johnson, Brian Gazzard, Clifford Leen, Deenan Pillay, Achim Schwenk, Jane Anderson, Kholoud Porter, Mark Gompels, and Caroline A. Sabrin for the UK CHIC Steering Committee

This very large HIV-positive cohort study examines a number of variables that predispose to the development of lymphoma in the HAART era. Despite a declining incidence of lymphoma, the authors define a close relationship between latest CD4 count and lymphoma risk, and thus advocate early initiation of HAART and more frequent HIV monitoring.

Disorders of Hemostasis

α1-antitrypsin Pittsburgh in a family with bleeding tendency
Baolai Hua, Liankai Fan, Yan Liang, Yongqiang Zhao, and Edward G.D. Tuddenham

A rare but naturally occurring mutation turns α1-antitrypsin into a potent antithrombin resulting in a bleeding tendency. This extremely rare phenomenon has been described before, but this additional family provides an interesting insight into the balance of coagulation.

Letters to the Editor

Disorders of Iron Metabolism

Regulation of serum hepcidin levels in sickle cell disease
Joyce J.C. Kroot, Coby M.M. Laarakkers, Erwin H.J.M. Kemna, Bart J. Biemond, and Dörre W. Swinkels

Chronic Lymphocytic Leukemia

Predictive value of β2-microglobulin levels in Binet A stage chronic lymphocytic leukemia
Massimo Gentile, Giovanna Cutrona, Antonino Neri, Stefano Molica, Manlio Ferrari, and Fortunato Morabito

Blood Doping

Detection of continuous erythropoietin receptor activator in blood and urine in anti-doping controls
Françoise Lasne, Laurent Martin, Jean Antoine Martin, and Jacques de Ceuriraz

Continuing Medical Education

H. pylori eradication therapy in patients with immune thrombocytopenic purpura

Gene expression profiling based on ZAP70 expression in patients with chronic lymphocytic leukemia

Relevance of hematopoietic chimerism at day +14 after umbilical cord blood transplantation

Matriptase-2 (TMPRSS6): in the regulation of iron homeostasis