

## Cover Figure

*Hematopoietic stem cell movement upon mobilization (A) and transplantation (B). This illustration is taken from the perspective article by Forsberg and Smith-Berdan on page 1477.*

## Editorials and Perspectives

- 1477 **Parsing the niche code: the molecular mechanisms governing hematopoietic stem cell adhesion and differentiation**  
E. Camilla Forsberg and Stephanie Smith-Berdan

*Hematopoietic stem cells are believed to reside in a limited number of specialized niches within the bone marrow. In this perspective article, Drs. Forsberg and Smith-Berdan review the prominent role that cell surface receptors play in integrating extrinsic and intrinsic cues to support effective hematopoiesis. See related article on page 1493.*

- 1481 **Hypercoagulability and thrombotic complications in hemolytic anemias**  
Kenneth I. Ataga

*Despite longstanding evidence for increased activation of coagulation in hemolytic anemias, its pathophysiology and its role in the vaso-occlusive crises of sickle disease remain unclear. Here Dr. Ataga reviews the latest evidence on this topic, emphasizing the likely multifactorial origin of the activation and the increasing evidence for the importance of cellular elements or their derived microparticles. See related articles on pages 1513 and 1520*

- 1484 **Blood cell activation in myeloproliferative neoplasms**  
Francisco Cervantes, Eduardo Arellano-Rodrigo, and Alberto Alvarez-Larrán

*Myeloproliferative neoplasms are characterized by overproduction of mature blood cells and increased risk of thromboembolic complications. However, the molecular lesions associated with these disorders also activate circulating blood cells. In this perspective article, Dr. Cervantes and his colleagues examine the role of blood cell activation in the pathophysiology of thrombosis in myeloproliferative neoplasms. See related article on page 1537.*

- 1488 **Mantle cell lymphoma**  
Stefano A. Pileri and Brunangelo Falini

*This perspective article by Drs. Pileri and Falini examines the diagnosis and bio-pathology of mantle cell lymphoma in the light of the criteria of the WHO Classification and recent reports. See related articles on pages 1555, 1563 and 1595.*

## Original Articles

- 1493 **Hematopoietic Stem Cells**  
**The integrin  $\alpha 9 \beta 1$  on hematopoietic stem and progenitor cells: involvement in cell adhesion, proliferation and differentiation**  
Thomas D. Schreiber, Carolin Steidl, Mike Essl, Harald Abele, Konstanze Geiger, Claudia A. Müller, Wilhelm K. Aicher, and Gerd Klein

*Integrins have been shown to play a major role in the interaction of hematopoietic stem cells with their supportive microenvironment. In this article, the authors show that integrin  $\alpha 9 \beta 1$ , in addition to the previously implicated integrin  $\alpha 4 \beta 1$ , contributes to the interaction of human CD34<sup>+</sup> cells with primary osteoblasts, and that selective inhibition of its function by inhibitory antibodies affects the proliferation and differentiation of CD34<sup>+</sup> cells. See related perspective article on page 1477.*

- 1502 **Phagocytes**  
**Endothelial cell-derived microparticles induce plasmacytoid dendritic cell maturation: potential implications in inflammatory diseases**  
Fanny Angelot, Estelle Seillès, Sabeha Büchlé, Yael Berda, Béatrice Gaugler, Joel Plumas, Laurence Chaperot, Françoise Dignat-George, Pierre Tiberghien, Philippe Saas, and Francine Garnache-Ottou

*Microparticles derived from vascular endothelium are thought to play a role in common inflammatory disorders. In this study, the authors show that microparticles derived from vascular endothelium specifically induce the maturation of plasmacytoid dendritic cells and production of inflammatory cytokines, suggesting that endothelial microparticles may serve as therapeutic targets for immune modulation.*

- 1513 **Sickle Cell disease**  
**Circulating erythrocyte-derived microparticles are associated with coagulation activation in sickle cell disease**  
Eduard J. van Beers, Marianne C.L. Schaap, René J. Berckmans, Rienk Nieuwland, Auguste Sturk, Frederiek E. van Doormaal, Joost C.M. Meijers, Bart J. Biemond, on behalf of the CURAMA study group

*It has long been known that patients with sickle cell disease have ongoing activation of their coagulation system, which is exacerbated during painful occlusive crises. In this paper, the authors explore the role of the increased numbers of erythrocyte derived microparticles in this phenomenon and suggest that a surprisingly large proportion of this is dependent on Factor XI. See related perspective article on page 1481.*

**1520** **Thalassemia Syndromes**  
**Hypercoagulability in splenectomized thalassemic patients detected by whole-blood thromboelastometry, but not by thrombin generation in platelet-poor plasma**

Armando Tripodi, Maria Domenica Cappellini, Veena Chantarangkul, Lidia Padovan, Maria Rosaria Fasulo, Alessia Marcon, and Pier Mannuccio Mannucci

*The increased incidence of thrombosis in patients with thalassemia is likely to be driven primarily by the abnormal erythrocytes, an impression supported by the higher incidence following splenectomy. The importance of the cellular components of blood is strikingly supported by this study in which a prothrombotic state can be detected by whole blood thromboelastometry but not by thrombin generation in platelet poor plasma. See related perspective article on page 1481.*

**1528** **Chronic Myeloid Leukemia**  
**ABC transporter A3 facilitates lysosomal sequestration of imatinib and modulates susceptibility in chronic myeloid leukemia cell lines**

Bjoern Chapuy, Melanie Panse, Ulf Radunski, Raphael Koch, Dirk Wenzel, Nobuya Inagaki, Detlef Haase, Lorenz Truemper, and Gerald G. Wulf

*Resistance to imatinib is a well-known clinical phenomenon. The intracellular protein ABC transporter A3 detoxifies agents by sequestering them in lysosomes. Here the authors examine A3 mediated lysosomal sequestration in chronic myeloid leukemia cell lines.*

**1537** **Myeloproliferative Neoplasms**  
**The JAK2V617F mutation induces constitutive activation and agonist hypersensitivity in basophils from patients with polycythemia vera**

Lisa Pieri, Costanza Bogani, Paola Guglielmelli, Maria Zingariello, Rosa Alba Rana, Niccolò Bartalucci, Alberto Bosi, and Alessandro M. Vannucchi

*The JAK2 (V617F) mutation is found in almost all patients with polycythemia vera and an important fraction of patients with essential thrombocythemia and primary myelofibrosis. This study shows that basophil counts are increased in JAK2 (V617F)-positive patients, and that the basophils contain an increased number of granules. See related article on page 1484.*

**1546** **Acute Myeloid Leukemia**  
**Genome wide molecular analysis of minimally differentiated acute myeloid leukemia**

Fernando P.G. Silva, Inês Almeida, Bruno Morolli, Geeske Brouwer-Mandema, Hans Wessels, Rolf Vossen, Harry Vrieling, Erik W.A. Marijt, Peter J.M. Valk, Hanneke C. Kluin-Nelemans, Wolfgang R. Sperr, Wolf-Dieter Ludwig, and Micheline Giphart-Gassler

*This study used single nucleotide polymorphism (SNP)-array technology to study copy number changes and to determine regions of loss of heterozygosity in minimally dif-*

*ferentiated acute myeloid leukemia. Several chromosomal regions were found to be deleted or duplicated, and mutations in RUNX1, ETV6, FLT3, RAS gene were the most frequent mutations detected.*

**1555** **Malignant Lymphomas**  
**SOX11 expression is highly specific for mantle cell lymphoma and identifies the cyclin D1-negative subtype**

Ana Mozos, Cristina Royo, Elena Hartmann, Daphne De Jong, Cristina Baró, Alexandra Valera, Kai Fu, Dennis D. Weisenburger, Jan Delabie, Shih-Sung Chuang, Elaine S. Jaffe, Carmen Ruiz-Marcellan, Sandeep Dave, Lisa Rimsza, Rita Brazier, Randy D. Gascoyne, Francisco Solé, Armando López-Guillermo, Dolores Colomer, Louis M. Staudt, Andreas Rosenwald, German Ott, Pedro Jares, and Elias Campo

*Cyclin D1-negative mantle cell lymphoma is difficult to distinguish from other small B-cell lymphomas. This study shows that SOX11 mRNA and nuclear protein expression is a highly specific marker for both cyclin D1-positive and negative mantle cell lymphoma. See related perspective article on page 1488.*

**1563** **Malignant Lymphomas**  
**Strong lymphoid nuclear expression of SOX11 transcription factor defines lymphoblastic neoplasms, mantle cell lymphoma and Burkitt's lymphoma**

Michael Dictor, Sara Ek, Maria Sundberg, Janina Warenholt, Czabafy György, Sandra Sernbo, Elin Gustavsson, Waleed Abu-Alsoud, Torkel Wadström, and Carl Borrebaeck

*The authors surveyed lymphomas to determine the range of expression of the mantle cell lymphoma-associated SOX11 transcription factor and its relation to cyclin D1. In addition to mantle cell lymphoma, SOX11 was strongly expressed only in lymphoblastic malignancies and Burkitt's lymphomas, and its expression was independent of cyclin D1. See related perspective article on page 1488.*

**1569** **Malignant Lymphomas**  
**Loss of HLA-DR expression and immunoblastic morphology predict adverse outcome in diffuse large B-cell lymphoma – analyses of cases from two prospectively randomized clinical trials**

Heinz-Wolfram Bernd, Marita Ziepert, Christoph Thorns, Wolfram Klapper Hans-Heinrich Wacker, Michael Hummel, Harald Stein, Martin-Leo Hansmann, German Ott, Andreas Rosenwald, Hans-Konrad Müller-Hermelink, Thomas F.E. Barth, Peter Möller, Sergio B. Cogliatti, Michael Pfreundschuh, Norbert Schmitz, Lorenz Trümper, Silvia Höller, Markus Löffler, and Alfred C. Feller for the German High Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL)

*The evaluation of biomarkers as prognostic factors in lymphomas requires studies in the context of well designed*

clinical trials. In this study, the authors show the predictive value of immunoblastic morphology and loss of HLA-DR but not the cell of origin immunohistochemical classification in diffuse large B-cell lymphoma treated in large clinical trials.

## Review Article

- 1581 **Lymphoproliferative disorders**  
**Genetic and immune-related factors**  
**in the pathogenesis of lymphoproliferative**  
**and plasma cell malignancies**  
Sigurdur Y. Kristinsson, Lynn R. Goldin,  
Magnus Björkholm, Jill Koshiol, Ingemar Turesson,  
and Ola Landgren

There are data to support a role for genetic and immune-related factors in the pathogenesis of lymphomas and plasma cell diseases. In this paper, the AUTHORS review relevant studies in Hodgkin's and non-Hodgkin's lymphomas, multiple myeloma, and the precursor condition monoclonal gammopathy of undetermined significance. Taken together, these novel insights raise complex medical considerations and imply ethical dilemmas.

## Brief Reports

- 1590 **Acute Myeloid Leukemia**  
**Human acute myeloid leukemia CD34<sup>+</sup>CD38<sup>-</sup>**  
**stem cells are susceptible to allorecognition**  
**and lysis by single KIR-expressing**  
**natural killer cells**  
Ulrich Langenkamp, Uwe Siegler, Simon Jörger,  
Stefan Diermayr, Alois Gratwohl,  
Christian P. Kalberer,  
and Aleksandra Wodnar-Filipowicz

In this study, the authors have investigated the anti-leukemic action of alloreactive single KIR positive natural killer cells on CD34<sup>+</sup>CD38<sup>-</sup> AML cells, showing that the HDAC inhibitor valproic acid augments this activity.

- 1595 **Malignant Lymphomas**  
**Differential diagnosis of cyclin D2<sup>+</sup> mantle cell**  
**lymphoma based on fluorescence *in situ***  
**hybridization and quantitative real-time-PCR**  
Leticia Quintanilla-Martinez, Julia Slotta-Huspenina,  
Ina Koch, Margit Klier, Eric D. Hsi, Laurence de Leval,  
Wolfram Klapper, Stefan Gesk, Reiner Siebert,  
and Falko Fend

The recognition of cyclin D1-negative mantle cell lymphoma is challenging. In this study the authors show that the quantification of cyclin D2 mRNA levels but not its immunohistochemical detection may be a useful tool to distinguish cyclin D1-negative mantle cell lymphoma with cyclin D2 translocations from other small B-cell lymphomas. See related perspective article on page 1488.

- 1599 **Multiple Myeloma**  
**Multiparameter flow cytometry quantification**  
**of bone marrow plasma cells at diagnosis**  
**provides more prognostic information**  
**than morphological assessment**  
**in myeloma patients**  
Bruno Paiva, Maria-Belén Vidrales, Jose J. Pérez,  
Gema Mateo, Maria Angeles Montalbán,  
Maria Victoria Mateos, Joan Bladé,  
Juan José Lahuerta, Alberto Orfao,  
and Jesús F. San Miguel

Quantification of bone marrow plasma cells in multiple myeloma patients using conventional morphology is of limited prognostic value. This study shows that multiparameter flow cytometry quantification of bone marrow plasma cells at diagnosis provides instead prognostic information.

- 1603 **Platelet Disorders**  
**High dose dexamethasone regulates**  
**interleukin-18 and interleukin-18 binding**  
**protein in idiopathic thrombocytopenic**  
**purpura**  
Ning-ning Shan, Xiao-juan Zhu, Qian Wang,  
Chun-yan Wang, Ping Qin, Jun Peng, and Ming Hou

Idiopathic thrombocytopenic purpura is no longer seen as a simple antibody mediated disorder and the role of T cells and T-regulatory cytokines such as IFN- $\gamma$  and IL-18 are now known to play an important role. This information should help better understanding of why some treatments are effective and in this study a down regulation of IL18 is reported in response to high dose dexamethasone.

- 1608 **Thrombosis**  
**Use of high intensity adjusted-dose low**  
**molecular weight heparin in women with**  
**mechanical heart valves during pregnancy:**  
**a single-center experience**  
John Quinn, Kate Von Klemperer, Ruth Brooks,  
Donald Peebles, Fiona Walker, and Hannah Cohen

This report describes the successful use of dose-escalating low molecular weight heparin thrombo-prophylaxis in pregnant women with prosthetic heart valves.

- 1613 **Stem Cell Transplantation**  
**Monitoring of donor chimerism in sorted**  
**CD34<sup>+</sup> peripheral blood cells allows**  
**the sensitive detection of imminent relapse**  
**after allogeneic stem cell transplantation**  
Martin Bornhäuser, Uta Oelschlaegel,  
Uwe Platzbecker, Gesine Bug, Karin Lutterbeck,  
Michael G. Kiehl, Johannes Schetelig,  
Alexander Kiani, Thomas Illmer, Markus Schaich,  
Catrin Theuser, Brigitte Mohr, Cornelia Brendel,  
Axel A. Fauser, Stefan Klein, Hans Martin,  
Gerhard Ehninger, and Christian Thiede

Detection of impending relapse following allogeneic stem cell transplantation in cases of acute leukemia or myelodysplastic syndrome is desirable for planning treatment intervention. Genetic changes harbored by tumor cells

are ideal for monitoring, but are not always available. Interestingly, analysis of serial donor chimerism in CD34<sup>+</sup> cells sorted from blood may provide an alternative.

1618 **Infectious Disorders**  
**Reactivation of DNA viruses in association with histone deacetylase inhibitor therapy: a case series report**

David Ritchie, Richard L. Piekartz, Piers Blombery, Laszlo J. Karai, Stefania Pittaluga, Elaine S. Jaffe, Mark Raffeld, John E. Janik, H. Miles Prince, and Susan E. Bates

Histone deacetylase inhibitors are a class of anti-cancer agents that induce growth arrest, differentiation, and apoptotic cell death of transformed cells. The authors report three instances of DNA viral reactivation in patients treated with romidepsin on a multicenter phase II trial in patients with cutaneous T-cell lymphoma and peripheral T-cell lymphomas. These observations suggest that vigilance for DNA virus reactivation is needed to quantify the risk in patients treated with histone deacetylase inhibitors.

## Letters to the Editor

1623 **Phagocytes**  
**Morphological evaluation of monocytes and monocyte precursors in bone marrow trephine biopsies - need for establishing diagnostic criteria**  
Kikkeri N. Naresh

1624 **Red Cell Disorders**  
**Chronic hemolytic anemia due to novel  $\alpha$ -globin chain variants: critical location of the mutation within the gene sequence for a dominant effect**  
Claude Préhu, Kamran Moradkhani, Jean Riou, Michel Bahuau, Pierre Launay, Natacha Martin, Henri Wajcman, Michel Goossens, and Frédéric Galactéros

1625 **Red Cell Disorders**  
**Safety of cardiovascular magnetic resonance gadolinium chelates contrast agents in patients with hemoglobinopathies**

Antonella Meloni, Brunella Favilli, Vincenzo Positano, Paolo Cianciulli, Aldo Filosa, Antonella Quarta, Domenico D'Ascola, Gennaro Restaino, Massimo Lombardi, and Alessia Pepe

1627 **Platelet Disorders**  
**Platelet morphological changes in 2 patients with von Willebrand disease type 3 caused by large homozygous deletions of the von Willebrand factor gene**  
Paquita Nurden, Alan T. Nurden, Silvia La Marca, Margherita Punzo, Luciano Baronciani, and Augusto B. Federici

## Errata

1630 **The incidence of hemorrhagic cystitis and BK-viruria in allogeneic hematopoietic stem cell recipients according to intensity of the conditioning regimen.**  
*Haematologica* 2006;91:401-4.  
Giraud G, Bogdanovic G, Priftakis P, Remberger M, Svahn BM, Barkholt L, Ringden O, Winiarski J, Ljungman P, Dalianis T

## Continuing Medical Education

Plasmacytoid dendritic cell activation by endothelial microparticles

SOX11 expression in mantle cell lymphoma

Familial clustering of lymphoproliferative and plasma cell malignancies

Molecular aberrations in minimally differentiated acute myeloid leukemia