

Cover Figure

Trephine bone marrow biopsy from a patient with hereditary thrombocythemia associated with a de novo splice donor mutation in the thrombopoietin gene. This illustration is taken from the article by Liu and coworkers on page 706.

Editorials and Perspectives

- 641 **Secondary genomic alterations in non-Hodgkin's lymphomas: tumor-specific profiles with impact on clinical behavior**
Silvia Beà and Elías Campo

Lymphoid neoplasms are associated with primary genetic alterations – mainly non-random reciprocal chromosomal translocations – and secondary alterations. In this perspective article, Drs. Beà and Campo discuss the importance of secondary chromosomal alterations in non-Hodgkin's lymphomas. See related articles on pages 670, 680, and 688.

- 646 **Molecular basis of thrombocytosis**
Mario Cazzola

Thrombocytosis can be classified into three major categories: hereditary or familial thrombocytosis, thrombocytosis associated with myeloproliferative and/or myelodysplastic disorders (clonal thrombocytosis), and reactive (secondary) thrombocytosis. In this perspective article, Dr. Cazzola examines the molecular basis of familial thrombocytosis. See related article on page 706.

- 649 **Interactions between genotype and phenotype in bleeding and thrombosis**
Massimo Franchini and Pier Mannuccio Mannucci

The clinical phenotypic variability of disorders of blood coagulation is often the result of gene-gene, or gene-environment interactions. Drs. Franchini and Mannucci discuss this only partially understood subject. See related article on page 729.

Original Articles

- 653 **Chronic Myeloid Leukemia**
Characterization of compound 584, an Abl kinase inhibitor with lasting effects
Miriam Puttini, Sara Redaelli, Loris Moretti, Stefania Brussole, Rosalind H. Gunby, Luca Mologni, Edoardo Marchesi, Loredana Cleris, Arianna Donella-Deana, Peter Drueckes, Elisa Sala, Vittorio Lucchini, Michael Kubbutat, Franca Formelli, Alfonso Zambon, Leonardo Scapozza, and Carlo Gambacorti-Passerini

Secondary resistance to imatinib is observed in patients with chronic myeloid leukemia. This study describes a novel Abl kinase inhibitor with long-lasting effects.

- 662 **Acute Myeloid Leukemia**
Effects of the aurora kinase inhibitors AZD1152-HQPA and ZM447439 on growth arrest and polyploidy in acute myeloid leukemia cell lines and primary blasts
Elisabeth Walsby, Val Walsh, Chris Pepper, Alan Burnett, and Ken Mills

Aurora kinase inhibitors are being considered for treatment of acute myeloid leukemia. Findings of this study suggest that two such inhibitors are effective apoptosis-inducing agents in primary myeloid leukemia cells.

- 670 **Malignant Lymphomas**
Comparative genome profiling across subtypes of low-grade B-cell lymphoma identifies type-specific and common aberrations that target genes with a role in B-cell neoplasia
Bibiana I. Ferreira, Juan F. García, Javier Suela, Manuela Mollejo, Francisca I. Camacho, Angel Carro, Santiago Montes, Miguel A. Piris, and Juan C. Cigudosa

Low-grade B-cell lymphomas are very heterogeneous. This study of comparative genome profiling identifies type-specific aberrations that target genes with a role in B-cell lymphoid neoplasms. See related perspective article on page 641.

- 680 **Malignant Lymphomas**
Genomic aberrations in mantle cell lymphoma detected by interphase fluorescence *in situ* hybridization. Incidence and clinicopathological correlations
Sandrine Sander, Lars Bullinger, Elke Leupolt, Axel Benner, Dirk Kienle, Tiemo Katzenberger, Jörg Kalla, German Ott, Hans Konrad Müller-Hermelink, Thomas F.E. Barth, Peter Möller, Peter Lichter, Hartmut Döhner, and Stephan Stilgenbauer

The primary genetic alteration of mantle cell lymphoma is a t(11;14)(q13;q32). Findings of this study provide novel insights into the pathogenesis of this lymphoid neoplasm, and in particular indicate that loss of chromosome 13q14 has additional prognostic relevance. See related perspective article on page 641.

- 688 **Malignant Lymphomas**
Gain of chromosome region 18q21 including the *MALT1* gene is associated with the activated B-cell-like gene expression subtype and increased *BCL2* gene dosage and protein expression in diffuse large B-cell lymphoma
Judith Dierlamm, Eva M. Murga Penas, Stefan Bentink, Swen Wessendorf, Hilmar Berger, Michael Hummel, Wolfram Klapper, Dido Lenze, Andreas Rosenwald, Eugenia Haralambieva, German Ott, Sergio B. Cogliatti, Peter Möller, Carsten Schwaenen, Harald Stein, Markus Löffler, Rainer Spang, Lorenz Trümper, and Reiner Siebert for the Deutsche Krebshilfe Network Project "Molecular Mechanisms in Malignant Lymphomas"

Diffuse large B-cell lymphoma is the most common lymphoma worldwide. Recent studies of gene expression profiling have identified subgroups of this lymphoid neoplasm

with different prognosis. This study suggests that a gain of chromosome 18q21 including the MALT1 gene may involve an unfavorable prognosis. See related perspective article on page 641.

- 697 **Lymphoproliferative Disorders**
Selective influences in the expressed immunoglobulin heavy and light chain gene repertoire in hairy cell leukemia

Francesco Forconi, Elisa Sozzi, Davide Rossi, Surinder S. Sahota, Teresa Amato, Donatella Raspadori, Livio Trentin, Lorenzo Leoncini, Gianluca Gaidano, and Francesco Lauria

Hairy cell leukemia is a rare, chronic B-cell neoplasm characterized by leukemic hairy cells. This immunogenetic analysis of the expressed immunoglobulin heavy and light chain gene repertoire suggests that immunoglobulin gene selection may play an important role in the pathogenesis of this neoplasm.

- 706 **Thrombocytosis**
A de novo splice donor mutation in the thrombopoietin gene causes hereditary thrombocythemia in a Polish family

Kun Liu, Robert Kralovics, Zbigniew Rudzki, Barbara Grabowska, Andreas S. Buser, Damla Olcaydu, Heinz Gisslinger, Ralph Tiedt, Patricia Frank, Krzysztof Okoń, Anthonie P.C. van der Maas, and Radek C. Skoda

Familial thrombocytosis may be associated with gain-of-function mutations in the thrombopoietin (THPO) gene, or an activating germline mutation of MPL, the gene encoding thrombopoietin receptor. This study of a large family with thrombocytosis associated with a germline THPO mutations illustrates the hematologic and clinical features of this rare condition. See related article on page 646.

- 715 **Disorders of Hemostasis**
Simultaneous genotyping of coagulation factor XI type II and type III mutations by multiplex real-time polymerase chain reaction to determine their prevalence in healthy and factor XI-deficient Italians

Giorgia Zadra, Rosanna Asselta, Maria Luisa Tenchini, Giancarlo Castaman, Uri Seligsohn, Pier Mannuccio Mannucci, and Stefano Duga

Factor XI deficiency is a rare autosomal recessive coagulopathy worldwide, although relatively common in Ashkenazi Jews. This study describes the presence of the F11 gene mutations in the Italian population and confirms their Jewish origin.

- 722 **Disorders of Hemostasis**
The Italian AICE-Genetics hemophilia A database: results and correlation with clinical phenotype

Maurizio Margaghione, Giancarlo Castaman, Massimo Morfini, Angiola Rocino, Elena Santagostino, Giuseppe Tagariello, Anna R. Tagliaferri, Ezio Zanon, Maria P. Biccocchi, Giuseppe Castaldo, Flora Peyvand, Rosa Santacroce, Francesca Torricelli, Elvira Grandone, Pier Mannuccio Mannucci, and the AICE-Genetics Study Group

This study reports a wide spectrum of factor 8 mutations in the large Italian database. Findings of the study indicate that the type of mutations is a strong predictor of the clinical phenotype.

- 729 **Thrombosis**
ABO blood group and risk of venous or arterial thrombosis in carriers of factor V Leiden or prothrombin G20210A polymorphisms

Antonia Miñano, Adriana Ordóñez, Francisco España, José R. González-Porras, Ramón Lecumberri, Jordi Fontcuberta, Pilar Llamas, Francisco Marín, Amparo Estellés, Ignacio Alberca, Vicente Vicente, and Javier Corral

Several studies have shown an effect of ABO blood group on hemostasis. Findings of this study indicate that non-O group increases the risk and severity of venous thrombosis in carriers of prothrombotic polymorphisms. See related perspective article on page 649.

- 735 **Stem Cell Transplantation**
Follow-up of healthy donors receiving granulocyte colony-stimulating factor for peripheral blood progenitor cell mobilization and collection. Results of the Spanish Donor Registry

Javier de la Rubia, Felipe de Arriba, Cristina Arbona, María J. Pascual, Concha Zamora, Andrés Insunza, Dorleta Martínez, Carmen Paniagua, Miguel A. Díaz, and Miguel A. Sanz

Information about the long-term follow-up and safety of granulocyte colony-stimulating factor administration to healthy donors is limited. Findings of this study indicate that clinical side effects are generally mild, and that development of secondary hematologic malignancy is unlikely.

Decision Making and Problem Solving

- 741 **Iron Overload**
Italian Society of Hematology practice guidelines for the management of iron overload in thalassemia major and related disorders

Emanuele Angelucci, Giovanni Barosi, Clara Camaschella, Maria Domenica Cappellini, Mario Cazzola, Renzo Galanello, Monia Marchetti, Antonio Piga, and Sante Tura

Three iron chelators are currently available for treatment of transfusion iron overload: deferoxamine, deferiprone, and deferasirox. This article reports the Italian Society of Hematology practice guidelines for the management of iron overload in thalassemia major and related disorders.

Brief Reports

- 753 **Iron Metabolism**
Deficiency of heme-regulated eIF2 α kinase decreases hepcidin expression and splenic iron in HFE^{-/-} mice
Sijin Liu, Rajasekhar N.V.S. Suragani, Anping Han, Wanting Zhao, Nancy C. Andrews, and Jane-Jane Chen

Heme-regulated eIF2 α balances heme and globin production by controlling globin synthesis. Its deficiency affects the phenotype of HFE^{-/-} mice by further decreasing hepcidin expression.

- 757 **Sickle Cell Disease**
Sickle cell disease-related organ damage occurs irrespective of pain rate. Implications for clinical practice
Eduard J. van Beers, Charlotte F.J. van Tuijn, Melvin R. Mac Gillavry, Anna van der Giessen, John-John B. Schmog, and Bart J. Biemond, on behalf of the CURAMA study group

This study shows that clinically relevant forms of organ damage occur irrespective of the frequency of painful crises in adults with sickle cell disease.

- 761 **Anemia of Renal Failure**
Anemia management in patients on peritoneal dialysis: efficacy and safety of epoetin δ
Bruce S. Spinowitz

In this clinical trial, subcutaneously administered epoetin δ was effective and well tolerated for treatment of anemia in patients on peritoneal dialysis.

- 765 **Chronic Myeloid Leukemia**
Phospho-CRKL monitoring for the assessment of BCR-ABL activity in imatinib resistant chronic myeloid leukemia or Ph⁺ acute lymphoblastic leukemia patients treated with nilotinib

Paul La Rosée, Susanne Holm-Eriksen, Heiko König, Nicolai Härtel, Thomas Ernst, Julia Debatin, Martin C. Mueller, Philipp Erben, Anja Binckebanck, Lydia Wunderle, Yaping Shou, Margaret Dugan, Ruediger Hehlmann, Oliver G. Ottmann, and Andreas Hochhaus

Findings of this study suggest that monitoring the actual BCR-ABL inhibition in nilotinib treated patients may be useful for establishing effective dosing and for detecting resistance against the drug.

- 770 **Chronic Myeloid Leukemia**
Front-line treatment of Philadelphia positive chronic myeloid leukemia with imatinib and interferon- α : 5-year outcome
Francesca Palandri, Ilaria Iacobucci, Fausto Castagnetti, Nicoletta Testoni, Angela Poerio, Marilina Amabile, Massimo Breccia, Tamara Intermesoli, Francesco Iuliano, Giovanna Rege-Cambrin,

Mario Tiribelli, Maurizio Miglino, Fabrizio Pane, Giuseppe Saglio, Giovanni Martinelli, Gianantonio Rosti, and Michele Baccarani, on behalf of the GIMEMA Working Party on CML

This study confirms the excellent response to imatinib front-line therapy in patients with chronic myeloid leukemia. By contrast, most patients discontinued pegylated interferon- α due to its side effects.

- 775 **Acute Myeloid Leukemia**
Cytoplasmic mutated nucleophosmin is stable in primary leukemic cells and in a xenotransplant model of NPMc⁺ acute myeloid leukemia in SCID mice

Brunangelo Falini, Maria Paola Martelli, Cristina Mecucci, Arcangelo Liso, Niccolò Bolli, Barbara Bigerna, Alessandra Pucciarini, Stefano Pileri, Giovanna Meloni, Massimo F. Martelli, Torsten Haferlach, and Susanne Schnittger

Findings of this study indicate that NPM1 mutations are stable in patients with acute myeloid leukemia, providing a rationale for monitoring of minimal residual disease.

- 780 **Malignant Lymphomas**
Clinical and demographic characteristics of Epstein-Barr virus-associated childhood Burkitt's lymphoma in Southeastern Brazil: epidemiological insights from an intermediate risk region

Rocio Hassan, Claudete Esteves Klumb, Fabricio E. Felisbino, Deisy M. Guiretti, Lidia R. White, Claudio Gustavo Stefanoff, Mario Henrique M. Barros, Héctor N. Seuánez, and Ilana R. Zalberg

This report describes clinical and demographic characteristics of Epstein-Barr virus-associated childhood Burkitt's lymphoma in Southeastern Brazil.

Letters to the Editor

- 784 **Thalassemia Syndrome**
A cross-sectional magnetic resonance imaging assessment of organ specific hemosiderosis in 180 thalassemia major patients in Hong Kong
Wing-Yan Au, Wynnie Wai-man Lam, Winnie W.C. Chu, Hui-Leung Yuen, Alvin Siu-Cheung Ling, Rever Chak-Ho Li, Helen Man-Hong Chan, Harold Kwok-Kuen Lee, Man-Fai Law, Herman Sung-Yu Liu, Raymond Liang, and Shau-Yin Ha

- 787 **Myeloproliferative Disorders**
The Janus kinase 2 (JAK2) V617F mutation in Chinese patients with chronic myeloproliferative disorders
Zhijian Xiao, Yue Zhang, Lin Li, Ling Nie, Lin Yang, and Shicai Xu

- Malignant Lymphomas**
789 A prospective study of the separate predictive capabilities of ¹⁸[F]-FDG-PET and molecular response in patients with relapsed indolent non-Hodgkin's lymphoma following treatment with iodine-131-rituximab radio-immunotherapy
Mark J. Bishton, Rodney J. Hicks, David A. Westerman, Miles H. Prince, Max Wolf, and John F. Seymour
- Multiple Myeloma**
791 Confirmation of the utility of the International Staging System and identification of a unique pattern of disease in Brazilian patients with multiple myeloma
Vania T.M. Hungria, Angelo Maiolino, Gracia Martinez, Gisele W.B. Colleoni, Érika O.D.M. Coelho, Laís Rocha, Renata Nunes, Rosane Bittencourt, Luciana C.O. Oliveira, Rosa Malena O. Faria, Ricardo Pasquini, Sílvia M.M. Magalhães, Cármino A. Souza, Jorge V. Pinto Neto, Luciana Barreto, Elizabeth Andrade, Maria do Socorro O. Portella, Vanessa Bolejack, and Brian G.M. Durie, on behalf of the International Myeloma Working Group Latin America
- Monoclonal Gammopathies**
793 Serum-free light chain elevation is associated with a shorter time to treatment in Waldenstrom's macroglobulinemia
Raphael Itzykson, Magali Le Garff-Tavernier, Sandrine Katsahian, Marie-Claude Diemert, Lucile Musset, and Veronique Leblond
- Platelet Disorders**
795 No evidence for B-cell clonality by spectratyping analysis in patients with idiopathic thrombocytopenic purpura undergoing rituximab therapy
Eleonora Toffoletti, Francesco Zaja, Alessia Chiarvesio, Angela Michelutti, Marta Battista, and Renato Fanin
- Platelet Disorders**
797 A simple, novel and robust test to diagnose type I Glanzmann thrombasthenia
Manasi Vijapurkar, Kanjaksha Ghosh, Shrimati Shetty, Mary Ann McLane, Ana Maria Moura-da-Silva, and Diego Butera^o
- Hemostasis**
799 A natural variant with a point mutation resulting in a homozygous Arg to His substitution at position 388 in prothrombin
Clément d'Audigier, Eric Pasmant, Odile Bournier, Yves Laurian, Marie Claude Guillin, and Annie Bezeaud

Online Only Articles

- e39 Surgical treatment of a foscavir-resistant atypical Cytomegalovirus pneumonia in an allogeneic stem cell transplant recipient
C. Bressollette-Bodin, A. Claver, D. Boutolleau, P. Chevallier, T. Guillaume, T. Gastinne, P. Moreau, J-L. Harousseau, B.M. Imbert-Marcille, S. Le Guill
- e42 No association of the hypercoagulable state with sickle cell disease related pulmonary hypertension
E.J. van Beers, H.M.H. Spronk, H. ten Cate, A.J. Duits, D.P.M. Brandjes, J.W.J. van Esser, B.J. Biemond, and J.B. Schnog on behalf of the CURAMA study Group
- e45 Early-onset haemochromatosis caused by a novel combination of TFR2 mutations (p.R396X/c.1538-2 A>G) in a woman of Italian descent
V. Gérolami, G. Le Gac, L. Mercier, M. Nezri, J-L. Bergé-Lefranc, C. Férec
- e47 Reply to: Reduced intensity conditioning haematopoietic stem cell transplantation with mesenchymal stromal cells infusion for the treatment of metachromatic leukodystrophy: a case report. Haematologica 2008;93:e11-13
L. Charnas, F. Eichler, A. Kohlschuetter, J. Tolar, P.J. Orchard
- e48 Reply to: [Reply to: Reduced intensity conditioning haematopoietic stem cell transplantation with mesenchymal stromal cells infusion for the treatment of metachromatic leukodystrophy: a case report. Haematologica 2008;93:e11-13]
N. Meuleman, T. Tondreau, G. Vanhaelen, L. Lagneaux, D. Bron