

Cover Figure

Megakaryocytes with round, non-lobulated nuclei from a patient with 5q- syndrome. Courtesy of Rosangela Invernizzi.

Editorials and Perspectives

- 961 **Hereditary red cell disorders and malaria resistance**
Pierre M. Durand and Theresa L. Coetzer

In this perspective article, Drs. Durand and Coetzer review evidence strongly indicating that pyruvate kinase deficiency evolved as a protective response to malaria. See also their recent contribution in this journal [Durand PM, Coetzer TL. Pyruvate kinase deficiency protects against malaria in humans. *Haematologica* 2008; 93:939-40. Epub 2008 May 6].

- 963 **Familial erythrocytosis: molecular links to red blood cell control**
Melanie J. Percy, and Frank S. Lee

Familial or hereditary erythrocytosis is a rare disorder of red cell production that can be inherited in either an autosomal dominant or recessive fashion. In this perspective article, Drs. Percy and Lee illustrate how identification of molecular lesions as the basis of erythrocytosis has provided a compelling correlation with, and indeed, physiological validation of proteins implicated in the pathway that senses oxygen and signals to erythropoiesis. Very interestingly, they show that all of the major elements in the oxygen sensing pathway have now been accounted for in the current OMM classification of familial erythrocytoses. See related articles on pages 1068 and 1072.

- 967 **Myelodysplastic syndrome with isolated 5q deletion (5q- syndrome). A clonal stem cell disorder characterized by defective ribosome biogenesis**
Mario Cazzola

The 5q- syndrome was first described by van den Berghe and co-workers in 1974. In this perspective article, Dr. Cazzola discusses its clonal nature and examines recent findings indicating that haploinsufficiency of genes mapping to chromosome 5q31-q32 leads to aberrant ribosome biogenesis. Dr. Cazzola also discusses the current uncertainties on the use of lenalidomide for treatment of myelodysplastic syndrome with deletion 5q. See related articles on pages 994 and 1001.

- 972 **Molecular pathophysiology of Philadelphia-negative myeloproliferative disorders: beyond JAK2 and MPL mutations**
Alessandro M. Vannucchi and Paola Guglielmelli

The discovery of the JAK2 and MPL mutations has been of enormous help in the diagnosis and characterization of chronic myeloproliferative disorders, and has opened new

perspectives for targeted therapy. In this perspective article, Drs. Vannucchi and Guglielmelli review additional molecular mechanisms that may contribute to the pathogenesis of these disorders, such as aberrant expression of microRNA. See related papers on pages 1009 and 1098.

- 976 **Molecular characterization of acute myeloid leukemia**
Konstanze Döhner and Hartmut Döhner

Acute myeloid leukemia is a genetically heterogeneous clonal disorder characterized by the accumulation of acquired somatic genetic alterations in hematopoietic progenitor cells that alter normal mechanisms of self-renewal, proliferation and differentiation. In this perspective article, Drs. K. Döhner and H. Döhner examine the molecular basis of acute myeloid leukemia and the prognostic relevance of mutations of genes such as NPM1, FLT3 and CEBPA. See related papers on pages 1017 and 1025.

- 982 **Gene expression signatures in follicular lymphoma: are they ready for the clinic?**
Nathalie A. Johnson and Randy D. Gascoyne

In this perspective article, Drs. Johnson and Gascoyne discuss clinical translation of gene expression signatures in follicular lymphoma. Genome-wide microarray studies offer a powerful discovery tool and should be built into the design of phase III clinical trials in follicular lymphoma. See related article on page 1033.

Original Articles

- 988 **Red Cell Disorders**
Influence of sickle cell disease and treatment with hydroxyurea on sperm parameters and fertility of human males
Isabelle Berthaut, Geoffroy Guignedoux, Frederique Kirsch-Noir, Vanina de Larouziere, Celia Ravel, Dora Bachir, Frédéric Galactéros, Pierre-Yves Ancel, Jean-Marie Kunstmann, Laurence Levy, Pierre Jouannet, Robert Giro, and Jacqueline Mandelbaum

The use of hydroxyurea has considerably modified the prognosis of sickle cell disease and many more patients now reach reproductive age. This study shows alterations of semen parameters due to sickle cell disease that seem to be exacerbated by hydroxyurea treatment. The authors suggest that a pre-treatment sperm analysis be performed and sperm cryopreservation be offered to patients before hydroxyurea treatment.

- 994 **Myelodysplastic Syndromes**
Genome-wide analysis of copy number changes and loss of heterozygosity in myelodysplastic syndrome with del(5q) using high-density single nucleotide polymorphism arrays
Li Wang, Carrie Fidler, Nandita Nadig, Aristoteles Giagounidis, Matteo G. Della Porta, Luca Malcovati, Sally Killick, Norbert Gattermann, Carlo Aul, Jacqueline Boulwood and James S. Wainscoat

This study shows a clear distinction between 5q- syndrome and other cases of myelodysplastic syndrome with del(5q) with regards to both copy number changes and the presence of large uniparental disomy, consistent with the different clinical behavior of patients with these two disorders. See related perspective on page 967.

- 1001 **Myelodysplastic Syndromes**
Fluorescence *in situ* hybridization improves the detection of 5q31 deletion in myelodysplastic syndromes without cytogenetic evidence of 5q-
Mar Mallo, Leonor Arenillas, Blanca Espinet, Marta Salido, Jesús M^a Hernández, Eva Lumbreras, Mónica del Rey, Eva Arranz, Soraya Ramiro, Patricia Font, Olga González, Mónica Renedo, José Cervera, Esperanza Such, Guillermo F. Sanz, Elisa Luño, Carmen Sanzo, Miriam González, María José Calasanz, José Mayans, Carlos García-Ballesteros, Victoria Amigo, Rosa Collado, Isabel Oliver, Félix Carbonell, Encarna Bureo, Andrés Insunza, Lucrecia Yañez, María José Muruzabal, Elena Gómez-Beltrán, Rafael Andreu, Pilar León, Valle Gómez, Angeles Sanz, Natalia Casasola, Esperanza Moreno, Adrián Alegre, María Luisa Martín, Carmen Pedro, Sergi Serrano, Lourdes Florensa, and Francesc Solé

The findings of this study indicate that fluorescence *in situ* hybridization improves the detection of deletion 5q31-32 in patients with myelodysplastic syndrome without cytogenetic evidence of del(5q). See related perspective on page 967.

- 1009 **Myeloproliferative Disorders**
Aberrant expression of microRNA in polycythemia vera
Hana Bruchova, Michaela Merkerova, and Josef T. Prchal
- The findings of this study indicate that peripheral blood cells from patients with polycythemia vera have microRNA signatures distinct from those of controls, underlining the complexity of the molecular basis of myeloproliferative disorders. See related perspective on page 972.

- 1017 **Acute Myeloid Leukemia**
Prognostic impact of genetic characterization in the GIMEMA LAM99P multicenter study for newly diagnosed acute myeloid leukemia
Francesco Lo-Coco, Antonio Cuneo, Fabrizio Pane, Daniela Cilloni, Daniela Diverio, Marco Mancini, Nicoletta Testoni, Antonella Bardi, Barbara Izzo, Niccolò Bolli, Roberta La Starza, Paola Fazi, Simona Iacobelli, Alfonso Piciocchi, Marco Vignetti, Sergio Amadori, Franco Mandelli, Pier Giuseppe Pelicci, Cristina Mecucci, Brunangelo Falini, Giuseppe Saglio for the Acute Leukemia Working Party of the GIMEMA group

The findings of this study reiterate the prognostic relevance of combining cytogenetic and mutational analysis (NPM1, FLT3) in the diagnostic work up of acute myeloid leukemia. See related perspective on page 976.

- 1025 **Acute Myeloid Leukemia**
M4 acute myeloid leukemia: the role of eosinophilia and cytogenetics

in treatment response and survival.

- The GIMEMA experience**
Alessandro Pulsoni, Simona Iacobelli, Massimo Bernardi, Marco Borgia, Andrea Camera, Nicola Cantore, Francesco Di Raimondo, Paola Fazi, Felicetto Ferrara, Franco Leoni, Vincenzo Liso, Marco Mancini, Filippo Marmont, Angela Maturro, Luca Maurillo, Lorella Melillo, Giovanna Meloni, Salvo Mirto, Giorgina Specchia, Caterina Giovanna Valentini, Adriano Venditti, Giuseppe Leone, Robin Foà, Franco Mandelli, and Livio Pagano

This analysis on a large GIMEMA population of patients with M4-acute myeloid leukemia confirmed the favorable prognostic role of inv(16), demonstrated the good prognostic role of eosinophilia and revealed an enhancement of the effect when the two factors were both present. See related perspective on page 976.

- 1033 **Malignant Lymphomas**
Gene expression analysis provides a potential rationale for revising the histological grading of follicular lymphomas
Pier Paolo Piccaluga, Andrea Califano, Ulf Klein, Claudio Agostinelli, Beatriz Bellosillo, Eva Gimeno, Sergi Serrano, Francisco Solé, Yonghui Zang, Brunangelo Falini, Pier Luigi Zinzani, and Stefano A. Pileri

The findings of this study support the hypothesis that grade IIIb follicular lymphoma belongs to the group of follicular lymphomas rather than to diffuse large B-cell lymphomas. See related perspective on page 982.

- 1039 **Lymphoproliferative Disorders**
The effect of FK506 on transforming growth factor β signaling and apoptosis in chronic lymphocytic leukemia B cells
Simona Romano, Maria Mallardo, Federico Chiurazzi, Rita Bisogni, Anna D'Angelillo, Raffaele Liuzzi, Giovanna Compare, and Maria Fiammetta Romano

Loss of response to transforming growth factor- β (TGF- β) is thought to contribute to the progression of chronic lymphocytic leukemia. This study shows that chronic lymphocytic leukemia cells do indeed escape the homeostatic control of TGF- β .

- 1049 **Multiple Myeloma**
A bioluminescence imaging based *in vivo* model for preclinical testing of novel cellular immunotherapy strategies to improve the graft-versus-myeloma effect
Henk Rozenmuller, Ellen van der Spek, Lijnje H. Bogers-Boer, Mieke C. Zwart, Vivienne Verweij, Maarten Emmelot, Richard W. Groen, Robbert Spaapen, Andries C. Bloem, Henk M. Lokhorst, Tuna Mutis, and Anton C. Martens

The development and preclinical testing of novel immunotherapy strategies for multiple myeloma can benefit substantially from a humanized animal model that enables quantitative real-time monitoring of tumor progression. This study describes a non-invasive bioluminescent imaging system for real-time monitoring of multiple myeloma cell growth in mice.

- 1058 **Transfusion Medicine**
Granulocyte concentrates: prolonged functional capacity during storage in the presence of phenotypic changes
Agata Drewniak, Jaap-Jan Boelens, Hans Vrieling, Anton T.J. Tool, Marrie C.A. Bruin, Marry van den Heuvel-Eibrink, Lynne Ball, Marianne D. van de Wetering, Dirk Roos, and Taco W. Kuijpers

Granulocyte transfusions may be an effective therapy for neutropenic pediatric patients suffering from life-threatening infections. This study shows that granulocyte concentrates can be stored without loss of in vitro viability and functionality for at least 24 hours.

Brief Reports

- 1068 **Erythrocytosis**
A novel heterozygous HIF2A^{M535I} mutation reinforces the role of oxygen sensing pathway disturbances in the pathogenesis of familial erythrocytosis
Maurizio Martini, Luciana Teofili, Tonia Cenci, Fiorina Giona, Lorenza Torti, Massimiliano Rea, Robin Foà, Giuseppe Leone, and Luigi Maria Larocca

This report shows that two members of a family with idiopathic erythrocytosis carried a mutation in the hypoxia-inducible factor-2A (HIF2A) gene. See related perspective article on page 963.

- 1072 **Erythrocytosis**
A study of 36 unrelated cases with pure erythrocytosis revealed three new mutations in the erythropoietin receptor gene
Maha Al-Sheikh, Elodie Mazurier, Betty Gardie, Nicole Casadevall, Frédéric Galactéros, Michel Goossens, Henri Wajcman, Claude Préhu, and Valérie Ugo

This report describes new mutations in the erythropoietin receptor (EPOR) gene in patients with erythrocytosis of unknown origin. See related perspective article on page 963.

- 1076 **Acute Myeloid Leukemia**
Molecular characterization of the MLL-SEPT6 fusion gene in acute myeloid leukemia: identification of novel fusion transcripts and cloning of genomic breakpoint junctions
Nuno Cerveira, Francesca Micci, Joana Santos, Manuela Pinheiro, Cecília Correia, Susana Lisboa, Susana Bizarro, Lucília Norton, Anders Glomstein, Ann E. Åsberg, Sverre Heim, and Manuel R. Teixeira

This report describes a detailed RNA and DNA analysis in three new patients with acute myeloid leukemia carrying the MLL-SEPT6 rearrangement.

- 1081 **Lymphoproliferative Disorders**
Transcriptional activation of the cardiac homeobox gene CSX1/NKX2-5 in a B-cell

- chronic lymphoproliferative disorder**
Xinying Su, Véronique Della-Valle, Eric Delabesse, Zahia Azgui, Roland Berger, Hélène Merle-Béral, Olivier A Bernard, and Florence Nguyen-Khac

This report describes the molecular characterization of the translocation t(5;14)(q35;q11) in a case of B-cell chronic lymphoproliferative disorder. The authors demonstrate the involvement of the TCR δ gene on chromosome 14 and of the NKX2-5 gene on chromosome 5.

- 1086 **Familial Hemophagocytic Lymphohistiocytosis**
Mutations affecting mRNA splicing are the most common molecular defect in patients with familial hemophagocytic lymphohistiocytosis type 3
Alessandra Santoro, Sonia Cannella, Antonino Trizzino, Giuseppe Bruno, Carmen De Fusco, Luigi D. Notarangelo, Daniela Pende, Gillian M. Griffiths, and Maurizio Arico

This report shows that UNC13D mutations leading to splicing errors are frequent in hemophagocytic lymphohistiocytosis type 3. Their detection and identification may be instrumental in the diagnosis of this disease.

- 1091 **Disorders of Hemostasis**
Severe and moderate hemophilia A: identification of 38 new genetic alterations
Pilar Casaña, Noelia Cabrera, Ana Rosa Cid, Saturnino Haya, Magdalena Beneyto, Carmen Espinós, Vicente Cortina, Maria Angeles Dasí, and José Antonio Aznar

This report describes new mutations of F8 in patients with severe and moderate hemophilia A.

Letters to the Editor

- 1095 **Thalassemia Syndromes**
No evidence of cardiac iron in 20 never- or minimally-transfused patients with thalassemia intermedia
Raffaella Origa, Susanna Barella, Giovanni Maria Argiolas, Patrizio Bina, Annalisa Agus, and Renzo Galanello

- 1096 **Hemoglobinopathies**
Defective mRNA levels are responsible for a β -thalassemia phenotype associated with Hb Federico II, a novel hemoglobin variant [β -106 (G8) Leu \rightarrow Val]
Michela Grosso, Ilaria Palumbo, Emanuela Morelli, Stella Puzone, Raffaele Sessa, and Paola Izzo

- 1098 **Myeloproliferative Disorders**
Oligoarray comparative genomic hybridization in polycythemia vera and essential thrombocythemia
Ioana Borze, Satu Mustjokio, Eeva Juvonen, and Sakari Knuutila

- 1100 **Myeloproliferative Disorders**
Low-dose thalidomide in myelofibrosis

Robert Weinkove, John T. Reilly,
Mary Frances McMullin, Natasha J. Curtin,
Deepti Radia, and Claire N. Harrison

- 1101** **Chronic Myeloid Leukemia**
Increased cortical bone mineralization in imatinib treated patients with chronic myelogenous leukemia
Sofia Jönsson, Bob Olsson, Claes Ohlsson, Mattias Lorentzon, Dan Mellström, and Hans Wadenvik
- 1103** **Acute Myeloid Leukemia**
Heterogeneous promoter activity of the telomerase reverse transcriptase gene in individual acute myeloid leukemia cells defined by lentiviral reporter assay
Seiichi Kobayashi, Yasushi Soda, Yuansong Bai, and Arinobu Tojo
- 1105** **Acute Myeloid Leukemia**
Expression of the nuclear oncogene Ski in patients with acute myeloid leukemia treated with all-trans retinoic acid
Sabine Teichler, Richard F. Schlenk, Konstantin Strauch, Nicole Hagner, Markus Ritter, and Andreas Neubauer
- 1107** **Malignant Lymphomas**
NOTCH2 mutations in marginal zone lymphoma
Gunhild Trøen, Iwona Wlodarska, Abdirashid Warsame, Silvia Hernández Llodrà, Christiane De Wolf-Peeters, and Jan Delabie
- 1109** **Monoclonal Gammopathies**
The IL6(-174G/C) polymorphism is a prognostic factor for survival after treatment initiation in Waldenström macroglobulinemia patients aged 65 years or less
Stéphanie Poulain, Isabelle Dervite, Xavier Leleu, Valérie Coiteux, Patrick Duthilleul, and Pierre Morel
- 1111** **Chronic Lymphocytic Leukemia**
The MDM2 -309 T/G promoter single nucleotide polymorphism does not alter disease characteristics in chronic lymphocytic leukemia
Thorsten Zenz, Sonja Häbe, Axel Benner, Dirk Kienle, Hartmut Döhner, and Stephan Stilgenbauer
- 1113** **Platelets**
A possible role for low-dose cyclosporine in refractory immune thrombocytopenic purpura
Giovanni Emilia, Mario Luppi, Monica Morselli, Fabio Forghieri, Leonardo Potenza, and Giuseppe Torelli
- 1115** **Thrombosis**
IgM anti-protein S antibodies as a risk factor for venous thrombosis
Montserrat Borrell, Isabel Tirado, José Mateo, Artur Oliver, Amparo Santamaría, and Jordi Fontcuberta
- 1117** **Thrombosis**
Antiplatelet drugs and risk of venous thromboembolism: results from the EDITH

case-control study

Karine Lacut, Jantien van der Maaten, Grégoire Le Gal, Géraldine Cornily, Dominique Mottier, and Emmanuel Oger

- 1119** **Gaucher Disease**
Persistent bone disease in adult type 1 Gaucher disease despite increasing doses of enzyme replacement therapy
Maaike de Fost, Carel J.M. van Noesel, Johannes M.F.G. Aerts, Mario Maas, Ruud G. Pöll, and Carla E.M. Hollak

Online Only Articles

Comment to: The clinical presentation and prognosis of diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC rearrangement. Haematologica 2007; 92:1335-1342

P. Bertrand, C. Maingonnat, P. Rumin, H. Tilly, C. Bastard

Reply to: [Comment to: The clinical presentation and prognosis of diffuse large B-cell lymphoma with t(14;18) and 8q24/c-MYC rearrangement. Haematologica 2007; 92:1335-1342]

Hervé Avet-Loiseau

Comment to: Recombinant erythropoietin found in seized blood bags from sportsmen. Haematologica 2008;93:313-4

G. Lippi, M. Franchini, B. Kayser

Reply to: [Comment to: Recombinant erythropoietin found in seized blood bags from sportsmen. Haematologica 2008;93:313-4]

J. Mallorqui, J. Segura, C. de Bolós, R. Gutierrez-Gallego, J.A. Pascual

Comment to: Secondary malignancies after treatment for indolent non-Hodgkin's lymphoma: a 16-year follow-up study. Haematologica 2008; 93:398-403

E. van der Spek, R. van der Griend

Reply to: [Comment to: Secondary malignancies after treatment for indolent non-Hodgkin's lymphoma: a 16-year follow-up study. Haematologica 2008; 93:398-403]

S. Sacchi