

Cover Figure

Simplified scheme of rRNA processing in human cells. This illustration is taken from the perspective article by Dianzani and Loreni on page 1601.

Editorials and Perspectives

- 1601 Diamond-Blackfan anemia: a ribosomal puzzle**
Irma Dianzani and Fabrizio Loreni

Diamond-Blackfan anemia is the first, and so far only known, inherited disease due to a defect in a structural ribosomal protein. In this perspective article, Drs. Dianzani and Loreni examine this ribosomal puzzle. See related articles on pages 1617 and 1627.

- 1605 ABO-incompatible allogeneic hematopoietic stem cell transplantation**
Nina Worel and Peter Kalks

Due to the fact that the HLA system is inherited independently of the blood group system, approximately 40 to 50% of all hematopoietic stem cell transplants are performed across the ABO-blood group barrier. In this perspective article, Drs. Worel and Kahls examine the features and outcome of ABO-incompatible allogeneic hematopoietic stem cell transplantation. See related paper on page 1686.

- 1607 Hematopoietic stem cell transplantation: 40 years of continuous progress and evolution**
Fulvio Porta, Franco Locatelli, and Giuseppe Roberto Burgio

Hematopoietic stem cell transplantation has represented one of the most innovative treatments of the last decades, as well as one of the most significant medical feats of human bio-solidarity. In this perspective article, Drs. Porta, Locatelli and Burgio analyze 40 years of continuous progress and evolution in the field.

- 1611 Pulmonary aspergillosis in hematologic malignancies: lights and shadows**
Livio Pagano, Luana Fianchi, and Morena Caira

The population of patients with hematological disorders at risk for pulmonary aspergillosis is expanding. In this perspective article, Drs. Pagano, Fianchi, and Caira analyze the recent advances in this field.

Original Articles

- 1617 Disorders of Erythropoiesis**
Enhanced alternative splicing of the FLVCR1 gene in Diamond Blackfan anemia disrupts FLVCR1 expression and function that are critical for erythropoiesis
Michelle A. Rey, Simon P. Duffy, Jennifer K. Brown, James A. Kennedy, John E. Dick, Yigal Dror, and Chetankumar S. Tailor

This study recapitulates the Diamond-Blackfan anemia hematologic features of reduced erythropoiesis but normal myelopoiesis by disrupting FLVCR1 in human hematopoietic stem cells. See related perspective article on page 1601.

- 1627 Disorders of Erythropoiesis**
Study of the effects of proteasome inhibitors on ribosomal protein S19 (RPS19) mutants, identified in patients with Diamond-Blackfan anemia

Aurore Crétien, Corinne Hurtaud, Hélène Moniz, Alexis Proust, Isabelle Marie, Orianne Wagner-Ballon, Valérie Choesmel, Pierre-Emmanuel Gleizes, Thierry Leblanc, Jean Delaunay, Gil Tchernia, Narla Mohandas, and Lydie Da Costa

The findings of this study demonstrate an important role for the proteasomal degradation pathway in regulating the levels of expression and nucleolar localization of certain mutant RPS19 proteins in Diamond-Blackfan anemia. See related perspective article on page 1601.

- 1635 Myeloproliferative Disorders**
Methylation of the suppressor of cytokine signaling 3 gene (SOCS3) in myeloproliferative disorders

Nasios Fourouclas, Juan Li, Daniel C. Gilby, Peter J. Campbell, Philip A. Beer, Elaine M. Boyd, Anne C. Goodeve, David Bareford, Claire N. Harrison, John T. Reilly, Anthony R. Green, and Anthony J. Bench

Suppressor of cytokine signaling 3 (SOCS3) is negative regulator of the JAK/STAT pathway. Methylation of this gene might, therefore, contribute to the pathogenesis of myeloproliferative disorders. In this study, SOCS3 promoter methylation was detected in about one third of patients with idiopathic myelofibrosis suggesting a possible role for SOCS3 methylation in this disorder.

- 1645 Myeloproliferative Disorders**
Prognostic factors for thrombosis, myelofibrosis, and leukemia in essential thrombocythemia: a study of 605 patients

Francesco Passamonti, Elisa Rumi, Luca Arcaini, Emanuela Boveri, Chiara Elena, Daniela Pietra, Sabrina Boggi, Cesare Astori, Paolo Bernasconi, Marzia Varettoni, Ercole Brusamolino, Cristiana Pascutto, and Mario Lazzarino

The findings from this study on a large series of patients treated according to current clinical practice provide reassurance that essential thrombocythemia is an indolent disorder and affected patients have a long survival.

- 1652 **Acute Lymphocytic Leukemia**
Anemia and survival in childhood acute lymphoblastic leukemia
Oliver Teuffel, Martin Stanulla, Gunnar Cario, Wolf D. Ludwig, Silja Rottgers, Beat W. Schafer, Martin Zimmermann, Martin Schrappe, and Felix K. Niggli

The inverse relationship between severity of anemia and survival found within specific subgroups of patients with childhood acute lymphoblastic leukemia suggests that very low hemoglobin levels at diagnosis are associated with more advanced disease in these subgroups.

- 1658 **Acute Lymphocytic Leukemia**
Impact of genotype on survival of children with T-cell acute lymphoblastic leukemia treated according to the French protocol FRALLE-93: the effect of *TLX3/HOX11L2* gene expression on outcome
Paola Ballerini, Judith Landman-Parker, Jean Michel Cayuela, Vahid Asnafi, Myriam Labopin, Virginie Gandemer, Yves Perel, Gérard Michel, Thierry Leblanc, Claudine Schmitt, Sylvie Fasola, Anne Hagemeyer, François Sigaux, Marie Françoise Auclerc, Luc Douay, Guy Leverger, and André Baruchel

The findings of this study suggest that *TLX3* gene expression is an independent risk factor predicting poor survival in childhood T-cell acute lymphoblastic leukemia.

- 1666 **Malignant Lymphomas**
Anthropometric characteristics and non-Hodgkin's lymphoma and multiple myeloma risk in the European Prospective Investigation into Cancer and Nutrition (EPIC)
Julie A. Britton, Aneire E. Khan, Sabine Rohrmann, Nikolaus Becker, Jakob Linseisen, Alexandra Nieters, Rudolf Kaaks, Anne Tjønneland, Jytte Halkjær, Marianne Tang Severinsen, Kim Overvad, Tobias Pischon, Heiner Boeing, Antonia Trichopoulos, Victoria Kalapothaki, Dimitrios Trichopoulos, Amalia Mattiello, Giovanna Tagliabue, Carlotta Sacerdote, Petra H.M. Peeters, H. Bas Bueno-de-Mesquita, Eva Ardanaz, Carmen Navarro, Paula Jakszyn, Jone M. Altzibar, Göran Hallman, Beatrice Malmer, Göran Berglund, Jonas Manjer, Naomi Allen, Timothy Key, Sheila Bingham, Hervé Besson, Pietro Ferrari, Mazda Jenab, Paolo Boffetta, Paolo Vineis, and Elio Riboli

The incidences of non-Hodgkin's lymphoma and multiple myeloma are increasing steadily. It has been hypothesized that this may be due, in part, to the parallel rising prevalence of obesity. This European Prospective Investigation into Cancer and Nutrition (EPIC) study supports an association between height and overall non-Hodgkin's lymphoma and multiple myeloma among women.

- 1678 **Thrombosis**
Nonsense-mediated mRNA decay in the *ADAMTS13* gene caused by a 29-nucleotide deletion
Isabella Garagiola, Carla Valsecchi, Silvia Lavoretano, Hale Oren, Martina Bohm, and Flora Peyvandi

This study demonstrates that two cases of severe *ADAMTS13* deficiency are mechanistically caused by the association of two different gene defects acting at two different levels.

- 1686 **Stem Cell Transplantation**
Impact of ABO-blood group incompatibility on the outcome of recipients of bone marrow transplants from unrelated donors in the Japan Marrow Donor Program
Fumihiko Kimura, Ken Sato, Shinichi Kobayashi, Takashi Ikeeda, Hiroshi Sao, Shinichiro Okamoto, Koichi Miyamura, Shin-ichiro Mori, Hideki Akiyama, Makoto Hirokawa, Hitoshi Ohto, Hiroshi Ashida, and Kazuo Motoyoshi for the Japan Marrow Donor Program

The findings of this study indicate that major and minor ABO incompatibility have specific effects on transplant-related mortality and acute graft-versus-host disease in recipients of bone marrow transplants from unrelated donors. See related perspective article on page 1605.

- 1694 **Stem Cell Transplantation**
Hematopoietic stem cell transplantation for hemophagocytic lymphohistiocytosis: a retrospective analysis of data from the Italian Association of Pediatric Hematology Oncology (AIEOP)
Simone Cesaro, Franco Locatelli, Edoardo Lanino, Fulvio Porta, Lucia Di Maio, Chiara Messina, Arcangelo Prete, Mimmo Ripaldi, Natasha Maximova, Giovanna Giorgiani, Roberto Rondelli, Maurizio Arico, and Franca Fagioli

This study confirms that hematopoietic stem cell transplantation represents a curative treatment for a large proportion of patients with hemophagocytic lymphohistiocytosis, irrespective of the underlying genetic defect.

Progress in Hematology

- 1702 **Stem Cell Transplantation**
B-cell involvement in chronic graft-versus-host disease
Rick Kapur, Saskia Ebeling, and Anton Hagenbeek

This article addresses the pathogenesis of chronic graft-versus-host disease, which is not yet completely understood, with a special focus on the possible role of B cells.

Decision Making and Problem Solving

- 1712** *Myelodysplastic Syndromes*
Diagnosis and classification of myelodysplastic syndrome: International Working Group on Morphology of myelodysplastic syndrome (IWGM-MDS) consensus proposals for the definition and enumeration of myeloblasts and ring sideroblasts
Ghulam J. Mufti, John M. Bennett, Jean Goasguen, Barbara J. Bain, Irith Baumann, Richard Brunning, Mario Cazzola, Pierre Fenaux, Ulrich Germing, Eva Hellström-Lindberg, Itsuro Jinnai, Atsushi Manabe, Akira Matsuda, Charlotte M. Niemeyer, Guillermo Sanz, Masao Tomanaga, Teresa Vallespi, and Ayami Yoshimi

This article details the proposals of the IWGM-MDS for the definition of myeloblasts, promyelocytes and ring sideroblasts in patients with myelodysplastic syndrome.

Brief Reports

- 1718** *Chronic Myeloid Leukemia*
Imatinib and leptomyacin B are effective in overcoming imatinib-resistance due to Bcr-Abl amplification and clonal evolution but not due to Bcr-Abl kinase domain mutation
Rama Krishna Kantha, Nikolas von Bubnoff, Cornelius Miething, Christian Peschel, Katharina S. Götze, and Justus Duyster
- The findings of this study indicate that the combination of imatinib and leptomyacin B effectively induces cell death in imatinib-resistant Ba/F3 cells which display Bcr-Abl amplification or signs of clonal evolution.*
- 1723** *Myeloproliferative Disorders*
Frequent reduction or absence of detection of the JAK2-mutated clone in JAK2V617F-positive patients within the first years of hydroxyurea therapy
François Girodon, Céline Schaeffer, Cédric Cleyrat, Morgane Mounier, Ingrid Lafont, Frédéric Dos Santos, Aurélie Vidal, Marc Maynadié, and Sylvie Hermouet

In this study, hydroxyurea treatment reduced the percentage of JAK2V617F mutant alleles by >30% in 13/25 patients with essential thrombocythemia or polycythemia vera within the first year after diagnosis.

- 1728** *Acute Myeloid Leukemia*
Transcriptional upregulation of p21/WAF/Cip1 in myeloid leukemic blasts expressing AML1-ETO
Tobias Berg, Manfred Fliegau, Jan Burger, Martin S. Staeger, Shaohua Liu, Natalia Martinez, Olaf Heidenreich, Stefan Burdach, Torsten Haferlach, Milton H. Werner, and Michael Lübbert

The increased expression of p21/WAF/Cip1 in primary leukemic blasts suggests that elevated p21/WAF/Cip1 levels may contribute to specific features observed in AML1-ETO positive leukemia.

- 1734** *Acute Lymphoblastic Leukemia*
An investigation into whether deletions in 9p reflect prognosis in adult precursor B-cell acute lymphoblastic leukemia: a multi-center study of 381 patients
Hareth Nahi, Hans Häggglund, Thomas Ahlgren, Per Bernell, Mats Hardling, Karin Karlsson, Vladimir Lj Lazarevic, Mats Linderholm, Bengt Smedmyr, Maria Åström, and Helene Hallböök

The findings of this study suggest that chromosomal abnormalities involving 9p may have a significant negative impact on survival in adult B-precursor acute lymphoblastic leukemia.

- 1739** *Multiple Myeloma*
Mobilization of peripheral blood stem cells in myeloma with either pegfilgrastim or filgrastim following chemotherapy
Guido Tricot, Bart Barlogie, Maurizio Zangari, Frits van Rhee, Antje Hoering, Jackie Szymonifka, and Michele Cottler-Fox

In this study on patients with multiple myeloma, peripheral blood stem cell mobilization after chemotherapy was feasible and similarly effective with pegfilgrastim and filgrastim.

- 1743** *Disorders of Hemostasis*
Novel point mutation in a leucine-rich repeat of the GPIIb/IIIa chain of the platelet von Willebrand factor receptor, GPIIb/IX/V, resulting in an inherited dominant form of Bernard-Soulier syndrome affecting two unrelated families: the N41H variant
Silvia Vettore, Raffaella Scandellari, Stefano Moro, Anna Maria Lombardi, Margherita Scapin, Maria Luigia Randi, and Fabrizio Fabris

This reports describes a new variant of heterozygous Bernard-Soulier syndrome with autosomal dominant inheritance.

Letters to the Editor

- 1748** *Disorders of Erythropoiesis*
Multiplex ligation-dependent probe amplification enhances molecular diagnosis of Diamond-Blackfan anemia due to RPS19 deficiency
Paola Quarello, Emanuela Garelli, Alfredo Brusco, Adriana Carando, Patrizia Pappi, Marco Barberis, Valentina Coletti, Maria Francesca Campagnoli, Irma Dianzani, and Ugo Ramenghi

- 1750 **Disorders of Erythropoiesis**
Immune-mediated pure red cell aplasia
in renal transplant recipients
*Julien Zuber, Kheira Beldjord, Nicole Casadevall,
Eric Thervet, Christophe Legendre, and Bruno Varet*
- 1752 **Red Cell Disorders**
Nonsense mutations of the α -spectrin gene
in hereditary pyropoikilocytosis
*Whitney Tolpinrud, Yelena D. Maksimova,
Bernard G. Forget, and Patrick G. Gallagher*
- 1754 **Red Cell Disorders**
First case of γ -thalassemia in association with
a β S allele: a pitfall in the neonatal screening
for sickle cell disease
*Caroline Lacoste, Nathalie Bonello-Palot, Katia Gonnet,
Françoise Merono, Nicolas Levy, Isabelle Thuret,
and Catherine Badens*
- 1755 **Red Cell Disorders**
Long term bi-weekly oral vitamin B₁₂ ensures
normal hematological parameters, but does
not correct all other markers of vitamin B₁₂
deficiency. A study in patients with inherited
vitamin B₁₂ deficiency
*Mustafa Vakur Bor, Mualla Çetin, Selin Aytaç,
Çigdem Altay, Per Magne Ueland, and Ebba Nexø*
- 1758 **Chronic Lymphocytic Leukemia**
Monitoring for cytomegalovirus and
Epstein-Barr virus infection in chronic
lymphocytic leukemia patients receiving i.v.
fludarabine-cyclophosphamide combination
and alemtuzumab as consolidation therapy
*Ester M. Orlandi, Fausto Baldanti, Annalisa Citro,
Lara Pochintesta, Marta Gatti, and Mario Lazzarino*

Erratum

- 1760 Erratum. [Oligoarray comparative genomic
hybridization in polycythemia vera and
essential thrombocythemia.
Haematologica 2008; 93:1098-1100]
*Ioana Borze, Satu Mustjoki, Eeva Juvonen, and Sakari
Knuutila*

Online Only Articles

Hepatitis B reactivation prophylaxis in immunosuppressed patients

A. Torresin, M. Feasi, G. Cassola

Risk of HBV liver disease in isolated anti-Hbc patients receiving immuno-chemotherapy for non-Hodgkin's lymphoma

C. Targhetta, M.G. Cabras, E. Angelucci

Use of hydroxyurea from childhood to adult age in sickle cell disease: semen analysis

A.K. Lukusa, C. Vermynen

Reply to: [Use of hydroxyurea from childhood to adult age in sickle cell disease: semen analysis. *Haematologica* 2008; 93:e67]

I. Berthaut, R. Giroi, J. Mandelbaum

Continuing Medical Education

Consensus proposals for the definition and enumeration of myeloblasts and ring sideroblasts in myelodysplastic syndrome

FVLCR1 gene expression in Diamond-Blackfan anemia

Prognostic factors for thrombosis, myelofibrosis, and leukemia in essential thrombocythemia

ABO-blood group incompatibility and the outcome of unrelated bone marrow transplantation