

## Cover Figure

Three-dimensional model of human FVa. This illustration is taken from the article by Dall'Osso and coworkers on page 1505.

## Editorials and Perspectives

### 1441 New and old players in the hepcidin pathway Clara Camaschella and Laura Silvestri

The identification of the liver peptide hepcidin at the beginning of the new millennium opened a new era in our understanding of iron metabolism. In this perspective article, Dr. Camaschella and Silvestri summarize current knowledge of the hepcidin pathway and of the regulation of the hepcidin expression. In particular, they discuss the function of matriptase-2, a transmembrane serine protease that is encoded by the *TMPRSS6* gene and suppresses hepcidin production. See related paper on pages 1466, 1473 and 1550.

### 1449 Novel thrombopoietic agents: a new era for management of patients with thrombocytopenia James N. George, and Deirdra R. Terrell

After many decades of an orphan existence, immune thrombocytopenic purpura is a central focus for the clinical development of multiple, novel thrombopoietic agents. In this perspective article, Drs. George and Terrell describe the molecular spectrum of thrombopoietic agents that are currently under development. See related paper on page 1495.

### 1449 Allogeneic hematopoietic stem cell transplantation for myelofibrosis Damiano Rondelli

Primary myelofibrosis or myelofibrosis secondary to polycythemia vera or essential thrombocythemia can be cured only by means of allogeneic hematopoietic stem cell transplantation at present. In this perspective article, Dr. Rondelli discusses which patients are the best candidates for transplantation, and the optimal transplantation procedures. See related paper on page 1514.

### 1452 Adoptive T-cell therapy for malignant disorders Daniel J. Powell Jr. and Bruce L. Levine

Adoptive cell transfer using *ex vivo* manipulated T lymphocytes has emerged as an important advance in cancer immunotherapy, allowing for re-education and re-setting of the host immune system. In this perspective article, Drs. Powell and Levine discuss the current situation in this field. See related paper on page 1523.

## Original Articles

### 1457 Hematopoietic Stem Cells Factors that influence short-term homing of human bone marrow-derived mesenchymal stem cells in a xenogeneic animal model Charalampia Kyriakou, Neil Rabin, Arnold Pizzey, Amit Nathwani and Kwee Yong

Human mesenchymal stem cells are potential agents for tissue regeneration, enhancing hematopoietic stem cell transplantation and delivering genes of therapeutic interest. This study shows that tissue homing of systemically administered mesenchymal stem cells can be increased by enforced expression of CXCR4, at least in irradiated hosts.

### 1466 Iron Metabolism Hemojuvelin N-terminal mutants reach the plasma membrane but do not activate the hepcidin response Alessia Pagani, Laura Silvestri, Antonella Nai, and Clara Camaschella

Hemojuvelin positively modulates the iron regulator hepcidin. Mutations of the gene encoding for hemojuvelin cause juvenile hemochromatosis, characterized by hepcidin deficiency and severe iron overload. This study shows that the delayed export and retention in the endoplasmic reticulum of some N-terminal mutants could contribute to the pathogenesis of juvenile hemochromatosis. See related perspective article on page 1441.

### 1473 Disorders of Iron Metabolism A mutation in the *TMPRSS6* gene, encoding a transmembrane serine protease that suppresses hepcidin production, in familial iron deficiency anemia refractory to oral iron Maria Antonietta Melis, Milena Cau, Rita Congiu, Gabriella Sole, Susanna Barella, Antonio Cao, Mark Westerman, Mario Cazzola, and Renzo Galanello

Previous studies have described a familial syndrome characterized by iron malabsorption, hypoferrremia, and microcytic anemia that did not respond to oral iron and responded only partly to parenteral iron. In this work, Melis and coworkers studied a Sardinian family with this inherited condition. They found a homozygous causal mutation in the *TMPRSS6* gene in affected members, who had inappropriately elevated levels of serum and urinary hepcidin. See related perspective article on page 1441.

### 1480 Acute Myeloid Leukemia Accumulation of hypoxia-inducible factor-1 $\alpha$ protein and its role in the differentiation of myeloid leukemic cells induced by all-trans retinoic acid Jing Zhang, Li-Ping Song, Ying Huang, Qian Zhao, Ke-Wen Zhao, and Guo-Qiang Chen

That hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) contributes to the differentiation of acute myeloid leukemia cells via transcriptional activity-independent mechanisms. This study

shows that increased HIF-1 $\alpha$  levels contribute to all-trans retinoic acid-induced differentiation of acute myeloid leukemia cells.

1488

**Acute Lymphoblastic Leukemia**  
Changes in antithrombin and fibrinogen levels during induction chemotherapy with L-asparaginase in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma. Use of supportive coagulation therapy and clinical outcome: the CAPELAL study

Mathilde Hunault-Berger, Patrice Chevallier, Martine Delain, Claude-Eric Bulabois, Serge Bologna, Marc Bernard, Ingrid Lafon, Jérôme Cornillon, Abdallah Maakaroun, Alexandra Tizon, Bruno Padrazzi, Norbert Ifrah and Yves Gruel for the GOELAMS (Groupe Ouest-Est des Leucémies Aiguës et Maladies du Sang)

The effects of L-asparaginase on hemostasis during induction chemotherapy of acute lymphoblastic leukemia of lymphoblastic lymphoma are less defined in adults than in children. This retrospective study suggests that antithrombin concentrates may have a beneficial effect on the outcome of adults treated for acute lymphoblastic leukemia with L-asparaginase.

1495

**Thrombopoiesis**  
The effect of a novel, small non-peptidyl molecule butyramide on human thrombopoietin receptor and megakaryopoiesis

Wataru Nogami, Hiroshi Yoshida, Kenzo Koizumi, Hajime Yamada, Kenji Abe, Akinori Arimura, Noriko Yamane, Koji Takahashi, Akiko Yamane, Atsushi Oda, Yoshikazu Tanaka, Hiroshi Takemoto, Yasuyuki Ohnishi, Yasuo Ikeda, and Yoshitaka Miyakawa

Thrombocytopenia is found in several conditions, and in many of them no treatment is available apart from platelet transfusion. Findings of this study suggest that butyramide, an orally bioavailable human Mpl activator, may increase platelet production. See related perspective article on page 1445.

1505

**Disorders of Coagulation**  
Molecular characterization of three novel splicing mutations causing factor V deficiency and analysis of the F5 gene splicing pattern

Claudia Dall'Osso, Iliaria Guella, Stefano Duga, Nadia Locatelli, Elvezia Maria Paraboschi, Marta Spreafico, Abdolreza Afrasiabi, Christoph Pechlaner, Flora Peyvandi, Maria Luisa Tenchini, and Rosanna Asselta

Factor V deficiency is a rare autosomal recessive hemorrhagic disorder, associated with bleeding manifestations of variable severity. This paper reports the functional consequences of three novel splicing mutations leading to FV deficiency.

1514

**Stem Cell Transplantation**  
Allogeneic hematopoietic stem cell transplantation in myelofibrosis: the 20-year experience of the Gruppo Italiano Trapianto di Midollo Osseo (GITMO)

Francesca Patriarca, Andrea Bacigalupo, Alessandra Sperotto, Miriam Isola, Franca Soldano, Barbara Bruno, Maria Teresa van Lint, Anna Paola Iori, Stella Santarone, Ferdinando Porretto, Pietro Pioltelli, Giuseppe Visani, Pasquale Iacopino, Renato Fanin and Alberto Bosi on behalf of the GITMO

In this GITMO study, Patriarca and coworkers evaluated the outcome of patients with myelofibrosis who underwent allogeneic stem cell transplantation, and the impact of prognostic factors. They conclude that the outcome of myelofibrosis patients who underwent allogeneic stem cell transplantation significantly improved after 1996 due to the reduction in transplant-related mortality. See related perspective article on page 1449.

1523

**Immunotherapy**  
The effect of artificial antigen-presenting cells with preclustered anti-CD28/-CD3/-LFA-1 monoclonal antibodies on the induction of ex vivo expansion of functional human antitumor T cells

Roberta Zappasodi, Massimo Di Nicola, Carmelo Carlo-Stella, Roberta Mortarini, Alessandra Molla, Claudia Vegetti, Salvatore Albani, Andrea Anichini and Alessandro M. Gianni

The aim of this study was to engineer an artificial APC-based system with the properties of a fluid cellular membrane and the flexibility derived from an artificial structure that could be tailored to carry the desired immunostimulatory molecules. The authors conclude that their artificial antigen-presenting cells might represent an efficient tool to rapidly obtain a sufficient number of functional T cells for adoptive immunotherapy in patients with cancer. See related perspective article on page 1452.

1535

**Immunotherapy**  
Genetic engineering of virus-specific T cells with T-cell receptors recognizing minor histocompatibility antigens for clinical application

Marieke Griffioen, H.M. Esther van Egmond, Helen Barnby-Porritt, Menno A.W.G. van der Hoorn, Renate S. Hagedoorn, Michel G.D. Kester, Nikolai Schwabe, Roel Willemze, J.H. Frederik Falkenburg and Mirjam H.M. Heemskerck

Donor lymphocyte infusion is an effective form of adoptive immunotherapy for hematologic malignancies after allogeneic stem cell transplantation, but is frequently associated with development of graft-versus-host disease. This study describes an efficient method for generating T-cell receptors-engineered virus-specific T cells, which may provide effective adoptive anti-tumor therapy after allogeneic stem cell transplantation, with a low risk of graft-versus-host disease.

## Decision Making and Problem Solving

- 1544 **Chronic Myeloid Leukemia**  
Recent trends in long-term survival of patients with chronic myelocytic leukemia: disclosing the impact of advances in therapy on the population level  
*Hermann Brenner, Adam Gondos, and Dianne Pulte*
- This analysis discloses a dramatic recent increase in long-term survival of younger patients with chronic myeloid leukemia, which most likely reflects rapid dissemination of advances in therapy on the population level.*

## Brief Reports

- 1550 **Disorders of Erythropoiesis**  
Serum hepcidin level and erythropoietic activity after hematopoietic stem cell transplantation  
*Junya Kanda, Chisaki Mizumoto, Hiroshi Kawabata, Hideyuki Tsuchida, Naohisa Tomosugi, Keitaro Matsuo, and Takashi Uchiyama*
- In this study, an inverse relationship between erythroid activity and serum hepcidin was found after hematopoietic stem cell transplantation.*
- 1555 **Disorders of Erythropoiesis**  
Long-term responses and outcomes following immunosuppressive therapy in large granular lymphocyte leukemia-associated pure red cell aplasia: a Nationwide Cohort Study in Japan for the PRCA Collaborative Study Group  
*Naohito Fujishima, Ken-ichi Sawada, Makoto Hirokawa, Kazuo Oshimi, Koichi Sugimoto, Akira Matsuda, Masanao Teramura, Masamitsu Karasawa, Ayako Arai, Yuji Yonemura, Shinji Nakao, Akio Urabe, Mitsuhiro Omine, and Kei-ya Ozawa*
- This report describes long-term responses following immunosuppressive therapy in large granular lymphocyte leukemia-associated pure red cell aplasia.*
- 1560 **Myeloproliferative Disorders**  
Rapid identification of JAK2 exon 12 mutations using high resolution melting analysis  
*Amy V. Jones, Nicholas C.P. Cross, Helen E. White, Anthony R. Green and Linda M. Scott*
- In this study, high resolution melting analysis was found to be a rapid, sensitive and high-throughput technique for screening for JAK2 exon 12 mutations.*
- 1565 **Acute Myeloid Leukemia**  
Nucleophosmin mutation in Southeast Asian acute myeloid leukemia: eight novel variants, FLT3 coexistence and prognostic impact of NPM1/FLT3 mutations  
*Chetsada Boonthimat, Wanna Thongnoppakhun, and Chirayu U. Auewarakul*

*This report shows that NPM1 mutations were most prevalent in Thai patients with acute myeloid leukemia with normal karyotype.*

- 1570 **Acute Myeloid Leukemia**  
Impaired dexamethasone related increase of anticoagulants is associated with the development of osteonecrosis in childhood acute lymphoblastic leukemia  
*Mariel L. te Winkel, Inge M. Appel, Rob Pieters, and Marry M. van den Heuvel-Eibrink*

*In childhood acute lymphoblastic leukemia, a hypercoagulable state may result from a lower dexamethasone-related increase of antithrombin and protein S and the subsequent decline of these anticoagulants below normal levels after introduction of asparaginase.*

- 1575 **Lymphoproliferative Disorders**  
CD49d expression is an independent risk factor of progressive disease in early stage chronic lymphocytic leukemia  
*Davide Rossi, Antonella Zucchetto, Francesca Maria Rossi, Daniela Capello, Michaela Cerri, Clara Deambroggi, Stefania Cresta, Silvia Rasi, Lorenzo De Paoli, Chiara Lobetti Bodoni, Pietro Bulian, Giovanni Del Poeta, Marco Ladetto, Valter Gattei, and Gianluca Gaidano*

*Findings of this study suggest that CD49d expression may be useful for the initial prognostic assessment of patients with chronic lymphocytic leukemia in the initial stage.*

## Letters to the Editor

- 1580 **Hematopoietic Stem Cells**  
The transcription factor nuclear factor Y regulates the proliferation of myeloid progenitor cells  
*Sake van Wageningen, Gorica Nikoloski, Gerty Vierwinden, Ruth Knops, Bert A. van der Reijden, and Joop H. Jansen*
- 1582 **Disorders of Heme Synthesis**  
Congenital sideroblastic anemia associated with germline polymorphisms reducing expression of FECH  
*Jonathan S. Caudill, Hamayun Imran, Julie C. Porcher, and David P. Steensma*
- 1584 **Thalassemia Syndromes**  
Correlation of liver iron concentration determined by R2 magnetic resonance imaging with serum ferritin in patients with thalassemia intermedia  
*Ali Taher, Fuad El Rassi, Hussain Isma'eel, Suzane Koussa, Adlette Inati, and Maria Domenica Cappellini*

- 1586 **Thalassemia Syndromes**  
Pregnancy outcome in patients with  $\beta$ -thalassemia intermedia at two tertiary care centers, in Beirut and Milan  
*Anwar H. Nassar, Mohammed Naja, Claudia Cesaretti, Bruno Eprassi, Maria Domenica Cappellini, and Ali Taher*
- 1588 **Thalassemia Syndromes**  
Continuous improvement of bone mineral density two years post zoledronic acid discontinuation in patients with thalassemia-induced osteoporosis: long-term follow-up of a randomized, placebo-controlled trial  
*Ersi Voskaridou, Dimitrios Christoulas, Marialena Konstantinidou, Evangelos Tsiftsakis, Panagiotis Alexakos, and Evangelos Terpos*
- 1590 **Disorders of Bilirubin Metabolism**  
Large deletion in *UGT1A1* gene encompassing the promoter and the exon 1 responsible for Crigler-Najjar type I syndrome  
*François M. Petit, Marylise Hébert, Vincent Gajdos, Liliane Capel, Ridha M'Rad, and Philippe Labrune*
- 1591 **Pediatric Leukemias**  
Two novel variants of *MOZ-CBP* fusion transcripts in spontaneously remitted infant leukemia with t(1;16;8) (p13;p13;p11), a new variant of t(8;16) (p11;p13)  
*Kiminori Terui, Tomohiko Sato, Shinya Sasaki, Ko Kudo, Takuya Kamio, and Etsuro Ito*
- 1593 **Myeloproliferative Disorders**  
Pulmonary extramedullary hematopoiesis in patients with myelofibrosis undergoing allogeneic stem cell transplantation  
*Sandeep Chunduri, Sujata Gaitonde, Stefan O. Ciurea, Ronald Hoffman, and Damiano Rondelli*
- 1595 **Acute Myeloid Leukemia**  
Exon 8 splice site mutations in the gene encoding the E3-ligase *CBL* are associated with core binding factor acute myeloid leukemias  
*Saman Abbas, Gabriëlle Rotmans, Bob Löwenberg, and Peter J.M. Valk*
- 1597 **Malignant Lymphomas**  
Genetic variation in genes expressed in the germinal center and risk of B cell lymphoma among Caucasians  
*Kathryn Scott, Peter J. Adamson, Eleanor V. Willett, Lisa J. Worrillow, and James M. Allan*

## Online Only Articles

Factor XI mutation and the origin of Ashkenazi Jews  
*Avshalom Zoosmann-Diskin*

Reply to: [Factor XI mutation and the origin of Ashkenazi Jews. *Haematologica* 2008; 93:e59]  
*G. Zadra, R. Asselta, M.L. Tenchini, G. Castaman, U. Seligsohn, P.M. Mannucci, S. Duga*

Efficacy of cyclosporine as a single agent therapy in chronic idiopathic thrombocytopenic purpura  
*D.R. Choudhary, R. Naithani, M. Mahapatra, R. Kumar, P. Mishra, R. Saxena*

Reply to: [Efficacy of cyclosporine as a single agent therapy in chronic idiopathic thrombocytopenic purpura]. *Haematologica* 2008; 93:e61]  
*G. Emilia, M. Luppi, M. Morselli, F. Forghieri, L. Potenza, G. Torelli*

Reply to: [Non-Hodgkin's lymphoma and residential proximity to toxic industrial waste in Southern Israel. *Haematologica* 2005; 90:1709-10]  
*R.S. Carel*

## Continuing Medical Education

Immunosuppressive therapy for large granular lymphocyte leukemia-associated pure red cell aplasia

Recent trends in long-term survival of patients with chronic myelocytic leukemia

A mutation in the *TMPRSS6* gene, encoding a serine protease that suppresses hepcidin production, in familial iron deficiency anemia refractory to oral iron

Allogeneic hematopoietic stem cell transplantation in myelofibrosis: the twenty-year experience of GITMO (Gruppo Italiano Trapianto di Midollo Osseo)