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, Drs. 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 myelosclerosis secondary to polycythemia vera or essential thrombocytosis 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 1453.

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 Mara Antonietta Melis, Milena Cau, Rita Congiu, Gabriella Sole, Susanna Barrella, 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 inappropriate elevated levels of serum and urinary hepcidin. See related perspective article on page 1441.

1480 Acute Myeloid Leukemia Accumulation of hypoxia-inducible factor-1α 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-1α (HIF-1α) contributes to the differentiation of acute myeloid leukemia cells via transcriptional activity-independent mechanisms. This study...
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, Jerome Cornillon, Abdallah Maakaroun, Alexandra Tizon, Bruno Padrazzi, Norbert Ibrah 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.

Thrombopoiesis

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

Wataru Nogami, Hiroshi Yoshida, Kenzo Koizumi, Hajime Yamada, Kenji Abe, Akioi Armura, Noriko Yamane, Koji Takahashi, Atsushi Oda, Yoshikazu Tanaka, Hiroshi Takemoto, Yasuyuki Omiishi, Yasuo Iceda, 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 butyramidamide, an orally bioavailable human Mpl activator, may increase platelet production. See related perspective article on page 1445.

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, Maria Guell, Stefano Dugo, Nadia Locatelli, Elvezia Maria Paraboschi, Marta Spreafico, Abdolreza Afsahi, 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.

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 Baciagalupo, Alessandra Sperotto, Miriam Isola, Franca Soldano, Barbara Bruno, Maria Teresa van Lint, Anna Paola Iori, Stella Santaroni, Ferdinando Porreto, Pietro Pioletti, 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.

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 Caro-Stella, Roberta Mortarini, Alessandra Molla, Claudia Veggetti, Salvatore Allrani, 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.

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 Willemsen, J.H. Frederik Falkenburg and Mirjam H.M. Heemskerk

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 erythropoietic 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
Naoko Fujishima, Ken-ichi Sawada, Makoto Hirokawa, Kazuo Oshimi, Koichi Sugimoto, Akira Matsuda, Masatomo Teramura, Masamitsu Kurasawa, Ayako Arat, Yui Yonemura, Shinji Nakao, Akio Urabe, Mitsuhiro Omine, and Keiya 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 Thongnopphakun, 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 de 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 Deambrogi, Stefania Cresta, Silvia Rasi, Lorenzo De Paoli, Chiara Lobetti Bodoni, Pietro Bulian, Giovanni Del Poeta, Marco Ladetto, Valter Gatte, 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

Disorders of Heme Synthesis
1582 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’eeel, Suzane Koussa, Adlette Inati, and Maria Domenica Cappellini
1586 Pregnancy outcome in patients with β-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 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

Disorders of Bilirubin Metabolism

1590 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 Gайдos, Liliane Capel, Ridha M’Rad, and Philippe Labrune

Pediatric Leukemias

1591 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

Myeloproliferative Disorders

1593 Pulmonary extramedullary hematopoiesis in patients with myelofibrosis undergoing allogeneic stem cell transplantation
Sanjeev Chunduri, Sujata Gaithonde, Stefan O. Ciurea, Ronald Hoffman, and Damiano Rondelli

Acute Myeloid Leukemia

1595 Exon 8 splice site mutations in the gene encoding the E3-ligase CBL are associated with core binding factor acute myeloid leukemias
Saman Abbass, Gabriëlle Rotmans, Bob Löwenberg, and Peter J.M. Valk

Malignant Lymphomas

1597 Genetic variation in genes expressed in the germinial center and risk of B cell lymphoma among Caucasians
Kathryn Scott, Peter J. Adamson, Eleanor V. Willett, Lisa J. Worrellow, and James M. Allison

Online Only Articles

Factor XI mutation and the origin of Ashkenazi Jews
Avshalom Zoossmann-Diskin
Reply to: [Factor XI mutation and the origin of Ashkenazi Jews. Haematologica 2008; 93:e59]

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. Morbelli, E. Forghieri, L. Potenza, G. Torrell

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 TMRSS6 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)