

## Cover Figure

The iron acquisition pathway in developing erythroblasts. This illustration is taken from the review article by Iolascon and co-workers on page 395.

## Editorials and Perspectives

- 307 **Towards explaining “unexplained hyperferritinemia”**  
Clara Camaschella and Erika Poggiali
- Elevated serum ferritin is found in a large spectrum of conditions both genetic and acquired, associated or not with iron overload. In this perspective article, Drs. Camaschella and Poggiali examine our current knowledge of the molecular basis of inherited hyperferritinemia. See related article on page 335.

- 310 **Immunosuppressive treatment for aplastic anemia: are we hitting the ceiling?**  
Jakob R. Passweg and André Tichelli
- The combination of antithymocyte globulin of horse origin and cyclosporine A is the standard treatment for aplastic anemia in patients not eligible for bone marrow transplantation. In this perspective article, Drs. Passweg and Tichelli discuss the current immunosuppressive therapy of aplastic anemia. See related article on page 348.

- 313 **Microparticles in endothelial cell and vascular homeostasis: are they really noxious?**  
Olivier Morel, Florence Toti, Nicolas Morel, and Jean-Marie Freyssinet
- Endothelial damage and release of membrane microparticles are key steps in the pathogenesis of inflammation. In this perspective article, Dr. Morel and co-workers discuss the biological and clinical significance of microparticles in endothelial cells. See related article on page 387.

## Original Articles

- 318 **Hematopoietic Stem Cells Green fluorescent protein transgene driven by Kit regulatory sequences is expressed in hematopoietic stem cells**  
Francesco Cerisoli, Letizia Cassinelli, Giuseppe Lamorte, Stefania Citterio, Francesca Bertolotti, Maria Cristina Magli, and Sergio Ottolenghi

The expression of Kit in multiple types of stem cells suggests that common transcriptional programs might regulate this gene in different stem cells. In this work, the authors used mouse lines expressing transgenic green fluorescent protein under the control of Kit promoter/first intron regulatory elements. This study provides the basis for the elucidation of DNA sequences regulating a stem cell gene in multiple types of stem cells.

- 326 **Erythropoiesis TAM receptors and the regulation of erythropoiesis in mice**  
Hongmei Tang, Song Chen, Haikun Wang, Hui Wu, Qingxian Lu, and Daishu Han

TAM receptors (Tyro3, Axl and Mer) are expressed in hematopoietic tissues, but their roles in hematopoiesis are largely unknown. This study shows that Axl and Mer play an important role in regulating erythropoiesis.

- 335 **Disorders of Iron Metabolism A new missense mutation in the L ferritin coding sequence associated with elevated levels of glycosylated ferritin in serum and absence of iron overload**  
Caroline Kannengiesser, Anne-Marie Jouanolle, Gilles Hetet, Annick Mosser, Françoise Muzeau, Dominique Henry, Edouard Bardou-Jacquet, Martine Mornet, Pierre Brissot, Yves Deugnier, Bernard Grandchamp, and Carole Beaumont
- The best known type of inherited hyperferritinemia not related to iron overload is the hyperferritinemia-cataract syndrome (OMIM #600886), caused by a mutation in the iron-responsive element in the 5-prime non-coding region of the ferritin light chain gene (FTL). This study describes a novel missense mutation of FTL responsible for genetic hyperferritinemia without iron overload. See related perspective article on page 307.

- 340 **Sickle Cell Disease Elevated tricuspid regurgitant jet velocity in children and adolescents with sickle cell disease: association with hemolysis and hemoglobin oxygen desaturation**  
Caterina P. Minniti, Craig Sable, Andrew Campbell, Sohail Rana, Gregory Ensing, Niti Dham, Onyinye Onyekwere, Mehdi Nouraie, Gregory J. Kato, Mark T. Gladwin, Oswaldo L. Castro, and Victor R. Gordeuk

An elevated echocardiography-determined tricuspid regurgitant jet velocity predicts high systolic pulmonary artery pressure and early mortality in adults with sickle cell disease. The study provides evidence for independent associations of elevated jet velocity with hemolysis and oxygen desaturation in children and adolescents with sickle cell disease.

- 348 **Aplastic Anemia**  
Treatment of severe aplastic anemia with a combination of horse anti-thymocyte globulin and cyclosporine, with or without sirolimus: a prospective randomized study  
Phillip Scheinberg, Colin O. Wu, Olga Nunez, Priscila Scheinberg, Carol Boss, Elaine M. Sloan, and Neal S. Young

As mentioned above, the combination of antithymocyte globulin of horse origin and cyclosporine A is the standard treatment for aplastic anemia in patients not eligible for bone marrow transplantation. The authors hypothesized that the addition of sirolimus to standard horse antithymocyte globulin and cyclosporine A would improve response rates in severe aplastic anemia, due to its complementary and synergistic properties to cyclosporine A. Despite a theoretical rationale for its use, unfortunately sirolimus did not improve the response rate. See related perspective article on page 310.

- 355 **Hodgkin's Lymphoma**  
Comparative analysis of oncogenic properties and nuclear factor- $\kappa$ B activity of latent membrane protein 1 natural variants from Hodgkin's lymphoma's Reed-Sternberg cells and normal B-lymphocytes  
Nathalie Faumont, Aurélie Chanut, Alan Benard, Nadine Cogne, Georges Delsol, Jean Feuillard, and Fabienne Meggetto

Latent membrane protein 1 (LMP1) was the first Epstein-Barr virus (EBV) latent protein found to be able to transform cell lines, and further the development of lymphomas in LMP1 transgenic mice due to its oncogenic potential. LMP1 polymorphism participates in EBV genetic diversity. In EBV-associated Hodgkin's lymphomas, neoplastic Reed-Sternberg cells and surrounding non-tumor B-cells contain different variants of LMP1. This study shows that LMP1 variants from Reed-Sternberg cells have enhanced proliferating and clonogenic potential.

- 364 **Chronic Lymphocytic Leukemia**  
A high number of losses in 13q14 chromosome is associated with a worse outcome and biological differences in patients with B-cell chronic lymphoid leukemia  
José Angel Hernández, Ana Eugenia Rodríguez, Marcos González, Rocío Benito, Celia Fontanillo, Virgilio Sandoval, Mercedes Romero, Guillermo Martín-Núñez, Alfonso García de Coca, Rosa Fisac, Josefina Galende, Isabel Recio, Francisco Ortuño, Juan Luis García, Javier de las Rivas, Norma Carmen Gutiérrez, Jesús F. San Miguel, and Jesús María Hernández

In B-cell chronic lymphoid leukemia, patients with 13q14 deletion generally have a favorable outcome. The findings of this study suggest that the number of malignant cells with 13q14 deletion may influence the outcome of patients with this cytogenetic abnormality as a single chromosomal aberration. A high number of malignant cells carrying the 13q14 deletion, as assessed by FISH, appears to be associated with short overall survival and time to progression.

- 372 **Multiple Myeloma**  
Cystatin-C is an independent prognostic factor for survival in multiple myeloma and is reduced by bortezomib administration  
Evangelos Terpos, Eirini Katodritou, Evangelos Tsiftsakis, Efstathios Kastritis, Dimitrios Christoulas, Anastasia Pouli, Eurydiki Michalis, Evgenia Verrou, Konstantinos Anargyrou, Konstantinos Tsionos, Meletios A. Dimopoulos, and Konstantinos Zervas, on behalf of the Greek Myeloma Study Group

Renal impairment is a common complication of multiple myeloma, and serum cystatin-C is considered an accurate marker of glomerular filtration rate. The findings of this study suggest that serum cystatin-C is not only a sensitive marker of renal impairment, but also reflects tumor burden and is of prognostic value in multiple myeloma.

- 380 **Amyloidosis**  
Translocation t(11;14) and survival of patients with light chain (AL) amyloidosis  
Alan H. Bryce, Rhett P. Ketterling, Morie A. Gertz, Martha Lacy, Ryan A. Knudson, Steven Zeldenrust, Shaji Kumar, Suzanne Hayman Francis Buadi, Robert A. Kyle, Philip R. Greipp, John A. Lust, Stephen Russell, S. Vincent Rajkumar, Rafael Fonseca, and Angela Dispenzieri

Little is known about cytogenetic abnormalities in patients with light chain (AL) amyloidosis. The findings of this study suggest that interphase FISH coupled to cytoplasmic staining of specific Ig on bone marrow cells could be useful in light chain (AL) amyloidosis, and that t(11;14) is an adverse prognostic factor in these patients.

- 387 **Thrombosis**  
Microparticle-associated endothelial protein C receptor and the induction of cytoprotective and anti-inflammatory effects  
Margarita Pérez-Casal, Colin Downey, Beatriz Cutillas-Moreno, Mirko Zuzel, Kenji Fukudome, and Cheng Hock Toh

The endothelial protein C receptor plays an important role within the protein C pathway in regulating coagulation and inflammation. This study provides information on the mechanisms by which activated protein C causes the release of the endothelial protein C receptor in microparticulate form from endothelial cells. See related perspective article on page 313.

## Review Article

- 395 **Red Cell Disorders**  
Molecular basis of inherited microcytic anemia due to defects in iron acquisition or heme synthesis  
Achille Iolascon, Luigia De Falco, and Carole Beaumont

This review article examines our present knowledge on the molecular basis of inherited microcytic anemia due to defects in iron acquisition or heme synthesis. The conditions examined include congenital sideroblastic anemias due to mutations in ALAS2, ABCB7 or GRX5, microcytic anemias due to DMT1 mutations, and the microcytic anemia associated with TMPRSS6 mutations.

Ronald J. deLeeuw, Ali Bashashati, Laurie H. Sehn, Joseph M. Connors, Mukesh Chhanabhai, Angela Brooks-Wilson, and Randy D. Gascoyne  
The findings of this study indicate that CD20 mutations involving the rituximab epitope are rare in both de novo and relapsed diffuse large B-cell lymphoma, and do not represent a significant cause of R-CHOP resistance.

## Brief Reports

- 409 **Bone Marrow Failure**  
Shwachman-Diamond syndrome neutrophils have altered chemoattractant-induced F-actin polymerization and polarization characteristics  
Claudia Orelia and Taco W. Kuijpers

The findings of this study indicate that Shwachman-Diamond syndrome neutrophils have aberrant chemoattractant-induced F-actin properties that might contribute to the impaired neutrophil chemotaxis present in this syndrome.

- 414 **Myeloproliferative Neoplasms**  
Detection of JAK2 exon 12 mutations in 15 patients with JAK2V617F negative polycythemia vera  
Susanne Schnittger, Ulrike Bacher, Claudia Haferlach, Thomas Geer, Peter Müller, Johann Mittermüller, Petro Petrides, Rudolf Schlag, Reiner Sandner, Johannes Selbach, Hans Rainer Slawik, Hans Werner Tessen, Jürgen Wehmeyer, Wolfgang Kern, and Torsten Haferlach

This study describes JAK2 exon 12 mutations in patients with polycythemia vera not carrying the classical JAK2 (V617F) mutation.

- 419 **Malignant Lymphomas**  
Expression pattern of XBP1(S) in human B-cell lymphomas  
Lorena Maestre, Reuben Tooze, Marta Cañamero, Santiago Montes-Moreno, Rocio Ramos, Gina Doody, May Boll, Sharon Barrans, Sara Baena, Miguel Angel Piris, and Giovanna Roncador

The transcription factor XBP1 (X-box-binding protein 1) is essential for plasma cell differentiation and immunoglobulin secretion. This study indicates that the active form of XBP1, XBP1(S), provides a specific marker of advanced plasma differentiation, and in lymphoid malignancies is restricted to plasma cell-derived neoplasms and plasmablastic diffuse large B-cell lymphomas.

- 423 **Malignant Lymphomas**  
CD20 mutations involving the rituximab epitope are rare in diffuse large B-cell lymphomas and are not a significant cause of R-CHOP failure  
Nathalie A. Johnson, Stephen Leach, Bruce Woolcock,

## Letters to the Editor

- 428 **Aplastic Anemia**  
Increased CD4<sup>+</sup> and CD8<sup>+</sup> effector memory T cells in patients with aplastic anemia  
Xiaojing Hu, Yan Gu, Yingxue Wang, Yaqin Cong, Xun Qu, and Conggao Xu

- 430 **Myelodysplastic Syndromes**  
The response to lenalidomide of myelodysplastic syndrome patients with deletion del(5q) can be sequentially monitored in CD34<sup>+</sup> progenitor cells  
Brigitte Mohr, Uta Oelschlaegel, Christian Thiede, Michelle Meredyth Stewart, Gerhard Ehninger, and Uwe Platzbecker

- 431 **Myeloproliferative Neoplasms**  
Myelofibrotic transformation in essential thrombocythemia  
Juergen Thiele, and Hans Michael Kvasnicka

- 433 **Myeloproliferative Neoplasms**  
Myelofibrotic transformation in essential thrombocythemia. Authors' reply  
Francesco Passamonti, Elisa Rumi, Emanuela Boveri, and Mario Lazzarino

- 433 **Acute Myeloid Leukemia**  
A JAK2-V617F activating mutation in addition to KIT and FLT3 mutations is associated with clinical outcome in patients with t(8;21)(q22;q22) acute myeloid leukemia  
Eisaku Iwanaga, Tomoko Nanri, Naofumi Matsuno, Toshiro Kawakita, Hiroaki Mitsuya, and Norio Asou

- 435 **Acute Lymphoblastic Leukemia**  
JAK1 mutation analysis in T-cell acute lymphoblastic leukemia cell lines  
Michaël Porcu, Olga Gielen, Jan Cools, and Kim De Keersmaecker

- 437 **Amyloidosis**  
A father and his son with systemic AL amyloidosis  
Stina Enqvist, Ulf-Henrik Mellqvist, Johan Mölne, Knut Sletten, Charles Murphy, Alan Solomon, Fred J. Stevens, and Per Westermark

- 439 **Amyloidosis**  
Donor lymphocyte infusions in amyloid light chain amyloidosis: induction of a "graft-versus-plasma cell-dyscrasia effect"  
*Stefan O. Schonland, Nicolaus Kröger, Christine Wolschke, Peter Dreger, Anthony D. Ho, and Ute Hegenbart*

- 441 **Platelet Disorders**  
In HPA 1a-immunized women the decrease in anti-HPA 1a antibody level during pregnancy is not associated with anti-idiotypic antibodies  
*Jens Kjeldsen-Kragh, Michael Kim, Mette Kjær Killie, Anne Husebekk, John Freedman, and John W. Semple*

- 443 **Platelet Disorders**  
Slow responses to standard dose rituximab in immune thrombocytopenic purpura  
*Kevin Kelly, Mary Gleeson, and Philip Thomas Murphy*

- 444 **Platelet Disorders**  
Slow responses to standard dose rituximab in immune thrombocytopenic purpura. Authors' reply  
*Francesco Zaja, and Renato Fanin*

## Obituary

Antonio López Borrasca (1926–2008)

## Continuing Medical Education

Treatment of severe aplastic anemia

Prognostic significance of translocation t(11;14) in light chain amyloidosis

The molecular basis of inherited microcytic anemia due to defects in iron acquisition or heme synthesis

Tricuspid regurgitant jet velocity in young patients with sickle cell disease