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Cover Figure

A simplified cross-section of the red cell membrane. This diagram is taken from the perspective article by Iolascon and Avvisati on page 1283.

Editorials and Perspectives

1281 **Variability and heritability of hemoglobin concentration: an opportunity to improve understanding of anemia in older adults**
Kushang V. Patel

Hemoglobin concentration varies substantially in humans. In this perspective article, Dr. Patel examines the many factors responsible for this variability, including genetic ones. The large interindividual variation in hemoglobin concentration has important implications for the diagnosis and treatment of anemia, particularly in older adults. See related paper on page 1372.

1283 **Genotype/phenotype correlation in hereditary spherocytosis**
Achille Iolascon and Rosa Anna Avvisati

Hereditary spherocytosis is found worldwide and has a prevalence of about 1 in 2000. This inherited hemolytic disease is caused by germline mutations in genes encoding proteins of the red cell membrane. In this perspective article, Drs. Iolascon and Avvisati examine genotype/phenotype relationships, and discuss their clinical implications. See related paper on page 1310.

1288 **Apoptotic pathways to death in myelodysplastic syndromes**
Michaela Fontenay and Emmanuel Gyan

The pathophysiology of myelodysplastic syndromes is largely unknown. In this perspective article, Drs. Fontenay and Gyan examine physiological cell death. They then discuss the dysregulated apoptotic pathways to death in myelodysplastic syndromes, and the usefulness of animal models for improving our understanding of this dysregulation. See related paper on page 1394.

1292 **The pathogenesis of classical Hodgkin's lymphoma: what can we learn from analyses of genomic alterations in Hodgkin and Reed-Sternberg cells?**
Martin Janz and Stephan Mathas

Classical Hodgkin's lymphoma is one of the most common malignant lymphomas. In the vast majority of cases it is curable at the early stages, but the treatment of advanced disease stages or refractory patients is challenging. In this perspective article, Drs. Janz and Mathas discuss the pathogenesis of classical Hodgkin's lymphoma and examine the numerous genetic defects identified so far. They conclude that the challenge for future work will be to identify the unifying molecular defects responsible for this malignancy. See related paper on page 1318.

1295 **Allogeneic transplantation in multiple myeloma**
Gösta Gahrton, Bo Björkstrand

Allogeneic stem cell transplantation from an HLA-identical sibling has proven to be useful in patients with multiple myeloma, possibly also because of a graft-versus-myeloma effect. In this perspective article, Drs. Gahrton and Björkstrand examine the results obtained so far, and discuss potential strategies to improve the outcome of patients with multiple myeloma undergoing this therapeutic procedure. See related paper on page 1343.

Original Articles

Hematopoiesis

1301 **The effect of mesenchymal stem cells on the viability, proliferation and differentiation of B-lymphocytes**
Soraya Tabera, José A. Pérez-Simón, María Díez-Campelo, Luis I. Sánchez-Abarca, Belén Blanco, Antonio López, Ana Benito, Enrique Ocio, Fermín M. Sánchez-Guijo, Consuelo Cañizo, and Jesús F. San Miguel

Mesenchymal stem cells are multipotent non-hematopoietic progenitor cells capable of differentiating into various lineages including osteoblasts, chondrocytes and adipocytes. The findings of this study indicate that mesenchymal stem cells promote survival and inhibit proliferation and maturation of B cells, and support a role of these cells in the immune response.

Red Cell Disorders

1310 **Clinical and hematologic features of 300 patients affected by hereditary spherocytosis grouped according to the type of the membrane protein defect**
Mariagabriella Mariani, Wilma Barcellini, Cristina Vercellati, Anna Paola Marcello, Elisa Fermo, Paola Pedotti, Carla Boschetti, and Alberto Zanella

The molecular basis of hereditary spherocytosis is highly heterogeneous, involving the genes encoding for spectrin, ankyrin, band 3 and protein 4.2. The findings of this retrospective study show that splenectomy corrected anemia in patients with all molecular subtypes of hereditary spherocytosis. Thus, the definition of the red cell membrane defect in hereditary spherocytosis has no major clinical implications, but may be useful for a differential diagnosis from other hematologic disorders that mimic this hemolytic anemia. See related perspective article on page 1283.

Malignant Lymphomas

1318 **Detection of genomic imbalances in microdissected Hodgkin and Reed-Sternberg cells of classical Hodgkin's lymphoma by array-based comparative genomic hybridization**
Sylvia Hartmann, José I. Martin-Subero, Stefan Gesk, Julia Hüsken, Maciej Giefing, Inga Nagel, Jennifer Riemke, Andreas Chott, Wolfram Klapper, Marie Parrens, Jean-Philippe Merlio, Ralf Küppers, Andreas Bräuninger, Reiner Siebert, and Martin-Leo Hansmann

Cytogenetic analysis of classical Hodgkin's lymphoma is limited by the low content of the neoplastic Reed-Sternberg

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cells in the affected tissues. The present study demonstrates that array comparative genomic hybridization of microdissected Hodgkin-Reed-Sternberg cells is suitable for identifying and characterizing chromosomal imbalances. Se related perspective article on page 1292.

Malignant Lymphomas

1327 **Chromosomal alterations detected by comparative genomic hybridization in subgroups of gene expression-defined Burkitt lymphoma**
Itziar Salaverria, Andreas Zettl, Silvia Beà, Elena M. Hartmann, Sandeep S. Dave, George W. Wright, Evert-Jan Boerma, Philip M. Kluin, German Ott, Wing C. Chan, Dennis D. Weisenburger, Armando Lopez-Guillermo, Randy D. Gascoyne, Jan Delabie, Lisa M. Rimsza, Rita M. Braziel, Elaine S. Jaffe, Louis M. Staudt, Hans Konrad Müller-Hermelink, Elias Campo, and Andreas Rosenwald for the Leukemia and Lymphoma Molecular Profiling Project (LLMPP)

This study of the Leukemia and Lymphoma Molecular Profiling Project (LLMPP) shows that pediatric and adult Burkitt's lymphoma are molecularly homogeneous, whereas 'discrepant Burkitt's lymphoma' differs in underlying genetic and clinical features from typical/atypical Burkitt's lymphoma.

Malignant Lymphomas

1335 **Second malignancies after treatment of diffuse large B-cell non-Hodgkin's lymphoma: a GISL cohort study**
Stefano Sacchi, Luigi Marcheselli, Alessia Bari, Raffaella Marcheselli, Samantha Pozzi, Paolo G. Gobbi, Francesco Angrilli, Maura Brugiatelli, Pellegrino Musto, and Massimo Federico

Improved treatment has increased the life expectancy of patients with non-Hodgkin's lymphoma, but the risk of second cancer in patients treated for diffuse large B-cell lymphoma is unclear. This Italian study shows that only young patients have an increased incidence ratio of second malignancies, while the incidence ratio in patients aged over 59 years matched that in the Italian general population.

Multiple Myeloma

1343 **Clinical impact of human Jurkat T-cell-line-derived antithymocyte globulin in multiple myeloma patients undergoing allogeneic stem cell transplantation**
Francis Ayuk, José A. Perez-Simon, Avichai Shimoni, Anna Sureda, Tatjana Zabelina, Rainer Schwerdtfeger, Rodrigo Martino, Herbert Gottfried Sayer, Adrián Alegre, Juan-José Lahuerta, Djordje Atanackovic, Christine Wolschke, Arnon Nagler, Axel R. Zander, Jesús F. San Miguel, and Nicolaus Kröger

Antithymocyte globulin is used in allogeneic stem cell transplantation to induce in vivo *T-cell depletion to facilitate engraftment and lower graft-versus-host disease. Antithymocyte globulin also has anti-myeloma activity* in vitro. *This study shows that inclusion of antithymocyte globulin in allogeneic stem cell transplantation protocols for patients with multiple myeloma may increase remission rates. See related perspective article on page 1295.*

Disorders of Hemostasis

1351 **Thrombomodulin-modified thrombin generation after *in vivo* recombinant factor VIII treatment in severe hemophilia A**
Arne W.J.H. Dielis, Wolfgang M.R. Balliël, René van Oerle, Wim T. Hermens, Henri M.H. Spronk, Hugo ten Cate, and Karly Hamulyák

Thrombin generation has been shown to reflect coagulation potential and factor VIII (FVIII) levels in patients with hemophilia A. This study shows that thrombin generation in the presence of thrombomodulin reflects plasma FVIII levels better.

Thrombosis

1358 **Endothelial protein C receptor polymorphisms and risk of myocardial infarction**
Pilar Medina, Silvia Navarro, Javier Corral, Esther Zorio, Vanesa Roldán, Amparo Estellés, Amparo Santamaría, Francisco Marín, Joaquín Rueda, Rogier M. Bertina, and Francisco España for the RECAVA thrombosis groups

Haplotypes A1 and A3 in the endothelial protein C receptor gene are tagged by the 4678G/C and 4600A/G polymorphisms, respectively, and have been reported to influence the risk of venous thromboembolism. This study shows that A1 and A3 haplotype carriers have a reduced risk of myocardial infarction.

Decision Making and Problem Solving

Malignant Lymphomas

1364 **Practice guidelines for the management of extranodal non-Hodgkin's lymphomas of adult non-immunodeficient patients. Part I: primary lung and mediastinal lymphomas. A project of the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation**
Pier Luigi Zinzani, Maurizio Martelli, Venerino Poletti, Umberto Vitolo, Paolo Gobbi, Tommaso Chisesi, Giovanni Barosi, Andrés J.M. Ferreri, Monia Marchetti, Nicola Pimpinelli, and Sante Tura

Extranodal non-Hodgkin's lymphomas constitute 20-25% of all cases of non-Hodgkin's lymphomas and can be managed with very different therapeutic strategies. This article summarizes ad hoc guidelines for the management of this disease.

Brief Reports

Erythropoiesis

1372 **Variation of hemoglobin levels in normal Italian populations from genetic isolates**
Cinzia Sala, Marina Ciullo, Carmela Lanzara, Teresa Nutile, Silvia Bione, Roberto Massacane, Pio d'Adamo, Paolo Gasparini, Daniela Toniolo, and Clara Camaschella

This study provides a dataset of hemoglobin levels for normal subjects of different geographical origin and indicates that hemoglobin levels are substantially influenced by heritable components. See related perspective article on page 1281.

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Erythropoiesis

1376 **Chronic preclinical safety evaluation of Hematide™, a pegylated peptidic erythropoiesis stimulating agent in monkeys**
Kathryn W. Woodburn, Susan D. Wilson, Kei-lai Fong, Peter J. Schatz, Thomas Ferrell, Charles B. Spainhour, and Daniel Norton

Hematide is a synthetic peptide-based, pegylated erythropoiesis stimulating agent in clinical development for treatment of anemia. In this study, hematide administration was associated with time and dose-dependent polycythemia in monkeys.

Thalassemia Syndromes

1380 **Significance of borderline hemoglobin A2 values in an Italian population with a high prevalence of β-thalassemia**
Antonino Giambona, Cristina Passarello, Margherita Vinciguerra, Rita Li Muli, Pietro Teresi, Maurizio Anzà, Gaetano Ruggeri, Disma Renda, and Aurelio Maggio

This study shows that borderline hemoglobin A2 values are not a rare event in a population with a high prevalence of beta-thalassemia carriers. These cases should be investigated at a molecular level, particularly if the partner is a carrier of beta-thalassemia.

Thalassemia Syndromes

1385 **Myocardial iron overload assessment by T2* magnetic resonance imaging in adult transfusion dependent patients with acquired anemias**
Anna Angela Di Tucci, Gildo Matta, Simona Deplano, Attilio Gabbas, Cristina Depau, Daniele Derudas, Giovanni Caocci, Annalisa Agus, and Emanuele Angelucci

In this study, gradient echo T2 magnetic resonance imaging provided a rapid and reproducible method for detecting myocardial iron overload which developed after a heavy transfusion burden equal to or greater than 290 mL/kg of packed red blood cell units.*

Chronic Myeloid Leukemia

1389 **ABL single nucleotide polymorphisms may masquerade as *BCR-ABL* mutations associated with resistance to tyrosine kinase inhibitors in patients with chronic myeloid leukemia**
Thomas Ernst, Jana Hoffmann, Philipp Erben, Benjamin Hanfstein, Armin Leitner, Rüdiger Hehlmann, Andreas Hochhaus and Martin C. Müller

The findings of this study indicate that analysis of normal ABL alleles enables an easy and fast differentiation between single nucleotide polymorphism and acquired mutations of BCR-ABL.

Myelodysplastic Syndromes

1394 **Impaired differentiation and apoptosis of hematopoietic precursors in a mouse model of myelodysplastic syndrome**
Chul Won Choi, Yang Jo Chung, Christopher Slape, and Peter D. Aplan

Expression of a NUP98-HOXD13 (NHD13) fusion gene, initially identified in a patient with myelodysplastic syndrome, leads to a highly penetrant myelodysplastic syndrome in mice that recapitulates all of the key features of the human disease. See related perspective article on page 1288.

Acute Myeloid Leukemia

1398 ***t(3;11)(q12;p15)/NUP98-LOC348801* fusion transcript in acute myeloid leukemia**
Paolo Gorello, Lucia Brandimarte, Roberta La Starza, Valentina Pierini, Loredana Bury, Roberto Rosati, Massimo F. Martelli, Peter Vandenberghe, Iwona Wlodarska, and Cristina Mecucci

This paper describes molecular cytogenetic findings of a t(3;11)(q12;p15), characterized as a new NUP98 translocation rearranging with LOC348801 at chromosome 3, in a patient with acute myeloid leukemia.

Multiple Myeloma

1402 **Long-term risk of myelodysplasia in melphalan-treated patients with immunoglobulin light-chain amyloidosis**
Morie A. Gertz, Martha Q. Lacy, John A. Lust, Philip R. Greipp, Thomas E. Witzig, and Robert A. Kyle

In this study, the actuarial risk of myelodysplasia at 10 years was 18% in patients with immunoglobulin light-chain amyloidosis treated with melphalan. As the survival of patients with plasma cell disorders improves, myelodysplasia may be a more common cause of morbidity and mortality for these patients.

Letters to the Editor

Red Cell Disorders

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Karen M.K. de Vooght, Richard van Wijk, Annet C. van Wesel, and Wouter W. van Solinge

Red Cell Disorders

1408 **Molecular studies reveal a concordant *KEL* genotyping between patients with hemoglobinopathies and blood donors in São Paulo City, Brazil**
Edmir Boturão-Neto, Akemi K. Chiba, Perla Vicari, Maria S. Figueiredo, and José O. Bordin

Red Cell Disorders

1410 **Association of asymmetric dimethylarginine with sickle cell disease-related pulmonary hypertension**
Precious P. Landburg, Tom Teerlink, Eduard J. van Beers, Frits A.J. Muskiet, Mies C. Kappers-Klunne, Joost W.J. van Esser, Melvin R. Mac Gillavry, Bart J. Biemond, Dees P.M. Brandjes, Ashley J. Duits, and John-John Schnog on behalf of the CURAMA study group

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Lymphoproliferative Disorders

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Lymphoproliferative Disorders

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Stem Cell Transplantation

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Angel Fernández, Felipe De Arriba, José Rivera, Inmaculada Heras, Vicente Vicente, and María Luisa Lozano

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Continuing Medical Education

Endothelial protein C receptor polymorphisms and the risk of myocardial infarction

Clinical and hematologic features of hereditary spherocytosis in relation to the type of membrane protein defect

The effect of mesenchymal stem cells on B-lymphocytes

Practice guidelines for the management of extranodal non-Hodgkin's lymphomas