Cover Figure

Strong cytoplasmic-restricted ALK positivity in Phoenix cells transfected with EML4-ALK. This illustration is taken from the article by Sozzi et al. on page 1307.

Editorials and Perspectives

1185 Genetic variation in hepcidin expression and its implications for phenotypic differences in iron metabolism
Henry K. Bayele, and Surjit Kalia S. Srai

At the core of iron homeostasis is hepcidin, a small acute phase antimicrobial peptide that now also appears to synchronously orchestrate the response of iron transporter and regulatory genes. In this perspective article, Drs Bayele and Srai discuss cis and trans acting factors that may influence hepcidin variation in humans and their potential role in iron metabolism control. See related papers on page 1293 and 1297.

1188 Hypereosinophilic syndrome variants: diagnostic and therapeutic considerations
Florence Roufosse

Hypereosinophilic syndromes are a group of disorders characterized by persistent and marked hypereosinophilia not due to an underlying disease known to cause eosinophil expansion, and which is directly implicated in damage or dysfunction of at least one target organ or tissue. In this perspective article, Dr. Roufosse provides an updated classification of these disorders and discusses the recent advances in this field, including fascinating pathogenic mechanisms and novel targeted therapeutic approaches. See related paper on page 1236.

1194 First-line therapy of CD20+ diffuse large B-cell lymphoma: facts and open questions
Ercole Brusamolino

CHOP chemotherapy, administered every 21 days, has been for years the standard therapy for advanced diffuse large B-cell lymphoma, with a long-term overall survival rate of about 40%. In this perspective article, Dr. Brusamolino discusses the recent advances in the treatment of this condition. See related paper on page 1250.

1198 Immune dysfunction in chronic lymphocytic leukemia T cells and lenalidomide as an immunomodulatory drug
Alan G. Ramsay and John G. Gribben

A new agent that is being used in chronic lymphocytic leukemia (CLL) and is receiving considerable interest is the immunomodulatory drug lenalidomide. The precise anti-CLL mechanism of action of lenalidomide is not yet completely defined. In this perspective article, Drs. Ramsay and Gribben examine the multiple biological effects of lenalidomide on various cell targets that likely contribute to its anti-CLL activity. See related paper on page 1326.

Original Articles

1203 First mutation in the red blood cell-specific promoter of hexokinase combined with a novel missense mutation causes hexokinase deficiency and mild chronic hemolysis

The red cell enzyme Hexokinase (HK), which catalyzes the phosphorylation of glucose to glucose-6-phosphate, is transcribed by an erythroid-specific promoter. Studying the molecular defect of a patient with hemolytic anemia due to HK deficiency, the authors identified the first mutation affecting the erythroid transcription of the HK gene and show its consequences in vivo.

1211 Imbalanced globin chain synthesis determines erythroid cell pathology in thalassemic mice
Kanitta Srinoun, Saovaros Svasti, Worrakavee Chamworathayave, Jim Vadolas, Phantip Vattanaviboons, Sudharth Fucharoen, and Pranne Winichagoon

Globin chain synthesis imbalance is the hallmark of thalassemia syndromes. In this study the authors have cross-bred human βIVSII-654 knock-in thalassemic mice with transgenic animals carrying four copies of the human β-globin gene and analyzed their progeny. The presence of multiple copies of the β-globin transgene significantly improved the globin chain synthesis ratio and the hematological phenotype of thalassemic mice.

1220 Incidence and risk factors of aplastic anemia in Latin American countries: the LATIN case-control study

Associations between aplastic anemia and numerous drugs, pesticides and chemicals have been reported. This study conducted in Latin American countries shows a low
incidence of aplastic anemia in this region of the world. Frequent exposure to benzene-based products increases this risk, while any association with specific drugs is uncertain.

**Chronic Myeloid Leukemia**

1227

A co-operative evaluation of different methods of detecting BCR-ABL kinase domain mutations in patients with chronic myeloid leukemia on second-line dasatinib or nilotinib therapy after failure of imatinib

Thomas Ernst, Franz X. Gruber, Oliver Pelz-Ackermann, Jacqueline Maier, Markus Pfirrmann, Martin C. Müller, Ingrid Mikkelø, Kimmo Pörkka, Dietger Niederwieser, Andreas Hochhaus, and Thoralf Lange

Various techniques have been employed to detect BCR-ABL kinase domain mutations in patients with chronic myeloid leukemia who are resistant to imatinib. The findings of this study suggest that denaturing high performance liquid chromatography combined with direct sequencing is a reliable screening technique for the detection of BCR-ABL kinase domain mutations.

**Myeloproliferative Neoplasms**

1236

T-cell abnormalities are present at high frequencies in patients with hypereosinophilic syndrome

Grzegorz Helbig, Agata Wieczorkiewicz, Joanna Dziaczkowska-Suszek, Miroslaw Majewski, and Slawomira Krycz-Krzemien

A T-cell clone, identified by clonal rearrangement of the T-cell receptor and by the presence of aberrant T-cell immunophenotype in peripheral blood, defines lymphocytic variant of hypereosinophilic syndrome. This study shows that T-cell abnormalities are present at high frequencies in patients with hypereosinophilic syndrome. See related perspective article on page 1194.

**Acute Promyelocytic Leukemia**

1242

Central nervous system involvement at first relapse in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline monotherapy without intrathecal prophylaxis

Pau Montesinos, Joaquín Díaz-Mediavilla, Guillermo Delío, Virginia Prates, Mar Torno, Vicente Rubio, Inmaculada Prez, Isolda Fernández, Marícriz Viguria, Chelo Rayón, José González, Javier de la Serna, Jordi Esteve, Juan M. Bergua, Concha Rivas, Marcos González, Jose D. González, Silvia Negri, Salut Brunet, Bob Lowenberg, and Miguel A. Sanz

With the advent of more effective therapy for the bone marrow in acute promyelocytic leukemia (APL) central nervous system (CNS) prophylaxis has been suggested to be useful. Using data from 739 patients treated on two Spanish national trials, the authors examine the incidence of CNS relapse in APL, and whether risk factors for such relapse can be identified.

**Chronic Lymphocytic Leukemia**

1259

Improved survival in chronic lymphocytic leukemia the past decade: a population-based study including 11,179 patients diagnosed 1973-2003 in Sweden

Sigríður Y. Kristinsson, Paul W. Dickman, Wyndham H. Wilson, Neil Caporaso, Magnus Björkholm, and Ola Landgren

Clinical management of chronic lymphocytic leukemia (CLL) patients has changed considerably over the last 30 years, reflected in an increased use of prognostic markers, new therapeutic agents and procedures, and supportive care measures. In this large population-based cohort study of over 11,000 CLL patients diagnosed in Sweden between 1973 and 2003, the authors found significantly improved 5-year and, most importantly 10-year CLL survival trends in all age groups. The observed improvements are likely due to improved therapeutic developments and supportive care.

**Malignant Lymphomas**

1266

Lenalidomide-induced upregulation of CD80 on tumor cells correlates with T-cell activation, the rapid onset of a cytokine release syndrome and leukemic cell clearance in chronic lymphocytic leukemia

Georg Aue, Nidgawa Njuggua, Xin Tian, Susan Soto, Thomas Hughes, Berengere Vire, Keyvan Keyvanfar, Federica Gibellini, Janet Valdez, Carol Boss, Leigh Samels, J. Philip McCoy Jr, Wyndham H. Wilson, Stefania Pittaluga, and Adrian Wiestner

In chronic lymphocytic leukemia (CLL) lenalidomide causes striking immune activation, possibly leading to clearance of tumor cells. This study shows that upregulation of CD80 on tumor cells and T-cell activation, which appears to be dispensable for the drug’s anti-tumor
Multiple Myeloma

A polymorphism in NFkB1 is associated with improved effect of interferon-α maintenance treatment of patients with multiple myeloma after high-dose treatment with stem cell support

Annette J. Vangsted, Tobias W. Klausen, Peter Gimsing, Niels F. Andersen, Niels Abildgaard, Henrik Gregersen, and Ulla Vogel

Interferon-α as maintenance therapy after high-dose therapy for multiple myeloma has been extensively debated during the last 30 years because several clinical studies have been published with conflicting results. In the present study, the authors addressed the question, of whether inborn variation in genes involved in inflammation influence treatment outcome in multiple myeloma patients receiving interferon-α as maintenance therapy. The findings suggest that a polymorphism in NFkB1 may be associated with improved effect of interferon-α in multiple myeloma patients, with homozygous carriers of the wild type allele having longer survival.

Stem Cell Transplantation

Is mobilized peripheral blood comparable with bone marrow as a source of hematopoietic stem cells for allogeneic transplantation from HLA-identical sibling donors? A case-control study

David Gallardo, Rafael de la Cámara, Jose B. Nieto, Ildelfonso Espigado, Arturo Iriondo, Antonio Jiménez-Velasco, Carlos Vallejo, Carmen Martín, Dolores Caballero, Salut Brunet, David Soriano, Carlos Solano, Josep M. Riberà, Javier de la Rubia, and Enric Carreras

The question of the relative efficacy of stem cell sources (bone marrow vs peripheral blood) for sibling allografts still remains, particularly in relation to quality of life. A study of a relatively homogeneous population has confirmed similar outcomes in terms of overall survival, transplant-related mortality or relapse incidence. However acute and chronic graft-vs-host disease showed increases in the peripheral blood group. Possibly as a consequence, although global quality of life did not differ, there was also a significant impairment of role and social functioning in this group.

Disorders of Iron Metabolism

Single nucleotide polymorphism genomic arrays analysis of t(8;21) acute myeloid leukemia cells

Tadayuki Akagi, Lee-Yung Shih, Seishi Ogawa, Joachim Gerst, Stephen R. Moore, Rhona Schreck, Norihiko Kawamata, Der-Cherng Liang, Masashi Sanada, Yasuhiro Nanna, Stefan Denenberg, Vasif K Zachariahs, Ann Nilorgren, Jee Hoon Song, Martin Dugas, Sören Lehmann, and H. Phillip Koelzer

In the AML1-ETO fusion gene, is associated with acute myeloid leukemia (AML). The findings of this study indicate that genomic alterations and KIT-D816 mutation confer a poor prognosis in t(8;21) AML patients.

Brief Reports

Thalassemia Syndromes

Two new β-thalassemia deletions compromising prenatal diagnosis in an Italian and a Turkish couple seeking prevention

Marjon Phylipsen, Antonio Amato,
Malignant Lymphomas

The EML4-ALK transcript but not the fusion protein can be expressed in reactive and neoplastic lymphoid tissues

Gabriella Sozzi, Maria Paola Martelli, Davide Conte, Piergiorgio Modena, Valentina Pettrissi, Stefano A. Pileri, and Brunangelo Falini

In the search for driver mutations that contribute to the development of cancer, translocations of ALK-EML4 were implicated as specific to non-small cell lung cancer. The author of this study clearly question the specificity of the rearrangement, showing that it is present in reactive lymph nodes and a number of different lymphomas.

Stem Cell Transplantation

Improving outcome of patients older than 30 years receiving HLA-identical sibling hematopoietic stem cell transplantation for severe acquired aplastic anemia using fludarabine-based conditioning: a comparison with conventional conditioning regimen

Sébastien Maury, Andrea Bacigalupo, Paolo Anderlini, Mahmoud Aljurf, Judith Marsh, Gérard Socié, Rosi Oneto, and Jakob R. Passweg on behalf of the Severe Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT-SAAWP)

Upfront or second line allogeneic hematopoietic stem cell transplantation (HSCT) offers a good disease-free survival option for patients suffering from severe idiopathic aplastic anemia. This report shows improved outcome of reduced-intensity versus conventional conditioning in HLA-identical sibling HSCT for older aplastic anemia patients.

Cell Therapy and Immunotherapy

Retroviral transfer of human CD20 as suicide gene for adoptive T-cell therapy

Marieke Griffioen, Esther H.M. van Egmond, Michel G.D. Kester, Roel Willemze, J.H. Frederik Falkenburg, and Mirjam H.M. Heemskerk

The aim of adoptive T-cell therapy of cancer is to selectively confer immunity against tumor cells. Autimmune side effects, however, remain a risk, emphasizing the relevance of a suicide mechanism allowing in vivo elimination of infused T cells. The findings of this study support the broad value of human CD20 as suicide gene in T-lymphocytes and safety switch in adoptive T-cell therapy.

Letters to the Editor

Erythrocytosis

Identification of high oxygen affinity hemoglobin variants in the investigation of patients with erythrocytosis

Melanie J. Percy, Naiman N. Butt, Gerard M. Crotty, Mark W. Drummond, Claire Harrison, Gail L. Jones, Matthew Turner, Jonathan Wallis, and Mary Frances McMullin

Acute Lymphoblastic Leukemia

Pyrurate kinase M2 and prednisolone resistance in acute lymphoblastic leukemia

Esther Hulleman, Mathilde J.C. Broekhuis, Rob Pieters, and Monique L. Den Boer

Acute Leukemia

Detection of twelve nucleotides insertion in the BCR-ABL kinase domain in an imatinib-resistant but dasatinib-sensitive patient with biphenotypic acute leukemia

Sandrine Hayette, Kaddour Chabane, Andrei Tchirkov, Marc G. Berger, Franck E. Nicolini, and Olivier Tournilhac

Platelet Disorders

Elevated profile of Th17, Th1 and Tc1 cells in patients with immune thrombocytopenic purpura

Jingbo Zhang, Daoxin Ma, Xiaojuan Zhu, Xin Qu, Chunyan Ji, and Ming Hou

Stem Cell Transplantation

Second bone marrow transplantation for patients with thalassemia: risks and benefits

Polina Stepensky, Reuven Or, Michael Y. Shapira, Shoshana Revel-Vilk, Jerry Stein, Igor B. Resnick

Obituary

Jean Dausset a scientific pioneer: intuition and creativity for the patients (1916-2009)

Laurent Degos

Continuing Medical Education

The effect of source of hematopoietic stem cells for transplantation from HLA-identical sibling donors

Introducing rituximab into primary treatment schemes for the poor prognosis diffuse large B-cell lymphoma

T-cell abnormalities in patients with hypereosinophilic syndrome

Central nervous system involvement in patients with acute promyelocytic leukemia