T-cell large granular lymphocytic leukemia. Peripheral blood smear showing lymphocytes with moderate to abundant cytoplasm and numerous azurophilic granules (MGG, x1250, courtesy of Rosangela Invernizzi, Italy).

Editorials and Perspectives

1333 Molecular basis of congenital neutropenia
Christoph Klein
In 1950 Rolf Kostmann discovered autosomal recessive severe congenital neutropenia and for more than 50 years its molecular etiology has remained enigmatic. In the last years, however, there have been impressive advances in this field. In this perspective article, Dr. Klein summarizes our current knowledge of the molecular basis of congenital neutropenia. See related paper on page 1449.

1336 Defective ribosome biogenesis in myelodysplastic syndromes
Naomi Galili, Samir Ahmed Qasim, and Azra Raza
Myelodysplastic syndromes are poorly understood at the biological level. In this perspective article, Drs. Galili, Qasim and Raza examine the role of defective ribosome biogenesis in the pathophysiology of myelodysplastic syndromes. See related paper on page 1453.

1338 Mutations of NOTCH1, FBXW7, and prognosis in T-lineage acute lymphoblastic leukemia
Charles G. Mullighan
From the genetic standpoint, T-lineage acute lymphoblastic leukemia is a heterogeneous disease and comprises a number of different subtypes. In this perspective article, Dr. Mullighan analyzes the relationship between somatic mutations in NOTCH1 or FBXW7 and the prognosis of T-lineage acute lymphoblastic leukemia. See related article on page 1383.

1341 Large granular lymphocyte disorders: new etiopathogenetic clues as a rationale for innovative therapeutic approaches
Renato Zambello, and Gianpietro Semenzato
The pathogenesis of large granular lymphocytic disorders is now being unravelled. Knowledge of the various cells of origin and the (often viral) drivers of proliferation is emerging. Leukemic transformation involves acquisition of mechanisms to escape death and to continue to proliferate. In this perspective article, Drs. Zambello and Semenzato examine new etiopathogenetic clues as a rationale for innovative therapeutic approaches. See related article on page 1407.

Phagocytes

1346 Citrullination of CXCL8 increases this chemokine's ability to mobilize neutrophils into the blood circulation
Tamara Loos, Ghislain Opdenakker, Jo Van Damme, and Paul Proost
The chemokine CXCL8 (interleukin 8) is a potent chemo-attractant of neutrophils. In this study, Loos and colleagues show that citrullination, a new post-translational modification of CXCL8, significantly increased this chemokine’s ability to attract neutrophils into the blood circulation, possibly by lowering the ability of CXCL8 to bind to the scavenging receptor DARC.

Red Cell Disorders

1354 4.1R-deficient human red blood cells have altered phosphatidylserine exposure pathways and are deficient in CD44 and CD47 glycoproteins
Phosphatidylserine exposure on the surface of the red cell membrane initiates the process of eryptosis, the red cell death program. The 4.1R protein is a phosphatidylserine binding protein. In this article, the authors demonstrate that erythrocytes from two patients with 4.1R deficiency show alterations of other proteins of the 4.1 multicomplex such as CD44 and CD47 and significantly increased phosphatidylserine exposure, suggesting a role for 4.1 protein in a signaling pathway relevant for red cell turnover.

Chronic Myeloid Leukemia

1362 Patients with chronic myeloid leukemia with the e13a2 BCR-ABL fusion transcript have inferior responses to imatinib compared to patients with the e14a2 transcript
Claire M. Lucas, Robert J. Harris, Athina Giannoudis, Andrea Davies, Katy Knight, Sarah J. Watmough, Liliu Wang, and Richard E. Clark
The clinical significance of the type of BCR-ABL transcript in newly diagnosed patients with chronic myeloid leukaemia treated with imatinib remains uncertain. The findings of this study suggest that the BCR-ABL fusion transcript type may have an impact on cytogenetic response to imatinib in patients with chronic myeloid leukemia.
1368 Myeloproliferative Disorders
Evidence for a founder effect of the MPL-S505N mutation in eight Italian pedigrees with hereditary thrombocytthemia
Kun Liu, Maurizio Martini, Bianca Rocca, Christopher I. Amos, Luciana Teefli, Fiornia Giona, Hainman Ding, Hirokazu Komatsu, Luigi M. Larocca, and Radek C. Skoda

Hereditary thrombocytthemia is a rare disease characterized by increased megakaryopoiesis and overproduction of platelets. Germ-line mutations have been identified in the genes for thrombopoietin (THPO) and its receptor, MPL. This study suggests that the recurrent MPL (S505N) mutation found in eight Italian families with hereditary thrombocytthemia is likely due to a founder effect.

1375 Acute Myeloid Leukemia
A phase 2 study of vorinostat in acute myeloid leukemia

The therapeutic potential of histone deacetylase inhibitors, such as vorinostat, in acute myeloid leukemia has raised considerable interest. Here the authors describe outcomes with two different schedules of this drug in patients with "poor-prognosis" or relapsed acute myeloid leukemia.

1383 Acute Lymphoblastic Leukemia
Prognostic implications of NOTCH1 and FBXW7 mutations in adult acute T-lymphoblastic leukemia
Claudia D Baldus, Julia Thibaut, Nicola Goekbuget, Andrea Stroux, Cornelia Schlee, Max Moxssner, Thomas Burmeister, Stefan Schwartz, Clara D. Bloomfield, Dieter Hoelzer, Eckhard Thiel, and Wolf-Karsten Hofmann

NOTCH1 mutations are found in more than 50% of patients with T-lineage acute lymphoblastic leukemia (T-ALL), and have been associated with a favorable outcome in pediatric T-ALL. FBXW7 mutations are found in a small subset of T-ALL, sometimes overlapping with the presence of NOTCH1 mutations. In this study, Baldus and colleagues investigated the prognostic impact of NOTCH1 and FBXW7 mutations in adult T-ALL. See related perspective article on page 1338.

1391 Acute Lymphoblastic Leukemia
Gene polymorphisms in folate metabolizing enzymes in adult acute lymphoblastic leukemia: effects on methotrexate-related toxicity and survival
Alessia Ongaro, Monica De Mattei, Matteo Giovanni Della Porta, GianMatteo Rigolin, Cristina Ambrosio, Francesco Di Raimondo, Agnese Pellati, Federica Francesca Masieri, Angelo Caruso, Linda Catozzi, and Donato Gemmati

Individual variations in response and/or toxicity to anti-cancer agents is common. The antifolate agent methotrexate is frequently used in maintenance therapy of acute lymphoblastic leukemia. The findings of this study suggest that genotyping of folate polymorphisms might be useful in adult acute lymphoblastic leukemia to optimize methotrexate therapy, reducing the associated toxicity with possible effects on survival.

1399 Acute Lymphoblastic Leukemia
Favorable outcomes with alemtuzumab-conditioned unrelated donor stem cell transplantation in adults with high risk Philadelphia chromosome-negative acute lymphoblastic leukemia in first complete remission

T-cell depletion is generally believed to effectively prevent graft-versus-host disease (GVHD), yet to impose an adverse effect on disease-free survival that eventually affects overall survival of leukemia patients undergoing allogeneic hematopoietic stem cell transplantation. In this study, however, Dr. Patel and co-workers demonstrate that T-cell-depleted hematopoietic stem cell transplantation from unrelated donors can result in good overall survival and low non-relapse mortality for adults with high-risk acute lymphoblastic leukemia in first complete remission.

1407 Lymphoproliferative Disorders
Therapeutic implications of variable expression of CD52 on clonal cytotoxic T cells in CD8 large granular lymphocyte leukemia
Sanjay R. Mohan, Michael J. Clemente, Manuel Afable, Heather N. Cazzolli, Nelli Bejanyan, Marcin W. Wlodarski, Alan E. Lichtin, and Jaroslaw P. Maciejewski

Clonal proliferations of large granular lymphocytes (LGL) are rare and heterogeneous in both origin and clinical behavior. They derive from either CD3+ T cells or NK-cell lineages and present a therapeutic challenge, with directed therapy using anti-CD52 (alemtuzumab) having a potentially useful role. Findings of this study indicate that the CD8+ subset can respond but, although numbers are small, responders may show down-regulation of CD52. This apparent escape from antibody attack adds to our understanding of antibody selection of variant tumor cells. See related perspective article on page 1341.
**Stem Cell Transplantation**

Type 1 regulatory T cells are associated with persistent split erythroid/lymphoid chimerism after allogeneic hematopoietic stem cell transplantation for thalassemia.

Giorgia Serafini, Marco Andreani, Manuela Testi, MariaRosa Battarra, Andrea Bontadini, Katharina Fleischhauer, Sarah Marktel, Guido Lucarelli, Maria Grazia Roncarolo, and Rosa Bacchetta

Allogeneic hematopoietic stem cell transplantation can cure thalassemia major. Persistent mixed chimerism develops in around 10% of transplanted thalassemic patients, but the biological mechanisms underlying this phenomenon are poorly understood. The findings of this study suggest that interleukin-10 and type 1 regulatory cells are associated with persistent mixed chimerism and may play an important role in sustaining long-term tolerance.

**Oncogenes**

Identification of protein tyrosine kinases with oncogenic potential using a retroviral insertion mutagenesis screen

Els Lierman, Helen Van Miegroet, Els Beullens, and Jan Cools

This report describes a novel retroviral insertion mutagenesis screen, which results in the generation of fusion genes consisting of a part of the viral vector and part of a cellular gene.

**Thalassemia Syndromes**

Association of α globin gene quadruplication and heterozygous β thalassemia in patients with thalassemia intermedia

Maria Carla Sollaino, Maria Elisabetta Paglietti, Lucia Perseu, Nicolina Giagu, Daniela Loi, and Renzo Galanello

The degree of the globin chain imbalance is the pathogenetic clue to the clinical phenotype of thalassemia syndromes. This paper reports a duplication of the α globin gene locus in a group of heterozygous β-thalassemia patients with the unexplained phenotype of thalassemia intermedia.

**Bone Marrow Failure**

G-CSF receptor (CSF3R) mutations in X-linked neutropenia evolving to acute myeloid leukemia or myelodysplasia

Karolien Beel, and Peter Vandenberghe

This paper shows for the first time that patients with X-linked neutropenia, caused by mutations in the Wiskott Aldrich syndrome gene, developed myelodysplasia/acute myeloid leukemia with acquisition of mutations in the CSF3R gene and loss of chromosome 7. See related perspective article on page 1336.

**Myelodysplastic Syndromes**

Low RPS14 expression is common in myelodysplastic syndromes without 5q- aberration and defines a subgroup of patients with prolonged survival

Akos Czibere, Ingmar Bruns, Bärbel Junge, Raminder Singh, Guido Kobbe, Rainer Haas, and Ulrich Gerning

This paper shows that the expression of the ribosomal protein S14 (RPS14) is reduced in about two thirds of patients with non-5q- myelodysplastic syndrome. See related perspective article on page 1336.
Malignant Lymphomas

Marked therapeutic efficacy of a novel polyethylene glycol-SN38 conjugate, EZN-2208, in xenograft models of B-cell non-Hodgkin’s lymphoma
Puja Sapra, Patricia Kraft, Mary Mehlig, Jennifer Malaby, Hong Zhao, Lee M. Greenberger, and Ivan D. Horak

This paper describes the results of preclinical animal model studies successfully treating human lymphoma xenograft using a topoisomerase I inhibitor. EZN-2208 is a pegylated form of irinotecan with marked improvements in solubility and shows promising efficacy in this lymphoma model.

Chronic Lymphocytic Leukemia

Prior history of non-melanoma skin cancer is associated with increased mortality in patients with chronic lymphocytic leukemia
Jorge R. Toro, Patrick W. Blake, Magnus Björkholm, Sigurdur Y. Kristinsson, Zhuoqiao Wang, and Ola Landgren

This study suggests that non-melanoma skin cancer may be a novel clinical predictor of worse chronic lymphocytic leukemia outcome.

Letters to the Editor

Disorders of Iron Metabolism

HAMP promoter mutation nc.-153C>T in 785 HEIRS Study participants
James C. Barton, Catherine Lenzedecker-Foster, Honggui Li, Susie DelRio-LaFreniere, Ronald T. Acton, John H. Eckfeldt, for the HEIRS Stud

Disorders of Iron Metabolism

HAMP promoter mutation nc.-153C>T in 785 HEIRS Study participants: authors’ reply
Olivier Loréal, Anne-Marie Jouanolle, Marie-Laure Island, Amnick Mosser, Yves Deugnier, Véronique David, and Pierre Brissot

Acute Myeloid Leukemia

Slow relapse in acute myeloid leukemia with inv(16) or t(16:16)
Thomas Clozel, Aline Renneville, Marion Venot, Claude Gardin, Chankleia Kelaïdi, Geneviève Leroux, Virginie Edache, Claude Preudhomme, Pierre Fenaux, and Lionel Adès

Obituary

Franco Rilke (1929-2009)
Stefano A. Pileri and Attilio Orazi

Continuing Medical Education

Persistent split erythroid/lymphoid chimerism after stem cell transplantation for thalassemia

Alentuzumab adults with high-risk acute lymphoblastic leukemia

Alentuzumab for the treatment of CD8⁺ large granular lymphocyte leukemia

Ribosomal protein S14 in myelodysplastic syndromes