Cover Figure

The ALL complex. This illustration is taken from the review article by Dr. Slany on page 984.

Editorials and Perspectives

891 Biphenotypic, bilineal, ambiguous or mixed lineage: strange leukemias!
Marie C. Béné

The criteria for "biphenotypic acute leukemia" have changed with improvements in the ability to distinguish blast cells of different lineages. In her perspective on the paper by Xu et al (page 918), Dr. Béné reviews these changes, proceeding up to the most recent WHO classification. See also related review article on page 984.

894 Novel lymphoid neoplasms – the borderland between diffuse large B-cell lymphoma and Burkitt’s lymphoma
Daphne de Jong

The recent update of the WHO classification of tumors of the lymphoid tissue has recognized a category with overlapping features between Burkitt lymphoma and diffuse large B-cell lymphoma. In this perspective article, Dr. de Jong reviews the conceptual basis and practical impact of this diagnosis. See related paper on page 935.

897 Anaplastic large cell lymphoma: changes in the World Health Organization classification and perspectives for targeted therapy
Brunangelo Falini, and Maria Paola Martelli

The accompanying perspective by Drs. Falini and Martelli provides a clear description of the current WHO classification with a focus on the distinction between ALK-positive anaplastic large cell lymphoma ALCL and ALK-negative disease. Additionally, they provide a rationale for potential new targets for therapy including flavopiridol. See related paper on page 944.

Original Articles

Hematopoietic Stem Cells

901 Mammalian target of rapamycin activity is required for expansion of CD34+ hematopoietic progenitor cells
Christian R. Geest, Fried J. Zwartkruis, Edo Vellenga, Paul J. Coffer, and Miranda Buitenhuis

The protein kinase mammalian target of rapamycin (mTOR) plays an essential role in the control of protein synthesis. In this paper, Geest and colleagues show that mTOR inhibition by rapamycin reduces the expansion of committed myeloid progenitors, but leaves the more primitive hematopoietic compartment unaffected.

Myeloproliferative Neoplasms

911 Elevated procoagulant microparticles expressing endothelial and platelet markers in essential thrombocythemia
Marijke C. Trappenburg, Muriel van Schilfgaarde, Marina Marchetti, Henri M. Spronk, Hugo ten Cate, Anja Leyte, Wim E. Terpstra, and Anna Falanga

Essential thrombocythemia is a myeloproliferative neoplasm characterized by an increased risk of both arterial and venous thrombosis. The findings of this study show that patients with this disorder have elevated levels of platelet-and endothelium-derived microparticles, which may support thrombin generation and play a role in the pathophysiology of thromboembolic complications.

Acute Leukemia

919 Clinical and biological characteristics of adult biphenotypic acute leukemia in comparison with that of acute myeloid leukemia and acute lymphoblastic leukemia: a case series of a Chinese population
Xiao-Qian Xu, Jian-Min Wang, Shu-Qing Lu, Li Chen, Jian-Min Yang, Wei-Ping Zhang, Xian-Min Song, Jun Hou, Xiong Ni, and Hui-Ying Qiu

Biphenotypic acute leukemia is rare, necessitating large series to provide information on prognosis. In this paper Xu and colleagues review Chinese experience with this condition. The findings of this study indicate that the prognosis of biphenotypic acute leukemia patients is poor when compared with de novo acute myeloid leukemia or acute lymphoblastic leukemia. See related perspective article on page 891 and related review article on page 984.

928 The anti-cancer drug, phenoxodiol, kills primary myeloid and lymphoid leukemic blasts and rapidly proliferating T cells
Patries M. Herst, Joanne E. Davis, Paul Neeson, Michael V. Bertridge, and David S. Ritchie

The plasma electron transport system is a relatively newly-discovered potential target for anti-leukemia drugs. In this paper Herst and coworkers describe the effects of phenoxodiol, an inhibitor of this pathway on leukemia cell lines and primary as well as on resting and activated T cells. The ability of phenoxodiol to kill rapidly proliferating lymphocytes might make this drug a promising candidate for the treatment of pathologically-activated lymphocytes.

Malignant Lymphomas

935 Clinicopathological features of lymphoma/leukemia patients carrying both BCL2 and MYC translocations
Naoto Tomita, Mami Tokunaka, Naoya Nakamura, Kengo Takeuchi, Junki Koike, Shigeki Motomura, Ko Miyanoto, Ako Kikuchi, Rie Hiy, Yoshihiro
Yakuushijin, Yusufumi Masaki, Soichiro Fujii, Takamasa Hayashi, Yoshiaki Ishigatsubo, and Ikuo Miura

Malignant lymphoid neoplasms carrying both MYC and BCL2 translocations ("double hit" lymphomas) are uncommon and have a very aggressive clinical behavior. This thorough study by Tomita and coworkers characterizes a large series of these patients recognizing their poor outcome and frequent extranodal and CNS involvement. See related perspective article on page 894.

Malignant Lymphomas
944 The effect of the cyclin-dependent kinase inhibitor flavopiridol on anaplastic large cell lymphoma cells and relationship with NPM-ALK kinase expression and activity
Paolo Bonvini, Elisa Zorzi, Lara Mussolin, Giovanni Monaco, Martina Pigazzi, Giuseppe Basso, and Angelo Rosolen

This study by Bonvini and coworkers describes in vitro data supporting a role for the CDK inhibitor flavopiridol in the treatment of anaplastic large cell lymphoma. Moreover, their studies establish a link between ALK over-expression and flavopiridol, as inhibition of ALK activity sensitizes the cells to flavopiridol-induced cell death. See related perspective article on page 897.

Stem Cell Transplantation
956 Imbalance of effector and regulatory CD4\(^+\) T cells is associated with graft versus host disease after hematopoietic stem cell transplantation using a reduced intensity conditioning regimen and alemtuzumab
Katie Matthews, Zhi Lim, Behdad Afsahi, Laurence Pearce, Atiyeh Abdallah, Shabram Kordasti, Antonio Pagliuca, Giovanna Lombardi, J. Alejandro Madrigal, Ghalam J. Mufti, and Linda D. Barber

Graft-versus-host disease (GVHD) remains the downside of the graft-versus-leukemia effect following allogeneic stem cell transplantation. This investigation of 25 patients with myelodysplastic malignancies treated with reduced intensity conditioning and with GVHD prophylaxis, has focused on cell populations and their correlation with outcome. Interesting imbalances of effector and regulatory CD4\(^+\) T cells were detected, which, if confirmed in larger cohorts, should provide insight into how the immunological storms accompanying allogeneic stem cell transplantation can be harnessed and weathered.

Cell Therapy and Immunotherapy
967 Adoptive immunotherapy mediated by ex vivo expanded natural killer T cells against CD1D-expressing lymphoid neoplasms
Davide Bagutti, Adalberto Ibbata, Mirko Corselli, Nadia Sessarego, Claudia Tenca, Amleto De Santanna, Andrea Mazzarello, Antonio Daga, Renzo Corvò, Giulio De Rossi, Francesco Frassoni, Ermanno Ciccone, and Franco Fais

Therapy of tumors by injection of T cells is gaining attention, although technical problems remain. This pre-clinical study investigates the potential of NKT cells, readily expanded in vitro and having a relatively wide specificity, determined by target expression of CD1d. This is attractive for lymphoid tumors and the data show attack on a xenograft in vivo in the presence of the CD1d-binding alpha-galactosylceramide. While clinical application is not immediate, the model allows useful dissection of an intriguing concept.

Cell Therapy and Immunotherapy
975 Treatment with bortezomib of human CD4\(^+\) T cells preserves natural regulatory T cells and allows the emergence of a distinct suppressor T-cell population
Belen Blanco, José A. Pérez-Simón, Luis I. Sánchez-Aburca, Teresa Caballero-Velazquez, Silvia Gutierrez-Cossio, Pilar Hernández-Campos, María Diez-Campeo, Carmen Herrera-Sánchez, Concepción Rodríguez-Serrano, Carlos Santana, Férmín M. Sánchez-Guijo, Consuelo del Canizo, and Jesús F. San Miguel

In vitro depletion of alloreactive T cells using the proteasome inhibitor bortezomib is a promising approach to prevent graft-versus-host disease (GVHD) after allogeneic stem cell transplantation. The findings of this study strengthen the idea of using bortezomib in the prevention of GVHD, not only because of its selective cytotoxic effect on activated T cells, but also due to its ability to preserve and/or generate regulatory T cells.

Review Article
984 The molecular biology of mixed lineage leukemia
Robert K. Slany

Mixed-lineage-leukemia is an aggressive leukemia that predominantly occurs in pediatric patients and is characterized by the expression of fusion genes involving the histone methyltransferase MLL and a variety of fusion partners. It is now clear that MLL fusion partners can activate transcription by two different mechanisms, which are discussed in this review article. Insights in these functions may open new avenues for rational drug development. See related papers on page 891 and 918.

Decision Making and Problem Solving
994 Morphological evaluation of monocytes and their precursors

This study establishes morphological definitions so that monocytes, including immature monocytes, can be reliably separated from the spectrum of monocyte precursors.
Infectious Disorders

Effect of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in lymphoma: a meta-analysis of published clinical trials and a decision tree addressing prolonged prophylaxis and maintenance
Panayiotis D. Ziakas, Petros Karsaliakos, and Eleftherios Mylonakis

Previous observations indicate that a lamivudine-prophylaxis strategy results in a decrease of hepatitis B virus (HBV) reactivation rates. This report evaluates the benefits from this strategy among lymphoma patients. The findings of this study indicate that extended anti-HBV prophylaxis can improve survival rates by 2.4% in HBsAg-positive lymphoma patients receiving chemotherapy.

Malignant Lymphomas

Identification of the gene encoding cyclin E1 (CCNE1) as a novel IGH translocation partner in t(14;19)(q32;q12) in diffuse large B-cell lymphoma
Inga Nagel, Takashi Akasaka, Wolfram Klapper, Stefan Gek, Sebastian Böttcher, Matthias Ritgen, Lana Harder, Michael Knebl, Martin J.S. Dyer, and Reiner Siebert

Cyclin D family members are known to be ectopically expressed in B-cell lymphomas due to their involvement in chromosomal translocations with the immunoglobulin loci (IGH). This study identified the gene encoding cyclin E1 (CCNE1) as a novel translocation partner of IGH in diffuse large B-cell lymphoma. These observations suggest that cyclin E1 may act as a novel oncogene in B-cell lymphomagenesis.

Sickle Cell Disease

Auto-adjusting positive airway pressure in children with sickle cell anemia: results of a phase I randomized controlled trial.
Melanie J. Marshall, Romola S. Bucks, Alexandra M. Hogan, Ian R. Hambleton, Susan E. Height, Morra C. Dick, Fenella J. Kirkham, and David C. Rees

Sleep related breathing disorders and especially low nocturnal oxygen saturation may favor complications of sickle cell disease (SCD). In this phase I trial, auto-adjusting continuous positive airway pressure (CPAP) was shown to be a feasible and safe therapy for SCD children. Sleep breathing disorders were improved, and there was evidence of a trend towards reduction of diurnal pain.

Bone Marrow Failure

Fanc1−/− hematopoietic stem cells demonstrate a mobilization defect which can be overcome by administration of the Rac inhibitor NSC23766
Michael D. Milson, Andrew W. Lee, Yi Zheng, and José A. Cancelas

In Fanconi anemia, gene and cell therapy trials using hematopoietic stem cells and progenitors have been hampered by poor mobilization of these stem cells to peripheral blood in response to G-CSF. This study shows that targeting Rac signaling may enhance G-CSF-induced hematopoietic stem cell mobilization in this bone marrow failure syndrome.

Acute Lymphoblastic Leukemia

Overexpression of CD123 correlates with the hyperdiploid genotype in acute lymphoblastic leukemia
Miroslav Djokic, Elisabet Björklund, Elisabeth Blemow, Joanna Mazur, Stefan Söderhäll, and Anna Porwit

This study on patients with acute lymphoblastic leukemia (ALL) shows that overexpression of CD123 is an aberrant phenotype present in a subset of precursor-B ALL with hyperdiploid genotype, and represents an additional marker of good prognosis in pediatric precursor-B ALL.

Multiple Myeloma

Loss of 1p and rearrangement of MYC are associated with progression of smouldering myeloma to myeloma: sequential analysis of a single case
Laura Checcchio, Gian Paolo Dagrada, Rebecca K.M. Protheroe, David M. Stockley, Alastair G. Smith, Kim H. Orchard, Nicholas C.P. Cross, Christine J. Harrison, and Fiona M. Ross on behalf of the UK Myeloma Forum

This case report suggests that loss of 1p and rearrangement of MYC are associated with progression of smoldering myeloma to multiple myeloma.

Amyloidosis

Hepatic response after high-dose melphalan and stem cell transplantation in patients with AL amyloidosis associated liver disease
Saulius Girnius, David C. Seldin, Martha Skinner, Kathleen T. Finn, Karen Quillen, Gheorghe Doros, and Vaishali Sanchorawala

In patients with AL amyloidosis and liver involvement, treatment with high-dose melphalan chemotherapy and autologous peripheral blood stem cell transplantation resulted in 61% overall survival at 5 years. Moreover, the transplant-related mortality (13%) was similar to that of patients with AL amyloidosis without associated liver disease.

Letters to the Editor

Acute Myeloid Leukemia

NRIP3: a novel translocation partner of MLL detected in a pediatric AML with complex chromosome 11 rearrangements
Brian V. Bulgarob, C. Michel Zwaan, Claus Meyer, Rolf Marschalek, Rob Pieters, H. Berna Beverloo, Marry M. van den Heuvel-Eibrink
Acute Lymphoblastic Leukemia

No evidence for association between TGFB1 promoter SNPs and the risk of childhood pre-B acute lymphoblastic leukemia among French Canadians
Jasmine Healy, Marie-Helene Roy-Gagnon, Daniel Sinnett

Malignant Lymphomas

Physiological PTEN expression in peripheral T-cell lymphoma not otherwise specified
Anna Gazzola, Clara Bertuzzi, Claudio Agostinelli, Simona Righi, Stefano A. Pileri, Pier Paolo Piccaluga

Continuing Medical Education

Morphological evaluation of monocytes and their precursors
Mixed lineage leukemia
The use of lamivudine to prevent hepatitis B reactivation
Clinicopathological features of lymphoma/leukemia patients with double hit lymphoma/leukemia