

Cover Figure

Aberrant cytoplasmic expression of nucleophosmin in acute myeloid leukemia with mutated NPM. This illustration is taken from the article by Falini et al. on page 439.

Editorials and Perspectives

- 321 Hematopoietic stem cell mobilization**
Roberto M. Lemoli and Alessandra D'Addio
- There are advantages from reinfusing autologous mobilized peripheral blood stem cells rather than bone marrow hematopoietic stem cells. This article focuses on the bio-molecular mechanisms underlying the release of hematopoietic stem cells from the bone marrow to help the understanding of novel strategies to make stem cell collection more effective. See related article on page 347.*

- 325 Towards the genetic treatment of β -thalassemia: new disease models, new vectors, new cells**
Paolo Moi and Michel Sadelain
- The transfer of a regulated globin gene in autologous hematopoietic stem cells is an attractive therapeutic approach to β -thalassemia, since, in principle, it is applicable to all patients. This commentary reviews recent advances in animal models, globin vector design and stem cell isolation. See related article on page 356.*

- 331 Prevention of thrombosis in polycythemia vera and essential thrombocythemia**
Raffaele Landolfi and Leonardo Di Gennaro
- Thrombotic events are a dominant clinical feature of polycythemia vera and essential thrombocythemia. Estimating the vascular risk and choosing the best antithrombotic strategy are crucial issues in the management of these disorders. This article reviews the most important risk factors for thrombosis and focuses on the available therapeutic strategies for reducing the vascular risk. See related article on page 372.*

- 336 Secondary malignancies after therapy of indolent non-Hodgkin's lymphoma**
Jonathan W. Friedberg
- Over the past decade the survival of patients with indolent non-Hodgkin's lymphoma has improved significantly. As a consequence, patients have more time to develop secondary effects of chemotherapy and radiation therapy. This perspective article focuses on risks and risk factors for the development of solid tumors in patients with such lymphomas. See related article on page 398.*

Original Articles

- 339 Hematopoiesis**
Multipotent mesenchymal stromal cells from amniotic fluid: solid perspectives for clinical application
Nadia Sessarego, Alessia Parodi, Marina Podestà, Federica Benvenuto, Massimo Moggi, Valentina Raviolo, Mario Lituania, Annalisa Kunkel, Guido Ferlazzo, Franca Dagna Bricarelli, Antonio Uccelli, and Francesco Frassonì

Mesenchymal stromal cells are multipotent cells potentially useful in regenerative medicine. These cells are usually obtained from the bone marrow; however, the cell dose may be a critical factor, and alternative sources need to be explored. This study suggests that amniotic fluid represents a rich source of mesenchymal stromal cells.

- 347 Hematopoietic Stem Cells**
Pegylated granulocyte colony-stimulating factor mobilizes CD34⁺ cells with different stem and progenitor subsets and distinct functional properties in comparison with unconjugated granulocyte colony-stimulating factor
Ingmar Bruns, Ulrich Steidl, Johannes C. Fischer, Akos Czibere, Guido Kobbe, Sascha Raschke, Raminder Singh, Roland Fenk, Michael Roszkopf, Sabrina Pechtel, Arndt von Haeseler, Peter Wernet, Daniel G. Tenen, Rainer Haas, and Ralf Kronenwett

Stem cells can be mobilized into the peripheral blood using cytokines, cytotoxic chemotherapy or a combination of both. Stimulation with pegylated-granulocyte colony-stimulating factor or granulocyte colony-stimulating factor results in different expression of key regulatory genes and different functional properties of mobilized hematopoietic stem and progenitor cells.

- 356 Thalassemia Syndrome**
A novel transgenic mouse model produced from lentiviral germline integration for the study of β -thalassemia gene therapy
Wei Li, Shuyang Xie, Xibing Guo, Xiuli Gong, Shu Wang, Dan Lin, Jingzhi Zhang, Zhaorui Ren, Shuzhen Huang, Fanyi Zeng, and Yitao Zeng

Lentiviral-mediated gene therapy has been successfully applied in the treatment of β -thalassemia. In this study transgenic mice with stable expression of a lentivirus carrying the human β -globin gene were obtained. These animals provide a useful model to investigate the stable effect of gene therapy in β -thalassemia.

- 363 Bone Marrow Failure**
SBDS-deficient cells undergo accelerated apoptosis through the Fas-pathway
Piya Rujkijyanont, Ken-ichiro Watanabe, Chhaya Ambekar, Hanming Wang, Aaron Schimmer, Joseph Beyene, and Yigal Dror

Ninety percent of patients with Shwachman-Diamond syndrome, an inherited bone marrow dysfunction, have mutations in the Shwachman-Bodian-Diamond syndrome

gene (SBDS). However, the relationship between SBDS and cell survival is unknown. This study shows that inhibition of SBDS results in accelerated apoptosis and investigates the mechanisms involved in this process.

- 372 **Myeloproliferative Disorders**
Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments
Valerio De Stefano, Tommaso Za, Elena Rossi, Alessandro M. Vannucchi, Marco Ruggeri, Elena Elli, Caterina Micò, Alessia Tieghi, Rossella R. Cacciola, Cristina Santoro, Giancarla Gerli, Nicola Vianelli, Paola Guglielmelli, Lisa Pieri, Francesca Scognamiglio, Francesco Rodeghiero, Enrico M. Pogliani, Guido Finazzi, Luigi Gugliotta, Roberto Marchioli, Giuseppe Leone, and Tiziano Barbui, for the GIMEMA CMD-Working Party

Polycythemia vera and essential thrombocythemia are typically complicated by thrombosis. According to this multicenter study recurrent thrombosis is observed in about one third of patients. Cytoreduction protects against recurrence of thrombosis. The contemporary use of oral anticoagulants or antiplatelet agents further reduce the incidence of re-thrombosis.

- 381 **Myeloproliferative Syndromes**
Activation of cytotoxic T-cell receptor $\gamma\delta$ T lymphocytes in response to specific stimulation in myelodysplastic syndromes
Jean-Jacques Kiladjian, Géraldine Visentin, Emilie Viey, Sylvie Chevret, Virginie Eclache, Jerome Stirnemann, Jean Henri Bourhis, Salem Chouaib, Pierre Fenaux, and Anne Caignard

Several immune defects have been shown to be present in patients with myelodysplastic syndromes. This study suggests that there are immune surveillance defects, which may contribute to the pathogenesis of these syndromes. Cytotoxic T-cell receptor $\gamma\delta$ T lymphocytes can be expanded in a high proportion of patients, which may be of particular value in the development of immunotherapy.

- 390 **Malignant Lymphomas**
Evaluation of response to fractionated radioimmunotherapy with ^{90}Y -epratuzumab in non-Hodgkin's lymphoma by ^{18}F -fluorodeoxyglucose positron emission tomography
Caroline Bodet-Milin, Françoise Kraeber-Bodéré, Benoît Dupas, Franck Morschhauser, Thomas Gastinne, Steven Le Gouill, Loïc Campion, Jean-Luc Harousseau, William A. Wegener, David M. Goldenberg, and Damien Huglo

FDG-PET imaging has been proven to be more accurate than conventional imaging for assessment of lymphoma response to therapy. This study evaluates the usefulness of FDG-PET for predicting response to radioimmunotherapy in patients with refractory lymphoma. The results suggest that positive FDG-PET findings 6 weeks after radioimmunotherapy predict significantly earlier relapse.

- 398 **Malignant Lymphomas**
Secondary malignancies after treatment for indolent non-Hodgkin's lymphoma: a 16-year follow-up study
Stefano Sacchi, Luigi Marcheselli, Alessia Bari, Raffaella Marcheselli, Samantha Pozzi, Stefano Luminari, Marco Lombardo, Gabriele Buda, Antonio Lazzaro, Paolo G. Gobbi, Caterina Stelitano, Fortunato Morabito, Giovanni Quarta, and Maura Brugiatielli

There is relatively little information on secondary cancers after non-Hodgkin's lymphomas. This long-term follow-up study determines the incidence rate and identifies subgroups of non-Hodgkin's lymphoma patients with increased incidences of secondary malignancy.

- 405 **Malignant Lymphomas**
A phase 2 pilot study of pegfilgrastim and filgrastim for mobilizing peripheral blood progenitor cells in patients with non-Hodgkin's lymphoma receiving chemotherapy
Nigel Russell, Rolf Mesters, Joerg Schubert, Marc Boogaerts, Hans E. Johnsen, Consuelo del Canizo, Nigel Baker, Philippa Barker, Tomas Skacel, and Norbert Schmitz

This phase 2 randomized, double-blind trial examines the efficacy of pegfilgrastim and filgrastim for mobilizing peripheral blood progenitors cells following chemotherapy in patients with non-Hodgkin's lymphoma. The results of the study suggest that pegfilgrastim may provide a suitable alternative to filgrastim in this setting.

- 413 **Chronic Lymphocytic Leukemia**
Clonal heterogeneity in chronic lymphocytic leukemia cells: superior response to surface IgM cross-linking in CD38⁺, ZAP-70⁺ positive cells
Giovanna Cutrona, Monica Colombo, Serena Matis, Marina Fabbi, Mauro Spriano, Vincenzo Callea, Ernesto Vigna, Massimo Gentile, Simonetta Zupo, Nicholas Chiorazzi, Fortunato Morabito, and Manlio Ferrarini

The reasons why immunoglobulin gene mutation status and expression of ZAP-70 and CD38 influence disease progression in chronic lymphocytic leukemia are still undefined. This study shows that CD38⁺, ZAP-70⁺ cells have a greater capacity for signalling through the B-cell receptor and suggests a function for B-cell receptor signaling in promoting cell expansion.

- 423 **Multiple Myeloma**
CD4⁺CD25⁺FOXP3⁺ T regulatory cells reconstitute and accumulate in the bone marrow of patients with multiple myeloma following allogeneic stem cell transplantation
Djordje Atanackovic, Yanran Cao, Tim Luetkens, Jens Panse, Christiane Faltz, Julia Arfsten, Katriin Bartels, Christine Wolschke, Thomas Eiermann, Axel R. Zander, Boris Fehse, Carsten Bokemeyer, and Nicolaus Kroger

Peripheral tolerance is largely maintained by immunosuppressive regulatory T cells, which typically co-express CD4, CD25 and FOXP3. This study analyzes lympho-

cyte subsets in myeloma patients treated with allogeneic stem cell transplantation, and shows that donor-derived regulatory T cells expand faster than conventional CD4⁺ T cells and have a strong inhibitory function.

Decision Making and Problem Solving

- 431 **Multiple Myeloma**
Report of the European Myeloma Network on multiparametric flow cytometry in multiple myeloma and related disorders
Andy C. Rawstron, Alberto Orfao, Meral Bekasac, Ludmila Bezdicikova, Rik A. Brooimans, Horia Bumbea, Klara Dalva, Gwenny Fuhler, Jan Gratama, Dirk Hose, Lucie Kovarova, Michael Lioznov, Gema Mateo, Ricardo Morilla, Anne K. Mylin, Paola Omede, Catherine Pellat-Deceunynck, Martin Perez Andres, Maria Petrucci, Marina Ruggeri, Grzegorz Rymkiewicz, Alexander Schmitz, Martin Schreder, Carine Seynaeve, Martin Spacek, Ruth M. de Tute, Els Van Valckenborgh, Nicky Weston-Bell, Roger G. Owen, Jesús San Miguel, Pieter Sonneveld, and Hans E. Johnsen on behalf of the European Myeloma Network

In multiple myeloma, the use of multiparametric flow cytometry in many laboratories is currently restricted to clinical research studies and the differential diagnosis of unusual cases. This article reports the indications of the European Myeloma Network for flow cytometry in patients with monoclonal gammopathies, and the technical recommendations for the analysis of plasma cells.

Brief Reports

- 439 **Acute Myeloid Leukemia**
NPM1 mutations and cytoplasmic nucleophosmin are mutually exclusive of recurrent genetic abnormalities: a comparative analysis on 2,562 patients with acute myeloid leukemia
Brunangelo Falini, Cristina Mecucci, Giuseppe Saglio, Francesco Lo Coco, Daniela Diverio, Patrick Brown, Fabrizio Pane, Marco Mancini, Maria Paola Martelli, Stefano Pileri, Torsten Haferlach, Claudia Haferlach, and Susanne Schnittger

NPM1 mutations, causing aberrant cytoplasmic expression of nucleophosmin, are the most frequent genetic alteration in acute myeloid leukemia with a normal karyotype. This study confirms in a large series of patients that NPM1 mutations and cytoplasmic nucleophosmin are mutually exclusive of recurrent genetic abnormalities.

- 443 **Acute Myeloid Leukemia**
Histone deacetylase inhibitor treatment downregulates VLA-4 adhesion in hematopoietic stem cells and acute myeloid leukemia blast cells
Ulrich Mahlknecht and Christiane Schönbein

The migration of hematopoietic progenitor cells depends on a number of cell surface molecules. This study shows that treatment with histone deacetylase inhibitors downregulates the integrin VLA-4 on acute myeloid leukemia blast cells and hematopoietic stem cells, resulting in decreased adhesion of these cells to mesenchymal stromal cells.

- 447 **Malignant Lymphomas**
Autoimmune thrombocytopenia in non-Hodgkin lymphomas

Alexander W. Hauswirth, Cathrin Skrabbs, Christian Schützinger, Markus Raderer, Andreas Chott, Peter Valent, Klaus Lechner, and Ulrich Jäger

Autoimmune thrombocytopenia is a potentially life-threatening complication in non-Hodgkin's lymphomas. This study focuses on the temporal relationship between autoimmune thrombocytopenia and lymphoma, the frequency in lymphoma subtypes, laboratory data and treatment outcome.

- 451 **Multiple Myeloma**
Normalization of the serum angiopoietin-1 to angiopoietin-2 ratio reflects response in refractory/resistant multiple myeloma patients treated with bortezomib

Konstantinos Anargyrou, Evangelos Terpos, Theodoros P. Vassilakopoulos, Anastasia Pouli, Sotirios Sachanas, Tatiana Tzenou, Stavroula Masouridis, Dimitrios Christoulas, Maria K. Angelopoulou, Evangelia M. Dimitriadou, Christina Kalpadakis, Konstantinos Tsionas, Panayiotis Panayiotidis, Meletios A. Dimopoulos, Gerassimos A. Pangalis, and Marie-Christine Kyrtsonis on behalf of the Greek Myeloma Study Group

Bortezomib is a proteasome inhibitor producing high response rates in patients with relapsed/resistant multiple myeloma patients. This study investigates the effect of bortezomib on circulating angiopoietins levels, and shows that the normalization of the angiopoietin-1/angiopoietin-2 ratio reflects the response to treatment.

- 455 **Multiple Myeloma**
High response rate and improved graft-versus-host disease following bortezomib as salvage therapy after reduced intensity conditioning allogeneic stem cell transplantation for multiple myeloma

Jean El-Cheikh, Mauricette Michallet, Arnon Nagler, Hugues de Lavallade, Franck E. Nicolini, Avichai Shimoni, Catherine Faucher, Mohamad Sobh, Daniela Revesz, Izhar Hardan, Sabine Fürst, Didier Blaise, and Mohamad Mohty

This study assesses the use of bortezomib as a salvage therapy in myeloma patients who relapse after allogeneic transplantation with reduced intensity conditioning. Bortezomib treatment is associated with a high response rate and improved graft-versus-host disease, suggesting that it is a safe and efficient therapeutic option.

- 459 Amyloidosis**
Evaluation of the serum-free light chain test in untreated patients with AL amyloidosis
Tilmann Bochtler, Ute Hegenbart, Christiane Heiss, Axel Benner, Friedrich Cremer, Martin Volkmann, Jochen Ludwig, Jolanta B. Perz, Anthony D. Ho, Hartmut Goldschmidt, and Stefan O. Schonland
- The diagnostic value of serum electrophoresis and urinary light chain excretion in AL amyloidosis is poor due to the usually low amount of monoclonal protein. This study evaluates immunoglobulin light chains in the serum of a large series of untreated patients with systemic AL amyloidosis, and proves that free light chain levels reflect disease severity.*

Letters to the Editor

- 463 Sickle Cell Disease**
Hospitalization of children with sickle cell disease in a region with increasing immigration rates
Raffaella Colombatti, Laura Visonà Dalla Pozza, Monica Mazzucato, Laura Sainati, Marta Pierobon, and Paola Facchin
- 465 Bone Marrow Failure**
Cytokines in combination to treat radiation-induced myelosuppression: evaluation of SCF + glycosylated EPO + pegylated G-CSF as an emergency treatment in highly irradiated monkeys
Michel Drouet, Christophe Delaunay, Nancy Grenier, Philippe Garrigou, Jean-François Mayol, and Francis Hérodin
- 467 ETV6/GOT1 fusion in a case of t(10;12)(q24;p13)-positive myelodysplastic syndrome**
Stephanie Struski, Laurent Mauvieux, Carine Gervais, Catherine Hélias, Kun Lun Liu, and Michel Lessard
- 469 Acute Myeloid Leukemia**
Drug-induced hypersensitivity syndrome with rapid hematopoietic reconstitution during treatment for acute myeloid leukemia
Hiroshi Suzuki, Takashi Asai, Zenshiro Tamaki, Akira Hangaishi, Shigeru Chiba, and Mineo Kurokawa
- 471 Lymphoproliferative Disorders**
Investigation of FDG-PET/CT imaging to guide biopsies in the detection of histologic transformation of indolent lymphoma
Caroline Bodet-Milin, Françoise Kraeber-Bodéré, Philippe Moreau, Loïc Campion, Benoît Dupas, and Steven Le Gouill

- 473 Chronic Lymphocytic Leukemia**
Recurrent cytogenetic findings in subsets of patients with chronic lymphocytic leukemia expressing IgG-switched stereotyped immunoglobulins
Anastasia Athanasiadou, Kostas Stamatopoulos, Maria Gaitatzi, Niki Stavroyianni, Athanasios Fassas, and Achilles Anagnostopoulos
- 475 Chronic Lymphocytic Leukemia**
High dose methylprednisolone and rituximab is an effective therapy in advanced refractory chronic lymphocytic leukemia resistant to fludarabine therapy
Moez Dungarwalla, Steve O. Evans, Unell Riley, Daniel Catovsky, Clare E. Dearden, and Estella Matutes
- 477 Disorders of Hemostasis**
Evaluation of factor V mRNA to define the residual factor V expression levels in severe factor V deficiency
Barbara Lunghi, Mirko Pinotti, Iva Maestri, Angelika Batorova, and Francesco Bernardi
- 479 Thrombosis**
Thrombophilia as a predictor of persistent residual vein thrombosis
Luca Spiezia, Daniela Tormene, Raffaele Pesavento, Laura Salmaso, Paolo Simioni, and Paolo Prandoni

Errata

- 480** Erratum in the article by Lokhorst HM et al. Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma. *Haematologica* 2008; 93:124-127

Online Only Articles

- e32** **Successful heart transplantation following melphalan plus dexamethasone therapy in systemic AL amyloidosis**
Aude Mignot, Frank Bridoux, Antoine Thierry, Shaida Varnous, Myriam Pujo, Annick Delcourt, Jean Marc Gombert, Jean-Michel Goujon, Frédéric Favreau, Guy Touchard, Daniel Herpin, and Arnaud Jaccard
- e36** **Transient global amnesia associated with the infusion of DMSO-cryopreserved autologous peripheral blood stem cells**
Zaher K. Otrock, Ahmad Beydoun, Wissam M. Barada, Rami Masroujeh, Rola Hourani, and Ali Bazarbachi
- e38** **Central nervous system relapse occurs in about 5% of cases of acute promyelocytic leukaemia**
Shailendra Kapoor