this issue, might be appropriate targets for potential immunotherapies aimed to enhance the antimyeloma activity in the near future.

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## Unrelated cord blood stem cell transplantation for AML

Postremission therapy for acute myeloid leukemia (AML) generally includes either consolidation with chemotherapy used in induction, or intensification using non–cross-resistant agents. Of approximately 60% of patients younger than 55 years who attain first remission with standard induction therapy, projected disease-free survival (DFS) rates range from 20% to 40%. Allogeneic transplantation performed in first remission can provide long-term DFS approximating 65% in young adults with histocompatible sibling grafts, with inferior outcomes observed in patients with advanced age (> 30 years), advanced disease, or infusion of unrelated adult or partially matched donors. Unrelated umbilical cord blood (UCB) has therefore been explored as a potential alternative graft source for AML patients lacking a sibling donor. However, low nucleated cell doses contained in a single UCB unit have limited its widespread use, particularly in adults, and initial reports of high-risk patients enrolled in phase 1 trials demonstrated inferior survival rates compared with conventional grafts.[1]

In this issue, Ooi and colleagues at the University of Tokyo (page 489) report clinical outcomes in 18 adults with de novo AML, of whom 14 were beyond first remission. These patients were treated with fully ablative total body irradiation (TBI)–based conditioning and infusion of allogeneic unrelated cord blood transplantation. The median age of the patients in this series was 43 years. No patient had a related or unrelated bone marrow donor available at the time of cord blood transplantation. Each patient received a single UCB unit thawed and infused without prior ex vivo expansion. Median cryopreserved UCB graft nucleated cell dose was $2.5 \times 10^7$/kg. Of these 18 adult patients, 17 demonstrated sustained donor engraftment, and median day to absolute neutrophil count of $0.5 \times 10^9$/L was 23 days. In the 17 patients demonstrating myeloid reconstitution, chimerism analyses confirmed full donor engraftment. On day 27, 1 patient died with organ toxicity, and 3 patients relapsed within the first 2 years after transplantation. The remaining 14 patients are alive and free of disease for up to 48 months of follow-up, and probability of DFS at 2 years was 76.6%. Further observations outlined in this issue parallel those reported in other adult patient series, that use of unrelated cord blood has been associated with a low incidence of severe acute and chronic graft-versus-host disease (GVHD). The majority (17) of these patients received standard cyclosporine + methotrexate as GVHD prophylaxis. One patient demonstrated severe (> grade II) acute GVHD and 3 patients demonstrated extensive chronic GVHD. All patients who are alive and disease-free received cord blood grafts containing more than $2 \times 10^7$ nucleated cells per kilogram, attributable in part to the shorter stature of these Japanese patients (median weight, 55.2 kg). These results confirm the importance of cord blood graft cell dose in determining optimal engraftment rates and survival in adults.

Recent advances in AML pathophysiology and proposed new therapeutic strategies include the following: identification of overexpressed differentiation antigens as targets of graft-versus-leukemia effect,[2] fms-related tyrosine kinase 3 (Flt3) mutations, and antibody-targeted chemotherapy with immunoconjugates of calicheamicin (gemtuzumab ozogamicin). Despite these advances, a large proportion of patients treated for AML succumb either to the disease or to complications related to its treatment. As outlined by the study reported by Ooi et al, the use of banked unrelated cord blood as an alternative allogeneic graft source results in durable remissions for adults with de novo AML, elicits low rates of severe GVHD, and is associated with acceptable survival rates. Further studies are warranted to determine the impact of improved HLA matching and higher graft cell dose threshold ($> 2 \times 10^7$/kg) on unrelated donor UCB stem cell transplantation outcomes in adults with AML.

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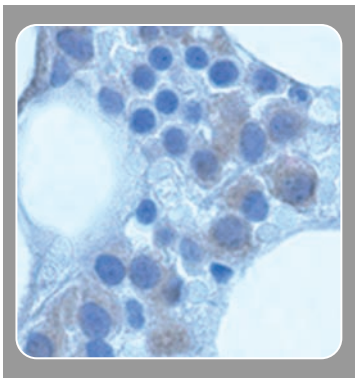
## BAFF and related proteins: a new therapeutic target for B-cell malignancies

For many years, investigation of new therapeutic agents for multiple myeloma (MM) and chronic lymphocytic leukemia (CLL) has been limited to empiricism based in part on our lack of understanding of the pathogenesis of each disease. During this time period, basic laboratory studies have led to a better understanding of the pathways that promote normal immunologic function in nontransformed B cells and how these pathways are effectively perturbed in the malignant transformed B-cell counterpart to promote the manifestations of disease. Such work has led to identification of several molecules that promote survival, including members of tumor necrosis factor superfamily ligand family B-cell–activating factor (BAFF) (also known as BlyS or B-lymphocyte stimulator) and a proliferation-inducing ligand (APRIL). BAFF and APRIL serve to enhance normal B-cell response to antigens, production of antibodies, and survival.[1] In several autoimmune

diseases, APRIL and BAFF are present in their most active form and likely play a role in the pathogenesis of these processes.[2] Recently the importance of APRIL and BAFF in the pathogenesis of several B-cell malignancies has been recognized. In this issue of *Blood*, Kern and colleagues (page 679) extend this knowledge further by providing a detailed functional assessment of both BAFF and related APRIL along with their corresponding receptors in primary CLL cells. Prior to this study and another by Novak et al,[3] the main source of BAFF and APRIL was believed to be monocytes, granulocytes, and dendritic cells. The compelling studies herein demonstrating expression of BAFF and APRIL from whole cellular lysates derived from patients' CLL cells confirm the previous observation of Novak et al.[3] The presence of BAFF and APRIL is also



demonstrated on the cell membrane and in the serum of samples derived from patients with CLL, suggesting an autocrine loop of stimulation from these cells. As with other inappropriate autocrine loops following neoplastic transformation, Kern and colleagues confirm quite rigorously that BAFF and APRIL promote cell survival of primary CLL cells against both spontaneous apoptosis in vitro and that induced by the potent lympholytic agent flavopiridol. Their studies extend beyond this functional assessment to definitively establish a potential autocrine cytokine network that mediates its biologic effect at least in part through activating the nuclear factor κB (NF-κB) pathway. Altering this signaling pathway by blocking BAFF interaction with the BAFF receptor disrupts a positive survival signal and leads to CLL cell apoptosis. Novak and colleagues (page 689) in an accompanying paper in this issue of *Blood* describe a similar important role for BAFF in multiple myeloma where BAFF expression has been noted and serves to disrupt apoptosis in multiple myeloma cell lines and primary tumor cells. This work extends previous important findings on BAFF and APRIL in CLL. Overall, both of these studies provide strong support for further investigation of the signaling pathways activated following ligation of these specific receptors and dissection of differences that might exist based on $V_H$ mutational status in CLL or cytogenetic group in both CLL and multiple myeloma. From a clinical standpoint, these data provide compelling justification to consider initiation of trials in CLL and multiple myeloma with agents such as LymphoStat-B, a neutralizing antibody to BAFF that has the potential to interrupt this important autocrine cytokine network. Additional efforts to develop antagonistic antibodies or small molecule inhibitors to these specific ligand-receptor signaling pathways would be of great future interest for therapeutic use in CLL and multiple myeloma.

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## Added challenges to gene therapy—immune responses in the setting of myeloablation

The genetic modification of hematopoietic stem cells (HSCs) holds promise as a therapeutic modality for a variety of disorders, including inherited metabolic disorders, malignancies, and HIV. The recent description of leukemia in children treated with HSC gene therapy[1] is a reminder that although this methodology has made significant advances, the ultimate application of a safe and effective stem cell gene therapy requires additional preclinical testing. It needs to be recognized that many HSC gene therapy strategies introduce a foreign gene as part of the therapy, and immune responses to such proteins are not fully understood. It has been demonstrated in studies in nonhuman primates that the delivery of foreign genes using oncoretroviral vectors does in fact elicit an immune response in certain instances, particularly in the setting of nonmyeloablative conditioning. In contrast, in previous reports that have described similar strategies using myeloablative conditioning, such immune responses were not observed, resulting in the conclusion that myeloablation was necessary for tolerance to develop to the transgene product(s). This further emphasizes the importance of suitable large-animal models to evaluate both the safety and efficacy of such approaches.

In this issue, Morris and colleagues (page 492) report the detection of cellular immune responses to foreign gene products in the setting of myeloablation. These observations raise the possibility that previous studies indicating that ablation facilitated the development of tolerance to a transgene product may not have fully appreciated the complexities of gene transfer strategies. In these studies the authors chose to evaluate the use of lentiviral vectors, which can transduce nondividing cells and therefore offer an advantage compared with oncoretroviral vectors. They had previously demonstrated that in baboons that received transplants of oncoretroviral vectors expressing green fluorescent protein (GFP) in a myeloablative transplantation setting, durable GFP expression was observed.[2] In contrast, in the studies presented here, using a similar conditioning protocol and lentiviral vectors, labeled cells disappeared relatively rapidly. This unexpected observation prompted the authors to evaluate whether the disappearance of the labeled cells was associated with a cellular immune response. Clear data establishing the evolution of a cellular immune response (cytotoxic T lymphocyte [CTL]) to the transgene product are presented, and development of this immune response was associated with the disappearance of labeled cells. Based on the fact that this was different from what they had observed with lentiviral vectors, the authors evaluated the frequency and phenotype of the transduced cells