Anti-cd20 antibodies with increased antigen binding affinity and enhanced effector function
H. Lowman (South San Francisco, USA)

Phenotypic and functional characterization of B-cell specific antigens: does targeting them modulate disease?
D.G. Maloney (Seattle, USA)

Targeting trail death receptors in lymphoma
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Immunotherapy of lymphoma
R. Levy (Palo Alto, USA)

Angiogenic mediators support growth and metastasis in myeloma and lymphoma
J.P. Leonard (New York, USA)
are decoy receptors.5 Thus, TRAIL preferentially kills cancer cells as they express TRAIL-R1 and TRAIL-R2. TRAIL has demonstrated antitumor activity against most human cancer cell lines, including lymphoma.6 Both TRAIL/Apo2L and anti-TRAIL-R1 and TRAIL-R2 agonistic antibodies can induce cell death in cancer cells by recruiting caspase 8 and 10 and activating the extrinsic apoptotic pathways.7 Several preclinical experiments demonstrated that activating TRAIL death receptors in lymphoma may have a potential therapeutic value.8 Preliminary data from a phase 2 study using the therapeutic monoclonal antibody mapatumumab targeting TRAIL-R1 demonstrated excellent safety but with modest clinical activity in NHL.9 Three patients (8%) with relapsed follicular lymphoma had a response to therapy, with one complete remission and two partial responses after a maximum of 6 cycles, with over 30% having stable disease. A phase 1 study using Apo2L/TRAIL recombinant protein also demonstrated an excellent safety profile. Based on preclinical experiments demonstrating synergy between TRAIL pathway and rituximab against B-cell lymphoma,2,10 a randomized study is currently being conducted comparing TRAIL/Apo2L with rituximab and the combination of rituximab plus Apo2L/TRAIL.11 Results from this ongoing study will provide valuable information on the clinical value of this approach in patients with relapsed follicular lymphoma.

Selected References:

IMMUNOTHERAPY OF LYMPHOMA
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Molecular Defined Target
Since B-cell lymphomas are the clonal proliferation of lymphocytes, the immunoglobulin they express is unique, and it can be regarded as a tumor-specific antigen. The first monoclonal antibodies used in human lymphoma were directed against this target and were successful.

Three phase 3 clinical trials have now been conducted (Biovest, Genitope, and Favrille). Two trials have finished accrual, and one has just announced results (Genitope). The Genitope trial showed no difference in the progression-free survival between the arm vaccinated with idiotype (Id)-KIH plus GM-CSF vs the control arm, which was vaccinated with KLH plus GM-CSF. However, there was a highly significant difference among the patients on the Id-specific vaccine arm who mounted a positive immune response compared to those who did not make an immune response. This result confirms the observations made in past phase 2 trials and leads to the conclusion that the ability to make an anti-idiotype immune response is some kind of biomarker for clinical outcome in follicular lymphoma (FL). It now becomes important to identify this subset of patients in other ways so that the biology of the disease can be better understood.

Forced Presentation of Tumor Antigens
We have now described a new strategy of therapeutic vaccination against lymphoma that combines tumor cell death induction with local injection of CpG oligonucleotides, a ligand for the Toll-like receptor 9 ligand. As a result, antigen-presenting cells pick antigens from dying tumor cells and are stimulated to present them to T cells. The ensuing T-cell response then eliminates systemic disease. These T cells can be further conditioned with hematopoietic stem cells into tumor-bearing donors and can expand to eliminate large, established tumors. In the animal model, we have shown that both cell-death induction and direct intratumoral injection of the CpG are necessary. We have now completed a pilot clinical trial and documented therapeutic efficacy of this maneuver in patients with low-grade lymphoma. In the future, direct intralymphatic injection of CpG could be combined with many different methods of tumor cell death induction.

ANGIOGENIC MEDIATORS SUPPORT GROWTH AND METASTASIS IN MYELOMA AND LYMPHOMA
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Angiogenesis, blood vessel formation, is required for tumor growth, and its importance is becoming increasingly evident in hematologic malignancies. Various studies have attempted to correlate the number and character of tumor-associated blood vessels with clinical outcome. Additionally, several angiogenic mediators appear to be important in tumor biology. Vascular endothelial growth factor (VEGF) is a signaling protein with several isoforms and is centrally important in vasculogenesis. Chemokines also play a role in tumor-associated angiogenesis. One example is SDF-1 alpha, a CXC chemokine that has been associated with tumor angiogenesis in multiple myeloma (MM) patients. Increased angiogenesis has been linked with decreased survival in MM and with relapse or resistance to chemotherapy in lymphoma. Therefore, it appears that antiangiogenic strategies may have a role in potentially improving outcomes for patients with MM or lymphoma. A relatively nonspecific strategy is the use of metronomic chemotherapy. Continuous or intermittent chronic use of low-dose oral cytotoxic agents can have antitumor effects in various settings, including those where higher dose, bolus chemotherapy is ineffective. An example of such a strategy is the PEP-C regimen, which has been explored by our group in a variety of settings and which is active and well-tolerated. Bevacizumab, a recombinant humanized antibody, inhibits angiogenesis by blocking VEGF receptors and is now being tested in lymphomas and multiple myeloma. Bevacizumab is undergoing testing with CHOP-based chemotherapy (+/- rituximab) in a variety of settings. In one study, diffuse large B-cell lymphoma (DLBCL) patients treated with a combination of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and bevacizumab had an 85% overall response rate. Immunomodulatory agents such as thalidomide and lenalidomide are also undergoing extensive evaluation in myeloma and lymphoma and clearly have important therapeutic activity. While they appear to work through a variety of pathways, one mechanism of action relates to effects on tumor angiogenesis. Finally, there are a number of novel compounds, including small molecule VEGF receptor inhibitors and heat shock protein 90 inhibitors, with antiangiogenic effects that are currently being studied. Emerging data suggest that the incorporation of strategies targeting tumor vasculature along with standard treatments or other novel agents is likely to ultimately contribute to improved outcomes for patients with lymphoma and myeloma.