of PECAM-1, including homophilic contact binding, intact immunoreceptor tyrosine-based inhibitory motifs (ITIMs), and, in part, recruitment and activation of the protein-tyrosine phosphatase, SHP-2. The authors propose that the formation of the PECAM-1/SHP-2 signaling complex may affect signal transduction pathways that modulate either the location and/or activation state of pre-existing pro- and antiapoptotic components of the cell-death pathway.

While the concept that homophilic engagement of PECAM-1 can result in the transduction of survival signals in vascular endothelial cells and in macrophage phagocytosis has been previously demonstrated (Noble et al, J Immunol. 1999;162:1376-1383; Brown et al, Nature. 2002;418:200-203), these workers attempt to define the complex molecular mechanisms by which PECAM-1 may exert cytoprotective effects in suppression of apoptosis. They show that PECAM-1 can negatively regulate intrinsic mitochondrial-dependent Bax-mediated apoptosis by preventing a post–Bax-translocation event, but not extrinsic Fas-mediated apoptosis. This cytoprotective effect of the PECAM-1/SHP-2 signaling pathway does not appear to involve phosphatidylinositol-3 (PI-3) kinase–serine/threonine kinase (Akt), or integrin activation. Further studies will be required to unravel the importance of PECAM-1 ITIM (inhibitory) and ITSM (switch)–signaling properties, the spatial-temporal organization of signaling complexes, and subcellular compartmentalization that lead to modulation of pre-existing signaling circuits, including the cell-death machinery.

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γδ T cells in cancer immunotherapy

The largest subset of human γδ T cells is the Vγ2 (alternate Vγ9) Vδ2 subset, comprising 2% to 5% of peripheral blood T cells. These Vγ2Vδ2 T cells uniformly recognize nonpeptide alkylamine, nitrogen-containing bisphosphonate, and organophosphate antigens in a T cell receptor (TCR)–dependent fashion. Such recognition enhances γδ T cell–mediated cytotoxicity, and secretion of IFN-γ and TNF-α, which are important antitumor effector mechanisms (Morita et al, Springer Sem Immunopath. 2000;22:191-217).

Mouse models provide strong evidence for γδ T cell–mediated resistance to tumors and infection. In humans, certain lymphoma and myeloma cells display cell-surface antigens that are recognized in a Vγ2Vδ2 TCR-dependent manner. Others display nonclassical major histocompatibility complex (MHC) class I–related proteins such as MHC class I–related chain A (MICA) and UL16 binding proteins (ULBPs) that can be recognized by NKG2D receptors on activated γδ T cells. Cells from common cancers metastatic to bone, such as those from breast cancer and prostate cancer, can be exposed to large concentrations of bone-avid nitrogen-containing bisphosphonates, such as pamidronate and risedronate. Such exposure may kill these cells directly, in several days, but γδ T cells can kill these sensitized cells in a matter of minutes. Thus, bisphosphonates can at once activate γδ T cells and sensitize tumor cells for elimination by γδ T cells (Das et al, Blood. 2001;98:1616-1618). Treatment of multiple myeloma with pamidronate has increased survival and decreased the incidence of metastatic lesions and pathologic fractures (Berenson et al, J Clin Oncol. 1998;16:593-602).

In this issue, Wilhelm and colleagues (page 200) report successful treatment of refractory lymphoma and myeloma with pamidronate and interleukin 2 (IL-2). Importantly, objective clinical responses correlated with proliferation of γδ T cells in vivo, strongly suggesting a role for γδ T cells in mediating the response. As more potent γδ T-cell antigens are coupled with treatments earlier in disease, we can soon expect even better results. These data represent an important initial step in manipulating γδ T cells in vivo to treat tumors and, perhaps, to treat or prevent infections that accompany them.

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Resistance to imatinib: more and more mutations

In the short time since the introduction of imatinib in 2001, investigators have already defined the primary mechanisms of drug resistance: mutations in the *BCR-ABL* gene that affect drug binding or an overall increase in the level of BCR-ABL protein due to gene amplification. In this issue, Branford and colleagues (page 276) report the first comprehensive mutation analysis of an unselected population of chronic myeloid leukemia (CML) patients treated with imatinib. The key finding is a very tight correlation between detection of a mutation and relapse, dispelling any remaining doubt about the causal role that mutations play in imatinib resistance.

A few additional points are worth noting. First, the authors find that mutations in the adenosine triphosphate (ATP)–binding loop confer a worse prognosis than other mutations, raising the possibility that early detection would mandate a change in treatment. Second, new clinical mutations are described here that were also picked up in a cleverly designed in vitro screen for imatinib resistance (Azam et al, Cell. 2003;112:831-843). Finally, the probability for finding a mutation increases with disease duration.

This last point is particularly important because it provides the first epidemiologic support for a clonal expansion model of imatinib resistance arising from pre-existing mutant subclones (Shah et al, Cancer Cell. 2002;2:117-125). The theory goes as follows. The CML clone makes sequence errors during DNA replication, some of which affect *BCR-ABL*. Over time, increasing clonal diversity raises the likelihood of generating imatinib-resistant subclones that expand in the setting of imatinib treatment. This model is based on data from patients who were treated with imatinib several years after their initial CML diagnosis. Will early imatinib treatment of newly diagnosed CML patients prevent this

clonal evolution? Or is it too late? Time will tell.

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New insight into myeloma lytic bone disease

Myeloma is intimately associated with changes in the bone marrow microenvironment. Transformation from the premalignant monoclonal gammopathy of unknown significance (MGUS) to overt myeloma is preceded and can be predicted as long as 3 years in advance by a coupled increase in bone turnover (Bataille et al, J Clin Invest. 1991;88:62-66). With transformation, coupling between bone resorption and formation is lost, so that osteoblast number and activity is diminished while osteoclast activity remains elevated, resulting in lytic bone disease, the most debilitating manifestation of myeloma. Increasing amounts of data from clinical studies and murine models suggest that the myeloma-associated changes in the bone marrow microenvironment are essential for maintaining the disease process, in addition to being responsible for disease manifestations.

In this issue, Oyajobi and coworkers (page 311) provide new insight into the role of macrophage inflammatory protein 1α (MIP-1α) in myeloma-associated lytic bone disease. MIP-1α is produced by myeloma cells and has been implicated in myeloma-associated osteoclastic bone destruction. The investigators demonstrate that MIP-1α alone is sufficient to produce osteolytic bone lesions. In the 5T murine model, neutralizing antibodies to MIP-1α reduced osteoclast-mediated osteolysis in myeloma-bearing mice, and reduction in lytic bone disease was associated with reduction in tumor burden. Experiments with RANKL$^{-/-}$ knockout mice convincingly demonstrate that MIP-1α–induced osteoclast formation is RANKL dependent.

These results give rise to an intriguing proposition of molecular cooperation between MIP-1α and RANKL in promoting myeloma-associated lytic bone disease: high concentrations of MIP-1α produced by myeloma cells attract monocytes/osteoclast progenitors to bone marrow areas infiltrated with myeloma cells, where RANKL expressed by myeloma cells (Heider et al, Clin Cancer Res. 2003;9:1436-1440) and other cells in the bone marrow microenvironment induce their differentiation into mature osteoclasts. This work also concurs with previous reports of the dependence of myeloma cells on osteoclast activity (Yaccoby et al, Br J Haematol. 2002; 116:278-270).

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