Advanced tumors, including leukemia, represent heterogeneous cell populations evolved from original malignant clones. Chemotherapy of leukemia is often associated with selection of drug-resistant cells followed by progression/relapse of the disease. Implementation of molecules that specifically target leukemia cells with minimal toxicity to normal tissues might significantly improve outcome of leukemia treatment. TRAIL belongs to the tumor necrosis factor (TNF) ligand family of cytokines. TRAIL triggers apoptosis in target cells via the receptor-mediated apoptotic pathway. Receptors for TRAIL can be divided into death receptors, TRAILR1/
DR4 , TRAIL-R2/DR5, and decoy receptors, TRAIL-R3/DcR1, TRAIL-R4/DcR2, osteoprotegerin/OPG/TRAIL-R5, based on their ability to transduce apoptotic signal. While normal tissues, including hematopoietic progenitor cells, are resistant to TRAIL-induced apoptosis, TRAIL induces programmed death in many tumor cell lines and primary cells. Various malignant cell lines and primary tumor cells, however, show resistance to TRAIL-induced apoptosis. TRAIL-resistance could represent important limitation for the potential TRAIL anti-tumor therapy. Combined *in vitro* application of TRAIL with other anti-cancer agents often increased sensitivity or overcame resistance of the tumor cells to the given chemotherapeutics or to TRAILinduced
apoptosis. The combination of TRAIL and cytotoxic agents improved therapeutic outcome compared to TRAIL or cytotoxic agents alone in several preclinical studies in tumor xenotransplanted immunodeficient mice models. Despite the work that has been accomplished the therapeutic potential of interactions between
TRAIL and a variety of established or experimental chemotherapeutical agents are still
incompletely understood. Several molecular mechanisms responsible for TRAIL

resistance have been described up to now. Most of the studies, however, focused on constitutive TRAIL resistance in solid tumors. Molecular mechanisms responsible for acquired TRAIL resistance in hematological malignancies remain to the large extent elusive.