Abstract:
Natural killer (NK) cells play critical roles in host defense against cancer. Our group is exploring a number of avenues to enhance NK cell function against leukemia. These include novel strategies to expand off-the-shelf cord blood (CB) derived NK cells based on their co-culture with genetically-modified feeder cells that express membrane-bound cytokines and co-stimulatory molecules. The methods ensure reliable expansion and activation of human CB NK cells and have been implemented in a GMP-grade large-scale setting to support ongoing clinical trials of CB-NK adoptive therapy.

To redirect NK cell specificity and enhance their in vivo persistence, we have successfully transduced expanded CB NK cells with a retroviral vector incorporating the genes for CAR-CD19, IL-15 and inducible caspase-9-based suicide gene (iC9), and demonstrated efficient killing of CD19-expressing cell lines and primary leukemia cells in vitro, with dramatic prolongation of survival in a xenograft Raji lymphoma murine model. IL-15 production by the transduced CB-NK cells critically improved their function. Moreover, iC9/CAR.19/IL-15 CB-NK cells were readily eliminated upon pharmacologic activation of the iC9 suicide gene. In conclusion, we have developed a novel approach to immunotherapy using engineered CB-derived NK cells which are easy to produce, exhibit striking efficacy and incorporate safety measures to limit toxicity. This approach should greatly improve the logistics of delivering this therapy to large numbers of patients, a major limitation to current CAR therapies.

Based on these promising preclinical data, we have initiated a Phase I/II clinical study to test the safety and efficacy of escalating doses of off-the-shelf iC9/CAR.19/IL-15 CB-NK cells in patients with relapsed or refractory B-lymphoid malignancies. Data from the trial will be presented at the meeting.