*Title & Author information populated by information given in the form field. *Does not need to be included in abstract field.*

INTERLEUKIN-21 ENHANCES NATURAL KILLER CELL ACTIVATION IN RESPONSE TO ANTIBODY-COATED TARGETS

Julie M Sands[1], Robin Pariha[2], James Lehman[3], Susheela Tridandapani[5], and William E. Carson[4].

1. Integrated Biomedical Sciences Graduate Program, 2. Molecular Virology, Immunology, and Medical Genetics, 3. Center for Biostatistics, 4. Department of Internal Medicine, 5. Department of Surgery, College of Medicine

Natural killer (NK) cells express an activating receptor for the Fc portion of IgG (FcγRIIIa) that mediates antibody-dependant cellular cytotoxicity (ADCC) and the production of immune modulatory cytokines in response to antibody (Ab)-coated targets. Interleukin (IL)-21, a member of the common gamma chain family of cytokines, has anti-tumor activity in murine models that depends in part on its ability to stimulate NK cells and promote the secretion of interferon-gamma (IFN-γ). We hypothesized that the FcR-mediated NK cell response to immobilized IgG would be enhanced by the administration of IL-21. Purified human NK cells cultured with IL-21 and immobilized IgG or human breast cancer cells coated with a therapeutic monoclonal Ab (trastuzumab) secreted large amounts of IFN-γ. Increased secretion of TNF-α and the chemokines IL-8, MIP-1α, and RANTES was also observed under these conditions. NK cell IFN-γ production was dependent on distinct signals mediated by the IL-21 receptor and the FcR and was abrogated in NK cells from STAT1-deficient mice. Supernatants derived from NK cells that had been stimulated with IL-21 and monoclonal Ab (mAb)-coated breast cancer cells were able to drive the migration of naïve and activated T cells in an *in vitro* chemotaxis assay. IL-21 also enhanced NK cell lytic activity against Ab-coated tumor cells. Co-administration of IL-21 and Ab-coated tumor cells to immunocompetent mice led to synergistic production of IFN-γ by NK cells. Furthermore, the administration of IL-21 augmented the effects of an anti-HER2/*neu* mAb in a murine tumor model. These findings demonstrate that IL-21 significantly enhances the NK cell response to Ab-coated targets and suggest that IL-21 would be an effective adjuvant to administer in combination with anti-tumor mAbs.