TRANSDUCTION OF NK-92 CELLS WITH A HIGH AFFINITY VARIANT OF THE FC RECEPTOR TO ENHANCE ANTIBODY DEPENDENT CELLULAR CYTOTOXICITY

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Natural Killer (NK) cells are part of the innate immune system. They play a key role in the body’s immunosurveillance and clearance of cells that have undergone malignant transformations. This has led to the investigation of various adoptive NK cell and NK cell line-based immunotherapies. Adoptive immunotherapy with primary NK cells has obstacles including limited ex vivo expansion and variations between patients. Using NK-derived cell lines bypasses these obstacles and thus has become attractive clinically. NK-92 is a human NK-derived cell line that is currently being tested in a phase I trial at Princess Margaret Cancer Centre.

One way to enhance current NK immunotherapies may be to genetically engineer them to express a factor that targets and activates them against cancer cells. One such molecule is the Fc receptor: CD16. Although primary NK cells already express CD16, NK-92 cells lack this polypeptide and kill cancer cells through other mechanisms. CD16 mediates antibody dependent cellular cytotoxicity (ADCC) by binding to the Fc portion of antibodies that are bound to tumor-associated antigens on the surface of cancer cells. Thus, adding CD16 onto NK-92 cells should enhance their specificity and cytotoxicity in the presence of cancer-specific antibodies by giving them another effective killing mechanism.

A high affinity variant, CD16a.F176V was subcloned into a lentivector (LV) construct. High-titer LV was packaged and used to effectively transduce NK-92 cells. The transduction has been shown to be stable. In vitro testing is currently underway to ascertain whether CD16a.F176V+ NK-92 cells demonstrate enhanced ADCC and if this makes them a superior immunotherapy effector over the NK-92 cell line currently in clinical trials. In our future work, we will test transductions of other receptors and other factors that might enhance the anticancer potential of the NK-92 (and similar) cell lines.