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

Elliot M Berinstein[1], Robyn AA Oldham[1], Brent Williams[2], Armand Keating[2], Jeffrey A Medin [1,3,4]

[1]Department of Medical Biophysics [2]Cell Therapy Program, Princess Margaret Hospital, 610 University Ave, Toronto, ON, Canada [3]Institute of Medical Sciences, [4]University of Toronto, Toronto, Ontario, Canada, 3 University Health Network, Toronto, Ontario, Canada.

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 F_C 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 F_C 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.