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## Xenogeneic Model of Anti-tumor Activity Mediated by Human Embryonic Stem Cell-Derived NK Cells

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The derivation of both myeloid and lymphoid cells from human embryonic stem cells (hESCs) clearly establishes hESCs as an important model system to study human hematopoiesis. However, the potential for clinical applications of hESC-derived hematopoietic cells still remain poorly characterized. Recent studies demonstrate in vitro activity of hESC-derived natural killer (NK) cells that have the ability to kill multiple human tumor cell lines. Now, we aim to more clearly characterize the in vivo function of hESC-derived NK cells and to determine their potential application for clinical therapy against human malignancy. One series of in vivo studies clearly demonstrate the ability of hESC-derived natural killer (NK) cells to eradicate human K562 erythroleukemia cells in a xenogeneic mouse model. In order to extend these findings to other malignancies, we are investigating in vivo activity of hESC-derived NK cells in two other tumor models, PC3 prostate cancer cells and MCF7 breast cancer cells. Dose titration experiments were conducted in which PC3 cells expressing firefly luciferase (luc) were subcutaneously injected into the dorsal flank of sub-lethally irradiated NOD/SCID mice. The luc<sup>+</sup> cells allow serial bioluminescent imaging to follow growth of the tumor cells non-invasively over a prolonged time course and sensitive detection of micro-metastasis. Our results demonstrate the ability of PC3 cells to engraft and proliferate within the mouse after injection. Additionally, luciferase expressing MCF7 breast cancer tumor cells were genetically engineered via nucleofection using currently existing expression plasmids. These cells have demonstrated stable luciferase and GFP-expression over several cell passages. Dose titration experiments utilizing luc<sup>+</sup> MCF7 cells are now underway and we expect results similar to those obtained for the PC3 tumor cells. Ultimately, investigation of the efficacy of hESC-derived NK cells to clear both established human tumors and metastatic disease in the xenogeneic mice will be compared to the efficacy of NK cells derived from human umbilical cord blood.



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