T-CELL ANTIGEN COUPLER (TAC TECHNOLOGY)

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Engineering T cells with chimeric antigen receptors (CARs) is proving to be an effective method for directing T cells to attack tumors in an MHC-independent manner. Current generation CARs aim to recapitulate T cell signalling by incorporating modular functional components of the TCR and co-stimulatory molecules. Development of next generation CARs has relied upon trial and error evaluation of signalling domains. We sought to develop an alternate method to re-direct the T cell receptor which does not rely upon the incorporation of signalling domains into the chimeric receptor. To this end, we developed the T-cell Antigen coupler (TAC) technology. The membrane-anchored TAC redirects the TCR in the presence of tumor antigen. We also included components of the CD4 co-receptor to provide requisite Lck signaling upon ligation of the tumor antigen. Our prototype receptor was directed against the HER-2 proto-oncogene. We have determined that engineering peripheral blood T cells with this novel receptor (CD4-TAC) engenders tumor-antigen specific activation of numerous T cell functions, including cytokine production, degranulation and cytolysis – equivalent to, if not greater than, a 2nd generation CAR bearing the CD28 and CD3zeta signalling domains. Future iterations of the engineered T cells will include chimeric co-stimulatory receptors to enhance T cell functionality and reduce off target toxicity. This research was supported by the Canadian Institutes of Health Research and the Terry Fox Foundation.