

# Updates in adoptive T cell therapy

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## Abstract

We are exploring the use of engineered T cells bearing chimeric receptors and strategies to augment their antitumor efficacy in adoptive transfer settings. The surface membrane glycoprotein mesothelin is a promising target for the immunotherapy of mesothelioma, ovarian, and pancreatic tumors due to the uniform overexpression of mesothelin and the benign phenotype of mesothelin null mice. We hypothesize that previous trials of adoptive immunotherapy for cancer that have used CTL have failed due to poor trafficking to sites of tumor, and insufficient effector functions to self antigens. Our preclinical data indicates that use of lentiviral engineered T cells with chimeric receptors that incorporate a 'tumor resistance genotype' should have improved function for cancer immunotherapy. We have tested mesothelin redirected T cells in humanized mouse models bearing tumor xenografts. The T cells are able to eradicate large, well established tumors at an E:T ratio of at least 1:70 *in vivo*. As a complementary strategy, we have engineered artificial antigen presenting cells (aAPC) to express ligands for either CD28 or ICOS. These aAPC appear to be useful to reprogram T cells, and increase the antitumor efficacy of mesothelin redirected T cells. Three routes of administration with redirected T cells have been tested in mice bearing xenografted flank tumors. The intraperitoneal route was found to be inferior to intravenous or direct intratumoral injection of the redirected T cells. Long term engraftment of the redirected T cells correlates with antitumor efficacy.