

Genetic Engineering of T-Cells to Benefit Anti-Tumor Immunotherapy

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Adoptive cell therapy with genetically engineered T-cells is providing a new approach to treat a variety of lymphomas, leukemias and solid tumors. For most cancer patients their T-cells, an important anti-tumor component of the immune system, become tolerant to tumor cell antigens. The inability of the immune system to respond to tumors has remained a major barrier to immune-mediated anti-cancer therapies, but novel modifications to patients' T-cells promise to overcome this problem.

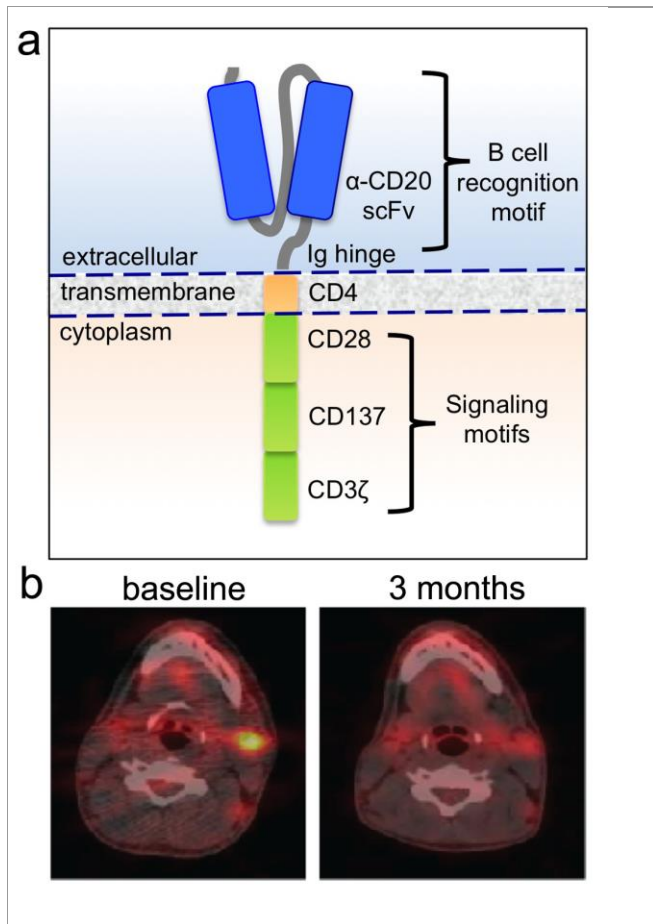
In adoptive T-cell therapy, patients' T-cells are isolated, stimulated to proliferate, and engineered to express a chimeric antigen receptor (CAR). The CAR specifically recognizes a tumor antigen and is capable of signaling the T-cell to proliferate and mount a cytotoxic response against the tumor.

A recent pilot study by Drs. Brian Till, Oliver Press and colleagues in the Clinical Research Division has combined recent advances in genetic engineering of T-cells with pre-transfer lymphodepletion to treat non-Hodgkin lymphoma patients. In this study, T-cells from three patients with relapsed indolent B-cell lymphomas were expanded and engineered to express a CAR recognizing CD20, a cell surface protein expressed on the patients' B-lineage tumor cells. In addition, the intracellular portion of the CAR contained the CD28 and CD137 co-stimulatory domains, a maneuver that has recently been shown to enhance T-cell activity compared to earlier generations of T-cell therapies. The inclusion of multiple co-stimulatory domains increased T-cell expansion and cytokine production *in vitro*, and was expected to produce better anti-tumor responses *in vivo*. Prior to T-cell transfer, patients were treated with cyclophosphamide chemotherapy to cause lymphodepletion, with the goal of improving engraftment of the transferred T-cells. Patients were then followed for the presence of the modified T-cells and their anti-tumor effects.

The treatment was generally well tolerated, and was associated with possible anti-tumor effects in all three patients. Similar patient groups not receiving adoptive T-cell therapy generally progress within 6 months; however, two patients in this study remained progression-free for one and two years following treatment. The third patient had a partial remission, but relapsed one year after the T-cell transfers. The engineered T-cells were detected in blood up to one year, and no host responses against the engineered T-cells were detected. Thus, this pilot study supports recent modifications to

CAR design and pretreatment lymphodepletion as promising anti-tumor immuno-therapies. Ongoing developments in *ex vivo* culturing and T-cell modifications, which are aimed at establishing greater CAR surface expression, T-cell proliferation and effector function *in vivo*, are hoped to provide more durable anti-tumor T-cell responses in future patients.

[Till BG, Jensen MC, Wang J, Qian X, Gopal AK, Maloney DG, Lindgren CG, Lin Y, Pagel JM, Budde LE, Rautitschek A, Forman SJ, Greenberg PD, Riddell SR, Press OW](#). CD20-specific adoptive immunotherapy for lymphoma using a chimeric antigen receptor with both CD28 and 4-1BB domains: pilot clinical trial results. *Blood*. DOI: 10.1182/blood-2011-10-387969.



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(a) Schematic of anti-CD20 chimeric antigen receptor (CAR). (b) PET-CT scan of a cervical lymph node at baseline and 3 months after receiving anti-CD20 CAR T-cell infusions, showing the clinical response of a B-cell lymphoma patient to the new 'third generation' CD20-specific adoptive immunotherapy.