How to Breed a Rare Bird: Endogenous T Cell Therapy Made Possible

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The human body has a number of defense mechanisms that kick in under the threat of foreign antigens, and one of the more important ones is the activation of white blood cells called T cells. A subset of these white blood cells, which attack virus-infected cells and tumor cells, expresses the glycoprotein CD8 at their surfaces, and are consequently called CD8+ or cytotoxic T cells. Although our immune systems capably manage a multitude of potentially harmful situations, even the best of frameworks need some external support on occasion. Among the more troublesome conditions is cancer, which has a particularly nasty way of hiding from its antagonists, necessitating sophisticated methods for boosting T cells to operate more efficiently.

In a recent publication in *Journal for Immunotherapy of Cancer*, Fred Hutch's Dr. Seth Pollack demonstrated a promising technique for enabling so called adoptive T cell therapy of various tumor types. Adoptive T cell therapy is a seemingly simple concept: T lymphocytes are taken from the patient's own body, multiplied and possibly modified *ex vivo*, and then re-infused into the patient. For instance, cells can be engineered with so called chimeric antigen receptors (CAR) and T cell receptors (TCR), which have been tested against various cancers demonstrating great promise for this new treatment modality. However, the practical use is unfortunately limited by the regulatory and logistical burdens following gene transfer approaches.

Another possibility is to explore the patient's blood and fish out any available T cells that are inherently antigen-specific, expand them, and subsequently re-introduce them to the patient. The feasibility of this endogenous T cell therapy has been proven for certain tumor antigens, but for other, more commonly expressed ones, the approach has been less successful due to low numbers of circulating antigen-specific cytotoxic T cells. Dr. Pollack and colleagues from the Clinical Research Division wanted to explore this track and chose to focus their efforts on NY-ESO-1, an antigen that is expressed in breast, lung and ovarian cancer, as well as in melanoma and sarcoma. They developed a strategy that exploits one of their previous discoveries: that the signaling protein interleukin-21 can aid the multiplication of T cells (Li et al., 2005).

Six patients with NY-ESO-1-expressing sarcomas (either synovial sarcoma or myoxid/round cell liposarcoma) were selected for the study, and their white blood cells harvested through

leukapheresis; a process which separates leukocytes from blood, the remainder of which is returned to the patient. Using an NY-ESO-1 tetramer they were able to sort the cells after stimulation, isolating the desired NY-ESO-1-specific cytotoxic T cells, which were then successfully expanded further to therapeutically relevant levels (> 20 billion cells). Their function was evaluated through specific lysis of T2 cells pulsed with varying concentrations of NY-ESO-1 peptide, in addition to an NY-ESO-1-expressing cell line (Mel A375). The results were clear: "The cells are capable of recognizing and killing tumor cells," Dr. Pollack said. NY-ESO-1-negative control cells (Mel 526) were not lysed to the same degree, demonstrating specificity of the produced cells.

The approach enables isolation and expansion of rare tumor-targeting cytotoxic T cells from peripheral blood under clinical manufacturing conditions, thereby opening a sought-after door for endogenous T cell therapy. In fact, a clinical trial of this kind of adoptive T cell therapy is already underway. Dr. Pollack: "We've treated six patients with tumor-specific T cells expanded using this method so far. A new trial starting soon will combine these cells with tumor-directed radiation in an effort to increase the efficacy of the T cells by manipulating the tumor microenvironment."

But it doesn't stop there; the process is easily adapted to other targets as well. "We've also used these methods to make cells specific for MAGE and PRAME family antigens," Dr. Pollack said. Exciting tidings for anyone who's on the lookout for new wings to add to the collective anti-cancer forces; rare birds are ready to get recruited.

Pollack SM, Jones RL, Farrar EA, Lai IP, Lee SM, Cao J, Pillarisetty VG, Hoch BL, Gullett A, Bleakley M, Conrad EU, Eary JF, Shibuya KC, Warren EH, Carstens JN, Heimfeld S, Riddell SR, Yee C. 2014. Tetramer guided, cell sorter assisted production of clinical grade autologous NY-ESO-1 specific CD8(+) T cells. *J Immunother Cancer*. 2(1):36.

See also: Li Y, Bleakley M, Yee C. 2005. IL-21 influences the frequency, phenotype, and affinity of the antigen-specific CD8 T cell response. *J Immunol*. 175(4):2261-9.

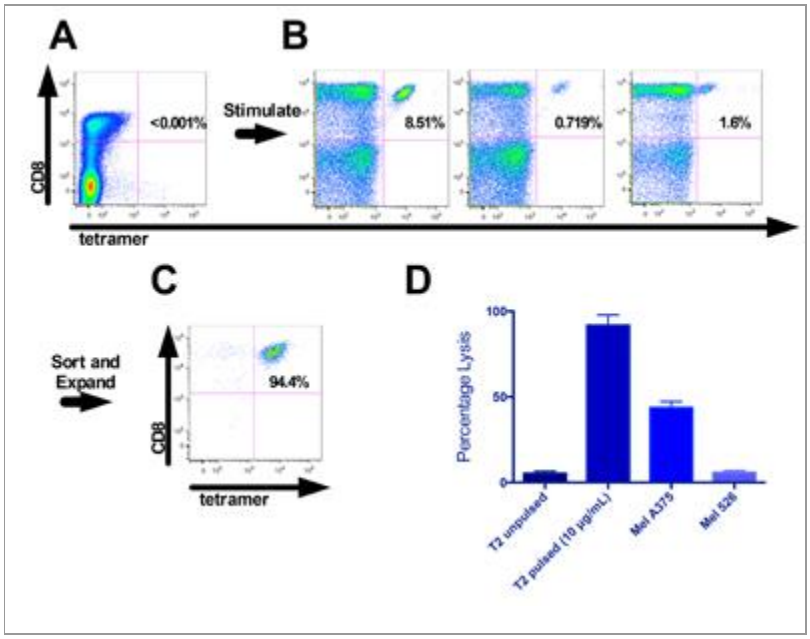

Image provided by Dr. Seth Pollack

Schematic of the production of NY-ESO-1-specific T cells from patient blood. A) Flow analysis with CD8 and tetramer staining of untreated mononuclear cells from peripheral blood showed no detectable population of the desired cells. B) After stimulation with peptide pulsed dendritic cells, 3/144 wells revealed modest populations. C) Cells in the positive wells were sorted and expanded. D) The produced T cells successfully lysed peptide pulsed targets and NY-ESO-1-expressing tumor cells, but not control cells.