Personalized immunotherapy for non-small cell lung cancer through identification of tumor-specific mutations by next generation sequencing and adoptive transfer of tumor infiltrating lymphocytes that recognize neoantigens

Ken-ichi Hanada1*, Christopher Chow1, Raul Gil Hoyos1, Jared J Gartner2, Todd D Prickett1, Robert Somerville1, Katherine Hogan1, Paul F Robbins2, Steven A Rosenberg1, James C Yang3

From 30th Annual Meeting and Associated Programs of the Society for Immunotherapy of Cancer (SITC 2015)
National Harbor, MD, USA. 4-8 November 2015

Background
Patients with metastatic melanoma can be successfully treated with adoptive transfer of tumor infiltrating lymphocytes (TIL). In 93 patients with over 5 year follow-up, the overall response rate was 56% and 20% achieved durable complete responses persisting in excess of 7 years. However, past attempts to apply TIL therapy to other solid cancers have not been successful and low frequency of tumor-specific T cells in other cancers has been suspected as a reason.

Recent progress in Next Generation Sequencing technology has enabled us to analyze genetic mutations in an individual patient’s tumor and identify immune cells that are reactive to these mutation-encoded neoantigens. The potential of this therapeutic approach recently was illustrated in a patient with cholangiocarcinoma who experienced major tumor regression when given such T cells. NSCLC is a cancer with a high number of genetic mutations and a recent report suggests that clinical response of NSCLC to anti-PD1 antibody therapy is positively associated with the number of genetic mutations.

Results
To identify neoantigen-reactive T cells from NSCLC and utilize them for adoptive therapy, we initiated clinical protocol (NCT02133196). Initial Whole Exome Sequence analysis of freshly resected metastases from four patients with NSCLC showed between 150 and 1500 non-synonymous mutations that could be confirmed by RNAseq. TIL cultures from these tumors tend to be initially dominated by CD3−, CD56+ cells, gradually converting to CD3+CD4+ dominant, CD3+CD8+ dominant, or a mixture of both at approximately 3 weeks. In all the cases, we were able to find CD4+ and/or CD8+ T cell populations that were reactive to one or more autochthonous neoantigens as confirmed by IFN-γ ELISPOT and FACS analysis based on 4-1BB and/or OX-40 up-regulation. In multiple TIL cultures, more than 50% of the cells were reactive to a neoantigen and in one case, single mutation in NPM1 (nucleophosmin) yielded both CD4+ and CD8+ T cell reactivity. These T cells can be grown to large numbers in vitro for patient adoptive transfer and these studies are underway.

Authors’ details
1NCI, NIH, Bethesda, MD, USA. 2Surgery Branch/National Cancer Institute / National Institutes of Health, Bethesda, MD, USA. 3National Institutes of Health, Bethesda, MD, USA.

© 2015 Hanada et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.