Cancer Immunity (12 March 2008) Vol. 8 Suppl.1, p. 13

CANCER IMMUNITY
Meeting Abstract

Protein-based vaccination targeting the cancer testis antigen NY-ESO-1

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Abstract

The Cancer Vaccine Collaborative (CVC) has pioneered vaccine approaches against Cancer Testis (CT) antigens. These molecules are characterized by expression in a wide variety of cancer types and very limited expression in non-malignant tissues. NY-ESO-1, which has been the focus of particular interest, is highly immunogenic and frequently induces spontaneous immunity, particularly in patients with advanced metastatic disease. It is not clear whether these immune responses modify the natural history of the cancer.

Vaccine trials with NY-ESO-1 have been undertaken using peptides, proteins and genetic vaccines. These trials have been undertaken in patients with fully resected cancer as well as those with advanced metastatic disease. Key observations include: (i) a broad integrated CD4, CD8 T cell and antibody response is induced in the majority of patients vaccinated with full length NY-ESO-1 and an appropriate adjuvant, (ii) the depth and breath of this response is complex and can involve many epitopes in an individual vaccine recipient, (iii) despite only being early phase trials, some strong indications of clinical activity have emerged, particularly in patients with minimal residual disease. We are currently performing a randomized international trial with NY-ESO-1 in such patients with resected melanoma under the aegis of the CVC in Australia and UK. If improved clinical outcomes are observed, this trial will establish the clinical value of targeting such molecules.

In contrast vaccination of patients with advanced metastatic melanoma resulted in attenuated immune responses and this difference appears to be due to tumor-related factors. A variety of regulatory mechanisms appear to be in play. Using immunohistochemistry and fl ow cytometric analysis of melanoma tissue, we detected expression of the transcription factor FoxP3 in the melanoma cells themselves as well as in regulatory T lymphocytes (Treg). Expression of FoxP3 may endow tumor cells with Treg-like activity, as demonstrated by contact-dependent suppression of T cell proliferation and contribute to tumor immune suppression. Although patients with advanced cancer may have NY-ESO-1 specific immune response, the quality of these responses may be critical for determining clinical outcomes and there is emerging evidence that antigen specific Treg may recognize peptides derived from CT antigens, including NY-ESO-1. Additionally, analysis of NY-ESO-1-specific T cells in patients with advanced ovarian cancer before and after depletion of Tregs revealed that Tregs masked spontaneous and vaccine induced effector T cells. The Treg suppressed effectors were generally of higher avidity than vaccine induced effector cells. Together, the CVC trials suggest that vaccine efficacy might be enhanced by targeting regulatory mechanisms via depletion of CD25+FOXP3+ Tregs and treatment with antibody against CTLA4.

References

1. Barrow C, Browning J, MacGregor D, Davis ID, Sturrock S, Jungbluth AA, Cebon J. Tumor Ag expression in melanoma varies according to Ag and stage. *Clin Cancer Res* 2006; **12:** 764-771. (PMID: 16467087)

2. Jackson H, Dimopoulos N, Mifsud NA, Tai TY, Chen Q, Svobodova S, Browning J, Luescher I, Stockert L, Old LJ, Davis ID, Cebon J, Chen W. Striking immunodominance hierarchy of naturally occurring CD8+ and CD4+ T cell responses to tumor Ag NY-ESO-1. *J Immunol* 2006; **176:** 5908-5917. (PMID: 16670298)

3. Davis ID, Chen W, Jackson H, Parente P, Shackleton M, Hopkins W, Chen Q, Dimopoulos N, Luke T, Murphy R, Scott AM, Maraskovsky E, McArthur G, MacGregor D, Sturrock S, Tai TY, Green S, Cuthbertson A, Maher D, Miloradovic L, Mitchell SV, Ritter G, Jungbluth AA, Chen YT, Gnjatic S, Hoffman EW, Old LJ, Cebon JS. Recombinant NY-ESO-1 protein with ISCOMATRIX adjuvant induces broad integrated antibody and CD4(+) and CD8(+) T cell responses in humans. *Proc Natl Acad Sci U S A* 2004; **101:** 10697-10702. (PMID: 15252201)

4. Chen Q, Jackson H, Parente P, Luke T, Rizkalla M, Tai TY, Zhu HC, Mifsud NA, Dimopoulos N, Masterman KA, Hopkins W, Goldie H, Maraskovsky E, Green S, Miloradovic L, McCluskey J, Old LJ, Davis ID, Cebon J, Chen W. Immunodominant CD4+ responses identified in a patient vaccinated with full-length NY-ESO-1 formulated with ISCOMATRIX adjuvant. *Proc Natl Acad Sci U S A* 2004; **101:** 9363-9368. (PMID: 15197261)

5. Svobodova S, Browning J, MacGregor D, Sturrock S, Pollara G, Azad A, Davis ID, Cebon J. Cancer-testis antigens are co-ordinately expressed in metastatic melanoma and are associated with poorer clinical outcomes in primary stage II melanoma disease. *Cancer & HIV Vaccines 2007: Shared Lessons* 2007; poster P-63.

6. Svobodova S, Pollara G, Maraskovsky E, Davis ID, Chen W, Cebon J. Antibody responses to the cancer antigen NY-ESO-1 identify highly immunogenic domains in melanoma patients before and after vaccination. *Cancer & HIV Vaccines 2007: Shared Lessons* 2007; poster P-62.

7. Ebert LM, Tan BS, Browning J, Svobodova S, Russell S, Kirkpatrick N, Gedye C, MacGregor D, Moss D, Davis ID, Cebon J, Chen W. The regulatory T cell-associated transcription factor FoxP3 is expressed by tumor cells. *Cancer & HIV Vaccines 2007: Shared Lessons* 2007; poster P-16.

8. Klein O, Ebert L, Nicholaou T, Browning J, Russell S, Tan BS, Zuber M, Dimopoulos N, Jackson H, Hoos A, Chen W, Davis ID, Cebon J.

T-lymphocytes recognising melanocyte differentiation antigens mediate tumour regression induced by ipilimumab. *Cancer & HIV Vaccines 2007: Shared Lessons* 2007; poster P-34.