

Vaccinating against cancer's Achilles' heel

Jonathan Cebon^{1*}, Craig Gedye¹, Ian Davis¹, Juliet Quirk¹, Weisan Chen¹, Andrew Simpson², Otavia Caballero² and Lloyd J. Old²

¹Ludwig Institute for Cancer Research, Melbourne, Australia

²Ludwig Institute for Cancer Research, New York, NY, USA

*Presenting author

Abstract

The Cancer Vaccine Collaborative (CVC) has pioneered vaccine approaches against Cancer Testis antigens (CTAg), most notably NY-ESO-1. Some clear insights have emerged from both the clinic and the laboratory: (i) NY-ESO-1 is spontaneously immunogenic particularly in patients with bulky disease, (ii) 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; the depth and breadth 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.

NY-ESO-1 distribution has been studied in detailed immunohistochemical studies of primary and metastatic melanomas. Unlike the widely-expressed differentiation antigens, CTAg are often only seen in a minority of cells within individual tumors. This raises the critical question of how can a vaccine approach that targets such an antigen affect clinical outcomes.

Although their biological function is still poorly understood, there is emerging evidence that some CTAg may play a role in the transcriptional regulation of germ cells. This putative role in germ cell biology, linked with the observation that they are frequently re-expressed in cancer provided the rationale to investigate CTAg expression in cancer stem cells.

There is increasing recognition that cancers are populated from a clonogenic subset of cells which have the property of stem cells. Many clinical and biological properties of cancer are consistent with this, such as clonality, the capacity of cancer to 'repopulate' after apparently effective therapy and the ability to migrate and invade. Cancer stem cells are critical targets for cancer therapy since cure can only be possible if they are eradicated. It has been proposed that melanoma is propagated by an intrinsic stem-cell-like population since only a fraction of cells are clonogenic in *in vitro* soft agar culture. Markers for these cells have included CD20, Hoechst 33342 dye exclusion, which can define a 'side-population' with stem cell-like properties and CD133 which is a stem cell marker in other systems including neuroepithelium, haemopoietic, renal, prostate and endothelial progenitors.

Our preliminary studies have confirmed the presence of a subpopulation of cells in melanoma cell lines that are defined by the presence of CD133. These have the capacity for clonogenicity and self-renewal. In a number of lines these represent a small subset (1-3%) of total cells. We have characterized highly enriched populations derived from these lines. Although they lack the capacity to differentiate into multiple lineages, all clonogenic potential appears to reside in this population. This is not the case for CD133lo cells derived from the same cell lines.

Using a series of melanoma cell lines which were sorted into highly enriched CD133hi and CD133lo cell fractions,

clonogenic cells were characterized biologically and evaluated for patterns of CTAg expression. The clonogenic cells were found to be highly enriched for several CTAg, particularly NY-ESO-1. Furthermore they could be selectively killed using NY-ESO-1-specific CD8+ T lymphocytes. This raises the possibility that vaccines against NY-ESO-1 may be able to eradicate melanoma stem cells.

We are currently performing a randomized international trial in patients with resected melanoma under the aegis of the CVC in Australia and UK. If improved clinical outcomes are observed, it may be through such a mechanism.

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