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Cancer Immunity, Vol. 3 Suppl. 2, p. 6 (12 December 2003)

**Use of monocyte-derived dendritic cells in cancer immunotherapy**

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**Abstract**

A novel approach to antigen-specific immunotherapy is to take advantage of dendritic cells (DCs) as "nature's adjuvant" and to actively immunize cancer patients with a sample of their own DCs charged with tumor antigens. DC vaccination is, however, still in an early stage, and most potentially important variables (e.g. type and maturational stage of DCs, type of antigen and loading method, schedule etc.) have yet to be addressed. Despite this need for establishing an optimized DC vaccine even in some of the initial exploratory clinical trials, vaccination with DCs loaded with tumor antigens in the form of peptides has induced a) tumor-specific killer and helper T cells ("proof of concept"), and b) occasional regression of metastases even in far-advanced cancer patients. This was reported for DCs directly isolated from blood as well as for DCs generated *ex vivo* from either CD34+ or CD14+ precursors (reviewed in [1](#), [2](#), [3](#)). Most of the studies including informative ones in volunteers have been performed by using DCs generated from CD14+ monocytes (so-called Monocyte-derived DCs or Mo-DCs), which are now considered as a gold standard. These Mo-DCs can be reproducibly generated within a few days in large numbers (300-800 million mature DCs per apheresis) from precursors in blood without any need for pretreating the patients with cytokines like GM-CSF or Flt3-L. Importantly, it is possible to obtain populations of immature Mo-DCs by exposing monocytes to GM-CSF + IL-4, which can then be transformed into homogeneously mature Mo-DCs by various stimuli such as TLR ligands (e.g. microbial products such as LPS or poly I:C), inflammatory cytokines like TNF-alpha, monocyte-conditioned medium or its mimic (IL-1beta + TNF-alpha + IL-6 + PGE<sub>2</sub>), or CD40L. The use of *mature* Mo-DCs is likely critical to induce strong immunity as it has become clear that antigen delivered on immature or incompletely matured Mo-DCs can even induce tolerance. Interestingly, it has recently also become evident that in the case of the Mo-DCs the choice of maturation stimulus is probably critical for success. Specifically, PGE<sub>2</sub> has to be part of the maturation stimulus in order to obtain CCR7-expressing Mo-DCs that migrate in response to CCL19 and CCL21 that guide DCs into lymphoid organs. Using such DCs loaded with tumor peptides we have demonstrated their migratory capacity *in vivo*, the induction of tumor-specific cytotoxic and helper T cells, and the presence of tumor-antigen specific T cells *in situ* in regressing metastases. Interestingly, immunizing to Mage-3A1 peptide by DCs has been shown to result in polyclonal T-cell responses while other vaccination strategies appear to yield only monoclonal ones. Currently, we are exploring in two-armed trials whether mature Mo-DCs exposed to CD40L and/or an unspecific helper protein ([4](#)) influence the quantity or quality of induced T-cell responses.

Recently, new approaches to charge DCs with antigens have become evident which promote the DC vaccination approach. The observation that DCs can take up naked RNA, express antigens encoded by the RNA and induce antigen-specific T cells *in vitro* as well as *in vivo* in patients has given an enormous additional momentum to the use of DCs as vectors for antigen delivery and cancer vaccination as this approach now allows one to administer to DCs both defined antigens, including universal ones such as telomerase or survivin as well as the total

antigenic repertoire of a given tumor (as total tumor or PCR amplified RNA). We have optimized protocols for the electroporation of RNA into both immature and mature Mo-DCs, and worked out an intracellular staining method that allows a reliable validation of the resulting DC vaccine. A clinical trial in melanoma patients employing mature Mo-DCs transfected with RNA encoding for MelanA, Mage-3 and survivin is ongoing.

The use of dying tumor cells, notably antibody-coated ones, is yet another loading technique. Other preclinical research has shown that the delivery of defined antigens as antigen-antibody complexes to DCs enhances cross presentation and allows for the potent induction of both CD4+ and CD8+ T-cell responses. Several recent results suggest that DCs might even be useful to directly trigger NK cells, and to mobilize the additional power of the innate immune system to attack tumor cells. Upon loading with alphaGalactosylCeramide DCs can also induce IFN-gamma producing NKT cells. It appears, therefore, rational and timely to optimize the use of DCs as vectors for the delivery of antigens to vaccinate against cancer.

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