ImmunoTools *multiplex* Award 2014

Ghaith Bakdash, PhD

Department of Tumor Immunology
Radboud Institute for Molecular Life Sciences, Radboudumc
Geert Grooteplein 26
6525 GA Nijmegen, The Netherlands

Novel dendritic cell subsets in cancer immunotherapy

Cancer immunotherapy, the scientific breakthrough of the year 2013 (*Couzin-Frankel 2013*), is a very attractive and promising therapeutic strategy for the treatment of cancer. One approach of cancer immunotherapy is dendritic cell (DC)-based immunotherapy. DCs are professional antigen presenting cells that can be loaded with tumor-derived antigens and used to mount an immune response against tumor cells by activating killer T cells. Thus, in a DC vaccination protocol, the patients' own DCs are utilized to induce anti-tumor immunity. This type of cellular therapy holds the promise to safely and effectively combat and prevent metastases in cancer patients and has shown promising results in some patients without exerting any treatment-related toxicity. Factually, no severe toxicity has been documented with DC immunotherapy and the encountered side effects are usually mild and include flu-like symptoms and local reaction at injection site, both common toxicity criteria (CTC) grade 1. The outstanding safety profile and extensive research efforts eventually led to the approval of Sipuleucel-T, a DC vaccine used in prostate cancer, by the FDA. Implementing a similar approach in our institute for the past decade, we have now treated well over 300 melanoma patients.

Despite the observed success with DC-based vaccines, the number of patients with increased overall survival is still limited (*Garbe, Eigentler et al. 2011*). This lack of optimal clinical outcome can be related to the fact that most clinical studies so far have been performed with *ex vivo* differentiated monocyte-derived DCs (MoDCs). However, recent studies carried out in our lab indicated that applying naturally occurring blood DCs, such as plasmacytoid DCs (pDCs) or the myeloid BDCA1$^+$ DCs, instead of the artificially generated MoDCs resulted in significantly enhanced overall survival of treated melanoma patients (*Tel et al 2013, Schreibelt et al unpublished data*). Thus, the type of DCs plays a major role in determining the clinical benefit of the vaccine.

In principle, blood DCs can be categorized into two major subsets: plasmacytoid (pDCs) and myeloid (mDCs) dendritic cells. The latter can be further subdivided into three subsets: BDCA1$^+$ DCs, BDCA3$^+$ DCs and CD16$^+$ DCs (*MacDonald et al 2002*). Transcriptional profiling revealed none overlapping qualities of theses subsets,

suggesting that they functionally complement each other to achieve an optimal immune reaction, crucial for tumor eradication (*Bakdash et al, in press*).

Despite the clear categorization of DC subsets, there are still unidentified types of DCs that can be instrumental in mediating immune responses. Among such types is the $CD34^+$ subset of DCs, which was initially identified in 2002 (*MacDonald et al 2002*). This subset was shown to be efficiently utilized to raise specific antileukemic cytotoxic T lymphocytes (CTL) (*Hsu et al 2006*). Similarly, we were able to identify a new subset characterized by the co-expression of BDCA1 and the monocytic marker CD14. Further characterization is required to delineate the functions of this novel subset (*Bakdash et al, unpublished data*).

Altogether, there is an urgent need to fully characterize novel DC populations and unravel yet unidentified DC subsets. The **Multiplex Array** will be a great tool to serve this purpose. This will be achieved by isolating those novel subsets from peripheral blood of healthy donors by means of Fluorescent activated cell sorting (FACS) and comparing them with the well characterized $BDCA1^+$ DCs by the Multiplex Array.

Not only will this award provide us with much needed information that can be further translated into clinical applications, but it may pave the way to establishing this technique in our lab and expanding its application to other types of immune cells involved in either the development or eradication of tumors.

ImmunoTools *multiplex* AWARD for **Ghaith Bakdash**

includes free analysis of samples on several antibody arrays with large range of antibodies against human CDs, human cytokines, and others