ImmunoTools *special* Award 2013

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Preclinical development of an innovative immunotherapy based on CD56$^+$ dendritic cells and interleukin-15: recruiting innate immunity against cancer

Recently, immunotherapy became a prominent research topic because of insights in the role of the immune system in suppressing and eliminating tumor cells, including leukemic cells. A very promising approach in the setting of cancer immunotherapy is dendritic cell (DC) vaccination. DC are namely the most professional antigen-presenting cells in the human body and are considered to be the central orchestrators of the immune system bridging innate and adaptive immunity. DC vaccination has already led to substantial, but often inconsistent clinical effects. The current protocol for the manufacturing of DC is therefore considered as not being optimal in view of generating DC with the best immunogenic characteristics.

In this context, the Tumor Immunology Group of the Laboratory of Experimental Hematology of the University of Antwerp, Belgium, developed a new protocol to generate DC with higher immune competence, namely so-called 'interleukin (IL)-15 DC' (Anguille *et al*, JTM 2009). These IL-15 DC are not only powerful inducers of the adaptive immune system against malign cells, but they have though a unique phenotype (i.e. CD56 positivity) and tumoricidal potential (so-called 'killer' DC) (Anguille *et al*, PLoS One 2012). Three major changes are made to the currently most used DC generation protocol: (1) the length of the differentiation culture is reduced from 6-8 days to 24-48 hours, (2) IL-4 in the differentiation cocktail is replaced by IL-15 and (3) a Toll-like receptor (TLR)7/8 agonist is added to a proinflammatory cytokine cocktail for maturation. The high potential of IL-15 (in the differentiation cocktail) is reflected by the fact that this pleiotropic cytokine is ranked as the most promising cytokine for the treatment of cancer on the list of the National Cancer Institute Immunotherapy (Immuno Therapy Agent Workshop 2007). The use of a TLR agonist in the maturation cocktail stands likewise in the centre of interest as a hopeful strategy to induce a powerful activation of the DC.

While much focus is being placed on augmenting T-cell immunity, the cells of the innate immune system are often overlooked in the setting of DC vaccination. Nevertheless, natural killer (NK) cells and γδ T cells play a pivotal role in antitumor immunity through direct cytotoxic activities, secretion of pro-inflammatory cytokines as well as through interaction between the different immune cells. This postulated bidirectional cross-talk between DC and NK cells or γδ T cells will be studied in

depth, with a focus on the induction of anti-leukemic immunity. In this study, the involvement of IL-15 and CD56 are of particular interest since IL-15 is known for its distinctive immunostimulatory properties and its critical role in homeostasis and activation of the innate and adaptive immune system and CD56 has recently been associated with cytotoxic effector functions (Roothans *et al*, OncoImmunology 2013).

Overall, my PhD project will create new insights into how the immune therapeutic potential of (IL-15) DC, NK cells and γδ T cells and their interactions can be used in the development of next-generation cancer vaccines. Hence, the requested cytokines and antibodies of ImmunoTools will be very useful in the preparation of the different types of DC vaccines (rh IL-4, rh IL-15, rh GM-CSF, rh IFN-γ, rh IL-1beta and rh TNFα), the phenotypic analysis of DC, NK cells and γδ T cells (anti-human antibodies) and the functional assays (rh IL-2, anti-human antibodies and ELISA sets) of which many are flow cytometry-based. Reagents of ImmunoTools are therefore appreciated assets at the commencement of my PhD.

ImmunoTools *special* AWARD for **Heleen Van Acker** includes 25 reagents

FITC - conjugated anti-human CD3, CD45RA, CD69, Control-IgG1, Control-IgG2b,

PE - conjugated anti-human CD7, CD25, CD27, Control-IgG1, Control-IgG2a,

APC -conjugated anti-human CD11c, CD16, CD56, Control-IgG1, Control-IgG2a,

recombinant human cytokines rh IL-15, rh IFNgamma, rh IL-2, rh GM-CSF, rh IL-4, rh IL-1beta, rh TNFα,

human IL-6 ELISA-set, IL-12p40 ELISA-set, TNF alpha ELISA set

DETAILS