ImmunoTools IT-Box-Cy55M-Award 2013

Tim Hutten

PhD Supervisor: Dr. Harry Dolstra & Dr. Willemijn Hobo

Laboratory of Hematology
Department of Laboratory Medicine
Radboud University Nijmegen Medical Centre,
Geert Grooteplein8, 6525GA, Nijmegen

Targeting co-inhibitory molecules in the tumor micro-milieu to improve anti-tumor T cell immunity

Myeloid malignancies are characterized by clonal expansion and accumulation of progenitor or immature cells of the myeloid lineage in the bone marrow. Allogeneic hematopoietic stem cell transplantation (allo-SCT) is an effective treatment option for these patients. This graft-versus-tumor efficacy is mainly mediated by alloreactive cytotoxic T- lymphocytes recognizing minor histocompatibility antigens (MiHA) which are expressed by malignant hematopoietic cells. Unfortunately in these patients relapses occur frequently due to the failure of the memory T cells to launch an effective MiHA-specific T cell response. This is probably due to immunosuppressive mechanisms within the tumor micro-environment. These can include disrupted antigen presentation, secretion of immunosuppressive cytokines, regulatory T cell recruitment and interactions between co-inhibitory receptors expressed by the MiHA-specific T cells and their corresponding co-inhibitory ligands on the tumor cells. Therefore, it is essential to develop potent adjuvant immunotherapy to interfere with these suppressive mechanisms, thereby augmenting anti-tumor T cell immunity, without causing severe systemic toxicity. In my PhD study we will focus on the question, whether we can potently boost anti-tumor T cell responses and prevent relapse in allo-SCT patients by local interference with suppressive mechanisms in the tumor-milieu using nanoparticles loaded with silencing RNAs (siRNA).

We are currently developing an acute myeloid leukemia (AML) mouse model to exploit the potential and efficacy of our nanoparticles loaded with siRNA to down regulate various co-inhibitory molecules in the tumor-environment. The *IT-Box-Cy55M* from ImmunoTools would be very useful for our experiments, as inflammatory cytokines (like IL-1β, IFN-γ and TNF-α) within the tumor micro-milieu could modulate the expression levels of co-inhibitory molecules on the tumor cells. In addition, in our mouse experiments we provide IL-2 and IL-15 to sustain MiHA-specific T cell survival, however we do not know what the effect of these cytokines is on expression levels of co-inhibitory molecules on the tumor cells. Therefore, with the help of ImmunoTools we would like to investigate whether presence of the following mouse cytokines: IL-2, IL-15, IL-1β, IFN-γ and TNF-α modulates the expression levels of co-inhibitory molecules expressed by AML cells. Furthermore, the mouse chemokines will allows us to investigate the responsiveness of MiHA-specific T cells in vitro.

ImmunoTools *IT-Box-Cy55M* for **Tim Hutten**

includes 55 recombinant mouse cytokines

rm EGF, rm Eotaxin / CCL11, rm FGF-a / FGF-1, rm FGF-b / FGF-2, rm FGF-8, rm Flt3L / CD135, rm G-CSF, rm GM-CSF, rm GRO-a / CXCL1, rm GRO-b / CXCL2, rm IFNgamma, rm IL-1alpha, rm IL-1beta, rm IL-2, rmIL-3, rm IL-4, rm IL-5, rm IL-6, rm IL-7, rm IL-9, rm IL-10, rm IL-11, rm IL-13, rm IL-15, rm IL-16, rm IL-17A, rm IL-17C, rm IL-17F, rm IL-19, rm IL-20, rm IL-21, rm IL-22, rm IL-25 / IL-17E, rm IL-27, rm IL-31, rm IL-33, rm IP-10 / CXCL10, rm LIF, rm MCP1 / CCL2, rm M-CSF, rm MIP-1α/ CCL3, rm MIP-1β / CCL4, rm MIP3α / CCL20, rm MIP3β / CCL19, rm NGF-beta, rm PDGF-AA, rm PDGF-BB, rm RANTES / CCL5, rm sCD40L / CD154, rm SCF, rm SDF-1α / CXCL12a, rm SDF-1β / CXCL12b, rm TNFα, rm TPO, rm VEGF DETAILS.