ImmunoTools IT-Box-Cy55M-Award 2013

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"Immunological danger signals and modulation of inflammation in hTNFα transgenic mice after LDRT and radon therapy"

Rheumatoid arthritis (RA) is characterized as a progressive chronic inflammatory autoimmune joint disease that is often accompanied by a symmetric Polyarthritis (PA) with synovial inflammation, cartilage degeneration and osteoclast-mediated bone-erosion. Although the exact cause of RA is yet to be determined, there are hints that it is triggered and sustained by the inappropriate expression of cytokines (such as: TNF-α, IL-1, IL-6, IL-10, IL-17, IL-19, IFNγ, G-CSF, and GM-CSF, all of which can be found inside the *IT-box-Cy55M*) alongside with genetic and environmental factors. During my thesis I will examine the effects of low-dose radiotherapy (LDRT) and radon exposure on modulation of inflammation in human tumor necrosis factor-α transgenic mice (hTNF-α tg mice) as well as on the development and activation of cells infiltrating the inflamed synovium in RA.

hTNF-α tg mice develop a chronic erosive polyarthritis (PA) that closely resembles clinical manifestations in patients with RA. Our group has already shown that whole body LDRT with 5x0.5Gy of X-ray of these mice results in a significant temporal improvement of the clinical progression of the disease (Frey B. *et al* (2009): Whole body low dose irradiation improves the course of beginning polyarthritis in human TNF-transgenic mice, *Autoimmunity* 42(4):346-348).

Among the cells that infiltrate the inflamed synovium are macrophages, T cells and osteoclasts, which is why I chose those cells for an *ex vivo* study to investigate their development and functions under the influence of selected cytokines alongside with radiation therapy (X-ray and radon). In order to do so, we have already established protocols in our lab to differentiate macrophages and osteoclasts from isolated bone marrow taken from hTNF-α tg and wild type C57/Bl6 mice using macrophage colony-stimulating factor (M-CSF) or M-CSF and receptor activator of NF-κB ligand (RANKL), respectively. Among the cytokines I would like to use for my experiments are: TNF-α, which is well known for driving inflammation and disease progression, and is a main target in RA therapy. Interleukin-10 (IL-10) which suppresses the release of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α, but also provides evidence that suggests a negative regulatory role in limiting osteoclastogenesis, inflammation, and immunopathology in various autoimmune models, amongst them arthritis. IL-19, which up-regulates TNF-α and IL-6 in the murine model and might therefore play an important role in inflammatory responses (Liao *et al*, (2002) IL-19 induces production of IL-6 and results in cell apoptosis through TNF-α, *J Immunol* 169:4288-4297). IL-6, which is known to be involved in bone homeostasis (Yoshitake *et al*. (2008)

Interleukin-6 directly inhibits osteoclast differentiation by suppressing receptor activator of NF-κB signaling pathways, *J Biol Chem* 283:11535-11540) where, under normal conditions, it suppresses osteoclastogenesis by inhibiting the differentiation of osteoclast progenitors. Under inflammatory circumstances, however, it provides discordant signals to osteoblasts and osteoclasts which could lead to the bone loss observed in RA (N. Nishimoto, (2006) Interleukin-6 in rheumatoid arthritis, *Curr Opin Rheumatol* 18: 277-281) making it an interesting target for my studies. With the help of the ImmunoTools *IT-box-Cy55M* I could also investigate the regulatory and stimulatory roles of various other cytokines involved in RA.

ImmunoTools *IT-Box-Cy55M* for **Lisa Deloch**
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