



**ONCOLille**

L'INSTITUT DE CANCÉROLOGIE DE LILLE

**Seminars**

On Thursday 20<sup>th</sup> of April. 2023 at **11 am**

**Silvia Gaggero, PhD**

**CANTHER, Team : « Factors of Persistence of Leukemic Cells » - Mitra Lab'**

**IL-2 is inactivated by the acidic pH environment of tumors enabling engineering of a pH-selective mutein**



Cytokines interact with their receptors in the extracellular space to control immune responses. How the physicochemical properties of the extracellular space influence cytokine signalling is incompletely elucidated. Here, we show that the activity of interleukin (IL-2), a critical cytokine in T cell immunity, is profoundly affected by low pH (~6.5), limiting IL-2 signalling in a IL-2Ra-dependent manner. Generation of lactic acid by tumours limits STAT5 activation, effector differentiation and anti-tumour immunity by CD8<sup>+</sup> T cells and renders high-dose IL-2 therapy poorly effective. Directed evolution by yeast display enabled selection of a pH-selective IL-2 mutein (Switch-2). Switch-2 binds the IL-2 receptor subunit IL-2Ra with higher affinity, triggers more potent STAT5 activation and drives CD8<sup>+</sup> T cell effector function at acidic pH than at pH 7.2 typical of normal tissues. Consequently, Switch-2 is mainly uptake by CD8<sup>+</sup> T cells localized in acidic tissues such as tumour and lymph-node, at the contrary of IL-2 that was found at a greater extent in CD8<sup>+</sup> T cells in blood and lungs. High-dose Switch-2 therapy induces anti-tumour immunity in different tumour models (B16, MC38, and 4T1) with reduced on-target toxicity in normal tissues, whereas high-dose IL-2 therapy resulted in toxicity alone. Phenotypical and single-cell analysis on CD8<sup>+</sup> tumour infiltrating lymphocytes (TILs) shows that Switch-2 increases cell proliferation, expansion of antigen specific cells, and cytokine expression as compared to IL-2. Therapeutic manipulation of the pH-selective activity of cytokines is a powerful approach to exploit the therapeutic efficacy of cytokines in pathological environments with reduced systemic side effects.

See you all in **Axel Khan Conference Room - ONCOLille**

If you can't make it, we will also stream through Zoom:

<https://univ-lille-fr.zoom.us/j/94766125424>

Passcode: OLille!

Meeting ID: 94766125424

Chann Lagadec

For the ONCOLille Animation Committee