Rufer team – Dpt of oncology, CHUV-UNIL

Title of project: Identifying high-avidity and high-quality individual T-cells in cancer patients

Summary of project: Immunotherapy mostly aims at strengthening the efficacy of anti-tumor T cell responses. However, while some cancer patients benefit well, others still experience disease progression, unfortunately. It is therefore important to determine the essential properties of anti-tumor T cells that provide lasting clinical benefit. Perhaps the most characteristic property is the affinity/avidity of the T receptors (TCR). TCR affinity/avidity controls all cellular functions and therefore determines the efficiency of T cells to recognize tumor cells and destroy them. Despite its importance, we still need to improve our knowledge regarding the contribution of TCR-pMHC avidity as a key biometric regulating the quality and potency of the T cell responses in well-defined clinical settings.

The Rufer team has generated a unique model of genetically engineered T-lymphocytes, by equipping them with TCRs of increased affinity against NY-ESO-1, a tumor antigen expressed in different types of cancer. In particular, we were able to demonstrate that the peak function of these modified T cells is "calibrated" by regulatory mechanisms linked to TCR affinity (1). We further described that sustained chronic interactions between affinity-increased TCR and self-MHC can directly adjust the functional potential of engineered T cells (2). Our research underlines the importance of identifying anti-tumor TCRs capable of generating optimal function without toxicity for effective clinical application. At present, we are developing the ULTRA (ULtimate T cell Receptor Affinity) platform, a working flow that will enable the generation and parallel validation of affinity-optimized TCRs against the HLA-A2/NY-ESO-1 tumor antigen. Such in-depth analyses should allow identifying essential binding properties within the TCR-pMHC ternary complex, which govern T cell activation, function and immune modulation in vivo.

Ref 1. Hebeisen M et al. SHP-1 phosphatase activity counteracts increased T cell receptor affinity. *J Clin Invest.* 2013;123(3):1044-56.

Ref 2. Duong MN, et al. Chronic TCR-MHC (self)-interactions limit the functional potential of TCR affinity-increased CD8 T lymphocytes. *J Immunother Cancer.* 2019;7(1):284