**ADAPTIVE IMMUNITY LABORATORY**

**Project title**
"The unexpected roles of T cells in pathology as a key to improved therapy"

**Pre-clinical Supervisor:** Marinos Kallikourdis

**Laboratory name:** Adaptive Immunity Laboratory


**Abstract**

The adaptive immune system (composed of T cells and B cells) evolved in vertebrates, permitting the defense of the self against pathogens. Yet the evolution of mammalian pregnancy, and the associated recognition and active tolerization of paternally-derived fetal antigens during placental pregnancy, may have brought about key changes in the ability of the adaptive immune system to define and defend the self, in a manner optimized up to but not beyond the reproductively active age of the female (Aluvihare, Kallikourdis and Betz, Nature Immunology 2004). However, in the last couple of centuries human lifespan has expanded substantially beyond the reproductively active age. This is likely to create problems, as the information-processing capabilities of adaptive immunity may not have been selected for dealing with the conditions found in aging tissues, when many of the above major diseases have their first incidence. We are interested in deciphering the interactions between the adaptive immune system and different tissues during disease pathogenesis. We study the mechanisms underlying these interactions, from a systemic down to molecular level. We then utilize the findings to attempt innovative, proof-of-principle therapeutic strategies for cancer and cardiovascular disease. Applying the above rationale, we have recently demonstrated that pro-inflammatory T cells, which are used therapeutically to treat tumors, may be simultaneously mediating pro-tumoral effects (Garetto et al., Oncotarget 2016). In an even more recent study, we identified, via immunophenotyping at different stages of the disease, an association between the presence of T cells and heart failure (HF), both in experimental models and in human HF patient biopsies. On the basis of this finding, we then utilized an FDA-approved drug that interferes with T cell function in order to treat experimentally-induced HF. Treatment resulted in a block of progression of HF, in a manner substantially more efficient than current standard drugs targeting cardiac disease (Kallikourdis et al, Nature Communications 2017). We are seeking a PhD student to extend the analysis of T cell-dependent responses in a context of human cancer therapy, as well in conditions of cardiovascular pathology. The aim is to help develop an efficient cancer therapy that eliminates the tumor without leading to off-target effects. The project involves immunoprofiling (FACS, ELISA) analysis of patients, closely matched by proof-of-principle interventionist experiments in in vivo models of disease. The



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latter will rely also on -omics technologies, which we make use of in the lab in a targeted and logic-driven manner.

**Main technical approaches**

Tumor immunology and cardio-immunology, FACS, IHC, 2 photon imaging, -omics.

**Scientific references**

1. Kallikourdis M. T cell responses to tumor: how dominant assumptions on immune activity led to a neglect of pathological functions, and how evolutionary considerations can help identify testable hypotheses for improving immunotherapy. Cancer Immunol Immunother.2018. 201829335855

2. Garetto S, Sardi C, Martini E et al. Tailored chemokine receptor modification improves homing of adoptive therapy T cells in a spontaneous tumor model. Oncotarget. 2016;7:43010-26.27177227

3. Kallikourdis M*, Martini E, Carullo P, Sardi C, Roselli G, Greco C, Vignali D, Riva F, Ormbostad Berre AM, Stølen TO, Fumero A, Faggian G, Di Pasquale E, Elia L, Rumio C, Catalucci D, Papait R, Condorelli G* (2017) T cell costimulation blockade blunts pressure overload-induced heart failure. Nat. Commun. 8, 14680 doi: 10.1038/ncomms14680



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