PhD project No. 21, Prof. Zippelius

Scientific Area	Immune-related diseases
Two project titles	A) Dissecting immune synapse polariziation in exhausted T cells B) Deciphering metabolic pathways in exhausted T cells
Host country	Switzerland
Supervisor, institution	Prof. Dr. Alfred Zippelius, University of Basel
Co-Supervisor, institution	A) Prof. Dr. Lukas Jeker, University Basel B) Dr. Christian Klein, Roche
Mentor, institution	A) and B) to be determined
Secondment institution	A) and B) to be determined

Short description of the supervisor's lab with introduction to the topic

Cancer immunotherapy is increasingly considered the most important advance in oncology following outstanding clinical successes with adoptive T cell therapies and immune checkpoint blockade. Despite these breakthroughs, therapeutic benefits are currently limited to a minority of treated patients. Intra-tumoral T cells have been demonstrated to have a critical role in predicting immunotherapy's effectiveness, these T cells gradually acquire a dysfunctional phenotype in the tumor microenvironment and often fail to control tumor growth. We have reported that intra-tumoral exhausted T cells frequently overexpress inhibitory receptors. We furthermore demonstrated that PD-1^{T} T cells (highly expressing PD-1) form a transcriptionally distinct subset that expresses a broad spectrum of inhibitory receptors, contain a largely unique TCR repertoire with highly enriched tumor reactivity, acquire a novel function by continuously secreting CXCL13, and are predictive for both response and survival in non-small cell lung cancer patients treated with PD-1 blockade. Consequently, a better mechanistic understanding of T cell exhaustion will facilitate innovative strategies to reinvigorate T cell effector functions and improve the clinical benefit in cancer patients, as shown previously in work from our group.

Topic description, including techniques to be used

Project A)

We recently discovered a multifunctional scaffold protein associated to the immune synapse in exhausted T cells. This project will mechanistically decipher the contribution of this protein and, more broadly, of synapse formation to T cell exhaustion. To this end, its localization to the immune synapse, its effect on TCR signalling and its contribution to modulate co-inhibitory/activating signals will be analyzed; this investigation will include the analysis of its interaction partners in the T cell receptor signalosome. Subsequently, targeting of the protein will be tested to improve the therapeutic efficacy of adoptive transfer strategies.

Project B)

The overall goal of this work is to deeply characterize the key metabolic pathways in the development of exhausted T cells and to develop novel strategies to reinvigorate terminally exhausted T cells. Different subsets of exhausted T cells and their differentiation stages upon prolonged TCR stimulation will be investigated by in-depth phenotypic characterization, measurement of metabolic activities, mitochondrial morphology, and quantification of effector functions. Subsequently, metabolism- and mitochondria-associated genes will be identified which can be targeted to improve T cell functionality in models of adoptive T cell transfers and in patient TIL populations.

Recommended applicant's training (technical expertise and knowledge)

Techniques: cell culture, flow cytometry, immune-monitoring,
Knowledge: cancer immunology, T cell biology, cancer immunotherapy, translational research

Maximum two relevant publications

The EURIdoc programme has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement number 101034170.

Thommen et al., 2018, Nature Medicine: A transcriptionally and functionally distinct PD-1 + CD8 + T cell pool with predictive potential in non-small-cell lung cancer treated with PD-1 blockade
Trüb et al., 2020, Journal of Immunotherapy of Cancer: Fibroblast activation protein-targeted-4-1BB ligand agonist amplifies effector functions of intratumoral T cells in human cancer

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Ethics description

1. Human Embryos/Foetus	
This research involves Human Embryonic Stem Cells (hESCs).	YES ☐ / NO ☒
This research involves the use of human embryos.	YES ☐ / NO ☒
This research involves the use of human foetal tissues / cells.	YES ☐ / NO ☒
2. Humans	
This research involves human participants.	YES ☐ / NO ☒
This research involves physical interventions on the study participants.	YES ☐ / NO ☒
3. Human Cells /Tissues	
This research involves human cells or tissues (other than from Human Embryos/ Foetuses, i.e. section 1).	YES ☒ / NO ☐
4. Personal Data	
This research involves personal data collection and/or processing.	YES ☐ / NO ☒
This research involves further processing of previously collected personal data (secondary use).	YES ☐ / NO ☒
5. Animals	
This research involves research involve animals.	YES ☒ / NO ☐

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