University of Basel

DBM Basel
Department of Biomedicine

MASTER THESIS PROJECT – INVESTIGATING THE IMPACT OF INTERFERON SIGNALING ON THE DURABILITY OF EXHAUSTED CD8 T CELL RESPONSES TO CHECKPOINT BLOCKADE (I.E. PD-1) IMMUNOTHERAPY

Field – Immunology – Cancer Immunotherapy – Crispr – Molecular engineering - Mouse models – Next generation sequencing
Key words – CD8 T cell exhaustion – Cytokine signals – cancer immunotherapy – checkpoint blockade

Scientific background

Cancer immunotherapies have revolutionized the field of clinical oncology. Over the last decade, strategies such has targeting the immune checkpoints (e.g. PD-1) have proven more efficient than standard cares and these approaches are now first or second line treatment, alone or in combination in more than 50 different cancer types. However, despite many clinical successes, current cancer immunotherapies still fail at achieving long-term benefits in a majority of patients. Exhaustion of CD8 T cells is a major limitation. This process gradually deprives anti-cancer CD8 T cells from their main effector functions and is reinforced by a stable epigenetic program. Developing complementary strategies to epigenetically reprogram exhausted CD8 T cells towards more durably protective cell-states is the next challenge. *However, our lack of understanding of the exhaustion process has hindered the design of relevant therapeutic interventions.* Recently, we have demonstrated that exhausted CD8 T cells, the primary target of PD-1 based immunotherapies, fail to mount durable responses to the therapy. This lack of sustained response likely explains the absence of durable benefits in many patients. Our preliminary observations suggest a role for type 1 interferon signaling in regulating the durability of exhausted CD8 T cell responses to PD-1 blockade.

Hypothesis

Based on these preliminary observations, we hypothesized that type 1 interferon signals may limit the durability of exhausted CD8 T cell responses to cancer immunotherapy. Understanding the physiological impact of chronic type 1 interferon signals and developing complementary approaches to specifically target this axis may improve the durability of immune responses to checkpoint blockade therapy and the cure of more patients.

Your role

Leveraging cutting-edge tools such as CRISPR and retroviruses, you will investigate the impact of type 1 interferon signaling on the CD8 T cell response to cancer immunotherapy using relevant mouse models. By analyzing scRNAseq datasets, you will identify specific targets downstream of type 1 interferon signaling responsible for the arrested response of exhausted CD8 T cells to PD-1 based therapy. Using gain-and-loss of function experiments in vivo, you will reveal the precise mechanism by which the identified target impairs CD8 T cell responses to immunotherapy. To achieve these goals, you will use and be trained for high dimensional flow cytometry, molecular engineering (CRISPR, Retroviruses design and production) and next generation sequencing approaches (scRNAseq and scATACseq).

Your profile

- B.Sc. in Biology or equivalent
- Familiar with basic molecular biology techniques (plasmid design/cloning)
- Strong interest and background in Immunology and/or Cancer Immunotherapy
- Fluent in French or English (required)

We offer

The successful candidate will join a vibrant cross-disciplinary and collaborative team with opportunities to master state-of-the-art immunological concepts and approaches as well as next generation sequencing techniques. The candidate will benefit from all the technological platforms available at the Department of Biomedicine, careful supervision by a Ph.D. student and an experienced research assistant and mentoring by the lab's head (Dr. Beltra). Within this dynamic environment, the candidate will have all the support needed for the success of his/her/their Master thesis and achievement of future career goals.

Contact

jeanchristophe.beltra@unibas.ch