PROJECT

Supervisor:	Prof. Daniela Latorre
Title:	Computational Analysis of autoreactive TCR Repertoires in Inflammatory Neuropathies
Curriculum:	Molecular Medicine; Basic and Applied Immunology and Oncology
Link to the personal page of the University or relevant hospital site website:	https://research.hsr.it/en/institutes/institute-of-experimental-neurology/units/neuro-immune-interactions/daniela-latorre.html

Description of the Project

Background/gap of knowledge

Autoimmune diseases arise from a failure of immune tolerance, leading to T cell-mediated recognition of self-antigens. Central to this process is the T-cell receptor (TCR), a highly variable molecule that determines antigen specificity through its interaction with peptides presented by major histocompatibility complex (MHC) molecules. TCR diversity is generated through V–J and V–D–J recombination of the α and β chains, resulting in a vast theoretical repertoire ($\sim 10^{15}$ possible TCRs), although only $\sim 10^{7}$–10^{8} unique clonotypes are observed in humans [1].

Despite evidence linking TCR repertoire alterations to autoimmune diseases, the specific sequences and molecular determinants driving pathogenic autoreactive T cell responses remain largely undefined. This is mainly due to the rarity and heterogeneity of autoreactive T cells in patient samples, which has limited their characterization. Defining the features of disease-relevant TCRs is essential to understand self-antigen recognition and immune dysregulation, and may enable the identification of disease-specific biomarkers and the development of targeted immunotherapies.

Rationale and hypothesis

A key limitation in the field is the reliable identification of antigen-specific TCRs and the prediction of antigen specificity from sequence. Most available datasets derive from tetramer-based experiments and are affected by significant biases, limiting their predictive power [2]. In addition, current computational approaches often rely predominantly on the β chain, despite antigen recognition depending on the combined contribution of both α and β chains and their biochemical properties.

To address these limitations, our lab has generated a unique dataset of over 300 paired α and β TCR sequences from autoreactive T cells isolated from patients with inflammatory peripheral neuropathies and healthy individuals, each annotated with defined epitope specificity and MHC restriction [3]. Building on this resource, we will integrate sequence-derived features, including length, hydrophobicity, and other physicochemical properties, to identify determinants of self-antigen recognition.

We hypothesize that combining paired α/β chain information with biochemical and structural features will provide substantial new insights into TCR autoreactivity, and will improve the prediction of TCR–antigen specificity.

Objectives and specific aims

Our objective is to define the molecular rules governing autoreactive T cell responses and improve antigen specificity prediction. We will (i) characterize TCR features using machine learning approaches [4][5], (ii) develop predictive models integrating α and β chain information and structural properties [6], and (iii) validate predictions in patient and healthy donor TCR repertoires.

Expected outcomes

We expect to identify TCR features distinguishing patients from healthy donors and to uncover determinants of autoreactivity. These results will improve prediction of TCR–antigen specificity and provide a framework for biomarker development and targeted immunotherapies in autoimmune diseases.

Skills that the student should acquire:

The student will gain skills in immunology, computational biology, and experimental validation, including TCR repertoire analysis, feature-based machine learning, structural modelling, functional assays, and data integration. The student will learn to critically evaluate dataset biases, connect computational predictions with experimental results, and communicate scientific findings effectively, preparing them for interdisciplinary research in immunology and bioinformatics.

References

[1]. Nose Y et al. TCR sequencing in cancer immunology and immunotherapy. *J Immunother Cancer*. 2026;14:e013499.

[2]. Messemaker M et al. A functionally validated TCR-pMHC database for specificity model development. *bioRxiv*2025;2025.04.28.651095.

[3]. Súkeníková L, et al. Autoreactive T cells target peripheral nerves in Guillain-Barré syndrome. Nature. 2024. Feb;626(7997):160-168

[4]. Linsley PS et al. Germline-like TCR-α chains shared between autoreactive T cells. *Nat Commun*. 2024;15:4971.

[5]. Dash P et al. Quantifiable predictive features define epitope-specific TCR repertoires. *Nature*. 2017;547:89-93.

[6]. Jumper J et al. Highly accurate protein structure prediction with AlphaFold. *Nature*. 2021;596:583-589