Integrative TCR:peptide:MHC modelling

Deeper understanding of the immune system's intricacies has led to clinical breakthroughs of personalized cancer vaccines in eliminating tumors in advanced-stage cancer patients[1-4]. Formulated with fragments from a patient's tumor DNA, cancer vaccines train a patient's own immune system to recognize a patient's mutated cancer proteins as 'foreign' and wage a lethal attack against tumors (see key concepts in **Box 1**). The major puzzle in this field is: *which of a patient's hundreds of tumor mutations can trigger the immune system to attack tumors*? Complementary to costly and time-consuming wet-lab screenings (e.g., Sipuleucel-T was priced at $93,000[5]), predictive algorithms that can quickly pinpoint neoantigens from a patient's tumor DNA are urgently needed, if personalized cancer vaccines are to be applied on a large scale.

Box 1. The TCR:peptide:MHC complex, neoantigens, and their pivotal role in the immune surveillance system and T-cell-mediated immune attacks on tumor cells[6]. Cells constantly break down proteins into peptides. The major histocompatibility complex (MHC) proteins present some of these peptides on the cell surface. T cells are fired up when their T-cell receptor (TCR) recognizes tumor-specific peptides presented on the tumor cell surface by MHC proteins forming the TCR:peptide:MHC (TCR:pMHC) complex[1,2] (**Figure 1**). MHC class I presents on the surface of every cell, while MHC II only presents on specific immune cells, e.g., dendritic cells. Tumor peptides presented by MHC-I can activate CD8+ T cells, which can directly kill tumor cells that present the peptides on their surface. Peptides presented by MHC-II can activate CD4+ T cells, which stimulate the production of antibodies and can provide help to CD8+ T cells. Such tumor-mutation derived peptides that are recognized by T cells as 'foreign' (i.e., immunogenic) are called **neoantigens**[7]. **MHC epitopes**: MHC-binding peptides. **TCR epitopes**: peptides that bind both MHC and TCR.

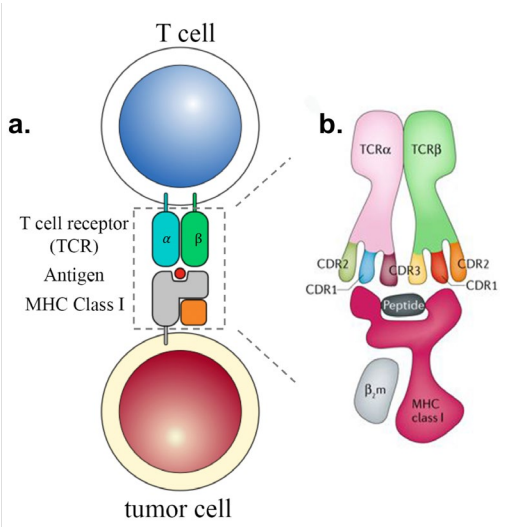

Figure 1. TCR nomenclature and the TCR:pMHC complex. A TCR has two chains (α and β) and each chain has 3 loops (CDR1-3). It mainly uses CDR3 to interact with the peptide. Source: Leem *et al.* 2018[8] for sub-figure **a.** and La Gruta *et al.* 2018[9] for **b.**

Our overall aim is to improve the efficacy, safety and development time of existing T cell based cancer vaccine approaches. This project focuses on a key comment of our cancer vaccine prediction project: 3D modelling of TCR:pMHC complexes. 3D models can provide critical insights on why and why not a vaccine works.

You will learn:
1. Advanced 3D modelling techniques for protein-protein complexes (HADDOCK[10-12], the flag-ship software in 3D modelling; homology modelling)
2. Deep understanding of 3D structures, especially T cell and antibody specific structural biology
3. Basic knowledge of T cell based immunotherapy
4. Although not required by this project, you will have opportunity to learning deep learning on these elegant molecules by joining our lab tutorial sessions and meetings.
5. Present your work
6. Summarize your work in manuscript

Your contributions:
1. Model high-quality (atomic resolution) 3D TCR:pMHC structures, which provide fundamental insights on how a T cell interacts with the peptide and the MHC molecule
2. Implement a python pipeline for large-scale modelling

Requirements:

1. Basic structural biology knowledge is needed.
2. Basic programming skills (ideally python) are preferred.

What you will do:
1. Start with a TCR:pMHC complex with known experimental structure: 1AO7 (PDB ID).
2. Define system-specific knowledge as restraints for integrative modelling
3. Model the TCR:pMHC complexes using HADDOCK
4. Study how to model CDR3-beta well
5. Study how to model the hinge movement well
6. Try several more TCR:pMHC complexes with known experimental structures
7. Write a python pipeline for large scale analysis
8. Prepare a presentation
9. Write a report in the form of a formal manuscript (there is a possibility of submitting it to a journal)

Time to start:
As early as possible.

Time last:
6-12 months

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References:

1. Ott, P. A. *et al.* An immunogenic personal neoantigen vaccine for patients with melanoma. *Nature* **547,** 217–221 (2017).
2. Sahin, U. *et al.* Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. *Nature* **547,** 222–226 (2017).
3. Harjes, U. Personal training by vaccination. *Nature Reviews Cancer* **17,** 451
4. Sahin, U. & Türeci, Ö. Personalized vaccines for cancer immunotherapy. *Science* **359,** 1355–1360 (2018).
5. Jaroslawski, S., Drugs, T. S.-T. B.2015. *Autopsy of an innovative paradigm change in cancer treatment: Why a single-product Biotech company failed to capitalize on its breakthrough Invention*.
6. Neefjes, J., Jongsma, M. L. M., Paul, P. & Bakke, O. Towards a systems understanding of MHC class I and MHC class II antigen presentation. *Nature Reviews Immunology 2018 18:7* **11,** 823–836 (2011).
7. Schumacher, T. N. & Schreiber, R. D. Neoantigens in cancer immunotherapy. *Science* **348,** 69–74 (2015).
8. Leem, J., de Oliveira, S. H. P., Krawczyk, K. & Deane, C. M. STCRDab: the structural T-cell receptor database. *Nucleic Acids Res.* **46,** D406–D412 (2018).
9. La Gruta, N. L., Gras, S., Daley, S. R., Thomas, P. G. & Rossjohn, J. Understanding the drivers of MHC restriction of T cell receptors. *Nature Reviews Immunology 2018 18:7* **18,** 467–478 (2018).
10. Dominguez, C. & Boelens, R. HADDOCK: A protein− protein docking approach based on biochemical or biophysical information. **125,** 1731–1737 (2003).
11. De Vries, S. J., Van Dijk, M. & Bonvin, A. The HADDOCK web server for data-driven biomolecular docking. *Nat Protoc* **5,** 883–897 (2010).
12. Xue, L. C., Rodrigues, J. P. G. L. M., Dobbs, D., Honavar, V. & Bonvin, A. Template-based protein-protein docking exploiting pairwise interfacial residue restraints. *Brief. Bioinformatics* bbw027 (2016). doi:10.1093/bib/bbw027