Universitat Pompeu Fabra Barcelona

Master in Bioinformatics for Health Sciences

Master project 2024-2025

Personal Information

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Project

Computational genomics

Project Title:

Identification of composite genomic biomarkers of upfront resistance to Immune CheckPoint Inhibitors across human cancers

Keywords:

cancer immunogenomics, cancer immunotherapy, up-front resistance biomarkers

Summary:

Immune Checkpoint Inhibitors (ICIs) have revolutionized the treatment of advanced tumors with high tumor mutation burden (TMB), such as skin melanoma, non-small cell lung cancer, and more recently, Mismatch Repair Deficient (MMRd) cancers[1,4]. However, response rates to ICIs, apart from MMRd tumors, are still suboptimal for most cancer types. Therefore, there is an urgent need to identify patients who are unresponsive to ICIs [5]. Identifying biomarkers of up-front ICI resistance would not only improve response rates but would also lessen the burden of long-term treatments for patients who will not eventually display positive responses. One of the most reasonable genomic events potentially associated with up-front ICI resistance are tumor-specific genetic immune escape (GIE) events. GIE alterations provide tumors with the capacity to evade immune system surveillance [6]. However, it is unclear whether GIE alterations may also negatively impact responses to ICI therapies. The goal of this project is to investigate the influence of GIE alterations on ICI treatment responses using an ICI-treated cohort of over 600 pan-cancer patients who underwent whole-genome/transcriptome tumor sequencing prior to treatment initiation [6,7]. Additionally, we plan to perform a genome-wide and cancer type-specific identification of up-front resistance genomic biomarkers beyond well-characterized GIE events, which may reveal novel up-front resistance mechanisms for ICI therapies in human cancers. This analysis results will provide essential insights for the cancer immunology field. First, it will reveal the impact of highly prevalent GIE alterations on ICI therapies. Furthermore, from a translational standpoint, it will address an unmet clinical need for ICI-based immunotherapies by providing novel genomic biomarkers for up-front ICI resistance. Implementing genomic biomarkers of negative ICI responses is relatively simple compared to other existing biomarkers of ICI treatment, and even for a modest fraction of patients, it could significantly improve their quality of life.

References:

1. Wei, S. C., Duffy, C. R. & Allison, J. P. Fundamental Mechanisms of Immune Checkpoint Blockade Therapy. Cancer Discov. 8, 1069–1086 (2018). 2. Das, S. & Johnson, D. B. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. J Immunother Cancer 7, 306 (2019). 3. Cercek, A. et al. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. N. Engl. J. Med. 386, 2363–2376 (2022). 4. Ramos-Casals, M. et al. Immune-related adverse events of checkpoint inhibitors. Nature Reviews Disease Primers 6, 1–21 (2020). 5. Cristescu, R. et al. Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy. Science 362, (2018). 6.Martínez-Jiménez F*^, Priestley P*, Shale C, Baber J, Rozemuller E, Cuppen E. Genetic immune escape landscape in primary and metastatic cancer. Nature Genetics. 2023;55(5):820-831. doi:10.1038/s41588-023-01367-1 7. Martínez-Jiménez F*, Movasati A, Brunner SR, et al. Pan-cancer whole-genome comparison of primary and metastatic solid tumours. Nature. 2023;618(7964):333-341. doi:10.1038/s41586-023-06054-z

Expected skills:

Cancer genomics, basic immunology, python programming, basic shell scripting, motivation to learn, motivation for a highly translational projects

Possibility of funding:

To be discussed

Possible continuity with PhD:

To be discussed