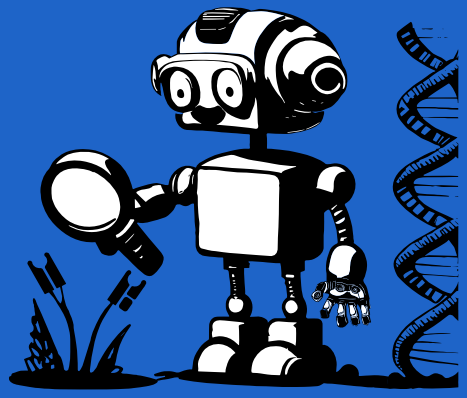
A Computational Exploration of MHC-based Immune Selection Signals in Large Cancer Genome Sequencing Datasets



Arne Claeys

2023

Thesis submitted to fulfil the requirements for the degree of Doctor in Health Sciences

GHENT UNIVERSITY

FACULTY OF MEDICINE AND HEALTH SCIENCES

Supervisors

Prof. Jimmy Van den Eynden
Dept. of Human Structure and Repair (GE38)
Ghent University, Belgium

Prof. Kathleen Marchal
Dept. of Plant Biotechnology and Bioinformatics (WE09),
Dept. of Information Technology (EA05)
Ghent University, Belgium

Members of the examination committee

Prof. Katleen De Preter (chair)
Dept. of Biomolecular Medicine (GE31)
Ghent University, Belgium

Prof. Jan Fostier
Dept. of Information technology (EA05)
Ghent University, Belgium

Prof. An Hendrix
Dept. of Human Structure and Repair (GE38)
Ghent University, Belgium

Prof. Pieter Mestdagh
Dept. of Biomolecular Medicine (GE31)
Ghent University, Belgium

Prof. Maxime Tarabichi
Institute of Interdisciplinary Research in Human and Molecular Biology
Université Libre de Bruxelles, Belgium

Prof. Karim Vermaelen
Dept. of Internal Medicine and Pediatrics (GE35)
Ghent University, Belgium

Scientific publications

Claeys, A., Merseburger, P., Staut, J., Marchal, K., & Van den Eynden, J. (2023). Benchmark of tools for in silico prediction of MHC class I and class II genotypes from NGS data. *BMC Genomics*, *24*(1), 247.

Claeys, A., & Van den Eynden, J. (2023). Quantification of Neoantigen-Mediated Immunoediting in Cancer Evolution—Letter. *Cancer Research*, *83*(6), 971–972.

Luijts, T., Elliott, K., Siaw, J. T., Van de Velde, J., Beyls, E., **Claeys, A.**, Lammens, T., Larsson, E., Willaert, W., Vral, A., & Van den Eynden, J. (2022). A clinically annotated post-mortem approach to study multi-organ somatic mutational clonality in normal tissues. *Scientific Reports*, *12*(1), 10322.

Borenäs, M., Umapathy, G., Lai, W., Lind, D. E., Witek, B., Guan, J., Mendoza-Garcia, P., Masudi, T., **Claeys, A.**, Chuang, T., El Wakil, A., Arefin, B., Fransson, S., Koster, J., Johansson, M., Gaarder, J., Van den Eynden, J., Hallberg, B., & Palmer, R. H. (2021). ALK ligand ALKAL2 potentiates MYCN-driven neuroblastoma in the absence of ALK mutation. *The EMBO Journal*, *40*(3).

Claeys, A., Luijts, T., Marchal, K., & Van den Eynden, J. (2021). Low immunogenicity of common cancer hot spot mutations resulting in false immunogenic selection signals. *PLOS Genetics*, *17*(2), e1009368.

Szydzik, J., Lind, D. E., Arefin, B., Kurhe, Y., Umapathy, G., Siaw, J. T., **Claeys, A.**, Gabre, J. L., Van den Eynden, J., Hallberg, B., & Palmer, R. H. (2021). ATR inhibition enables complete tumour regression in ALK-driven NB mouse models. *Nature Communications*, *12*(1).

Claeys, A., & Van den Eynden, J. (2023). *MHC class I and class II genotypes are independent predictors of anti-PD1 immunotherapy response in melanoma* [Preprint]. *In Review*.

Gabre, J. L., Merseburger, P., **Claeys, A.**, Siaw, J., Bekaert, S.-L., Speleman, F., Hallberg, B., Palmer, R. H., & Van den Eynden, J. (2023). *Preclinical exploration of the DNA Damage Response pathway using the interactive neuroblastoma cell line explorer CLEAN* (p. 2023.09.17.557904) [Preprint]. *bioRxiv*.

Siaw, J. T., **Claeys, A.**, Lai, W.-Y., Borenäs, M., Hilgert, E., Bekaert, S.-L., Speleman, F., Durinck, K., Hallberg, B., Palmer, R., & Van den Eynden, J. (2023). *RUVBL1 and RUVBL2 as Novel Druggable DNA Damage Response Regulators in the N-Myc Regulatory Network in Neuroblastoma* [Preprint]. *SSRN*.

Presentations

EMBL Cancer Genomics
poster session
November 2023, Heidelberg

PrIOMiC-OncoPoint
storm presentation
May 2023, Ghent

ICGEB Cancer Bioinformatics Tools
invited speaker
December 2021, Muğla

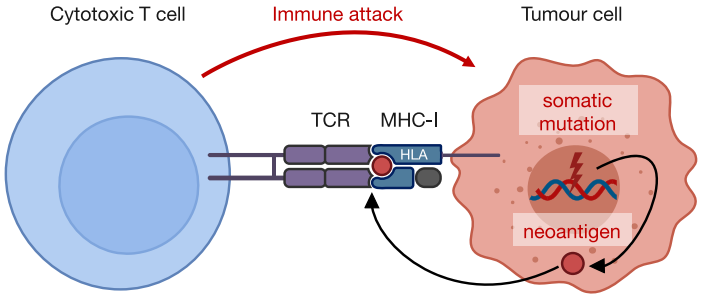
EMBL Cancer Genomics
poster session
November 2021, Heidelberg

EACR Bioinformatics in Cancer
poster session
May 2021, Cambridge

OncoDot.2
storm presentation
January 2021, Ghent

Objective

Cancer arises as the result of an evolutionary process where mutations accumulate in the DNA of normal cells. Some mutations give cells an advantage over their neighbours, allowing them to grow uncontrollably or to escape cell death. However, this is balanced by the immune system which can detect and eliminate abnormal cells by recognizing small protein chunks (neoantigens) presented on the cell surface by Major Histocompatibility Complex (MHC) molecules. In my PhD project, I used computational methods to study this process and its implications for cancer immunotherapy.



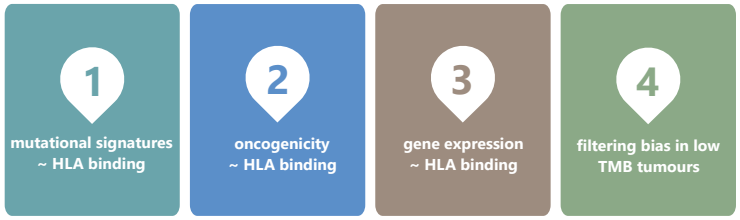
Mutations lead to the formation of neoantigens.

Earlier reports of MHC binding affinity-based immune selection signals were confounded.

At the start of my PhD, we investigated an apparent contradiction in previous studies on immunogenic selection in human genomic data.

Two *Cell* papers suggested that the mutations that are observed in cancer patients are those that are poorly presented to their immune system, depending on the MHC genotype. Another study reported immunoediting signals in a large cancer genomics dataset using two newly developed metrics that quantify a difference in cancer cell fraction and mRNA expression between neoantigenic and non-neoantigenic mutations.

However, these conclusions contrasted with a study from our own group that showed a lack of immune selection signals in human genomic data. In my first two papers, I resolved this contraction and identified multiple confounding factors that affect MHC binding affinity-based immune selection studies.



Four confounding factors were identified.

HLA-HD is the most accurate *in silico* NGS-based MHC-II genotyping method.

Apart from the long-established role of MHC-I in tumour immunology, there is also an emerging role of MHC-II presentable neoantigens. To investigate their role in cancer, accurate methods that can derive the MHC-II genotype of the patient from NGS data are required. Prior to the start of my PhD, there was no consensus on the optimal approach for this task.

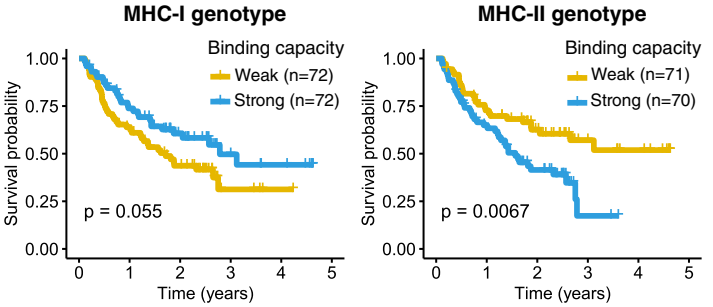
Therefore, we benchmarked the performance of 13 publicly available tools for MHC genotyping and provided practical guidelines for the field. For WES data, *Optitype* and *HLA-HD* are the best performing individual tools for MHC class I and MHC class II typing, respectively. For RNA data, the same tools are recommended when sufficient computational resources are available.

MHC-II genotypes are predictors of ICB immunotherapy.

Immune checkpoint blockade (ICB) therapies have demonstrated a remarkable efficacy in many cancer patients, but responses remain variable. The best outcomes are observed in mutagen-exposed tumours with a high tumour mutational burden (TMB) and high total neoantigen load. However, these two biomarkers are not independent: the neoantigen load is in fact a combined effect of the TMB and the probability that a mutation results in neoantigens. In turn this depends on the presentability of peptides to the MHC in that patient, which is influenced by the patient's MHC genotype. Following this reasoning, we hypothesized that the MHC genotypes have a potential value as biomarkers for ICB responses.

Previous studies have reported associations between a few individual MHC-I alleles and clinical outcomes of ICB therapy. However, classical association studies between Human Leukocyte Antigen (HLA) alleles and clinical response are underpowered due to the low allele frequency of each individual allele. Furthermore, rather than a single HLA allele, the entire ensemble of MHC-I and MHC-II alleles in an individual defines the repertoire of peptides that can be presented to the immune system. To overcome this limitation, we used an alternative approach where we quantified the overall MHC-I and MHC-II presentability in a patient using two novel metrics, which were named MGBS-I and MGBS-II, respectively.

Using this metric, we demonstrated that the MHC class II genotype is a predictor of anti-PD-1 immunotherapy responses in melanoma, independently of TMB.



Melanoma patients with a strong MHC-II binding capacity have worse overall survival in response to anti-PD1 ICB therapy.

CONTACT

Department of Human Structure and Repair
Computational Cancer Genomics and Tumour Evolution Lab
ccgg.ugent.be
arne.claeys@ugent.be

GHENT UNIVERSITY

Kom op tegen Kanker