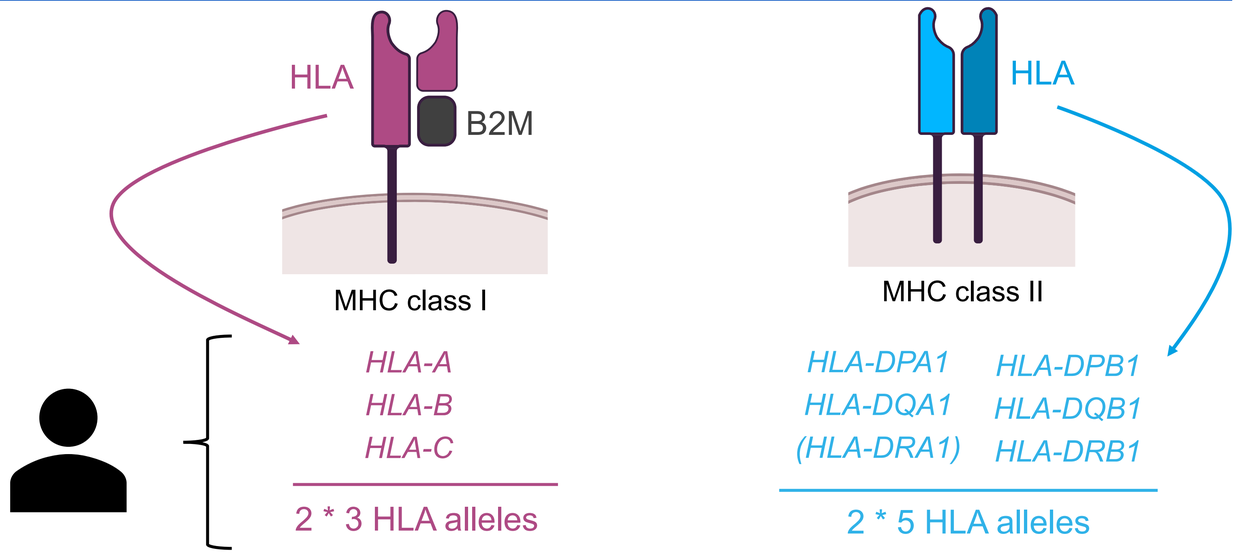
MHC-II genotypes are independent predictors of anti-PD1 immunotherapy response in melanoma.

Arne Claeys and Jimmy Van den Eynden

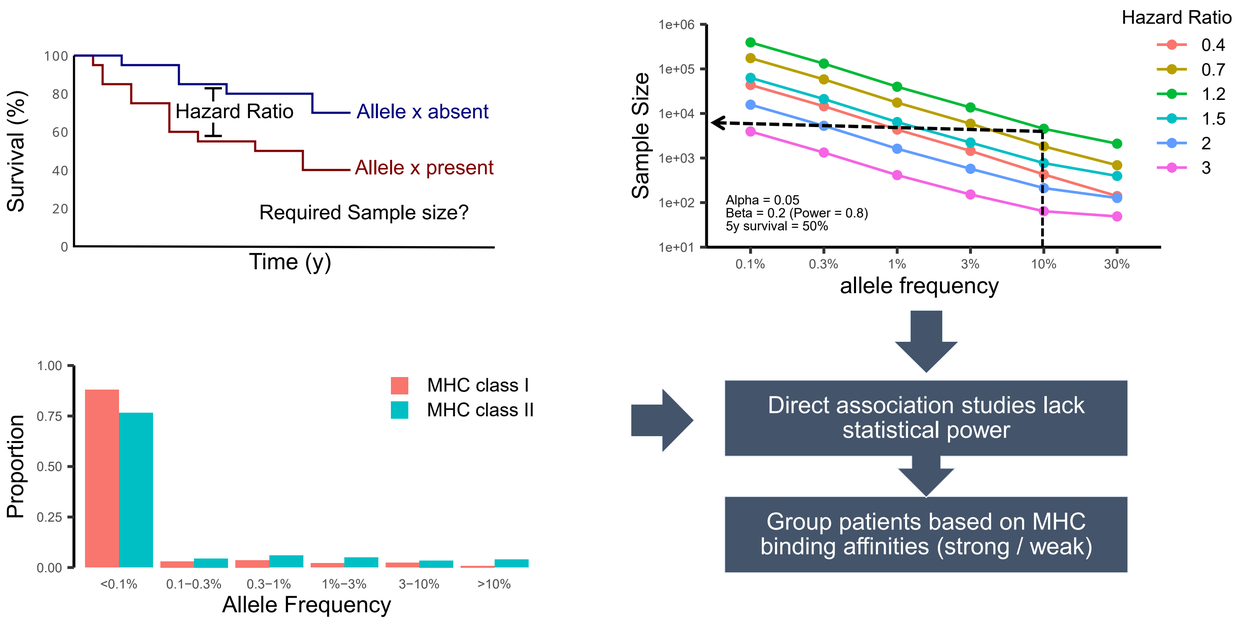
Anatomy and Embryology, Department of Human Structure and Repair, Ghent University, Belgium
Cancer Research Institute Ghent, Ghent, Belgium

Background

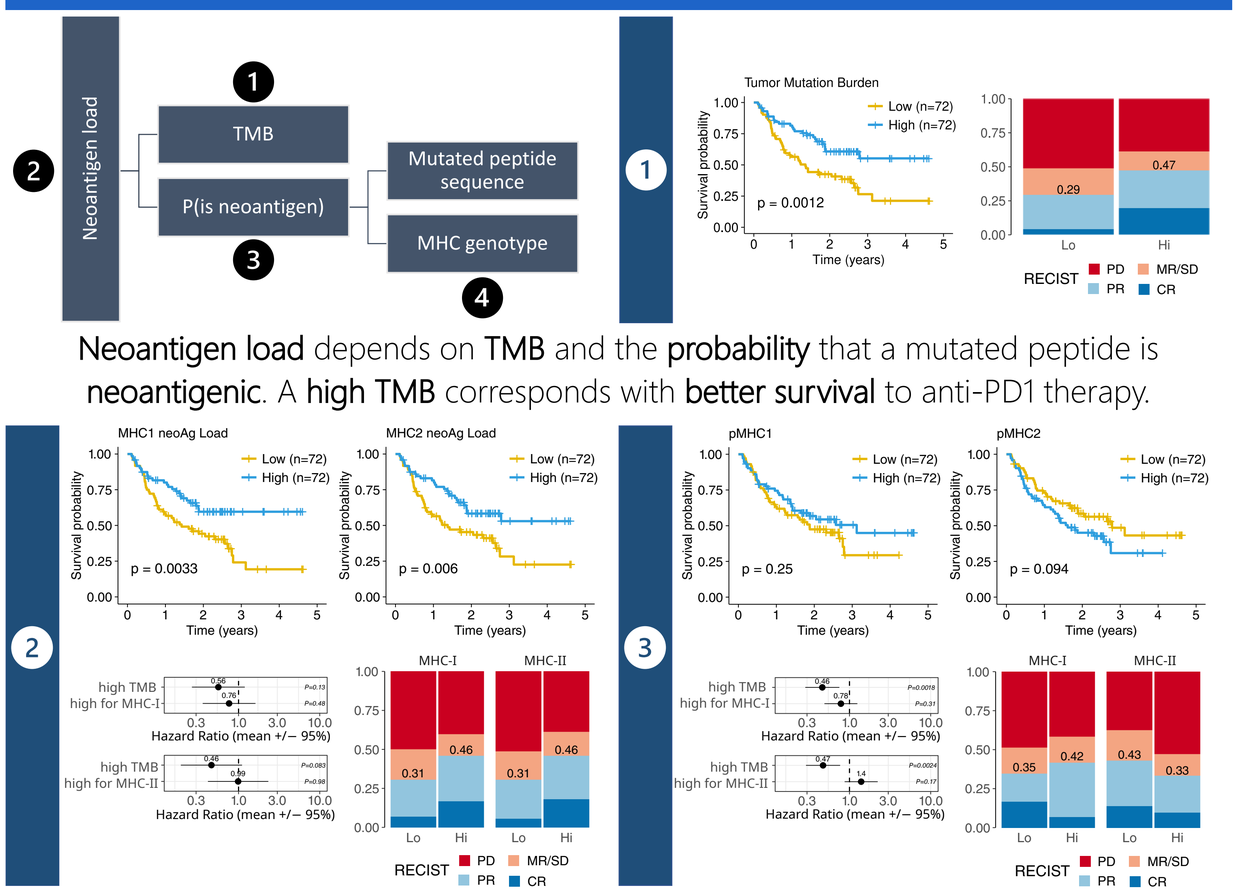
- **Immune checkpoint blockade** (ICB) therapies have shown remarkable success in the treatment of cancer, but their **efficacy varies widely** among patients.
- **Tumour mutation burden** (TMB) and **total neoantigen load** are regarded as the **most accurate** genomic biomarkers, yet **outcomes** remain **hard to predict**.
- **ICB responses** are mediated through the **presentation of neoantigens** by the highly polymorphic **Major Histocompatibility Complex** (MHC).
- **Neoantigen** prediction **accuracies** are extremely **low** *(Claeys et al., Cancer Research, 2023)*.
- We hypothesize the **MHC genotype could** be an essential **determinant** of treatment **outcomes**.



1: Direct association studies with MHC genotypes are unfeasible

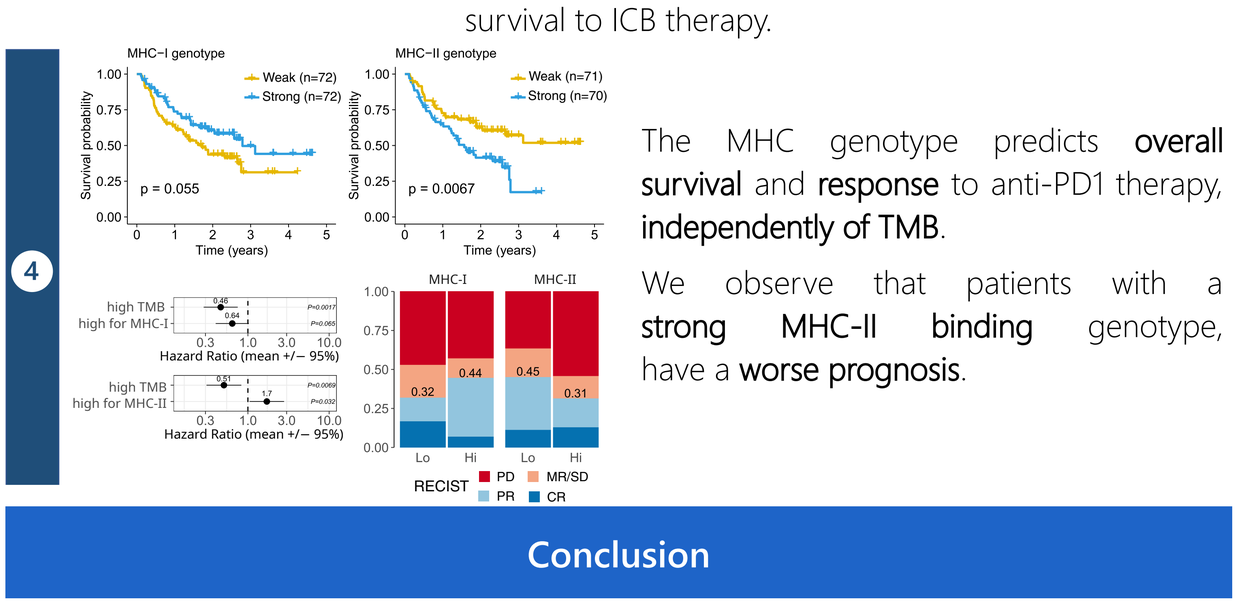


2: MHC genotypes are independent predictors of ICB response



Neoantigen load depends on TMB and the probability that a mutated peptide is neoantigenic. A high TMB corresponds with better survival to anti-PD1 therapy.

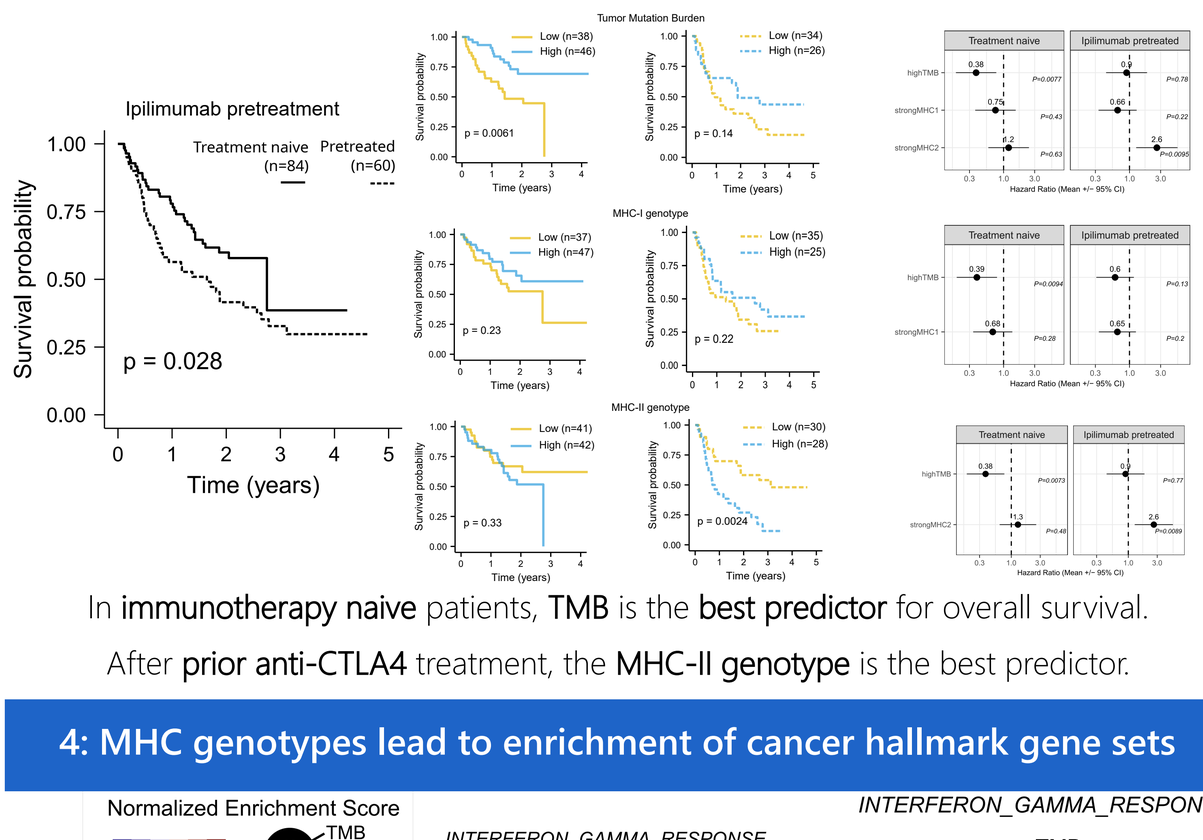
Total neoantigen burden is confounded by TMB and does not independently predict survival to ICB therapy.



The MHC genotype predicts **overall survival** and **response** to anti-PD1 therapy, **independently of TMB**.

We observe that patients with a **strong MHC-II binding** genotype, have a **worse prognosis**.

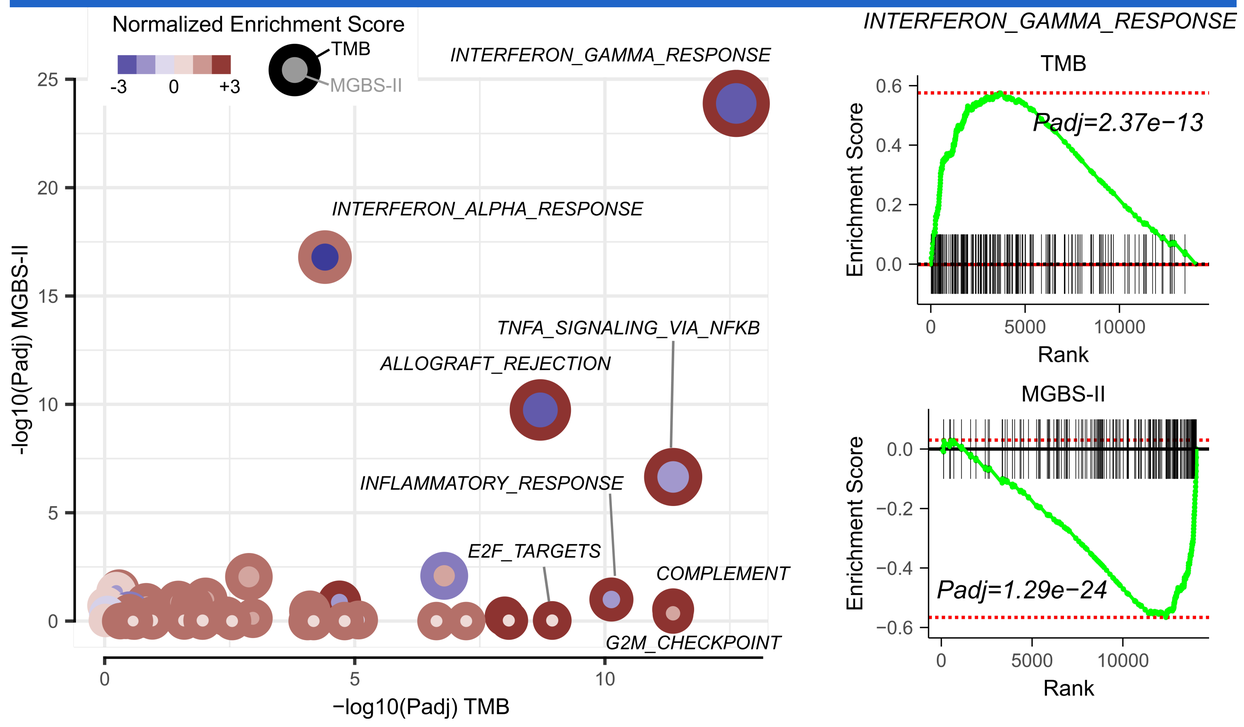
3: Observed survival effect depends on prior anti-CTLA4 treatment



In **immunotherapy naive** patients, **TMB** is the **best predictor** for overall survival.

After **prior anti-CTLA4** treatment, the **MHC-II genotype** is the best predictor.

4: MHC genotypes lead to enrichment of cancer hallmark gene sets



Gene set enrichment analysis was performed on genes differentially expressed between patients with a **high vs low TMB** or **strong vs weak** binding MHC-II genotypes.

Conclusion

- The **MHC genotype**, quantified using a simple metric, has potential as a new **genomic biomarker** for **ICB response** in melanoma.
- The **MHC class II genotype** is associated with responses to **sequential anti-CTLA4 and anti-PD1** treatment.
- Obtaining the MHC genotype is **non-invasive** (only requires a blood sample). It can be determined using common **sequencing technologies** (WGS, WES and RNA-Seq).
- Our proposed biomarker is **static** and not influenced by prior mutational selection or immunoediting.
- **Further validation** of our biomarker in **larger clinical datasets** and across **different cancer types** is required.

CRIG · FACULTY OF MEDICINE AND HEALTH SCIENCES · Kom op tegen Kanker · GHENT UNIVERSITY