

# Dissecting neoantigen drivers of immunotherapy response in Merkel Cell Carcinoma

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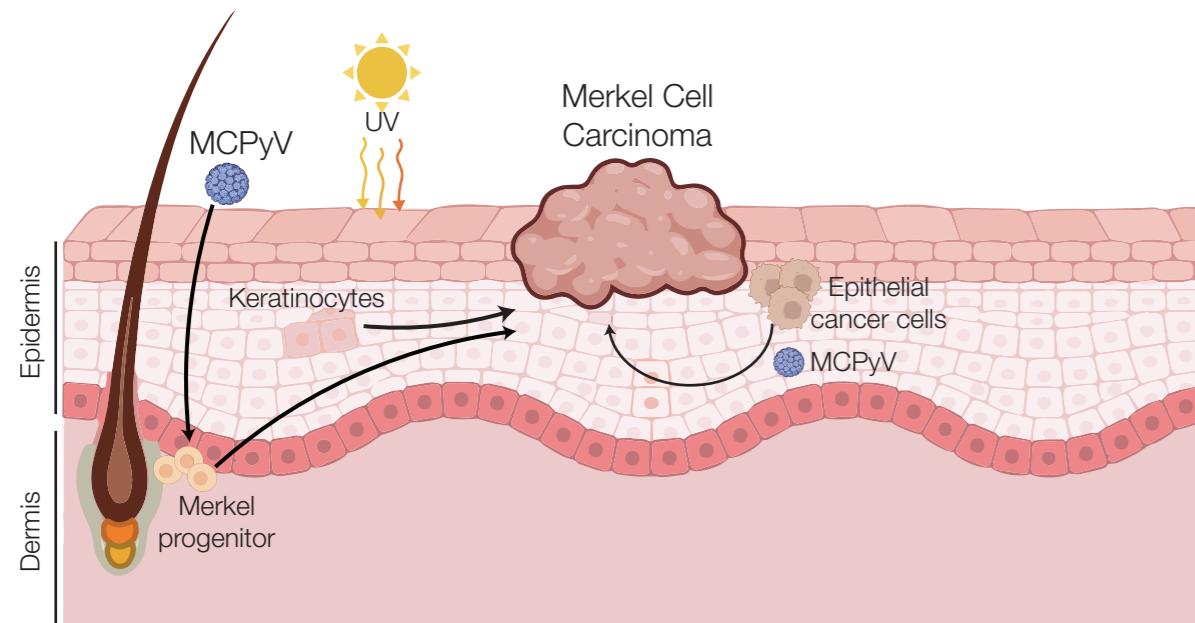
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ii



Higher mutational rate  
Lower mutational rate

The etiology of Merkel Cell Carcinoma could be caused by UV exposure or by the integration and replication of the Merkel Cell Polyoma Virus (MCPyV)<sup>1</sup>.

**Immunotherapy** with immune checkpoint inhibitors (ICB) is the first line therapy for **MCC patients**, for both MCPyV<sup>+</sup> and MCPyV<sup>-</sup> cases.

However **no dedicated approaches for neoantigens profiling in MCC exists**, leading to a scarce understanding of the prognostic factors of successfully response to ICB therapy.

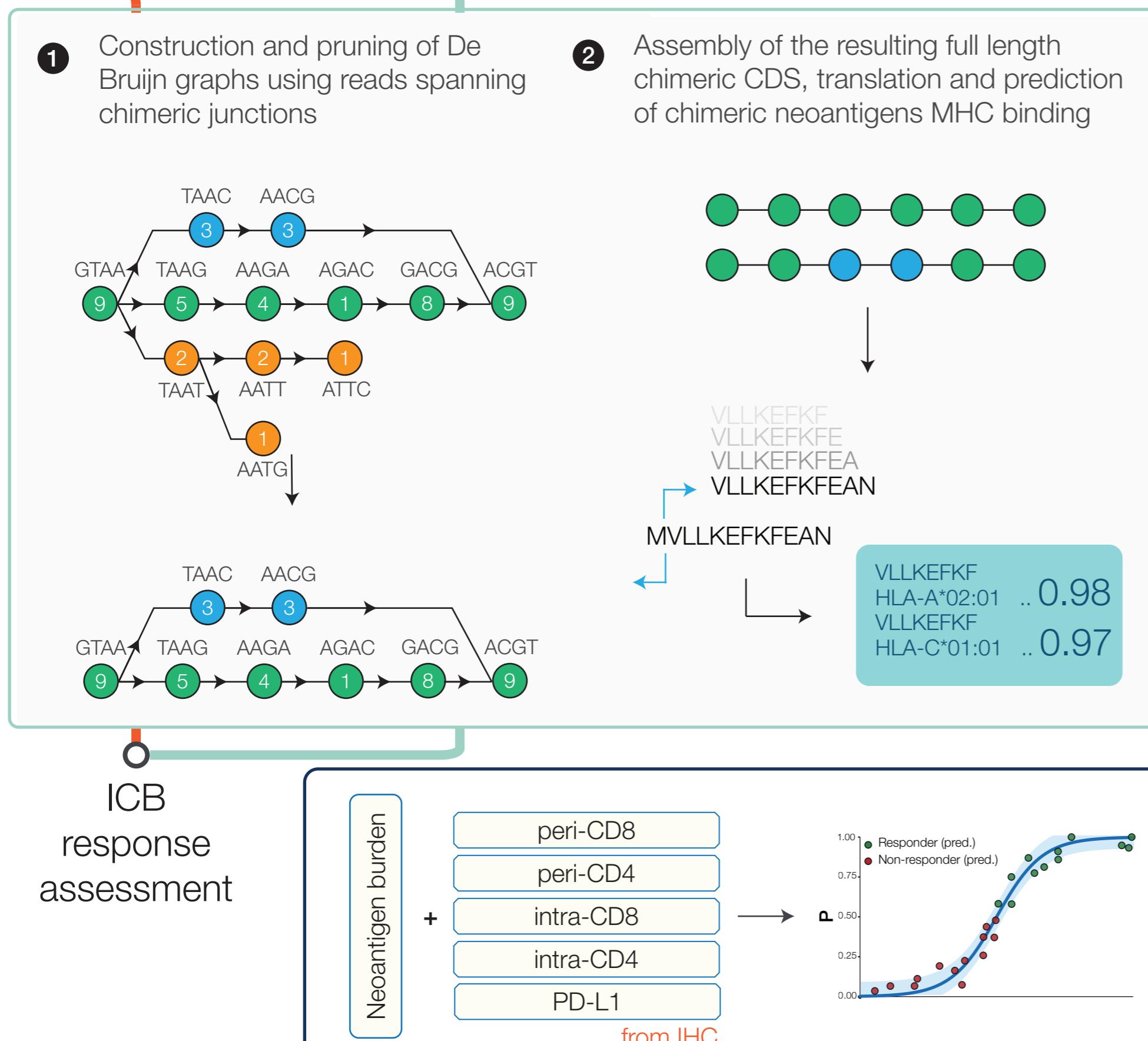
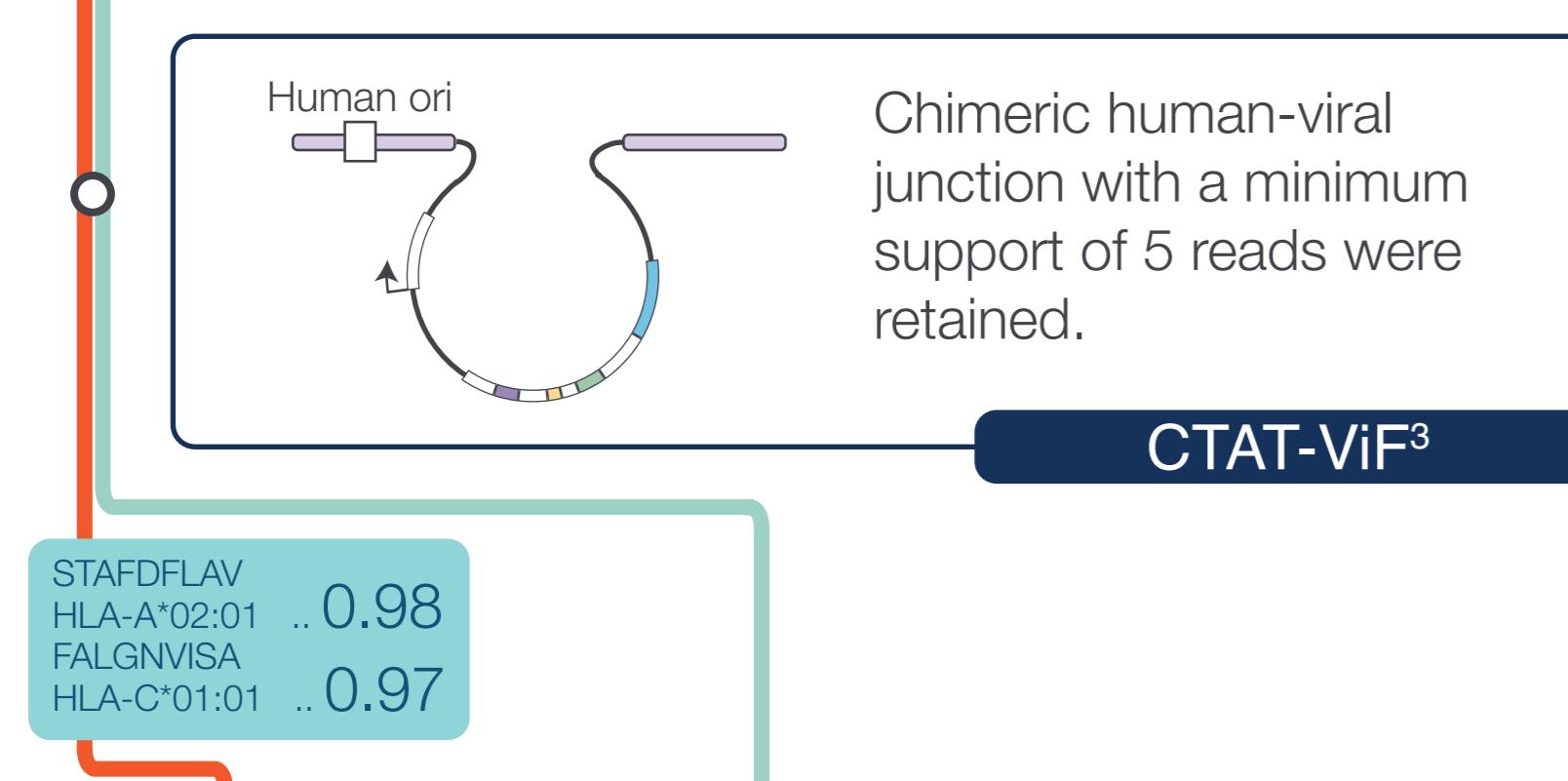
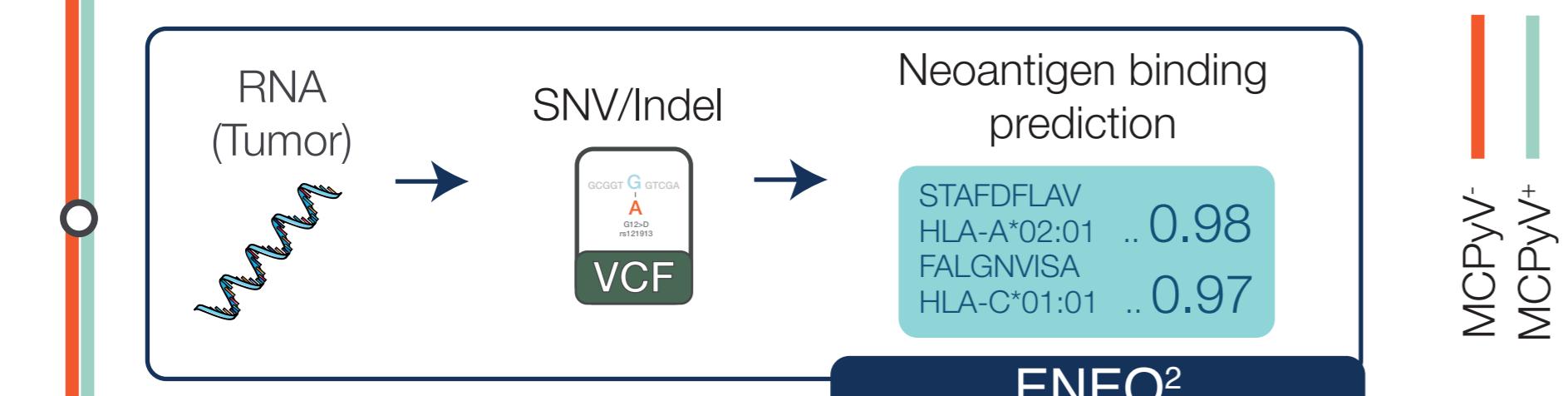


## AIM OF THE WORK

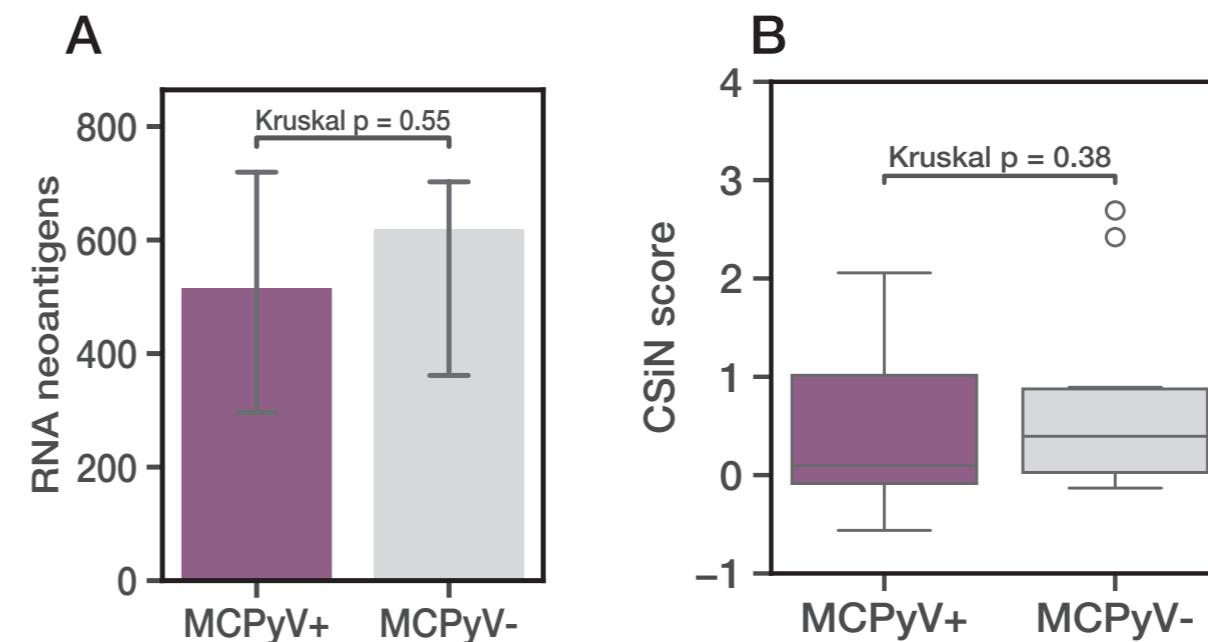
- Developing an comprehensive approach for **tumor neoantigens prediction in MCC patients using just tumor RNA-seq**
- Exploring drivers of successful response to ICB immunotherapy

## METHODS AND DATA

RNA was extracted and sequenced from 27 microdissected biopsies collected from a retrospective cohort of treatment naive MCC patients before starting anti-PD1 immunotherapy.

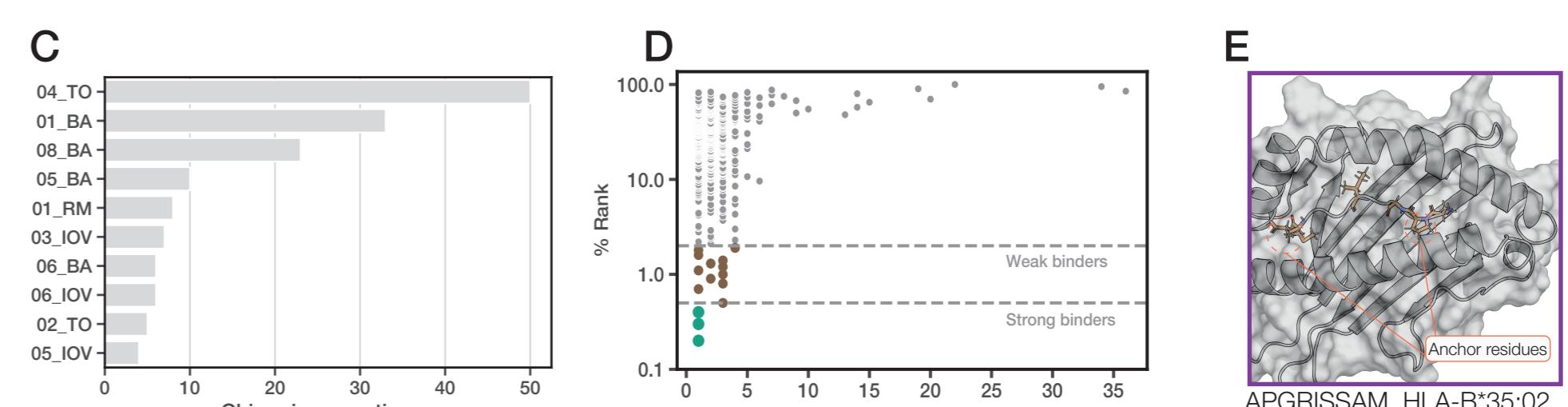


## RESULTS

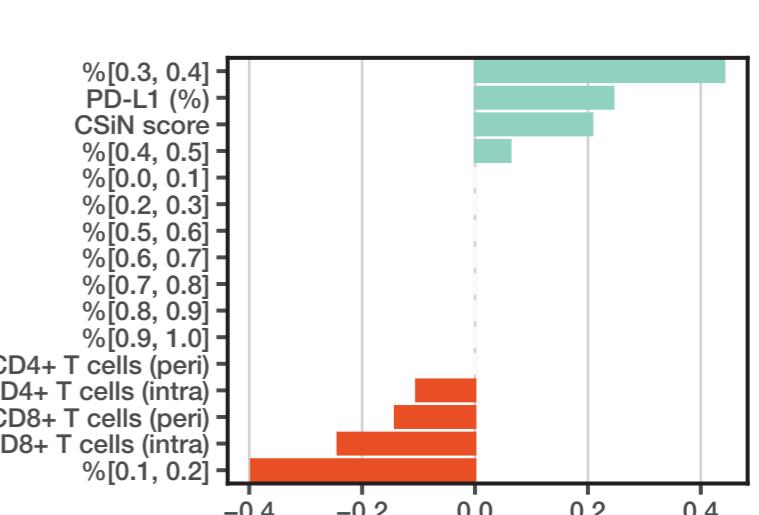


Neoantigens derived from somatic RNA-mutations does not differ significantly in both quantity (A) and quality, measured using the Cauchy-Schwarz index of Neoantigens (CSIN)<sup>4</sup> score (B).

We identified a variable number of viral junctions across the cohort, leading to a diverse range of **chimeric neoantigens (C)**. These neoantigens showed a **favorable binding potential**, as determined by the %Rank (D). We further confirmed the binding goodness of them via structural modeling of the pMHC complex (E).



Patients with a higher percentage of **clonal neoantigens** (VAF > 0.2) and **elevated PD-L1 expression** were more likely to respond to ICB therapy. Our logistic regression model suggests these factors are key markers of a pre-existing but stalled immune response that can be unlocked by ICB treatment.



## CONCLUSIONS

- We implemented a integrated approach for **somatic/viral neoantigens prediction in MCC patients using just tumor RNA-seq**
- We reported **multiple neoantigens arising from chimeric CDS**, opening for the route for highly-specific **personalized immunotherapies**

## REFERENCES

- https://doi.org/10.1038/s41419-025-07892-7
- https://doi.org/10.1093/nar/gab/lqa026
- https://doi.org/10.1101/2025.03.10.642430
- https://doi.org/10.1126/scimmunol.aaz3199

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