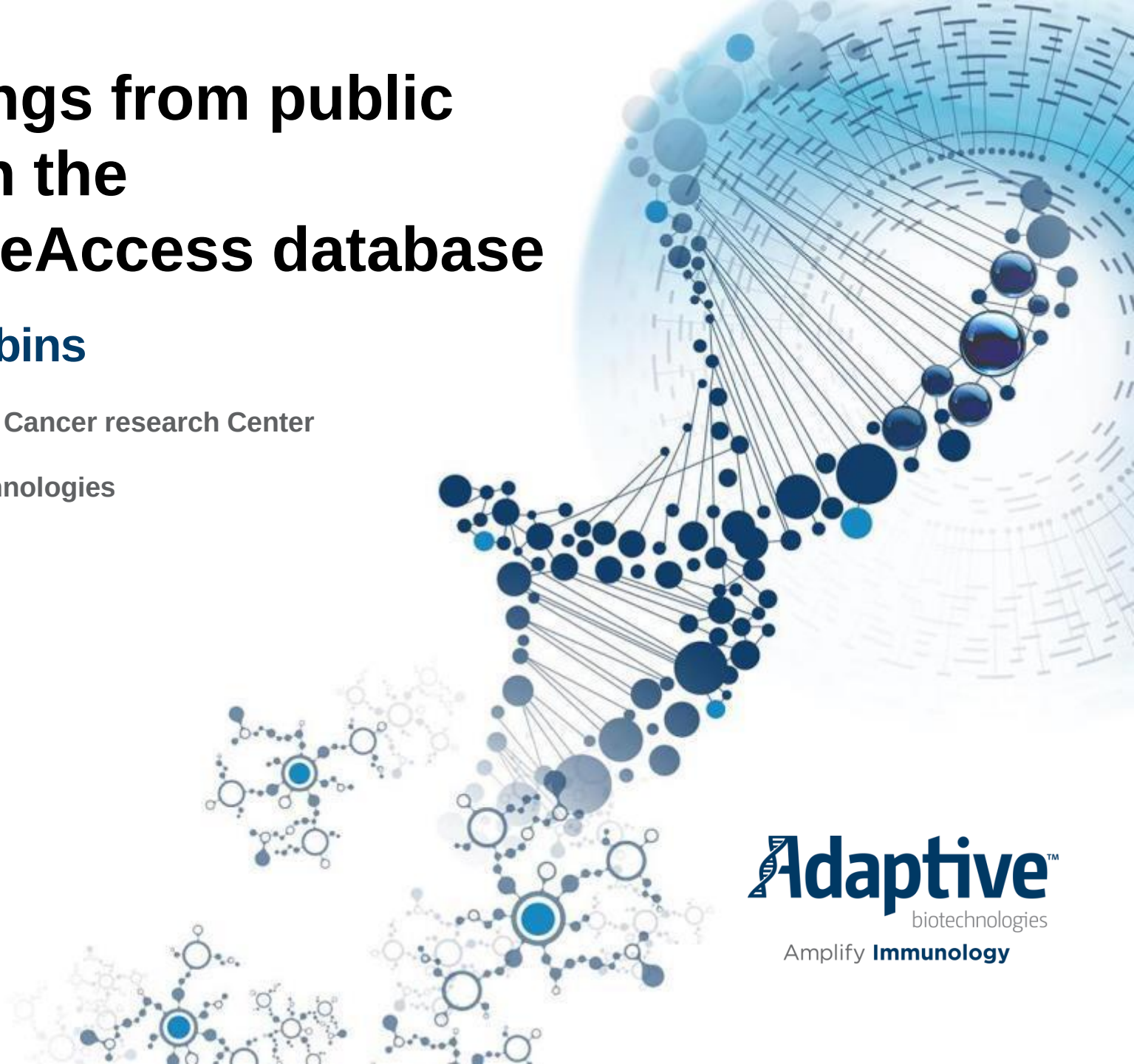
Learnings from public data on the ImmuneAccess database

Harlan Robins

Fred Hutchinson Cancer research Center

Adaptive Biotechnologies



Adaptive™ biotechnologies

Amplify **Immunology**

Available Data at Adaptive on ImmuneAccess (www.immuneaccess.com)

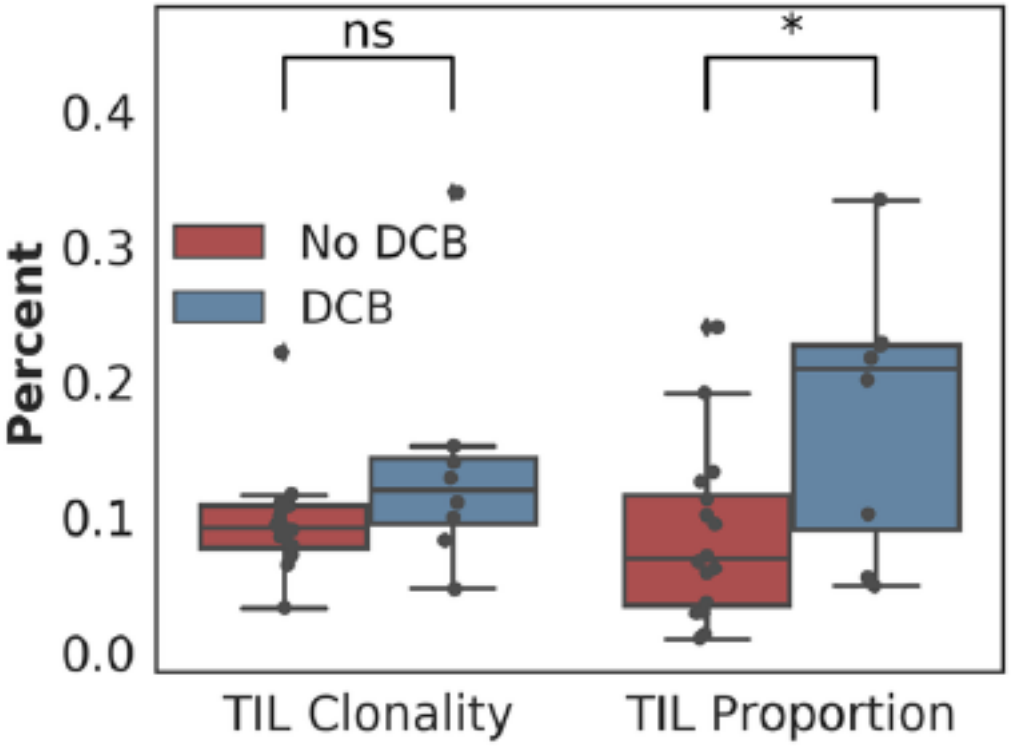
Uses of TCR Sequences

- Properties of the repertoire
- Tracking clones
- Mapping to antigen

- Contribution of systemic and somatic factors to clinical response and resistance to PD-L1 blockade in urothelial cancer: An exploratory multi-omic analysis
  - Snyder et al. Plos Medicine. 2017.

TCRB repertoire in the pre-treatment tumor microenvironment correlates with clinical benefit to IOs

Urothelial cancer patients treated with Atezolizumab



Key Takeaways

- Hallmarks of immune activation in pre-treatmet tumor tissue correlate with response to checkpoint inhibitors.
- 81% of patients without DCB had below median TIL clonality or TIL infiltration (proportion) in the tissue (p = 0.02)

*DCB = Durable Clinical Benefit = PFS > 6 mo

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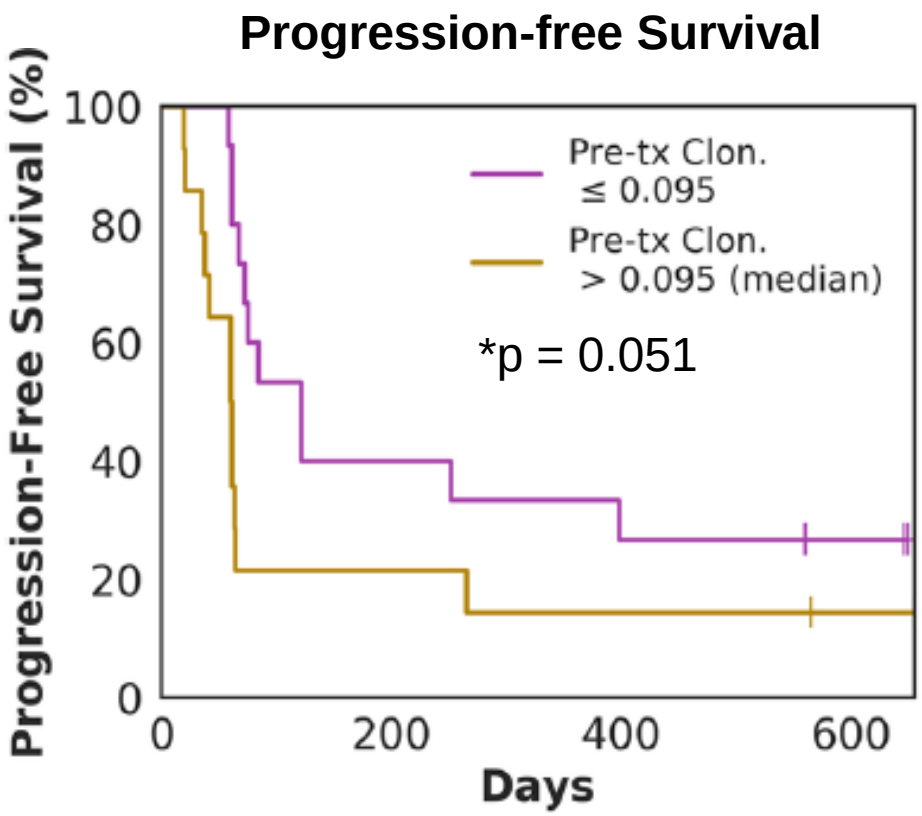
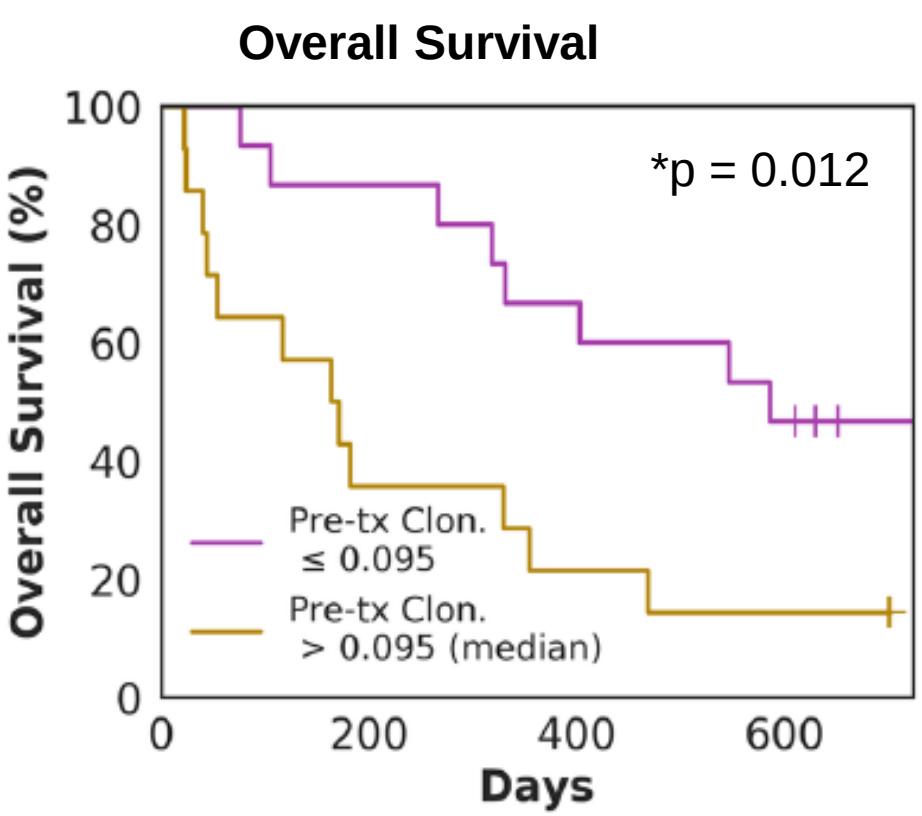
Pre-treatment Clonality in Peripheral Blood Correlates with Survival

Baseline peripheral clonality in patients with urothelial cancer treated with Atezolizumab was Prognostic





*Analysis was from a COX PH model

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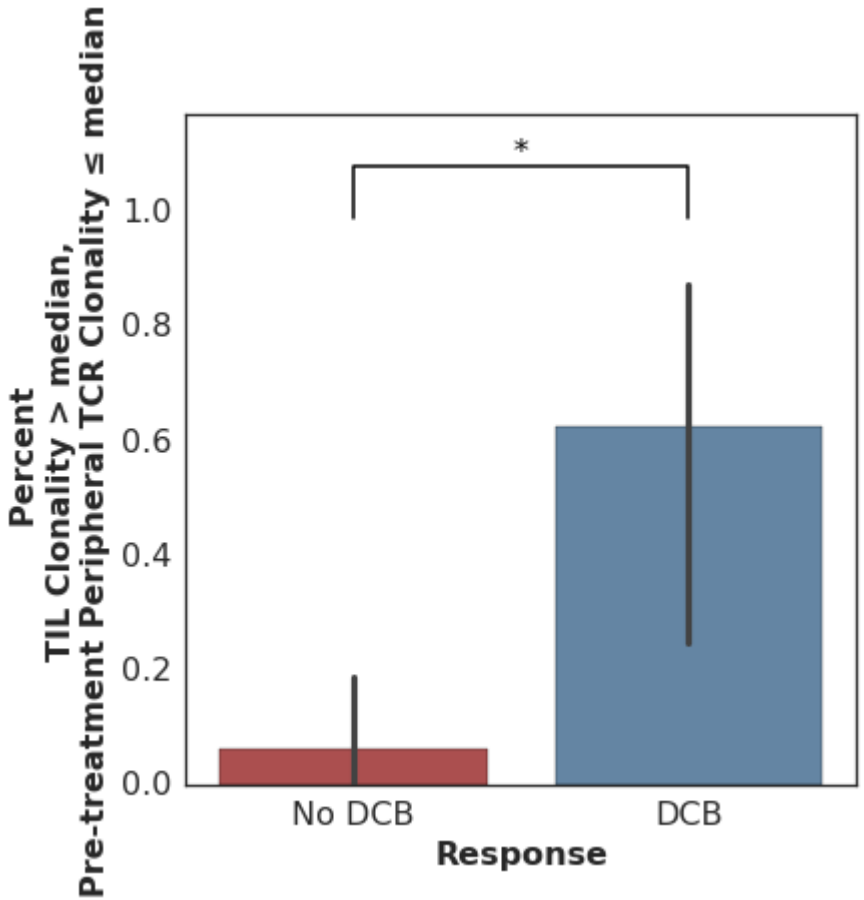
The combination of pre-treatment TIL assessment and peripheral clonality may be predictive of clinical benefit

Proportion of Patients with High TIL Clonality and Low Peripheral Clonality



Key Takeaways

- The combination of a healthy peripheral immune repertoire (low peripheral clonality) and an activated immune repertoire in the TME strongly correlates with clinical benefit.
- A comprehensive immune assessment or pre-treatment peripheral blood and tumor repertoires may facilitate patient stratification.

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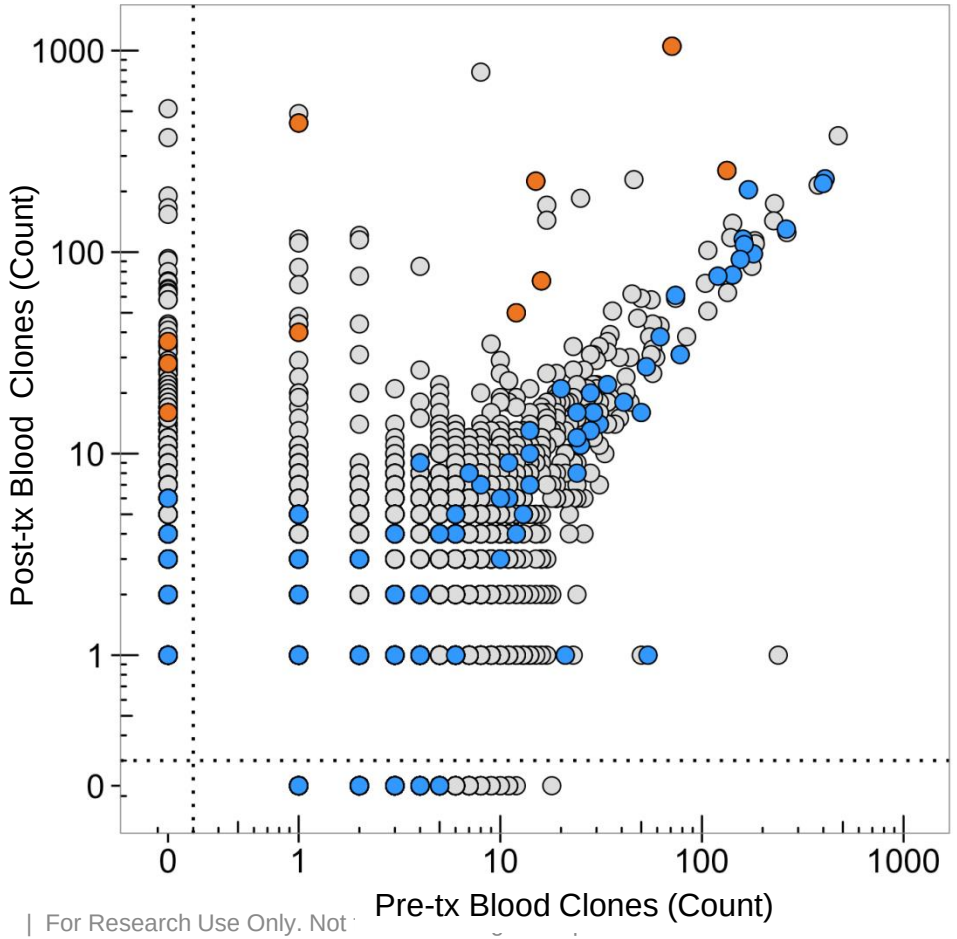
On-treatment monitoring identifies patients receiving clinical benefit.

Expansion of tumor-associated (TA) clones was detected in blood and correlated with response after the 1st dose of Atezo (anti-PD-L1) in patients with metastatic urothelial cancer

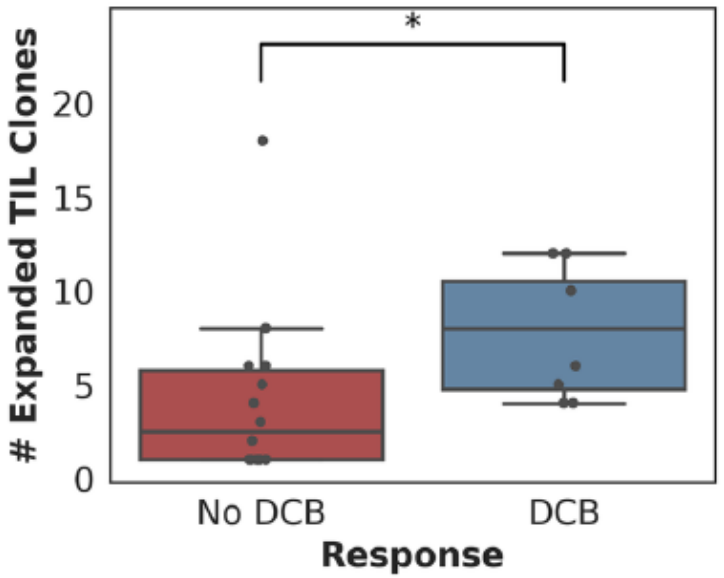
TA clones expanding in the blood

TA clones detected the blood

Clones only in blood



TIL Clones Expanding in the Blood



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Clinical Cancer Research

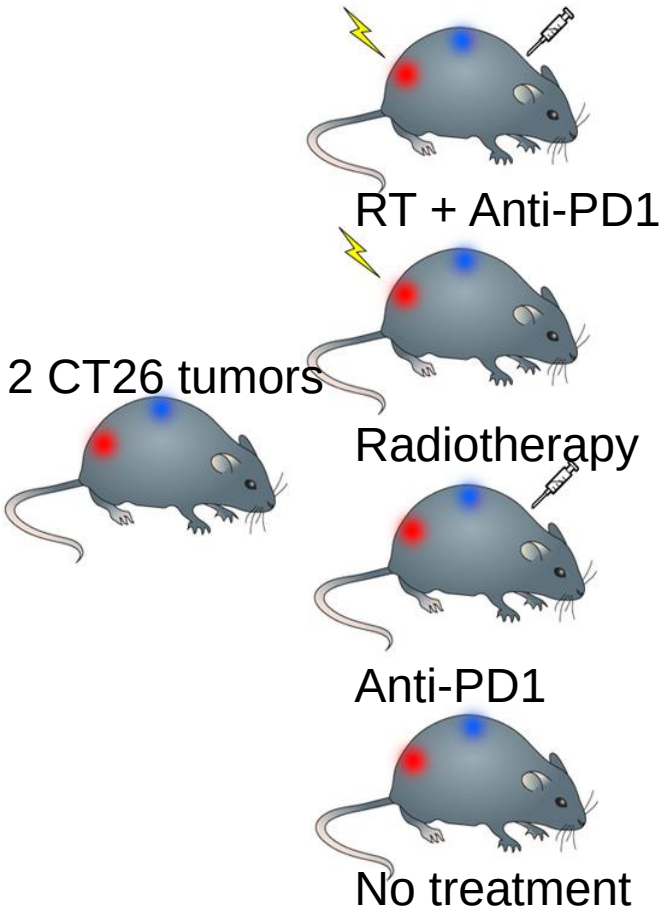
Cancer Therapy: Preclinical

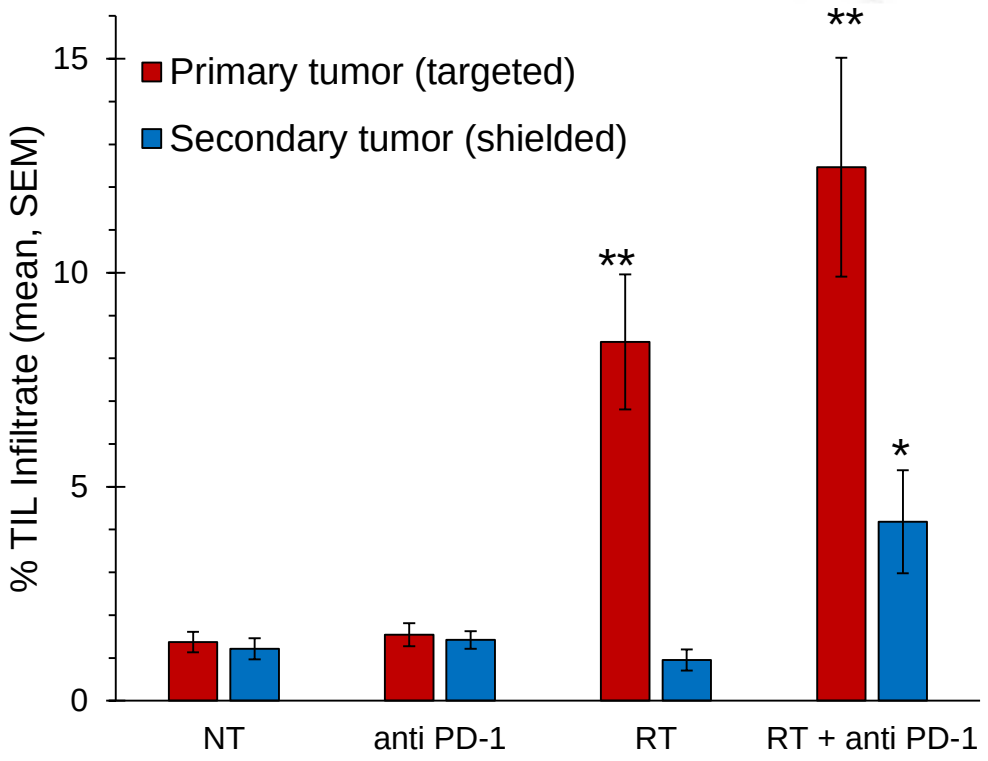
Fractionated radiation therapy stimulates anti-tumor immunity mediated by both resident and infiltrating polyclonal T-cell populations when combined with PD1 blockade

Simon J Dovedi, Eleanor J Cheadle, Amy Popple, Edmund Poon, Michelle Morrow, Ross Stewart, Erik Yusko, Catherine Sanders, Marissa Vignali, Ryan Emerson, Harlan Robins, Robert W Wilkinson, Jamie Honeychurch, and Timothy Illidge

DOI: 10.1158/1078-0432.CCR-16-1673

TIL Infiltrate doubles in the shielded tumor after combination treatments





PD-1 may replicate the immune effects of radiotherapy at a distant tumor that received no radiation

Dovedi and Illidge. Oral Presentation 2016 AACR

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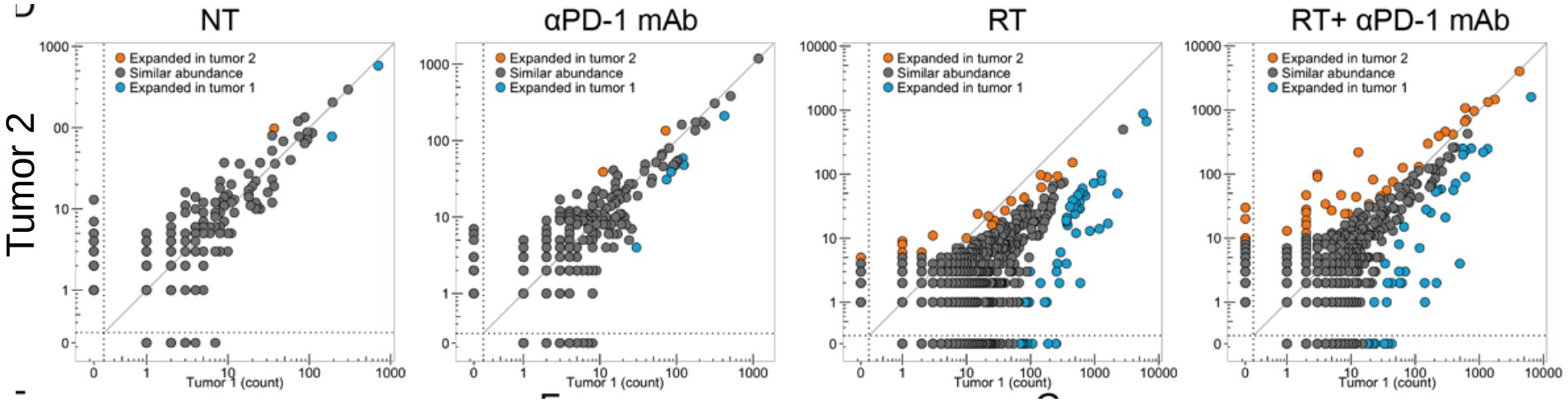
RT in combination with checkpoint blockades

- Strong concordance in tumors (NT and anti-PD1) indicates similar TCR repertoires, derived from common clones is established prior to therapy.
- The abscobal tumor TIL repertoires does not mirror the irradiated tumor unless anti-PD-1 mAb is administered.
- The combination of anti-PD-1 and RT may generate an abscopal effect.



Tumor 1 - irradiated

Dovedi and Illidge. Oral Presentation 2016 AACR

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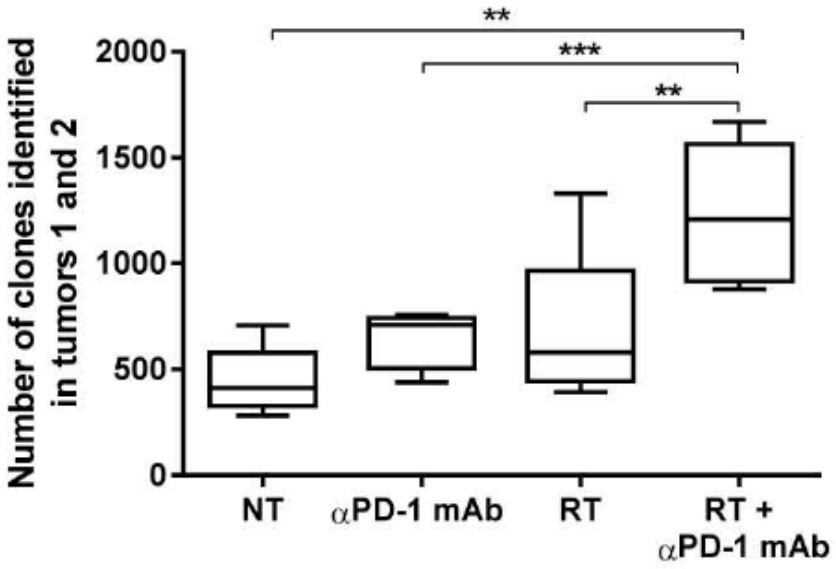
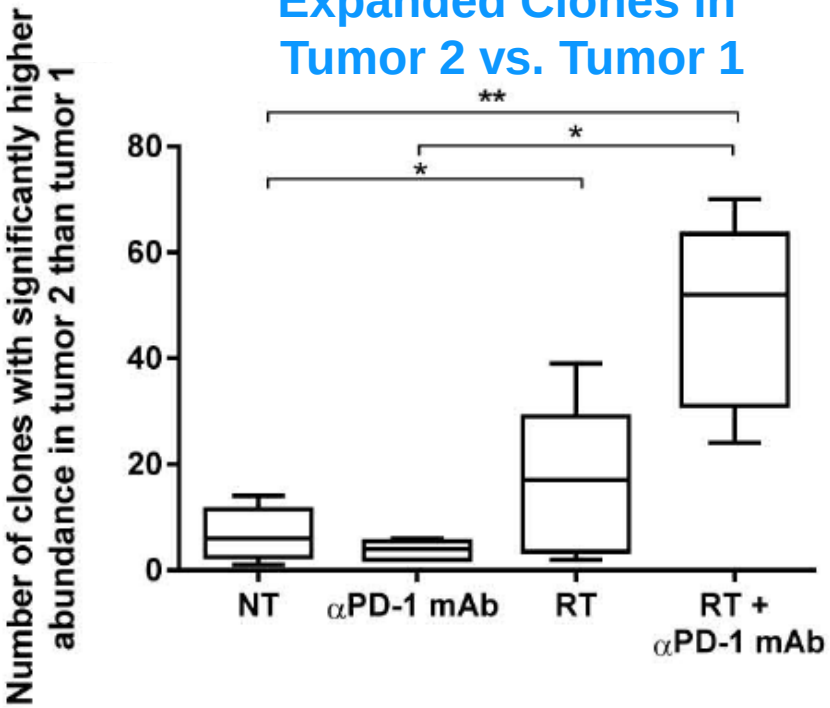
RT in combination with anti-PD1

Shared Clones



Expanded Clones in Tumor 2 vs. Tumor 1



- Quantitation of clone sharing between the irradiated and abscopal tumors indicates that many of the clones in the systemic tumor derived form the same progenitor.
- The clone response is not equal however, in that many clones despite being detected in both tumors have a statistically different frequency in tumor 2 vs. tumor 1.

Clonal expansion of CD8 T cells in the systemic circulation precedes development of ipilimumab-induced toxicities

Sumit K. Subudhi[a,1], Ana Aparicio[a,1], Jianjun Gao[a], Amado J. Zurita[a], John C. Araujo[a], Christopher J. Logothetis[a], Salahaldin A. Tahir[a], Brinda R. Korivi[b], Rebecca S. Slack[c], Luis Vence[d], Ryan O. Emerson[e], Erik Yusko[e], Marissa Vignali[e], Harlan S. Robins[e,f], Jingjing Sun[g], James P. Allison[d,g,2], and Padmanee Sharma[a,d,g,2]

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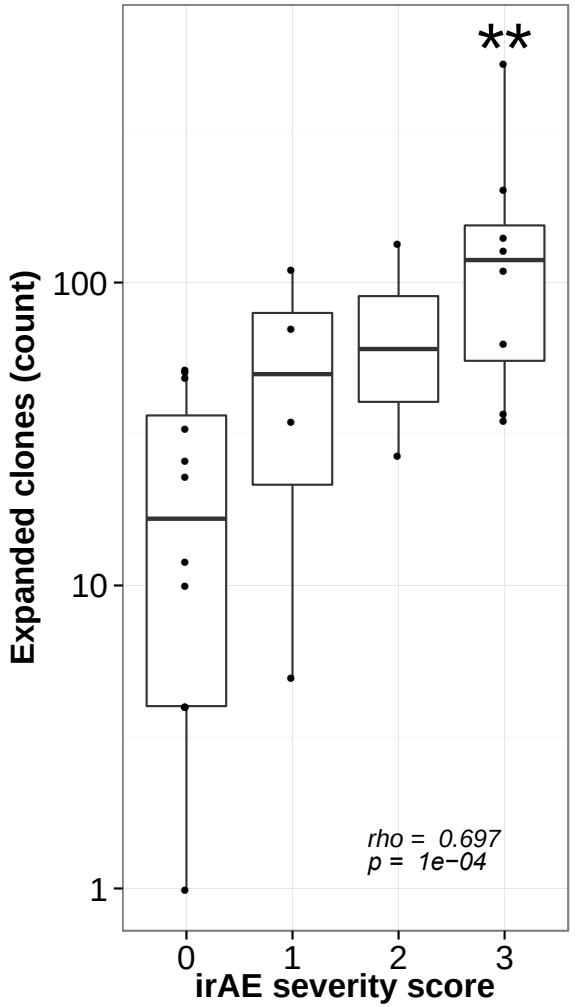
Contributed by James P. Allison, August 17, 2016 (sent for review May 31, 2016; reviewed by Nina Bhardwaj, Charles G. Drake, and Owen N. Witte)

Clonal expansion correlates with AE severity in CRPC

Pre- and post-Ipilimumab comparison
of clonal expansion and repertoire turnover

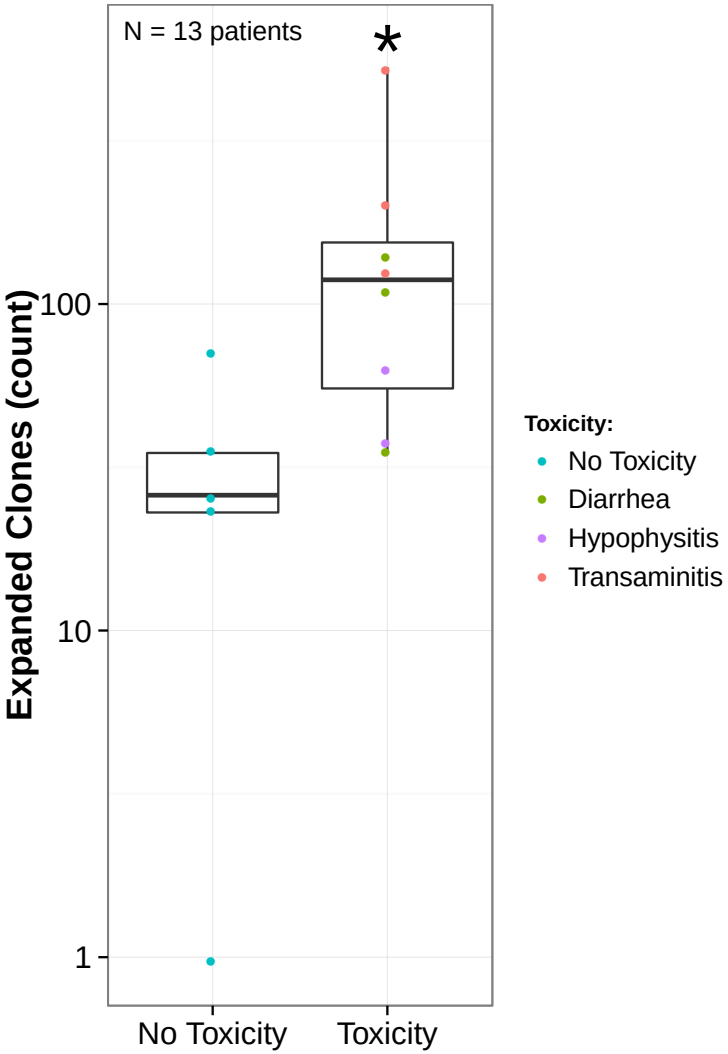


Source: Pam Sharma, MDACC – AACR 2015

Key Takeaways

- Castration-resistant prostate cancer (CRPC) patients were treated with **androgen deprivation therapy** followed by **multiple doses of ipilimumab** (10mg/kg)
- **Higher** than average **toxicities** caused the trial to stop prematurely
- **Patients experiencing AEs** compared to patients with little or no toxicities showed **increased clonal expansion** and **repertoire turnover**

Clonal expansions detected in blood draws prior to the onset of AEs



Source: Pam Sharma, MDACC – AACR 2015

Key Takeaways

- Patients with Grade 3 AEs showed greater clonal expansion in blood draws (PBMCs) just prior to onset of toxicities
- Most common toxicities include:
  - Diarrhea
  - Hypophysitis
  - Transaminitis

CMV Public TCRs – Dataset

- 640 healthy bone marrow donors
- HLA typing
- CMV serostatus: 45% CMV+, 55% CMV-
- ~100 million different TCRs detected
- Are some TCRs statistically associated with CMV status?

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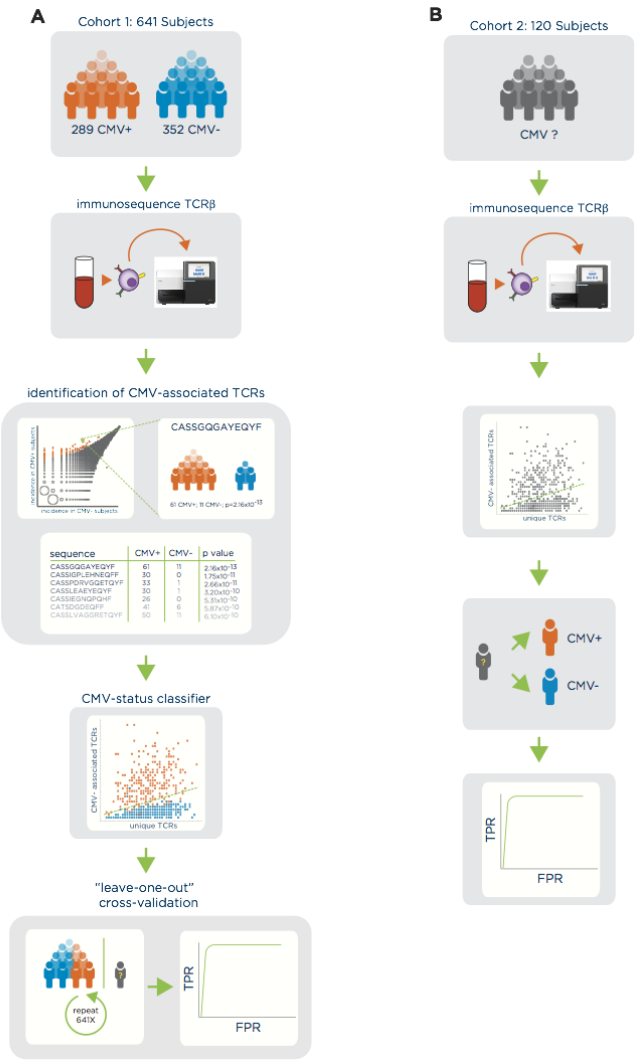
Search for public TCRs to diagnose CMV



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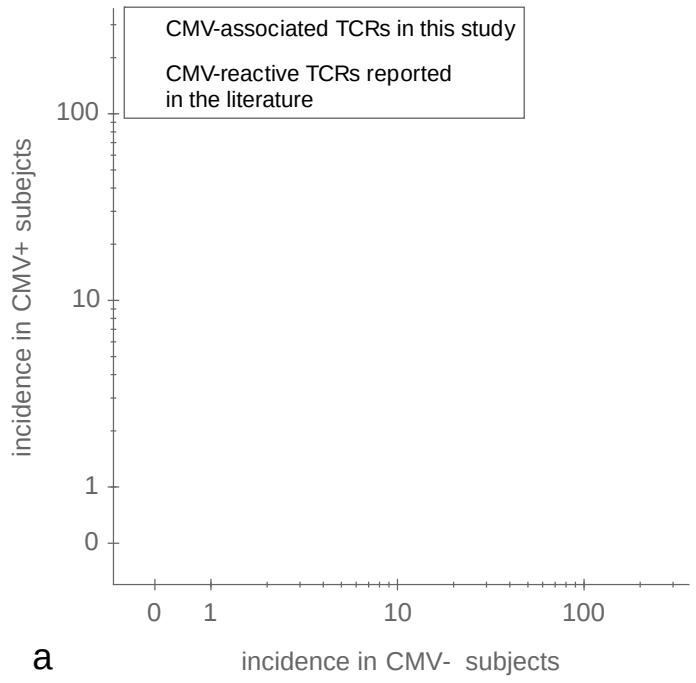
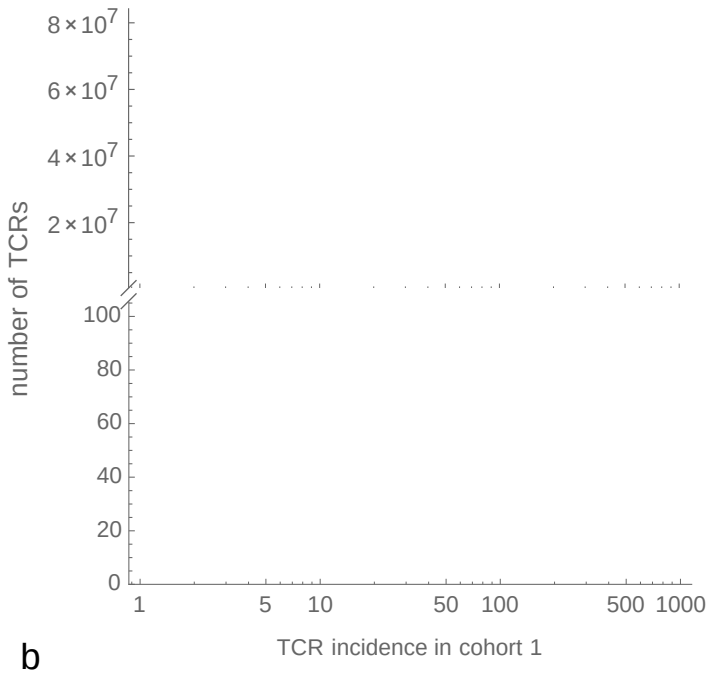
We find many CMV specific clones

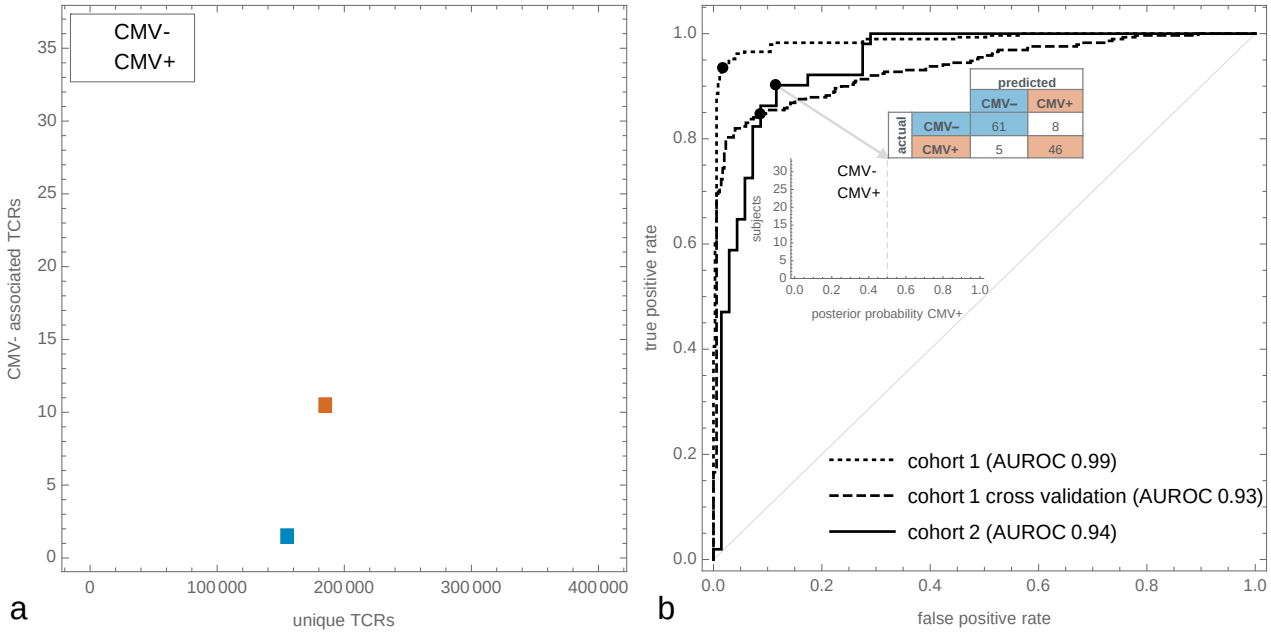


a

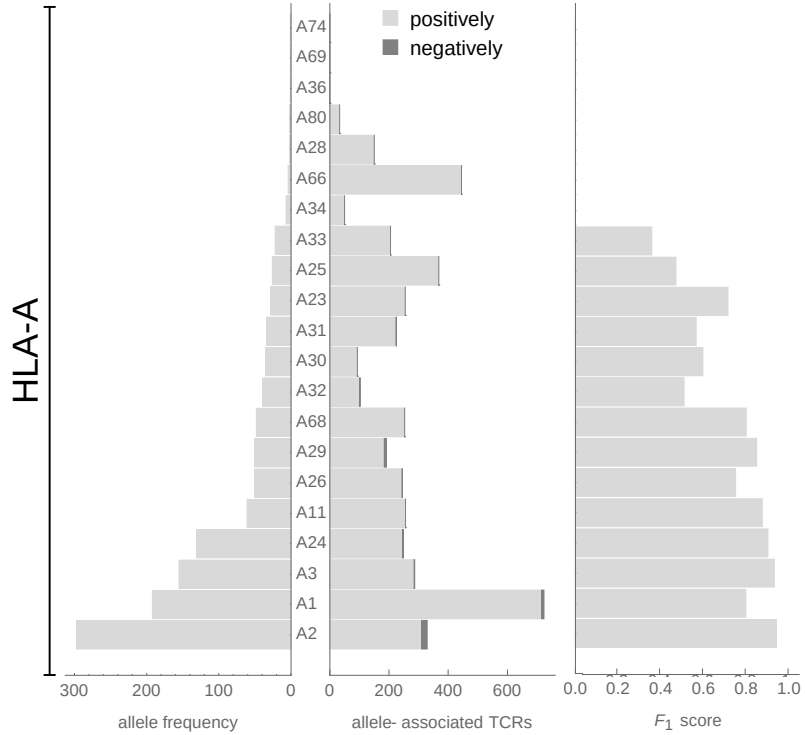


b

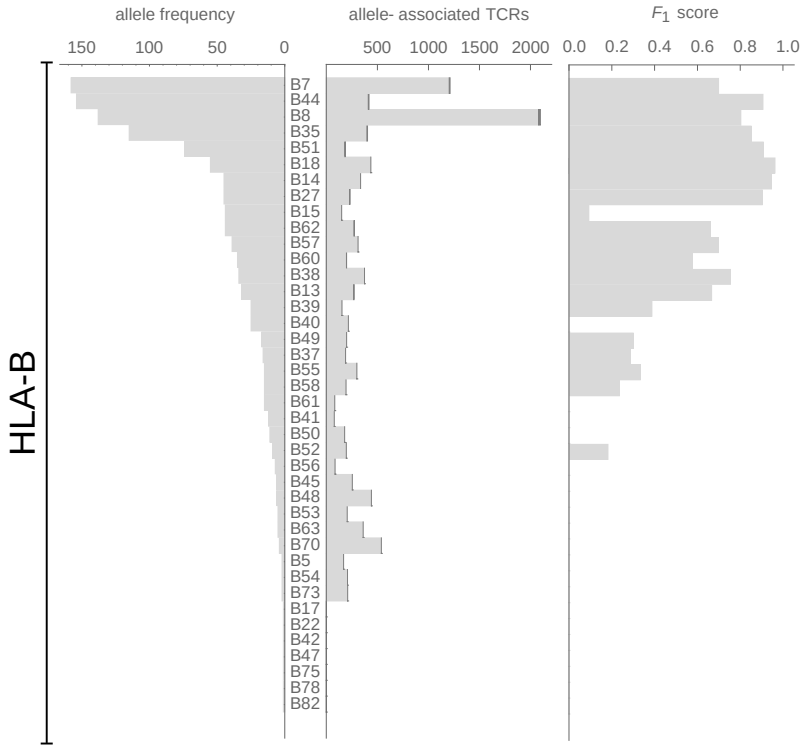
These clones are sufficient to diagnose CMV



We can consider HLA a feature and use public TCRs to HLA type



For HLA class II as well



The players

Will deWitt
Ryan Emerson
Marissa Vignali
Annie Sherwood
Bryan Howie
Edward Osborne
Alex Snyder

Paul Lindau

John Hansen
Hootie Warren
Karen Makar
Pam Sharma
Jim Allison
Simon Dovedi