Learnings from public data on the ImmuneAccess database

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

DATA AT A GLANCE

5,545 human samples
See all

464 mouse samples
See all

545,429,843 nucleotide sequences

48 journal articles

14 research areas
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
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-treatment 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 $> 6 \text{ mo}$
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

*Progression-free Survival

*Overall Survival

*\( p = 0.051 \)

*\( p = 0.012 \)
The combination of pre-treatment TIL assessment and peripheral clonality may be predictive of clinical benefit.

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.
**On-treatment monitoring identifies patients receiving clinical benefit.**

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

<table>
<thead>
<tr>
<th>Pre-tx Blood Clones (Count)</th>
<th>Post-tx Blood Clones (Count)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA clones expanding in the blood</td>
<td>TA clones detected in the blood</td>
</tr>
<tr>
<td>TA clones detected in the blood</td>
<td>Clones only in blood</td>
</tr>
</tbody>
</table>

**TIL Clones Expanding in the Blood**

![Graph showing the correlation between pre-treatment and post-treatment blood clone counts.](image)

- Pre-tx Blood Clones (Count) vs. Post-tx Blood Clones (Count)
- TA clones expanding in the blood
- TA clones detected in the blood
- Clones only in blood

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![Box plot comparing response with No DCB and DCB conditions.](image)
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

2 CT26 tumors
Radiotherapy
Anti-PD1
No treatment

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

Dovedi and Illidge. Oral Presentation 2016 AACR
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.

Dovedi and Illidge. Oral Presentation 2016 AACR
RT in combination with anti-PD1

- 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

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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

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

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

Source: Pam Sharma, MDACC – ACR 2015
Clonal expansions detected in blood draws prior to the onset of AEs

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

Source: Pam Sharma, MDACC – AACR 2015
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?
Search for public TCRs to diagnose CMV

A  Cohort 1: 641 Subjects

283 CMV+  352 CMV-

Immunosequence TCRs

Identification of CMV-associated TCRs

CMV-status classifier

"Leave-one-out" cross-validation

B  Cohort 2: 120 Subjects

CMV+  CMV-

Immunosequence TCRs

Identification of CMV-associated TCRs

CMV-status classifier

"Leave-one-out" cross-validation

For Research Use Only. Not for use in diagnostic procedures.
We find many CMV specific clones

![Graph showing CMV-associated TCRs and CMV-reactive TCRs reported in the literature]
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

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

Paul Lindau