Historical perspective and future directions: Computational science in immuno-oncology

Eliezer (Eli) Van Allen, MD
Associate Professor, Harvard Medical School
Chief, Division of Population Sciences, Dana-Farber Cancer Institute
Associate Member, Broad Institute of MIT and Harvard

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Outline

• Genomics and immuno-oncology biomarkers
• Pivoting to reverse translation and genomics
• Creating more complex molecular representations for discovery and prediction
• Next steps
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Clinical genomics and cancer immunotherapy ca. 2015

Tumor mutational burden

CTL4 Ab and melanoma

PD-1 Ab and NSCLC

Snyder et al *NEJM* 2014
Van Allen et al *Science* 2015
Rizvi et al *Science* 2015
Le et al *NEJM* 2015
Is TMB necessary and/or sufficient?


Miao, Margolis, Vokes et al. *Nature Genetics* 2018

[Graph showing box plots for mutation load and neoantigen load, with different colors representing minimal or no clinical benefit, long-term survival with no clinical benefit, and clinical benefit.]

249 tumors across multiple histologies

AUC = 0.66
Practical challenges with clinical use of TMB
Practical challenges with clinical use of TMB, cont.

Of the 1739 randomly assigned patients, 1649 (94.8%) had tumor samples available to attempt assessment of tumor mutational burden, and 1004 (57.7%) had valid data for tumor mutational burden–based efficacy analyses (Table S2 in the Supplementary Appendix). Baseline char-
Practical challenges with clinical use of more complex signatures
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“First order” genomic events and response to immune checkpoint blockade?

<table>
<thead>
<tr>
<th>Tumor cell (response mechanisms)</th>
<th>Tumor antigens</th>
<th>Neoantigens, viral antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased tumor mutation burden</td>
<td></td>
<td>Mismatch repair deficiency</td>
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</table>

**PBRM1** mutations and anti-PD-1 response

- **Graph 1:**
  - x-axis: MutSig2CV significance: \(-\log_{10}(p\text{-value})\)
  - y-axis: Responder significance: \(-\log_{10}(q\text{-value})\)
  - Genes: PBRM1, GUCY2C, VHL, KDM5C, SETD2, ATXN7L1
  - Patients with truncating mutation in gene:
    - Gene significantly mutated (p<0.05)
    - Gene significantly mutated and mutations enriched in CB (q<0.10)

- **Graph 2:**
  - Survival vs. time from start of anti-PD-1 therapy (years)
  - p-value: 0.0074
  - Groups:
    - PBRM1 LOF (n=19)
    - PBRM1 intact (n=16)

- **Graph 3:**
  - Progression-free survival vs. time (years)
  - Groups:
    - Not first-line anti-PD-(L)1
    - First-line anti-PD-(L)1

- **Graph 4:**
  - Progression-free survival vs. time (years)
  - Groups:
    - PBRM1-LOF
    - PBRM1-intact

- **PBRM1** mutations and anti-PD-1 response

Miao et al. Science 2018
Linking clinical genomics to functional biology

Miao, et al Science 2018; Kaelin Lab

Pan, et al Science 2018

Canadas et al Nature Med 2018

Endogenous retrovirus signature
Clinical validation in similar clinical contexts in kidney cancer?

Original Miao et al validation cohort

*Adjusted for lines of therapy prior to ICI

Biology vs. biomarker for immuno-oncology

• Numerous interactions suggest complex interplay with other modifiers in distinct clinical contexts
• Additional lineage-specific, tumor heterogeneity, and microenvironmental factors at play
• Functional and larger clinical investigations needed/underway

• NOT A CLINICAL BIOMARKER!

McDermott et al Nature Medicine 2018
Zhou et al CIR 2022
PI3K/PTEN and cancer immunotherapy resistance?
Placing single-gene correlates in broader molecular contexts

**PIK3CA**

Melanoma, HNSCC, bladder cancer

Miao, Margolis, Vokes et al *Nature Genetics* 2018

Litchfield et al *Cell* 2021
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From "first order" genomics to integrated tumor-immune representations

![Graph showing PD-L1 expression versus tumor mutation burden. The graph displays two datasets: CR/PR (blue) and SD/PD (gray). The x-axis represents tumor mutation burden, while the y-axis shows the percentage of PD-L1 expression.}

![Receiver Operating Characteristic (ROC) curve comparing multivariate and univariate models. The ROC curve plots sensitivity against specificity. Two curves are shown: red for the multivariate model and dashed red for the univariate model. The x-axis represents specificity, ranging from 0.0 to 1.0, and the y-axis represents sensitivity, ranging from 0.0 to 1.0.]

Hellmann et al Cancer Cell 2017
Linking transcriptional programs, mutations, and clinical outcomes

Bi, He et al. Cancer Cell 2021
Toward convergent spatial representations of integrated molecular states
Linking integrated molecular representations with complete clinical features

Liu et al. Nature Medicine 2019
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More (and better!) data needed
Considering genomics and neoantigen discovery

\[ R^2 = 0.99 \]

Predicted neoantigens/exome (rank < 2%) vs. Nonsynonymous mutations/exome

\[
\text{Predicted neoantigen burden} = 2.24 \times (\text{nonsynonymous mutation burden}) - 12.4
\]

Team Median Overlap

Miao, Margolis, Vokes et al *Nature Genetics* 2018
Well et al *Cell* 202
Considering resistance heterogeneity
Toward integrating biology and machine learning for immunogenomics discovery

NCI IOTN CIDC CIMAC Bioinformatics working group (Yi Xing, Alan Hutson); ElMarakeby, et al Nature 2021; Lu et al Nature Machine Intell 2021
Toward representative clinicogenomic cohorts: The Metastatic Prostate Cancer Project & Count Me In

You can have a direct impact on the future of men with prostate cancer

The Metastatic Prostate Cancer Project is a nationwide genomic research study for men with advanced or metastatic prostate cancer. We seek to generate the most comprehensive database that will be shared with the entire research community to accelerate discoveries.

www.mpcproject.org
joincountmein.org
The Metastatic Prostate Cancer Project
MPCProject.org

Over **1100 men** with metastatic prostate cancer have joined the MPCproject since our launch in January 2018.

http://www.mpcproject.org
@PrCaProject
The Metastatic Prostate Cancer Project
MPCproject.org

- NCI-Designated Cancer Center (n = 50)
- Physician shortage area
- Medically underserved

Total: 238 (38%)

Pathogenic germline variant
- None
- At least one

Patient-partners with germline sequencing

Self-reported family history
- No
- Yes
- Don't know

Pathogenic germline variants
- NBN
- MSH6
- HOXB13
- BRCA2
- CHEK2

Crowdis, Balch et al bioRxiv 2021
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Phil Abbosh
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Many others...

Funding

Let's work together!
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• Type your question in the Q&A box, then click “Send”
• Questions will be answered in the Question & Answer session at the end of the webinar (as time permits)