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Breakout session II Somatic and epigenetic changes related to the cancer immune landscape

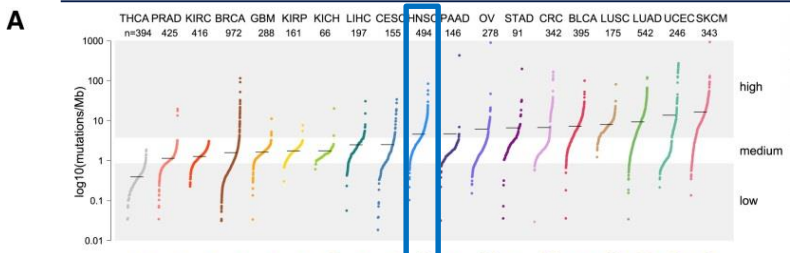
Josue Samayoa, Richard Simon, Vésteinn Thorsson, Daniel De Carvalho, Michele Ceccarelli, Maulik Patel,

05/15/2018

Disclosures

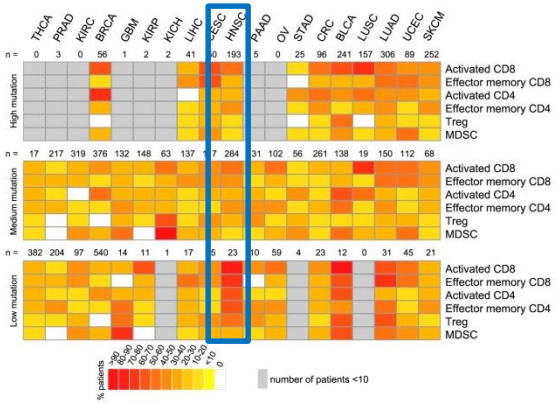
Currently employed as a Principal research scientist, AbbVie Inc.

Impact of inter-and-intra tumor type TMB variability to Immune landscape



High Mutation

Low Mutation

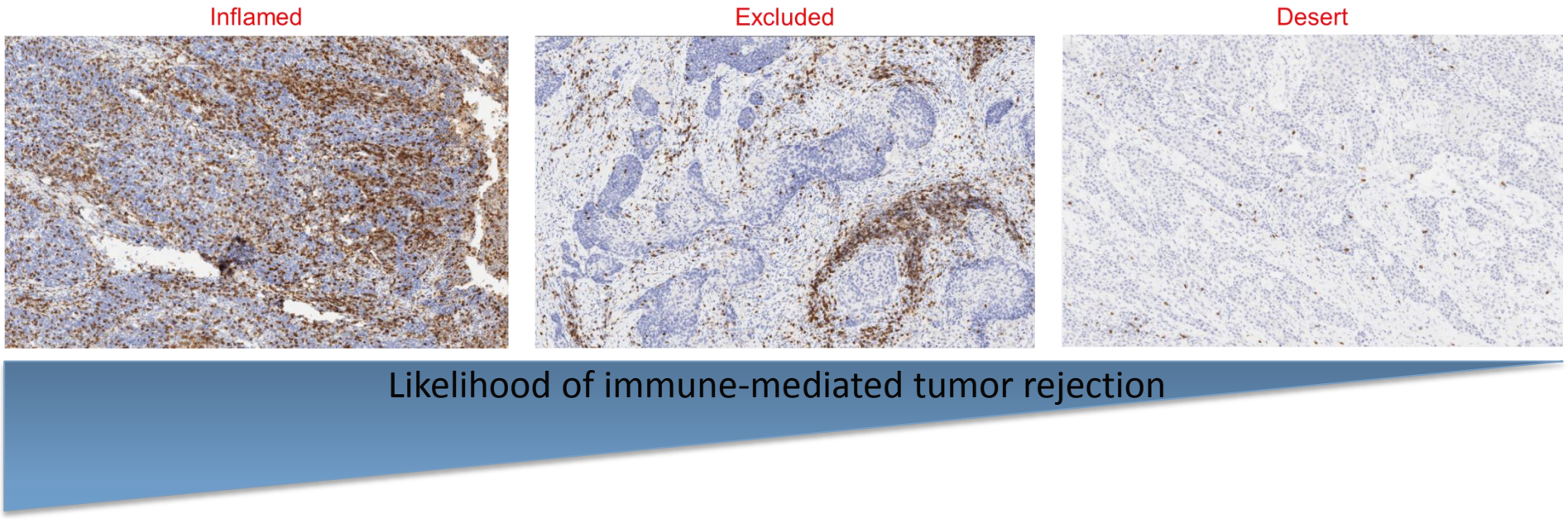


Heterogeneity upon heterogeneity:

- **There is heterogeneity in the immune landscapes of different tumor types**
- **There is also heterogeneity between high and low TMB tumors of the same type**
- **The immune landscape is comprised of multiple dimensions that all play a role in determining response**

Charoentong et al., 2017, Cell Reports 18, 248–262

The cancer immune landscape is a relevant phenotype for IO-responsiveness

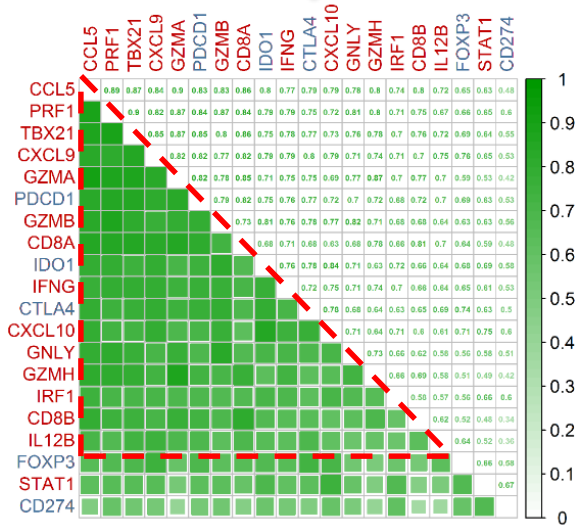


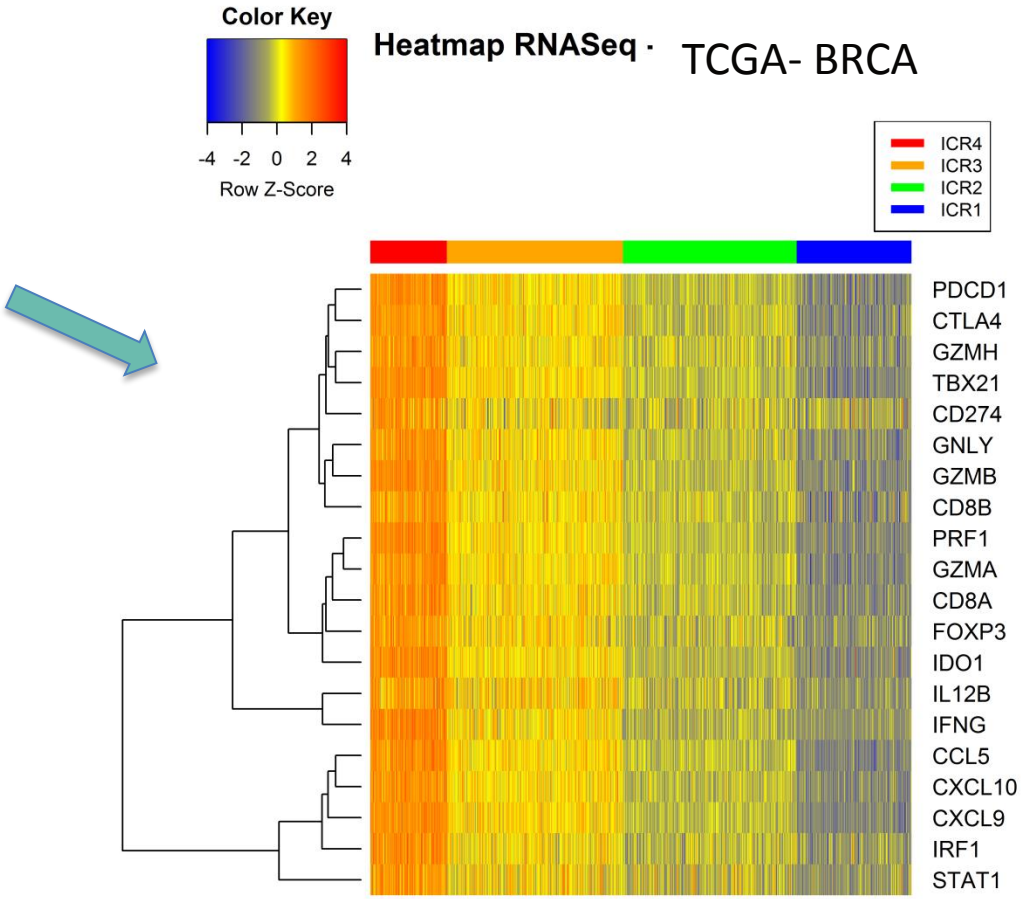
- The focus of this session will be to investigate the interplay between epigenetic and somatic alterations, their influence on the cancer immune landscape, and ultimately their role in determining response to IO-based therapies.

Immunological Constant of Rejection (ICR) – Hendrickx et al, 2017

Immunologic Constant of Rejection

CXCR3/CCR5 Chemokines	Th1 signaling	Effector functions	Immune regulatory
CXCL9	IFNG	GNLY	CD274
CXCL10	TBX21	PRF1	CTLA4
CCL5	CD8	GZMA	FOXP3
	IL12B	GZMB	IDO1
	CD8	GZMH	PDCD1
	STAT1		
	IRF1		





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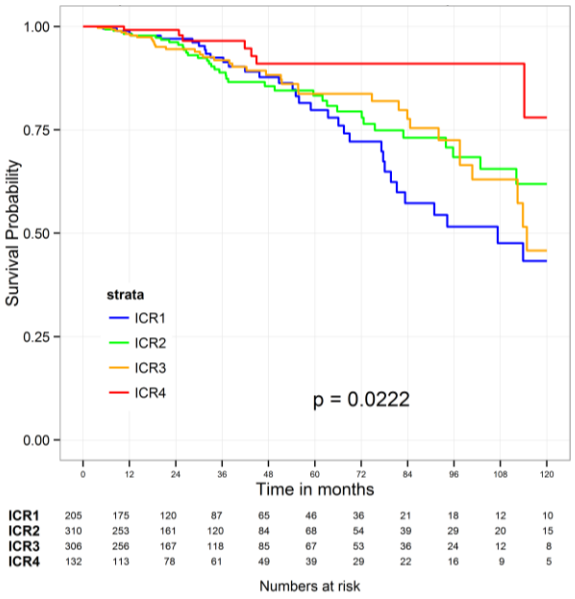

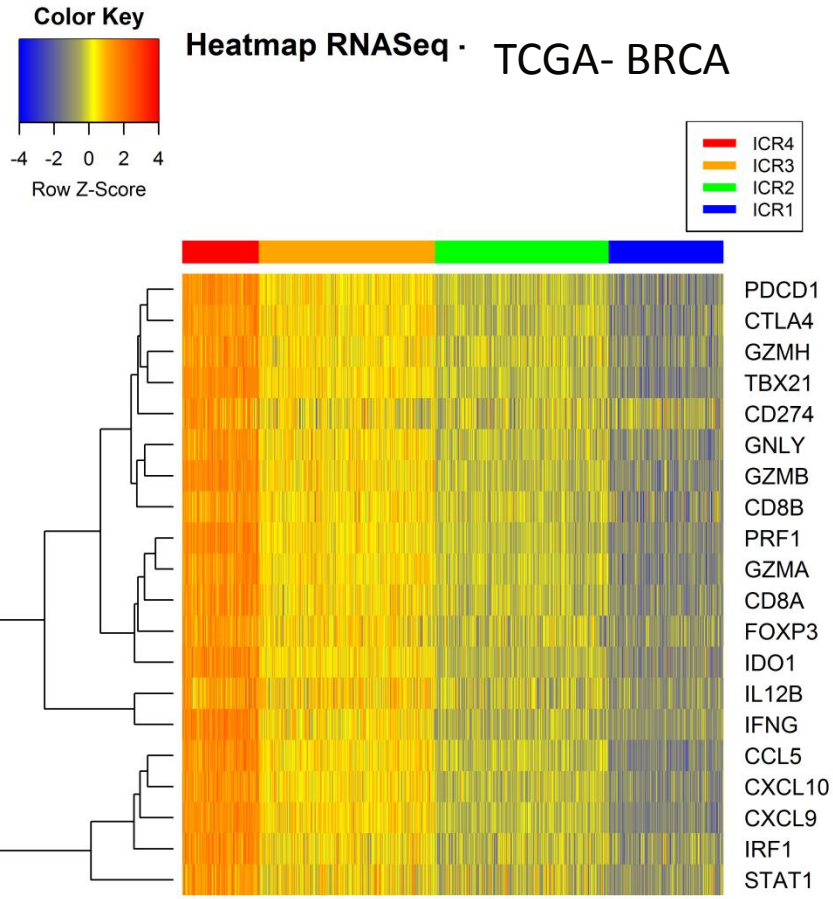

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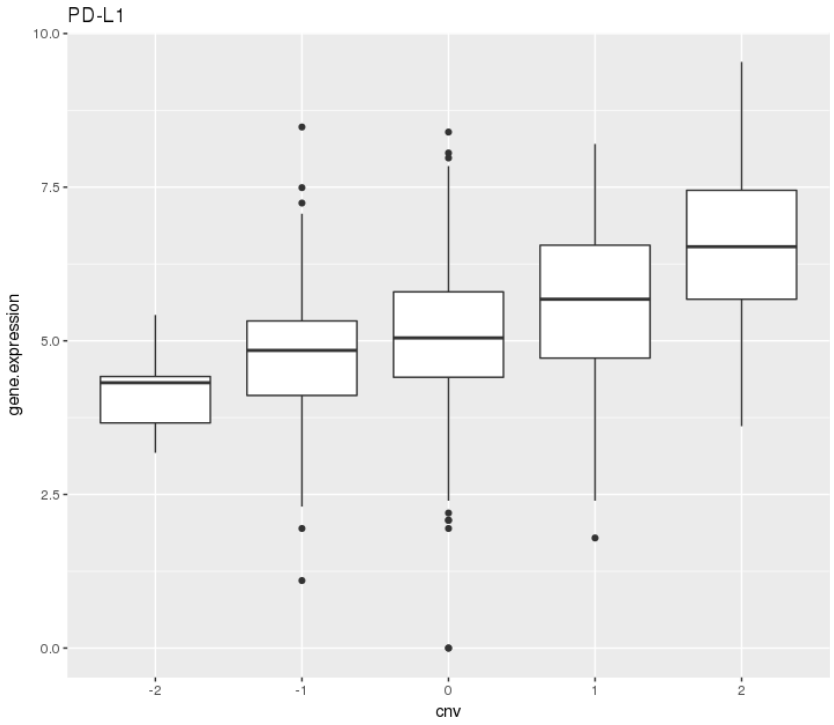
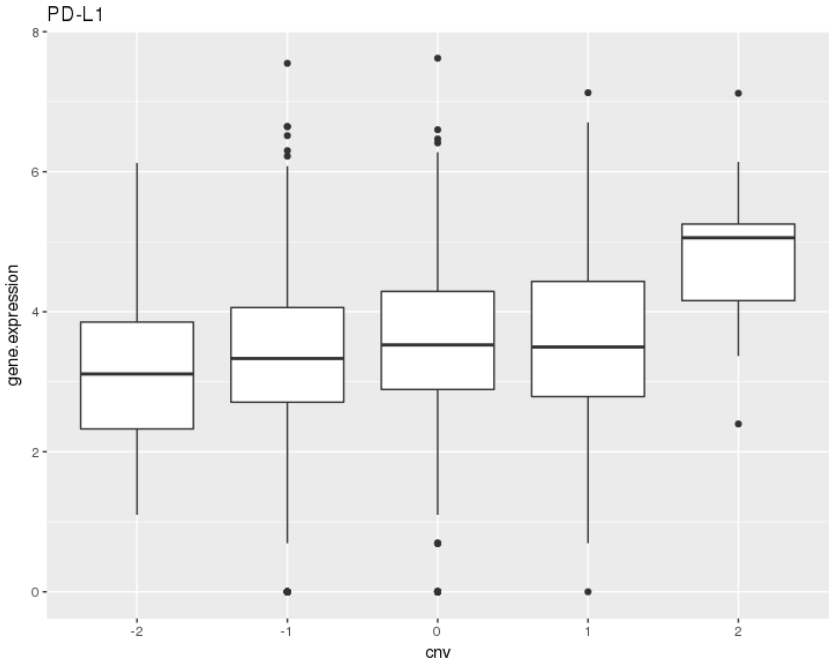
PD-L1 amplification level is significantly correlated with expression among inflamed tumors

Pan-Cancer ICR4



Pan-Cancer ICR1



Kyle Halliwill

Questions for breakout sessions

1. What are the underlying genomic alterations that explain the variability of response to IO based therapies for tumors with high TMB? Specifically, what molecular alterations are associated with cases that have high TMB and yet fail to respond to IO?

   Maulik Patel, PharmD/PhD, Senior Clinical Scientist II, AbbVie Inc., Redwood City, CA

2. How can knowledge of how somatic alterations influence the tumor microenvironment help us optimize immunotherapy combinations? Specifically, are there shared themes in these effects that can be exploited for improving therapy?

   Vésteinn Thorsson, PhD, Senior Research Scientist, Institute for Systems Biology, Seattle, WA

3. What molecular alterations have a direct effect on epigenetics and how does this correlate with the cancer immune landscape and IO responsiveness?

   Daniel D. De Carvalho, PhD, Assistant Professor, Department of Medical Biophysics, Faculty of Medicine, University of Toronto

4. What are the regulatory networks downstream of molecular alterations that are correlated with the cancer immune immune-phenotypes and response to IO-based therapies. How do we identify the main regulators of these networks as potential targets to revert the immune silent phenotypes?

   Michele Ceccarelli, PhD, Research Fellow, AbbVie Inc., Redwood City, CA

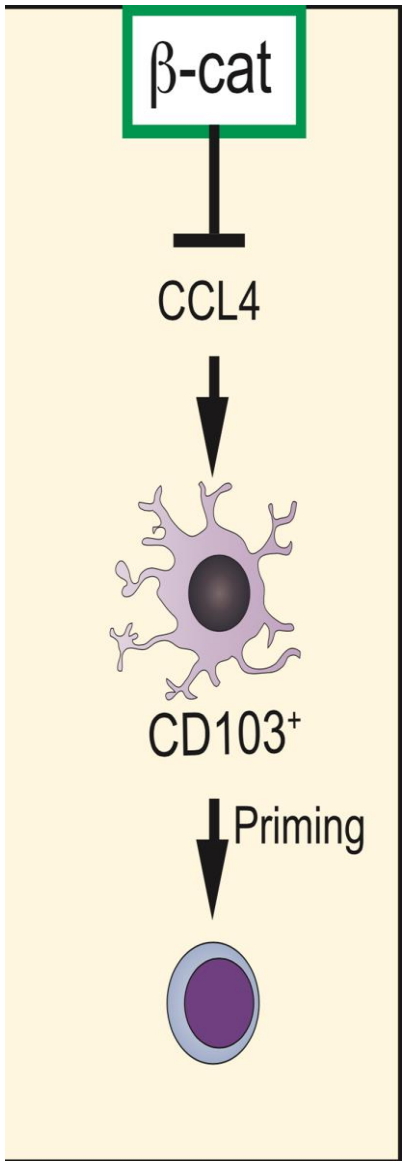
Guidance for discussion

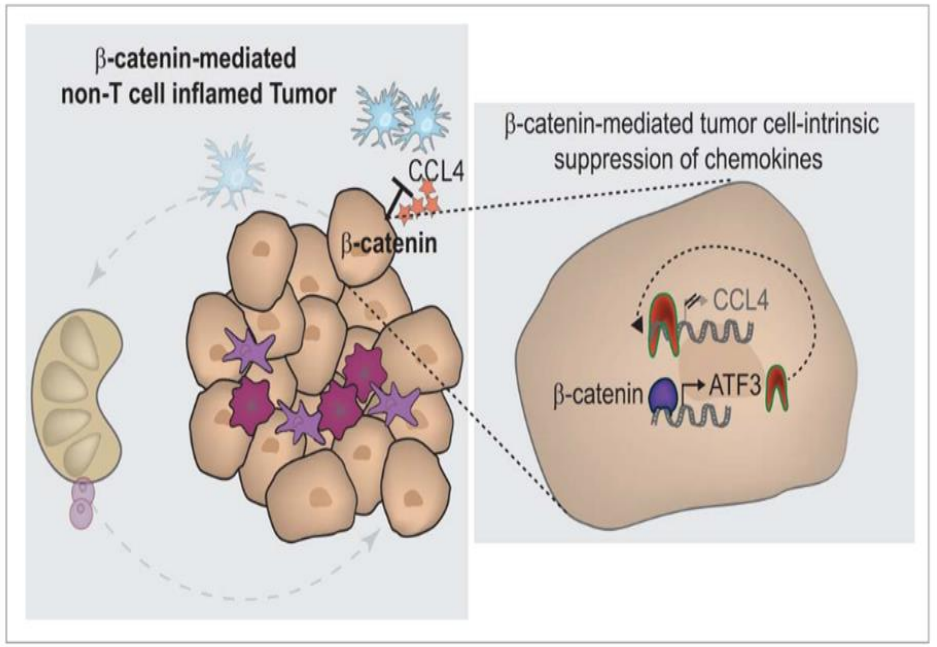
Start with what we know.

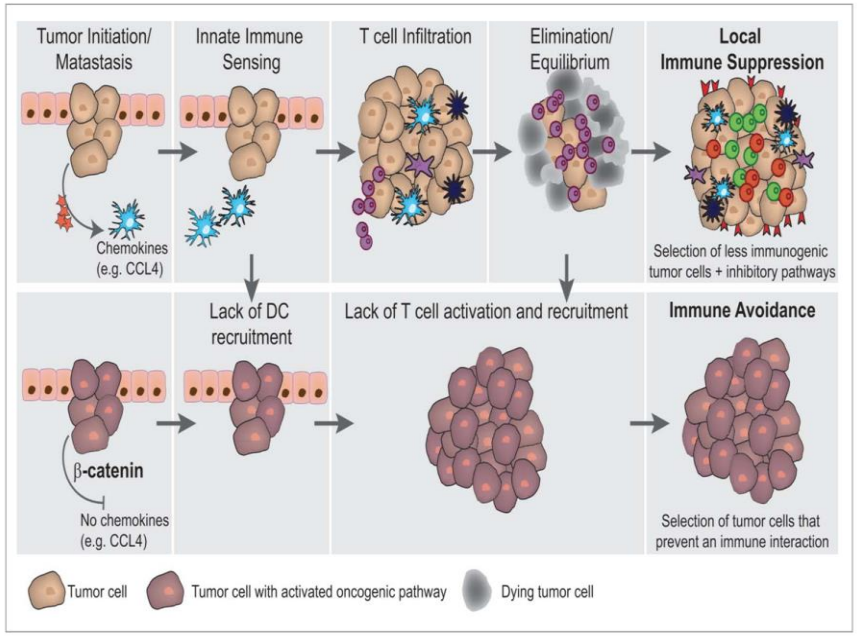
What questions still remain to be answered?

What is our strategy to address these questions?

Example 1: Wnt beta-catenin







Example 3: IDH1 mutation and glioma

Mutant IDH1 regulates the tumor-associated immune system in gliomas

Nduka M. Amankulor,[1] Youngmi Kim,[2] Sonali Arora,[2] Julia Kargl,[2,3,4] Frank Szulzewsky,[2] Mark Hanke,[2,3] Daciana H. Margineantu,[2,3] Aparna Rao,[1] Hamid Bolouri,[2,5] Jeff Delrow,[6] David Hockenbery,[2,3] A. McGarry Houghton,[2,3,7] and Eric C. Holland[2,5]

Gliomas harboring mutations in isocitrate dehydrogenase 1/2 (IDH1/2) have the CpG island methylator phenotype (CIMP) and significantly longer patient survival time than wild-type IDH1/2 (wtIDH1/2) tumors. Although there are many factors underlying the differences in survival between these two tumor types, immune-related differences in cell content are potentially important contributors. In order to investigate the role of IDH mutations in immune response, we created a syngeneic pair mouse model for mutant IDH1 (muIDH1) and wtIDH1 gliomas and demonstrated that muIDH1 mice showed many molecular and clinical similarities to muIDH1 human gliomas, including a 100-fold higher concentration of 2-hydroxygluratate (2-HG), longer survival time, and higher CpG methylation compared with wtIDH1. Also, we showed that IDH1 mutations caused down-regulation of leukocyte chemotaxis, resulting in repression of the tumor-associated immune system. Given that significant infiltration of immune cells such as macrophages, microglia, monocytes, and neutrophils is linked to poor prognosis in many cancer types, these reduced immune infiltrates in muIDH1 glioma tumors may contribute in part to the differences in aggressiveness of the two glioma types.

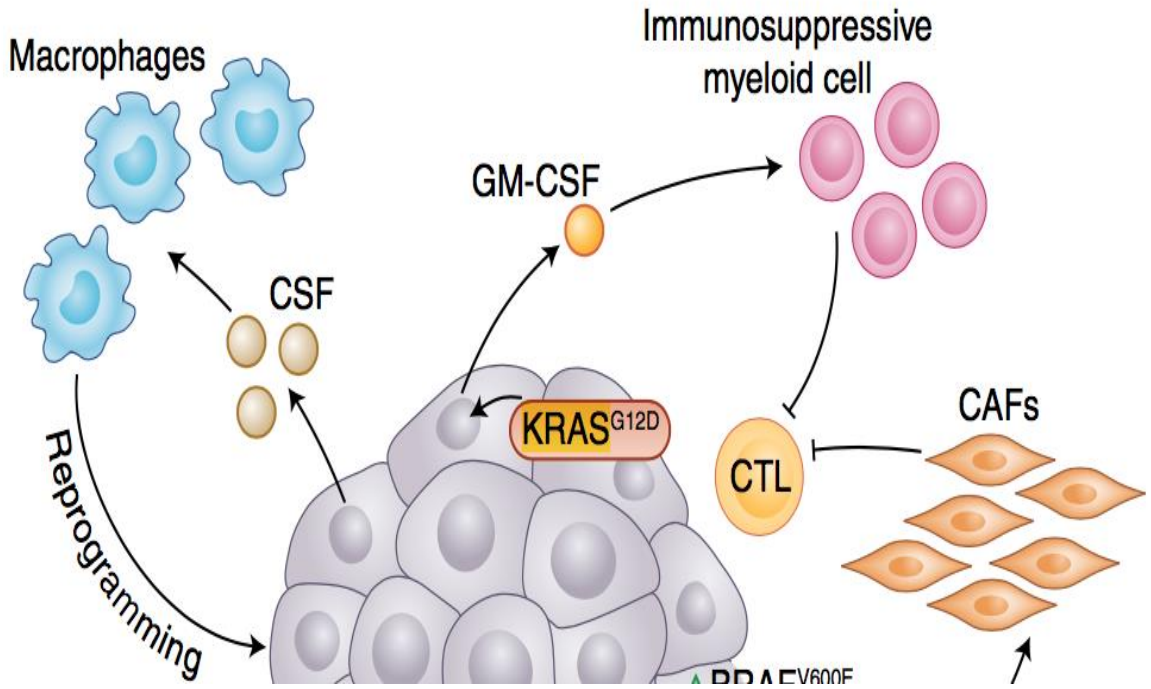
GENES & DEVELOPMENT 31:1–13

Decoupling genetics, lineages, and microenvironment in IDH-mutant gliomas by single-cell RNA-seq

Andrew S. Venteicher[1,2,3,*], Itay Tirosh[2,*,†], Christine Hebert[1,2], Keren Yizhak[1,2], Cyril Neftel[1,2,4], Mariella G. Filbin[1,2,5], Volke Hovestadt[1,2], Leah E. Escalante[1,2], McKenzie L. Shaw[1,2], Christopher Rodman[2], Shawn M. Gillespie[1], Danielle Dionne[2], Christina C. Luo[1], Hiranmayi Ravichandran[1], Ravindra Mylvaganam[1], Christopher Mount[6], Maristela L. Onozato[1], Brian V. Nahed[3], Hiroaki Wakimoto[3], William T. Curry[3], A. John Iafrate[1], Miguel N. Rivera[1,2], Matthew P. Frosch[1], Todd R. Golub[2,5,7], Priscilla K. Brastianos[8], Gad Getz[1,2], Anoop P. Patel[3], Michelle Monje[6], Daniel P. Cahill[3], Orit Rozenblatt-Rosen[2], David N. Louis[1], Bradley E. Bernstein[1,2], Aviv Regev[2,7,9,†,‡], Mario L. Suvà[1,2,†,‡]

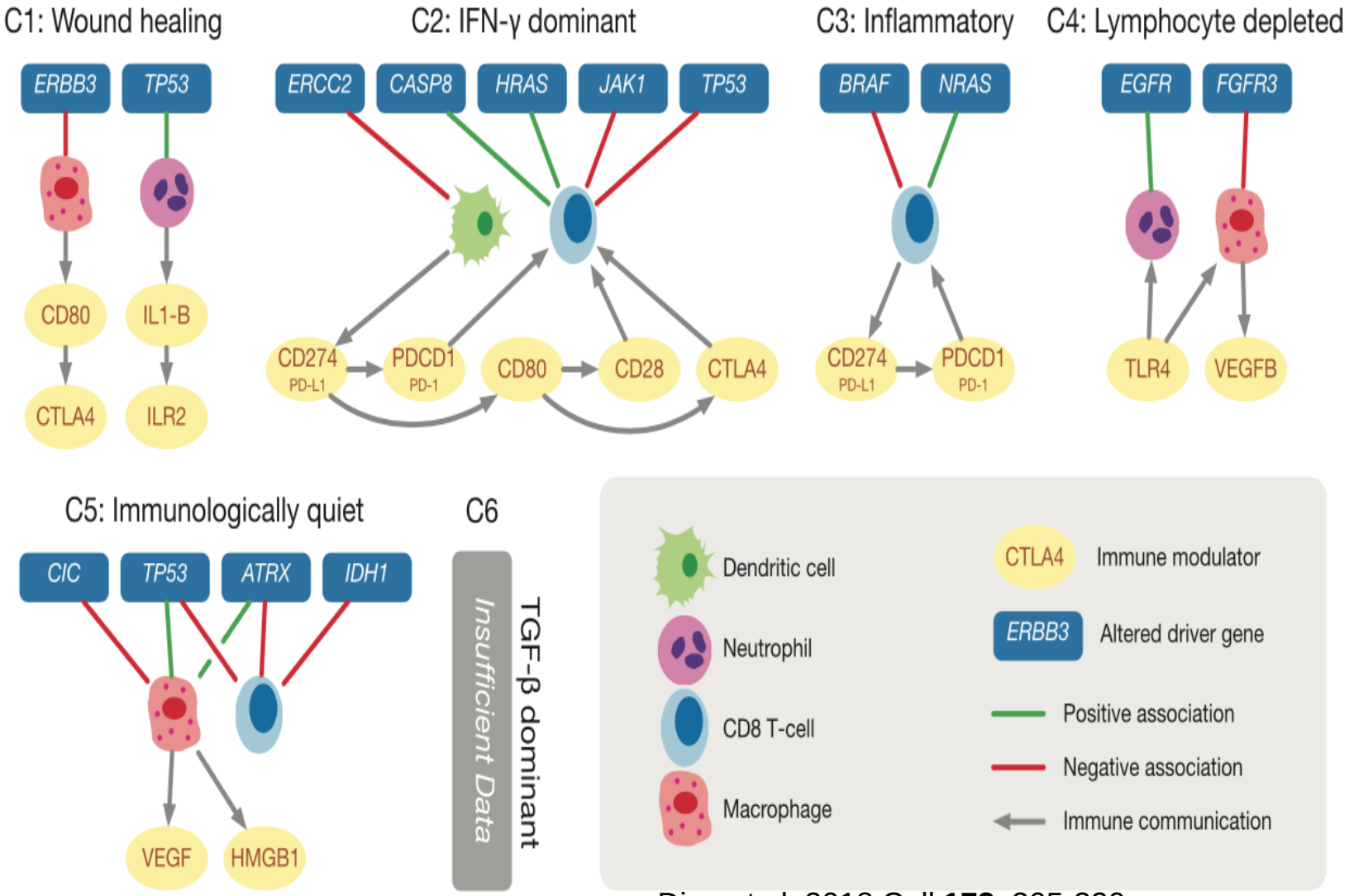
Science 31 Mar 2017:
Vol. 355, Issue 6332, eaai8478
DOI: 10.1126/science.aai8478

KRAS mutations lead to immunosuppresive myeloid cells by increasing GM-CSF



PRAD, NSCLC

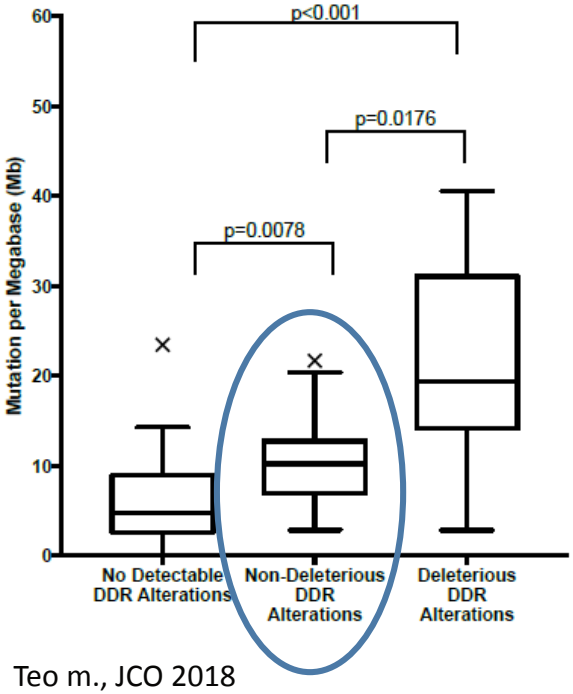
Cancer immunogenomics can be used to identify other possible assocations



Ding et al. 2018 Cell **173**, 305-320

Genomic Alterations and High TMB:

Alterations in DDR and Repair Genes - Impact on Mutational Burden and an Independent Effect of DDR Status on PFS and OS in mUC.

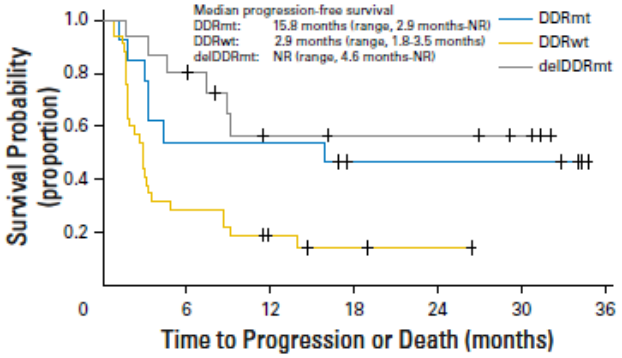


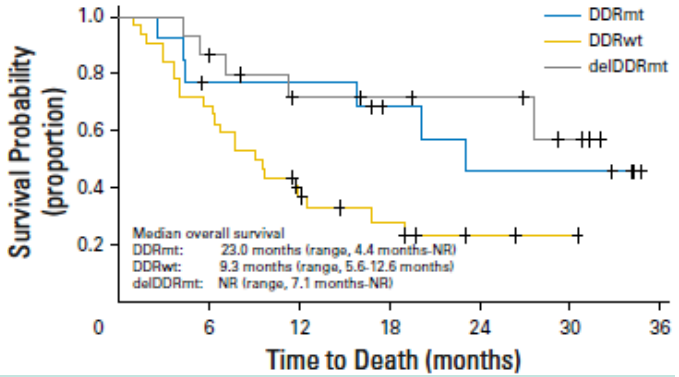
Teo m., JCO 2018

DDR:

- DSB related (HR, FA, DSB detection)
- MMR
- NER
- Other

DDR Status	ORR
Any DDR Alts Vs WT	68% vs 19% (p<0.001)
Functional DDR Alts Vs WT	80% vs 19% (p<0.001)
VUS DDR Alts vs WT	54% vs 19% (p<0.001)





- **In mUC , alterations in DDR genes were strongly associated with clinical benefit to anti-PD1/L1 treatment.**
- **Q. What is the frequency of DDR genes alteration in UC and other solid malignancies? And, do DDR alterations, beyond MMR, impart similar IO response that can also be characterized as histotype-agnostic phenomena?**
- **Q. How can we better characterize VUS alterations ? Clear need not just for DDR gene panel but also with other oncogenes/TSG?**
- **Harmonization of targeted gene panels to include all high frequency DDR genes (FoundationOne Dx etc.,), and the need for inclusion of additional low frequency DDR genes in the panel?**
- **Macroscale: How do we evaluate the mechanisms that link DDR alterations, to TMB and neoantigen load, and IO response?**

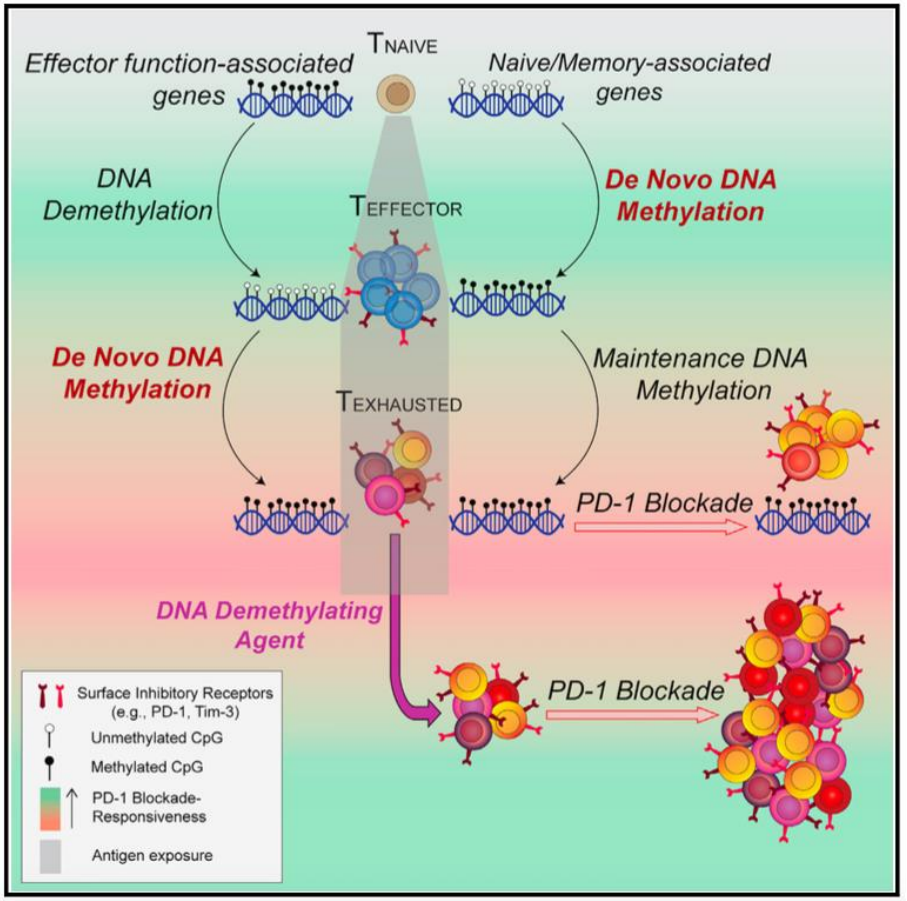
Cancer Cell Extrinsic

Example 1: DNA methylation in
T cell exhaustion

Cell

De Novo Epigenetic Programs Inhibit PD-1 Blockade-Mediated T Cell Rejuvenation

Hazem E. Ghoneim,[1] Yiping Fan,[2] Ardiana Moustaki,[1] Hossam A. Abdelsamed,[1] Pradyot Dash,[1] Pranay Dogra,[1] Robert Carter,[2] Walid Awad,[1] Geoff Neale,[3] Paul G. Thomas,[1] and Ben Youngblood[1,4,*]
[1]Department of Immunology
[2]Department of Computational Biology
[3]Hartwell Center for Bioinformatics & Biotechnology
St. Jude Children's Research Hospital, Memphis, TN 38105, USA
[4]Lead Contact
*Correspondence: benjamin.youngblood@stjude.org
http://dx.doi.org/10.1016/j.cell.2017.06.007



Cancer Cell Intrinsic

Example 2: PBAF complex in Kidney Cancer

REPORT

Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma

Diana Miao[1,2], Claire A. Margolis[1,2], Wenhua Gao[1], Martin H. Voss[3,4], Wei Li[5], Dylan J. Martini[1], Craig Norton[1], Dominick Bossé[1], Stephanie M. Wankowicz[1,2], Dana Cullen[6], Christine Horak[6], Megan Wind-Rotolo[6], Adam Tracy[2], Marios Giannakis[1,2], Frank Stephen Hodi[1], Charles G. Drake[7], Mark W. Ball[8], Mohamad E. Allaf[8], Alexandra Snyder[3,*], Matthew D. Hellmann[3,4], Thai Ho[9], Robert J. Motzer[3,4], Sabina Signoretti[1], William G. Kaelin Jr.[1,10], Toni K. Choueiri[1,†,‡], Eliezer M. Van Allen[1,2,†,‡]

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[2]Broad Institute of Massachusetts Institute of Technology (MIT) and Harvard, Cambridge, MA 02142, USA.

[3]Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA.

[4]Weill Cornell Medical College, New York, NY 10065, USA.

[5]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA 02215, USA.

[6]Bristol-Myers Squibb, New York, NY 10154, USA.

[7]Columbia University Medical Center, New York, NY 10032, USA.

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[9]Mayo Clinic, Scottsdale, AZ 85259, USA.

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Science

RESEARCH ARTICLES

Cite as: D. Pan *et al.*, *Science* 10.1126/science.aao1710 (2018).

A major chromatin regulator determines resistance of tumor cells to T cell–mediated killing

Deng Pan,[1]* Aya Kobayashi,[1]* Peng Jiang,[2]* Lucas Ferrari de Andrade,[1] Rong En Tay,[1] Adrienne Luoma,[1] Daphne Tsoucas,[2] Xintao Qiu,[3] Klothilda Lim,[3] Prakash Rao,[3†] Henry W. Long,[3] Guo-Cheng Yuan,[2] John Doench,[4] Myles Brown,[3] Shirley Liu,[2‡] Kai W. Wucherpfennig[1,5‡]

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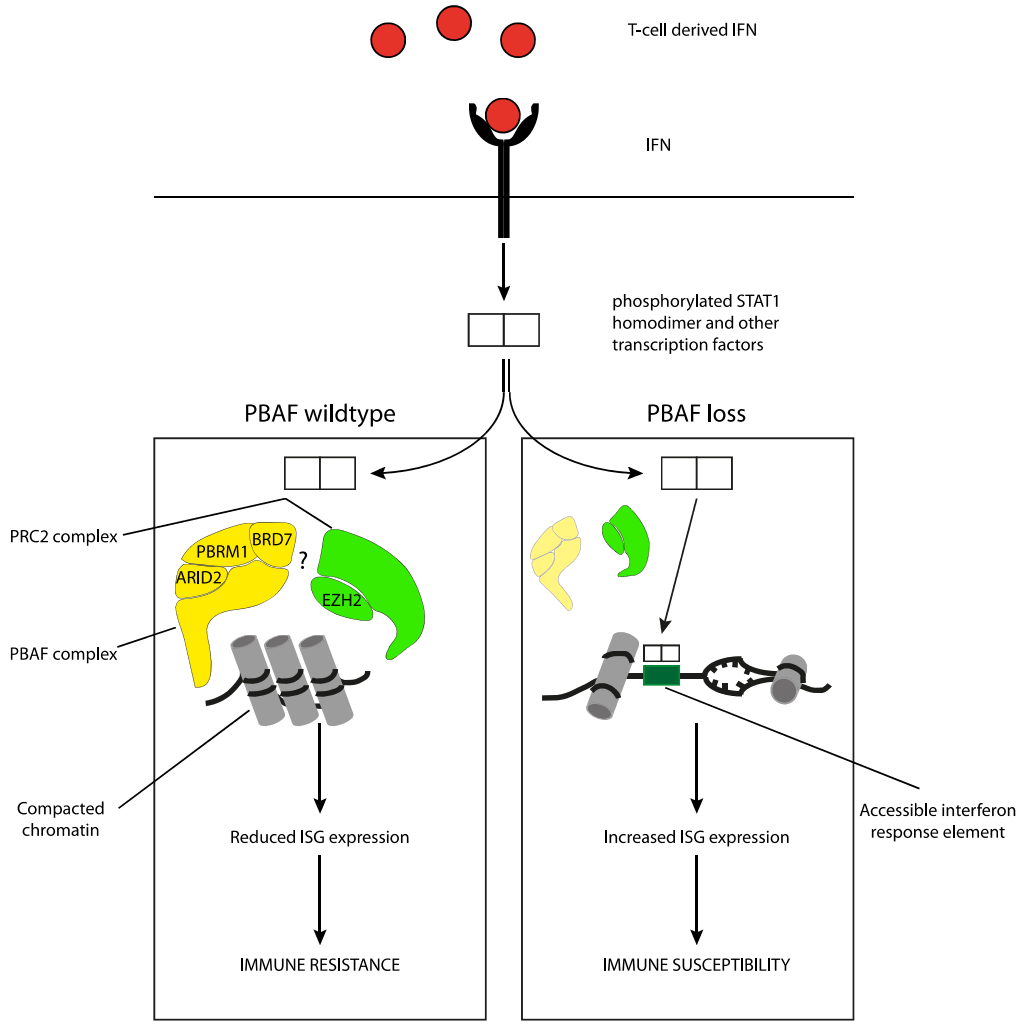
Cancer Cell Intrinsic

Example 2: PBAF complex in Kidney Cancer



Ghorani et al., Science 2018

Cancer Cell Intrinsic

Example 4: Expression of repetitive elements in Cancer is predictive to response to IO

Cell Reports
Article

Global Cancer Transcriptome Quantifies Repeat Element Polarization between Immunotherapy Responsive and T Cell Suppressive Classes

Alexander Solovyov,[1,2,10] Nicolas Vabret,[1,2,3,10] Kshitij S. Arora,[4,5,10] Alexandra Snyder,[6] Samuel A. Funt,[6,7] Dean F. Bajorin,[6,7] Jonathan E. Rosenberg,[6] Nina Bhardwaj,[1,2,3] David T. Ting,[4,8,11] and Benjamin D. Greenbaum[1,2,3,9,11,12,*]

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[10]These authors contributed equally
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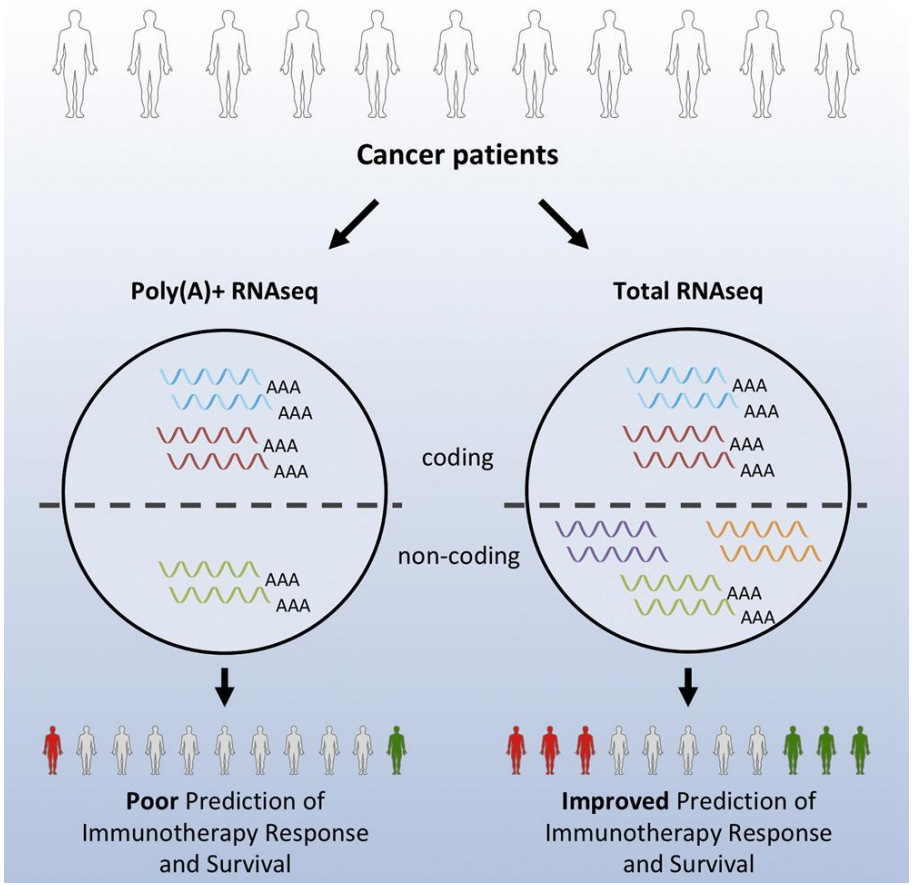
*Correspondence: benjamin.greenbaum@mssm.edu
https://doi.org/10.1016/j.celrep.2018.03.042



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[2]Department of Oncological Sciences and Department of Pathology, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[3]Precision Immunology Institute at the Icahn School of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[4]Massachusetts General Hospital Cancer Center, Boston, MA, USA
[5]Department of Pathology and Department of Surgery, Harvard Medical School, Charlestown, MA, USA
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[8]Department of Medicine, Harvard Medical School, Boston, MA, USA
[9]Icahn Institute for Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[10]These authors contributed equally
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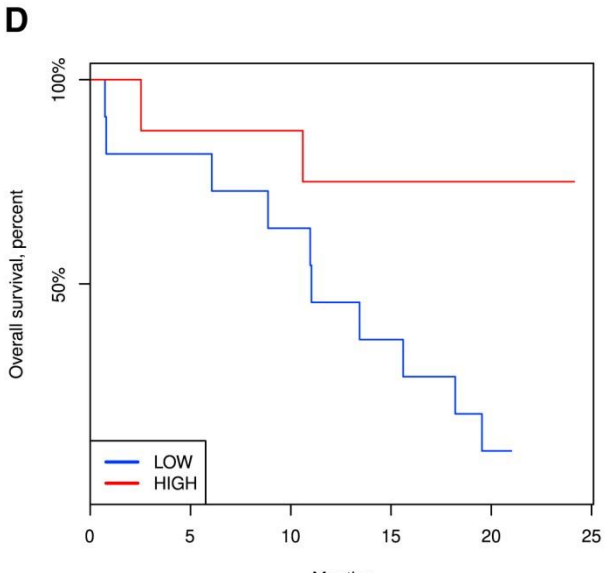

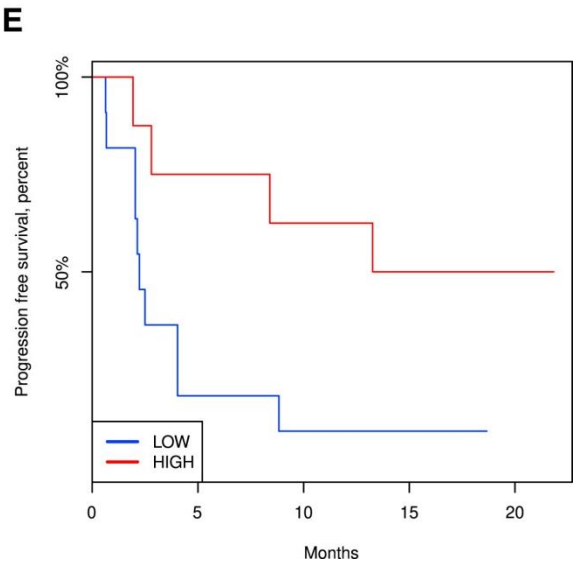

Questions from breakout sessions

- To what extent is the immune landscape directed by the tumor?
  - What are the known alterations that impact the environment?
  - how do we modify this relationship for therapeutic IO potential?
- How do we standardize TMB in the clinical setting?
  - How does response vary with the degree or number of mutations?
  - And how do we translate this understanding to a threshold in the clinic?
  - Should we use genomic alterations in DNA Damage Repair and Response genes instead of TMB? Would that be a better predictor of response?
- How do we incorporate functional impact assessment into mutation assessment
- Why haven't epigenetic based therapies worked against solid tumors?
  - Is it just due to poor drugs?
  - What did we miss?
  - How do we look at the impact on the immune landscape post epigenetic therapy?
  - Do we need targeted demethylating agents?

Recommendations

- More data!!!!!
  - High quality data and samples
  - multi-dimensional data (Somatic, epigenetics, metabolomics)
  - definitive immune landscape estimate
- Clinical outcomes tied to genomic information
- Standardizations across clinical measurements
- Complete patient phenotypic annotation including prior therapies
- Integrative modeling analysis
- Pre-competitive consortium wide effort is needed (NCI-PACT)
- There will be a presentation at the SITC Bio-marker meeting?
-