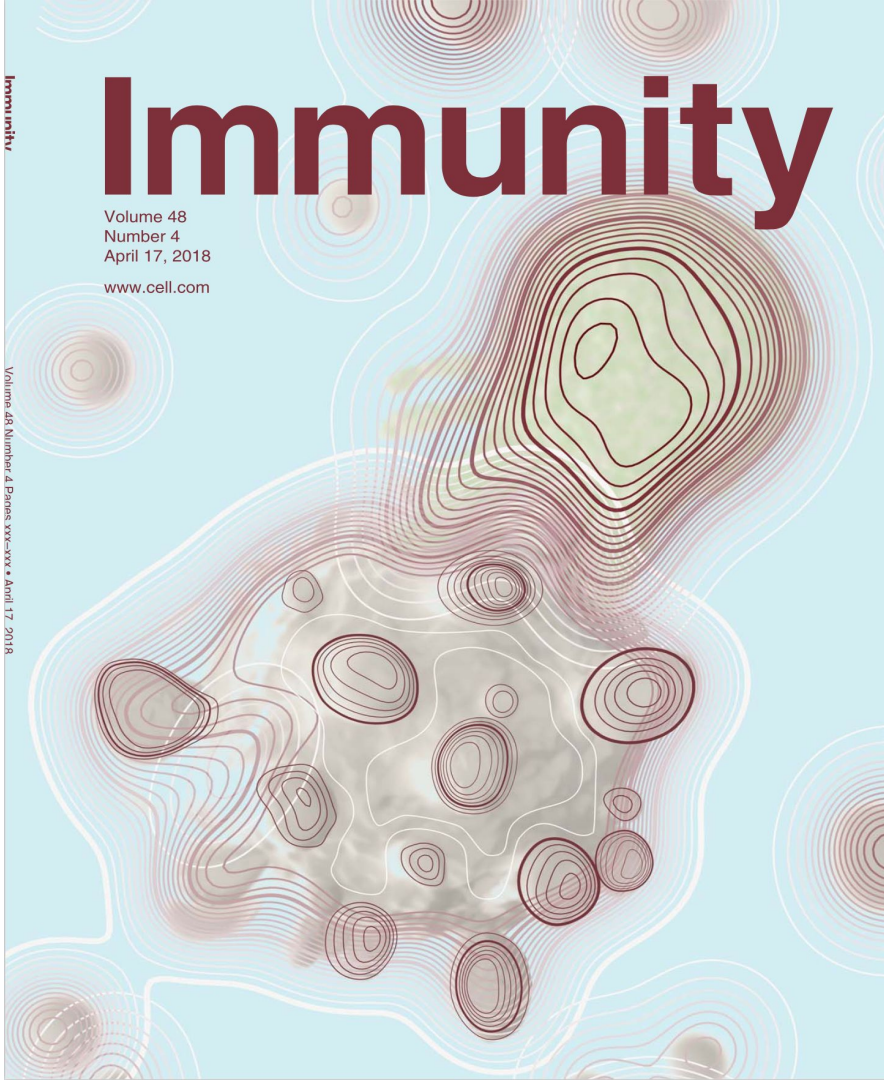
Immune Response in 10,000 Tumor Samples and Correlation with Somatic Alterations

Vésteinn Þórsson
Institute for Systems Biology, Seattle

Cancer Immune Responsiveness Workshop
Session II: Somatic Genetics/Epigenetics of Immune Landscape
May 14, 2018



Overview

- TCGA and PanCancer Atlas Overview
- Immune Subtypes Across Cancers
- Composition of the Microenvironment
- Somatic Correlates

The Cancer Genome Atlas

- 2009-2016
- ISB - MDACC Genome Data Analysis Center (GDAC)
  - PIs: Ilya Shmulevich and Wei Zhang
- 33 tumor types
- 10,000+ primary tumor samples
- Multi-omics measurement and analysis
- Development of analysis methods
- 2.5 PB of data

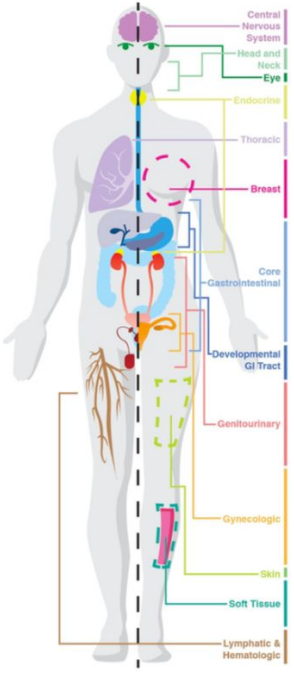


Image source: Pathways Marker Paper, Cell, 2018

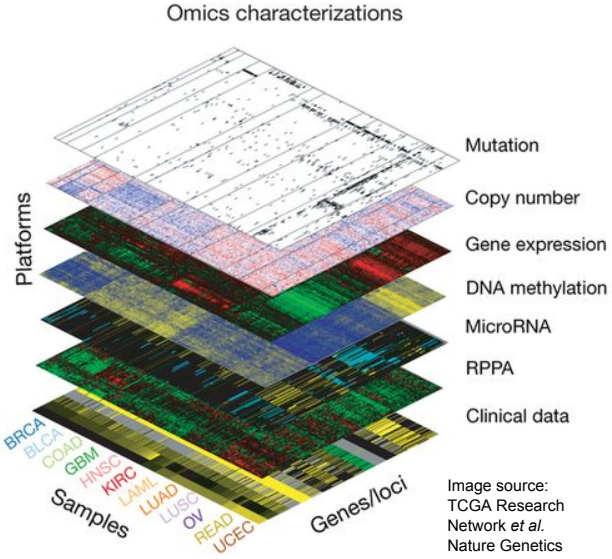


Image source: TCGA Research Network *et al.* Nature Genetics 2013

mutation calling
copy number estimation
integrative clustering
purity estimation
visualization
web portals

Welcome to the Pan-Cancer Atlas

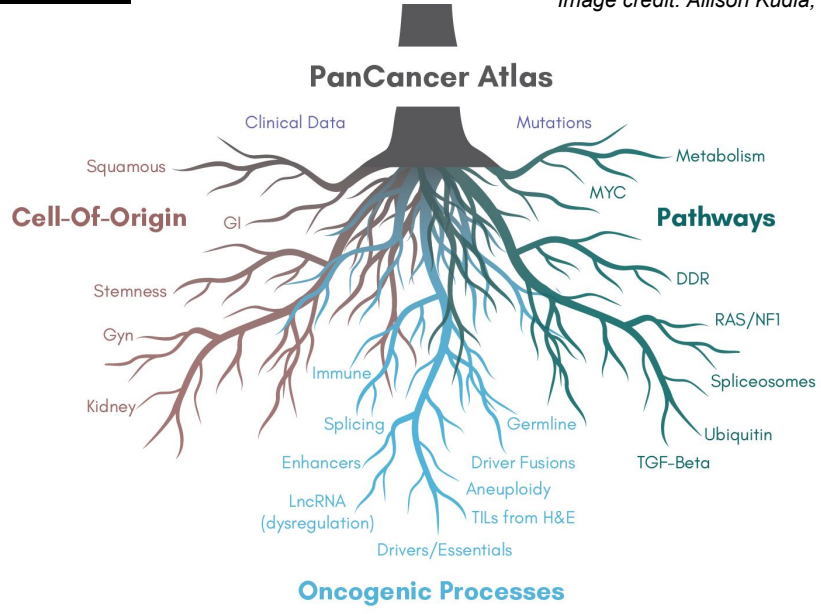
From The Cancer Genome Atlas (TCGA) consortium, a large-scale collaboration initiated and supported by the National Cancer Institute (NCI) and National Human Genome Research Institute (NHGRI).

From the analysis of over 11,000 tumors from 33 of the most prevalent forms of cancer, the Pan-Cancer Atlas provides a uniquely comprehensive, in-depth, and interconnected understanding of how, where, and why tumors arise in humans. As a singular and unified point of reference, the Pan-Cancer Atlas is an essential resource for the development of new treatments in the pursuit of precision medicine.

The visualization below presents the Pan-Cancer Atlas as a series of shaded rings that join together to create a beautiful, singular spectrum. Like the research itself, the full impact of this visualization is found in its cohesion. As you scroll below you will see a collection of 27 papers divided into three main categories: cell-of-origin patterns, oncogenic processes, and signaling pathways. Each

CellPress

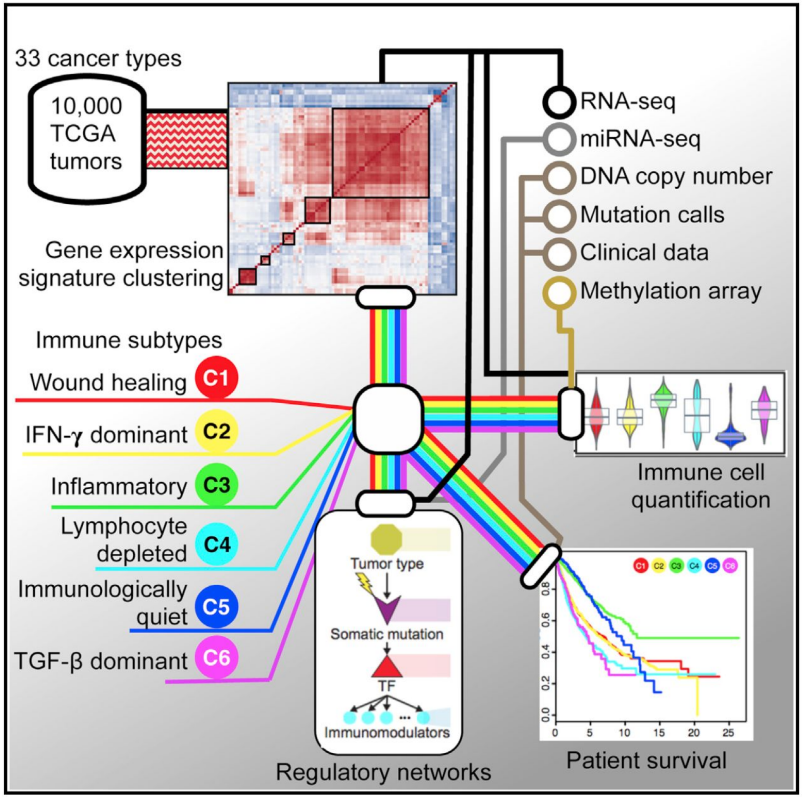
Image credit: Allison Kudla, ISB



TCGA | Immune Subtypes | TME Composition | Somatic Correlates

Immunity

The Immune Landscape of Cancer

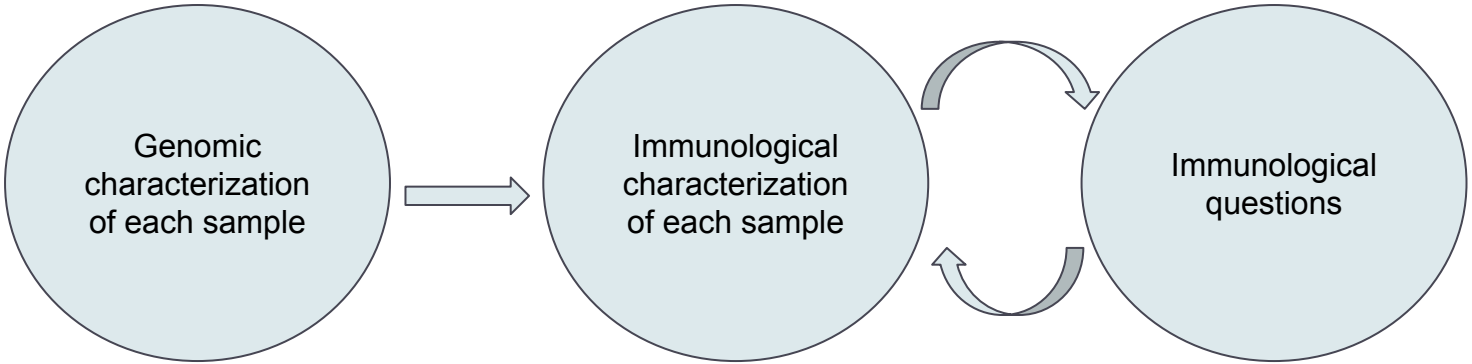


Highlights

- Six identified immune subtypes span cancer tissue types and molecular subtypes
- Immune subtypes differ by somatic aberrations, microenvironment, and survival
- Multiple control modalities of molecular networks affect tumor-immune interactions
- These analyses serve as a resource for exploring immunogenicity across cancer types

Immunity , Volume 48 , Issue 4 , p812 - 830.e14, 2018

TCGA PanCancer Atlas Immune Response Working Group



- Consensus somatic variants
- Normalized gene expression
- Tumor subtypes
- Pathways

- Immune signatures
- TCR/BCR repertoire
- Neo-antigens
- Microenvironment composition

- Immunological subtyping
- Molecular correlates of immune response
- Survival analysis
- Therapeutic implications

UCSF School of Medicine

DANA-FARBER CANCER INSTITUTE

Michael Smith Genome Sciences Centre

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Mount Sinai Hospital

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

BROAD INSTITUTE

Institute for Systems Biology

COLUMBIA UNIVERSITY

UNIVERSITY of WASHINGTON

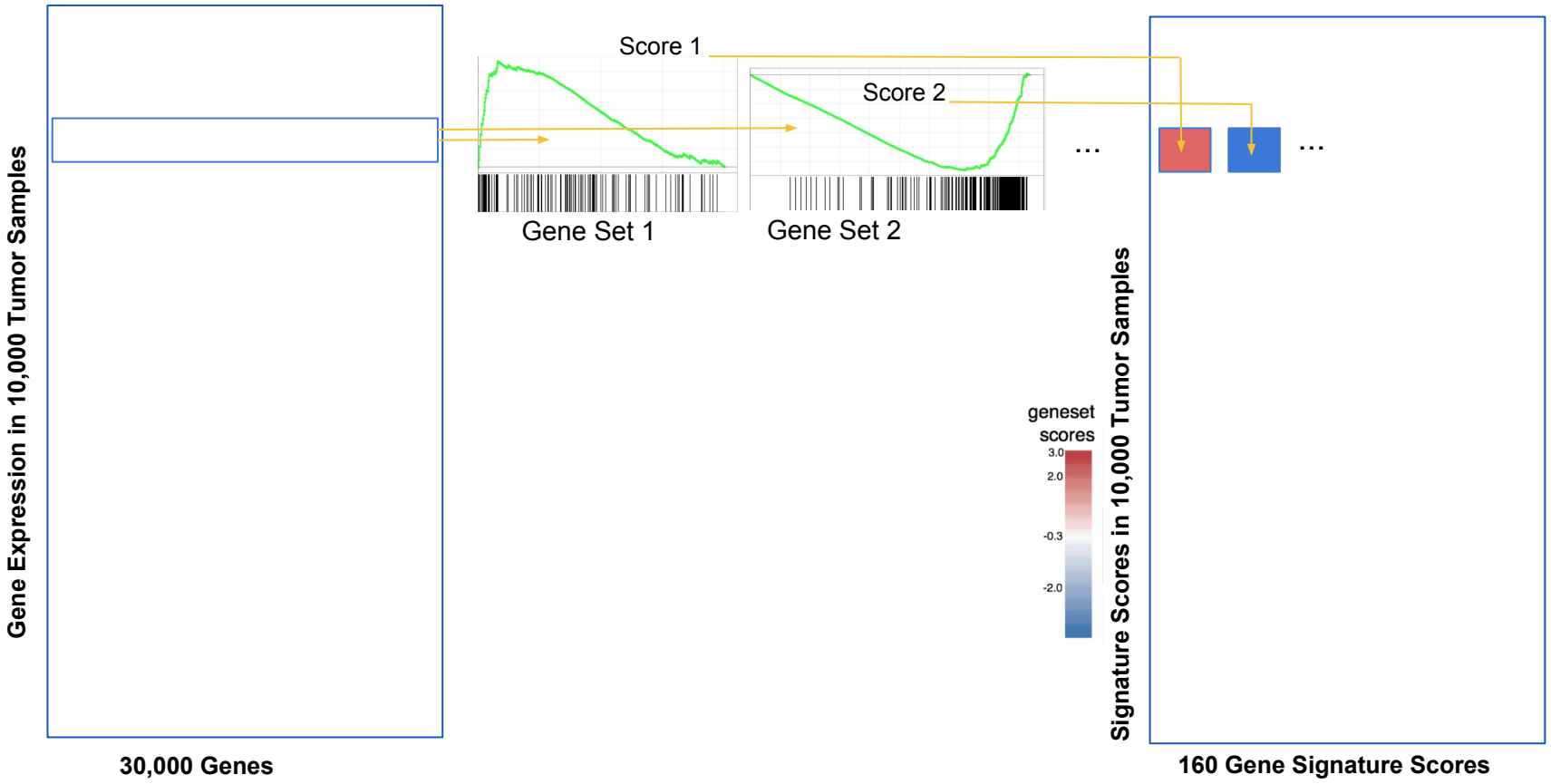
Sage BIONETWORKS

CSH Cold Spring Harbor Laboratory

HARVARD UNIVERSITY

STANFORD UNIVERSITY

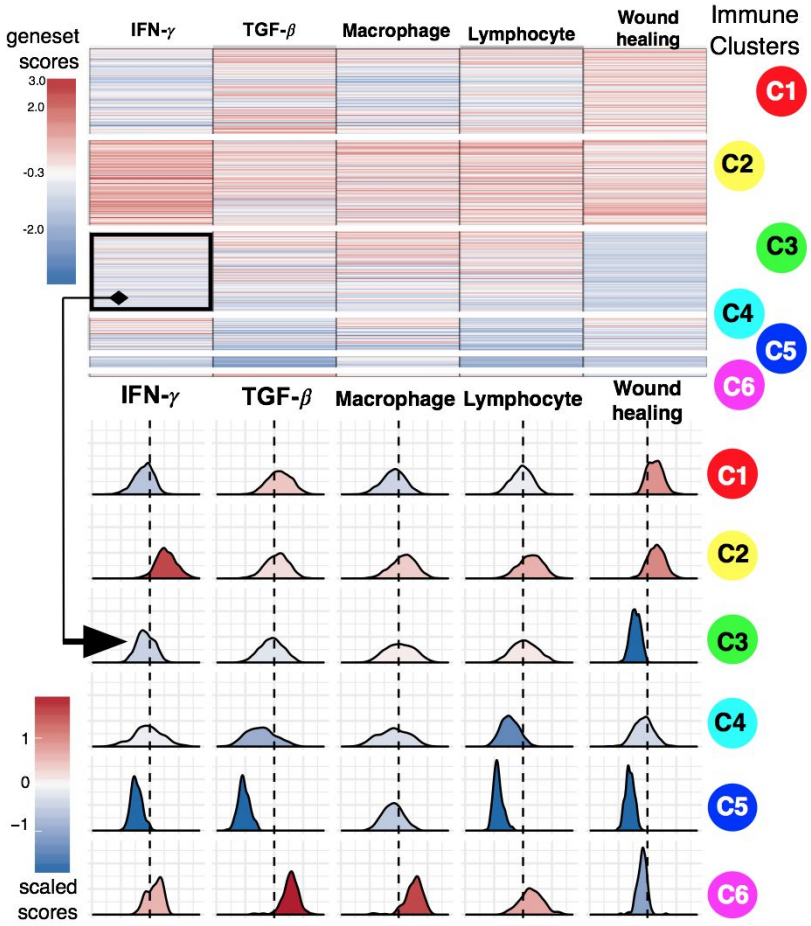
Score All Tumor Samples With Tumor Immune Gene Signature Sets



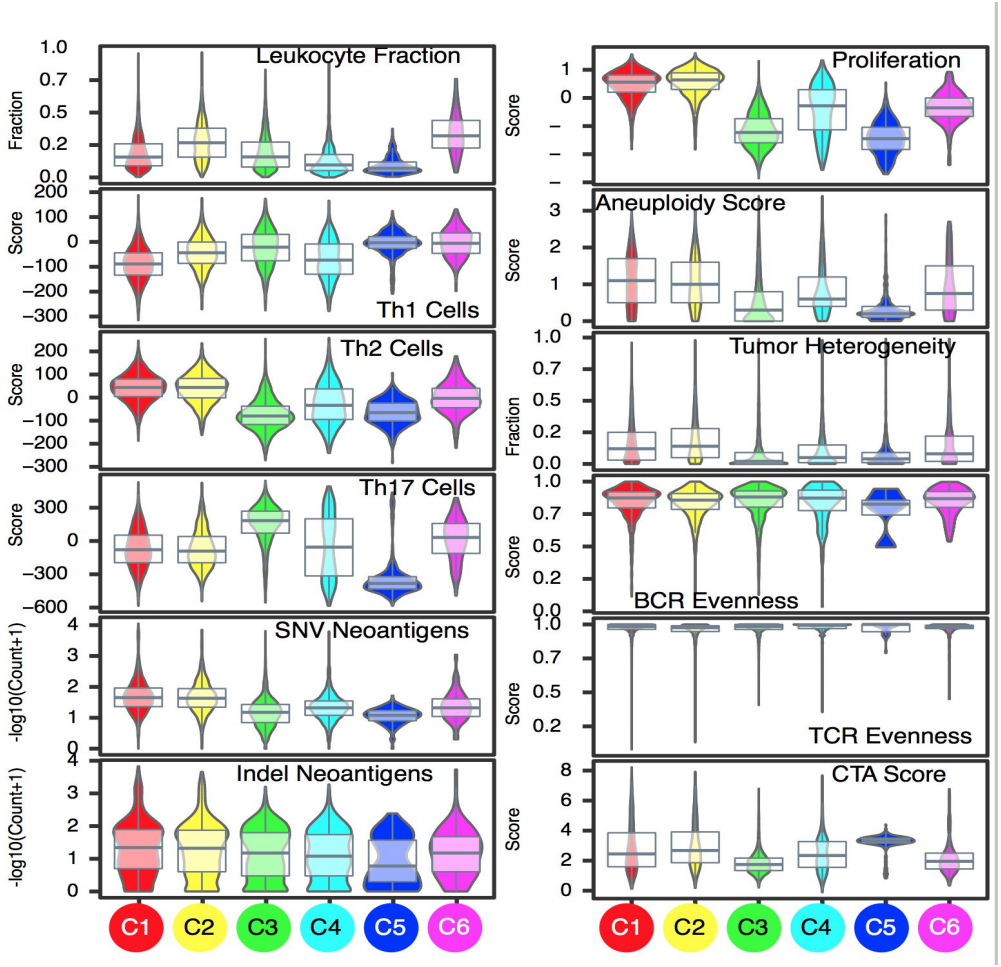
Clustering

&

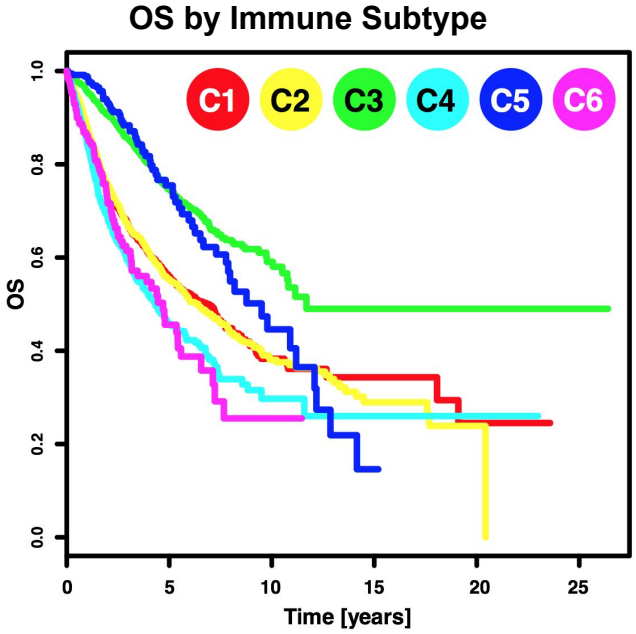
Distributions of scores



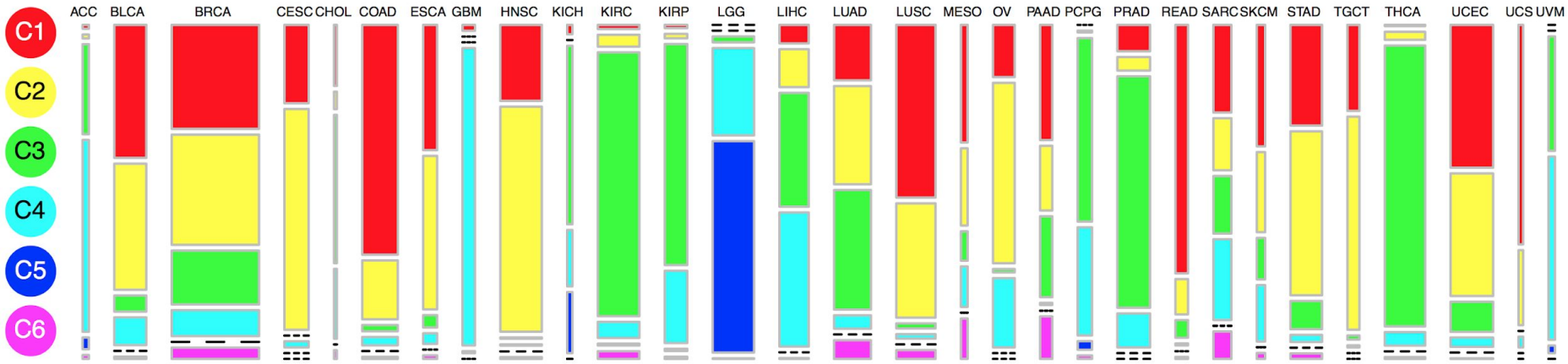
Characterize immune subtypes



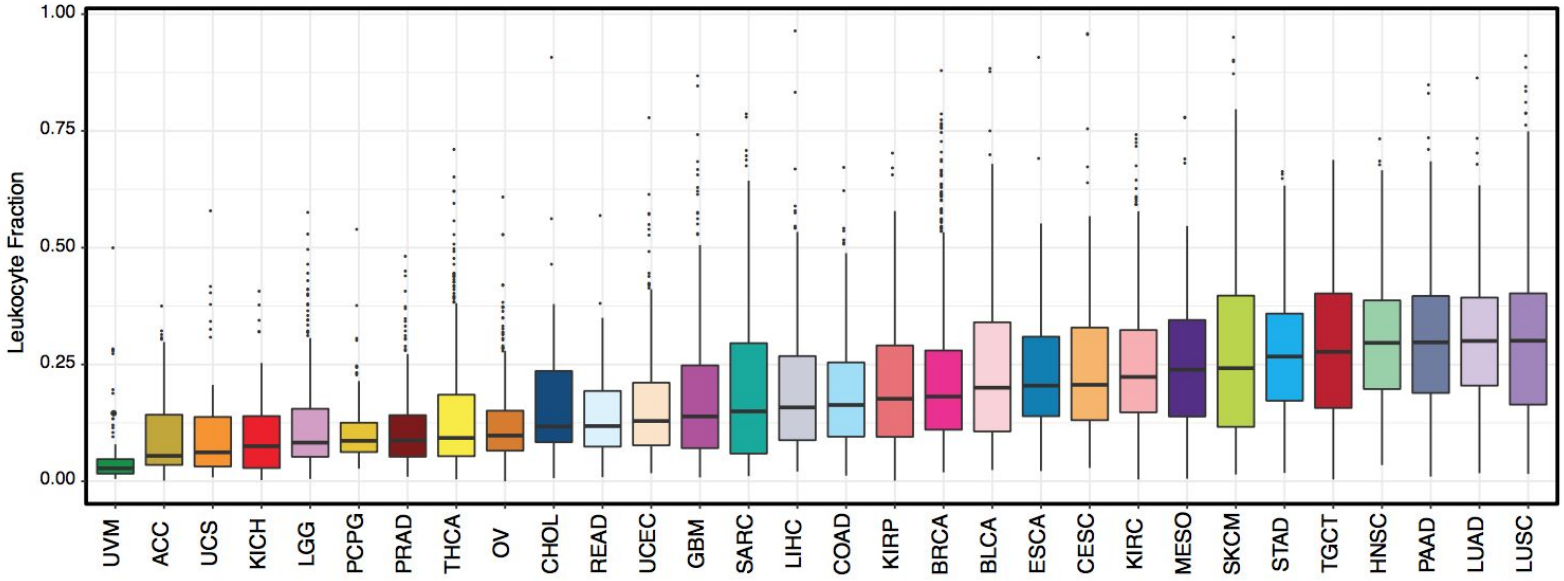
		Macrophage: lymphocyte	Th1:Th2	Proliferation	Intratumoral heterogeneity	Other
C1	Wound Healing	Balanced	Low	High	High	
C2	IFN-g dominant	Lowest	Lowest	High	Highest	Highest M1 and highest CD8 T cells
C3	Inflammatory	Balanced	High	Low	Lowest	Highest Th17
C4	Lymphocyte Depleted	High	Minimal Th	Moderate	Moderate	
C5	Immunologically quiet	Highest	Minimal Th	Low	Low	Highest M2
C6	TGF-b dominant	High	Balanced	Moderate	Moderate	Highest TGF-β signature


OS by Immune Subtype
C1
C2
C3
C4
C5
C6
OS
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
25
Time [years]

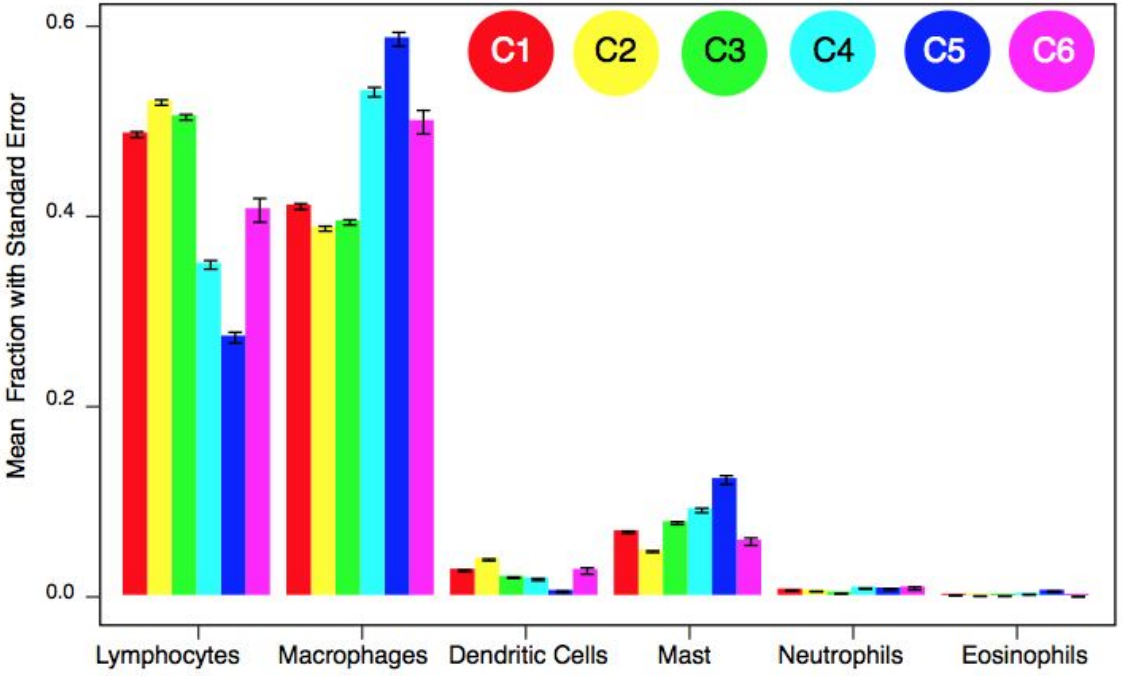
Immune Subtypes and TCGA Tumor Types



Leukocyte Fraction in 33 Tumor Types



Immune Cell Fractions



CIBERSORT

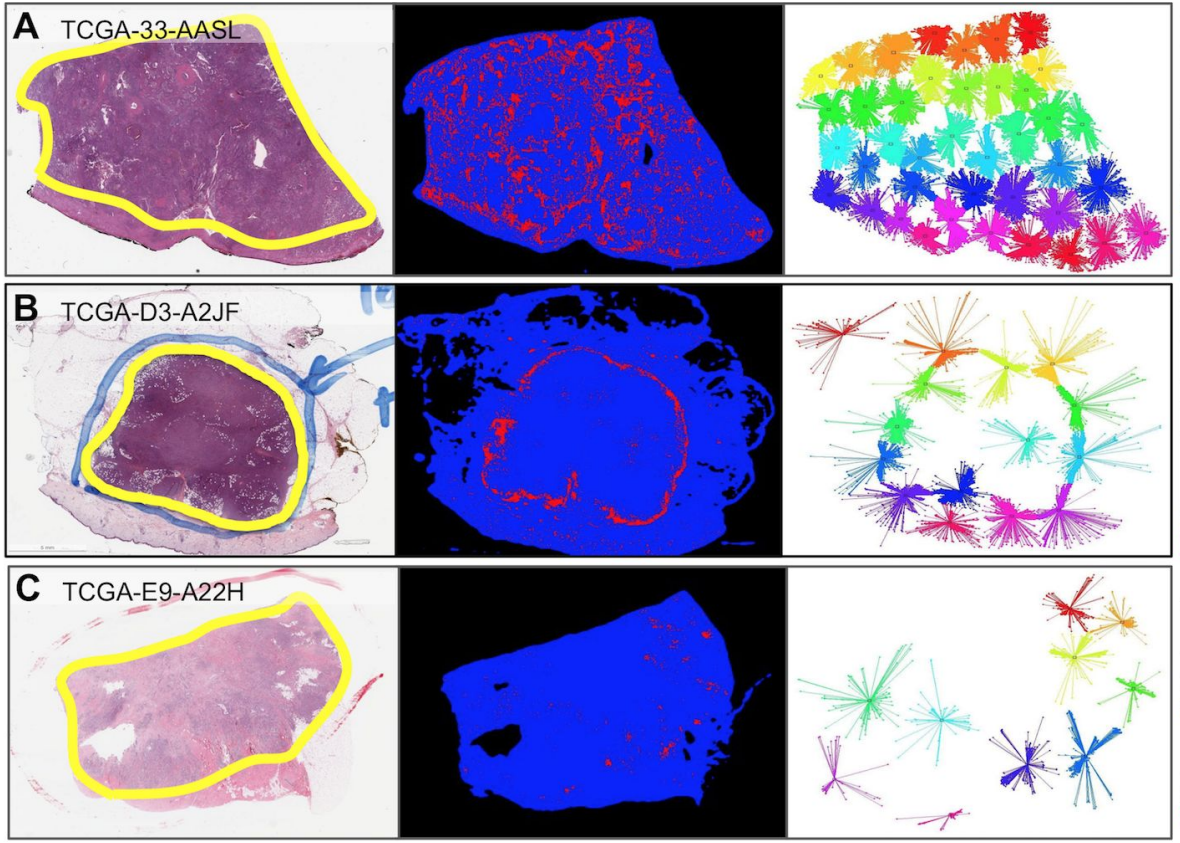
Andrew Gentles, Stanford

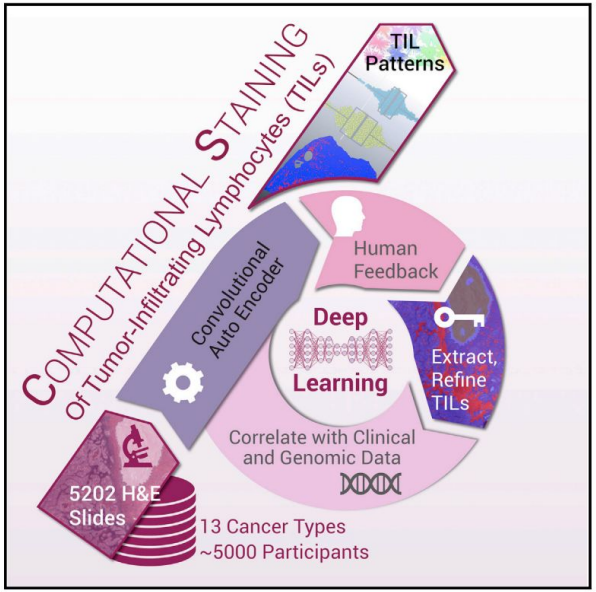
Lymphocyte Spatial Density and Organization

Spatial Organization and Molecular Correlation of Tumor-Infiltrating Lymphocytes Using Deep Learning on Pathology Images

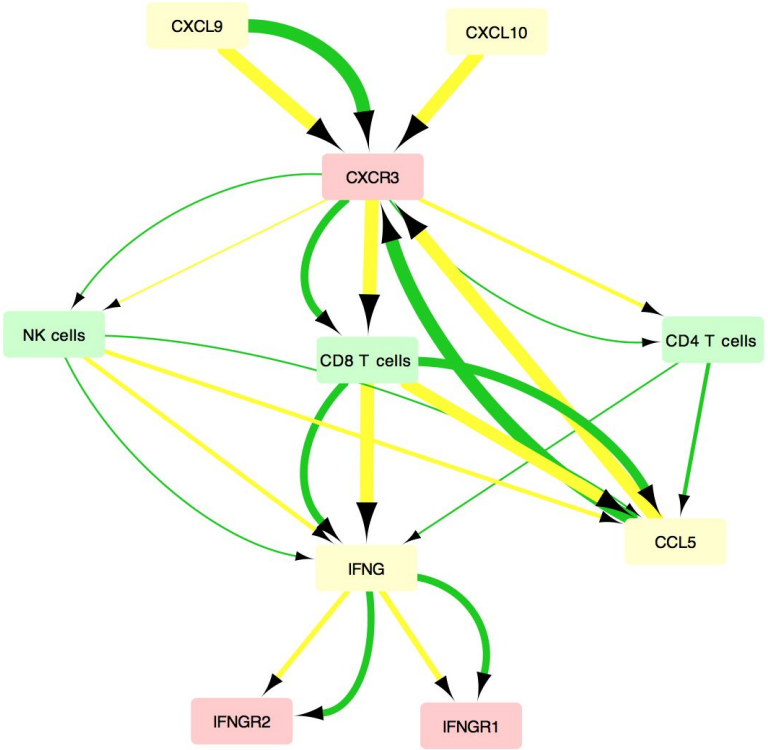
Joel Saltz,[1,*] Rajarsi Gupta,[1,4] Le Hou,[2] Tahsin Kurc,[1] Pankaj Singh,[3] Vu Nguyen,[2] Dimitris Samaras,[2] Kenneth R. Shroyer,[4] Tianhao Zhao,[4] Rebecca Batiste,[4] John Van Arnam,[5] The Cancer Genome Atlas Research Network, Ilya Shmulevich,[6] Arvind U.K. Rao,[3,7] Alexander J. Lazar,[8] Ashish Sharma,[9] and Vésteinn Thorsson[6,10,*]

Cell Reports 23, 181–193, April 3, 2018





Predicting the Immune Cellular Communication Network



Node types

Cells

Ligands

Receptors

Subtype-derived interactions

C2

C3

C4

C6

David Gibbs, Vesteinn Thorsson, Ilya Shmulevich

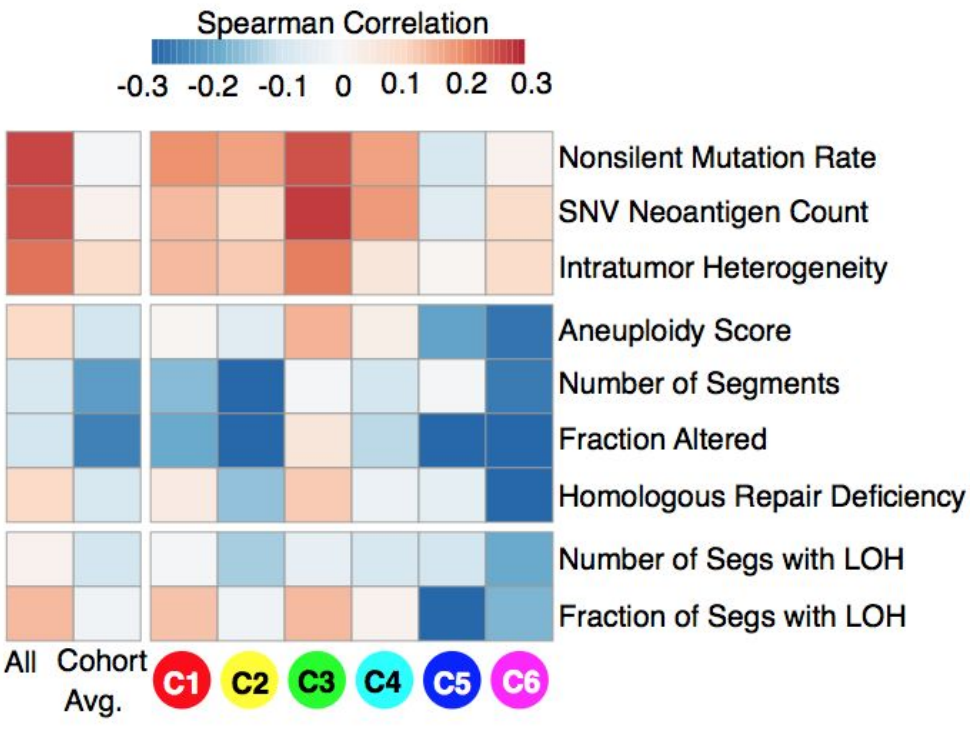
Somatic Correlations with TME studied in this work

Correlations with

- Overall DNA alteration burden
- Amplified/deleted genomic regions / genes
- Driver mutations
- Pathway-level alterations

Causal connections to transcriptional control - intracellular networks

Correlations with DNA Alteration Show Differences by Type of Alteration



Cell Reports
Resource

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Genomic and Molecular Landscape of DNA Damage Repair Deficiency across The Cancer Genome Atlas

Theo A. Knijnenburg,[1,25] Linghua Wang,[2,10,25] Michael T. Zimmermann,[3,23,25] Nyasha Chambwe,[1,25] Galen F. Gao,[4] Andrew D. Cherniack,[4] Huihui Fan,[5] Hui Shen,[5] Gregory P. Way,[6] Casey S. Greene,[6] Yuexin Liu,[7] Rehan Akbani,[7] Bin Feng,[8] Lawrence A. Donehower,[9] Chase Miller,[10] Yang Shen,[11] Mostafa Karimi,[11] Haoran Chen,[11] Pora Kim,[12] Peilin Jia,[12] Eve Shinbrot,[10] Shaojun Zhang,[2] Jianfang Liu,[13] Hai Hu,[13] Matthew H. Bailey,[14,15] Christina Yau,[16,17] Denise Wolf,[16] Zhongming Zhao,[12] John N. Weinstein,[7] Lei Li,[18] Li Ding,[14,15,19,20] Gordon B. Mills,[21] Peter W. Laird,[5] David A. Wheeler,[10] Ilya Shmulevich,[1] The Cancer Genome Atlas Research Network, Raymond J. Monnat, Jr.,[22,*] Yonghong Xiao,[8,*] and Chen Wang[23,24,26,*]
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[8]TESARO Inc., Waltham, MA 02451, USA
[9]Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX 77030, USA

Cancer Cell
Article

Genomic and Functional Approaches to Understanding Cancer Aneuploidy

Alison M. Taylor,[1,2,3] Juliann Shih,[2] Gavin Ha,[1,2,3] Galen F. Gao,[2] Xiaoyang Zhang,[1,2,3] Ashton C. Berger,[2] Steven E. Schumacher,[1,2] Chen Wang,[4,5] Hai Hu,[6] Jianfang Liu,[6] Alexander J. Lazar,[7] The Cancer Genome Atlas Research Network, Andrew D. Cherniack,[1,2,3] Rameen Beroukhim,[1,2,3] and Matthew Meyerson[1,2,8,9,*]
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[3]Department of Medicine, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA
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[6]Chan Soon-Shiong Institute of Molecular Medicine at Windber, Windber, PA 15963, USA
[7]Departments of Pathology, Genomic Medicine, and Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 85, Houston, TX, USA
[8]Department of Pathology, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA
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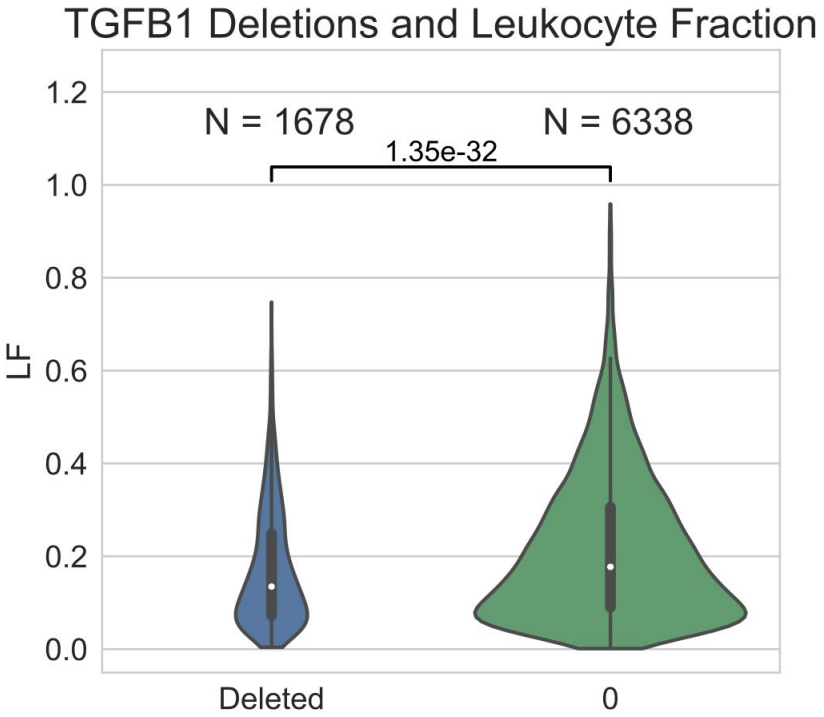
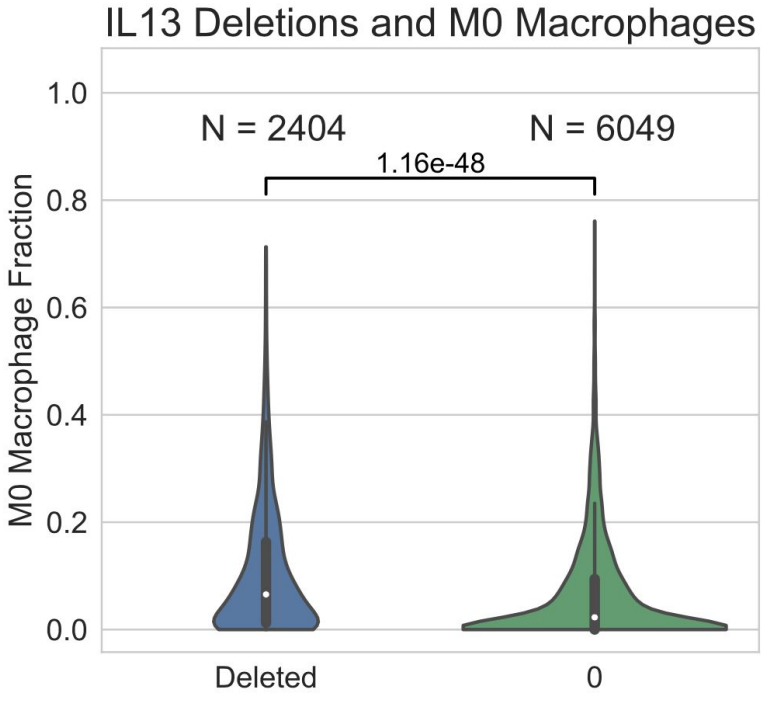
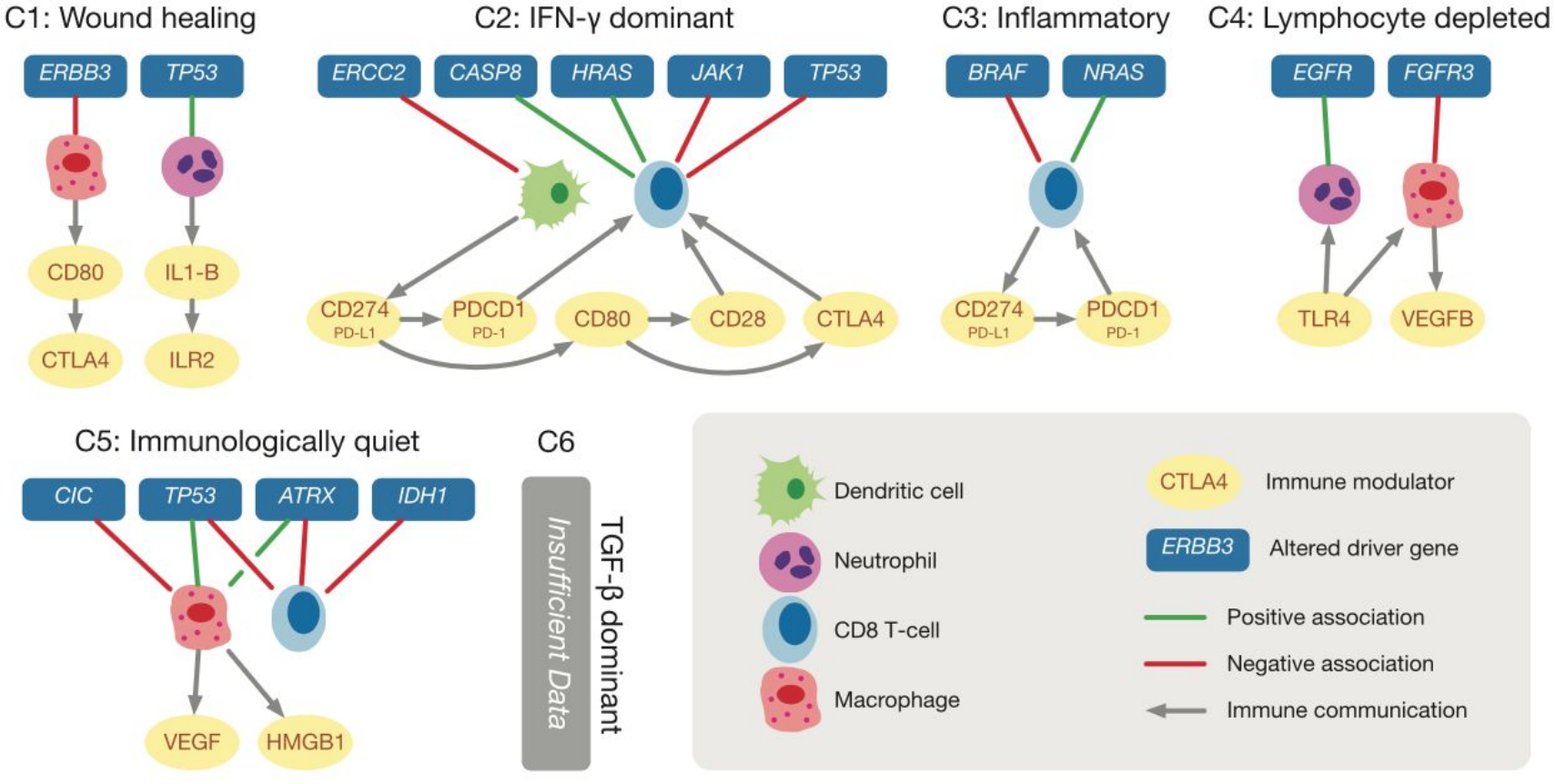
*Correspondence: matthew_meyerson@dfci.harvard.edu
https://doi.org/10.1016/j.ccell.2018.03.007

Gene Alteration Association Examples





Galen Gao, Andrew Cherniack, Broad Institute

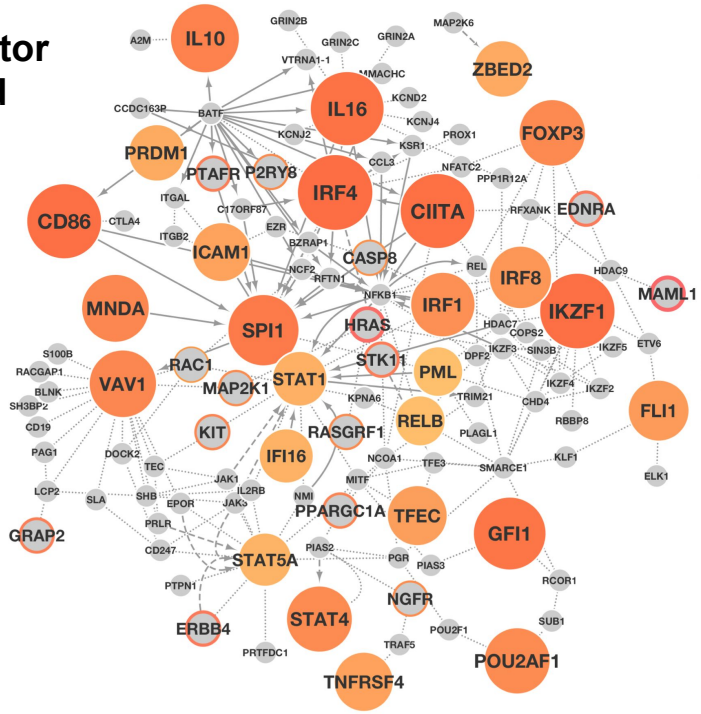


Ding et al., 2018, Cell *173*, 305–320

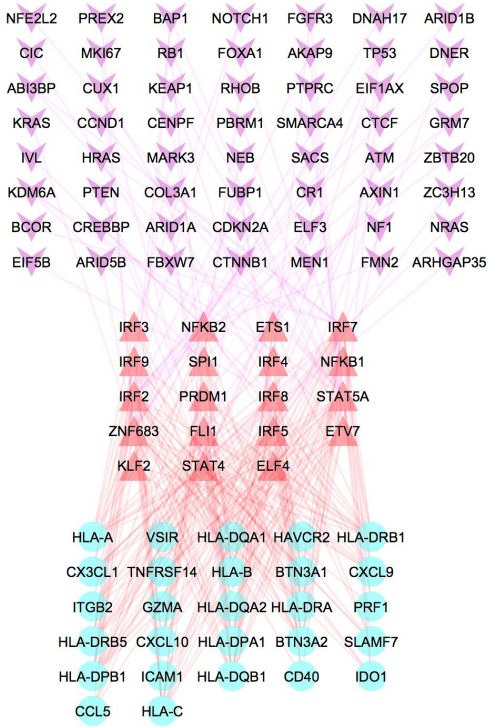
Eduard Porta-Pardo, David Gibbs, Vesteinn Thorsson

Including physical assocations/links

Master Regulator Method



SYGNAL



Evan O Paull and Andrea Califano, Columbia

Chris Plaisier, ISB, Arizona State

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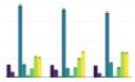
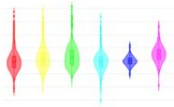
Tumor Microenvironment



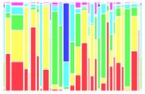
Explore the immune cell proportions in your sample groups.

Immunomodulators



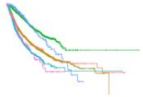
Explore the expression of genes that code for immunomodulating proteins, including checkpoint proteins.

Sample Group Overview



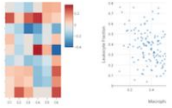
This module provides short summaries of your selected groups, and allows you to see how they overlap with other groups.

Clinical Outcomes



Plot survival curves based on immune characteristics and identify variables associated with outcome.

Immune Feature Trends



This module allows you to see how immune readouts vary across your groups, and how they relate to one another.

Thank you

ISB Team David Gibbs, Sheila M. Reynolds, Ilya Shmulevich

TCGA Immune Response Working Group *Benjamin Vincent* (UNC), *Ilya Shmulevich* (ISB), David L. Gibbs* (ISB), Scott D. Brown (BCGSC), Denise Wolf (UCSF), Dane S. Bortone (UNC), Tai-Hsien Ou Yang (Columbia), Eduard Porta-Pardo (Barcelona SC), Galen F. Gao (Broad), Chrisopher Plaiser, James Eddy, Elad Ziv, … , Davide Bedognetti, … , Alexander J. Lazar (MD Anderson), Jonathan S. Serody (UNC), Elizabeth G. Demicco* (Mt. Sinai), Mary L. Disis* (U Washington)

TIL Map Collaboration: Joel Saltz Le Hou, Rajasri R. Gupta, Tahsin Kurc, Vu Nyugen, Dimitri Samaras, Rebecca Batiste, John Van Arnam (Stony Brook), Ashish Sharma, Lee Cooper (Emory), Arvind Rao, Pankaj J. Singh, Alexander Lazar (MDAnderson), Ilya Shmulevich (ISB)

CRI iAtlas Team Justin Guinney, James Eddy (Sage Bionetworks), David Gibbs, Ilya Shmulevich (ISB)

TCGA Research Network, TCGA Patients and Families

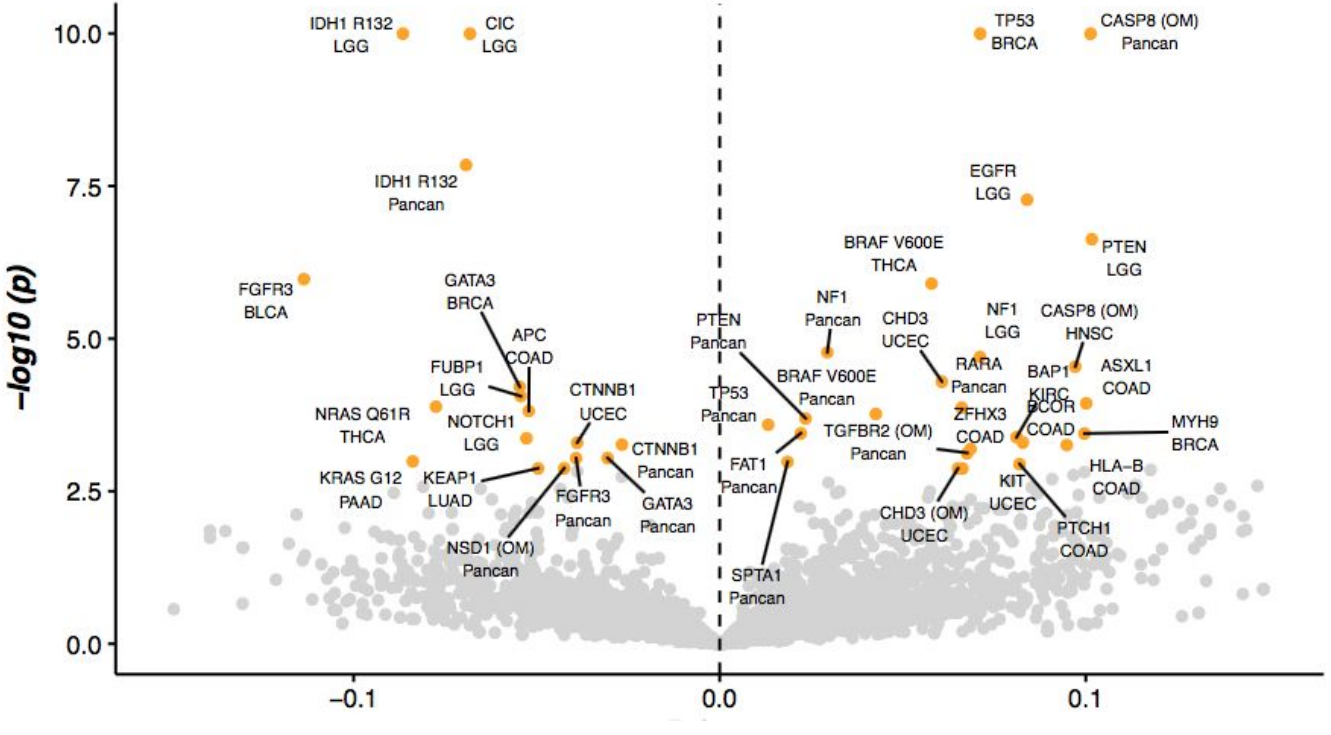
Funding from
Cancer Research Institute; National Cancer Institute U24CA143835

Extra Slides

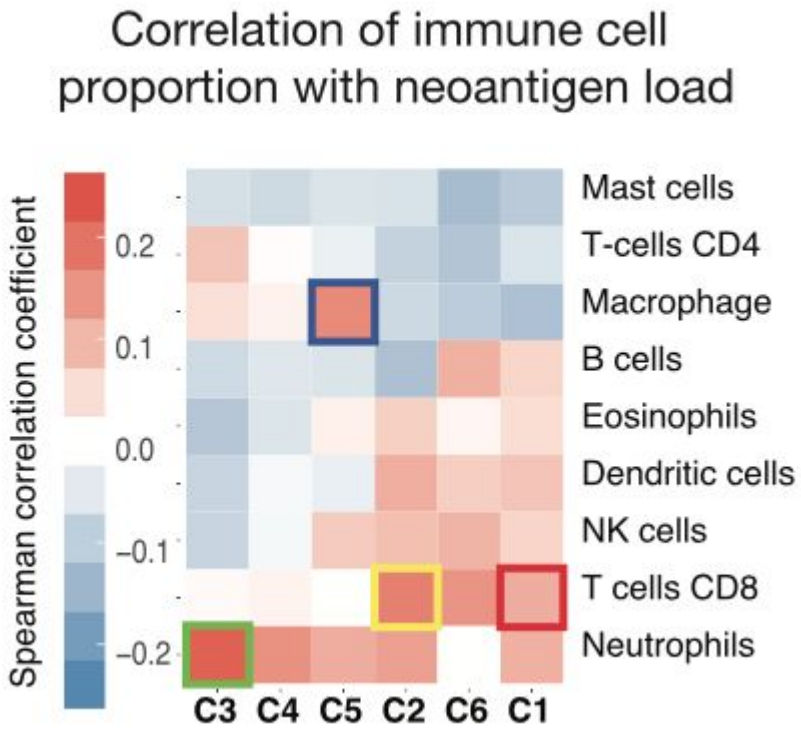
See Manuscript for Further Discussions

- Prognostic Associations of Tumor Immune Response Measures
- Immune Response Correlates of Demographic and Germline Variation
- Survey of Immunogenicity
- The Adaptive Immune Receptor Repertoire in Cancer
- Regulation of Immumodulatory Proteins

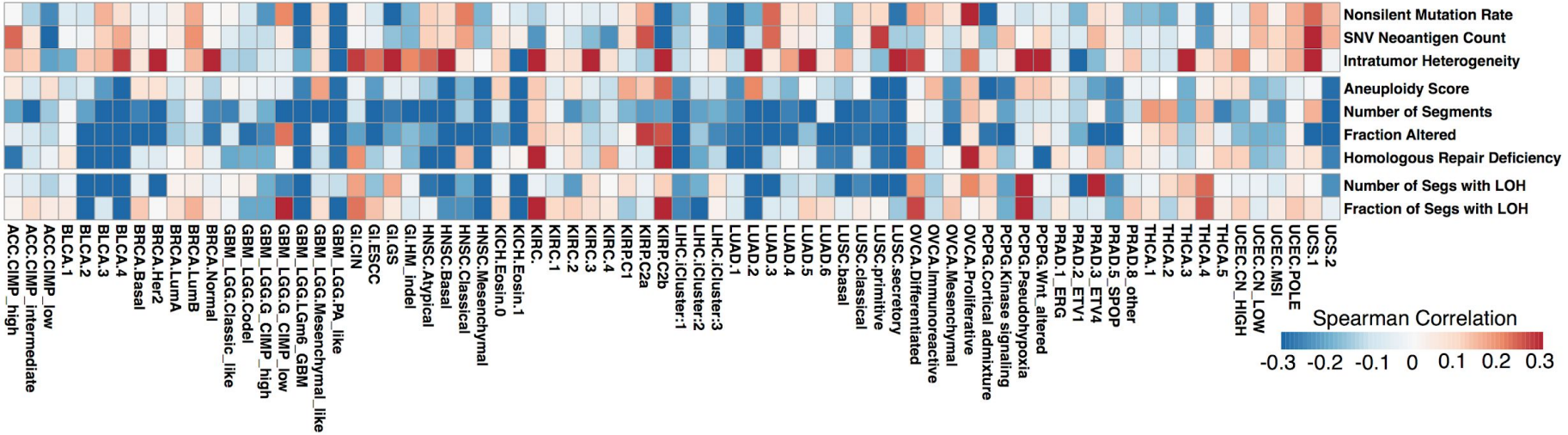
Driver mutations that associate with Leukocyte Fraction



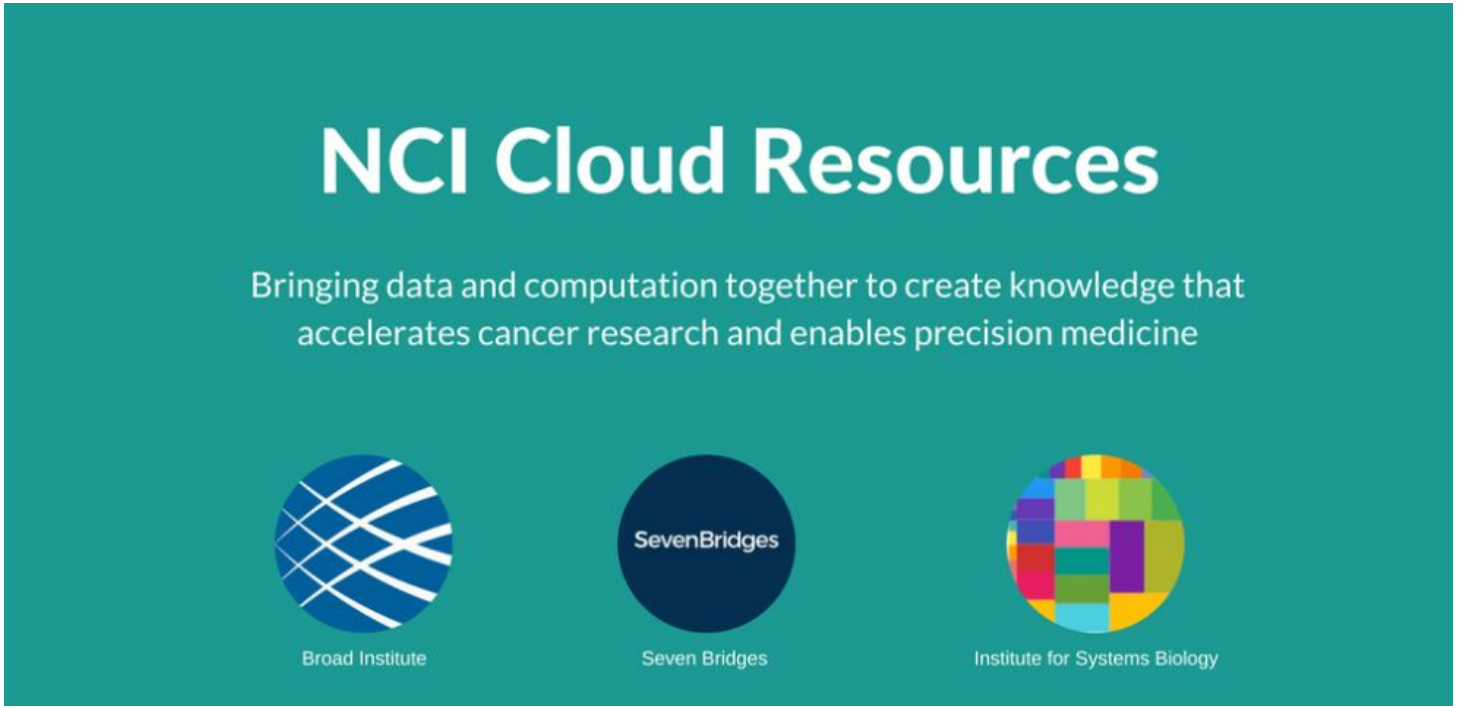
B


Correlation of immune cell proportion with neoantigen load
Spearman correlation coefficient
0.2
0.1
0.0
−0.1
−0.2
Mast cells
T-cells CD4
Macrophage
B cells
Eosinophils
Dendritic cells
NK cells
T cells CD8
Neutrophils
C3
C4
C5
C2
C6
C1

.. and by tumor (molecular) subtype



Data Management and Integration



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Example Query: CTLA-4 Gene Expression

Google Cloud Platform

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select * from [isb-cgc-01-0008:Filtered.EBpp_AdjustPANCAN_RNASeqV2_filtered] where Symbol="CTLA4"
```

Row	ParticipantBarcode	SampleBarcode	AliquotBarcode	SampleTypeLetterCode	SampleType	Study	Symbol	Entrez	normalized_count
1	TCGA-OR-A5JB	TCGA-OR-A5JB-01A	TCGA-OR-A5JB-01A-11R-A29S-07	TP	Primary solid Tumor	ACC	CTLA4	1493	60.1537
2	TCGA-OR-A5LG	TCGA-OR-A5LG-01A	TCGA-OR-A5LG-01A-11R-A29S-07	TP	Primary solid Tumor	ACC	CTLA4	1493	1.365
3	TCGA-4Z-AA7N	TCGA-4Z-AA7N-01A	TCGA-4Z-AA7N-01A-11R-A39I-07	TP	Primary solid Tumor	BLCA	CTLA4	1493	346.102
4	TCGA-DK-A6AV	TCGA-DK-A6AV-01A	TCGA-DK-A6AV-01A-12R-A30C-07	TP	Primary solid Tumor	BLCA	CTLA4	1493	55.1331
5	TCGA-FD-A5BR	TCGA-FD-A5BR-01A	TCGA-FD-A5BR-01A-11R-A26T-07	TP	Primary solid Tumor	BLCA	CTLA4	1493	105.179

Can query directly from R using the

bigrquery

library, then do a plot