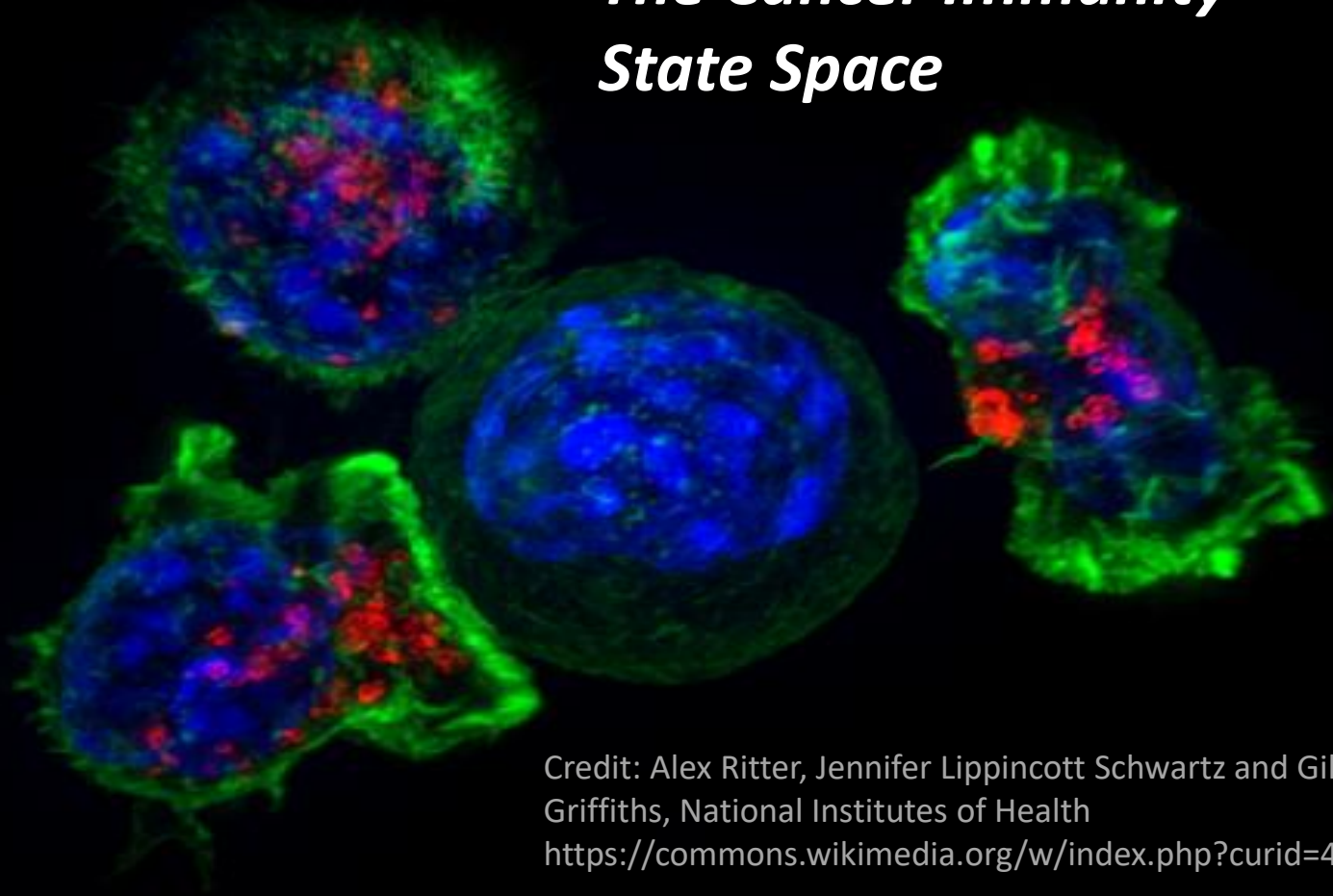
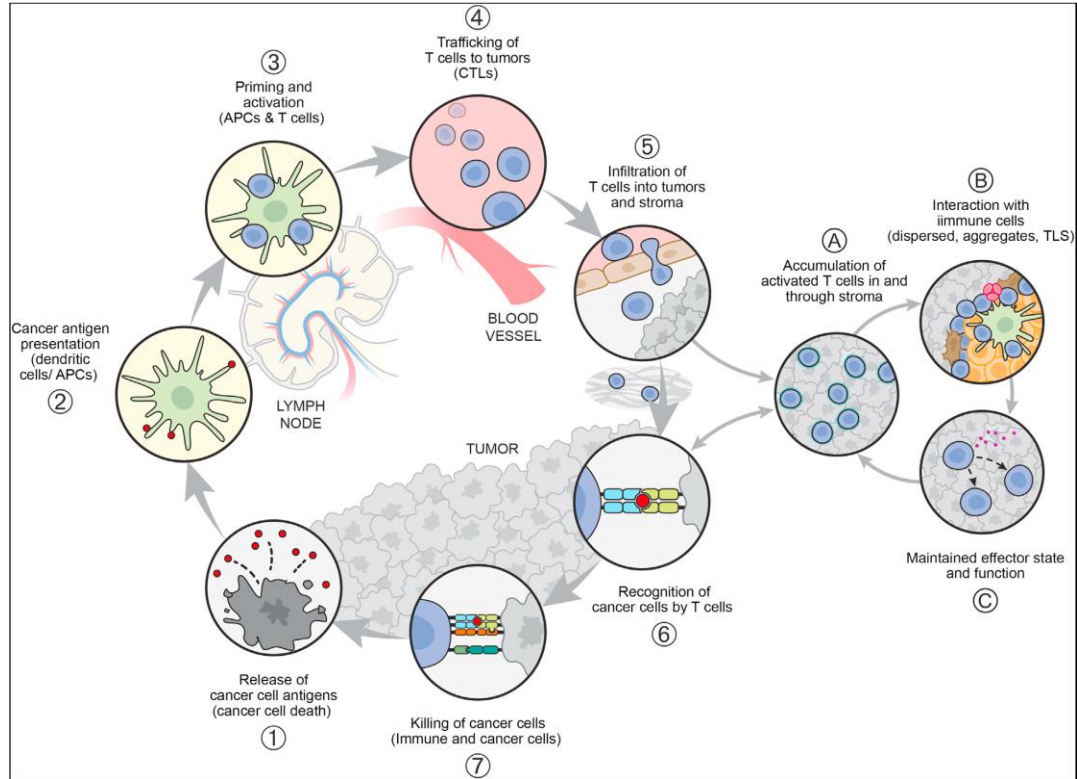


The Cancer Immunity State Space



Credit: Alex Ritter, Jennifer Lippincott Schwartz and Gillian
Griffiths, National Institutes of Health
<https://commons.wikimedia.org/w/index.php?curid=49182097>

A conceptual model - The Cancer Immunity Cycle



CellPress
OPEN ACCESS

Review

The cancer-immunity cycle: Indication, genotype, and immunotype

Ira Mellman,^{1,*} Daniel S. Chen,^{2,3} Thomas Powles,⁴ and Shannon J. Turley¹

¹Genentech, South San Francisco, CA, USA

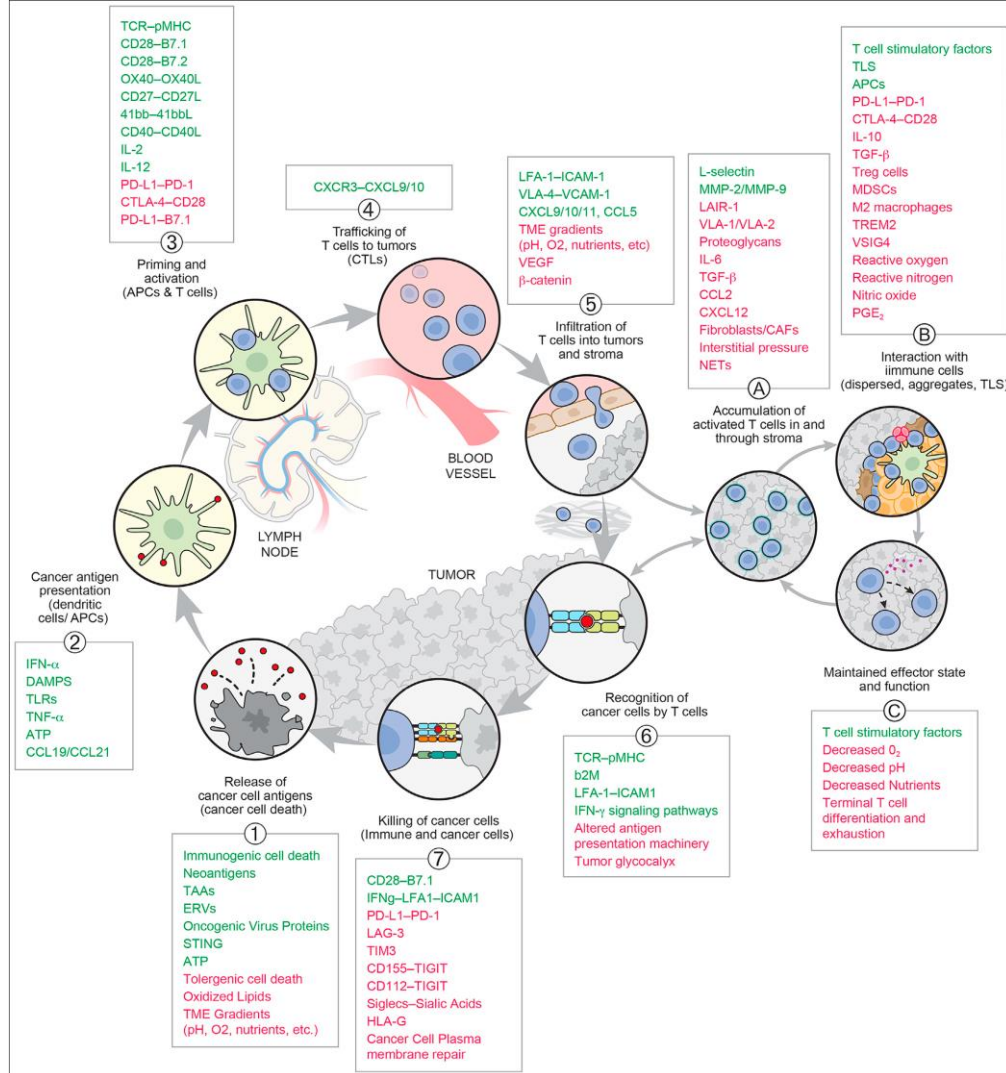
²Engenuity Life Sciences, Burlingame, CA, USA

³Synthetic Design Lab, Burlingame, CA, USA

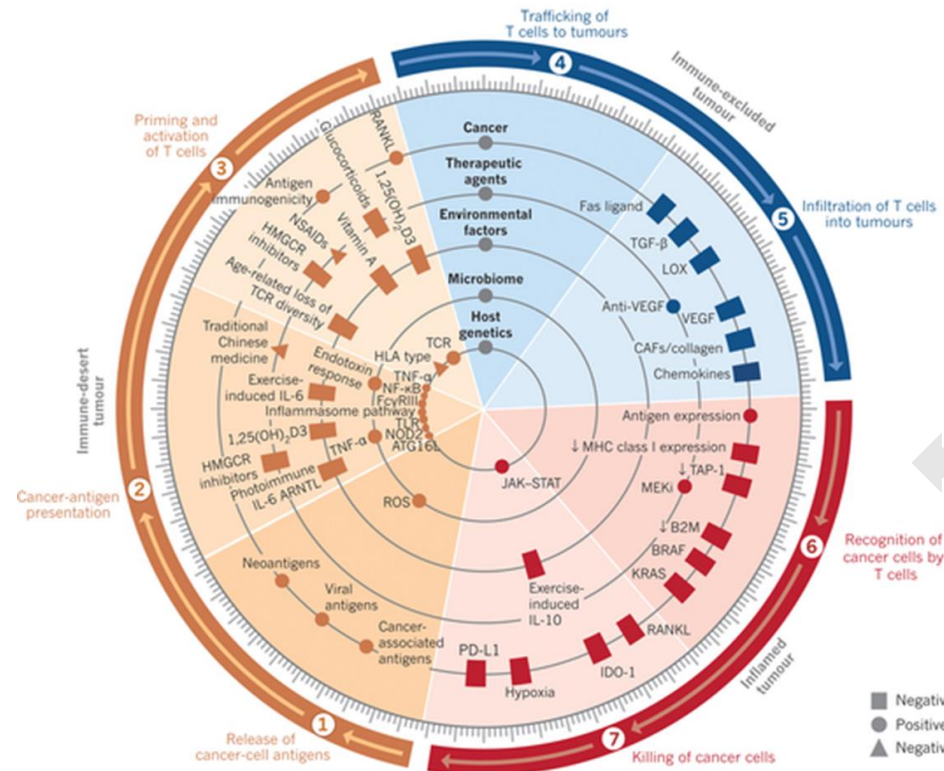
⁴Barts Cancer Institute, London, UK

*Correspondence: mellman.ira@gene.com

<https://doi.org/10.1016/j.immuni.2023.09.011>



The “CI set point” and how to “map Cancer Immunity”?



Nature 541, 321–330 (19 January 2017) doi:10.1038/nature21349

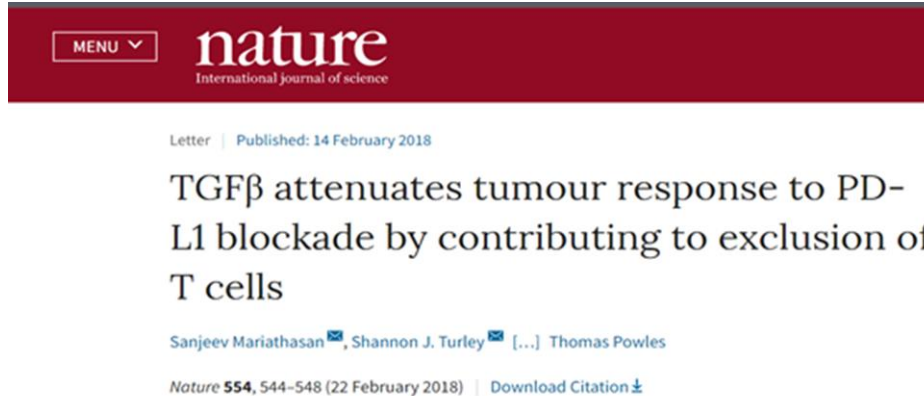
Factors that influence the cancer-immune set point.

The CI set point defined by:

$$\int (F_{\text{stim}}) - \int (F_{\text{inhib}}) \geq 1 / \sum_{n=1,y} (\text{TCR}_{\text{affinity}} \times \text{frequency})$$

- Negative eff...
- Positive effect
- ▲ Negative or positive effect

Example: Imvigor210 -Stationary bulk mRNA expression tumor micro environment (TME) data:



Pre-treatment tumour samples from Imvigor 210, a large phase 2 trial investigating the clinical activity of PD-L1 blockade with atezolizumab in mUC.

TGF- β attenuates tumor response to PD-L1 blockade by contributing to exclusion of T cells

Dorothee Nickles, Yasin Senbabaoglu, Daniel Sheinson

2018-02-14 21:57:03

- Introduction
- Downloading the IMvigor210CoreBiologies package
- Installing the IMvigor210CoreBiologies package
- Data provided with this package
 - Preprocessed data
 - Transcriptome wide gene expression data
 - Genomic alterations as assessed by FMO panel (Foundation Medicine, Inc.)
 - Data from in vivo experiments
 - Statistical analysis of immune cell infiltration
 - Other data
 - Gene signatures
 - R functions used in analyses
 - Color palettes
 - Supplementary Tables
 - Raw image data
- Running analyses
 - Locating the IMvigor210CoreBiologies analysis directory
 - Generating results shown in Figure 1 and related Extended Data
 - Generating results shown in Figure 2 and related Extended Data
 - Generating results shown in Figure 3 and related Extended Data
 - Generating results shown in Figure 4 and related Extended Data

Introduction

The IMvigor210CoreBiologies package provides methods and processed data for Mariathasan S, Turley S, Nickles D et al., "TGF- β attenuates tumor response to PD-L1 blockade by contributing to exclusion of T cells."

The human raw gene expression data will be available at the European Genome-phenome archive (EGA) under the accession number EGAS00001002556.

Downloading the IMvigor210CoreBiologies package

Accessing data and R based analytics:

<http://research-pub.gene.com/IMvigor210CoreBiologies/>

“Response was associated with CD8+ T-effector cell phenotype and, to an even greater extent, high neoantigen or tumour mutation burden (TMB). Lack of response was associated with a signature of transforming growth factor β (TGF- β) signalling in fibroblasts, particularly in patients with CD8+ T cells that were excluded from the tumour parenchyma and instead found in the fibroblast- and collagen-rich peritumoural stroma”

“TGF- β attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells”

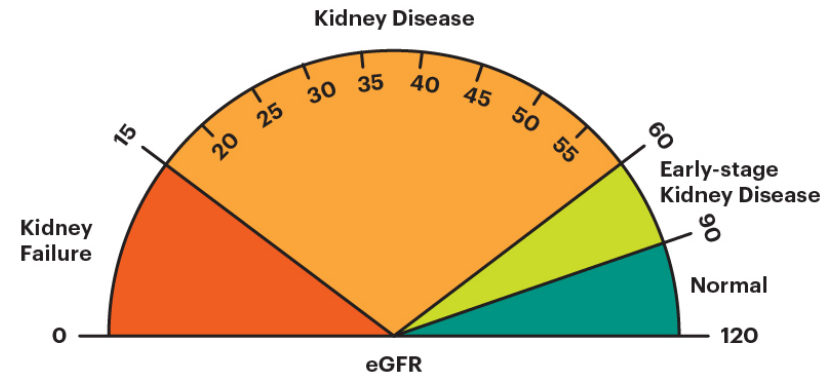
Sanjeev Mariathasan et al

Nature. 2018 February 22; 554(7693): 544–548. doi:10.1038/nature25501.

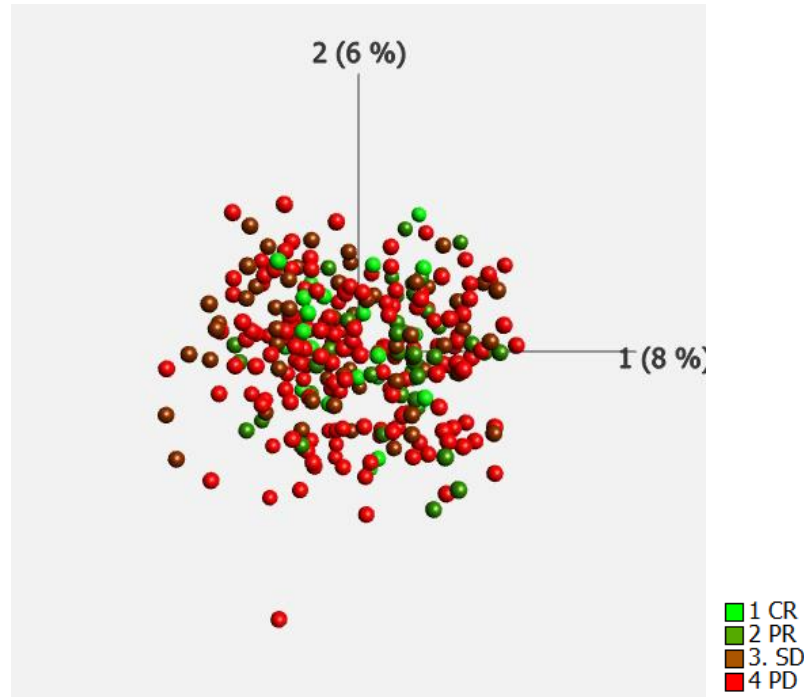
- Cohort 1 (n=119) as patients who were treatment naive for metastatic urothelial carcinoma, had an ECOG performance status ≤ 2 , and were ineligible for cisplatin by at least one of the following criteria: GFR > 30 and < 60 mL/min, $\geq$ G2 hearing loss or peripheral neuropathy or ECOG performance status 2.
- Cohort 2 (n=310) as patients progressed after platinum-based chemotherapy and had ECOG performance status ≤ 1 and GFR ≥ 30 mL/min.
- Atezolizumab 1200 mg IV was given every three weeks until disease progression (Cohort 1) or loss of clinical benefit (Cohort 2). The following endpoints were evaluated: RECIST v1.1 ORR by central review, duration of response, and OS.

ECOG PERFORMANCE STATUS*	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
 Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.:
 Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol
 5:649-655, 1982.



Invigor210: Sample 3d PCA plot capture 19% of the variance in the data



Stationary baseline bulk mRNA expression tumor micro environment (TME) data:

- 300 samples/patients
- 28204 variables/genes

Response as per RECIST 1.1:

CR = Complete Response

PR = Partial Response

SD = Stable Disease

PD = Progressive Disease

There seems to be favorable domains.

Can we find statistically robust representations of the signals by reducing noise in an objective way?

The Projection Score optimization indicates 7 degrees of freedom

Fontes and Soneson *BMC Bioinformatics* 2011, **12**:307
<http://www.biomedcentral.com/1471-2105/12/307>



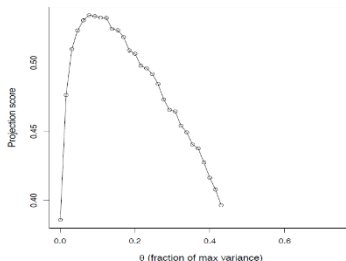
RESEARCH ARTICLE

Open Access

The projection score - an evaluation criterion for variable subset selection in PCA visualization

Magnus Fontes* and Charlotte Soneson

$$\alpha_2(\mathbf{\Lambda}_X, S) = \frac{\sum_{k \in S} \lambda_k^2}{\sum_{k=1}^r \lambda_k^2}.$$
$$\tau(\phi_m(\mathbf{X}), S, \mathcal{P}_{\phi_m(\mathbf{X})}) = (\alpha_2(\mathbf{\Lambda}_{\phi_m(\mathbf{X})}, S))^{1/2} - \mathbb{E}_{\mathcal{P}_{\phi_m(\mathbf{X})}} \left[(\alpha_2(\mathbf{\Lambda}_{\phi_m(\mathbf{X})}, S))^{1/2} \right].$$



Ross DT, Scherf U, Eisen MB, Perou CM, Rees C, Spellman P, Iyer V, Jeffrey SS, Van de Rijn M, Waltham M, Pergamenschikov A, Lee JC, Lashkari D, Shalon D, Myers TG, Weinstein JN, Botstein D, Brown PO: Systematic variation in gene expression patterns in human cancer cell lines. *Nat Genet* 2000, **24**:227-235.

A Projection Score optimization indicates that the main signal in the mRNA Invigor 210 data is 7 dimensional

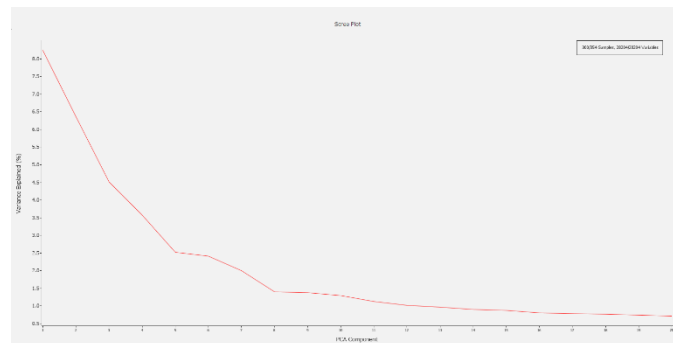
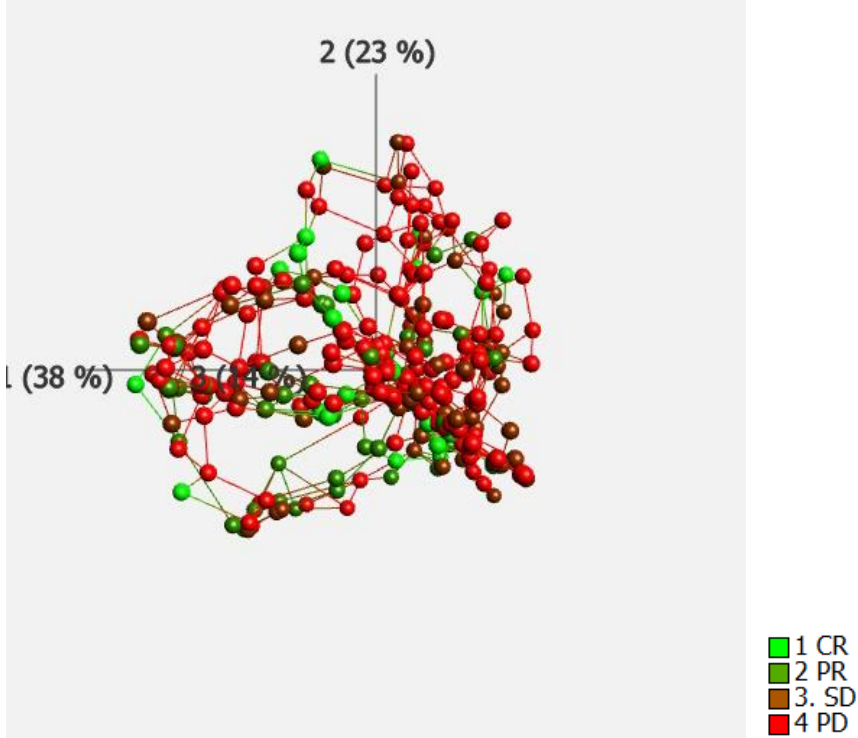
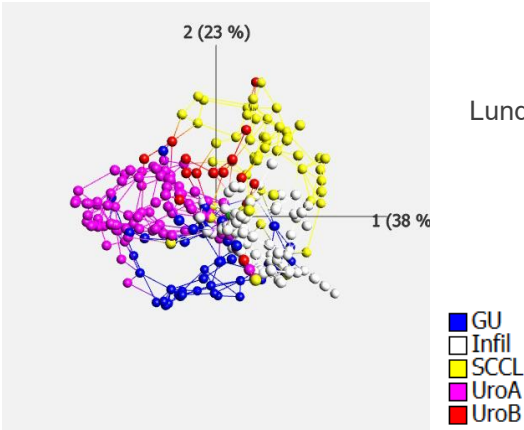


Illustration by a *Scree plot*

Projection Score 7d optimization followed by an ISOMAP embedding illustrate biologically meaningful subdomains of state space:

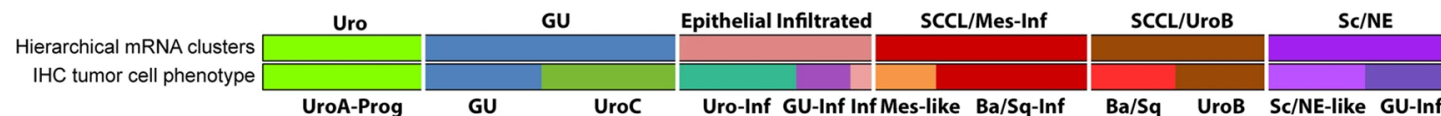


Projection Score 7d Optimization leaves 4246 genes. No statistical testing has been performed, but we can distinguish some regions of the space connected with NonResponders. In addition, subdomains e.g. correspond to different taxonomy sub phenotypes according to e.g. the *Lund* or *TCGA* taxonomy:



Ex: Lund sub-typing based on IHC and mRNA expression

A) Lund advanced cohort (n=307)



B)



Supervised approach to generate a tumor cell phenotype informed mRNA centroid classifier (LundTax)

SCIENTIFIC REPORTS

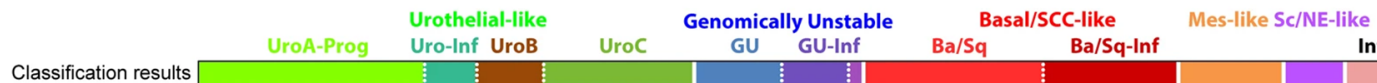
OPEN A validation and extended description of the Lund taxonomy for urothelial carcinoma using the TCGA cohort

Received: 11 July 2017
Accepted: 19 February 2018
Published online: 27 February 2018

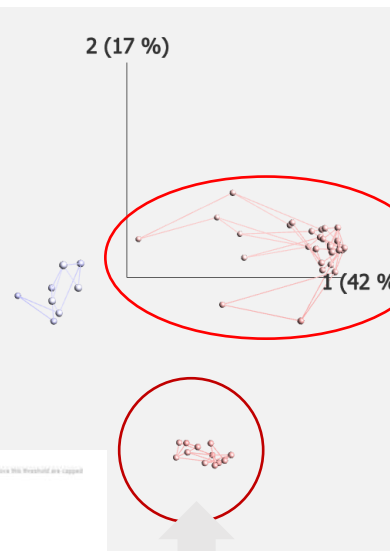
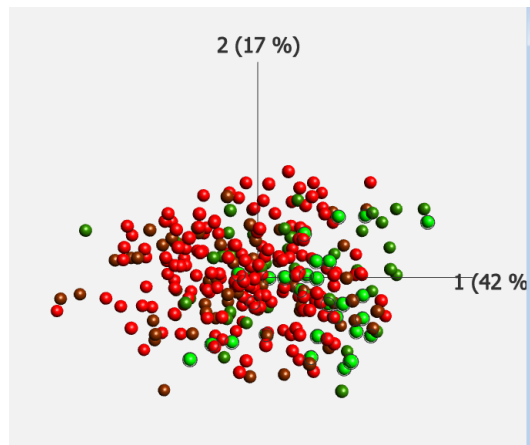
Nour al-dain Marzouk¹, Pontus Eriksson², Carlos Rovira³, Fredrik Liedberg⁴, Gertraud Sjöblad¹ & Mattias Höglund¹

C) TCGA cohort (n=407)

Classification of TCGA cohort with LundTax centroids



Performing rank-regression w.r.t. CR > PR > SD > PD with a False Discovery Rate (FDR) cut off of 0.05 produce 50 genes. A PCA bi-plot show distinct variable clusters driving the signal:



A *gprofiler* run identifies two of the gene clusters as significant:

Cellcycle

Variables colored according to mean expression in the Complete Response (CR) group and connected by a graph based on correlation distance

Type II Interferon signalling (INFG)
CXCR3 chemokine receptor binding

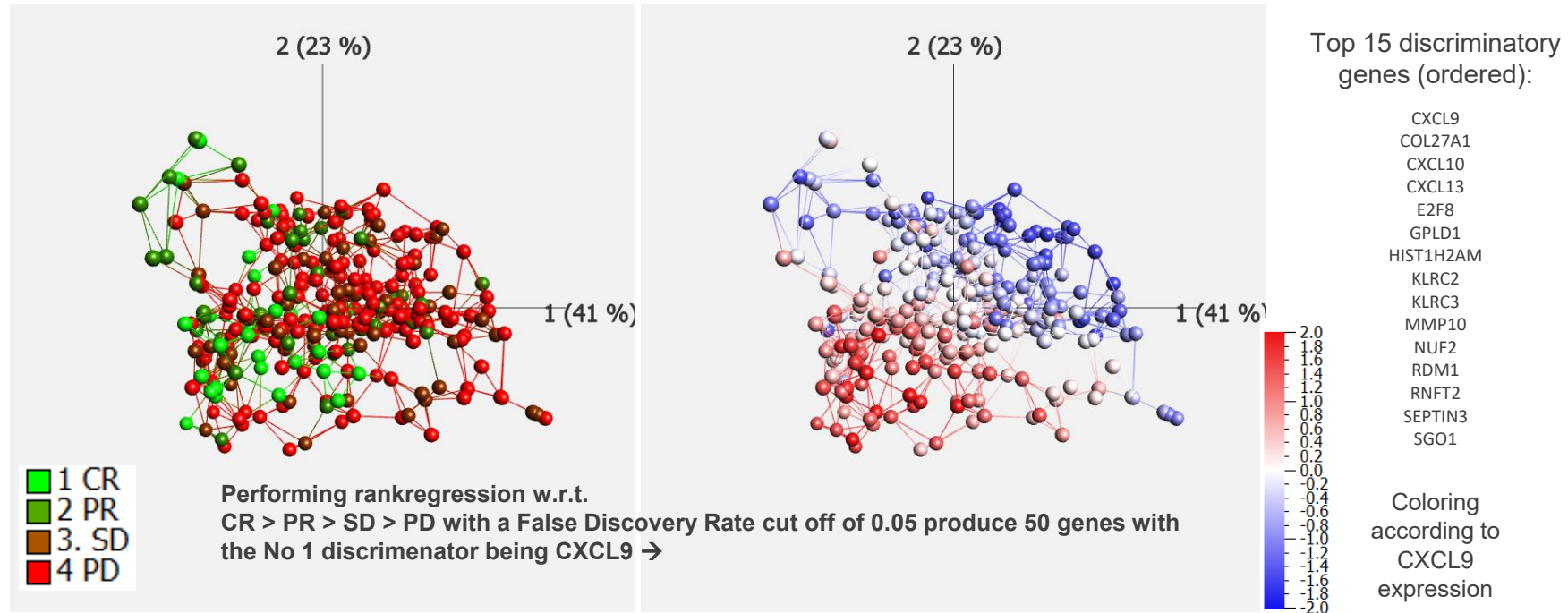


version
date
organism

s102_eg19_p15_7allb4d5
3/17/2021, 9:07:07 PM
Hsapiens

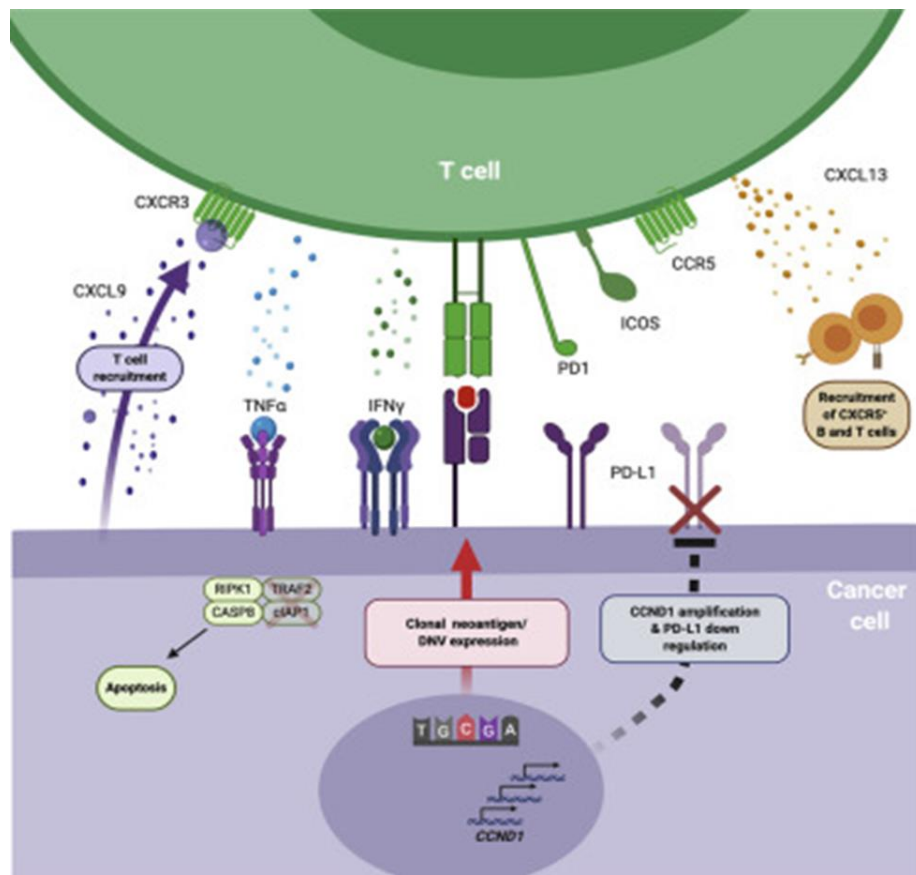
g:Profiler

Response to CPI in Imvigor210 is highly correlated with CXCL9 expression



Response to CPI has the strongest correlation with CXCL9 expression. Illustrated using an ISOMAP embedding.

The CXCL9 signature for CPI response generalizes to other indications



Cell

Volume 184, Issue 3, 4 February 2021, Pages 596-614.e14



Article

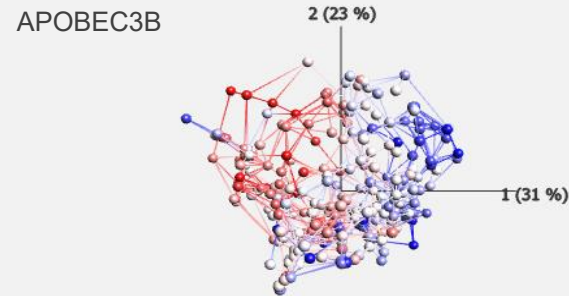
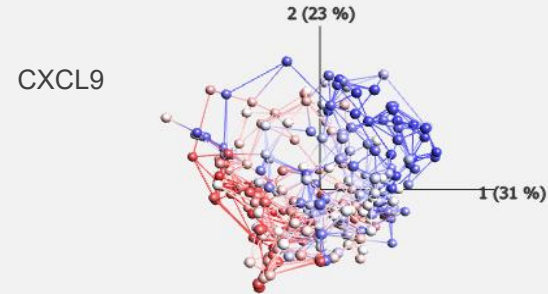
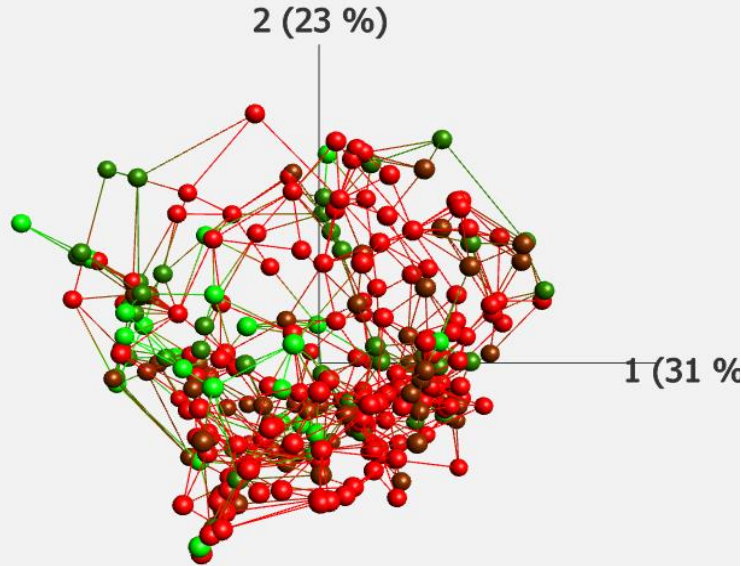
Meta-analysis of tumor- and T cell-intrinsic mechanisms of sensitization to checkpoint inhibition

Kevin Litchfield ^{1, 3, 13}, James L. Reading ^{2, 3, 13}, Clare Puttick ^{1, 13}, Krupa Thakkar ^{1, 3}, Chris Abbosh ³, Robert Benthall ³, Thomas B.K. Watkins ¹, Rachel Rosenthal ¹, Dhruva Biswas ¹, Andrew Rowan ¹, Emilia Lim ¹, Maise Al Bakir ¹, Virginia Turati ⁴, José Afonso Guerra-Assunção ⁵, Lucia Conde ⁵, Andrew J.S. Furness ⁶, Sunil Kumar Saini ⁷, Sine R. Hadrup ⁷ ... Charles Swanton ^{1, 3, 14}

Highlights

- Large-scale meta-analysis of >1,000 CPI-treated cases with exome/transcriptome data
- Clonal TMB and CXCL9/CXCL13 expression are the strongest predictors of CPI response

An APOBEC signature complements the CXCL9 signature and correlate with Response to CPI in the Imvigor210 data:



Looking to complement the CXCL9 signature, we find a statistically significant APOBEC signature

REVIEW | ONLINE NOW

APOBECs orchestrate genomic and epigenomic editing across health and disease

Karla Cervantes-Gracia ² • Anna Gramalla-Schmitz ² • Julian Weischedel • Richard Chahwan  [Show footnotes](#)Open Access • Published: August 02, 2021 • DOI: <https://doi.org/10.1016/j.tig.2021.07.003>

PDF [2 MB]



Figures



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Reprints

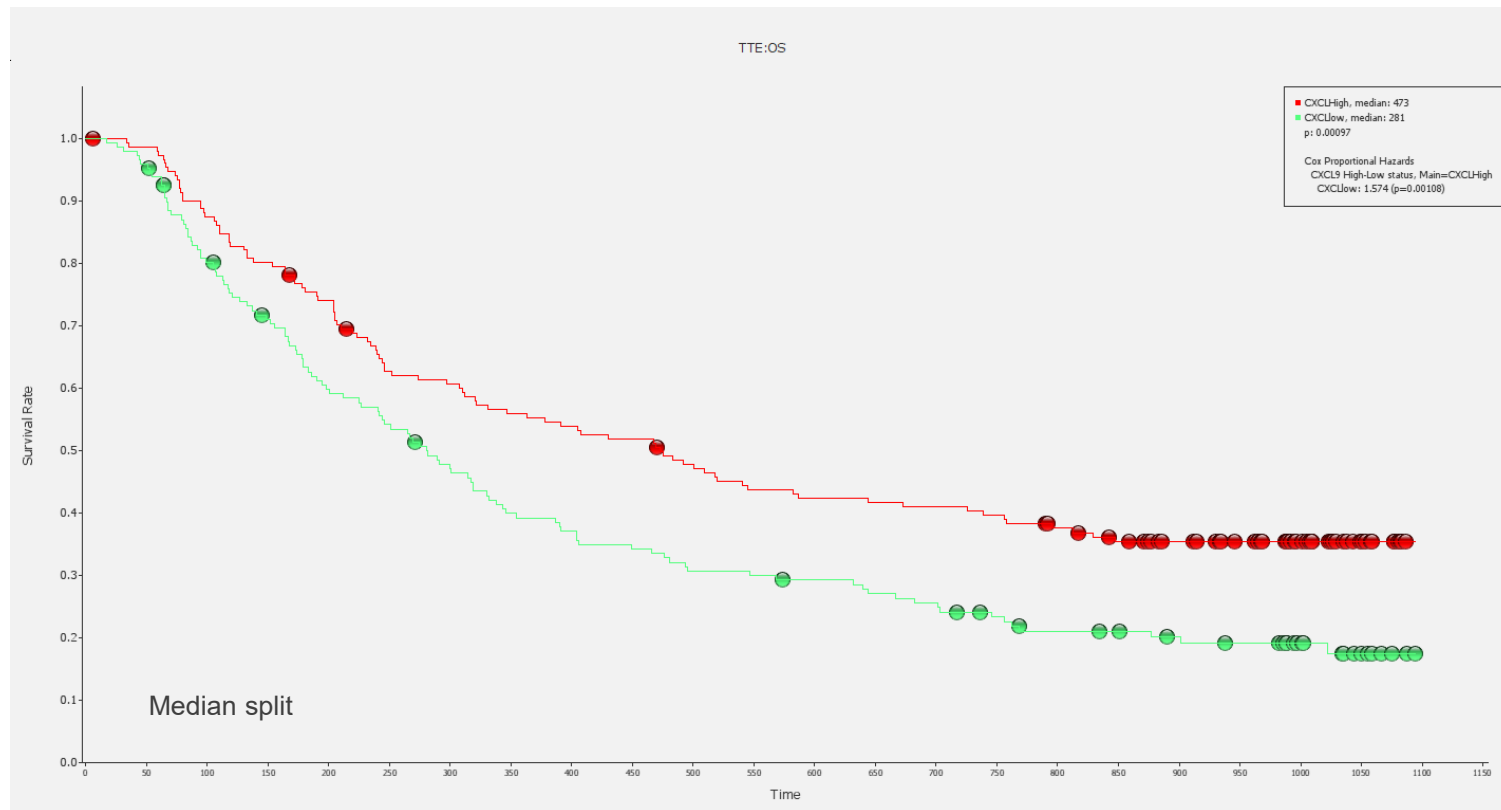


Request

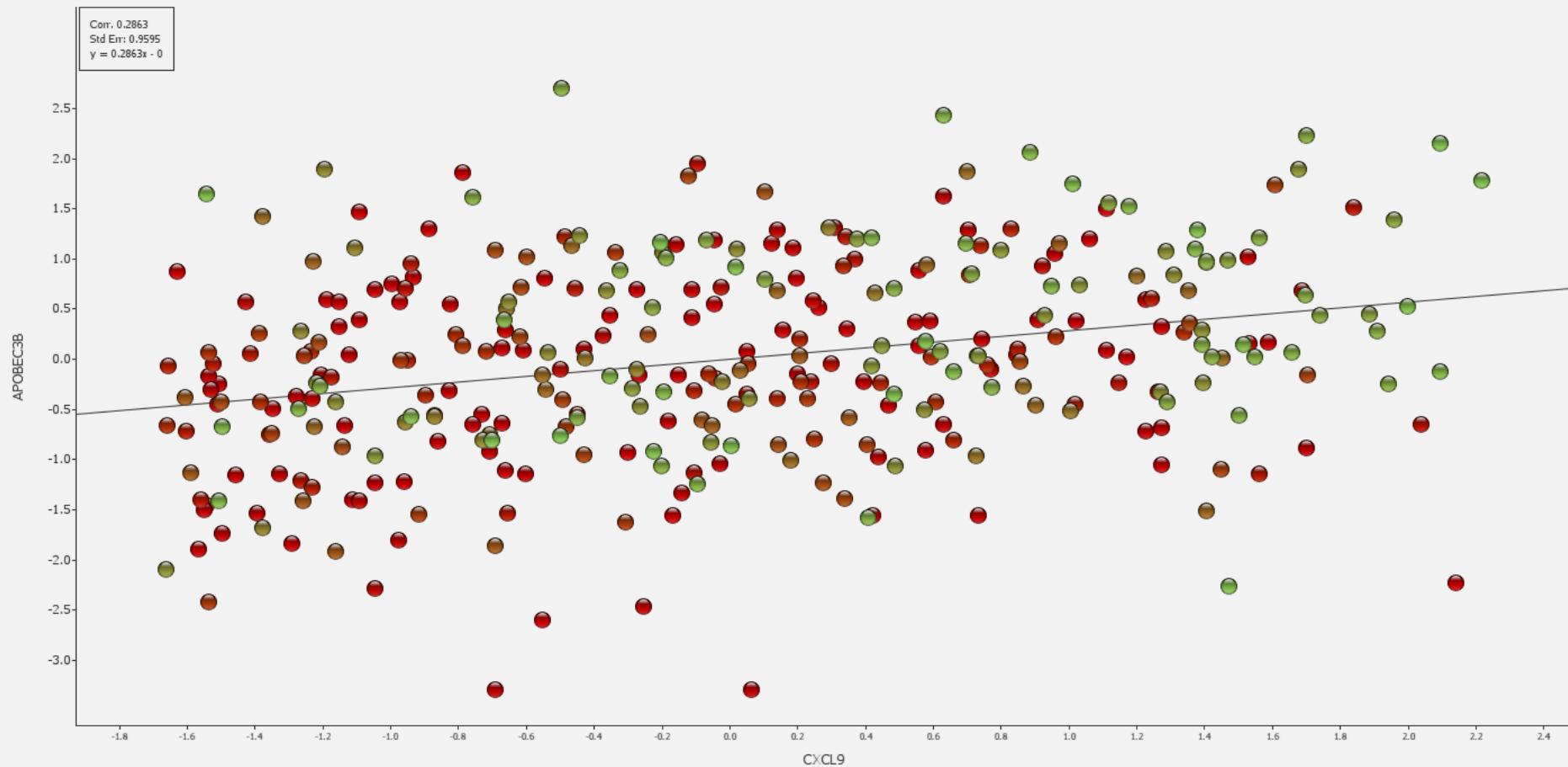
 PlumX Metrics

- *APOBEC proteins can deaminate cytosine residues in DNA and RNA. This can lead to somatic mutations, DNA breaks, RNA modifications, or DNA demethylation in a selective manner.*
- *They orchestrate a wide array of genomic and epigenomic modifications, thereby affecting various cellular functions positively or negatively, including immune editing, viral and retroelement restriction, DNA damage responses, DNA demethylation, gene expression, and tissue homeostasis.*

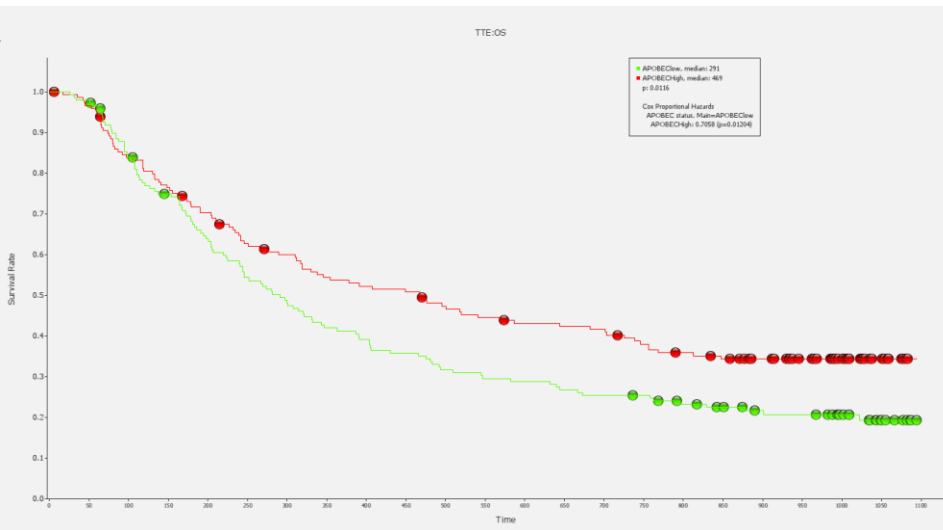
Kaplan Meier Plot showing the impact of the CXCL9 signature on OS in Imvigor210



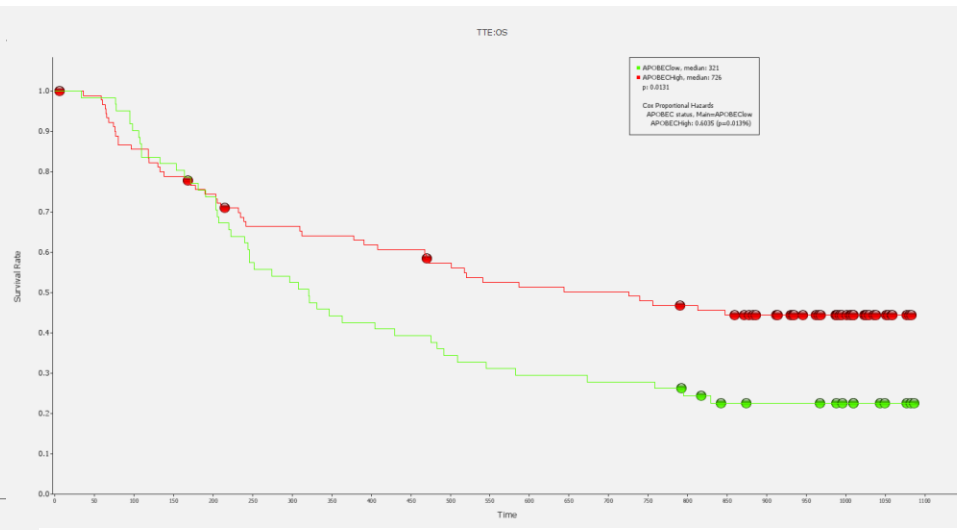
CXCL9 vs APOBEC3B Colored according to OS



OS Kaplan-Meier plots for the APOBEC3B signature in Imvigor210



KM plot for APOBEC3B (using a median split)



Survival benefit for APOBEC-High shown in a KM plot involving exclusively the CXCL9-High group (using a median split)



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journal homepage: www.ejancer.com



Original Research

Tertiary lymphoid structures marker *CXCL13* is associated with better survival for patients with advanced-stage bladder cancer treated with immunotherapy

Clarice S. Groeneveld^{a,b,1}, Jacqueline Fontugne^{b,c,1}, Luc Cabel^b,
Isabelle Bernard-Pierrot^b, François Radvanyi^b, Yves Allory^{b,c,2},
Aurélien de Reyniès^{a,*,2}



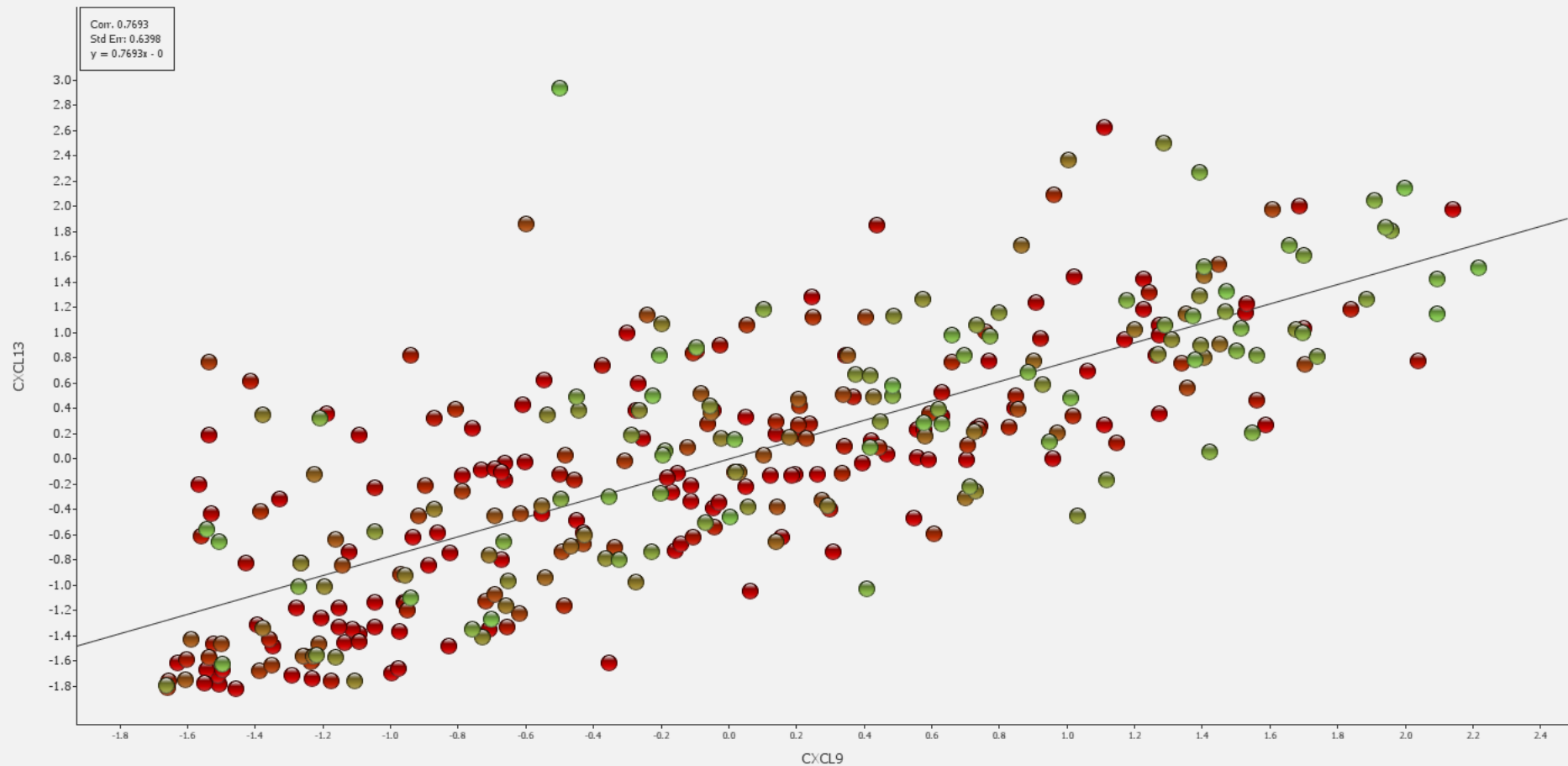
Response to immunotherapy in soft-tissue sarcoma, melanoma and renal cell carcinoma have been recently linked to the presence of tertiary lymphoid structures (TLS) in the tumour. TLS are organised aggregates of T, B and dendritic cells, participating in adaptive antitumor immune response. The chemokine CXCL13 is involved in the formation of TLS, and is reported as a reliable transcriptomic marker of TLS.

Objectives: In this study, we sought to assess whether CXCL13 transcript expression can be a prognostic biomarker for ICI-treated MIBC patients and also investigated whether it can serve as a biomarker of TLS in MIBC.

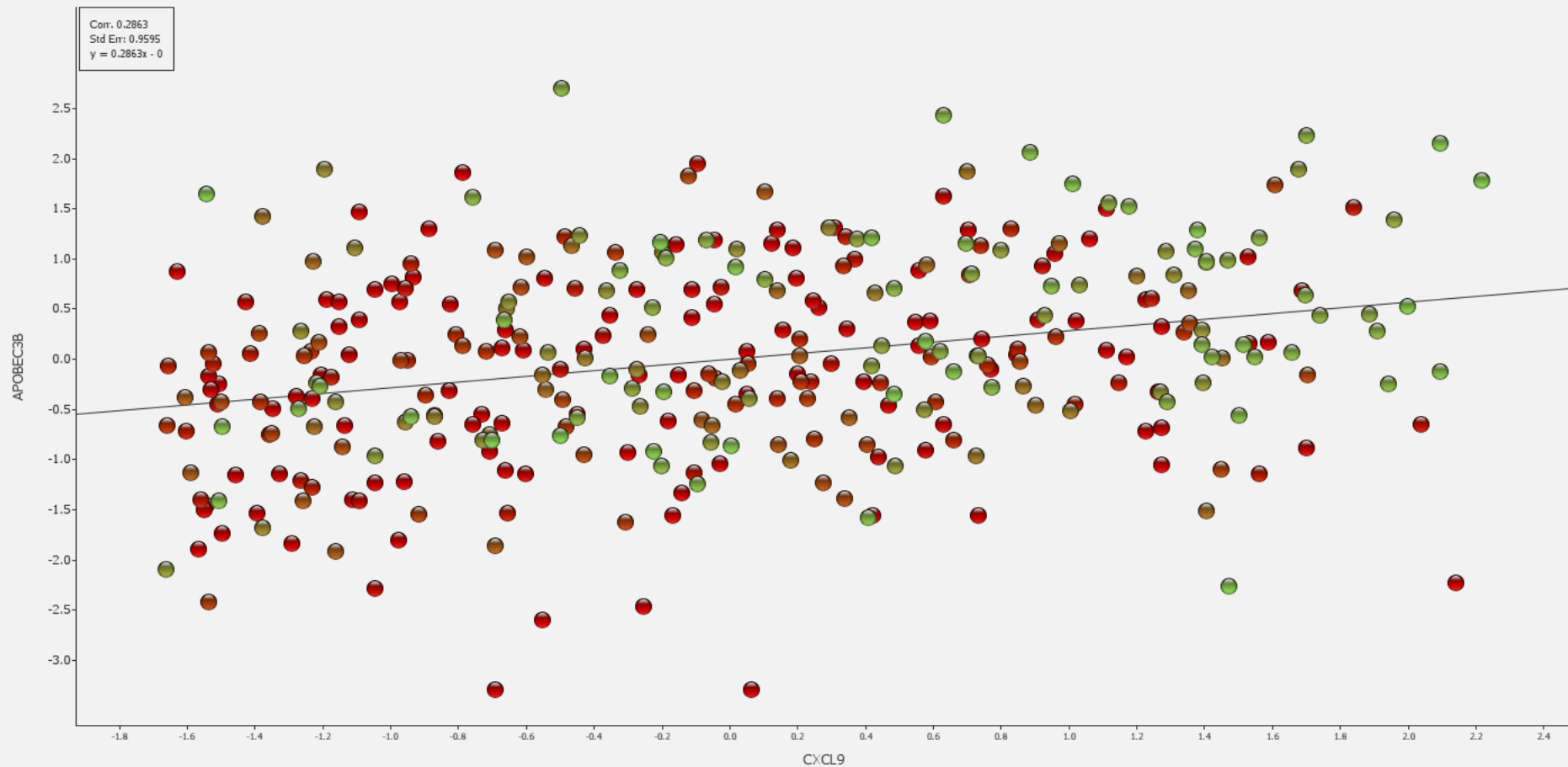
Methods: We analysed transcriptomic data from three publicly available MIBC cohorts and evaluated pathological slides from the TCGA-BLCA cohort for TLS presence and stage of maturation.

Results: We showed that CXCL13 was independently associated with both prolonged survival (HR 2.08, 95% CI [0.68e0.94]) and objective response ($p < 0.0001$) in patients treated with ICI.

CXCL9 vs CXCL13 Colored according to OS



CXCL9 vs APOBEC3B Colored according to OS



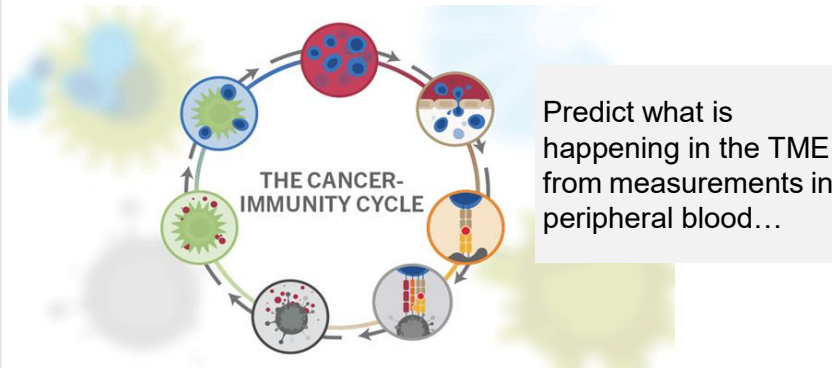
How do we gain future knowledge around cancer immunity?

Focus areas in data driven CIT research to find new biomarkers & targets:

- Integrative Modeling & Analysis & Visualization
- Dynamical modeling in the Cancer Immunity State Space.
Mapping initial state and exploring dynamics.

Compartmental Modeling of

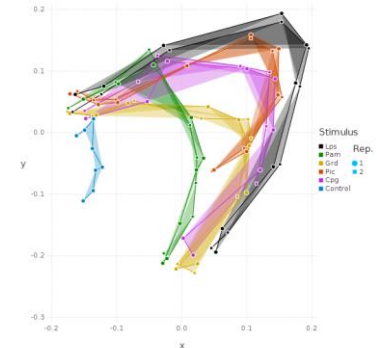
- Blood
- Tumor Micro Environment
- Lymph system
-



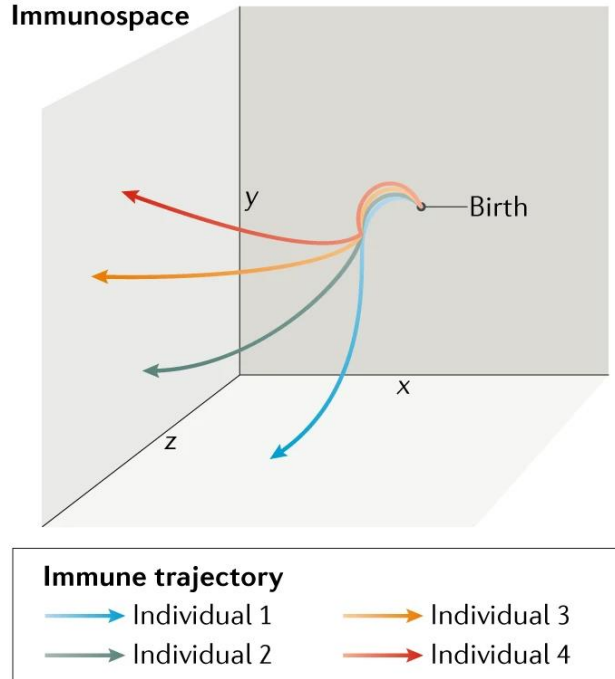
Time Series Data Sources:

- Circulating Tumor DNA (ctDNA)
- T-Cell Receptor Repertoire Sequencing
- Complementary exvivo systems (Organoid models, TruCulture system)
- ...

Find robust “dynamical biomarkers” for early and clinically actionable prediction of response...



General Systems Immunology for Biomedicine: Predicting and controlling dynamics under perturbations



- “Human immune systems are relatively stable within individuals over the course of weeks to months, but incredibly variable between individuals”
- “...induced responses to pathogens differ markedly among different age groups and... these differences are unique to different kinds of stimuli”
- Functional gene expression responses of human blood cells to common pathogens differ broadly across age groups.
- Divergent immune cell composition with advanced age is associated with chromatin changes that are induced by environmental influences over the course of life.