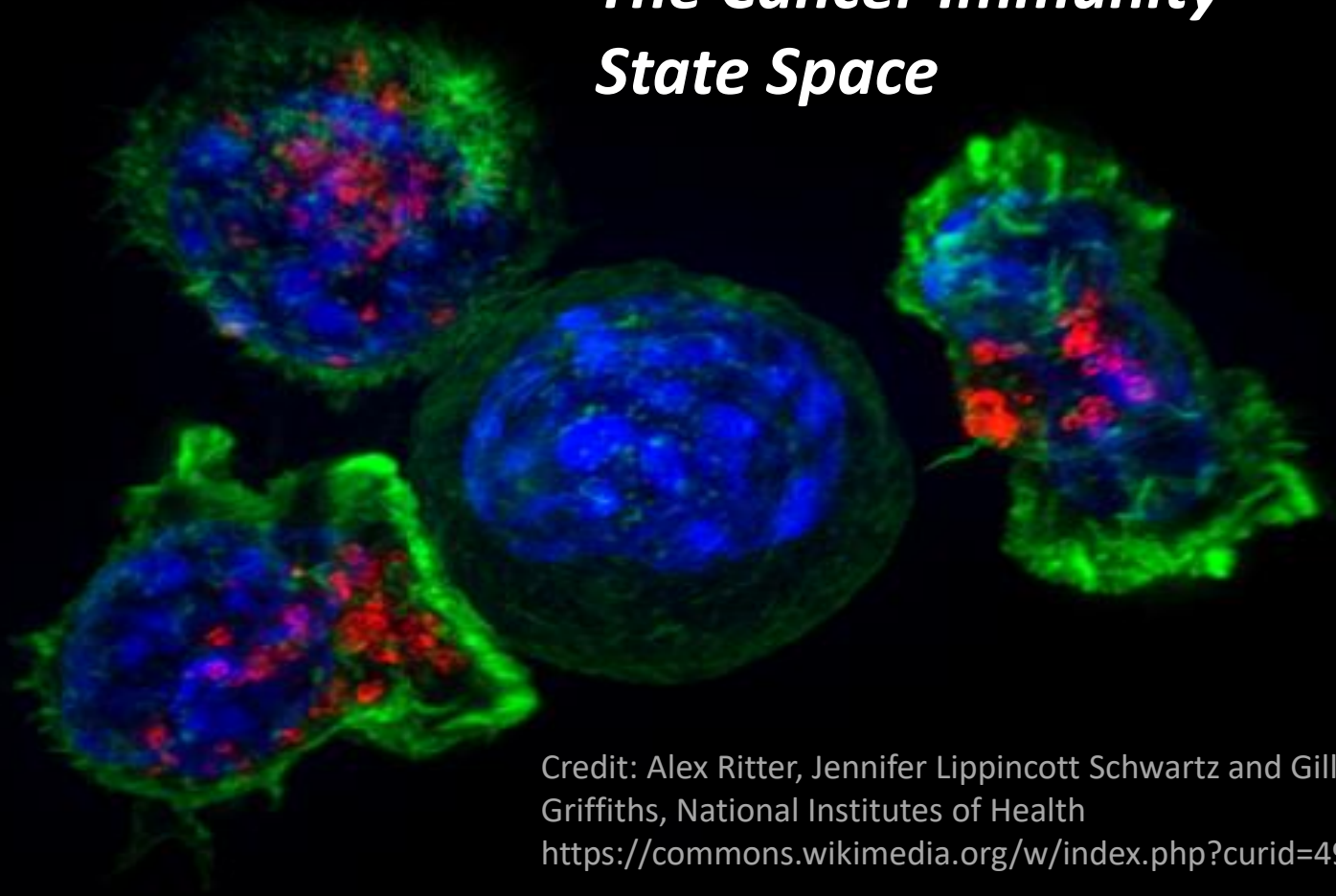
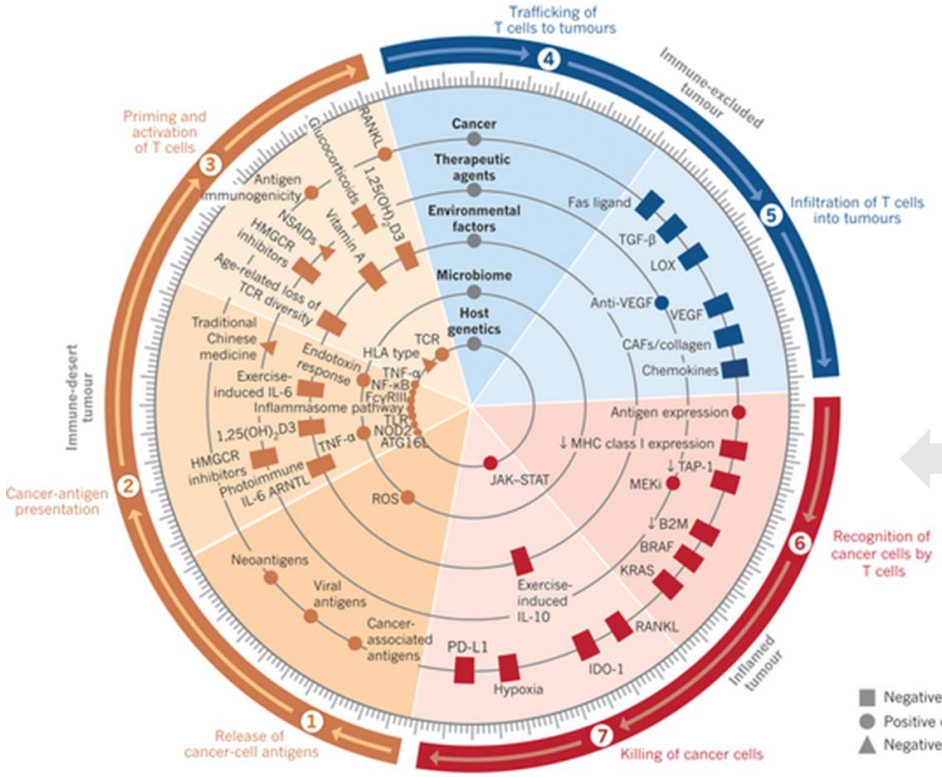
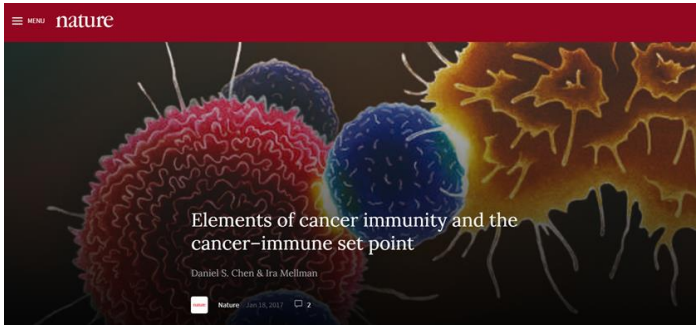
The Cancer Immunity State Space



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

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





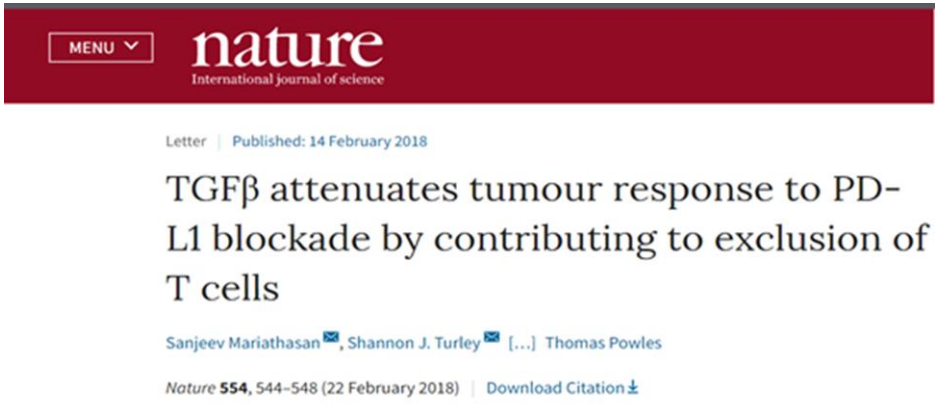
Nature 541, 321–330 (19 January 2017) doi:10.1038/nature21349

Factors that influence the cancer–immune set point.

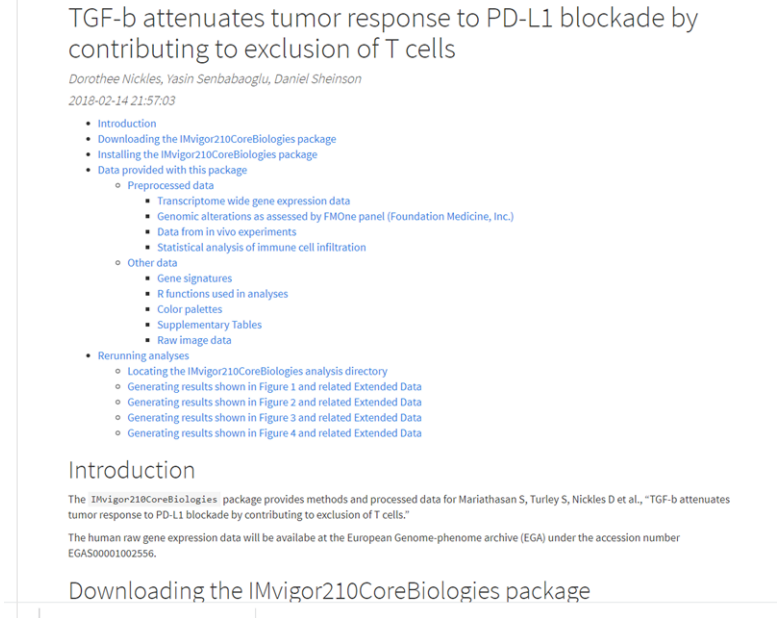
The CI set point defined by:

$$\int (F_{stim}) - \int (F_{inhib}) \geq 1/\Sigma_{n=1,y} (TCR_{affinity} \times frequency)$$

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.



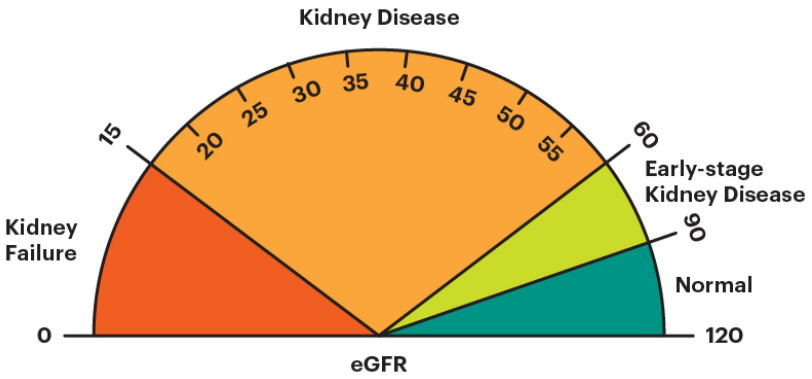
Accessing data and R based analytics:
http://research-pub.gene.com/IMvigor210CoreBiologies/

- 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, ≥ 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.

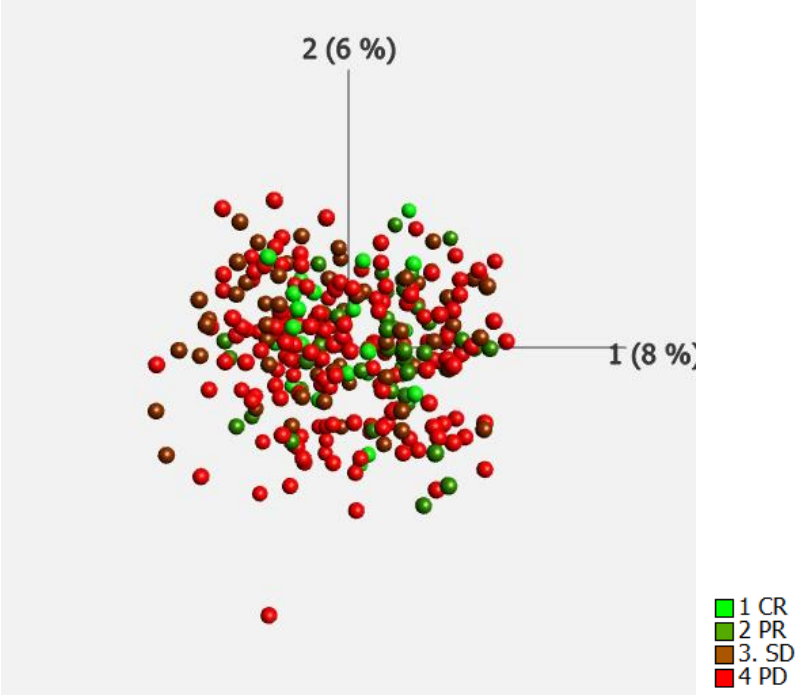
ECOG PERFORMANCE STATUS*

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.



Imvigor210: 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

BMC Bioinformatics

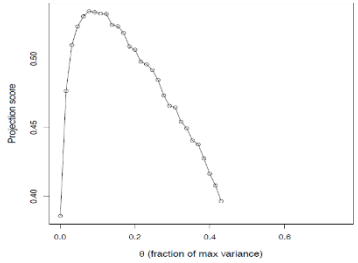
RESEARCH ARTICLE Open Access

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

Magnus Fontes* and Charlotte Soneson

$$\alpha_2(\mathbf{\Lambda}_X, S) = \frac{\sum_{k\in S}\lambda_k^2}{\sum_{k=1}^{r}\lambda_k^2}.$$

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



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 Imvigor 210 data is 7 dimensional

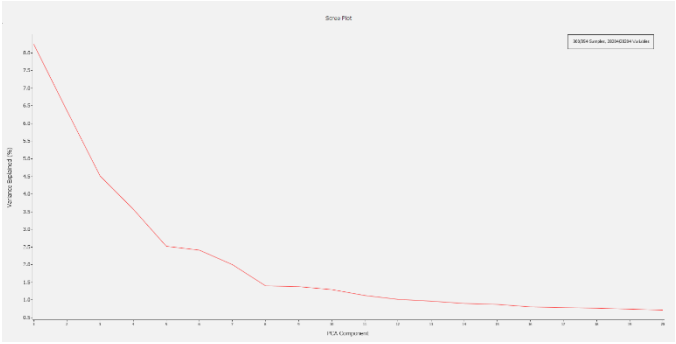
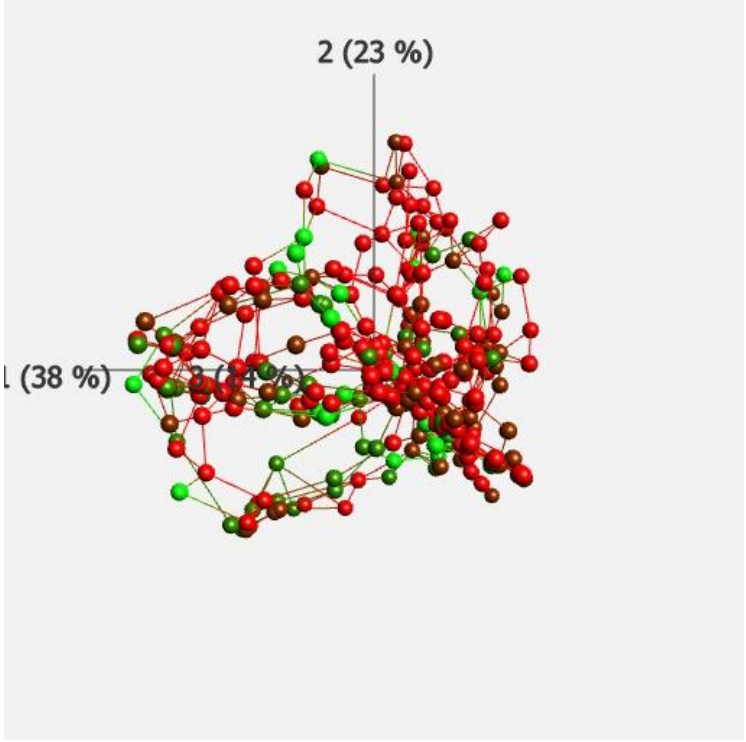
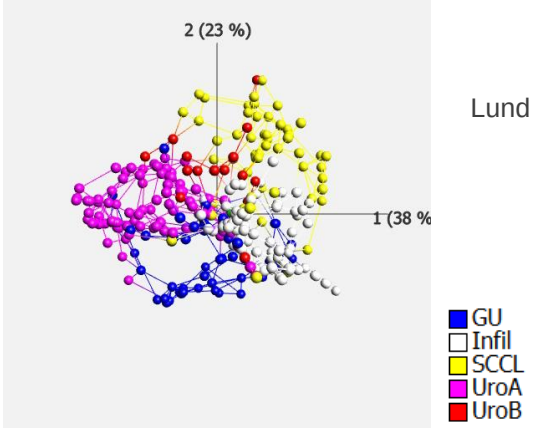


Illustration by a *Scree plot*

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

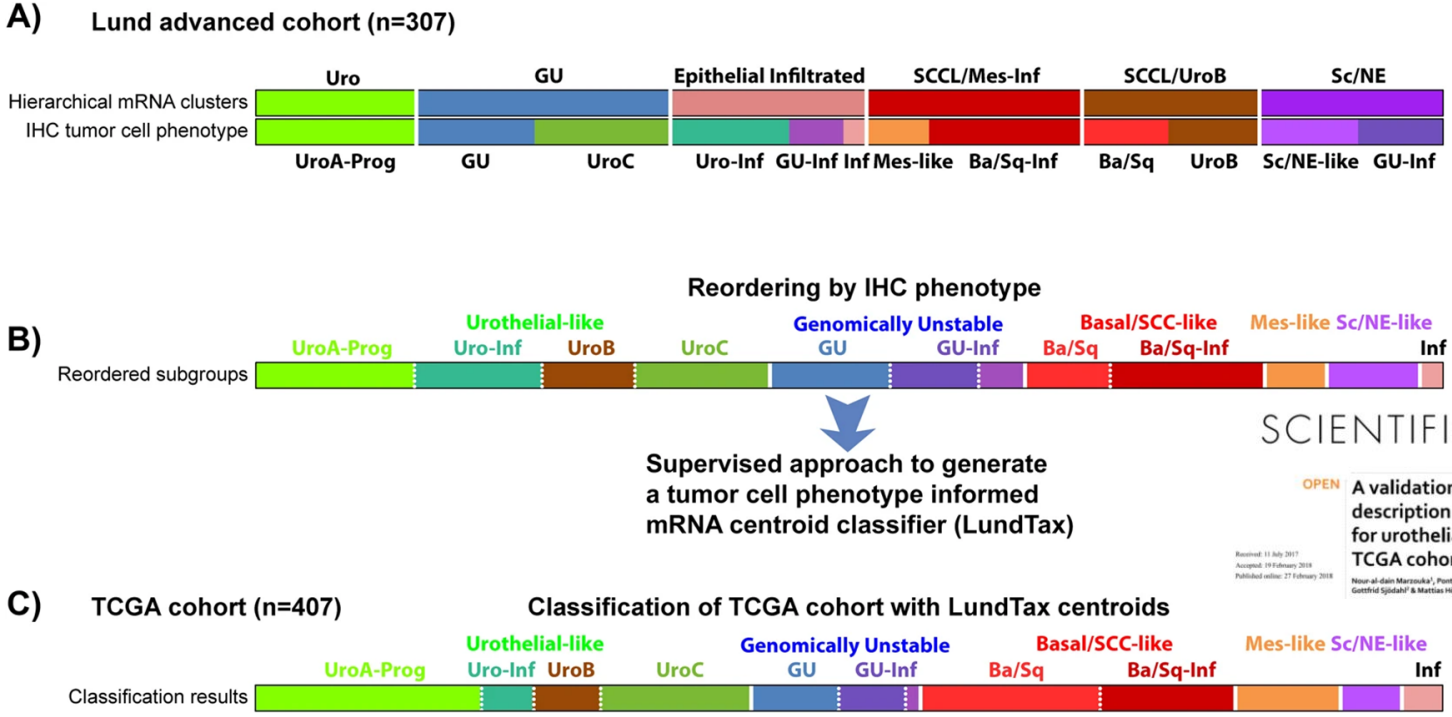


Projection Score 7d Optimization leaves 4246 genes.
No statistical testing has been performed, but we can distinguish some regions of the space connected with NonResponders.
In addition, subdomains e.g. correspond to different taxonomy sub phenotypes according to e.g. the *Lund or TCGA taxonomy*:



Lund Taxonomy:

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



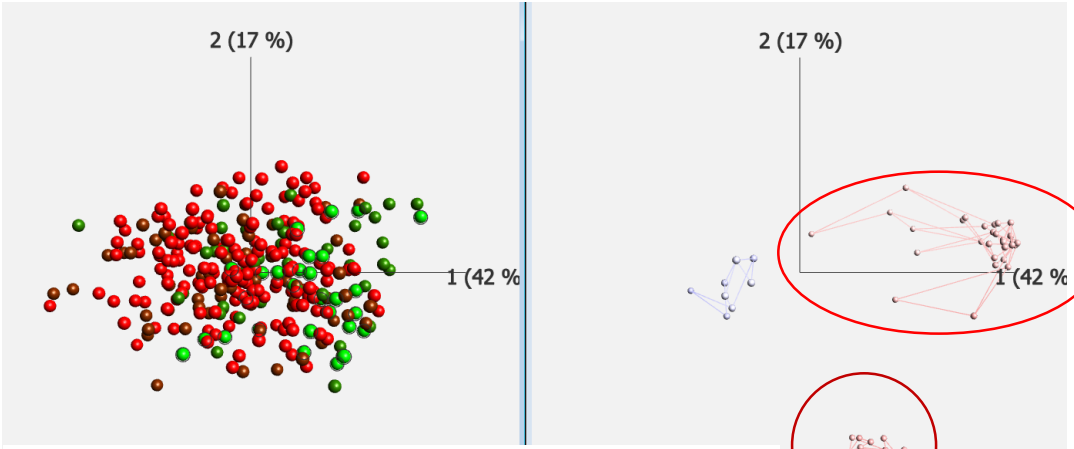
SCIENTIFIC REPORTS

OPEN

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

Nour-al-dain Marzouka[1], Pontus Eriksson[1], Carlos Rovira[1], Fredrik Liedberg[1], Gottfrid Sjödahl[1] & Mattias Höglund[1]

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:

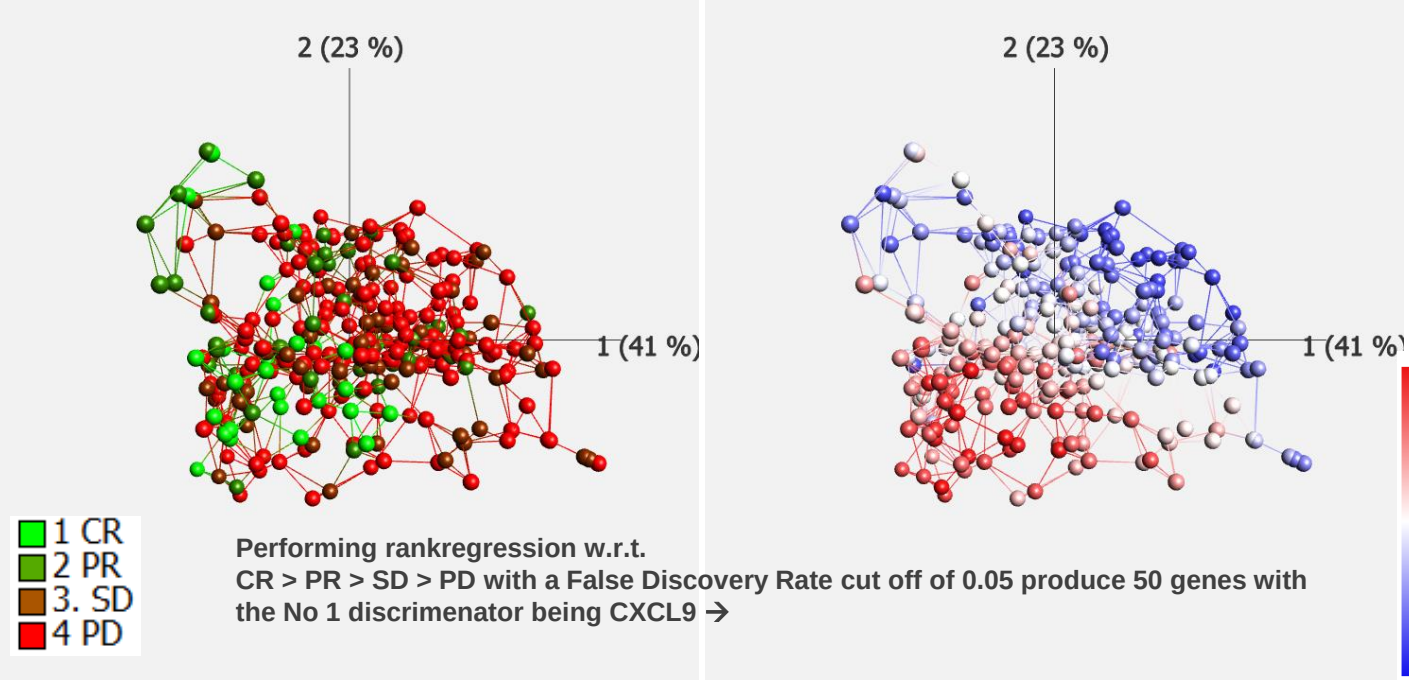
Cellcycle

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

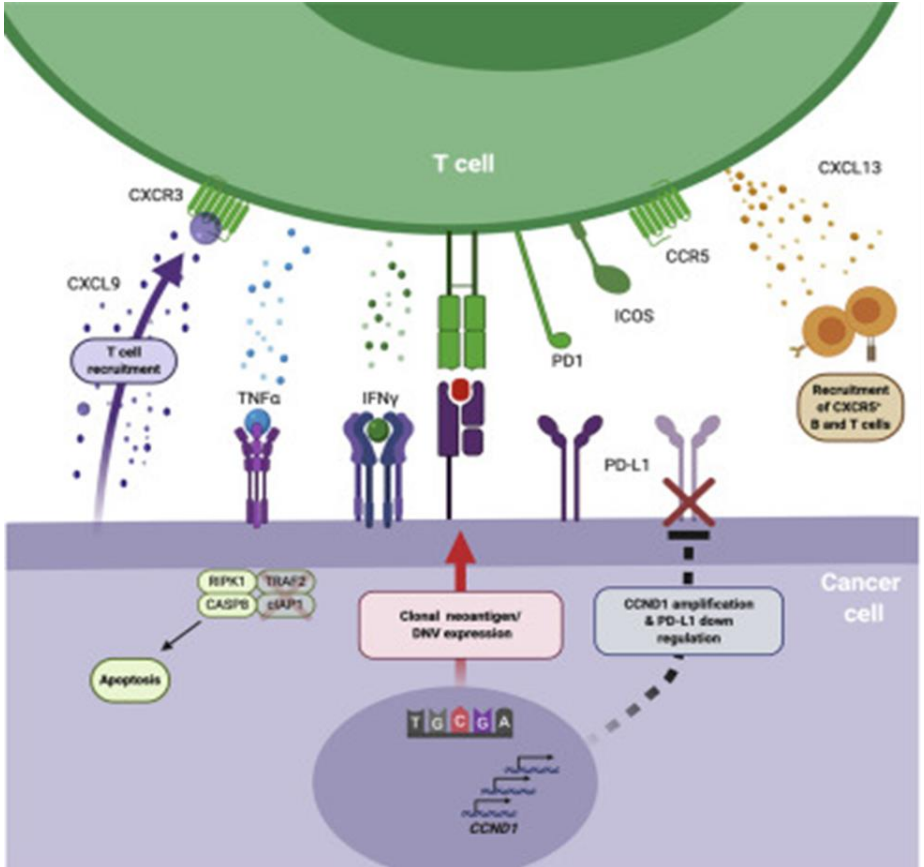
https://biit.cs.ut.ee/gprofiler/gost

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
CellPress

Article

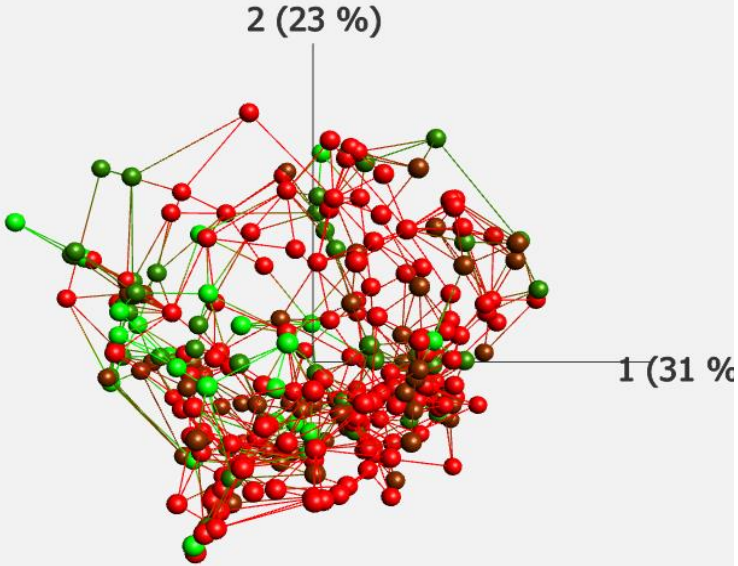
Meta-analysis of tumor- and T cell-intrinsic mechanisms of sensitization to checkpoint inhibition

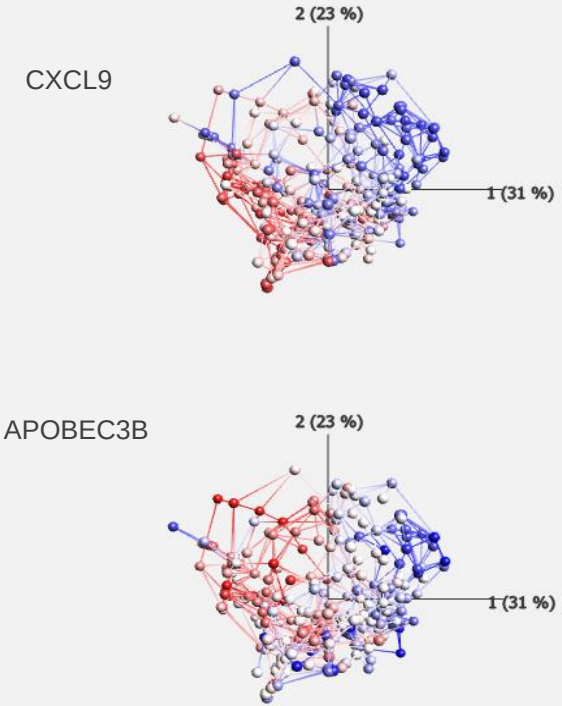
Kevin Litchfield [1, 3, 13], James L. Reading [2, 3, 13], Clare Puttick [1, 13], Krupa Thakkar [1, 3], Chris Abbosh [3], Robert Bentham [3], Thomas B.K. Watkins [1], Rachel Rosenthal [1], Dhruva Biswas [1], Andrew Rowan [1], Emilia Lim [1], Maise Al Bakir [1], Virginia Turati [4], José Afonso Guerra-Assunção [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:



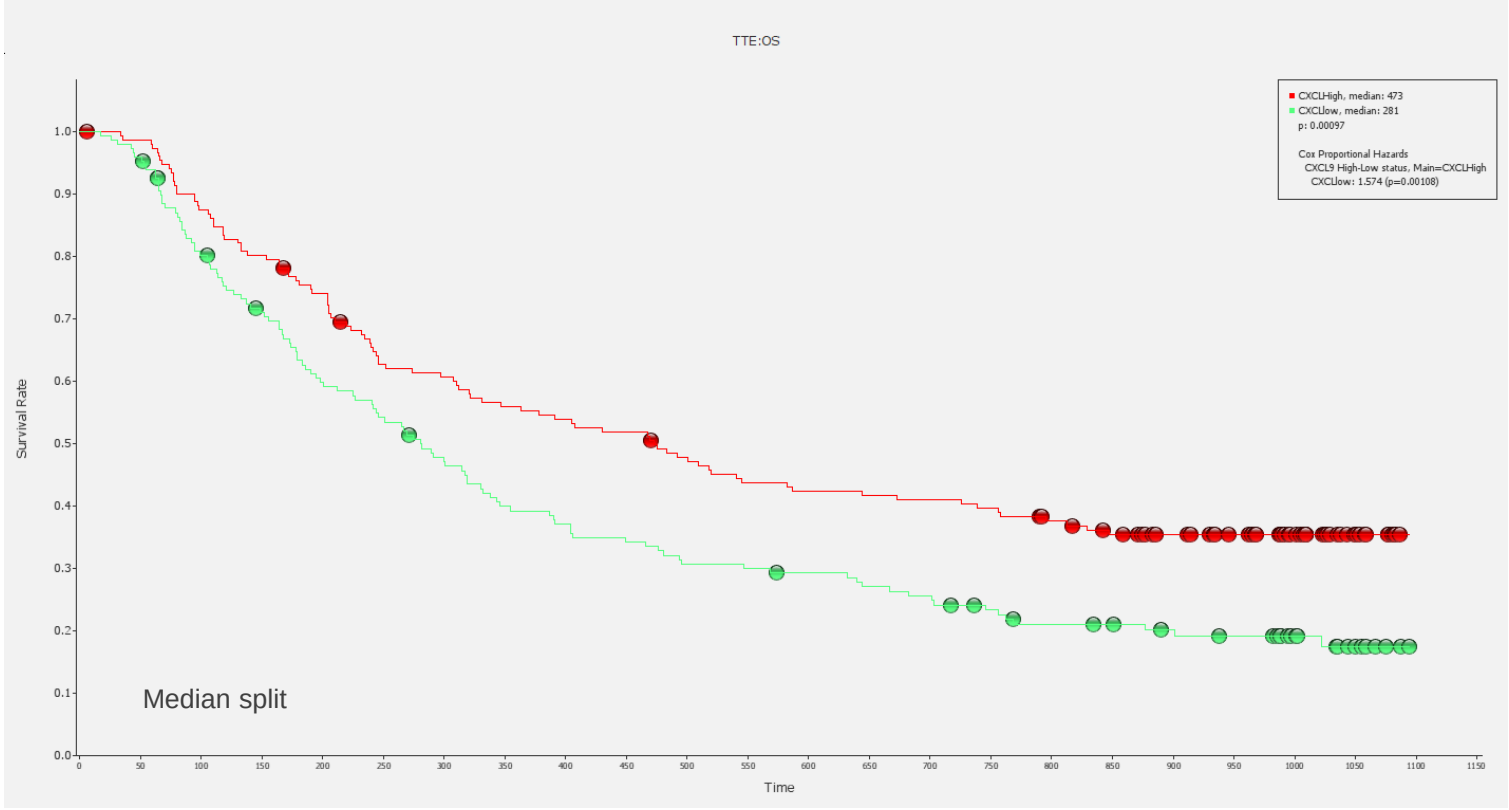


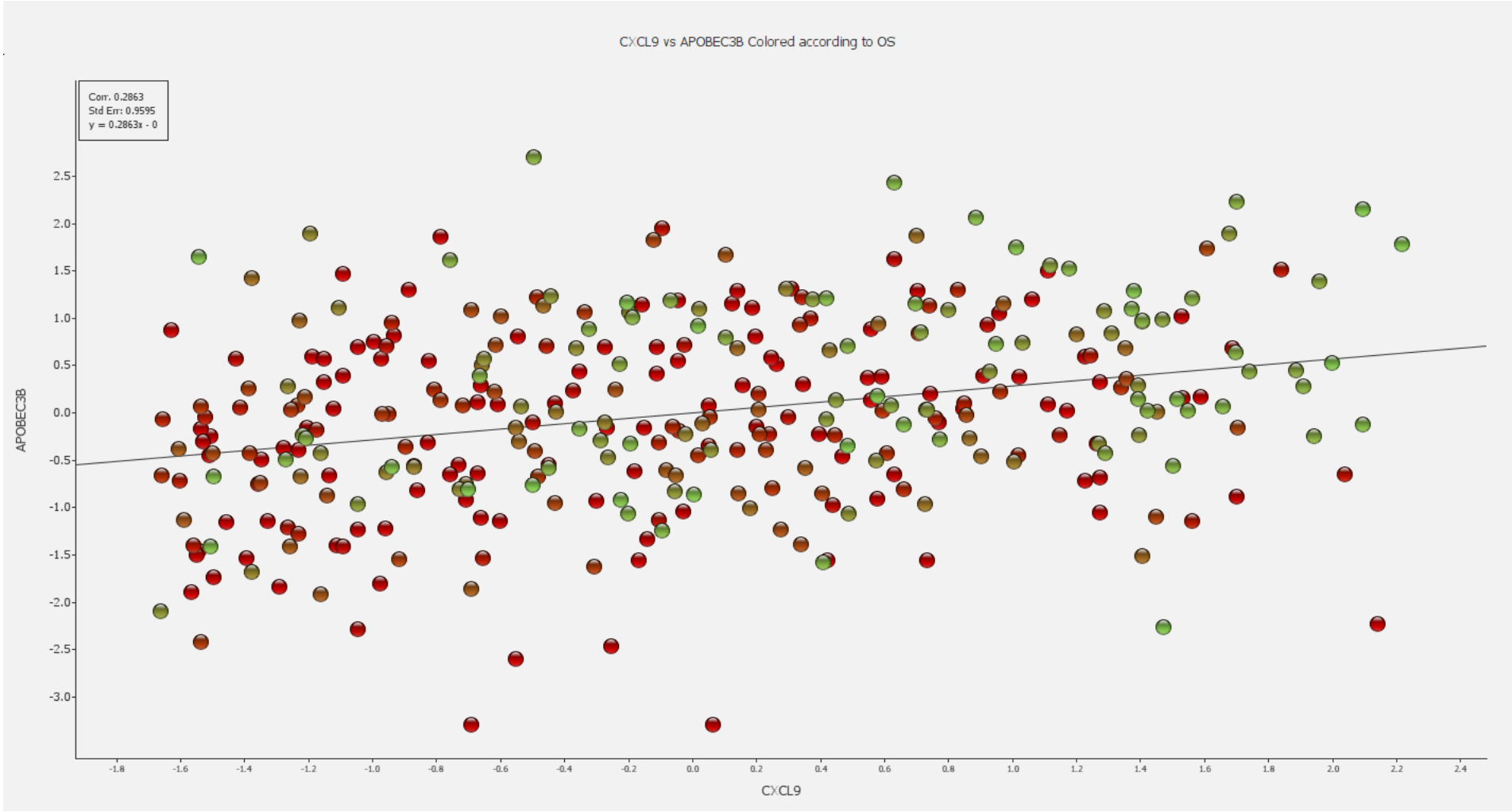
Looking to complement the CXCL9 signature, we find a statistically significant APOBEC signature

- *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.*

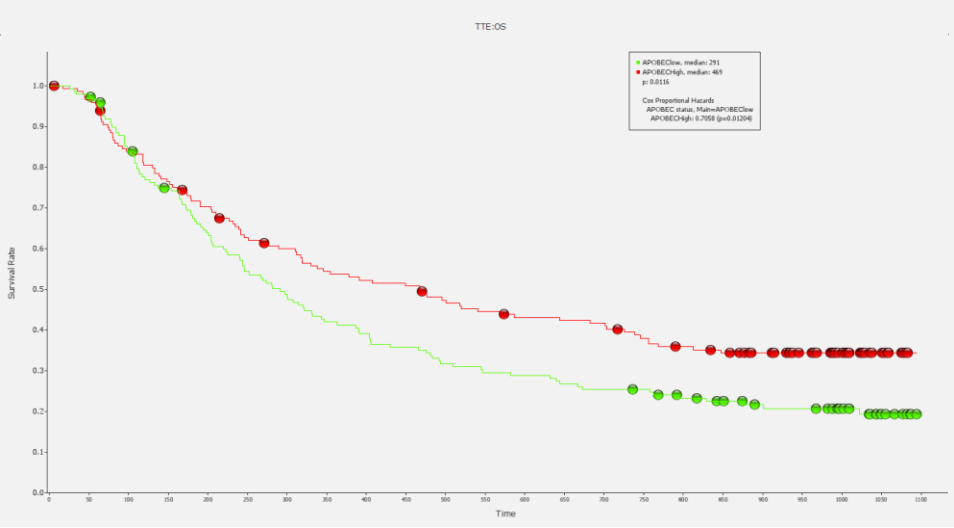
- *They orchestrate a wide array of genomic and epigenomic modifications, thereby affecting various cellular functions positively or negatively, including immune editing, viral and retroelement restriction, DNA damage responses, DNA demethylation, gene expression, and tissue homeostasis.*

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

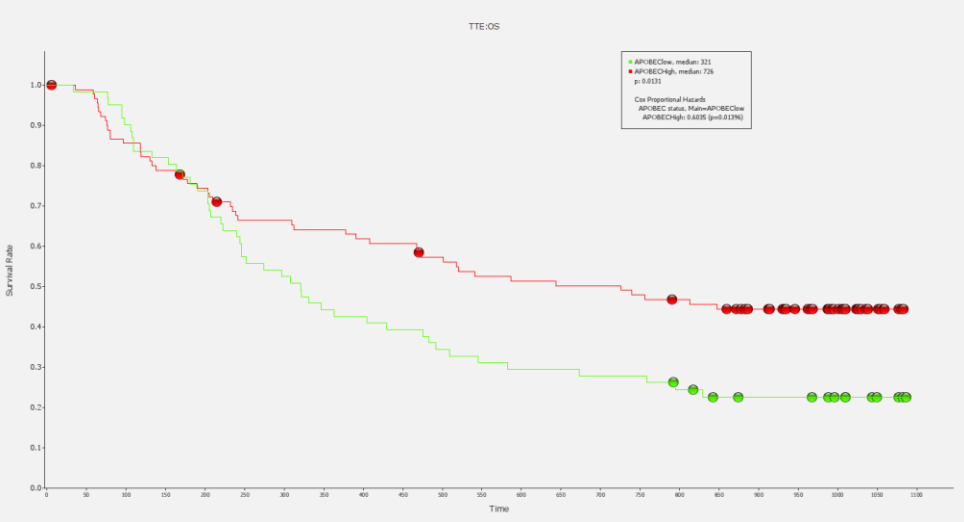



CXCL9 vs APOBEC3B Colored according to OS
Corr. 0.2863
Std Err: 0.9595
y = 0.2863x - 0
APOBEC3B
CXCL9
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-1.8
-1.6
-1.4
-1.2
-1.0
-0.8
-0.6
-0.4
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4

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)

European Journal of Cancer 148 (2021) 181–189

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

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

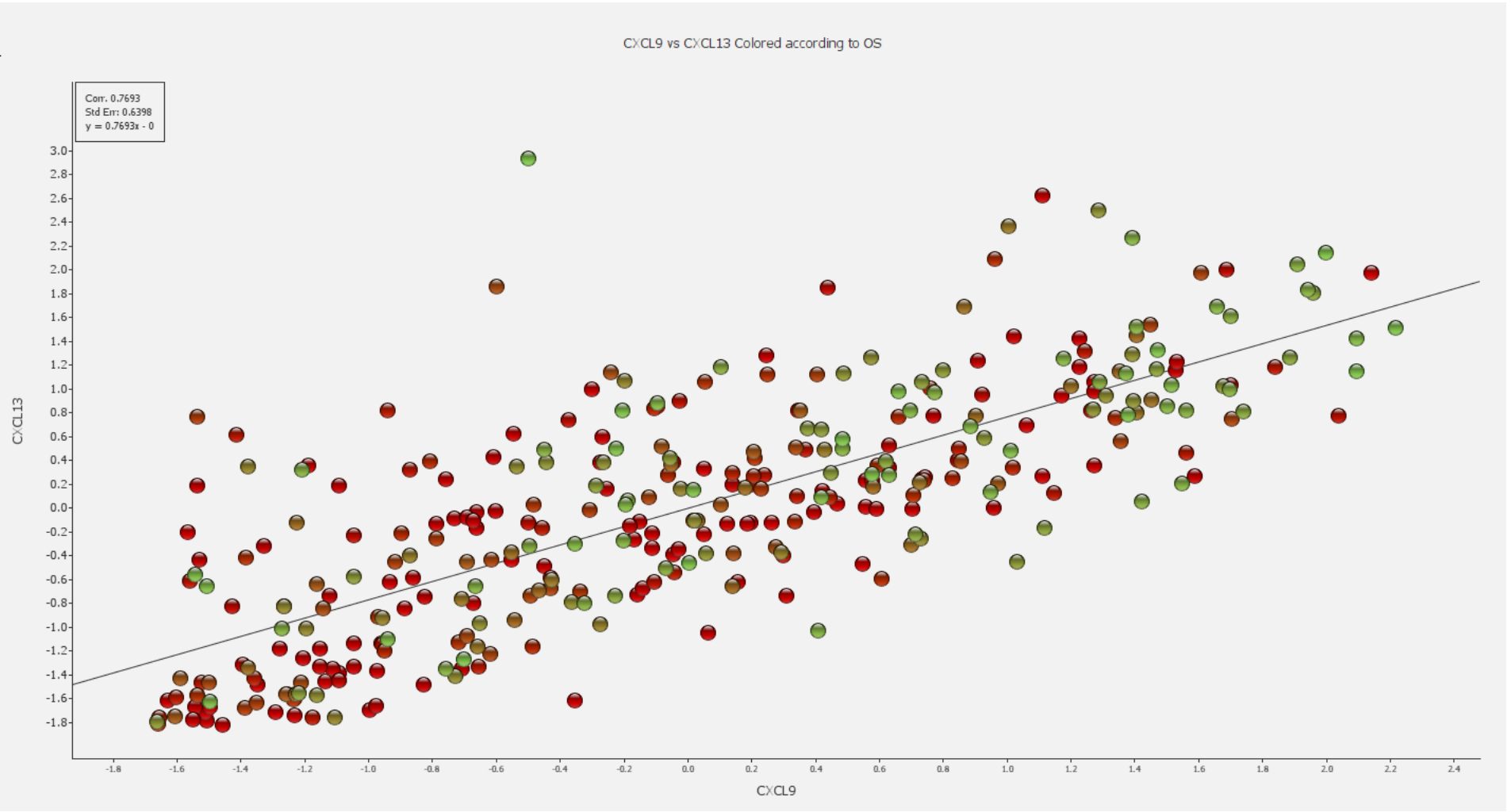
Clarice S. Groeneveld [a,b,1], Jacqueline Fontugne [b,c,1], Luc Cabel [b], Isabelle Bernard-Pierrot [b], François Radvanyi [b], Yves Allory [b,c,2], Aurélien de Reyniès [a,*,2]

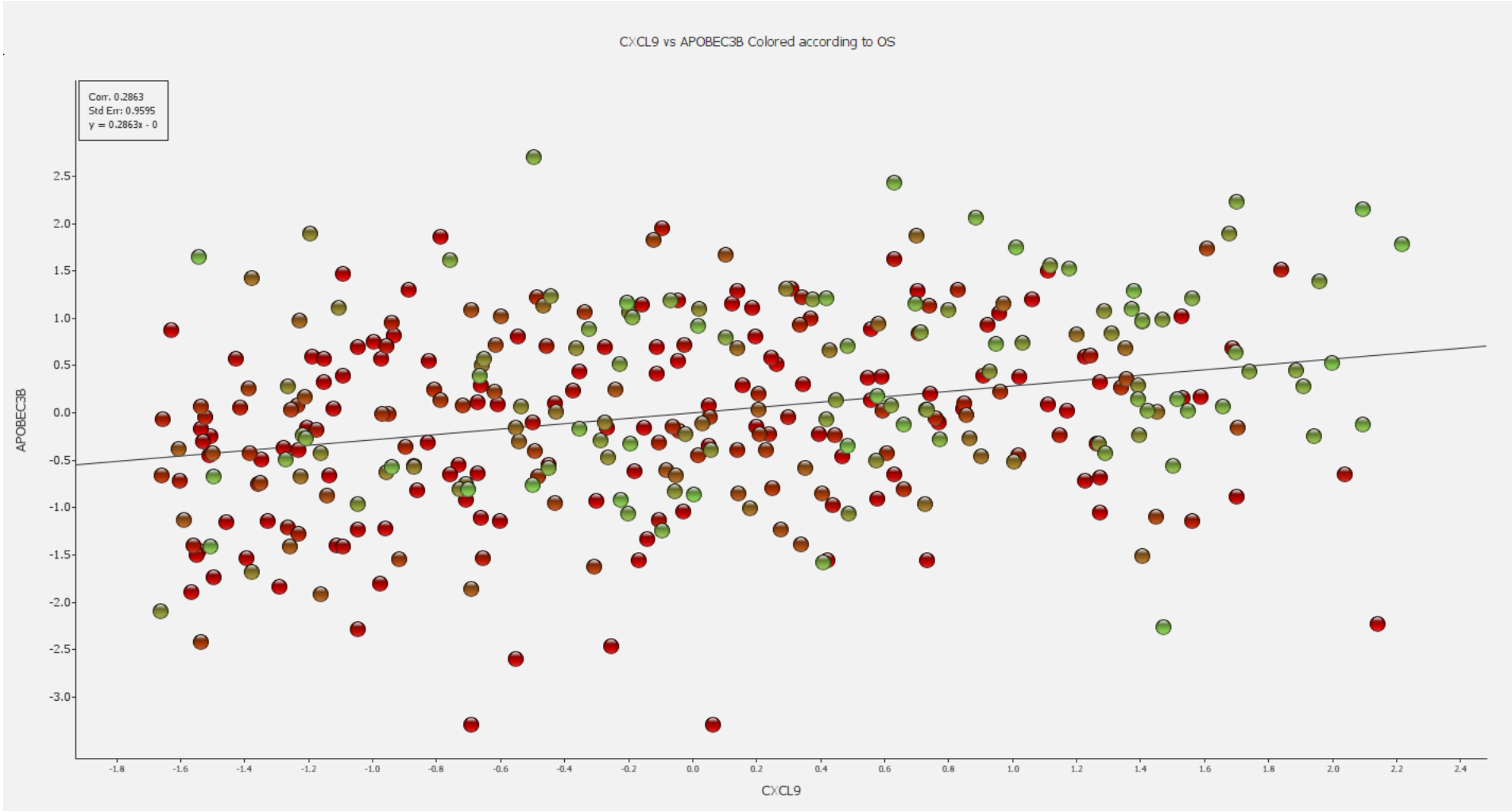
Response to immunotherapy in soft-tissue sarcoma, melanoma and renal cell carcinoma have been recently linked to the presence of tertiary lymphoid structures (TLS) in the tumour. TLS are organised aggregates of T, B and dendritic cells, participating in adaptive antitumor immune response. The chemokine 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 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 Z 0.8, 95% CI [0.68e0.94]) and objective response ($p < 0.0001$) in patients treated with ICI.


CXCL9 vs CXCL13 Colored according to OS
Corr. 0.7693
Std Err: 0.6398
y = 0.7693x - 0
CXCL13
CXCL9
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
-1.8
-1.8
-1.6
-1.4
-1.2
-1.0
-0.8
-0.6
-0.4
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4


CXCL9 vs APOBEC3B Colored according to OS
Corr. 0.2863
Std Err: 0.9595
y = 0.2863x - 0
APOBEC3B
CXCL9
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-1.8
-1.6
-1.4
-1.2
-1.0
-0.8
-0.6
-0.4
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4

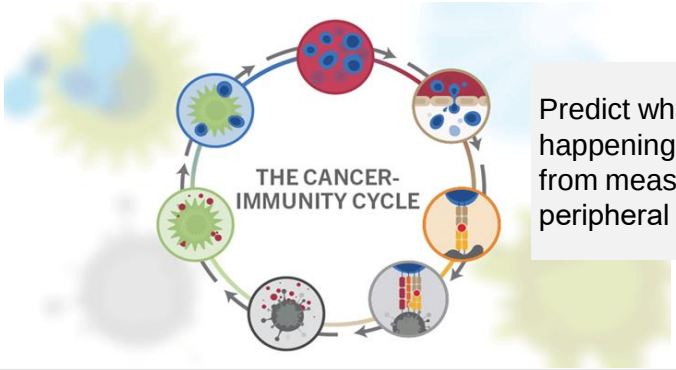
How do we gain future knowledge around cancer immunity?

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
- ….

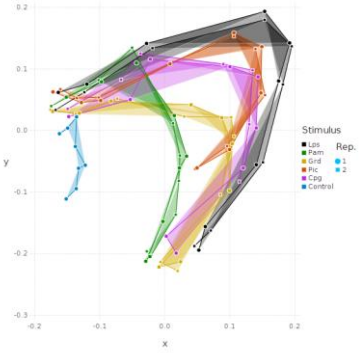


Predict what is happening in the TME from measurements in peripheral blood…

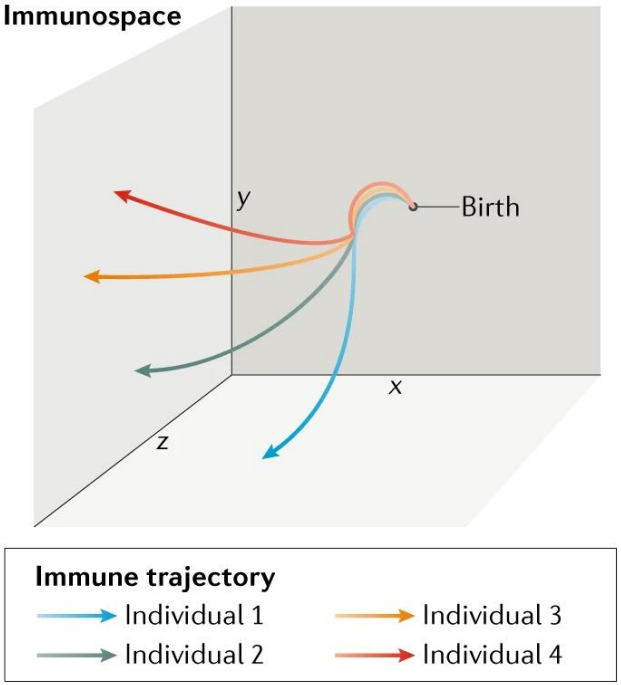
Time Series Data Sources:

- 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.

Petter Brodin
Nature Reviews | Immunology volume 19 | February 2019 | 87