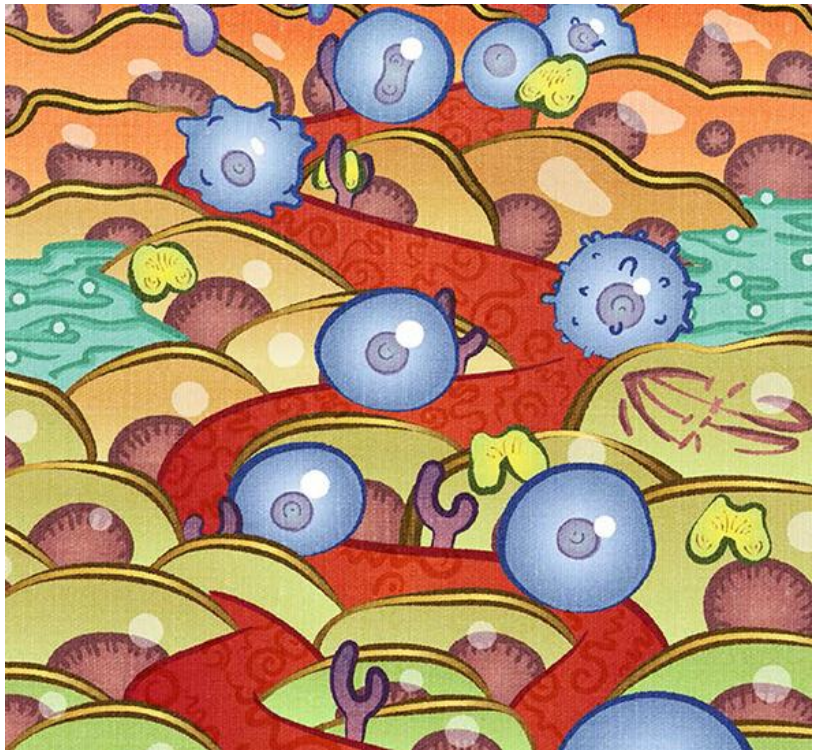
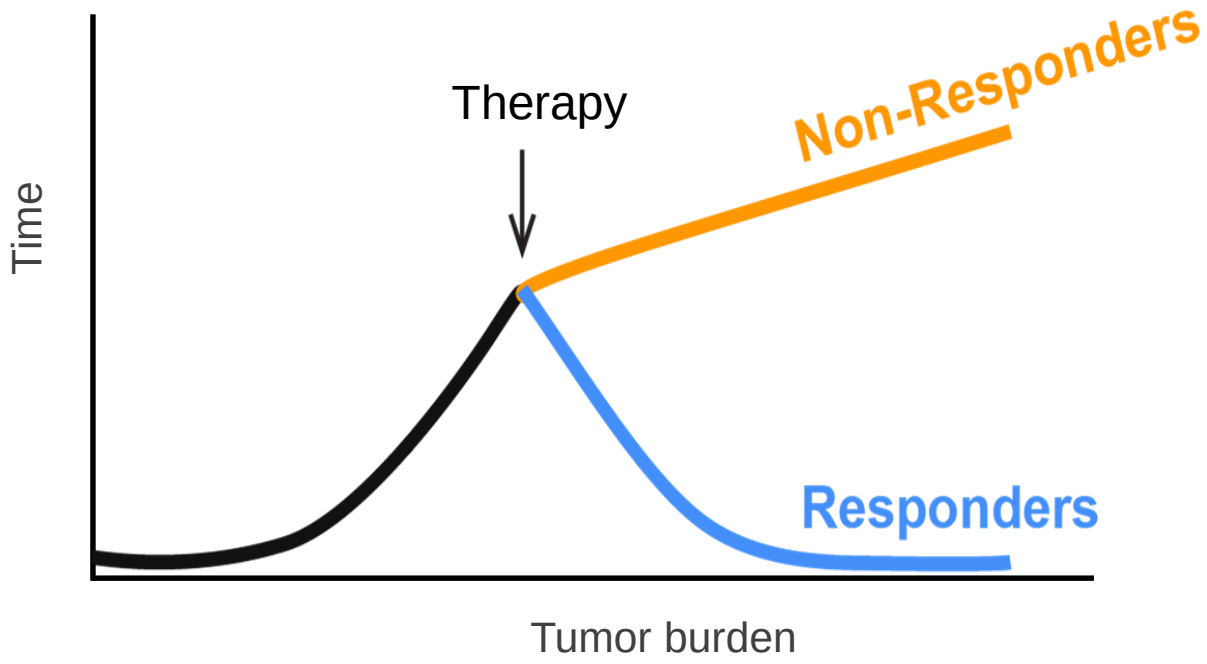
Data Driven Approaches for Modeling Response and Resistance



Dana Pe'er
Sloan Kettering Institute

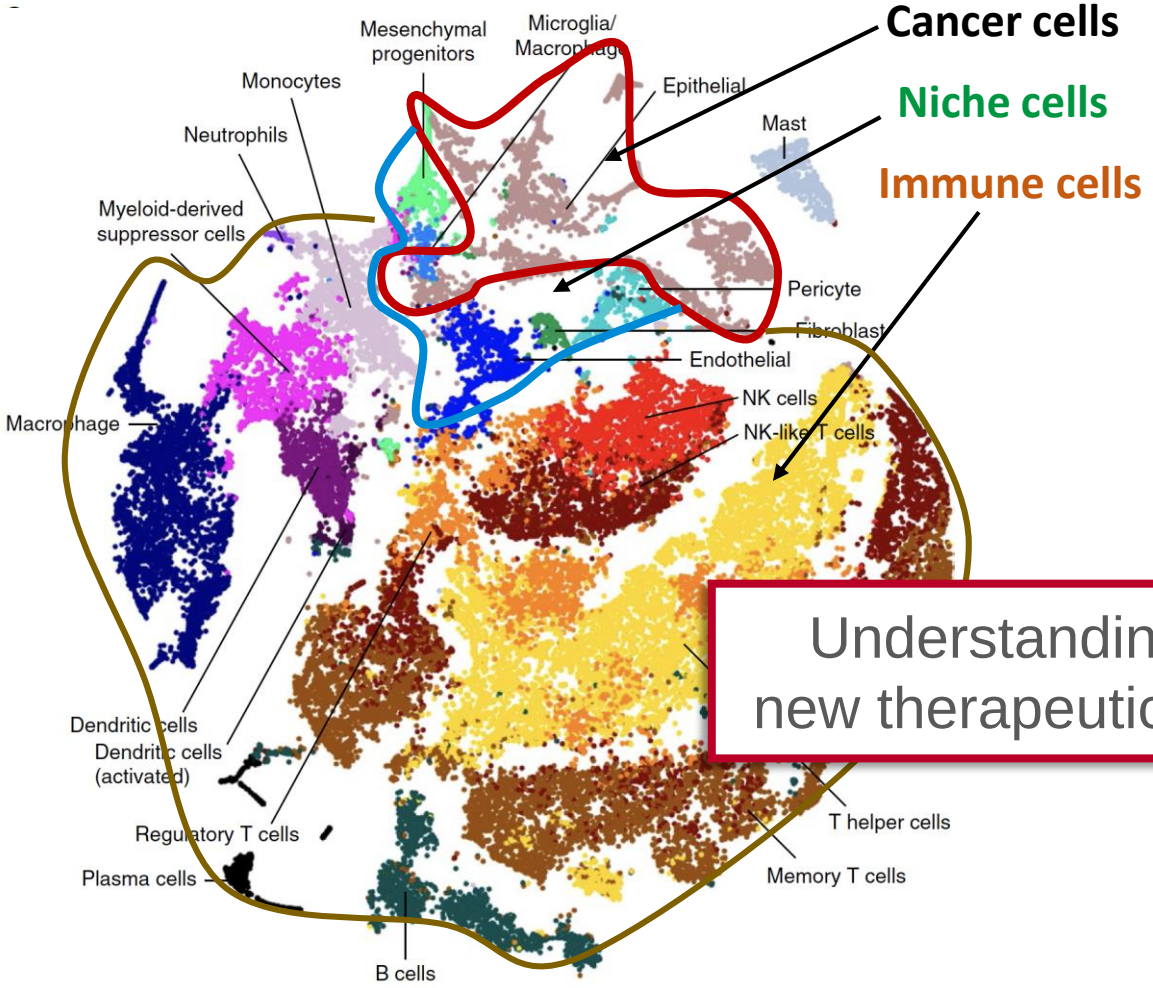
Memorial Sloan Kettering Cancer Center

The challenge

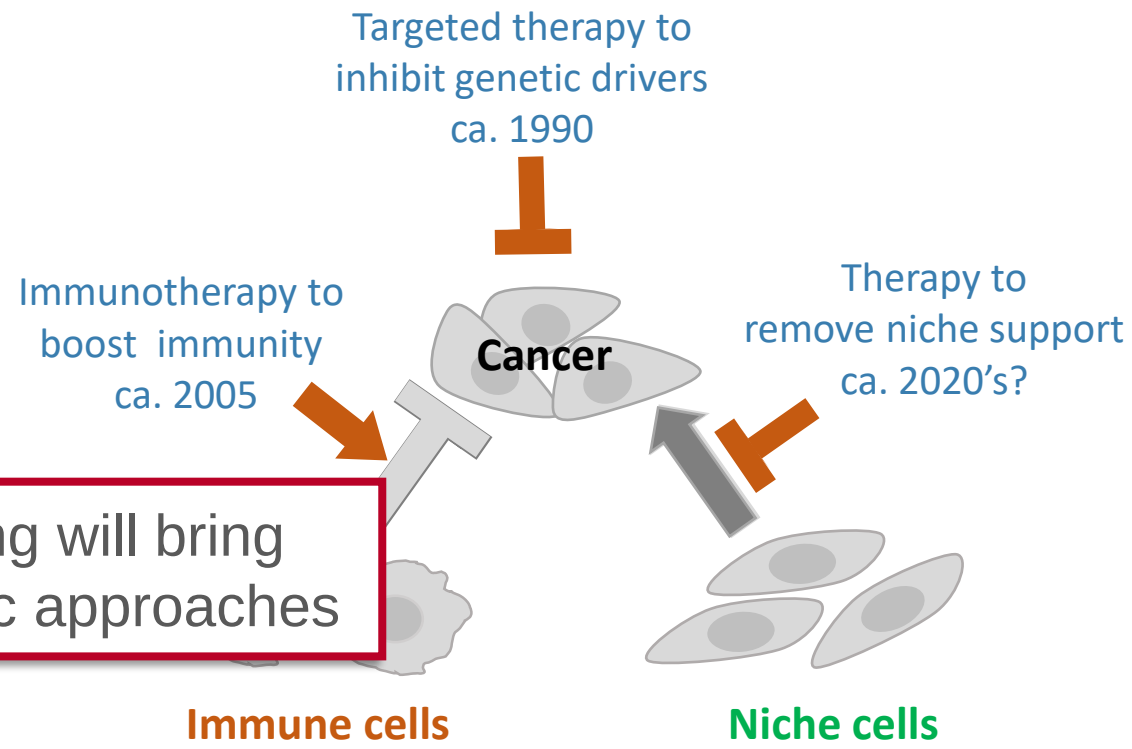


- What differs between responders and non-responders?
- Can we find therapeutic approaches for the non-responders?
- Molecular data at single-cell resolution can help

Single-cell sequencing characterizes the TME



Cell composition of the tumor microenvironment (TME) of metastatic lung cancer

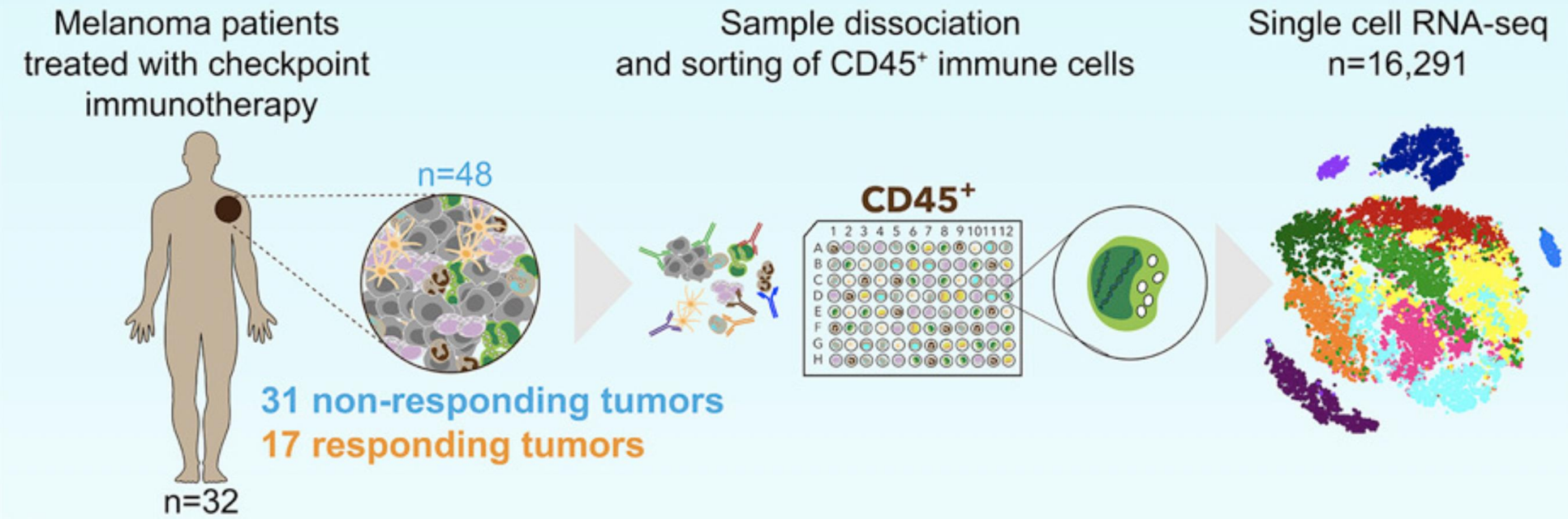


Understanding will bring new therapeutic approaches

with Joan Massagué Lab

Laughney et al. *Nat Med* 2019

T-cell states are associated with ICT response

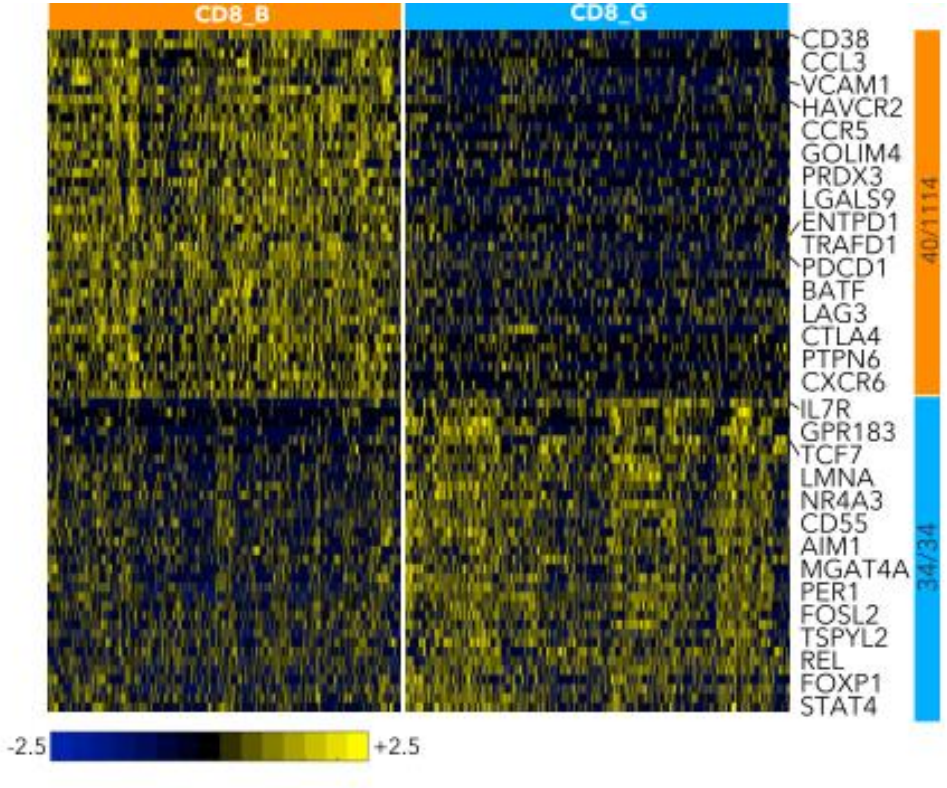


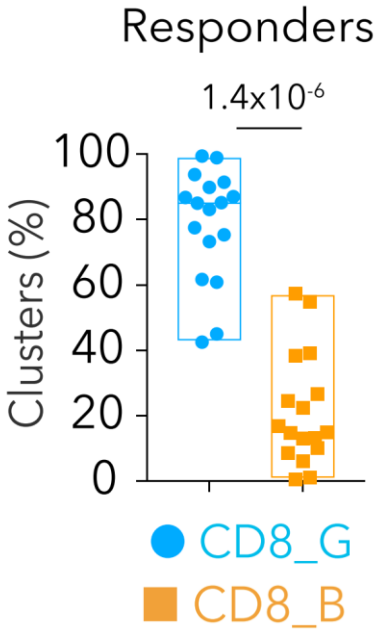
Response to immune checkpoint therapy in melanoma

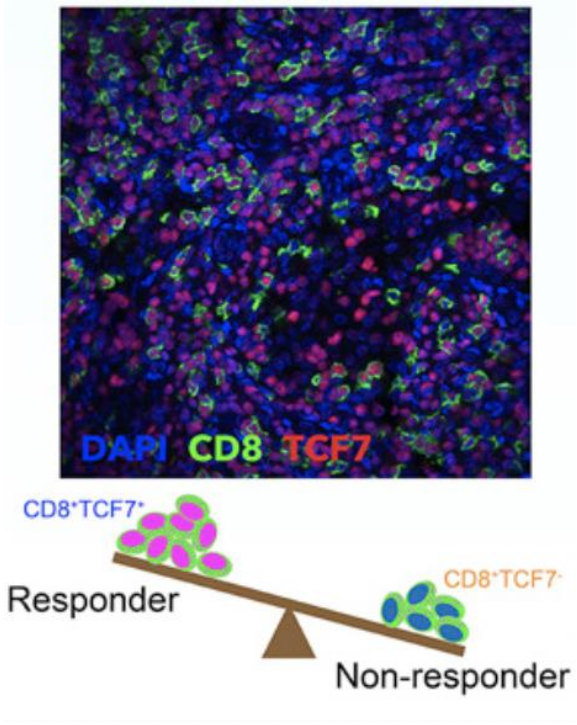
Nir Hacohen Lab

Sade-Feldman et al. *Cell* 2018

Genes that predict ICT response







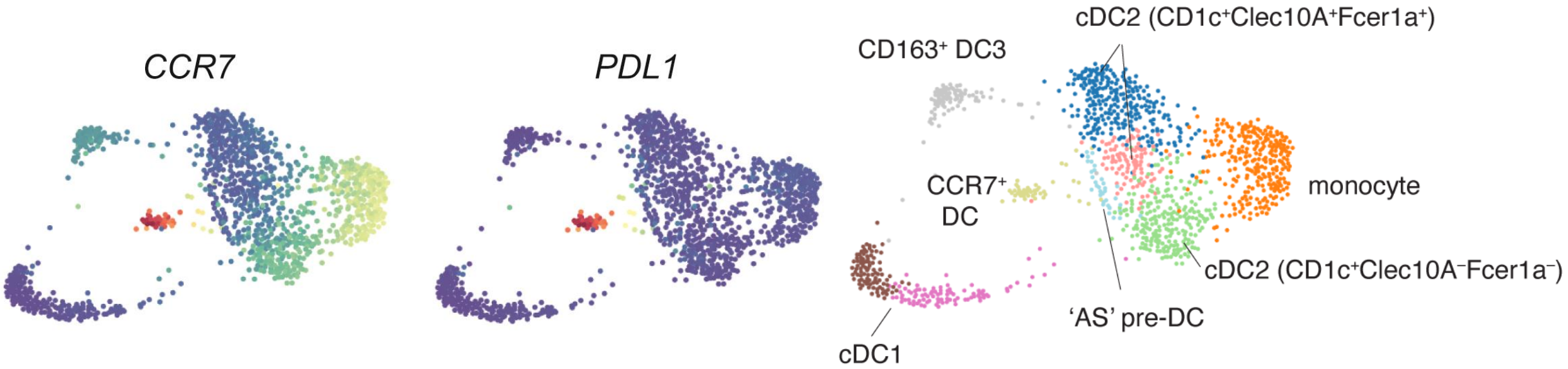
TCF7⁺ CD8⁺ T-cell frequency in tumor tissue predicts better response and survival

- scRNA-seq identifies T-cell gene programs corresponding to responders and non-responders
- Approach is **genome-wide and unbiased**

Nir Hacohen Lab

Sade-Feldman et al. *Cell* 2018

Novel dendritic cell phenotypes play a role in ICT



scRNA-seq of sorted clinical melanoma dendritic cells

→ **rare populations matter**

Discovered and characterized a **new dendritic cell subset**

nature cancer
ARTICLES
https://doi.org/10.1038/s43018-020-0075-x
Check for updates

PD-L1 expression by dendritic cells is a key regulator of T-cell immunity in cancer

Soyoung A. Oh[1], Dai-Chen Wu[1,5], Jeanne Cheung[1], Armando Navarro[1], Huizhong Xiong[1], Rafael Cubas[1], Klara Totpal[1], Henry Chiu[1], Yan Wu[1], Laetitia Comps-Agrar[1], Andrew M. Leader[2,3,4], Miriam Merad[2,3,4], Merone Roose-Germa[1], Soren Warming[1], Minhong Yan[1], Jeong M. Kim[1,6], Sascha Rutz[1] and Ira Mellman[1]✉

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

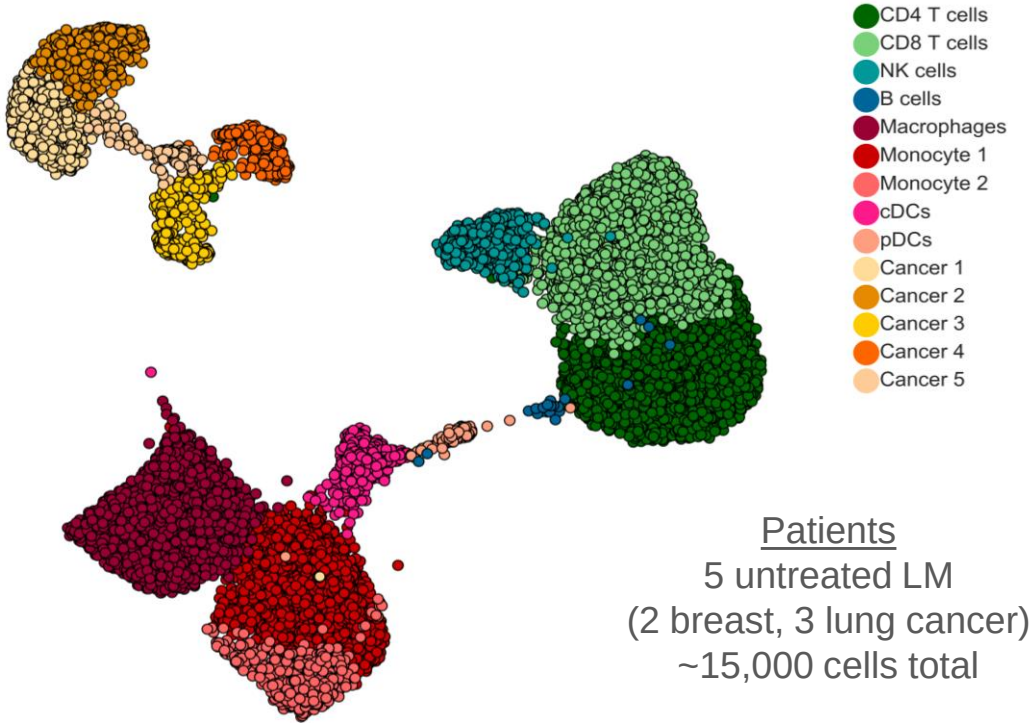
Dendritic cells dictate responses to PD-L1 blockade cancer immunotherapy

Maud Mayoux[1], Andreas Roller[2], Vesna Pulko[1], Stefano Sammicheli[1], Stanford Chen[1], Eva Sum[1], Christian Jost[1], Marieke F. Fransen[3], Regula B. Buser[1], Marcin Kowanetz[4], Karolin Rommel[1], Ines Matos[1], Sara Colombetti[1], Anton Belousov[5], Vaios Karanikas[1], Ferry Ossendorp[3], Priti S. Hegde[4], Daniel S. Chen[6], Pablo Umana[1], Mario Perro[1], Christian Klein[1], Wei Xu[1]*†

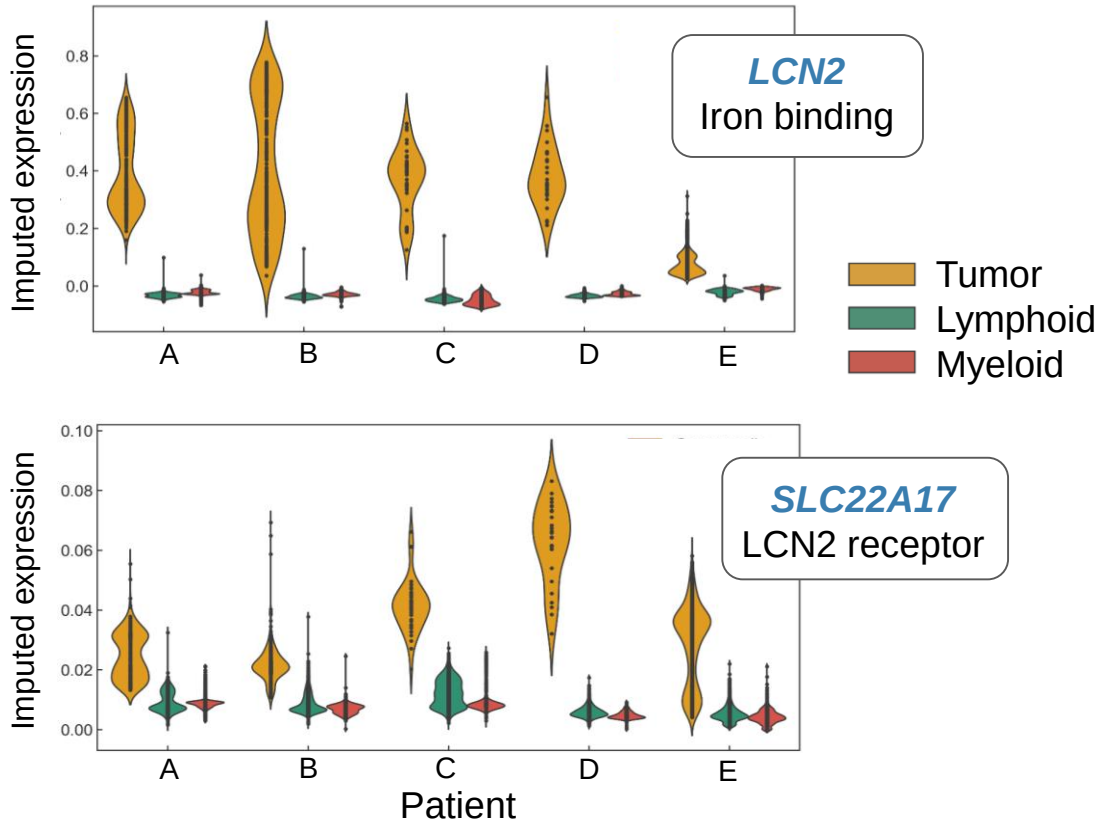
with Sasha Rudensky Lab

Brown, Gudjonson et al. *Cell* 2019

Cancer cells co-opt an immune survival strategy



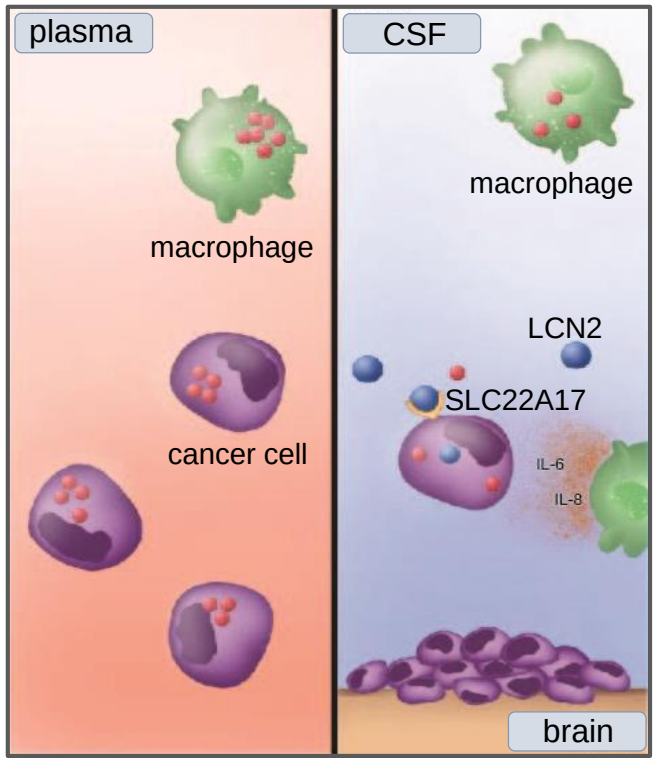
Patients
5 untreated LM
(2 breast, 3 lung cancer)
~15,000 cells total



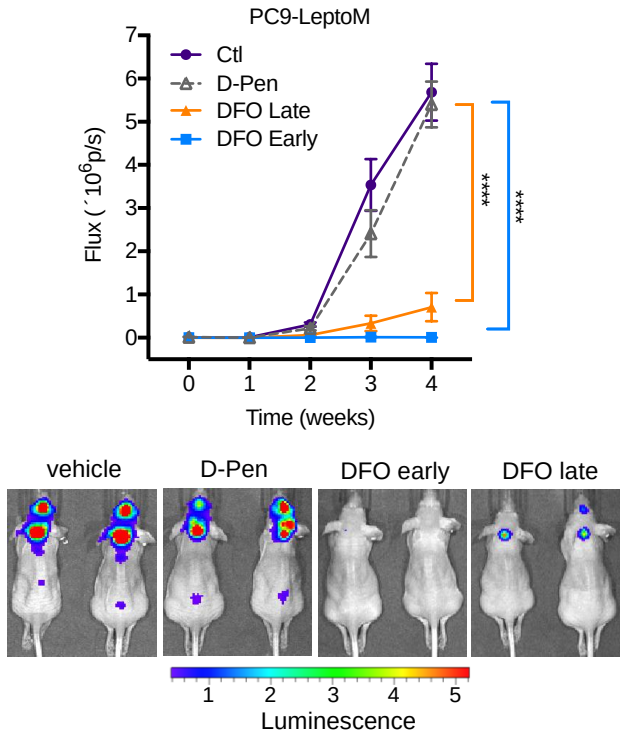
- Leptomeningeal metastases: 3.5 months median survival
- CSF is low in iron, rich in immune cells—**how do cancer cells survive**?
- Cancer cells from all patients overexpress two iron transport genes

with Adrienne Boire Lab
Chi et al. *Science* 2020

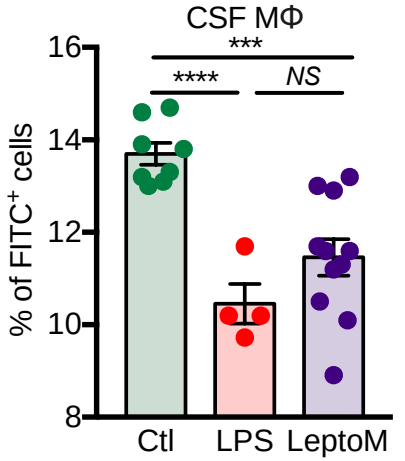
Cancer cells co-opt an immune survival strategy



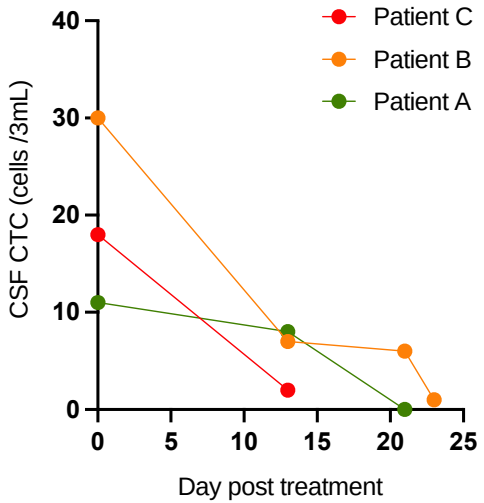
Iron chelation vs. control



Macrophage activity



Phase I trial (ongoing)
(Deferoxamine)



- Iron chelation inhibits cancer cell growth in CSF
- Genome-wide view provided an unexpected mechanism for cancer cell survival and immune suppression: competition for resources
- From **data to clinical trial in 8 months**

with Adrienne Boire Lab
Chi et al. *Science* 2020

Single-cell data is not ‘big data’

Single-cell data feels like ‘big data’, but it is actually ‘complex data’

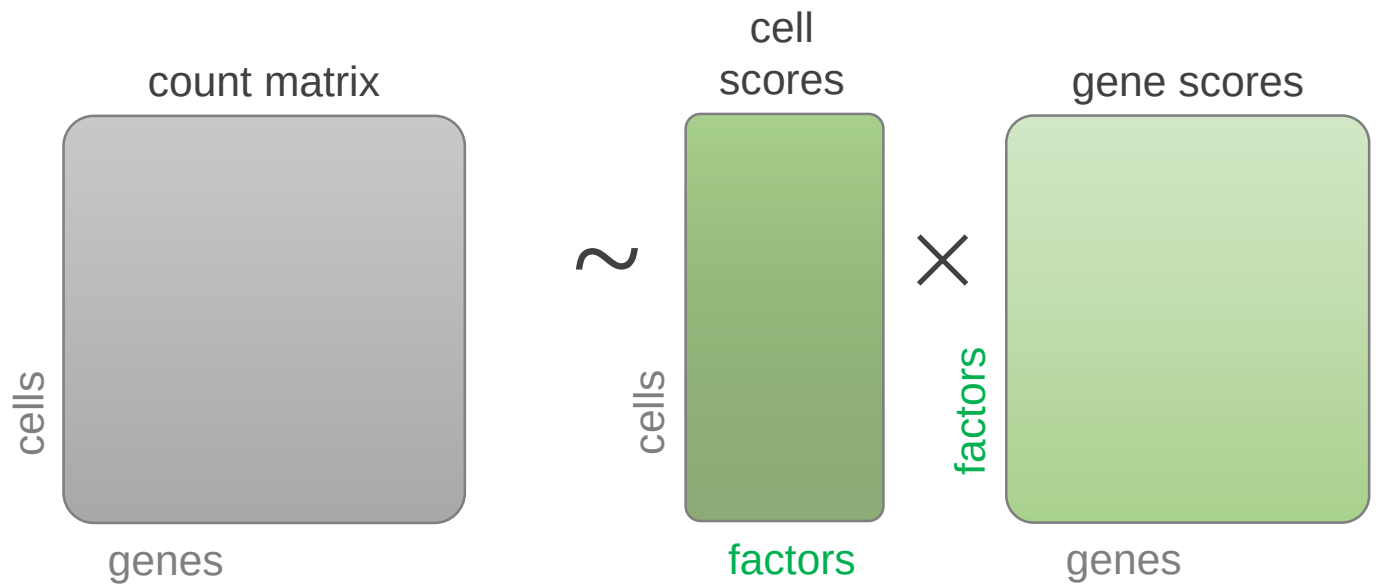
Problem

- Typical dataset is a matrix of 100,000 cells x 20,000 genes (~200 million values)
  - Yet, it is only derived from 10–40 patients, insufficient for most clinical questions
- Clinical trials inherently contain small sample sizes

Solutions

- Meta-analysis of multiple clinical trials
- Integrate single-cell data with large bulk genomics or H&E datasets
- Incorporate prior biological knowledge into the modeling

Factor analysis to characterize gene programs

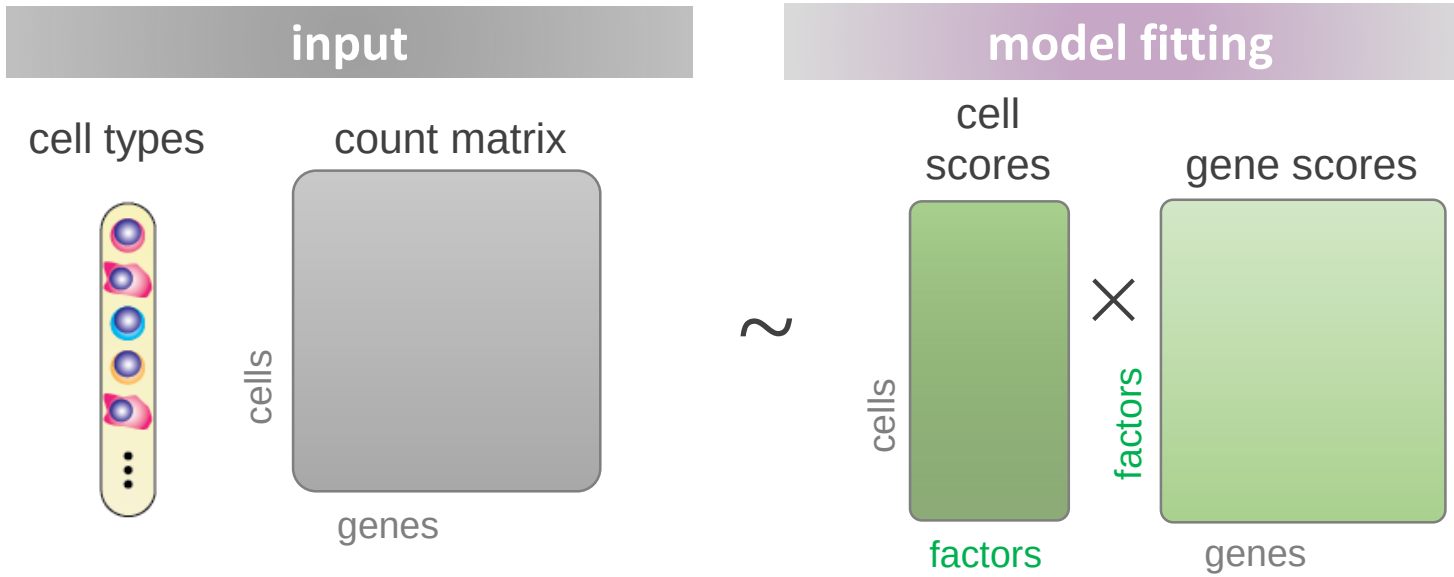


$$\mathbf{x}_i \approx \theta_{i,1}\mathbf{F}_1 + \cdots + \theta_{i,k}\mathbf{F}_k$$

- Goal of factor analysis: **decompose a cellular profile into gene programs**
- This is an unconstrained problem (many ways to slice and dice the matrix)
- Many factors are confounded by cell type or technical noise

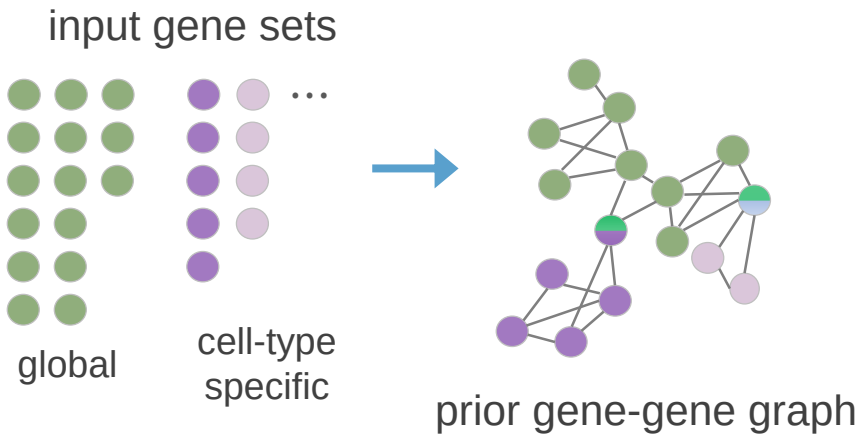
Spectra factor analysis

Spectra: Supervised pathway deconvolution of interpretable gene programs

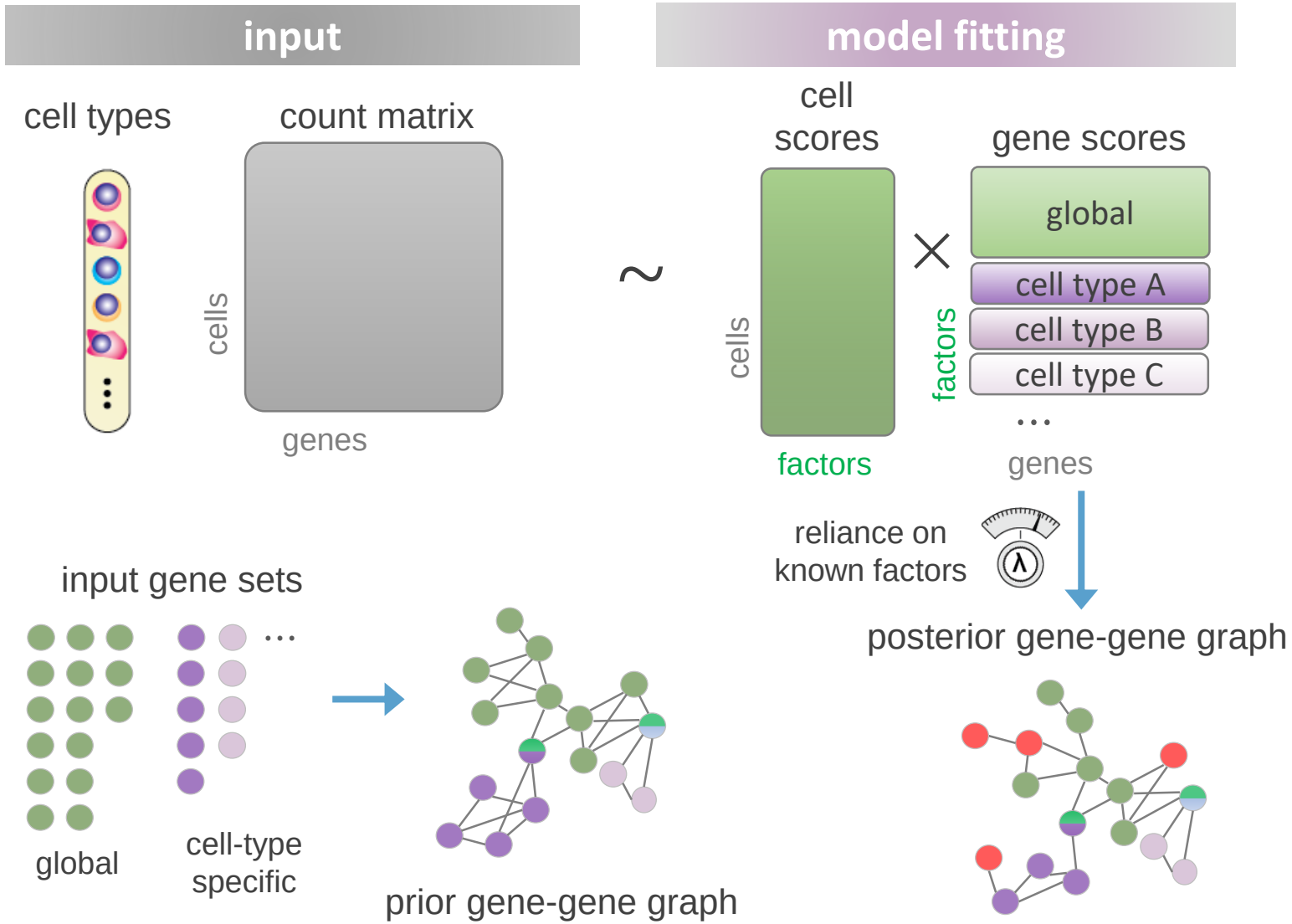


Input: cell-type annotation for each cell

Bias the factorization towards prior gene programs to **generate interpretable programs**



Spectra factor analysis



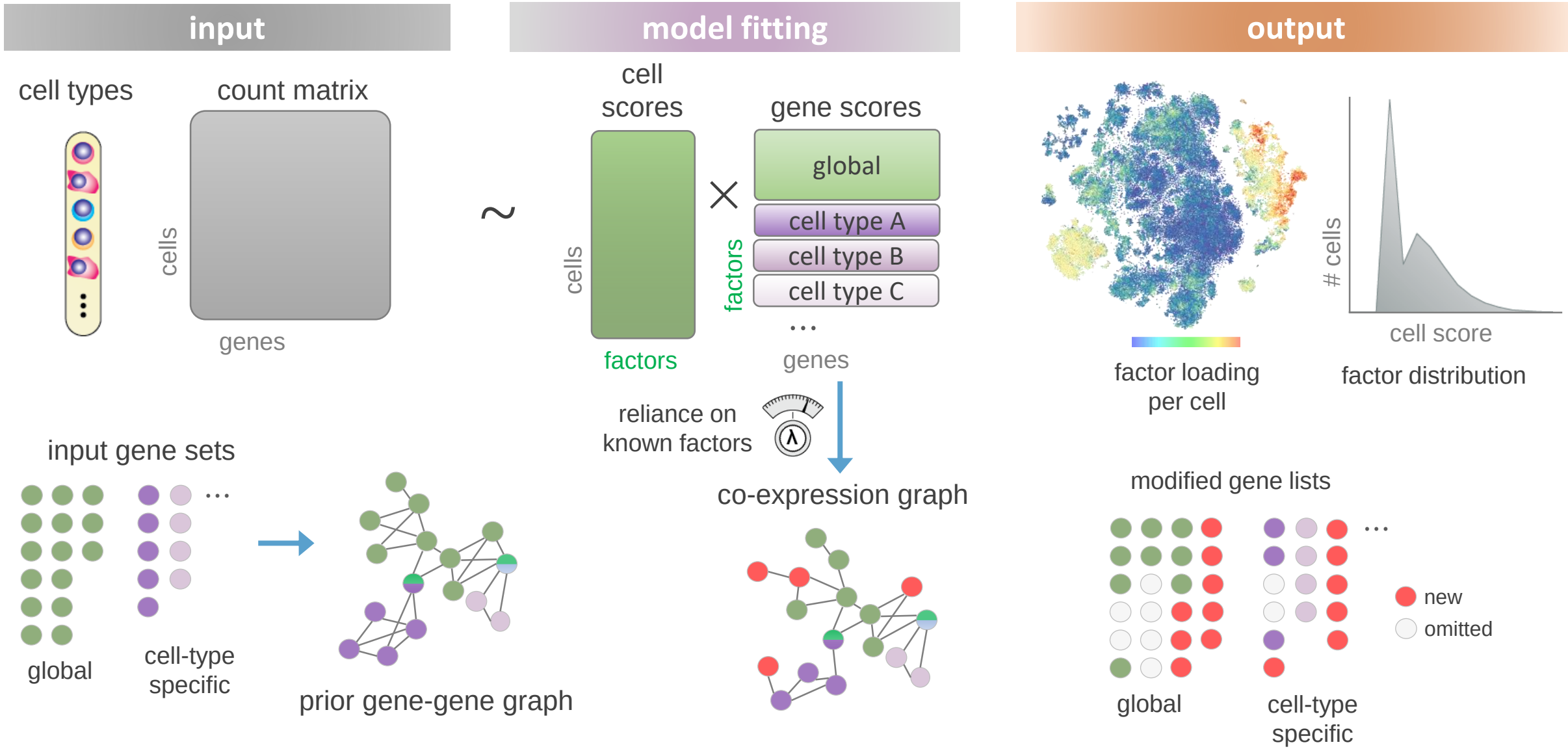
Factors are **scored by**

- how well they match the data
- support for knowledge graph

Factors are **fit to the data by** adding and removing genes

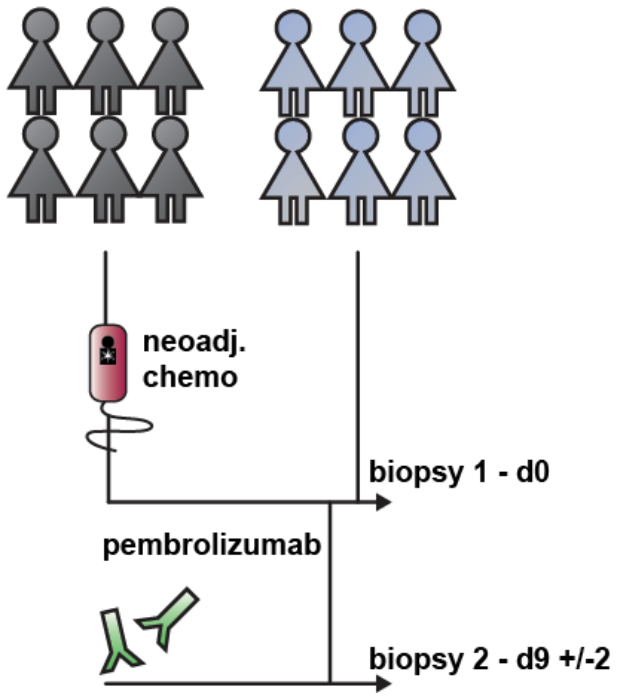
Novel factors can be found by detaching them from the graph

Spectra factor analysis

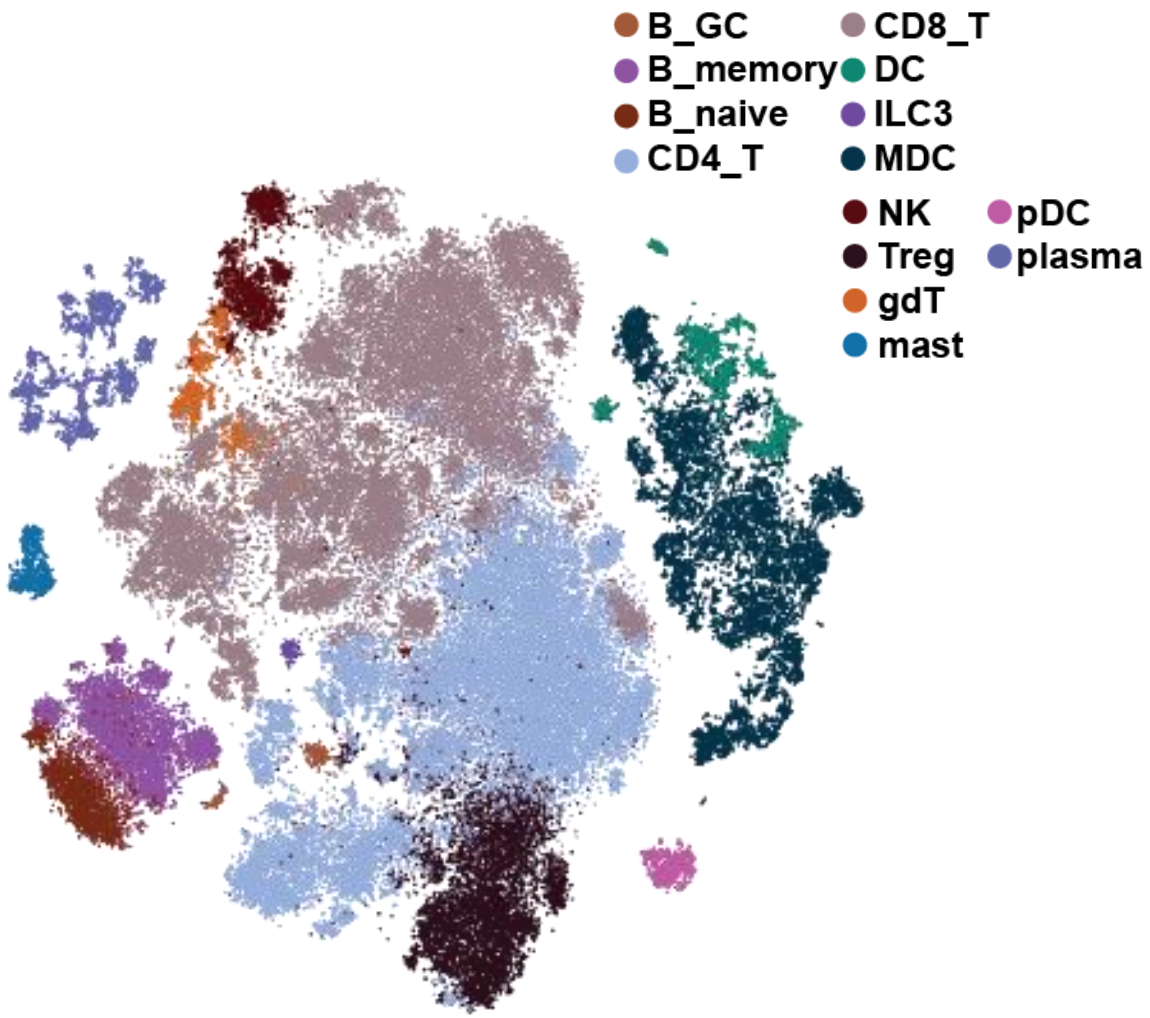


Spectra dissects breast cancer response to immunotherapy

Response to anti-PD-1 treatment in breast cancer



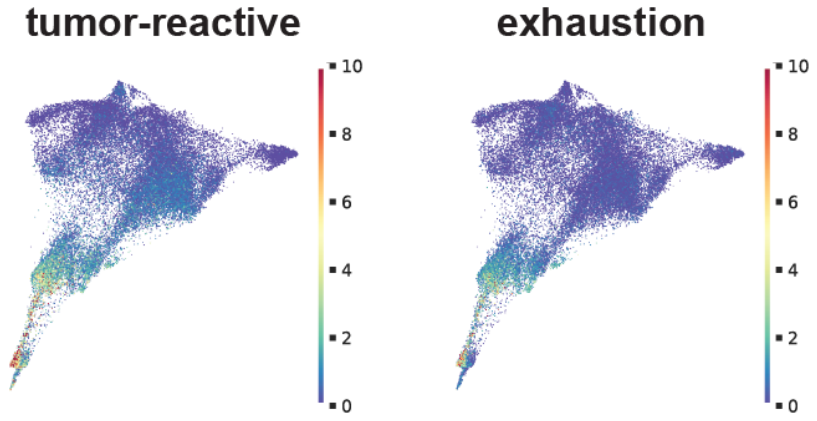
42 BRCA patients (all histologies)
Pre- and on-therapy biopsies (1 cycle anti-PD-1)
scTCR-seq and scRNA-seq

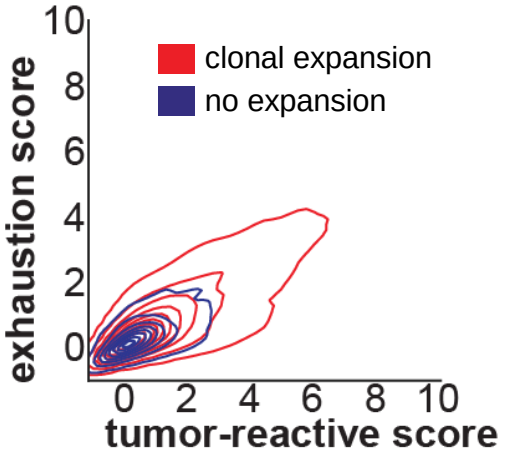


Diether Lambrechts Lab
Bassez, Vos et al. *Nat Med* 2021

Tumor-reactive T cells respond to immunotherapy

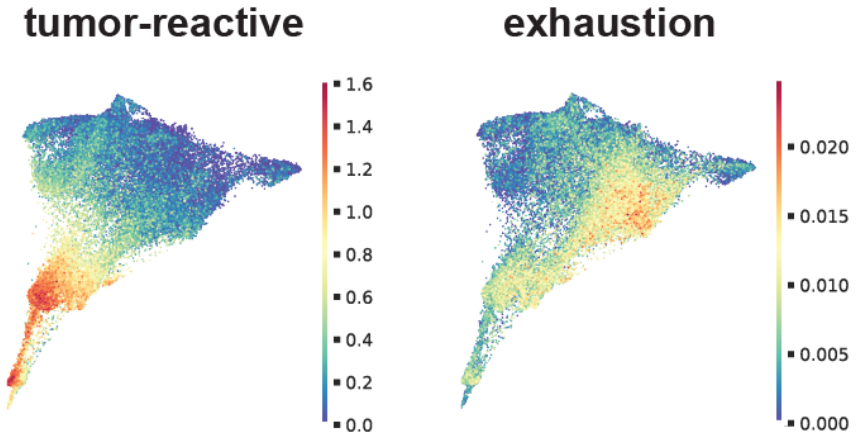
Input gene sets

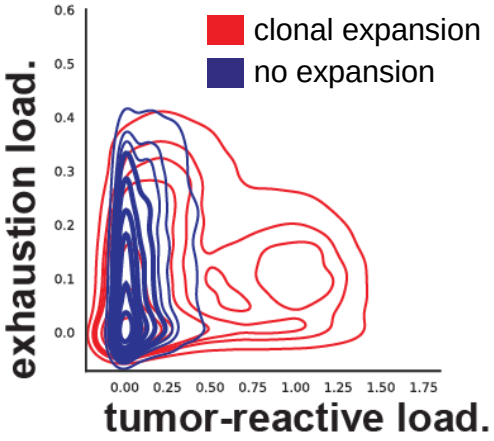


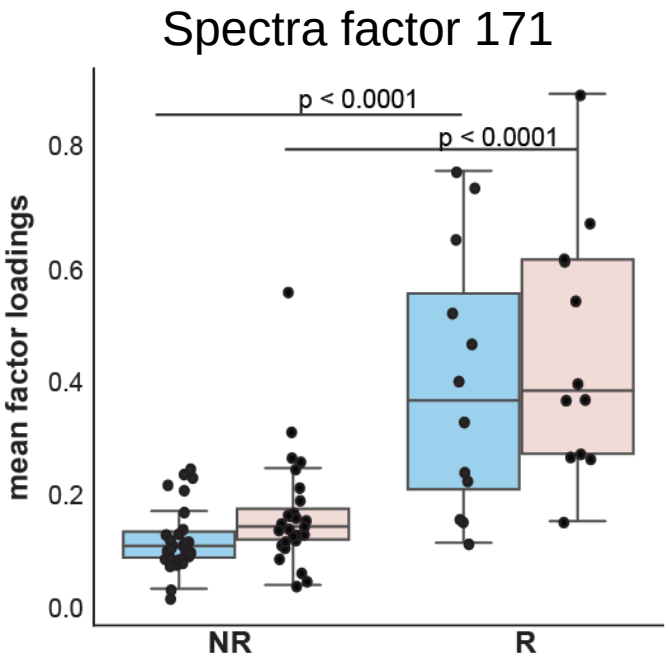


- Tumor-reactive and exhausted gene-sets are highly overlapping and correlated
- Spectra can deconvolve these highly related processes

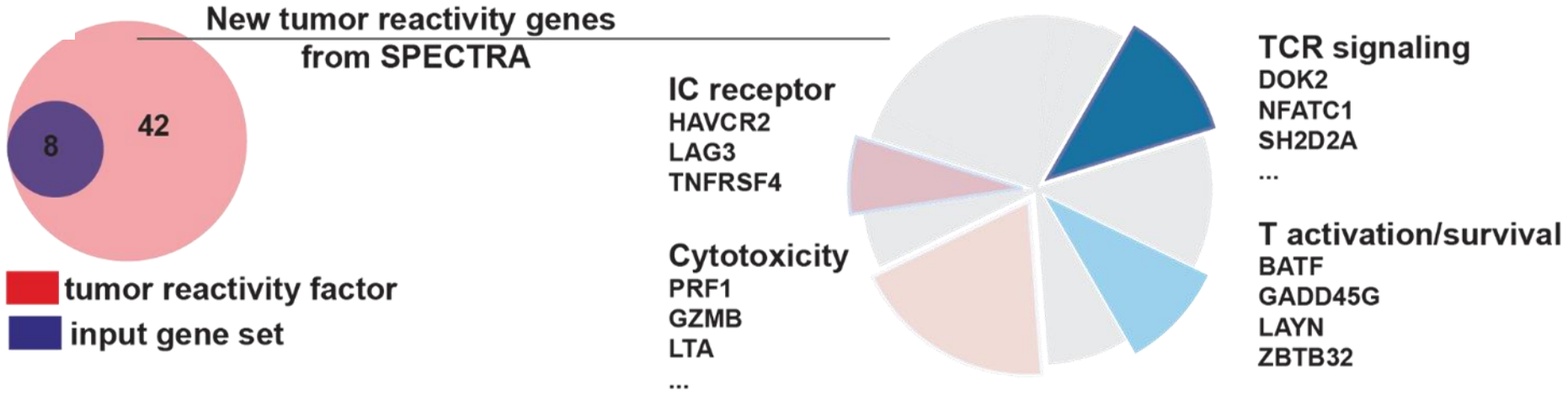
Spectra output (factors)







Spectra adapts the genes to the data



Spectra identifies putative new mediators replicated in a validation dataset

PNAS

Combination OX40 agonism/CTLA-4 blockade with HER2 vaccination reverses T-cell anergy and promotes survival in tumor-bearing mice

Stefanie N. Linch[a], Melissa J. Kasiewicz[a], Michael J. McNamara[a], Ian F. Hilgart-Martiszus[a], Mohammad Farhad[a,b], and William L. Redmond[a,1]

[a]Robert W. Franz Cancer Research Center, Earle A. Chiles Research Institute, Providence Portland Medical Center, Portland, OR 97213; and [b]Cell, Developmental, and Cancer Biology Department, Oregon Health and Science University, Portland, OR 97239

nature immunology ARTICLES
https://doi.org/10.1038/s41590-021-00964-8
Check for updates

BATF and IRF4 cooperate to counter exhaustion in tumor-infiltrating CAR T cells

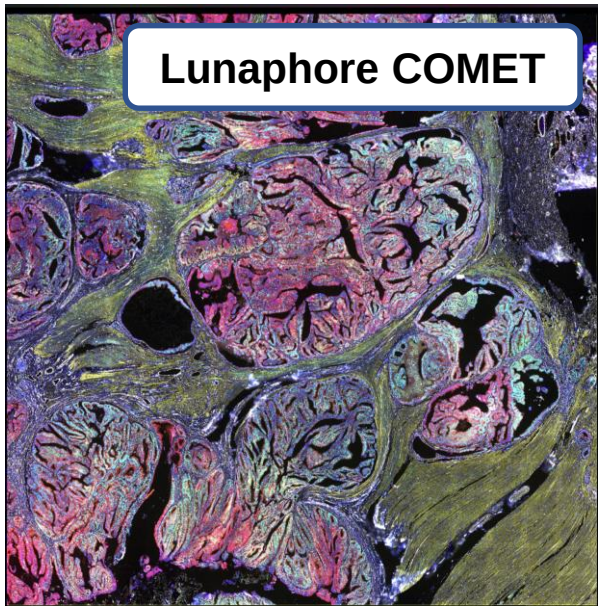
Hyungseok Seo[1,9,11], Edahí González-Avalos[1,2,11], Wade Zhang[1,3], Payal Ramchandani[1,4,9], Chao Yang[1], Chan-Wang J. Lio[1,10], Anjana Rao[1,5,6,7,8] and Patrick G. Hogan[1,7,8]

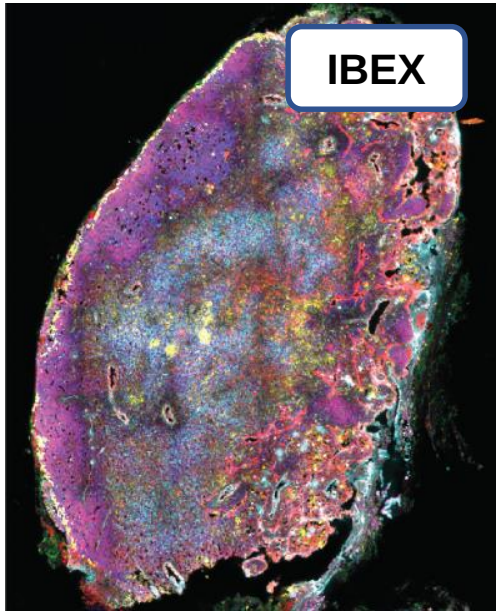
European Journal of Immunology

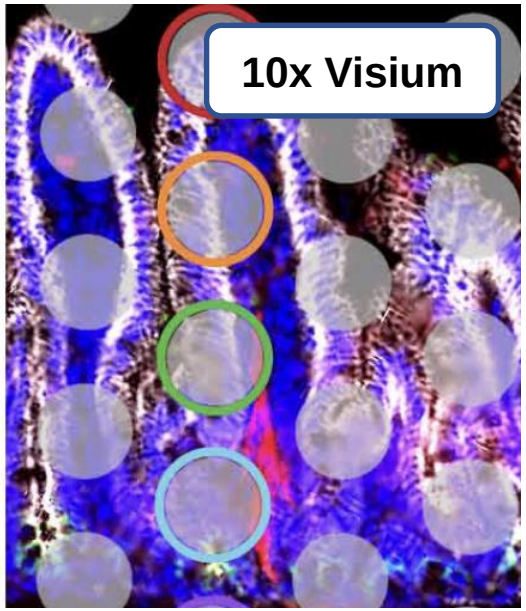
Gadd45b and Gadd45g are important for anti-tumor immune responses

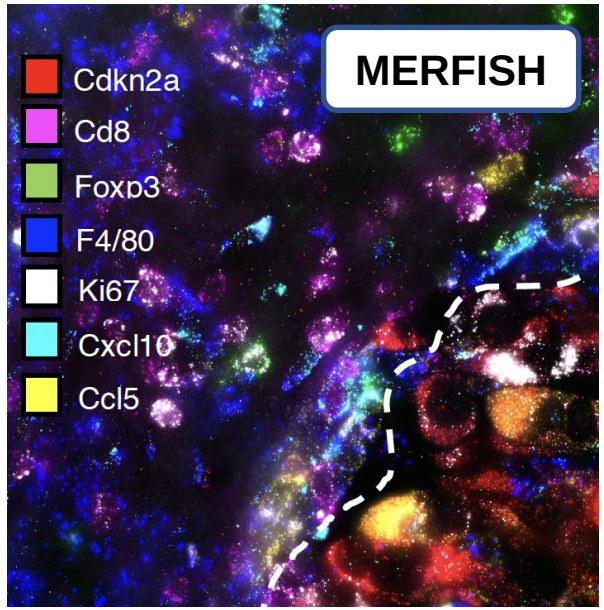
*Songguang Ju[1,2], Yibei Zhu[1,2], Lin Liu[1], Shao Dai[1], Changyou Li[1], Elizabeth Chen[1], Yukai He[3], Xueguang Zhang[*2] and Binfeng Lu[1,4]*

Understanding cells in their tissue context









- Spatial context is needed to understand cell-cell interactions
- New spatial technologies are emerging
- Cell-cell interactions can serve as potent drug targets

What we need to do

- Collect well-designed longitudinal cohorts, including responders and non-responders; profile with single-cell and spatial technologies
- Work in teams of immuno-oncology and computational experts to design new algorithms suited for this data
- Aggregate cohorts (with careful statistics), integrate with other data modalities