OMICS APPLIED TO HOST RESPONSE: METHODS AND GENERAL APPLICATIONS

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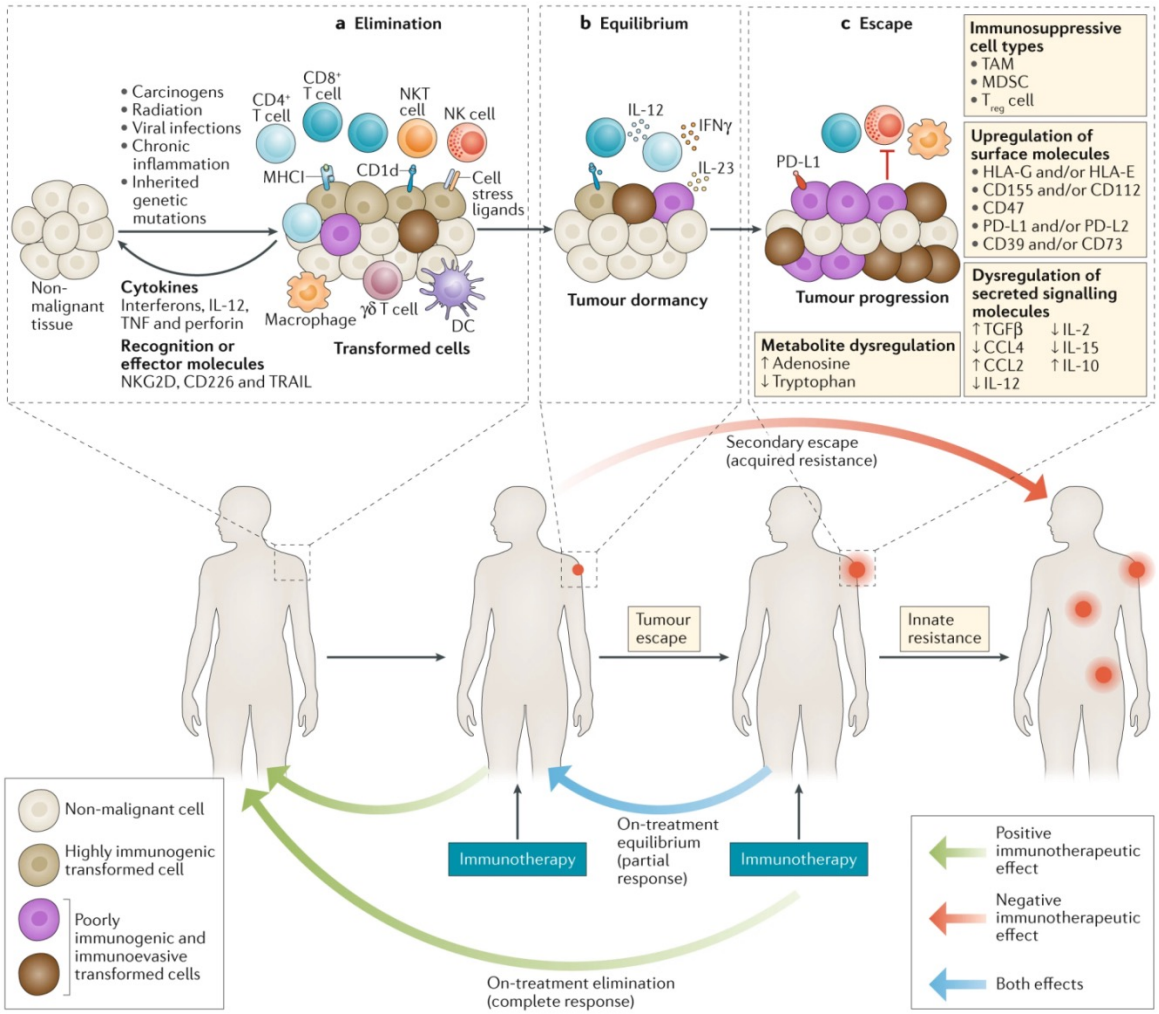
MRO . ART
MODERN RADIATION ONCOLOGY: MULTIDISCIPLINARITY IN THE ERA OF OMICS AND AI GUIDED ONCOLOGY
32° RESIDENTIAL COURSE

17-19 October, 2022

Cancer immunoediting and response to immunotherapy



A deep understanding of tumor-host interaction and co-evolution is needed to make immunotherapy a precise application in the clinical setting

Figure adapted from O'Donnell, Nat Rev Clin Oncol, 2019

High dimensional omics in immuno-oncology

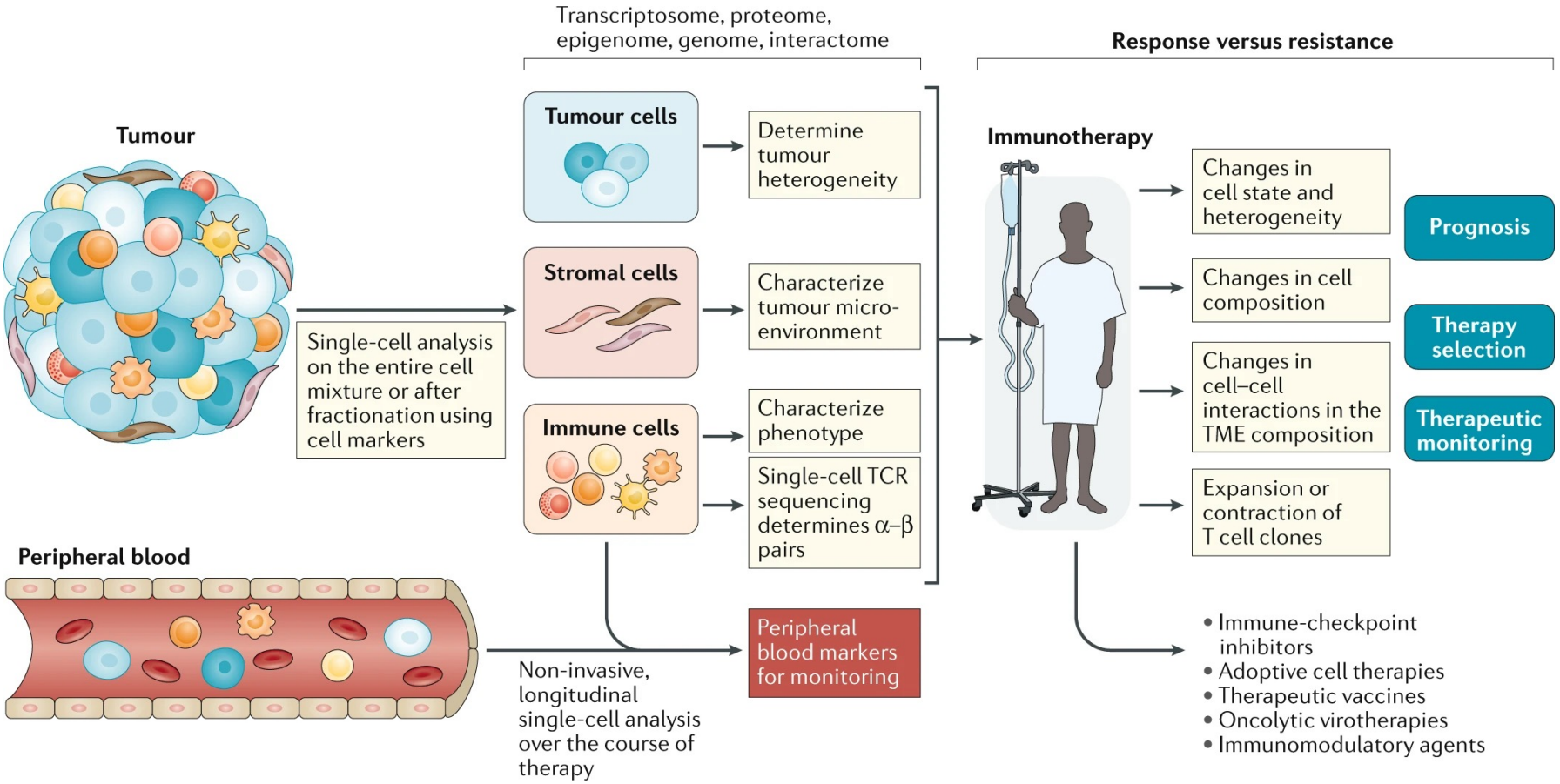


Figure adapted from Gohil, Nat Rev Clin Oncol, 2021

omics and tumor microenvironment (TME)

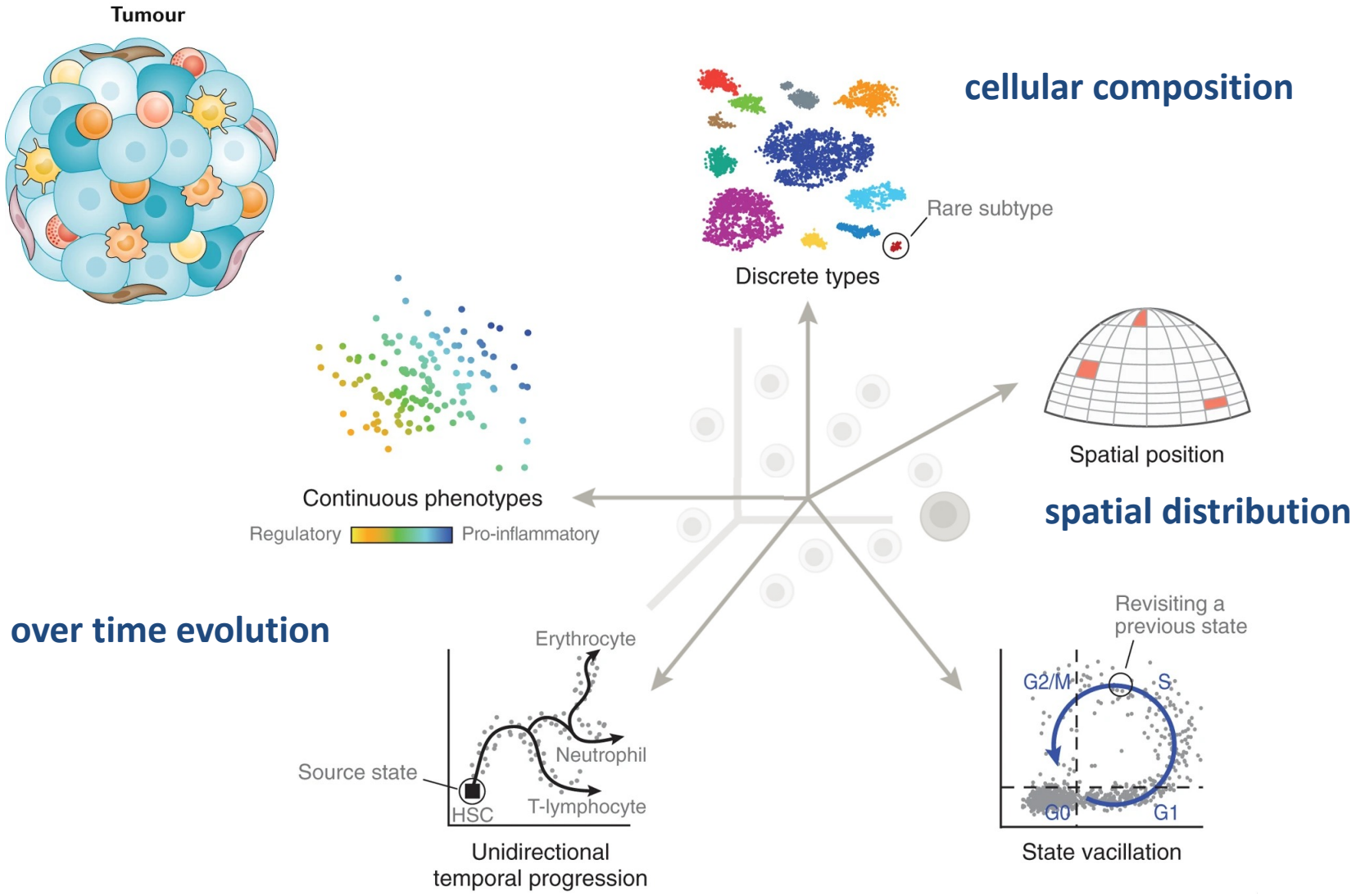


Figure adapted from Wagner, Nat Biotech, 2016

omics and TME: cellular composition

Omics profiling technologies in immuno-oncology

Population level		Single-cell (sc) level
WGS-seq WES-seq	**Genomics**	scWGS-seq scWES-seq
RNA-seq	**Transcriptomics**	scRNA-seq
ATAC-seq ChiP-seq	**Epigenomics**	scATAC-seq scChiP-seq
Flow cytometry MS RPPA	**Proteomics**	CyTOF scMS

omics and TME: cellular composition

- ✓ HCC patients > nivolumab
- ✓ PDAC patients > GVAX+ipilimumab
- ✓ Melanoma patients > ipilimumab

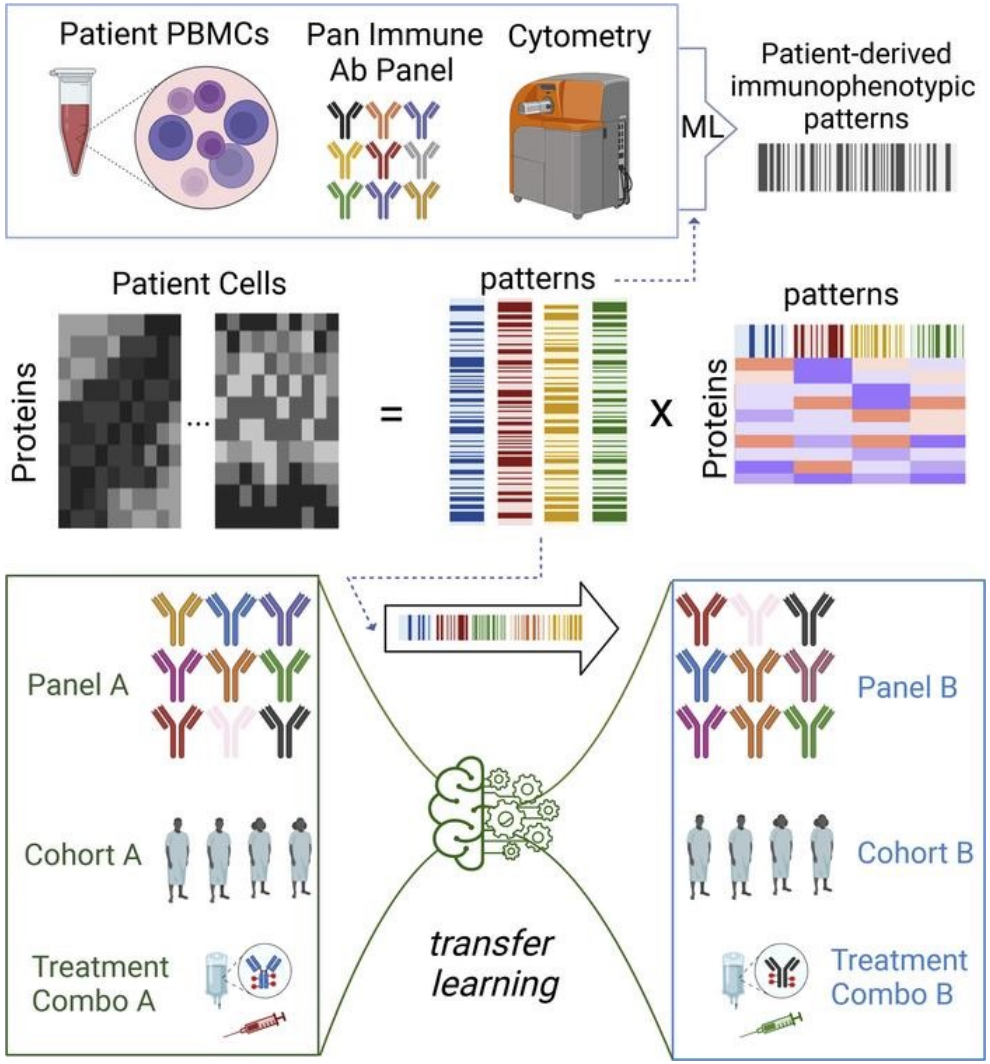
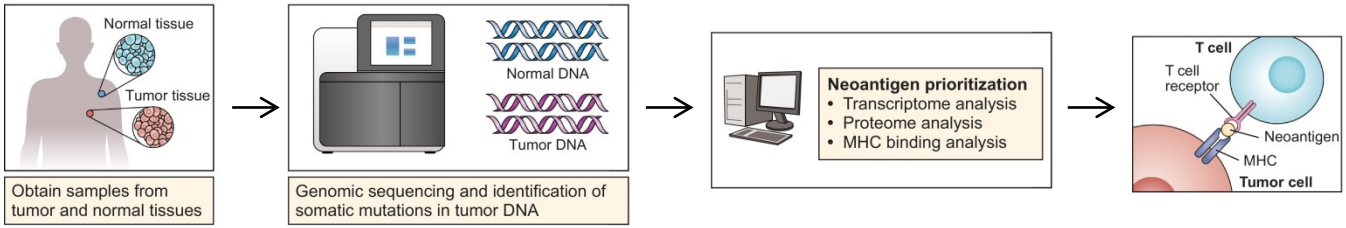


Figure adapted from Sidiropoulos, JCI, 2022

omics and TME: cellular composition

RNA-seq+WGS/WES

✓ to predict patient-specific cancer immunogenic neoantigens



LETTER

doi:10.1038/nature23003

Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer

Ugur Sahin[1,2], Evelyna Derhovanessian[1], Matthias Miller[1], Björn-Philipp Kloke[1], Petra Simon[1], Martin Löwer[1], Valesca Bukur[1,2], Arbel D. Tadmor[1], Ulrich Luxemburger[1], Barbara Schrörs[1], Tana Omokoko[1], Matthias Vormehr[1], Anna Panzyniak[1], Andreas N. Kuhn[1], Janina Buck[1], Sandra Heesch[1], Katharina H. Schreeb[1], Isabel Vogler[1], Eva Gedeharde[1], Sebastian Attig[2,1], Richard Rae[2], Andrea Breitkreuz[1], Claudia T[1], Goran Martic[1], Alexander Hobbeger[1], Patrick Sorn[1], Jan Diekmann[1], Janko Ciesla[1], Olga Wa[1], Alexandra-Kemmer Brück[1], Meike Witt[1], Martina Zillgen[1], Andree Rothermel[2], Barbara Kaze[1], Stefanie Rohe[1], Mustafa Diken[1,2], Sebastian Kreiter[1,2], Romina Nemecek[3], Christoffer Gebhar[1], Christoph Huber[3], Jochen Utikal[4,5], Christoph Huber[1,2,3], Carmen Loquai[1,6] & Özlem Türeci[1,6]

LETTER

doi:10.1038/nature22991

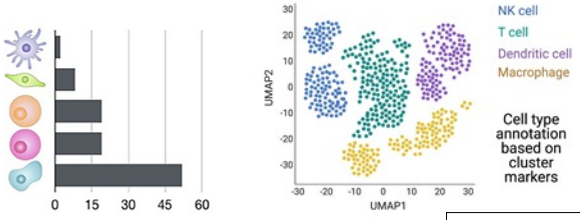
An immunogenic personal neoantigen vaccine for patients with melanoma

Patrick A. Ott[1,2,3]*, Zhuting Hu[1]*, Derin B. Keskin[1,3,4], Sachet A. Shukla[1,4], Jing Sun[1], David J. Bozym[1], Wandi Zhang[1], Adrienne Luoma[5], Anita Giobbie-Hurder[6], Lauren Peter[7,8], Christina Chen[1], Oriol Olive[1], Todd A. Carter[4], Shuqiang Li[6], David J. Lieb[6], Thomas Eisenhaure[6], Evisa Gjini[6], Jonathan Stevens[10], William J. Lane[10], Indu Javeri[11], Kalappanadar Nellaiappan[11], Andres M. Salazar[12], Heather Daley[1], Michael Seaman[1], Elizabeth I. Buchbinder[1,2,3], Charles H. Yoon[2,13], Maegan Harden[1], Niall Lennon[4], Stacey Gabriel[4], Scott J. Rodig[8,10], Dan H. Barouch[3,7,8], Jon C. Aster[2,13], Gad Getz[1,4,14], Kai Wucherpfennig[3,5], Donna Neuberg[6], Jerome Ritz[1,2,3], Eric S. Lander[3,4], Edward F. Fritsch[1,4]†, Nir Hacohen[1,4,11] & Catherine J. Wu[1,2,3,4]

omics and TME: cellular composition

RNA-seq

✓ to quantify different cell types of the TME (G



Finotello *et al. Genome Medicine* (2019) 11:34
https://doi.org/10.1186/s13073-019-0638-6

Genome Medicine

METHOD Open Access

Molecular and pharmacological modulators of the tumor immune contexture revealed by deconvolution of RNA-seq data

Cancer Therapy: Clinical

Clinical Cancer Research

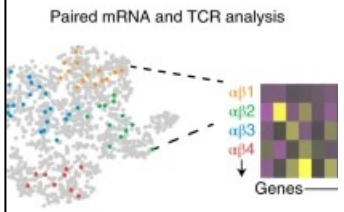
CTLA4 Blockade Broadens the Peripheral T-Cell Receptor Repertoire

Lidia Robert[1], Jennifer Tsoi[2], Xiaoyan Wang[1,3], Ryan Emerson[7,8], Blanca Homet[1,9], Thinle Chodon[1], Stephen Mok[1,2], Rong Rong Huang[4], Alistair J. Cochran[4], Begoña Comin-Anduix[5,6], Richard C. Koya[5,6], Thomas G. Graeber[2,6], Harlan Robins[7,8], and Antoni Ribas[1,2,5,6]

Cell

Tumor and Microenvironment Evolution during Immunotherapy with Nivolumab

Nadeem Riaz,[1,2,3,15] Jonathan J. Havel,[1,15] Vladimir Makarov,[1,3,15] Alexis Desrichard,[1,15] Walter J. Urba,[4] Jennifer S. Sims,[1,3] F. Stephen Hodi,[5] Salvador Martín-Algarra,[6] Rajarsi Mandal,[7] William H. Sharfman,[8] Shailender Bhatia,[9] Wen-Jen Hwu,[10] Thomas F. Gajewski,[11] Craig L. Slingluff, Jr.,[12] Diego Chowell,[1,3] Sviatoslav M. Kendall,[1,3] Han Chang,[13] Rachna Shah,[1] Fengshen Kuo,[3] Luc G.T. Morris,[3,7] John-William Sidhom,[14] Jonathan P. Schneck,[14] Christine E. Horak,[13] Nils Weinhold,[2,*] and Timothy A. Chan[1,2,3,16,*]



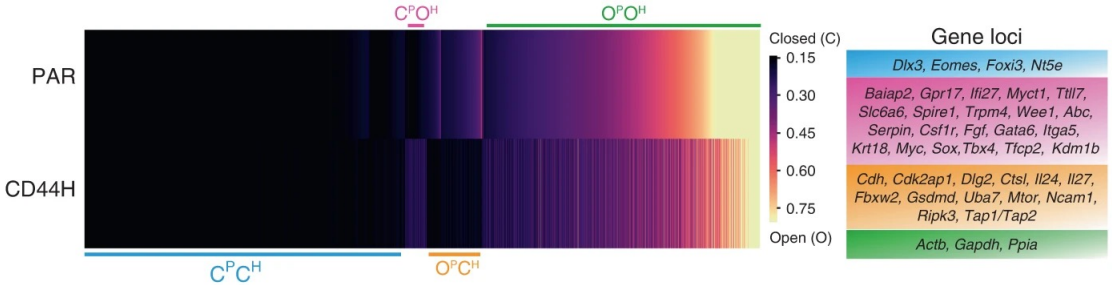
omics and TME: cellular composition

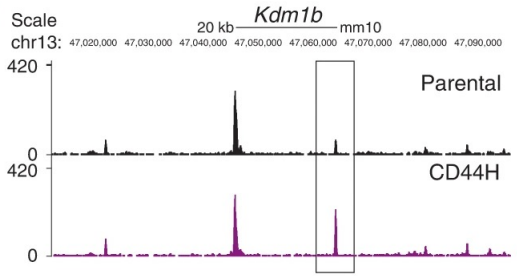
nature immunology
ARTICLES
https://doi.org/10.1038/s41590-022-01290-3
Check for updates

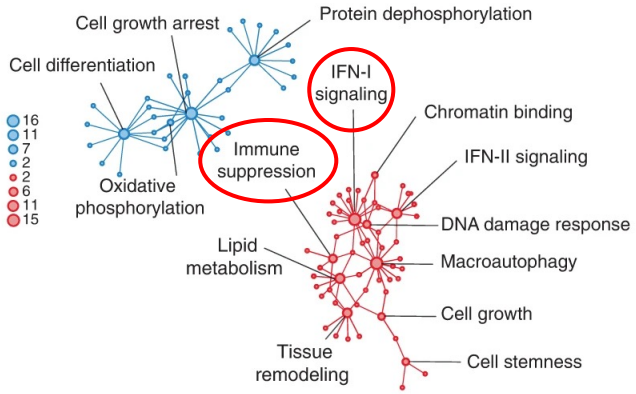
OPEN

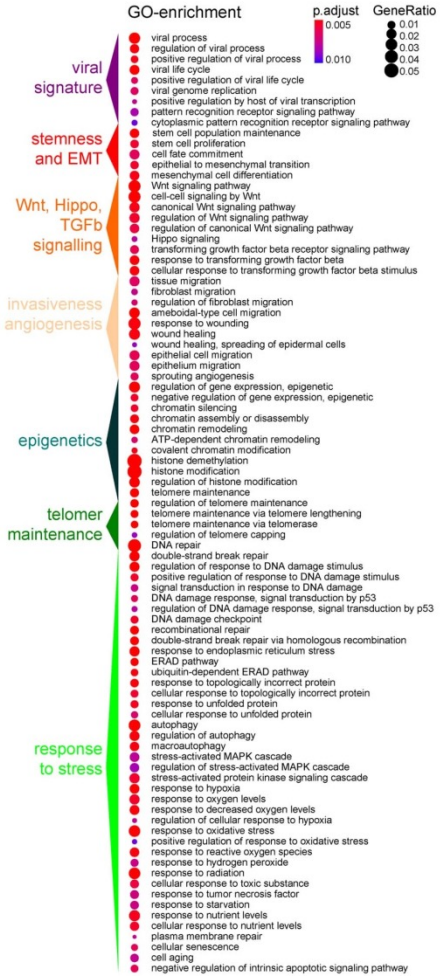
Type I IFNs promote cancer cell stemness by triggering the epigenetic regulator KDM1B

cture and histone modification









Musella, Nat Immunol, 2022

omics and TME: cellular composition

RNA-seq+ATAC-seq/CHIP-seq

- ✓ this intra-modality integration is allowing researchers to build the tumor immune atlas, that provide a comprehensive compendium of immune cells and an inspection of gene expression patterns in different immune cell types within the TME

HUMAN CELL ATLAS
IMMUNE SYSTEM

From the Human Cell Atlas to dynamic immune maps in human disease

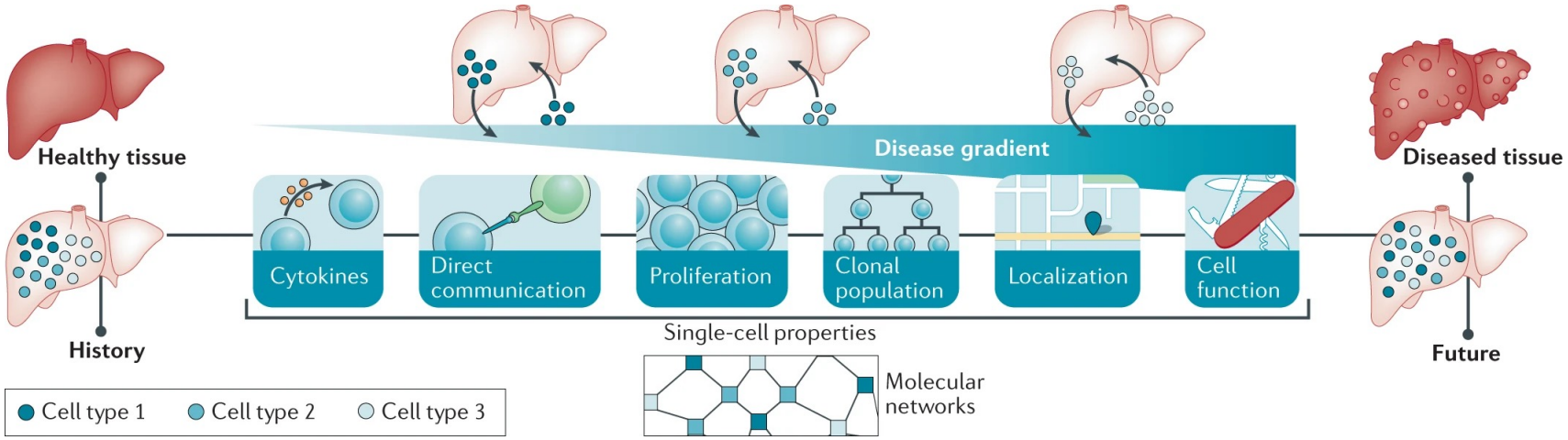


Figure adapted from Adlung Nat Rev Immunol, 2018

omics and TME: spatial distribution

The relative spatial distribution of cells impacts therapeutic response

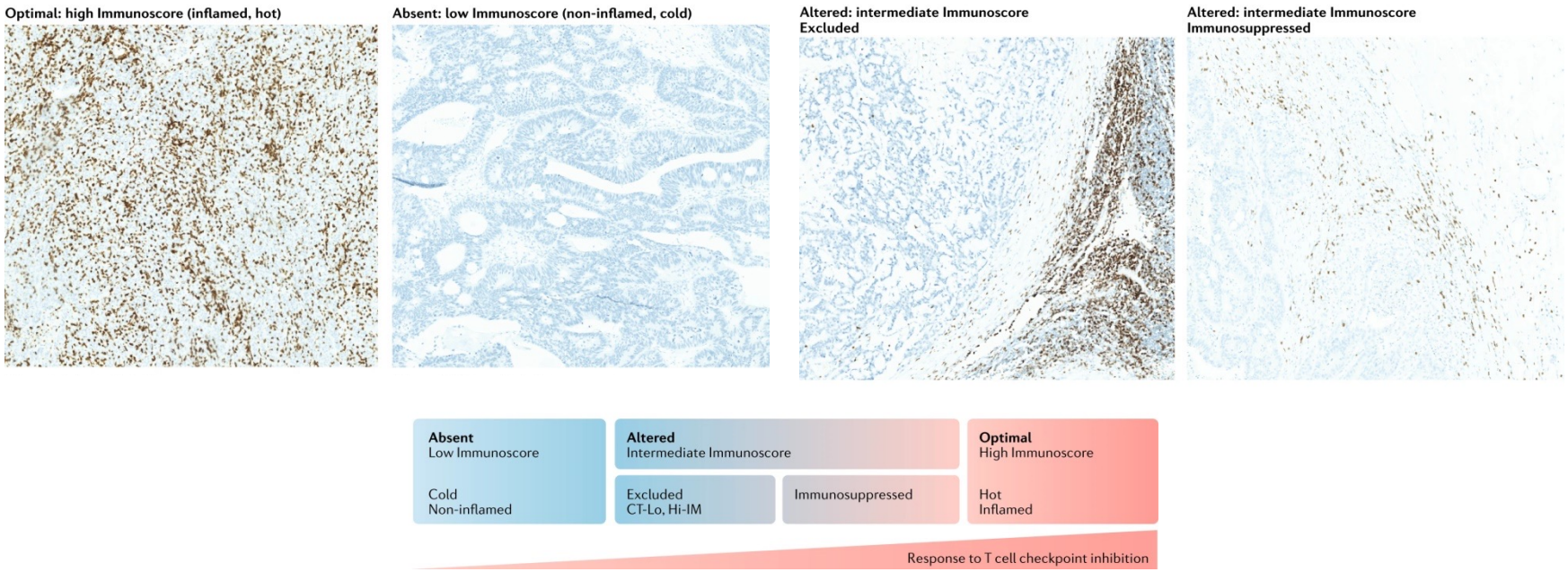


Figure adapted from Galon Nat Rev Drug Discov, 2019

High dimensional spatial proteomics

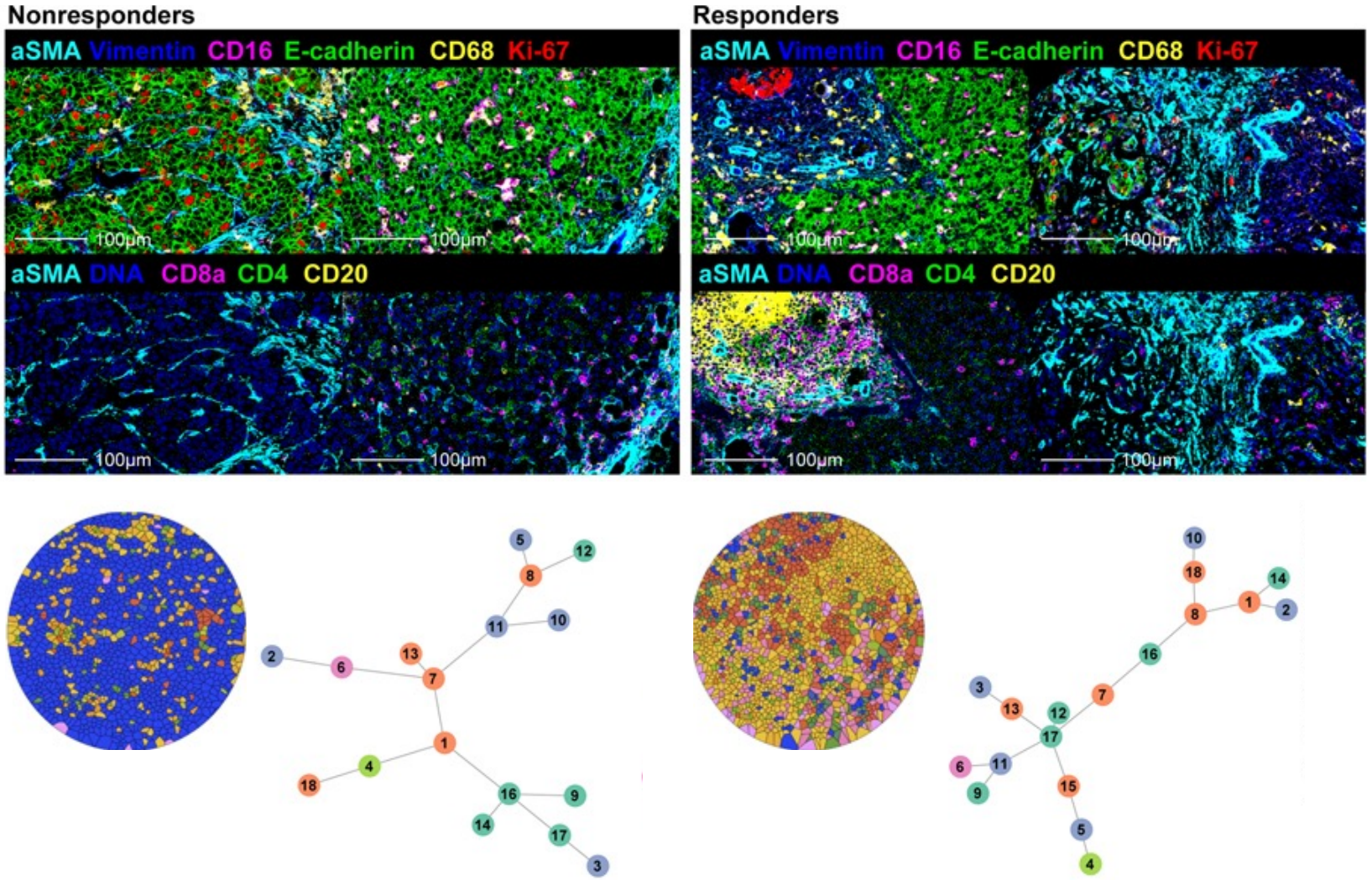
- ✓ Image mass cytometry (IMC)
- ✓ Multiplexed ion beam imaging
- ✓ Cyclic imaging detection (CODEX)
- ✓ Cyclic immunofluorescence (CyCIF)
- ✓ Multiplexed immunofluorescence (MxIF)

High dimensional spatial transcriptomics

- ✓ Slide-seq
- ✓ 10X Genomics Visium
- ✓ Sequential fluorescence *in situ* hybridization (seqFISH)
- ✓ MERFISH

omics and TME: spatial distribution

The relative spatial distribution of cells impacts therapeutic response

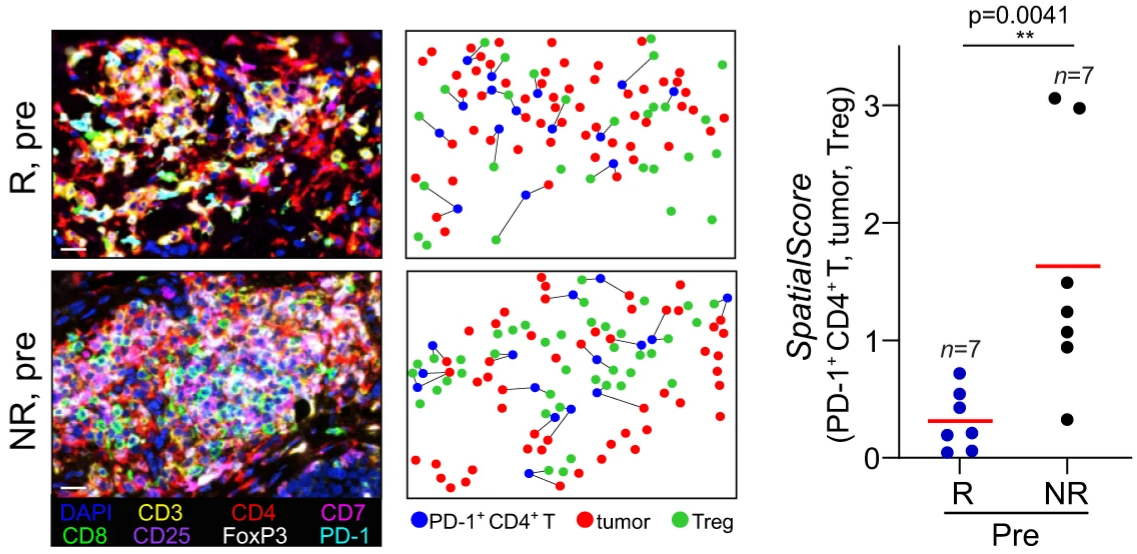


HCC patients treated with cabozantinib+nivolumab

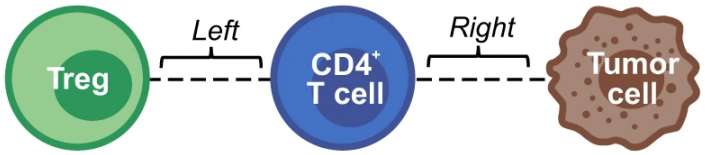
Figure adapted from Ho Nat Cancer, 2021

omics and TME: spatial distribution

The immuno *SpatialScore*
Cell-cell interactions impact on tumor's (immune)therapeutic response



***SpatialScore* distance ratio = Right / Left**



***SpatialScore* = T cell effector / suppressive activity**

Cutaneous T cell lymphoma patients treated with pembrolizumab

Figure adapted from Phillips Nat Commun 2021

omics and TME: spatial distribution

Spatial multi-omics for precision immuno-oncology

Spatial multi-omics help to reveal patient –specific TMEs enabling personalized therapies

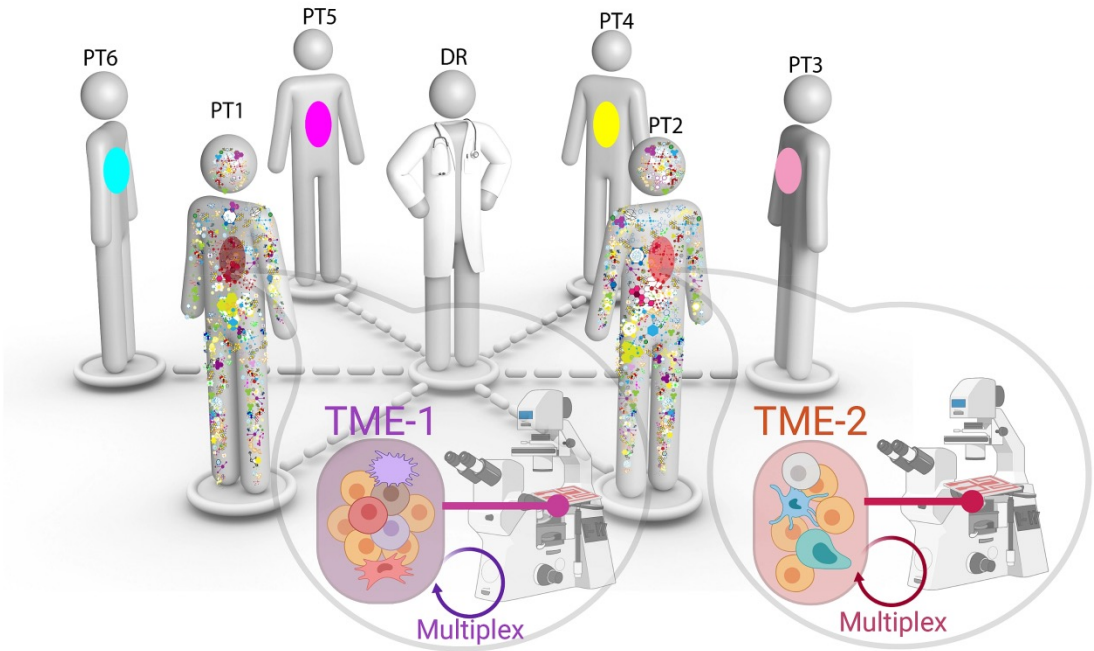


Figure adapted from https://cancercommunity.nature.com/posts/spatial-multi-omics-analysis-in-single-cells-for-precision-oncology

omics and TME: over time evolution

Tumor-immune interactions during (immune)therapeutic response are dynamic

TCR/BCR-seq

- ✓ to follow clonal evolution and immuno dominance during cancer progression and response to (immuno)therapy

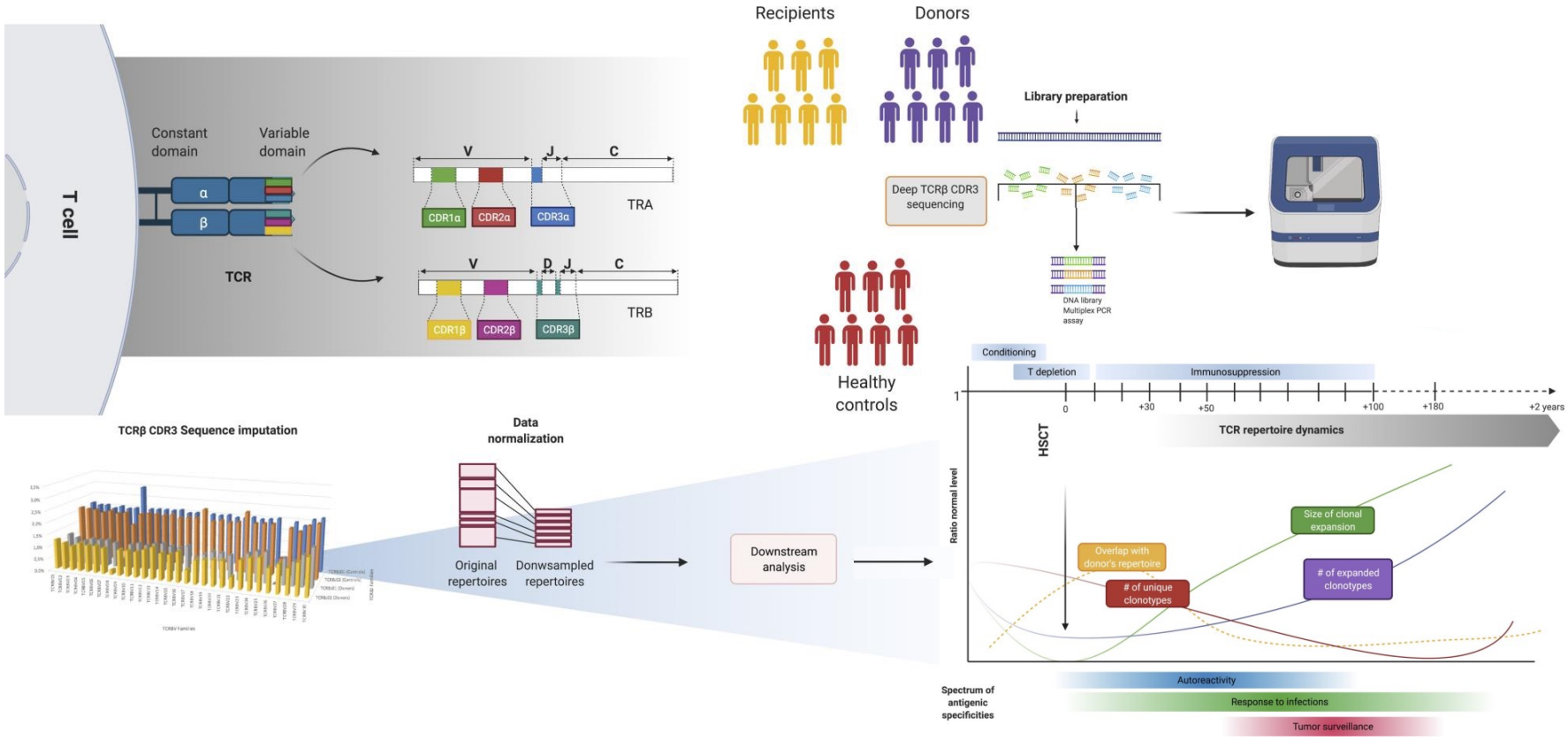
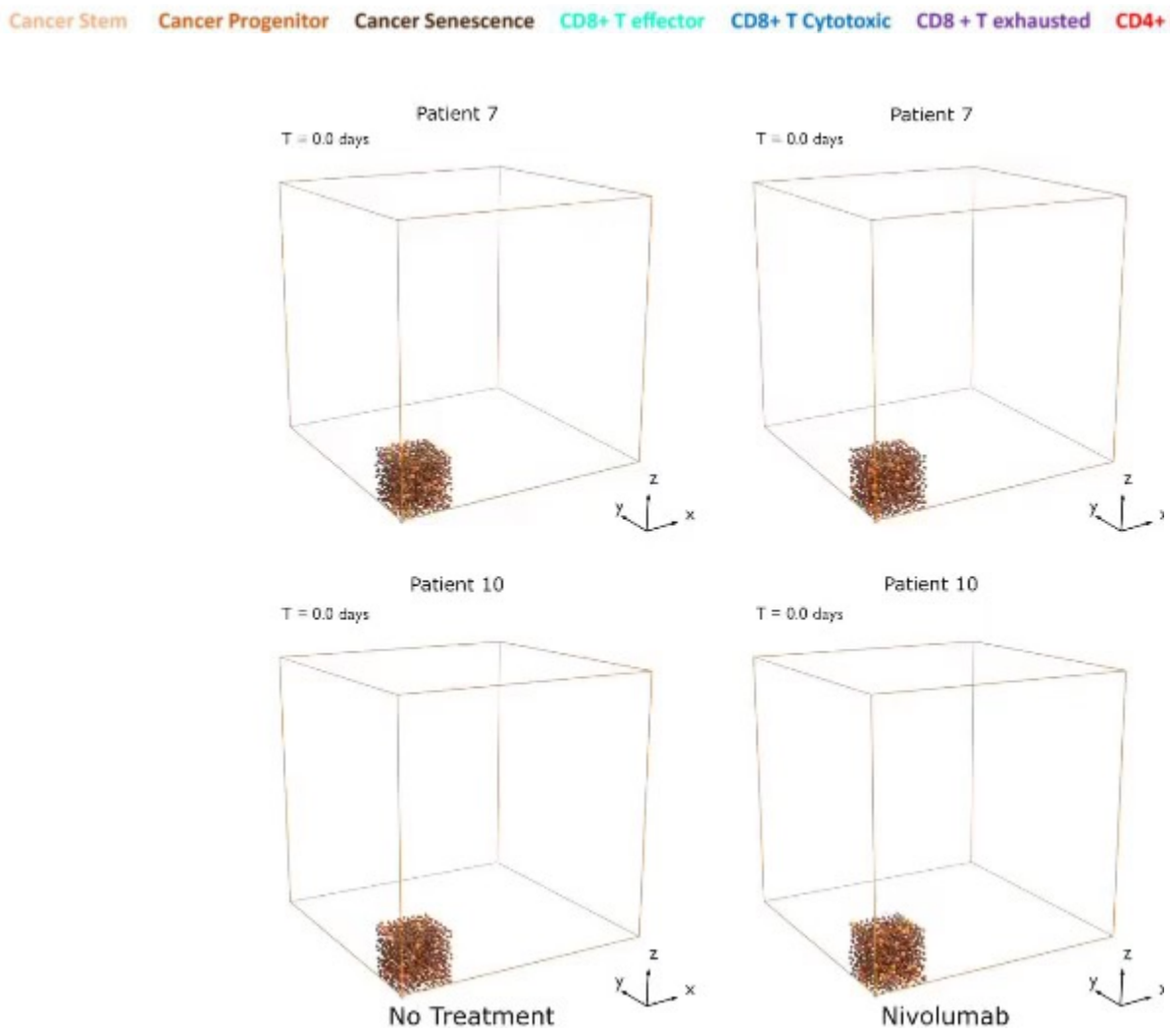


Figure adapted from Pagliuca, JCI, 2021

omics and TME: over time evolution

Tumor-immune interactions during (immune)therapeutic response are dynamic



Movie adapted from Zhang ImmunoInform 2021

Conclusions

- ✓ Therapeutic response and resistance depends on the cellular compositon of tumors and their microenvironments, the spatial distribution of cells and the cellular evolution over time.

- ✓ Bulk and single cell omics together with emerging spatial molecular technologies are ideally suited to resolve the molecular and cellular mechanisms of therapeutic response and resistance.

- ✓ Integrating mathematical modeling with multi-omics can model intercellular networks and co-evolution over time, which finally tip the balance between therapy response or resistance.

Thank you for the attention!