SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER

BLOOMBERG~KIMMEL INSTITUTE FOR CANCER IMMUNOTHERAPY

JOHNS HOPKINS MEDICINE

July 16, 2018

Endpoints for Evaluating the Efficacy of PD-1/PD-L1 Combination Therapies

National Academy of Medicine

Elizabeth M. Jaffee, M.D.
Dana and Albert Broccoli Professor of Oncology
The Skip Viragh Pancreatic Cancer Center
President, American Association for Cancer Research

Disclosure Information

Elizabeth M. Jaffee, M.D.

I have the following financial relationships to disclose

I will be discussing the investigational use of:

- GVAX
- Listeria Monocytogenes – mesothelin

Both licensed to Aduro Biotech with potential to receive royalties

Consultation activity: Adaptive Biotech, MedImmune, Genocea

Grants: Aduro and BMS

What are the goals for testing PD-1/PD-L1 combination therapies?

- Enhance the efficacy of single agent PD-1/PD-L1 blocking agents in ”inflammed or hot” tumors
  - Presumes existing T cells available for activation
  - Enhance numbers, quality, and activation state of existing T cells
  - Prevent T cell exhaustion

- Increase the number of patients with less “inflammed or cold” tumors to respond to I-O agents
  - Presumes lack of good quality T cells
  - Will require T cell induction followed by activation and T cell exhaustion prevention

- Achieve more durable responses in all patients responding to I-O agents
  - Increase the rate of responses as well

What types of PD-1/PD-L1 combination therapies are currently in clinical trials?

- PD-1/PD-L1 blockade with other checkpoint and targeted blocking agents
  - CTLA-4, Lag-3, Tim-3, IDO1, CSFR1, TIGIT, IL-8 blockade
  - Daratumumab, (CD38) Brentuximab (CD30),
  - Cabozantinib, Sunitinib, Bevacivumab
  - PARP, PI3K, and MEK inhibitors
- PD-1/PD-L1 blockade with epigenetic agents
  - HDACi and demethylating agents
- PD-1/PD-L1 blockade with agonist antibodies
  - OX-40, CD137, or CD40
- PD-1/PD-L1 blockade with vaccines
- PD-1/PD-L1 blockade with chemotherapy or radiation

Best Endpoints: Durable tumor responses and longer survival

- Tumor response measured by radiographic changes is best measure but these come in different flavors
  - Quick regression
  - Pseudo-progression followed by regression
  - True progression followed by regression

- In inflammed or “hot” tumors this can usually be observed quickly in weeks due to existing T cells that require activation

- In non-inflammed or ”cold” tumors this can take months
  - T cell induction is preceded by checkpoint activation and takes time to get adequate numbers of effective T cells

RECIST does not provide adequate assessment of immunotherapeutics

- Anti-tumor response takes longer when compared to chemotherapy
- Clinical responses to immunotherapies can occur after conventional progression on CAT scan - pseudoprogression
- Immune-related response criteria (irRC) is a newer method that allows for insignificant progressive disease (slight increase in some lesions while others respond on CAT scan)
- Durable stable disease may represent an antitumor immune response

Wolchek, et al, Clin Ca Res, 2009

How can we design and measure the best PD-1/PD-L1 combinations?

- Biomarkers are needed to determine early response
- Best biomarkers for determining response to combinations should take into account the mechanisms of action of the contributing therapeutics
- Biomarkers that assess the interaction of the targeted combination pathways can be used to optimize sequence and dosing

More science is needed to design the best combinations!

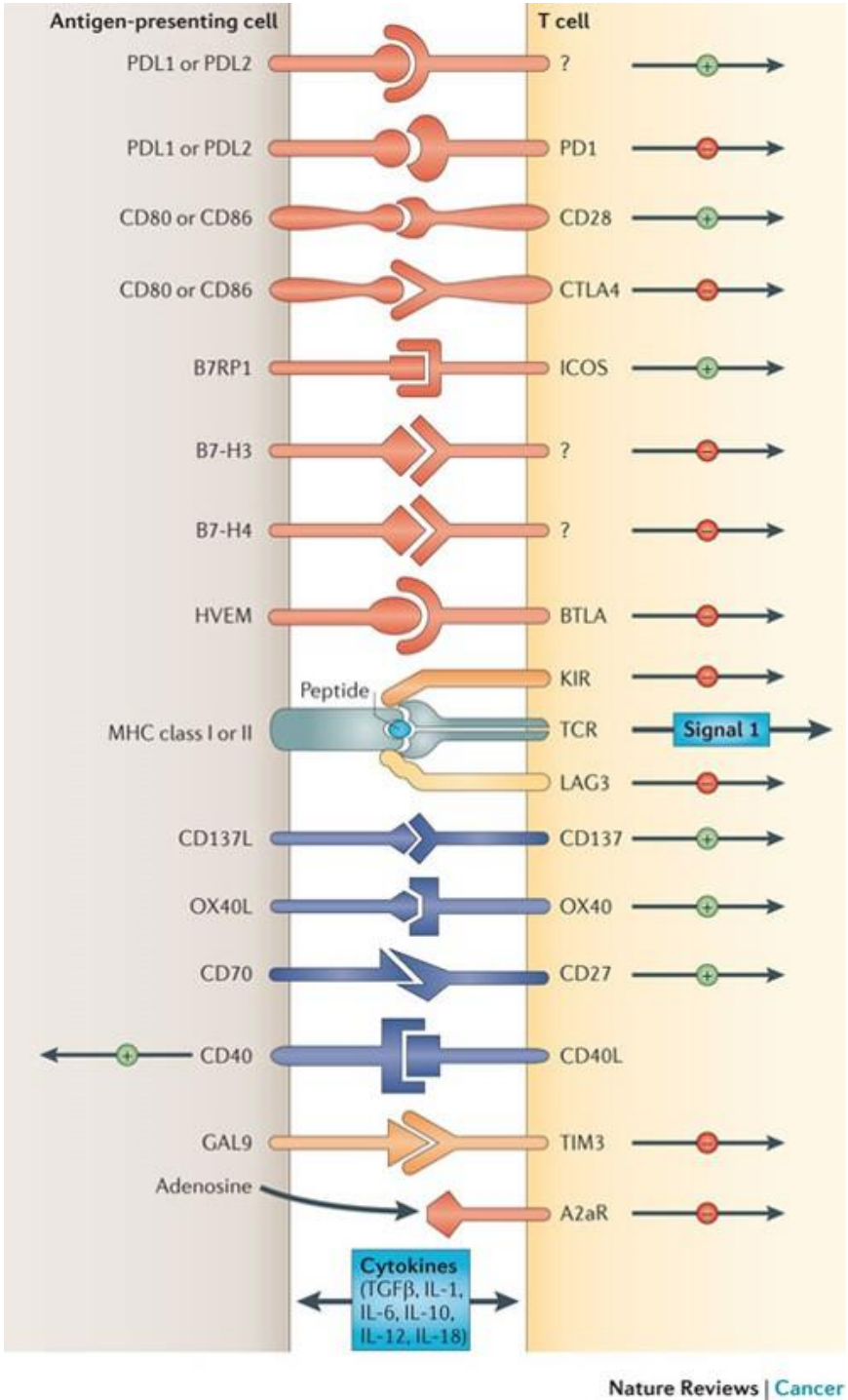
- Science needs to drive the rationale for PD-1/PD-L1 combinations
  - Knowledge of inhibitory pathways that are co-expressed or upregulated in response to PD-1/PD-L1 blockade
  - Knowledge of primary and adaptive resistance to PD-1/PD-L1 blockade
  - Knowledge of the specific suppressive populations within the TME
  - Knowledge of the agonist signals that may enhance T cell activation, prevent exhaustion, induce memory

- Uncovering the pathways will lead to biomarkers for optimizing combinations
  - Biomarkers that can predict synergistic activity
  - Biomarkers that can optimize dosing and sequencing

T cell activation is the summation of both activating and inhibitory signals

APC

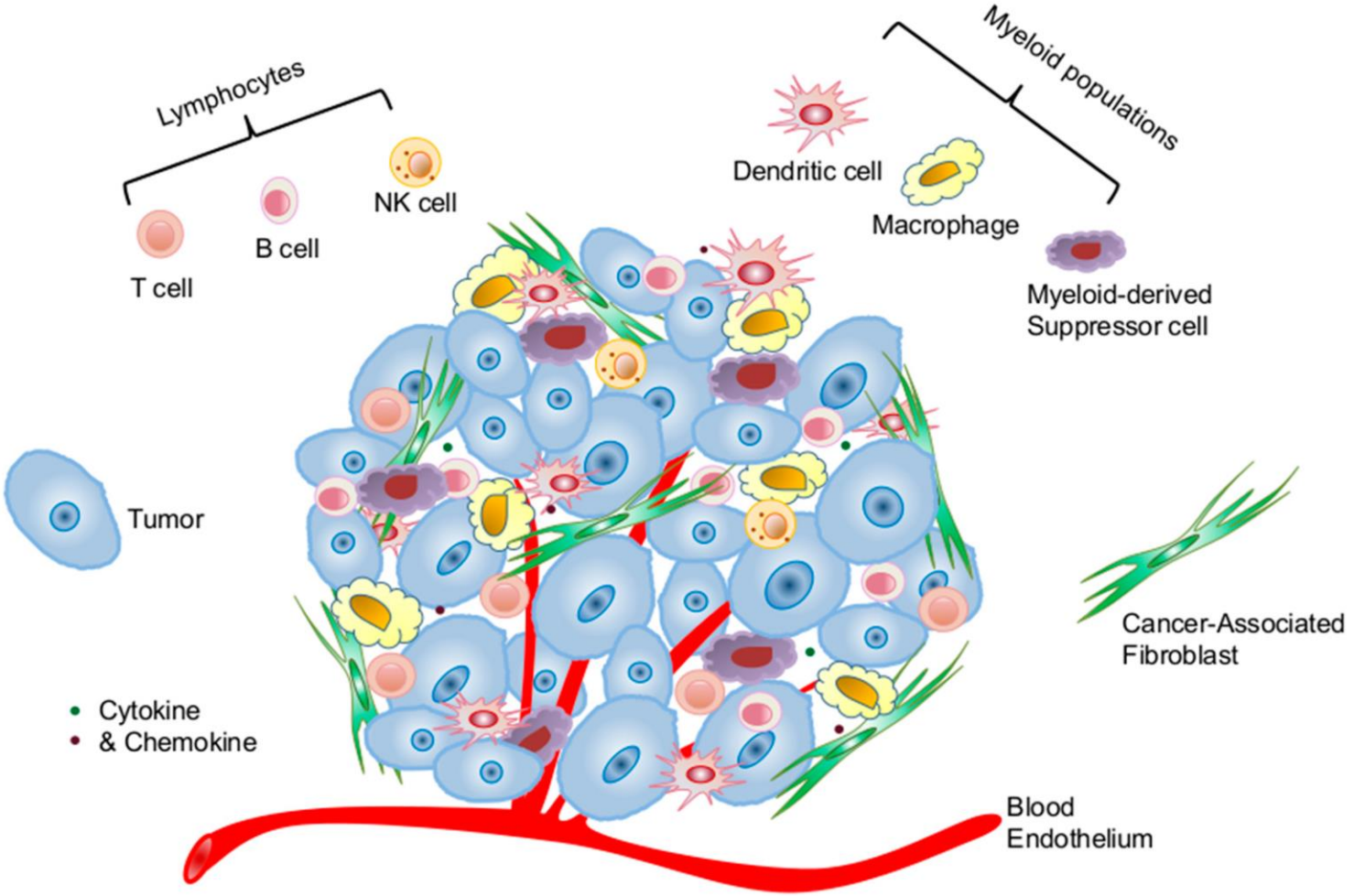
Tumor Cell



T Cell

The Tumor Micro-environment has multiple signaling pathways for suppressing T cell trafficking and anti-tumor function

We have yet to understand how these different signaling pathways interact to alter the balance between cancer development and anti-cancer immunity



Cui Y, et al. Int. J. Mol. Sci. 2016.

Optimizing PD-1/PD-L1 combinations requires a better understanding of T cells and TME

- The optimal signals for activating and maintaining quality T cells

- T cell resistance – multiple mechanisms are at play including exhaustion, inactivation/apoptosis
  - How do we best prevent resistance
  - How do we know when specific mechanisms are likely to occur

- Signaling within the tumor microenvironment is a dynamic process
  - Shaped by the constantly evolving genetic, epigenetic and inflammatory processes
  - Likely differs between tumors in the same patient at different sites
  - Adaptive resistance occurs with T cell infiltration

Technologies are rapidly developing to assist with better understanding these complexities

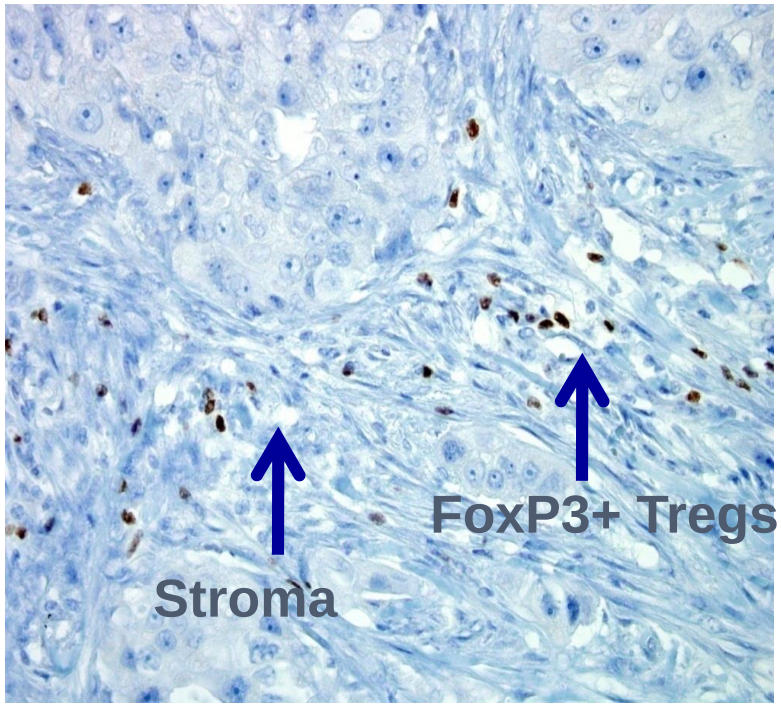
- Multiplex assays can define immune cell composition and delineate their function within the TME and peripheral blood
  - Multiplex immunohistochemistry with computational analyses
  - Single cell and bulk RNAseq and Nanostring
  - Multiplex flow cytometry/mass cytometry
- TCR sequencing has shown promise in predicting responders to both PD-1/PD-L1 and CTLA-4 blockade
  - PD-1 blockade increases the clonality of activated T cells
  - CTLA-4 blockade increases the diversity of naïve T cells undergoing activation
  - This biomarker could assist with sequencing of some combinations
- Molecular imaging of specific immune signals and T cells is making progress
- Liquid biopsies are emerging for detecting immune signals

What are we learning from these technologies?

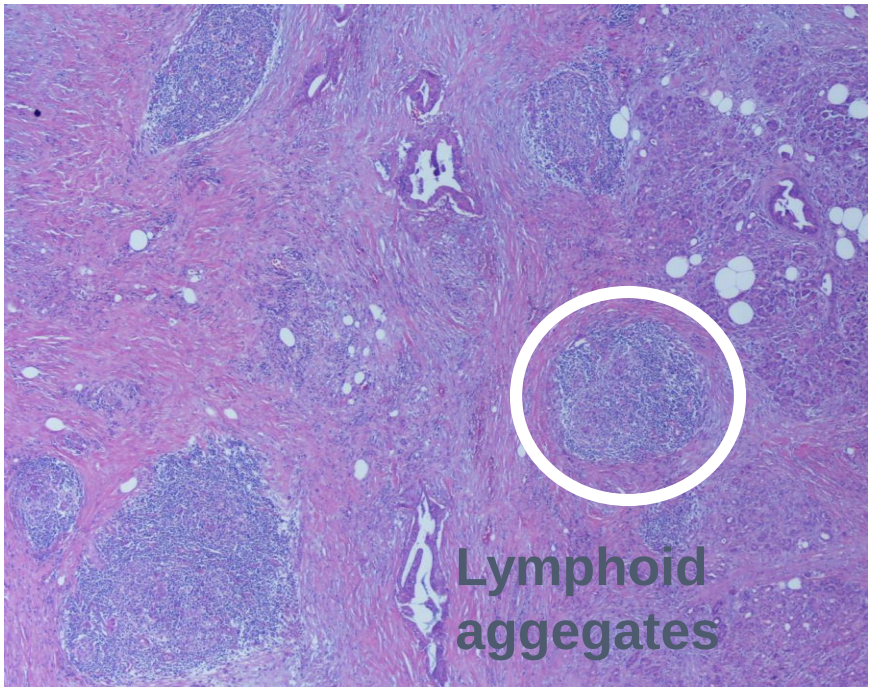
Example: Multiplex analysis provides evidence for successful combination of vaccine and anti-PD-1 blockade

- Neo-adjuvant GM-CSF secreting whole tumor cell vaccine turns uninflammed pancreatic cancers into inflammed tumors
  - Multiplex-IHC identifies predictors of response
- Same vaccine in combination with anti-PD-1 blockade induces PRs in metastatic patients
  - Multiplex-IHC shows invigorated T cell infiltration in regressing tumor

Lymphoid Aggregates found in 2 location patterns in vaccinated patients 2 weeks after a single vaccine



Pre–vaccination

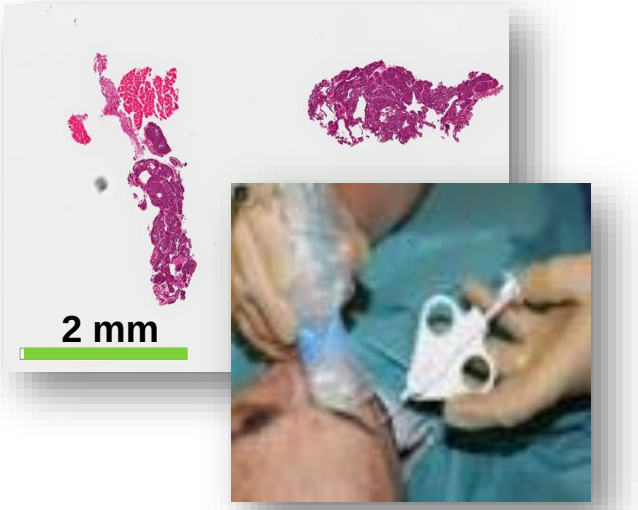


Post–vaccination intratumoral T cells

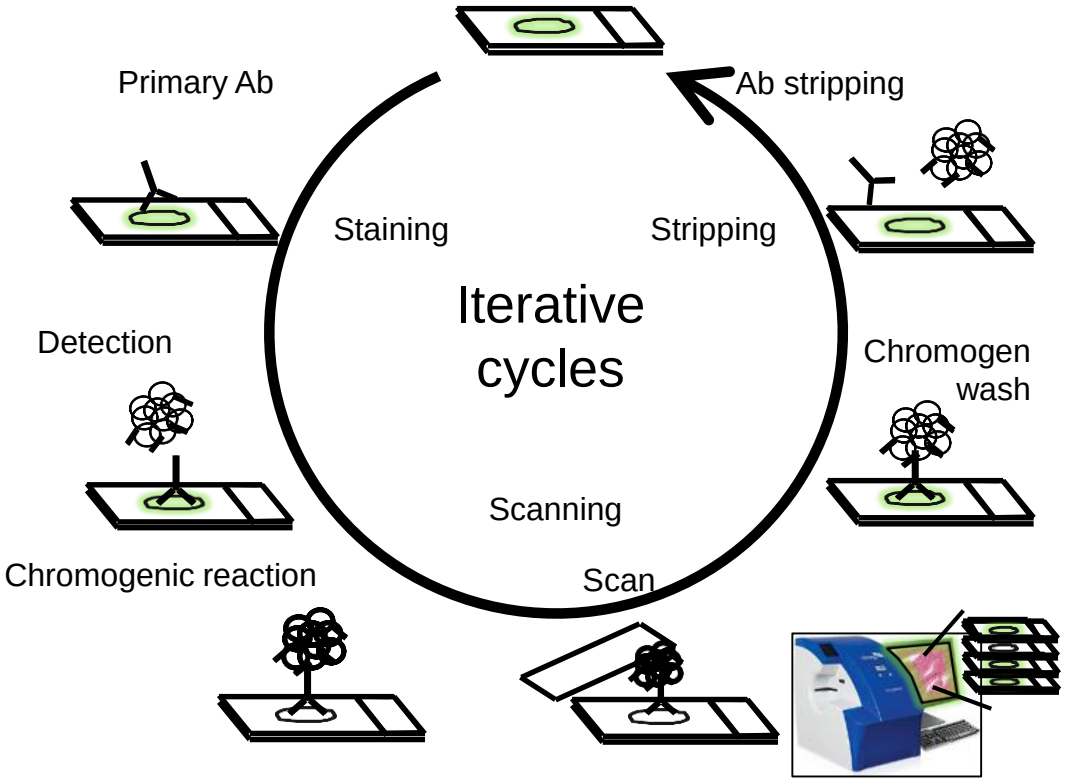
Multiplex Immunohistochemistry Approach To Interrogate The TME

surgical

20 ga core biopsy, x2



Sequential cycles of IHC



Modified from

Tramu G, et al. J Histochem Cytochem 1978
Glass G, et al. J Histochem Cytochem, 2009
Stack EC, et al. Methods, 2014

Tsujikawa T, et al. Cell Reports, 2017

SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER
BLOOMBERG~KIMMEL INSTITUTE FOR CANCER IMMUNOTHERAPY
JOHNS HOPKINS MEDICINE

STAND UP TO CANCER

Multiplex IHC enables detection of 12-different epitopes in a single FFPE section

Sequential IHC

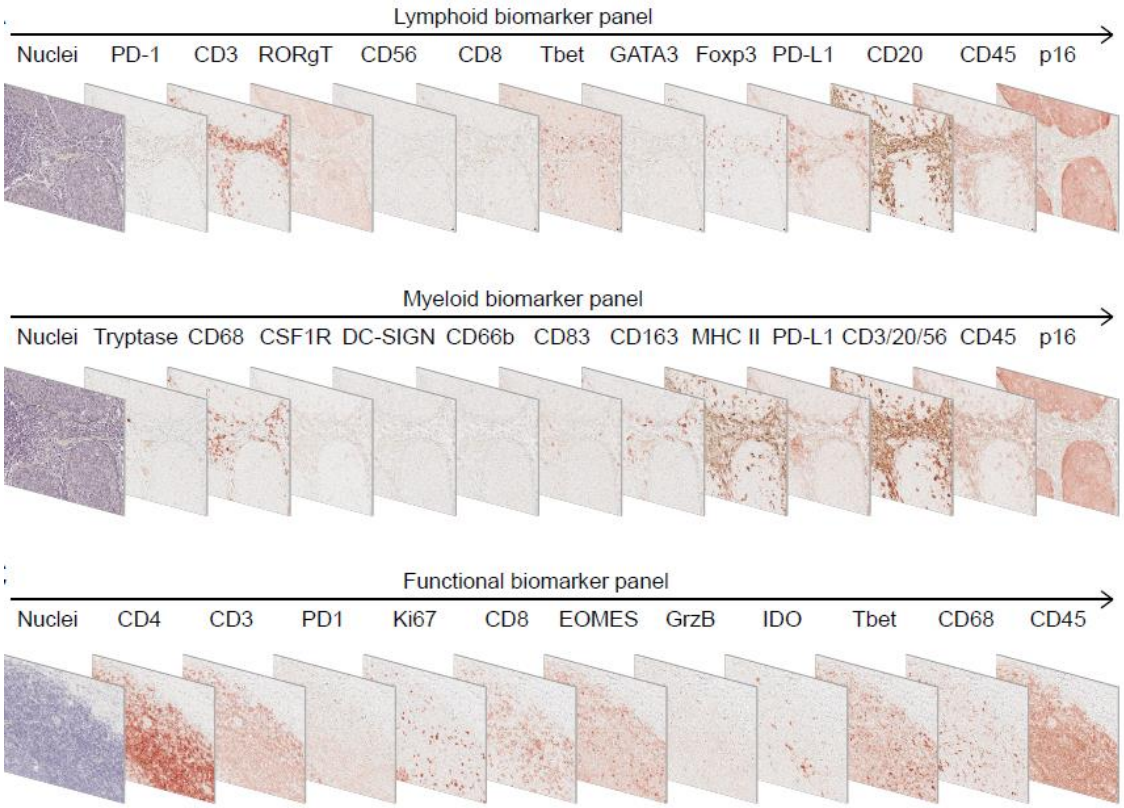
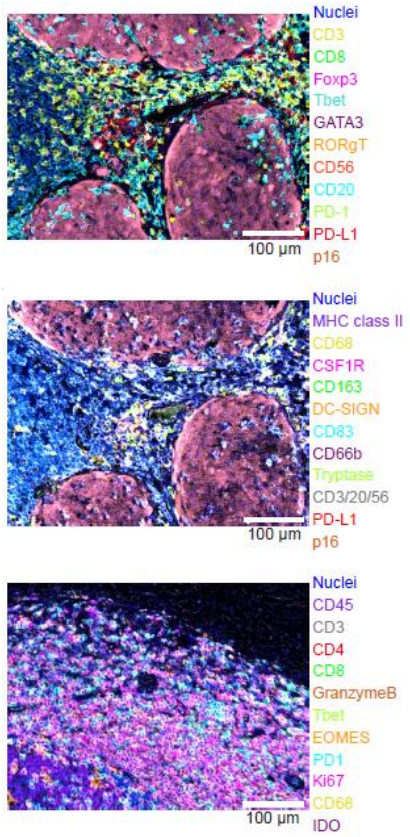


Image Co-registration

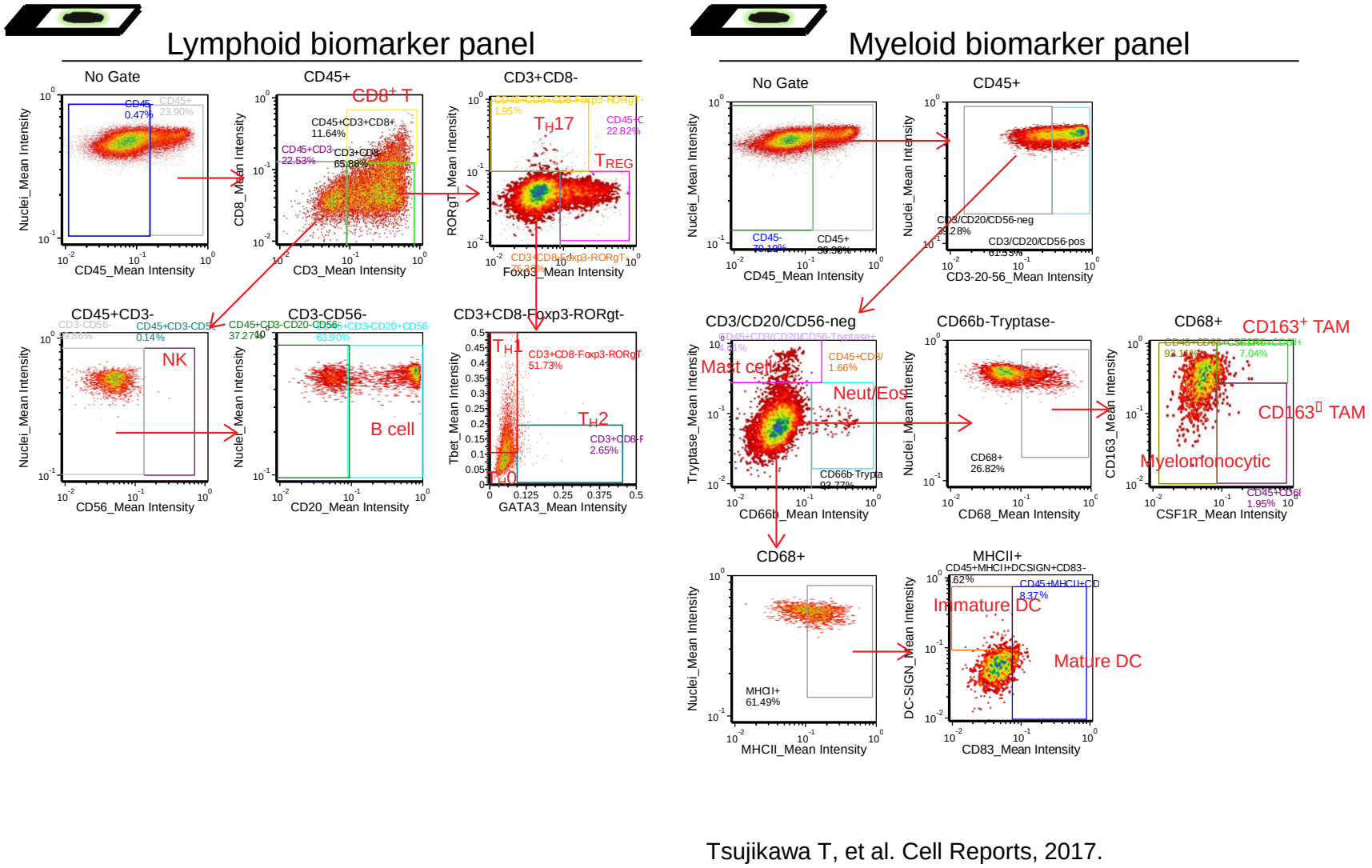
Color Deconvolution

Visualization



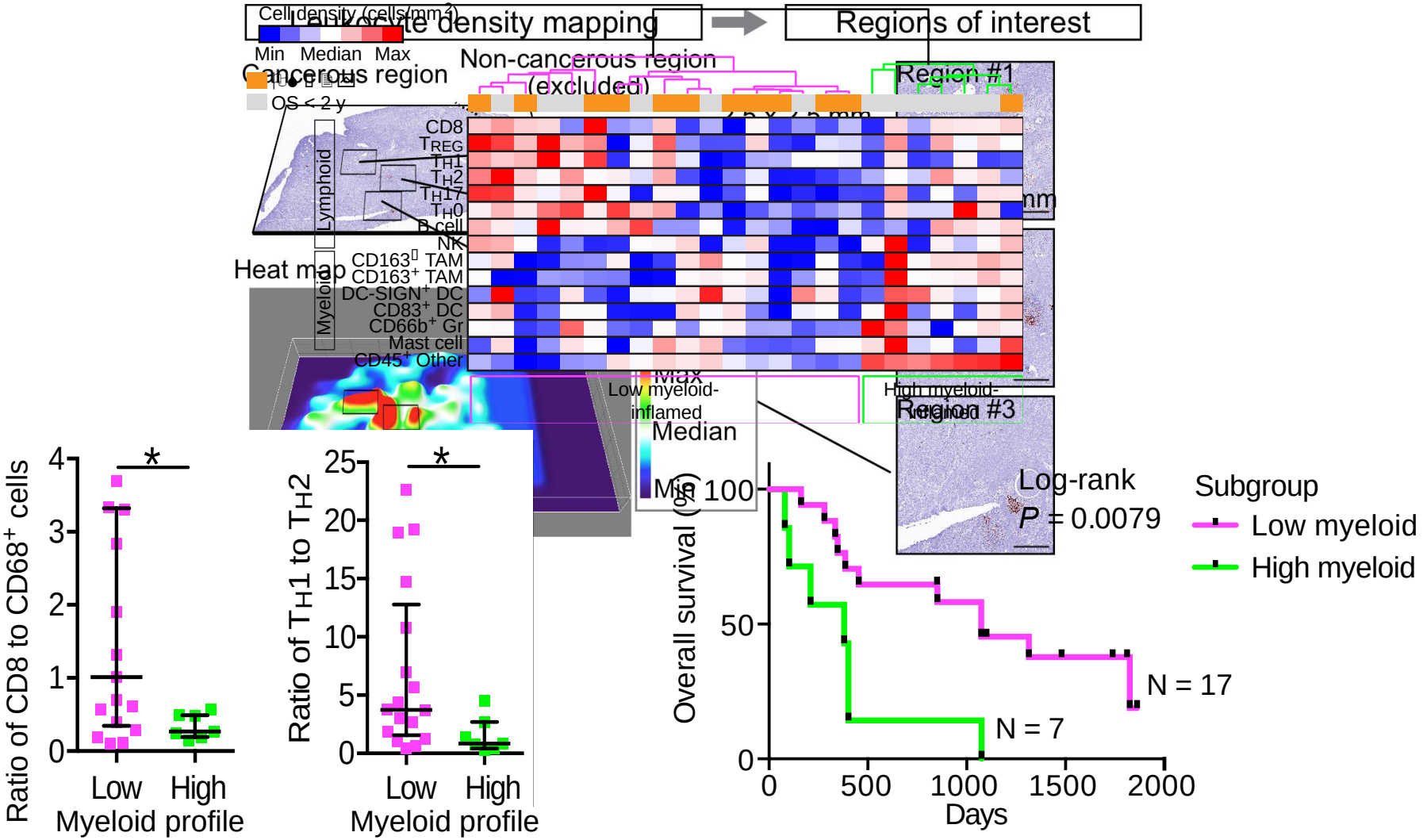
Tsujikawa T, et al. Cell Reports, 2017

Image cytometry enables quantification of 16-different cell lineages



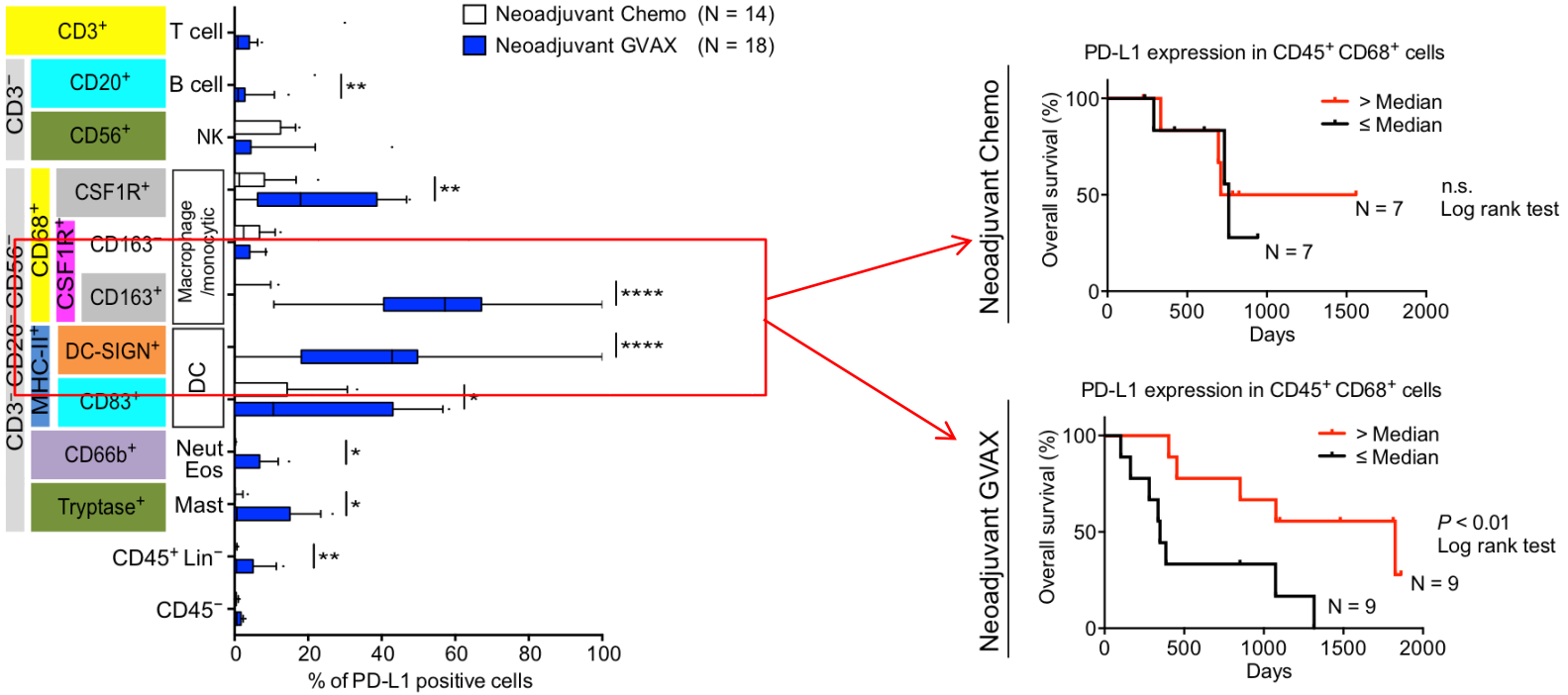
Tsujikawa T, et al. Cell Reports, 2017.

Low versus High Myeloid Content in CD45+ inflammed" Areas



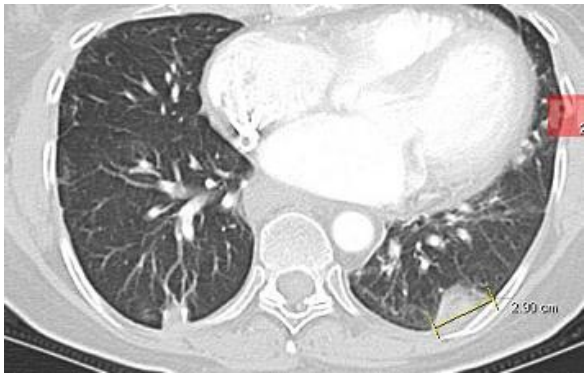
Tsujikawa, et al. *Cell Reports*, 2017.

Neoadjuvant GVAX therapy is associated with PD-L1 upregulation in myeloid cell lineages correlating with prognosis

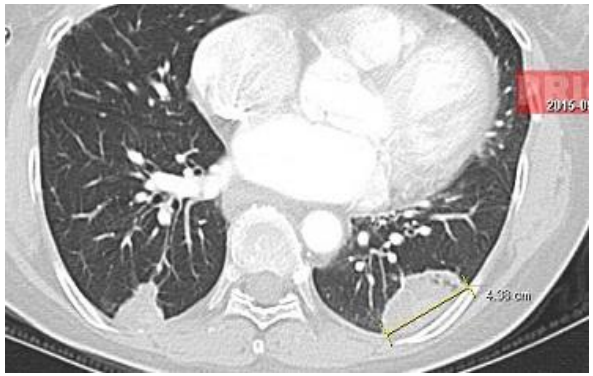


Tsujikawa T, et al. Cell Reports, 2017

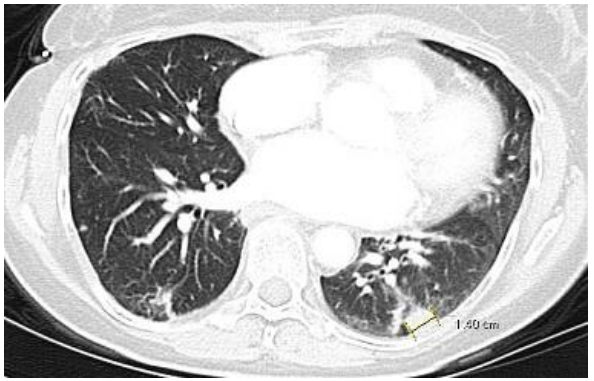
GVAX + CRS-207 Heterologous Prime Boost Vaccination with Programmed Death-1 (PD-1) Blockade



Baseline

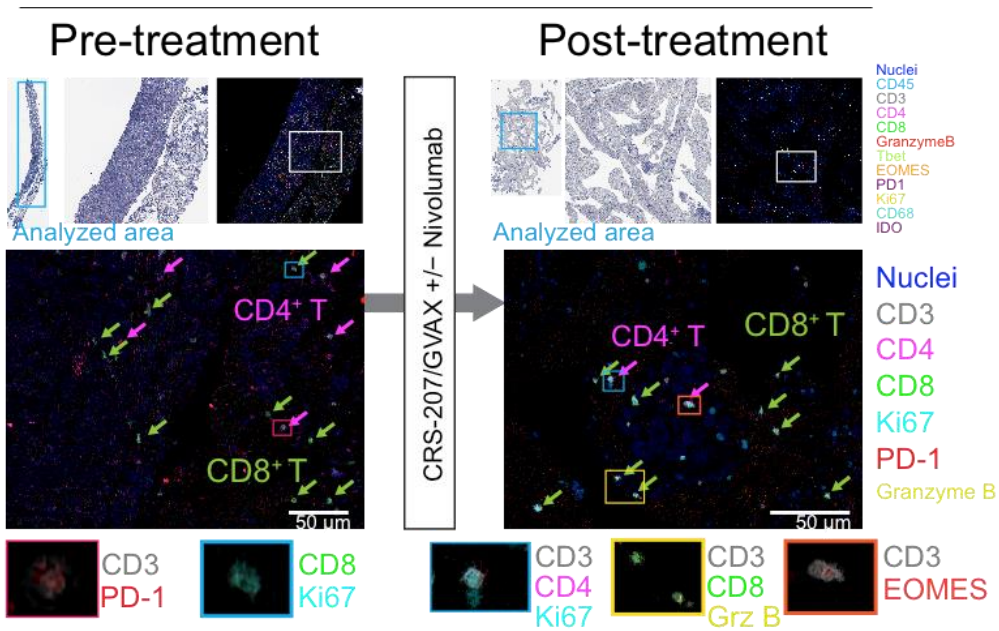


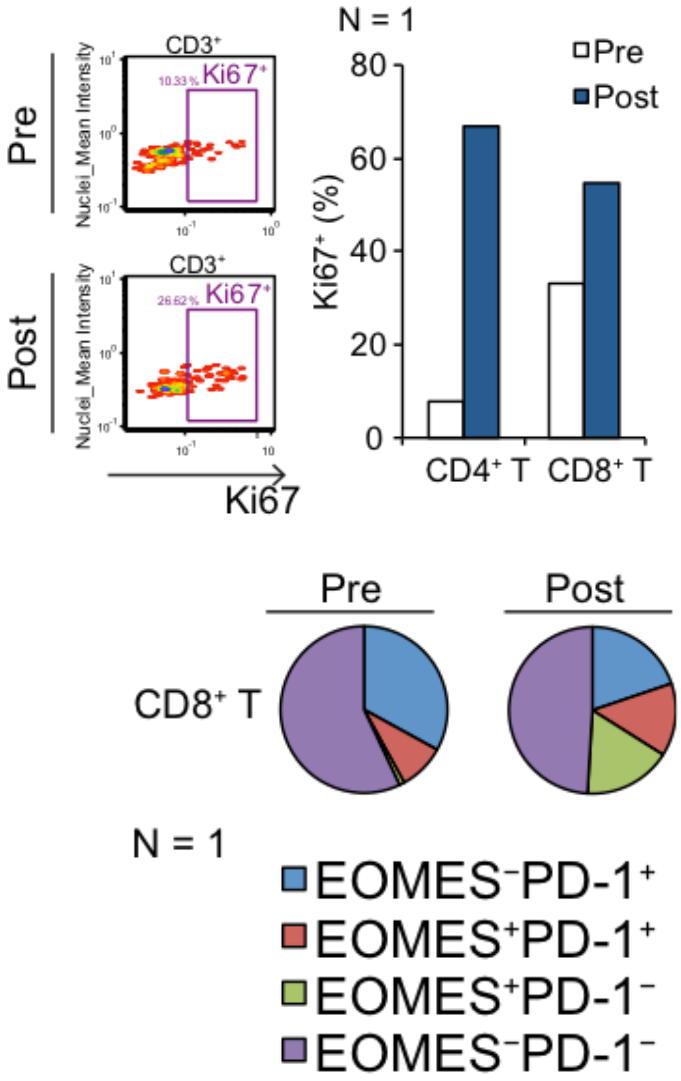
Week 10



Week 30

Multiplex IHC depicts evidence of T cell reinvigoration with GVAX/CRS207 + nivolumab





Post-vaccine increased EOMES expression which enhances T cell infiltration and is associated with a less exhaution

Le, Tsujikawa T, et al. Unpublished data

Example Mass Cytometry
Systemic Immunity Is Required for Effective Cancer Immunotherapy

Spitzer MH, Carmi Y, Reticker-Flynn NE, Kwek SS, Madhireddy D, Martins MM, Gherardini PF, Prestwood TR, Chabon J, Bendall SC, Fong L, Nolan GP, Engleman EG.
Cell, 2017

Used Mass Cytometry which enables evaluation of over 50 parameters to be quantified by replacing fluorophores with mass tags

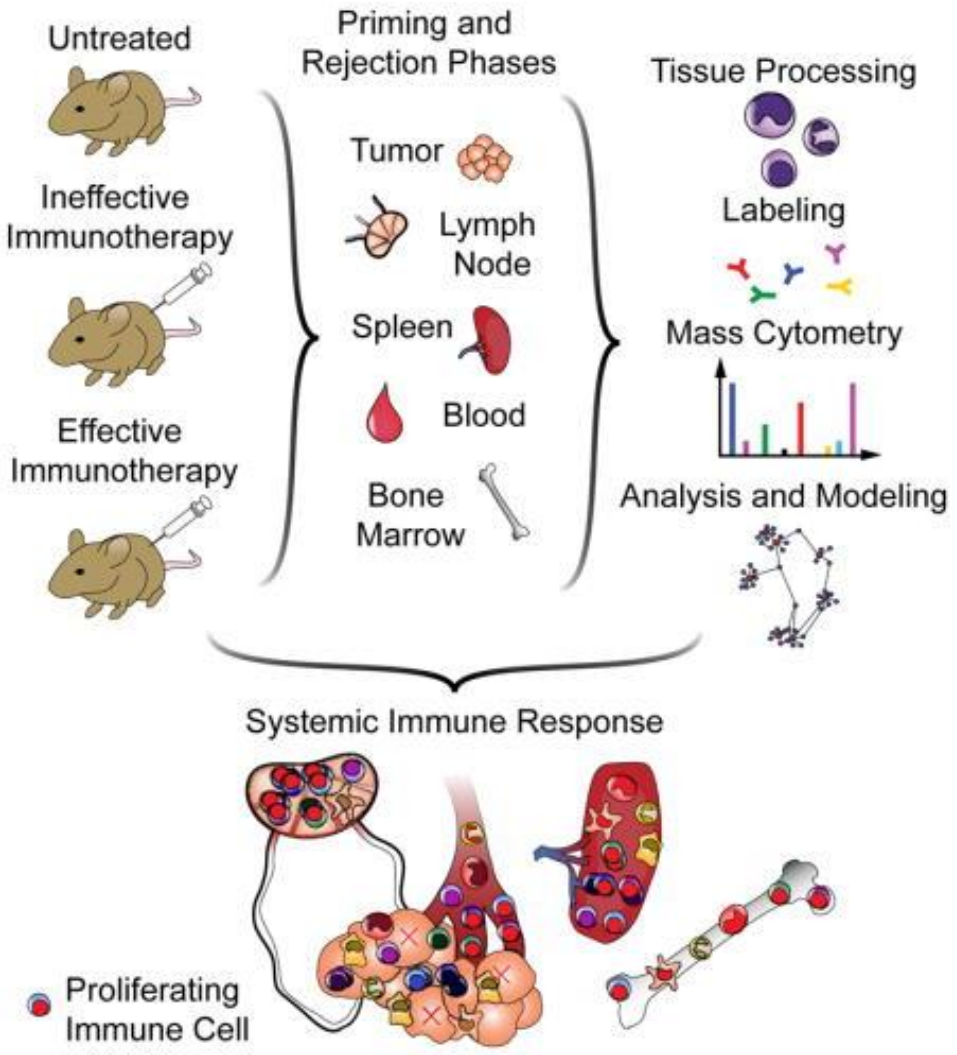
High throughput - 50 Parameters used to study a single cell among tens of thousands within a tumor

Evaluated immune responses in multiple tissues

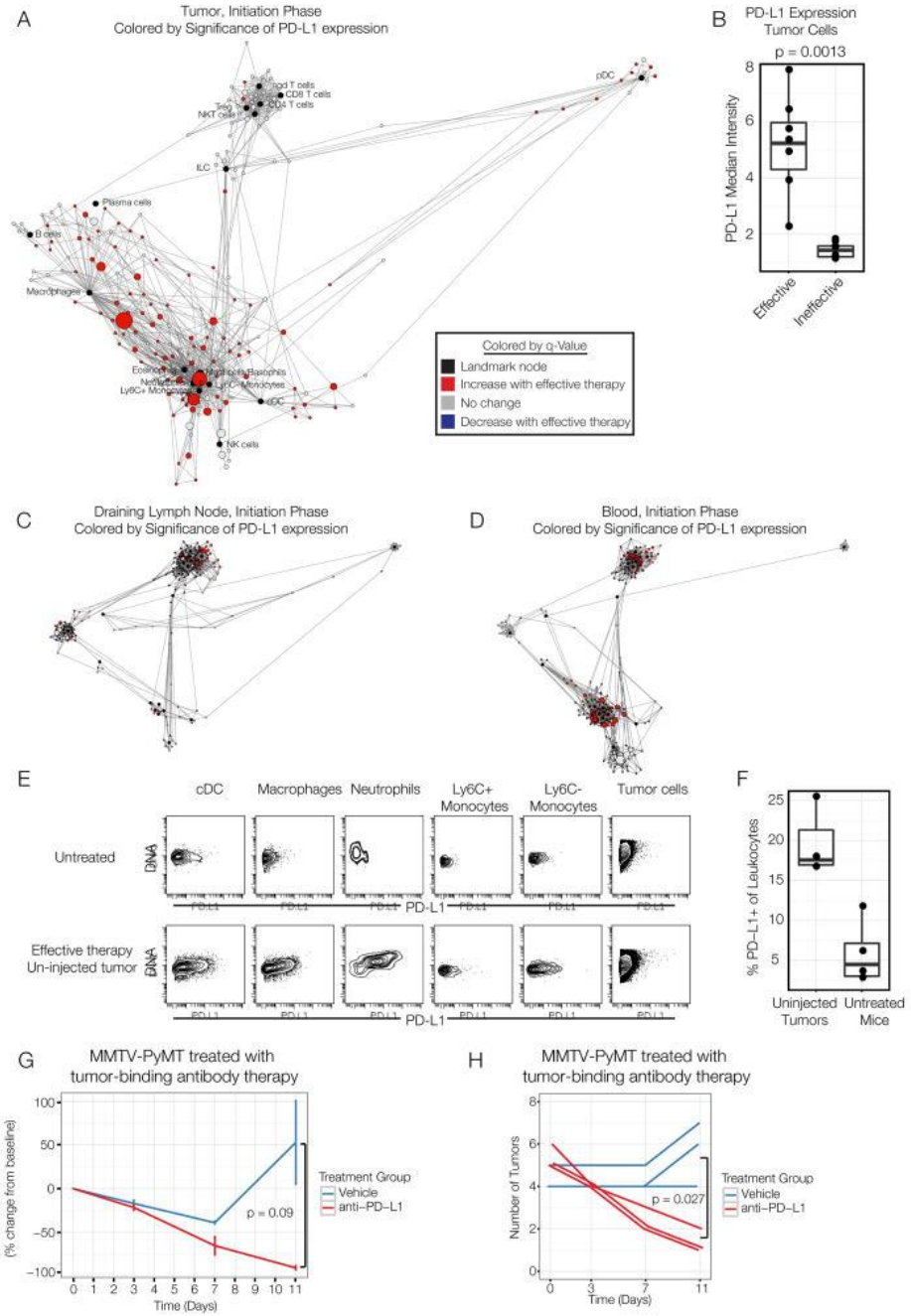
Immune cell proliferation is not maintained in the TME

Requires systemic proliferation to maintain an antitumor response

Response required CD4 T cells

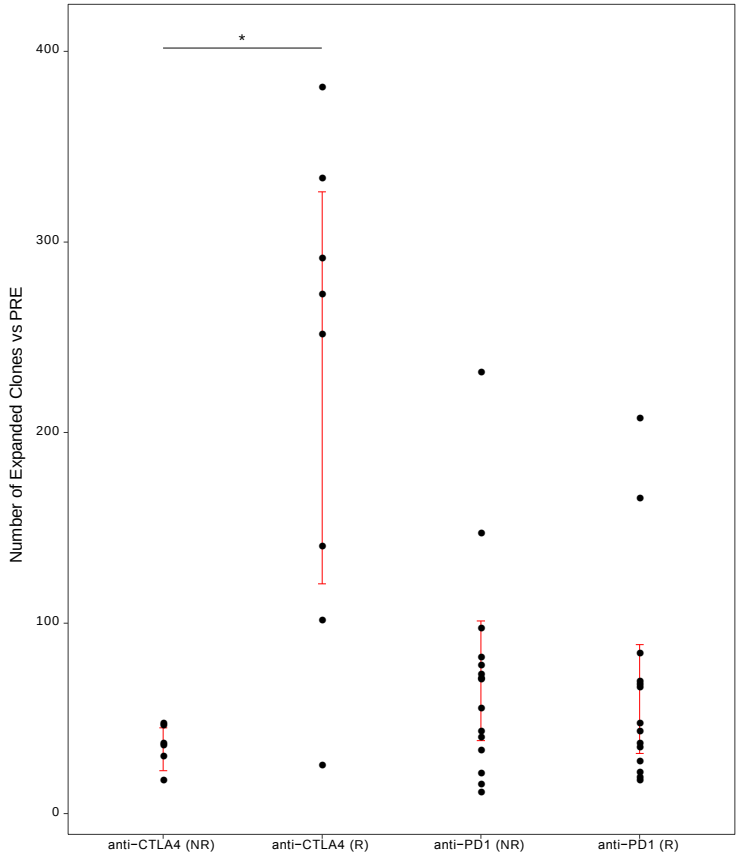


PD-L1 blockade + Anti-tumor antibody Enables distal tumor rejection



Example: TCR Sequencing of PBL Reflects Tumors and Suggests Mechanism for Combining CTLA-4 with PD-1/PD-L1

Responders had significantly more expanded clones than non-responders only in the anti-CTLA4 study



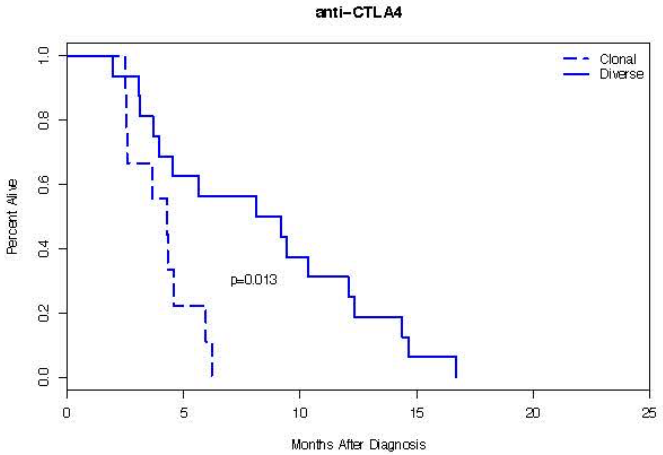
Alex Hopkins
JCI Insights, 2018

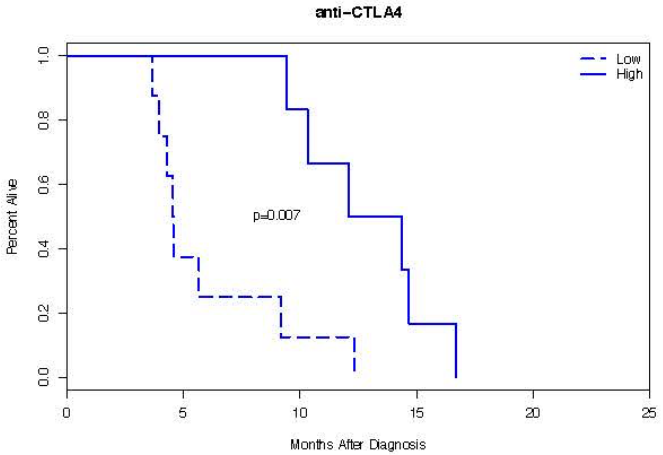
Kaplan Meier survival curves based on TCR clonality status or number of expanded clones

Clonality

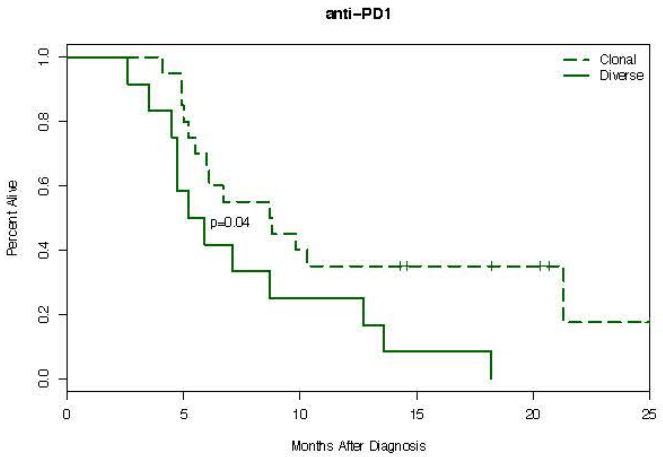
Expanded Clone

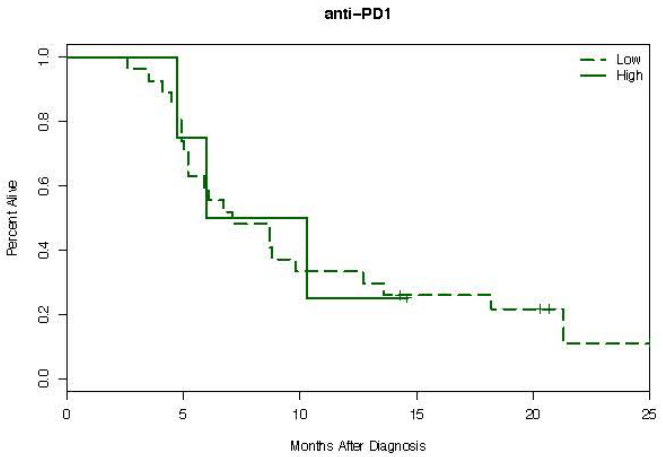
Anti-CTLA4





Anti-PD-1





>100 expanded clones

<100 expanded clones

Hopkins, et al., JCI Insights, 2018

Evolving TCRseq Methods: ImmunoMAP

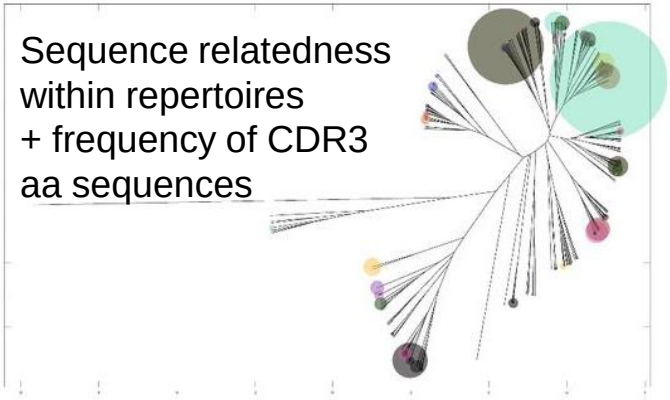
Sidhom et al, Cancer Immunology Research 2017

- Improves on standard TCRseq by taking into account sequence similarity or relatedness instead of identity alone
- Technique uses clustering of CDR3 sequences based on similarities and creates structural diversity metrics for whole TCR repertoires
- Assesses similarities between TCR sequences that recognize the same antigen while also evaluating the scope of diversity among different repertoires

ImmunoMAP

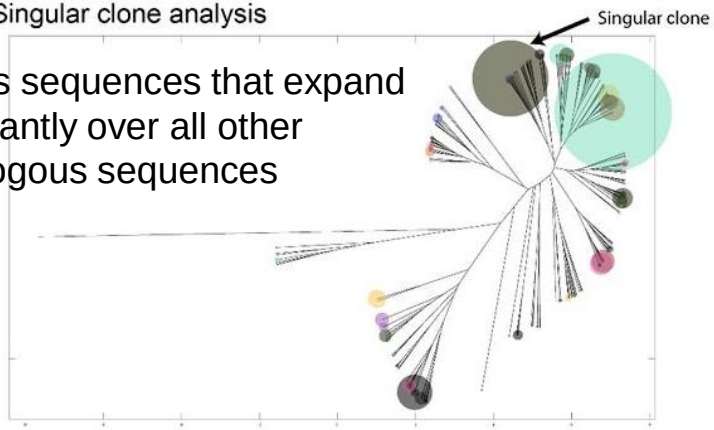
A Weighted repertoire dendogram

Sequence relatedness within repertoires + frequency of CDR3 aa sequences



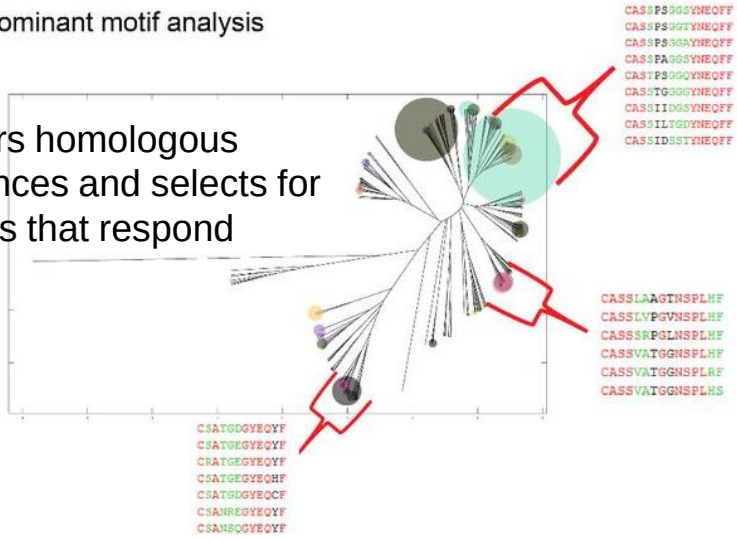
C Singular clone analysis

Defines sequences that expand significantly over all other homologous sequences



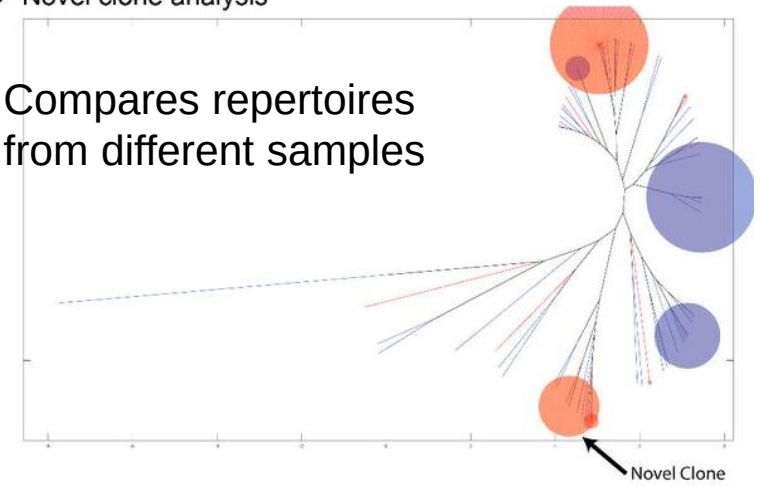
B Dominant motif analysis

Clusters homologous sequences and selects for clusters that respond

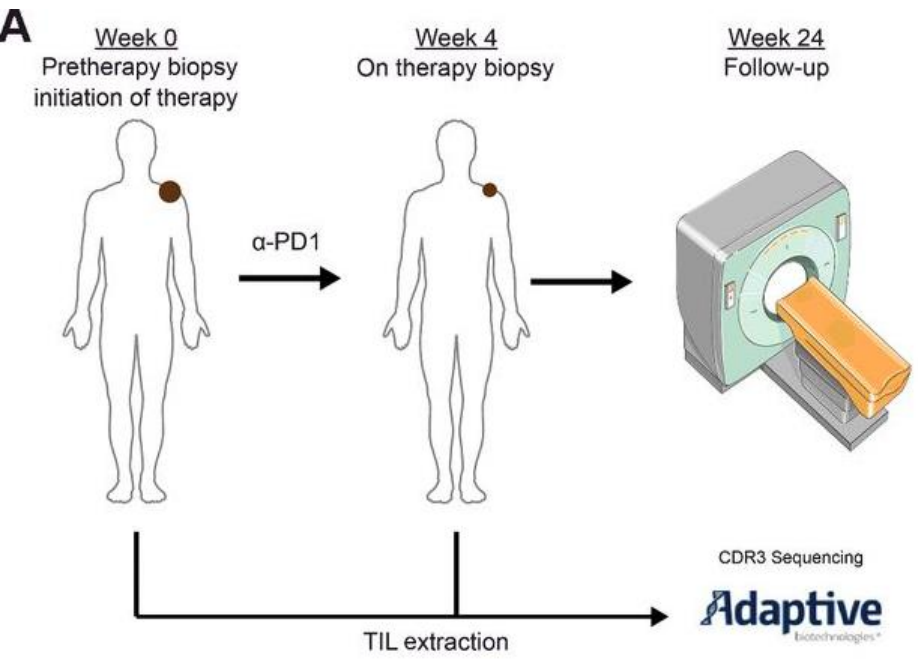


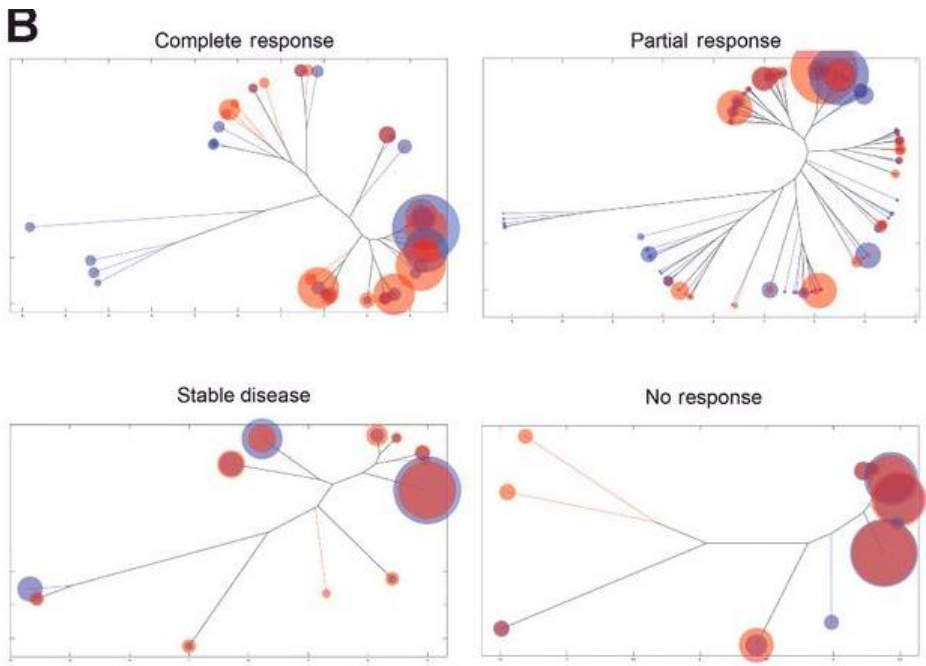
D Novel clone analysis

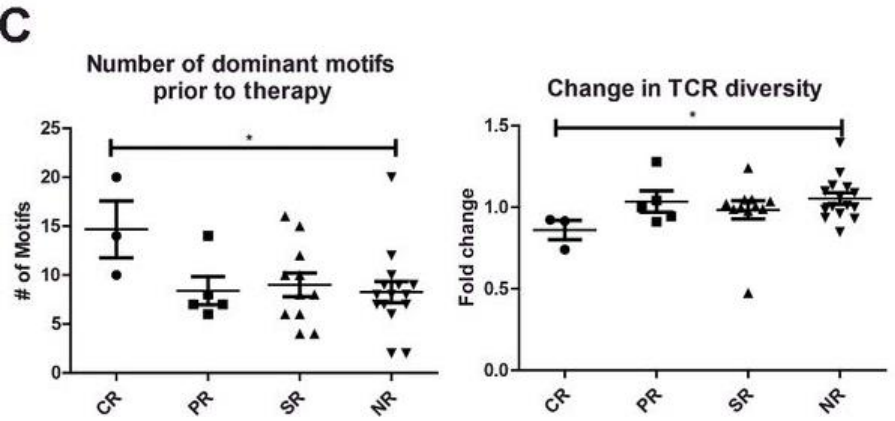
Compares repertoires from different samples

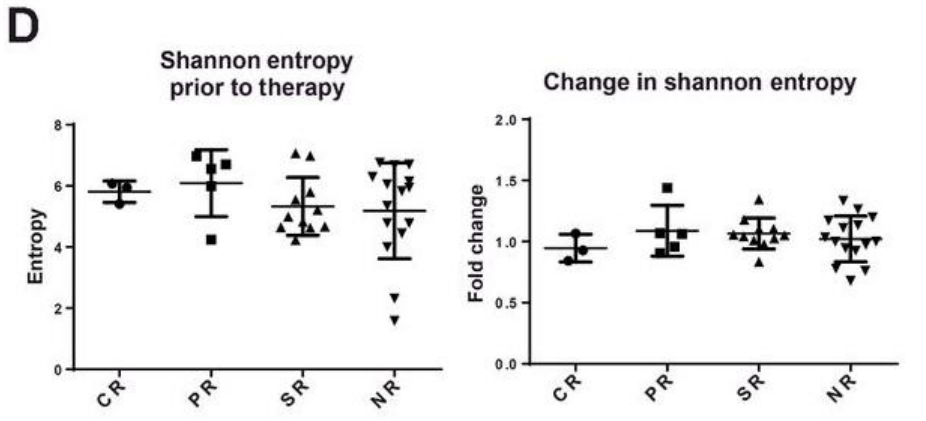


Diversity of dominant motifs predicts response to PD-1 blockade







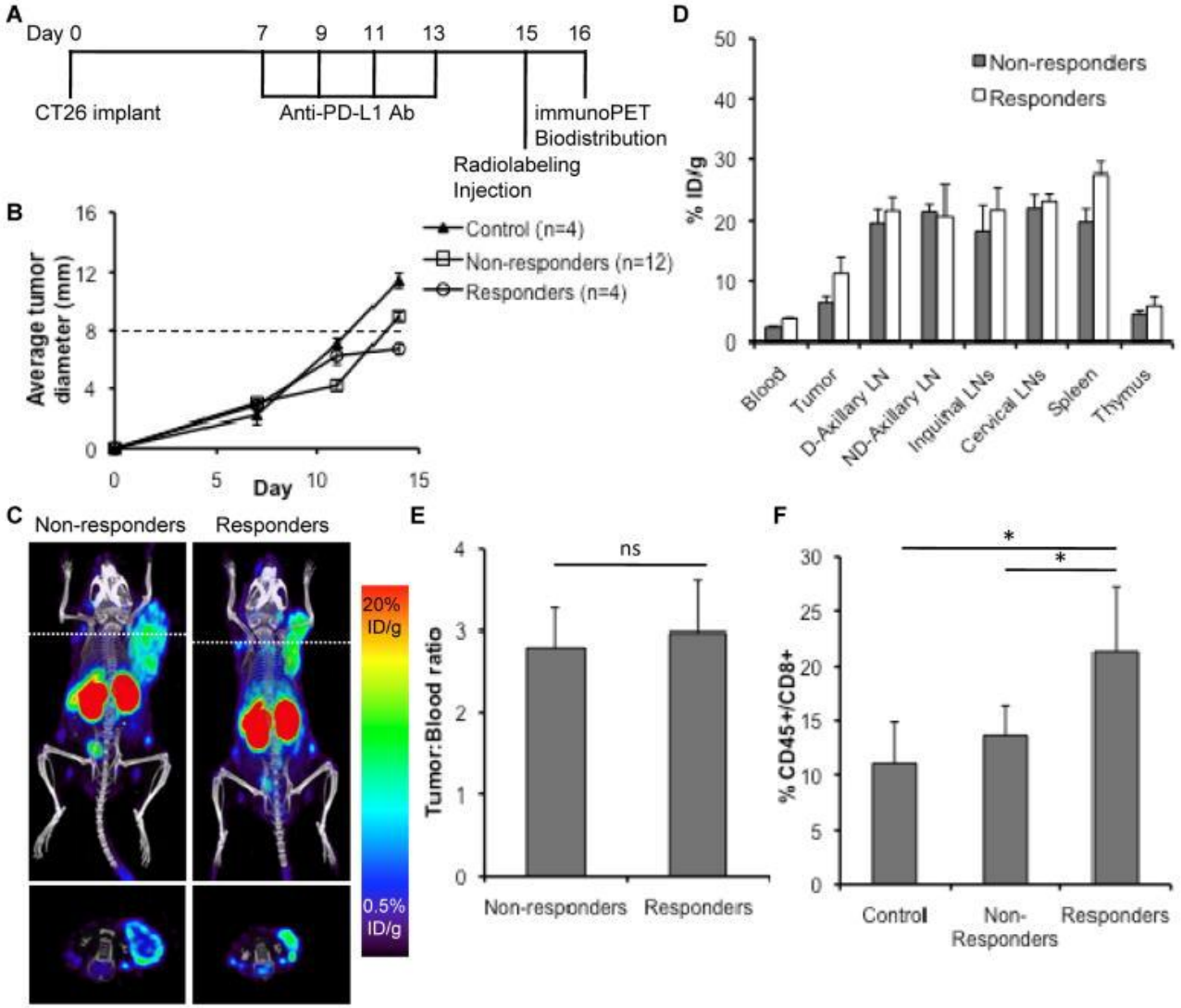


Example Imaging:
Anti-CD8 immunoPET of89Zr-malDFo-169 CDb in mice with colorectal cancer treated with anti-PD-L1

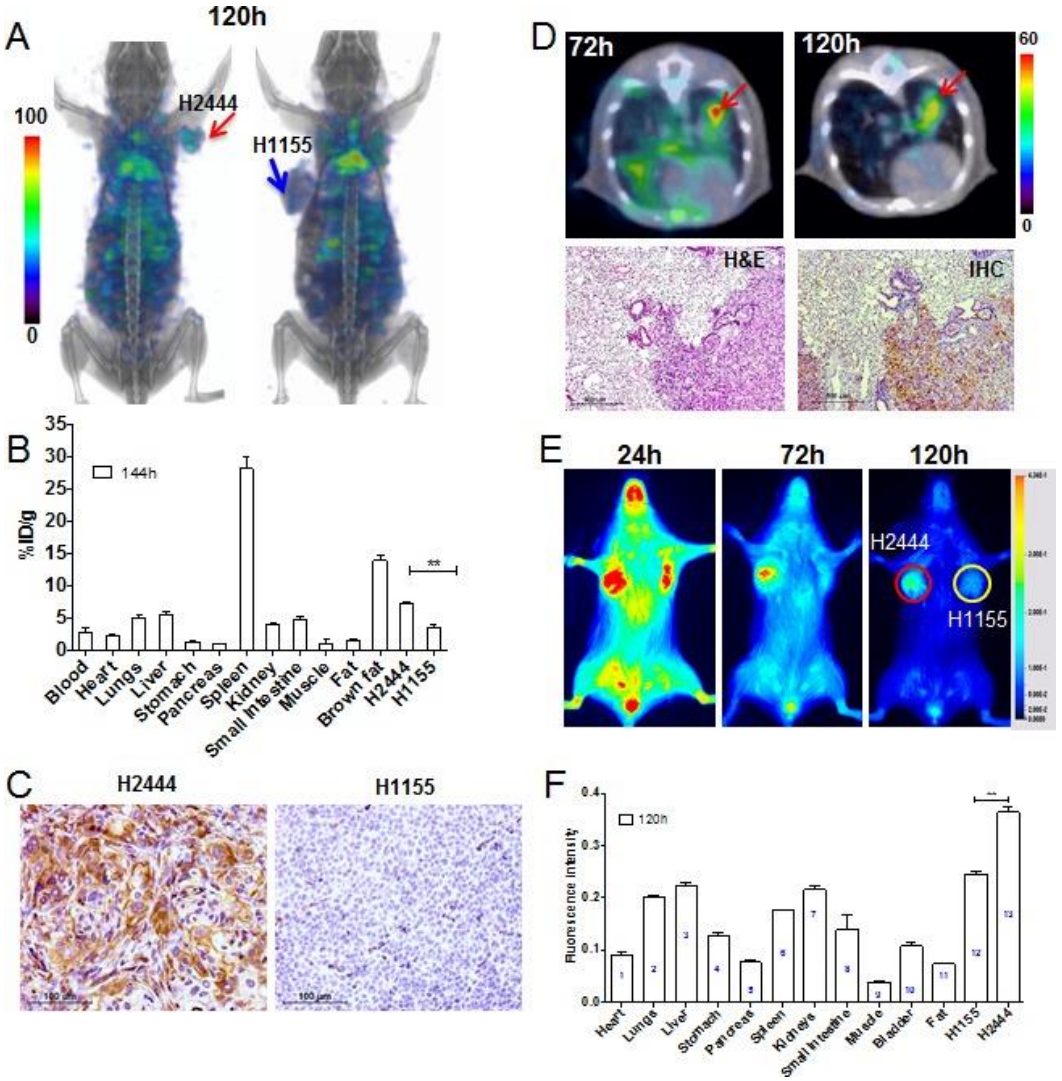
Other targets are being studied

Other methods are being developed to minimize background and immune cell modulation with the imaging agent

Tavere R et al, Ca Res 2016



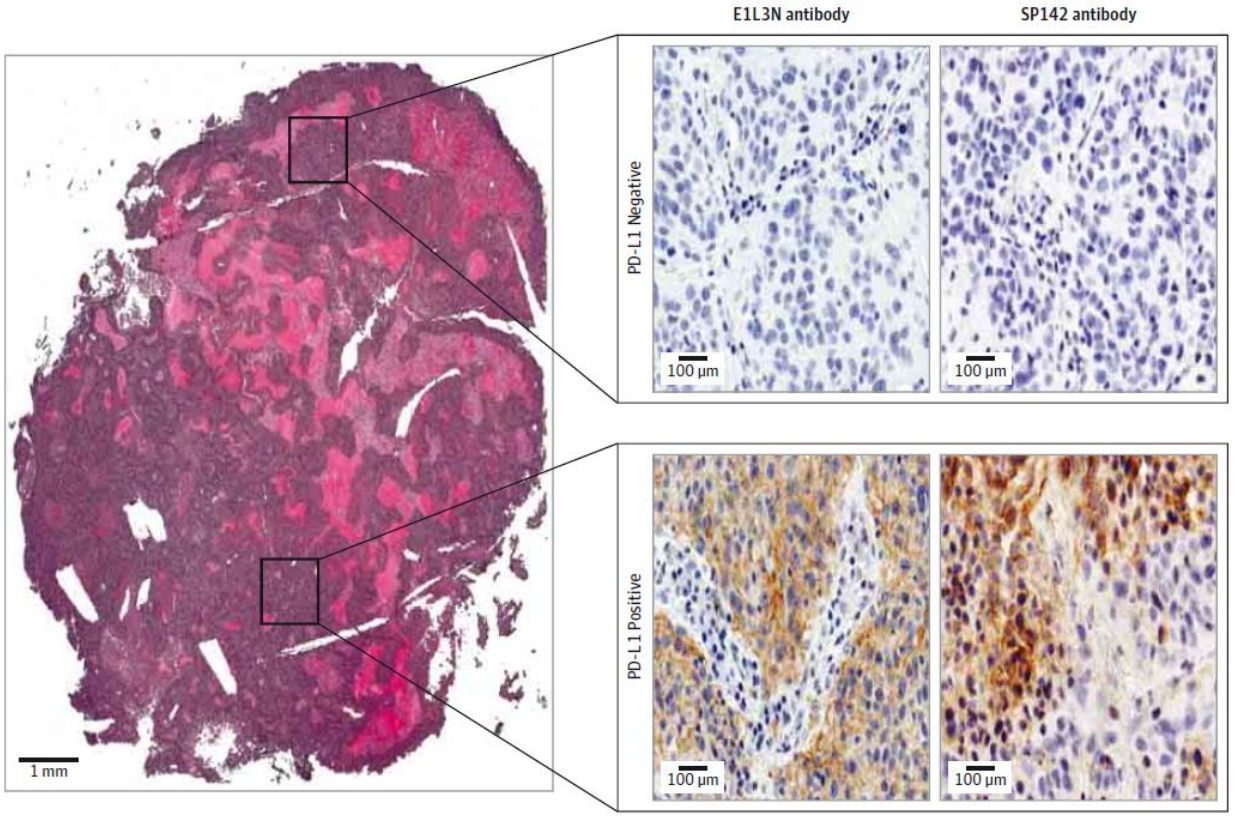
Example Imaging:
Anti-PD-L1 immunoPET with in mice with 111In anti-PD-L1 Monoclonal Ab in human lung cancer xenografts



Chatterjee et al, Oncotarget 2016

Cautionary Note:
Factors Limiting Biomarker Assessment: Spatial Heterogeneity And tumor site heterogeneity – where best to sample?

- Discordance between lesions
- Sampling error within a lesion
- Changes over time



McLaughlin J et al JAMA Oncology (2015)

Knowledge is Immune Power!

- Science needs to drive the rationale for PD-1/PD-L1 combinations
- Current approaches are mixed – often combining two agents because both showed some activity as single agent
- We need to develop the right biomarkers to study combinations
- New technologies are providing the opportunity to study combinations but we need to take into account each agent's mechanism
- Less invasive methods will provide the best opportunities for repetitive assessment and combination optimization

THANK YOU!