

# How to get a prognostic biomarker out of every clinical trial!

Lisa H. Butterfield, PhD.  
Vice President, PICI Research and Development  
Adjunct Professor, Microbiology and Immunology, UCSF  
Past President, SITC



## Disclosures:

StemImmune/Calidi Scientific and Medical Advisory Board, April 6, 2017-present

SapVax Advisory Board meetings Nov. 15, 2017; Dec. 6, 2018

NextCure, Scientific Advisory Board, 2018-2020

Western Oncolytics, Scientific Advisory Board, 2018-present

Torque Therapeutics, Scientific Advisory Board, 2018-2020

Khloris, Scientific Advisory Board, 2019-present

Pyxis, Scientific Advisory Board, 2019-present

Cytomix, Scientific Advisory Board, 2019-present

Vir, Scientific Advisory Board meeting, Feb. 2020

DCprime, Scientific Advisory Board meeting, Nov. 2020

RAPT, Scientific Advisory Board, 2020-present

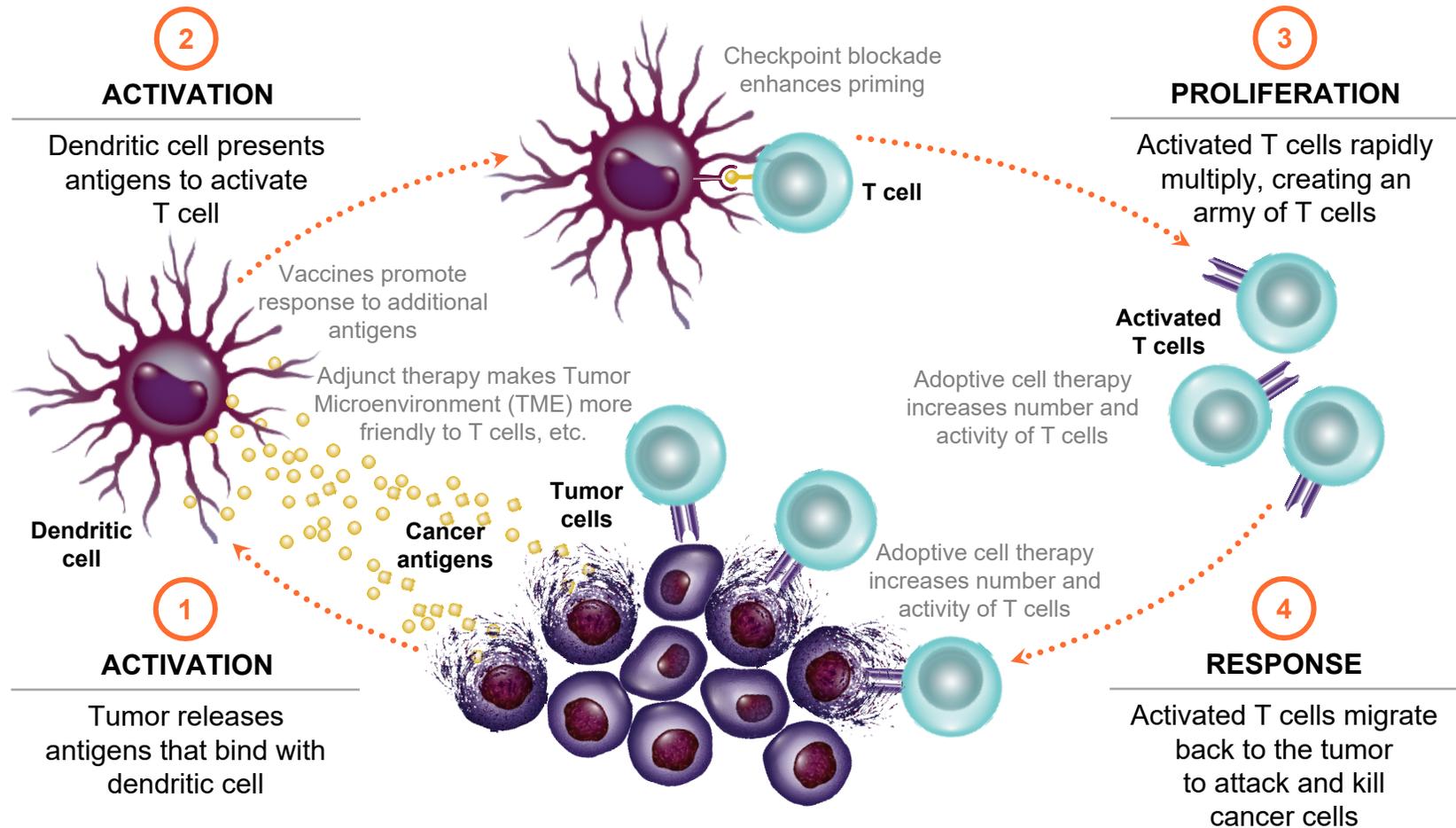
# Why don't we have more useful Biomarkers?

There did not use to be populations of clinical trial objective *clinical* responders:

1. We need the right specimens saved under standardized conditions. Variably banked specimens give noisy data. Some trials bank non-viable tumor (FFPE), minimal blood (poorly functional PBMC) and plasma samples.

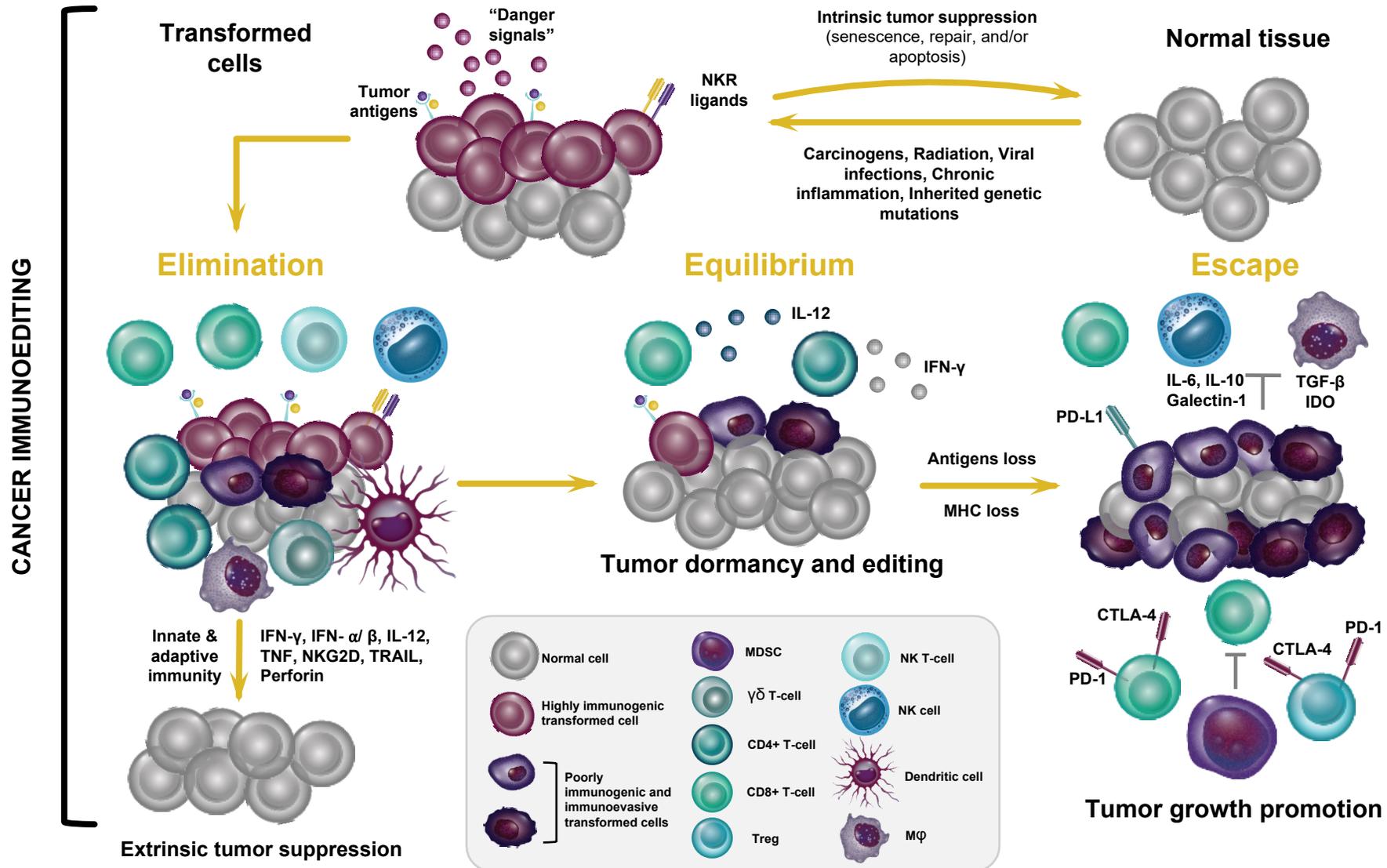
2. Immune assays can be costly; testing small numbers don't give robust, reproducible signals; guessing at 1-2 assays may miss the true biomarker.

# At the core: T cell Activation

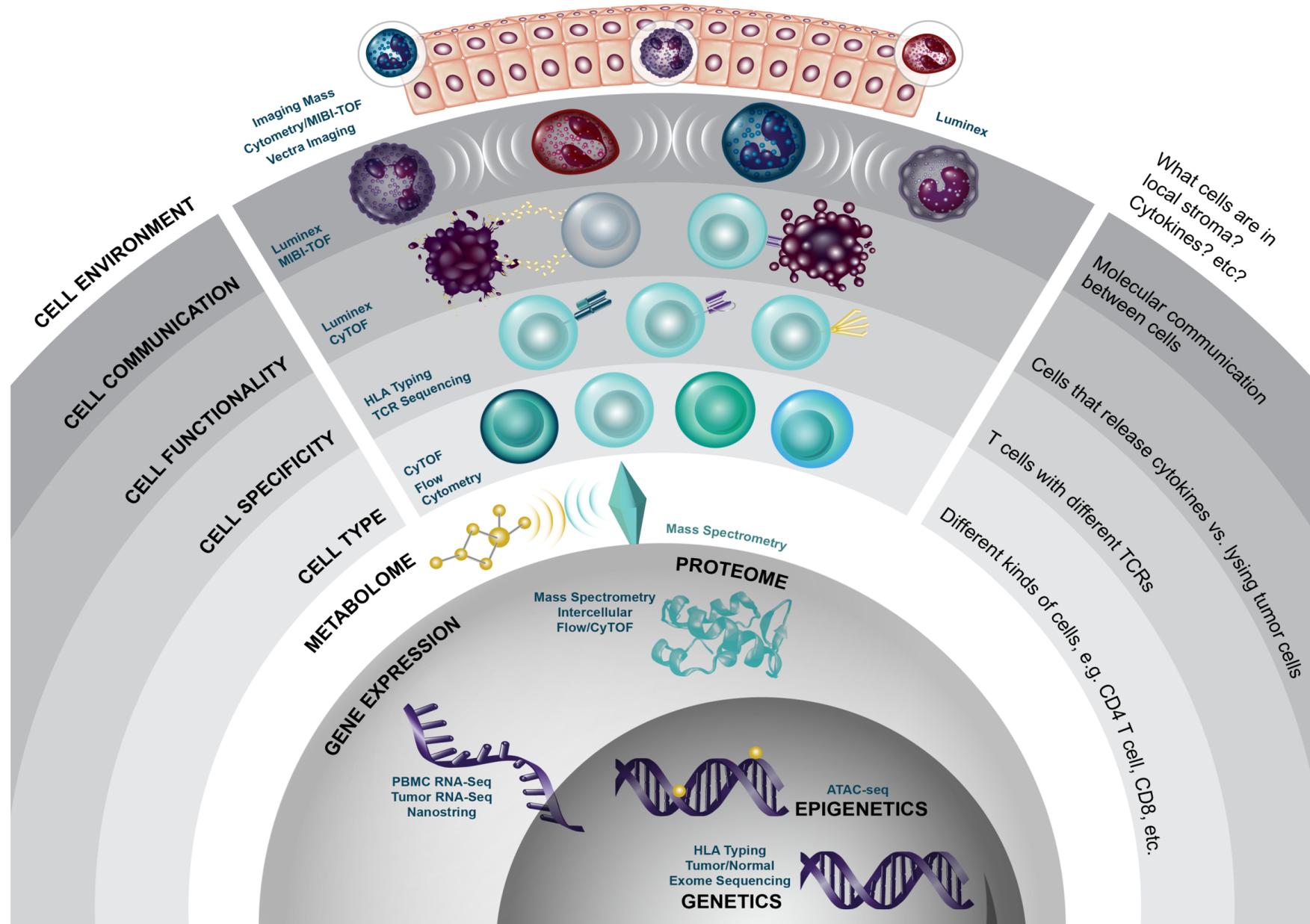




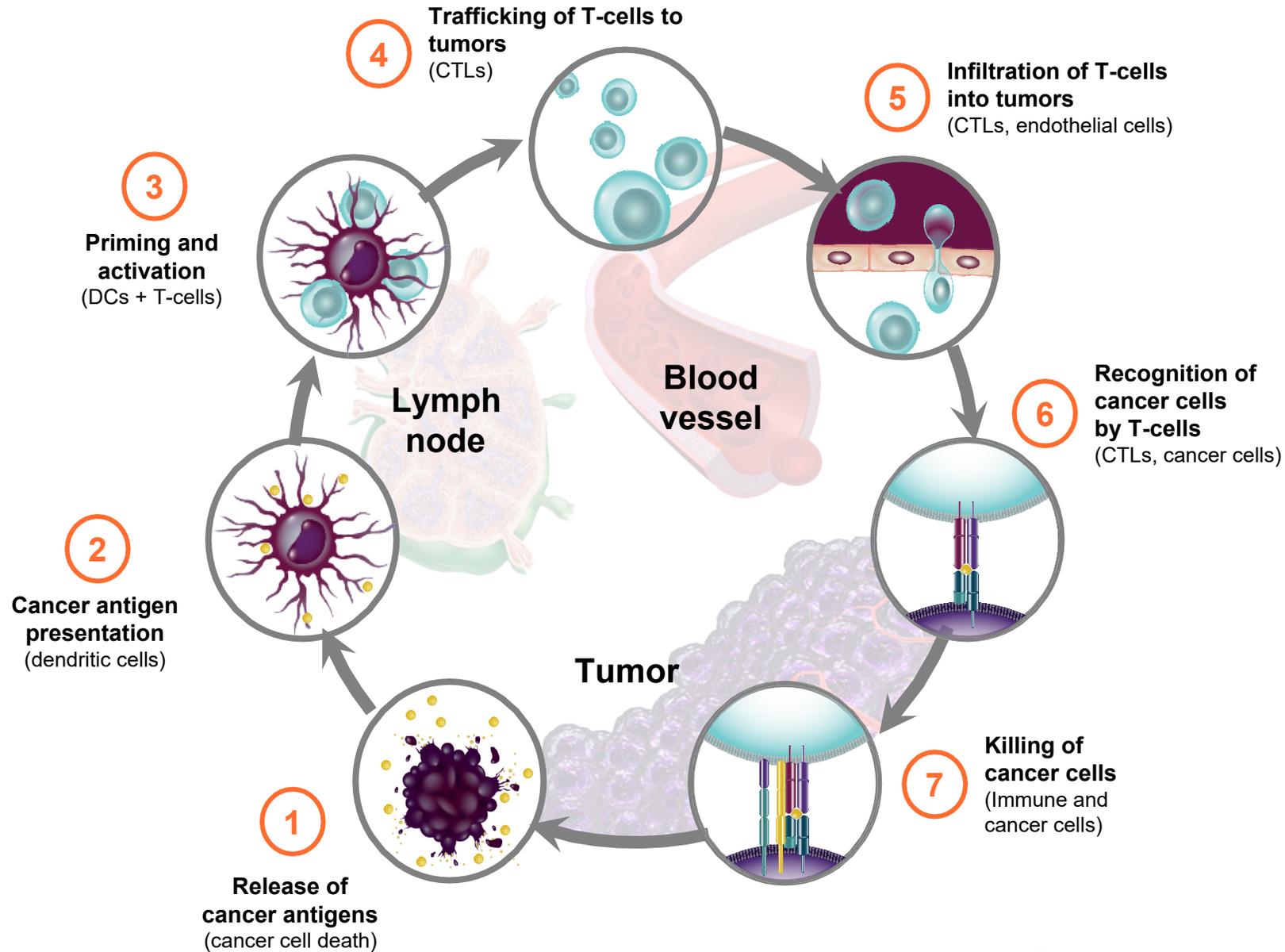
# Cancer Immunoediting



# Cellular Communications and Heterogeneity



# The Key: Cancer Immunity Cycle



# No sample left behind

...the reality is that most immune profiling efforts remain at a pilot scale. ...require greater attention to how samples are acquired and analyzed and community agreement on how store, share and interpret data.

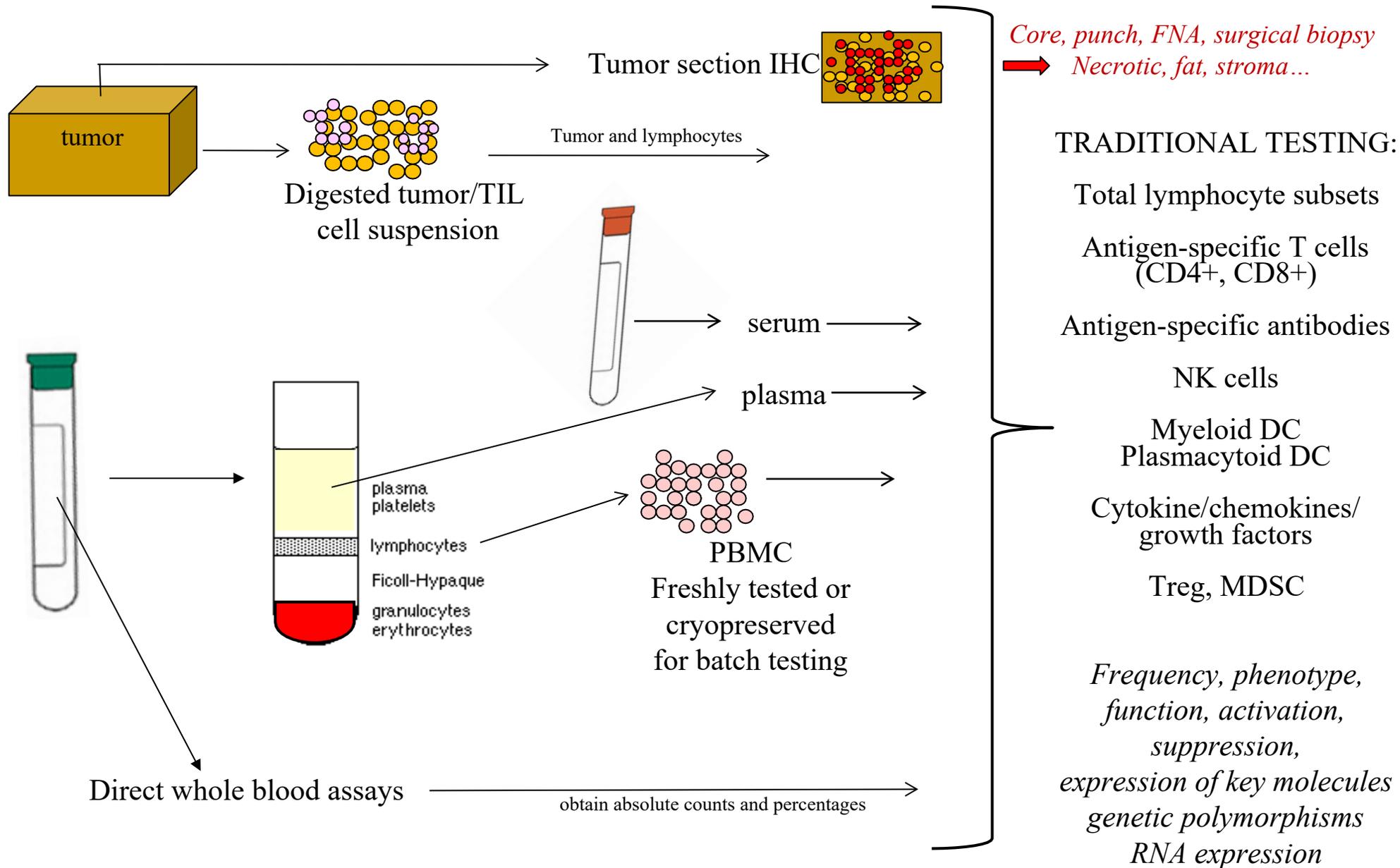
...samples are acquired for specific purposes, such as tumor biopsies for diagnosis or blood draws for determining tumor burden.

Once a sample has been used to answer a research question, often the remaining tissue or cell sample is lost. ...

in industry-sponsored studies, samples often remain sequestered in company freezers....Drug companies have little incentive to fund unsupervised analyses of their patient cohorts.

Grants focus on an investigator's one-dimensional analysis of samples and fail to provide funding for sample studies beyond that analysis.

...institutional support is often a hard-fought gain....



Patient-derived specimens used in immunologic monitoring

# Measuring Immunity in Immunotherapy Clinical Trials:

- Was the cytokine induced (right time/place/level)?
- Did the vaccine activate tumor-specific T cells?
- Did the adoptively transferred effector cells survive/traffic to the tumor/kill the tumor?
- Was immune suppression reversed?
- Were the target cells/molecules activated?
- Did the target cells/molecules get to the tumor site and show activity?
  
- *Was the therapeutic intervention an improvement?*
- *Why or why not?*



Need: reliable, standardized measures of immune response.

**CLIA** (Clinical Laboratory Improvements Amendments) rules:

Test Accuracy (close agreement to the true value),

Precision (agreement of independent results: same day, different day),

Reproducibility (intra-assay and inter-assay)

Reportable range (limits of detection)

Normal ranges (pools of healthy donors, accumulated patient samples),

Personnel competency testing

Equipment validation, monitoring

Reagent tracking

# Central Immunology Laboratory

Clinical Site

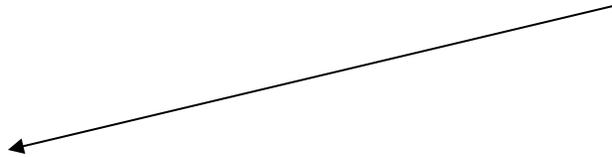
Central Lab

Screen or enrollment:  
fax blood kit request



Kit prepared and  
shipped ground

Pt. blood draw  
mailed O/N to lab

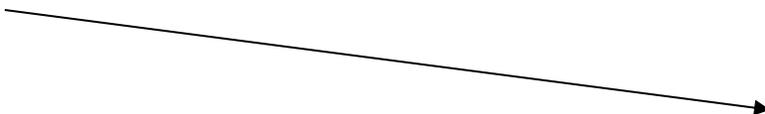


Blood processed and  
banked according to  
SOPs within 24 hours



Assays performed per  
SOPs, send results

Gather lab and  
clinical data;  
biostatistics



Results to PI  
publish

**Memorandum DATE:** July 12, 2013

**FROM:** James A. Zwiebel, M.D.  
Chief, Investigational Drug Branch, Cancer Therapy Evaluation Program  
Division of Cancer Treatment and Diagnosis

Tracy Lively, Ph.D.  
Deputy Associate Director, Cancer Diagnosis Program  
Division of Cancer Treatment and Diagnosis

**SUBJECT:** Guidelines for Biomarker Assays Used in CTEP-Sponsored, Early Phase Clinical Trials Performed Under CTEP IND

**TO:** Investigators and Company Collaborators

Briefly, markers are **integral** when they are essential for conducting the study as they *define eligibility, stratification, disease monitoring or study endpoints.*

Markers are considered **integrated** when they actually are *testing a hypothesis based on preexisting data* and not simply generating hypotheses. Such integrated markers need to be performed ideally on all patients in a trial and *the assay should already have been tested in human subjects with the disease in question and demonstrated reproducible analytic qualities.*

In contrast, **exploratory biomarkers** may not be performed on all subjects in a trial, and collection of these exploratory markers by investigators participating in the trial may be voluntary.

# SITC cancer immunotherapy resource document: a compass in the land of biomarker discovery

Siwen Hu-Lieskovan,<sup>1,2</sup> Srabani Bhaumik,<sup>3</sup> Kavita Dhodapkar,<sup>4,5</sup>  
Jean-Charles J B Grivel,<sup>6</sup> Sumati Gupta,<sup>7</sup> Brent A Hanks,<sup>8</sup> Sylvia Janetzki,<sup>9</sup>  
Thomas O Kleen,<sup>10</sup> Yoshinobu Koguchi,<sup>11</sup> Amanda W Lund,<sup>12</sup> Cristina Maccalli,<sup>6</sup>  
Yolanda D Mahnke,<sup>13</sup> Ruslan D Novosiadly,<sup>14</sup> Senthamil R Selvan,<sup>15</sup>  
Tasha Sims,<sup>16</sup> Yingdong Zhao,<sup>17</sup> Holden T Maecker,<sup>18</sup> (*JITC 2020*)

Tried, true and very well standardized  
functional benchmark

*(albeit single functional parameter  
usually):*

the IFN $\gamma$  ELISPOT assay

# Standardized ELISPOT Assays

## **E4697** (*n=20, 2008-2009*)

	<u>spontaneous</u>	<u>PMA/I (+)/OKT3</u>
Healthy control ave.:	4.9 (54%CV)	304 (19.2%CV <i>intra-assay</i> ) (48% CV inter-assay)
Patient ave.:	0.7 (35%CV)	81 (38.7 %CV)

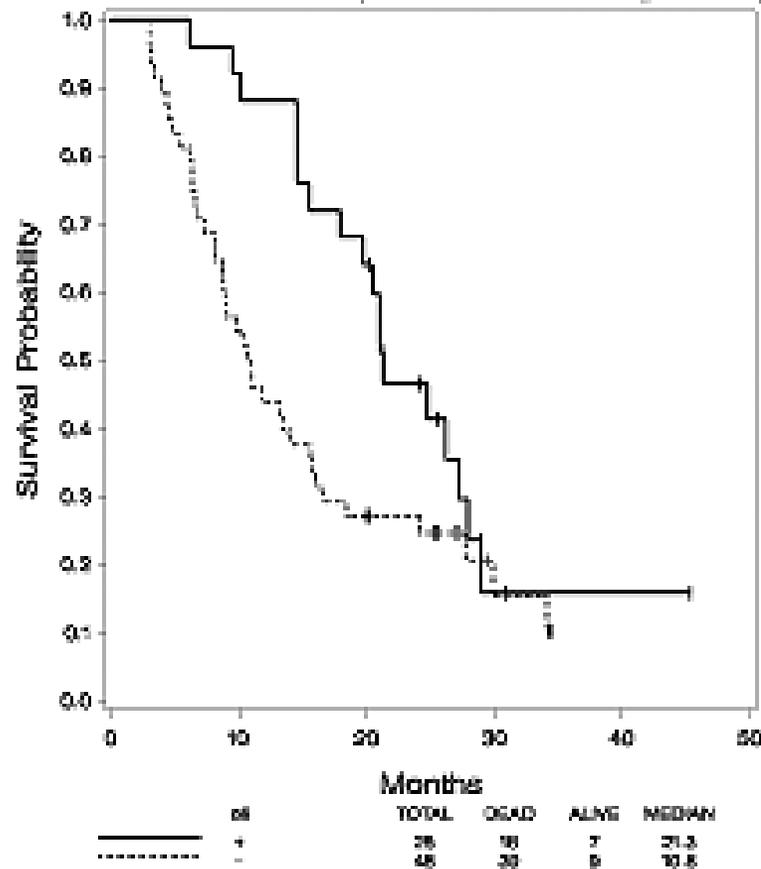
## **E1696** (*n=20, 2002-2003*)

	<u>spontaneous</u>	<u>PMA/I (+)/PHA</u>
Healthy control ave.:	5.4 (56%CV)	284 (15.5%CV <i>intra-assay</i> ) (51% CV inter-assay)
Patient ave.:	19 (40%CV)	171 (18.8 %CV)

# Immune Response Correlates with Overall Survival

## Multiple melanoma antigen peptide vaccine ± GM-CSF ± IFNα2b

Fig 4: Overall Survival by ELISPOT Response (n = 73)



The Kaplan-Meier plot for OS by immune response status is shown for E1696 (Phase II).

*There was a significant difference in OS by immune response status. Immune responders lived longer than the non-immune responders (median OS 21.3 versus 10.8 months, p=0.033).*

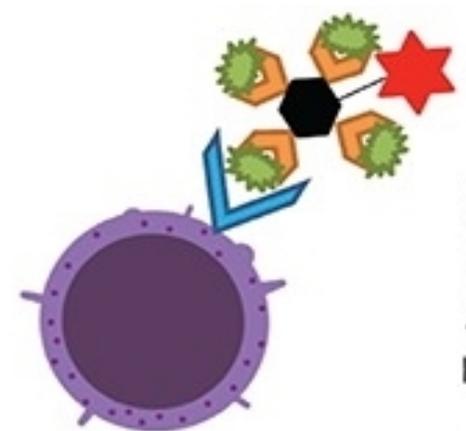
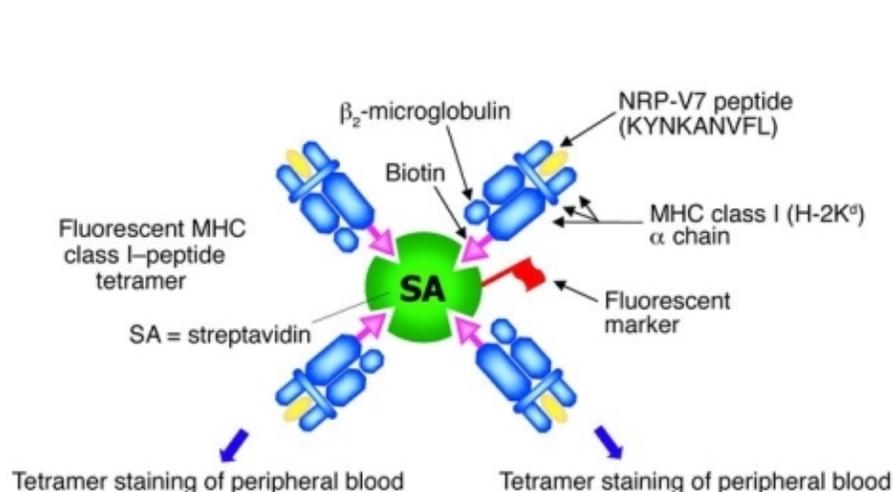
*(Kirkwood, J.M., Clin. Cancer Res. 2009)*

Peptide-specific and phenotypic:

## MHC multimer

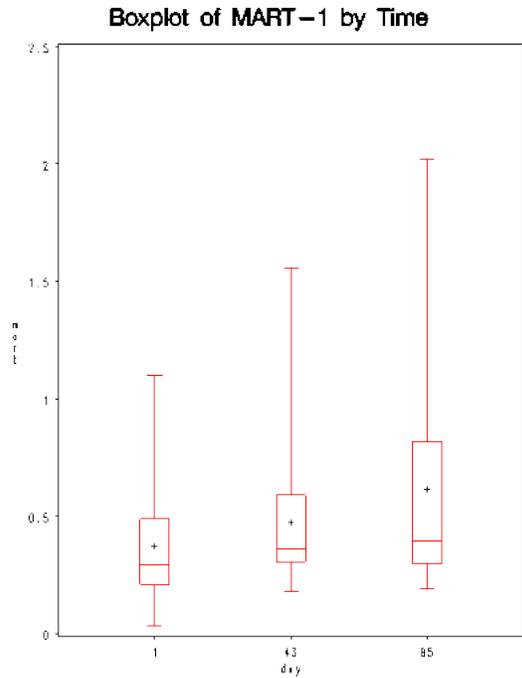
(tetra-, penta-...dextra-...):

count the cell, grab the cell, profile the cell

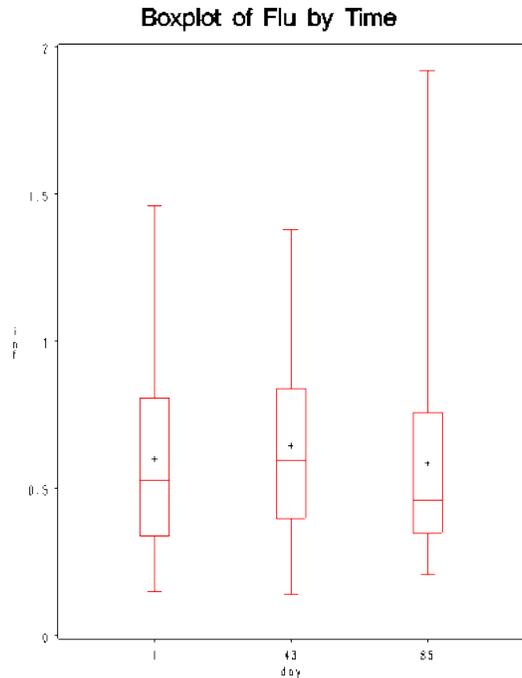


# Immune Response: E1696

## Melanoma antigen peptide-specific CD8+ T cells



%MART-1  
CD8+ cells: .29% .36% .39%



.53% .53% .43%

%effector  
cells: 10% 16% 18%  
(p=0.048)

17% 17% 16%  
(p = ns)

### MHC Tetramer Analysis:

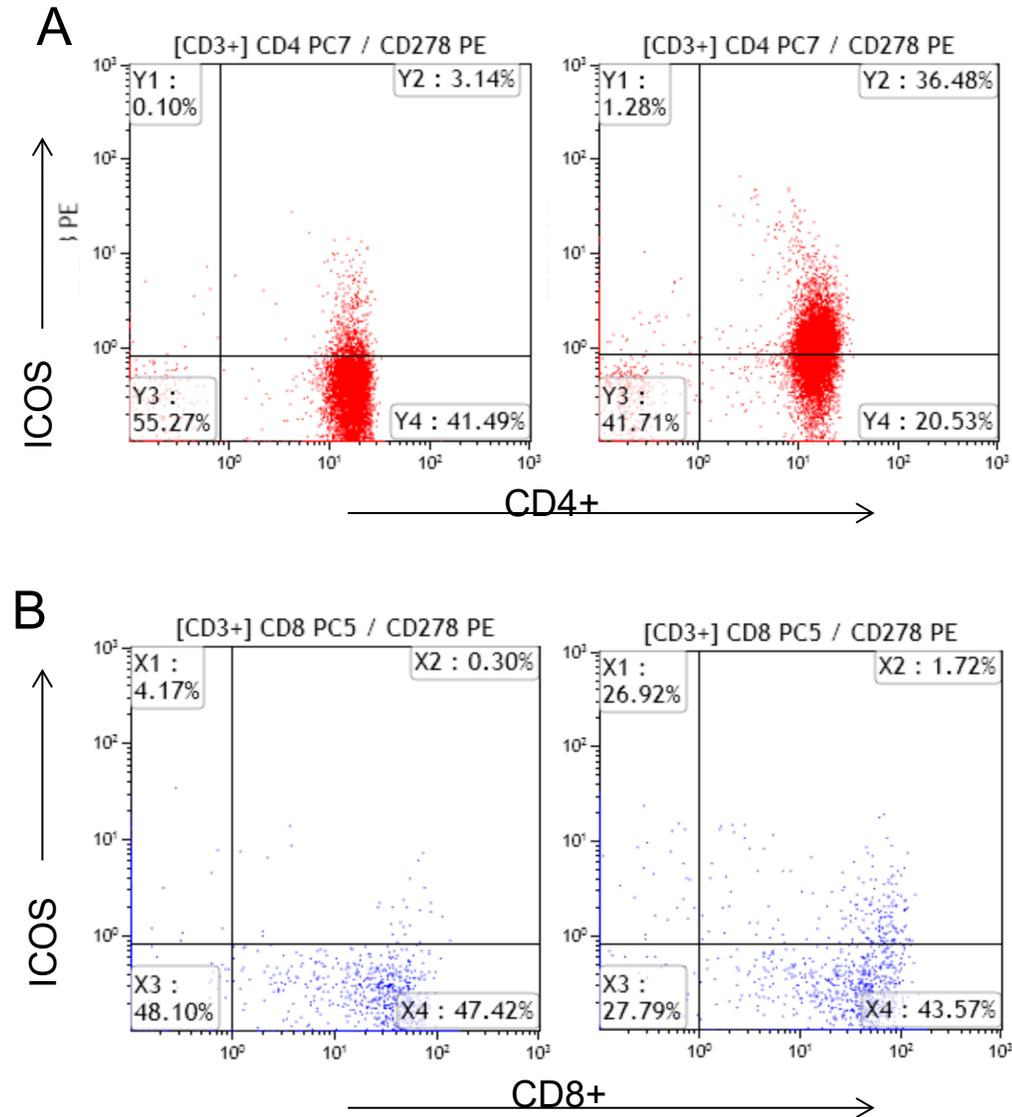
The frequency of vaccine peptide-specific CD8+ T cells was measured by MHC tetramers, showing significant increases for all 3 melanoma antigen peptides (not Flu).

The MART-1 and gp100-specific cells differentiated towards effector cells with vaccination.

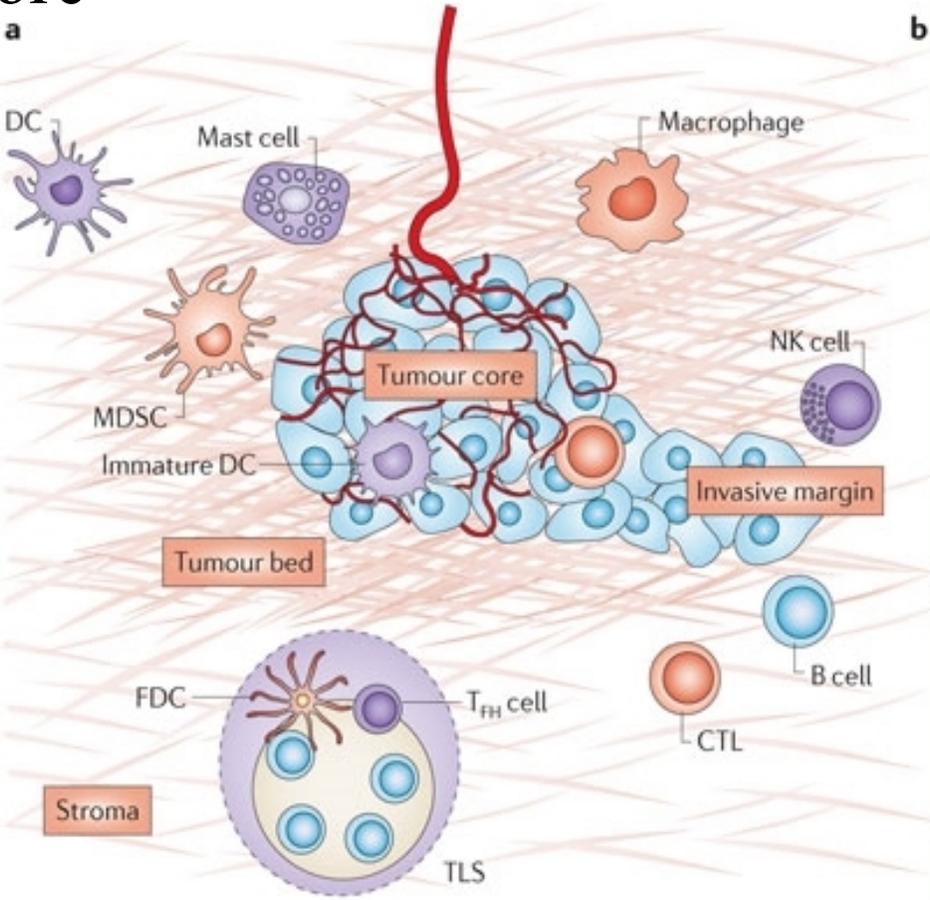
# Multicenter, Randomized Phase II Trial of GM-CSF plus Ipilimumab (Ipi) vs. Ipi Alone in Metastatic Melanoma: E1608

The addition of GM-CSF to ipilimumab significantly improves OS in patients with metastatic melanoma. Improved tolerability was seen in patients receiving GM-CSF.

Biomarkers (*mechanistic insights*): Increased ICOS on CD4+ and CD8+ T cells correlates with clinical outcome. *Now being tested in other clinical trials.*



# ImmunoScore



Immune contexture	Parameters: positive association with survival
Type	CTLs (CD3 <sup>+</sup> CD8 <sup>+</sup> ) Memory T cells (CD45RO <sup>+</sup> )
Location	Core of the tumour Invasive margin
Density	<p>Number of cells per mm<sup>2</sup></p> <p>1    10    100    1,000    10,000</p> <p>CD3<sup>+</sup><sub>CT</sub>    —————</p> <p>CD3<sup>+</sup><sub>IM</sub>    —————</p> <p>CD8<sup>+</sup><sub>CT</sub>    —————</p> <p>CD8<sup>+</sup><sub>IM</sub>    —————</p> <p>CD45RO<sup>+</sup><sub>CT</sub>    —————</p> <p>CD45RO<sup>+</sup><sub>IM</sub>    —————</p>
Functional orientation	T <sub>H</sub> 1 cell-associated factors (IFN $\gamma$ , IL-12, T-bet and IRF1) Cytotoxic factors (granzymes, perforin and granulysin) Chemokines (CX3CL1, CXCL9, CXCL10, CCL5 and CCL2) T <sub>H</sub> 17 cells, T <sub>Reg</sub> cells and T <sub>H</sub> 2 cells have a variable effect on survival, depending on tumour type
TLS	Presence and quality

Nature Reviews | Cancer

Tumor anatomy showing the features of the immune contexture, including the tumor core, the invasive margin, tertiary lymphoid structures (TLS) and the tumor microenvironment. The distribution of different immune cells is also shown.

CT, core of the tumor; DC, dendritic cell; FDC, follicular dendritic cell; IM, invasive margin; IRF1, interferon regulatory factor 1. *J. Galon, W. Fridman*

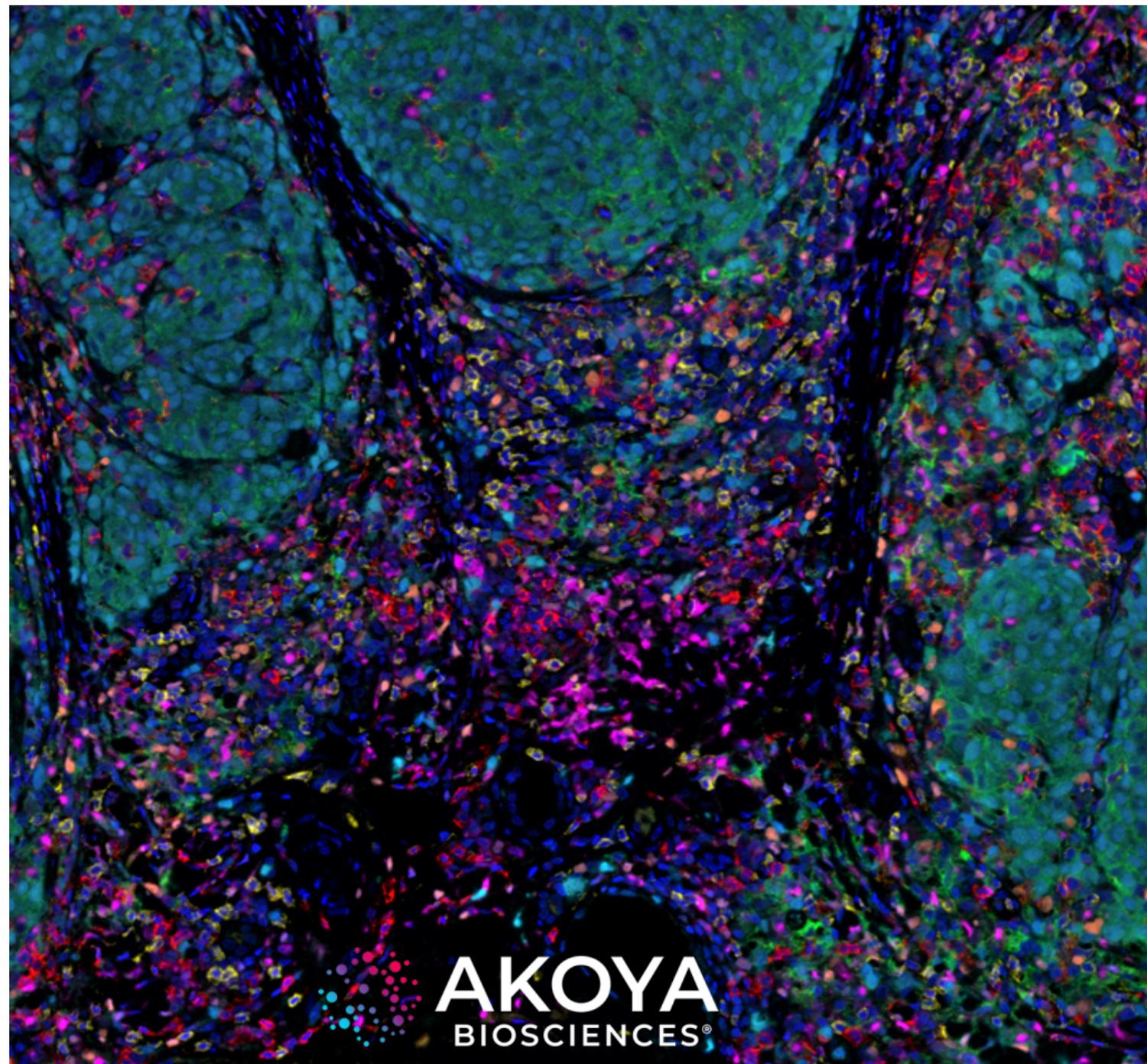
# TME analysis: multiplex tissue staining:

Assessments of T cell density, location, and phenotype in baseline and on-treatment tumor samples provide important insights into the role of these cells in patients with cancer and immune checkpoint therapy.

It is apparent that complex immune monitoring approaches and robust computational solutions are needed to better characterize the tumor immune contexture.

**Melanoma,**  
Vectra platform,  
Phenoptics 2.0  
Analytically validated.  
High-throughput.

Melanoma  
FoxP3  
PD-L1  
Sox10/S100  
PD-1  
CD8  
CD68  
DAPI



## Melanoma, CODEX imaging platform

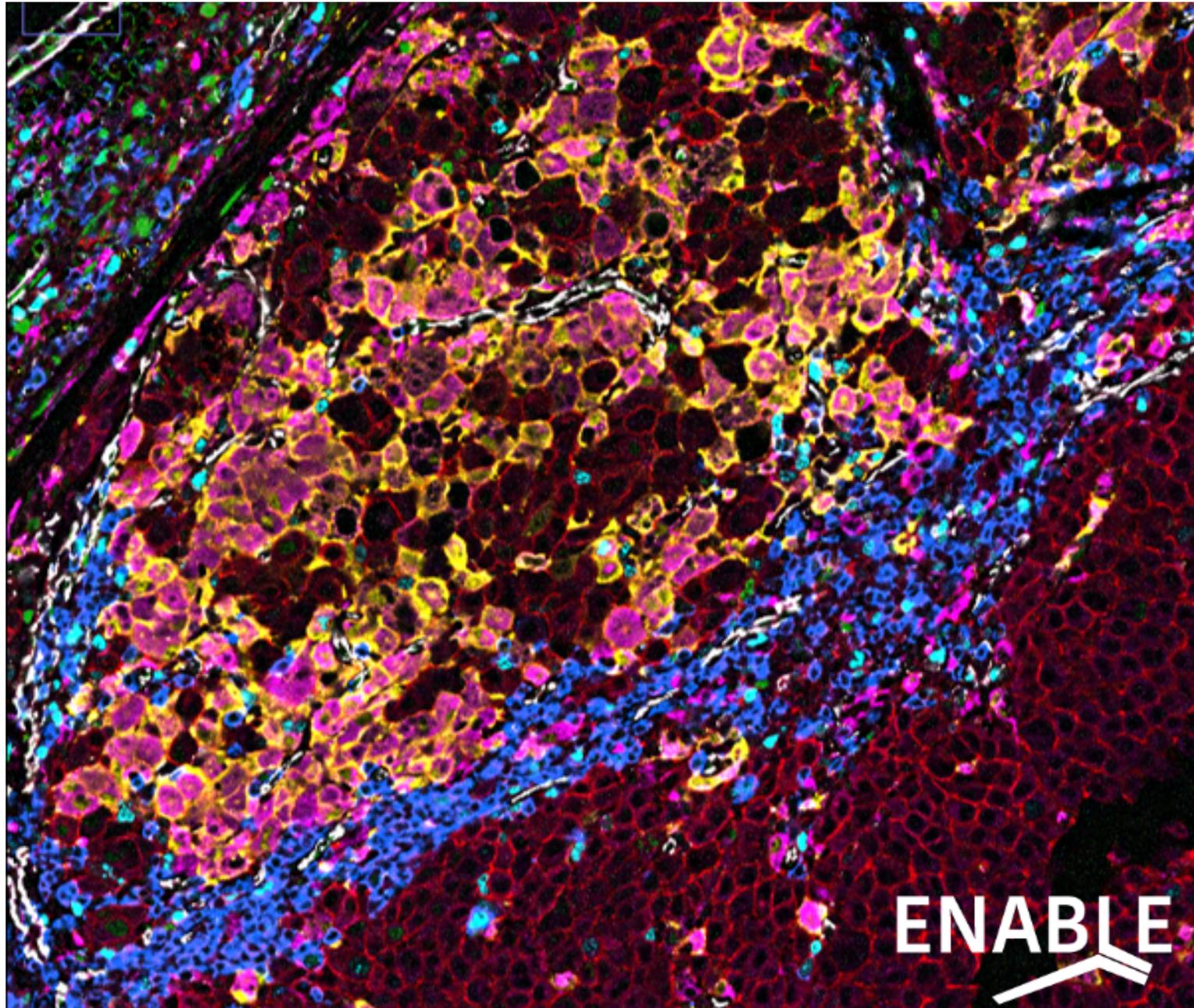
Cell 2020: “Coordinated Cellular Neighborhoods Orchestrate Antitumoral Immunity at the Colorectal Cancer Invasive Front” G. Nolan lab

FFPE-CODEX multiplexed tissue imaging of 56 markers in 140 tissues of 35 CRC patients.

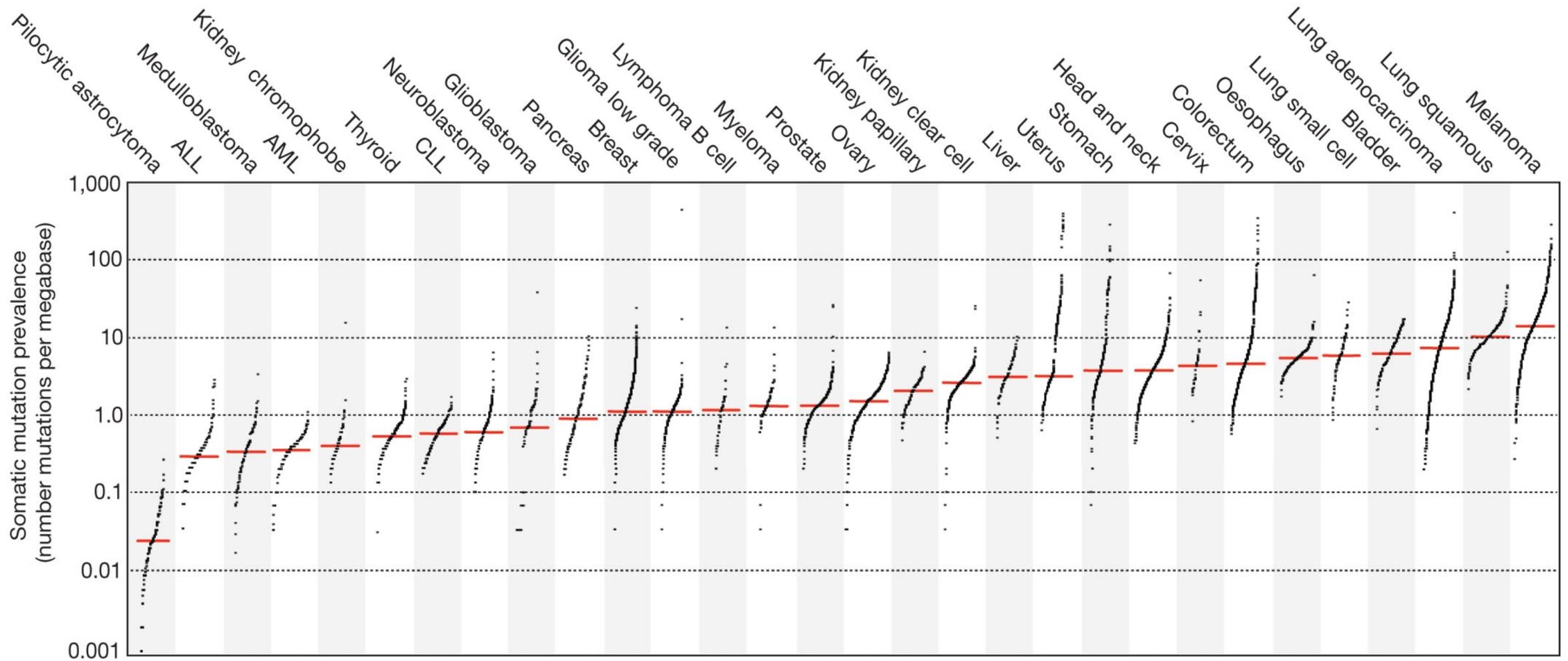
Cellular neighborhoods reveal spatial organization of the tumor microenvironment

Altered organization of tumor and immune components in low- versus high-risk patients

Local enrichment of PD-1+ CD4+ T cells correlates with survival in high-risk patients.



# The prevalence of somatic mutations across human cancer types.



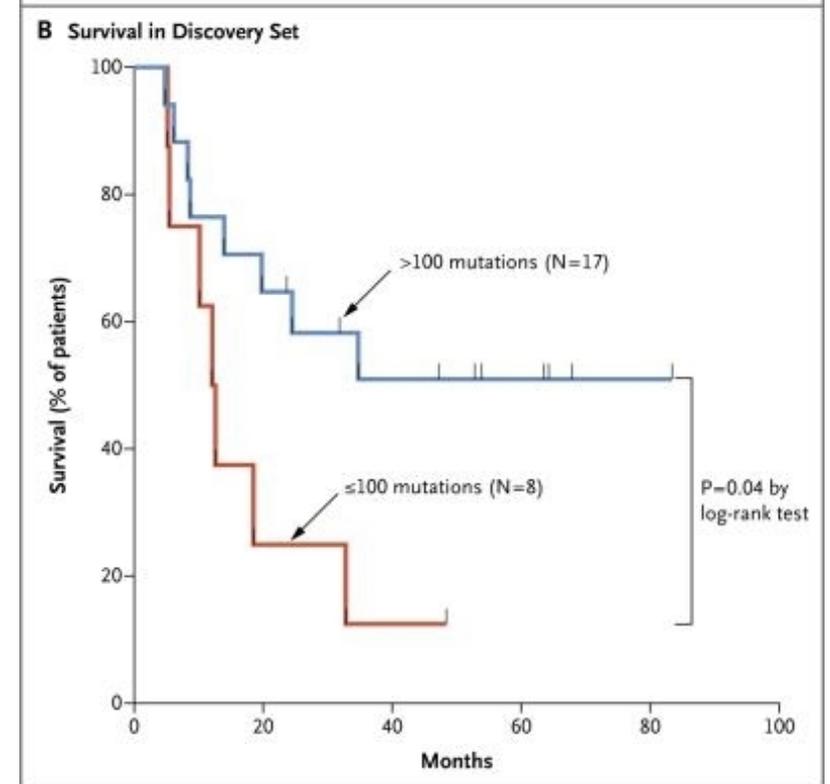
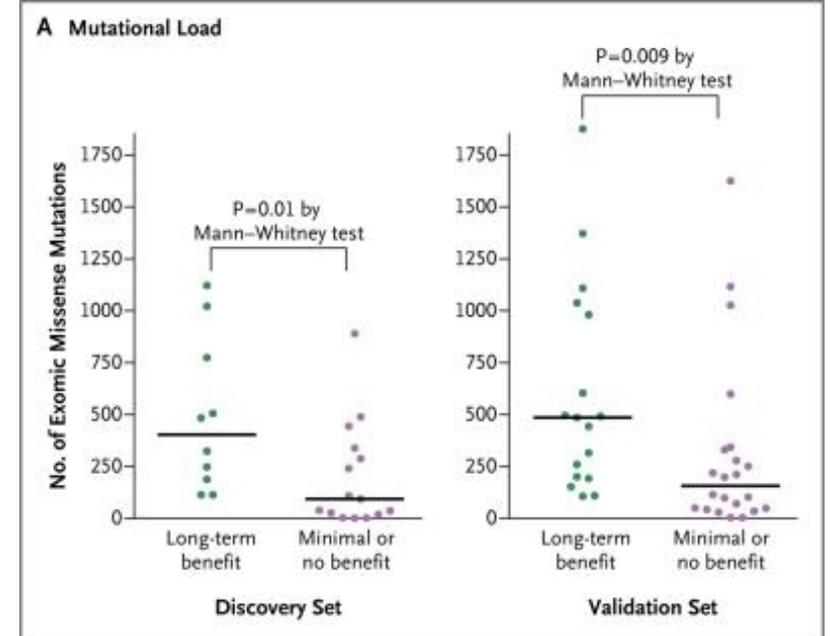
# Genetic basis for clinical response to CTLA-4 blockade in melanoma

*Snyder A, N Engl J Med. 2014*

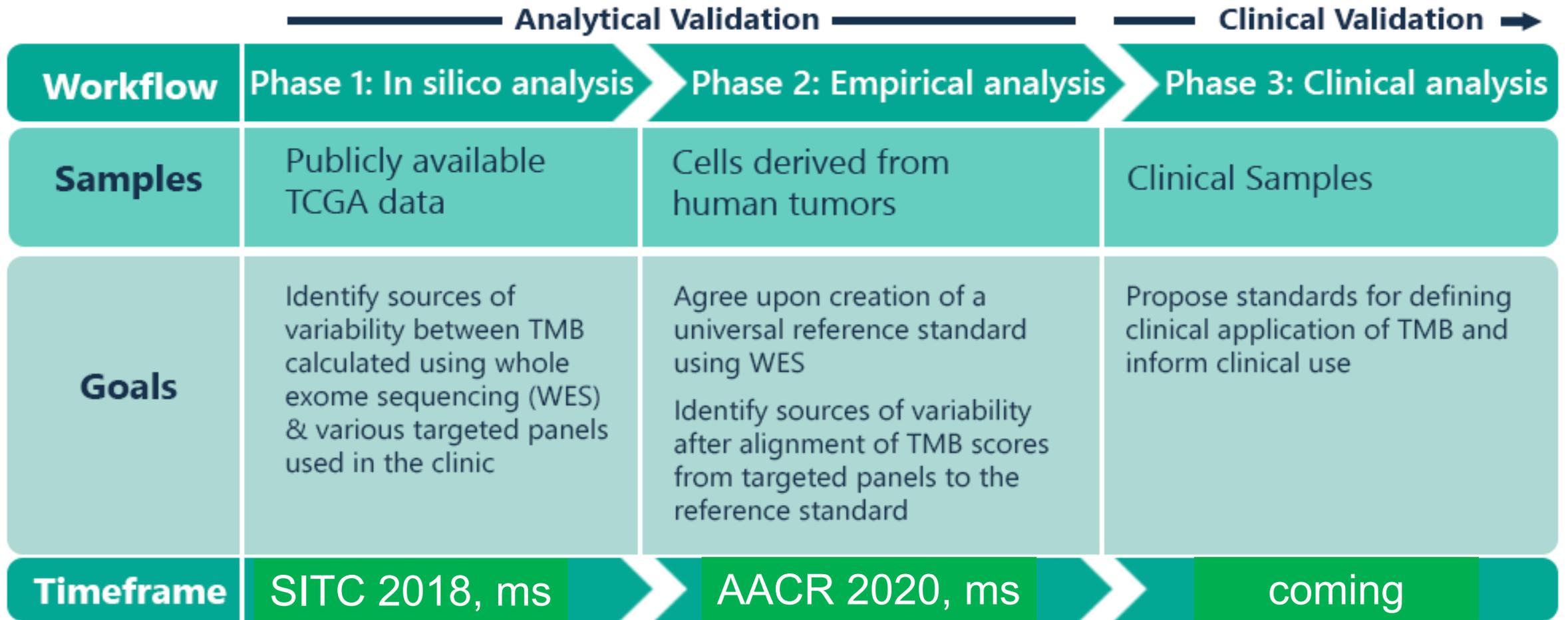
## More mutations = better checkpoint blockade response

TMB and other genetic determinants have demonstrated the potential to make immune checkpoint therapy more precise. Clinical data in support of the predictive value of TMB in the context of ICIs are encouraging but not fully conclusive, and challenges remain. It remains to be seen if tumor and/or bTMB can help identify patients who are likely to benefit from combination immunotherapies, including, but not limited to, angio-immunotherapy and chemoimmunotherapy combinations.

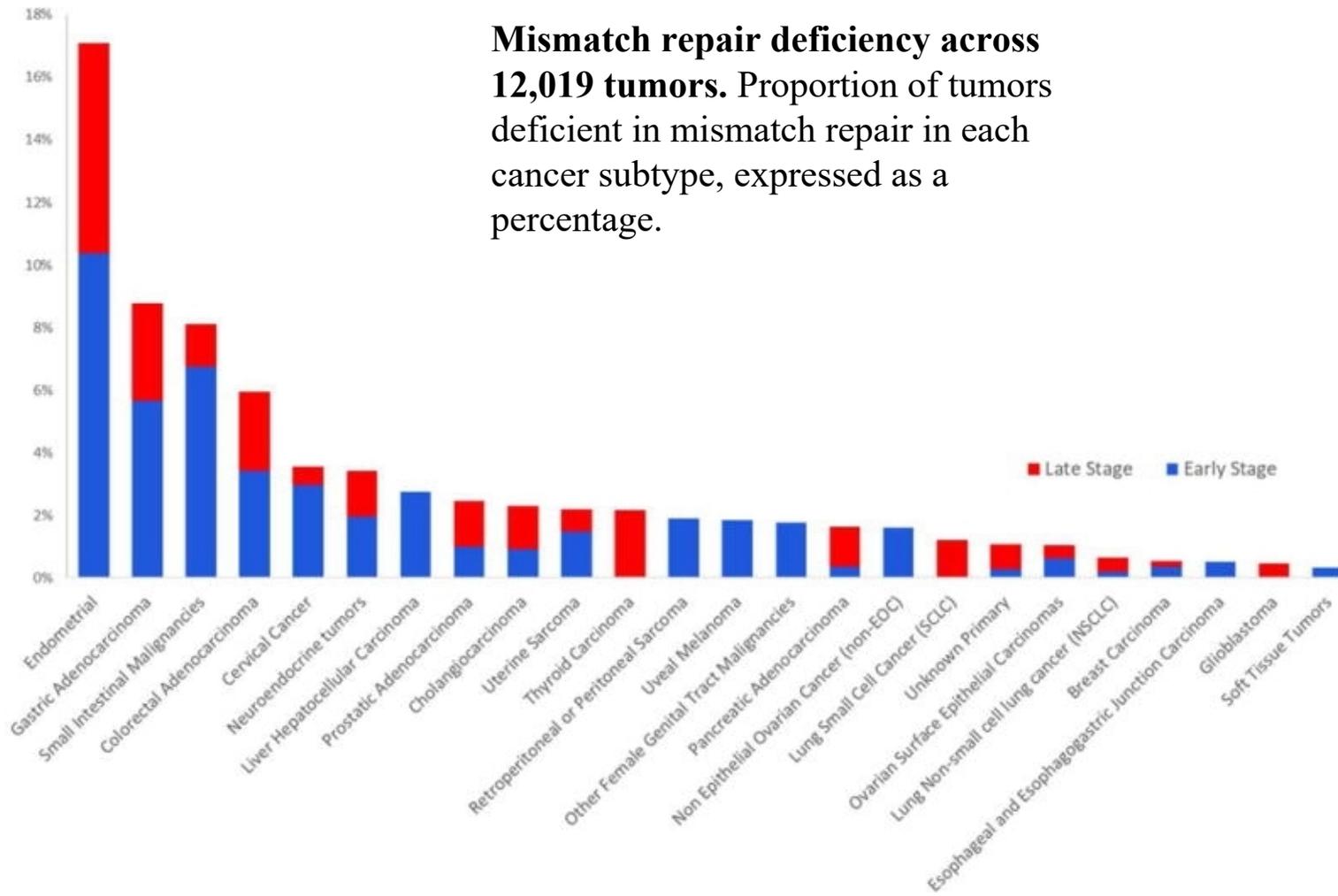
Additionally, the variability in the current methods of TMB assessment may complicate therapeutic decisions in the clinic. This highlights the need for standardization and harmonization of TMB analysis and reporting across assays and laboratories.



# TMB Harmonization Project Overview (Friends of Cancer Research)



# Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade



The genomes of cancers deficient in mismatch repair contain exceptionally high numbers of somatic mutations. We evaluate the efficacy of PD-1 blockade in patients with advanced mismatch repair-deficient cancers across 12 different tumor types. The large proportion of mutant neoantigens in mismatch repair-deficient cancers make them sensitive to immune checkpoint blockade, regardless of the cancers' tissue of origin.

## Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *Brahmer J., N Engl J Med. 2015*

**The expression of the PD-1 ligand (PD-L1) was neither prognostic nor predictive of benefit.**

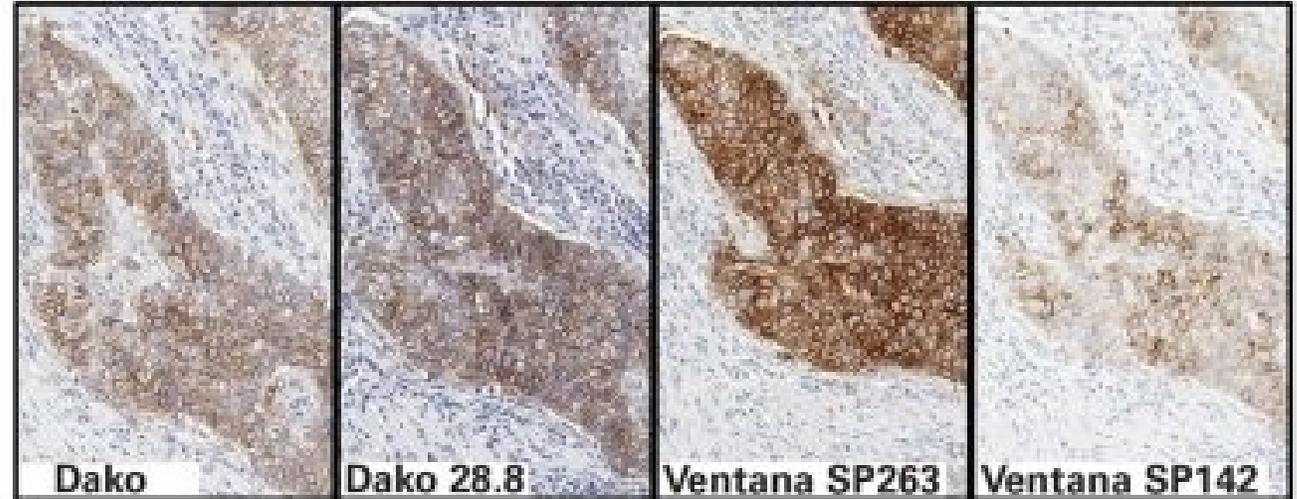
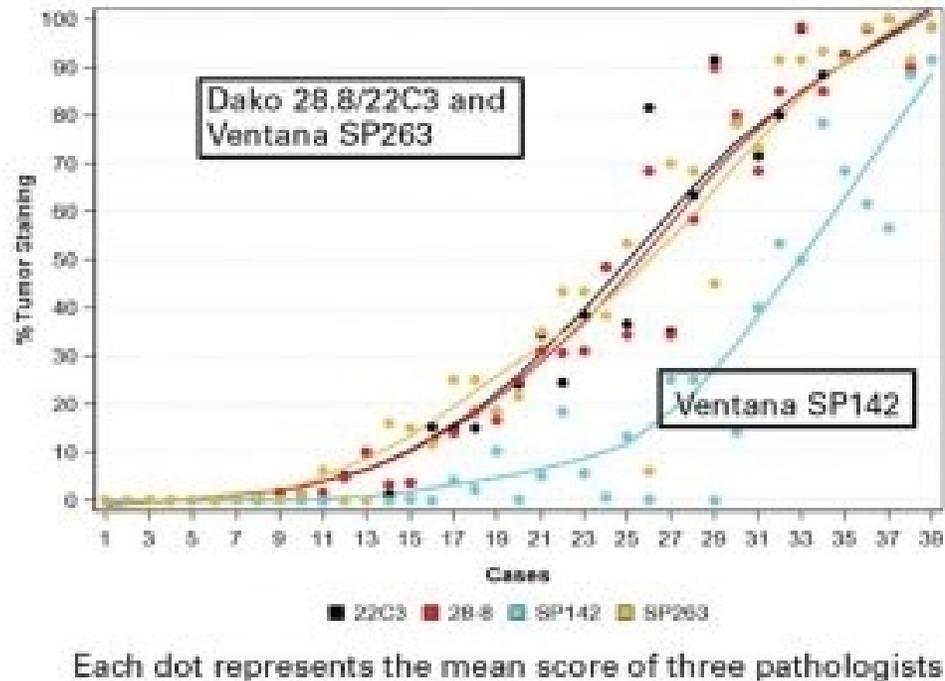
Among patients with advanced, previously treated squamous-cell NSCLC, overall survival, response rate, and progression-free survival were significantly better with nivolumab than with docetaxel, regardless of PD-L1 expression level.

PD-L1 IHC has demonstrated clinical utility by allowing patient selection and enrichment for clinical benefit from single-agent treatment with anti-PD-1 checkpoint inhibitors.

A number of PD-L1 IHC tests were independently codeveloped to support specific anti-PD-(L)1 programs, and the lack of standardization between these IHC requires harmonization of these assays in the clinic, as well as consensus on the scoring algorithms and cut-off levels to define positive PD-L1 status across various tumor types.

While PD-L1 IHC tests allow for enrichment of patients who are likely to derive clinical benefit from anti-PD-(L)1 agents, their clinical utility is less clear in the context of combination immunotherapies (eg, nivolumab/ipilimumab, angio-immunotherapy, and chemoimmunotherapy) which, based on currently available data, appear to be efficacious irrespective of tumor PD-L1 status.

# Consistency in PD-L1 staining by IHC on tumor cells: The Blueprint Project

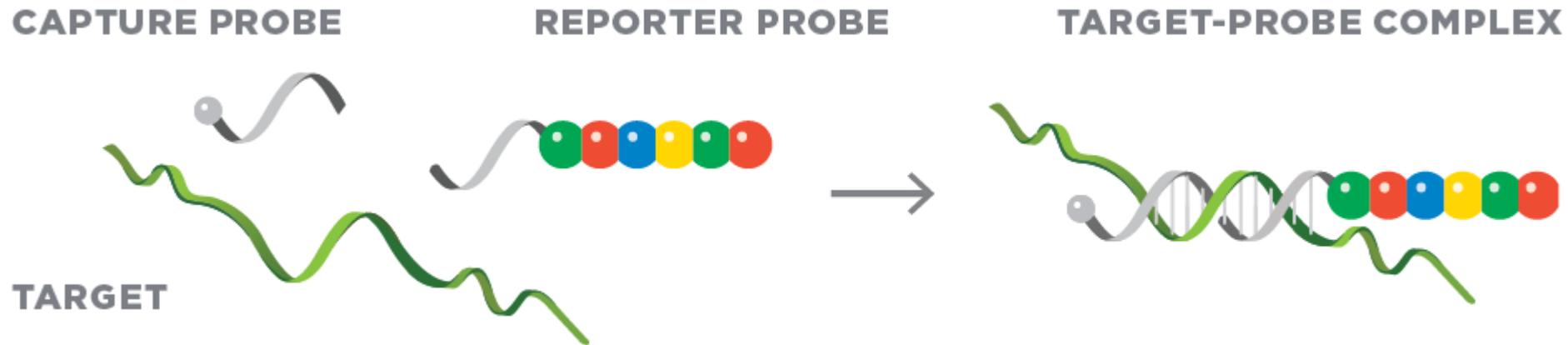


**Conclusion: 1:** Three assays showed similar staining characteristics for PD-L1 staining on tumor cells, but Ventana SP142 comparatively showed fewer tumor cells stained.

**Fig. 1. PD-L1 Expression on Tumor Cells** Hirsch FR, McElhinny A, Stanforth D, et al. PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phases 1 of the Blueprint PD-L1 IHC Assay Comparison Project. J Thor Oncol. 2017;12(2) 208-222

# HIGHLY MULTIPLEXED SINGLE MOLECULE COUNTING

NanoString's patented molecular barcodes provide a true digital detection technology capable of highly multiplexed analysis



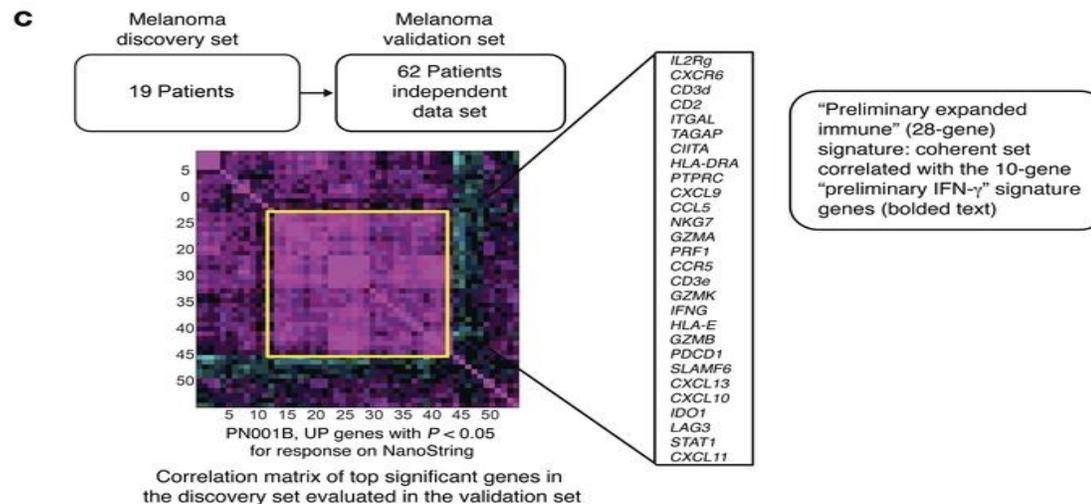
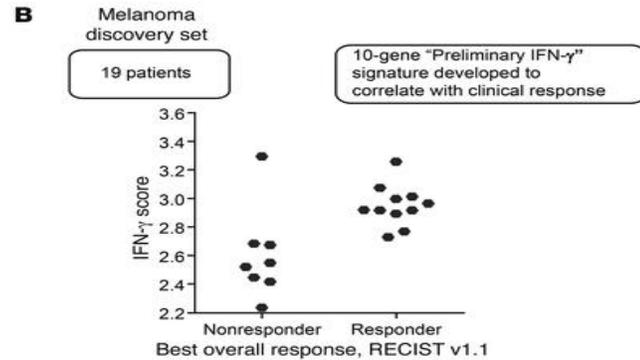
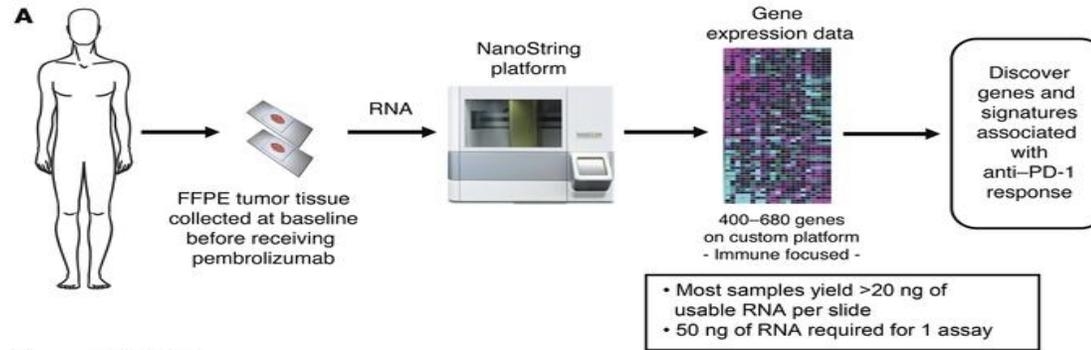
# Tumor Microenvironment (TME) Gene Expression Profiles

We report validation of the hypothesis that immune-related gene signatures can predict clinical response to PD-1 checkpoint blockade. Signatures related to IFN- $\gamma$  signaling and activated T cell biology were initially delineated in a small pilot melanoma cohort, then confirmed and refined in a larger independent cohort of patients with melanoma.

The cross-tumor predictive value of these signatures was demonstrated by testing in head and neck squamous cell carcinoma (HNSCC) and gastric cancer cohorts, followed by a modeling exercise to determine a final T cell–inflamed gene expression profile that predicted response across 9 different cancer cohorts to arrive at a final signature, forming the basis of a clinical-grade assay for evaluation of clinical utility in select ongoing pembrolizumab clinical trials ([18](#)).

Our data definitively confirm that a T cell–inflamed microenvironment, characterized by active IFN- $\gamma$  signaling, cytotoxic effector molecules, antigen presentation, and T cell active cytokines, is a common feature of the biology of tumors that are responsive to PD-1 checkpoint blockade. Moreover, these data demonstrate that a focused set of genes can be used to identify this PD-1 checkpoint blockade–responsive biology and predict clinical response across a wide variety of tumor types.

# IFN $\gamma$ -related mRNA profile predicts clinical response to PD-1 blockade



**Table 2. IFN- $\gamma$  and expanded immune gene signatures**

IFN- $\gamma$	Expanded immune gene signature	
<i>IDO1</i>	<i>CD3D</i>	<i>IL2RG</i>
<i>CXCL10</i>	<i>IDO1</i>	<i>NKG7</i>
<i>CXCL9</i>	<i>CIITA</i>	<i>HLA-E</i>
<i>HLA-DRA</i>	<i>CD3E</i>	<i>CXCR6</i>
<i>STAT1</i>	<i>CCL5</i>	<i>LAG3</i>
<i>IFNG</i>	<i>GZMK</i>	<i>TAGAP</i>
	<i>CD2</i>	<i>CXCL10</i>
	<i>HLA-DRA</i>	<i>STAT1</i>
	<i>CXCL13</i>	<i>GZMB</i>

# Serum (or supernatant) profiling

**Luminex:** Screening **65-plex** (cytokines/chemokines/growth factors, also 14+ soluble checkpoints and costimulatory molecules; pg/ml)

**Olink: Target 96:** Targeted protein biomarker discovery 96-plex panels, qPCR readout;

**Explore 1536:** Measure 1,536 proteins. Readout on NGS

**Phage display:** rationally designed libraries encompassing the entire human proteome have been implemented. With next-generation sequencing as a readout, researchers can quantify the enrichment of millions of individual phage clones simultaneously and identify sequences that bind to the target or antibody of interest (“phage immunoprecipitation and sequencing (PhIP-Seq)”)

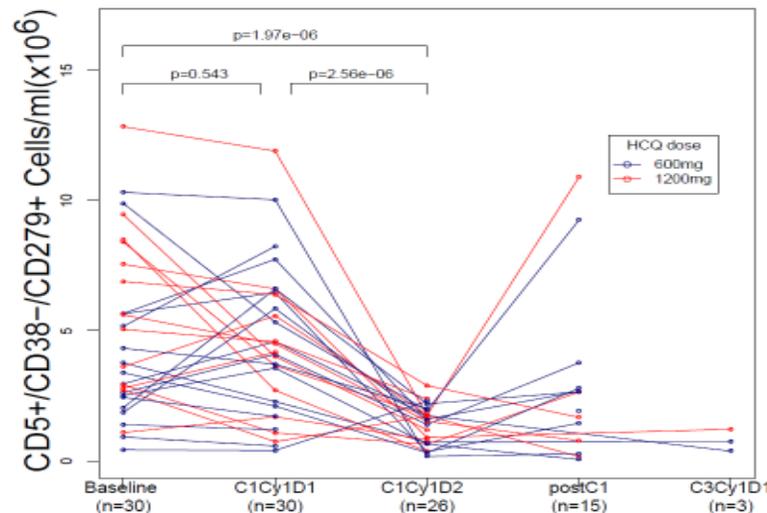
# Soluble Checkpoints/Costimulatory Molecules

## Safety and activity of hydroxychloroquine and aldesleukin in metastatic renal cell carcinoma: A cytokine working group phase II study (ASCO 2018 poster)

Leonard J. Appleman<sup>1</sup>, Daniel P. Normolle<sup>1</sup>, Theodore F. Logan<sup>2</sup>, Paul Monk<sup>3</sup>, Thomas Olencki<sup>3</sup>, David F. McDermott<sup>4</sup>, Marc S. Ernstoff<sup>5</sup>, Jodi K. Maranchie<sup>1</sup>, Rahul Parikh<sup>1</sup>, David Friedland<sup>1</sup>, Mary Jo Buffo<sup>1</sup>, Shuyan Zhai<sup>1</sup>, Herbert Zeh<sup>1</sup>, Xiaoyan Liang<sup>1</sup>, Lisa H. Butterfield<sup>1</sup>, Michael T. Lotze<sup>1</sup>

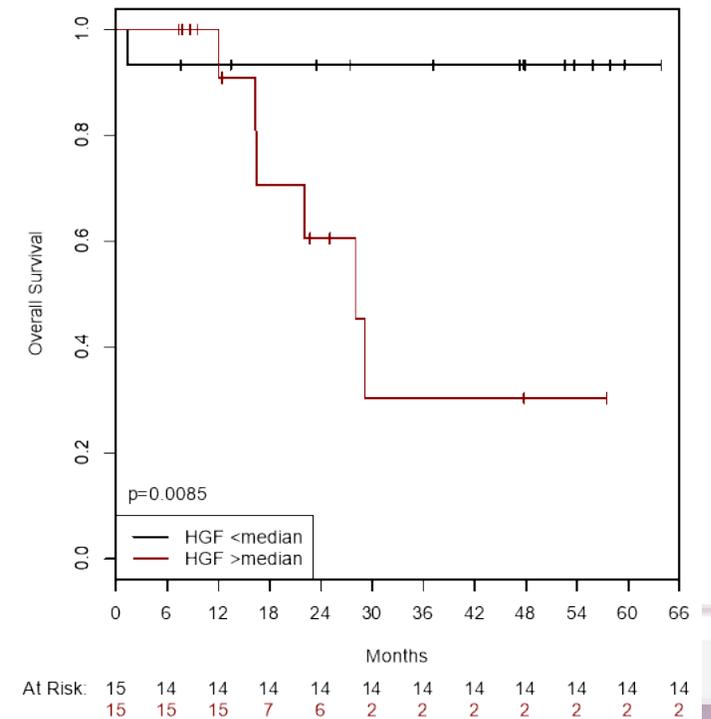
**Overall Survival (OS)** was compared to each baseline biomarker. Test 1) split markers at the median, and then used a log-rank test to compare the dichotomized biomarker to OS 2) a proportional hazards (Cox) model. Those with at least one p-value <0.01 from 64 cytokines **and 14 checkpoints**:

	Median split	-----Proportional Hazards-----	
	p-value	Hazard Ratio (95% CI)	p-value
sLAG-3	0.8506	1.022 (1.0033,1.042)	0.0087
HGF	0.0085	1.010 (0.999,1.021)	0.0360
sCD-30	0.0066	1.0005 (0.999,1.001)	0.34



PD1+/CD38-/CD5+ Cells  
Migrate Out of Circulation  
with IL-2

### Decreased OS in Patients with Increased HGF



# Themes Emerge

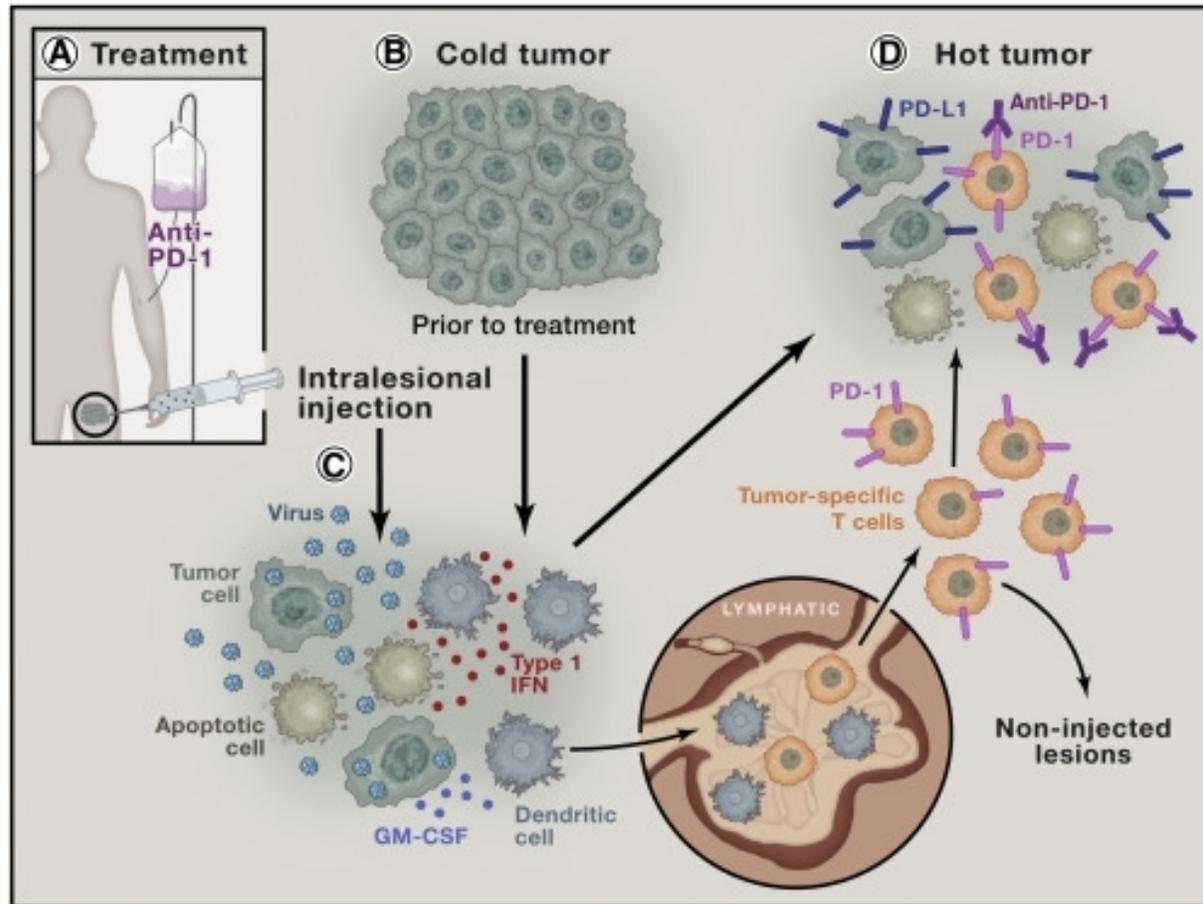
Biomarkers for prediction, prognostication and mechanism-of-action in cancer immunotherapy are still largely exploratory, although exciting signals are being validated (analytically and clinically). Biomarkers identified in tissue might ultimately be testable in blood.

New high throughput technologies can yield important insights:

Could “multiple TAA T cell responses” in blood = “determinant spreading” from “*in vivo* cross-presentation” = “greater TCR diversity” in blood, driven in part by “higher mutation loads” in tumors with “IFN $\gamma$  signatures” showing they are permissive for immune infiltration?

Common mechanisms: PD-L1 on tumors, Tumor Mutation Burden (TMB), CD8+ T cell infiltrate, IFN $\gamma$  (or related type 1 T cell response) gene expression signature (*related but not the same and not completely overlapping with each other*)

# T-VEC oncolytic virus + PD-1 Blockade



Phase 1b trial testing [oncolytic virotherapy](#) with T-VEC on [cytotoxic T cell](#) infiltration and therapeutic efficacy of the anti-PD-1 [antibody pembrolizumab](#). Twenty-one patients with advanced melanoma were treated with T-VEC followed by combination therapy with pembrolizumab. Confirmed objective response rate was 62%, with a complete response rate of 33% per immune-related response criteria. Patients who responded to combination therapy had increased [CD8<sup>+</sup>](#) T cells, elevated [PD-L1 protein expression](#), as well as [IFN- \$\gamma\$](#)  gene expression on several cell subsets in tumors after T-VEC treatment. Response to combination therapy did not appear to be associated with baseline CD8<sup>+</sup> T cell infiltration or baseline IFN- $\gamma$  signature.

---

# Biomarkers

Who should be enrolled?

Who will benefit and why?

Who will experience an adverse event/toxicity and why?

*Predictive, prognostic, mechanism of action*

# Addressing inherent variability in immunologic monitoring of clinical trials

## Recommendations from the iSBTc-SITC/FDA/NCI Workshop on Immunotherapy Biomarkers, CCR 2011

Source of Variability	Recommendation
Patient	Save DNA/RNA/cells/tumor to understand host variation include healthy donor control
Blood draw	Standardized tubes and procedures
Processing/cryopreservation/ thaw	Standardized procedures and reagents
Cellular product	Phenotypic and functional assays to characterize the individual product, development of potency assays
Assay choice	Standardized functional tests
Assay conduct	Standardized operating procedures (SOPs)
Assay analysis	Appropriate biostatistical methods
Data reporting	Full details, controls, quality control/assurance (QA/QC) MIATA guidelines
Newest, non-standardized technology	Sufficient blood/tissue to interrogate the samples <i>now</i> , as well as <i>later</i> , to generate new hypotheses

# Immunotherapy Biomarkers Task Force: 2015-2019

GROUP 1: “Immune monitoring assay standardization and validation—update” *Leaders: Magdalena Thurin, PhD and Giuseppe Massucci, MD*

GROUP 2: “New developments in biomarker assays and technologies”  
*Leader: Jianda Yuan, MD*

GROUP 3: “Assessing Immune Regulation and Modulation Systematically (high throughput approaches)” *Leader: David Stroncek, MD*

Group 4: “Baseline Immunity, tumor immune environment and outcome prediction” *Leader: Sacha Gnjatic, PhD*

Taskforce Contributions to the field:

1. Preamble/overview commentary (JITC March 2015)
2. Recommendations/white paper 1/WG (JITC Mar. 2016)
3. Biomarker Technology short reports (1/month in JITC x 12)
4. Clinical trial analysis project: standard cellular/cytokine assays and high throughput molecular analyses—ongoing (CTLA-4 +/- GM-CSF)
  5. Summary meeting: April 1st 2016
  6. Workshop for next projects: May 2018
7. Now: Data sharing, Immunoscore images, multispectral imaging, updates (2019-2020)

# Pathology Task Force

- **Chair:** Carlo B. Bifulco, MD; **Co-Chair:** Janis M. Taube, MD, MSC
- White Paper 1 - *“Best practices for Multiplex IHC/IF Staining and Validation, and Future Directions”*
- White Paper 2 - *“Best practices for Multiplex IHC/IF Image analysis, Harmonization Efforts, and Data Sharing”*

# Emerging Biomarker Themes

Multiple TAA T cell responses

Epitope spreading

Greater TCR diversity

Multiple antigens, polyclonal response

High mutation loads

IFN $\gamma$  signatures

Tumor clonal TCR expansion

Immune infiltrated tumor, active cellular infiltrate

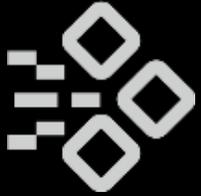
PD-L1 on tumors (+/-infiltrate): expression cut-off?

TMB: which measure? Cut-off?

CD8+ T cell infiltrate/"ImmunoScore" (CD3/CD8/CD45RO)

Gene expression signatures: validation?

# Focus Areas



## CAR-T and Cell Therapy: The Next Wave

To engineer a smarter army of next-gen cell therapies that seek out specific targets and attack cancer — again and again.



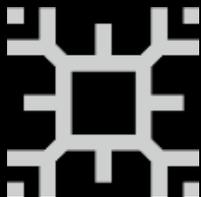
## Checkpoint Inhibitors: Overcoming Resistance

To uncover why some patients respond to checkpoint inhibitors for cancer while others don't. If we know when and how immunotherapy resistance arises, we can prevent or even reverse it.



## Tumor Antigen Discovery: Targeting Cancer

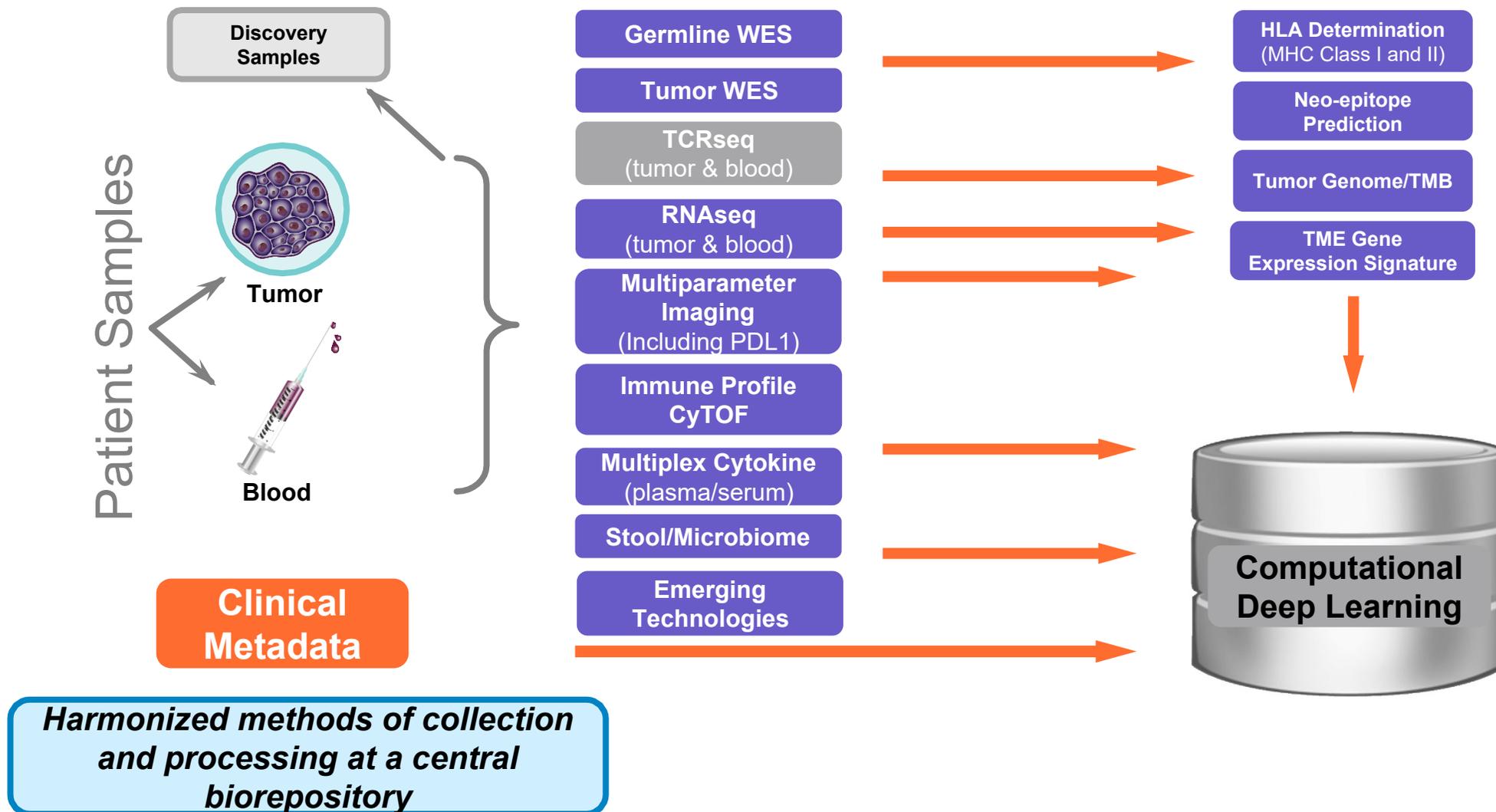
To find the “red flags” that show us where cancer is hiding. By pinpointing these antigens that fire up our immune system, we can create more effective personalized anti-cancer therapies.



## Tumor Microenvironment

To infiltrate a solid tumor's defenses. How can we break down the tumor microenvironment that walls off cancer from immunotherapy treatments?

# The Parker Translational Suite: Deep Immune Profiling



# Conclusions

Biomarkers for prediction, prognostication and mechanism-of-action in cancer immunotherapy are still largely exploratory, although exciting signals are being validated (analytically and clinically). Biomarkers identified in tissue might ultimately be testable in blood.

New high throughput technologies can yield important insights (*and lots of candidate biomarkers!*)

Could “**multiple TAA T cell responses**” in blood = “**determinant spreading**” from “**in vivo cross-presentation**” = “**greater TCR diversity**” in blood, driven in part by “**higher mutation loads**” in tumors with “**IFN $\gamma$  signatures**” showing they are permissive for immune infiltration?

Common mechanisms: PD-L1 on tumors, Tumor Mutation Burden, CD8+ T cell infiltrate, IFN $\gamma$  gene signature