Targeting immune inhibitory pathways in the tumor microenvironment

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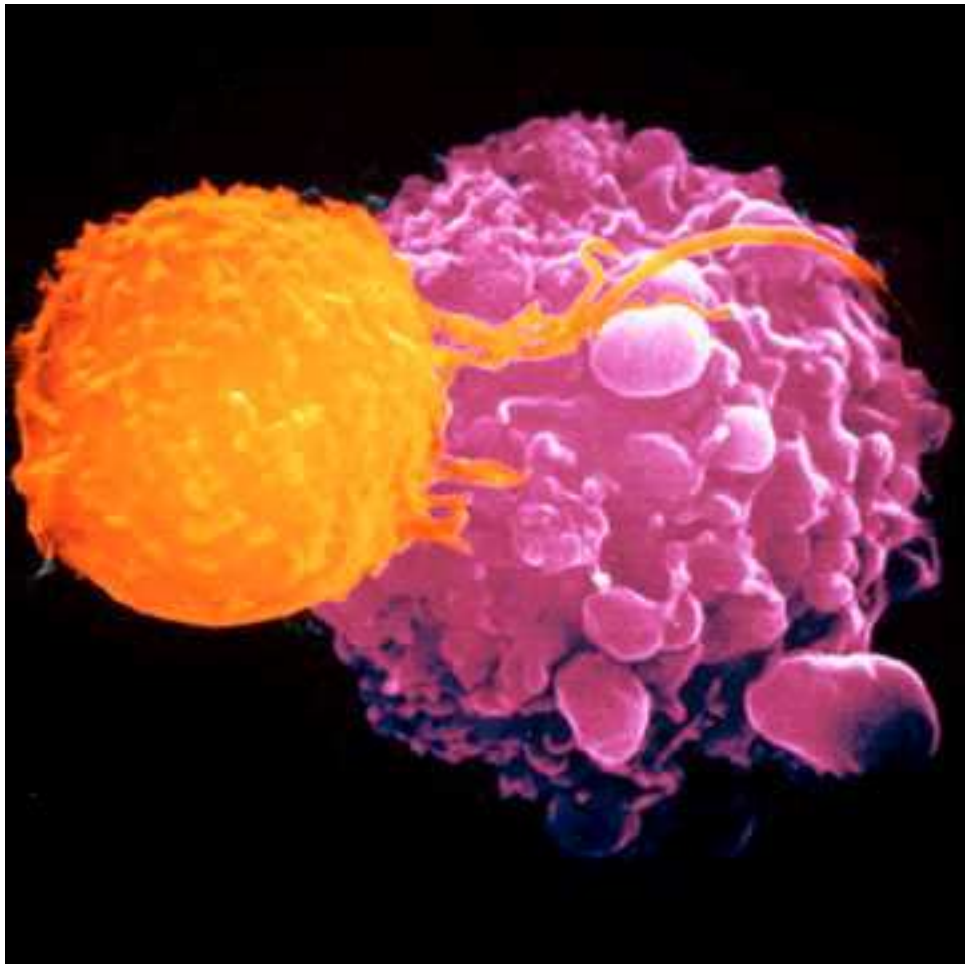
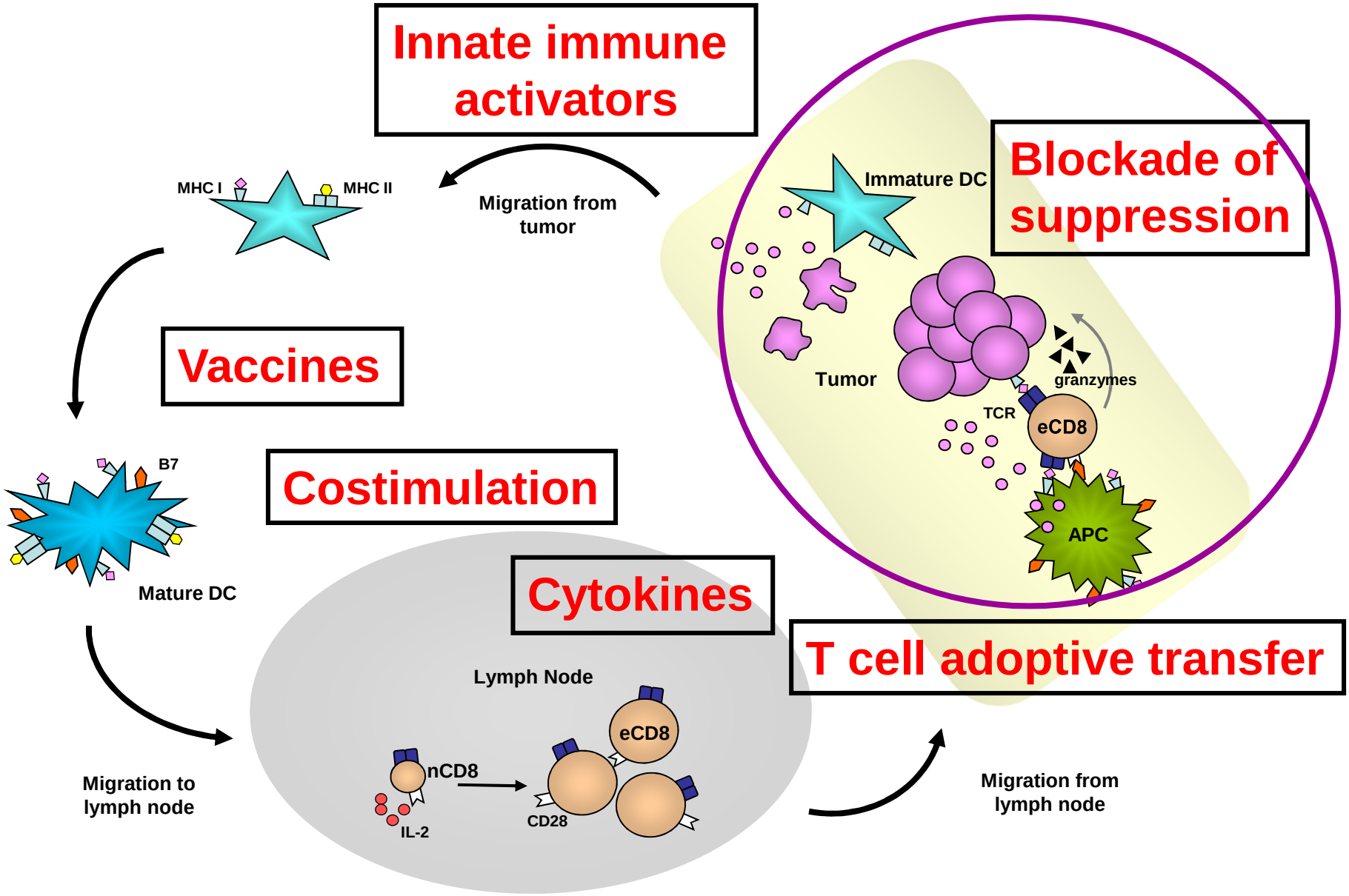
Disclosures

- Advisory boards:
  - Roche-Genentech, Merck, Abbvie, Jounce, Bayer
- Research support:
  - GSK-Bio, Roche-Genentech, BMS, Incyte, Ono, Seattle Genetics
- There will be discussion about the use of products for non-FDA approved indications in this presentation.

$CD8^+$ cytotoxic T lymphocyte killing an antigen-expressing tumor cell



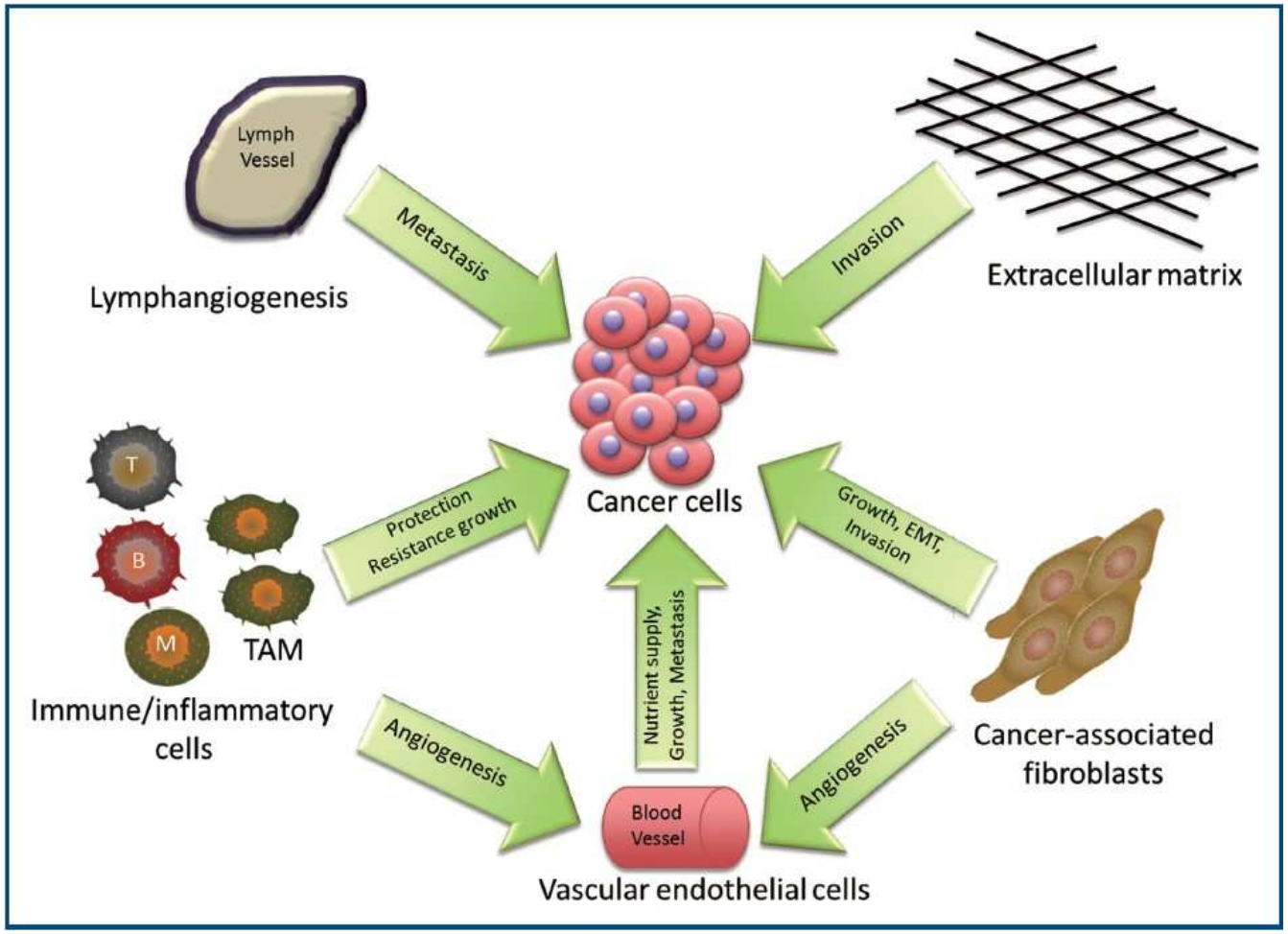
Model for CD8$^+$ T cell-mediated anti-tumor immune response *in vivo:* Interventions



In vivo, a tumor is more than cancer cells

- Three dimensional mass/tissue
- Extracellular matrix
- Supported by the neovasculature, fibroblasts, macrophages
- Variable presence of inflammatory cells
  - T cells (and subsets thereof)
  - Dendritic cell subsets
  - Macrophage subsets
- The functional phenotypes of these cells may or may not be permissive for an effective anti-tumor immune response (either priming phase or effector phase)

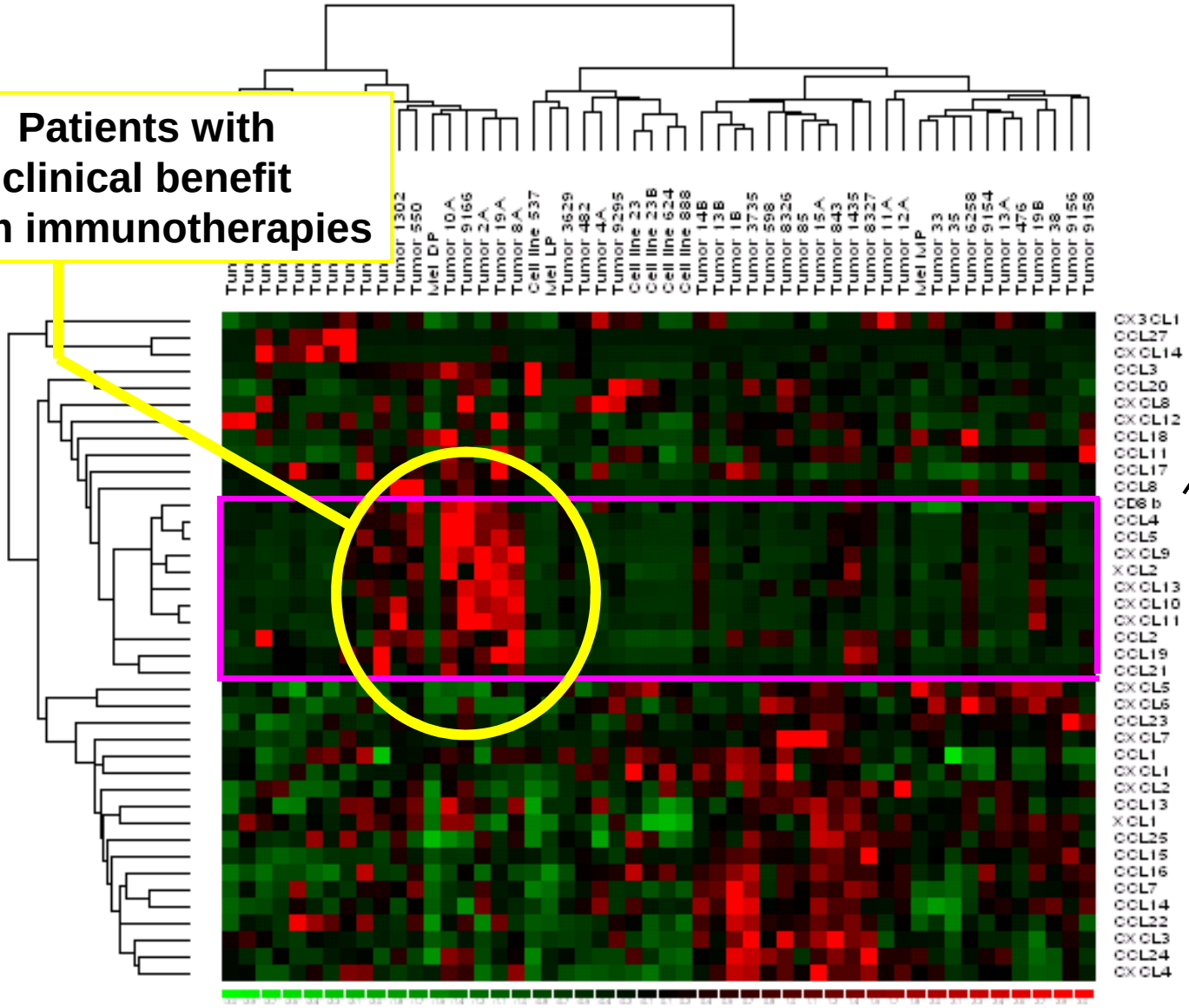
Complexity of stromal elements in solid tumors



DeMorrow et al. 2011

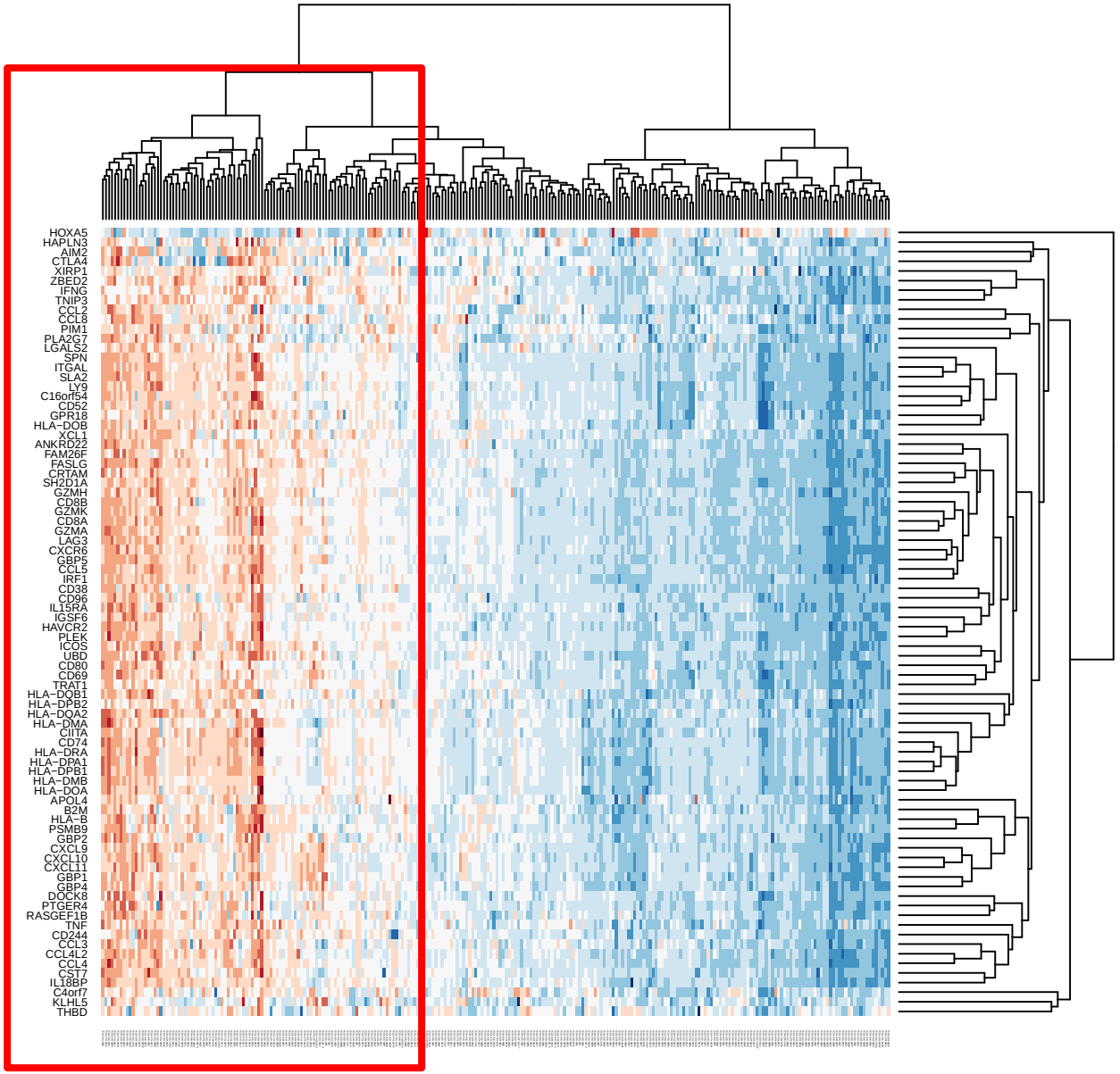
Expression of a subset of chemokine genes is associated with presence of CD8$^+$ T cells in melanoma metastases

Patients with clinical benefit from immunotherapies



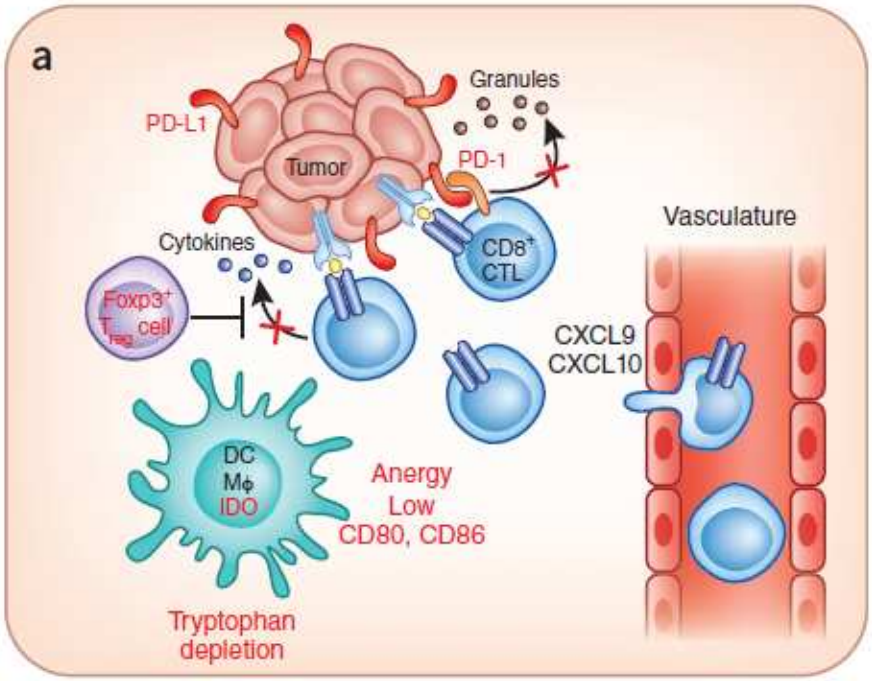
Harlin et al. Can. Res. 2009

T cell/chemokine signature detected in a major subset of melanoma metastases: TCGA



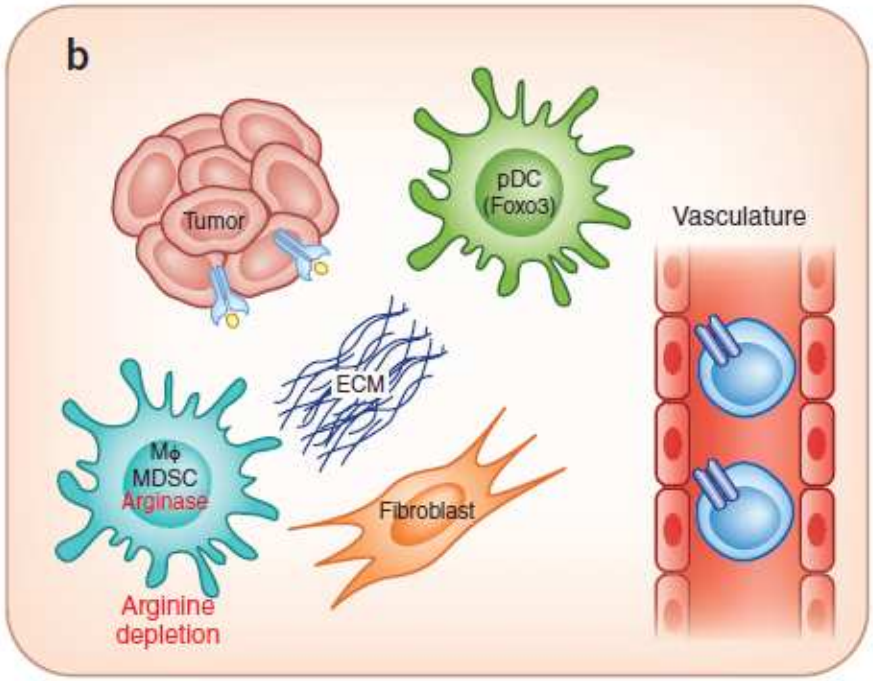
Working model: immunobiology of T cell-inflamed and non-inflamed tumor microenvironment

T cell-inflamed



- Chemokines
- CD8⁺ T cells
- Type I IFN signature
- Immune escape: Inhibitory pathways
- *Most immunotherapy responders have this phenotype*

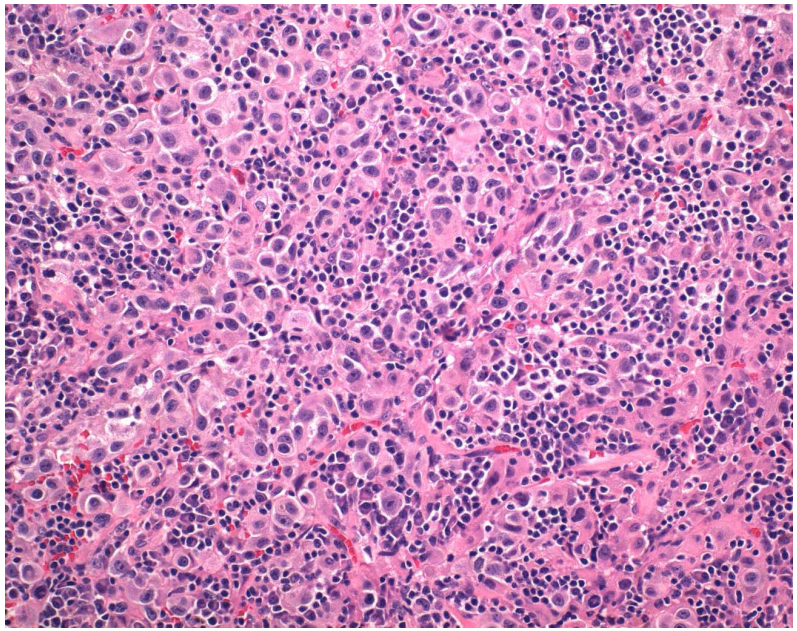
Non- T cell-inflamed



- Low inflammatory signature
- Absent intratumoral CD8⁺ T cells
- Immune escape: T cell exclusion

Nature Immunol. 2013

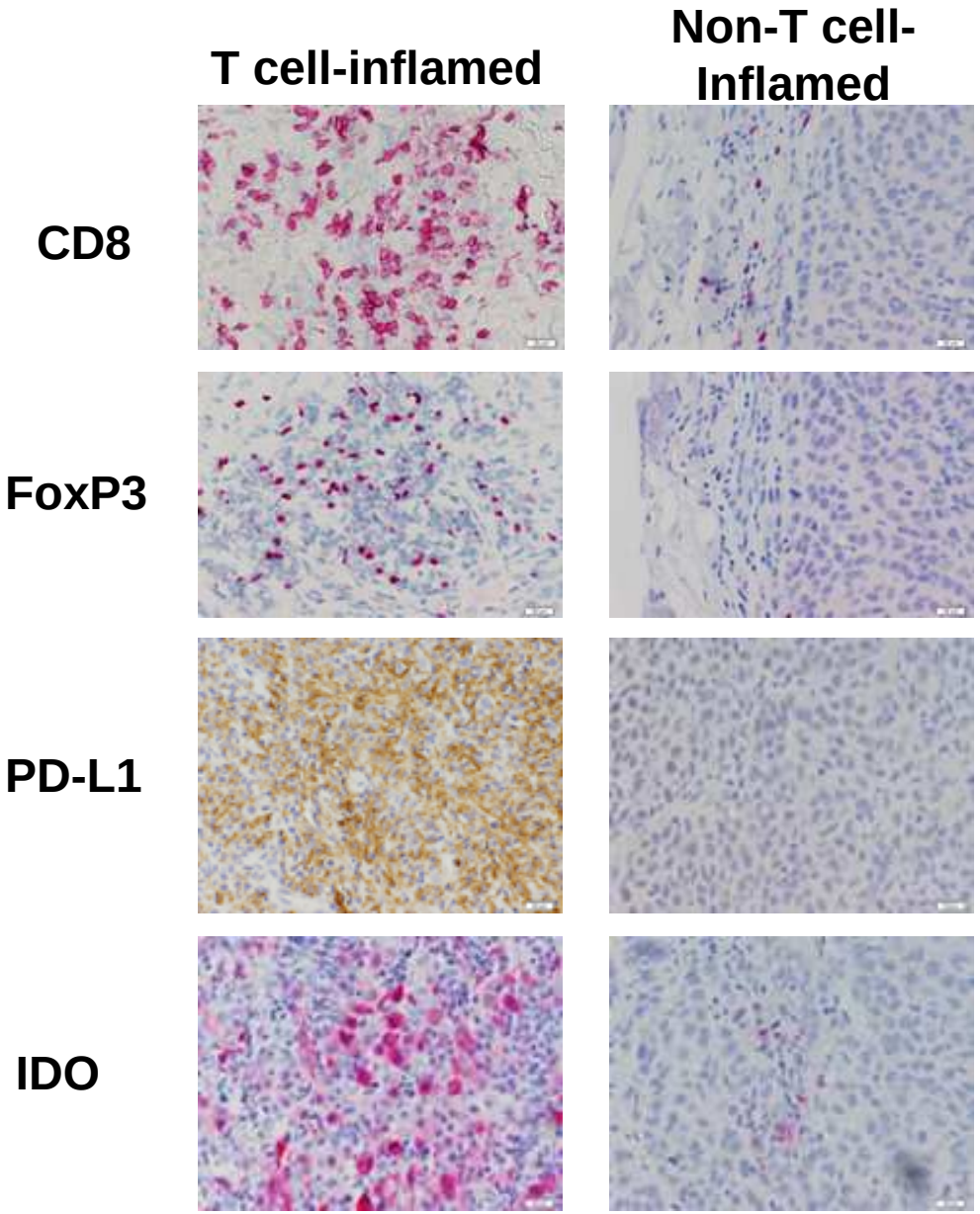
Why are tumors that do attract $CD8^+$ T cell not rejected spontaneously?



- **CTLA-4** (inhibitory receptor on activated T cells)
- **PD-L1** (engages 2nd inhibitory receptor PD-1 on T cells)
- **IDO** (indoleamine-2,3-dioxygenase; degrades tryptophan)
- $CD4^+CD25^+FoxP3^+$**Tregs** (extrinsic suppression)
- T cell **anergy** (B7-poor➔ T cell intrinsic dysfunction)

Immunol. Rev. 2006, Clin. Can. Res. 2007

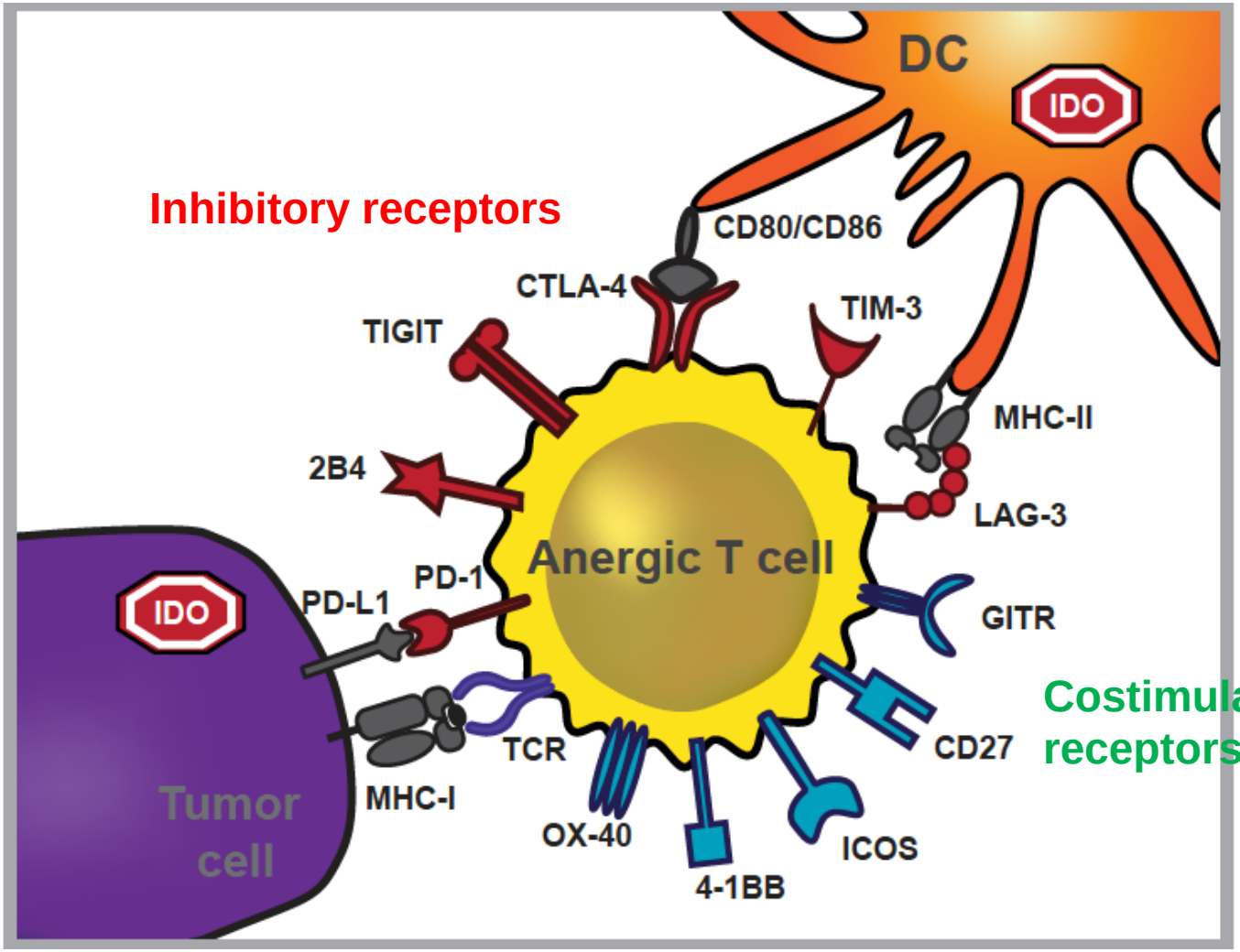
Presence of Tregs and expression of PD-L1 and IDO are associated with a CD8$^+$ T cell infiltrate



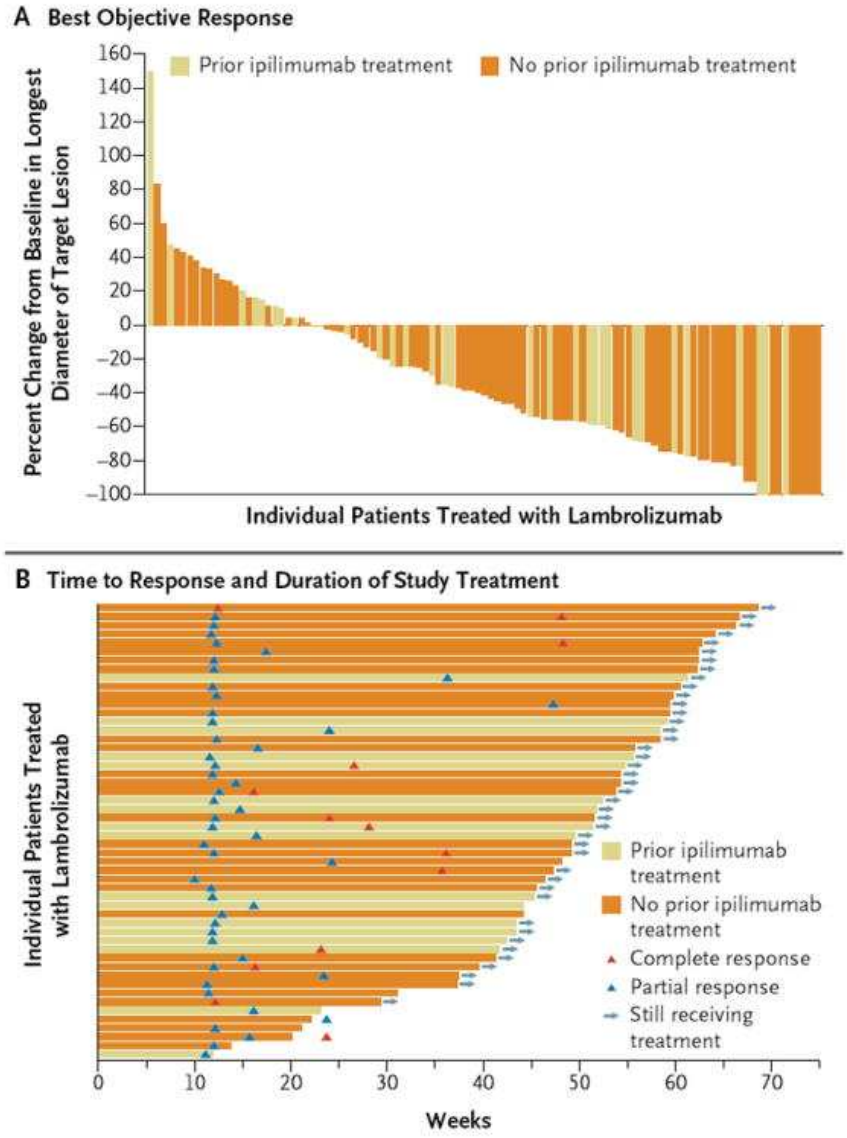
- Immune-intrinsic negative feedback loop
- CD8$^+$ T cell-derived IFN-γ upregulates PD-L1 and IDO, and CCL22 recruits Tregs
- Current immuno Rx appears to re-activate CD8$^+$ T cells already in tumor

Spranger et al., Science Trans. Med. 2013

Dysfunctional T cells in the tumor microenvironment express both negative and positive regulatory receptors that are targetable



Activity of pembrolizumab (anti-PD-1) in metastatic melanoma



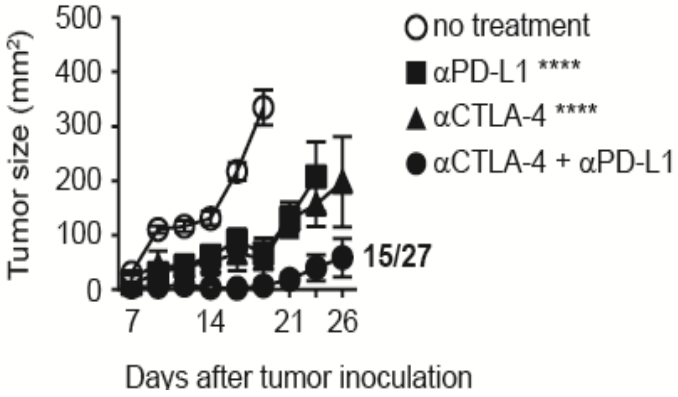
- 38% response rate
- High durability
- FDA approved 9/4/14

- 2015: Second anti-PD-1 mAb (nivolumab) approved for melanoma and also NSCLC (SC)
- Activity in at least 12 additional cancers

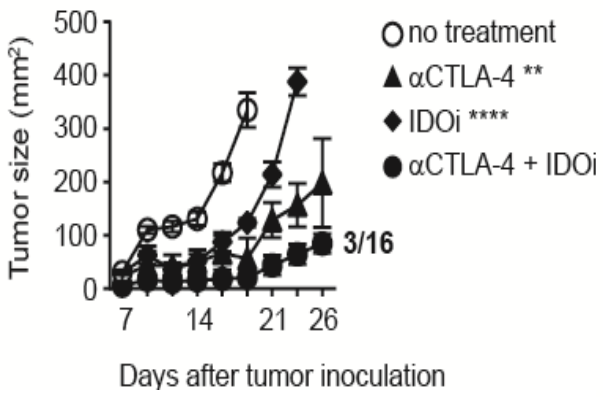
Hamid et al., NEJM 2013

Combinatorial targeting of CTLA4 ± PDL1 ± IDO results in improved tumor control

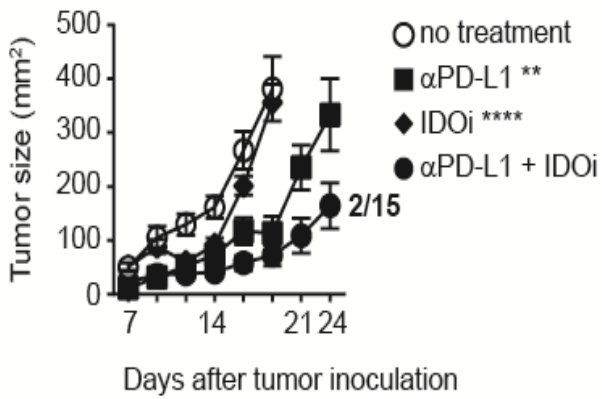
CTLA4 + PDL1



CTLA4 + IDOi

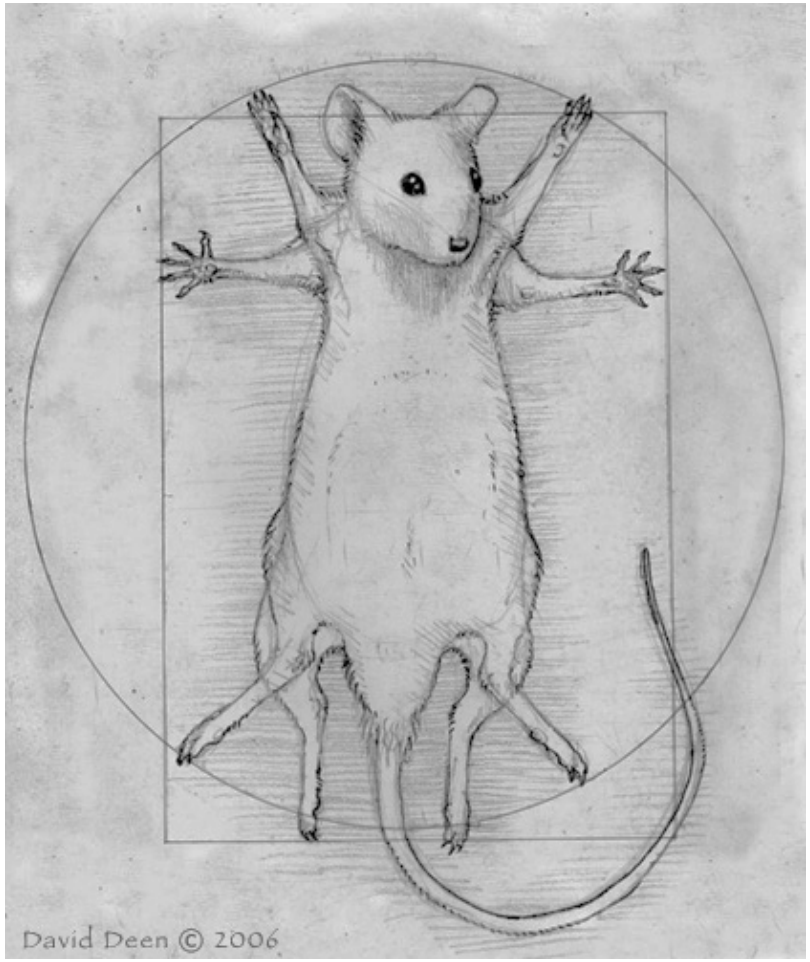


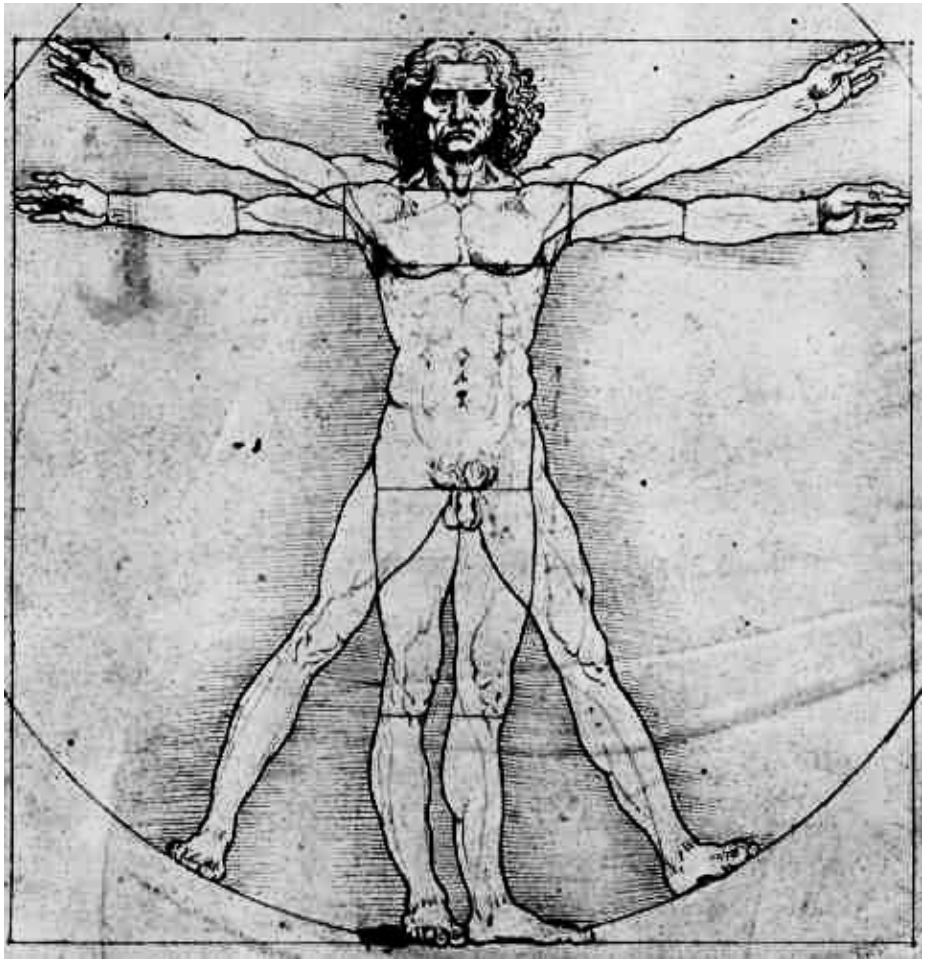
PDL1 + IDOi



Spranger et al; JITC 2014

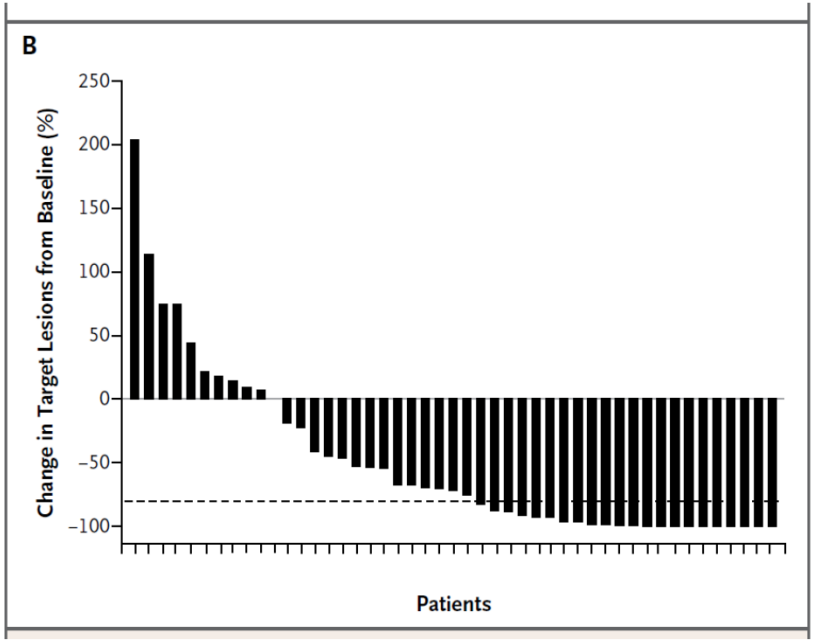
Translation of these therapeutic approaches from the laboratory to the clinic





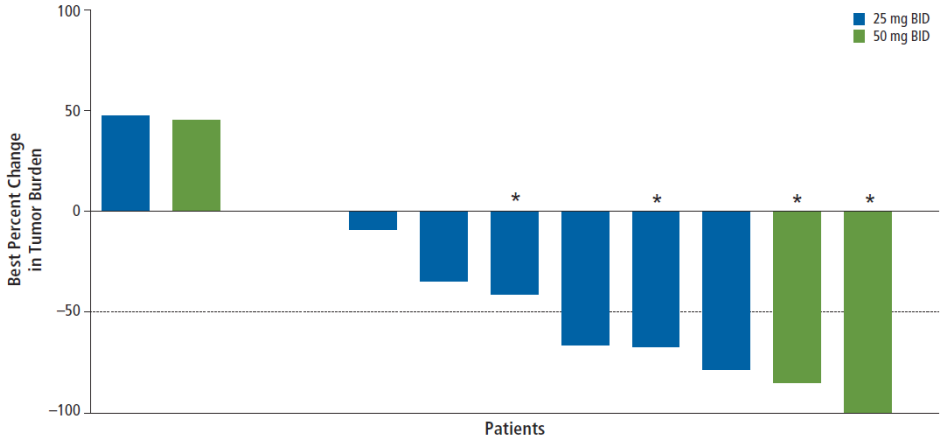
Combination immunotherapy clinical trials in metastatic melanoma: anti-CTLA-4 + anti-PD-1 and anti-CTLA-4 + IDOi

Anti-CTLA-4 + anti-PD-1



Wolchok et al. NEJM. 2013

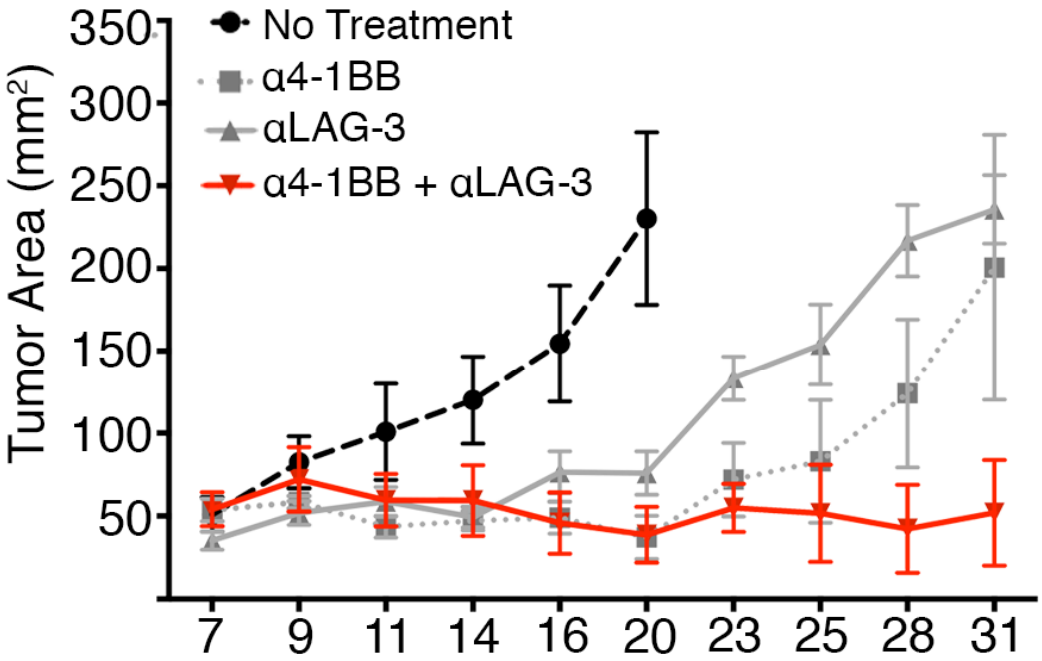
Anti-CTLA-4 + IDOi

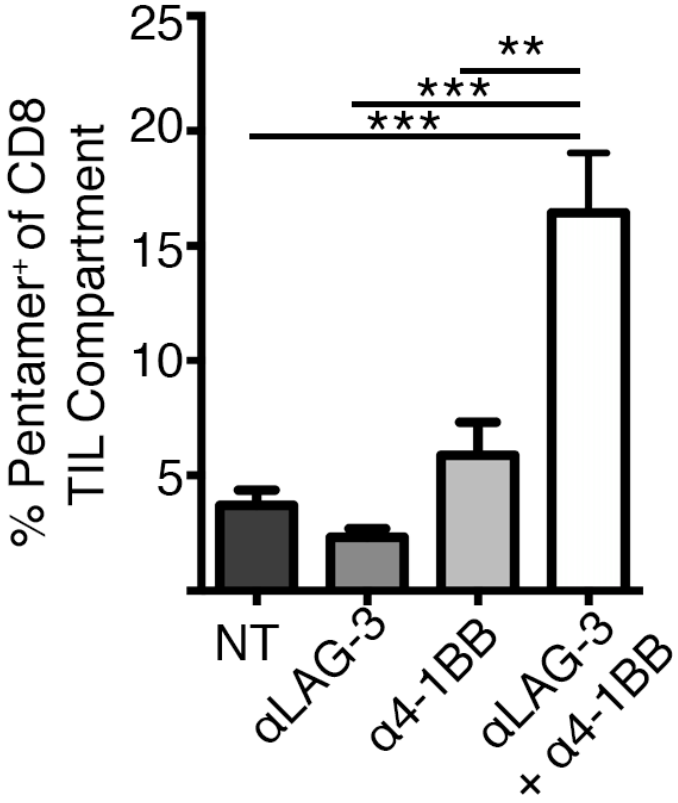


Gibney et al; ASCO 2014

Numerous additional logical combinations also being pursued, including anti-PD-1 + IDOi

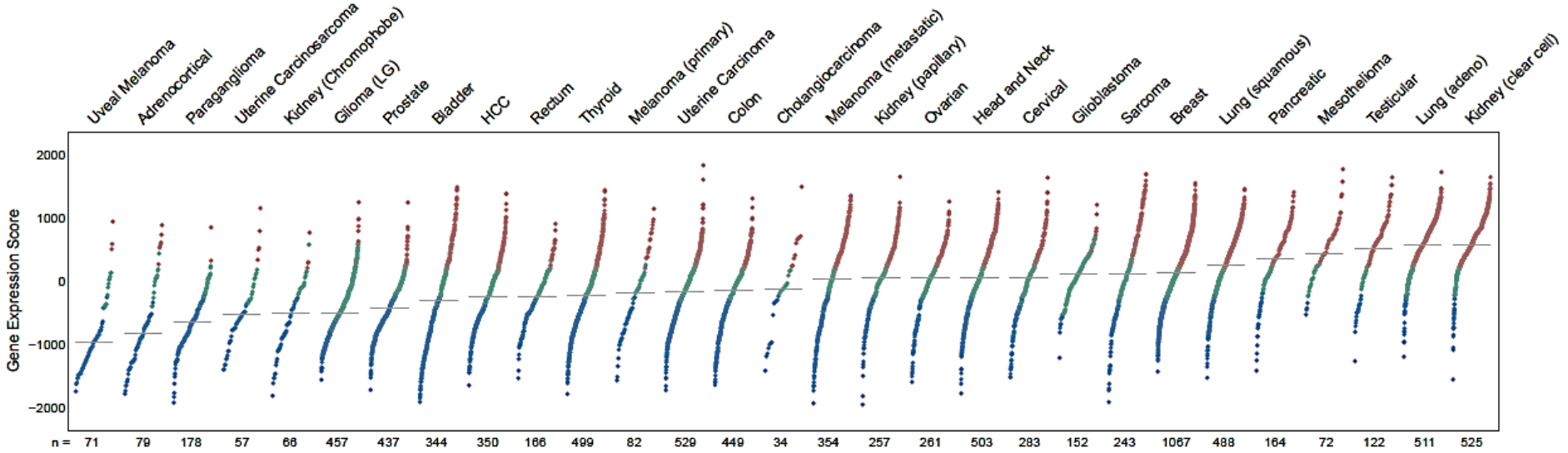
Administration of blocking anti-LAG-3 + agonistic anti-4-1BB mAb shows potent anti-tumor activity





Brendan Horton

Fraction of tumors with T cell-inflamed tumor microenvironment gene signature analyzed by cancer type

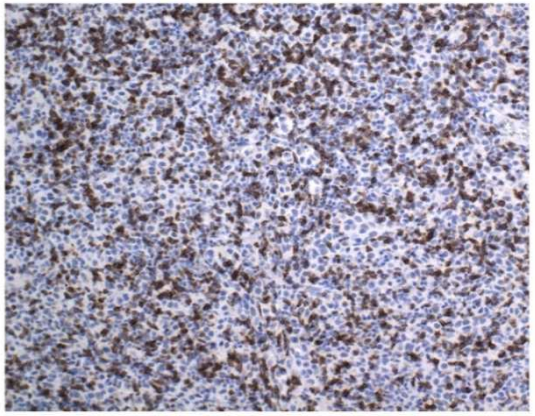


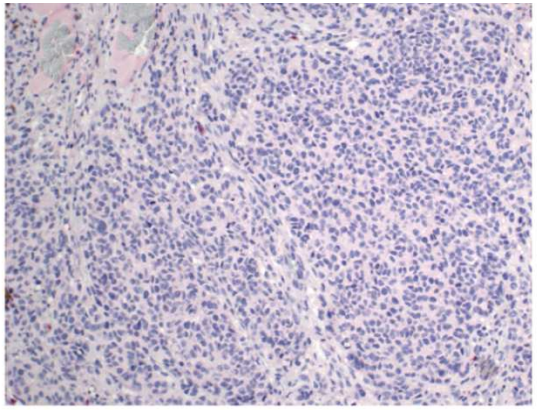
Jason Luke
Stefani Spranger
Riyue Bao

If the presence of a baseline T cell-inflamed tumor microenvironment defines a ceiling for efficacy of current immunotherapies, how can we approach the non-T cell-infiltrated tumors?

What are the molecular mechanisms that explain the T cell-inflamed versus non-inflamed tumor microenvironments?

Three major hypotheses





1. Somatic differences at the level of tumor cells
   - Distinct oncogene pathways activated in different patients
   - Mutational landscape and antigenic repertoire
2. Germline genetic differences at the level of the host
   - Polymorphisms in immune regulatory genes
3. Environmental differences
   - Commensal microbiota
   - Immunologic/pathogen exposure history of patients

Currently evaluating these possibilities in melanoma patients and multiple genomics platforms

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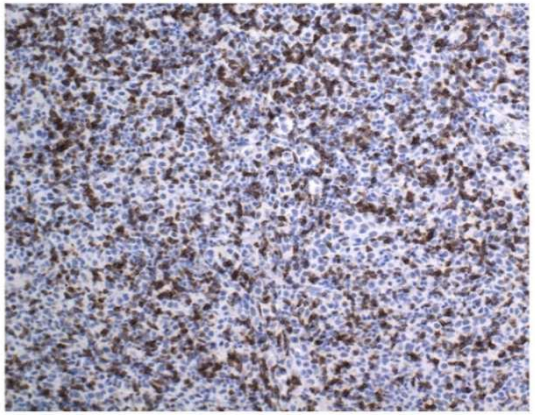
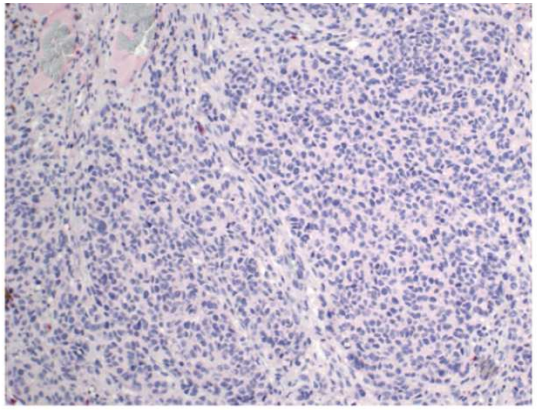
Three major hypotheses





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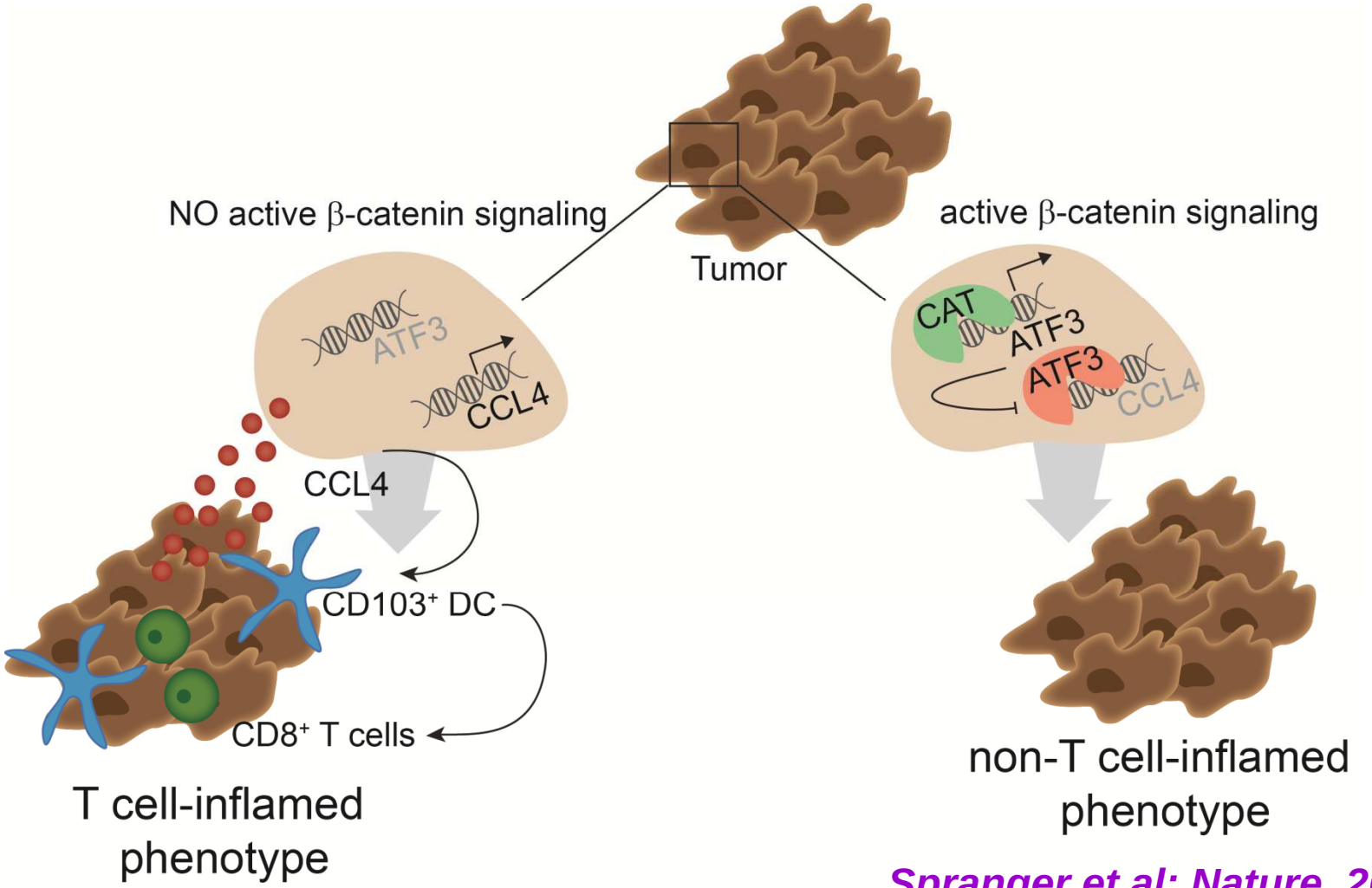
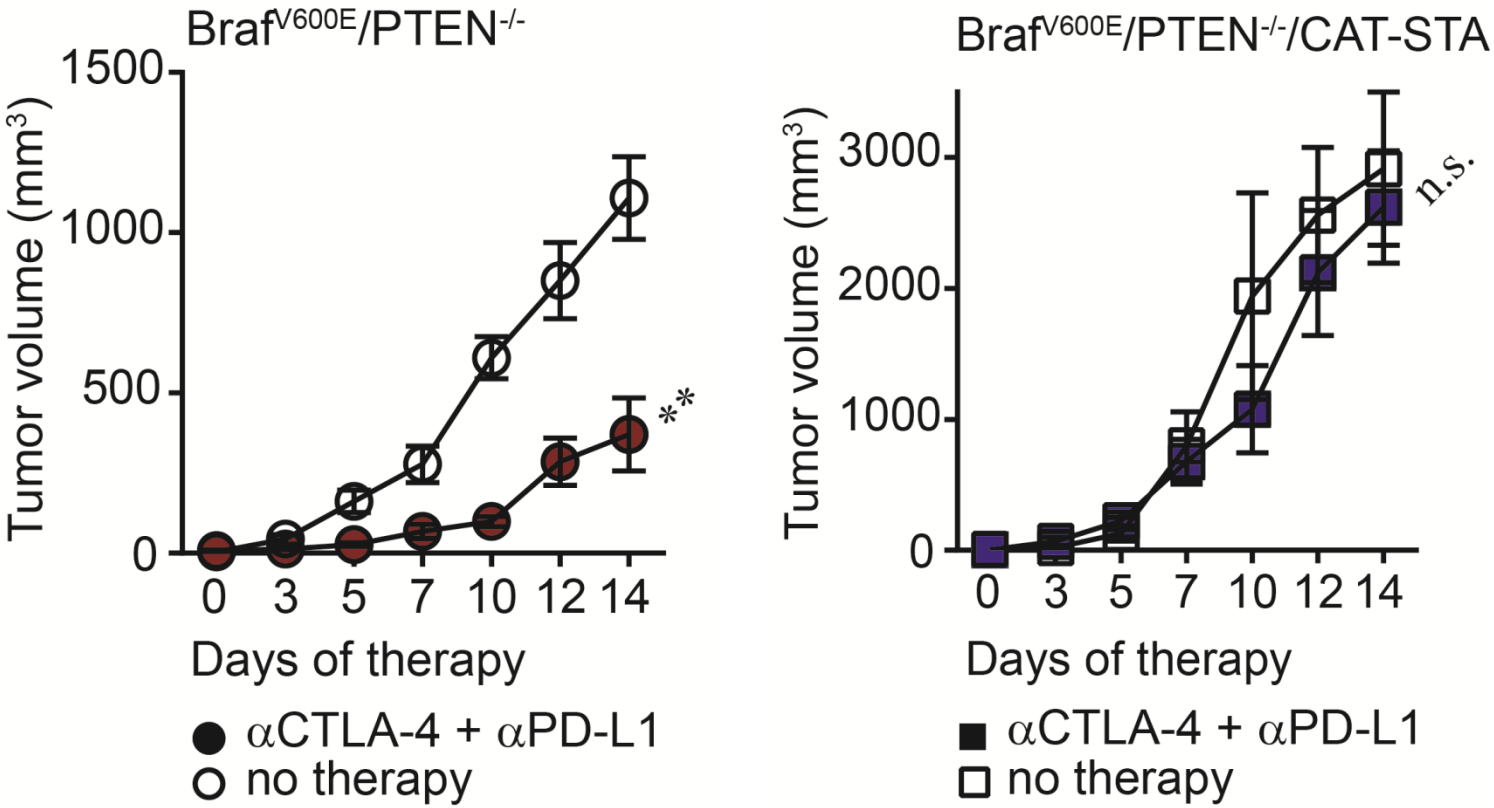
Model of how melanoma-intrinsic β-catenin activation prevents host anti-tumor immune response

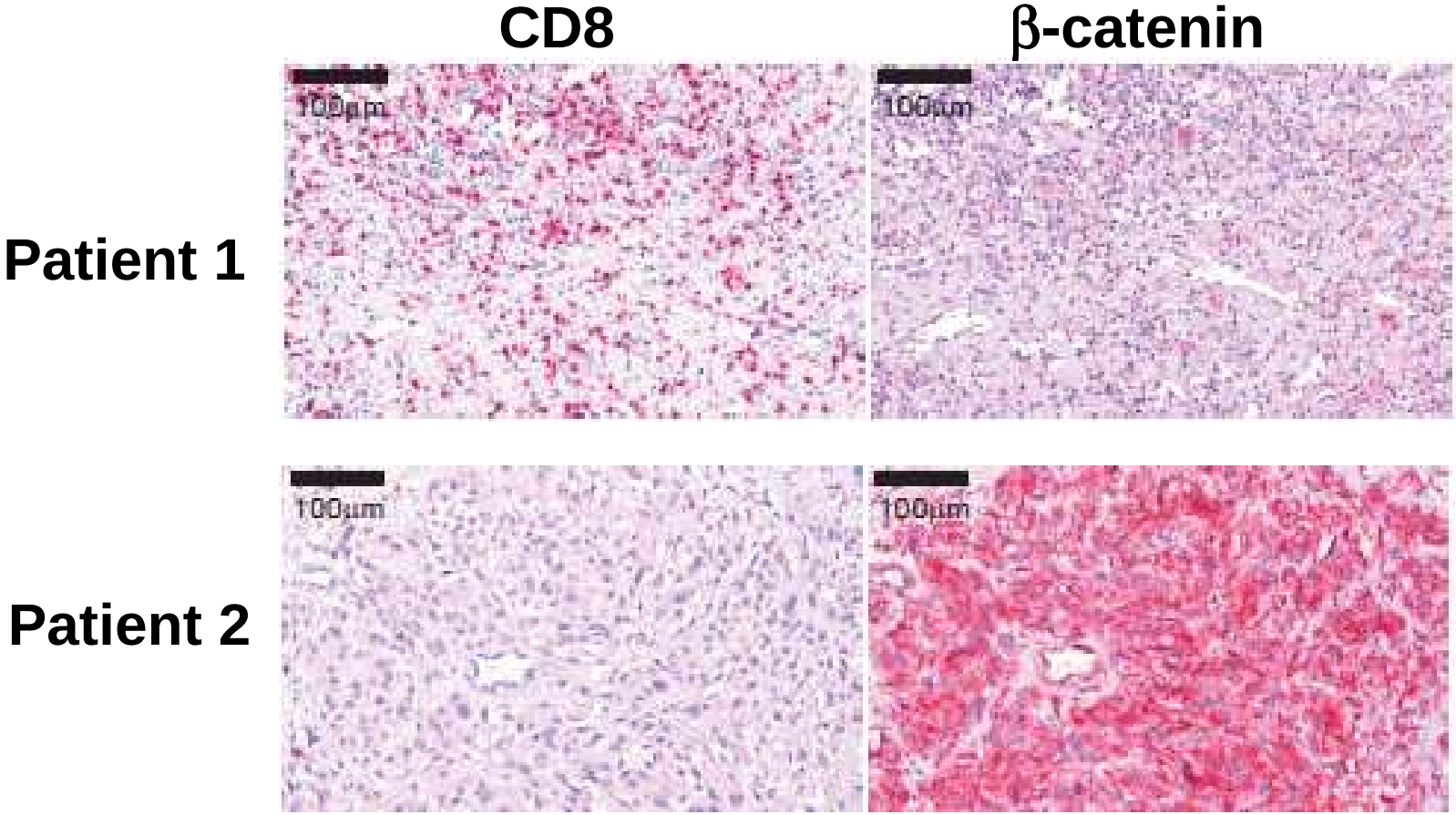


Spranger et al; Nature. 2015

Immunotherapy with anti-CTLA-4 + anti-PD-L1 is ineffective if induced B-Raf-driven melanomas express active β-catenin



$CD8^+$ T cells inversely correlate with stabilized β-catenin in melanoma



Major points

- The tumor microenvironment plays a major role in determining the functional outcome of anti-tumor immunity
- Most cancer types can be subseted based on the presence or absence of a T cell-inflamed tumor microenvironment
- Several current immunotherapy strategies, including anti-PD-1 mAbs, exert their major activity by restoring the function of specific T cells already in the tumor site
- Multiple additional immune targets have been identified in the tumor microenvironment, and combination immunotherapies are being pursued that may synergize
- New biologic principles and treatment strategies are being investigated to enable immunotherapies to be active in the non-T cell-inflamed subset of cancers