Biomarcatori e Tecniche di Diagnostica per Immagini nella Valutazione dell'Infiammazione in Oncologia

Overview sui meccanismi biologici legati all'infiammazione delle patologie tumorali e rilevanza clinica

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IRCCS – Istituto Nazionale Tumori «Regina Elena»

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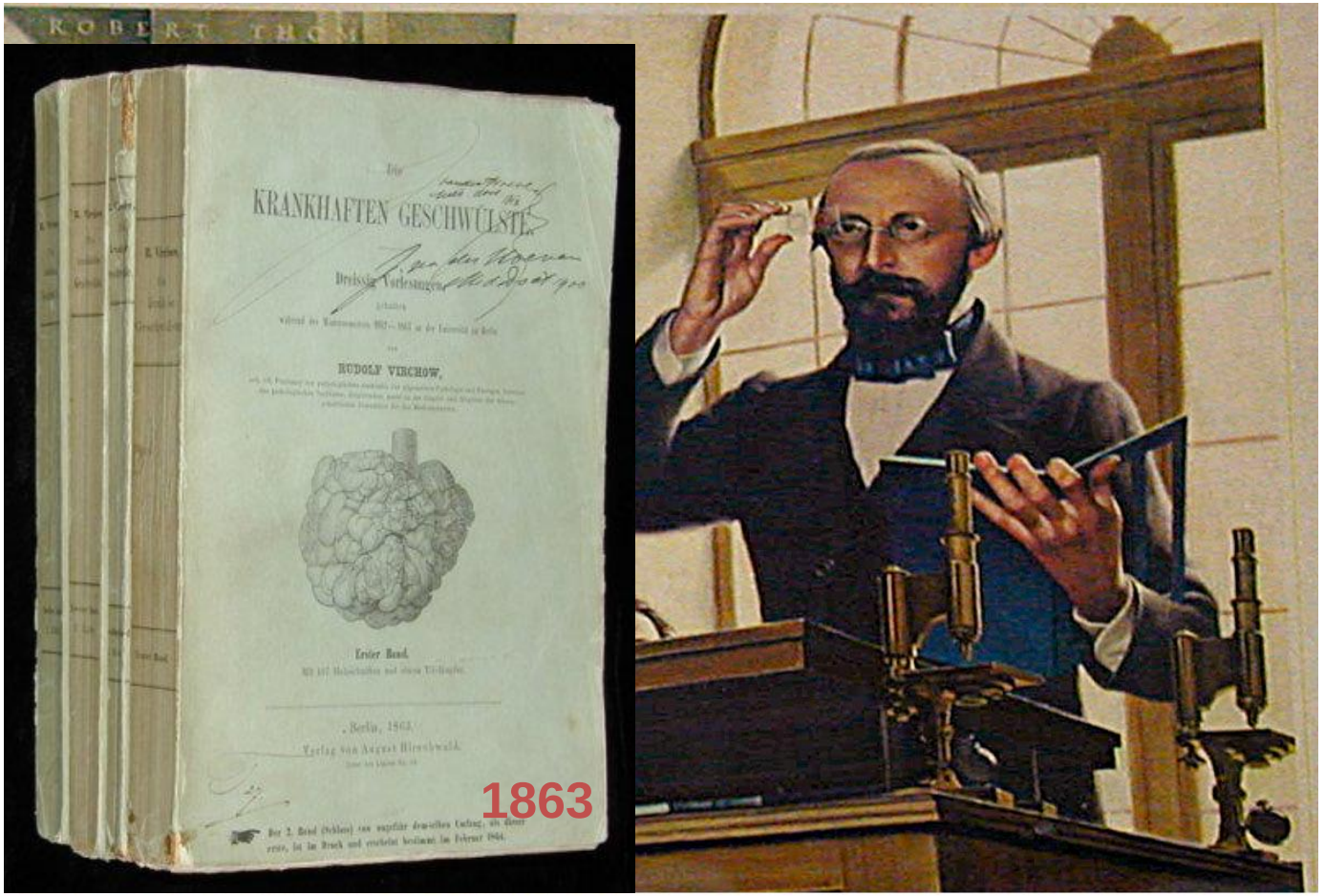
Istituto Superiore di Sanità

RUDOLF VIRCHOW



In 1863, Wirchow first postulated that cancer originates at sites of CHRONIC INFLAMMATION

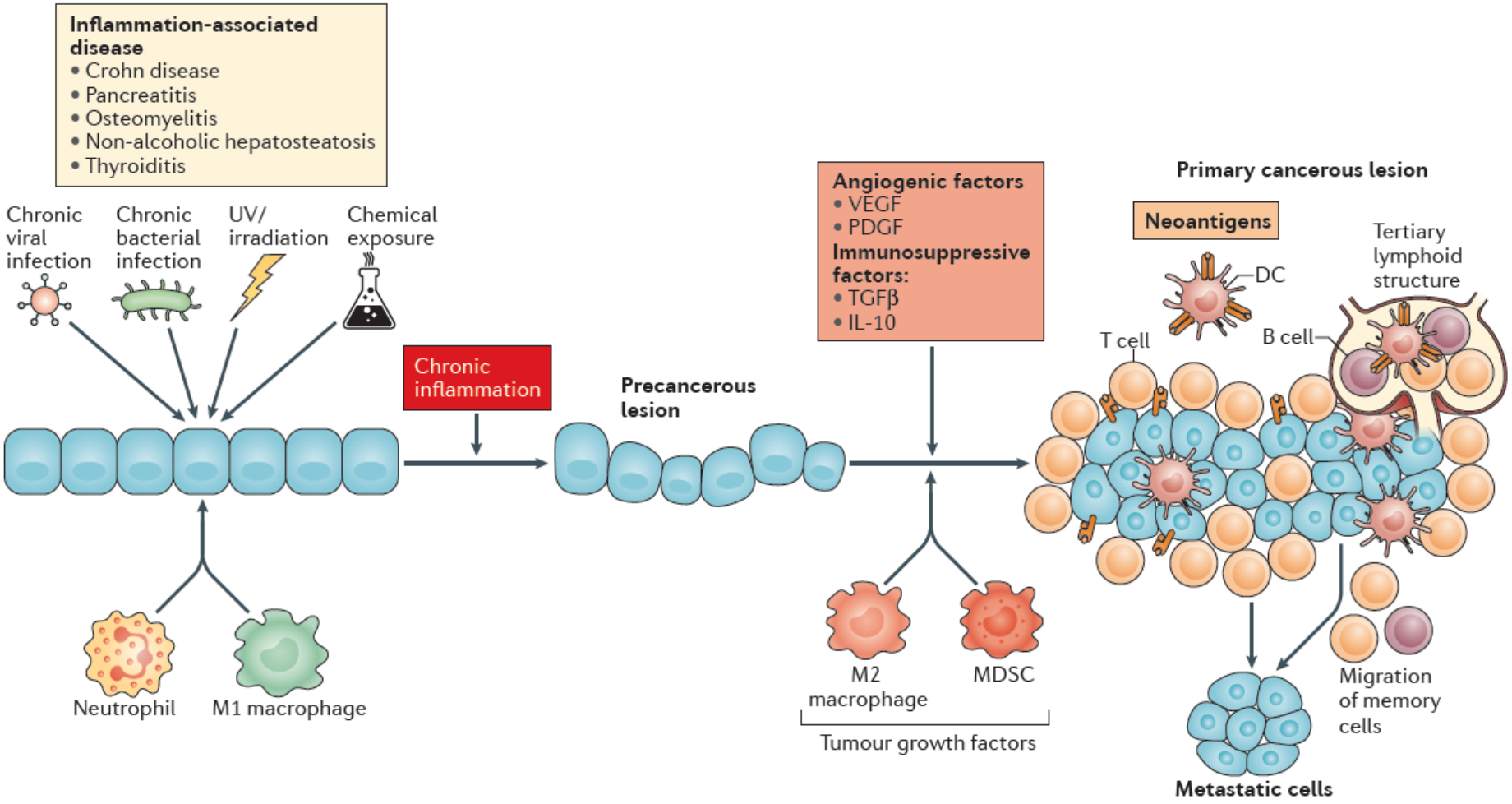
A functional link exists between inflammation and cancer

- **Increased cancer incidence in individuals affected by chronic inflammatory disorders**

- **Reduced cancer incidence in patients treated with long term anti-inflammatory drugs**

- **The anti-inflammatory therapy with canakinumab targeting the interleukin-1β innate immunity pathway could significantly reduce incident lung cancer and lung cancer mortality (Trial of canakinumab in 10061 patients)** ***Ridker, et al The Lancet 2017***

Tumorigenesis goes *hand in hand* with chronic inflammation at the tumor sites

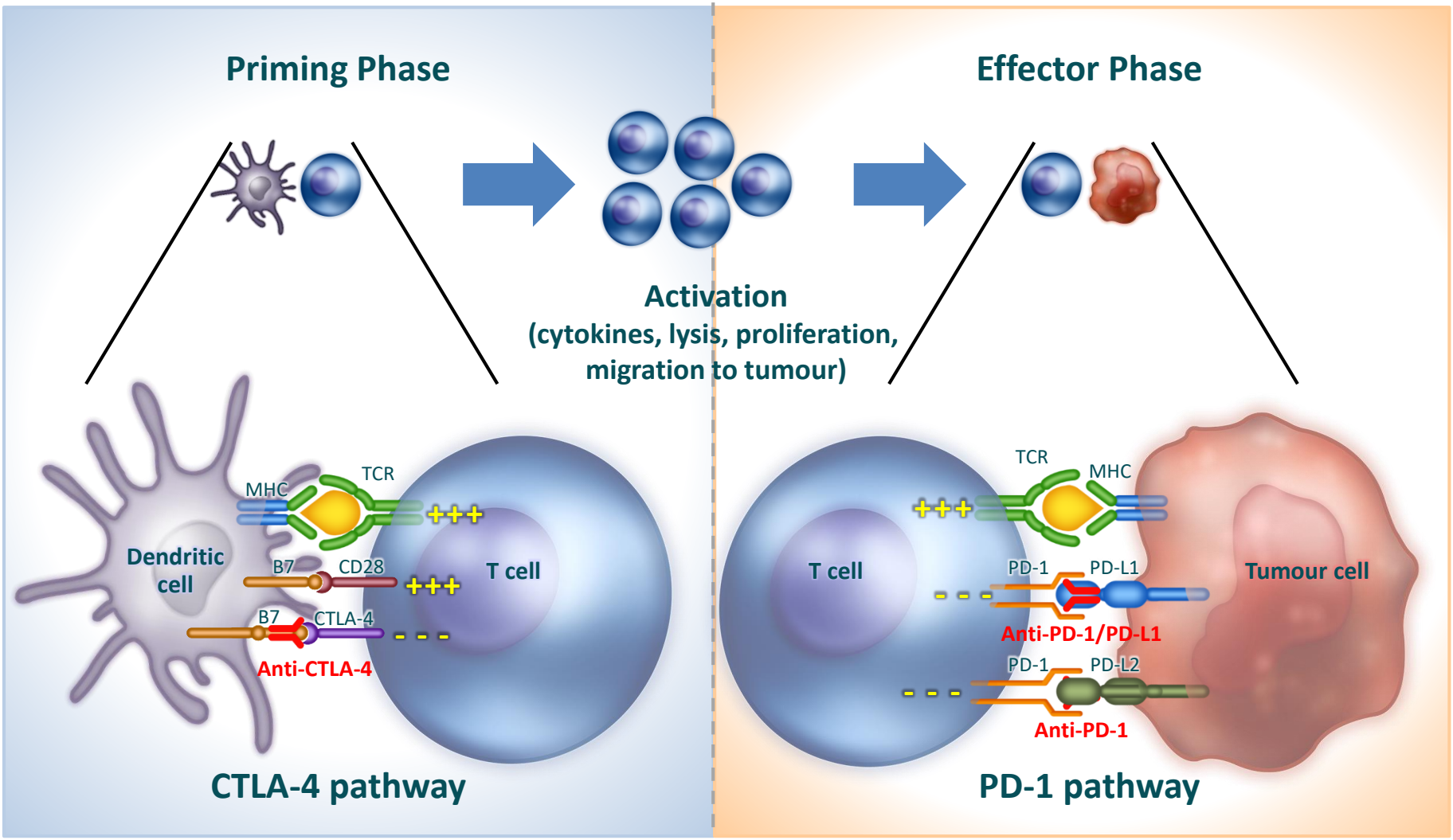


Fridman WH et al., Nat Rev, 2017

Key Concept

Cancer has to be conceived as a complex organ, not anymore as a mass composed just of tumor cells

This concept is at the basis of the success (or lack thereof) of ICI



Intrinsic features of Tumor Cells do not explain alone response to ICI

The case of Tumor Mutational Burden

Tumor mutational burden predicts ONLY PARTIALLY resonse to ICI

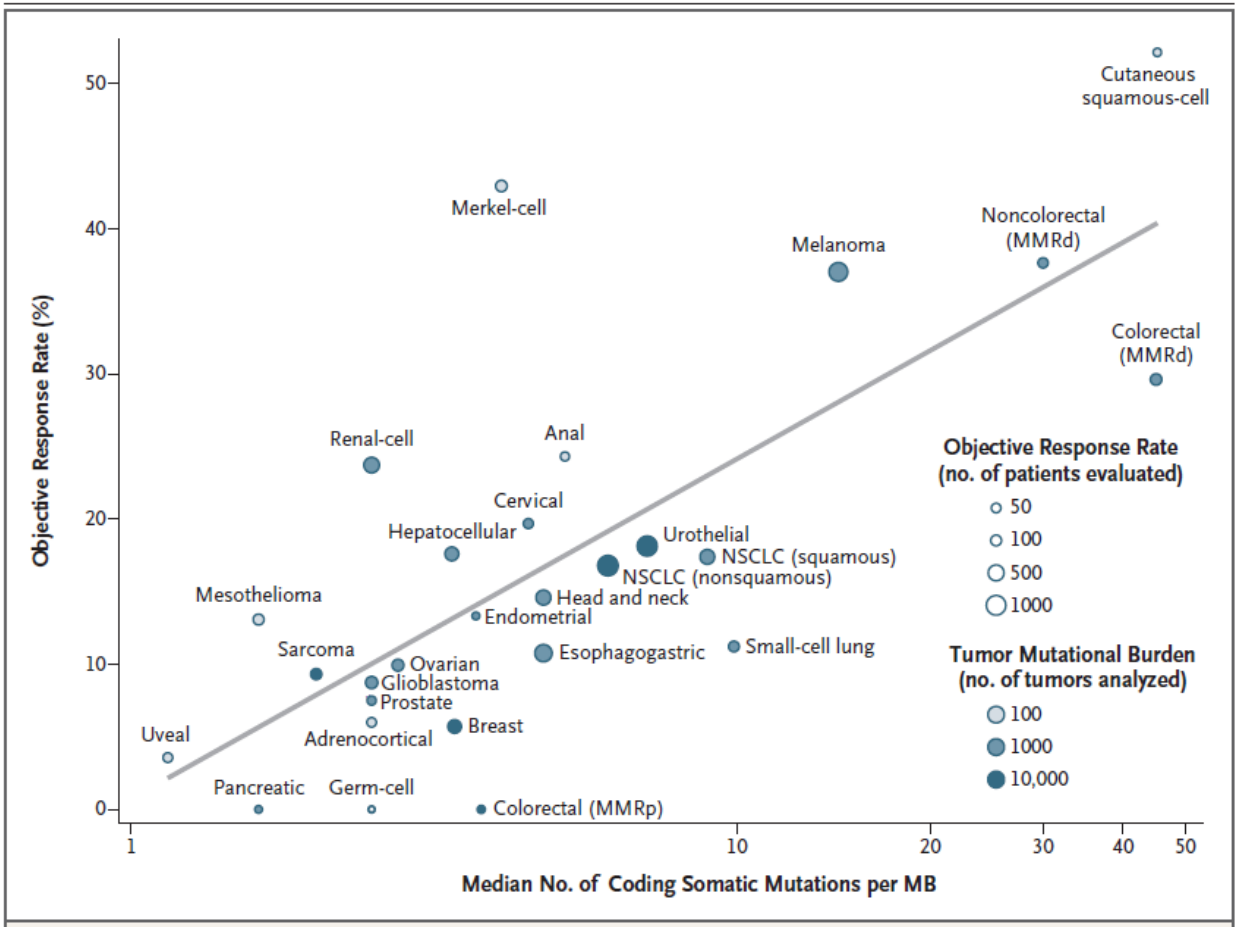
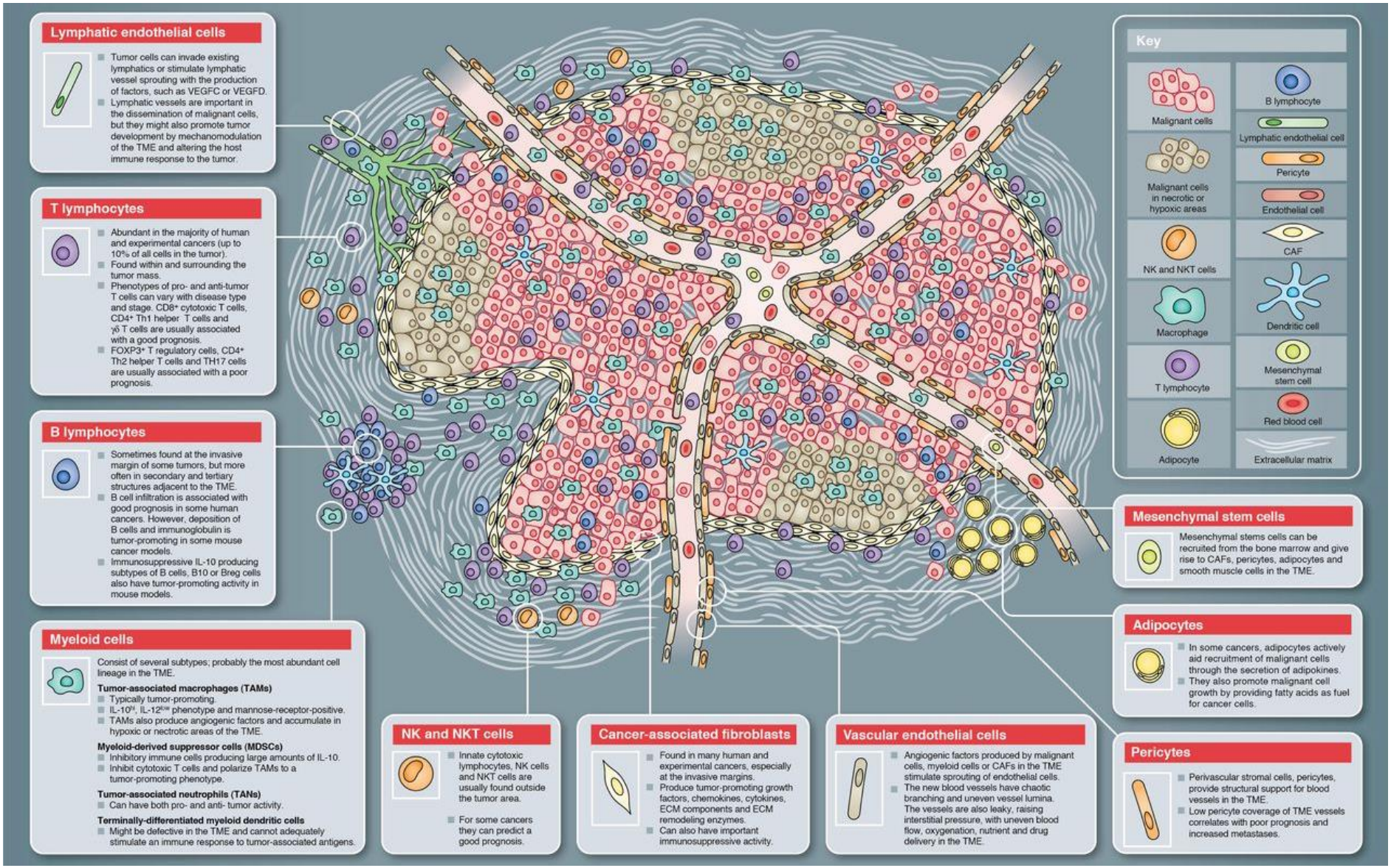


Figure 1. Correlation between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 or Anti–PD-L1 Therapy in 27 Tumor Types.

Intrinsic features of Tumor Cells do not explain alone response to ICI

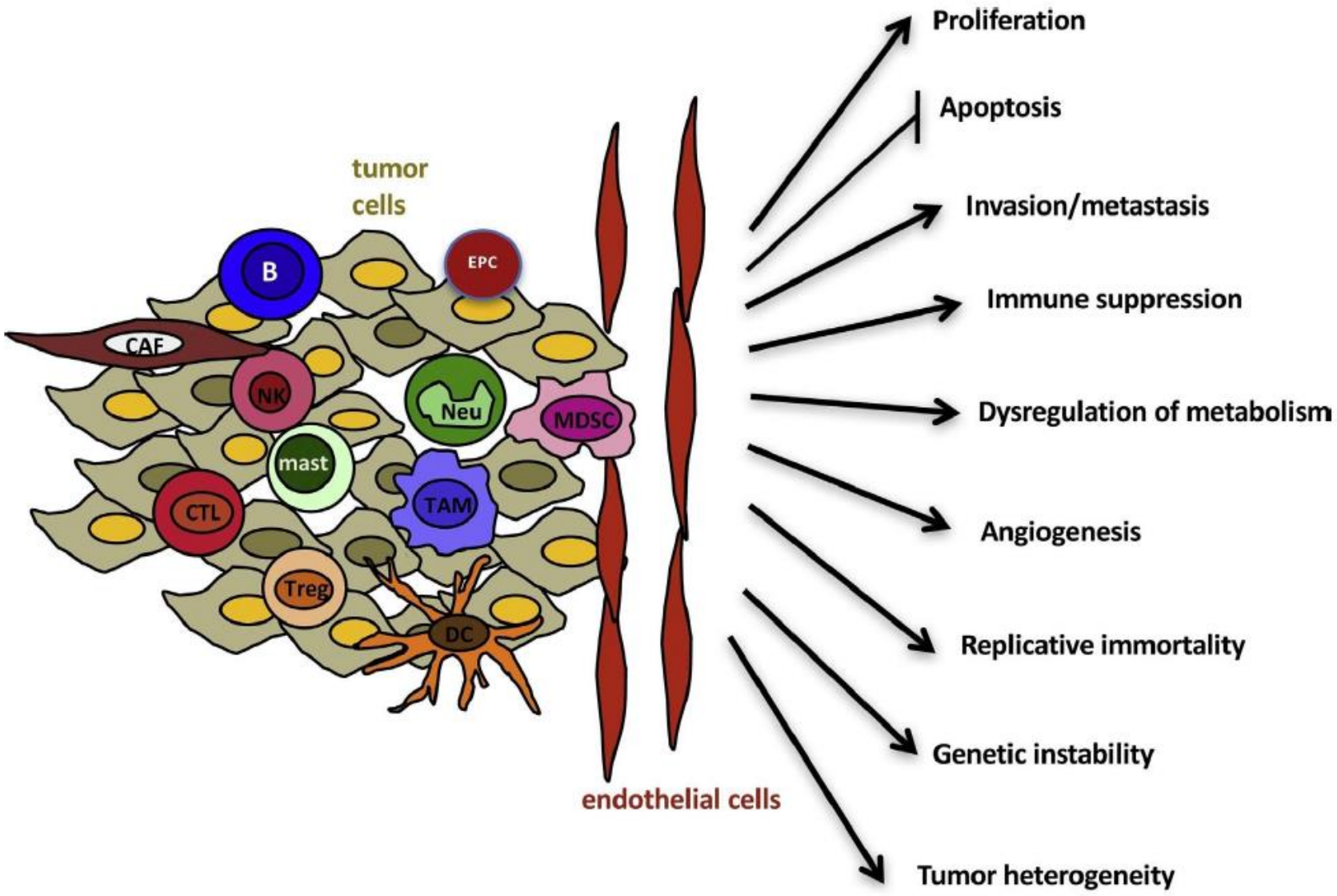
Response to ICI depends on something more: the interplay with the tumor microenvironment

Cancer cells are embedded in a complex tumor microenvironment: a highly trafficked network



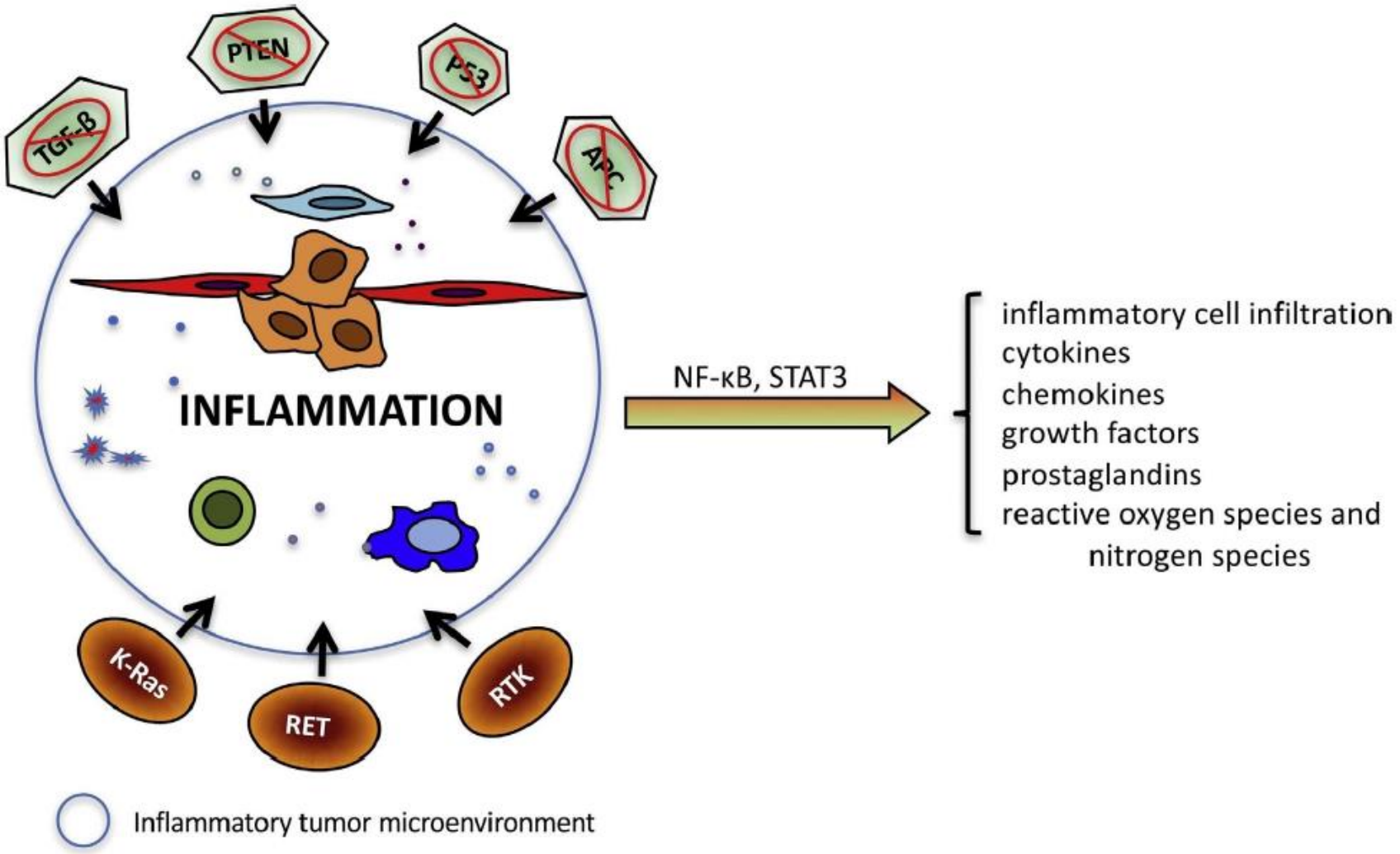
Balkill et al., Cell Science 2012

Players in the TME and the outcome resulting from tumor-associated inflammation



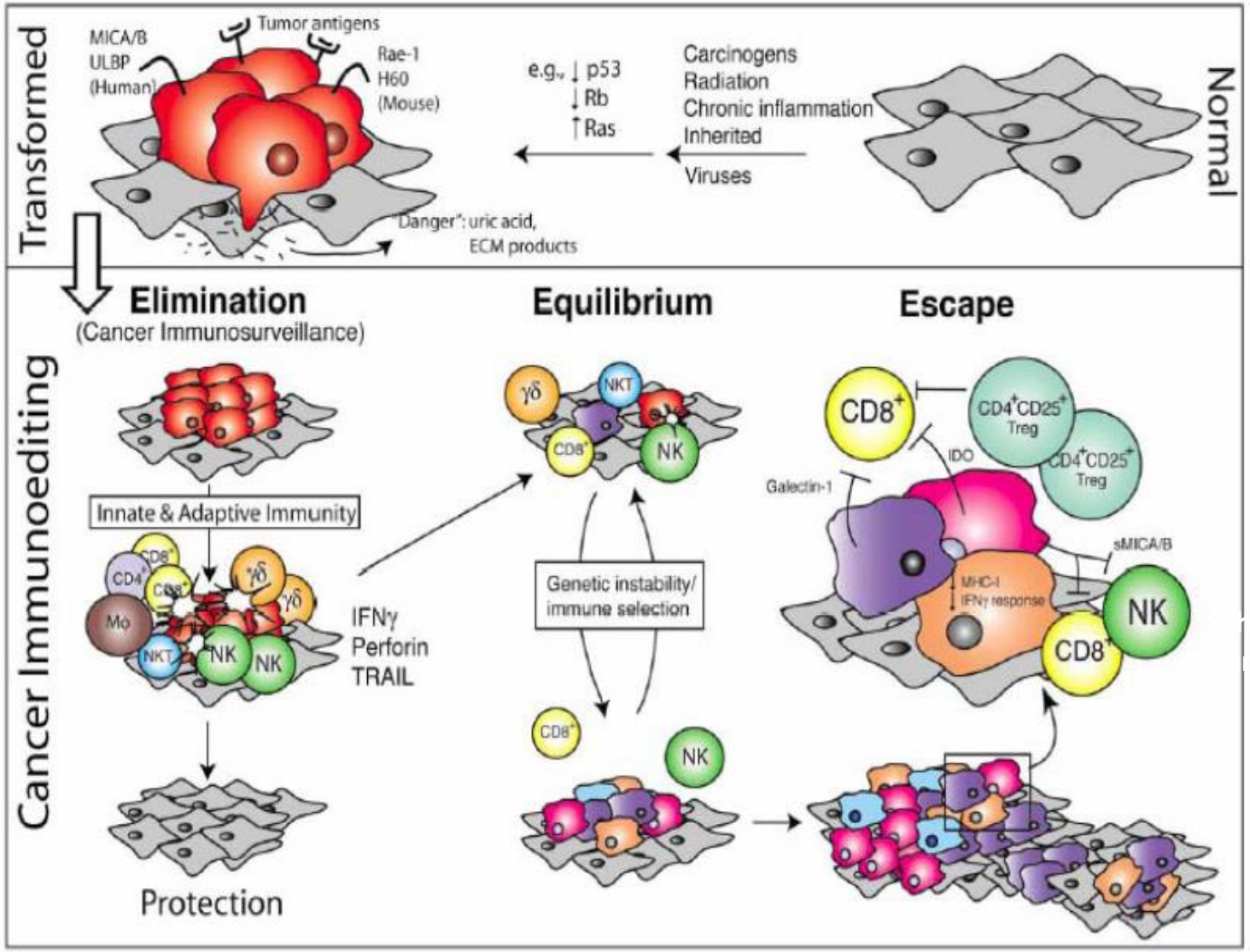
Yanga and Linb, Seminars in Cancer Biology 2017

Loss of tumor suppressors and/or activation of oncogenes induces the inflammatory microenvironment

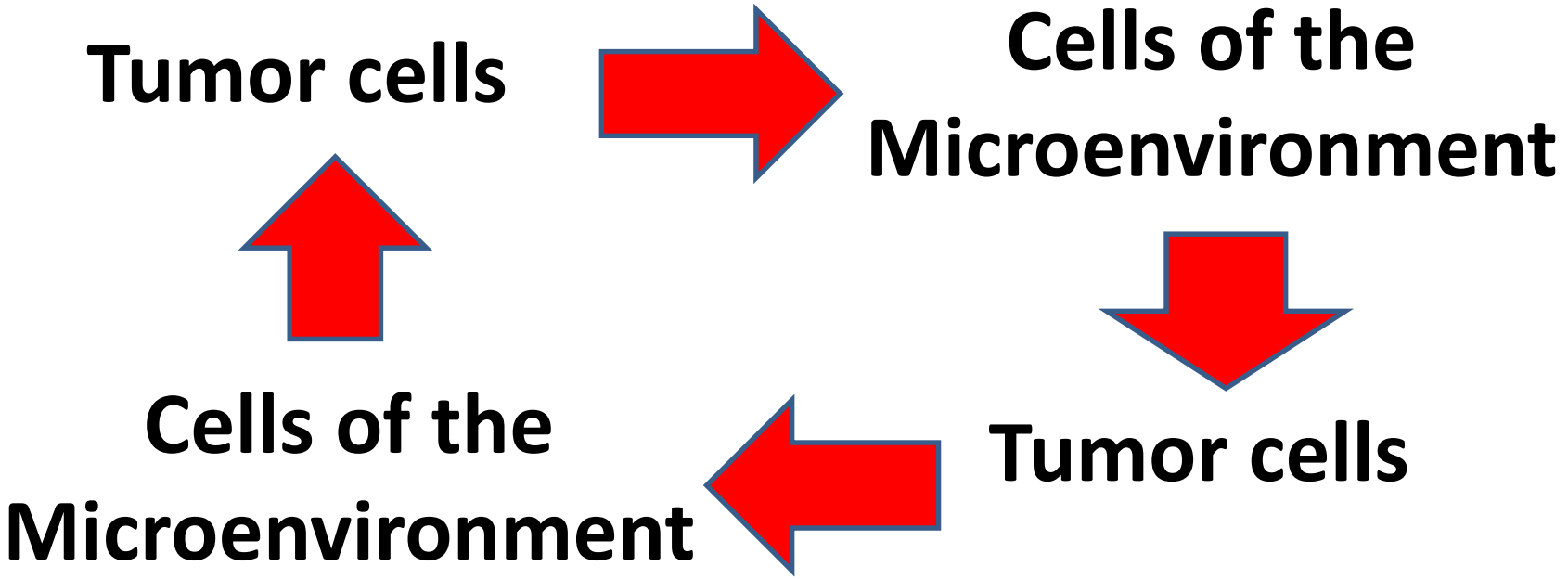


Yanga and Linb, Seminars in Cancer Biology 2017

Cancer growth is shaped by Immunoediting: a dymanic interplay with the tumor microenvironment



A dynamic interplay



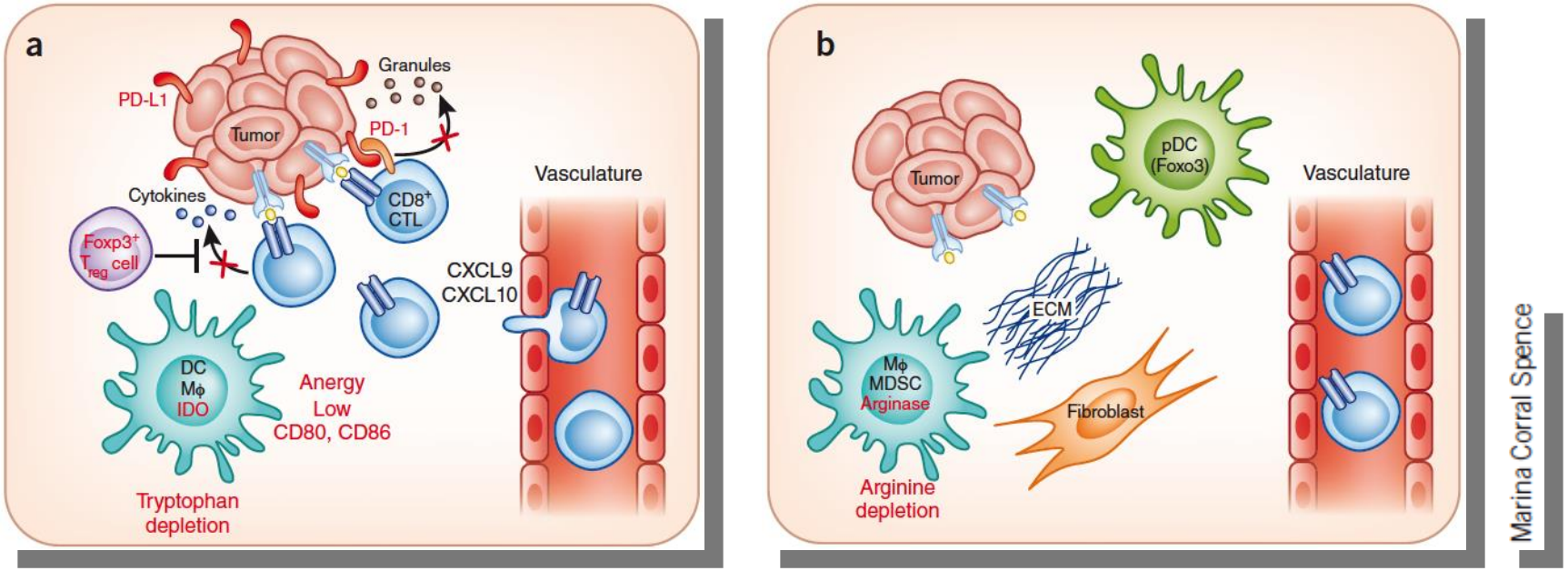
Hot tumors and cold tumors

Innate and adaptive immune cells in the tumor microenvironment

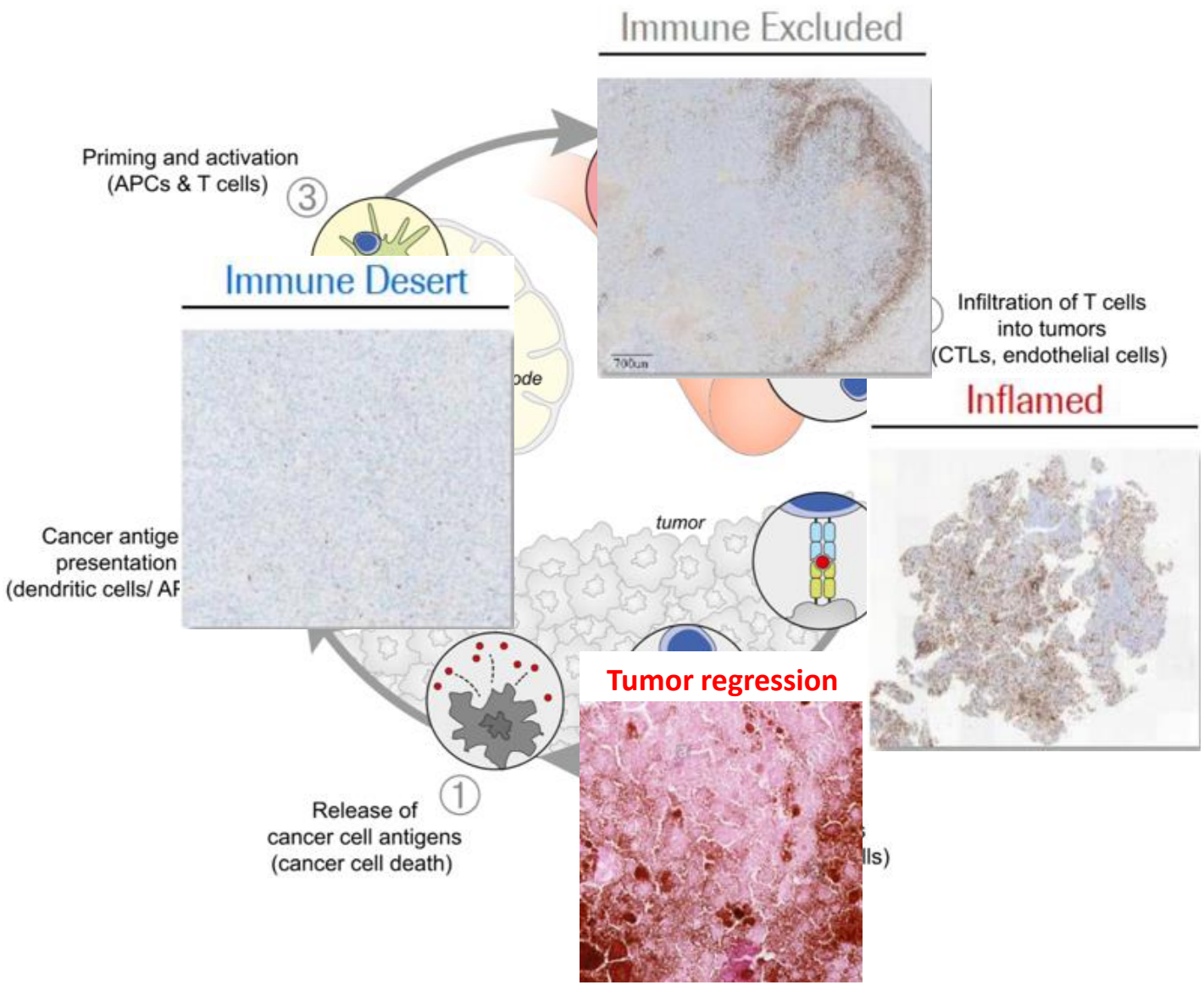
Thomas F Gajewski, Hans Schreiber & Yang-Xin Fu

inflamed tumor

Non-inflamed tumor

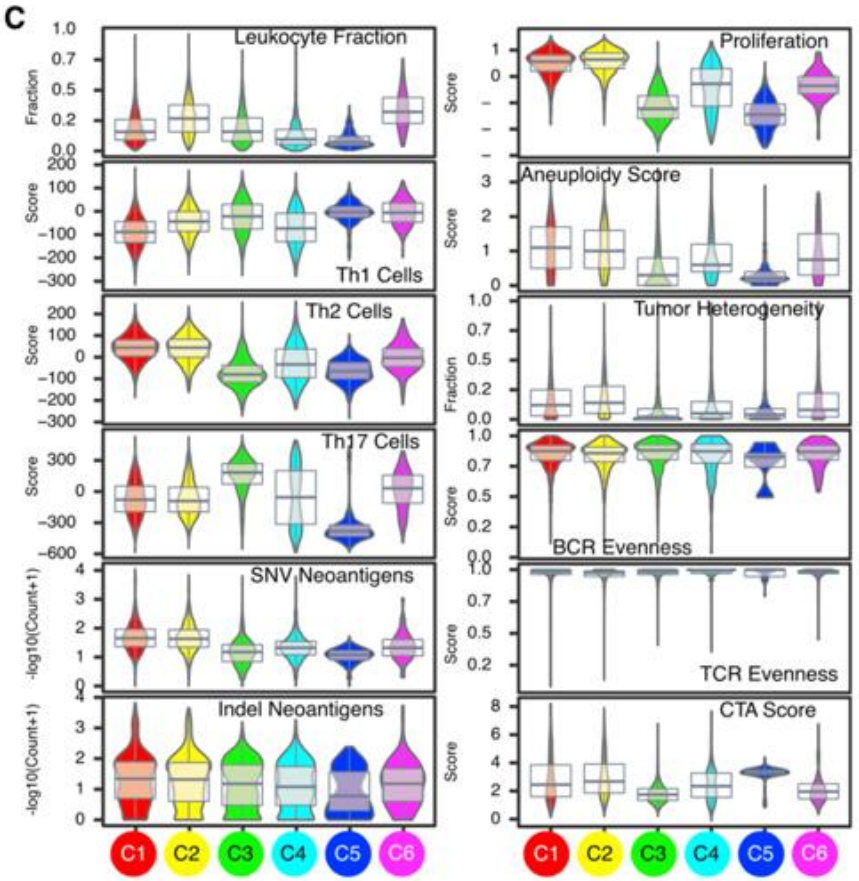


OCTOBER 2013 NATURE IMMUNOLOGY



Chen DS, Mellman I. Immunity 2013

Evolving technologies highlight higher levels of complexity



Immunity

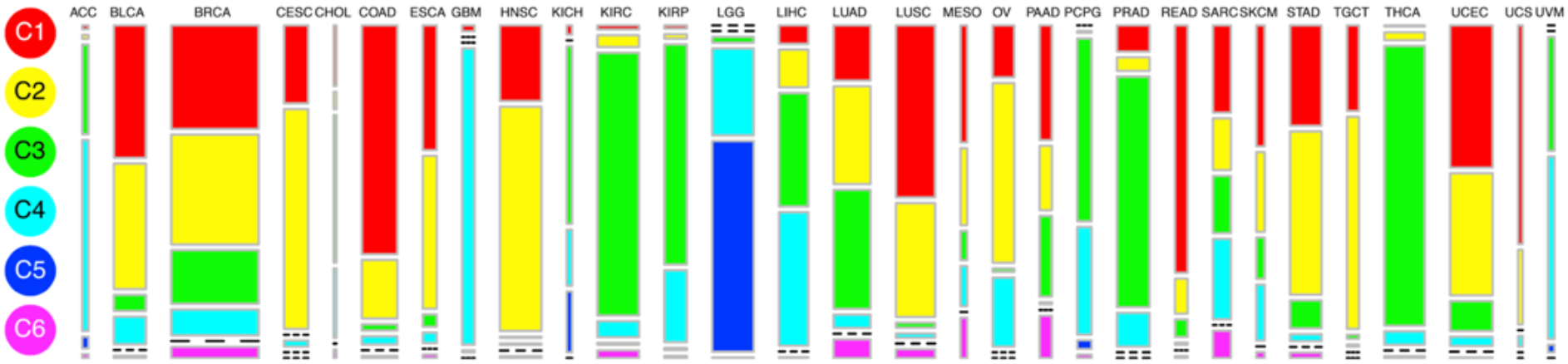
The Immune Landscape of Cancer

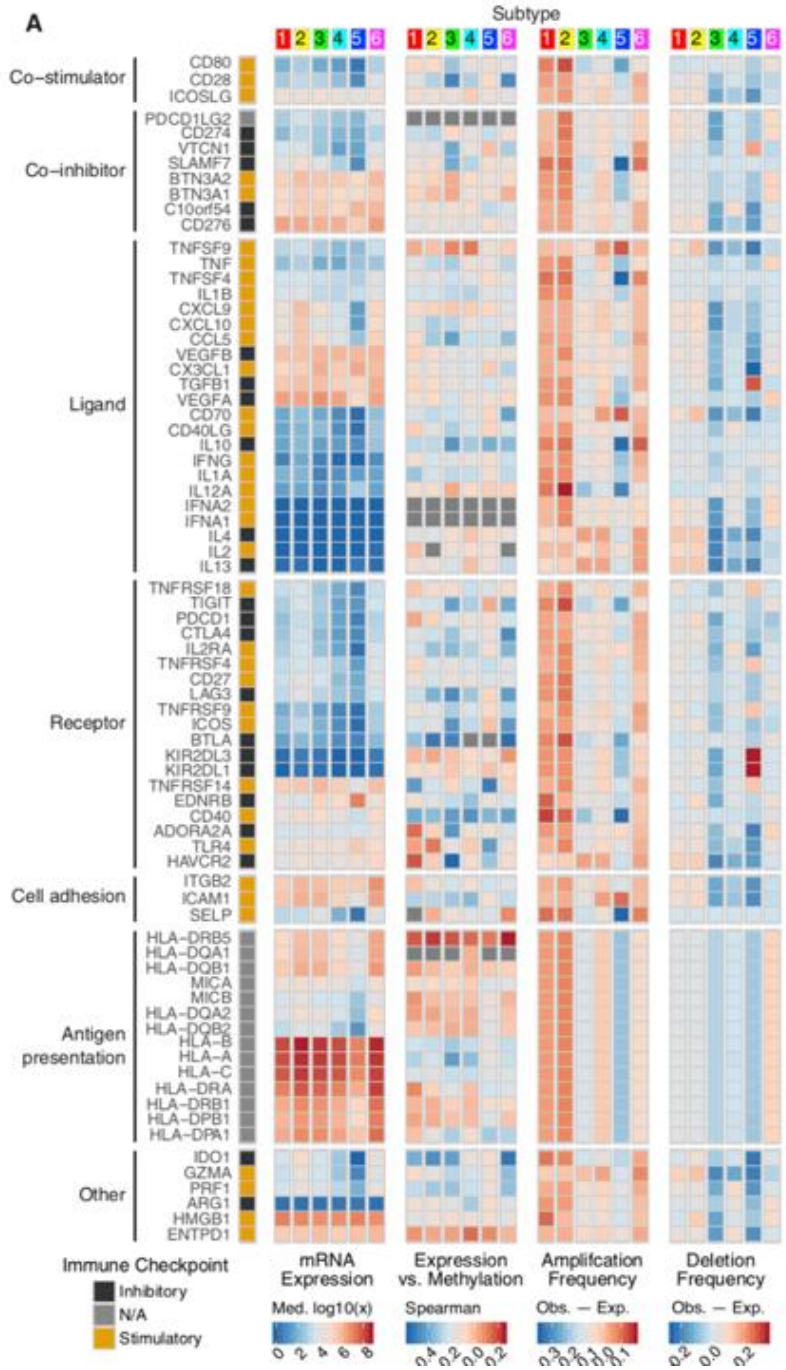
Thorsson et al. Immunity 2018

	Macrophage: lymphocyte	Th1:Th2	Proliferation	Intratumoral heterogeneity	Other
Wound healing	Balanced	Low	High	High	
IFN-γ dominant	Lowest	Lowest	High	Highest	Highest M1 and highest CD8 T cells
Inflammatory	Balanced	High	Low	Lowest	Highest Th17
Lymphocyte depleted	High	Minimal Th	Moderate	Moderate	
Immunologically quiet	Highest	Minimal Th	Low	Low	Highest M2
TGF-β dominant	High	Balanced	Moderate	Moderate	Highest TGF-β signature

Evolving technologies highlight higher levels of complexity

	Macrophage: lymphocyte	Th1:Th2	Proliferation	Intratumoral heterogeneity	Other
C1 Wound healing	Balanced	Low	High	High	
C2 IFN-γ dominant	Lowest	Lowest	High	Highest	Highest M1 and highest CD8 T cells
C3 Inflammatory	Balanced	High	Low	Lowest	Highest Th17
C4 Lymphocyte depleted	High	Minimal Th	Moderate	Moderate	
C5 Immunologically quiet	Highest	Minimal Th	Low	Low	Highest M2
C6 TGF-β dominant	High	Balanced	Moderate	Moderate	Highest TGF-β signature





Differential expression of immunomodulatory molecules among different immunotypes

Thorsson et al. Immunity 2018

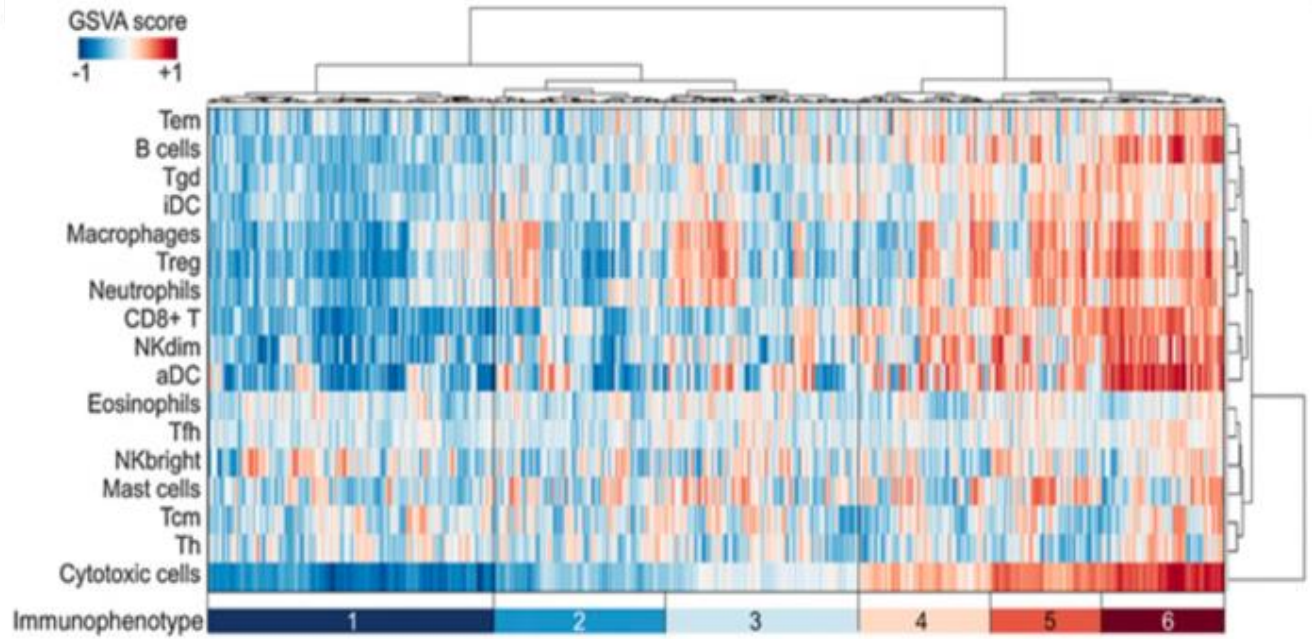
Evolving technologies highlight higher levels of complexity

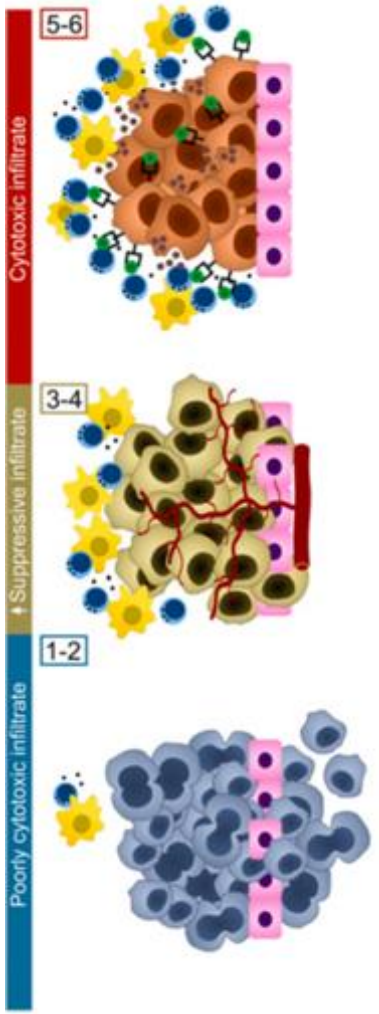
Translational Cancer Mechanisms and Therapy

Clinical Cancer Research

A Pan-cancer Landscape of Interactions between Solid Tumors and Infiltrating Immune Cell Populations

David Tamborero[1,2], Carlota Rubio-Perez[1,2], Ferran Muiños[2], Radhakrishnan Sabarinathan[2], Josep M. Piulats[3], Aura Muntasell[4], Rodrigo Dienstmann[5,6], Nuria Lopez-Bigas[1,2,7], and Abel Gonzalez-Perez[1,2]





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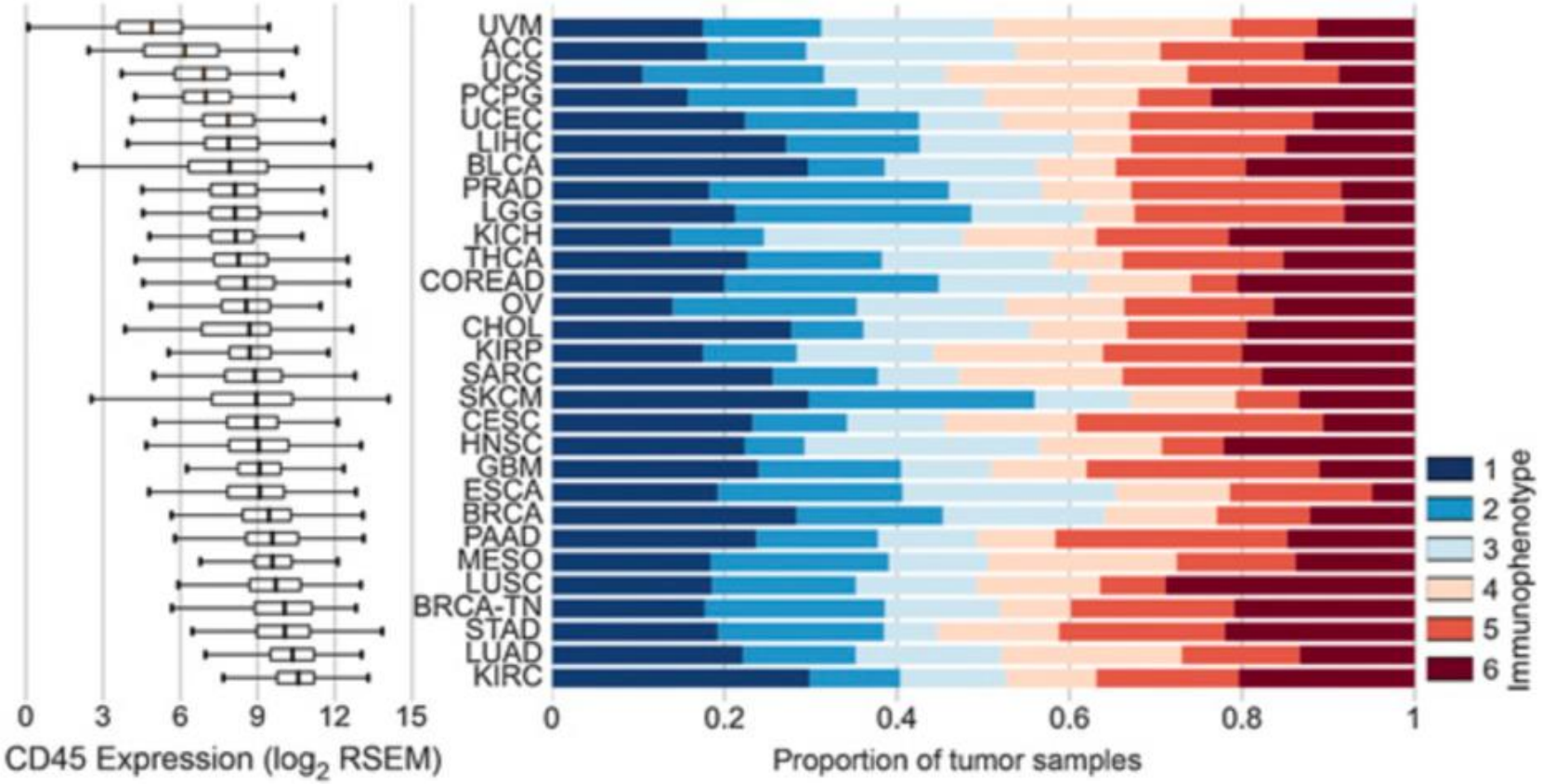
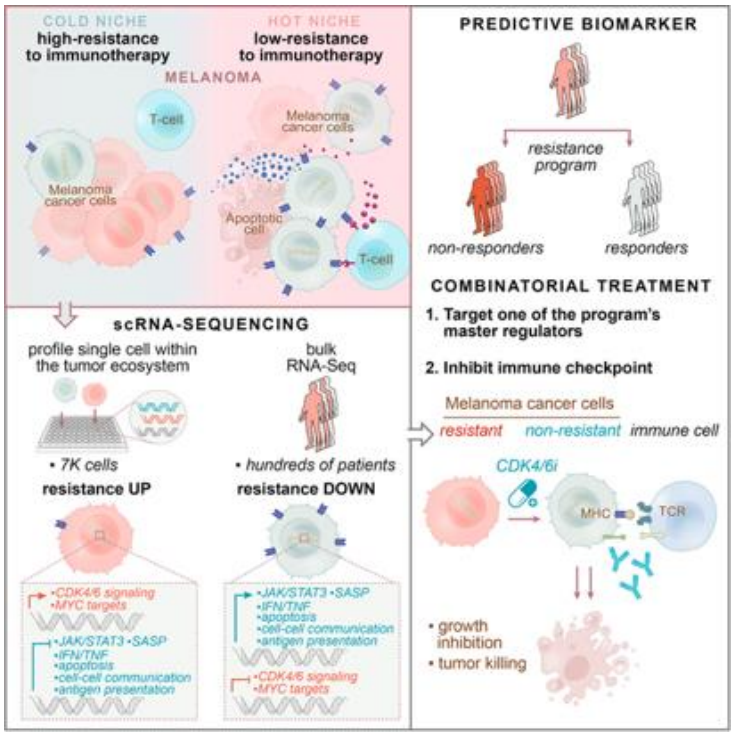


We are starting to understand the origin of microenvironment immunotypes

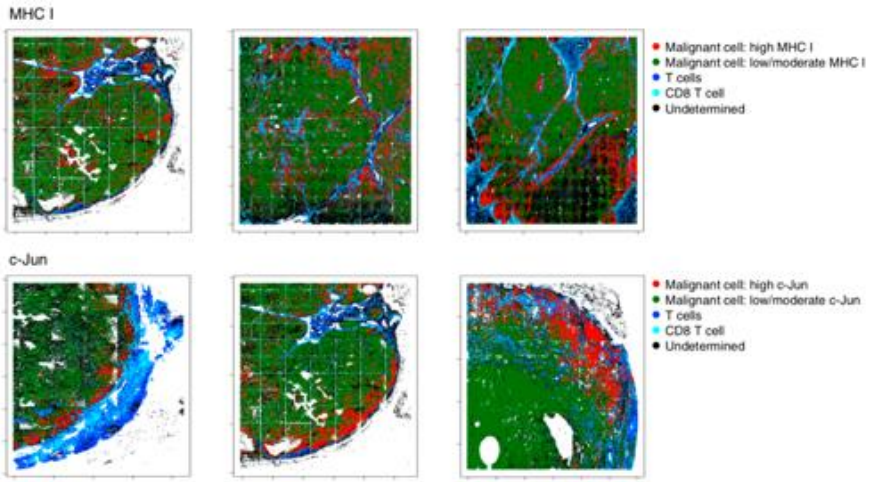
Cell

A Cancer Cell Program Promotes T Cell Exclusion and Resistance to Checkpoint Blockade

Jerby-Arnon et al Cell *175*, 984–997, November 1, 2018



Malignant Cells in T Cell-Depleted Niches Express Features of the Resistance Program *In Situ*



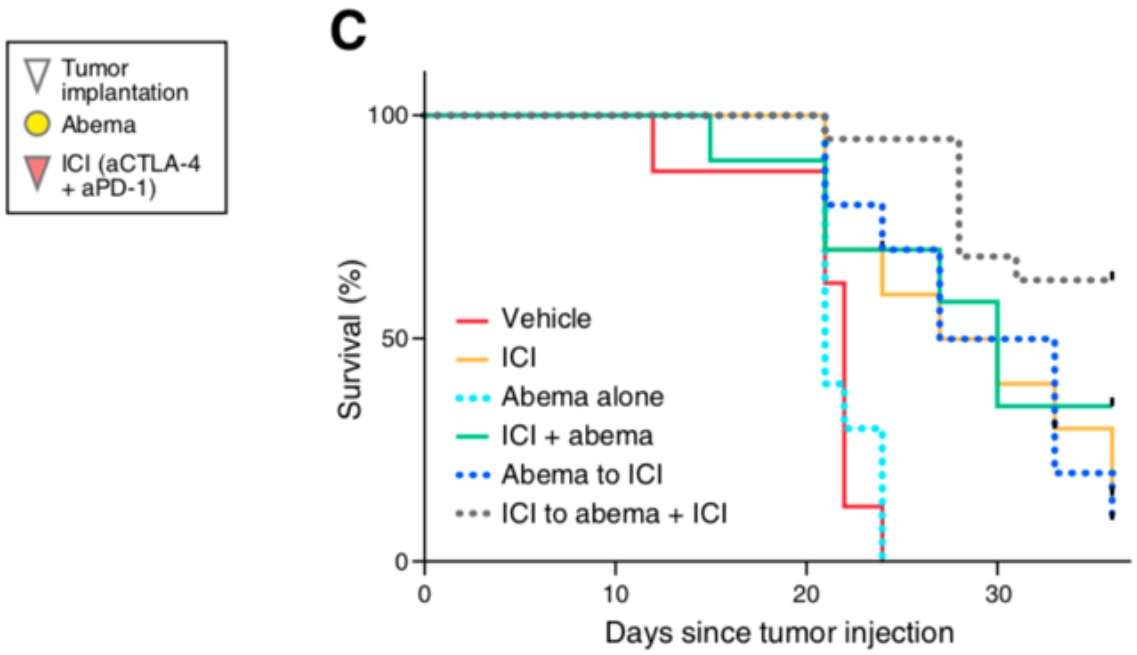
The Resistance Program Is Expressed Prior to Treatment and Is Enhanced following Immunotherapy in Resistant Lesions

The Resistance Program Predicts ICI Responses in Melanoma Patients

We are starting to understand the origin of microenvironment immunotypes

The Resistance Program Is Coherently Controlled by CDK4/6

CDK4/6 Inhibitors Repress the Resistance Program in Melanoma Cells



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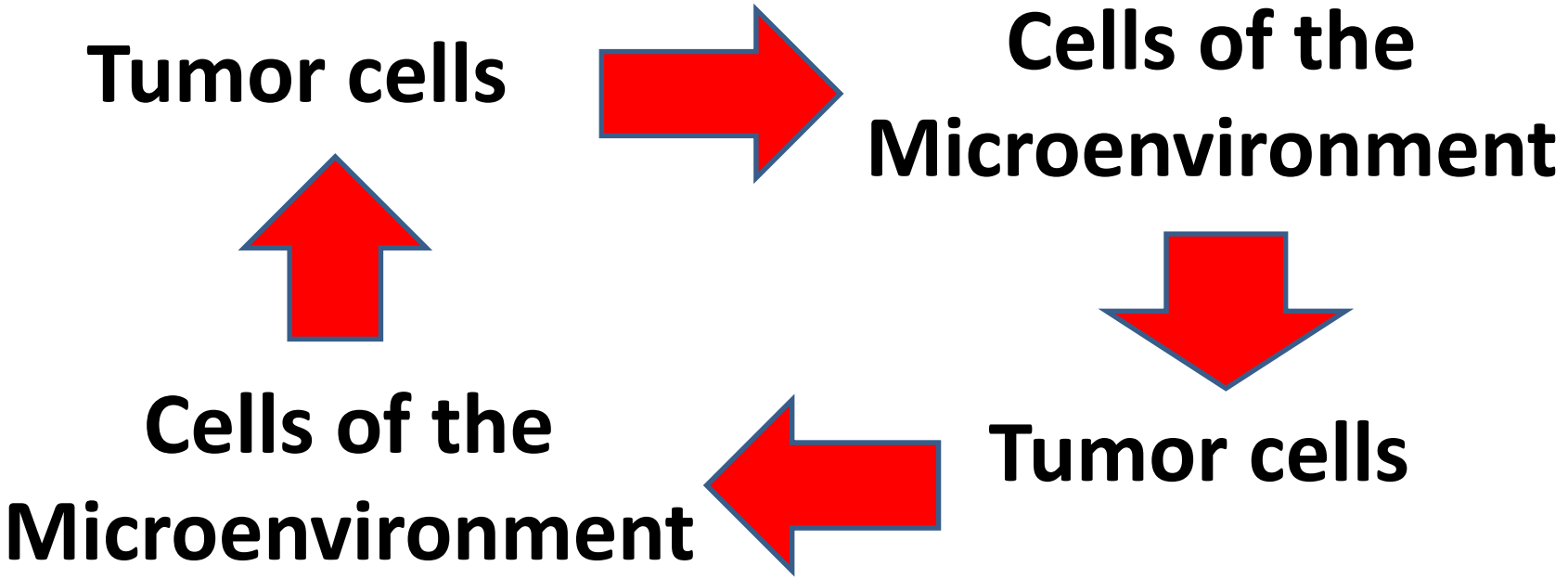
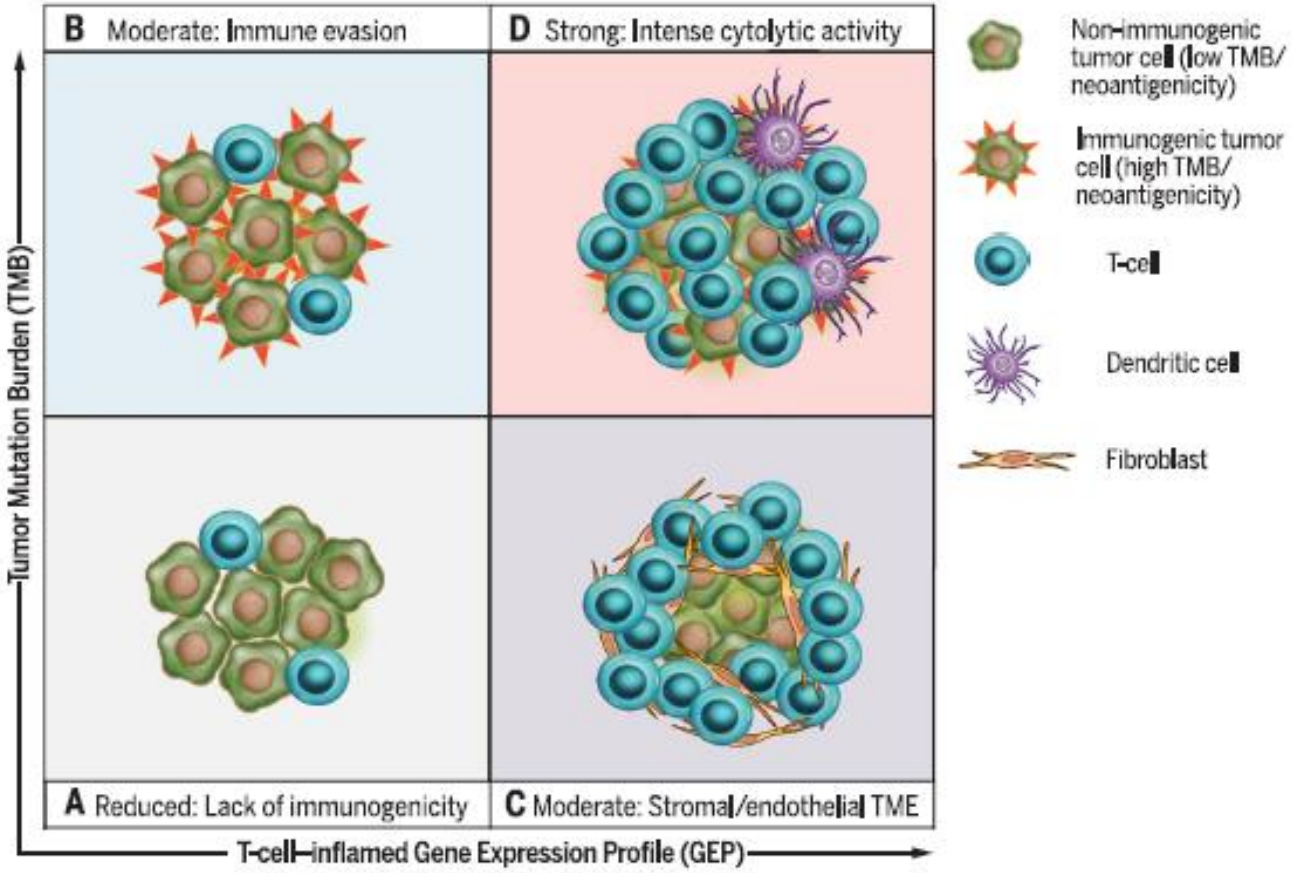


Potential diagnostic and therapeutic implications

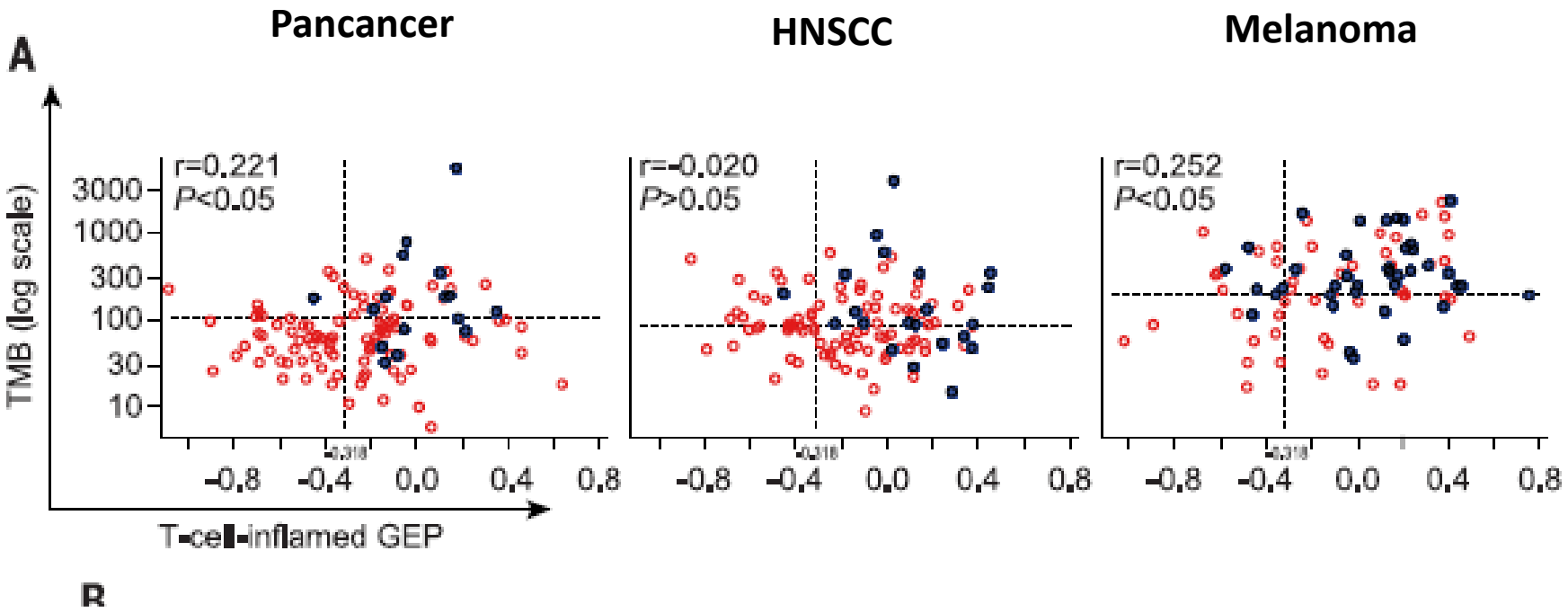
Diagnostic Implications: combinations of biomarkers increases the predictive value of ICI



Biomarker-defined responses to pembrolizumab monotherapy identify targetable-resistance biology. (**A**) Tumors have low TMB and low neoantigenicity and lack a

Cristescu et al, 2018

Diagnostic Implications: combinations of biomarkers increases the predictive value of ICI

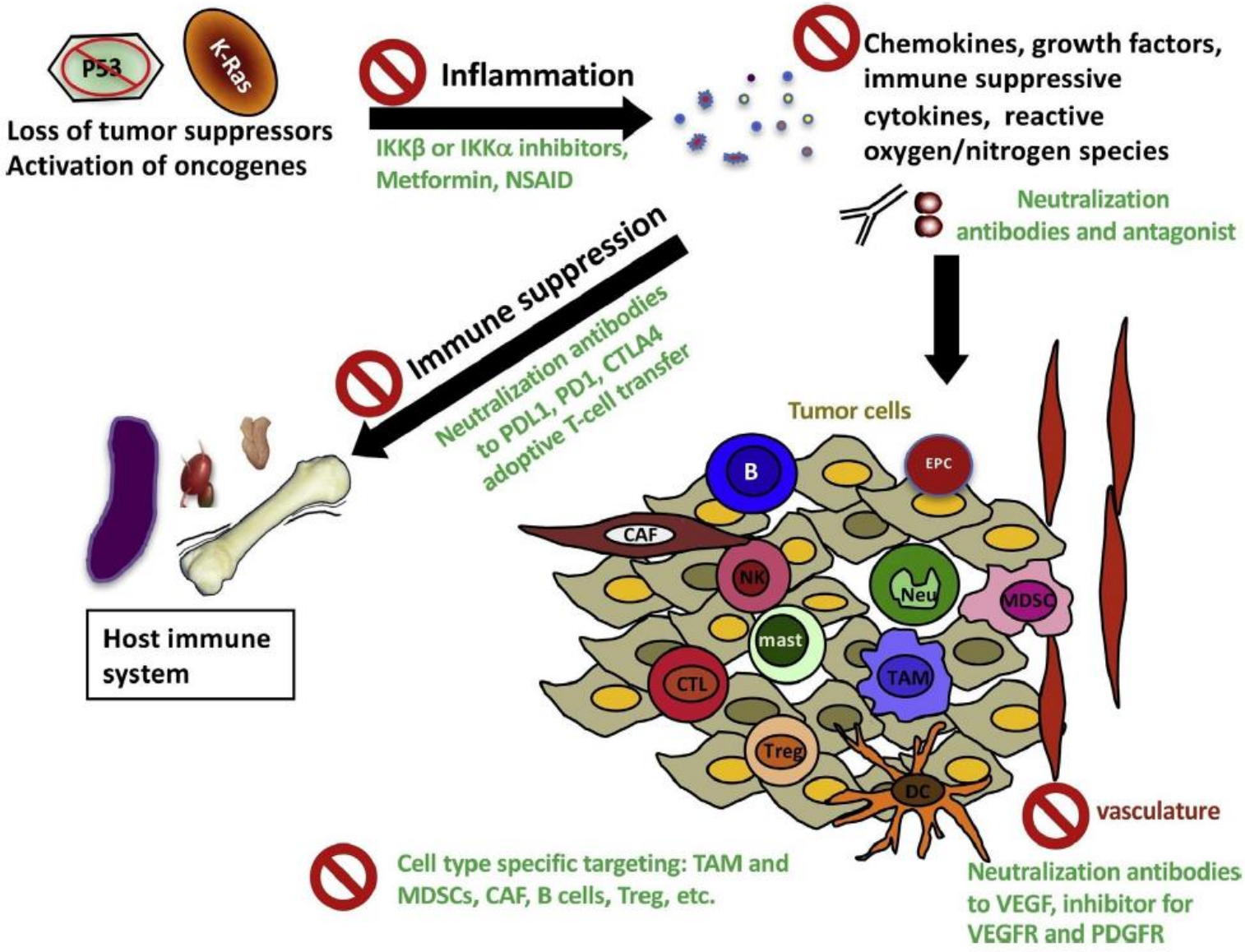


Cristescu et al, 2018

Alliance Against Cancer (ACC)

- ACC Immunotherapy
- Several centers involed
- Goal of the project: define a predictive signature of response to ICI through multiplex profiling of fast progressors vs long term responders

Therapeutic Implications



Yanga and Linb, Seminars in Cancer Biology 2017

Suggested Reading

The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy

*Jonathan J. Havel[1,2,4], Diego Chowell[1,2,4] and Timothy A. Chan[1,2,3]**

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