Obstacles to Driving an Immune Response

Margaret Callahan, MD, PhD
Memorial Sloan-Kettering Cancer Center

‘Driving’ An Immune Response

T-cell receptor:
Antigen-MHC

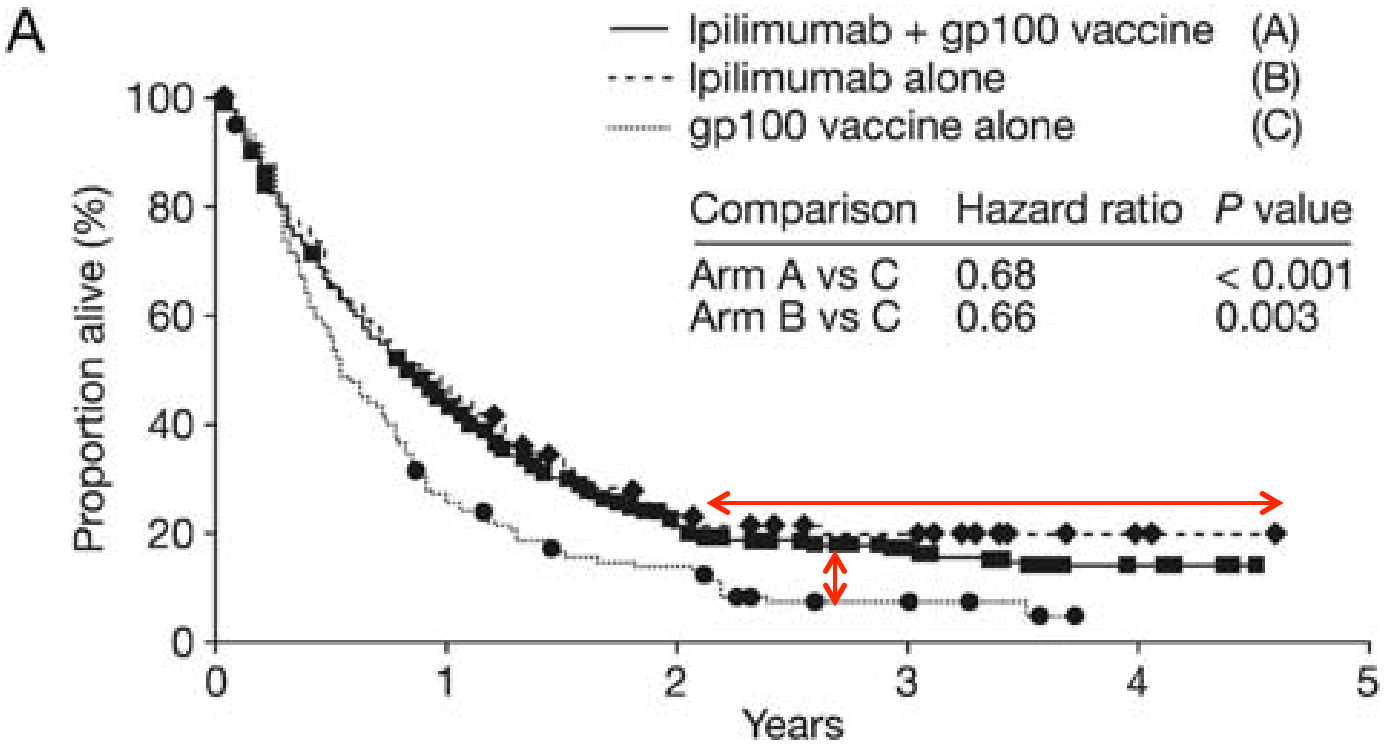
CD28:B7

CTLA-4: B7

PD-1: PD-L1

Jedd Wolchok

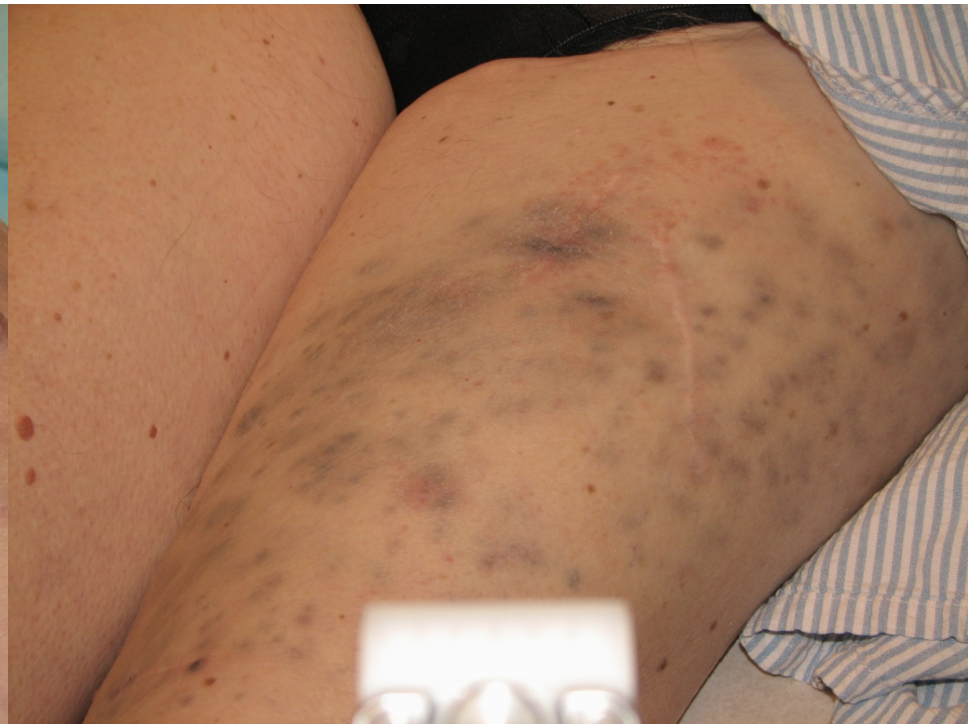
Ipilimumab Demonstrates a Survival Benefit



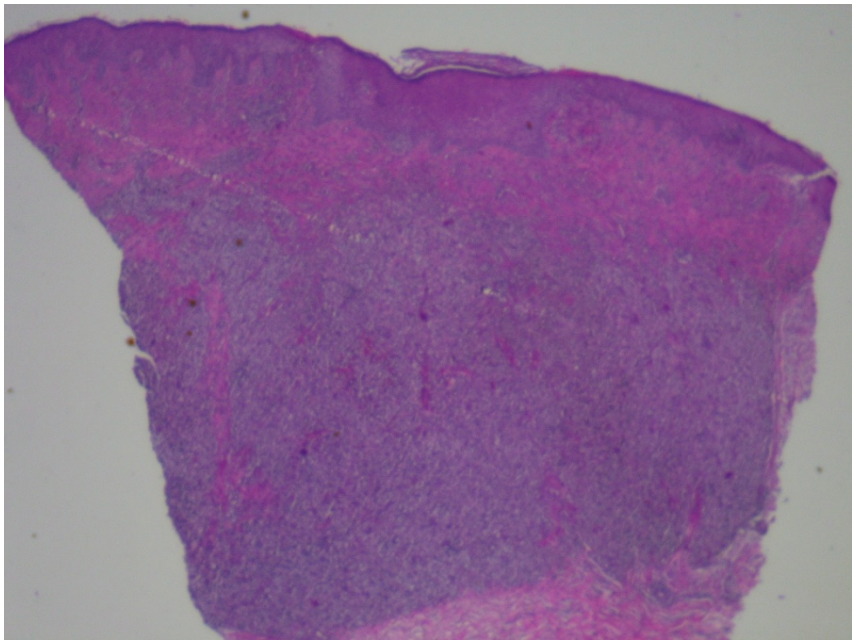
	Ipilimumab + gp100 (*n* = 403)	Ipilimumab + placebo (*n* = 137)	gp100 + placebo (*n* = 136)
1-year OS rate (%)	44	46	25
2-year OS rate (%)	22	24	14
Median OS (months)	10.0	10.1	6.4

Hodi et al. NEJM 2010

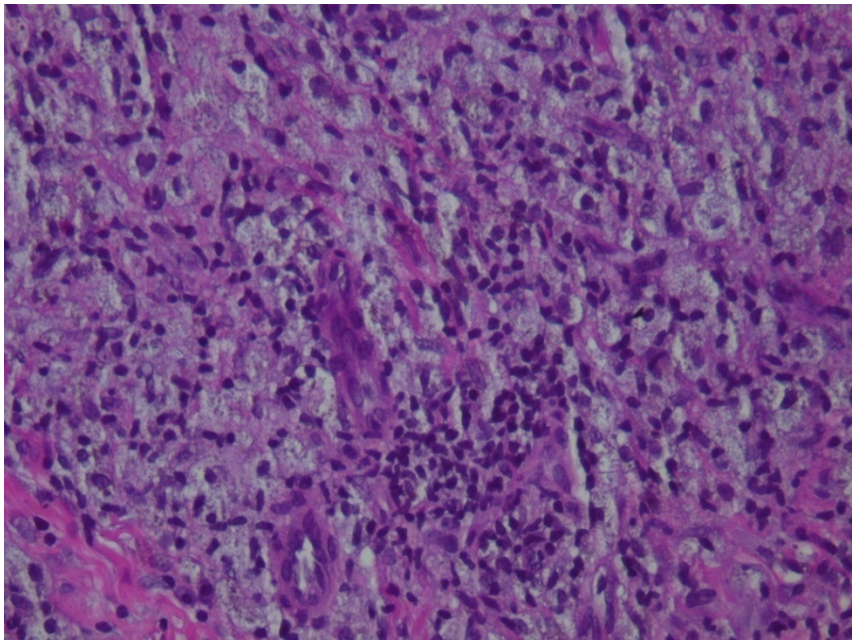
11/28/06 1/9/07



Jedd Wolchok

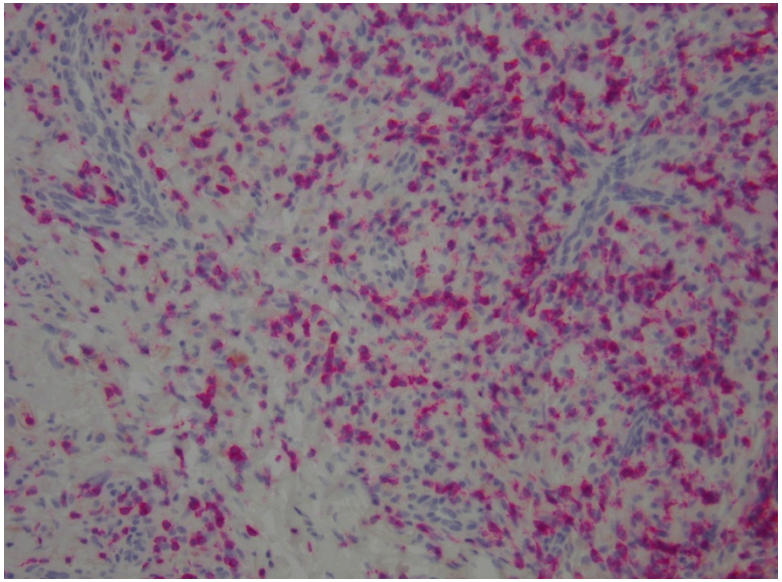


Tumorous nodule
with melanin pigment
(macrophages and
lymphocytes;
no melanocytes)

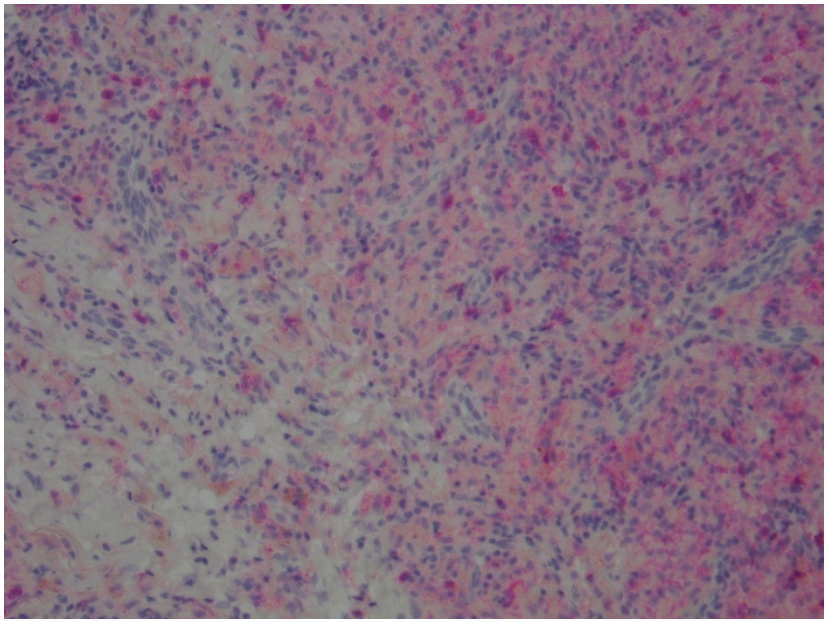


Macrophages and
lymphocytes are present,
but no tumor cells

Klaus Busam



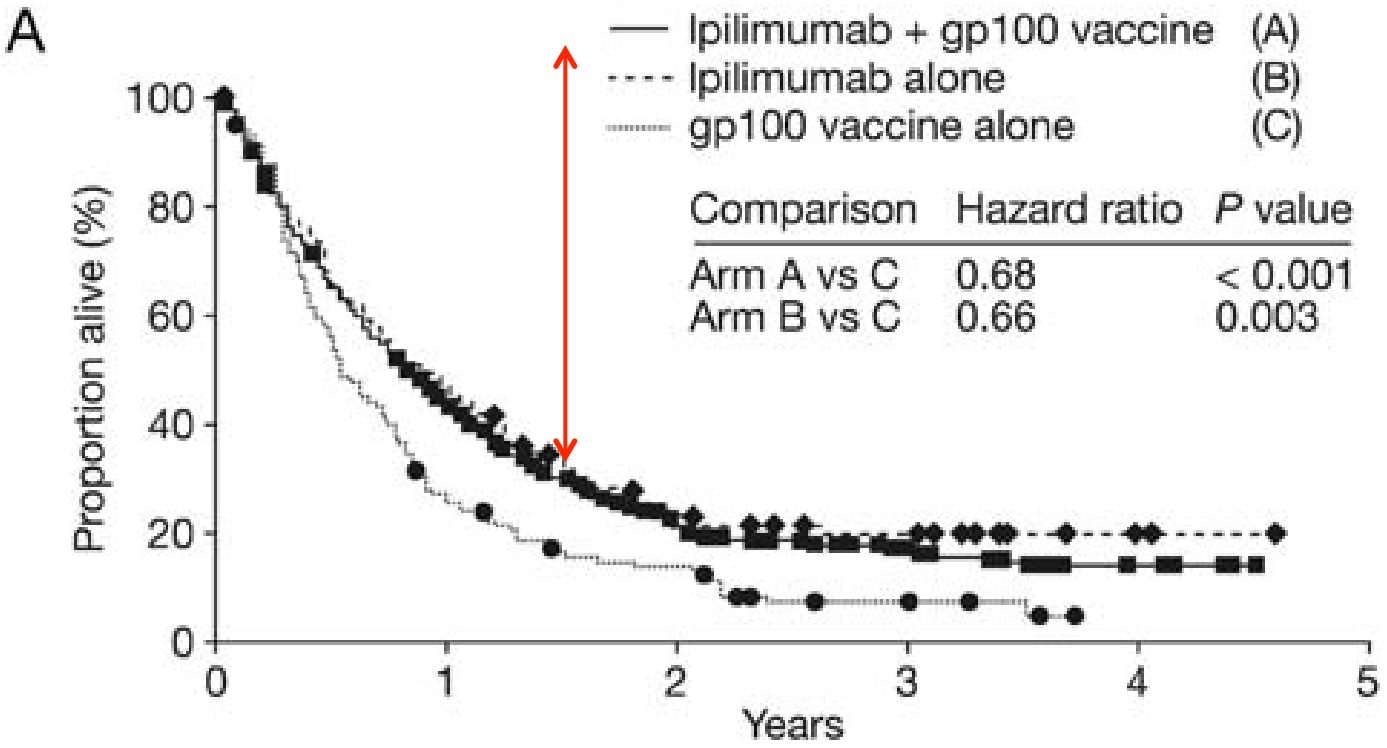
CD8-positive T-cells



CD4-positive T-cells
(macrophages are also
weakly pos for CD4)

Klaus Busam

Ipilimumab Demonstrates a Survival Benefit



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Hodi et al. NEJM 2010

What Prevents This From Happening ?
(How do tumor evade immune elimination)

Immune Surveillance

Proposed: L Thomas and M Burnet

Disproved: O Stutman

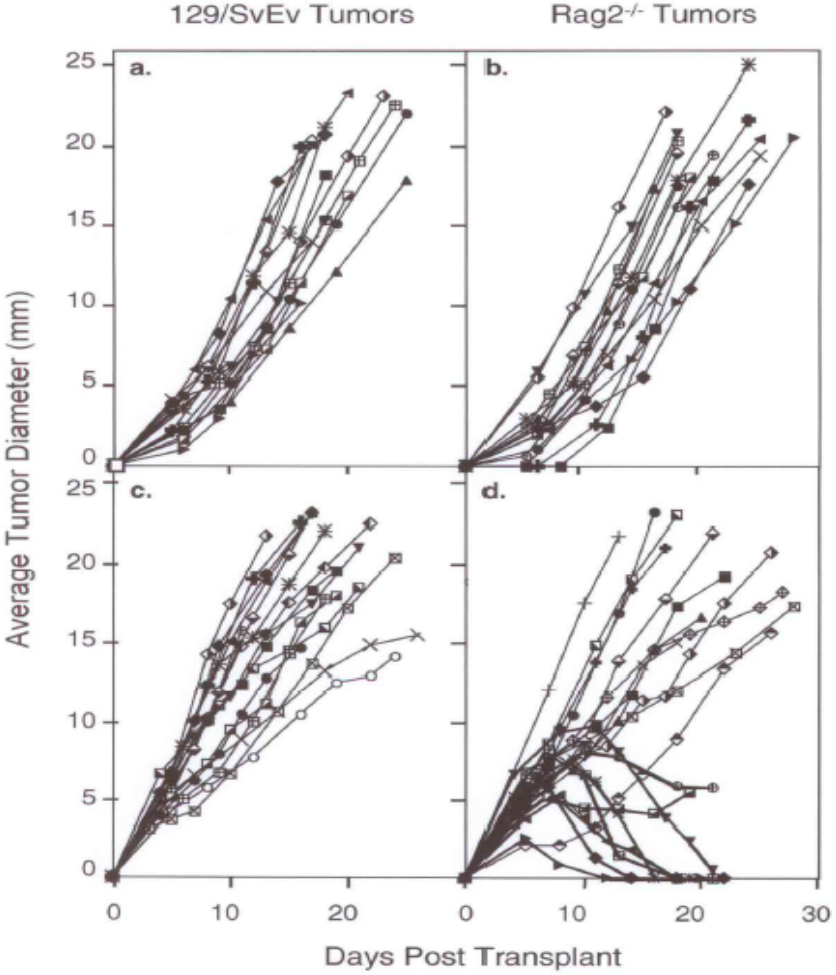
Resurrected: R Schreiber

Jedd Wolchok

Immune Surveillance 2.0 (Cancer Immunoediting)

Tumors transplanted from:

Immune-competent mice Immune-compromised mice



Recipient

Tumors transplanted to:

Rag2-/-

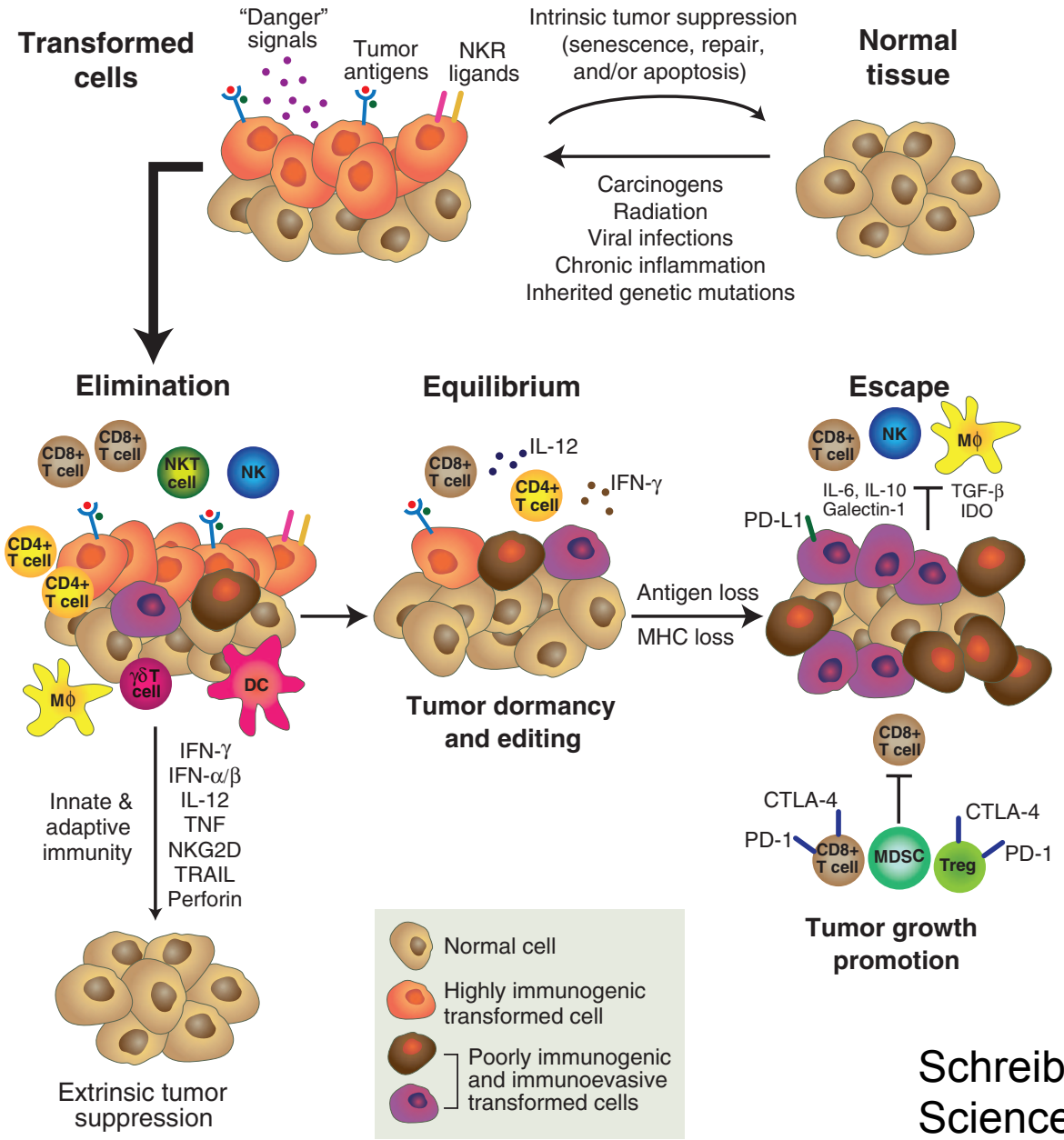
Immune-compromised mice

WT

Immune-competent mice

Shakaran et al. Nature, 410, 1107 (2001)

Cancer Immunoediting



Schreiber, Old, Smyth, Science 331, 2011

What Prevents This From Happening ?
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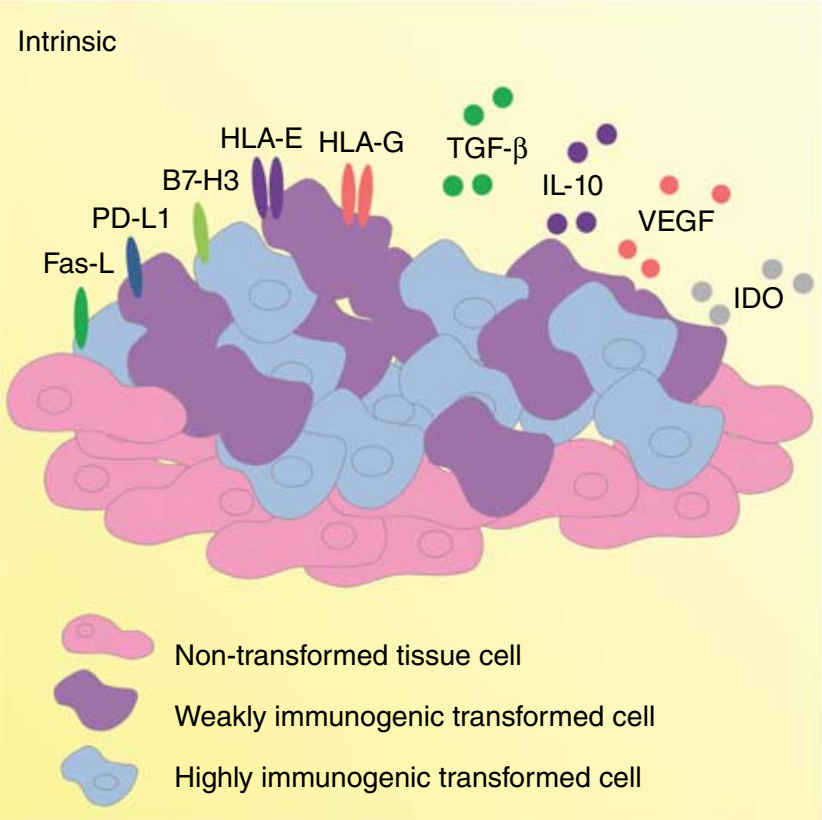
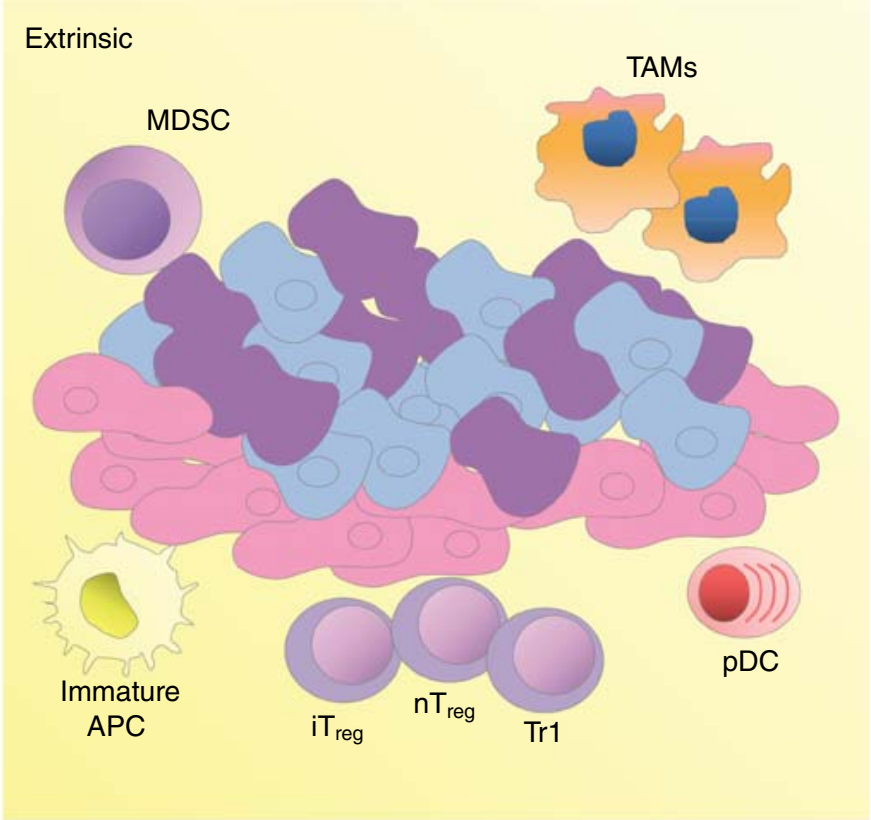
(How do tumor evade immune elimination)

1. Tumor adaptations that allow immune evasion
2. Tumor microenvironment, trafficking, physical barriers
3. Suppressive/Regulatory cell populations
4. Regulation of anti-tumor immune cells

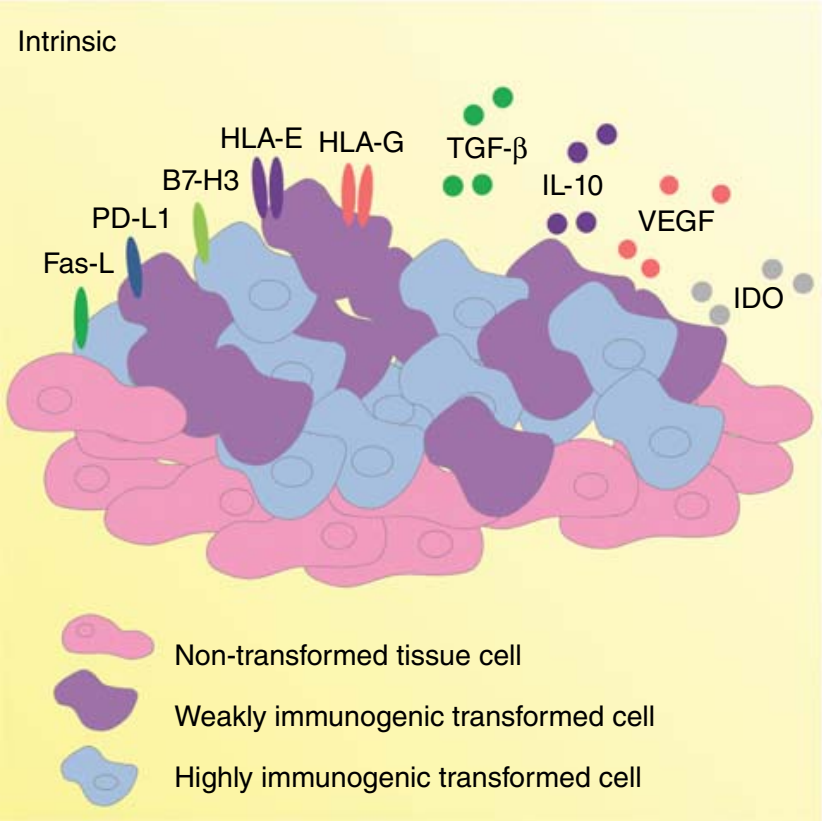
How Tumors Evade Immune Elimination ?





Oleinika et al. Clinical & Exp Immunology 2013

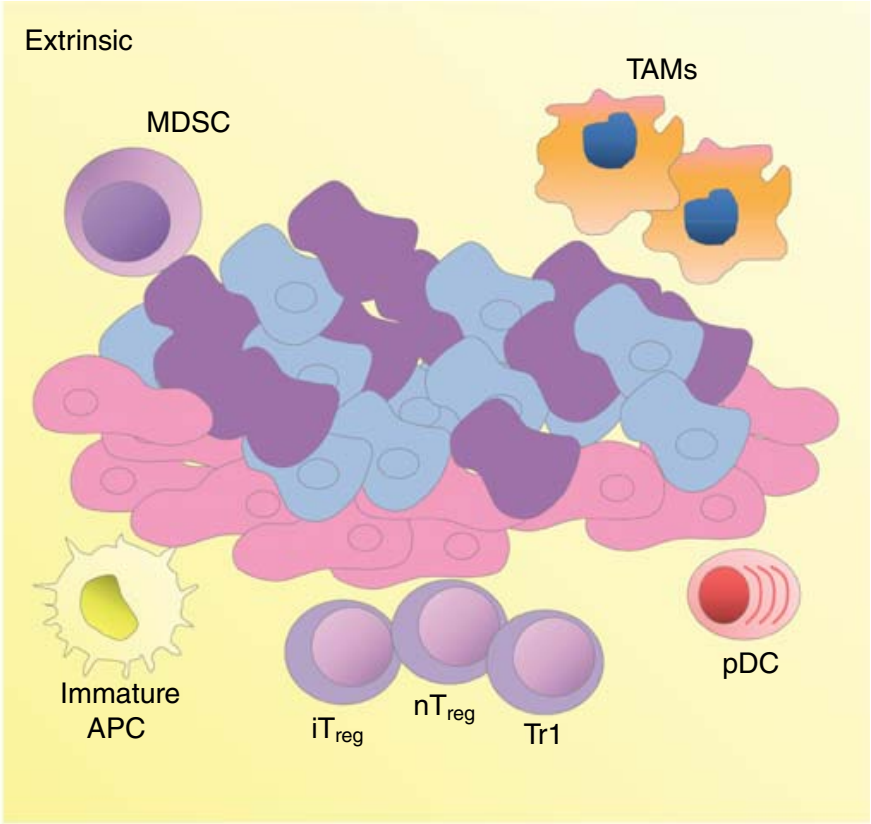
Tumor/Intrinsic Factors



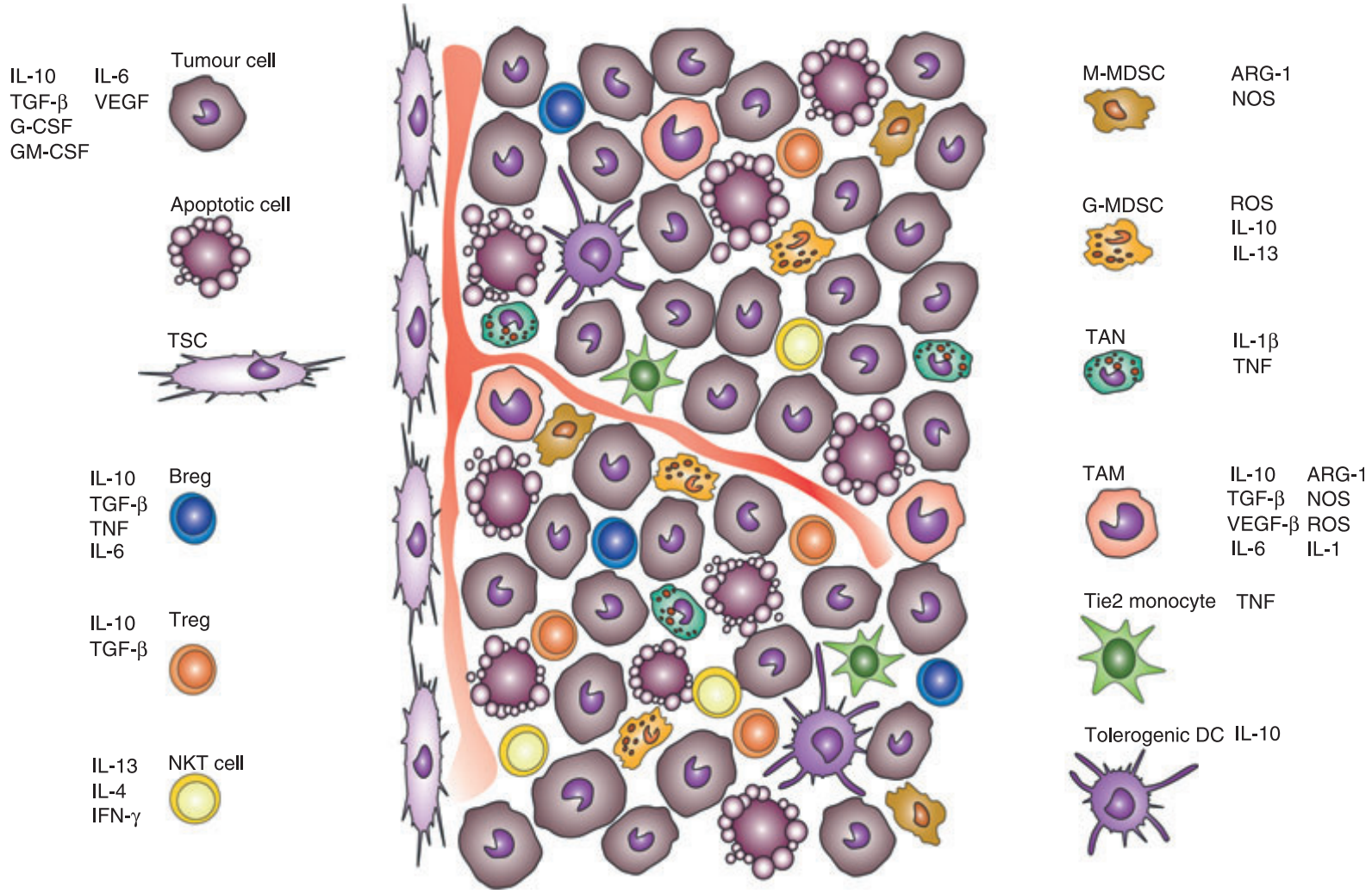
- Antigen Loss
- MHC Loss (or any other step in antigen presentation)
- Expression of molecules that impair anti-tumor immune responses (PD-L1)
- Expression of soluble factors to down-regulate anti-tumor immune responses (TGF-b, IDO)
- Others …

Microenvironment/Extrinsic Factors

- Geographic Barriers
- Myeloid Derived Suppressor Cells (MDSC)
- Regulatory T cells (iTreg, nTreg)
- Tumor Associated Macrophages (TAMs)
- Tolerogenic DCs
- Others …

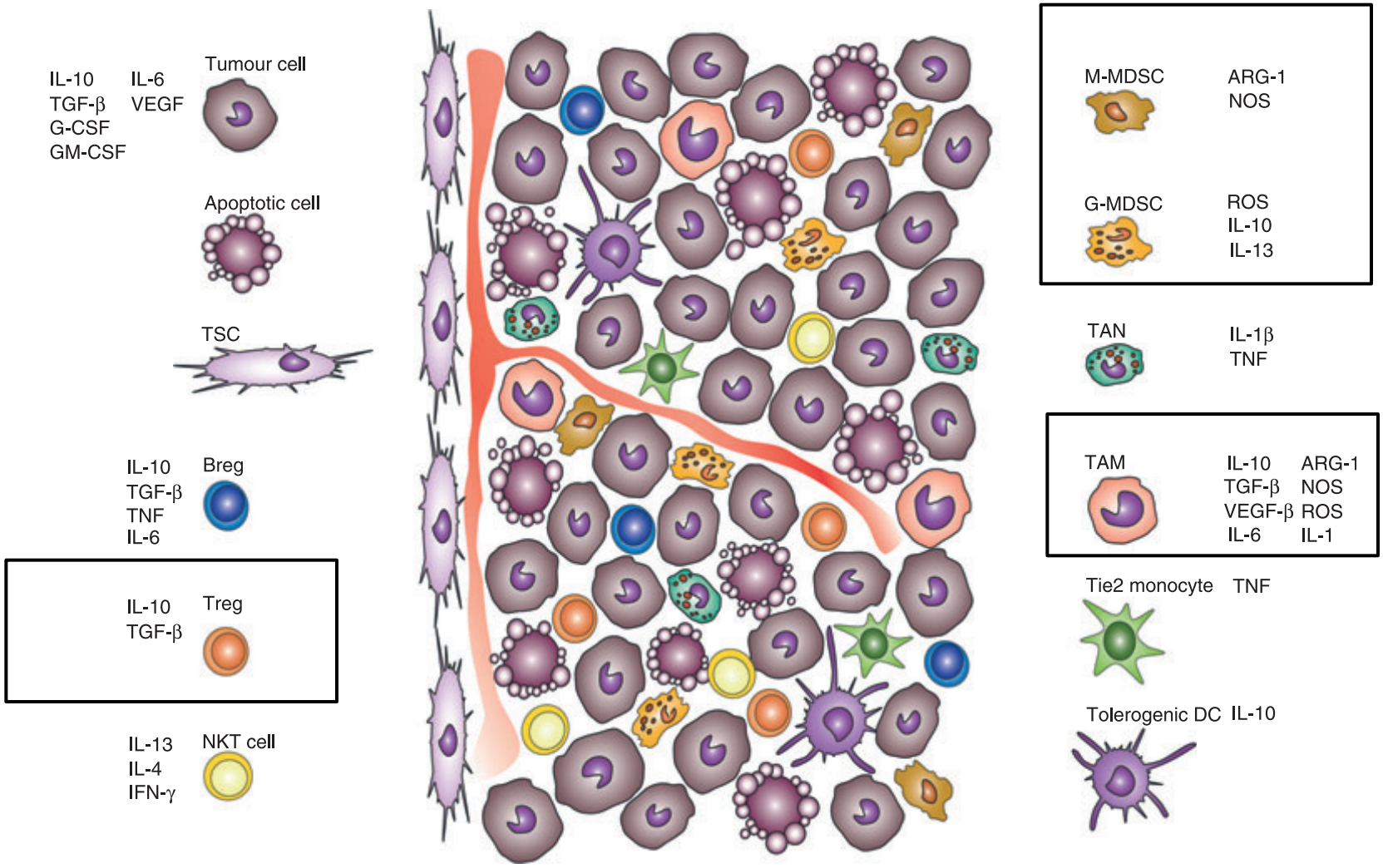


The Immunosuppressive Tumor Microenvironment



Lindau *et al.* The immunosuppressive tumor network: myeloid derived suppressor cell, regulatory T cells and natural killer cells. **Immunology.** 2012

The Immunosuppressive Tumor Microenvironment



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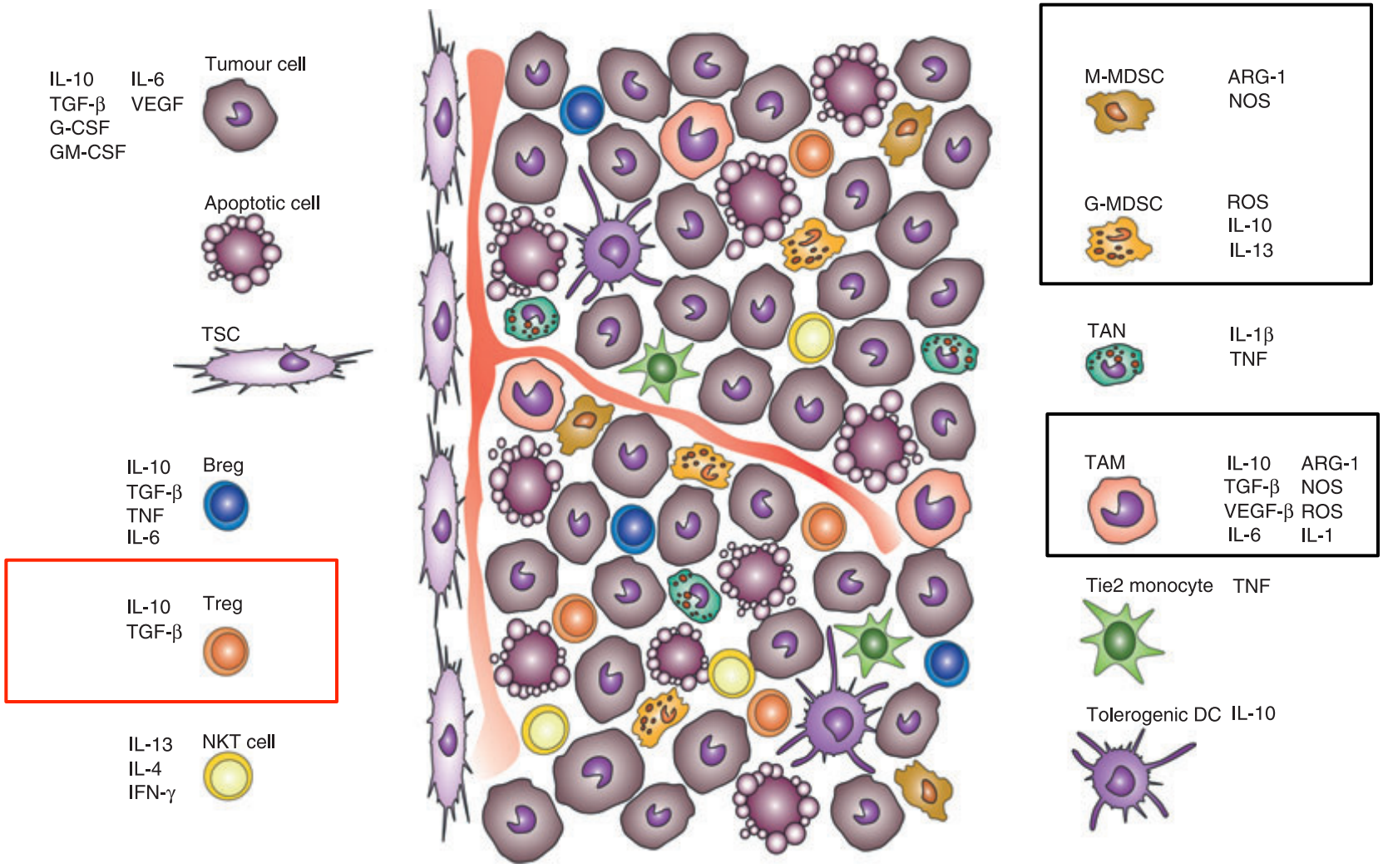
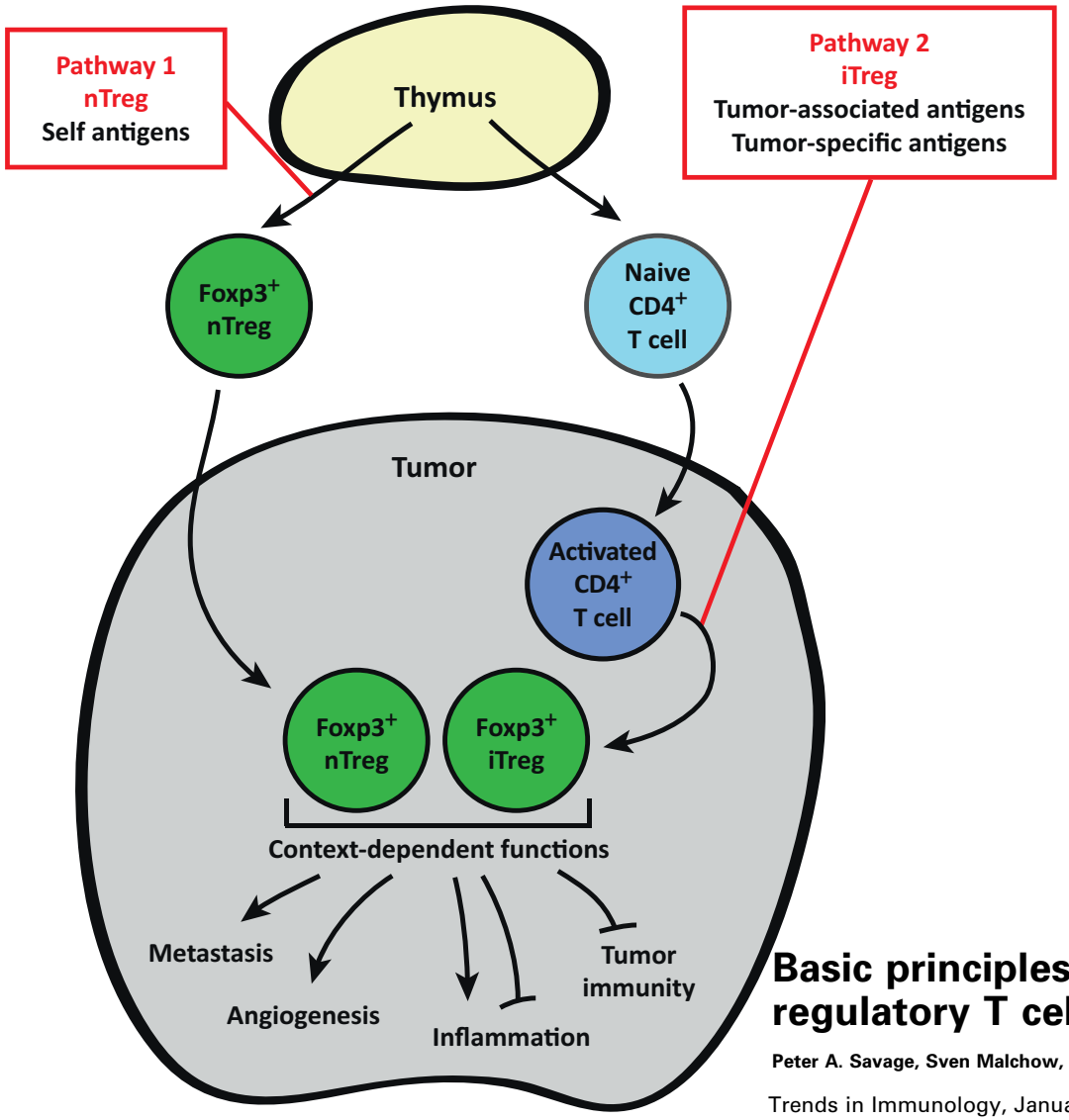
The Immunosuppressive Tumor Microenvironment



Lindau *et al.* The immunosuppressive tumor network: myeloid derived suppressor cell, regulatory T cells and natural killer cells. **Immunology.** 2012

Regulatory T cells



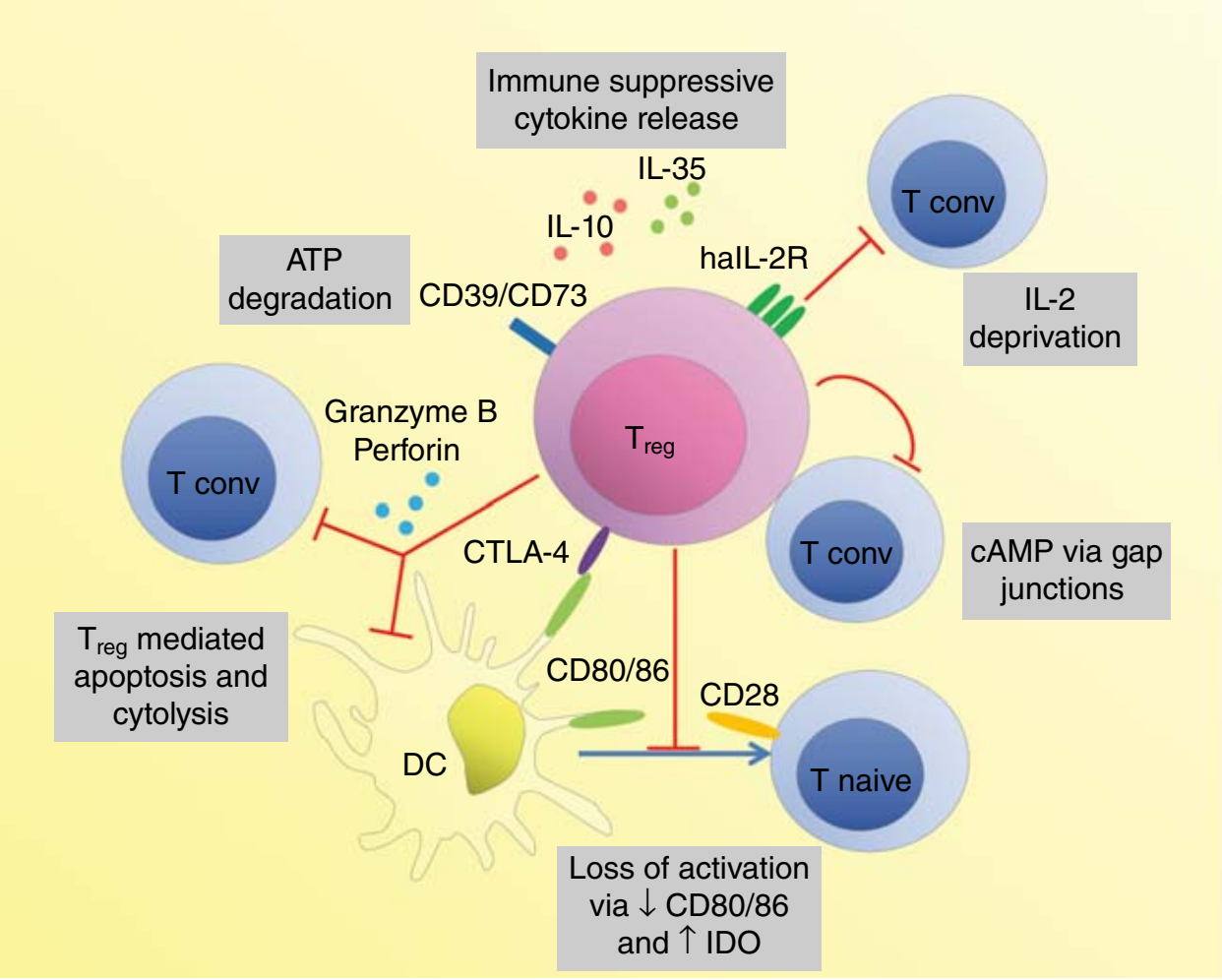
Basic principles of tumor-associated regulatory T cell biology

Peter A. Savage, Sven Malchow, and Daniel S. Leventhal

Trends in Immunology, January 2013, Vol. 34, No. 1

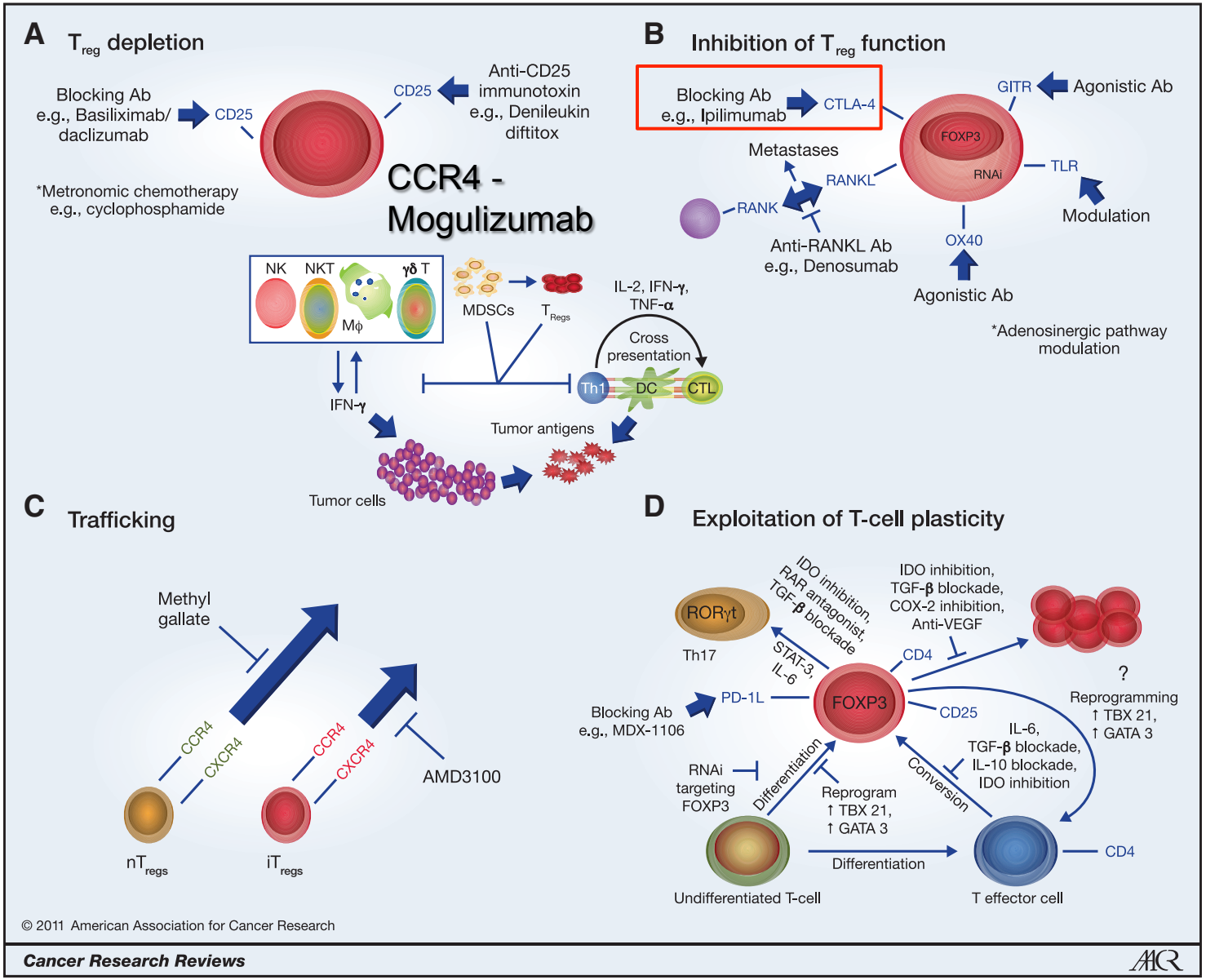
TRENDS in Immunology

Regulatory T cells in anti-tumor immunity



Oleinika et al. Clinical & Exp Immunology 2013

Opportunities for Targeting Tregs ?



CTLA-4 blocking antibodies and Regulatory T cells

JEM

Article

Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti–CTLA-4 therapy against melanoma

B16

Tyler R. Simpson,[1,2,3] Fubin Li,[4] Welby Montalvo-Ortiz,[1] Manuel A. Sepulveda,[3] Katharina Bergerhoff,[6] Frederick Arce,[6] Claire Roddie,[6] Jake Y. Henry,[6] Hideo Yagita,[5] Jedd D. Wolchok,[3] Karl S. Peggs,[6] Jeffrey V. Ravetch,[4] James P. Allison,[1] and Sergio A. Quezada[6]

Research Article

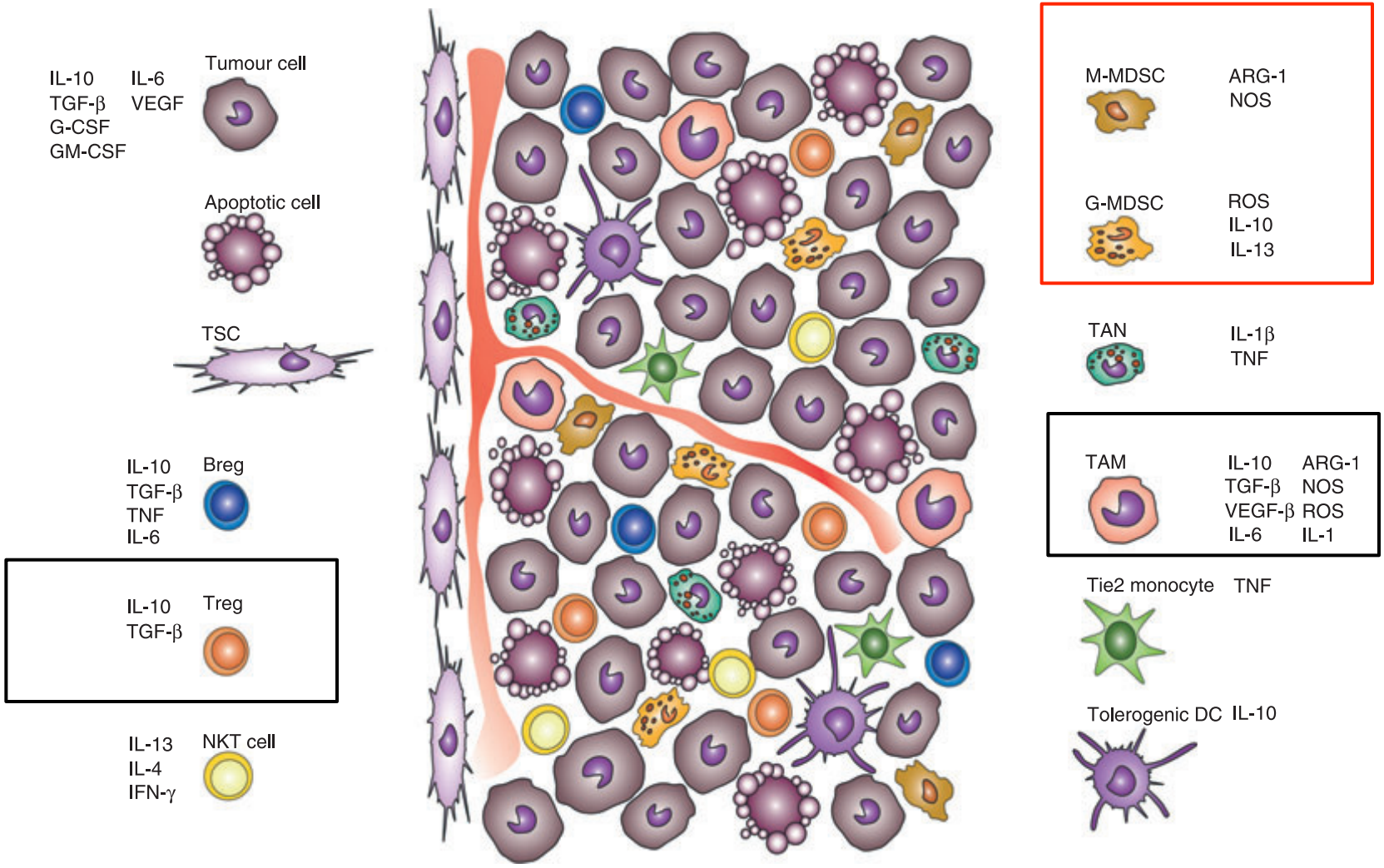
Cancer Immunology Research

Anti-CTLA-4 Antibodies of IgG2a Isotype Enhance Antitumor Activity through Reduction of Intratumoral Regulatory T Cells

MC38, CT26

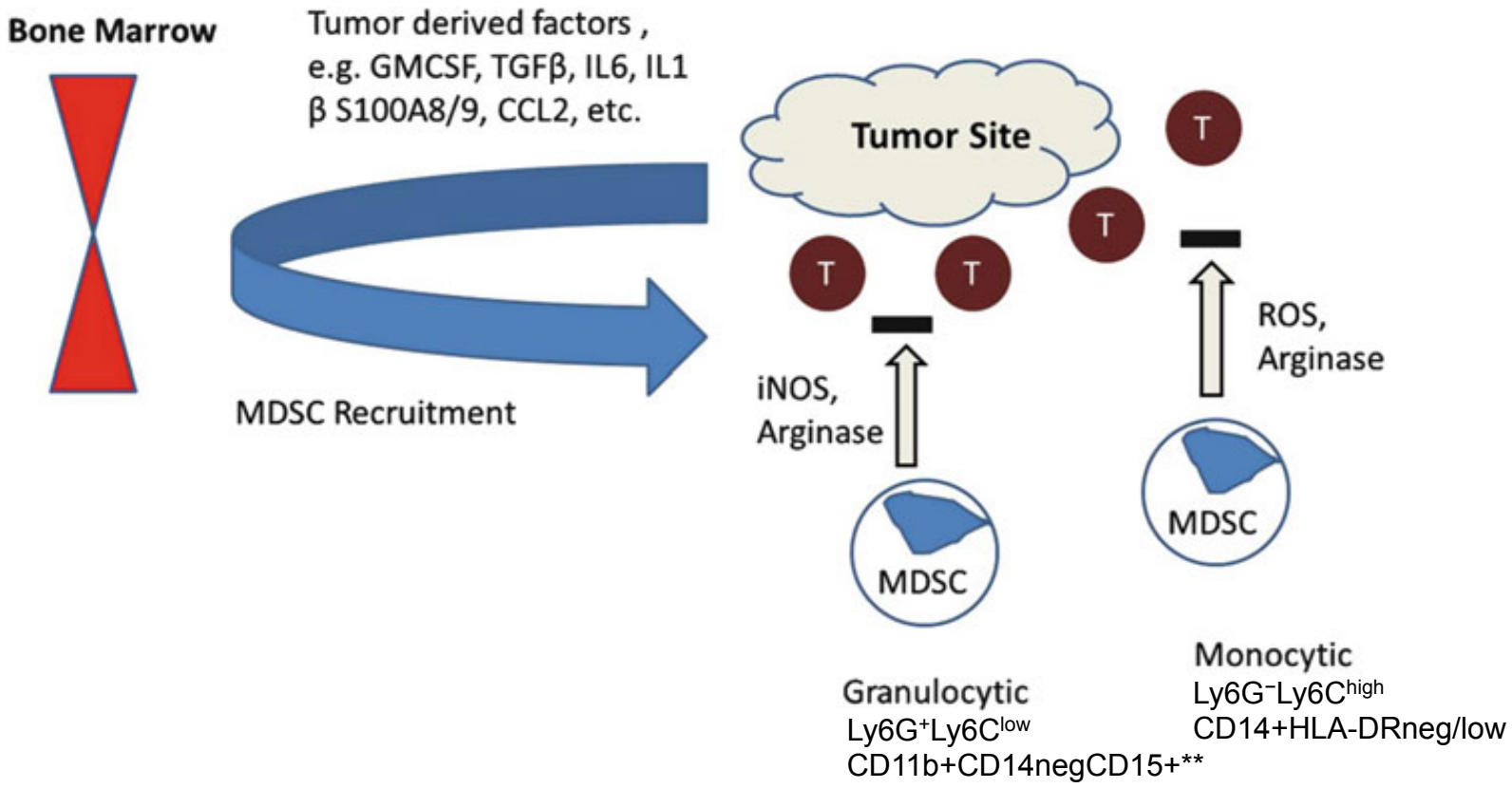
Mark J. Selby, John J. Engelhardt, Michael Quigley, Karla A. Henning, Timothy Chen, Mohan Srinivasan, and Alan J. Korman

The Immunosuppressive Tumor Microenvironment



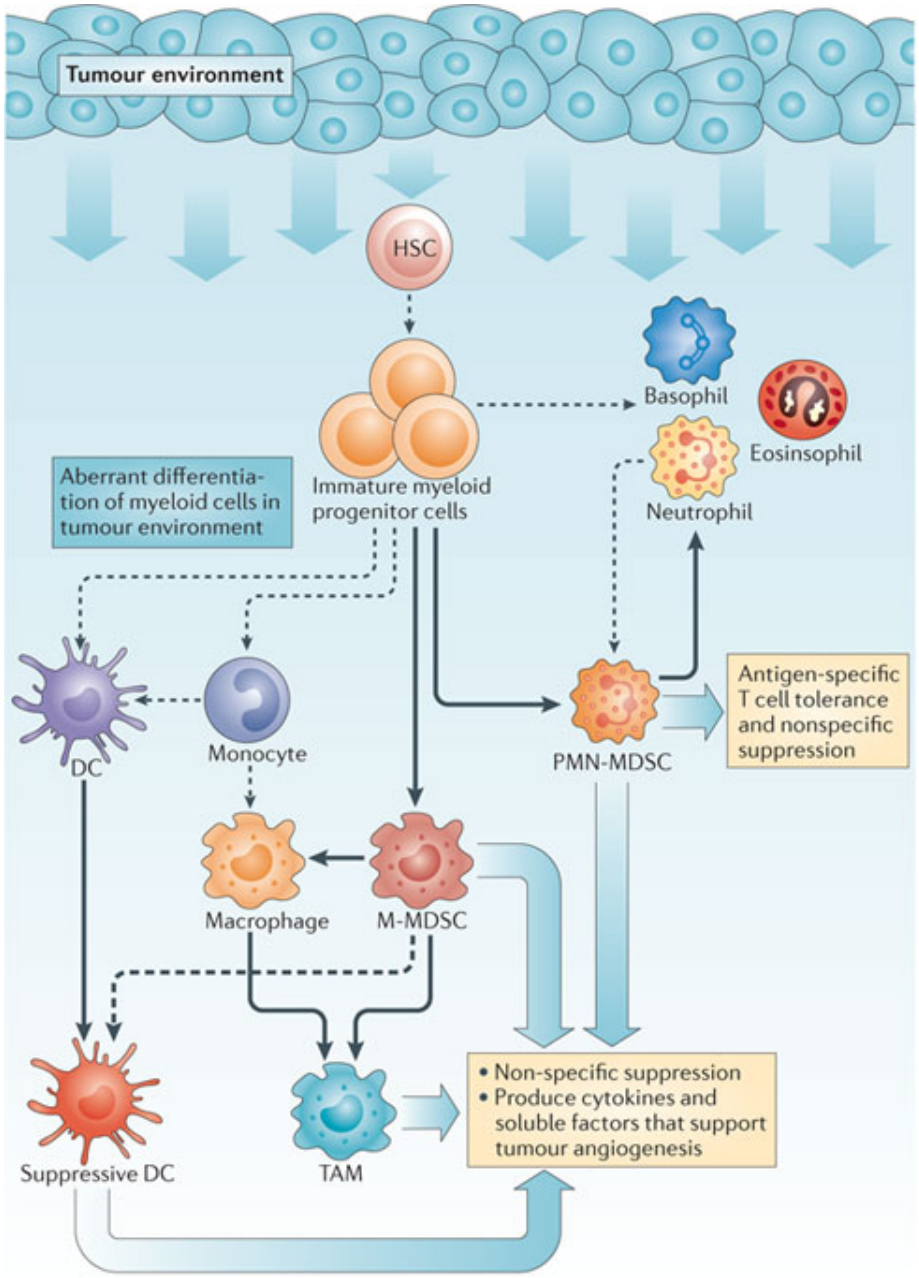
Lindau *et al.* The immunosuppressive tumor network: myeloid derived suppressor cell, regulatory T cells and natural killer cells. **Immunology.** 2012

Myeloid-Derived Suppressor Cells



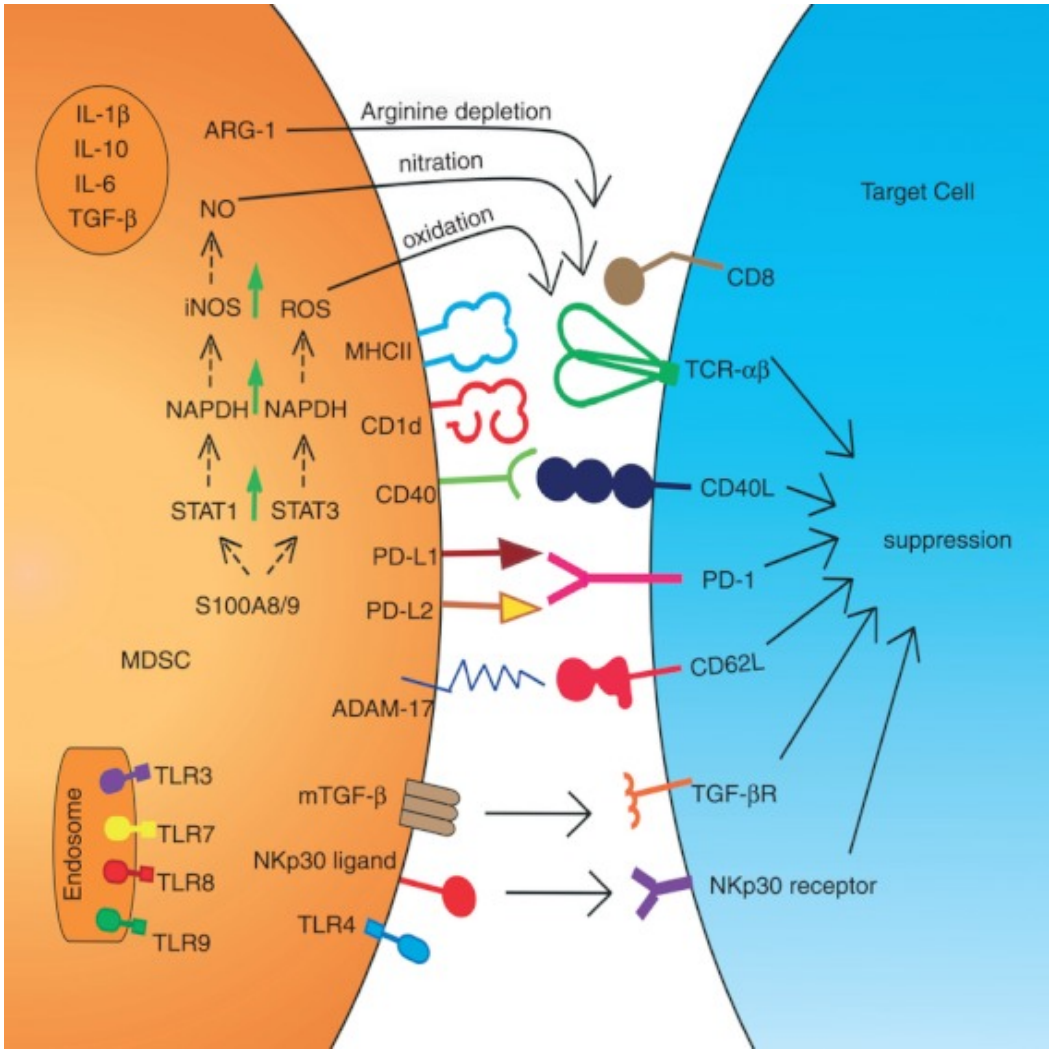
What markers to use ?
How stable are these populations ?

MDSC



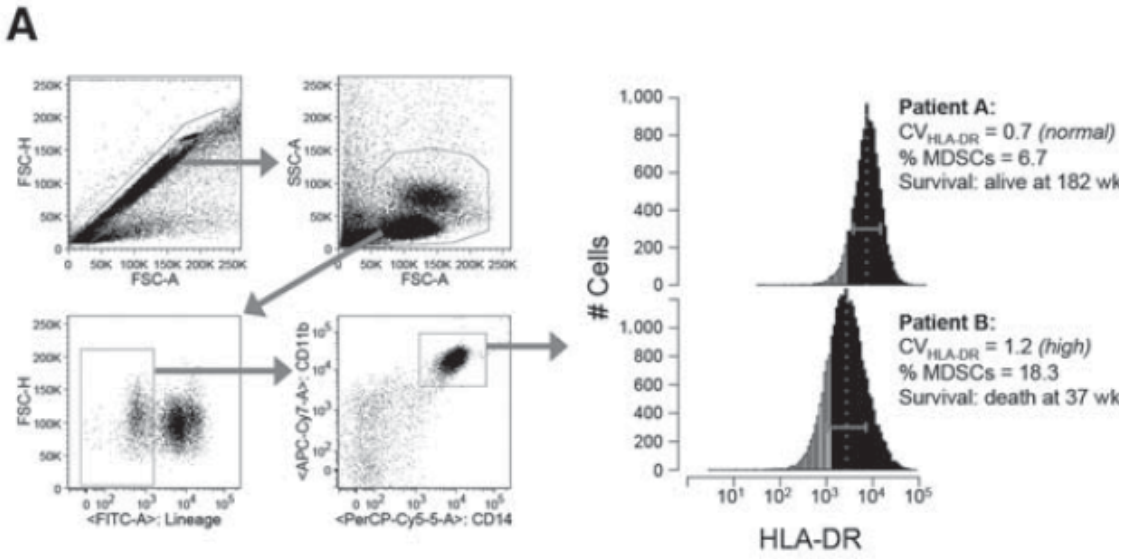
Gabrilovich et al. Coordinated regulation of myeloid cells by tumours. **Nat Rev Immunology**. 2012

Myeloid-Derived Suppressor Cells

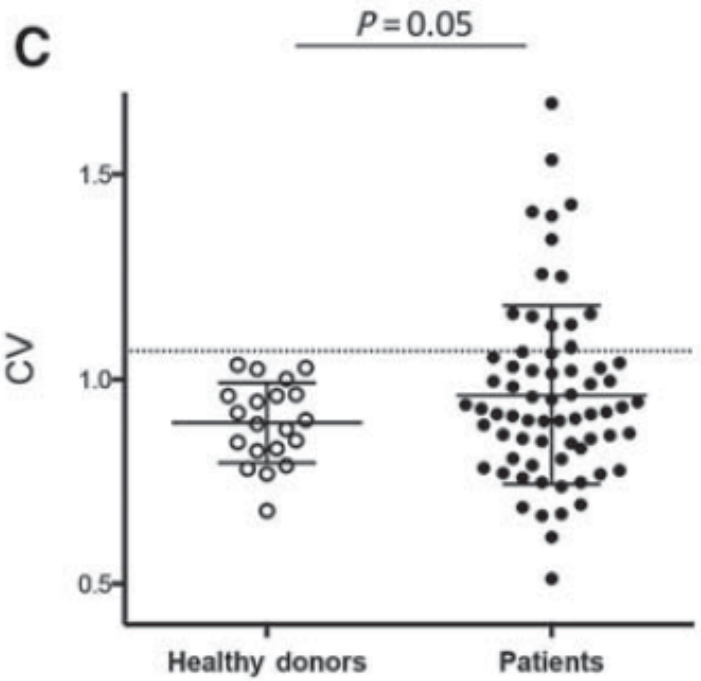


Lindau *et al.* The immunosuppressive tumor network: myeloid derived suppressor cell, regulatory T cells and natural killer cells. **Immunology.** 2012

Metastatic Melanoma Patients Have an Increased Quantity of MDSC

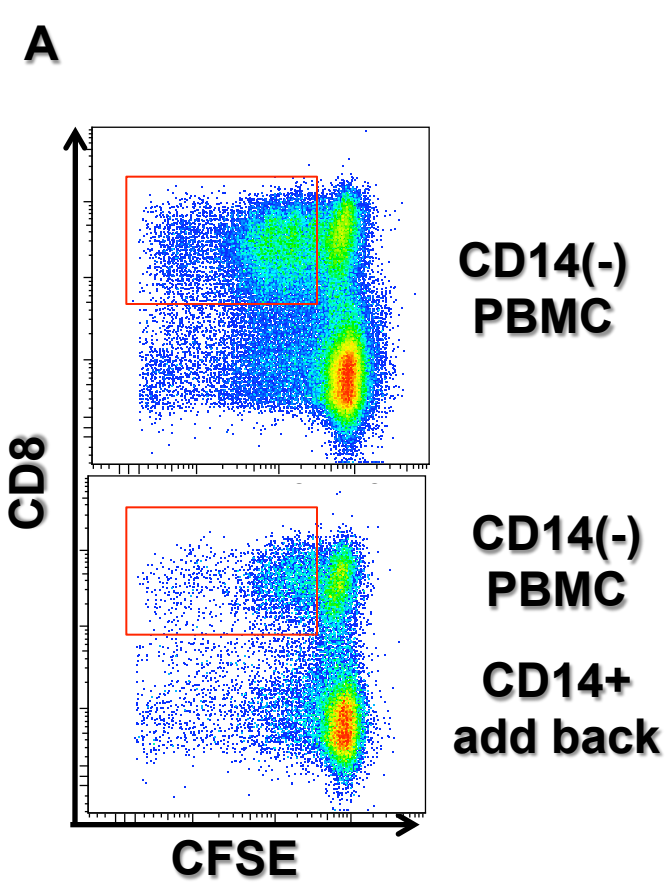


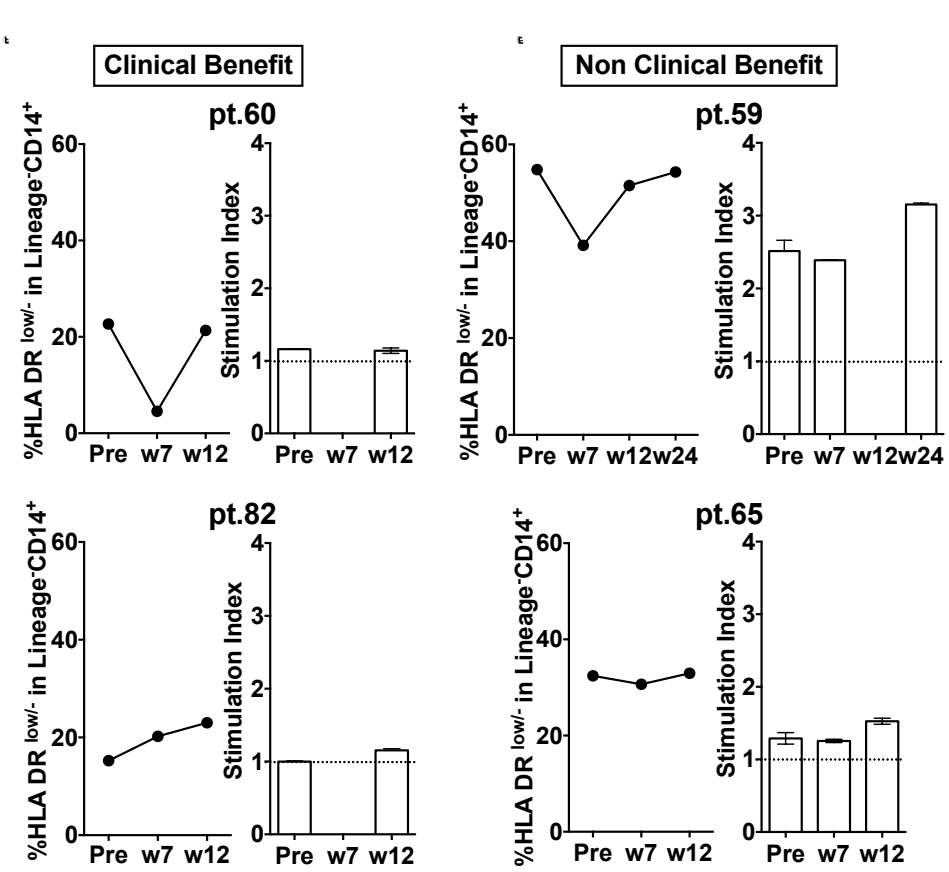
$CD14^{+}HLA\text{-}DR^{low/-}$



Kitano S, Postow M, et al. Computational Algorithm-Driven Evaluation of Monocytic Myeloid-Derived Suppressor Cell Frequency for Prediction of Clinical Outcomes. **CIR** 2014

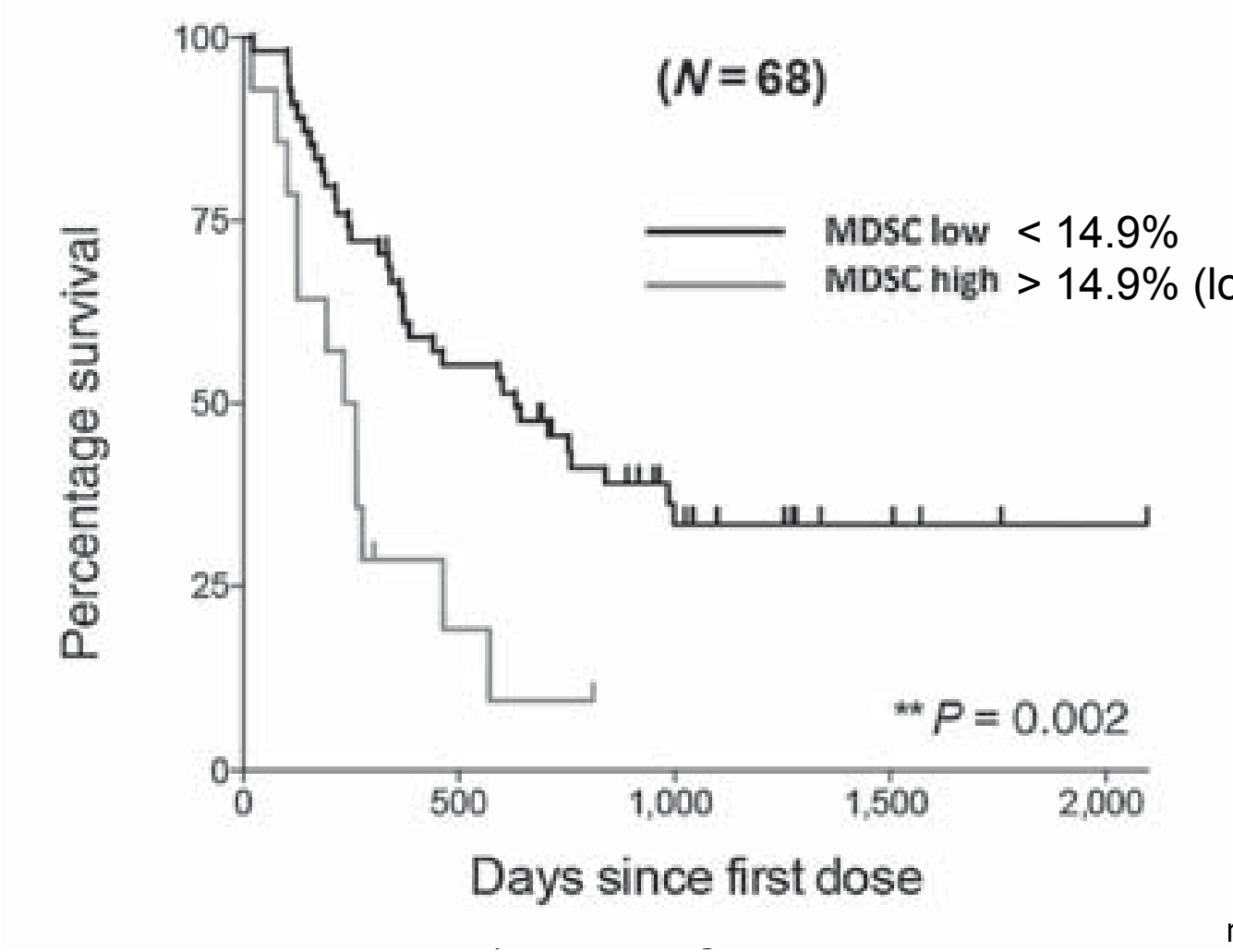
CD14+ Cells From Melanoma Patients Suppress T cell Proliferation





Kitano S, Postow M, et al. Computational Algorithm-Driven Evaluation of Monocytic Myeloid-Derived Suppressor Cell Frequency for Prediction of Clinical Outcomes. **CIR** 2014

MDSC are increased in patients with poorer survival outcomes after treatment with ipilimumab

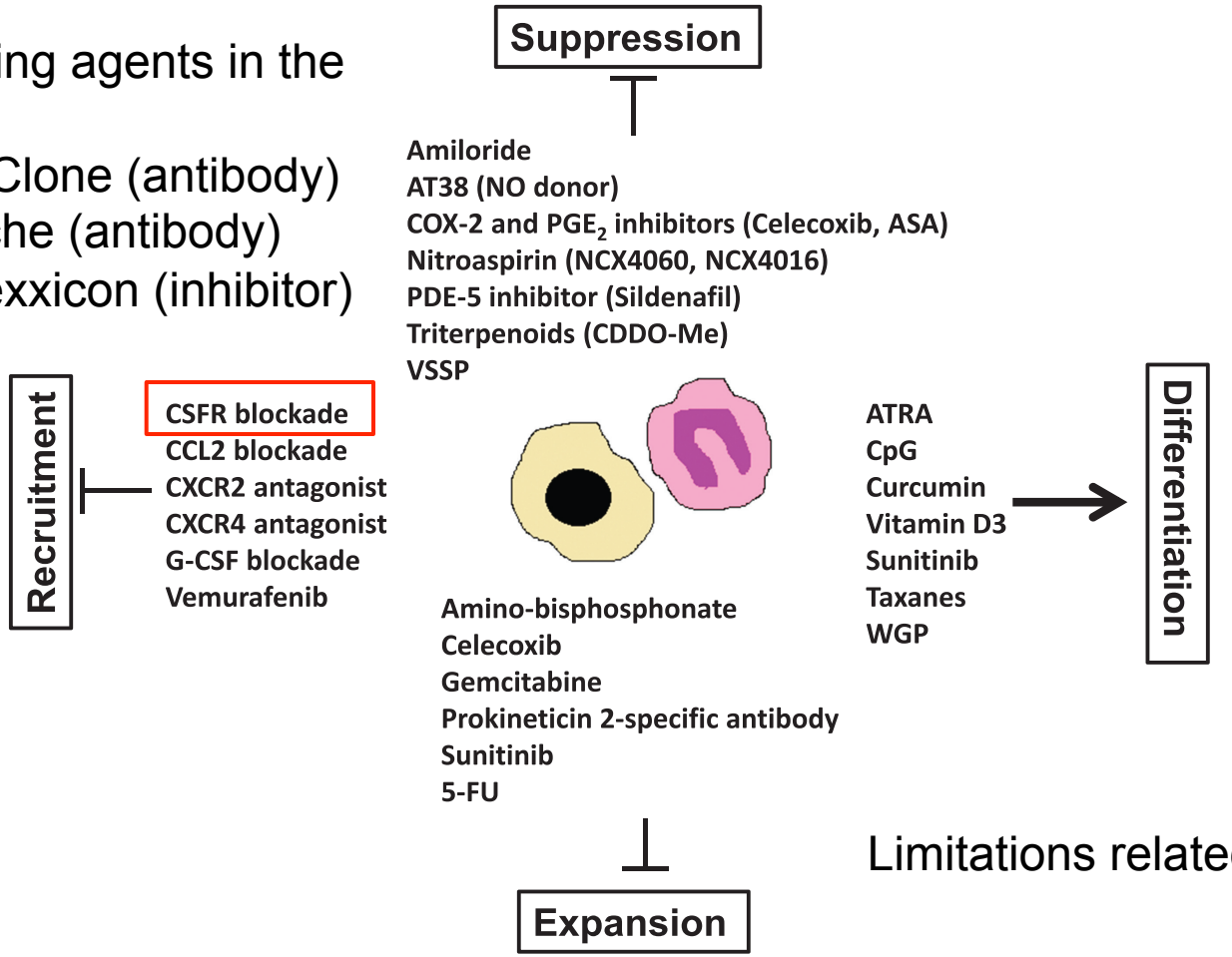


nocytic Myeloid-Derived

Suppressor Cell Frequency for Prediction of Clinical Outcomes. **CIR** 2014

Opportunities for Targeting MDSC?

CSF1-R blocking agents in the clinic:
- IMC-CS4 ImClone (antibody)
- RG7155 Roche (antibody)
- PLX3397 Plexxicon (inhibitor)

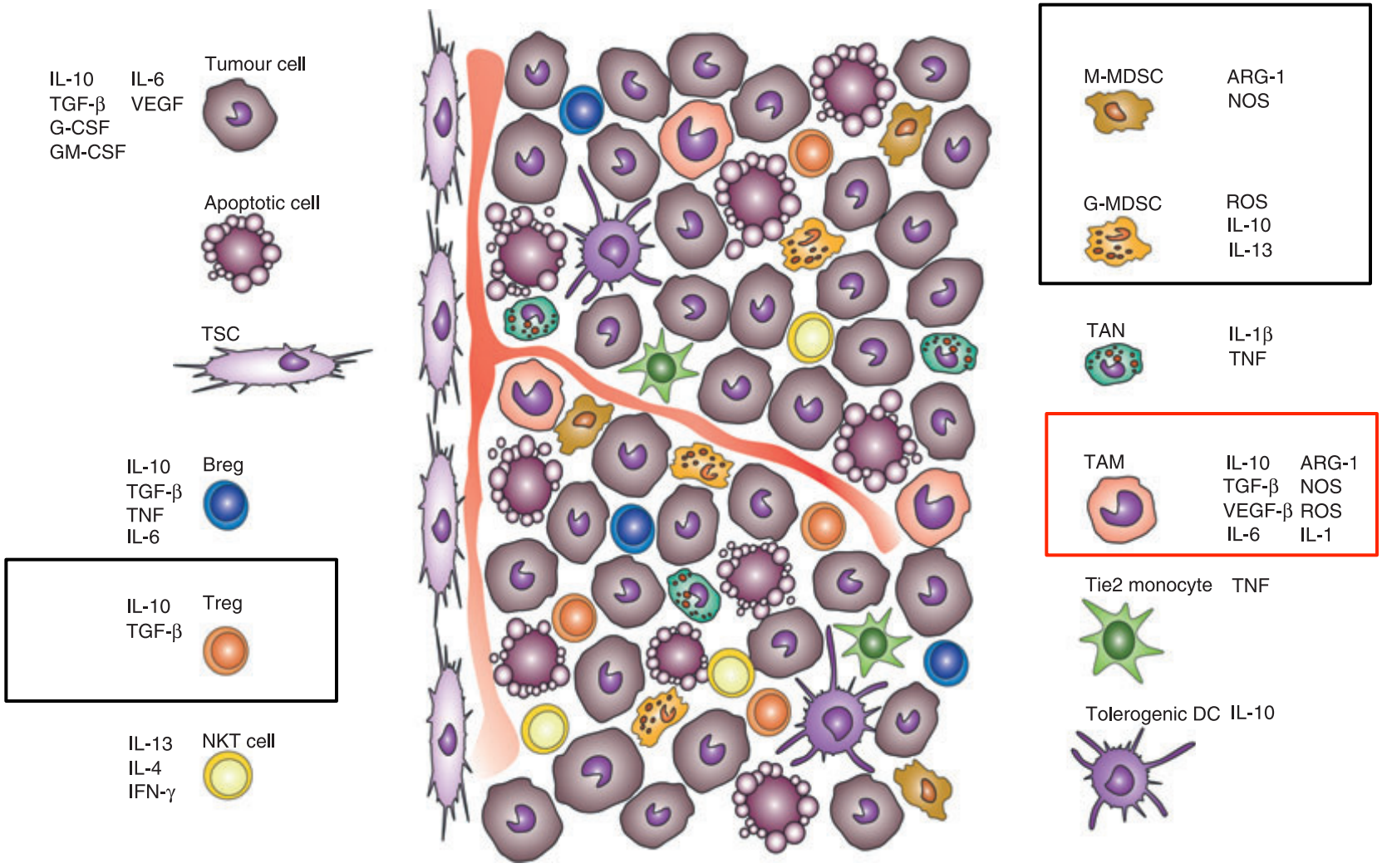


Limitations related to specificity

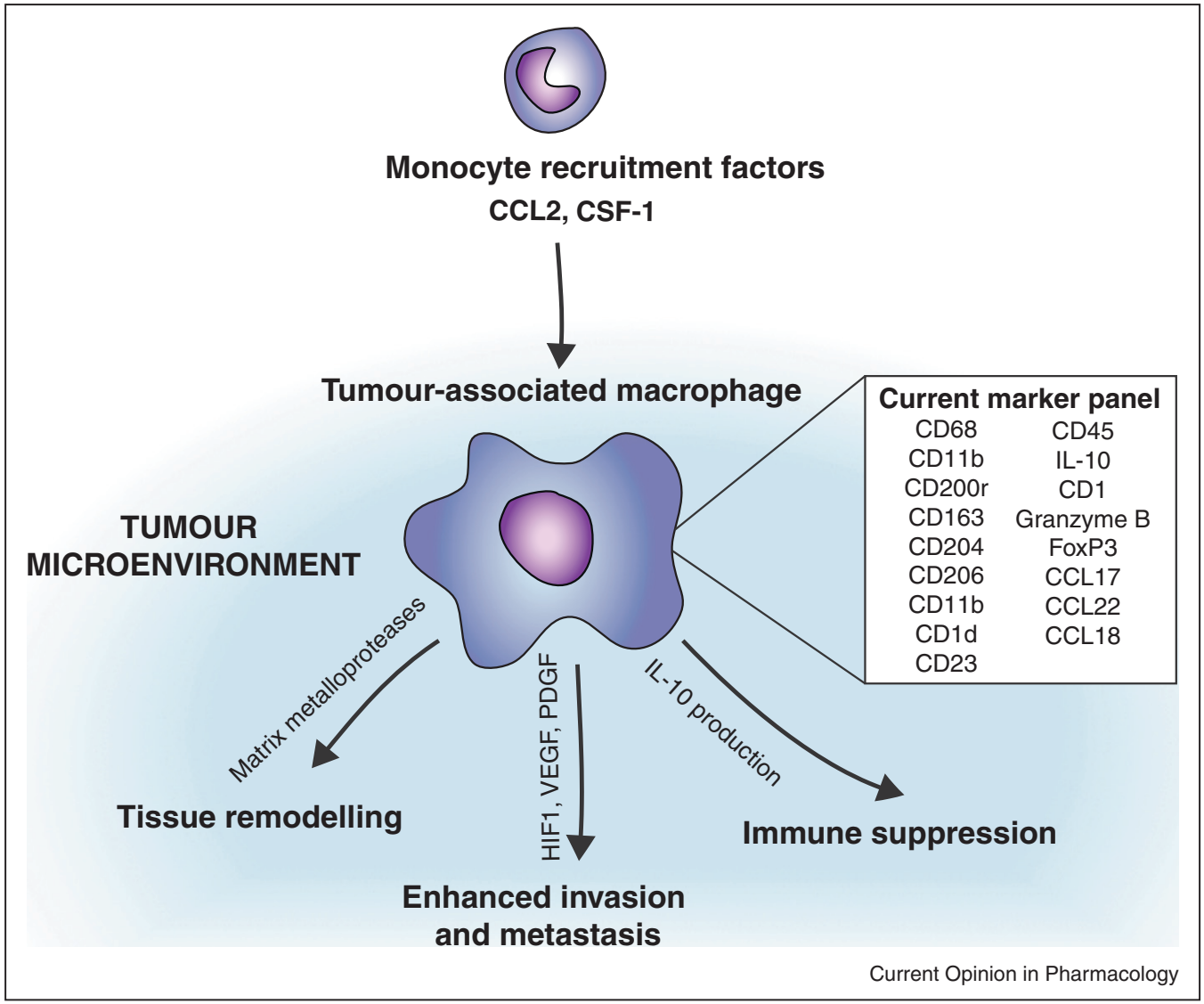
FIGURE 1 . The main therapeutic compounds targeting MDSC suppression, expansion, recruitment, and differentiation in cancer.

Albeituni *et al.* Hampering Immune Suppressors: Therapeutic Targeting of Myeloid-Derived Suppressor Cells in Cancer. **The Cancer Journal.** 2013

The Immunosuppressive Tumor Microenvironment



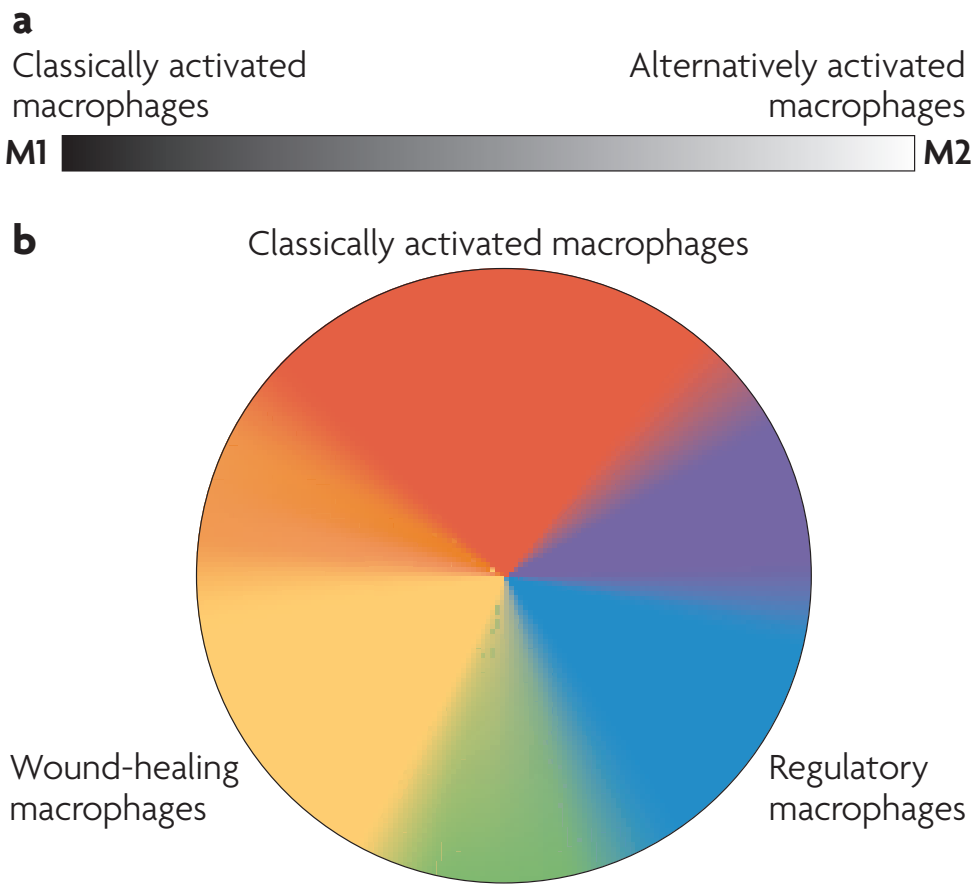
Tumor Associated Macrophages



Cook and Hagemann. Tumour-associated macrophages and cancer. **Curr. Opinion in Pharmacology.** 2013.

TAMs may have positive or negative effects on anti-tumor immunity

"good"
IFN-g



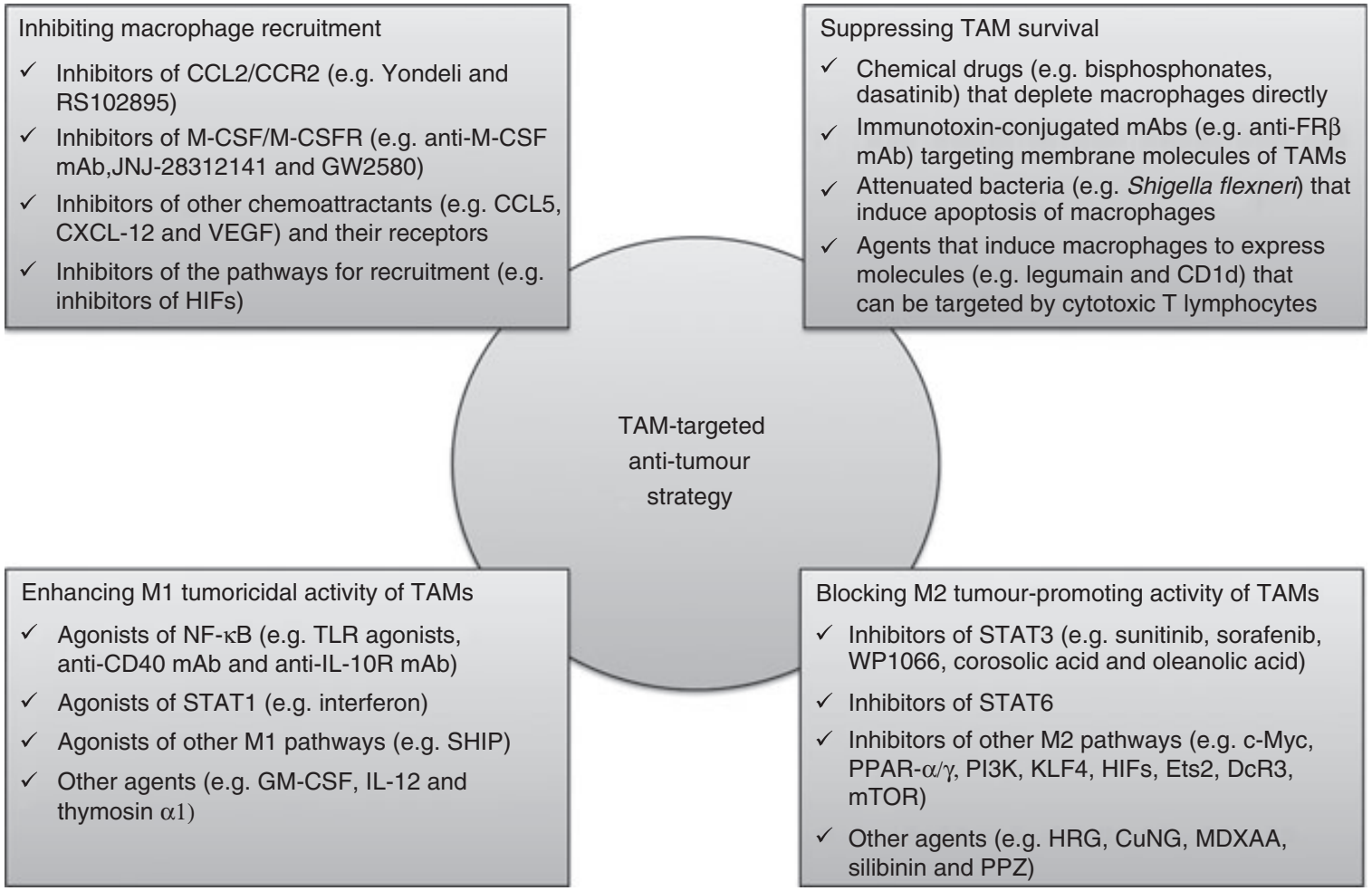
"bad"
IL-10

Plasticity,
Exists on a spectrum of phenotypes

Figure 1 | **Colour wheel of macrophage activation.**

Moser and Edwards. Exploring the full spectrum of macrophage activation. **Nat Rev Immunol.** 2008

Opportunities for Targeting TAMs?



Tang *et al.* Anti-tumour strategies aiming to target tumour-associated macrophages. **Immunology.** 2012

What Prevents This From Happening ?
(How do tumor evade immune elimination)

1. Tumor adaptations that allow immune evasion (antigen loss, PD-L1)
2. Tumor microenvironment, trafficking, physical barriers
3. Suppressive/Regulatory cell populations
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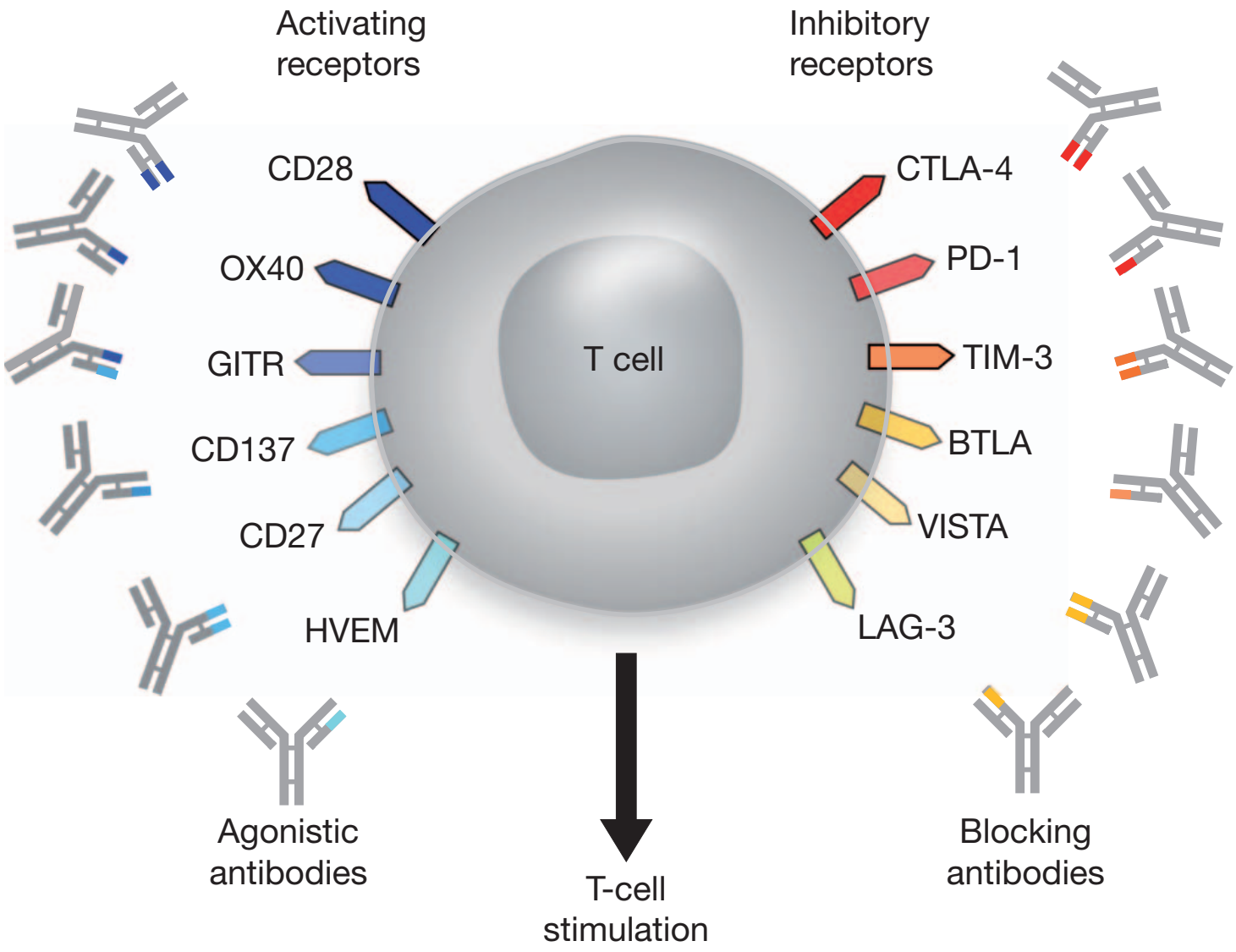
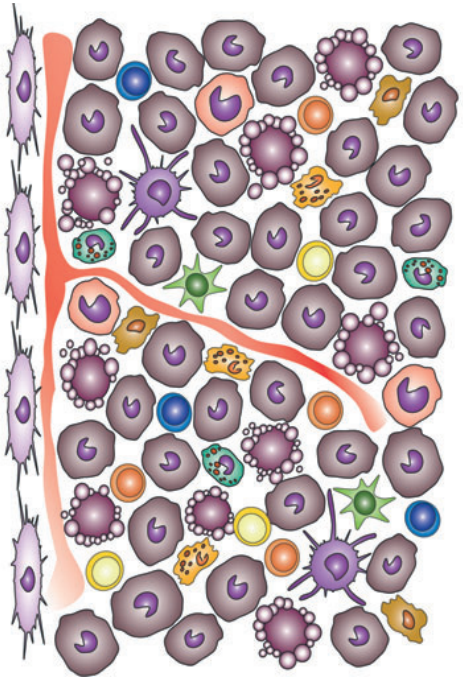
Checkpoint Molecules Regulate T cell Activation



Mellman et al. Nature 2011

Obstacles to Driving an Immune Response

Tregs MDSC

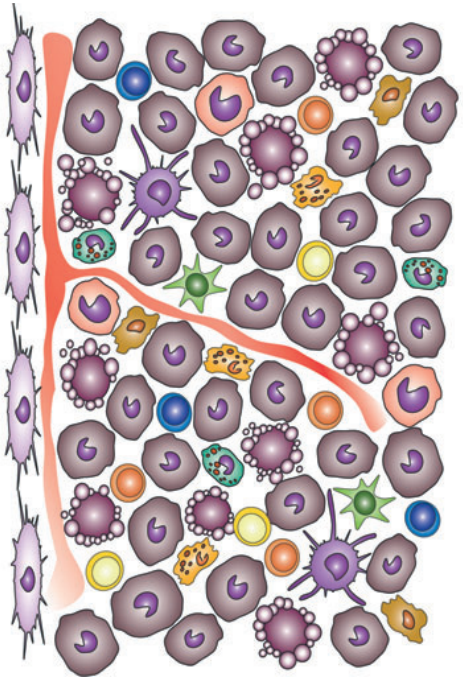


TAMS

Tumor Microenvironment

Tumor immuno-editting

Obstacles to Driving an Immune Response



Represent Opportunities to Improve Upon the Potential for Immunotherapies in the Future

Thank you !

Question 1. Cancer Immunoediting describes a process by which:

A. All tumors are destroyed by the immune system
B. All tumors escape detection by the immune system
C. Oncologists detects typos
D. The immune system interacts with and exerts selective pressure on tumors in a dynamic process that may result in tumor elimination, equilibrium, or escape.

Question 2. The following cells may prevent an effective anti-tumor immune response :

A. Myeloid-derived suppressor Cells
B. M1 Macrophages
C. M2 Macrophages
D. Regulatory T cells
E. All of the Above
F. A, B, C
G. A, C, D

Question 3. Tumor cells may avoid immune elimination by:

A. Upregulating MHC molecules
B. Expressing higher levels of tumor antigens
C. Expression of PD-L1
D. Production of soluble factors like Interferon-γ