
SITC
2017
November 8-12
NATIONAL HARBOR
MARYLAND
Gaylord National Hotel
& Convention Center
sitc
Society for Immunotherapy of Cancer

SITC 2017

Monocytes and Macrophages in Cancer

Vincenzo Bronte
Verona University Hospital

sitc
Society for Immunotherapy of Cancer

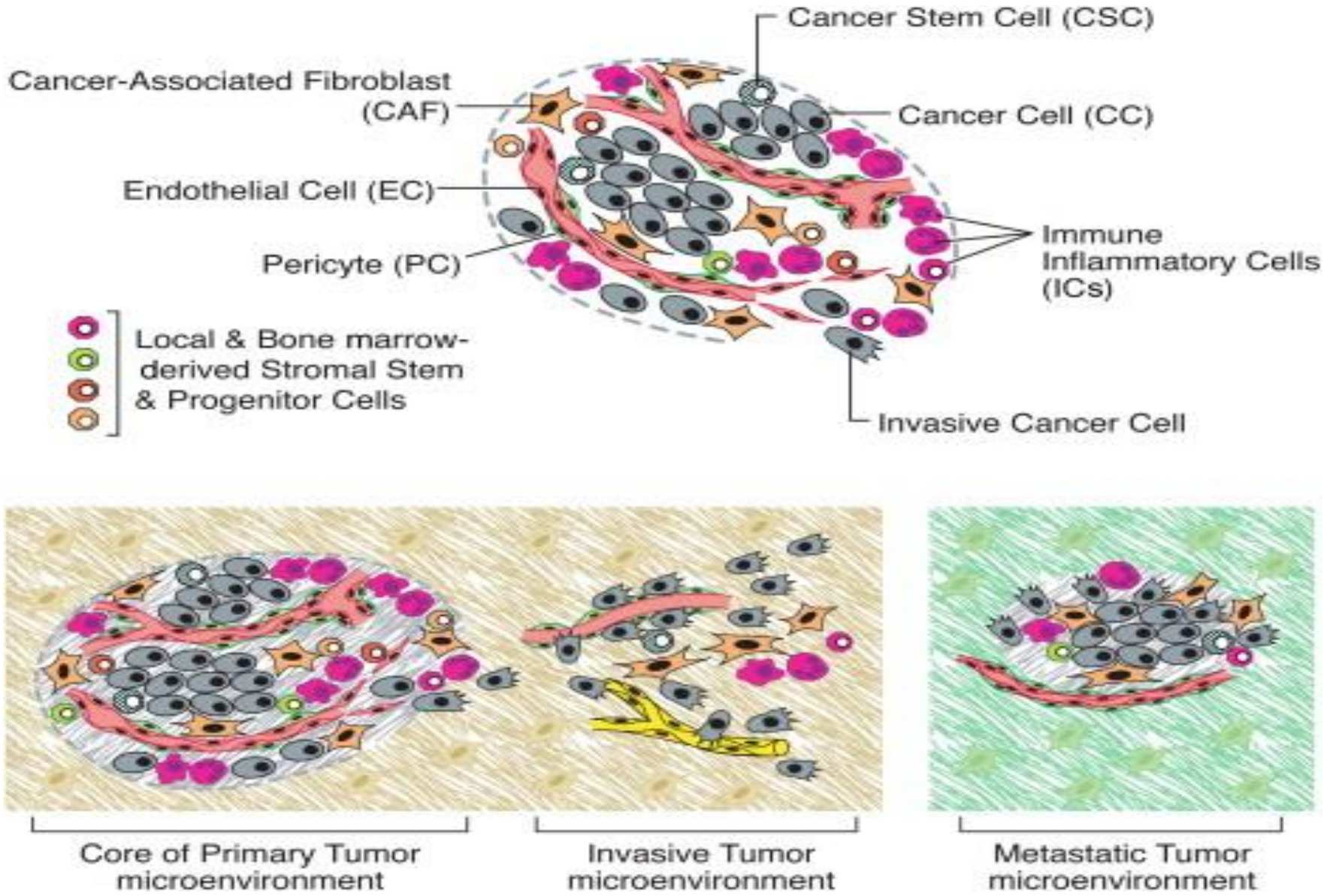
Presenter Disclosure Information

Vincenzo Bronte

The following relationships exist related to this presentation:

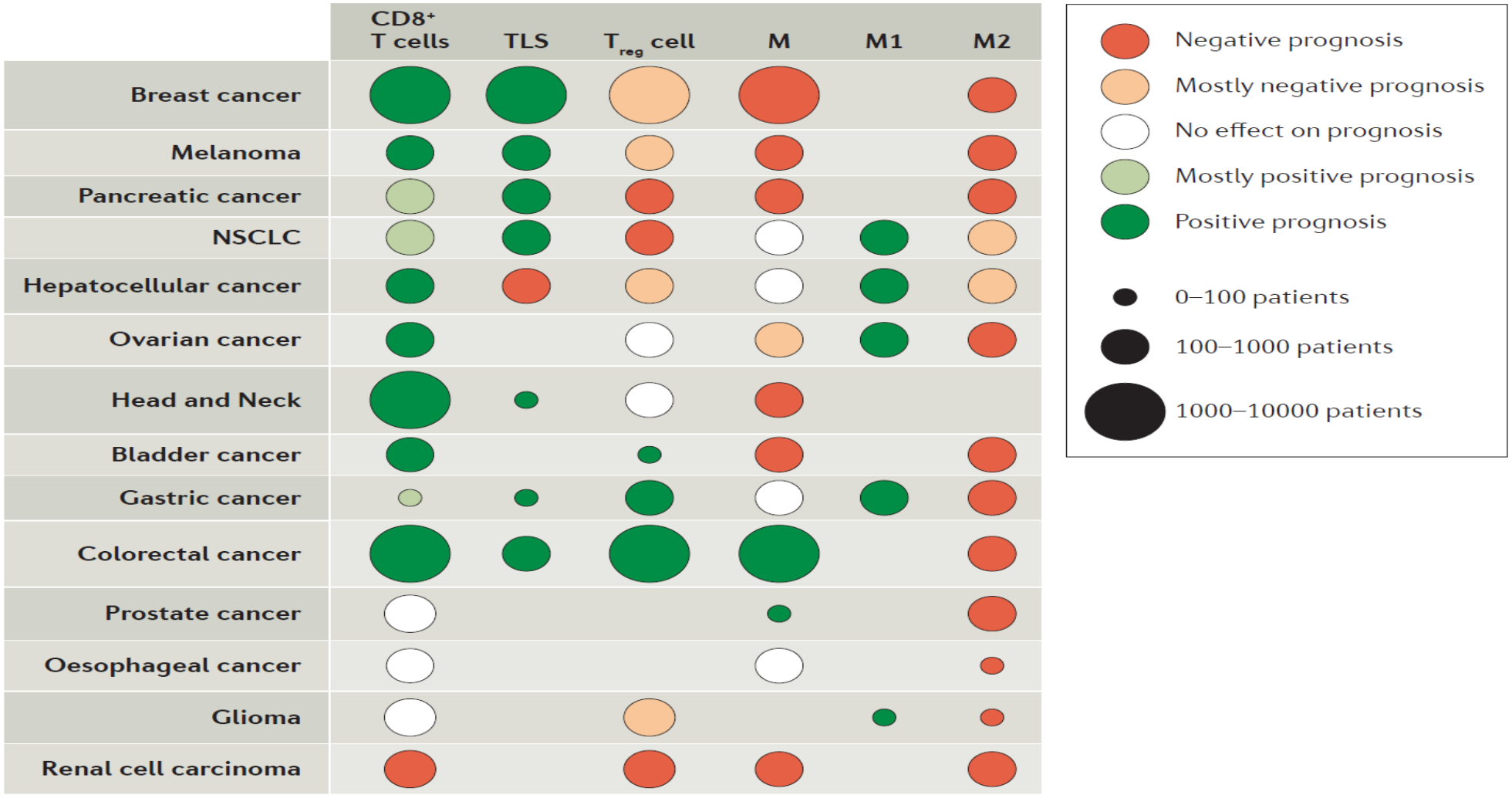
iTeos Therapeutics SA, scientific advisory board and research collaboration
Tusk Therapeutics Ltd, scientific advisory board, research support and collaboration
IO Biotech ApS, shareholder and scientific advisory board
BioNTech AG, patent and research collaboration
Ganymed Pharmaceuticals AG, research collaboration
Xios Therapeutics, scientific advisory board

Cancer stroma comprises different immune cells



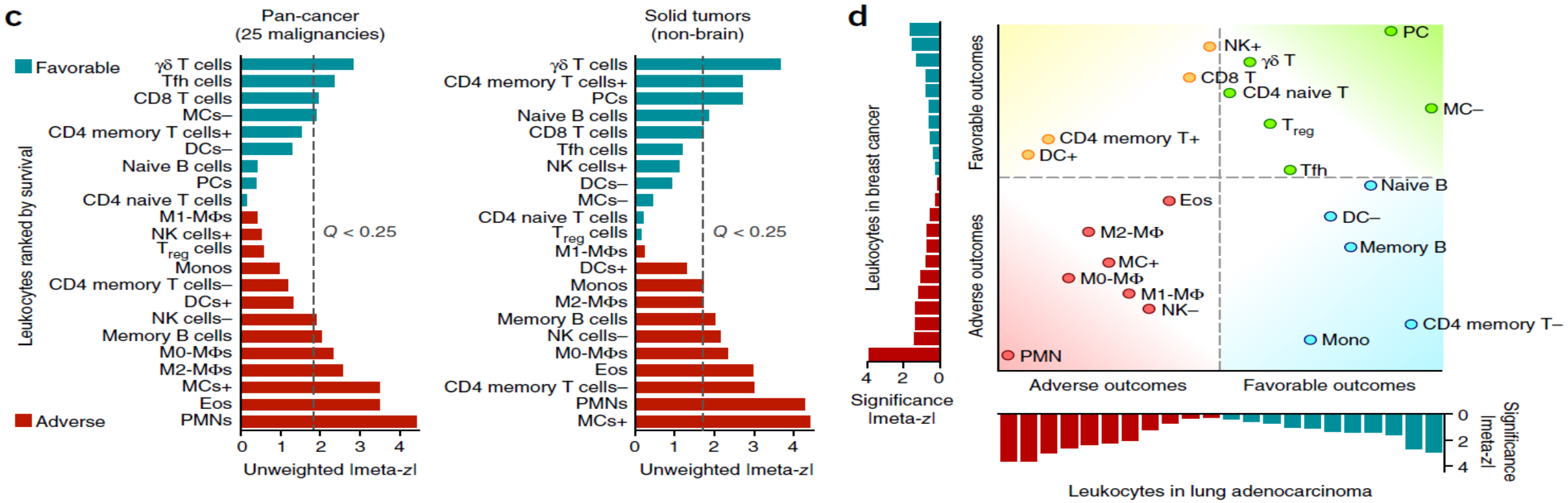
D. Hanahan , R. A. Weinberg, Cell, 2011

Meta-analysis of 200 published articles studying the impact of cytotoxic T cells, tertiary lymphoid structures, T regulatory lymphocytes and macrophages with regards to prognosis of patients with cancer



W. H. Fridman et al., Nat. Rev. Clin. Oncol., 2017

Computational meta-analysis of expression signatures from 18,000 human tumors reveals positive and negative correlations between tumor-infiltrating leukocytes and patient survival

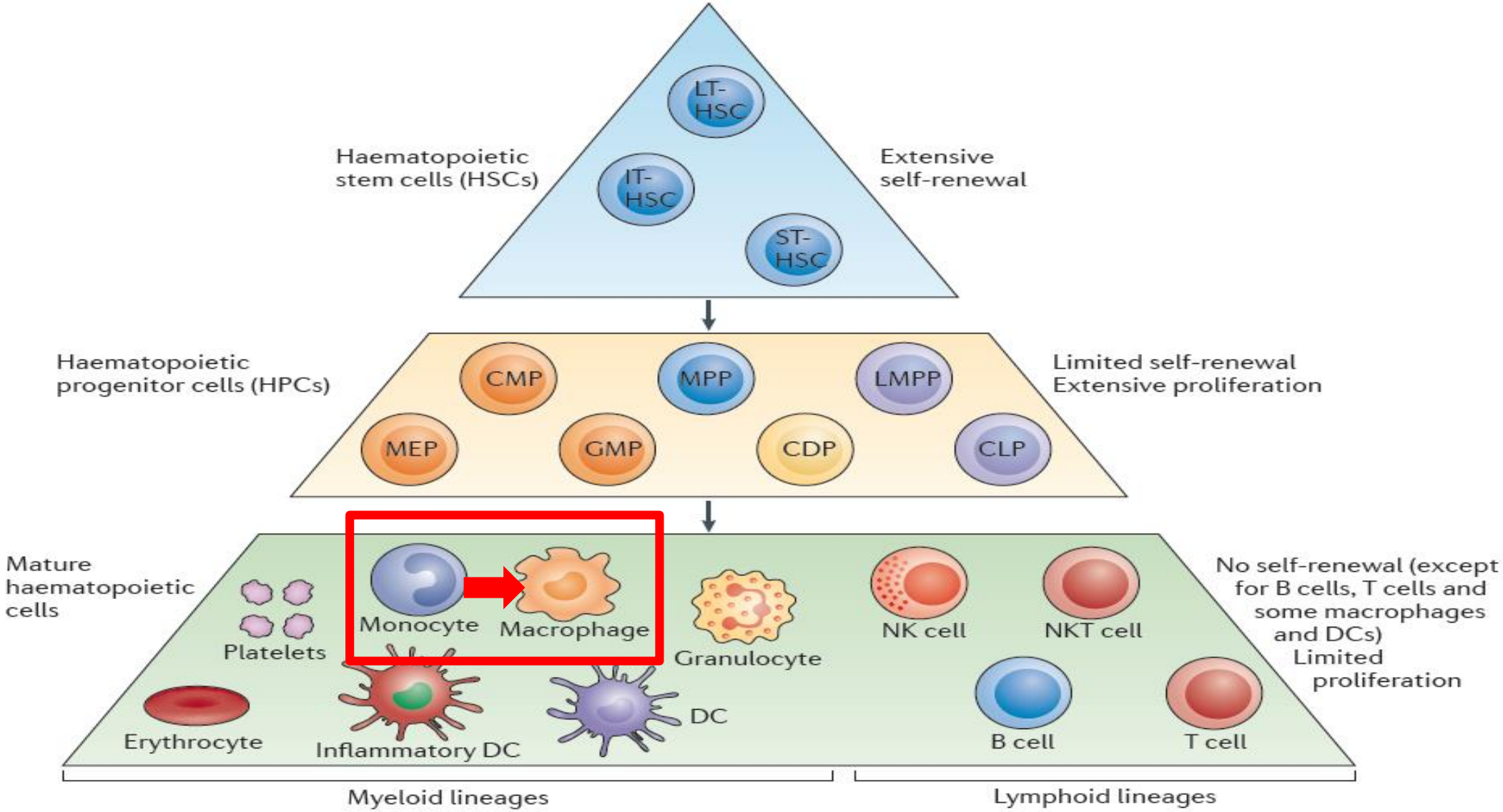


A. J. Gentles et al., Nat. Med., 2015

Myeloid cells of innate immunity

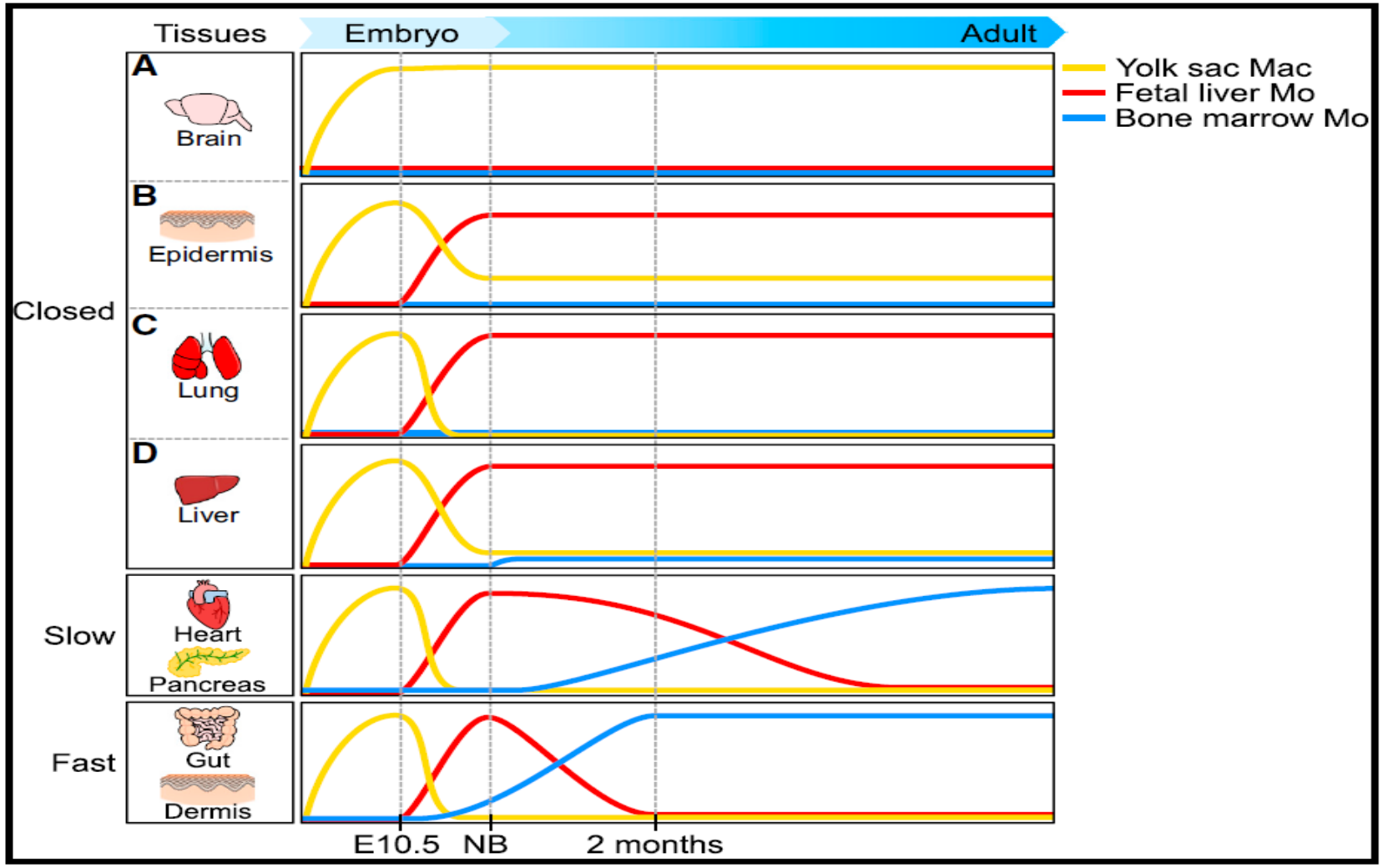
Cell type	*Main function in immune response*
Monocytes/Macrophages	**Phagocytosis, inflammation, tissue repair**
Neutrophils	**Phagocytosis, inflammation, anti-microbial peptide production**
Dendritic cells	**Activation of naïve T cells**
Mast cells	**Inflammation, vascular permeability**
Eosinophils	**Defense against parasites**

Steady-state hematopoyesis



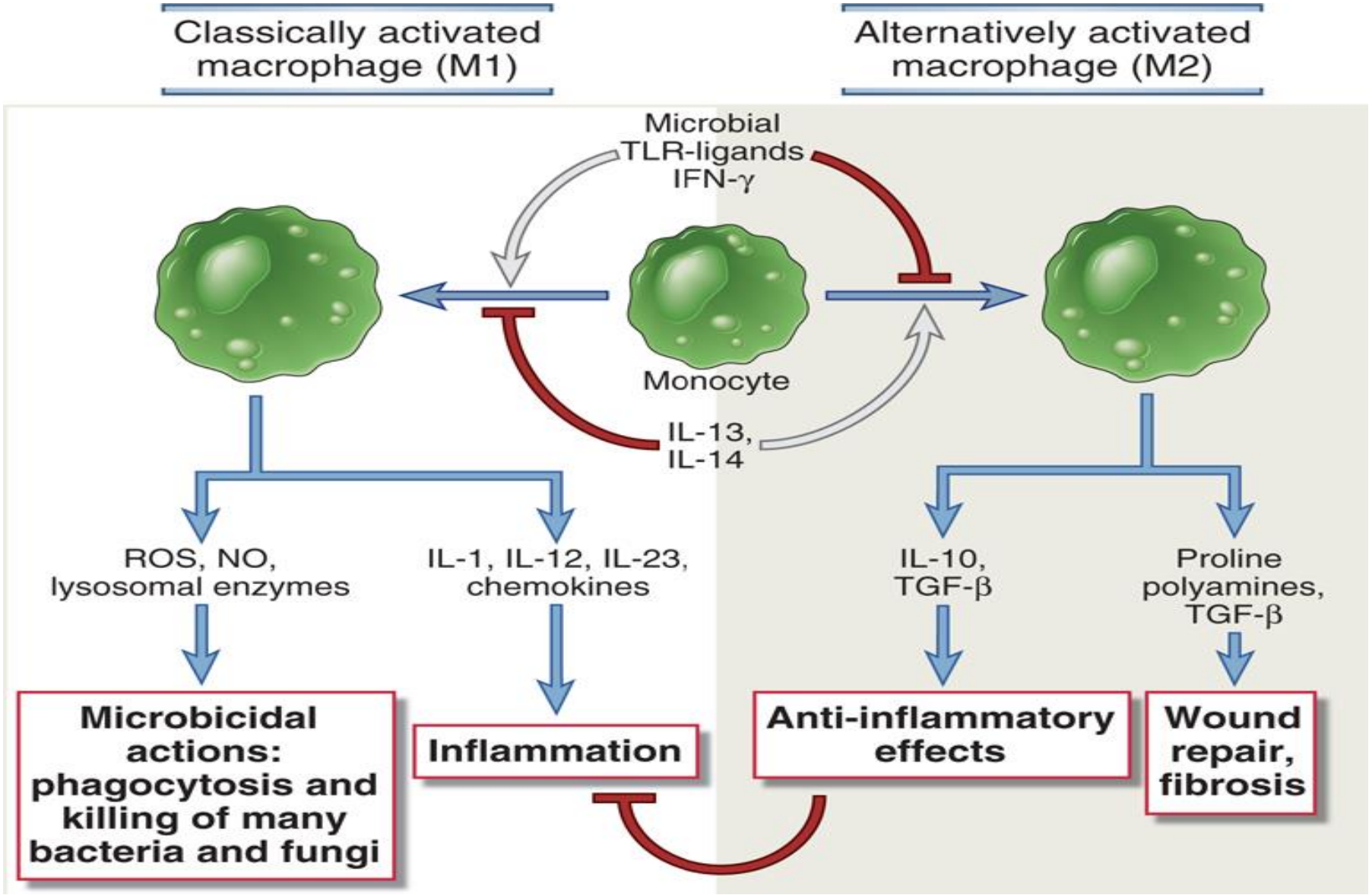
M. G. Manz and S. Boettcher, Nat. Rev. Immunol., 2014

Monocyte and macrophage developmental pathways (before birth and under steady-state condition)



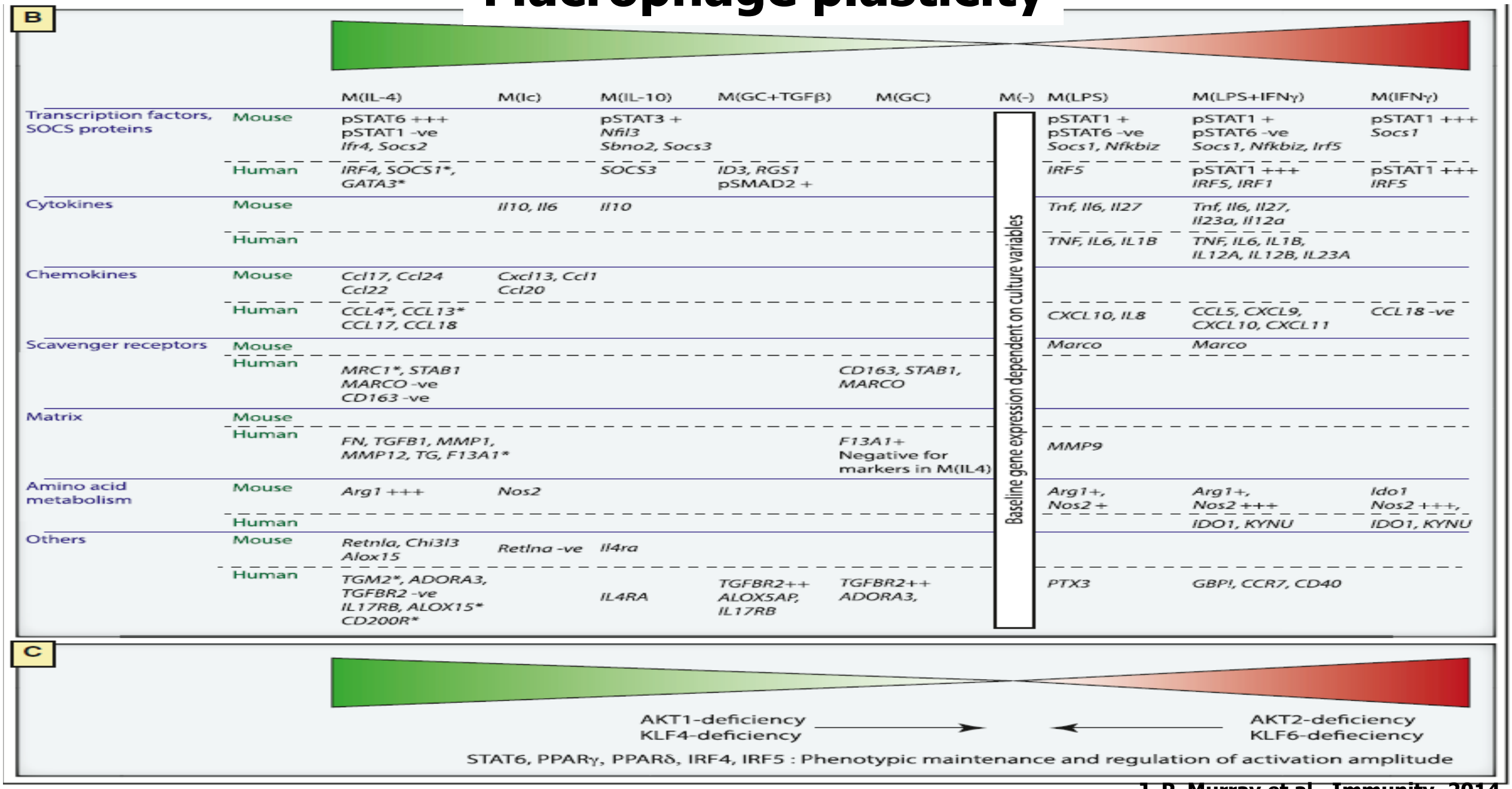
F. Ginhoux and S. Jung, Nat Rev Immunol., 2014
F. Ginhoux and M. Guilliams, Immunity, 2016

Classic and alternative activation of macrophages



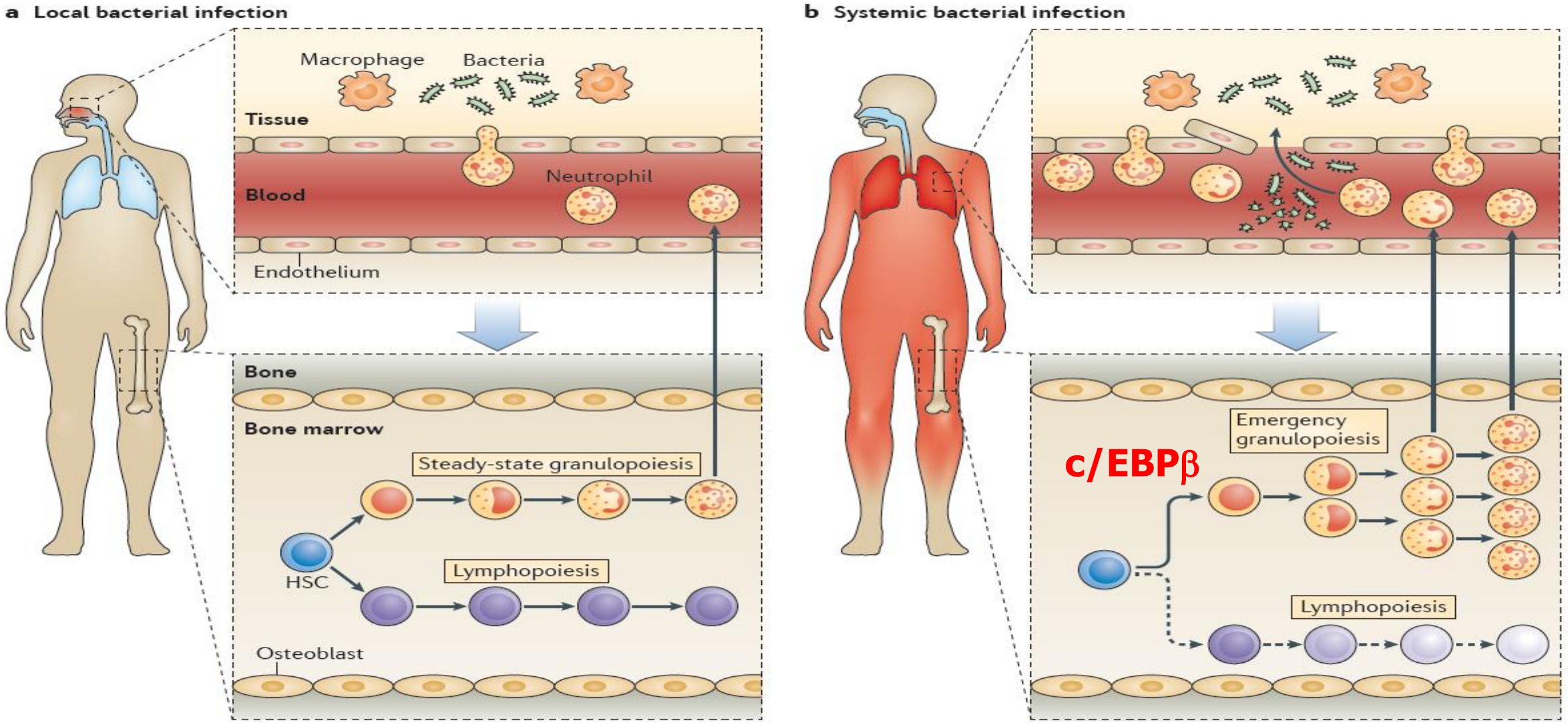
K. Abbas K, A. H. Lichtman. Cellular and Molecular Immunology, 7th Edition

Macrophage plasticity



J. P. Murray et al., Immunity, 2014

Emergency granulopoiesis



M. G. Manz and S. Boettcher, Nat. Rev. Immunol., 2014

Tumor-induced myelopoiesis

REVIEW

Received 4 Nov 2015 | Accepted 2 Jun 2016 | Published 6 Jul 2016

DOI: 10.1038/ncomms12150 OPEN

Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards

Vincenzo Bronte[1,*], Sven Brandau[2], Shu-Hsia Chen[3], Mario P. Colombo[4], Alan B. Frey[5], Tim F. Greten[6], Susanna Mandruzzato[7,8], Peter J. Murray[9], Augusto Ochoa[10], Suzanne Ostrand-Rosenberg[11], Paulo C. Rodriguez[12], Antonio Sica[13,14], Viktor Umansky[15,16], Robert H. Vonderheide[17] & Dmitry I. Gabrilovich[18,*]

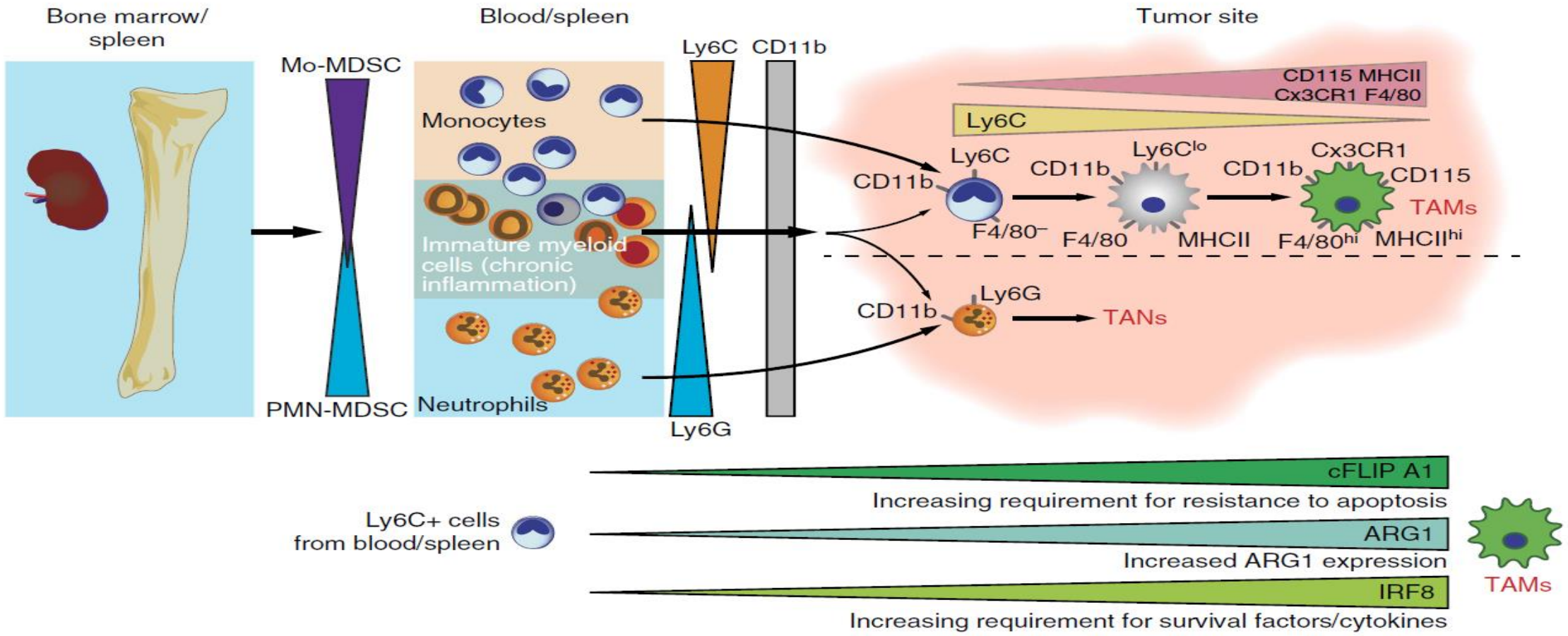


Table 1 | Minimal phenotypic characteristics necessary to identify cells as MDSC.

Mouse	Phenotype	Human (in PBMC fraction)	Phenotype
Total MDSC (not sufficient for MDSC characterization)	$Gr\text{-}1^{+}CD11b^{+}$	Total (mixed) MDSC	Not clearly determined
PMN-MDSC	$CD11b^{+}Ly6C^{lo}Ly6G^{+}$	PMN-MDSC	$CD14^{-}CD11b^{+}CD15^{+}$ (or $CD66b^{+}$)
M-MDSC	$CD11b^{+}Ly6C^{hi}Ly6G^{-}$	M-MDSC	$CD11b^{+}CD14^{+}HLA\text{-}DR^{low/-}$ $CD15^{-}$
eMDSC	Not clearly determined	e-MDSC	Lin^{-} (CD3/14/15/19/56)/ $HLA\text{-}DR^{-}/CD33^{+}$

eMDSC, early-stage MDSC; MDSC, myeloid-derived suppressor cell; M-MDSC, monocytic-MDSC; PBMC, peripheral blood mononuclear cell; PMN-MDSC; polymorphonuclear-MDSC.
Although phenotype is the first necessary step for defining MDSC, please note that, it cannot be used as the sole parameter for distinction between PMN-MDSC and neutrophils and M-MDSC and monocytes.
It is important, wherever possible, to use cells from control mice or healthy donors as controls.

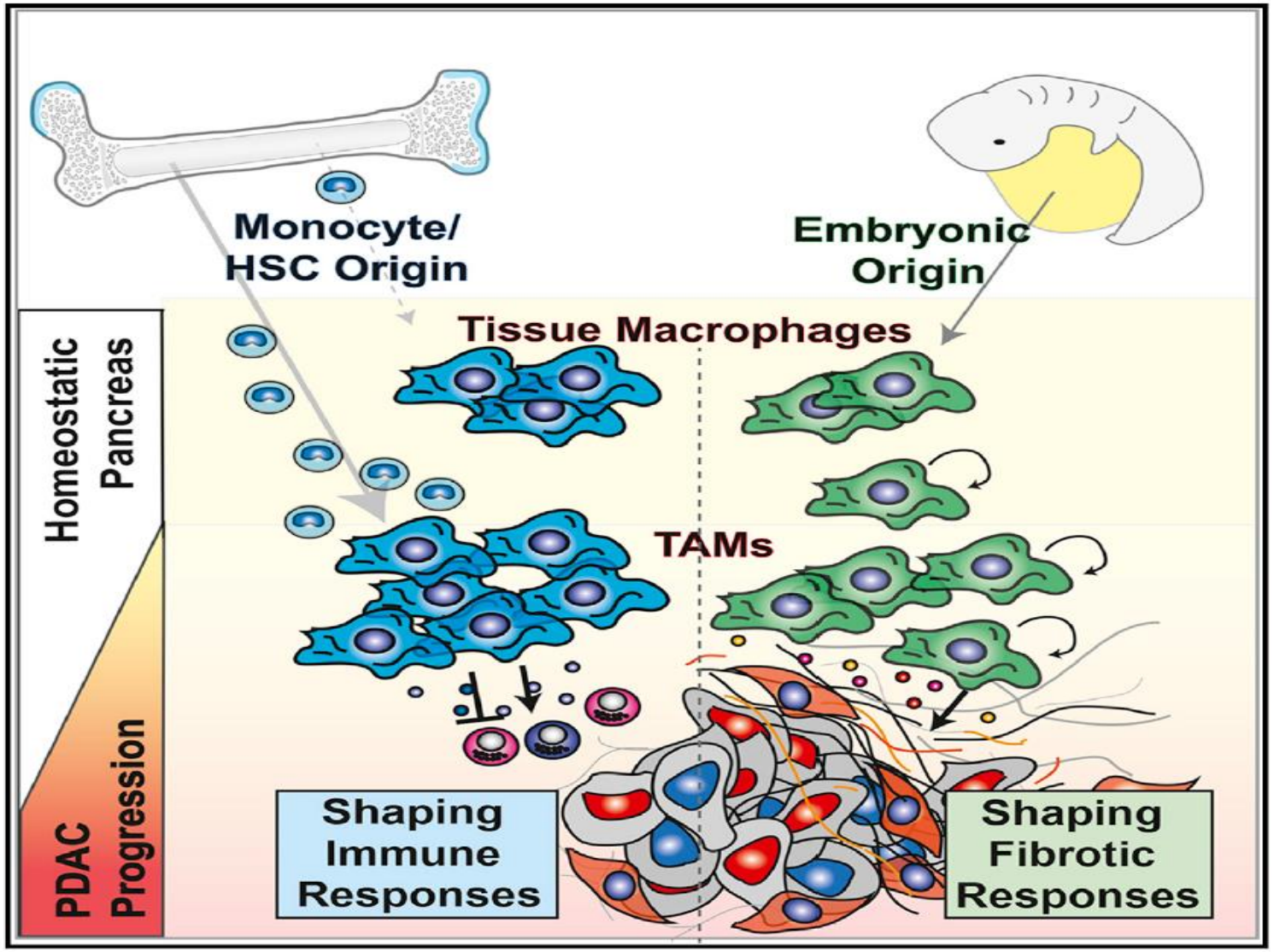
Table 2 | Minimal functional characteristics necessary to identify cells as MDSC.

Mouse functional tests		Human functional tests	
Type of immune response	**Assays**	**Autologous system**	**Allogeneic system**
• Inhibition of antigen-non-specific function (anti-CD3/CD28 or ConA induced) • Inhibition of antigen-specific function using antigen-specific T cells (induced after immunization with peptides or from transgenic mice)	• Inhibition of ^{3}H-thymidine incorporation or CFSE dilution • Inhibition of CTL activity • Inhibition of IFN-γ production by T cells in ELISPOT or intracellular staining • Inhibition of expression of CD3ζ chain on T cells • Inhibition of IL-2 production	• Inhibition of anti-CD3/CD28 (or PHA) induced T-cell proliferation or IFN-γ production (in ELISPOT or by intracellular staining) by the addition of candidate MDSC populations • Improved T-cell proliferation after removal of candidate MDSC populations	• Inhibition of proliferation or IFN-γ production by T cells (in ELISA, ELISPOT or by intracellular staining) by the addition of selected MDSC populations

CTL, cytotoxic T lymphocyte; ELISA, enzyme-linked immunosorbent assay; IFN, interferon; IL, interleukin; MDSC, myeloid-derived suppressor cell.
It is important, wherever possible, to use cells from control mice or healthy donors as controls.
For either antigen-specific or antigen-non-specific response, one assay is usually sufficient.

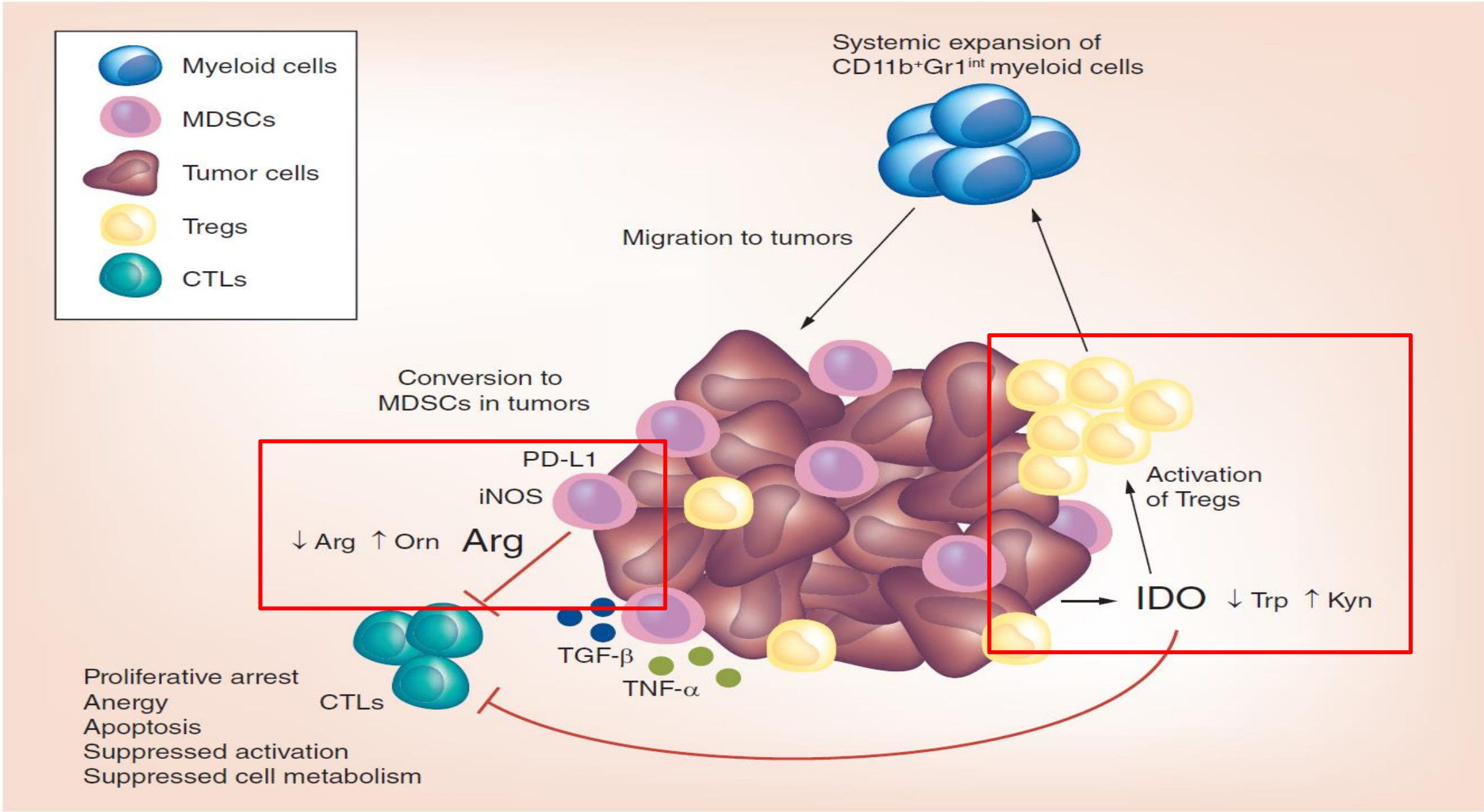
V. Bronte et al., Nat. Comm., 2016

TAMs of different origin in cancer



Zhu et al., Immunity, 2017

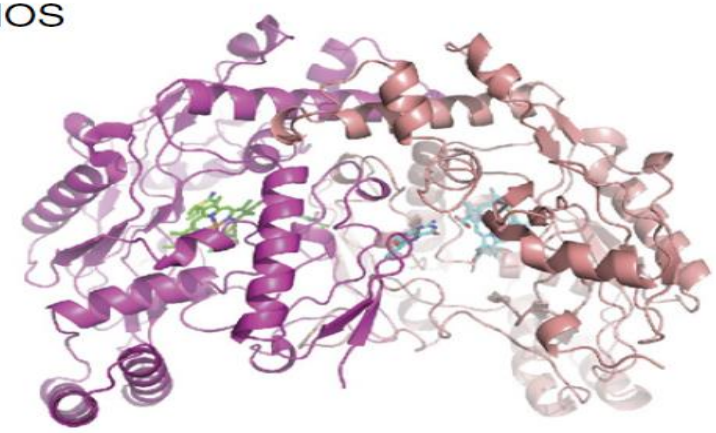
The metabolic control of T cell activation by myeloid cells



E. Timosenko et al., Immunotherapy, 2016

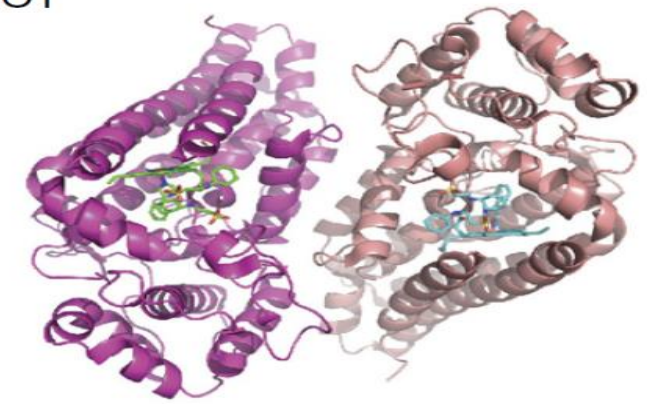
Amino acid metabolizing enzymes with immuno regulatory activity

iNOS



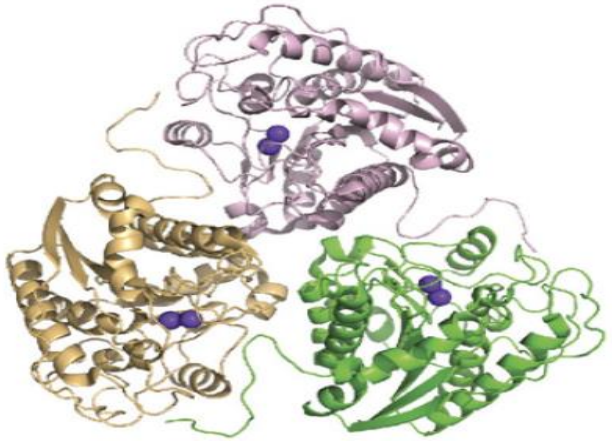
$$\text{Arginine} + 4\ O_2 + 3\ H^+ + 3\ \text{NADPH} \longrightarrow 2\ \text{citrulline} + 4\ H_2O + 3\ \text{NADPH}^+ + 2\ \text{NO}$$

IDO1



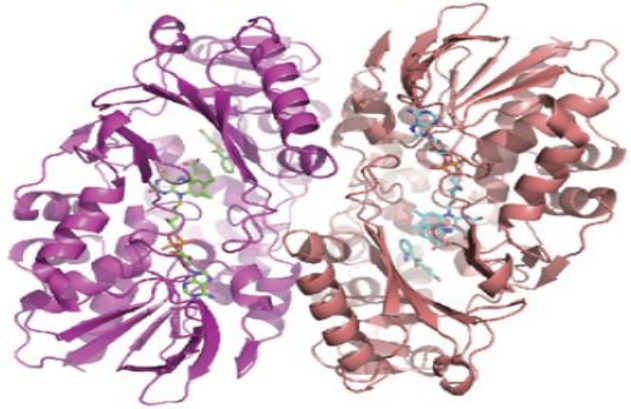
$$\text{Tryptophan} + O_2 \longrightarrow \text{formylkynurenine}$$

Arg1



$$\text{Arginine} + H_2O \longrightarrow \text{ornithine} + \text{urea}$$

IL4i1 model
(Malayan pit viper LAAO)



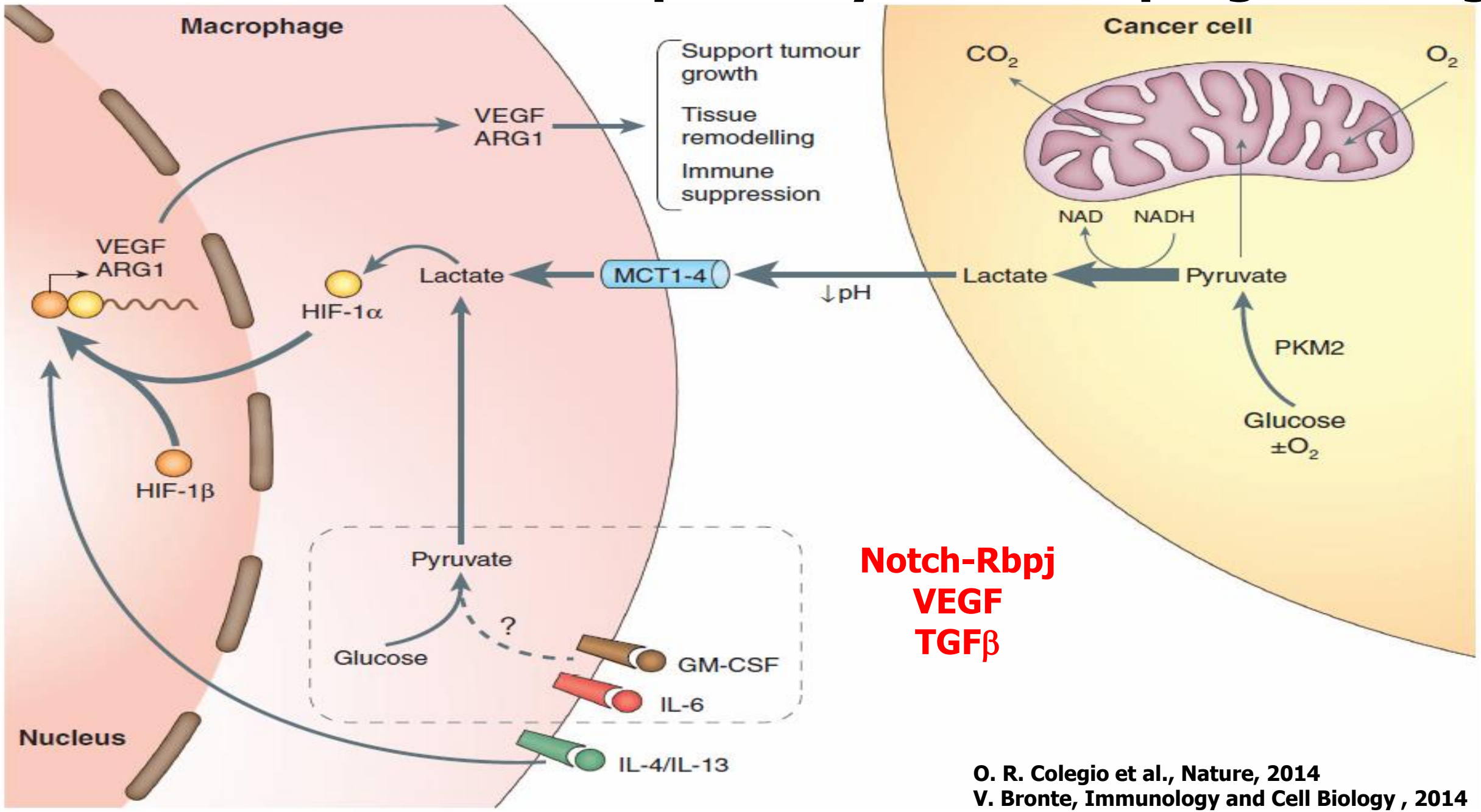
$$\text{AA} + H_2O + O_2 \longrightarrow \text{oxo acid} + H_2O_2 + NH_3$$

P. J. Murray, Nat. Immunol., 2016

Amino acid metabolizing enzymes and control of immune response

Enzyme	Substrate	Effects of enzymatic activity	Main cytokine controlling expression	Cell type
Indoleamine 2,3-dioxygenase 1	L-tryptophan	L-tryptophan depletion and kinurenine	IFN-γ	Plasmacitoid DC, MØ, DC subsets, some tumors
Arginase 1	L-arginine	L-arginine depletion, urea and polyamines	IL-4/IL-13	MDSC, MØ, some tumors
Nitric Oxide Synthase 2	L-arginine	NO	IFN-γ	MDSC, MØ
Interleukin-4-induced gene 1 (oxidase)	L-phenylalanine and other	H_2O_2 and phenylpyruvate	IL-4/IL-13	DC, B lymphocytes

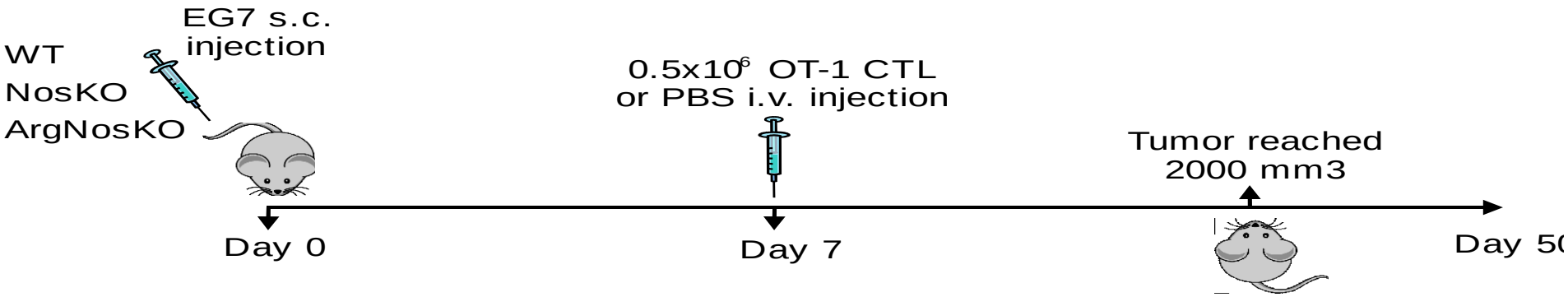
Metabolic and molecular pathways for TAM programming

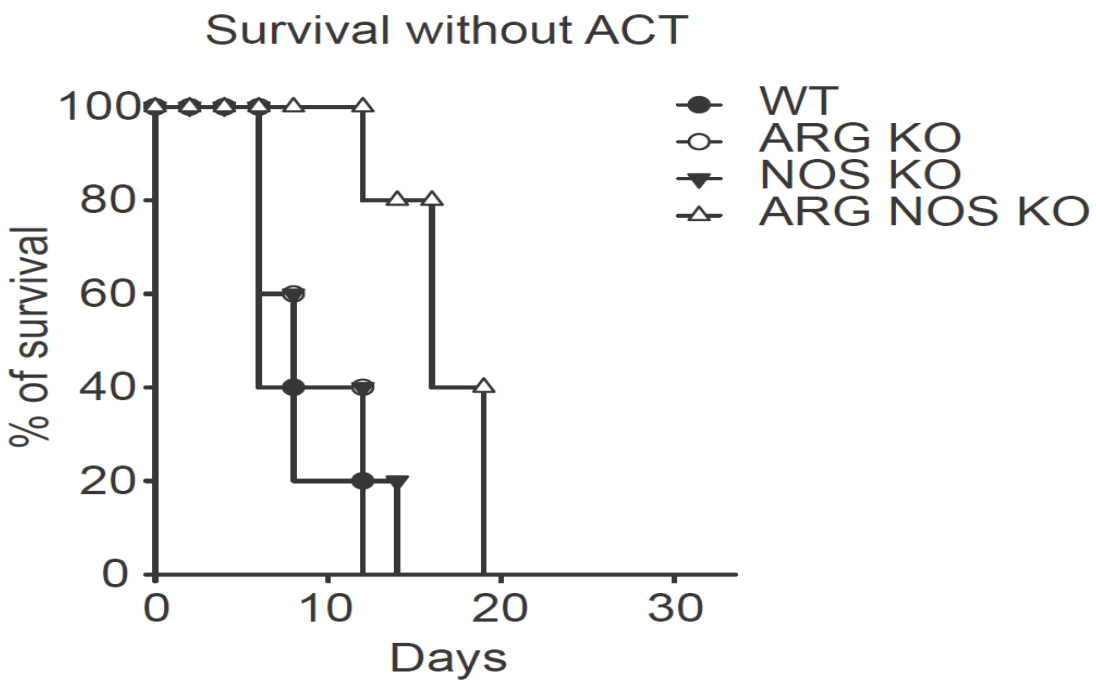


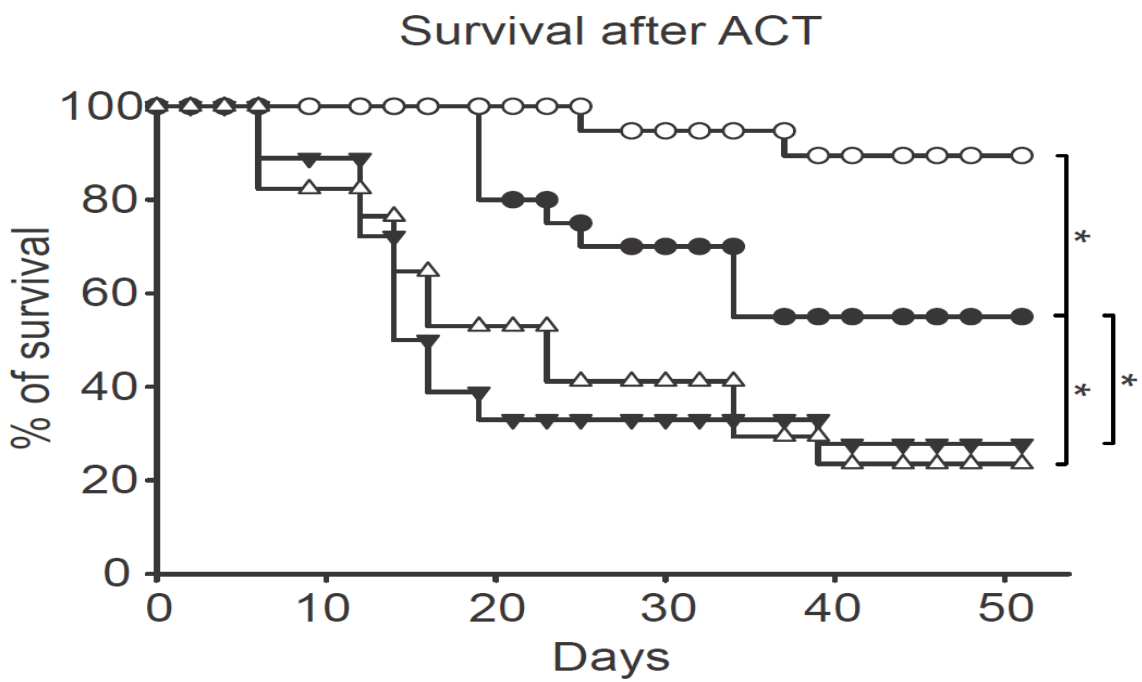
Notch-Rbpj
VEGF
TGFβ

O. R. Colegio et al., Nature, 2014
V. Bronte, Immunology and Cell Biology , 2014

ARG1 genetic ablation favors immunotherapy

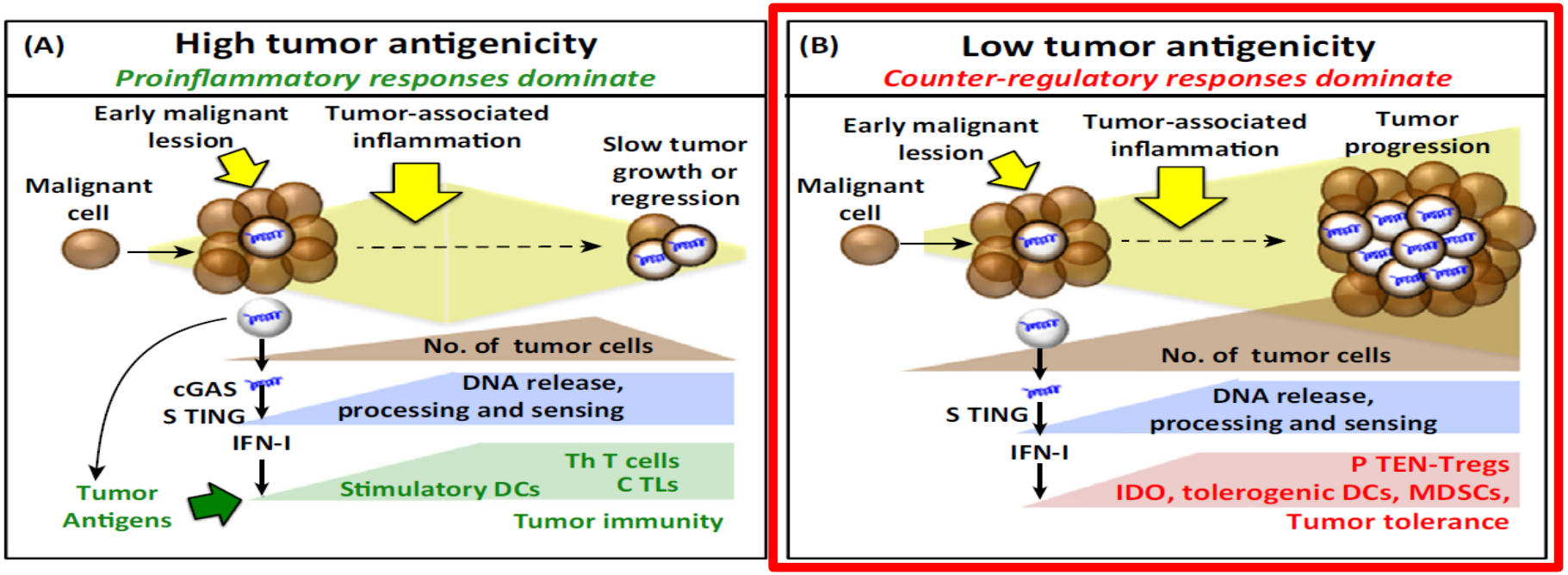


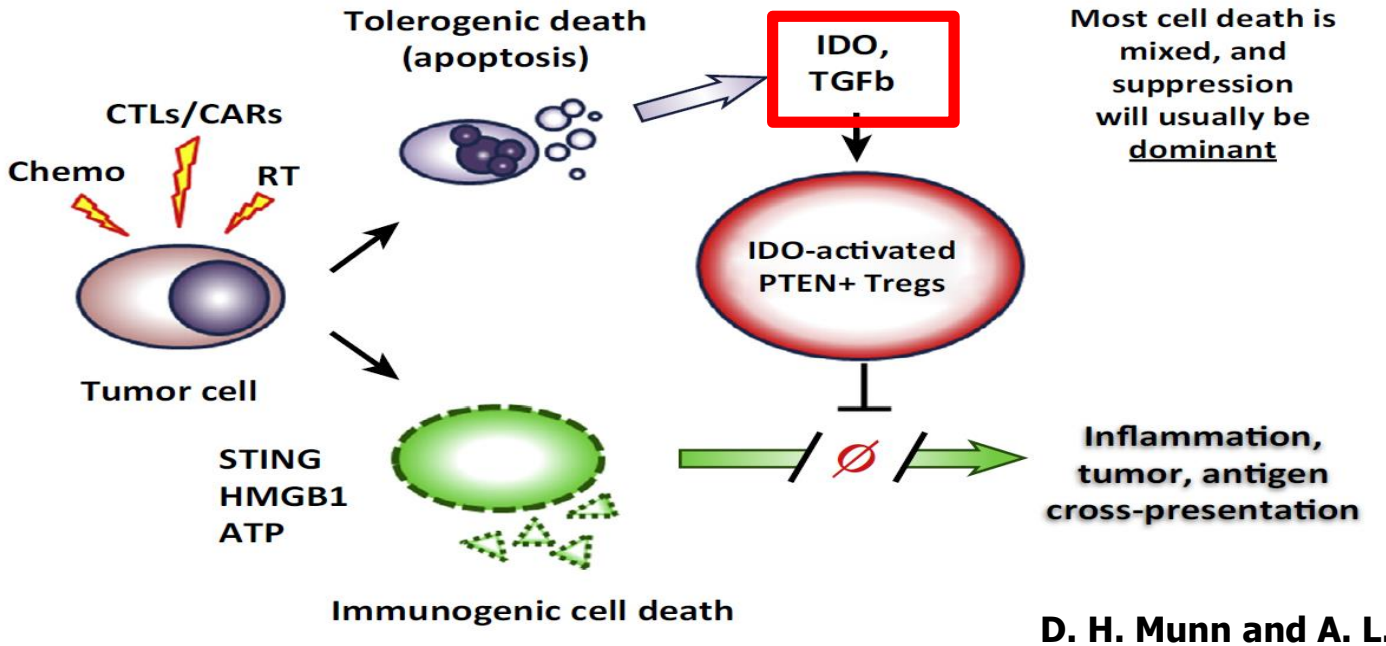




I. Marigo et al., Cancer Cell, 2016

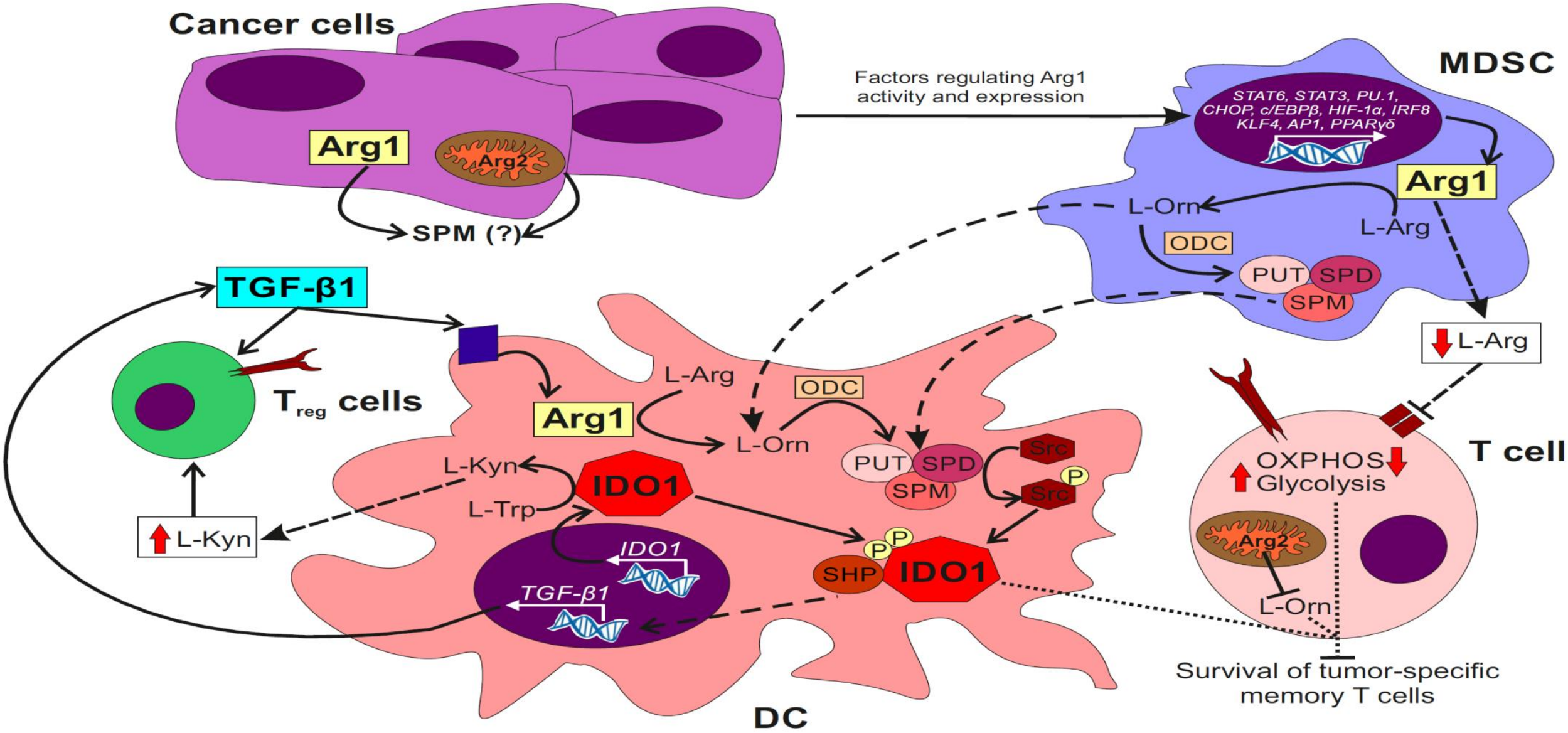
The different environment can determine variable outcomes





D. H. Munn and A. L. Mellor, Trends Immunol., 2016

ARG1 and IDO1 cross-talk



G. Montanelli et al., Curr. Opin. Pharmacol, 2017
G. Montanelli et al., Immunity, 2017

Current clinical trials

Indoleamine 2 3-dioxygenase 1 (IDO1)

- About 24 clinical trials in cancers (mostly in combination with checkpoint inhibitors or other cancer therapies)
- 4 small molecule inhibitors and one vaccine

Arginase 1 (ARG1)

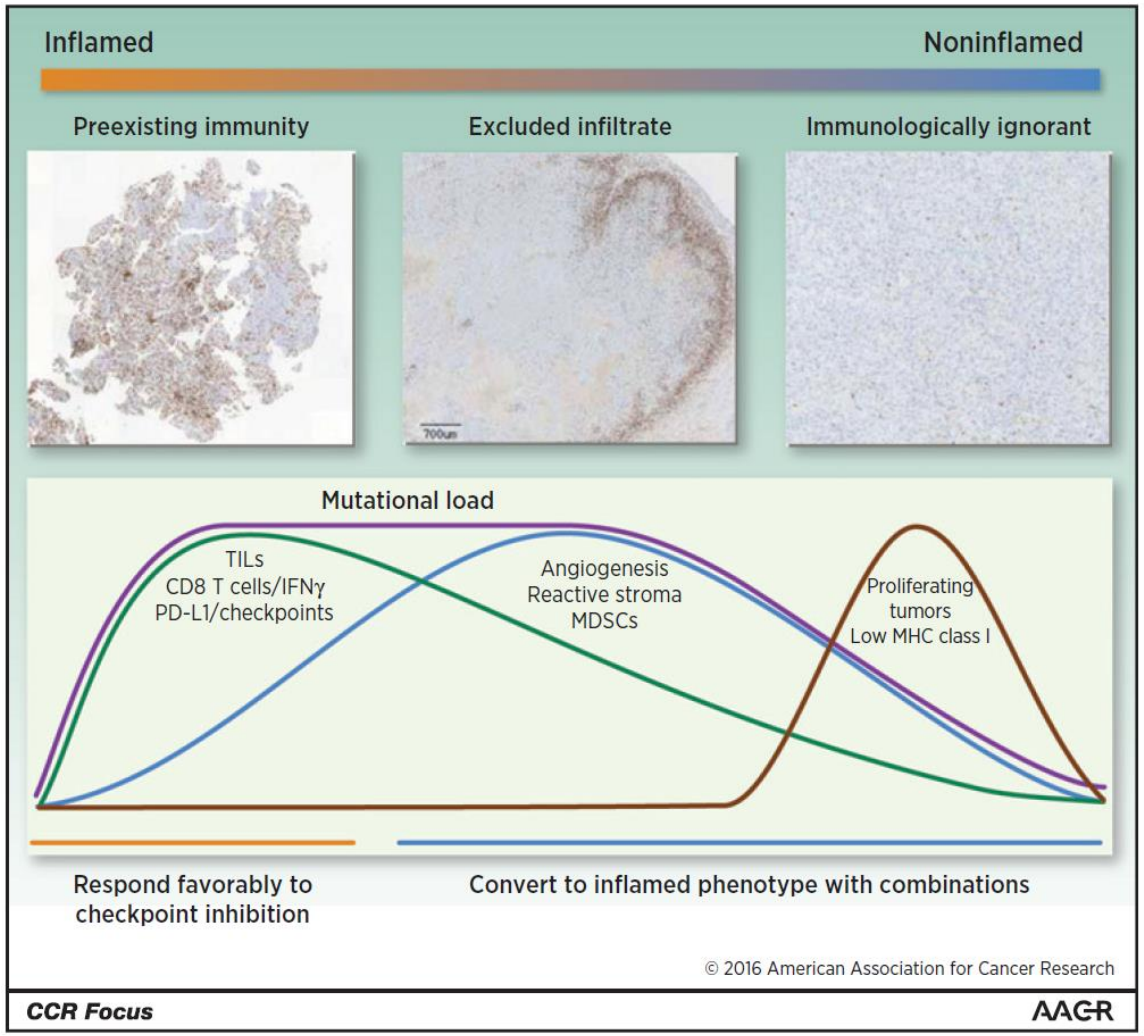
- 3 clinical trials, only one in cancer
- Small molecule inhibitor

Ornithine decarboxylase (ODC)

- About 34 clinical trials (Trypanosoma infections, cancer prevention and treatment, alone or in combination)
- Small molecule inhibitor

More info in: G. Montanelli et al., Curr. Opin. Pharmacol., 2017

Cold and immune-evasive tumors: the micro-environment as target



P.S. Hegde et al., Clin. Can. Res. Focus, 2016

Cold and immune-evasive tumors: the micro-environment as target

- **Cancer cell molecular programs**

β-catenin, c-Met

- **Enzymes**

IDO1, Arginase 1

- **Chemochines, cytokines and chemoattractants**

CCL2, CSF-1

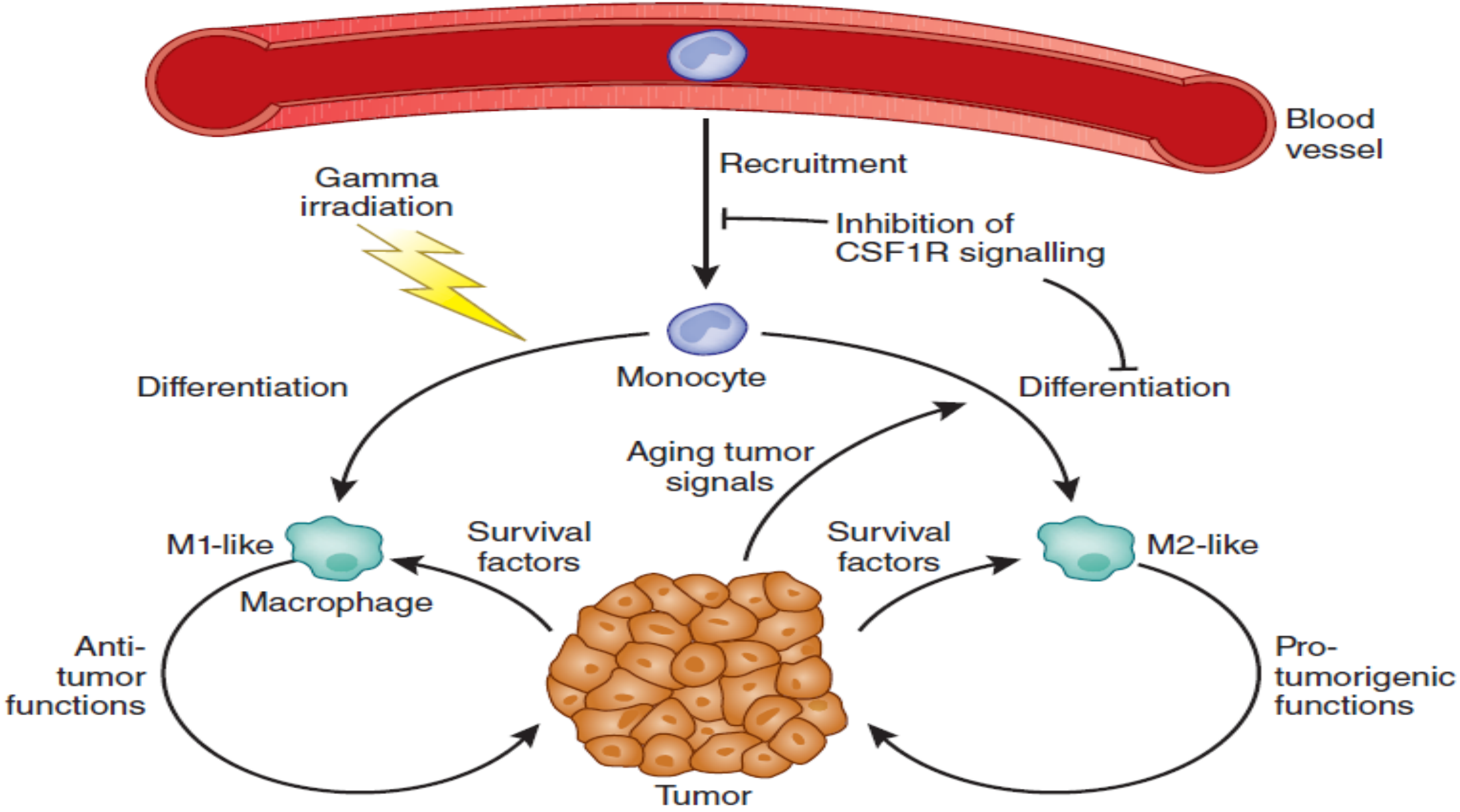
- **Signaling and transcription factors in myeloid infiltrating cells**

PI3Kγ, c/EBPβ

- **Myeloid cell activation and biology**

Anti-CD40, TLR4 agonists, STING agonists, TLR9 agonists

Therapeutic interventions on TAMs to improve cancer therapy



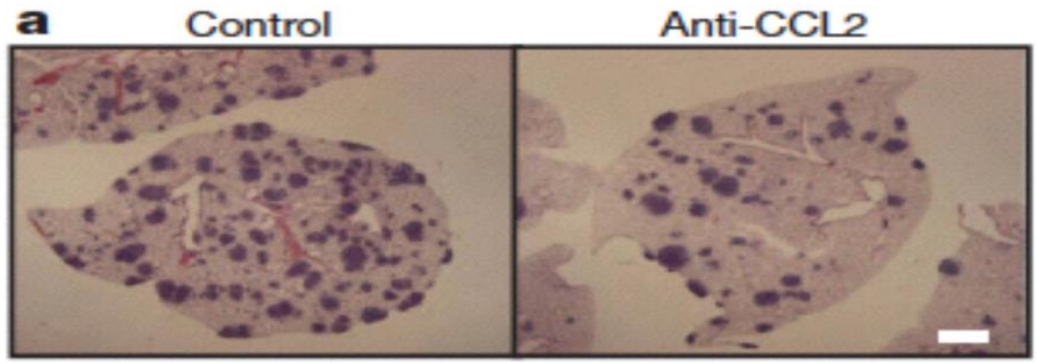
V. Bronte and P. J. Murray. Nat. Med. 2015

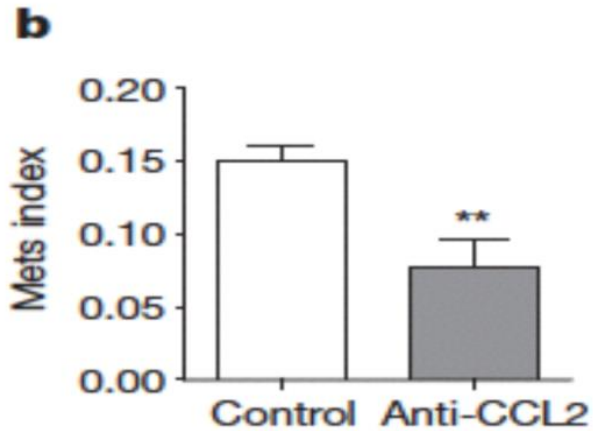
LETTER

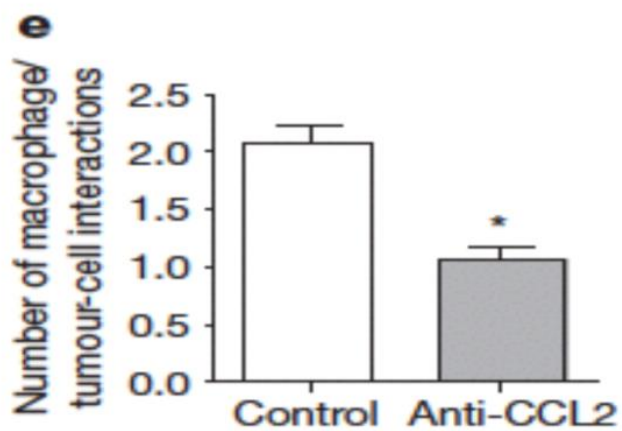
doi:10.1038/nature10138

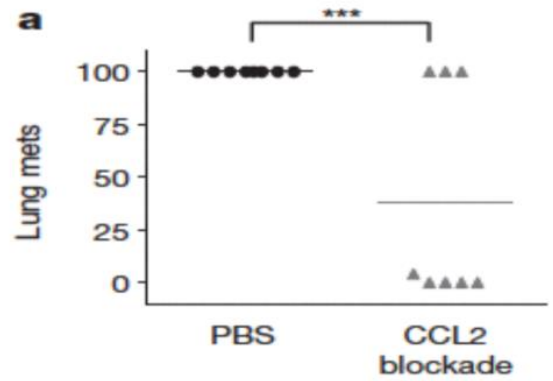
CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis

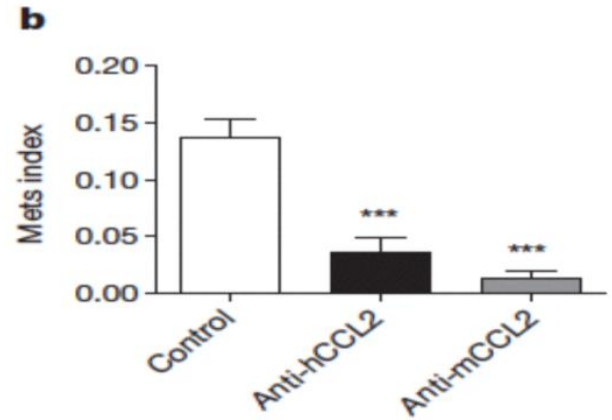
Bin-Zhi Qian[1], Jiufeng Li[1], Hui Zhang[1], Takanori Kitamura[1], Jinghang Zhang[2], Liam R. Campion[3], Elizabeth A. Kaiser[3], Linda A. Snyder[3] & Jeffrey W. Pollard[1]









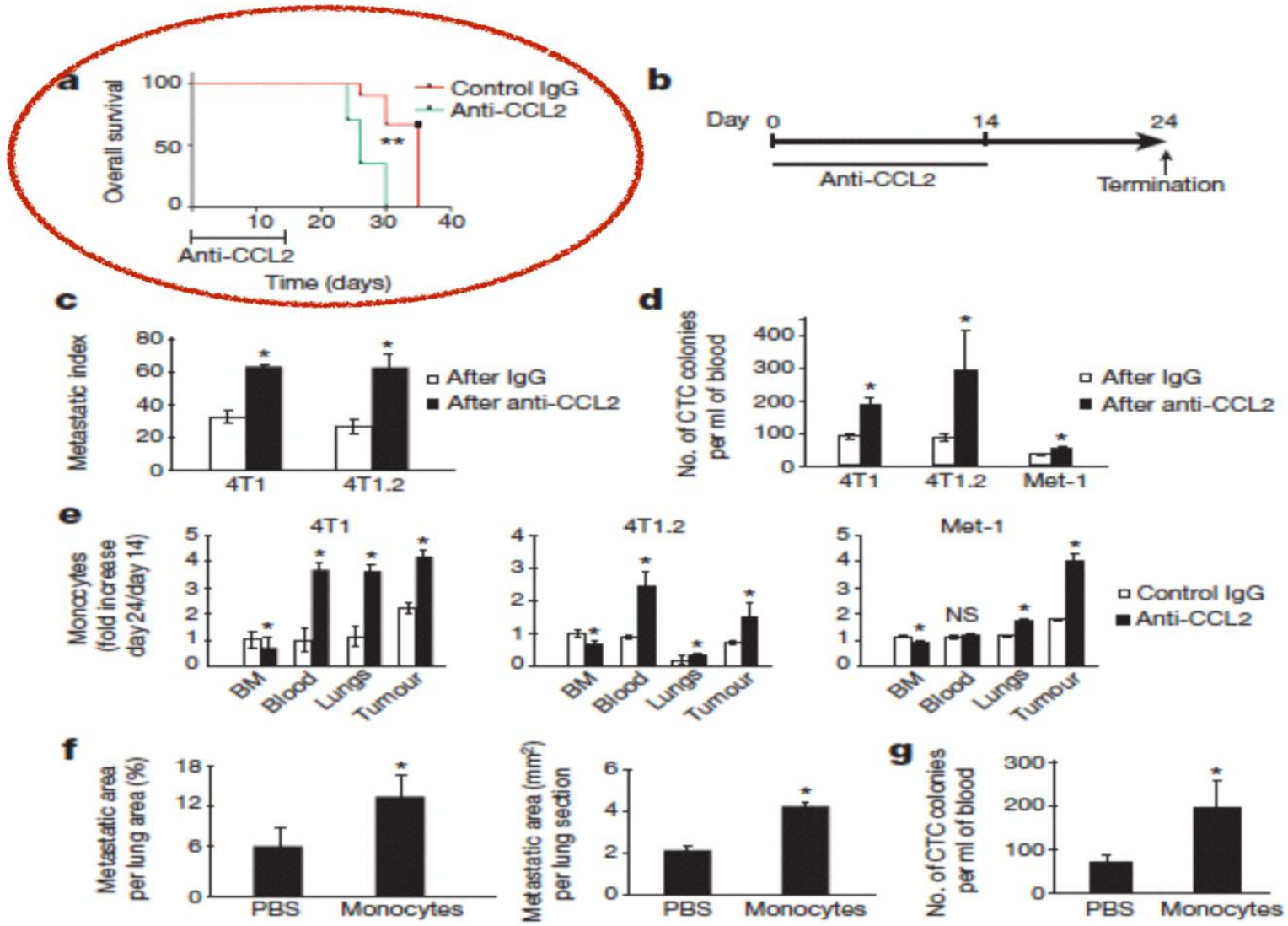


LETTER

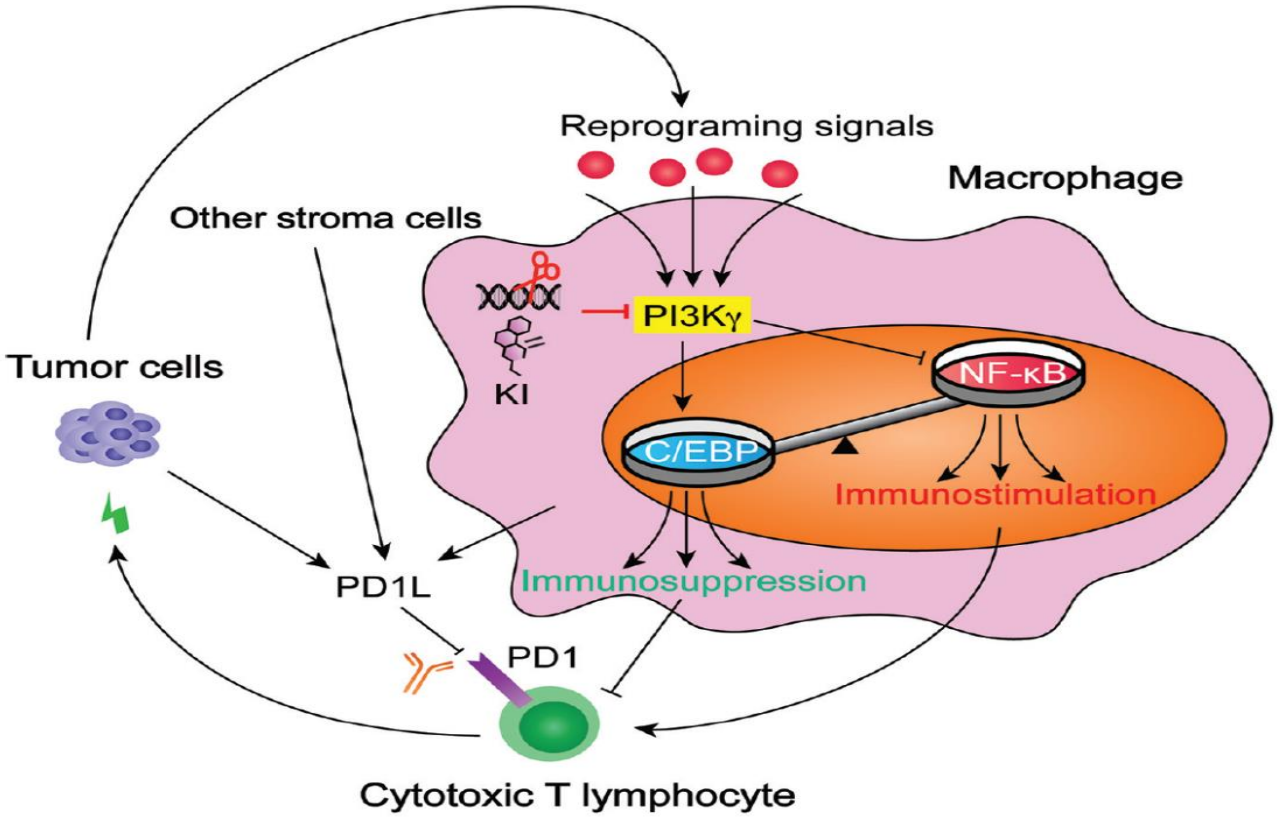
doi:10.1038/nature13862

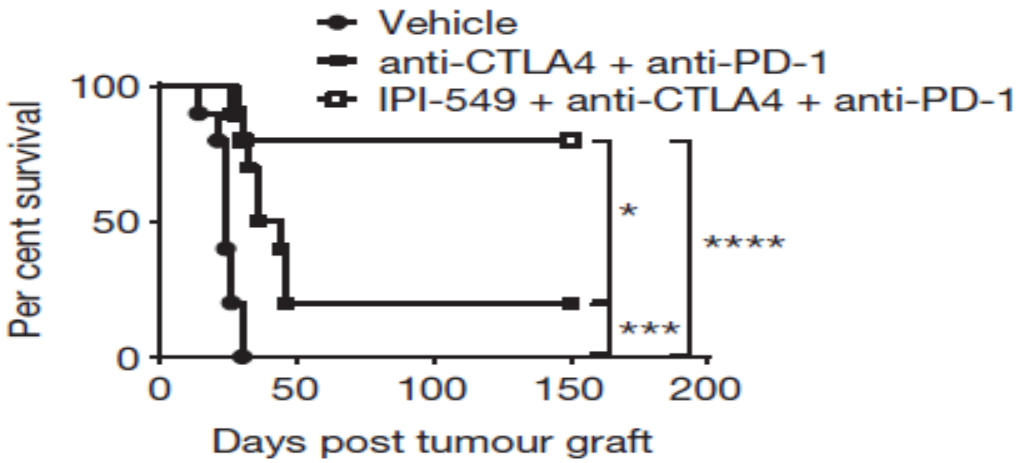
Cessation of CCL2 inhibition accelerates breast cancer metastasis by promoting angiogenesis

Laura Bonapace[1,2]*, Marie-May Coissieux[1]*, Jeffrey Wyckoff[1]†, Kirsten D. Mertz[3,4], Zsuzsanna Varga[3], Tobias Junt[2]* & Mohamed Bentires-Alj[1]*



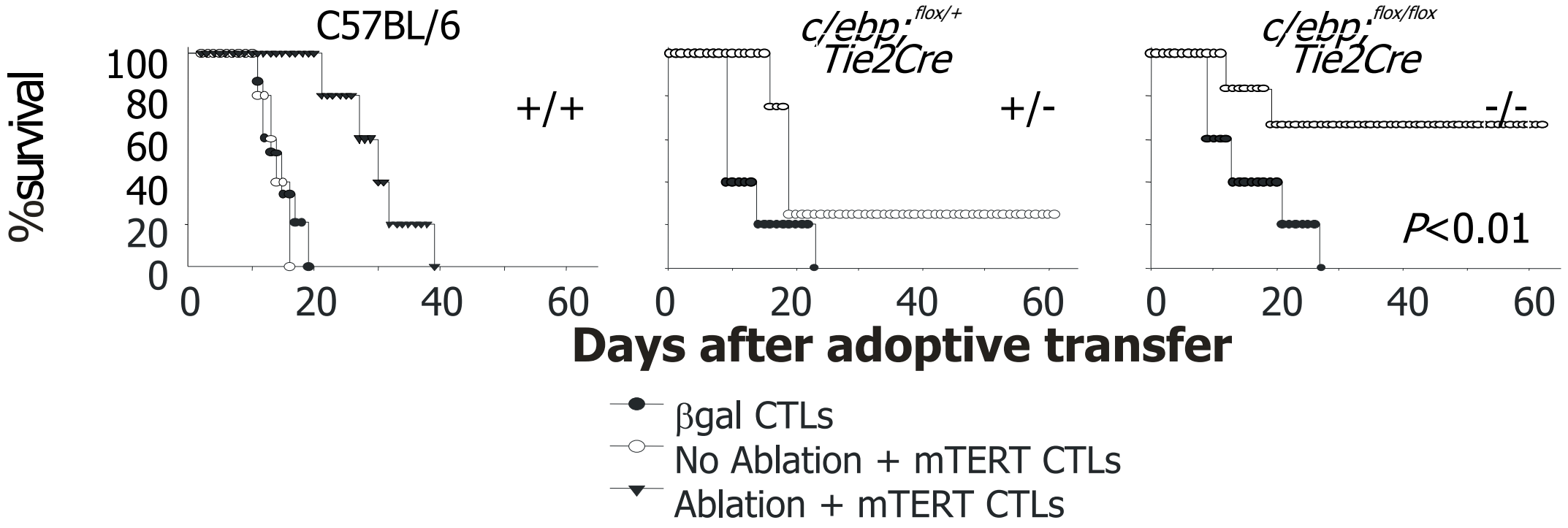
Targeting PI3Kγ in myeloid cells





W. Zheng and J. W. Pollard, Cell Research, 2016
M. M. Kaneda et al., Nature, 2016
O. De Henau et al., Nature, 2016

Targeting cEBPβ in myeloid cells



I. Marigo et al., Immunity, 2010

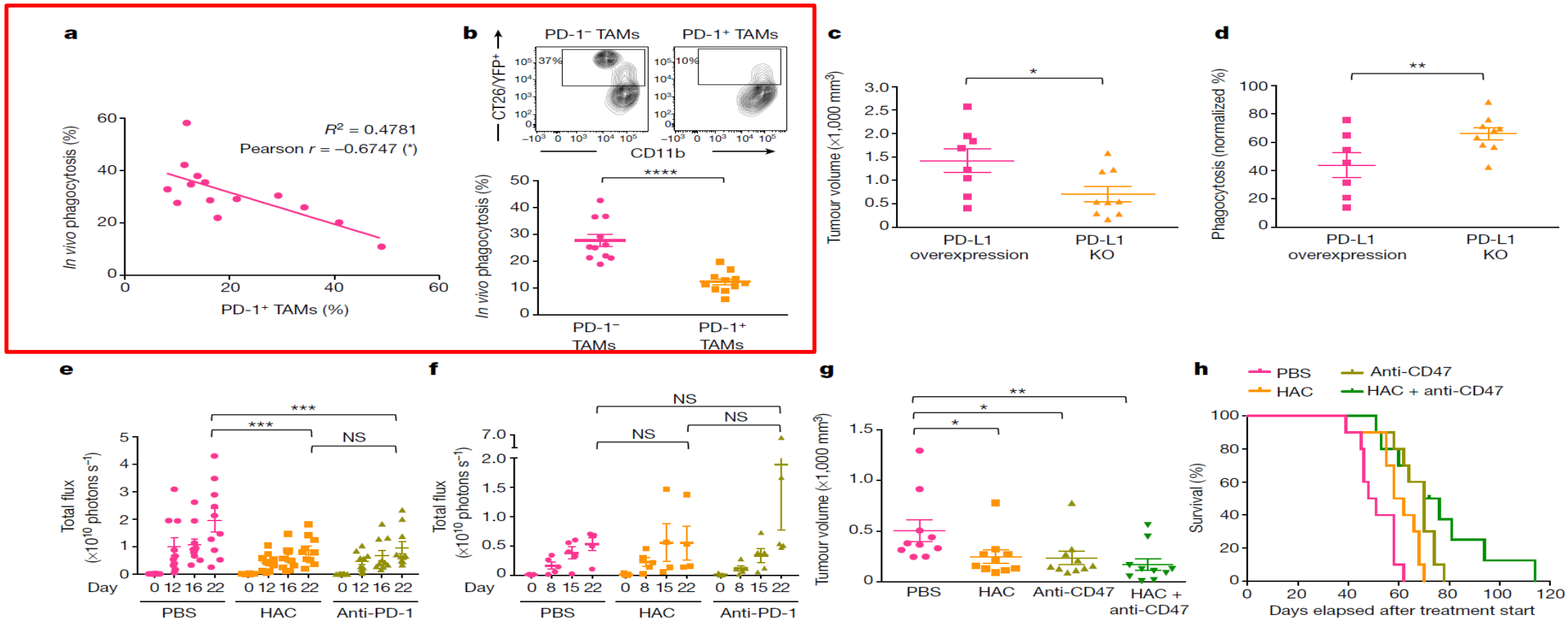
LETTER

doi:10.1038/nature22396

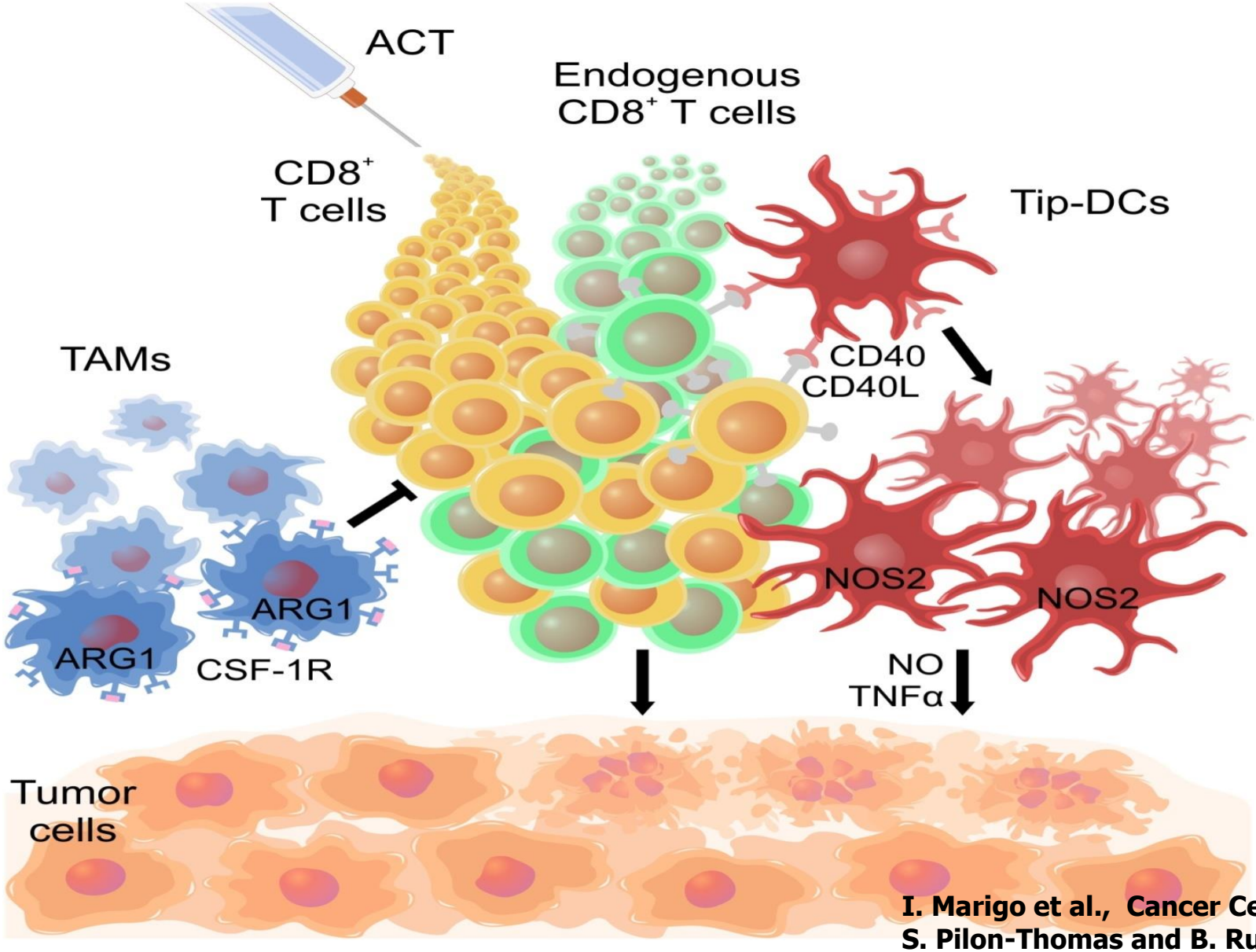
PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity

Sydney R. Gordon[1,2,3,4,5], Roy L. Maute[1,3,4,5], Ben W. Dulken[1,6], Gregor Hutter[1,7,8], Benson M. George[1,3,4,5,6], Melissa N. McCracken[1,3,4,5], Rohit Gupta[9], Jonathan M. Tsai[1,3,4,5,6], Rahul Sinha[1,3,4,5], Daniel Corey[1,3,4,5], Aaron M. Ring[10], Andrew J. Connolly[5] & Irving L. Weissman[1,3,4,5]

RESEARCH LETTER



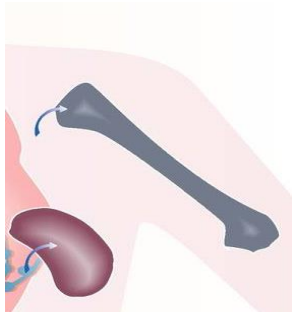
Tumor-specific CD8⁺ T cells collaborate with monocyte-derived Tip-DCs

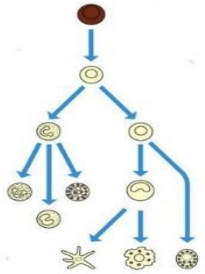


I. Marigo et al., Cancer Cell, 2016
S. Pilon-Thomas and B. Ruffell, Cancer Cell, 2016

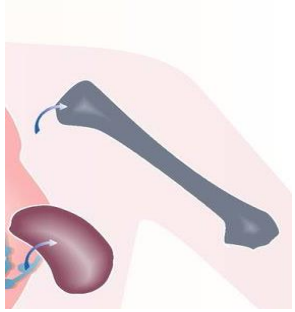
Refining therapeutic strategies to alter myeloid compartment in cancer

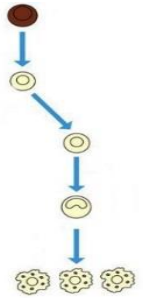
Chemotherapy
Radiotherapy



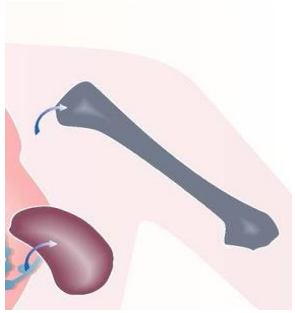


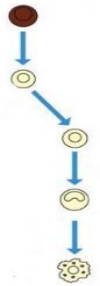
CD11b
CSF1R
CCL2





cEBPβ
PI3Kγ
miR-142-3p





Lessons and Take Home Messages

- Targeting myeloid cells is likely not going to be effective as single therapy but can enhance cancer immunotherapy.
- Single or combinatorial approaches depleting macrophages for prolonged times might have secondary effects on tissues homeostasis.
- Treatments that acts on cell plasticity might offer some advantages over simple depletion.
- Intra-tumoral activation can promote a sustained T cell response.
- Further (single cell) characterization of tumor-infiltrating myeloid cells might provide better molecular targets for intervention.