Altered myelopoiesis in cancer

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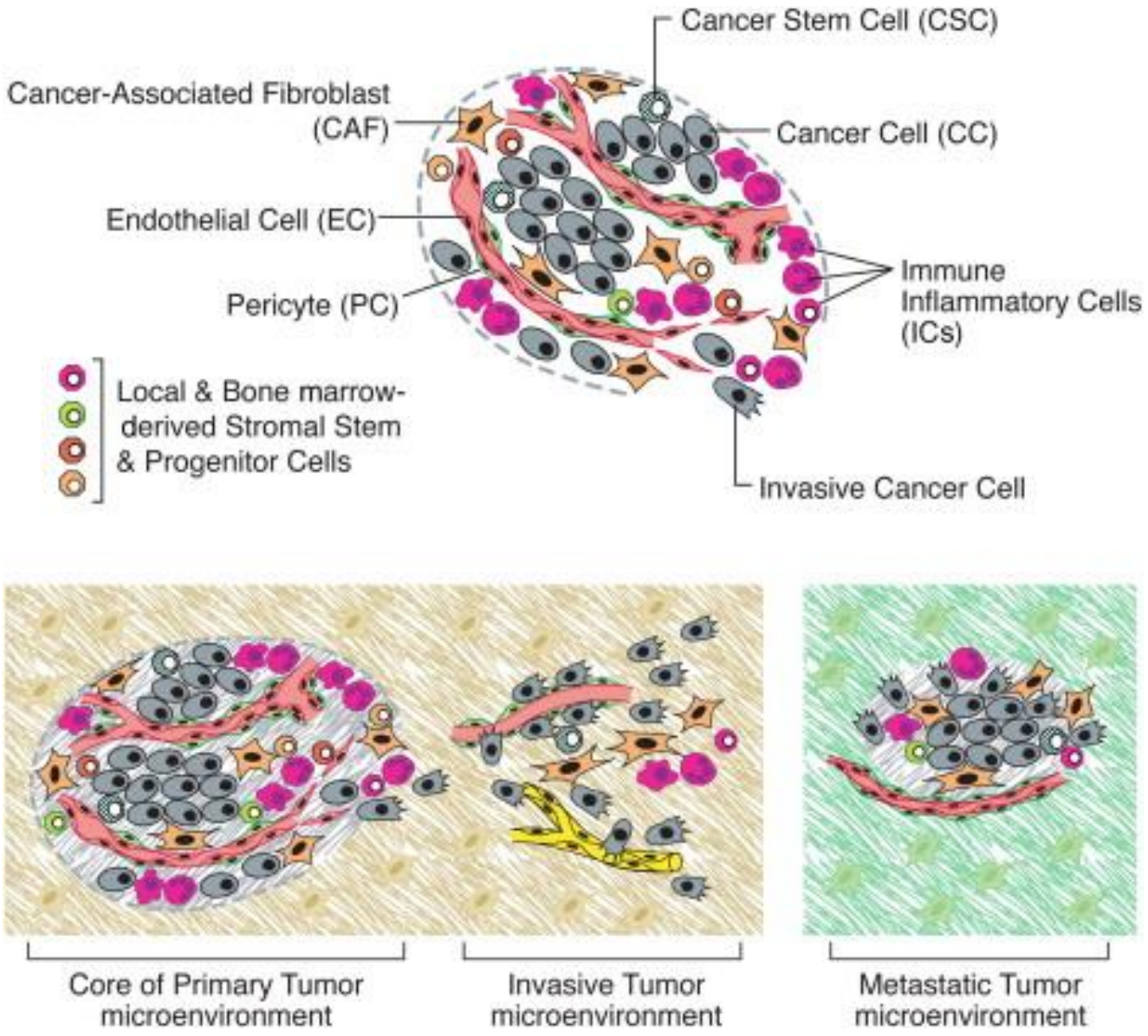
Disclosure

- **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
- **Codiak BioSciences**, scientific advisory board

Cancer stroma comprises different immune cells



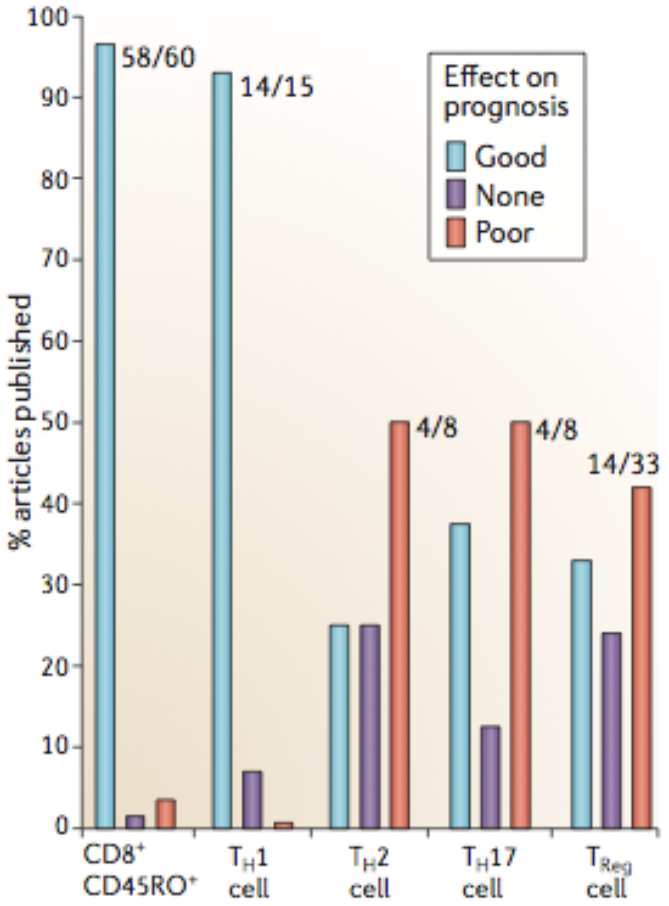
D. Hanahan , R. A. Weinberg, Cell, 2011

Meta-analysis of 124 published articles studying the impact of cytotoxic T cells, memory T cells, and T-helper subpopulations with regards to prognosis of patients with cancer

20 cancer types analyzed

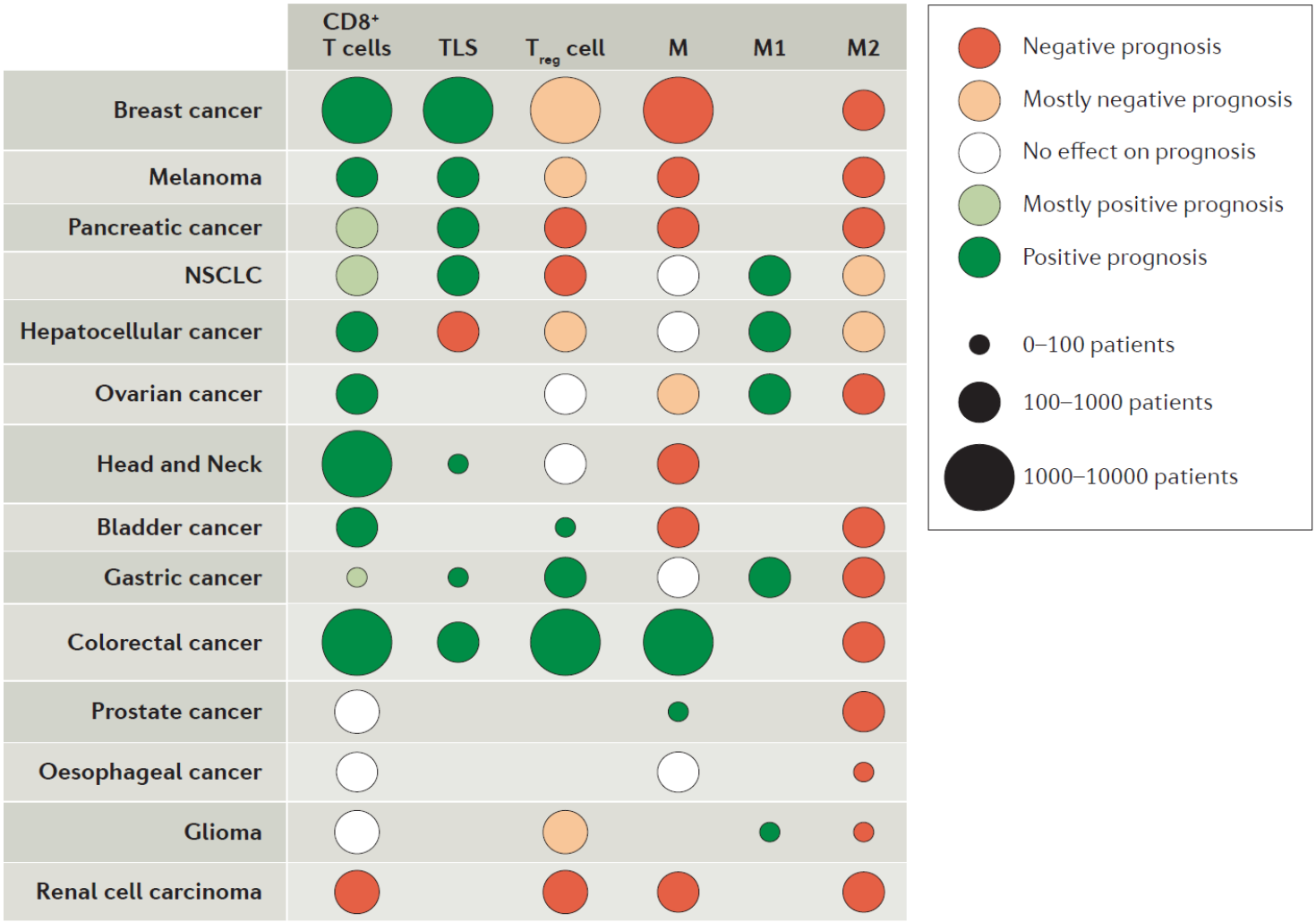
Table 1 | **The association of immune cell infiltrates with prognosis**

Cells	$CD8^+CD45RO^+$ T cells	T_H1 cells
Melanoma	Good[103–106]	
Head and neck cancers	Good[80,109,110]	
Breast cancer	Good[111–114]	• Good[115,116] • None[117]
Bladder cancer	Good[118,119]	
Ovarian cancer	Good[120–122]	Good[123,124]
Oesophageal cancer	Good[126,127]	Good[128]
Colorectal cancer	Good[6,26,35,36,63,79,130–148]	Good[5,16,70]
Renal cell carcinoma	• Good[75] • Poor[75]	Good[71]
Prostatic adenocarcinoma	Good[151–153]	
Lung carcinoma	• Good[13,154–157] • None[158]	Good[13]
Pancreatic cancer	Good[163]	
Cervical cancer		Good[166]
Anal squamous cell carcinoma		
Brain cancer		
Hepatocellular carcinoma	• Good[167,168] • Poor[77]	Good[169]
Gastric cancer		Good[171]
Medulloblastoma		Good[173]
Merkel cell carcinoma	Good[174]	
Urothelial cell carcinoma	Good[175]	
Follicular lymphoma and Hodgkin's lymphoma		



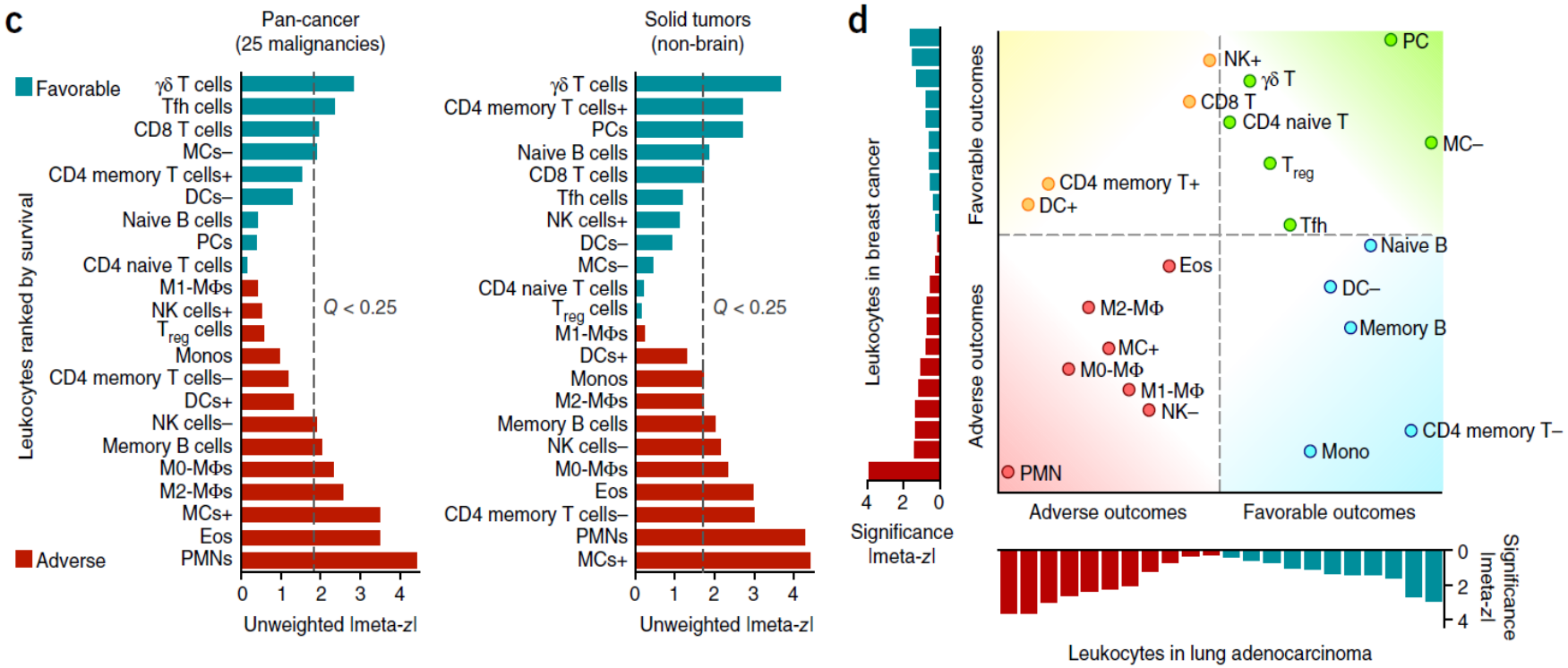
W. H. Fridman et al., Nat. Rev. Cancer, 2012
Courtesy of Jerome Galon

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



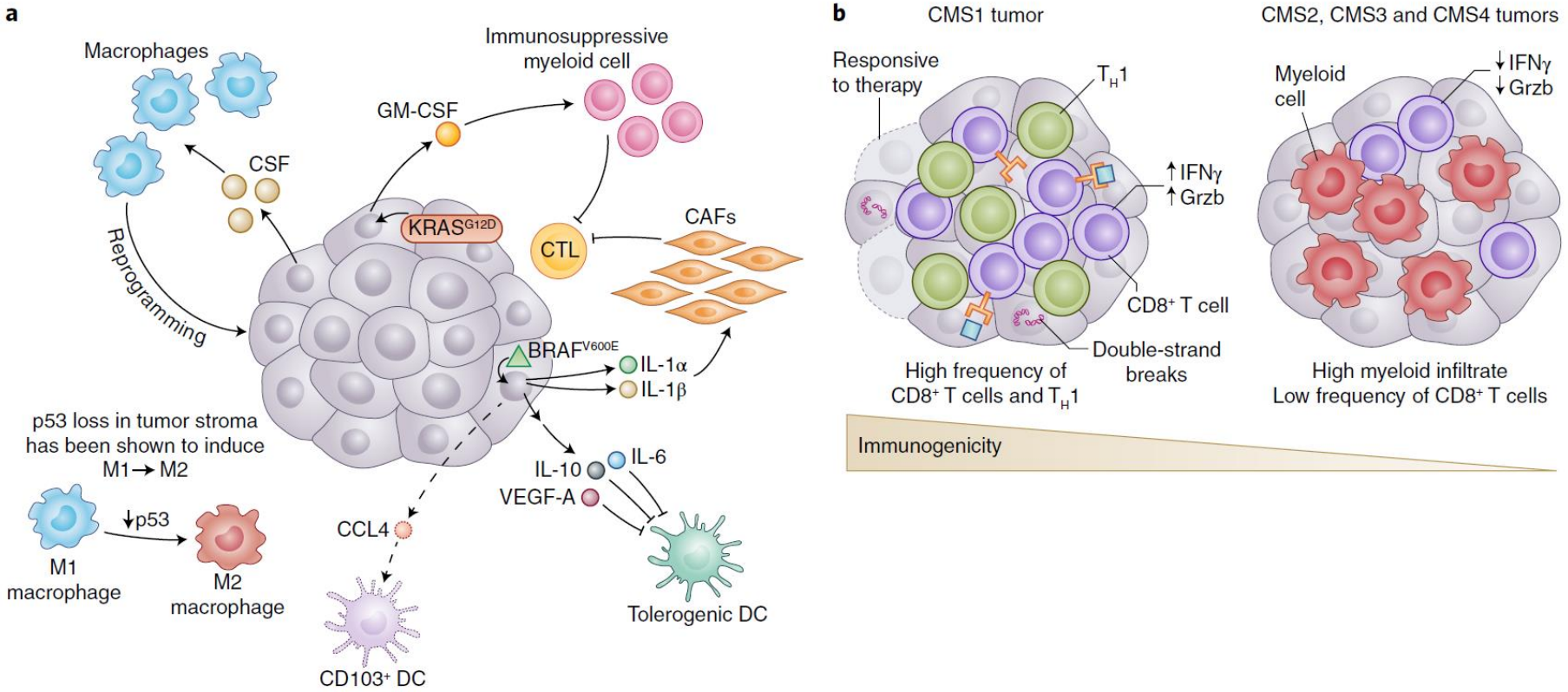
W. H. Fridman et al., Nat. Rev. Clin. Oncol., 2017

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

The oncogene-dependent control of the immune landscape

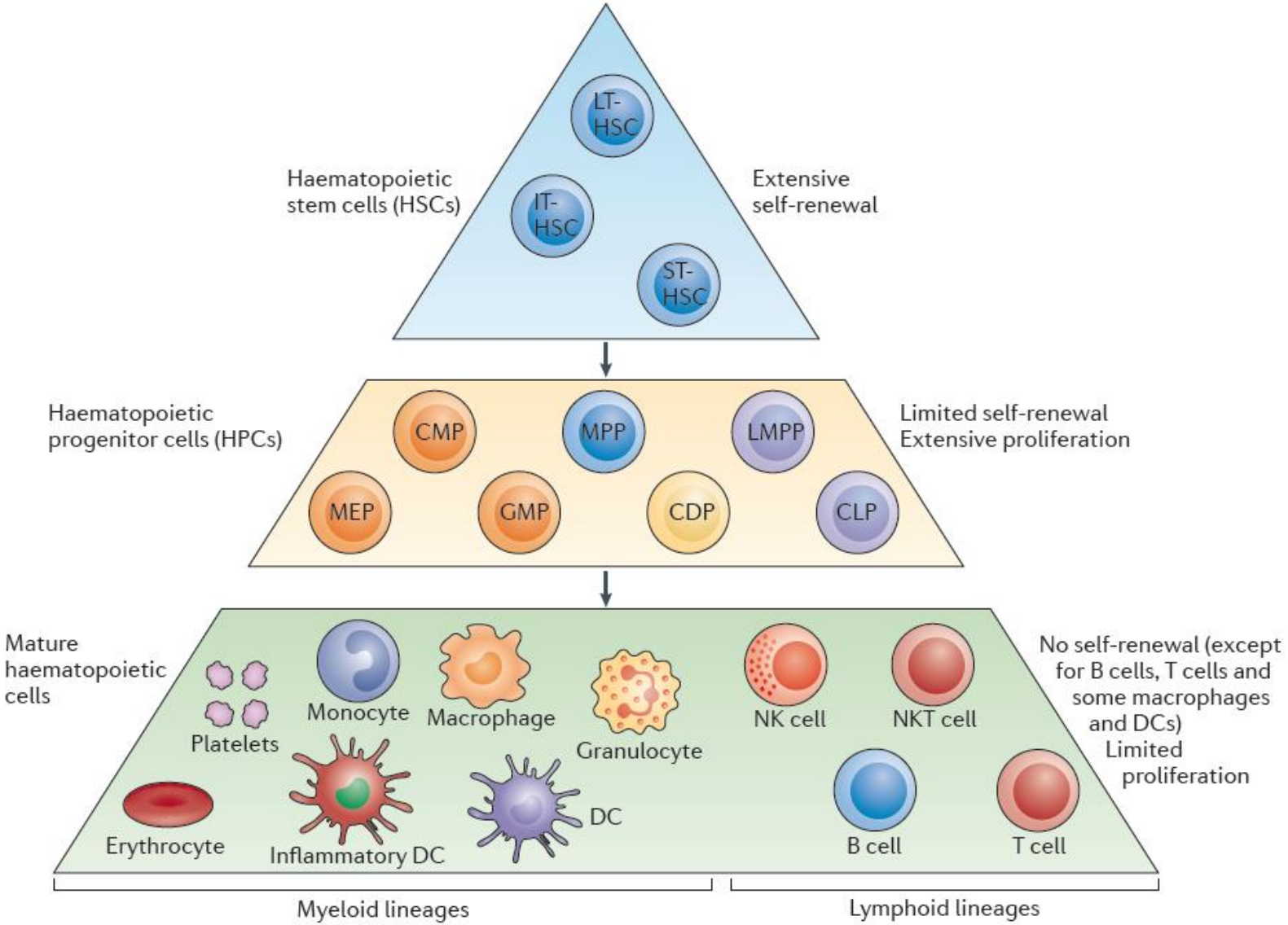


M. Binnewies et al., Nat. Med., 2018

Myeloid cells of innate immunity

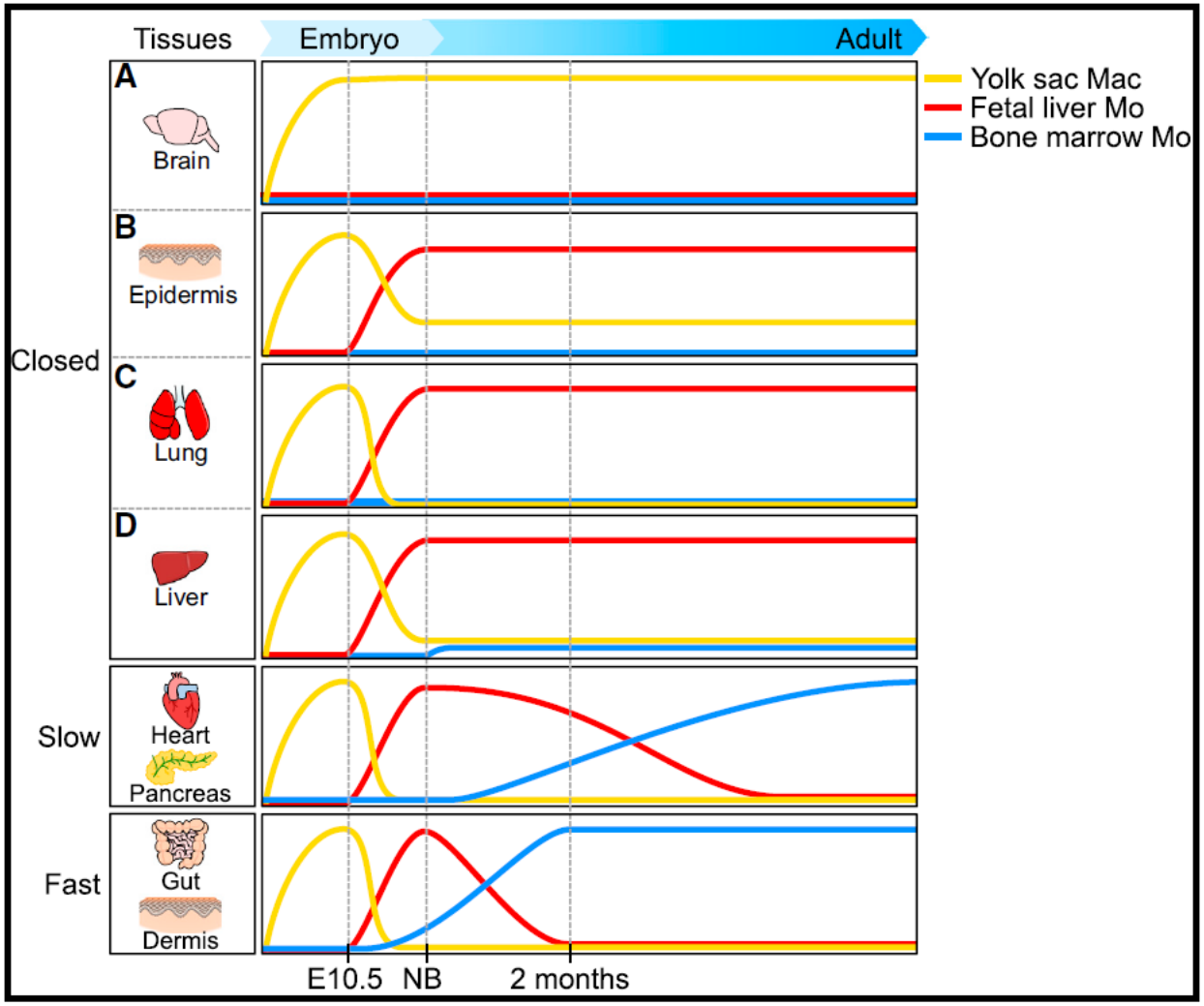
Cell type	*Main function in immune response*
Monocytes/Macrophages	Phagocytosis, inflammation, tissue repair
Neutrophils	Phagocytosis, inflammation, anti-microbial peptide production
Dendritic cells	Activation of naïve T cells
Mast cells	Inflammation, vascular permeability
Eosinophils	Defense against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

Steady-state hematopoyesis



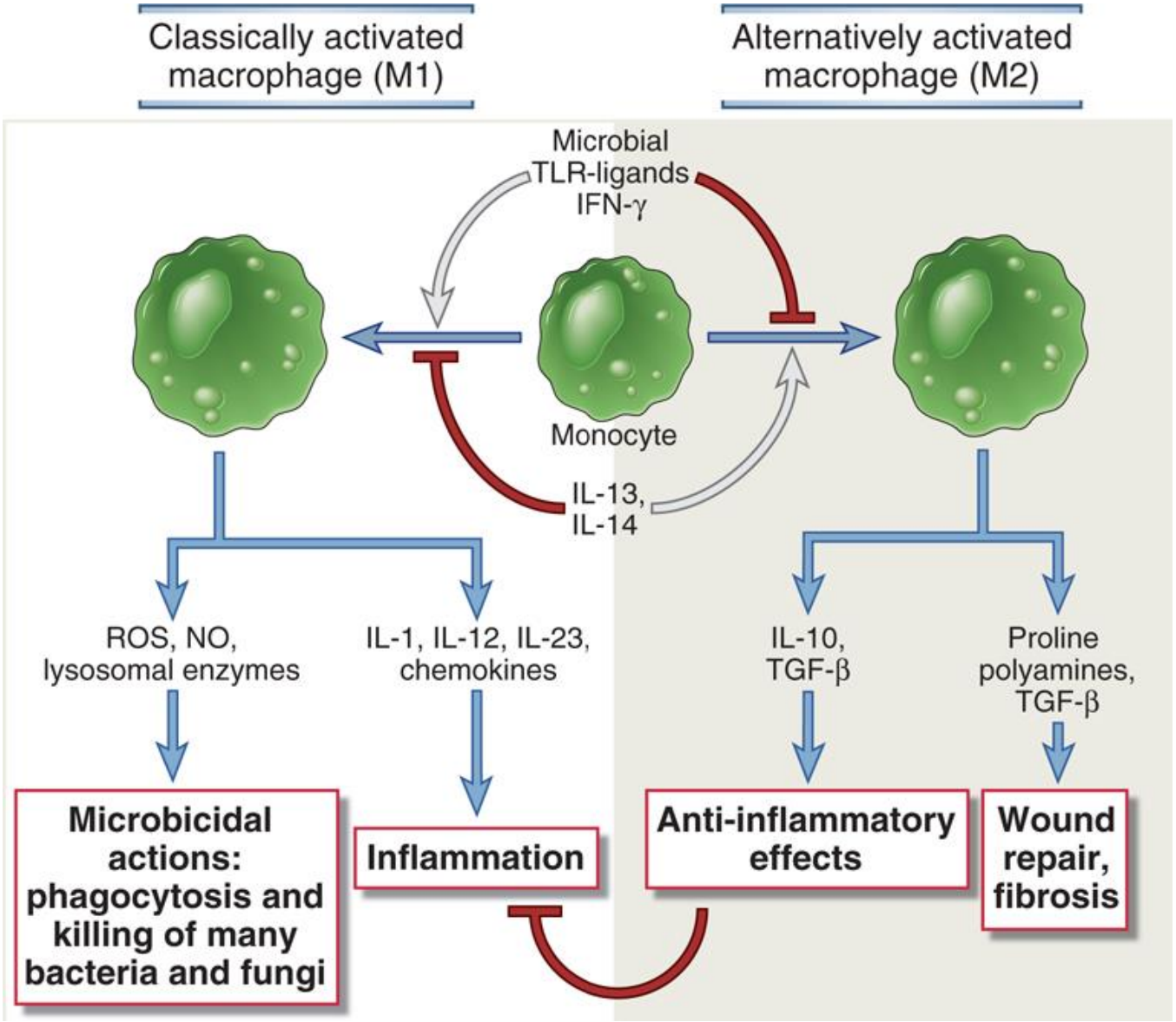
M. G. Manz and S. Boettcher, Nat. Rev. Immunol., 2014

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



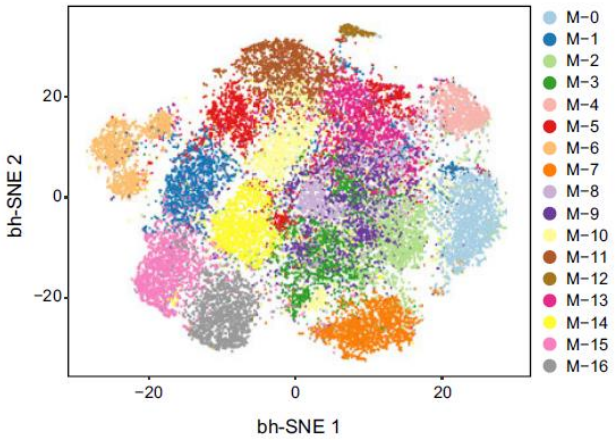
F. Ginhoux and S. Jung, Nat Rev Immunol., 2014
F. Ginhoux and M. Guilliams, Immunity, 2016

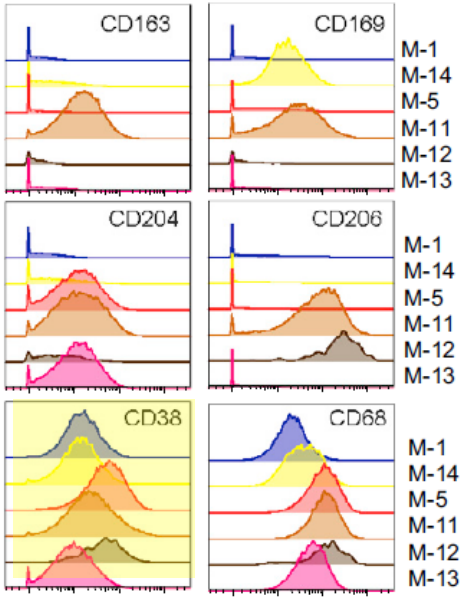
Classic and alternative activation of macrophages

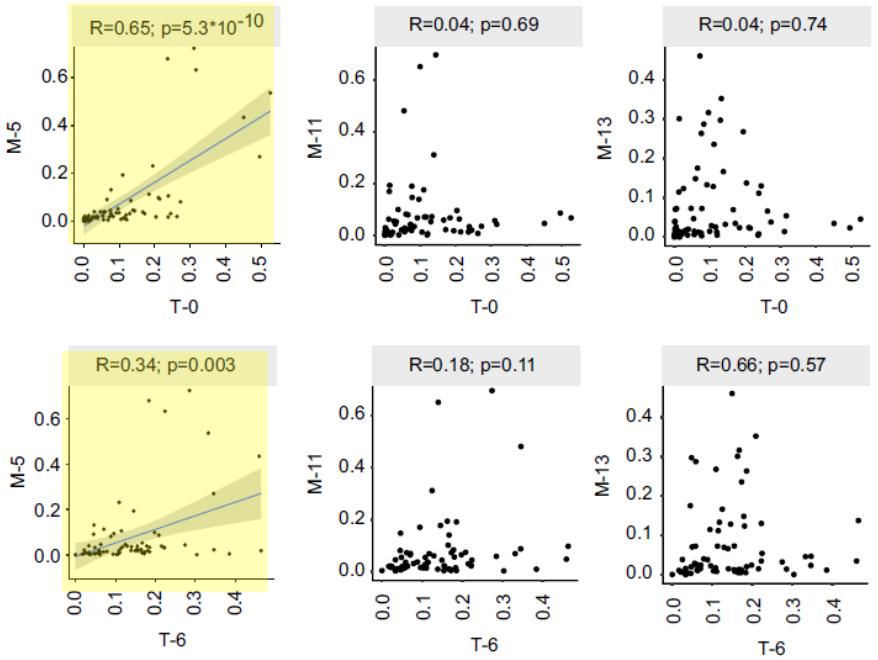


K. Abbas K, A. H. Lichtman. Cellular and Molecular Immunology, 7th Edition

TAM heterogeneity in clear cell renal carcinoma unveiled by mass cytometry



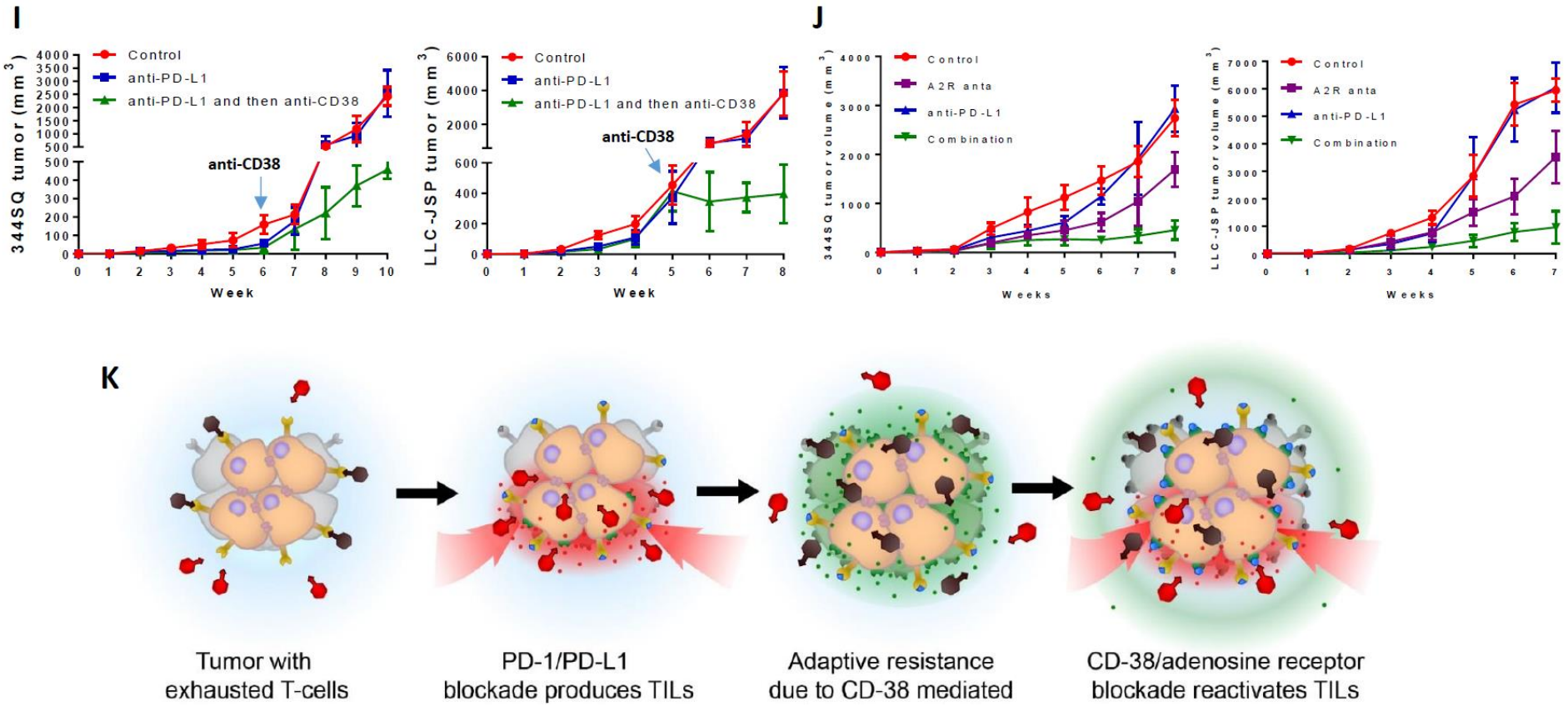




CD38+CD204+CD206 TAMs correlate with immunosuppression (PD-1+ T cells and Treg)

S. Chevrier et al., Cell, 2017

CD38 as mechanism of acquired resistance to PD-1/PD-L1 blockade through the activation of adenosine receptor



L. Chen et al., Cancer Discovery, 2018

Genmab Announces that Janssen Will Stop Studies of Daratumumab in Combination with Anti-PD-(L)1

Company Announcement

- Based on a recent planned review, the Data Monitoring Committee (DMC) recommends Phase Ib/II study of daratumumab plus atezolizumab (anti PD-L1 antibody) in patients with previously treated non-small cell lung cancer to be terminated.
- Phase I MMY2036 study of daratumumab plus JNJ-63723283 (anti PD-1 antibody) in patients with multiple myeloma, discontinued
- Health Authorities have been informed about these events and Janssen has contacted its partner companies conducting daratumumab and anti-PD-(L)1 combination studies to discuss ceasing enrollment and dosing of the combination while the data is being further investigated

Copenhagen, Denmark; May 26, 2018 – Genmab A/S (Nasdaq Copenhagen: GEN) announced

REVIEW

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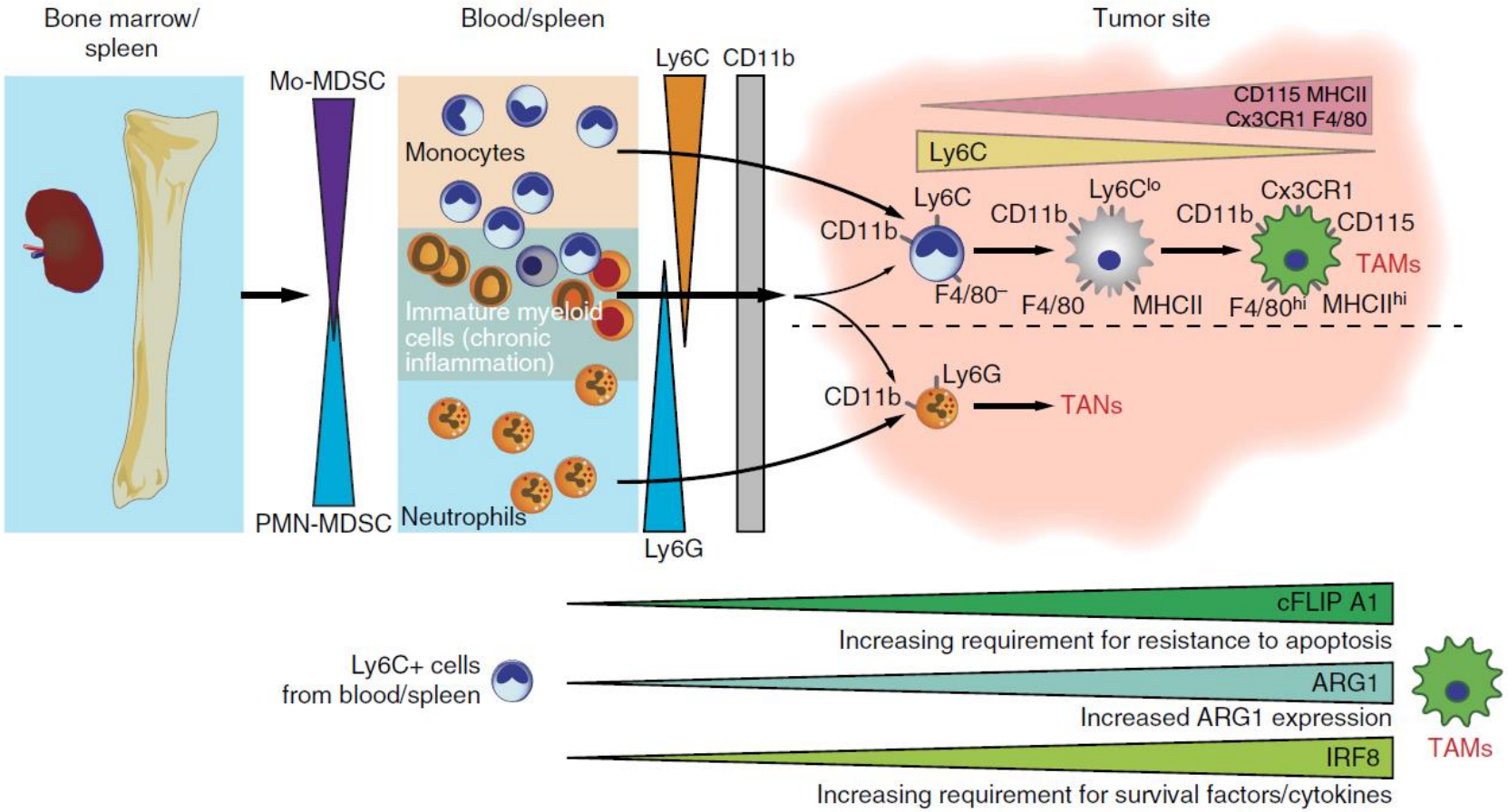
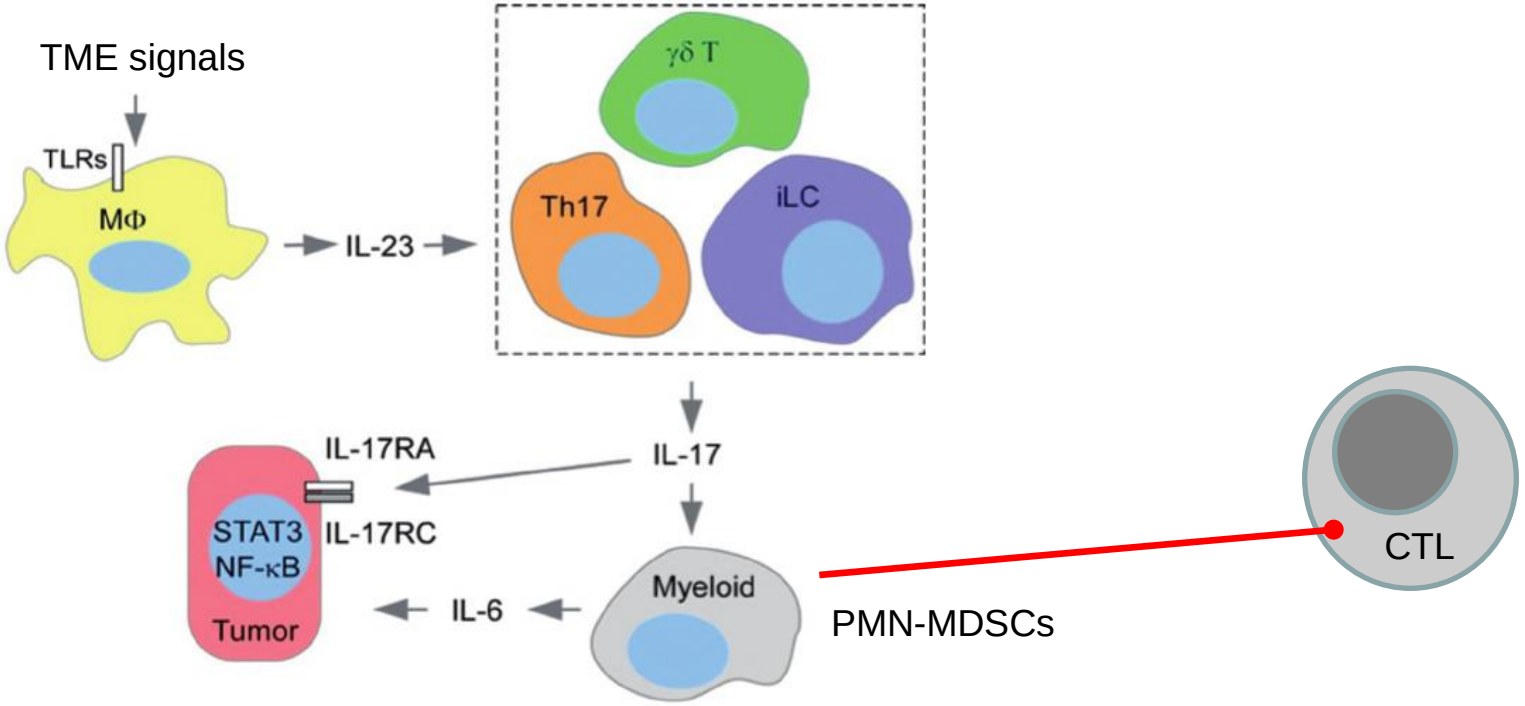
Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards

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,*]



The IL-23/IL-17 axis in inflammation and cancer

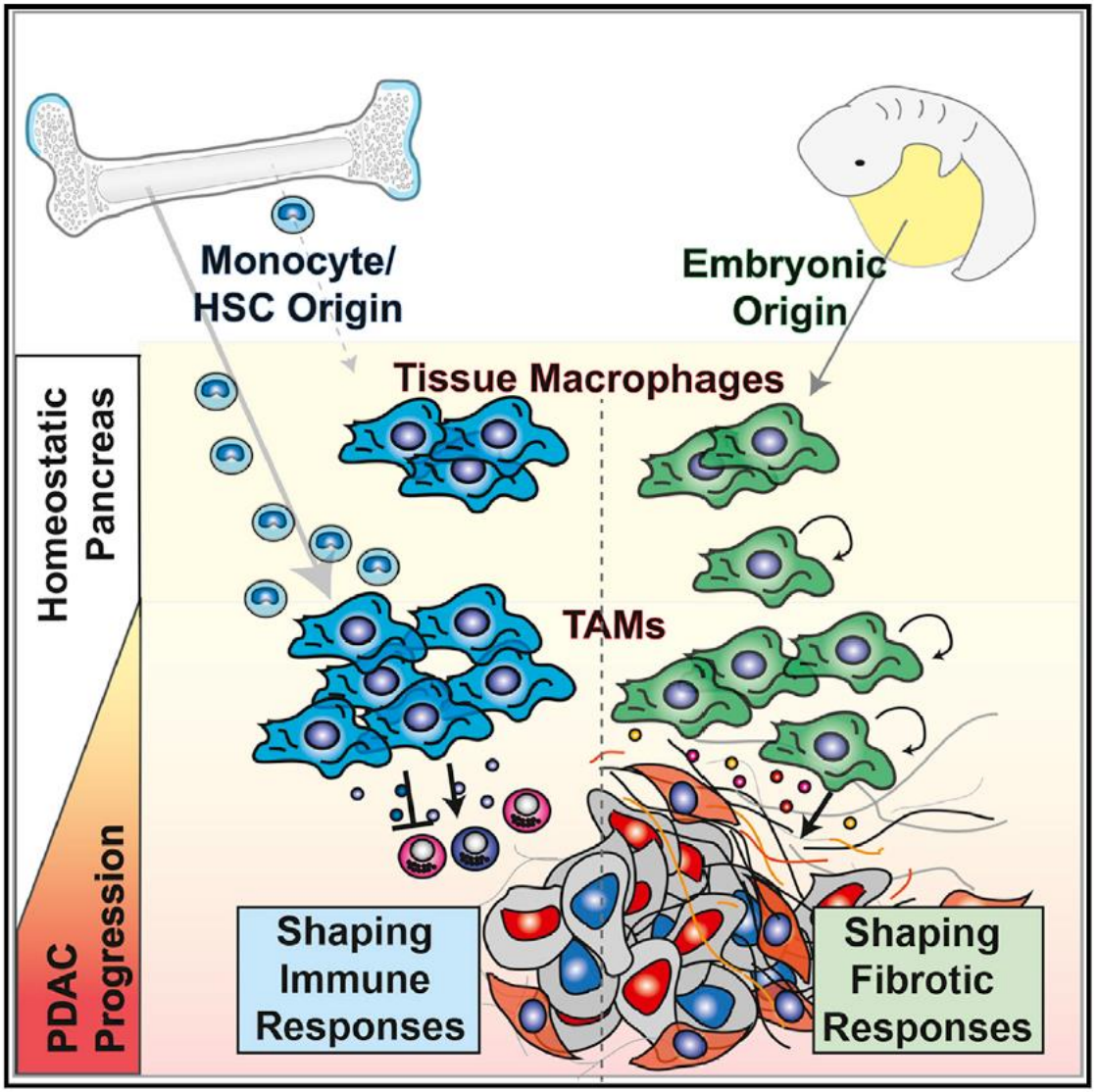


Calcinotto A, et al. IL-23 secreted by myeloid cells drives castration-resistant prostate cancer. Nature. 2018

Kortlever RM, et al. Myc cooperates with Ras by programming inflammation and immune suppression. Cell. 2017

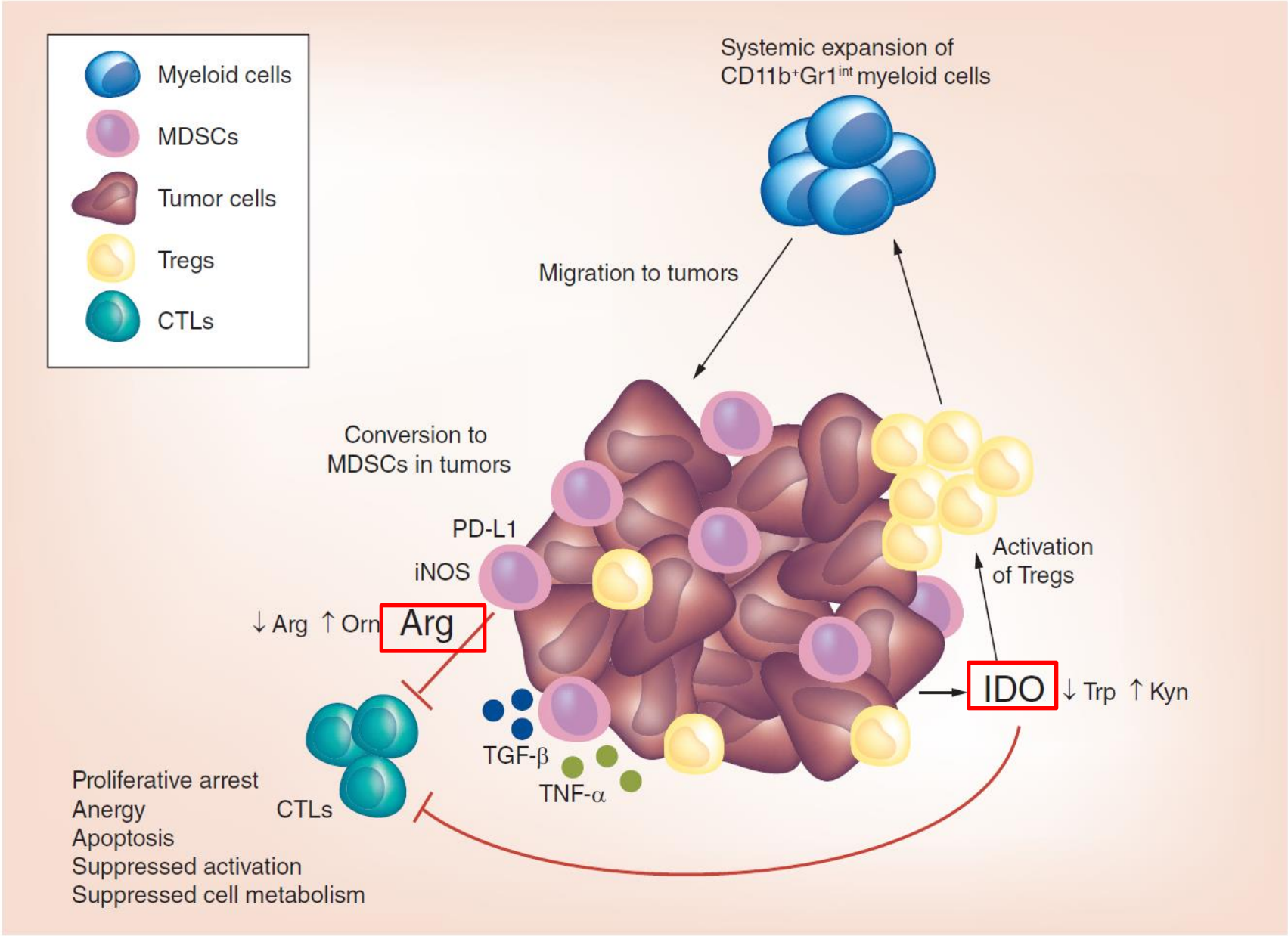
Coffelt SB, et al., IL-17-producing γδ T cells and neutrophils conspire to promote breast cancer metastasis. Nature. 2015

TAMs of different origin in pancreatic cancer



Zhu et al., Immunity, 2017

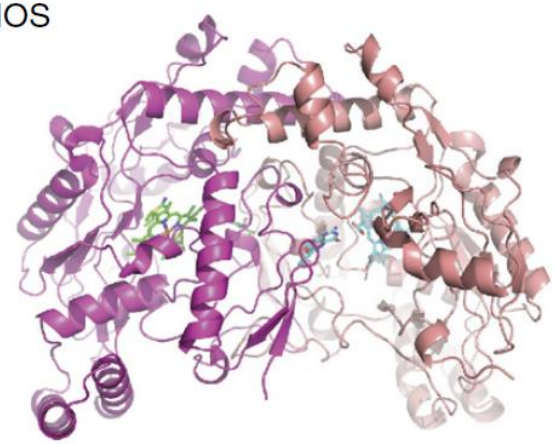
The metabolic control of T cell activation by myeloid cells



E. Timosenko et al., Immunotherapy, 2016

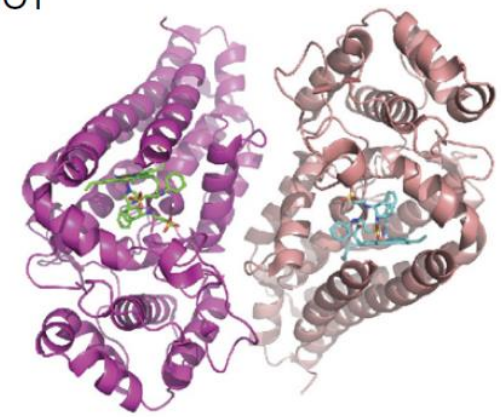
Amino acid metabolizing enzymes with immuno regulatory activity

iNOS



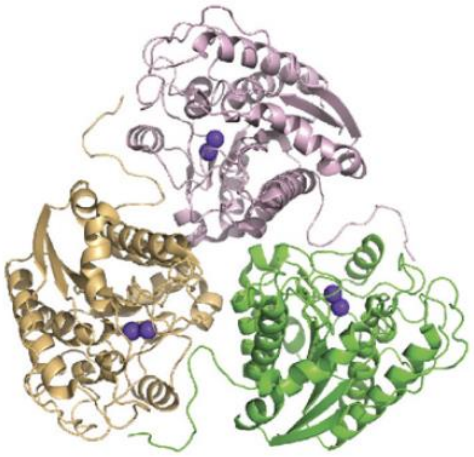
Arginine + 4 O_2 + 3 H^+ + 3 NADPH ⟶
2 citrulline + 4 H_2O + 3 $NADPH^+$ + 2 NO

IDO1



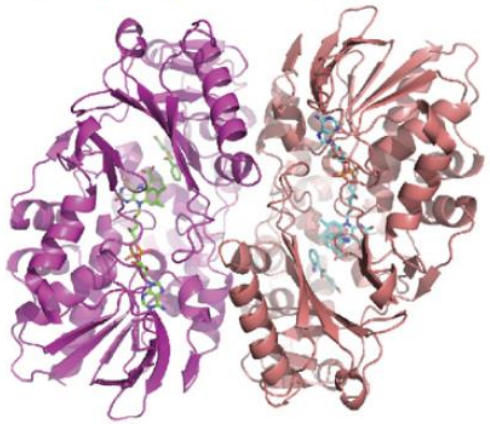
Tryptophan + O_2 ⟶ formylkynurenine

Arg1



Arginine + H_2O ⟶ ornithine + urea

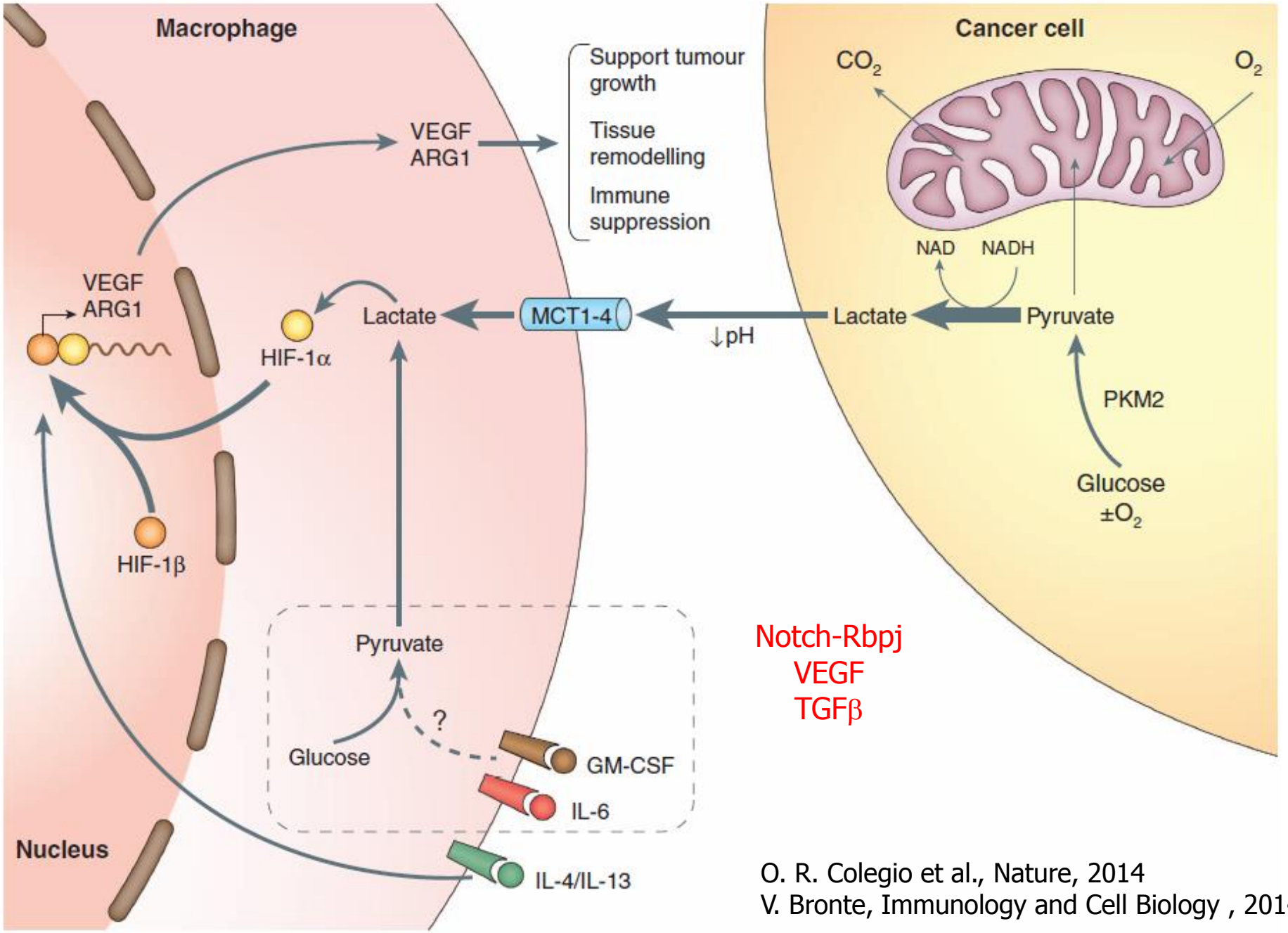
IL4i1 model
(Malayan pit viper LAAO)



AA + H_2O + O_2 ⟶ oxo acid + H_2O_2 + NH_3

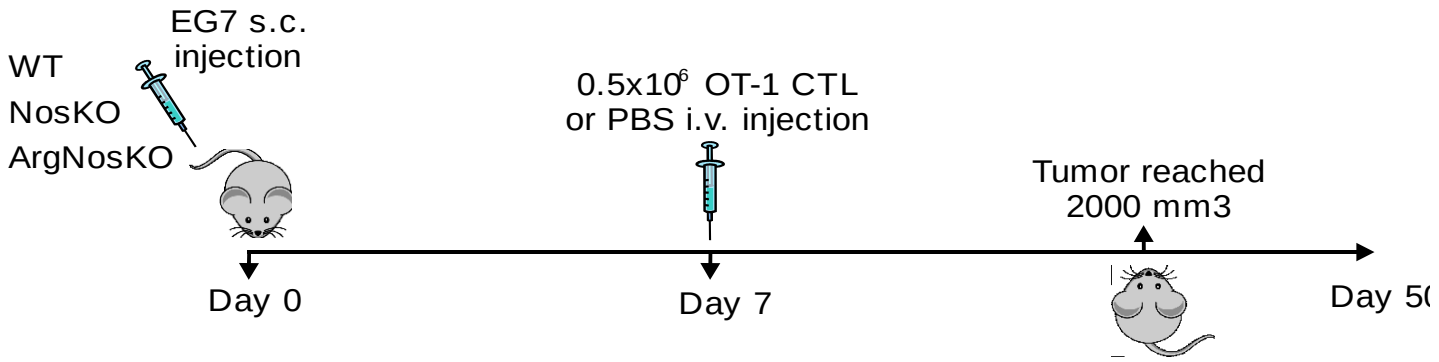
P. J. Murray, Nat. Immunol., 2016

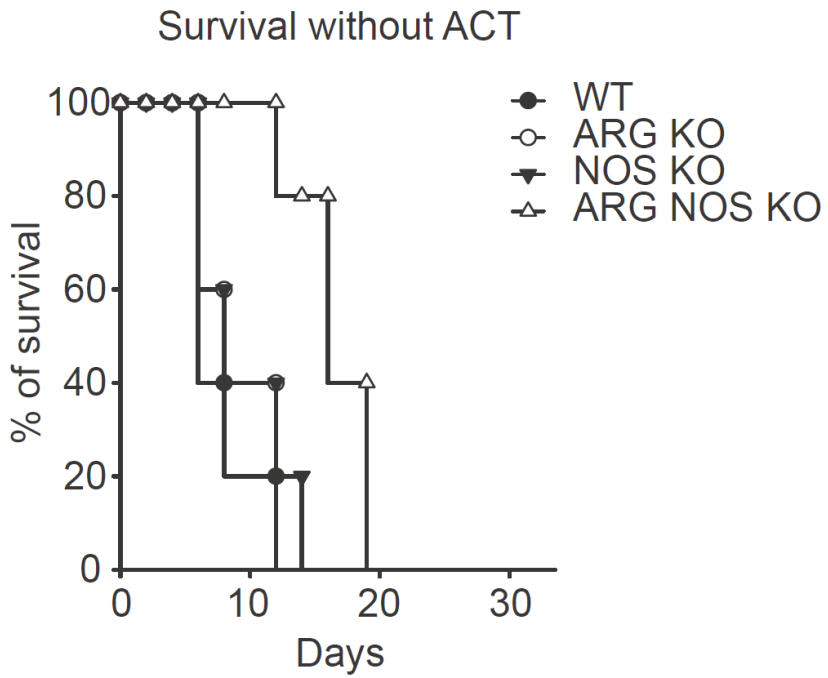
Metabolic and molecular pathways for ARG1 induction

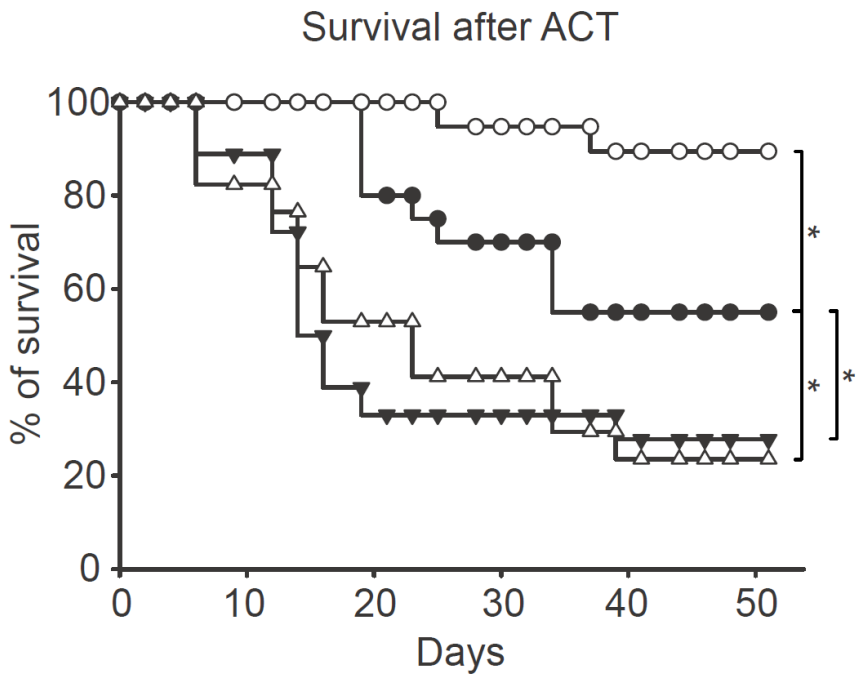


O. R. Colegio et al., Nature, 2014
V. Bronte, Immunology and Cell Biology , 2014

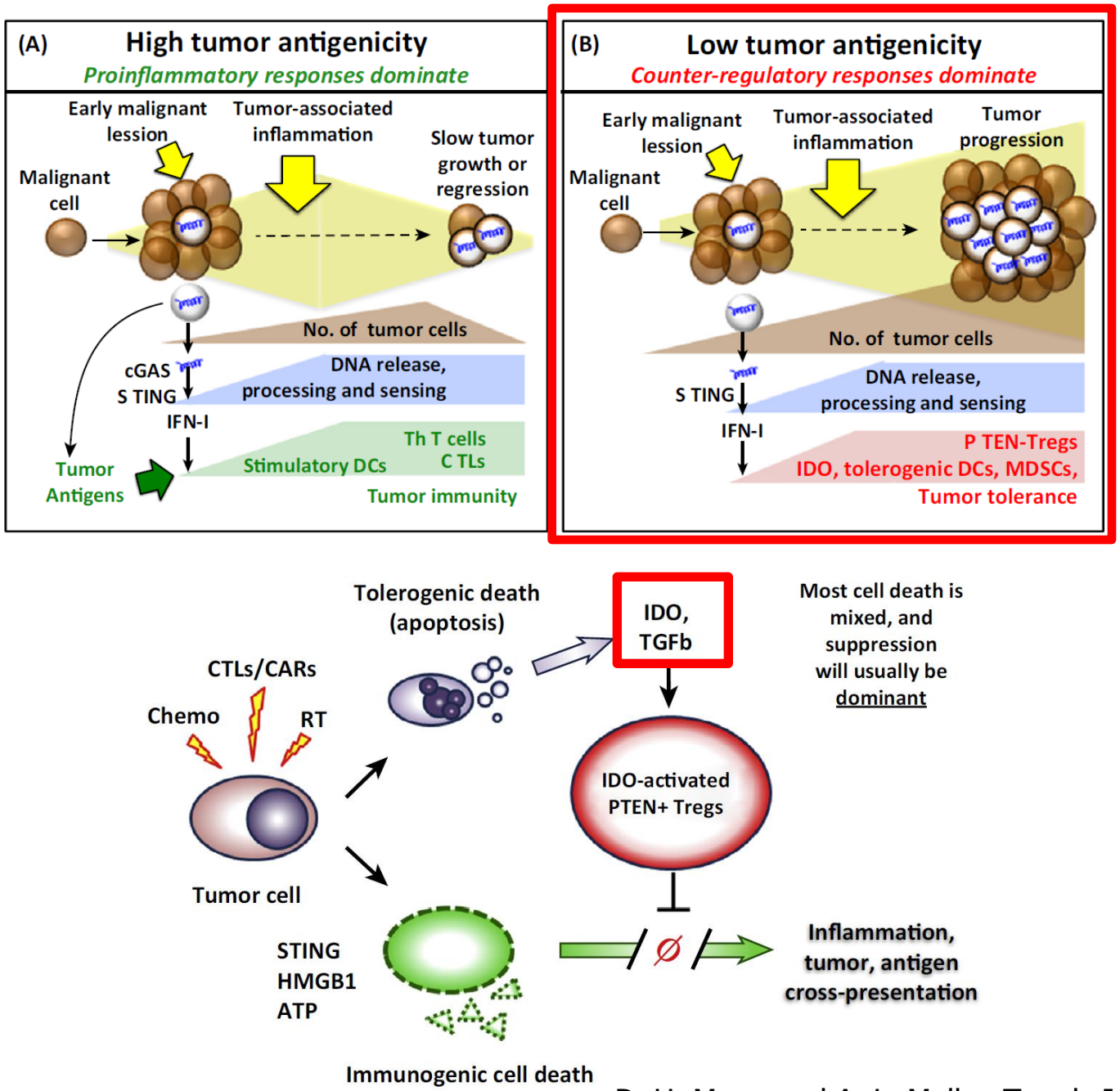
ARG1 genetic ablation favors immunotherapy







I. Marigo et al., Cancer Cell, 2016



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

IN THE PIPELINE

By Derek Lowe

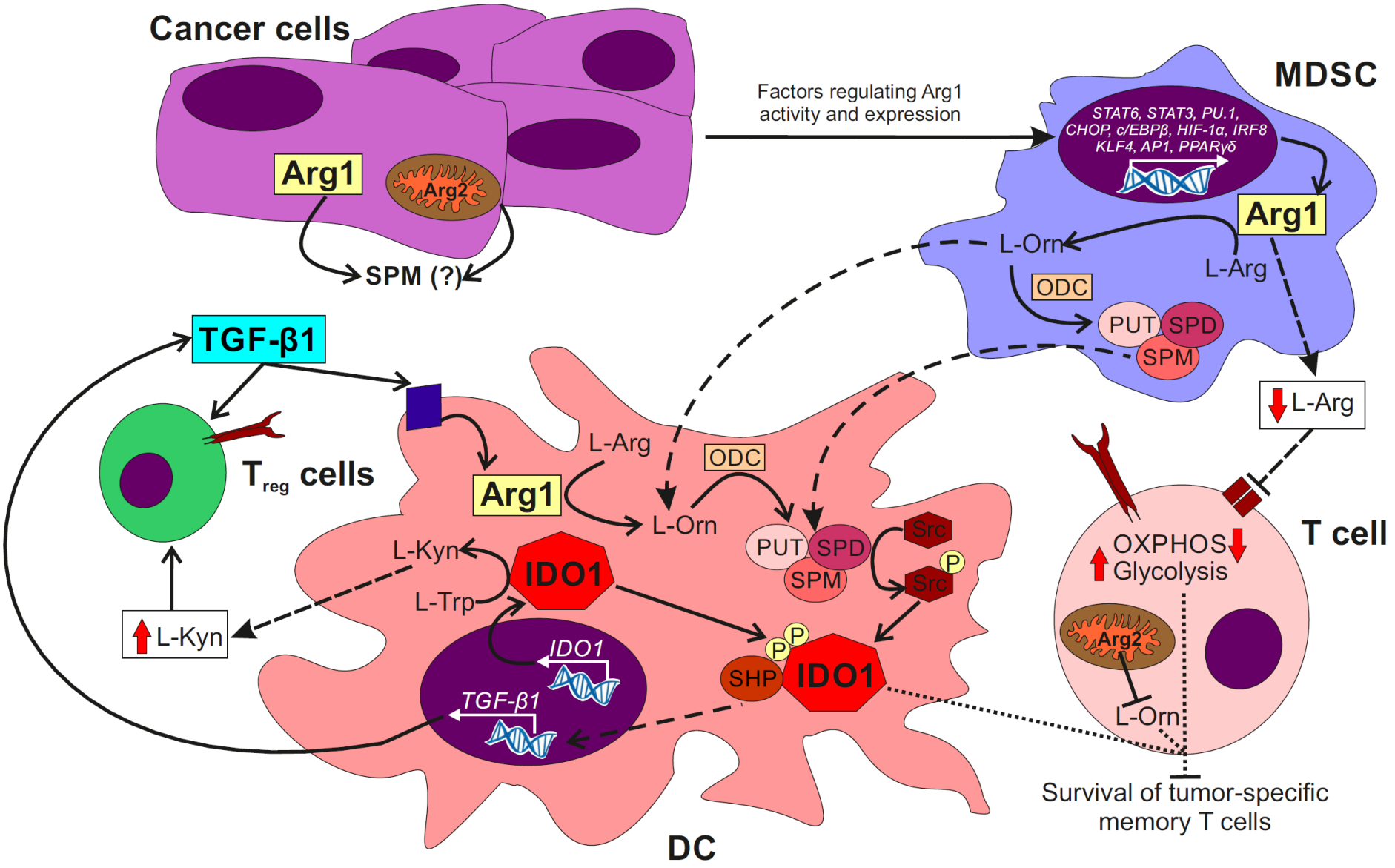
Derek Lowe's commentary on drug discovery and the pharma industry. An editorially independent blog from the publishers of *Science Translational Medicine*. All content is Derek's own, and he does not in any way speak for his employer.

CANCER

IDO Inhibitors Hit a Wall

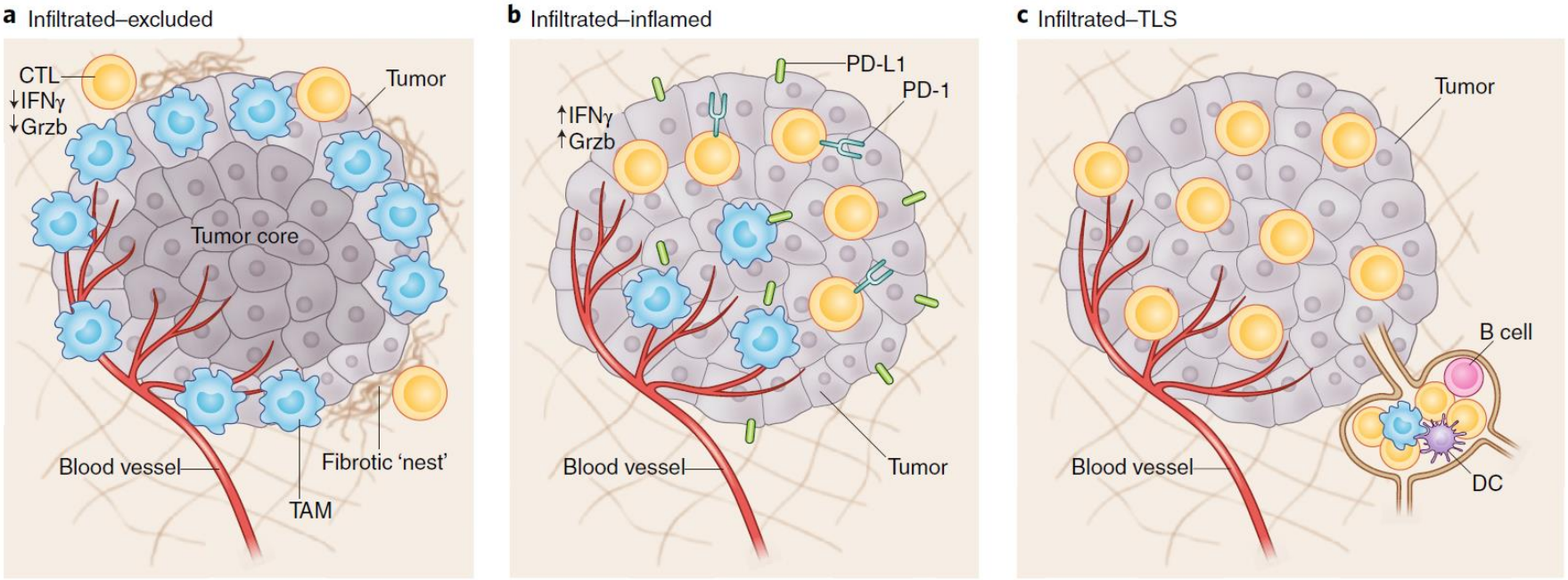
By Derek Lowe | 9 April, 2018

ARG1 and IDO1 cross-talk



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

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



M. Binnewies et al., Nat. Med., 2018

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

- **Cancer cell molecular programs**

β-catenin

- **Enzymes**

IDO1, Arginase 1

- **Chemochines, cytokines and chemoattractants**

CCL2, CCL3, CCL4, CSF-1

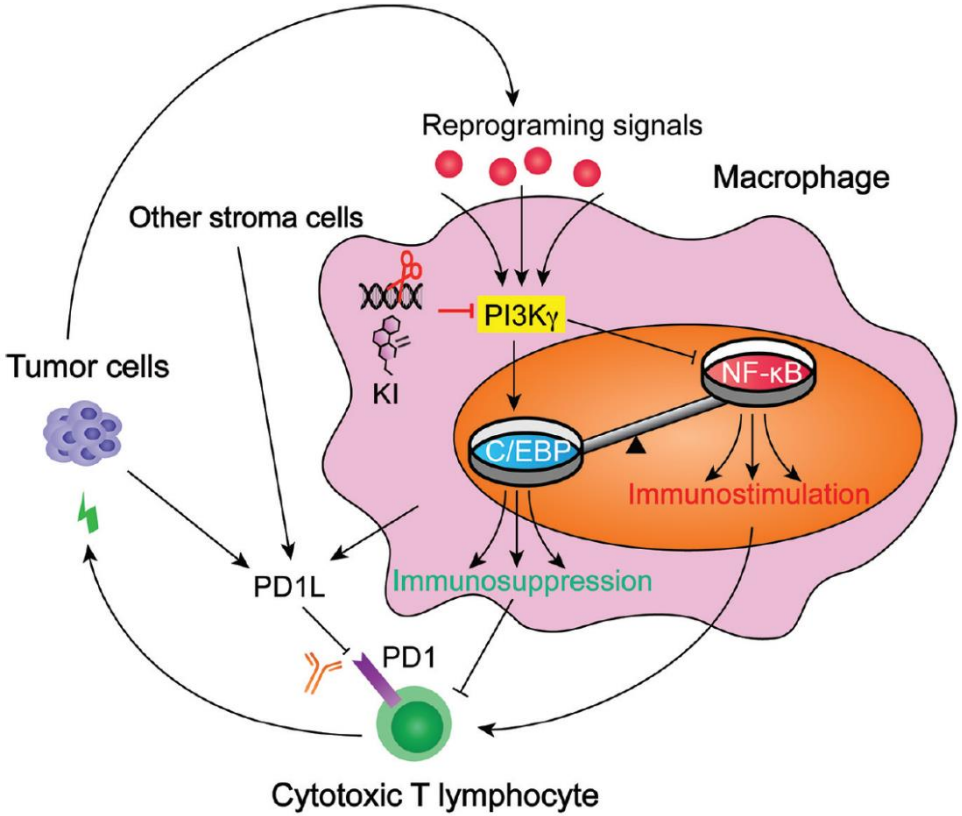
- **Signaling and transcription factors in myeloid infiltrating cells**

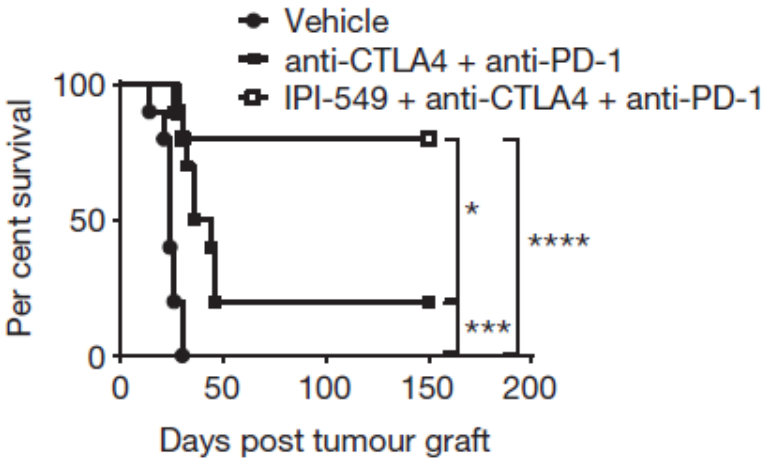
PI3Kγ, c/EBPβ, miR142-3p

- **Myeloid cell activation and biology**

Anti-CD38, TLR4 agonists, STING agonists, TLR9 agonists

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

Conclusions

- Targeting myeloid cells is likely not going to be effective as single therapy but can enhance cancer immunotherapy.

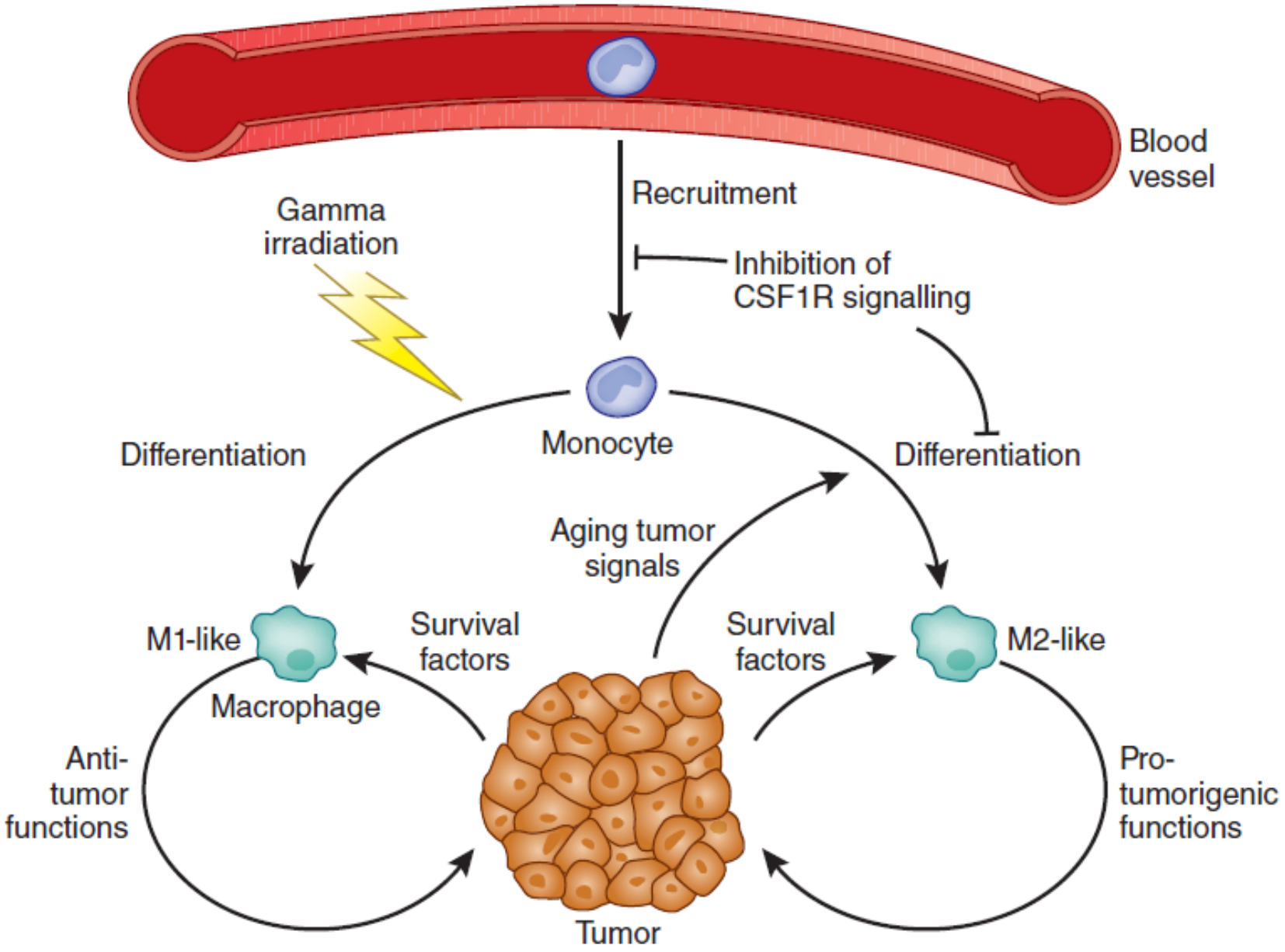
- Single or combinatorial approaches depleting macrophages for prolonged times might have secondary effects on tissues homeostasis.

- Treatments that acts on cell plasticity might offer some advantages over simple depletion.

- Intratumoral activation can promote a sustained T cell response.

- Further characterization of tumor-infiltrating myeloid cells might provide better molecular targets for intervention.

Therapeutic interventions on TAMs to improve cancer therapy



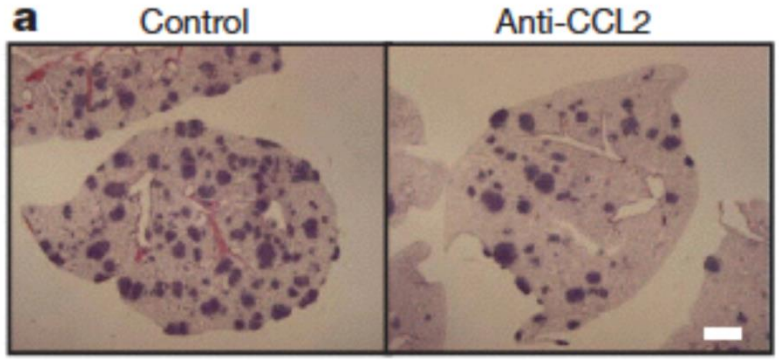
V. Bronte and P. J. Murray. Nat. Med. 2015

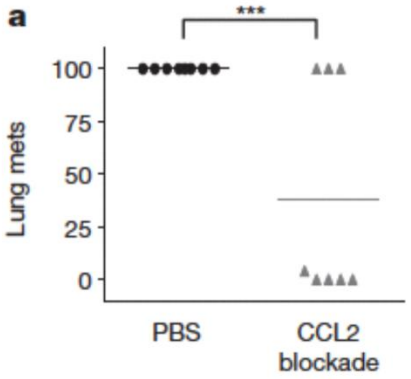
LETTER

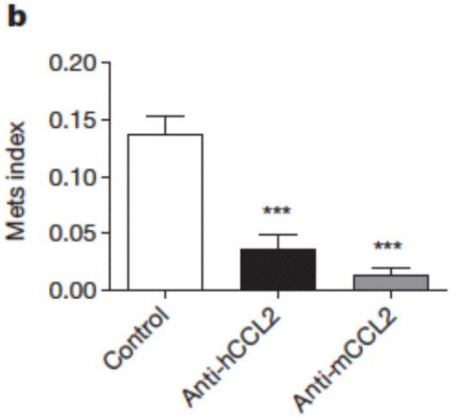
doi:10.1038/nature10138

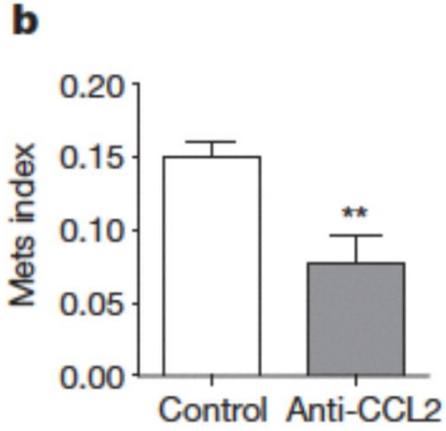
CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis

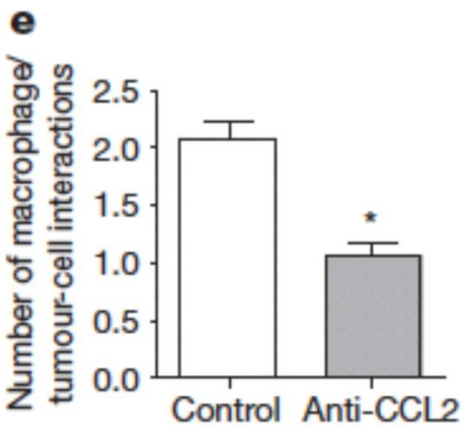
Bin-Zhi Qian[1], Jiufeng Li[1], Hui Zhang[1], Takanori Kitamura[1], Jinghang Zhang[2], Liam R. Campion[3], Elizabeth A. Kaiser[3], Linda A. Snyder[3] & Jeffrey W. Pollard[1]









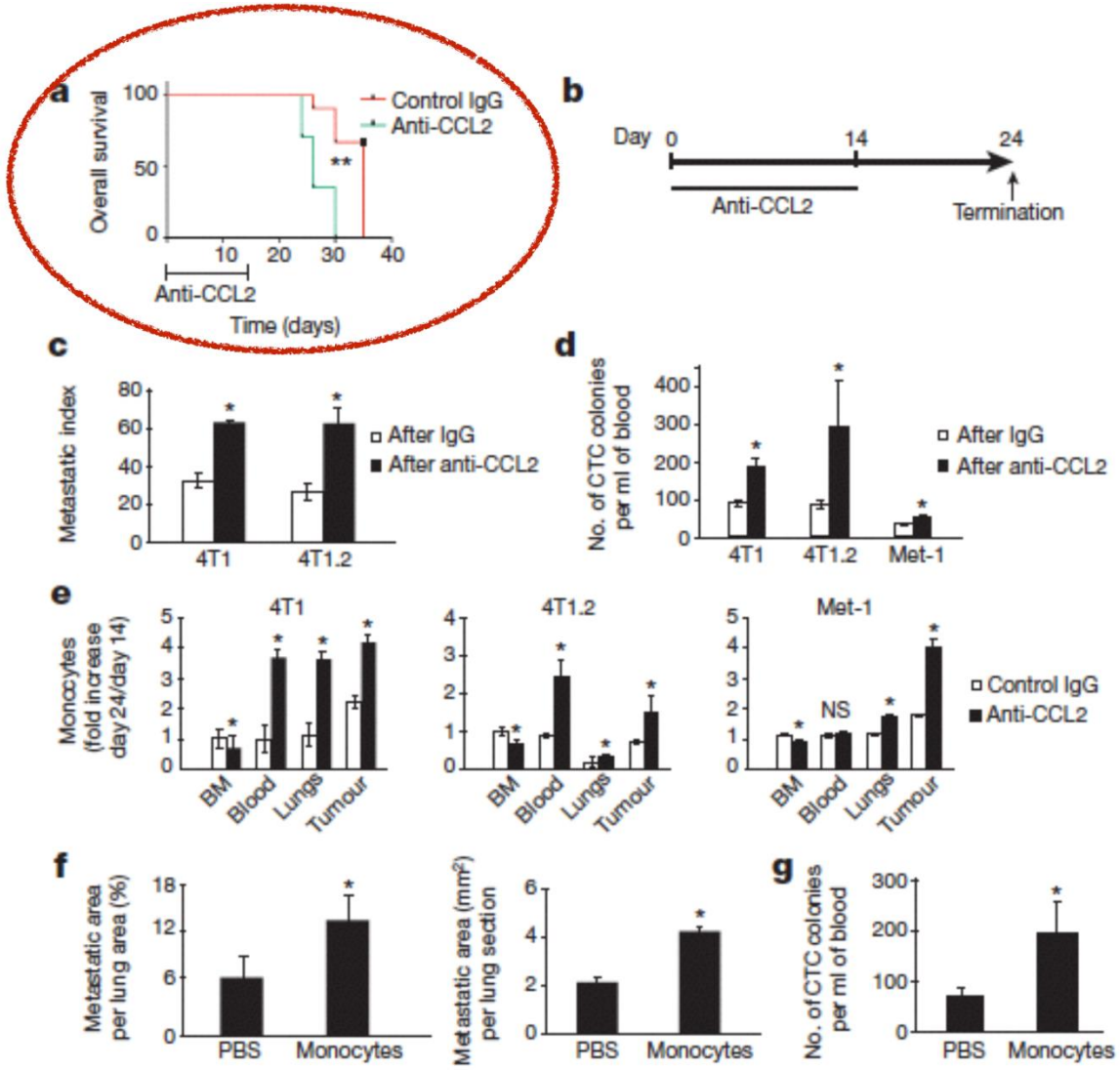


LETTER

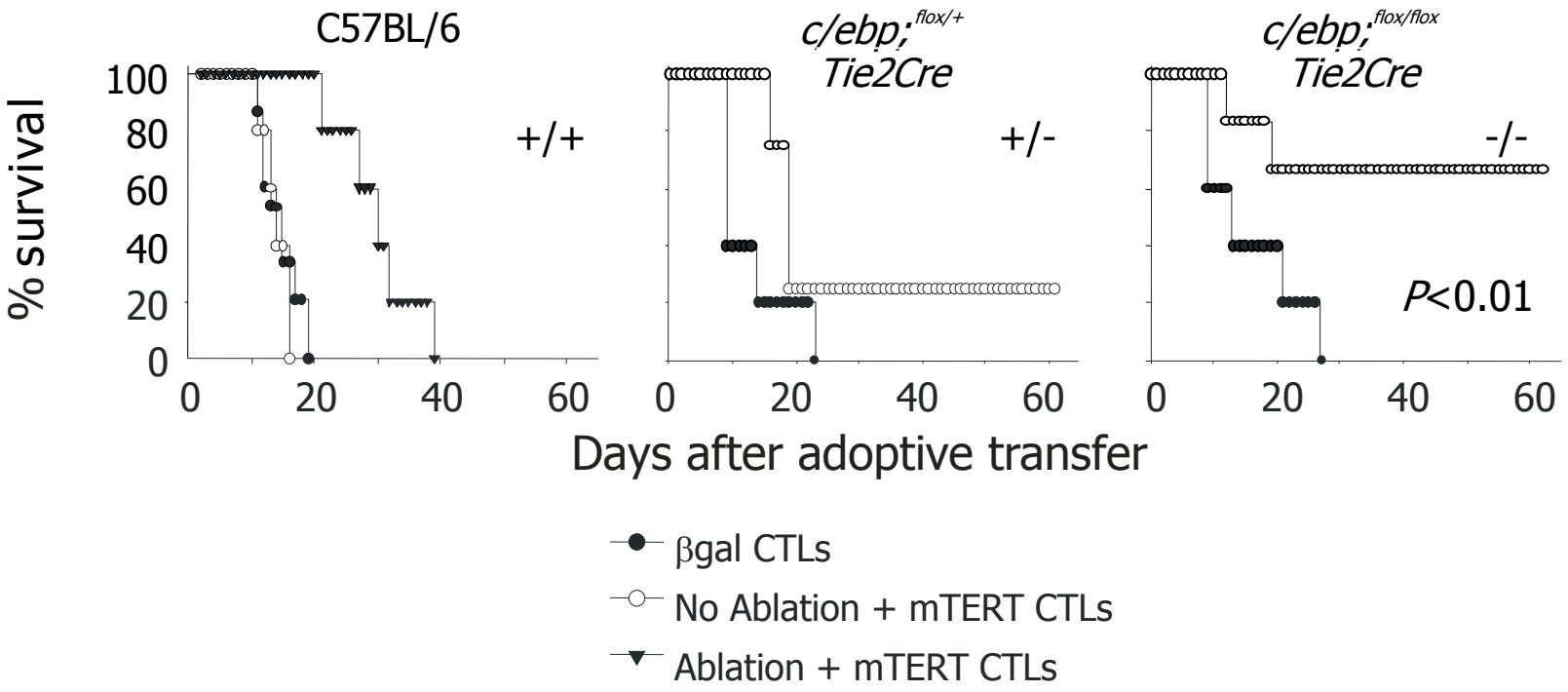
doi:10.1038/nature13862

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]*

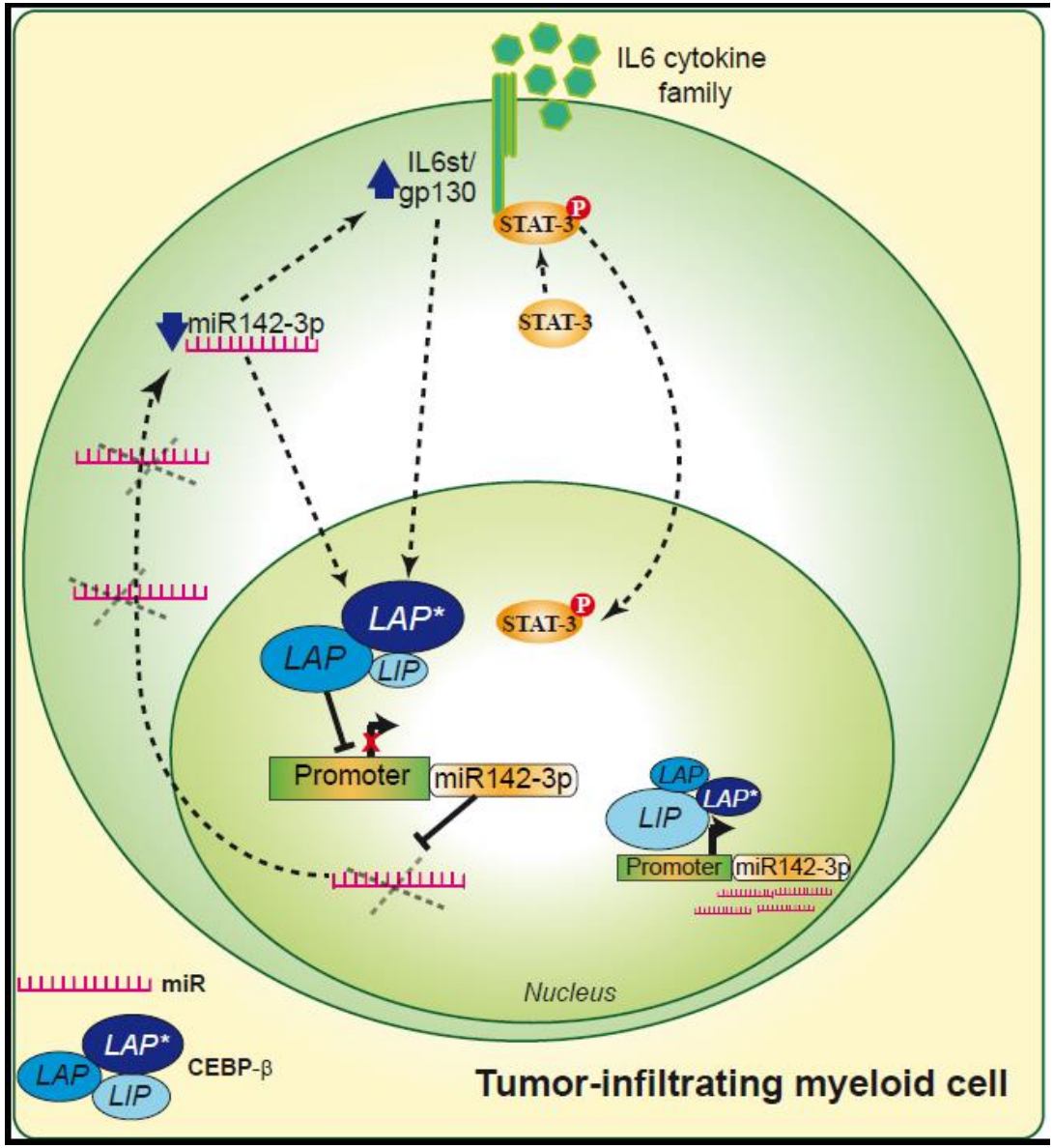


Targeting cEBPβ in myeloid cells



I. Marigo et al., Immunity, 2010

Among miRs down-regulated in tumor-infiltrating myeloid cells, miR-142-3p promotes the macrophage differentiation by controlling cEBPβ



N. Sonda et al., 2013, Immunity

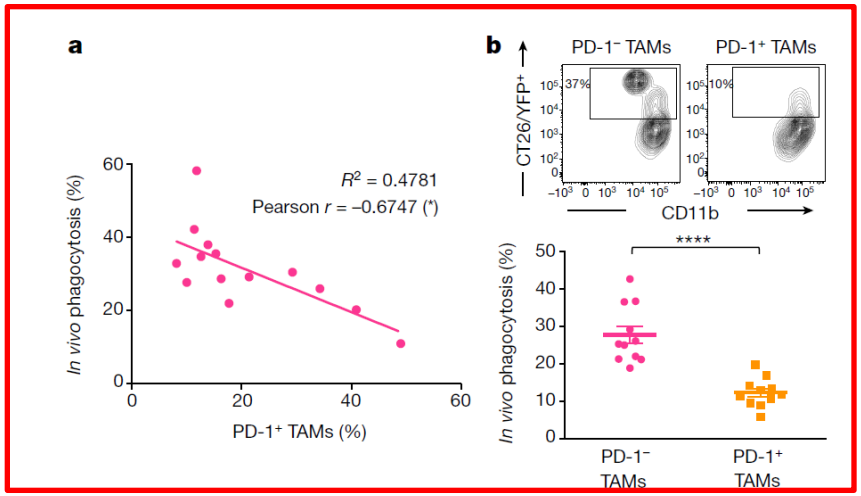
LETTER

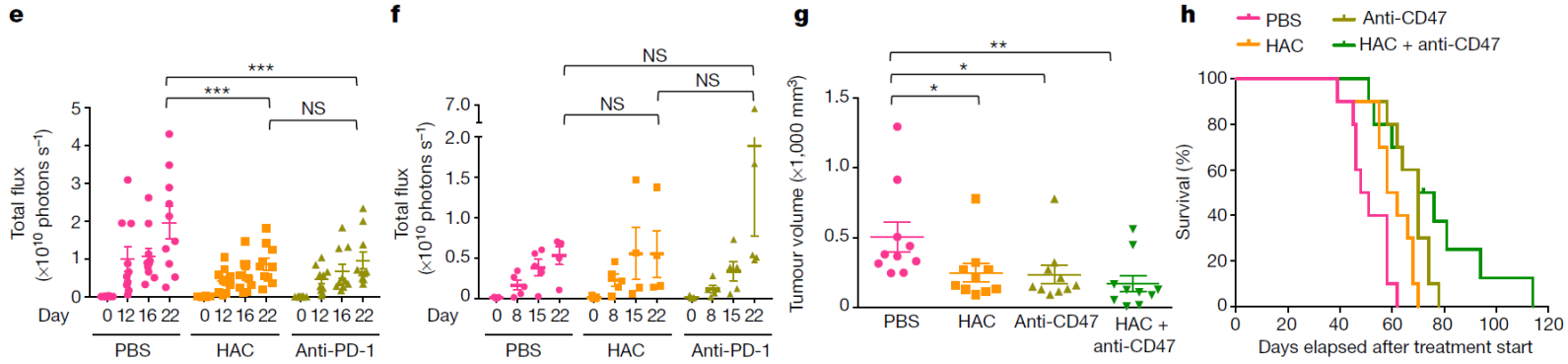
doi:10.1038/nature22396

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

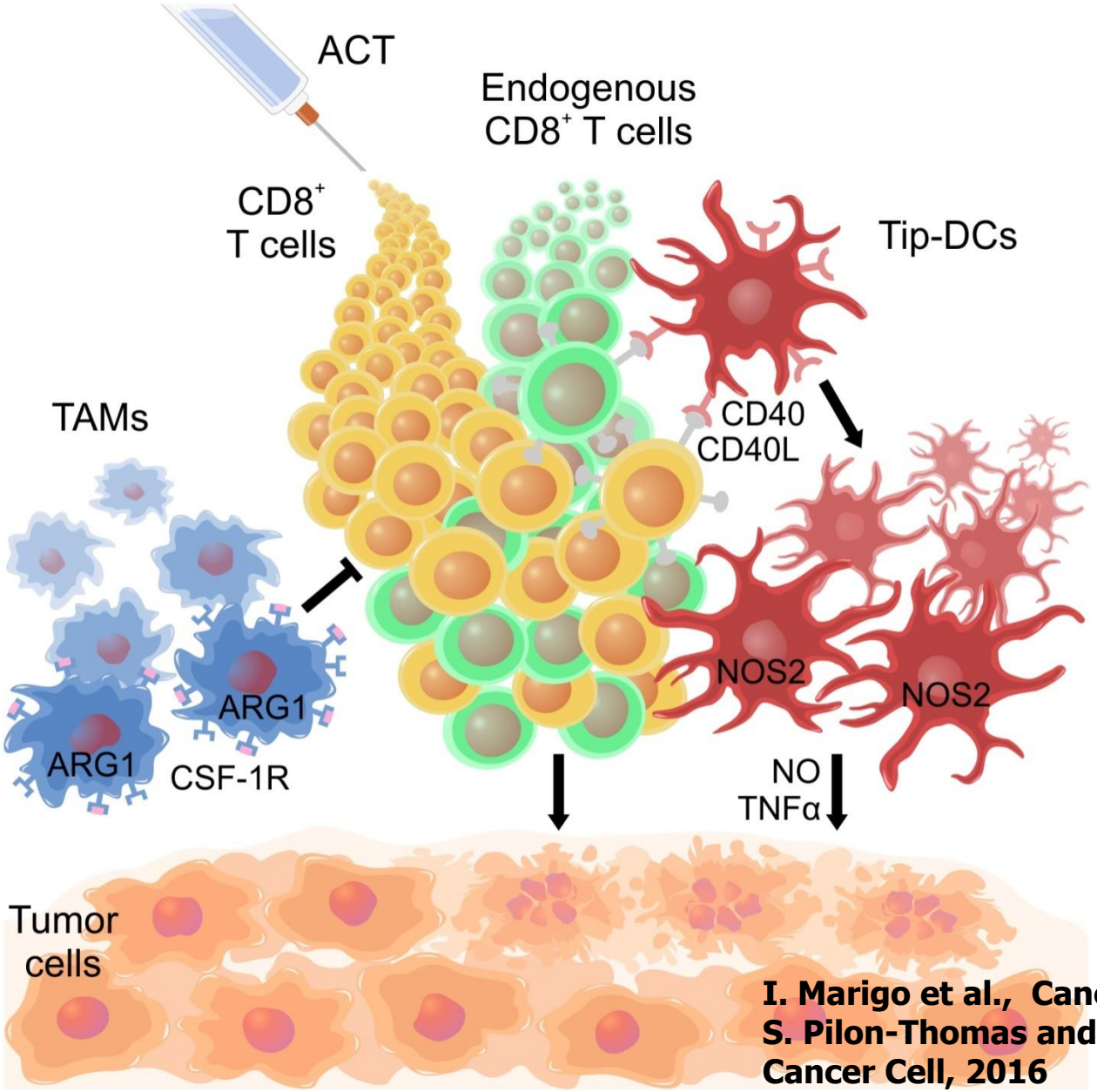
Sydney R. Gordon[1,2,3,4,5], Roy L. Maute[1,3,4,5], Ben W. Dulken[1,6], Gregor Hutter[1,7,8], Benson M. George[1,3,4,5,6], Melissa N. McCracken[1,3,4,5], Rohit Gupta[9], Jonathan M. Tsai[1,3,4,5,6], Rahul Sinha[1,3,4,5], Daniel Corey[1,3,4,5], Aaron M. Ring[10], Andrew J. Connolly[5] & Irving L. Weissman[1,3,4,5]

RESEARCH LETTER



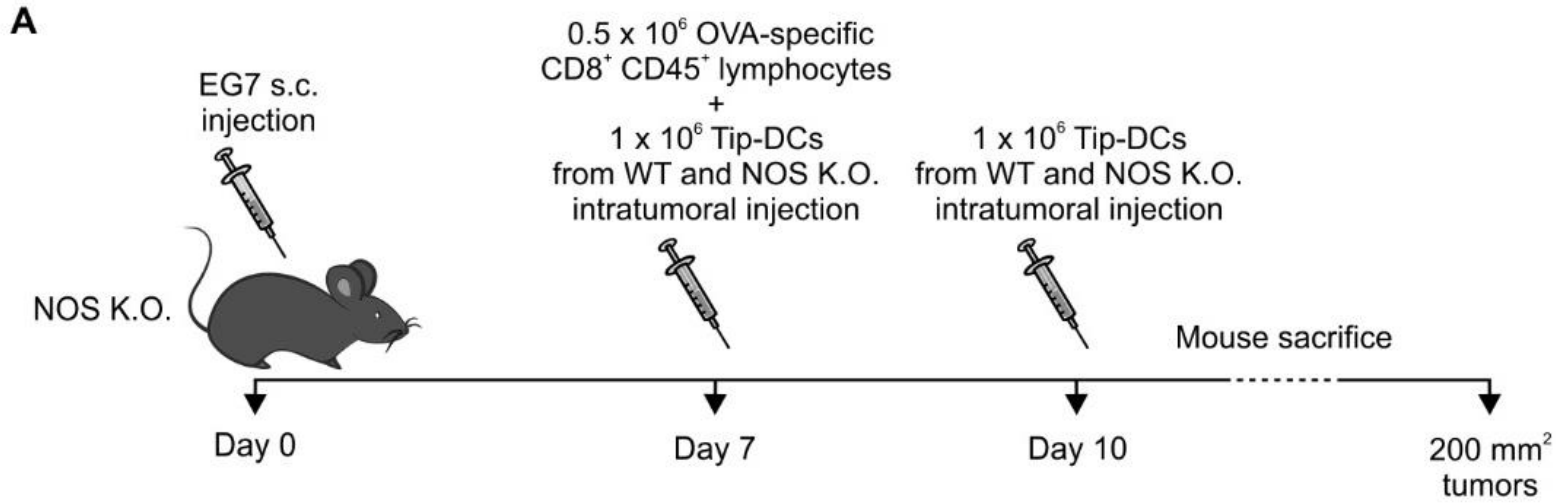


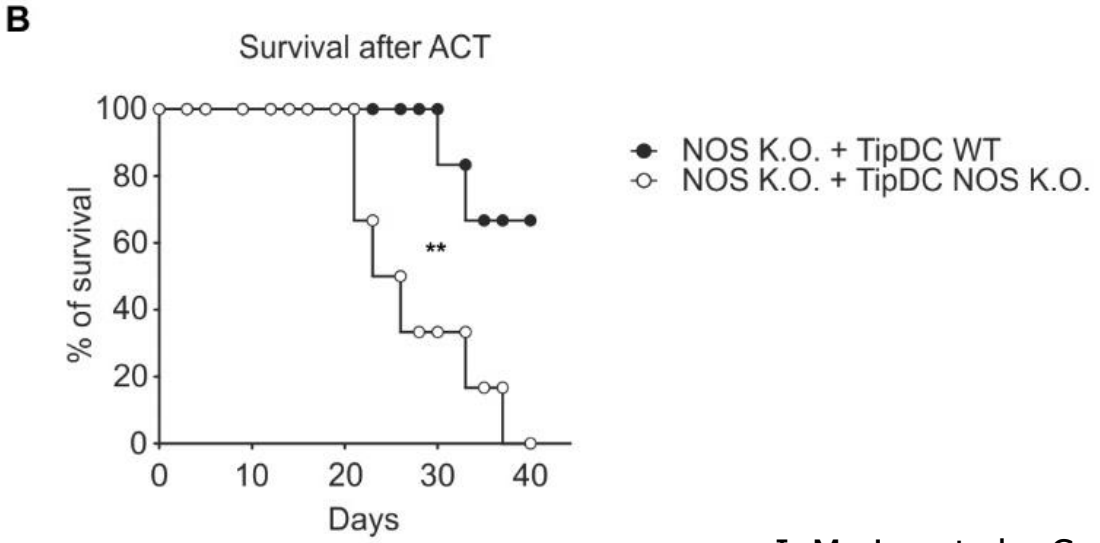
Tumor-specific CD8$^+$ T cells collaborate with monocyte-derived Tip-DCs



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

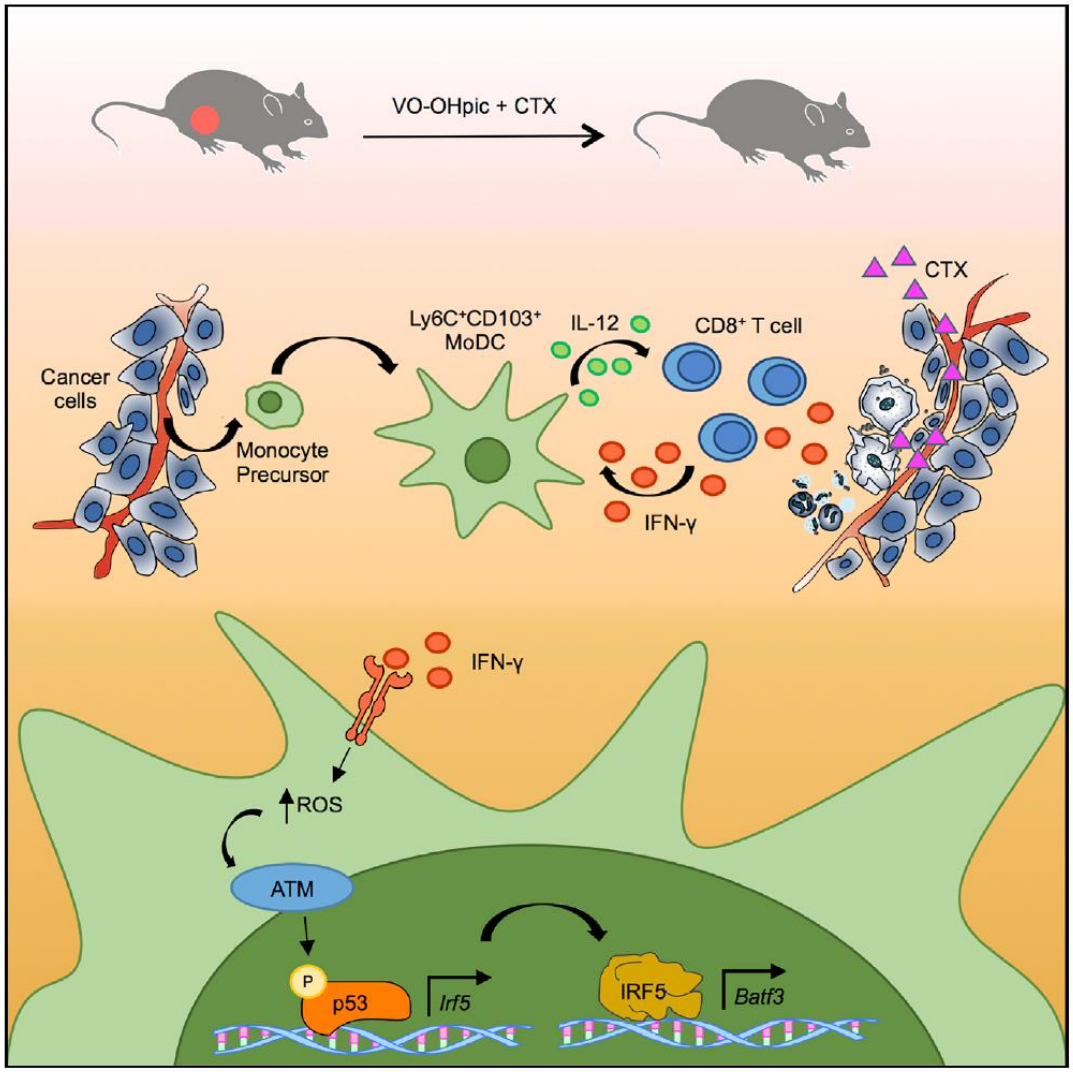
Intratumoral transfer of Nos2^{+} TipDCs is required for tumor rejection following ACT





I. Marigo et al., Cancer Cell, 2016

Interference with Treg triggers a CD8$^+$ T cell-dependent maturation of monocytes into Batf3 dendritic cells



Gardner and Ruffel, Immunity, 2018
Sharma et al., l, Immunity, 2018

Conclusions

- 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.

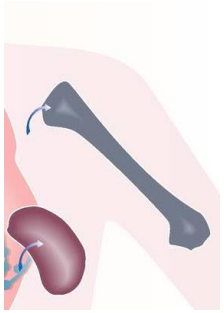
- Treatments that acts on cell plasticity might offer some advantages over simple depletion.

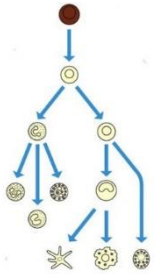
- Intratumoral activation can promote a sustained T cell response.

- Further characterization of tumor-infiltrating myeloid cells might provide better molecular targets for intervention.

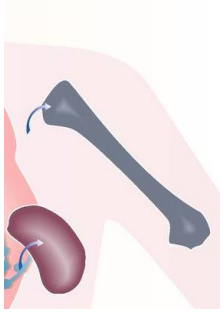
Refining therapeutic strategies to alter myeloid compartment in cancer

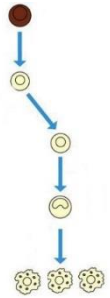
Chemotherapy
Radiotherapy





CD11b
CSF1R
CCL2





cEBPβ
Gata6
PI3Kγ
miR-142-3p