Immunoterapia e microambiente

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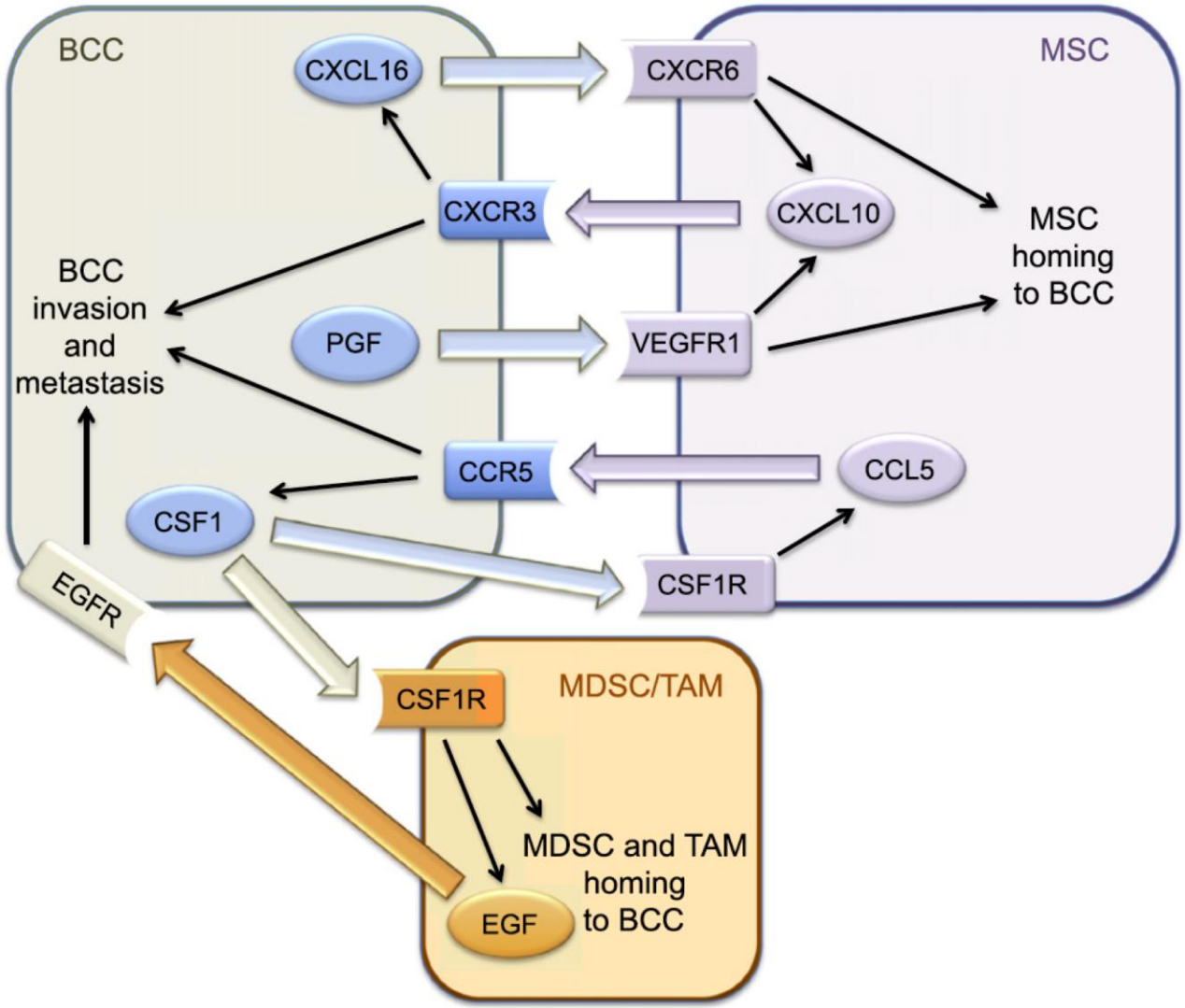
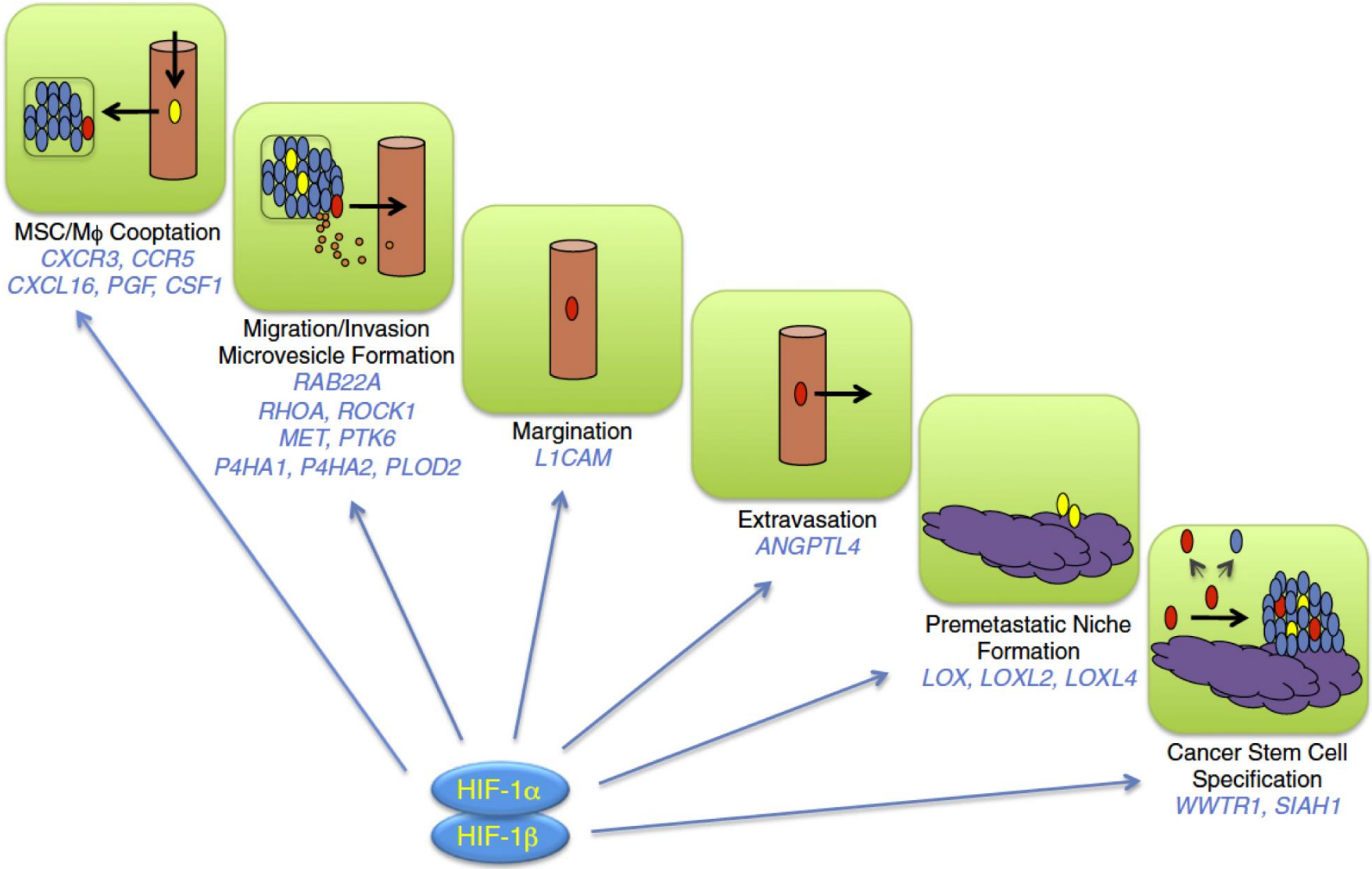
Università di Pisa

Signaling between breast cancer cells (BCCs), mesenchymal stem cells (MSCs), myeloid-derived suppressor cells (MDSCs), and tumor associated macrophages (TAMs) stimulates metastasis



G.L. Semenza. Biochim Biophys Acta 1863 (2016) 382–391

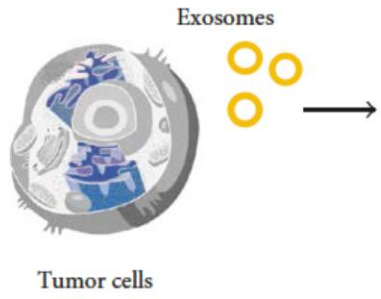
HIF-1 activates the transcription of genes that control multiple steps in the metastatic process

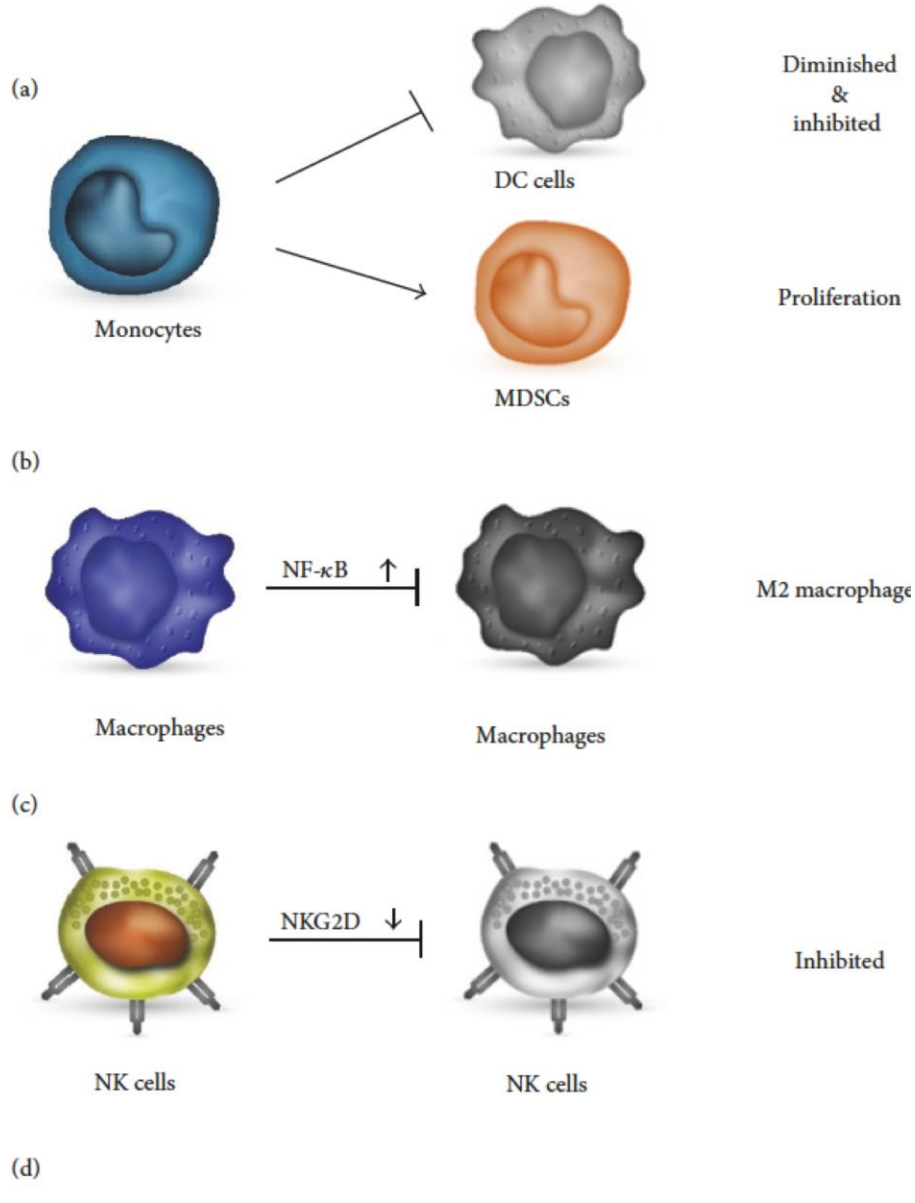


G.L. Semenza. Biochim Biophys Acta 1863 (2016) 382–391

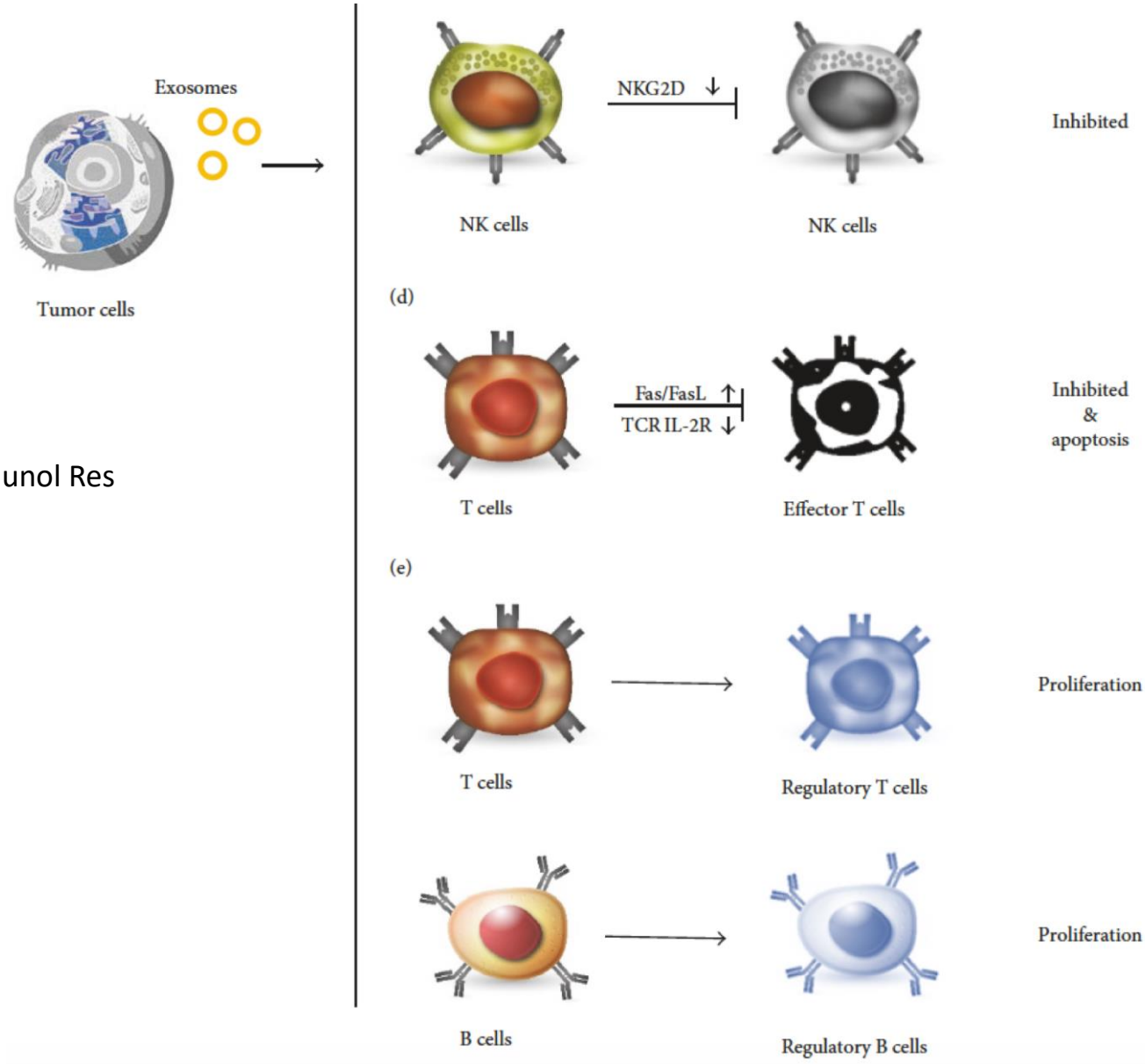
Tumor-released exosomes could mediate immune suppression

Wuzhen Chen et al. J Immunol Res
2017, Article ID 1073947



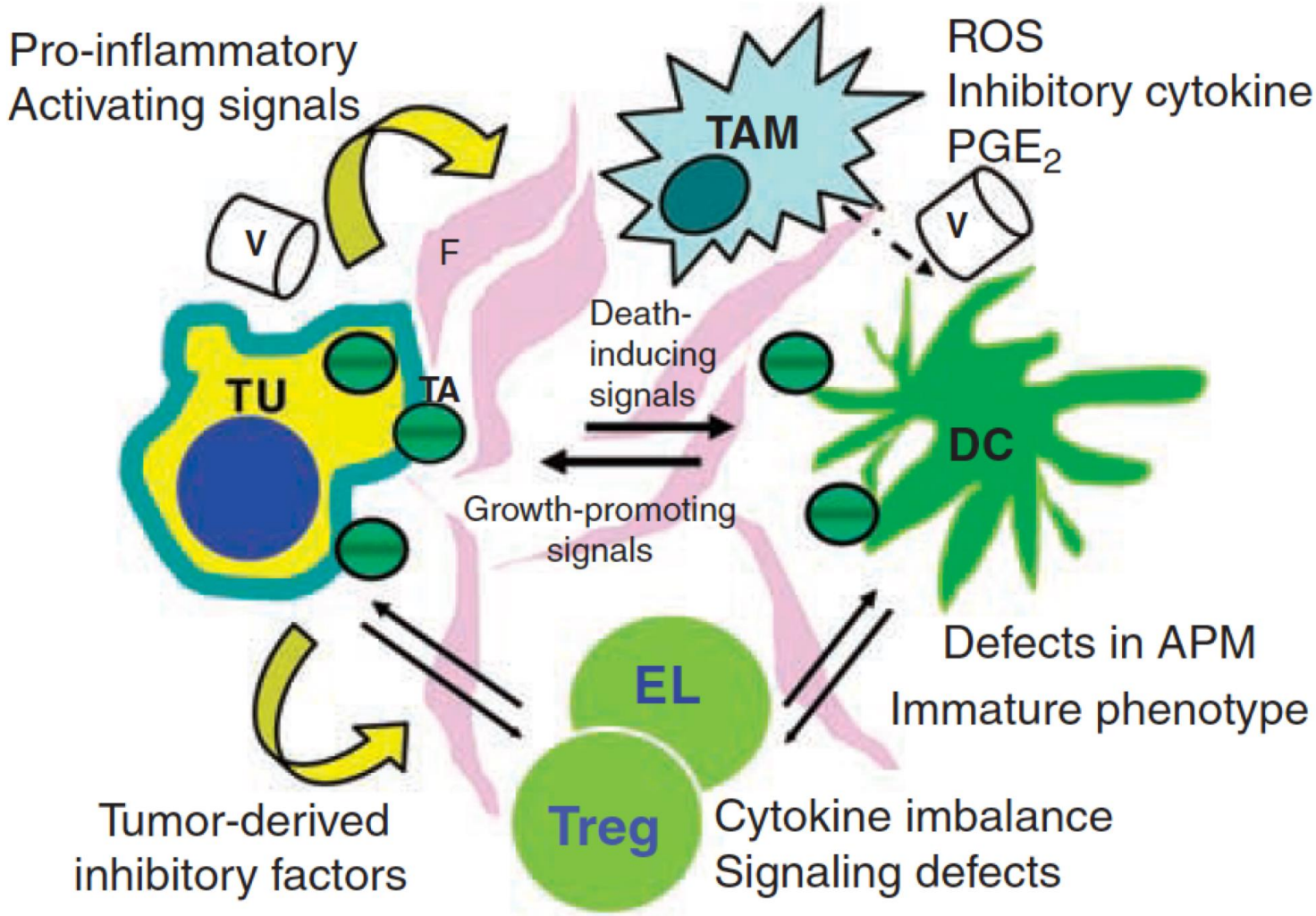


Tumor-released exosomes could mediate immune suppression



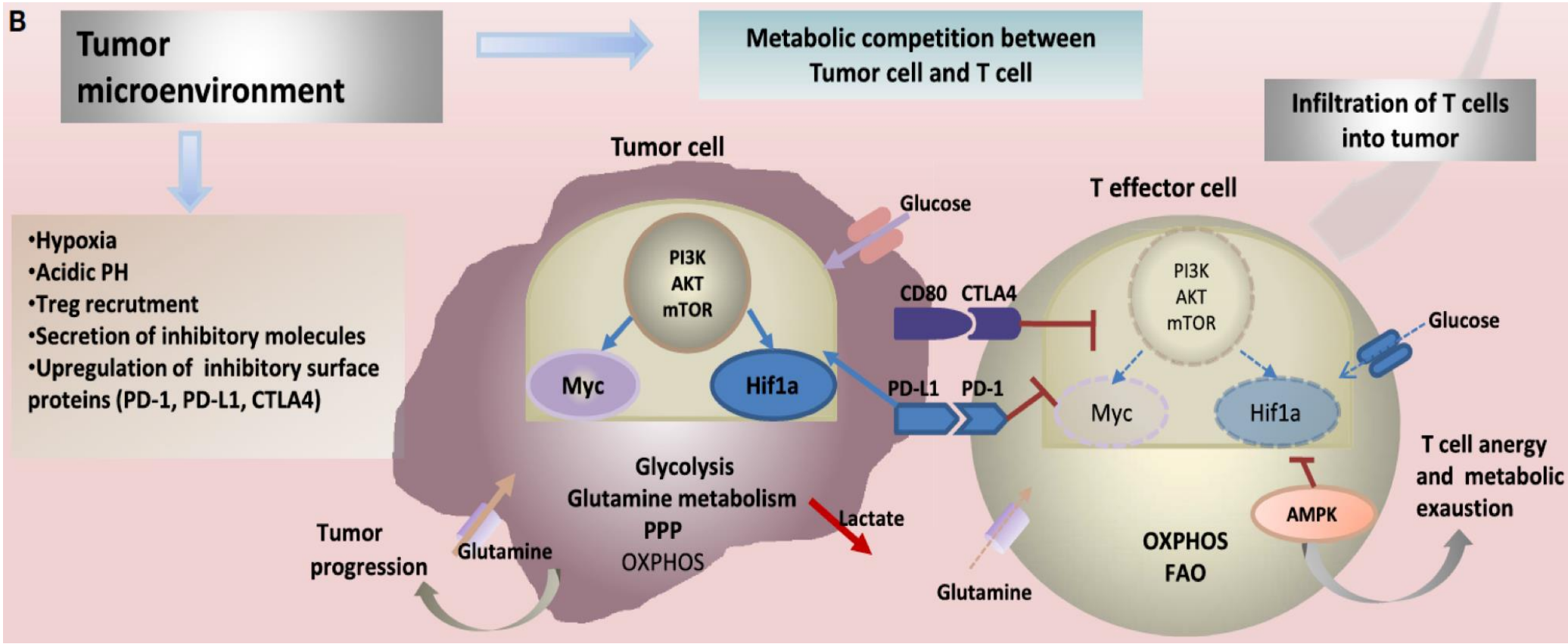
Wuzhen Chen et al. J Immunol Res 2017, Article ID 1073947

A diagram depicting the tumor microenvironment



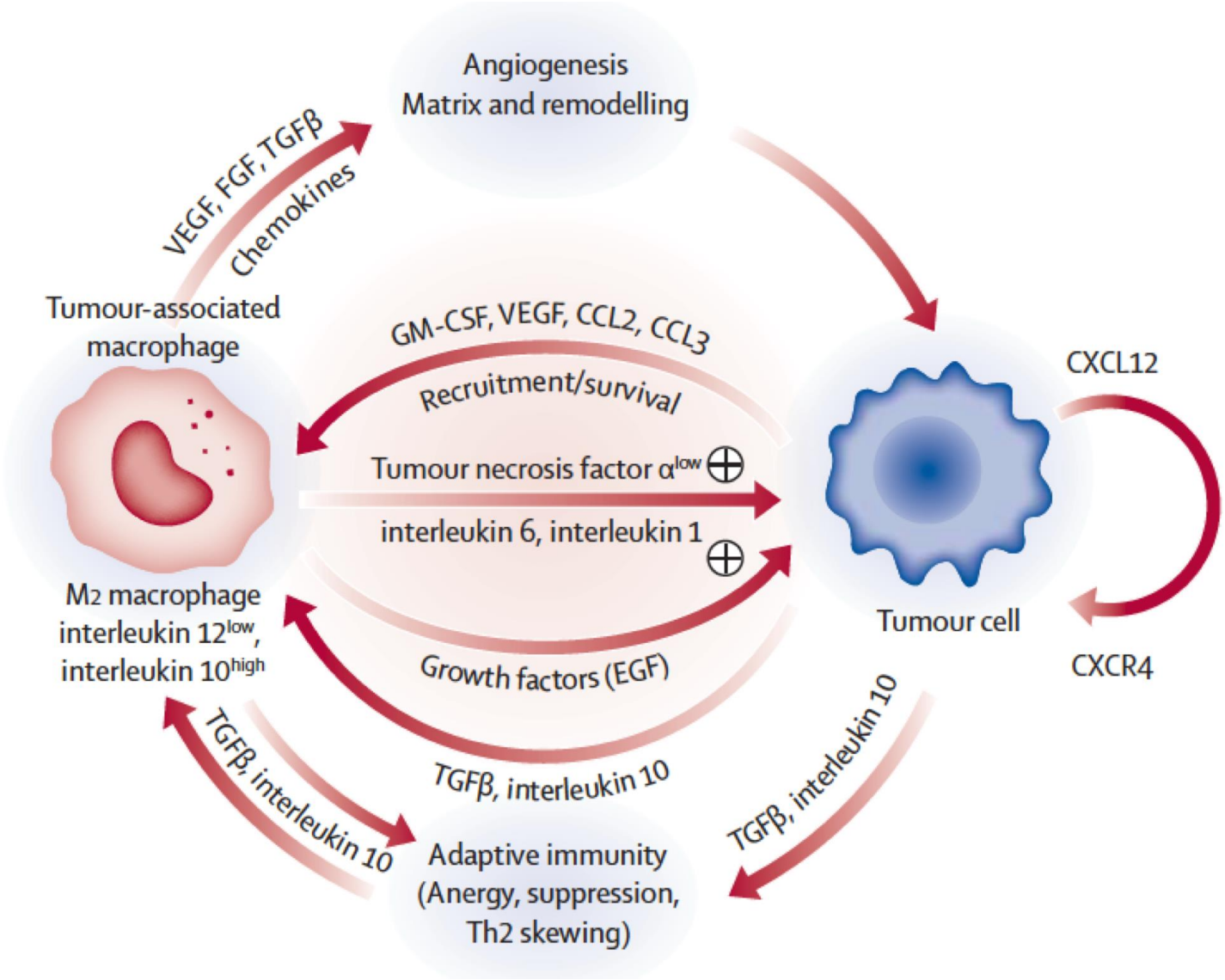
TL Whiteside. Oncogene (2008) 27, 5904–5912

Tumor orchestrates T-cell metabolism



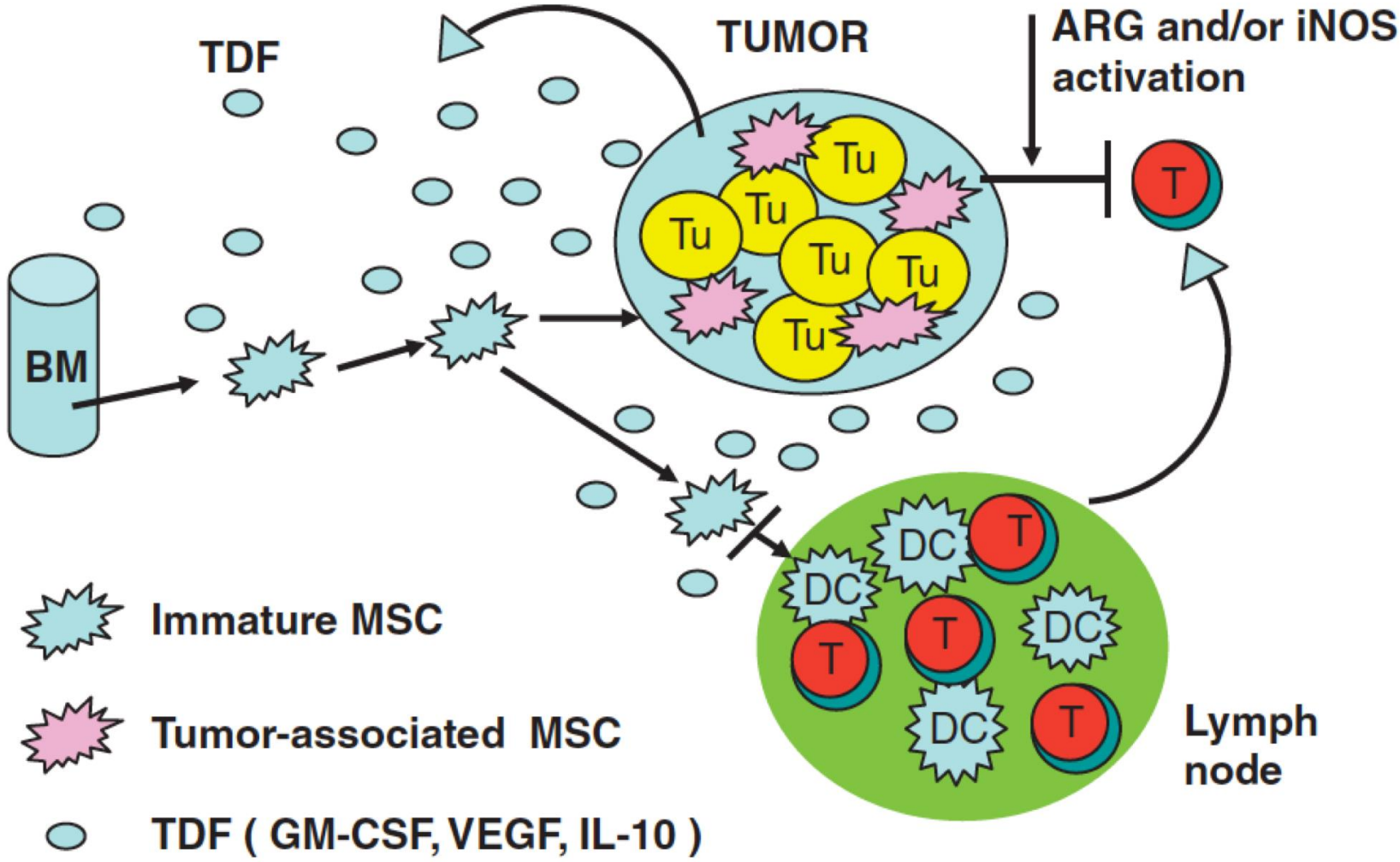
Kouidhi S, Elgaaied AB and Chouaib S (2017) Front. Immunol. 8:270

Interplay between tumour-associated macrophages and cancer cells in established tumours



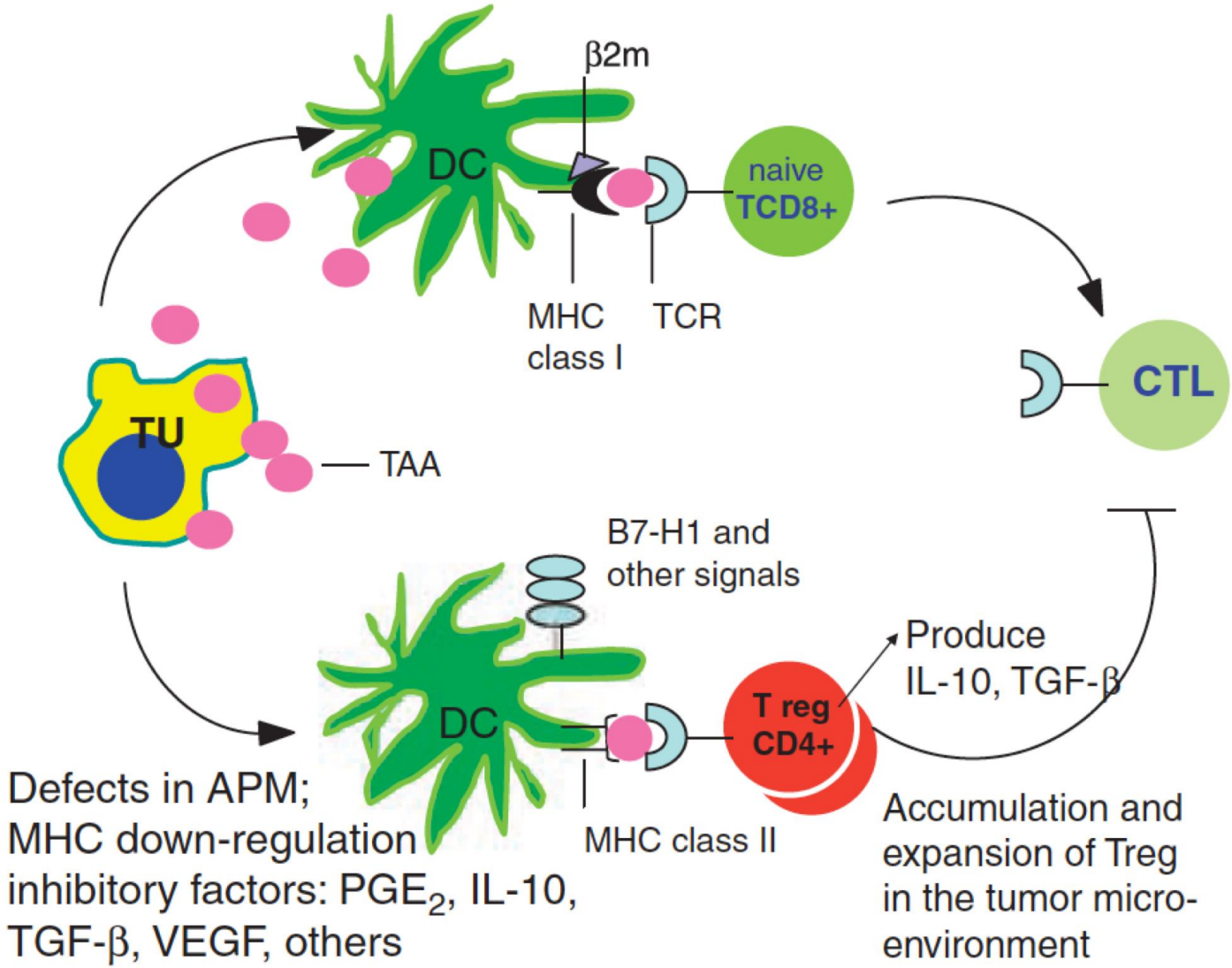
Mantovani A et al. Lancet 2008; 371: 771–83

Tumors recruit MSC from the bone marrow



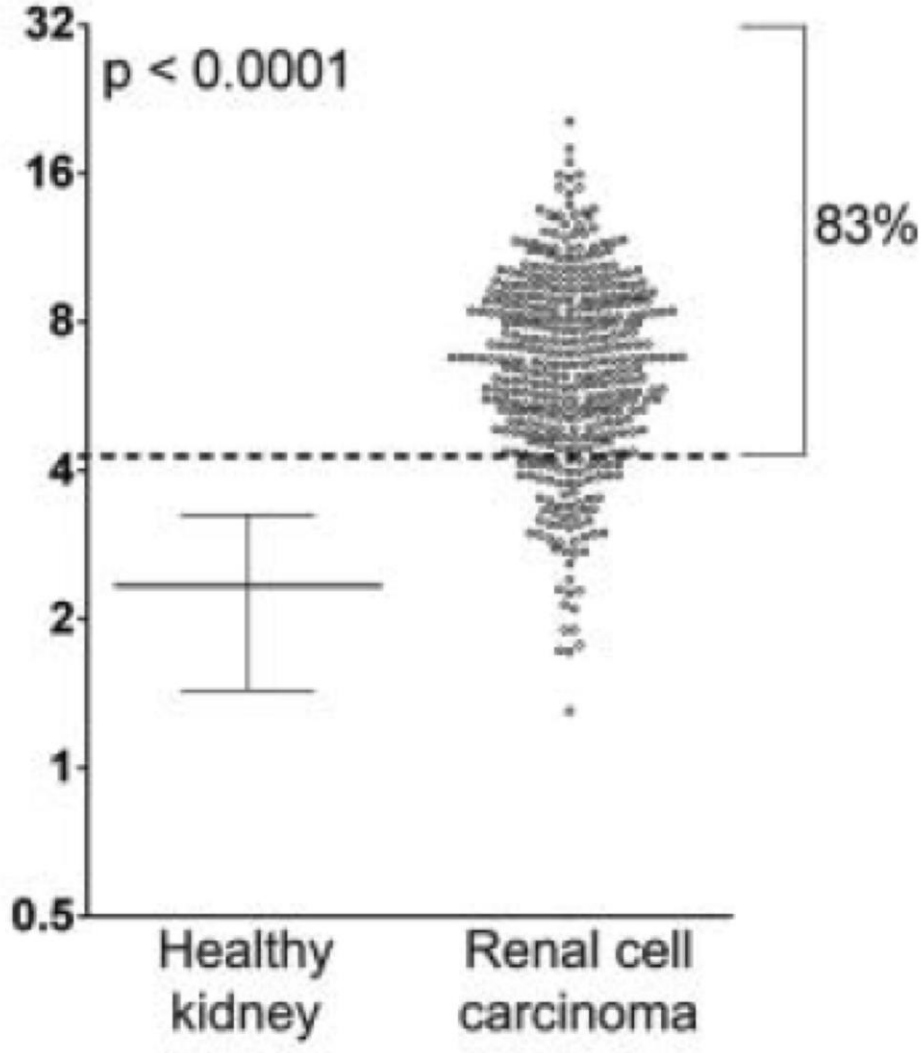
TL Whiteside. Oncogene (2008) 27, 5904–5912

Accumulation and expansion of Treg in the tumor microenvironment



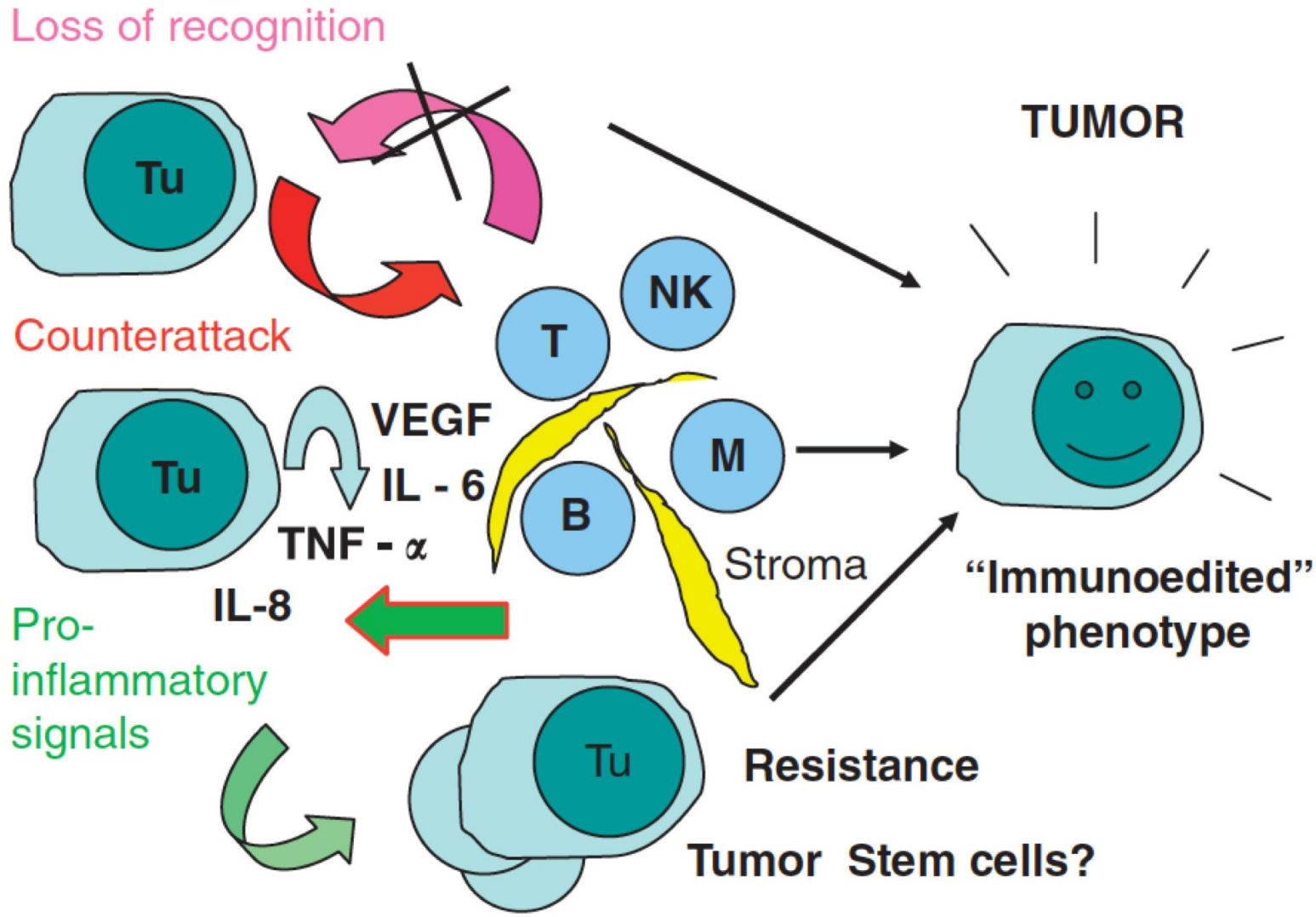
TL Whiteside. Oncogene (2008) 27, 5904–5912

mRNA expression of the best Treg marker in kidney cancer samples and the corresponding HTs



Cari L et al. Oncoimmunology 2017, e1387705

Mechanisms responsible for 'immunoediting' of tumor cells in the tumor microenvironment



TL Whiteside. Oncogene (2008) 27, 5904–5912

Mechanisms orchestrated by the tumor that contribute to its escape from the host immune system

- Interference with the induction of anti-tumor immune responses:
  - Decreased expression of costimulatory molecules on the tumor or APC
  - Alterations in TCR signaling in TIL
  - Death receptor/ligand signaling and 'tumor counterattack'
  - Dysfunction of DC and inadequate cross-presentation of TAA to T cells
  - DC apoptosis in the tumor microenvironment

TL Whiteside. Oncogene (2008) 27, 5904–5912

Mechanisms orchestrated by the tumor that contribute to its escape from the host immune system

- Inadequate effector cell function in the tumor microenvironment:
  - Suppression of T-cell responses by Treg
  - Suppression of immune cells by myeloid suppressor cells (MSC)
  - Apoptosis of effector T cells in the tumor and in the periphery
  - Microvesicles (MV, exosomes) secreted by human tumors and inducing apoptosis of CD8+ effector T cells

TL Whiteside. Oncogene (2008) 27, 5904–5912

Mechanisms orchestrated by the tumor that contribute to its escape from the host immune system

- Insufficient recognition signals:
  - Downregulation of surface expression of HLA molecules on tumor cells
  - Downregulation of surface TAA displayed by tumor cells: antigen loss variants
  - Alterations in APM component expression in tumor cells or APC
  - Suppression of NK activity in the tumor microenvironment

TL Whiteside. Oncogene (2008) 27, 5904–5912

Mechanisms orchestrated by the tumor that contribute to its escape from the host immune system

- Development of immunoresistance by the tumor:
  - Lack of susceptibility to immune effector cells
  - Immunoselection of resistant variants
  - Tumor stem cells

TL Whiteside. Oncogene (2008) 27, 5904–5912

Conclusions

- Mechanisms evolved by tumors for disarming host defenses and escape from the immune control vary in different cancers, and the unique signature of each tumor is reflected by its microenvironment.
- Therefore, understanding of cellular and molecular interactions operative in the tumor microenvironment is of crucial importance.
- Changing of chronic to acute inflammation at the tumor site might be therapeutically beneficial.
- Molecular tools are now available for devising novel and more effective anticancer therapies targeting not only the tumor but also its microenvironment.

TL Whiteside. Oncogene (2008) 27, 5904–5912

Gli anticorpi monoclonali in immuno-oncologia

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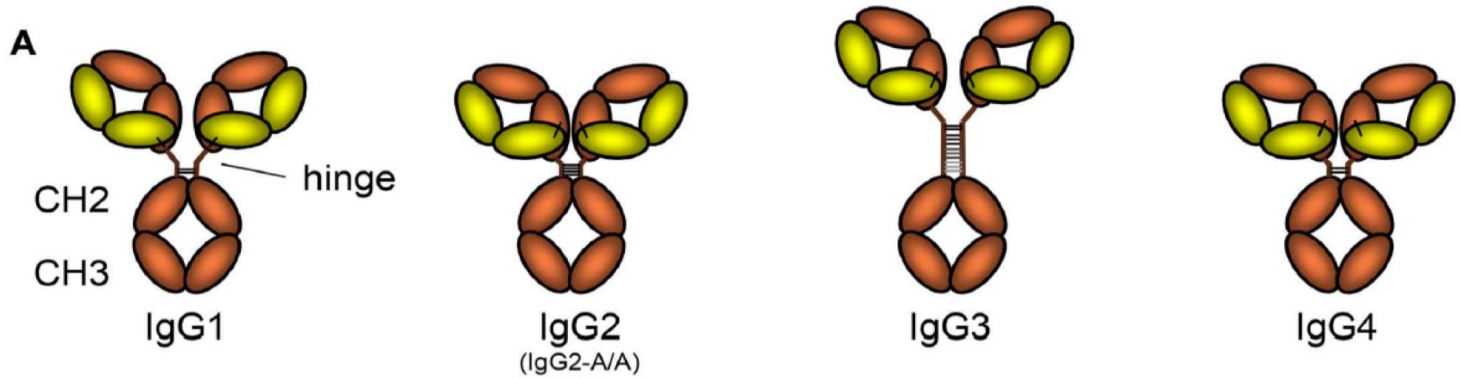
CORSO DI IMMUNOTERAPIA IN ONCOLOGIA
"CARCINOMA DEL RENE E DELLA VESCICA"

Biological agents targeting PD-1 or PD-L1 in cancer clinical trials

Biological agent	Class	Target
CT-011 (pidilizumab)	Humanized IgG1	PD-1
MK-3475 (lambrolizumab, pembrolizumab)	Humanized IgG4	PD-1
BMS-936558 (nivolumab)	Human IgG4	PD-1
AMP-224 (B7-DC-Fc fusion protein)	PD-L2 IgG2a fusion protein	PD-1
BMS-936559	Human IgG4	PD-L1
MEDI4736 (durvalumab)	Humanized IgG	PD-L1
MPDL3280A (atezolizumab)	Human IgG	PD-L1
MSB0010718C (avelumab)	Human IgG1	PD-L1

Kim C. Ohaegbulam et al. Trends Mol Med 2015, Vol. 21, No. 1

Properties of human IgG subclasses

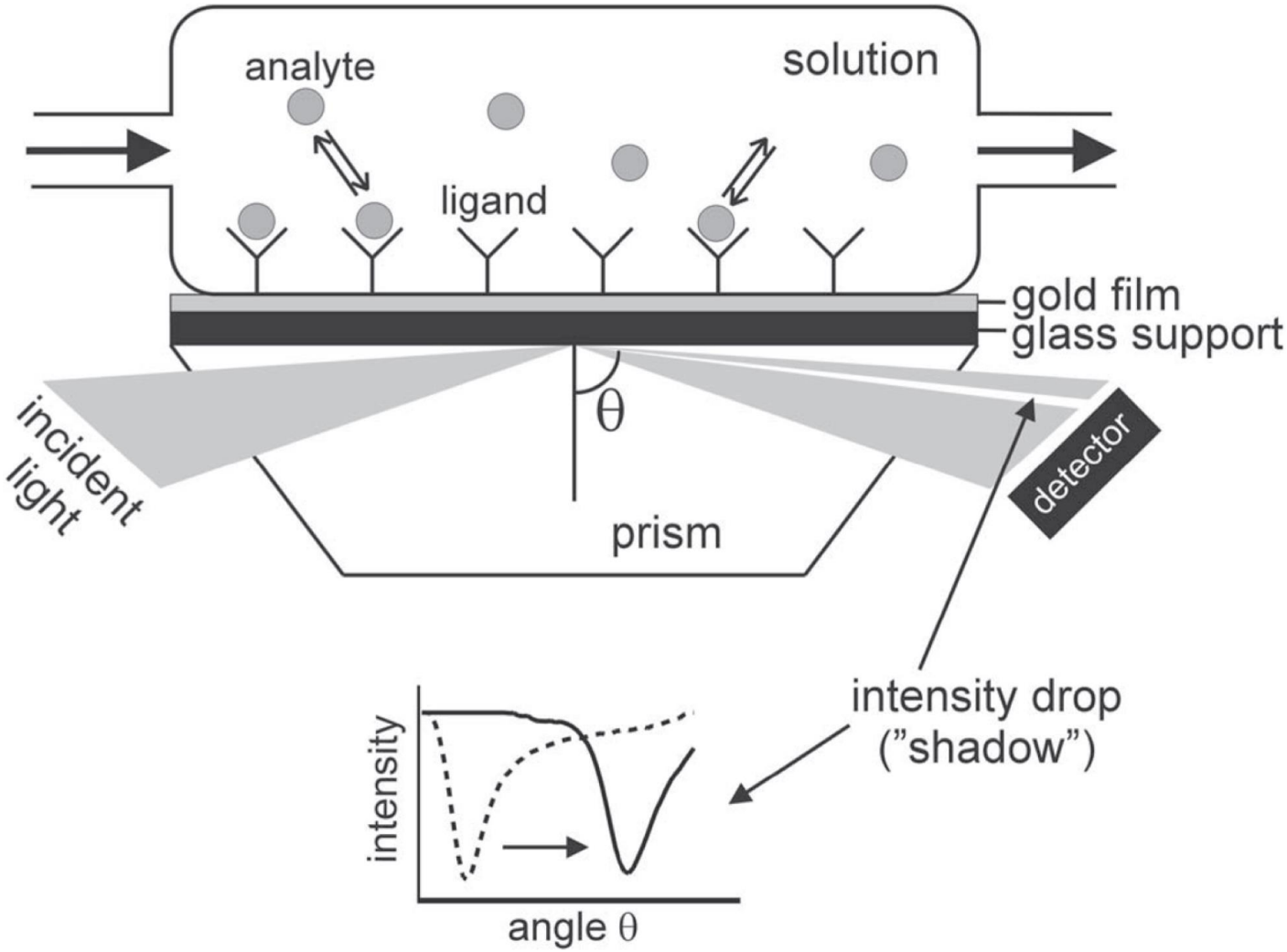


	IgG1	IgG2	IgG3	IgG4
General				
Molecular mass (kD)	146	146	170	146
Amino acids in hinge region	15	12	62[a]	12
Inter-heavy chain disulfide bonds	2	4[b]	11[a]	2
Mean adult serum level (g/l)	6.98	3.8	0.51	0.56
Relative abundance (%)	60	32	4	4
Half-life (days)	21	21	7/~21[a]	21
Placental transfer	++++	++	++/++++[a]	+++

Vidarsson G et al. Frontiers in Immunology 2014 (5) A 520: 1-17

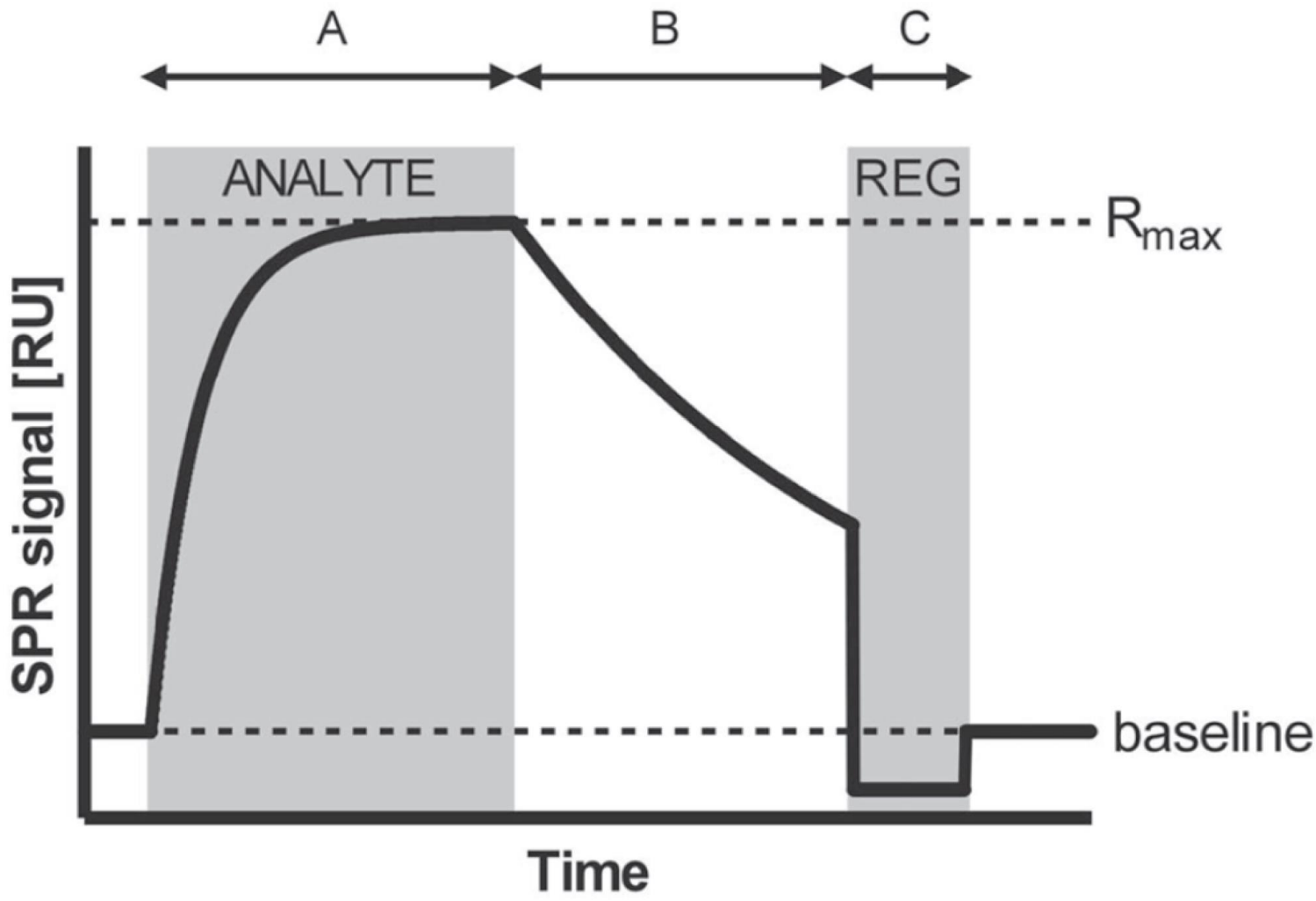
Differenziazione tra moAbs anti-PD-L1: dinamica di interazione con l'antigene

Schematic view of a surface plasmon resonance (SPR) detector



Hahnefeld, Drewianka, and Herberg. Methods in Molecular Medicine, vol. 94. J. Decker and U. Reischl Eds. Humana Press Inc., Totowa, NJ

Basic parts of a sensorgram



Hahnefeld, Drewianka, and Herberg. Methods in Molecular Medicine, vol. 94. J. Decker and U. Reischl Eds. Humana Press Inc., Totowa, NJ

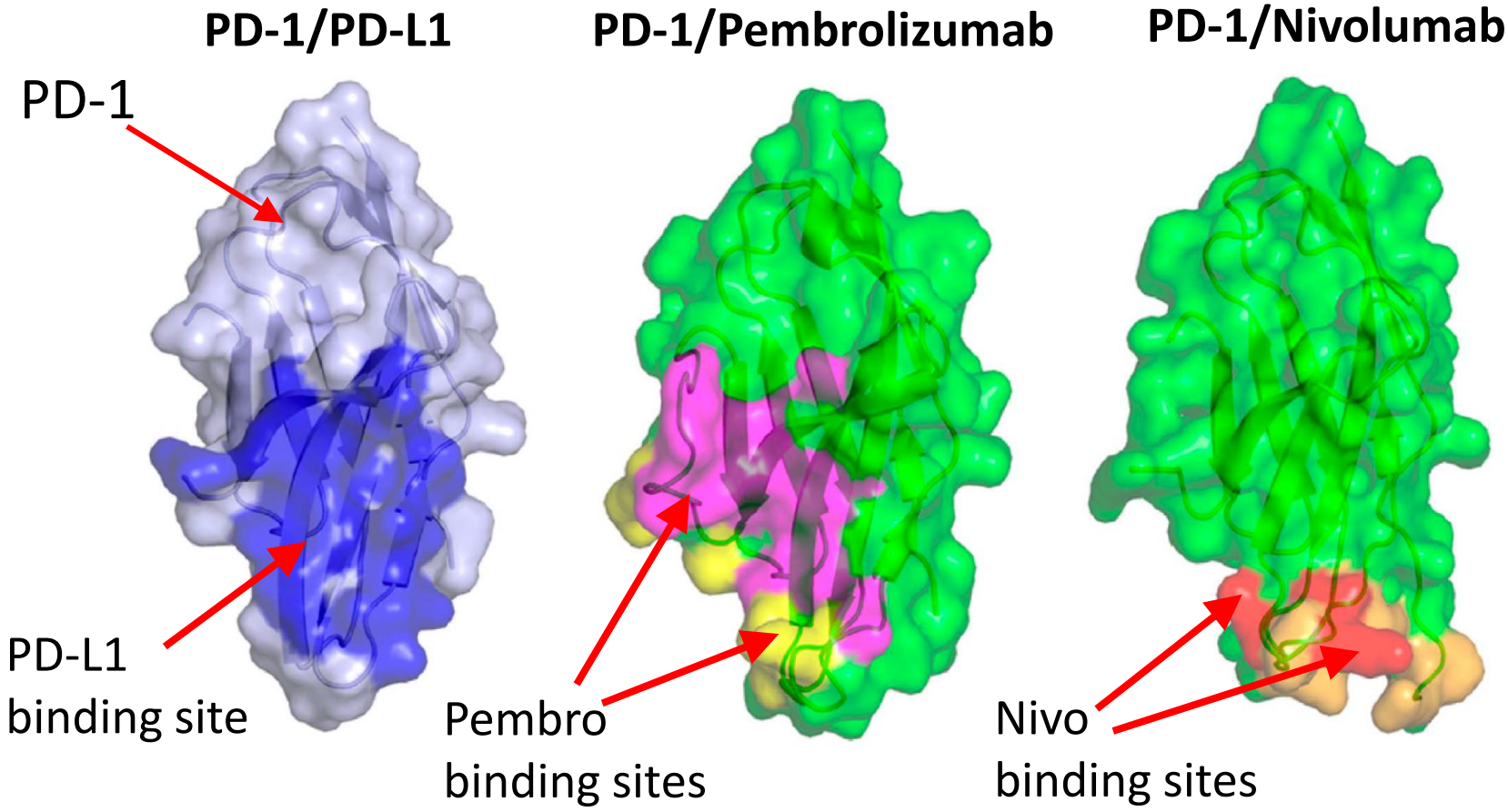
Activation of ADCC/CDC by immune-checkpoint inhibitors

Checkpoint Inhibitor	Killer Isotype	Nonkiller Isotype
Anti-CTLA-4	Ipilimumab (IgG1)	Tremelimumab (IgG2)
Anti-PD-1	Pidilizumab (IgG1)	Nivolumab (IgG4), pembrolizumab (IgG4)
Anti-PD-L1	Avelumab	BMS-936559 (IgG4), Atezolizumab
		Durvalumab

ADCC = antibody-dependent cell-mediated cytotoxicity; CDC = complement dependent cytotoxicity; CTLA = cytotoxic T-lymphocyte antigen; Ig = immunoglobulin; PD = programmed cell death protein.

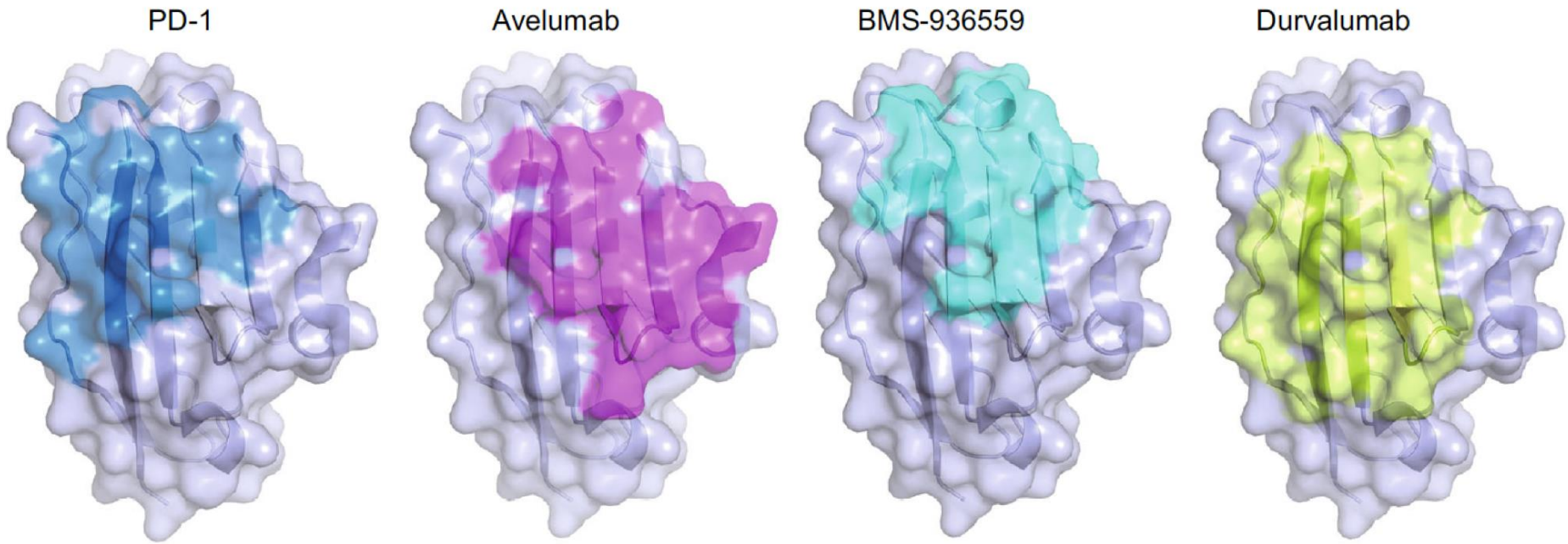
Kathleen M. Mahoney et al. Clin Ther. 2015;37:764–782

Interactions between PD-1 and anti-PD-1 drugs



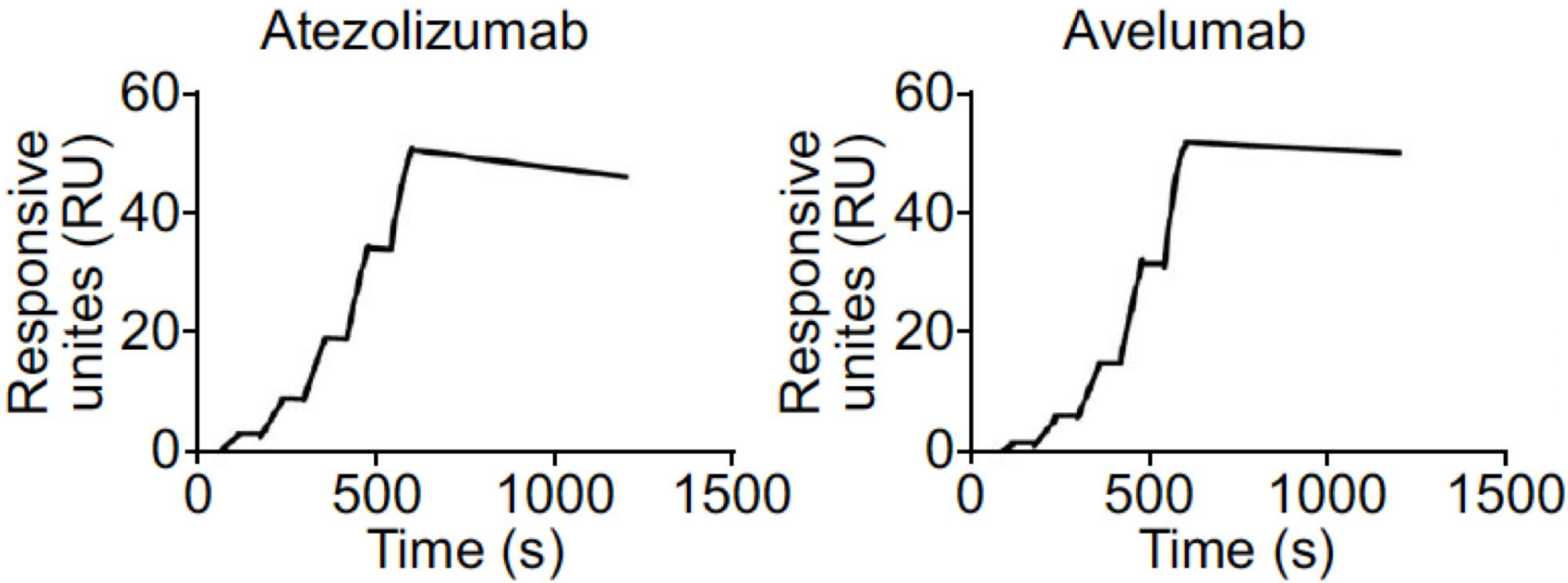
Ju Yeon Lee et al. Nature Communications 2016 DOI: 10.1038/ncomms13354

Binding surface of PD-1 and binding epitopes of avelumab, BMS-936559, and durvalumab on PD-L1



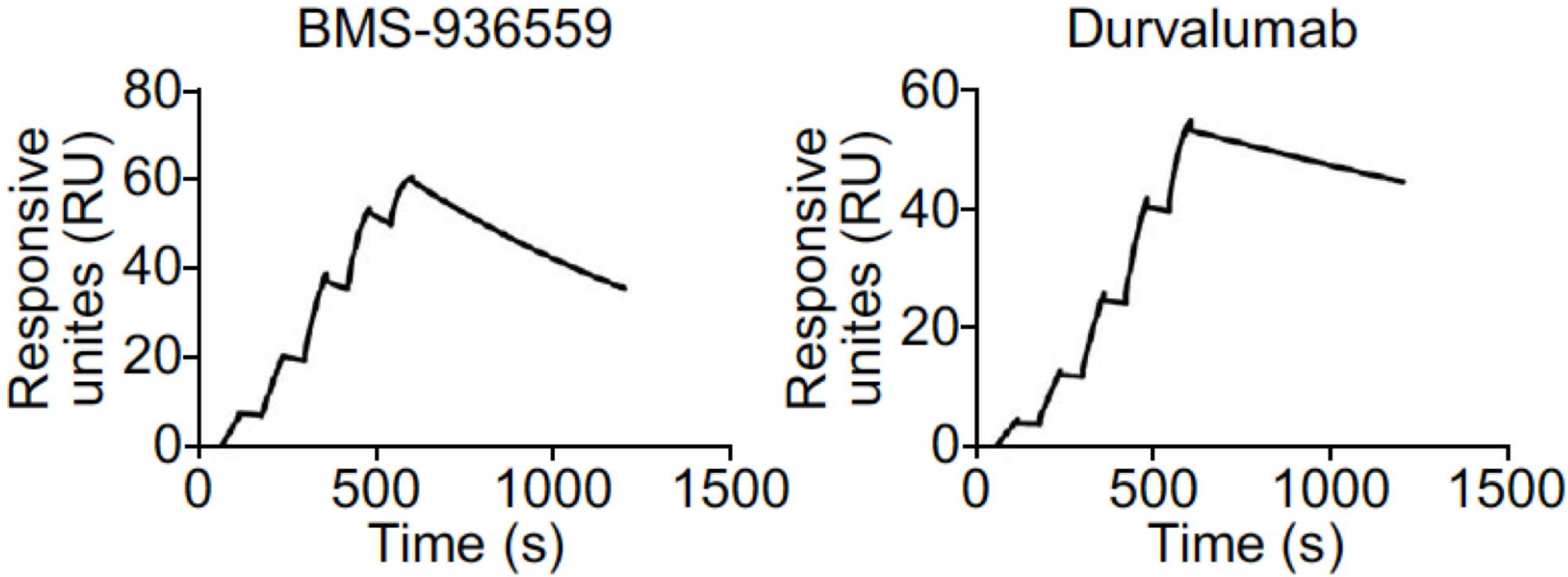
Shuguang Tan et al., Protein Cell DOI 10.1007/s13238-017-0412-8

Binding kinetics of anti-PD-L1 moAbs and PD-L1



Shuguang Tan et al., Protein Cell DOI 10.1007/s13238-017-0412-8

Binding kinetics of anti-PD-L1 MAbs and PD-L1



Shuguang Tan et al., Protein Cell DOI 10.1007/s13238-017-0412-8

Binding profiles of the four MAbs to PD-L1

MAbs	ka[1] (10^4/Ms)	kd[2](10^{-4}/s)	KD (nM)
atezolizumab	8.93	1.56	1.75
durvalumab	42.8	2.85	0.667
avelumab	161	0.753	0.0467
BMS-936559	105	8.68	0.83

[1] ka, association rate constant.

[2] kd, dissociation rate constant.

Shuguang Tan et al., Protein Cell DOI 10.1007/s13238-017-0412-8

Kd of PD-L1 and PD-L2 for PD-1

PD-1

PD-1:PD-L1

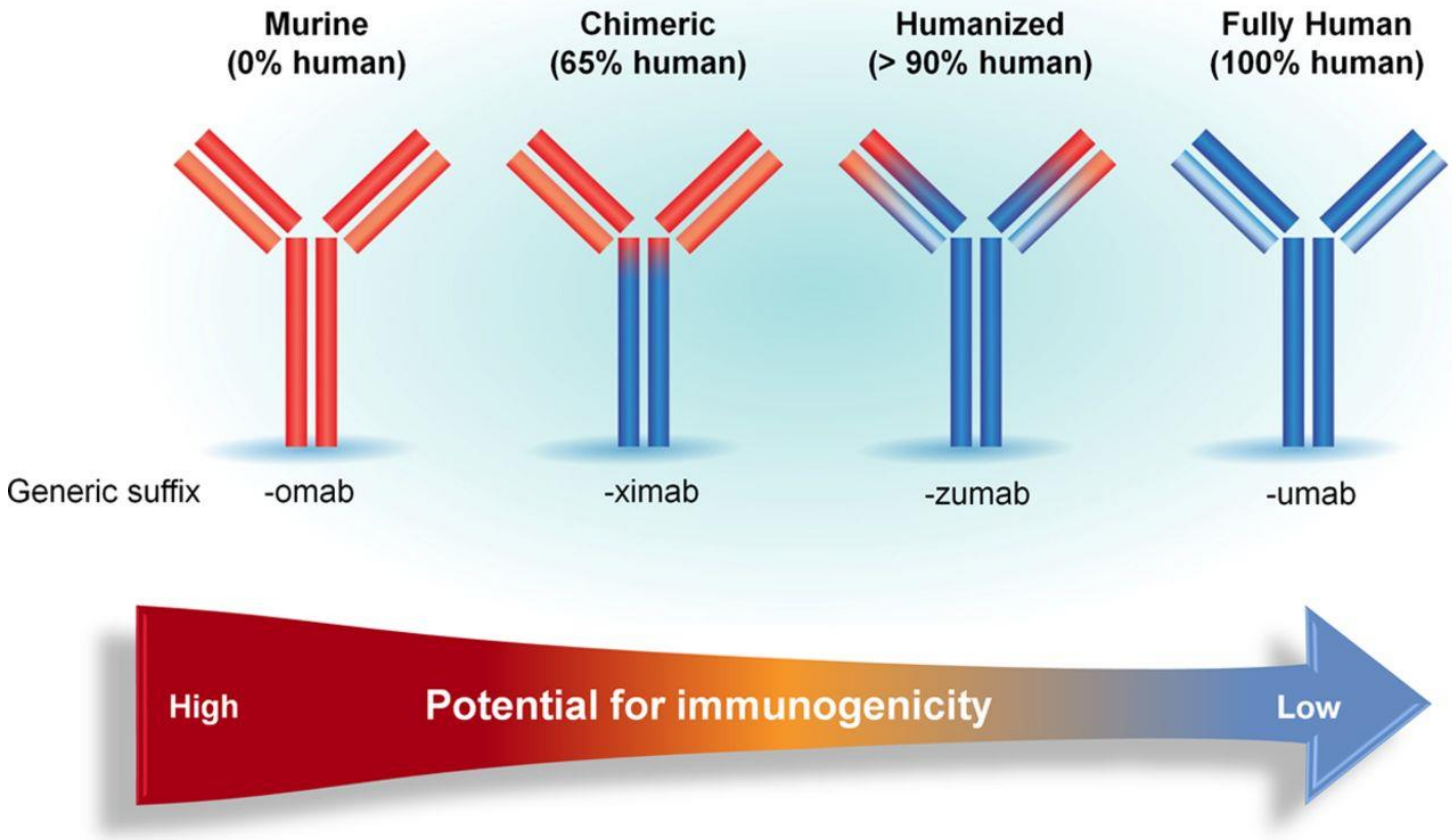
270–526 nM	Youngnak et al[49] (Scatchard plots analysis)
590–770 nM	Butte et al[48] (Scatchard plots analysis)
770 nM	Butte et al[48] (equilibrium binding†)

PD-1:PD-L2

89–106 nM	Youngnak et al[49] (Scatchard plots analysis)
590 nM	Butte et al[48] (equilibrium binding†)

Kathleen M. Mahoney et al. Clin Ther. 2015;37:764–782

Humanization of therapeutic antibodies has reduced their immunogenicity



Ian N. Foltz et al. Circulation. 2013;127:2222-2230

American Heart Association.

Comparison table of moAbs anti-PD-1

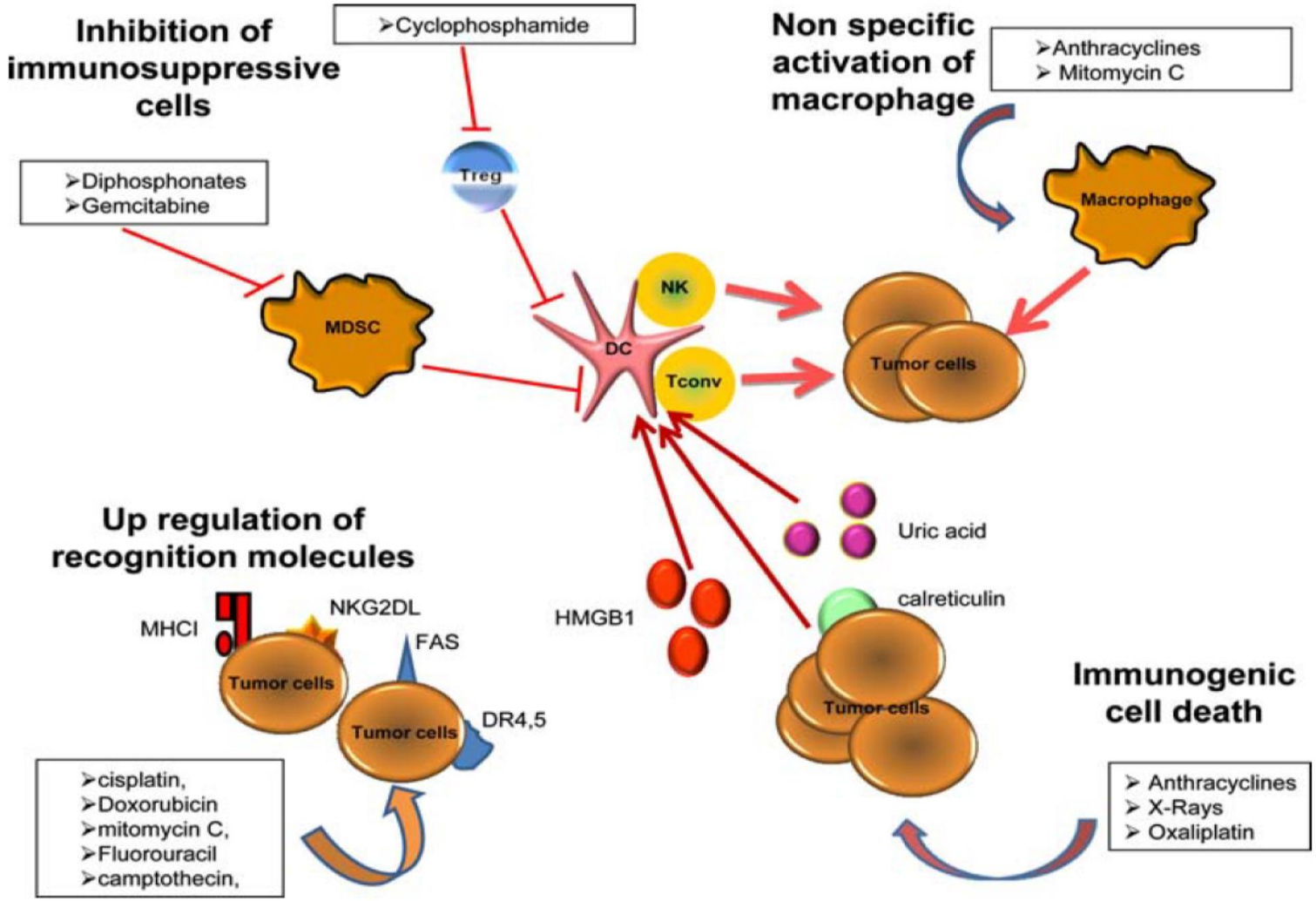
	Nivolumab	Pembrolizumab	Pidilizumab	AMP-224
Humanized	--	✓	✓	--
Fully human	✓	--	--	--
Ig subclass	IgG4	IgG4	IgG1	Fusion protein
ADCC/CDC	--	--	✓	✓
K_D	+/++	++	+	?

Comparison table of moAbs anti-PD-L1

	Atezolizumab	Durvalumab	Avelumab	BMS-936559
Humanized	✓	--	--	--
Fully human	--	✓	✓	✓
Ig subclass	IgG1 modified	IgG1 modified	IgG1	IgG4
ADCC/CDC	--	--	✓	--
K_D	+/++	++	+++	++

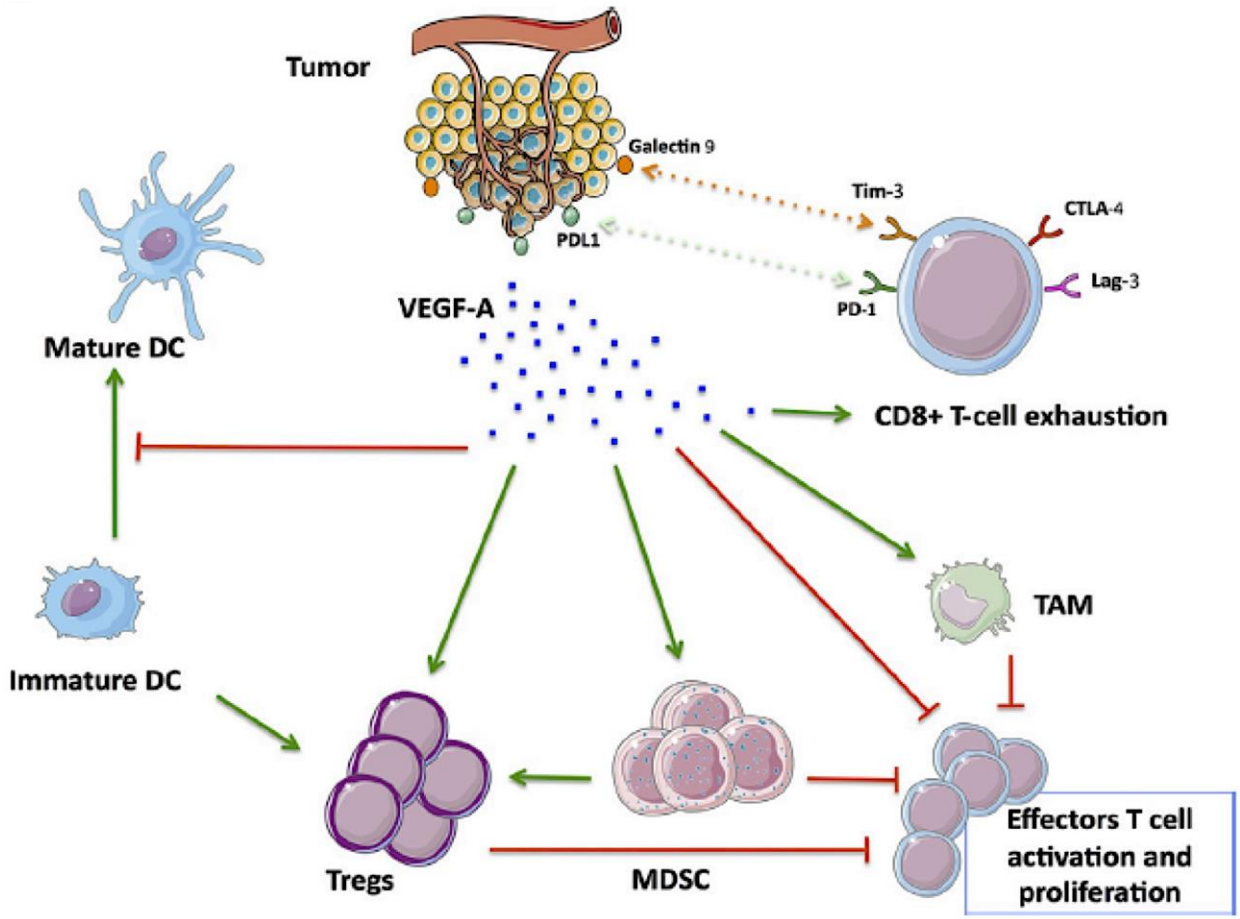
Interazioni VEGF, PD-1/PD-L1 e chemioterapia

Chemotherapy as an adjuvant for antitumor immunity



Cédric Ménard et al., Cancer Immunol Immunother (2008) 57:1579–1587

VEGF-A promotes tumor-induced immunosuppression



VEGF-A promotes T-cell exhaustion, proliferation of immunosuppressive cells, and limits tumor T-cell recruitment

Lapeyre-Prost A et al. Int Rev Cell Mol Biol. 2017;330:295-342

Conclusions

- Immune checkpoint inhibitors have profoundly changed the management of selected diseases, including melanoma, NSCLC and renal cancer
- The reason of lack of activity in other cancers needs to be evaluated.
- Response biomarkers in addition to PD-L1 in cancer cells should be identified.
- Anti-PD-1 and anti-PD-L1 antibodies can be integrated into current treatment regimens