An overview on immuno-oncology

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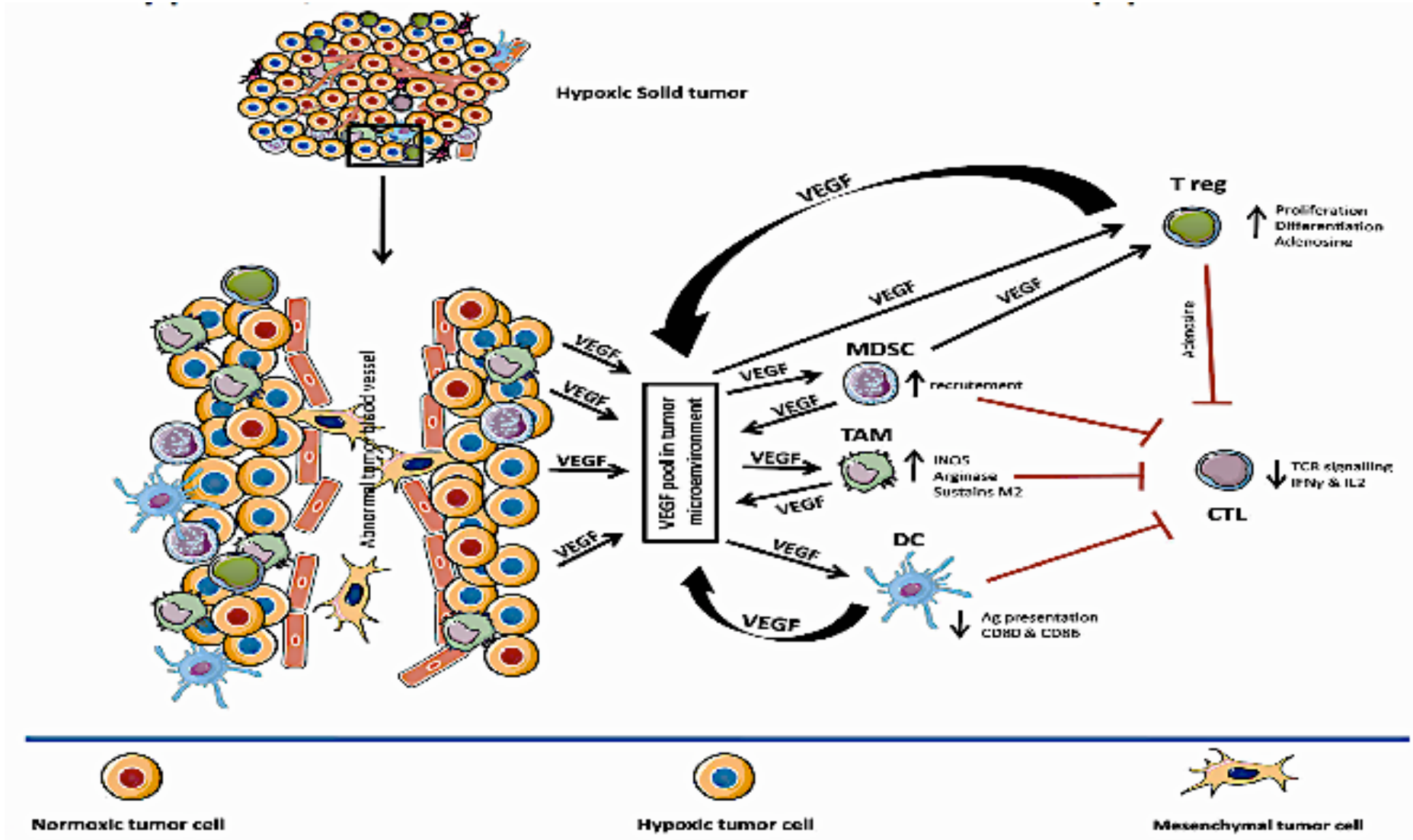
Tumor-derived immune suppression

- Systematic studies have identified multiple mechanisms by which cancers defeat the immune response:
  - Immunosuppressive cytokines: TGF-β, IL-4, -6, -10, VEGF
  - Immunosuppressive immune cells: T-regs, macrophages
  - Disruption of immune activation signaling: loss of MHC receptor, IDO (indoleamine-dioxygenase) production
- Goal: therapy strategies that "**liberate**" underlying anticancer immune responses
- Immune checkpoints not even in the picture in 2008!

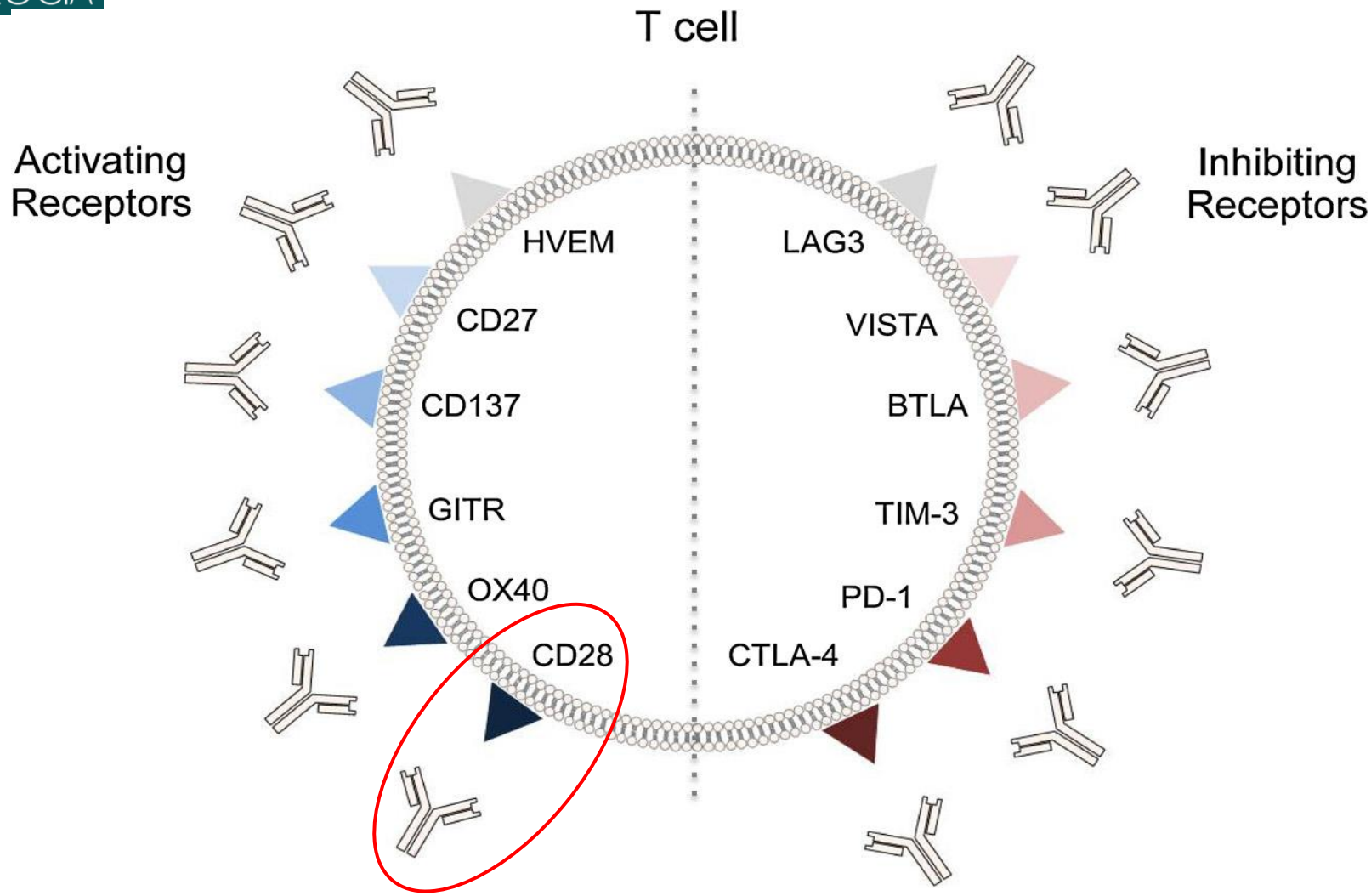
Weiner LM. N Engl J Med. 2008;358:2664-2665; Atkins MB, Brahmer J. Immunotherapy in cancer: from principles to practice – Clinical Care Options Oncology 2014

Hypoxia, inflammation and immune suppression



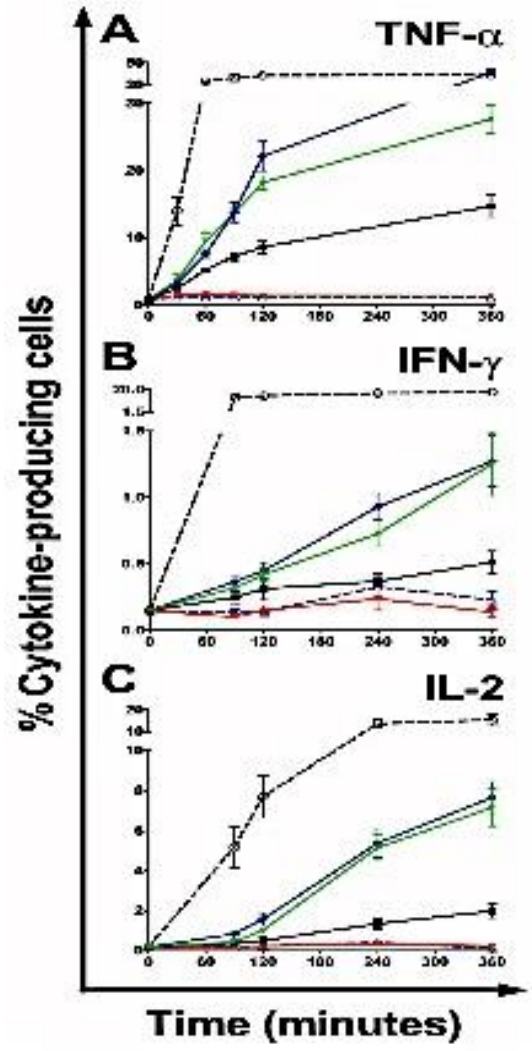
Chouaib S et al. Front Immunol. 2012; 3:21

Immunotherapeutic targets

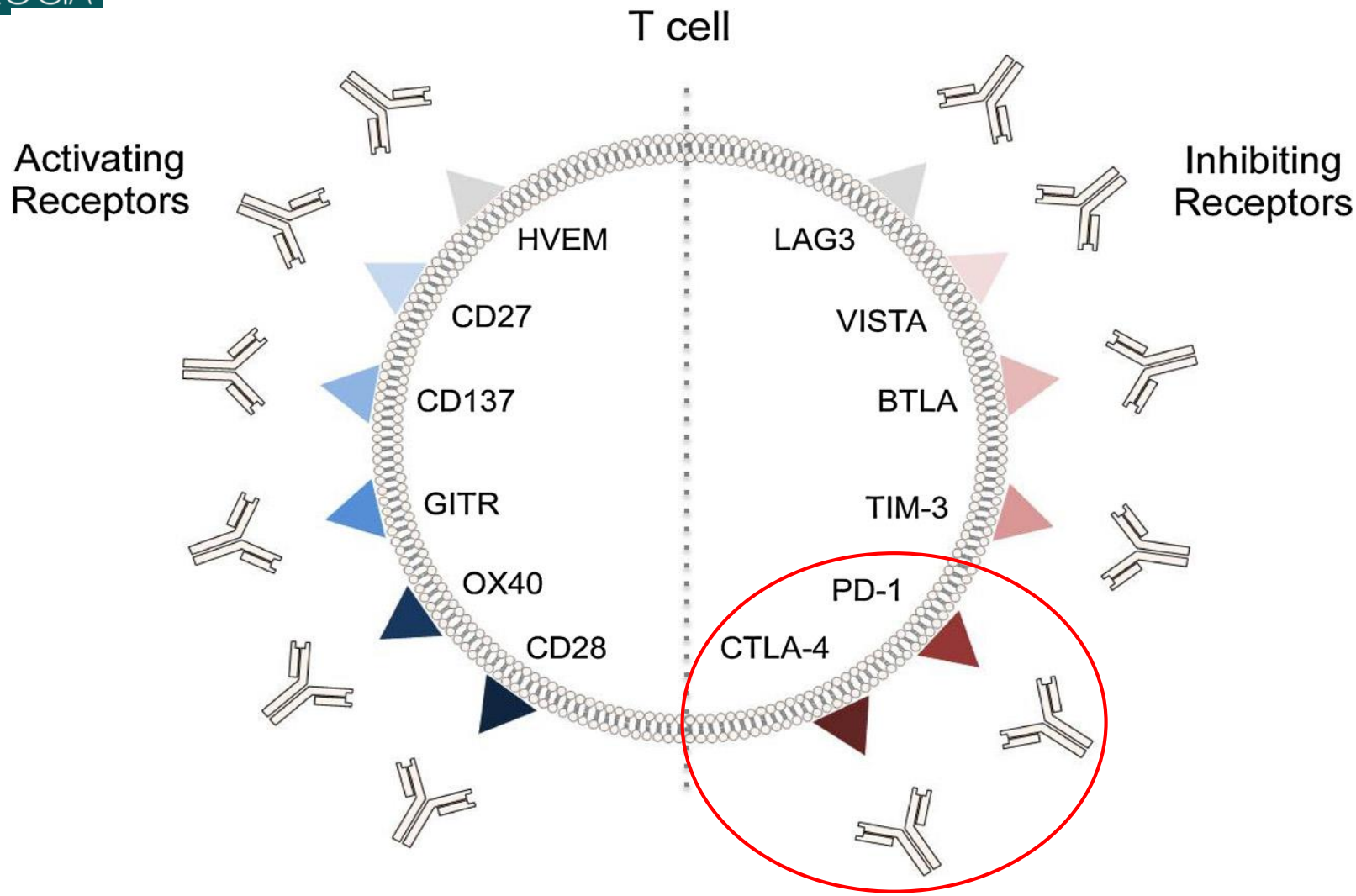


B. Merelli et al. Critical Reviews in Oncology/Hematology 89 (2014) 140–165

TGN1412 SADRs due to species differences in CD28 expression on CD4+ effector memory T-cells



Immunotherapeutic targets



B. Merelli et al. Critical Reviews in Oncology/Hematology 89 (2014) 140–165

Comparisons between CTLA-4 and PD-1

	PD-1	CTLA-4
Biological function	Inhibitory receptor	Inhibitory receptor
Expression on	Activated T cells, activated B cells, activated NK cells, TILs in different tumor types	T cells at the time of their initial response to antigen (activated CD8+ effector T cells)
Major role	• Limitation of T cells activity in peripheral tissues following inflammatory responses • Limitation of autoimmunity	Regulation of the early stage of T cells activation
Ligands	• PD-L1 (B7-H1/CD274) • PD-L2 (B7-CD/CD273)	• CD80 (B7.1) • CD86 (B7.2)
Mechanism of action	• PD-1 binds to the ligand ↓ • Recruitment of phosphatase SHP-2 • Decreased expression of the cell survival protein Bcl-xL ↓ • PD-1 inhibits kinases (PI3K/AKT) that are involved in T cells activation	• CTLA-4 interacts with the ligand ↓ • Binding with PI3K, phosphatases SHP-2 and PP2A • Blockade of lipid-raft expression • Blockade of microcluster formation

B. Merelli et al. Critical Reviews in Oncology/Hematology 89 (2014) 140–165

Prima Edizione
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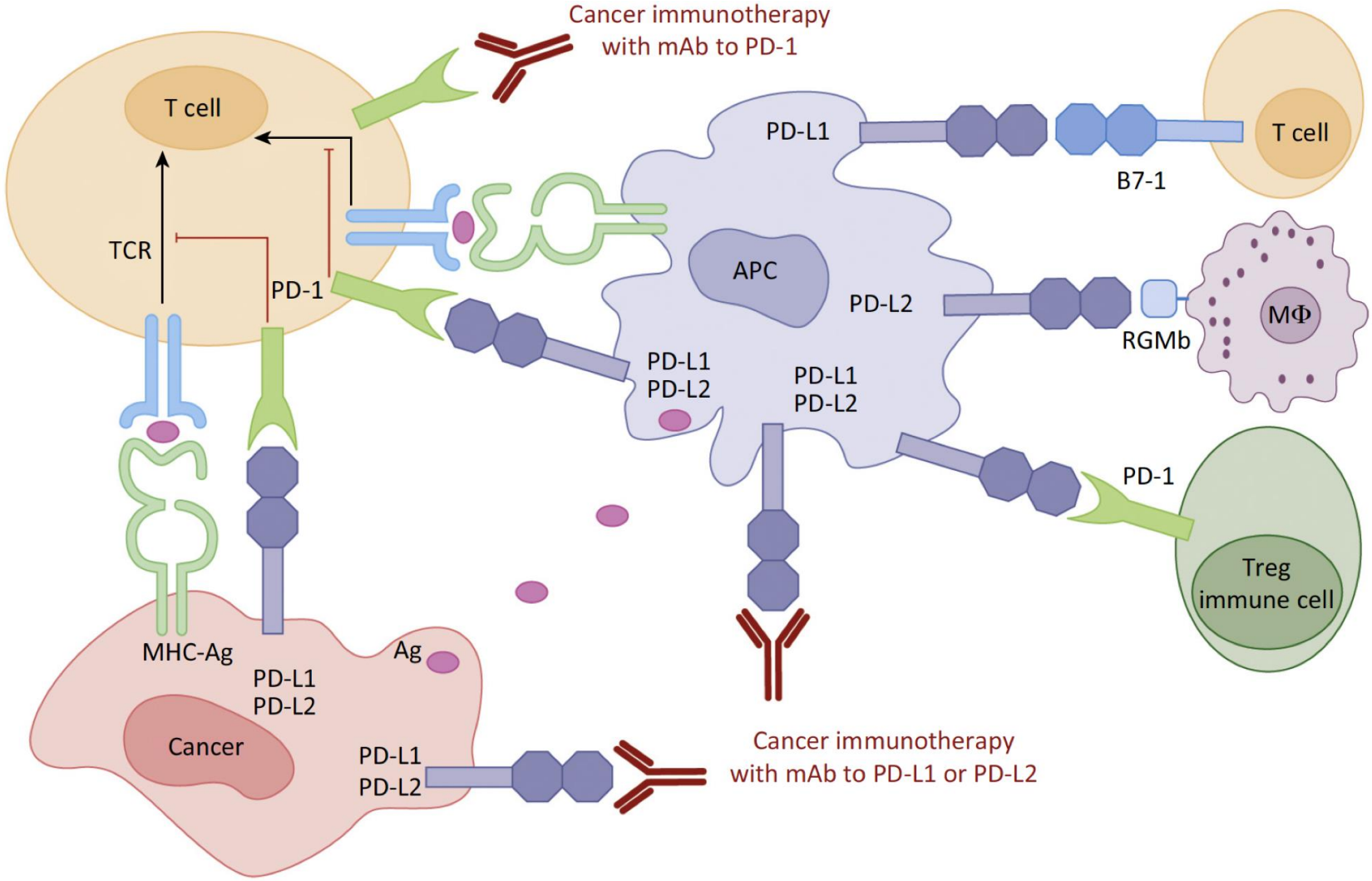
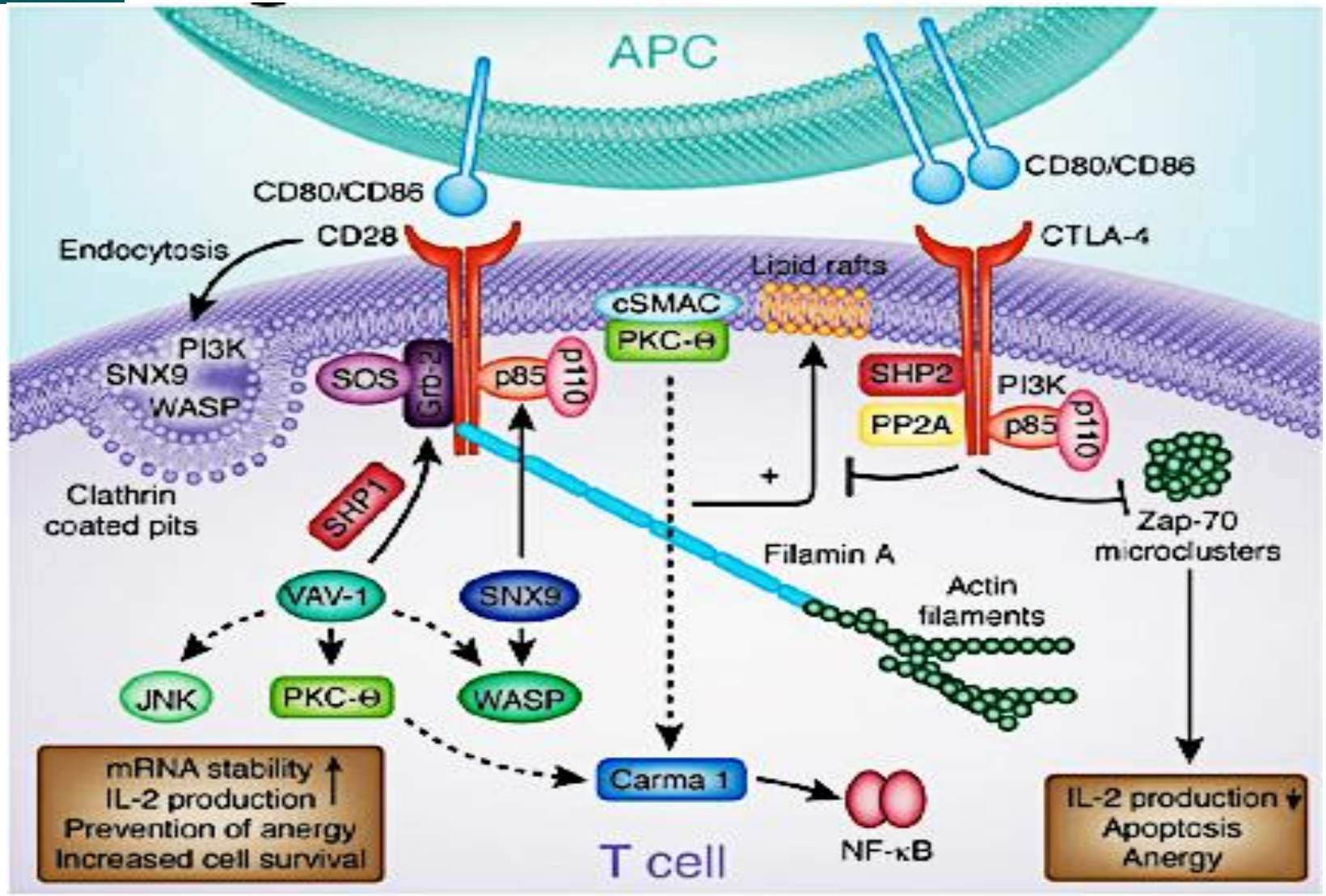
Cancer immunotherapy with anti-PD-1 and anti-PD-L1/L2 antibodies



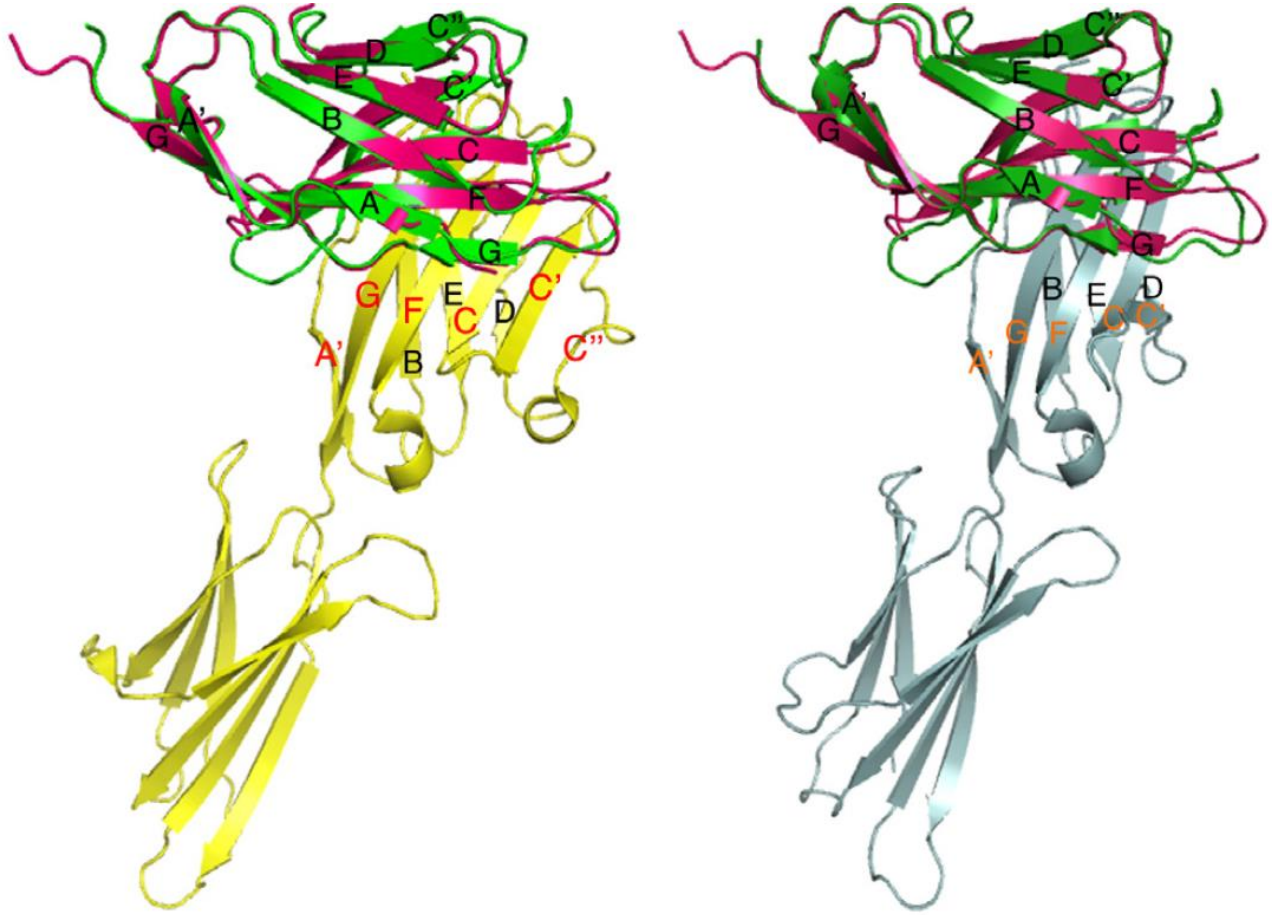
Kim C. Ohaegbulam et al. Trends in Molecular Medicine 2015, Vol. 21, No. 1

CTLA-4 signal transduction



Rudd C et al. Immunological Reviews 2009, 229: 12–26

Crystal structures of PD-1/PD-L1 (left) and PD-1/PD-L2 complexes (right)



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

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

PD-1

PD-1:PD-L1

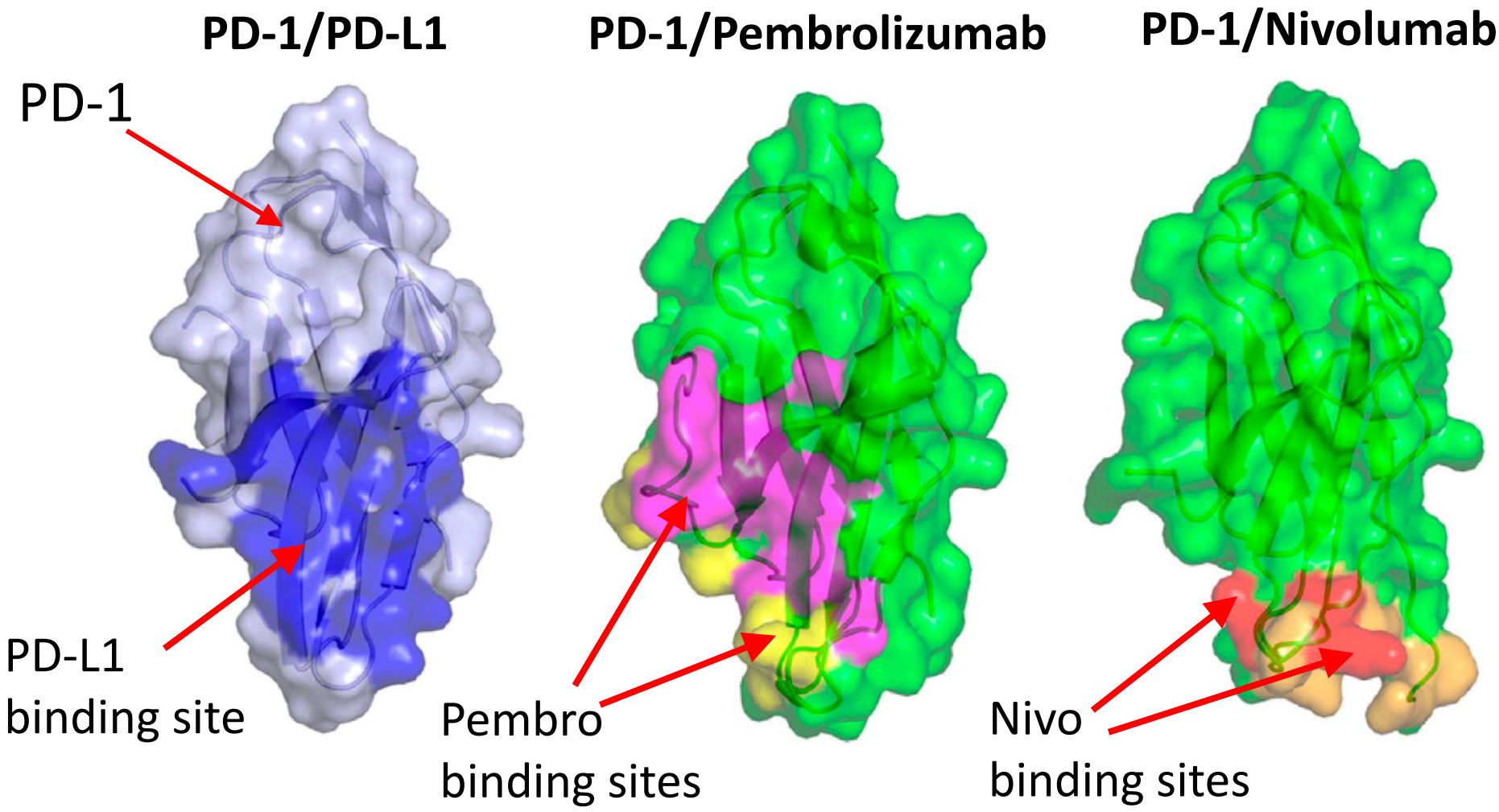
270–526 nM	Youngnak et al[49] (Scatchard plots analysis)
590–770 nM	Butte et al[48] (Scatchard plots analysis)
770 nM	Butte et al[48] (equilibrium binding†)

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

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



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

Prima Edizione
CORSO DI IMMUNOTERAPIA IN ONCOLOGIA

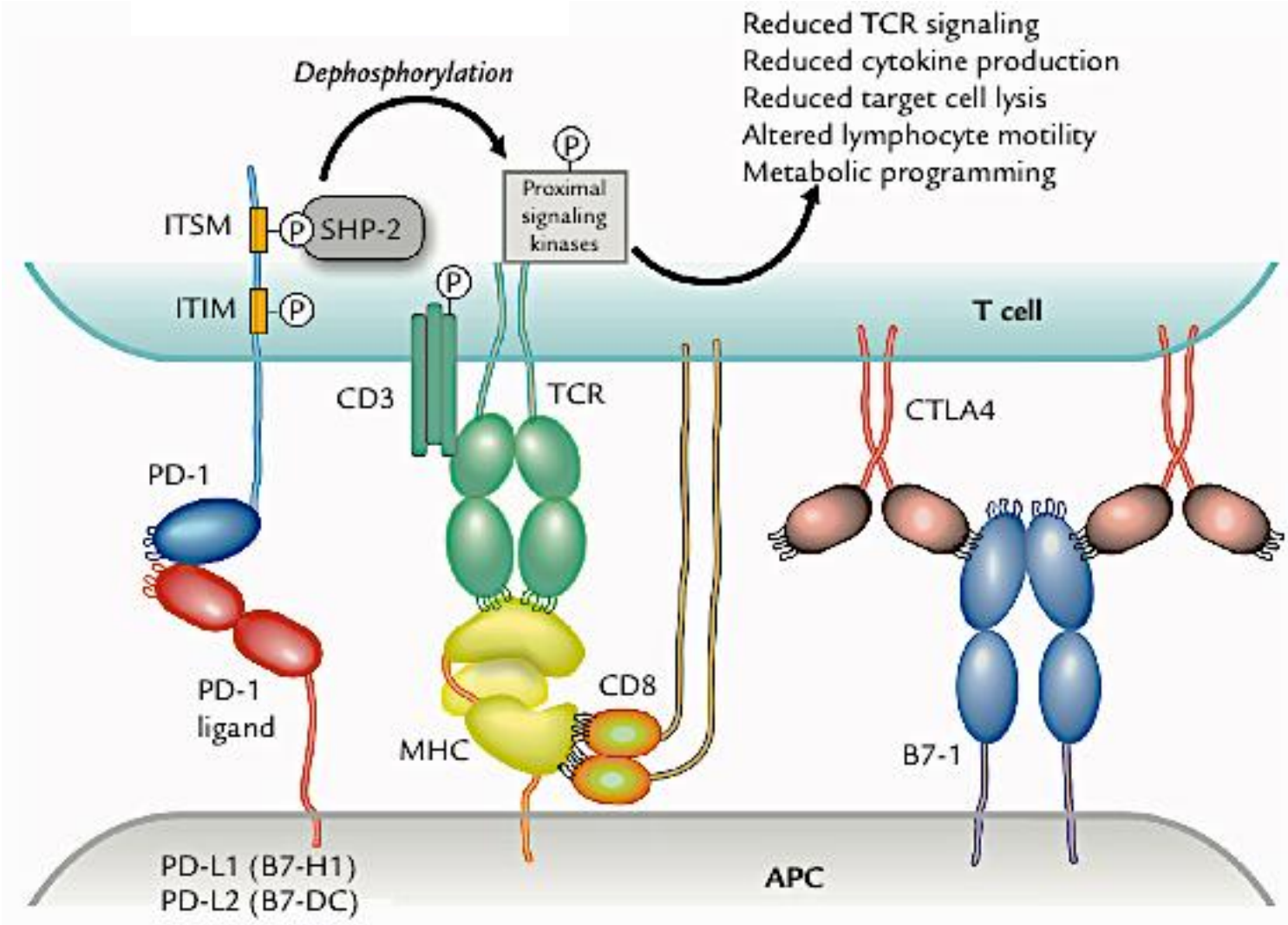
PD-1 polymorphisms

- −606A>G, 7146G>A, 7625G>A, 7785C>T, 7786G>C, 8669A>G, and 8737G>A

  - Liu C et al., Int J Genomics 2014;2014:247637

  - Dong W et al., PLoS One 2016;11(3):e0152448

PD1/PD-L1 signal transduction



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

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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

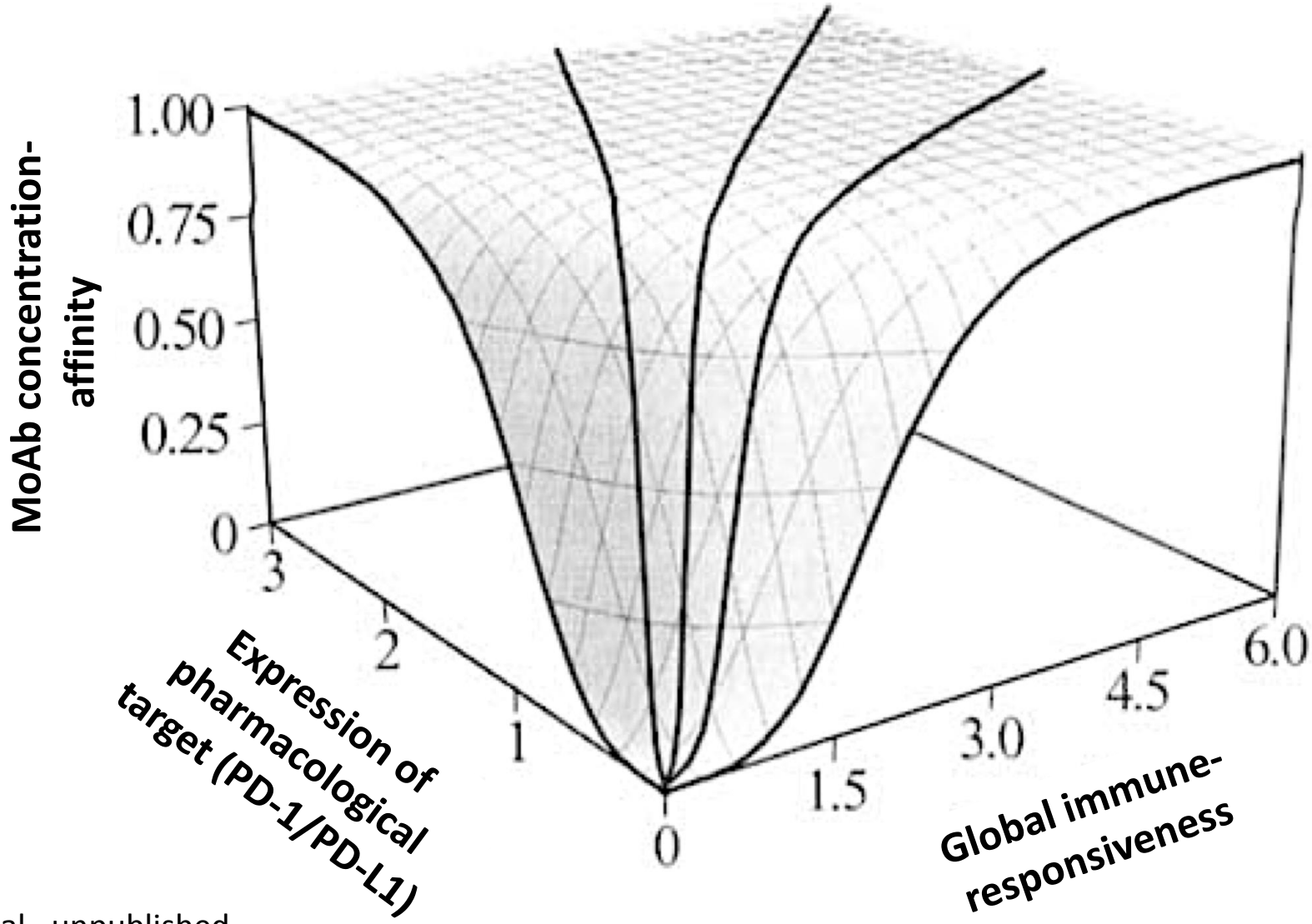
Activation of ADCC/CDC by immune-checkpoint inhibitors

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	-	BMS-936559 (IgG4), MPDL-3280A (mutated IgG1 that eliminates ADCC and CDC)

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

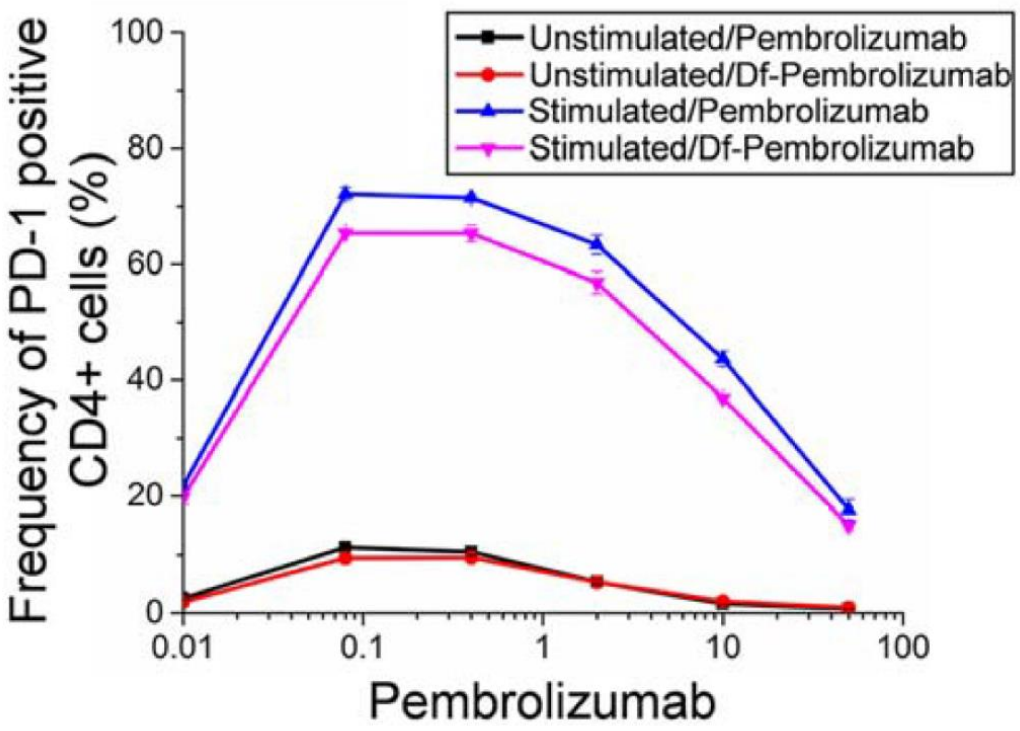
Kathleen M. Mahoney et al. Clin Ther. 2015;37:764–782

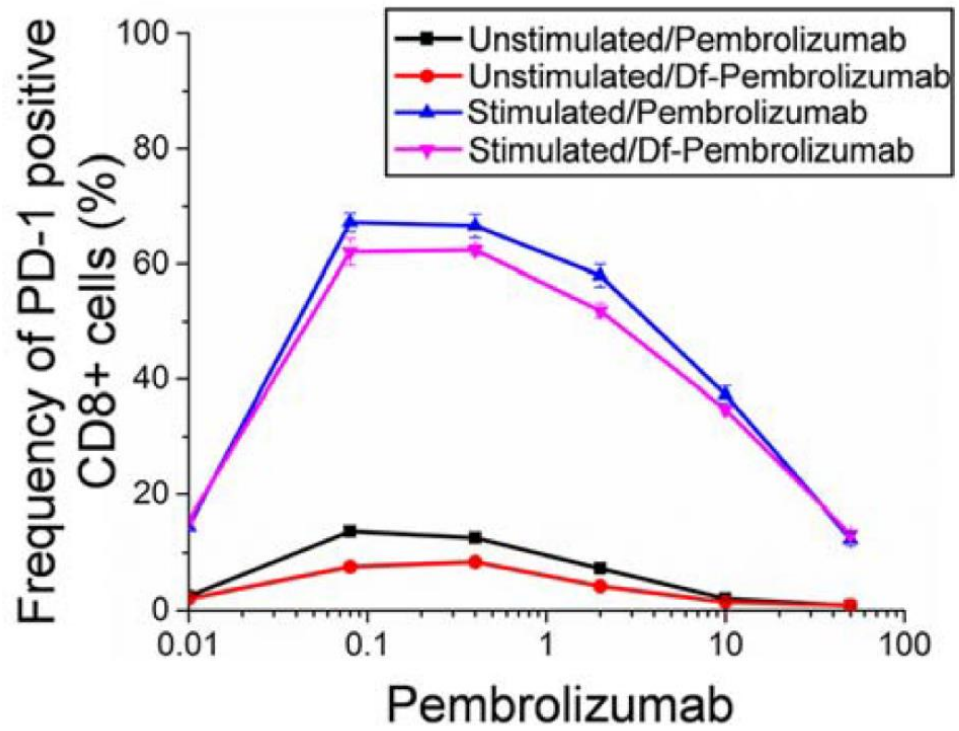
Tri-dimensional model of drug-target-immune-activation for immune checkpoint inhibitors



Danesi et al., unpublished

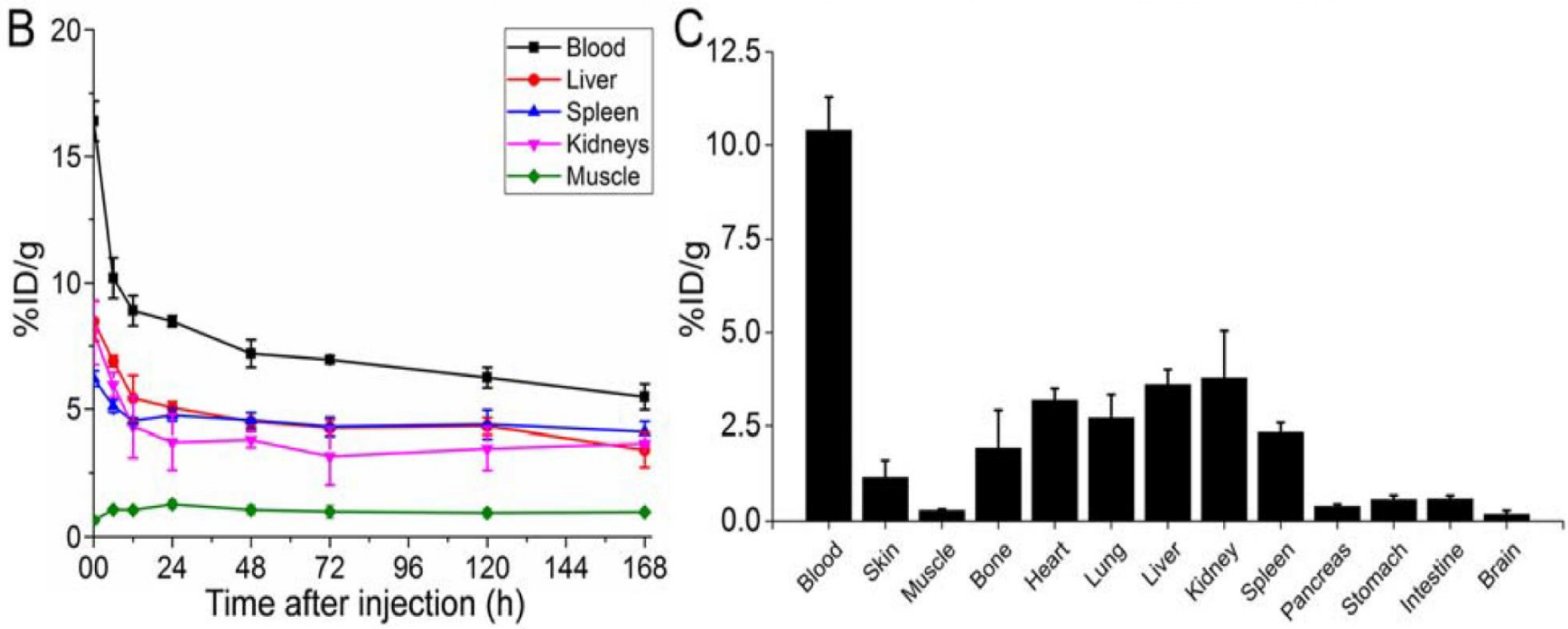
Pembrolizumab displays higher binding to stimulated T-cells





Christopher G. England et al J Nucl Med Doi: 10.2967/jnumed.116.177857

Biodistribution of [89Zr]-Df-pembrolizumab in ICR mice



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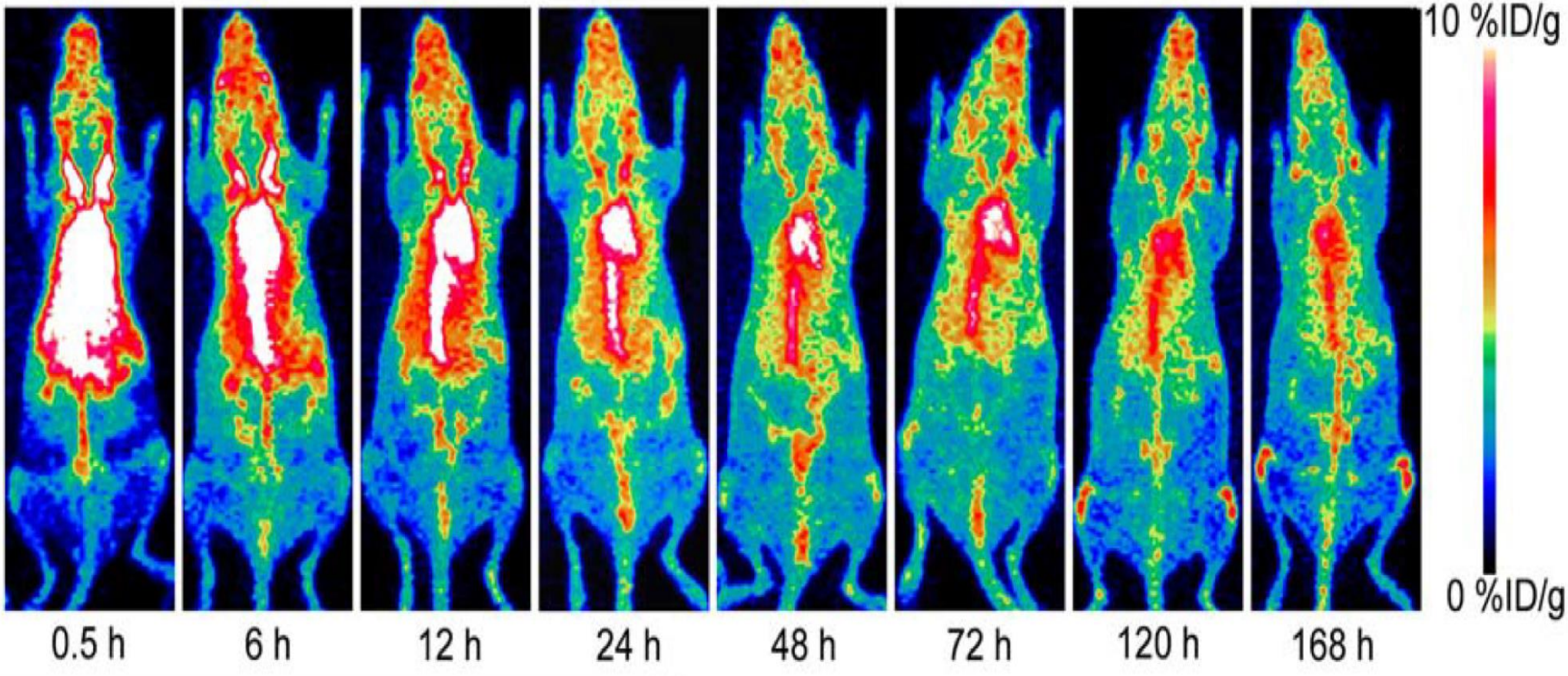
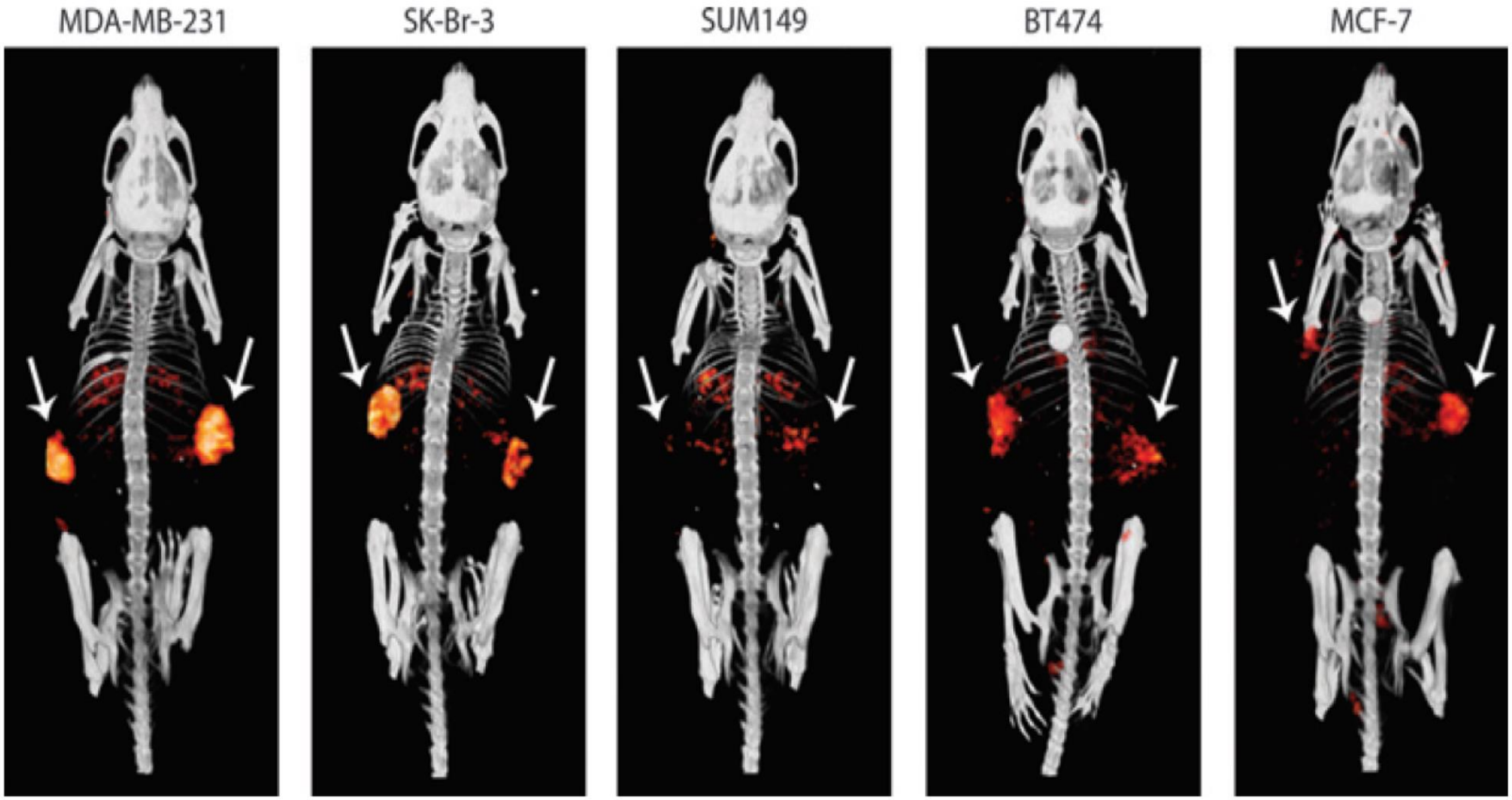


Imaging of tumor PD-L1 expression using radiolabeled anti-PD-L1 antibody



Sandra Heskamp et al. Cancer Res 2015;75:2928-2936

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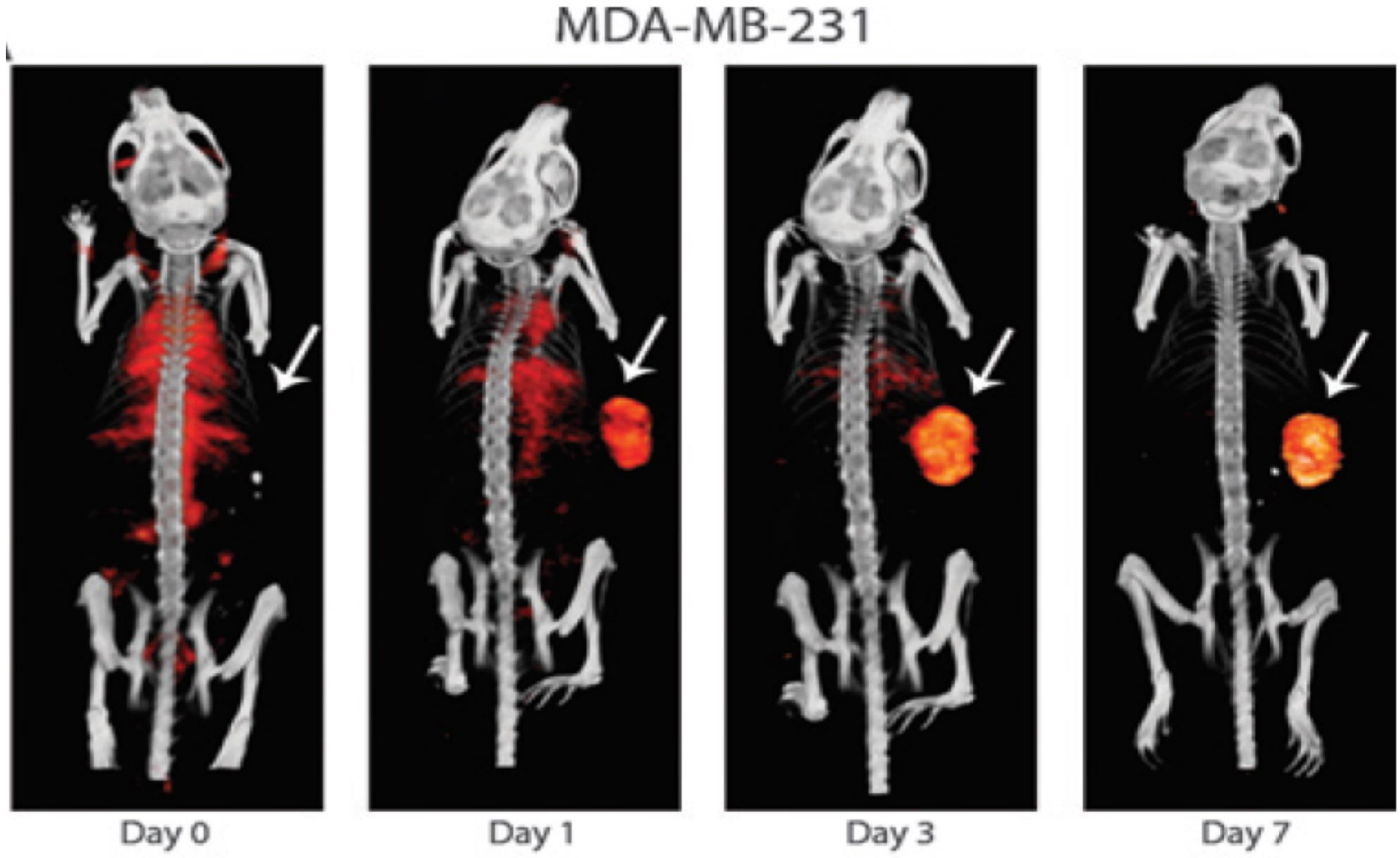

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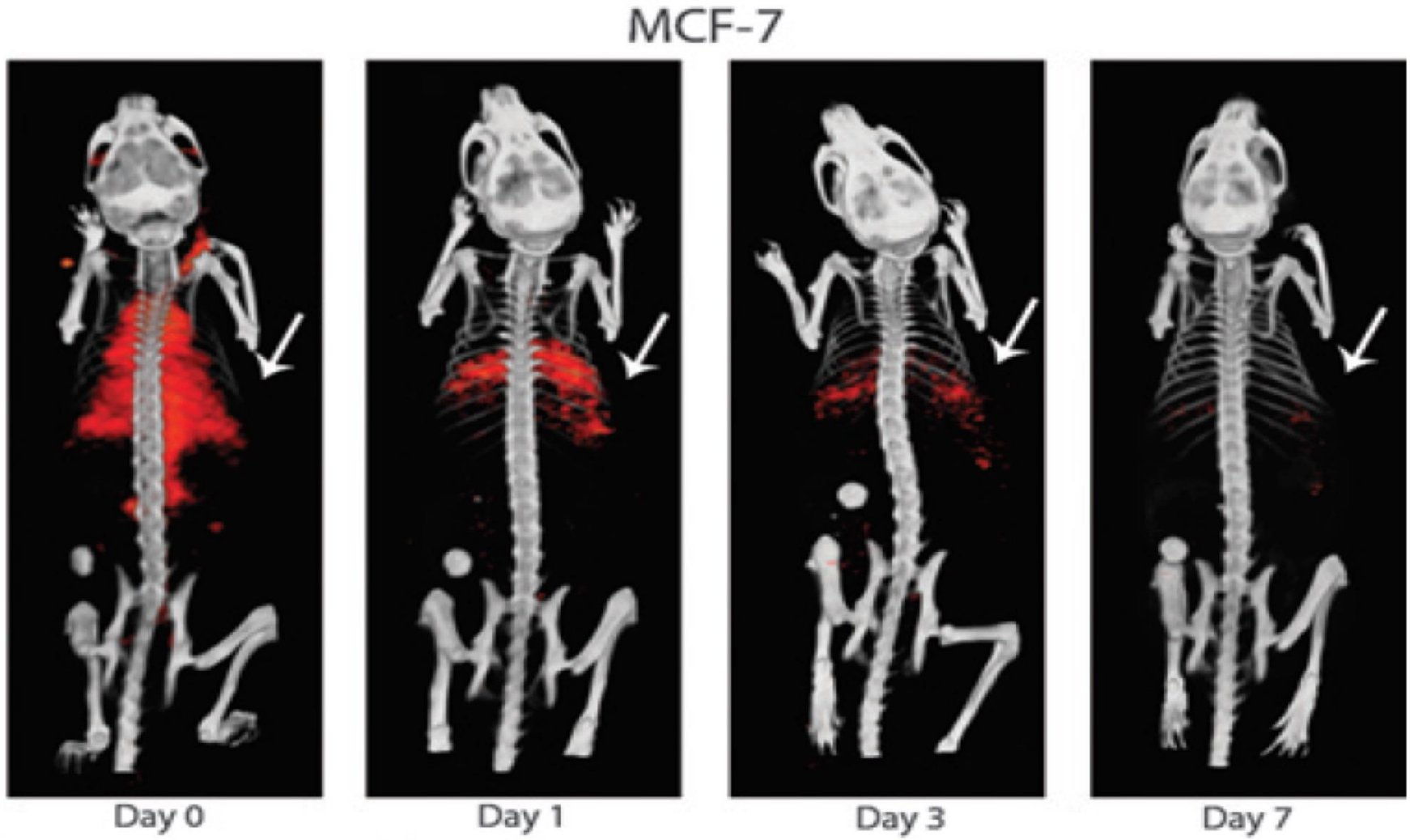

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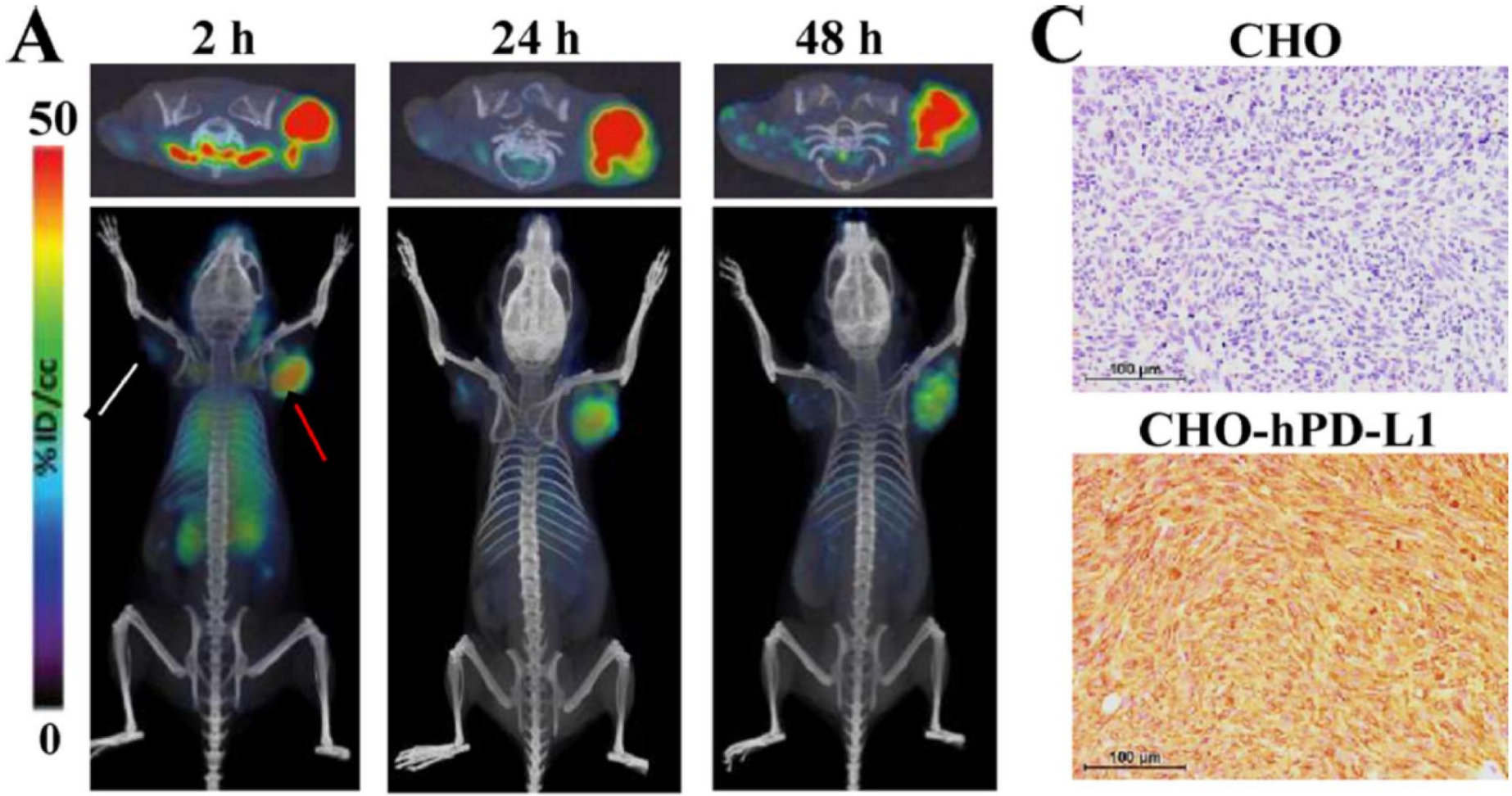
PD-L1 Detection in Tumors Using [64Cu]atezolizumab with PET



Wojciech G. Lesniak et al. Bioconjug Chem 2016; 27(9): 2103–2110

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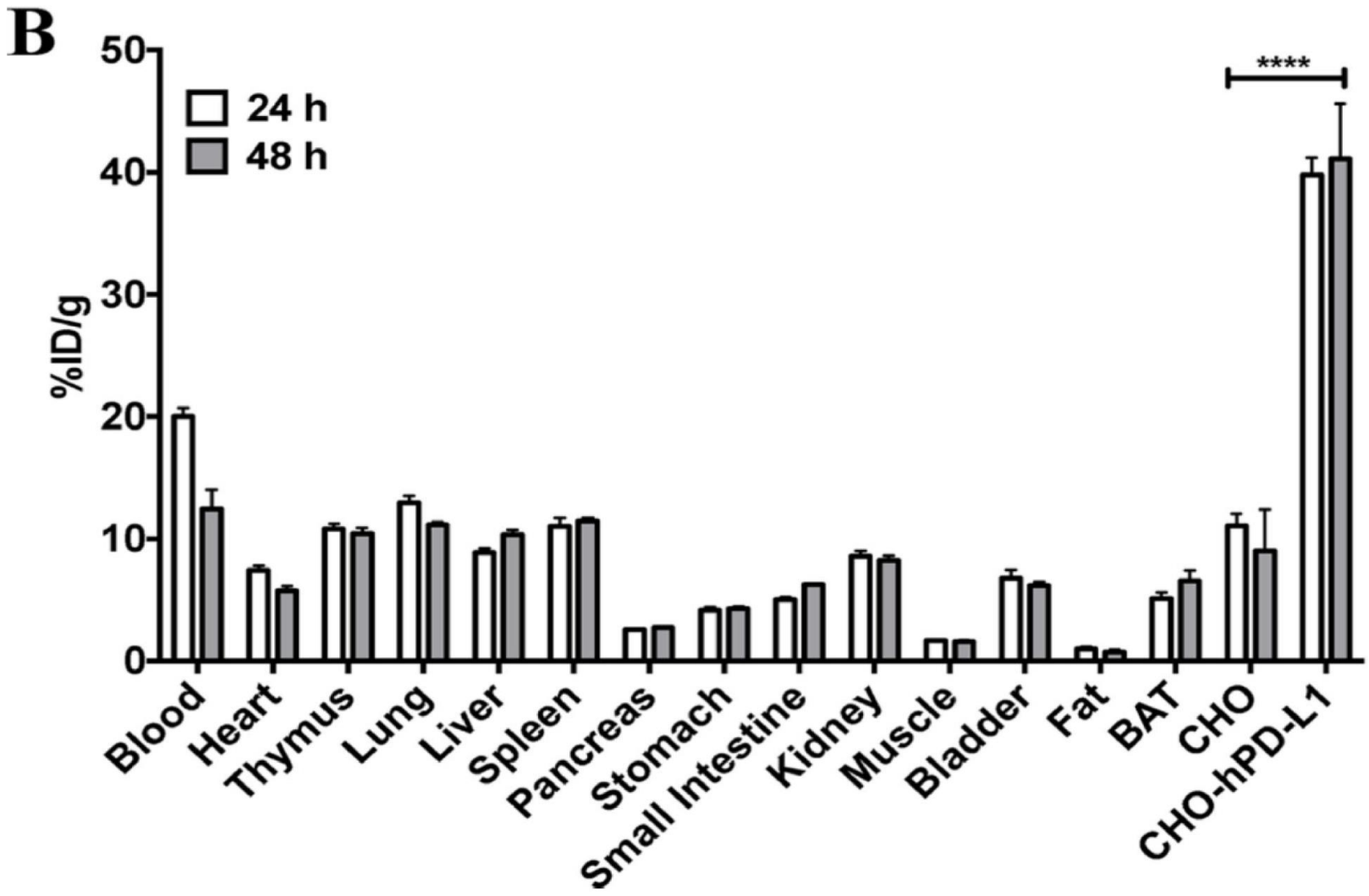
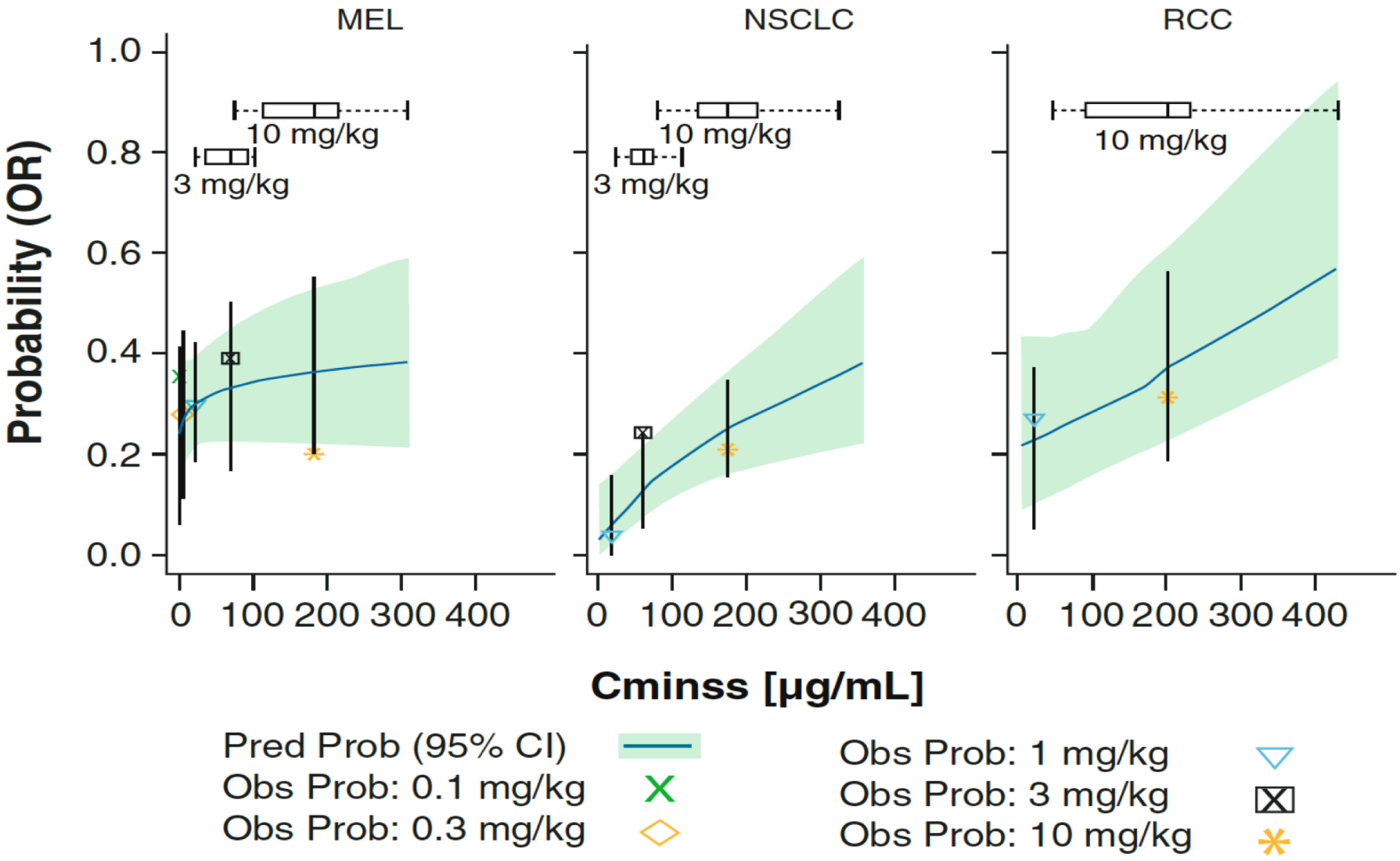


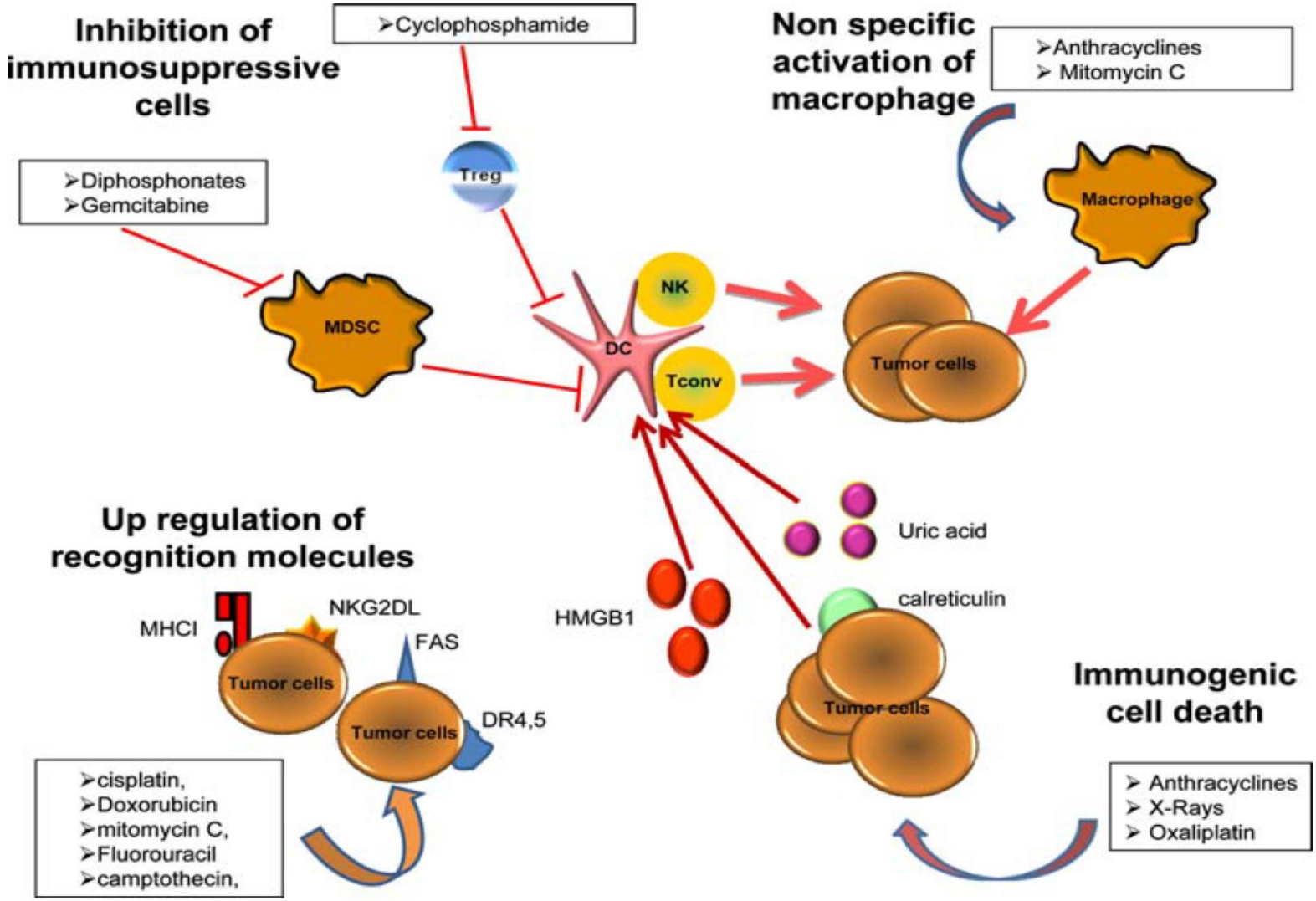
Wojciech G. Lesniak et al. Bioconjug Chem 2016; 27(9): 2103–2110

Exposure-response efficacy analysis of nivolumab by tumor type



Agrawal et al. Journal for ImmunoTherapy of Cancer (2016) 4:72

Chemotherapy: not only a cytotoxic effect, but also an adjuvant for antitumor immunity



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

Open questions

- Why are the response rates of anti-PD-1 and anti-PD-L1 variable among different cancers?
- Can response biomarkers be identified and how can these be integrated into clinical practice?
- How can anti-PD-1 and anti-PD-L1 antibodies be integrated into current treatment regimens in upfront and relapsed settings?
- Does PD-1 expressed on immune cells other than T cells play a role in anti-PD-1/PD-L1 therapy?