Come potenziare la terapia con immune checkpoint inhibitors

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HIGHLIGHTS IN EMATOLOGIA

Treviso, Ospedale Ca' Foncello

22-23 Novembre 2019

AO S.Croce e Carle
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Medicina Sperimentale

DISCLOSURES:

MASSIMO MASSAIA

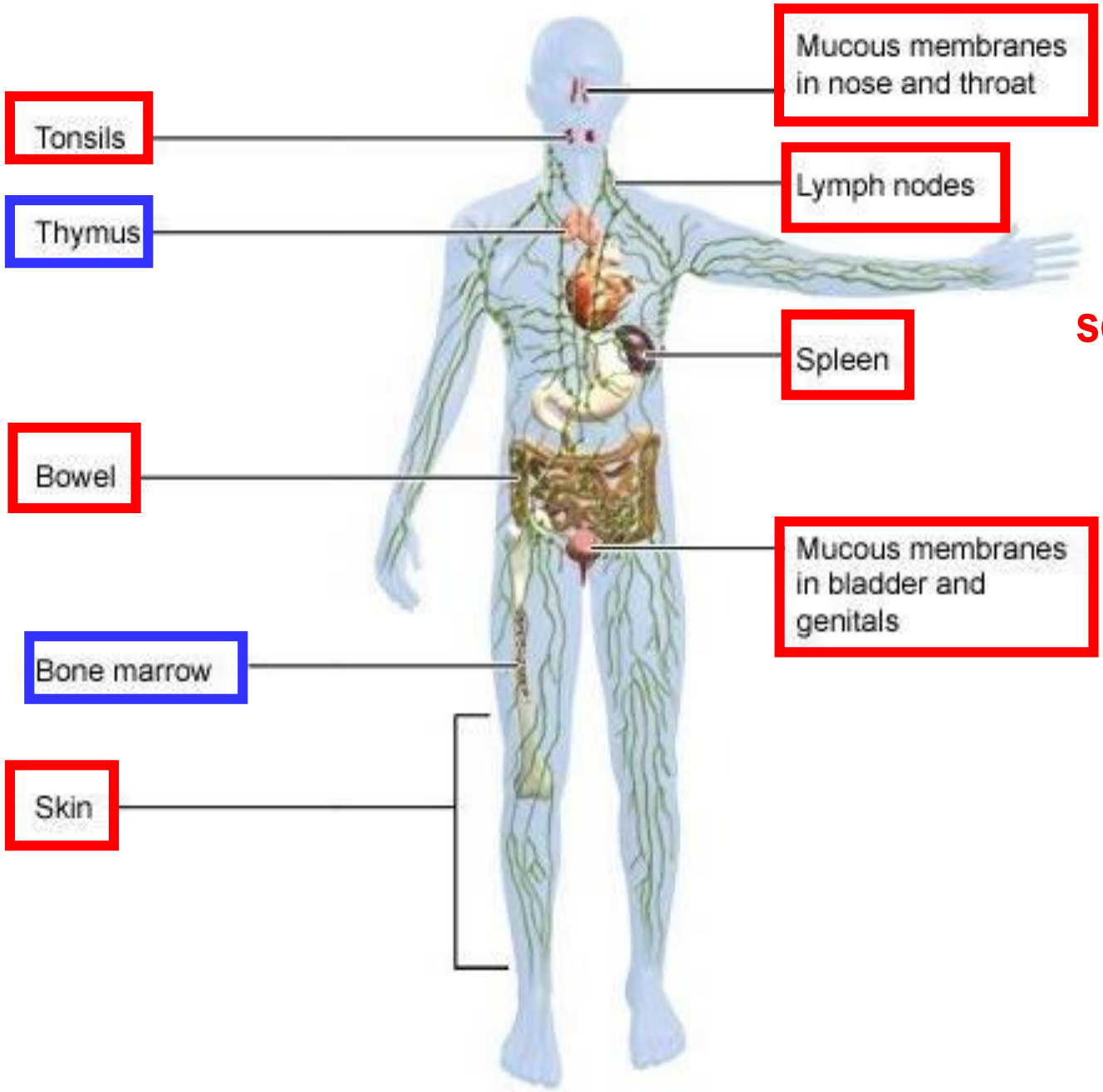
Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario: *Gilead, Novartis*

- Partecipazione ad Advisory Board: *Abbvie*, *Janssen*

The human immune system

primary lymphoid organs



secondary lymphoid organs

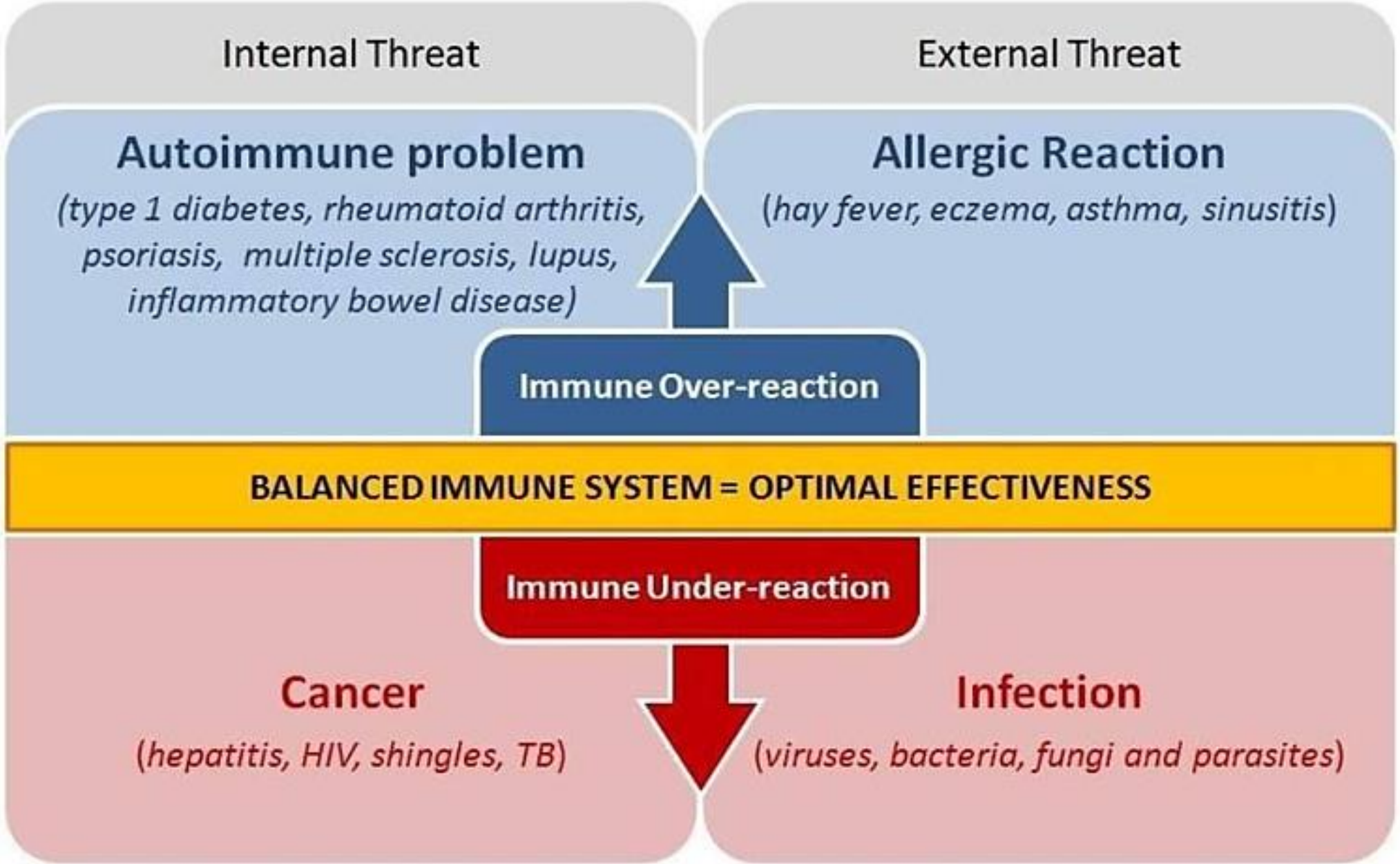
The main functions of the immune system

Immune system belongs to the basic homeostatic mechanisms

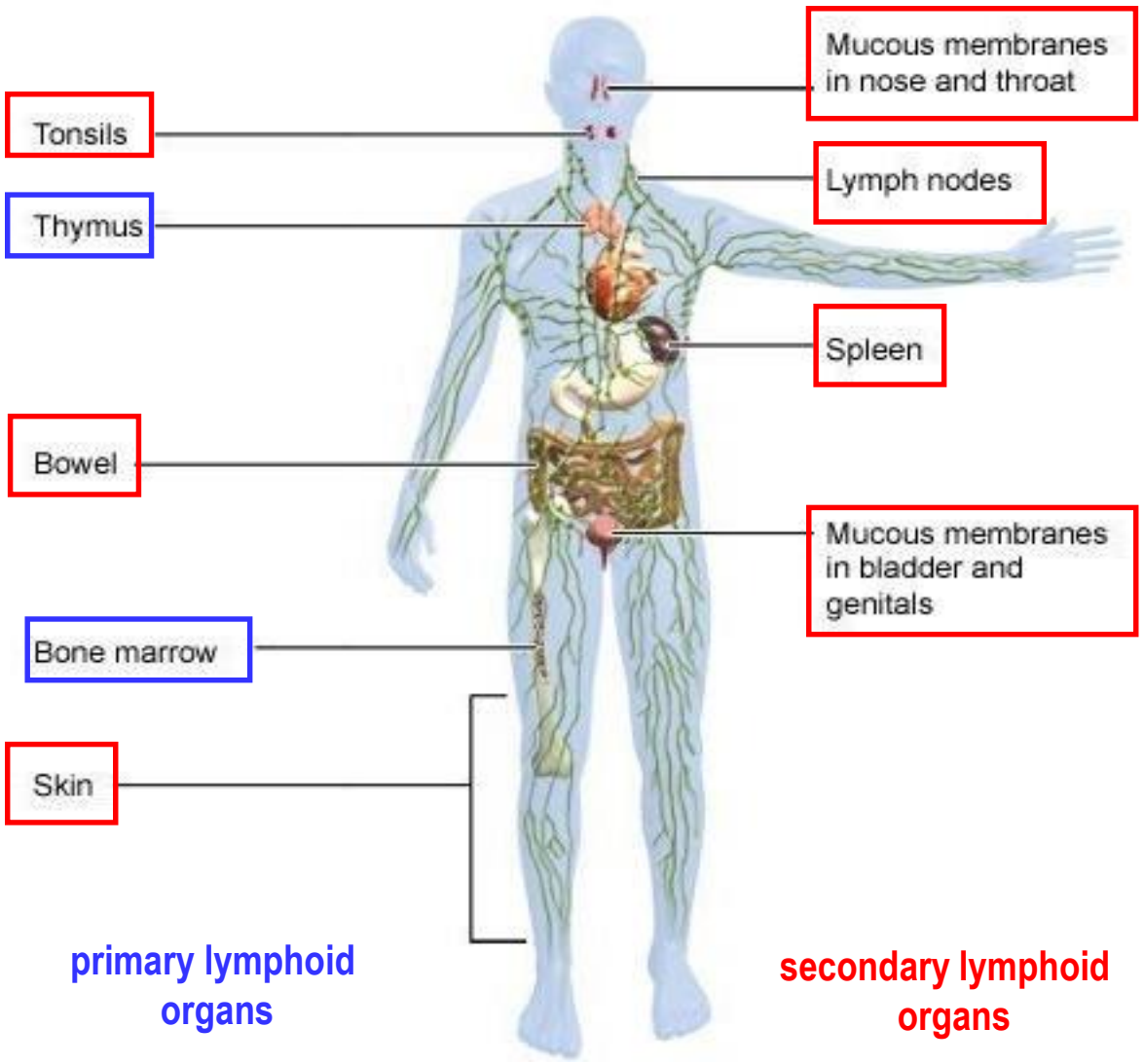
Defense - identification and protection against pathogenic microorganisms and their toxins

Autotolerance – recognition of own tissues and keeping tolerance to them

Immune surveillance - identifying and removing the old , damaged and otherwise changed cells

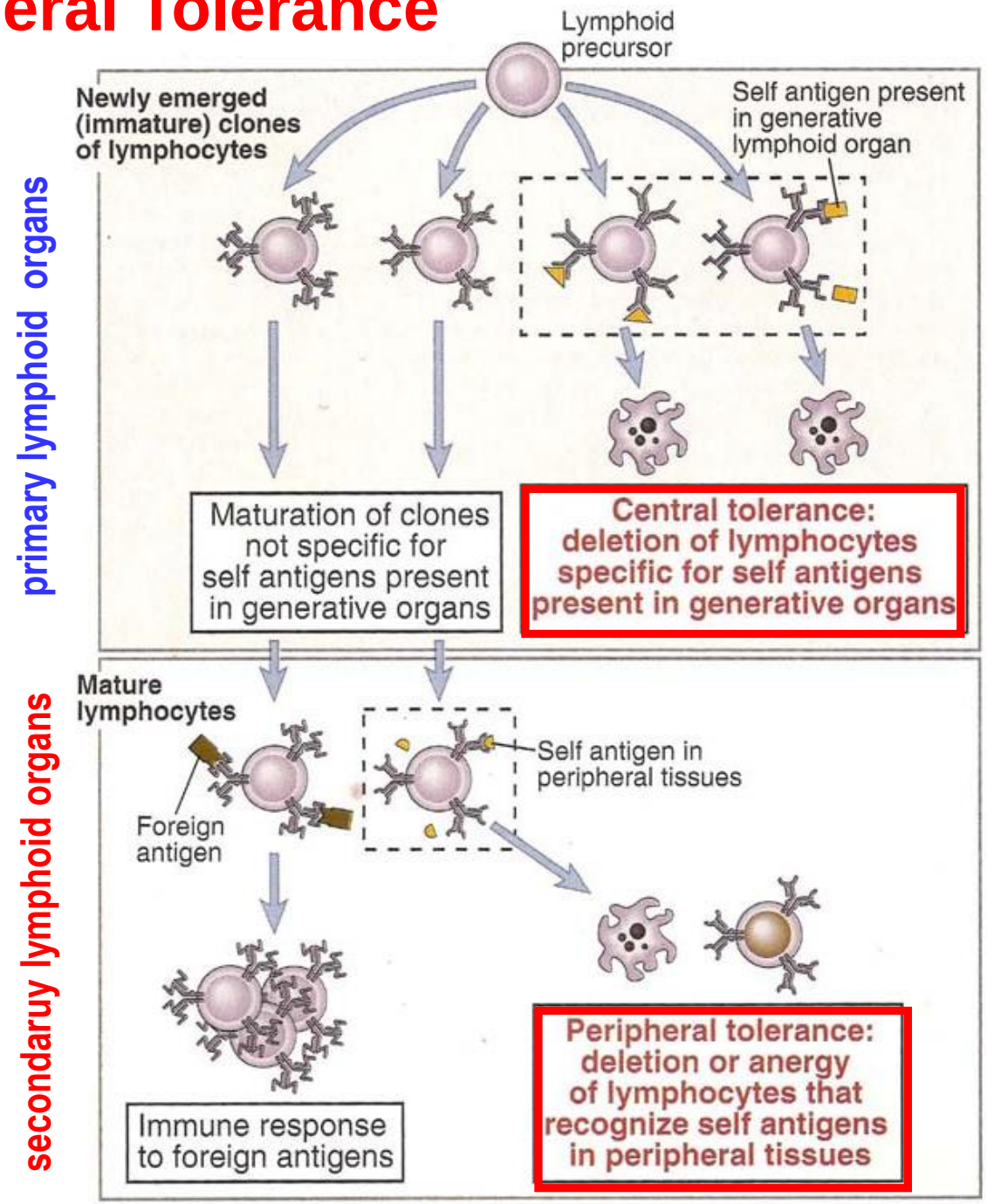

Internal Threat
External Threat
Autoimmune problem
(type 1 diabetes, rheumatoid arthritis, psoriasis, multiple sclerosis, lupus, inflammatory bowel disease)
Allergic Reaction
(hay fever, eczema, asthma, sinusitis)
Immune Over-reaction
BALANCED IMMUNE SYSTEM = OPTIMAL EFFECTIVENESS
Immune Under-reaction
Cancer
(hepatitis, HIV, shingles, TB)
Infection
(viruses, bacteria, fungi and parasites)

Central and Peripheral Tolerance

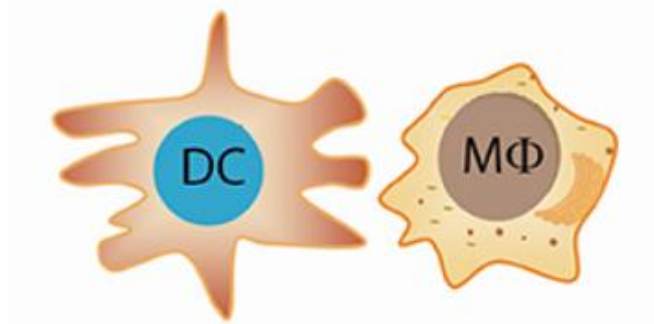


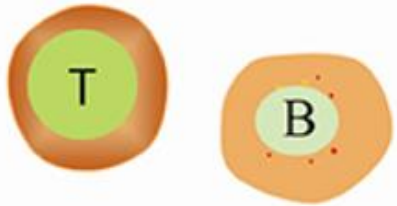
primary lymphoid organs

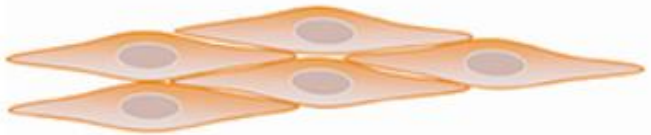
secondary lymphoid organs



Peripheral tolerance maintained by multiple negative regulatory mechanisms controlling multiple levels and phases of immune responses







Peripheral Tissue/Tumor

General Regulatory Mechanisms

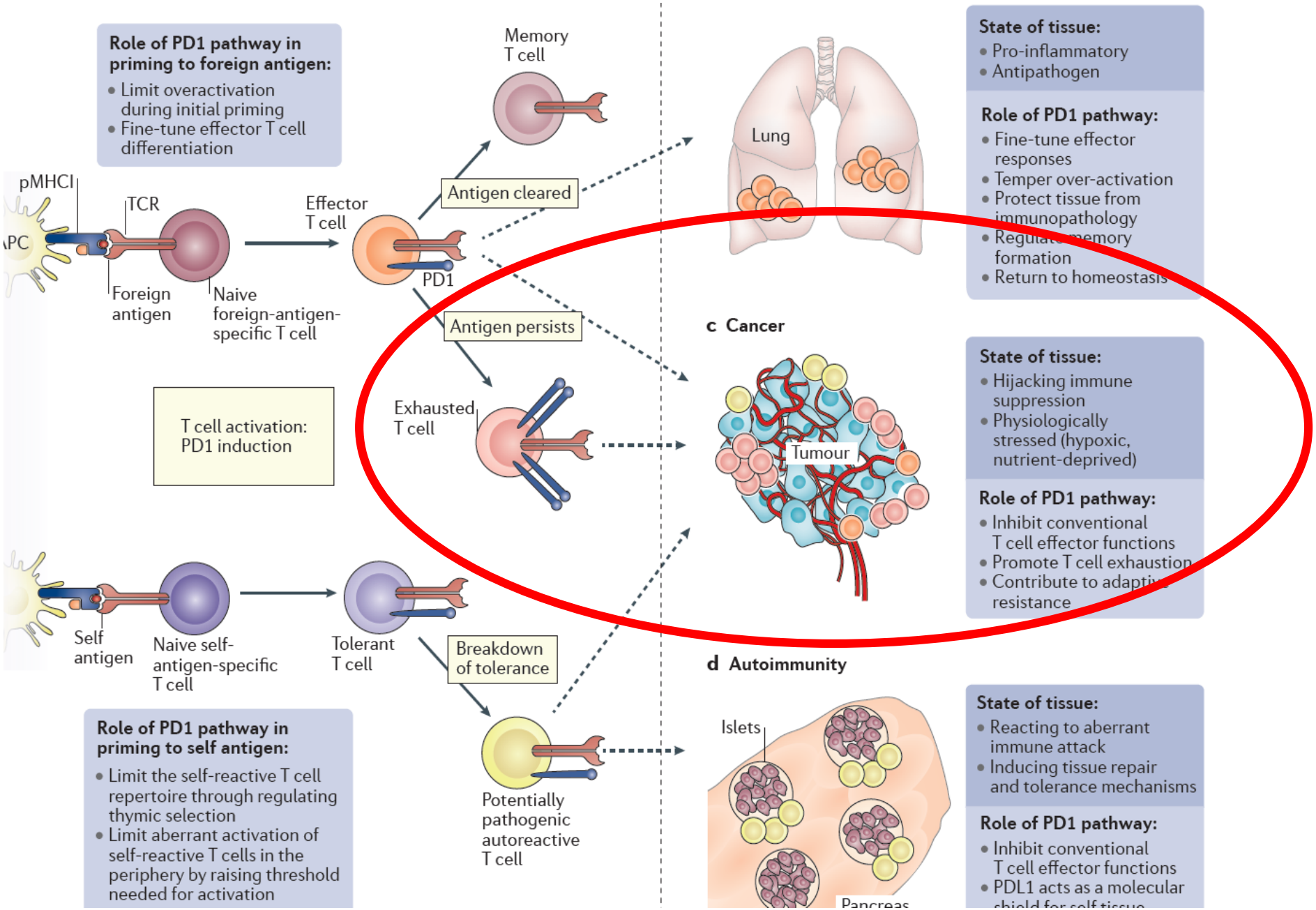
Negative regulatore (NR) of inflammatory signaling
NR of TLRs: A20, Twist, Foxj1, Foxoa3, IRAK-M, IRF-4, sTLR, MKP, etc.
NR of cytokine receptors: SOCS, PTP, PIAS & SLIM
NR of other signaling pathways: cbl, Blimp-1, etc

Inhibitory surface receptors & ligands
B7-CD28 superfamily members: CTLA4, PD1/PD-L1, B7-H4, etc.
TRIAL-R, FasL, RP105, Inhibitory Fc receptor, etc.

Soluble anti-inflammatory factors
TWEAK, IL-10, TGFb, IDO, etc

Regulatory cell subsets
Foxp3+ Treg, regulatory DCs?

Guram K, et al., *Front Immunol.* 2019 Mar 18;10:491.



Sharpe AH, et al., *Nat Rev Immunol*. 2018 Mar;18(3):153-167

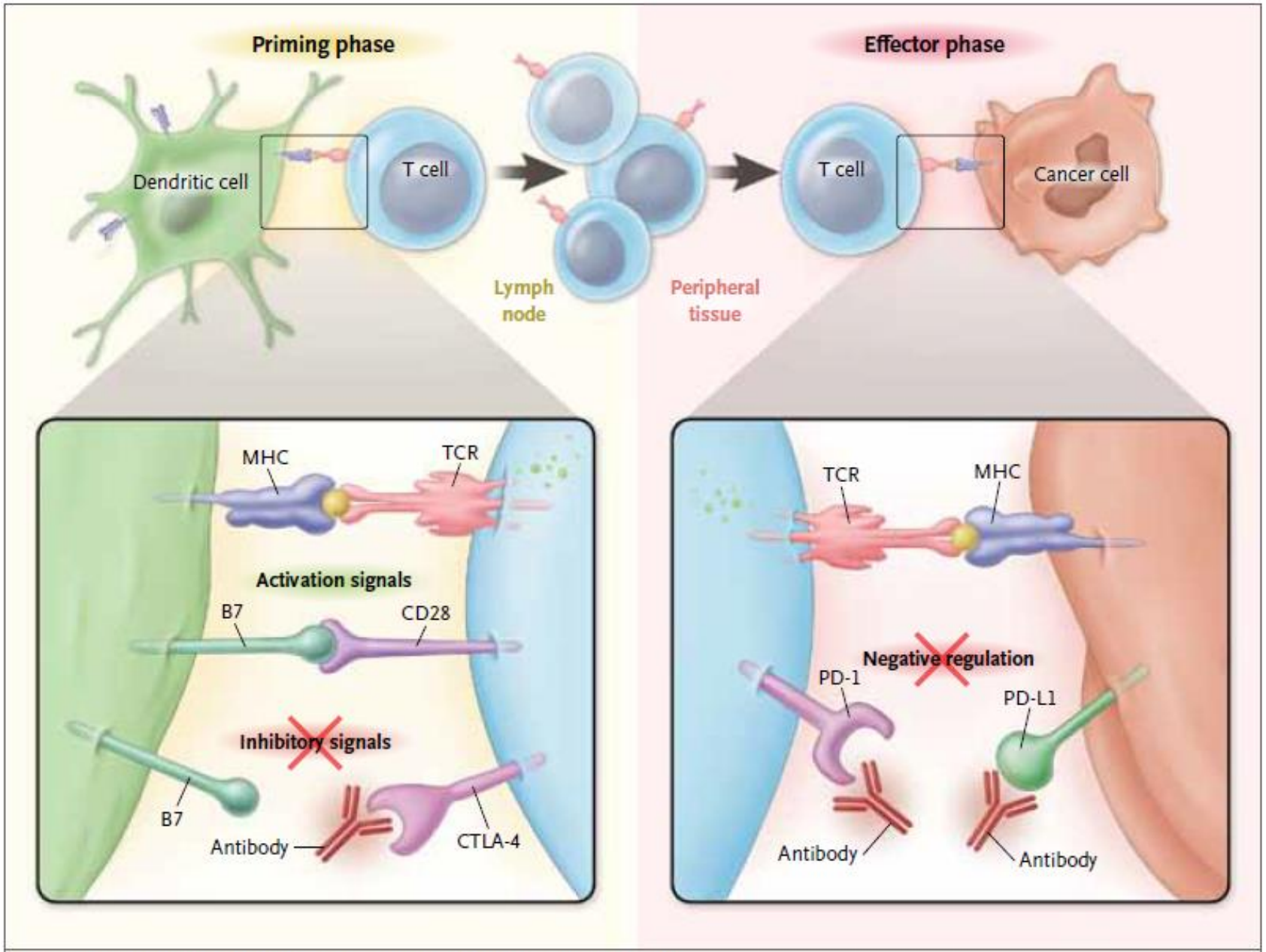
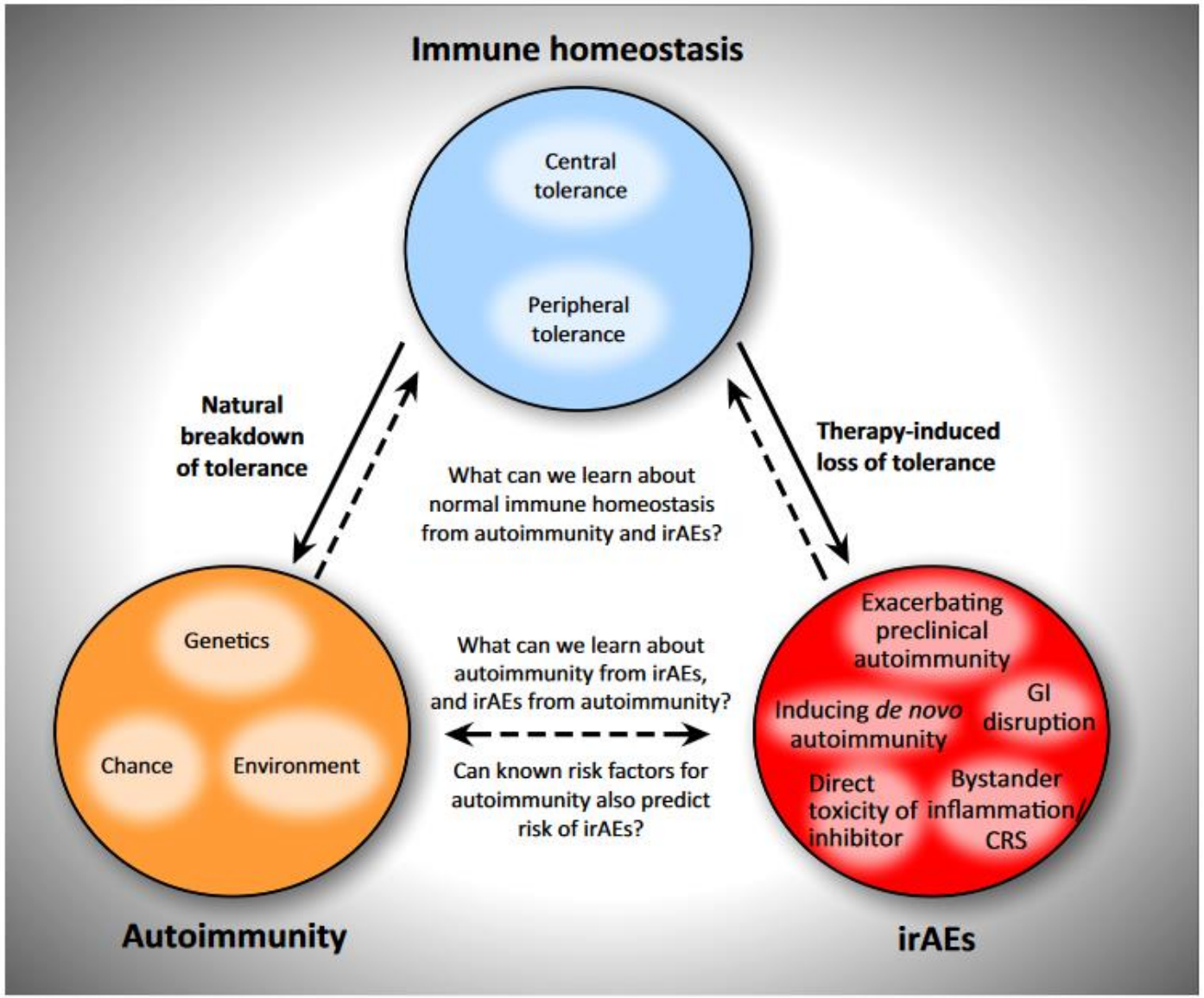


Figure 1. Blockade of PD-1 or CTLA-4 Signaling in Tumor Immunotherapy.

Ribas A.. *N Engl J Med*. 2012 Jun 28;366(26):2517-9

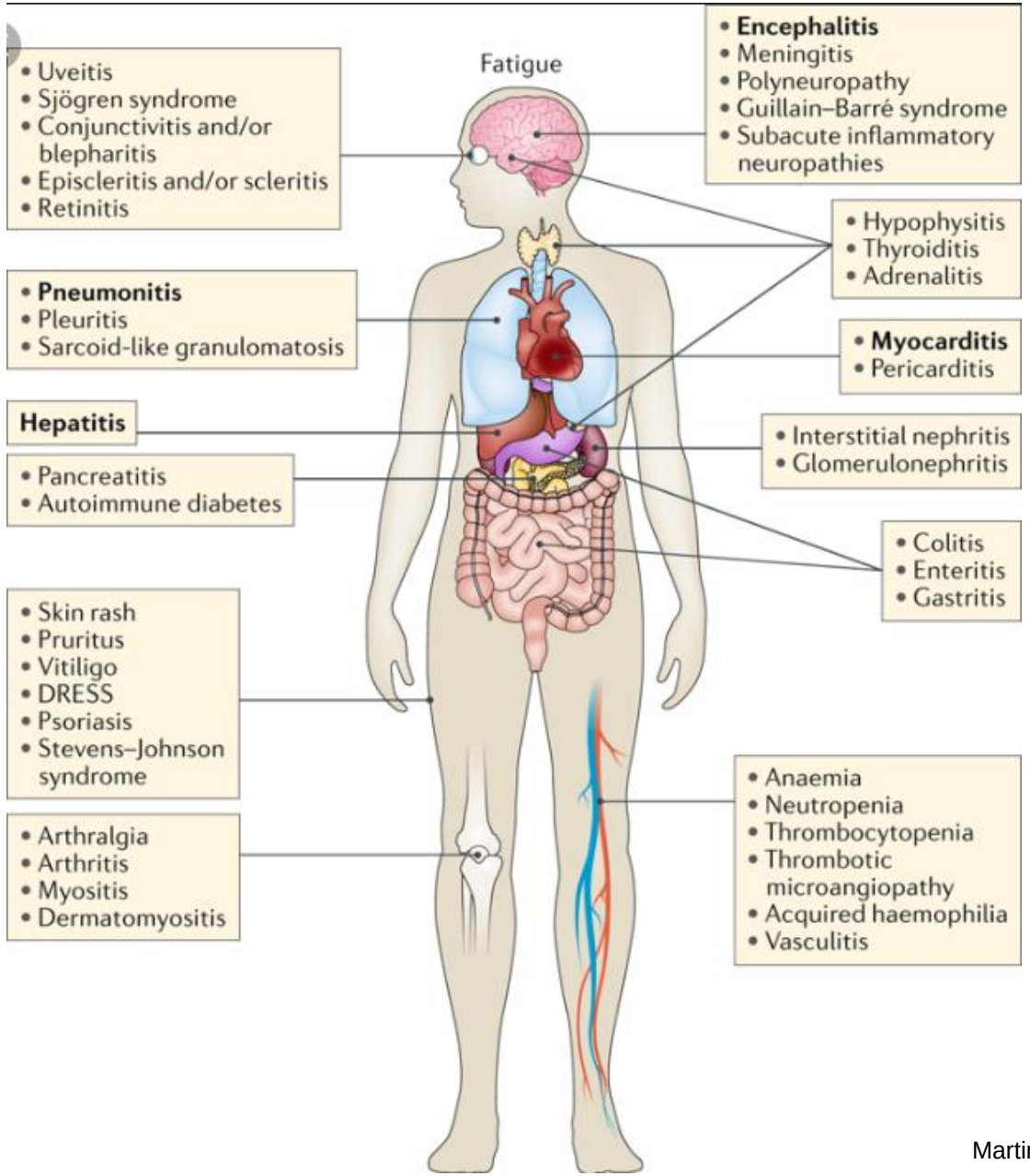
Key Figure

Pathogenic Immune Responses and Onset of Autoimmunity or irAEs



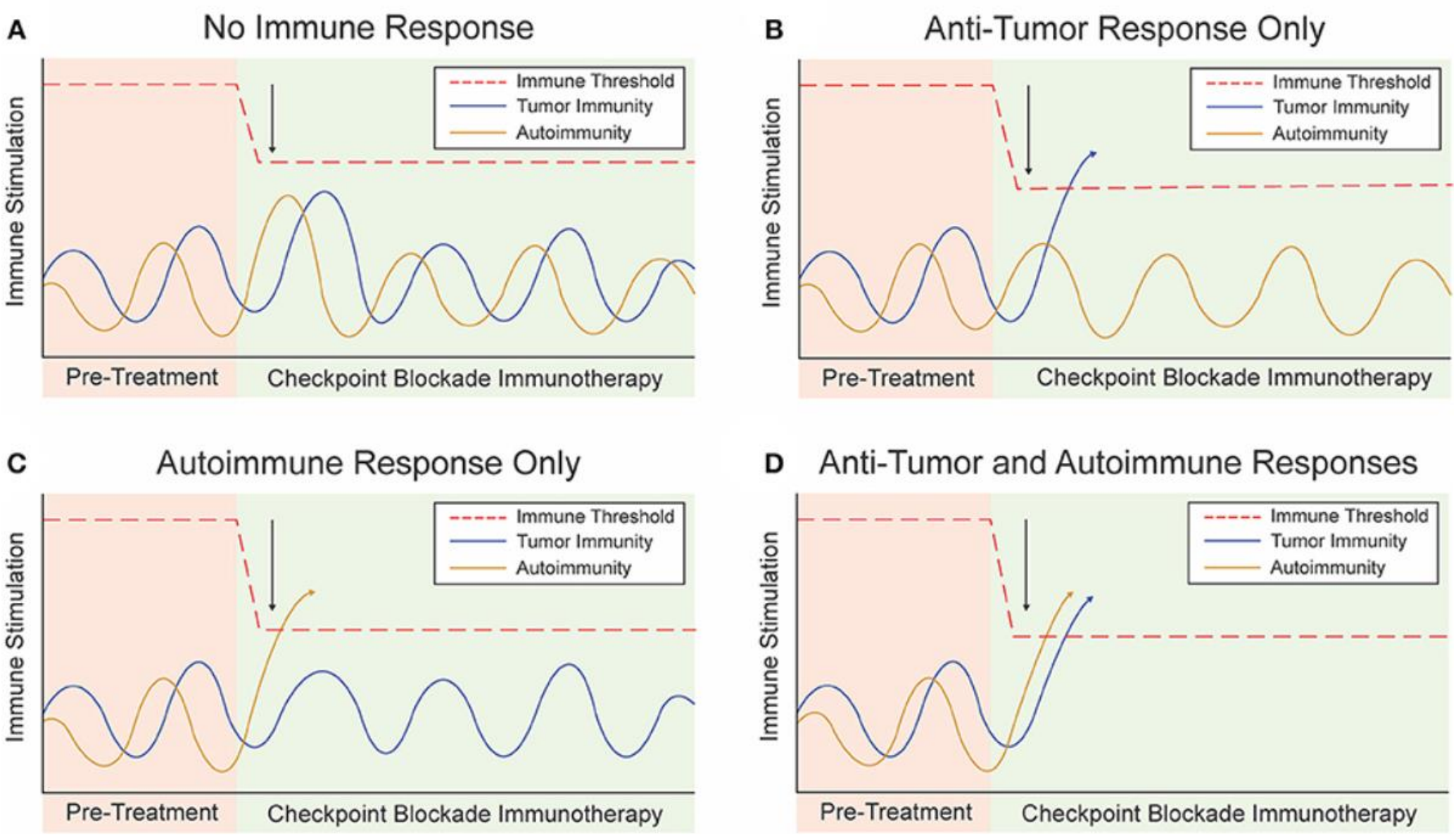
Pauken KE, et al., *Trends Immunol*. 2019 Jun;40(6):511-523.

The spectrum of IRAEs induced by ICP blockade



Martins F, et al., Nat Rev Clin Oncol. 2019 Sep;16(9):563-580.

A Threshold Model for Immune Activation



Guram K, et al., *Front Immunol.* 2019 Mar 18;10:491.

Das and Johnson *Journal for ImmunoTherapy of Cancer* (2019) 7:306
https://doi.org/10.1186/s40425-019-0805-8

Journal for ImmunoTherapy of Cancer

REVIEW Open Access

Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors

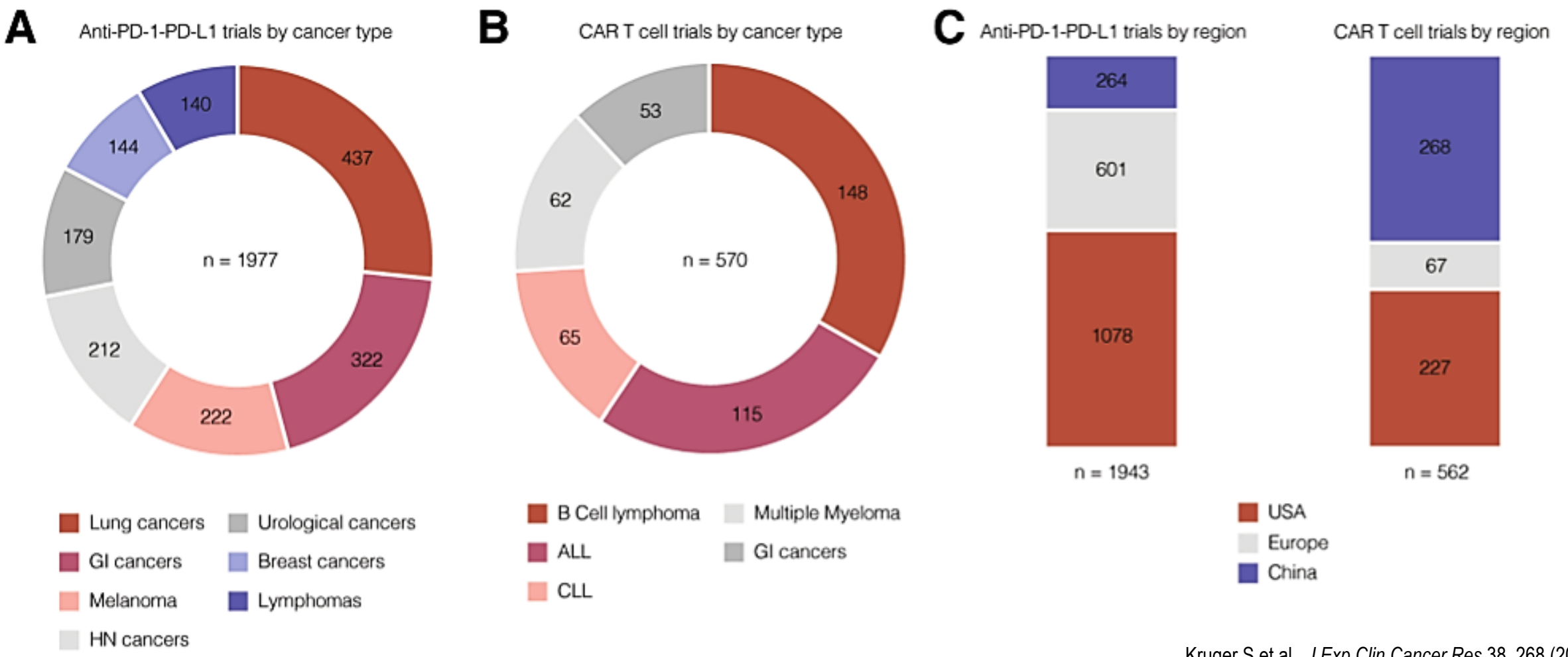
Satya Das* and Douglas B. Johnson

ORR, PFS and OS mucch better in IRAES+ vs IRAES- pts after treatment with α-PD-1/PD-1L

Das S et al., . *J Immunother Cancer*. 2019 Nov 15;7(1):306

REVIEW Open Access

Advances in cancer immunotherapy 2019 – latest trends



Kruger S et al., *J Exp Clin Cancer Res* 38, 268 (2019)

Critical Reviews in Oncology / Hematology 135 (2019) 47–58

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Programmed cell death protein receptor and ligands in haematological malignancies – Current status

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[c] Dept. of Cancer Prevention and Therapy, Wroclaw Medical University, Poland

Table 1
Clinical trials with use of PD-1 or PD-L1 inhibitors in haematological malignancies.

Disease	PD-1 or PD-L1 inhibitor	Phase of clinical trial	Author	Cinical outcome
Multiple myeloma	Pembrolizumab + Lenalidomide + Low-Dose Dexamethasone for Relapsed/Refractory Multiple Myeloma	I	Mateos et al.	ORR = 76% VGPR = 24% PR = 53% [illegible] 94%
	Pembrolizumab + Pomalidomide + Low-Dose dexamethasone for relapsed/refractory multiple myeloma	II	Bardos A. et al.	ORR = 60% sCR = 6% [illegible] = 174 months
Chronic Lymphocytic Leukemia	Pembrolizumab in chronic lymphocytic leukemia with Richter's transformation (RT) and relapsed CLL	II	Ding W. et al.	ORR in patients with [illegible] = 44% ORR in CLL patients = 0% OS in patients with RT = 107 months
Relapsed or Refractory Hematologic Malignancy:	Nivolumab	Ib	Lesokhin, A.M et al.	ORR for FL = 40% ORR for DLBCL = 36% ORR for other BCL = 15% ORR for MF = 40%
	Nivolumab + Ipilumab	Ib	Ansell S et al.	ORR for HL = 74% ORR for B-cell NHL = 20% ORR for T-cell NHL = 9% ORR for MM = 0%
	Pidilizumab	I	Berger R. et al.	ORR = 33%
Acute myeloid leukemia (AML)	Nivolumab + Azacitidine in with Relapsed Acute Myeloid Leukemia (AML)	I/II	Daver N. et al.	ORR = 69% CR = 18% Median OS = 9,3 months
Myelodysplastic syndrome (MDS)	Nivolumab with Azacitidine in untreated patients with Myelodysplastic Syndromes and [illegible] vs Nivolumab as single after treatment wih Hypomethylating Agents	I/II	Garcia-Manero G. et al.	ORR in AZA + Nivo = 69% CR in AZA + Nivo = 15% HI in AZA + Nivo = 15% Nivo vs Ipi monotherapy ORR = 0% vs 22% (p = 0.156)
	Pembrolizumab	II	Garcia-Manero G. et al.	ORR = 4% PR = 4% Marrow CR = 11% HI = 11% Overall Survival Rate after 24 weeks = 49%
Hodgkin lymphoma (HL)	Nivolumab in Relapsed or Refractory Hodgkin's [illegible]	I	Ansell S. et al.	ORR = 87% CR = 17% PFS at 24 weeks = 86%
	Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma	II	Timmerman J.M et al.	ORR = 68% CR = 8% PFS after 6 months = 77% PFS after 12 months = 546%
	Nivolumab in in Japanese patients with relapsed or refractory classical Hodgkin lymphoma.	II	Maruyama D. et al.	ORR = 81.3% CR = 23% PR = 53% OS after 6 months = 100%
	Pembrolizumab in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure	I	Armand P. et al.	ORR = 65% CR = 16% PFS rate after 24 weeks 69% PFS rate after 52 weeks = 46%
	Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma.	II	Chen R. et al.	ORR = 69% CR = 224%
Diffuse large B-cell lymphoma (DLBCL)	Pidilizumab after autologous hematopoietic stem-cell transplantation for diffuse large B-cell lymphoma	II	Armand P. et al.	ORR = 51% PFS rate after 16 months = 70% CR = 34%
	Pembrolizumab in relapsed/refractory primary mediastinal large B-cell lymphoma.	Ib	Zinzani PL. Et al.	ORR = 41% CR = 12%
Non-Hodgkin lymphoma (FL + DLBCL)	Atezolizumab + Obinutuzumab in relapsed /refractory NHL	Ib	Palomba M.L. et al.	ORR for FL = 57% ORR for DLBCL = 16%
Follicular lymphoma	Pidilizumab + Rituximab in relapsed follicular lymphoma	II	Westin J.R. et al.	ORR = 66% CR = 52%
Mycosis Fungoides and Sezary Syndrome	Pembrolizumab in Relapsed/Refractory Mycosis Fungoides and Sezary Syndrome	II	Khodadoust M. et al.	ORR = 38% CR = 4% PFS rate after one year = 69%

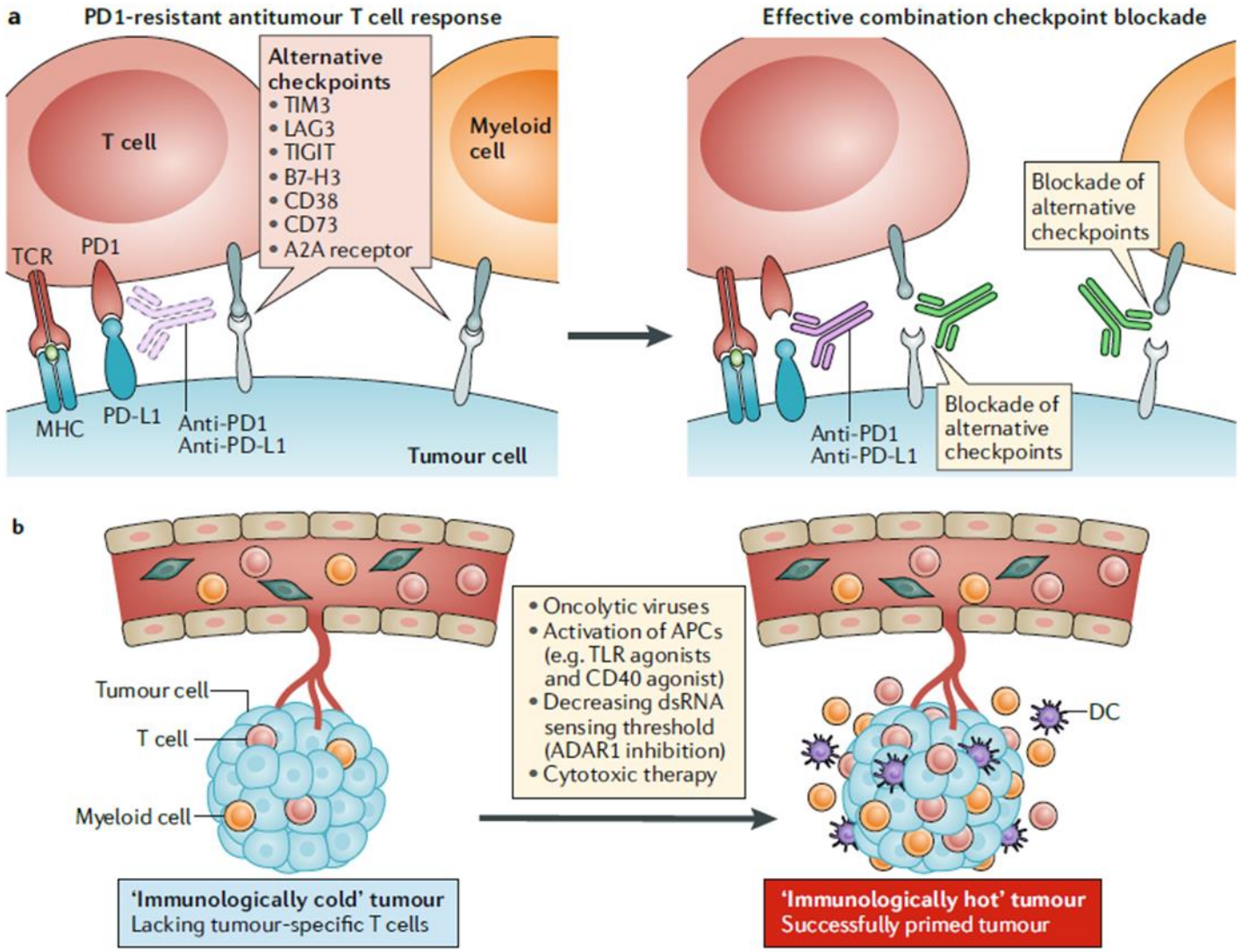
: Sokołowski M et al., *Crit Rev Oncol Hematol*. 2019 Mar;135:47-58.

ICP blockade in myeloid malignancies: a promise under investigation

Intervention	Outcomes
Nivolumab + 5-AZA	75% CR/CRp; 50% 1-year survival
Nivolumab + 5-AZA	ORR: 33% (22% CR/CRi); median OS 6.3 months
Idarubicin + cytarabine ± nivolumab	77% CR/CRi; median OS 18.54 (nivolumab group) vs 13.2 months (I + A alone), p = 0.2
Pembrolizumab + decitabine	1 MRD-negative CR; median OS 7 months
Ipilimumab + 5-AZA	71% CR/CRp; 68% 1-year survival

1: Bewersdorf JP, et al., *Expert Rev Anticancer Ther*. 2019 May;19(5):393-404

Mechanisms of innate and acquired resistance to immune checkpoint inhibition (I)



Kalbasi A, et al., *Nat Rev Immunol.* 2019 Sep 30.

Mechanisms of innate and acquired resistance to immune checkpoint inhibition (III)

a Oncogenic signalling pathways

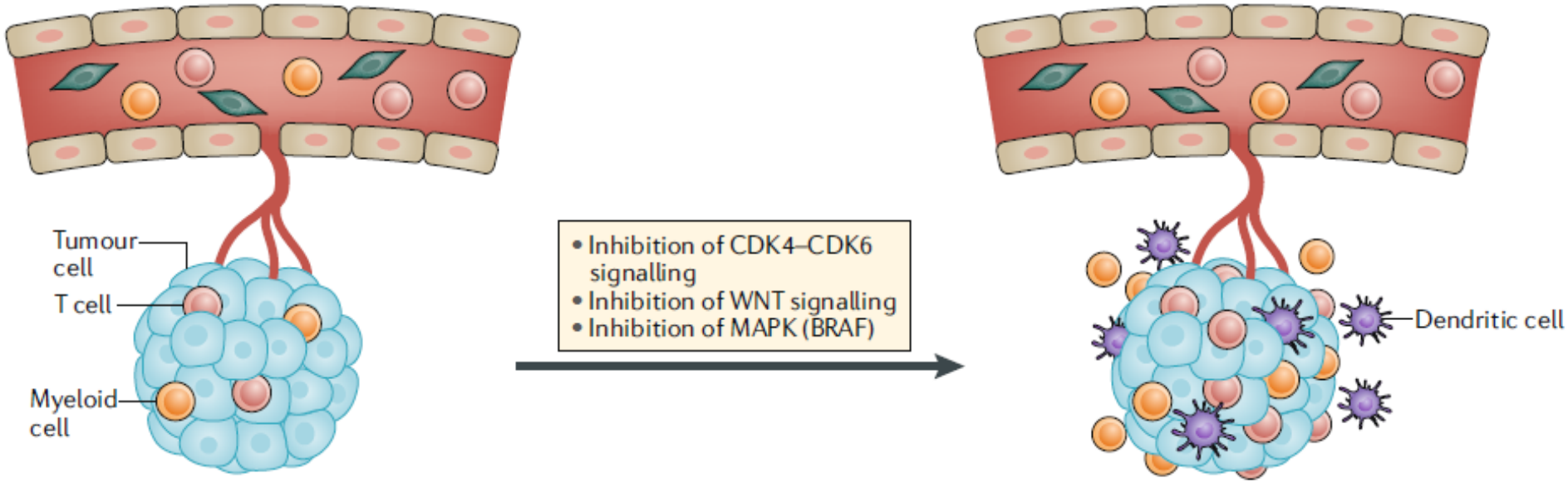
MAPK signalling
- Increased production of immunosuppressive cytokines IL-6 and IL-10
- Negative regulation of antigen presentation
- Suppression of differentiation antigens (melanoma)
- Reduced sensitivity to antiproliferative effects of IFNγ and TNF

WNT–β-catenin signalling
- Increased production of immunosuppressive cytokines
- Disruption of $BATF3^{+}$ dendritic cell recruitment by CCL4
- T_{reg} cell development

CDK4–CDK6 signalling
- Decreased sensitivity to dsRNA via DNMT1
- Decreased antigen presentation
- Decreased interferon target gene activation

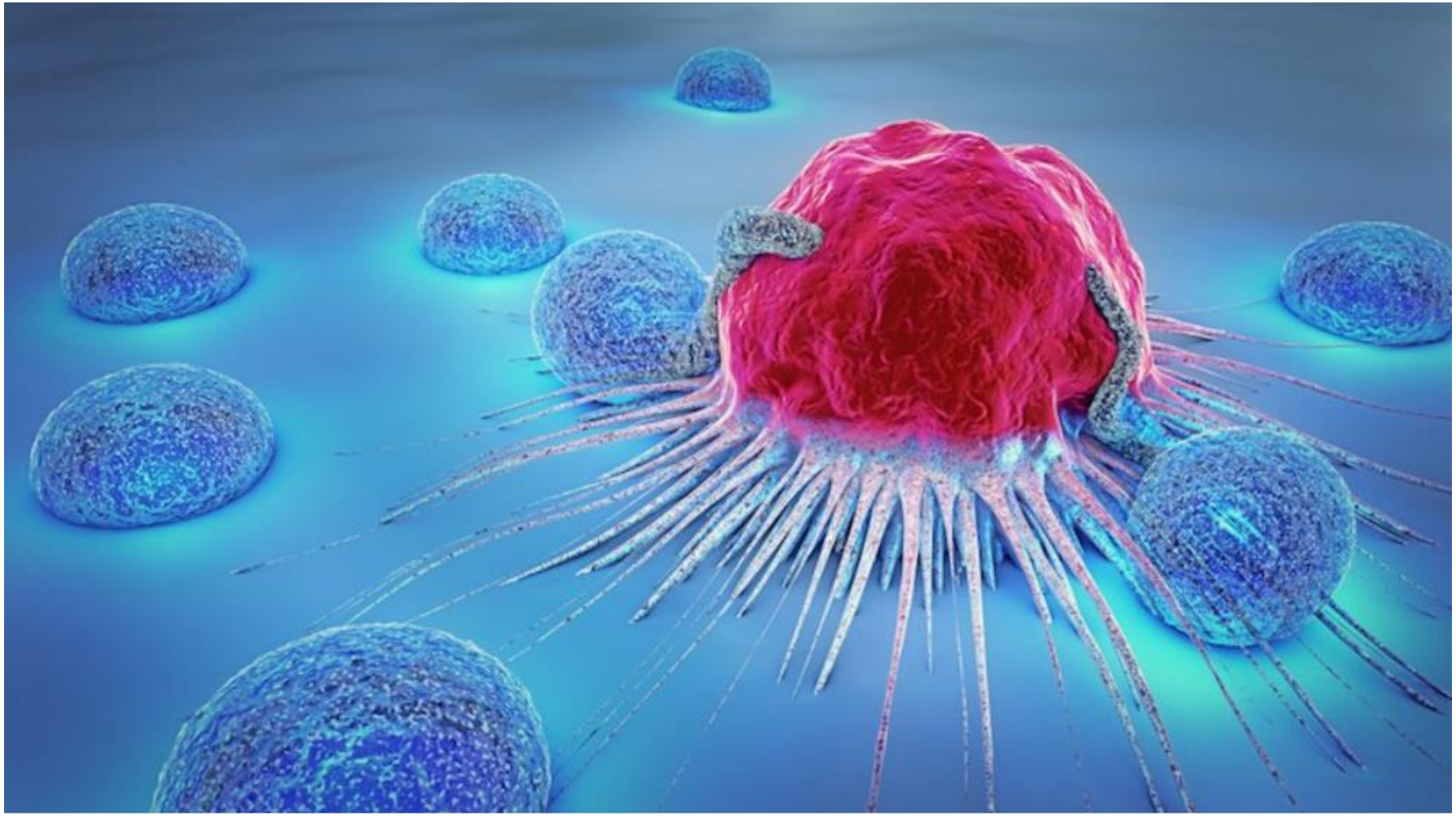
Pathways activated after PTEN loss
- Diminished type I interferon response to PAMPs
- Poor T cell recruitment via activation of autophagosome

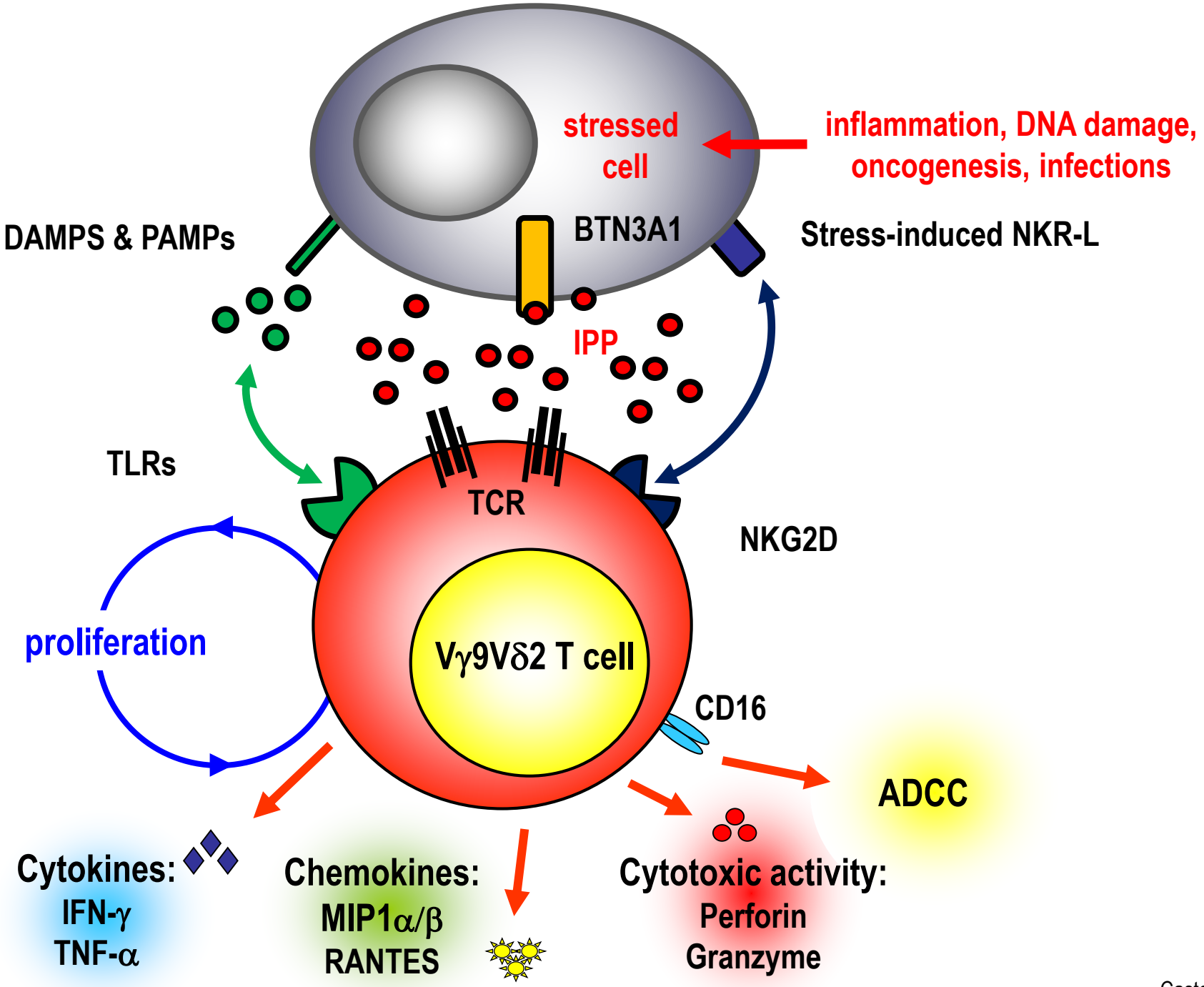
b



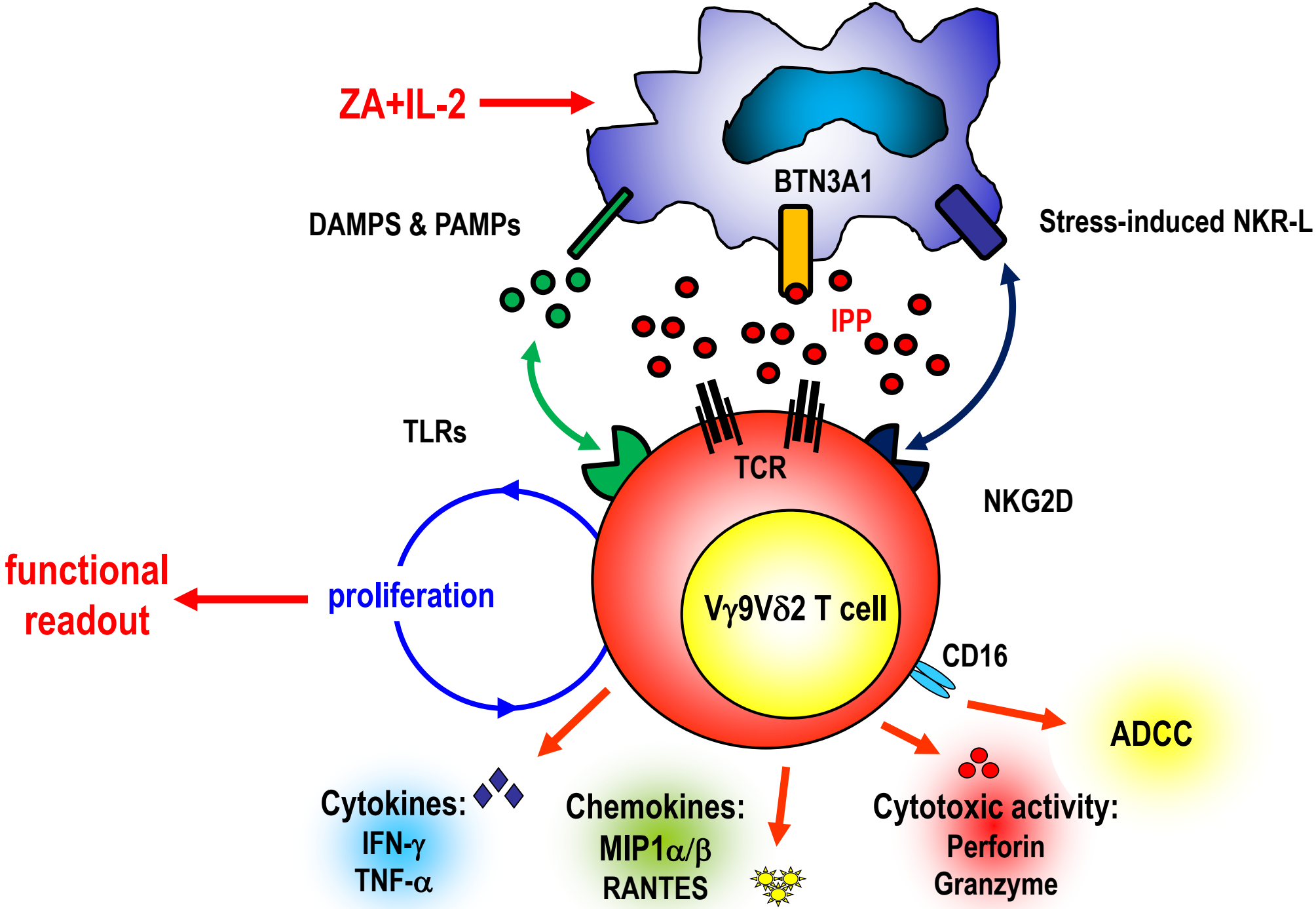
Kalbasi A, et al., *Nat Rev Immunol.* 2019 Sep 30.

Vγ9Vδ2 T cells as cellular decoders of the immune suppression network in the BM of MM patients



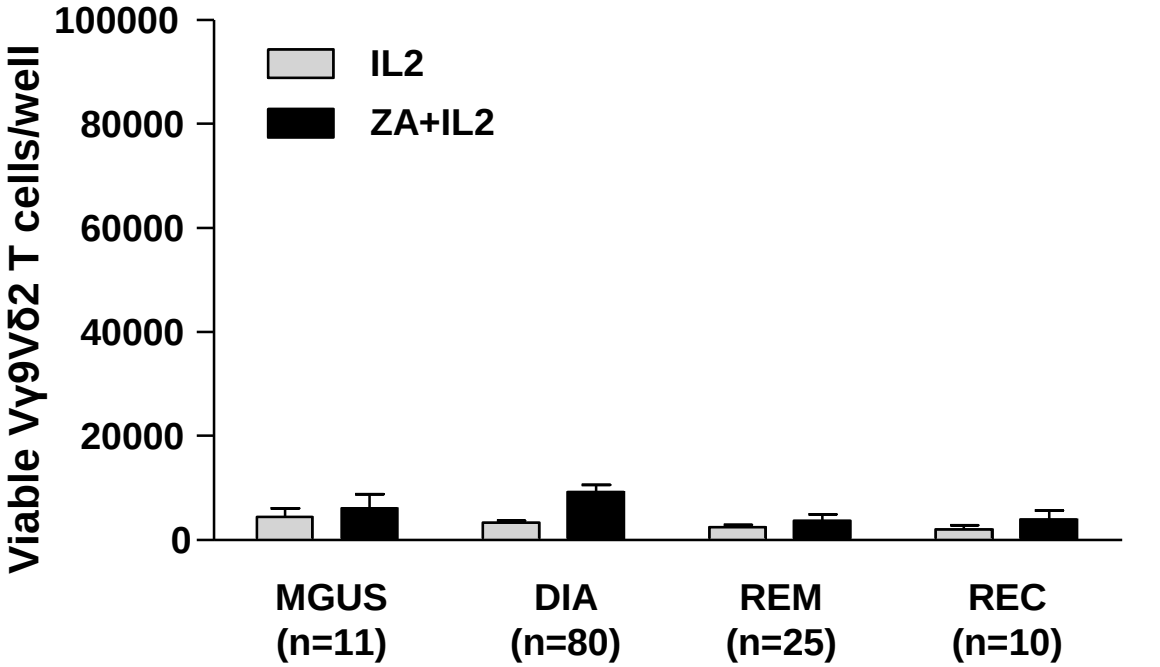


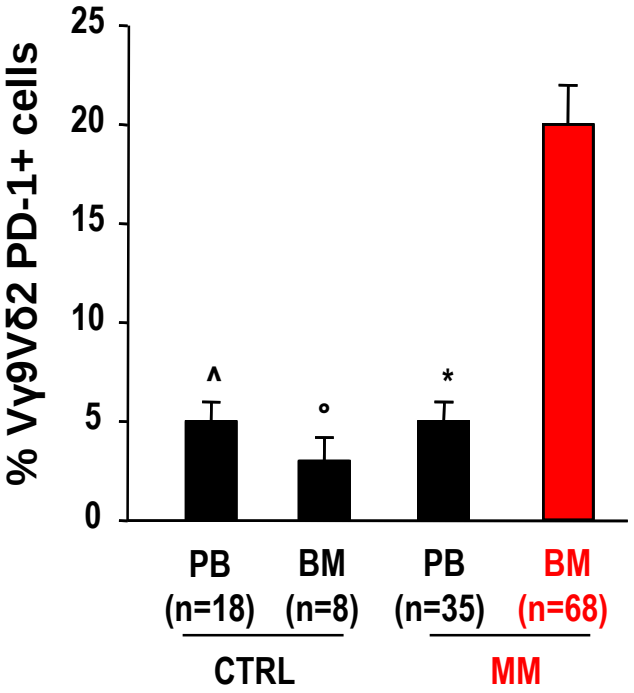
Castella B & Massaia M, 2019

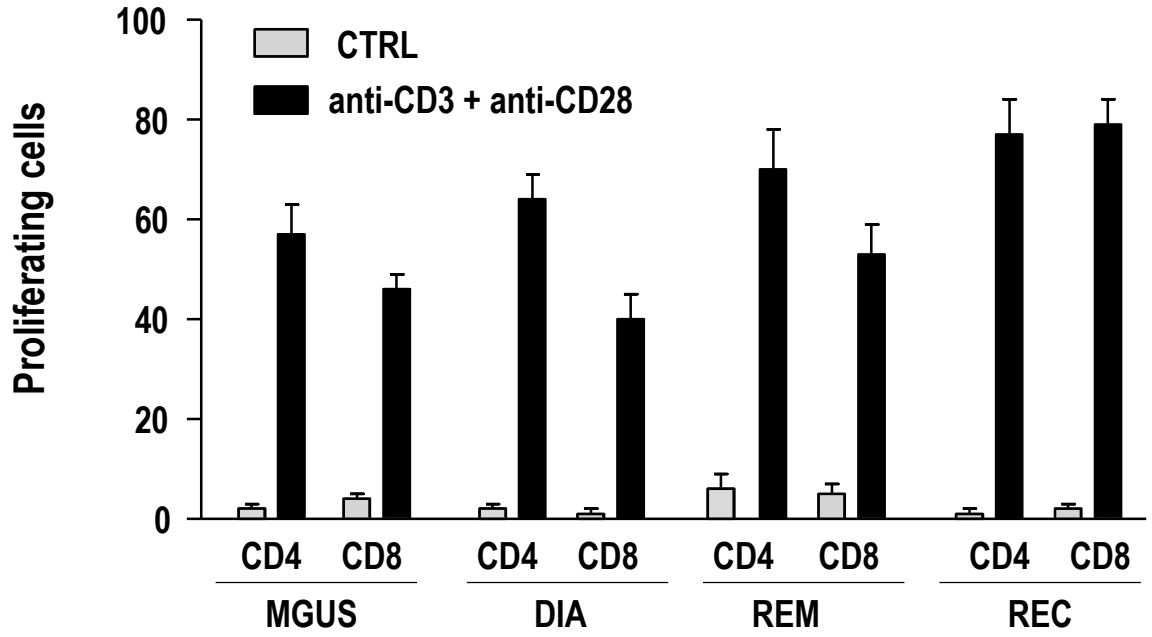


Castella B & Massaia M, 2019

MM BM Vγ9Vδ2 T cells are anergic to pAg stimulation

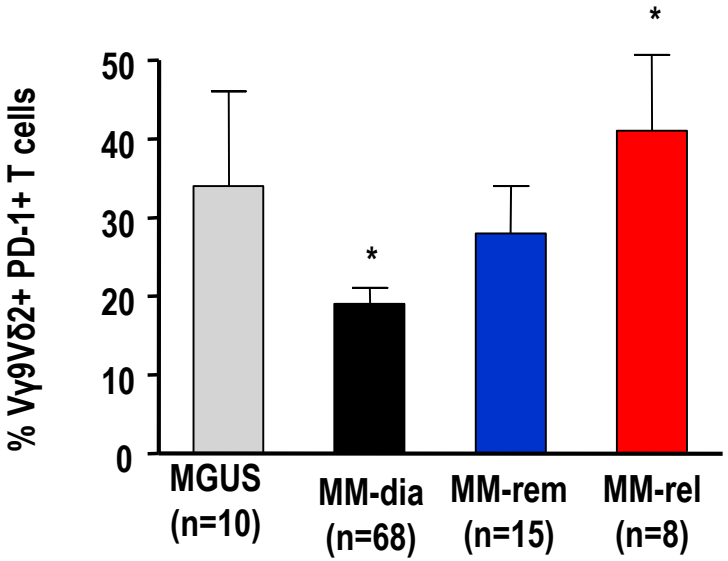


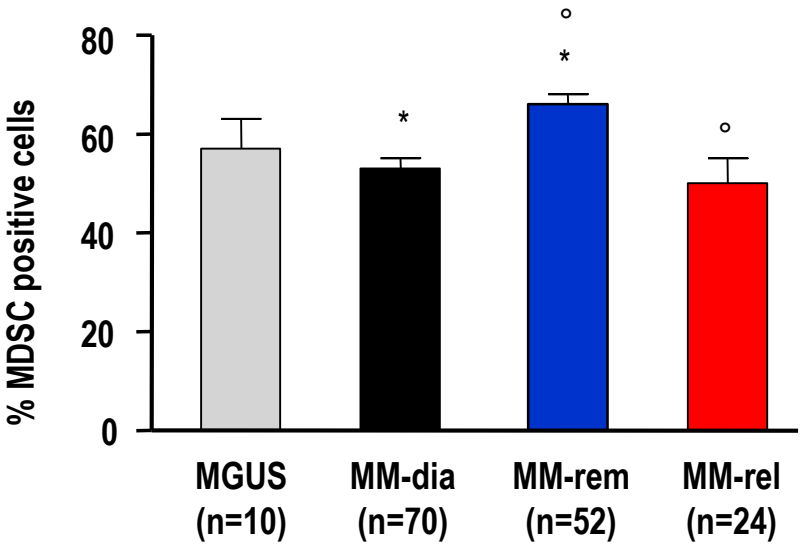


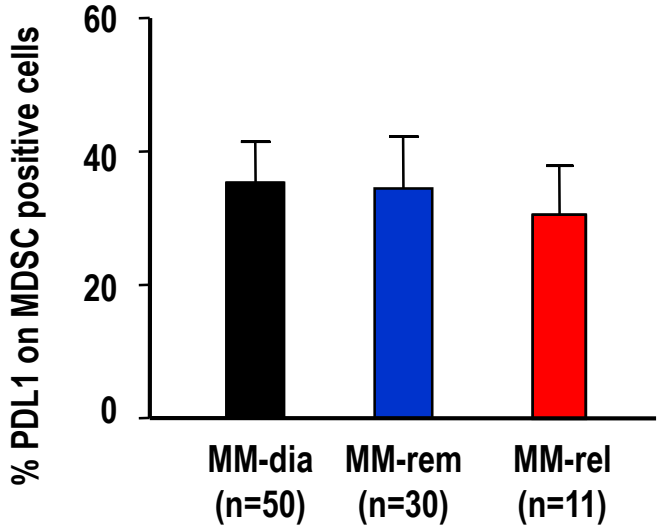


Castella, et al. *Oncoimmunology*. 2015 May 26;4(11):e1047580

Early and long-lasting immune suppressive TME commitment







Castella, et al. *Oncoimmunology*. 2015 May 26;4(11):e1047580

JCI insight

RESEARCH ARTICLE

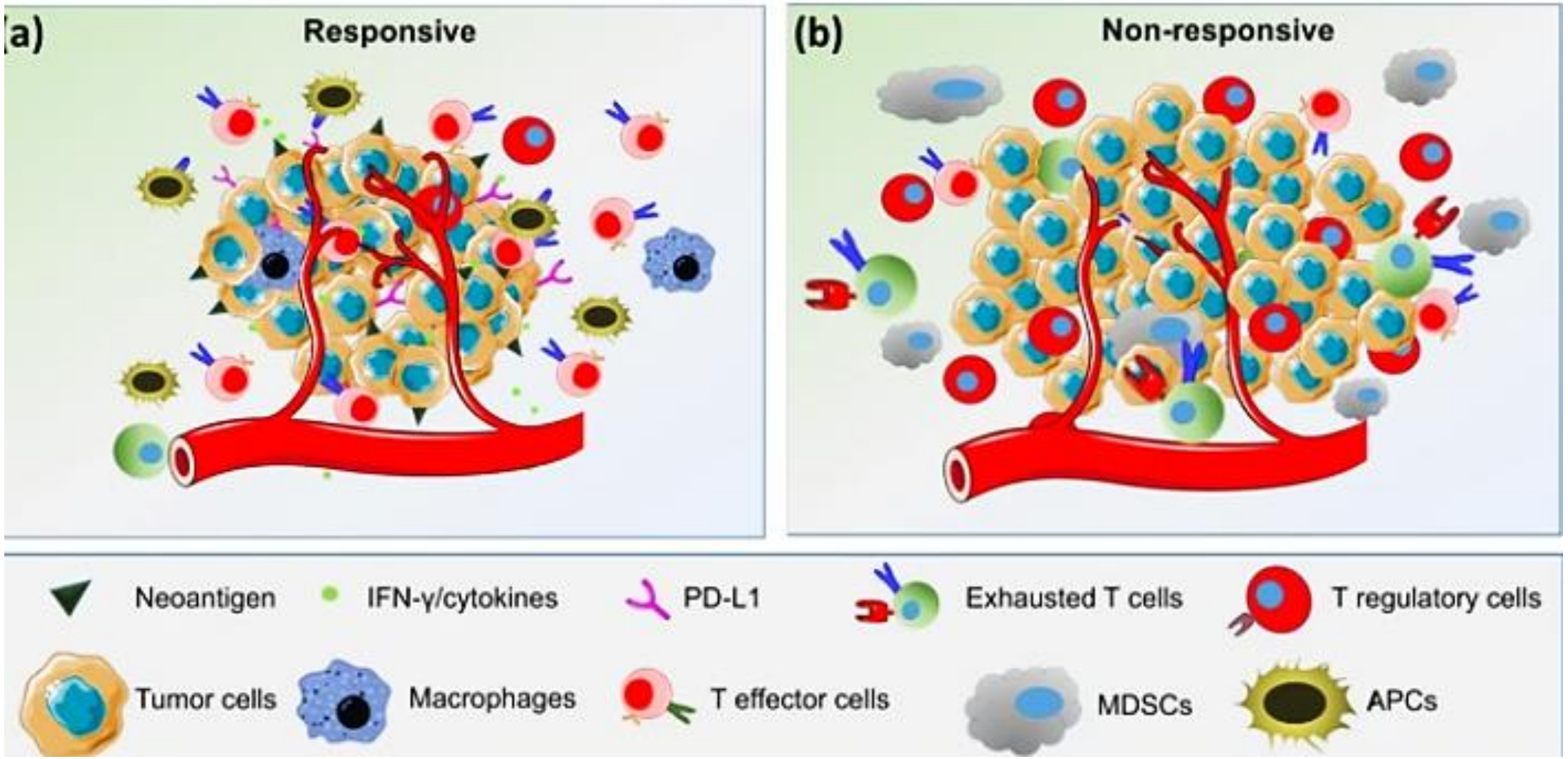
Early alterations in stem-like/marrow-resident T cells and innate and myeloid cells in preneoplastic gammopathy

Jithendra Kini Bailur,[1] Samuel S. McCachren,[1,2] Deon B. Doxie,[1] Mahesh Shrestha,[1] Katherine Pendleton,[1] Ajay K. Nooka,[1,3] Natalia Neparidze,[4] Terri L. Parker,[4] Noffar Bar,[4] Jonathan L. Kaufman,[1,3] Craig C. Hofmeister,[1,3] Lawrence H. Boise,[1,3] Sagar Lonial,[1,3] Melissa L. Kemp,[2] Kavita M. Dhodapkar,[3,5] and Madhav V. Dhodapkar[1,3]

Early and complex alterations in the immune landscape in MGUS, including both innate and adaptive immune cells

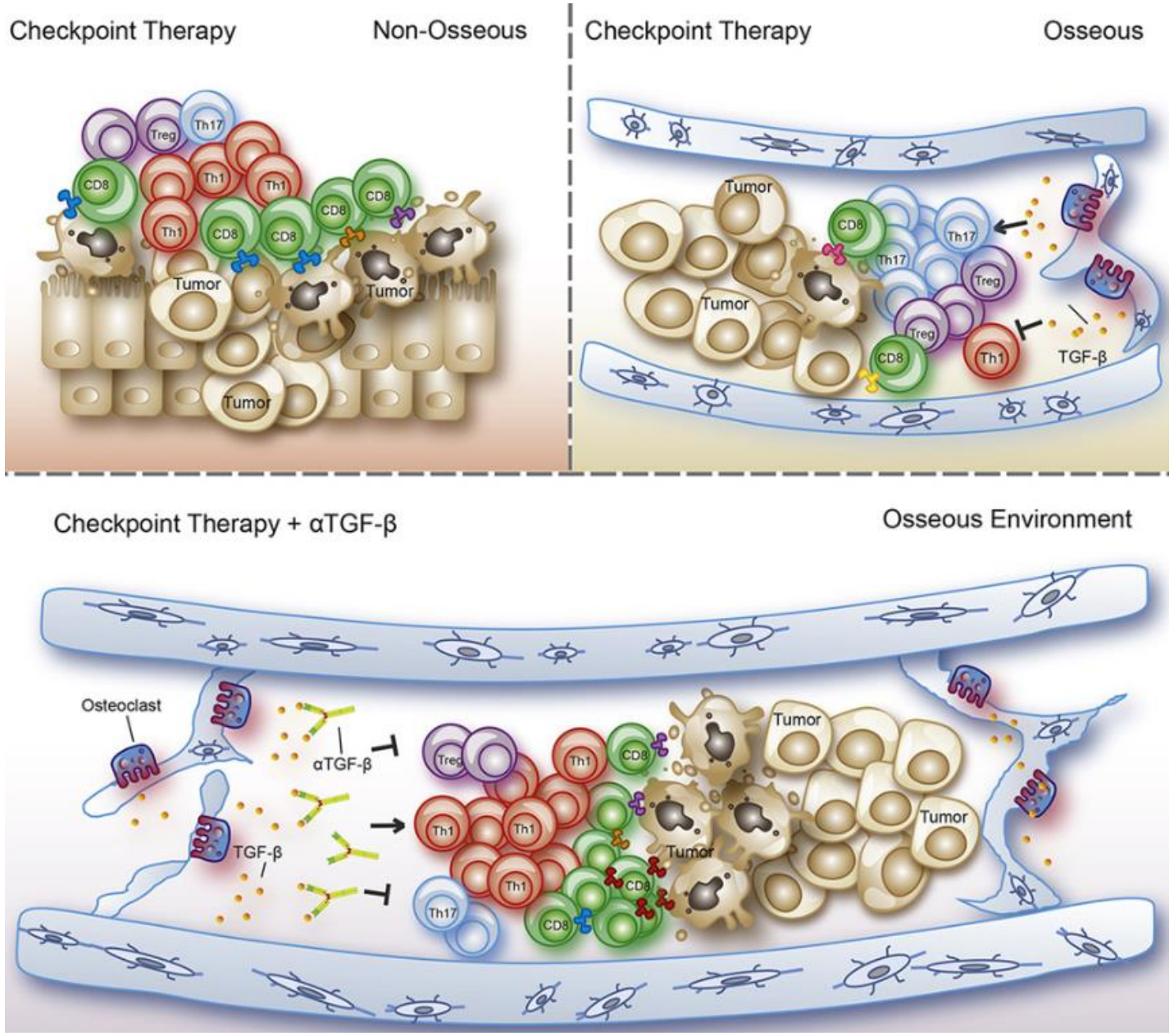
JCI Insight. 2019;4(11):e127807. https://doi.org/10.1172/jci.insight.127807.

Predictive biomarkers for response to ICP blockade

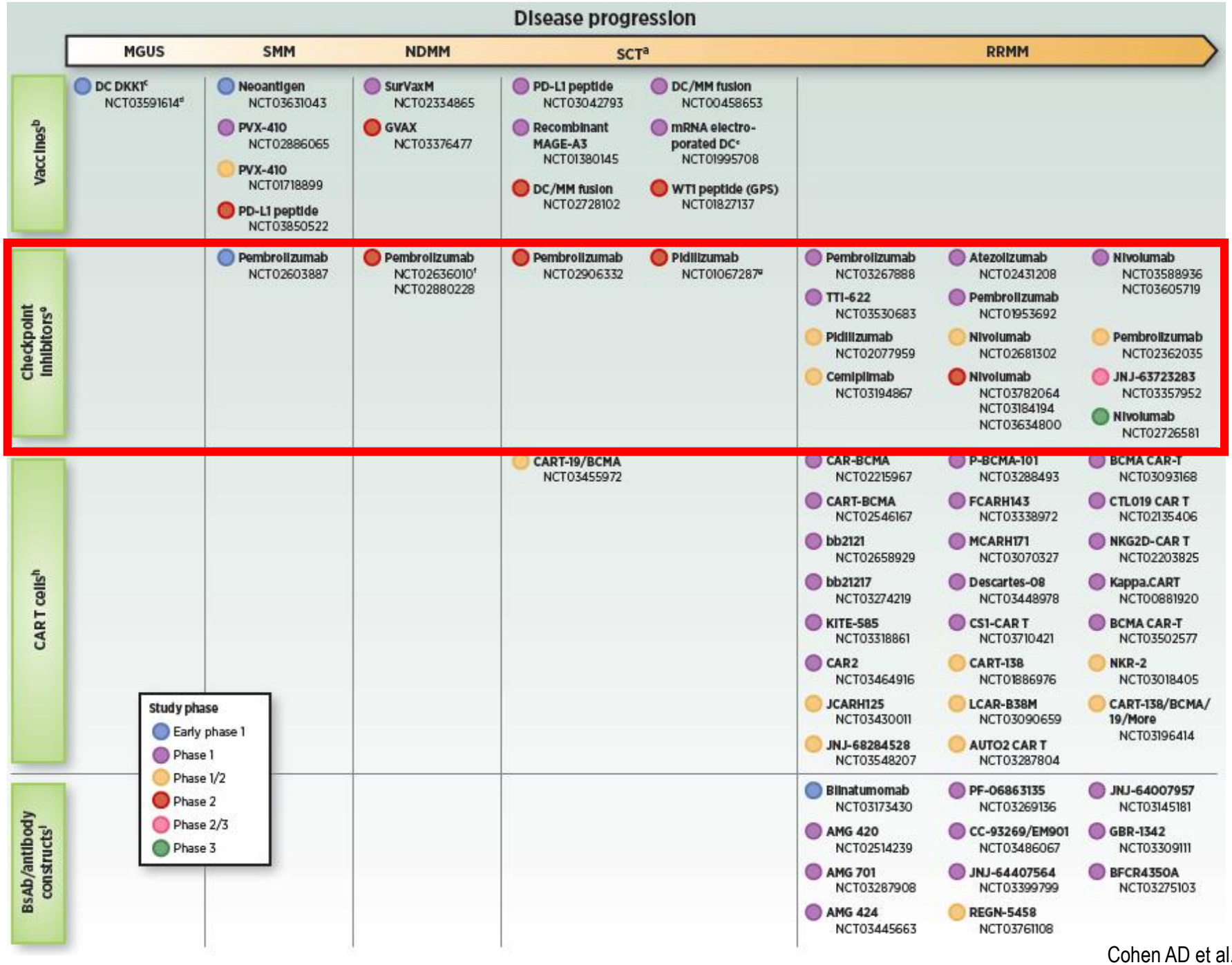


Darvin P et al.,. *Exp Mol Med.* 2018 Dec 13;50(12):165.

Tissue-Specific Checkpoint Immunotherapy Evasion

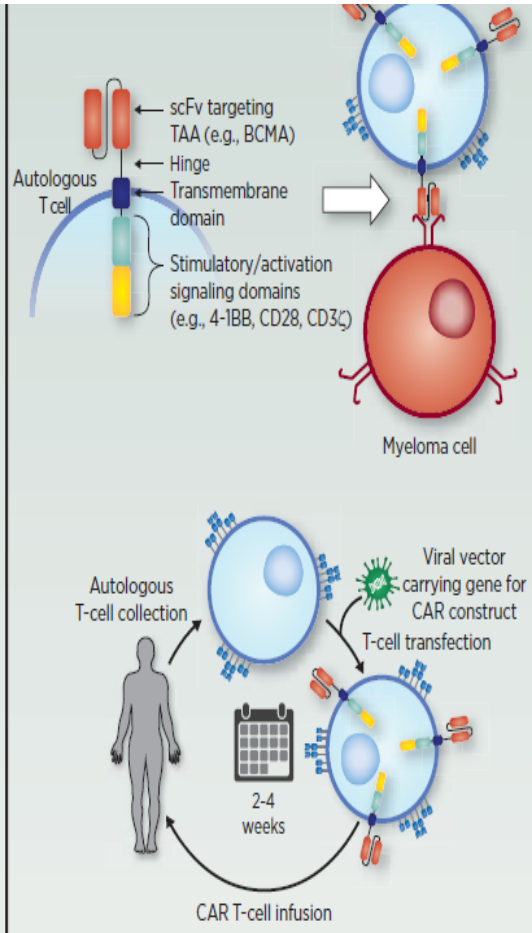


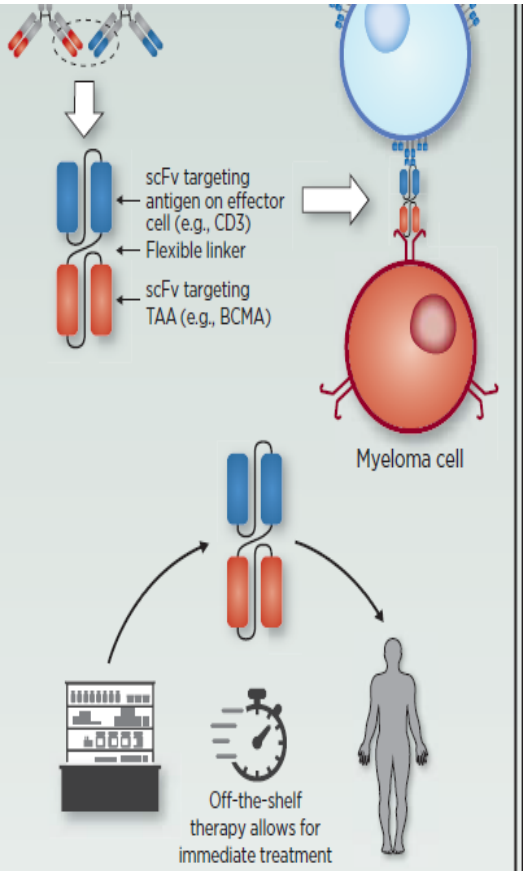
Jiao S et al., Cell. 2019 Nov 14;179(5):1177-1190.e13.



Cohen AD et al., Clin Cancer Res. 2019 Oct 31.

STRUCTURE AND MANUFACTURING





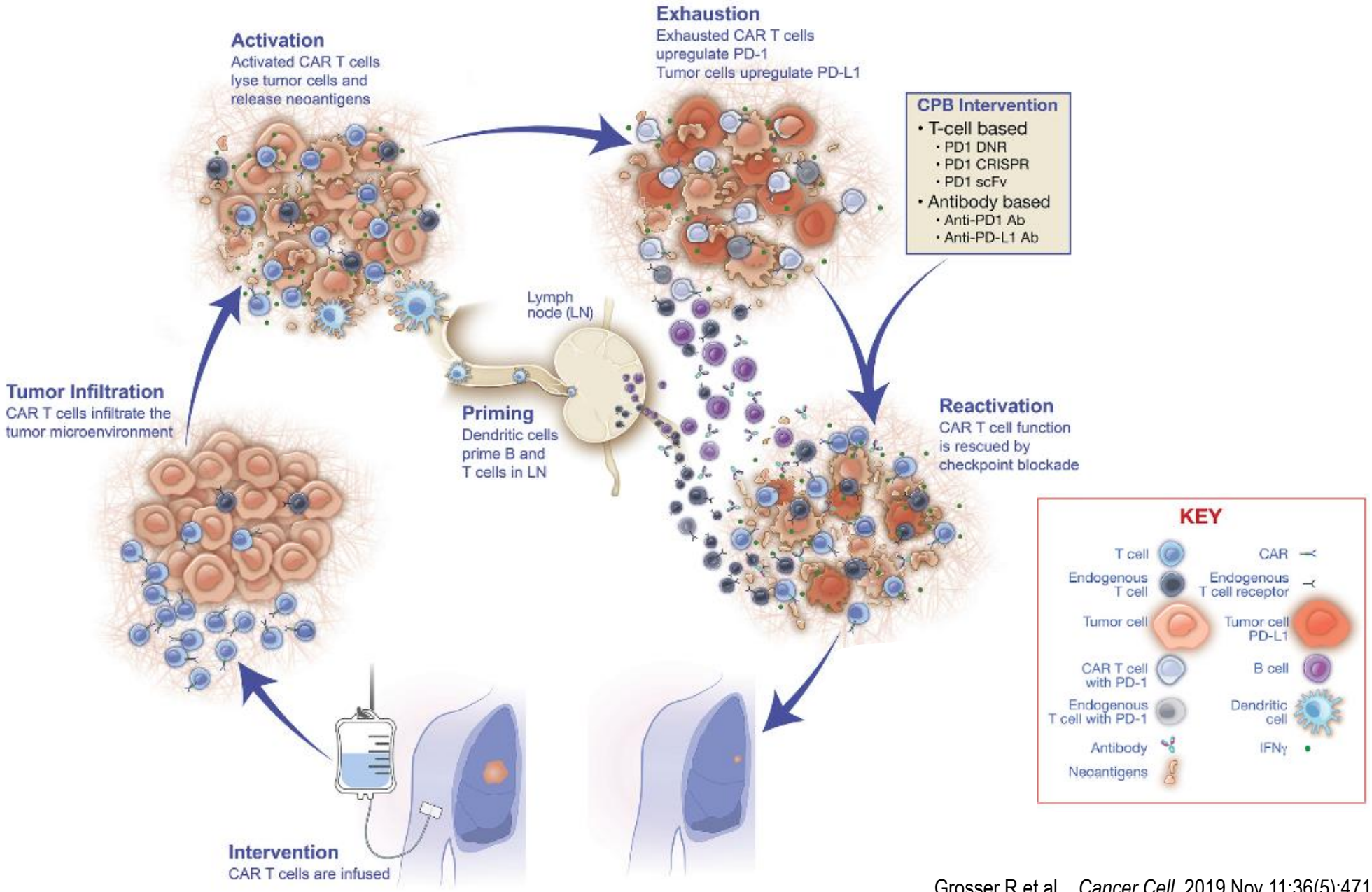
CHALLENGES AND STRATEGIES FOR IMPROVEMENT

Challenge	Strategies for Improvement
Immunogenicity (e.g., HAMA)	• Fully human product
Manufacturing time	• Allogeneic product • More rapid manufacturing protocols
Target antigen loss/ antigen-negative relapse	• Gamma-secretase inhibition for BCMA (e.g., NCT03502577) • Dual antigen-targeting product
Persistence	• MIL-based product • Preferential transduction of T_{CM} and T_{SCM} cell • PI3K inhibitor during manufacturing • Product with defined CD4:CD8 ratio

Challenge	Strategies for Improvement
Immunogenicity (e.g., HAMA)	• Humanize mAbs • Generate mAbs from phage display libraries based on human sequence
Target antigen loss/ antigen-negative relapse	• Infusion of 2 bsAbs/antibody constructs targeting separate TAAs
Frequency of administration	• Extended half-life product
Safety (CRS, neurotoxicity, infections)	• Tocilizumab to treat or prevent therapy-associated CRS • Consensus grading criteria and management algorithms for CRS and neurologic toxicity

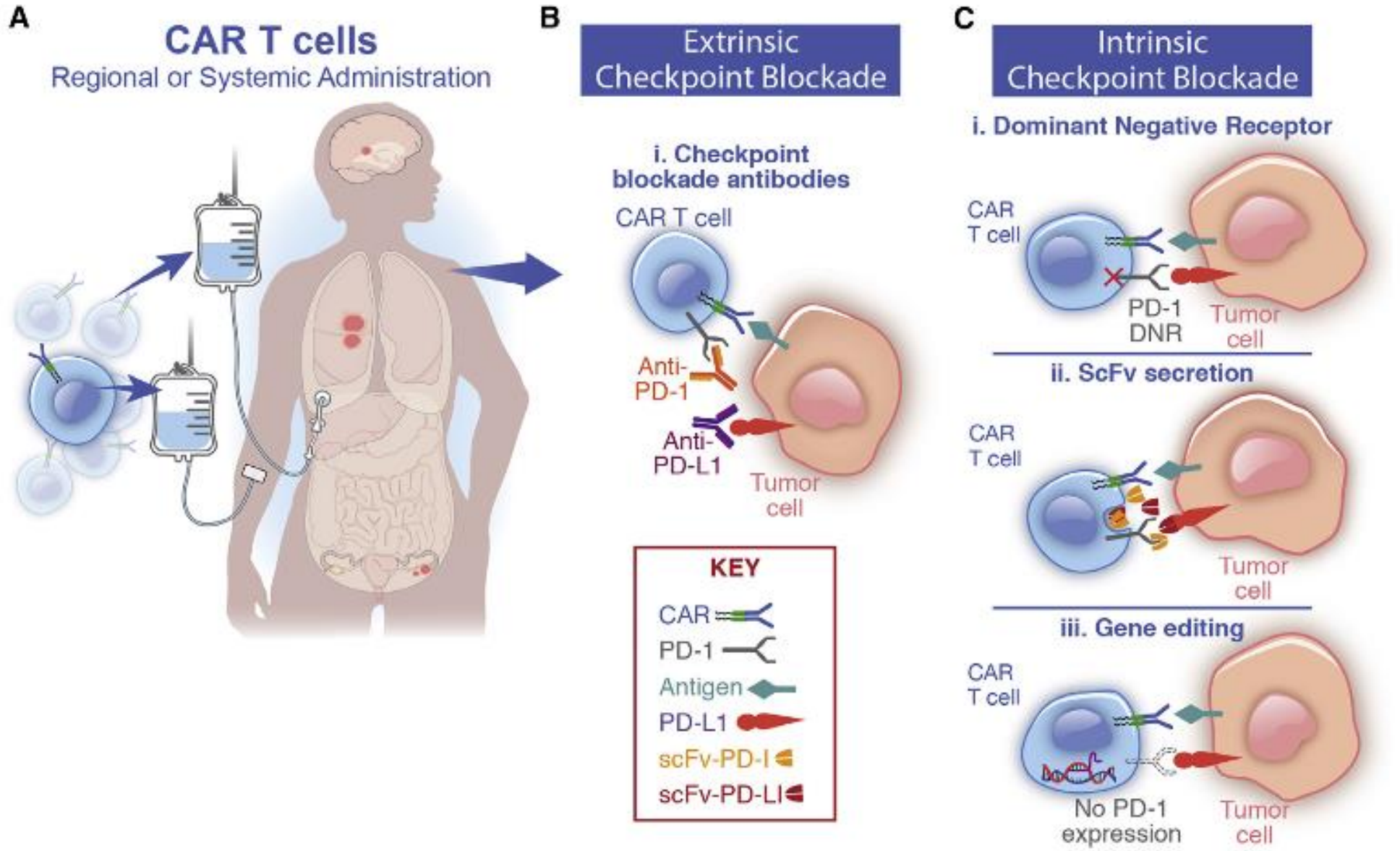
Cohen AD et al., Clin Cancer Res. 2019 Oct 31.

Rescue of CAR-T cell exhaustion with ICP blockade



Grosser R et al., ,*Cancer Cell.* 2019 Nov 11;36(5):471-482.

Strategies to combine CAR-T cells and ICP blockade

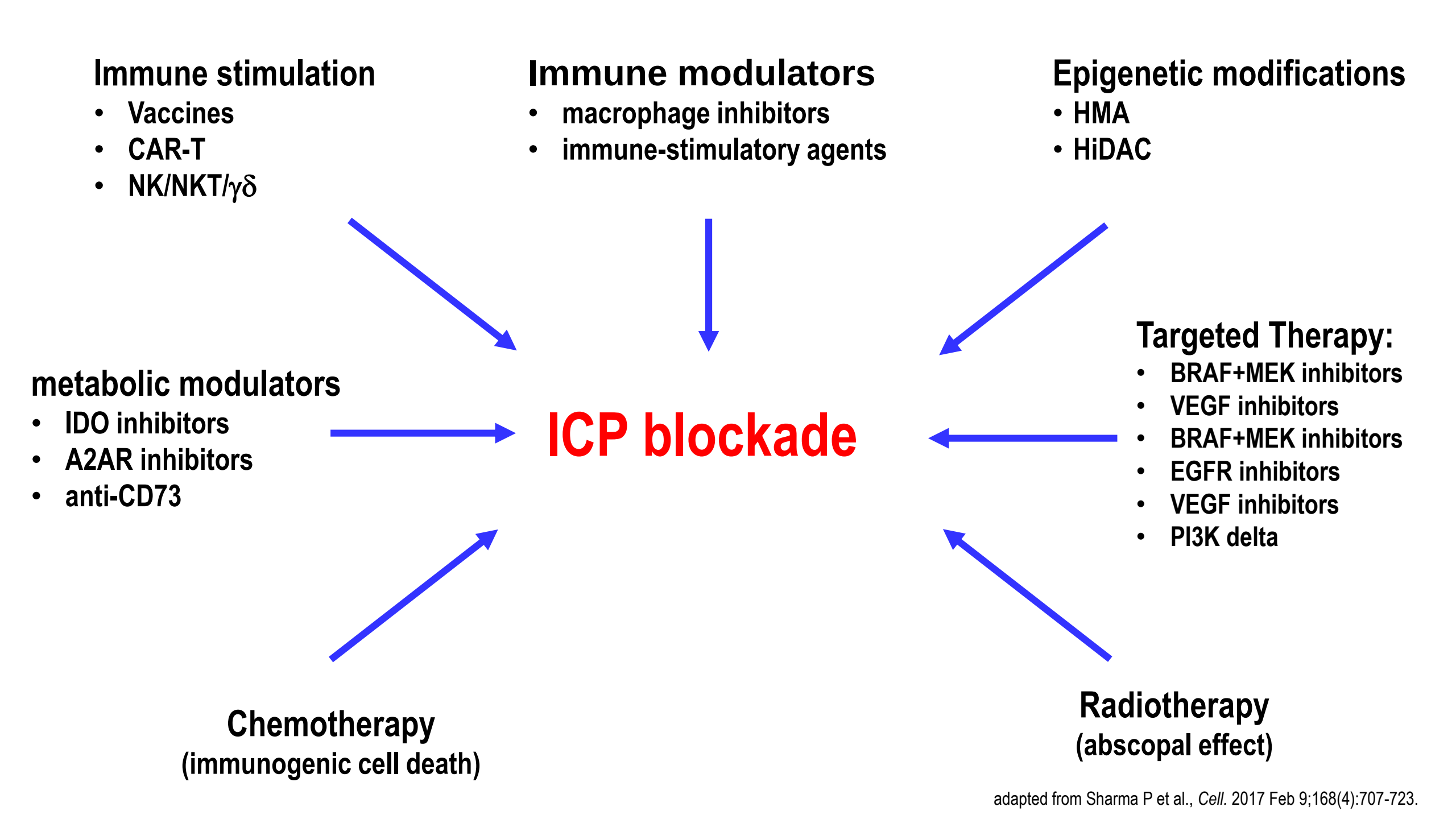


Grosser R et al., ,*Cancer Cell.* 2019 Nov 11;36(5):471-482.

Table 1. Clinical Trials Exploring Combination Therapy with CAR T Cells and Checkpoint Blockade

Trial	Launch	Phase	Center(s)	CPB Agent	CAR Target/Design	Cancer Diagnosis
NCT00586391	2009	I	Baylor	ipilimumab	CD19/CD19CAR-28-zeta T cells	B cell lymphoma, chronic lymphocytic leukemia, acute lymphocytic leukemia
NCT01822652	2013	I	Baylor	pembrolizumab	GD2/iC9-GD2-CD28-OX40 (iC9-GD2) T cells	neuroblastoma
NCT02650999	2016	I/II	University of Pennsylvania	pembrolizumab	anti-CD19 CARs	$CD19^+$ diffuse large B cell lymphoma, follicular lymphoma, mantle cell lymphoma
NCT02706405	2016	I	Fred Hutchinson	durvalumab	autologous anti-CD19CAR-4-1BB-CD3ζ-EGFRt-expressing $CD4^+$/$CD8^+$ central memory T lymphocytes JCAR014	diffuse large B cell lymphoma
NCT02926833	2016	I/II	City of Hope, Stanford, Moffitt, Dana Farber, MD Anderson	atezolizumab	CD19/KTE-C19	diffuse large B cell lymphoma
NCT03310619	2017	I/II	City of Hope, Northwestern University, Massachusetts General, University of Nebraska, University of Pennsylvania, MD Anderson	durvalumab	JCAR017	lymphoma, non-Hodgkin lymphoma, diffuse large B cell lymphoma, follicular lymphoma
NCT03726515	2018	I	University of Pennsylvania	pembrolizumab	CART-EGFRvIII T cells	glioblastoma

Grosser R et al., ,*Cancer Cell.* 2019 Nov 11;36(5):471-482.



adapted from Sharma P et al., *Cell.* 2017 Feb 9;168(4):707-723.

Credits

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Barbara Castella (Senior Lab Investigator)

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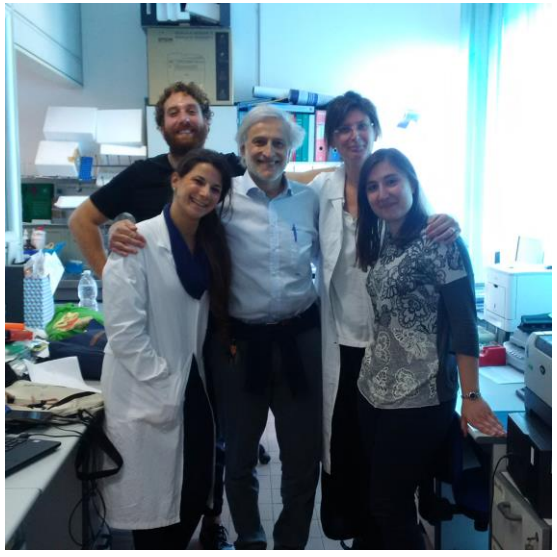

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2ST CUNEO CITY IMMUNOTHERAPY CONFERENCE (CCITC)
IMMUNOTHERAPY IN HEMATOLOGICAL MALIGNANCIES 2020
JUNE 18-20, 2020
ORGANIZED BY MASSAIA M, SC EMATOLOGIA AO S.CROCE E CARLE, CUNEO, ITALY
& CENTRO INTERDIPARTIMENTALE DI RICERCA IN BIOLOGIA MOLECOLARE (CIRBM), TORINO, ITALY