New Immunotherapeutic Strategies: Checkpoint Inhibitors and Beyond

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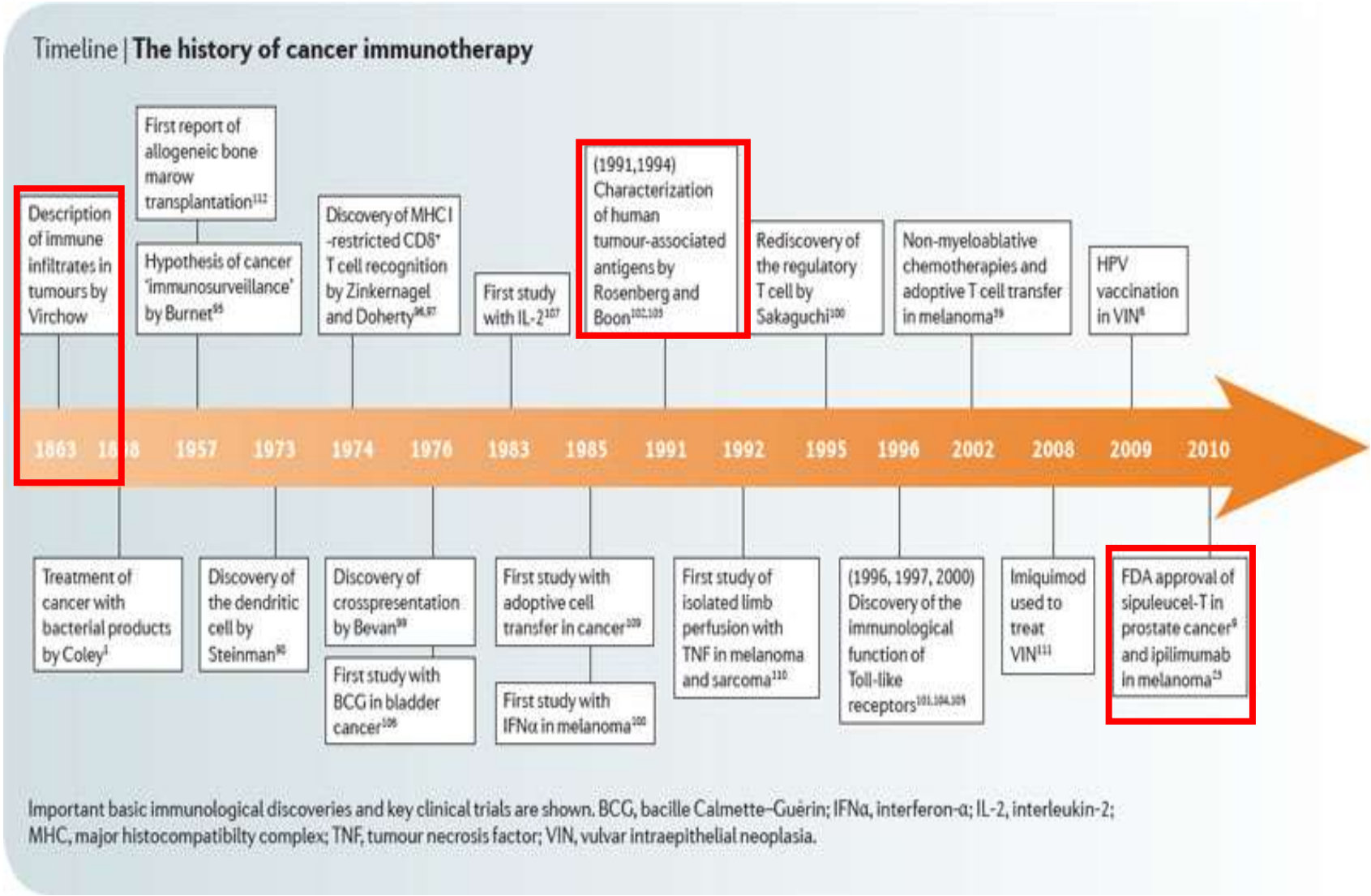
I have no declarations.

Definition of Cancer Immunotherapy

- Treatments that harness patients' immune system for cancer therapy
- Monoclonal antibodies
  - Target cancer cells
  - Modulate immune function
- Cytokines
- Cancer vaccines (+/- dendritic cells)
- Adoptive cellular therapy (+/- engineered receptors: TCR or chimeric antigen receptor, CAR)

Cancer immunotherapy: Timeline



Lesterhuis WJ, et al. *Nature Reviews Drug Discovery* 2011;10(8):591-600.

Approved Cancer Immunotherapies

2010: Sipuleucel-T (dendritic cell vaccine) for prostate cancer

2011: Ipilimumab (anti-CTLA4 Ab) for advanced melanoma

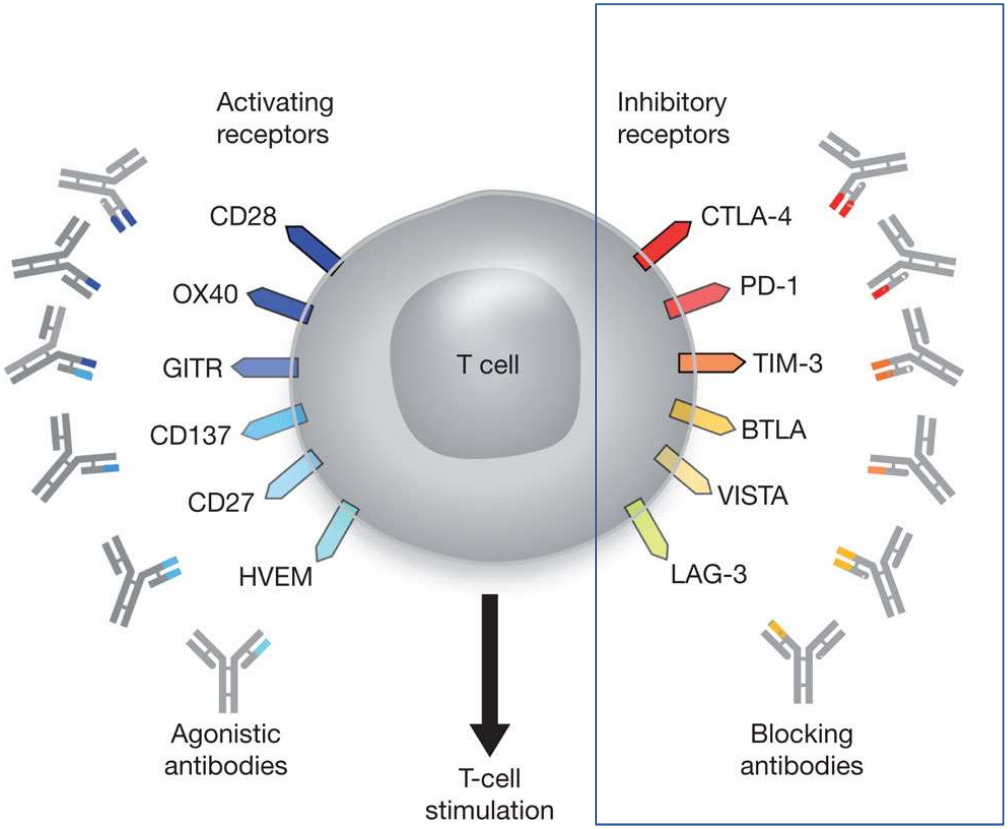
2014: Pembrolizumab and Nivolumab (anti-PD1 Ab) for advanced melanoma; Blinatumomab (CD3xCD19 BiTE) for B-ALL

2015: Nivolumab for lung cancer and kidney cancer; Nivo/Ipi combination for melanoma; T-VEC (oncolytic virus) for melanoma

2016 on: multiple other cancer types; MSI tumors

These treatments still only work for subsets of patients and some cancer types

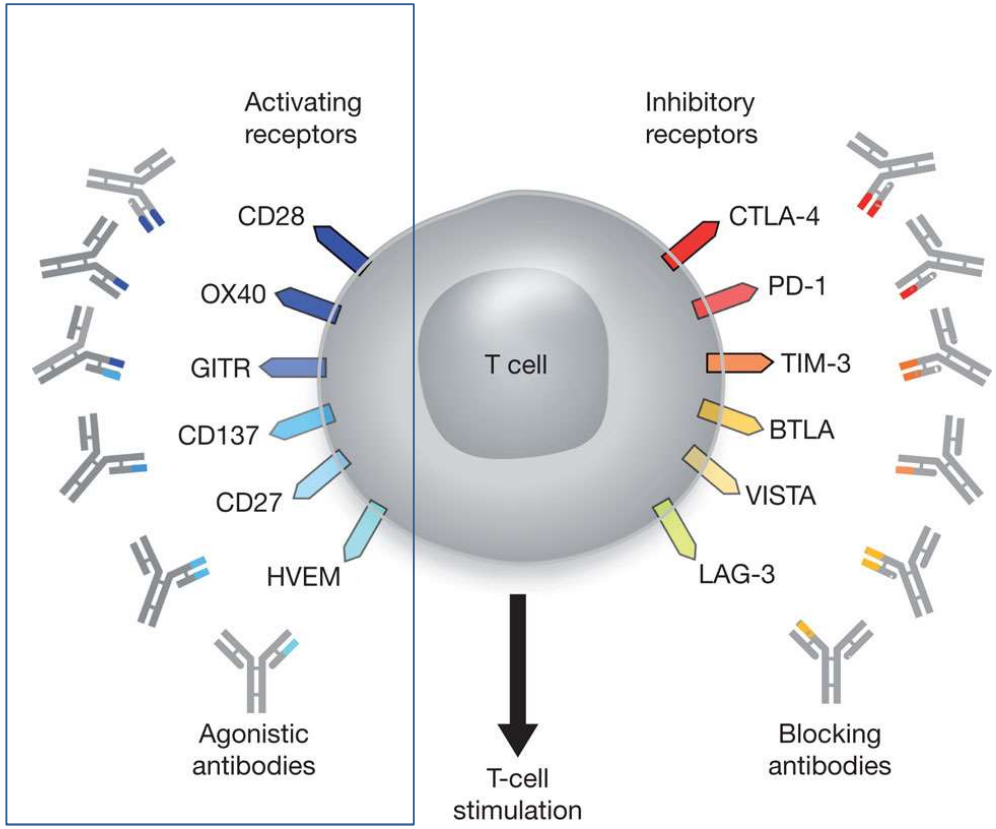
Inhibitory Immune Checkpoints



I Mellman *et al. Nature* **480**, 480-489 (2011) doi:10.1038/nature10673

nature

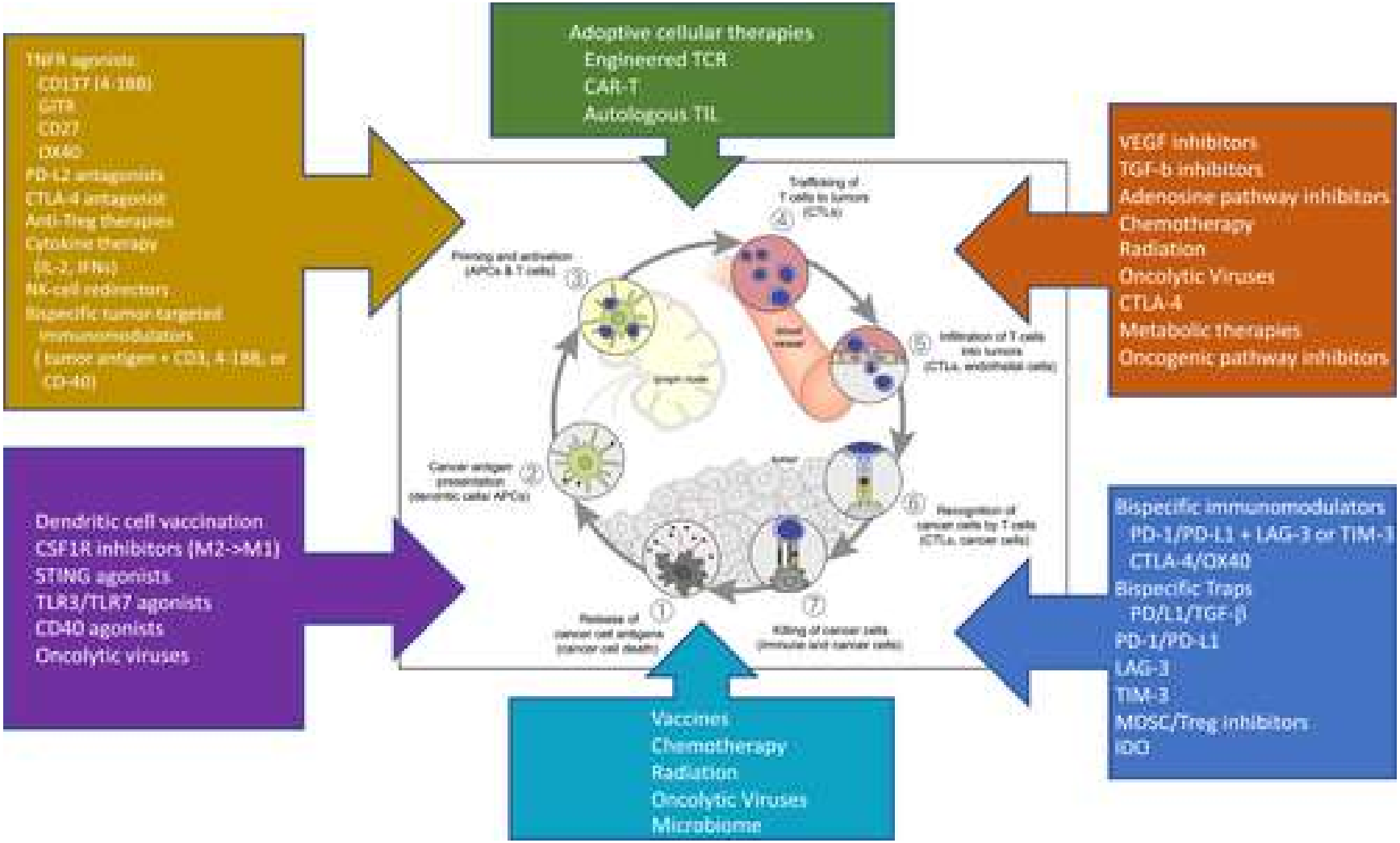
Activating Immune Checkpoints



I Mellman *et al. Nature* **480**, 480-489 (2011) doi:10.1038/nature10673

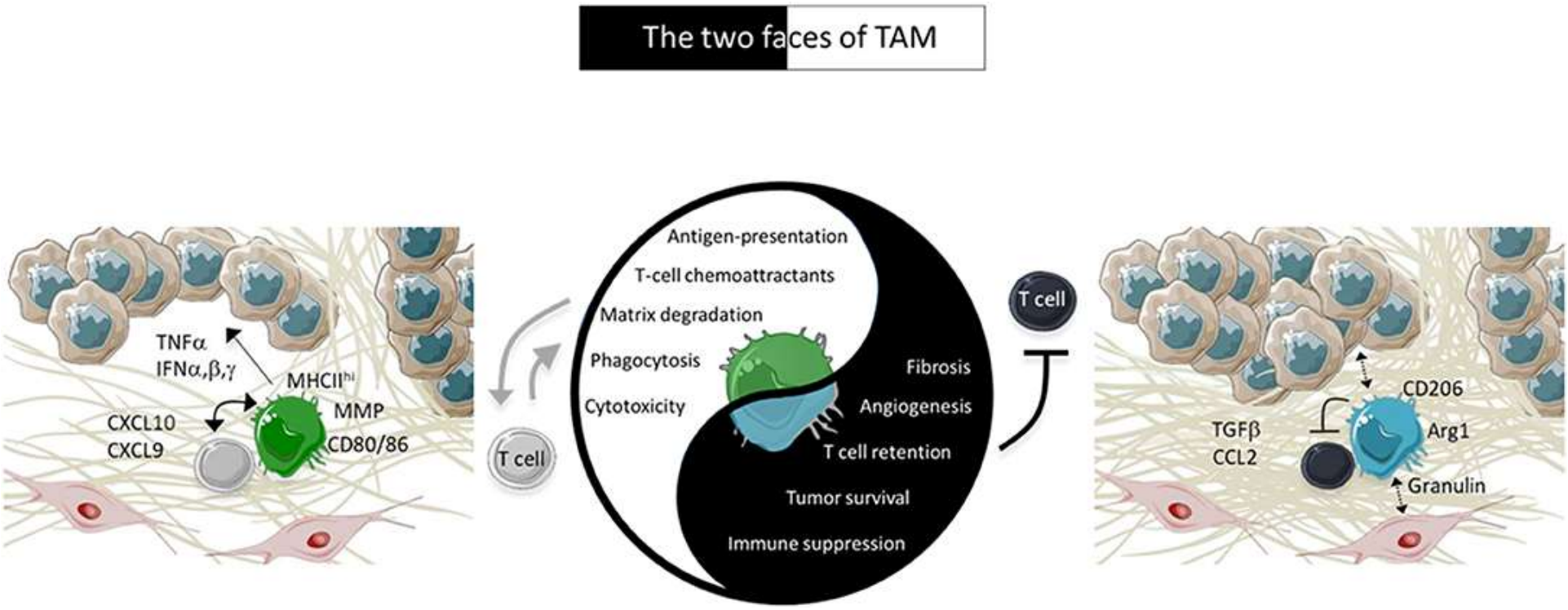
nature

Cancer Immunotherapy 2019



Immunological Reviews, Volume: 290, Issue: 1, Pages: 6-23, First published: 29 July 2019, DOI: (10.1111/imr.12766)

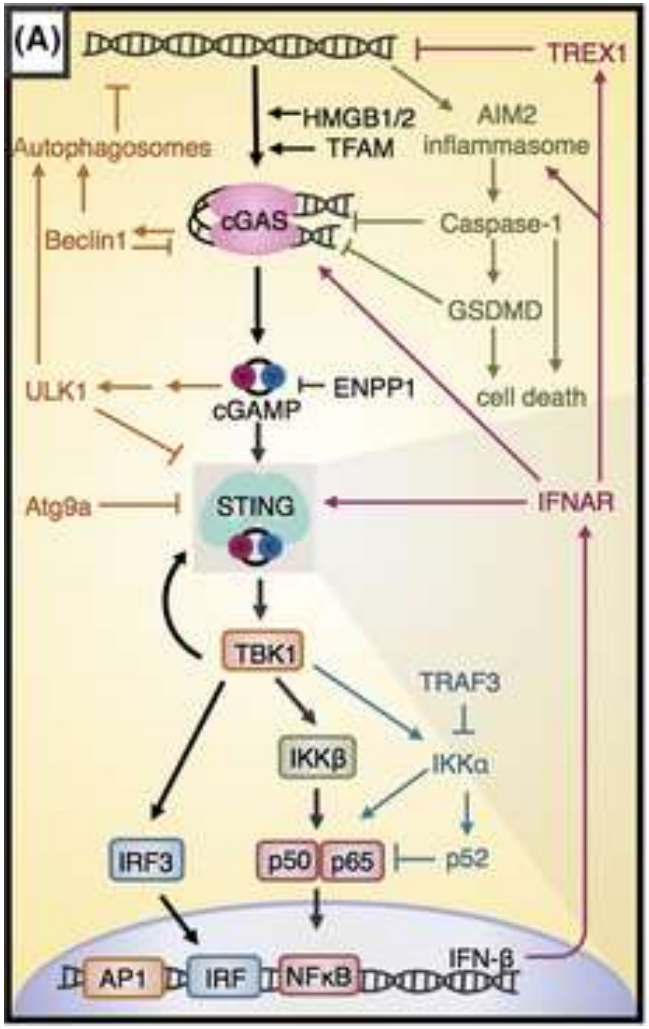
Tumor-associated Macrophages (TAM)



Targeting TAMs

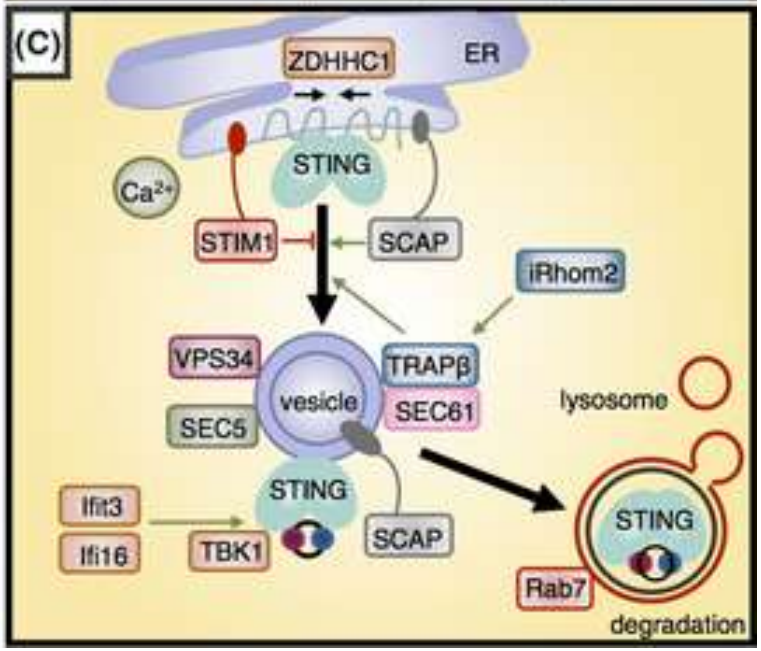
	Macrophage/TIL targets	Clinical trial number	Investigators	Indications	Study design	Immune response evaluation	Phase
Depletion of pro-tumoral TAM	Anti-CCR2/CCR5/anti-PD1	NCT03184870	Bristol-Myers Squibb	Solid tumors	aCCR2/CCR5 vs. aCCR2/CCR5 + aPD1 vs. aCCR2/CCR5+ chemotherapies	Decrease in regulatory T cells & tumor-associated macrophages	I
	Anti-CFS1R/anti-PD1	NCT02526017	Five Prime Therapeutics, Inc.	Solid tumors	aCSF1R + aPD1 vs. aCSF1R alone	Changes in macrophage and T-cell levels/Changes in gene expression in peripheral T-cell and other leukocyte phenotypes, and levels of peripheral myeloid-derived suppressor cells	I
	Anti-CFS1R/anti-PDL1	NCT03238027	Syndax Pharmaceuticals, Inc.	Solid tumors	aCSF1R alone vs. aCSF1R + aPDL1	Inflammatory cytokines/TIL expansion	I
	Anti-CSF1R/anti-PDL1	NCT02323191	Hoffmann-La Roche	Solid tumors	aCSF1R + aPDL1	TAM depletion	I + II
Inhibition of pro-tumoral TAM activity	Anti-CTLA-4, Anti-PDL1/OX40L Ig	NTC02705482	MedImmune LLC	Advanced solid tumors	OX40L Ig + aPDL1 vs. OX40L Ig + aCTLA4	TIL expansion	I
	Anti-PDL1/OX40L Ig	NTC02221960	MedImmune LLC	Recurrent or Metastatic Solid Tumors	OX40LIg alone vs. OX40L Ig + aPDL1	Biomarkers activity on TIL	I
	PD1-Fc-OX40L	NTC03894618	Shattuck Labs	Solid tumors and lymphomas	1 or 2 inejctions i.t		I
	TGFbRI inhibitor/anti-PDL1	NCT02937272	Eli Lilly and Company	Solid tumors	TGFbRI inh orally alone vs. TGFbRI inh orally + anti-PDL1 i.v		I
	TGFb inhibitor/anti-PD1	NCT02423343	Eli Lilly and Company	Solid tumors (NLSC/HCC)	TGFB inh orally + anti-PD1 i.v		I + II
Activation of anti-tumoral TAM activity	TLR7, 8 agonist/anti-PDL1	NTC02556463	MedImmune LLC	Solid tumors	aTLR7/8 alone vs. aTLR7/8 + aPDL1	TIL expansion/Inflammatory cytokine levels	I
	TRL9 agonist/OX40 agonist	NCT03831295	Stanford Cancer Institute Palo Alto	Solid neoplasms	TLR9 agonist x3 i.t + OX40 agonist x2 i.v and x3 i.t vs. TLR9 agonist x3 i.t + OX40 agonist x3 i.v and x3 i.t		I
	TLR4 agonist/anti-PD1, ICOS agonist, OX40 agonist	NCT03447314	GlaxoSmithKline	Neoplasms	OX40 + TLR4 agonists vs. ICOS + TLR4 agonists vs. aPD1 + TRL4 agonists vs. OX40 + ICOS + TLR4 agonists		I
	STING agonist/anti-PD1	NCT03172936	Novartis Pharmaceuticals	Solid tumors and lymphomas	One vs. 3 doses of STING agonist (i.t) + 1 injection of anti-PD1 (i.v)	Cytokines, TIL expansion in targeted and non-targeted lesions	I
	STING agonist/anti-CTLA4	NCT02675439	Novartis Pharmaceuticals	Solid tumors and lymphomas	3 injections of STING agonist (i.t) vs. 2 injections of STING agonist (i.t) + 1 injection of aCTLA4	Measurement of CD8-TIL counts/RNA expression analysis of IFN gamma and immunomodulatory genes	I
	CD40 agonist/anti-PDL1	NCT02304393	Hoffmann-La Roche	Advanced/ metastatic solid tumors	1 dose of CD40 agonist i.v + aPDL1 vs. 1 dose of CD40 agonist s.c + aPDL1	TIL expansion, PDL1 expression on tumor and immune infiltrating cells	I
	anti-CD47, IFN-α2/anti-PD1, anti-PDL1	NCT02890368	Trillium Therapeutics Inc.	Solid tumors	aCD47 Monotherapy/aCD47 + PD-1/PD-L1 Inhibitor/aCD47 + pegylated IFN-α2/aCD47 + T-Vec/aCD47 + radiation	Anti-tumor activity	I
	GMCSF/iNeo-Vac-P01 (peptides)	NCT03662815	Sir Run Run Shaw Hospital	Solid tumors	iNeo-Vac-P01 (peptides)+ GM-CSF x7 doses	IFN-gamma measurement/CD4 and CD8 T cells subsets	I
	Ad-IFNγ/TIL adoptive transfer	NCT01082887	Nantes University Hospital	Metastatic melanoma	2 injections of Ad-IFNγ (i.t) +2 injections of TIL (i.v)		I+II

STING pathway agonism



(B)

Post-translational modifications		Positive regulators	Negative regulators
cGAS	Glutamylation	CCP5, CCP6	TTLL4, TTLL6
	Phosphorylation	TRIM14, TRIM41, TRIM56	Akt
	Sumoylation	TRIM38	Senp2
STING	Phosphorylation	TBK1	ULK1
	Ubiquitination	AMFR/INSIG1, MUL1, RNF26, TRIM32, TRIM56, UBXN3B	EIF3S5, RNF5, TRIM29, TRIM30a



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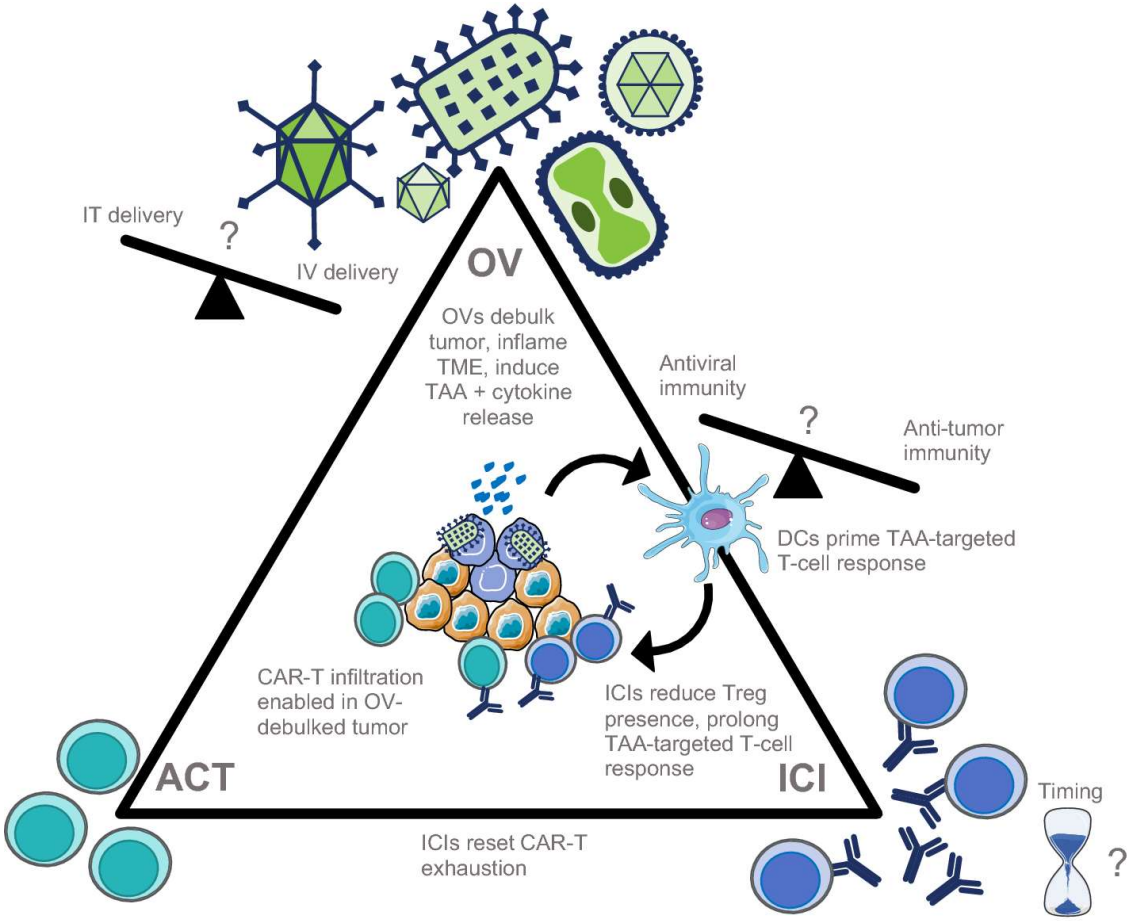
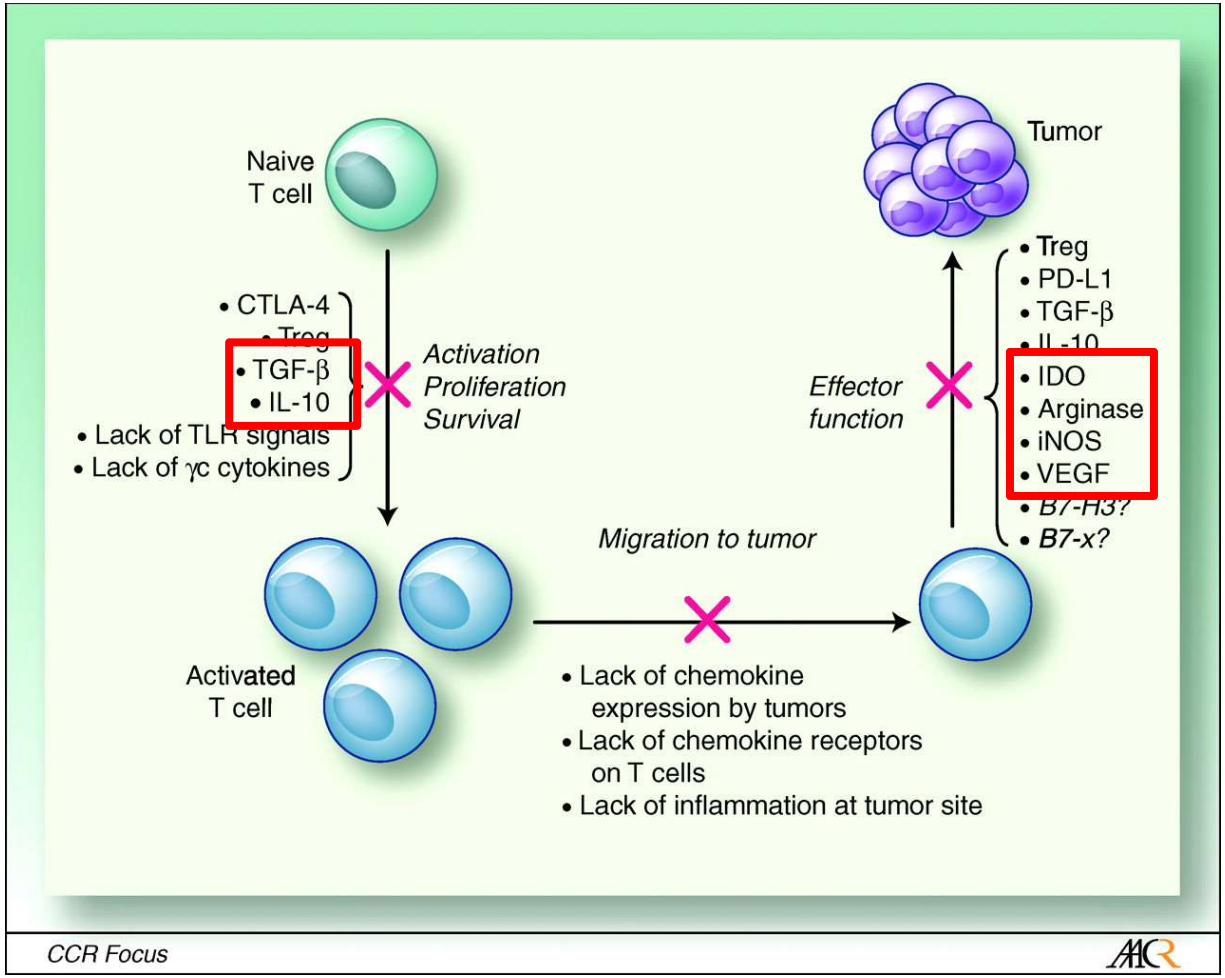
Oncolytic Viruses (OV)

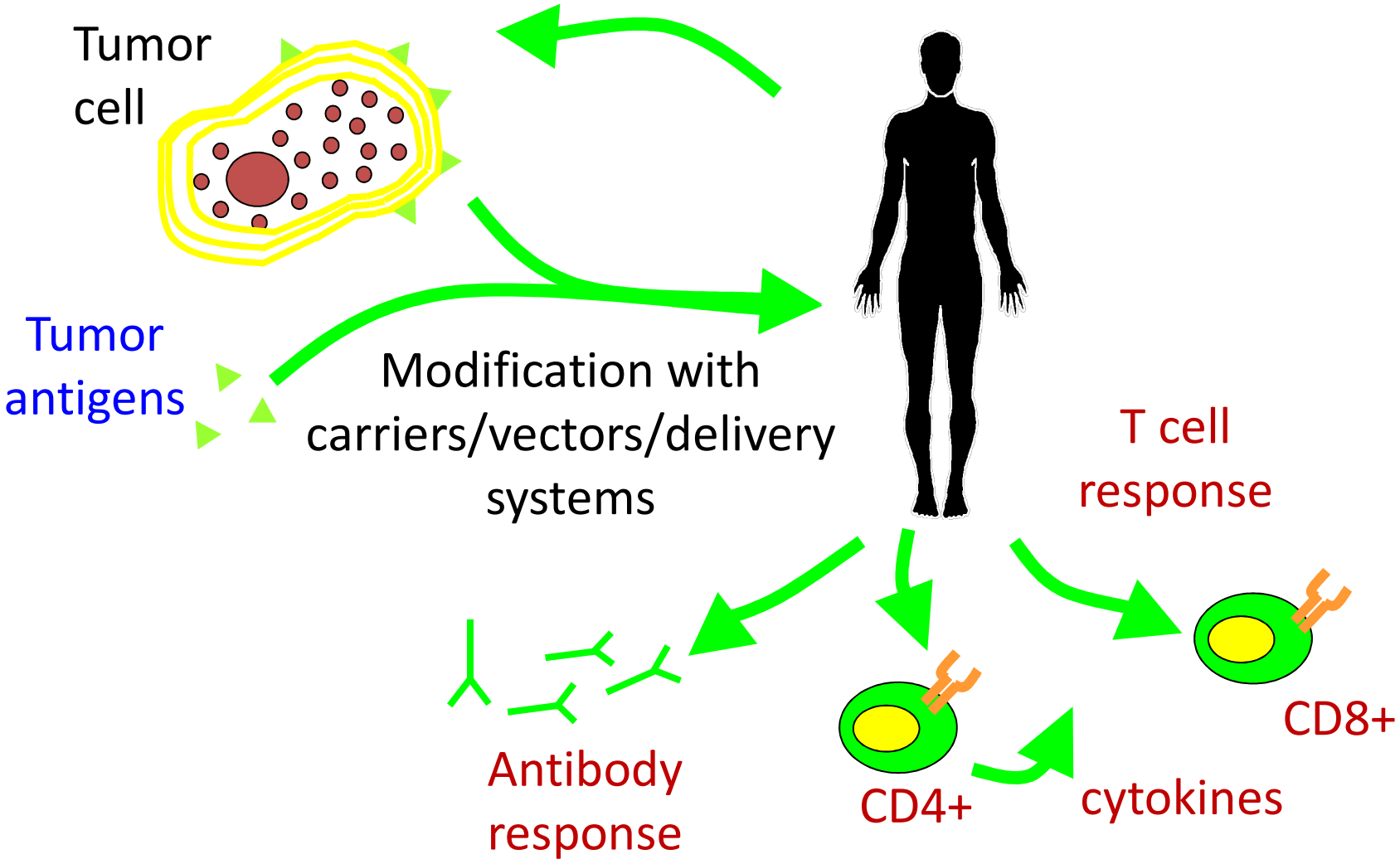


Other barriers to effective antitumor T-cell immunity

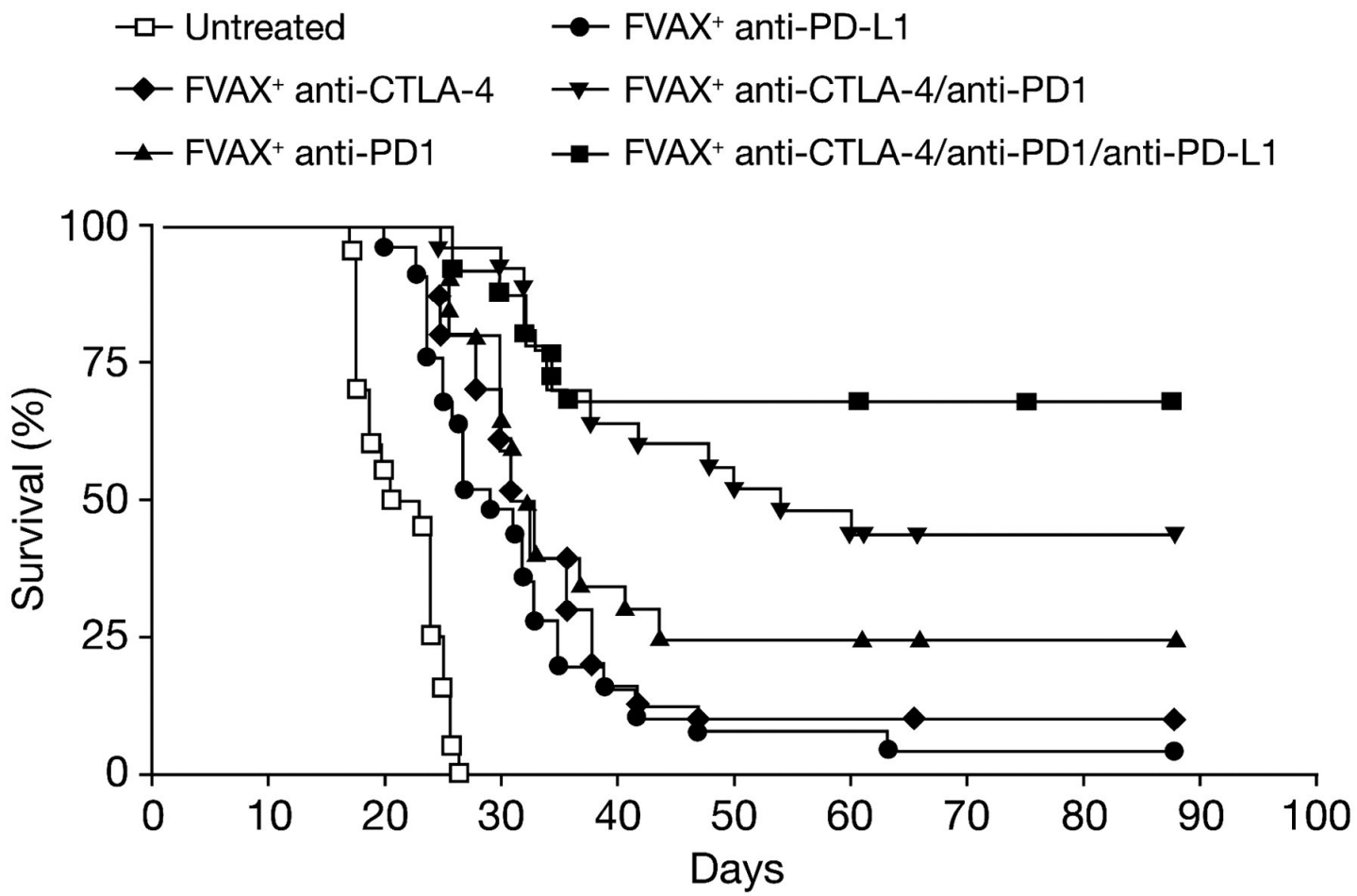


Lizée G et al. *Clin Cancer Res* 2007;13:5250-5255

Therapeutic vaccination against cancer



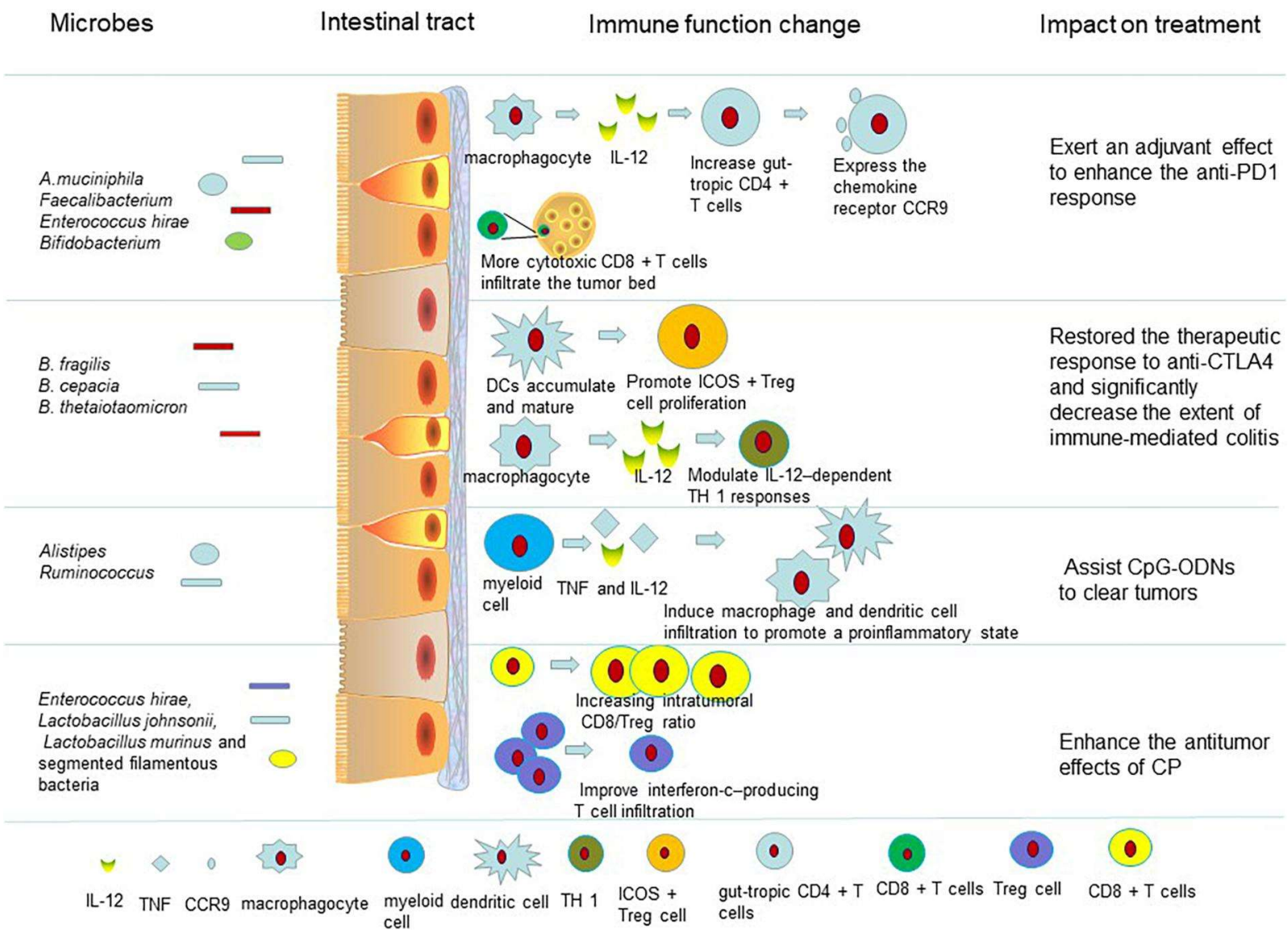
Need for Synergistic combinations



Drake C G Ann Oncol 2012;23:viii41-viii46

Annals of Oncology

GI Microbiome



Biomarkers/Patient Selection

Table. Comparison of Pooled Diagnostic Sensitivity and Specificity and Predictive Values for Responders vs Nonresponders After Anti–PD-1/PD-L1 Therapy Between Different Assay Modalities[a]

Modality	Pooled Sensitivity	Pooled Specificity	Pooled PPVs	Pooled NPVs
PD-L1 IHC (n = 24)	0.50 (0.48-0.53)	0.63 (0.62-0.65)	0.34 (0.32-0.36)	0.78 (0.76-0.79)
TMB (n = 10)	0.57 (0.51-0.62)	0.70 (0.66-0.73)	0.42 (0.38-0.47)	0.80 (0.77-0.83)
GEP (n = 9)	0.71 (0.67-0.75)	0.51 (0.48-0.54)	0.42 (0.39-0.46)	0.77 (0.74-0.81)
mIHC/IF (n = 7)	0.60 (0.53-0.66)	0.78 (0.73-0.82)	0.63 (0.56-0.70)	0.75 (0.70-0.80)
Multimodality (n = 6)	0.58 (0.50-0.65)	0.79 (0.75-0.82)	0.41 (0.33-0.48)	0.88 (0.85-0.91)

Abbreviations: GEP, gene expression profiling; mIHC/IF, multiplex immunohistochemistry/immunofluorescence; PD-L1 IHC, programmed cell death ligand 1 immunohistochemistry; TMB, tumor mutational burden.

[a] All data are reported as a proportion (95% CI). Nonoverlapping 95% CIs suggest statistical significance.

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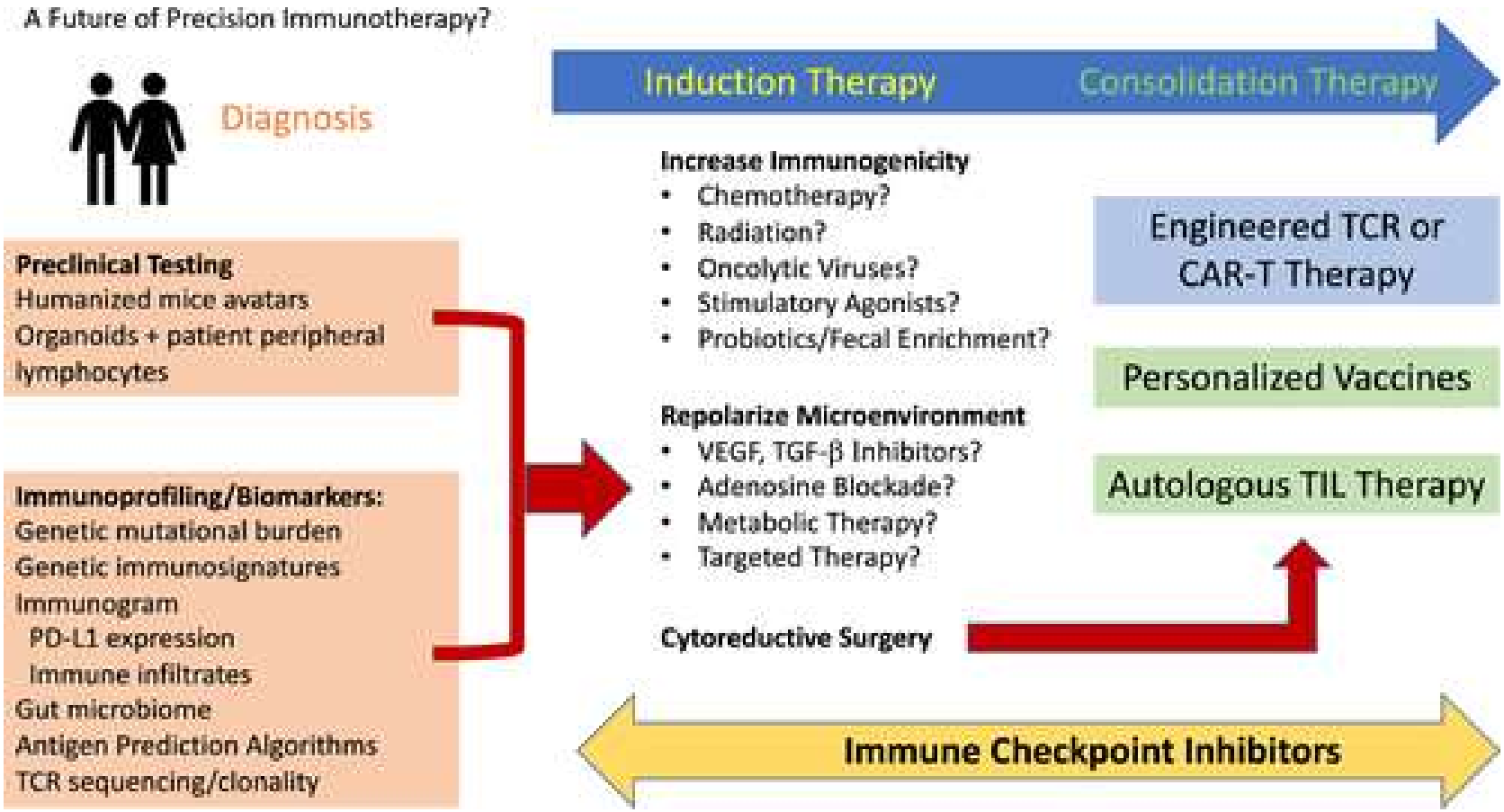
From: **Comparison of Biomarker Modalities for Predicting Response to PD-1/PD-L1 Checkpoint Blockade: A Systematic Review and Meta-analysis**

JAMA Oncol. Published online July 18, 2019. doi:10.1001/jamaoncol.2019.1549

Precision Immunotherapy



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Summary and Future Directions

Response	Resistance	Future Directions
High tumor mutational burden	Lack of T cell infiltration	Refining PD-L1 antibody precision
Checkpoint protein expression (PD-L1)	High quantities of T-regs, TAMs, MDSCs	Biomarkers for CTLA-4 response
High quantities of infiltrating CD8+ T cells	Expression of alternative checkpoint proteins	Neoantigen signatures superior to TMB in some tumors
Low circulating neutrophil:lymphocyte ratio	High stromal burden (cancer-associated fibroblasts)	Implementing new technologies to assess immune microenvironment
Higher diversity of gut microbiomes	High suppressive cytokines (VEGF, cofactors, IL-6, TGF-β)	Statistical models to incorporate multiple biomarkers
High expression of immune-related genes (Tumor Inflammation immunosignature)	Genetic mutations (JAK 1/2, PTEN loss, β-catenin/Wnt signaling)	

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