Basic Principles of Tumor Immunotherapy

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Disclosure

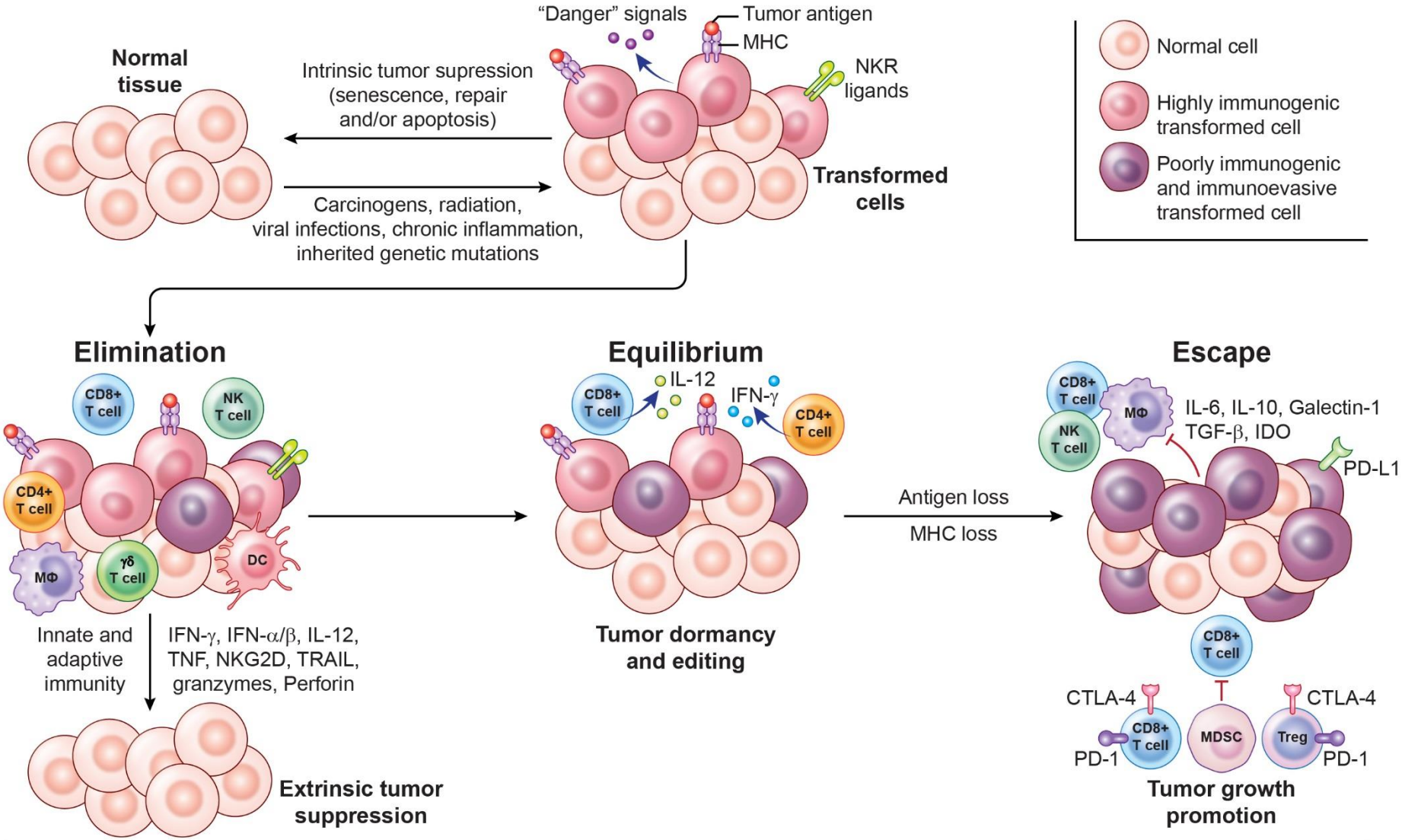
Research funding from Provectus Inc. and Lion Biotechnologies Inc.

I will be discussing non-FDA approved treatments/indications during my presentation

Why does the immune system fail to eliminate cancer?

Cancer cells grow progressively in immunogenic hosts without evidence of T cell exhaustion or systemic anergy.

The 3 Es of cancer immunoediting



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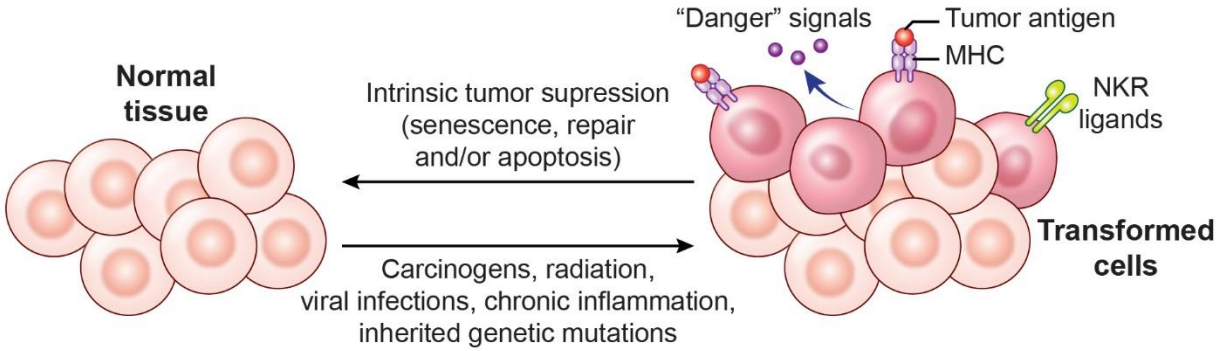
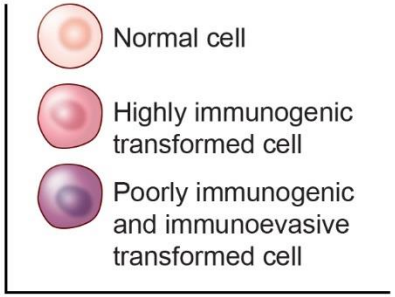
The 3 Es of cancer immunoediting





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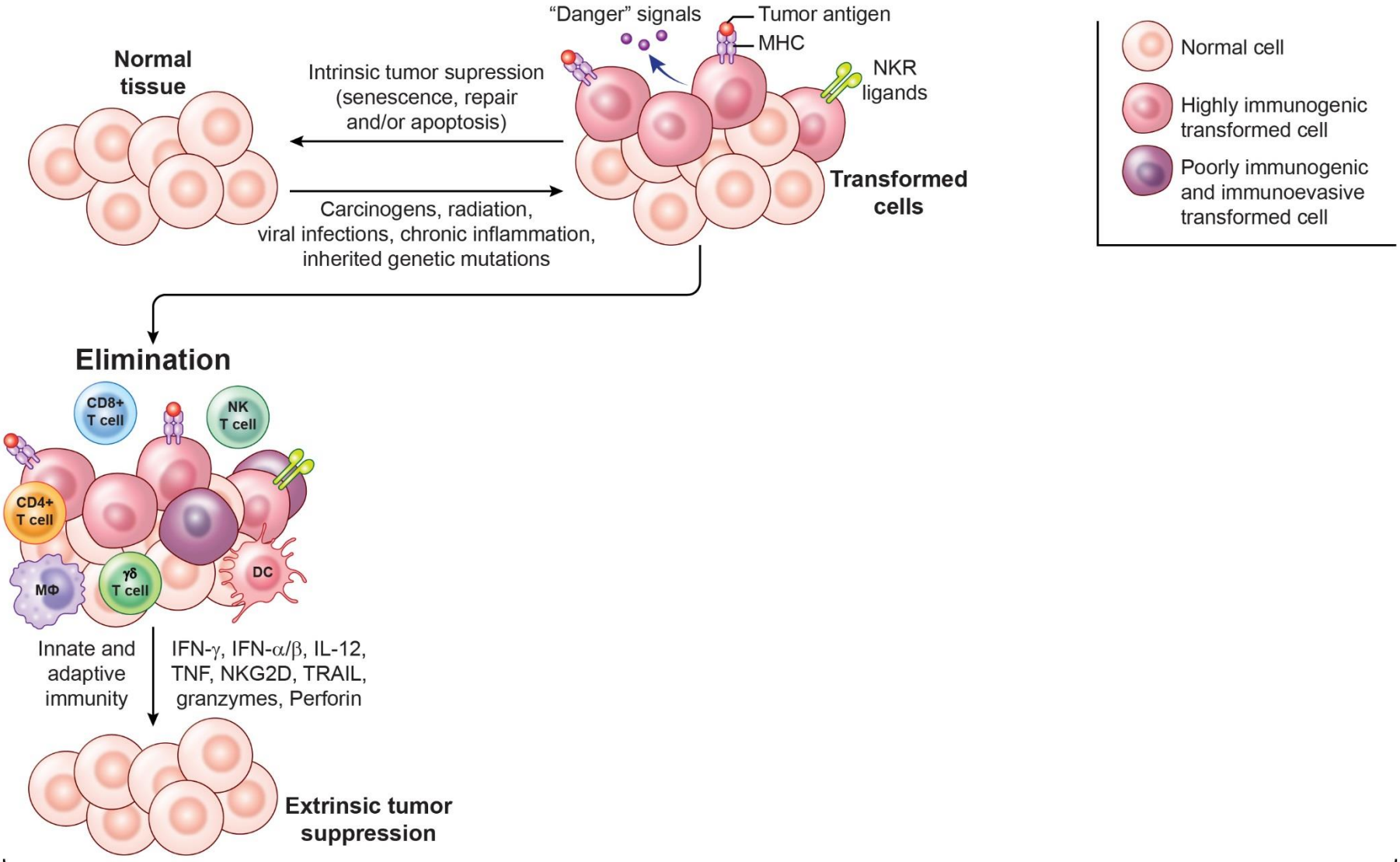

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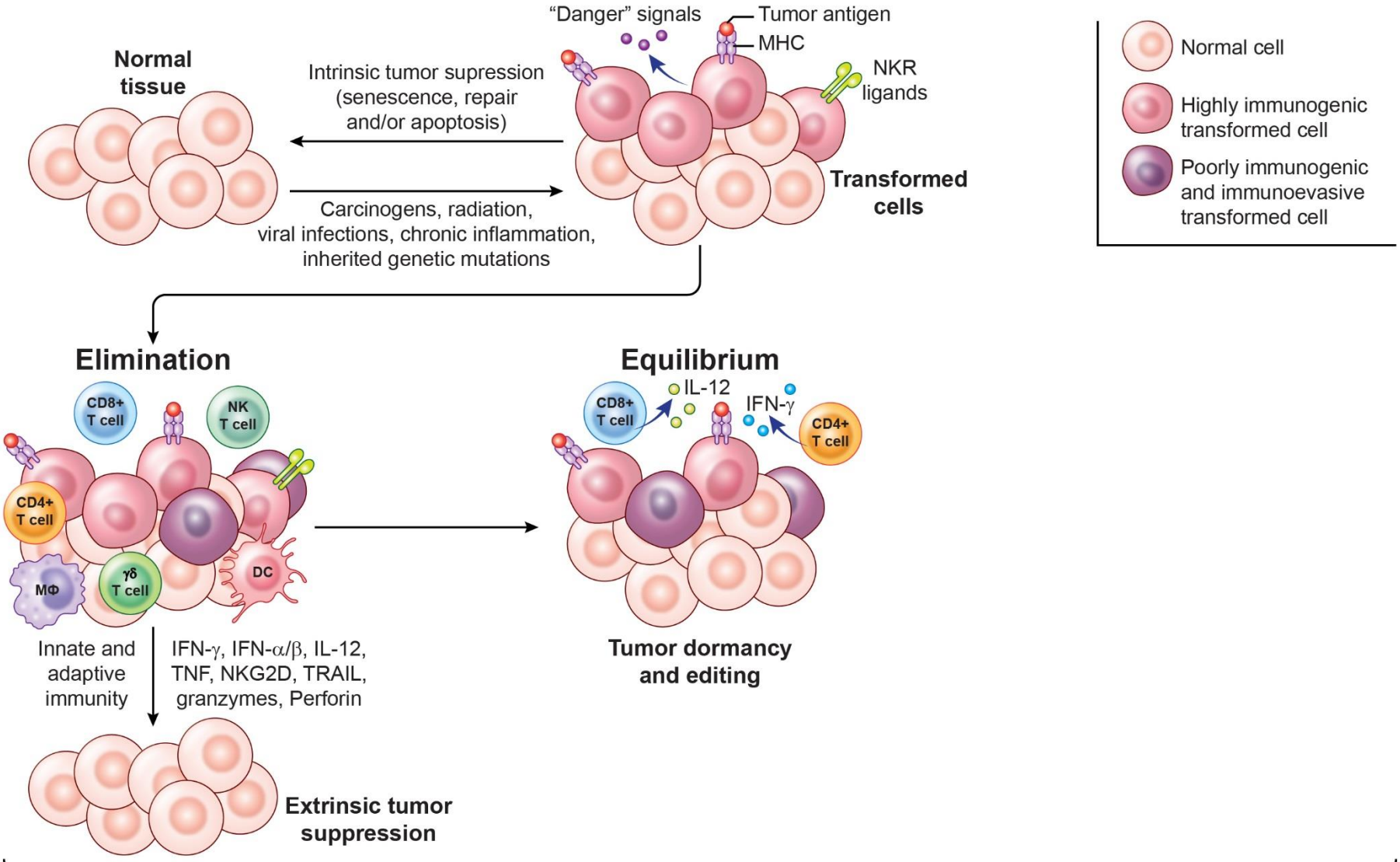

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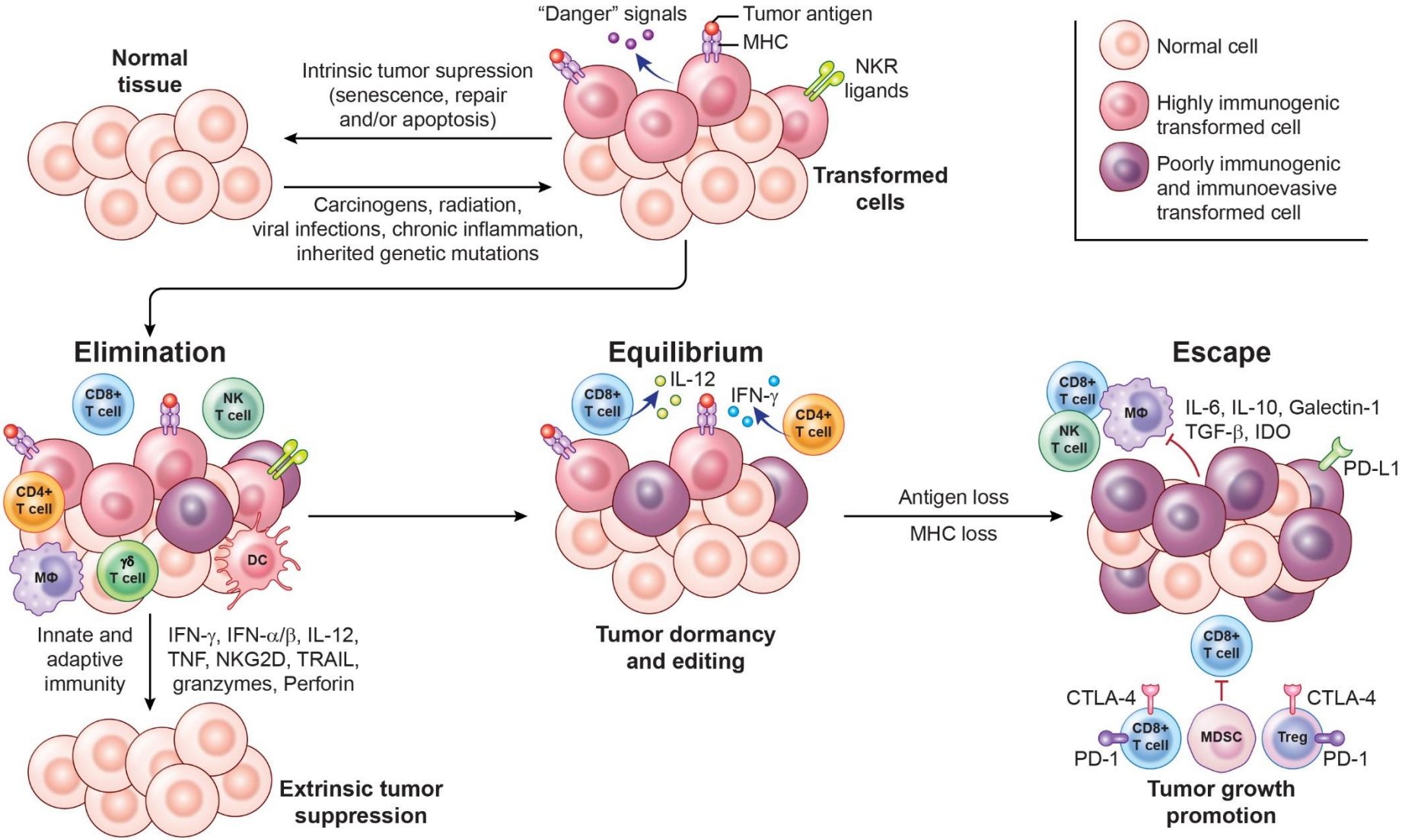

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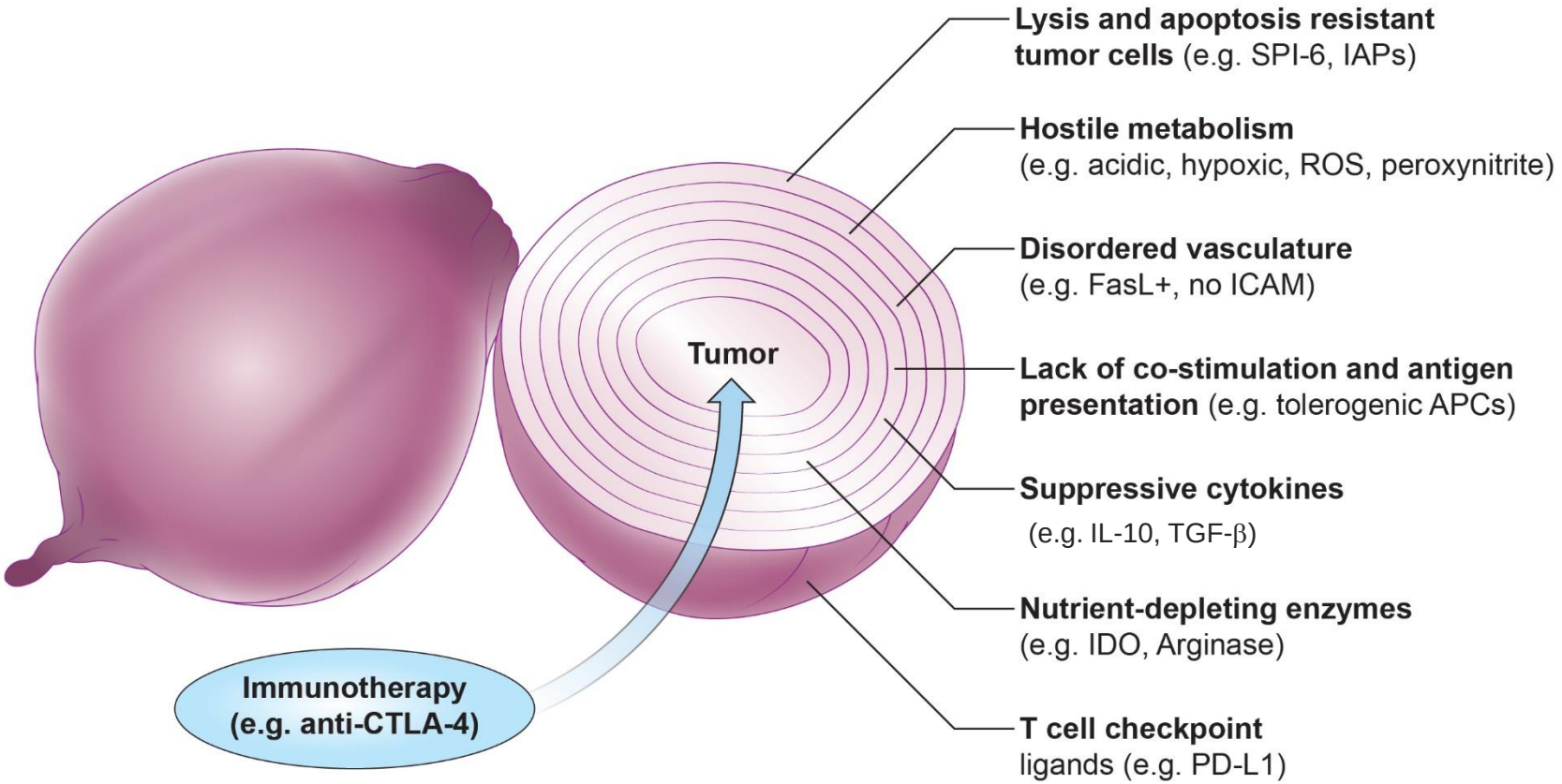
Multi-layered immunosuppression



- Tumors insulate themselves with dense layers of immunosuppressive stroma
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can "peel back" the layers of local immune suppression, thereby restoring the capacity of T cells to eradicate the tumor

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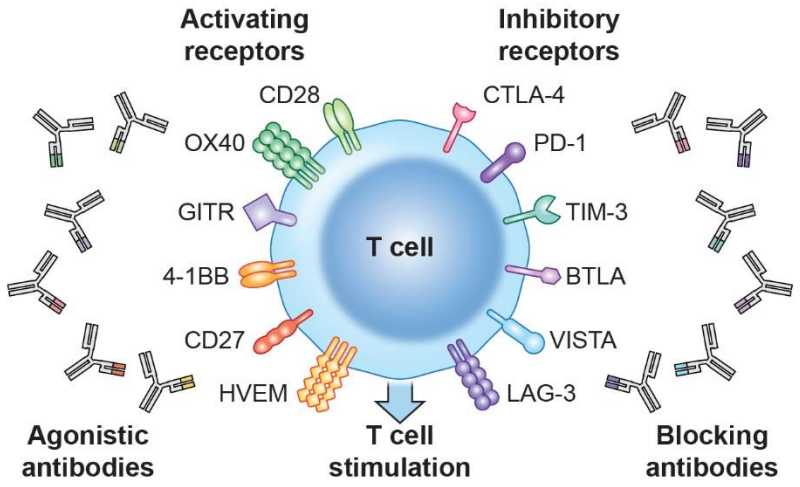
To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

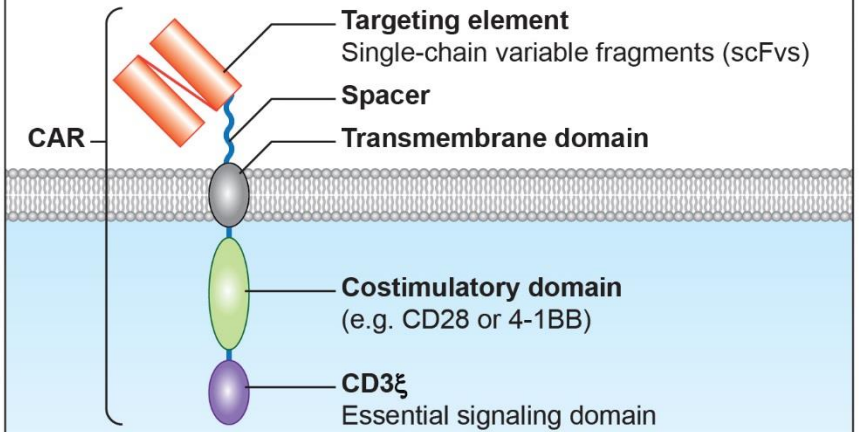
The goal of immunotherapy, then, is to restore the capacity of the immune system to recognize and reject cancer.

Types of immunotherapy

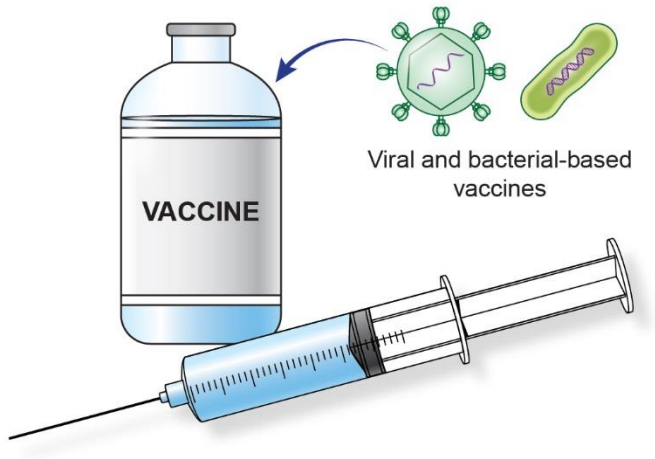
T cell checkpoint modulation



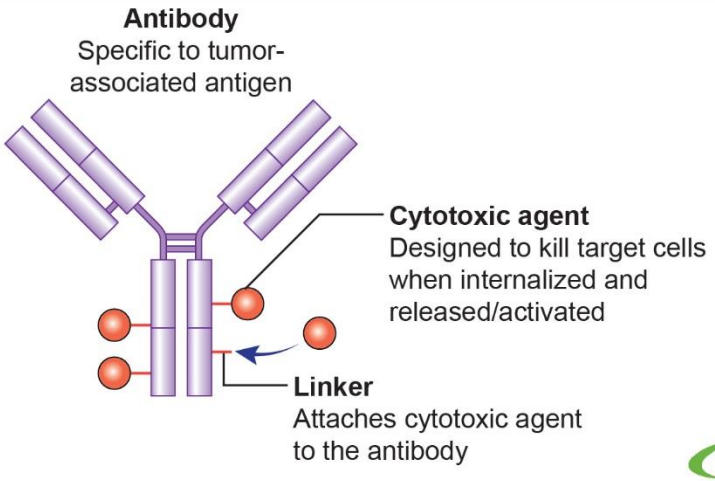
T cell adoptive transfer



Therapeutic cancer vaccines



Effector antibodies and antibody-drug conjugates



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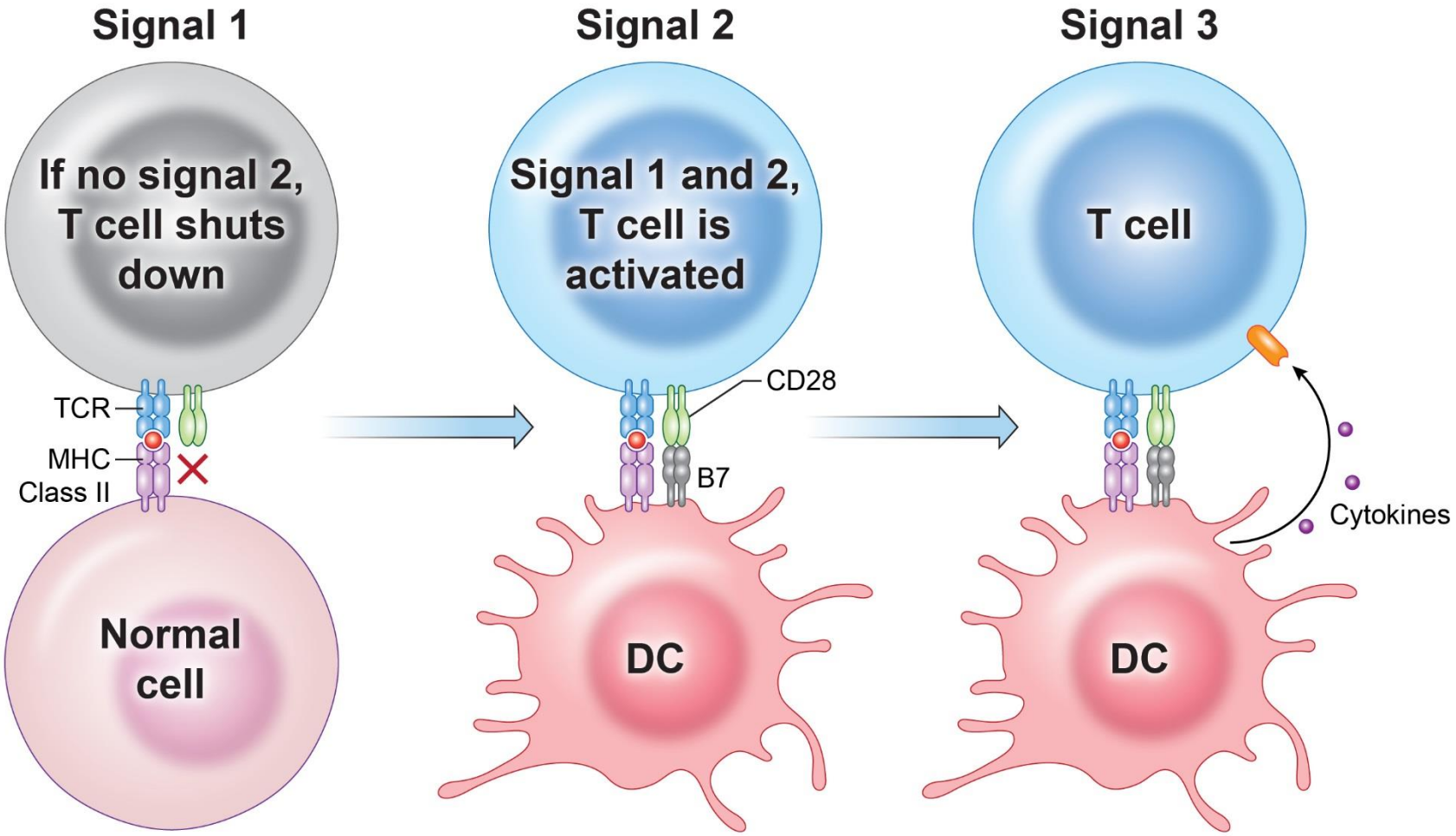
T cell Checkpoint Modulation

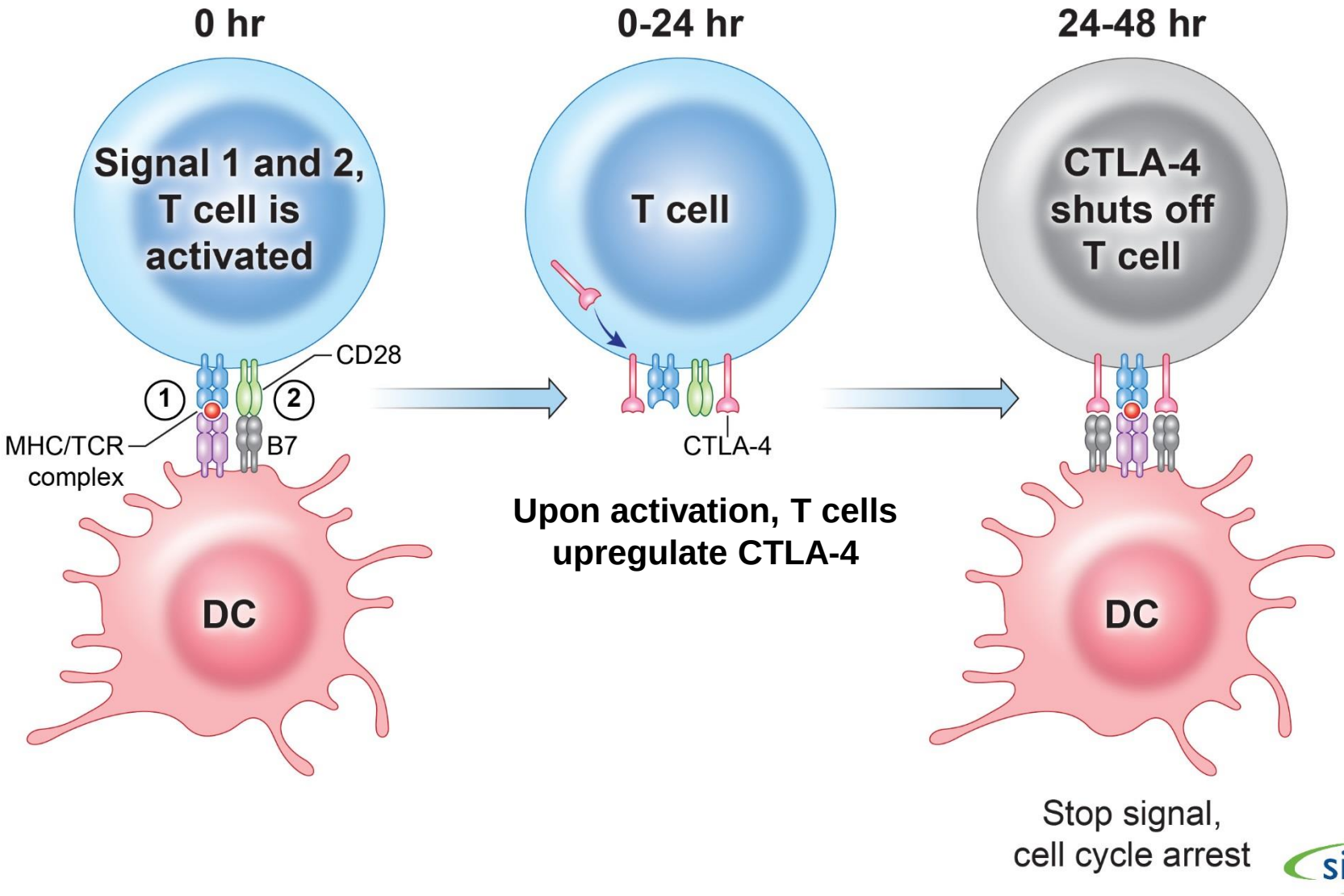
To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

The goal of T cell checkpoint blockade is to make T cell “off-switches” inaccessible to tumor cells, thus restoring tumor-specific immunity.

Three signals for antigen-specific T cell activation



CTLA-4, a negative regulator of T cell activity, limits the responsiveness of activated T cells



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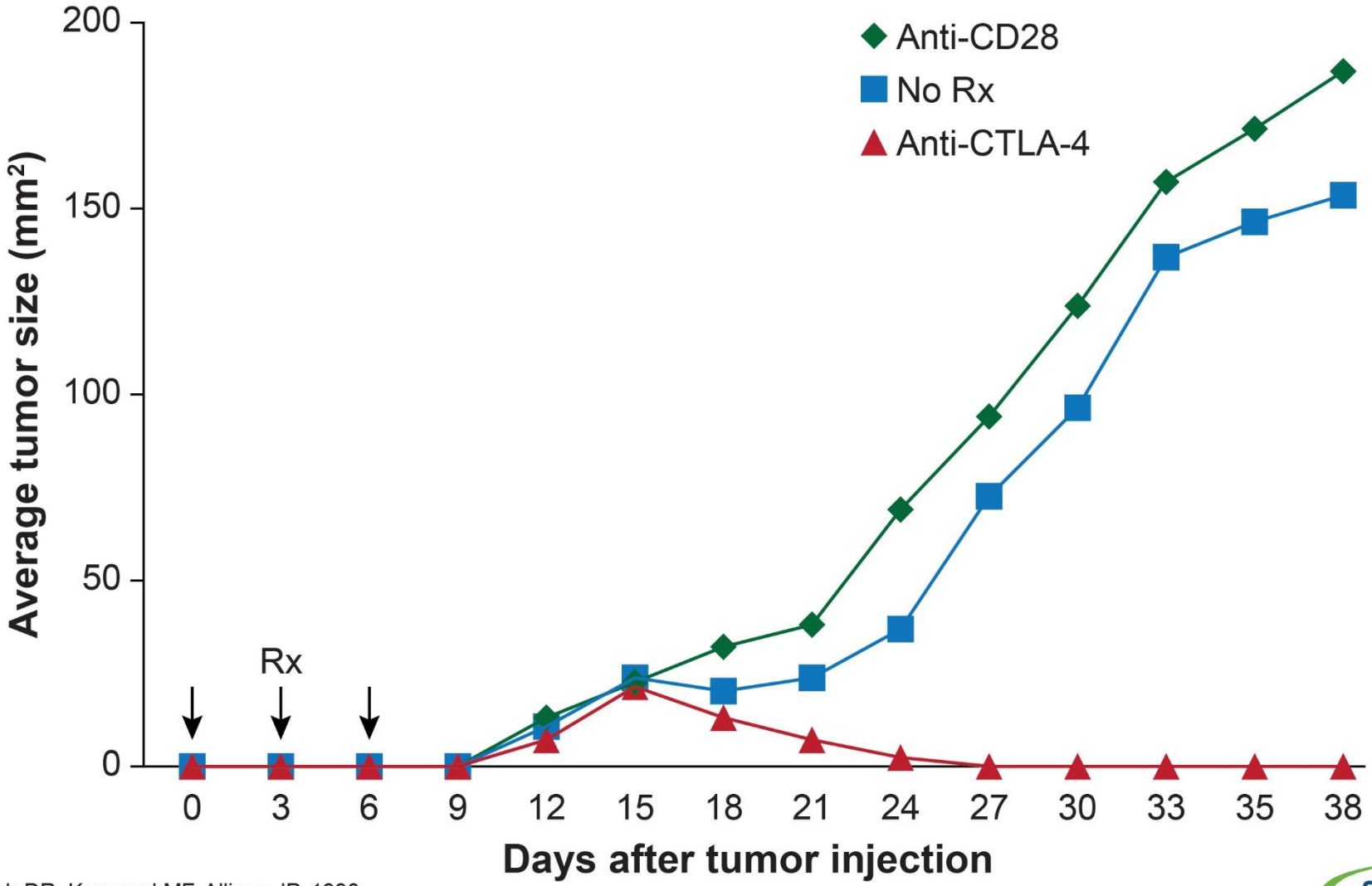
Anti-CTLA-4 induces regression of transplantable colon carcinoma



Leach DR, Krummel MF, Allison JP. 1996.
Enhancement of antitumor immunity by CTLA-4 blockade.
Science. 217(5256): 1734-6.

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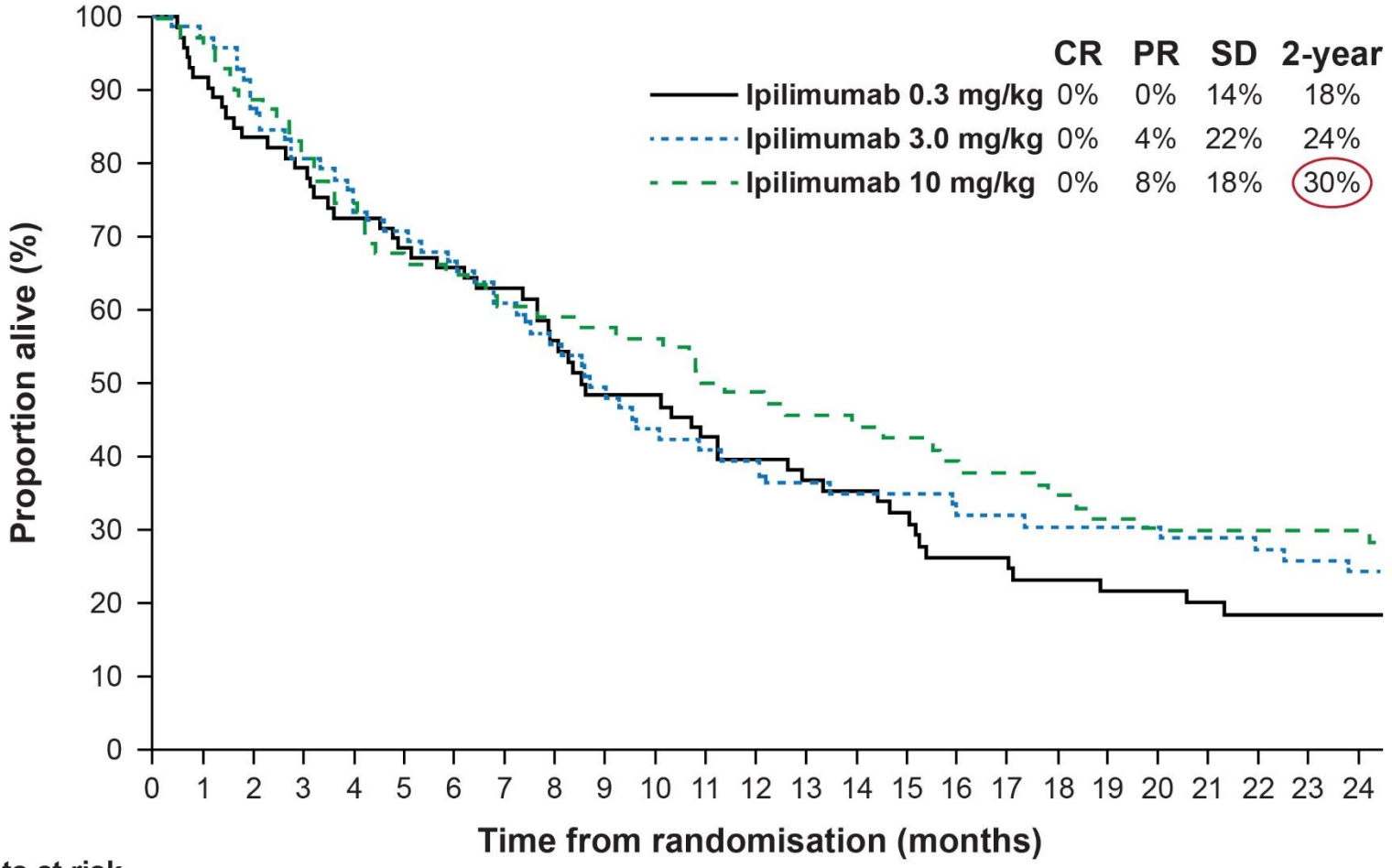
Ipilimumab (human anti-CTLA-4) was approved for the treatment of metastatic melanoma by the FDA in 2010



Patients at risk

0.3 mg/kg	73	67	61	58	53	50	47	45	38	33	33	29	27	25	24	21	17	17	15	14	14	13	12	12	12
3.0 mg/kg	72	70	64	58	54	50	47	43	39	34	30	28	26	24	23	23	22	21	20	20	20	19	18	17	16
10 mg/kg	72	70	63	58	53	47	45	42	41	40	39	33	31	29	28	27	25	24	22	20	19	19	19	18	18

Wolchok et al. 2010. Lancet Oncol.

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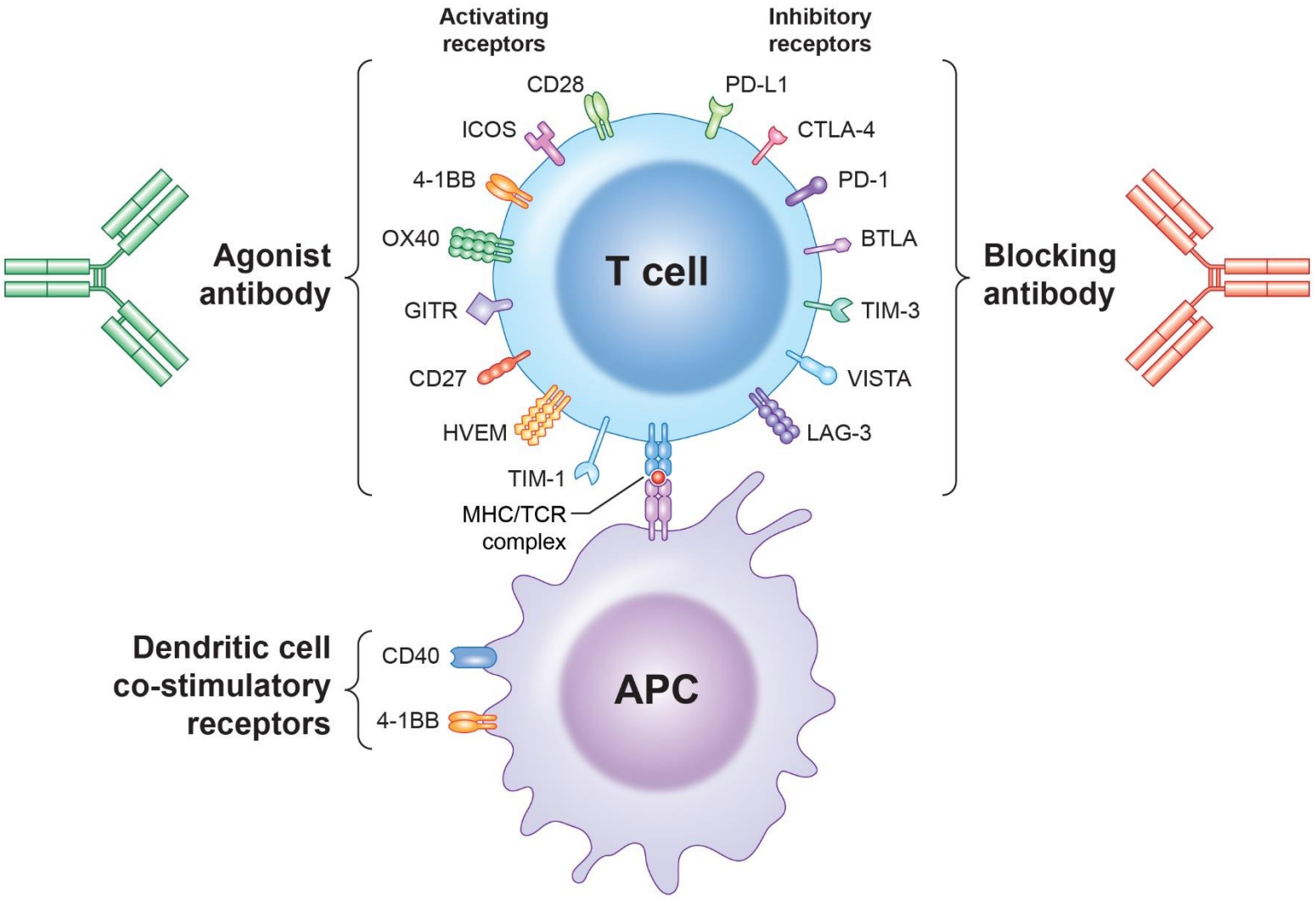
T cell checkpoint modulation



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Immune checkpoint-modulating antibodies currently in the clinic

T cell immune checkpoint-modulating antibodies in the clinic

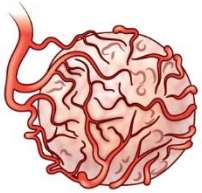
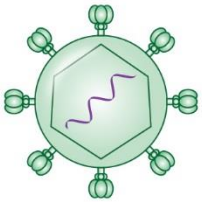
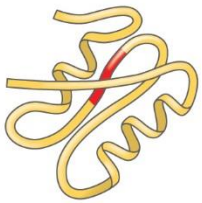
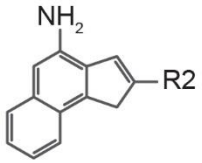
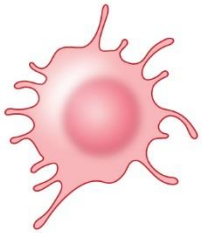
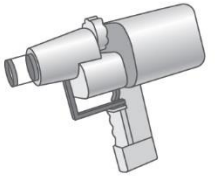
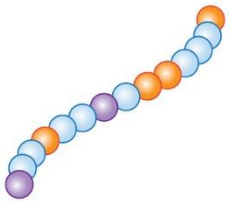
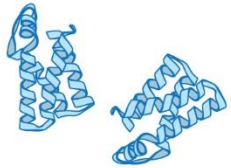
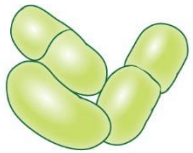
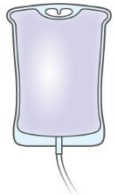
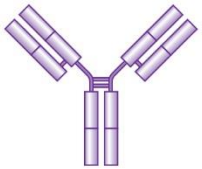
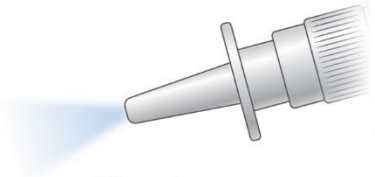
Target molecule	Drug	Development stage
CTLA-4	Ipilimumab	FDA approved
	Tremelimumab	Phase III trial
PD-1	Pembrolizumab	FDA approved
	Nivolumab	FDA approved
	AMP-514/MEDI0680	Phase I trial
PD-L1	Atezolizumab	FDA approved
	Durvalumab	Phase III trial
	Avelumab	Phase III trial
	BMS-936559	Phase I trial
4-1BB	Urelumab	Phase I trial
	PF-05082566	Phase I trial
OX-40	MEDI6469	Phase I trial
	MEDI6383 (rOX40L)	Phase I trial
	MOXR0916	Phase I trial
GITR	TRX518	Phase I trial
CD27	CDX-1127	Phase I trial
CD40	CP-870, 893	Phase I trial
LAG3	BMS-986016	Phase I trial

Therapeutic Cancer Vaccines

To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

The goal of therapeutic cancer vaccination is to increase the frequency of tumor-specific T cells.

Components of a cancer vaccine

Antigen	Adjuvant	Vector	Vehicle
 Whole tumor	 Emulsifiers	 Viral vectors	 Injection
 Protein antigen	 Innate agonists	 Dendritic cells	 Gene gun
 Antigenic peptide(s)	 Cytokines	 Attenuated bacteria	 Systemic infusion
	 Antibodies		 Nasal spray

Active immunotherapies in phase III development

The first therapeutic cancer vaccine approved for human use was Sipuleucel-T for prostate cancer in 2010. Many others are in Phase III development as shown here and dozens more are currently in Phase I and Phase II. There is increasing interest in targeting the mutated antigens unique to each patient's cancer which are the targets for the most efficacious anti-tumor responses.

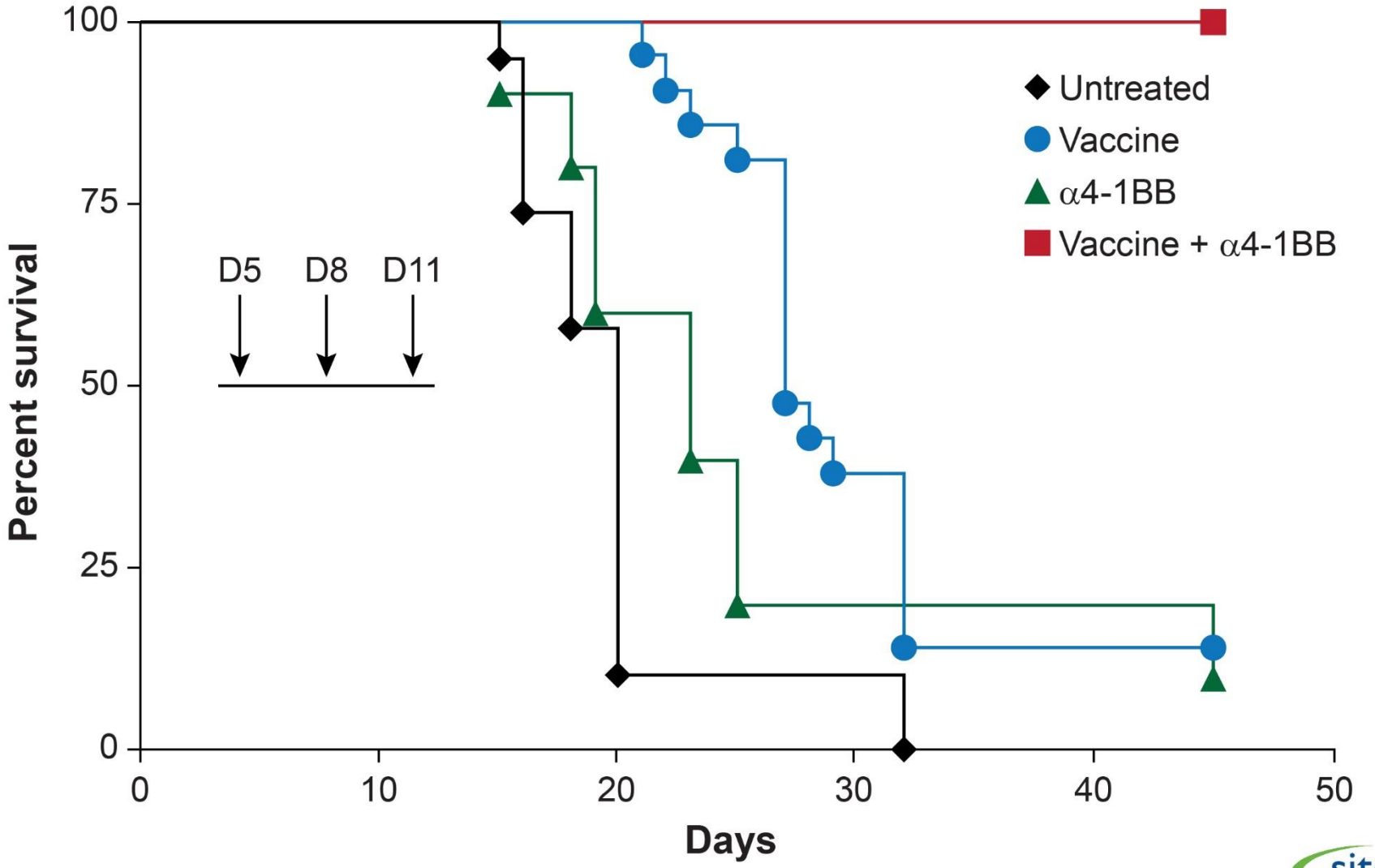
Immunotherapy	Targeted antigens	Adjuvants/ immune modulators	Study population	n	Outcomes
Prostate cancer					
Autologous cell vaccine: sipuleucel-T Provenge®	PAP	GM-CSF	Metastatic, castration-resistant prostate cancer	512	OS: 25.8 months vs 21.7 months (HR 0.78; *P*=0.03) PFS: 3.7 months vs 3.6 months (HR 0.95; *P*=0.63) T cell response in 74.0% vs 12.1% of patients
Allogeneic tumor cell vaccine: GVAX	Tumor cell	GM-CSF	Castration-resistant prostate cancer	626	OS: 20.7 months vs 21.7 months with docetaxel plus prednisone (HR 1.03; P=0.78)
Viral vector vaccine: Prostvac	PSA	GM-CSF	Castration-resistant prostate cancer	408	OS 25.1 months with Prostvac vs. 16.6 months with control vaccine (HR 0.56, P=0.0061)
Breast cancer					
Peptide vaccine: Theratope	Sialyl-Tn	KLH	Metastatic breast cancer, in remission after first-line chemotherapy	1,028	Median OS: 23.1 months vs 22.3 months (P=0.916) With concomitant endocrine therapy, OS: 39.6 months vs 25.4 months (P=0.005) Median TTP: 3.4 months vs 3.0 months (P=0.353) With concomitant endocrine therapy: 10.6 months vs 6.3 months (P=0.078)
Lung cancer					
Peptide vaccine: tecemotide (L-BLP25)	MUC1	Liposomal monophosphoryl lipid A plus cyclophosphamide	Unresectable stage II NSCLC; after chemo-radiotherapy	1,239	Median OS: 25.6 months vs 22.3 months (HR 0.88; P=0.123); OS with concurrent chemotherapy: 30.8 months vs 20.6 months (HR 0.78; P=0.016); OS with sequential chemotherapy: 19.4 months vs 24.6 months (HR 1.12; P=0.38)
Peptide vaccine: GSK1572932A	MAGE-A3	Liposomal AS15	Completely resected stage IB-II NSCLC	182	Trial terminated owing to failure to meet primary end points of extended DFS. Not possible to identify gene signature predicting benefit

Active immunotherapies in phase III development

(Continued)

Immunotherapy	Targeted antigens	Adjuvants/ immune modulators	Study population	n	Outcomes
Lung cancer					
Allogeneic tumor cell vaccine: belagenpumatucel-L Lucanix™	Tumor cell	Anti-TGF-β	Stage IIIB-IV NSCLC	532	Median OS: 20.3 months vs 17 months (HR 0.94; P=0.594) Non-adenocarcinoma: 19.9 months vs 12.3 months (HR 0.55; P=0.036)
Melanoma					
Peptide vaccine	gp100	IL2 plus Montamide™ ISA51	Locally-advanced stage III or stage IV melanoma	185	OS: 17.8 months vs 11.1 months (P=0.06) PFS: 2.2 months vs 1.6 months (P=0.08) T cell responses in 7 of 37 (19%) patients Higher levels of CD4 'foxp3' cells in patients with clinical response (P=0.01)
Peptide vaccine: GSK 2132231A	MAGE-A3	QS-21	Resected melanoma	1,349	Failed to meet primary end point of DFS; ongoing for end point of DFS in patients with predictive gene signature
Pancreatic cancer					
Peptide vaccine: GV1001	Telomerase	GM-CSF	Locally-advanced and/or metastatic pancreatic cancer	1,062	OS: 8.4 months (concurrent with chemotherapy) and 6.9 months (sequential chemotherapy) vs 7.9 months with chemotherapy alone (NS)
Colorectal cancer					
Autologous tumor cell vaccine: OncoVAX®	Tumor cell	BCG	Resected stage II-III colon cancer; after resection	254	42% reduction in the risk of recurrence and/or death (P=0.032); greatest effect in stage II disease with 60% reduction in risk of recurrence and/or death (P=0.007) and 54% reduction in risk of death
Haematological malignancies					
Autologous anti-idiotype vaccine	Idiotype	KLH	Advanced follicular lymphoma, with complete response after chemotherapy	177	PFS: 23.0 months vs 20.6 months (P=0.256) ≥1 blinded vaccination: 44.2 months vs 30.6 months (P=0.047)

4-1BB agonist antibody and HPV E6/E7 vaccine synergize in curing TC-1 tumors



Todd Bartkowiak, M.S.

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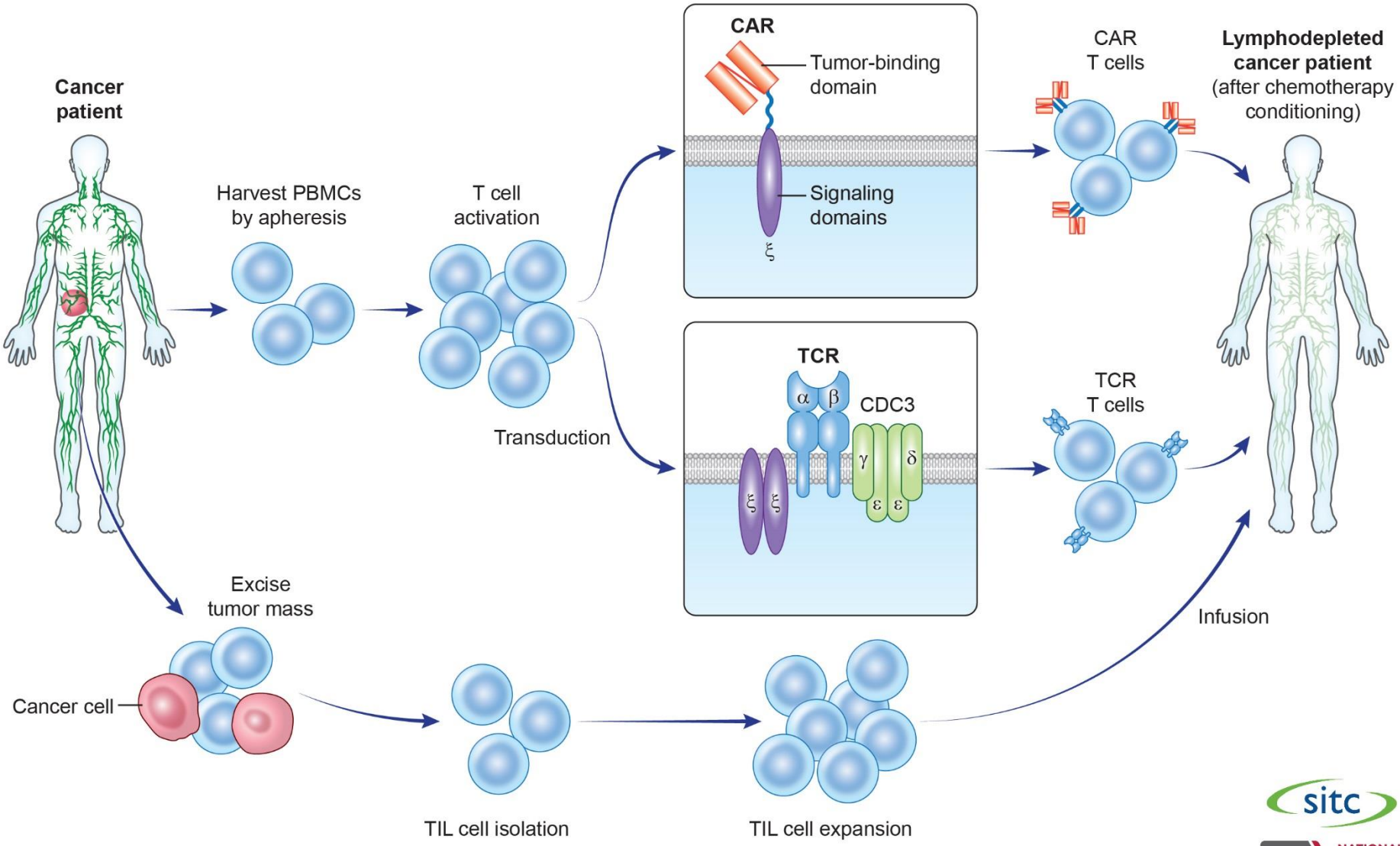
T cell Adoptive Transfer

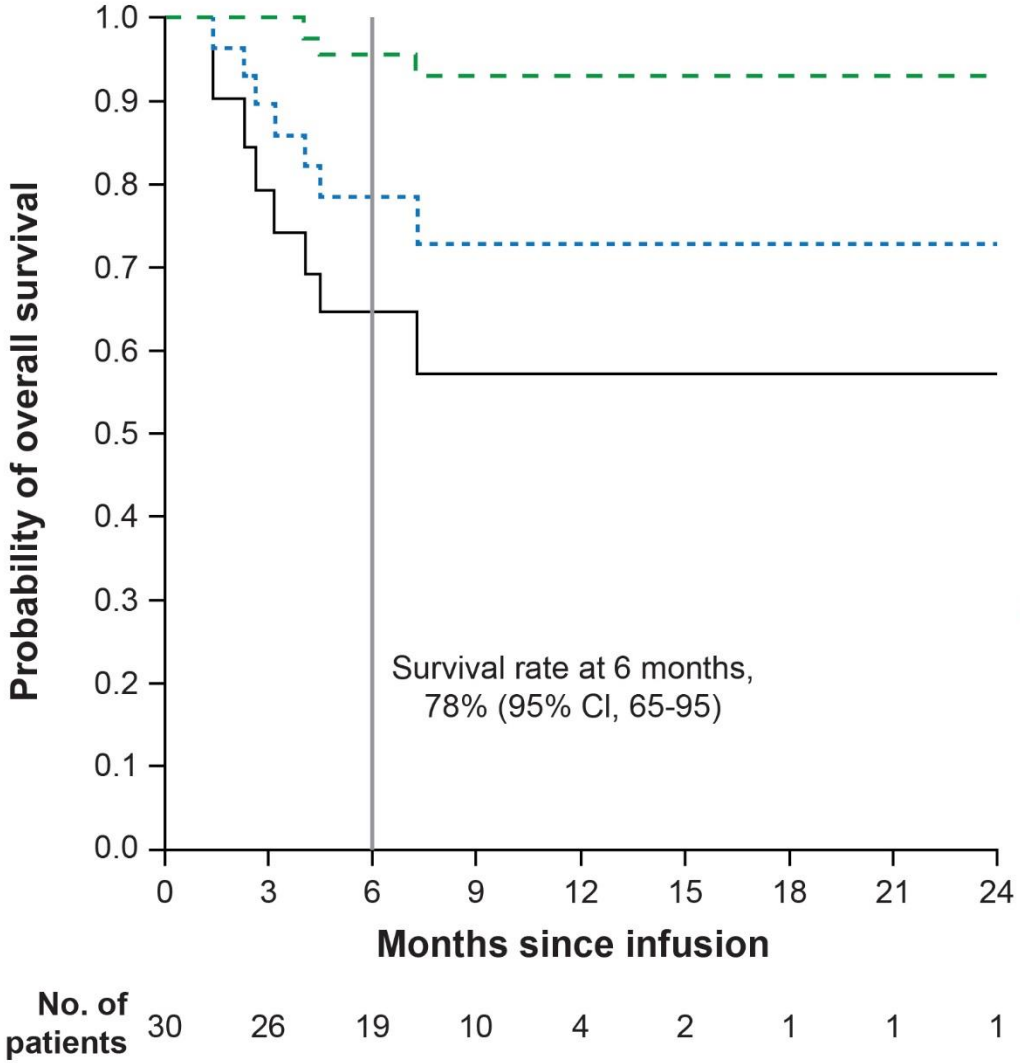
To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

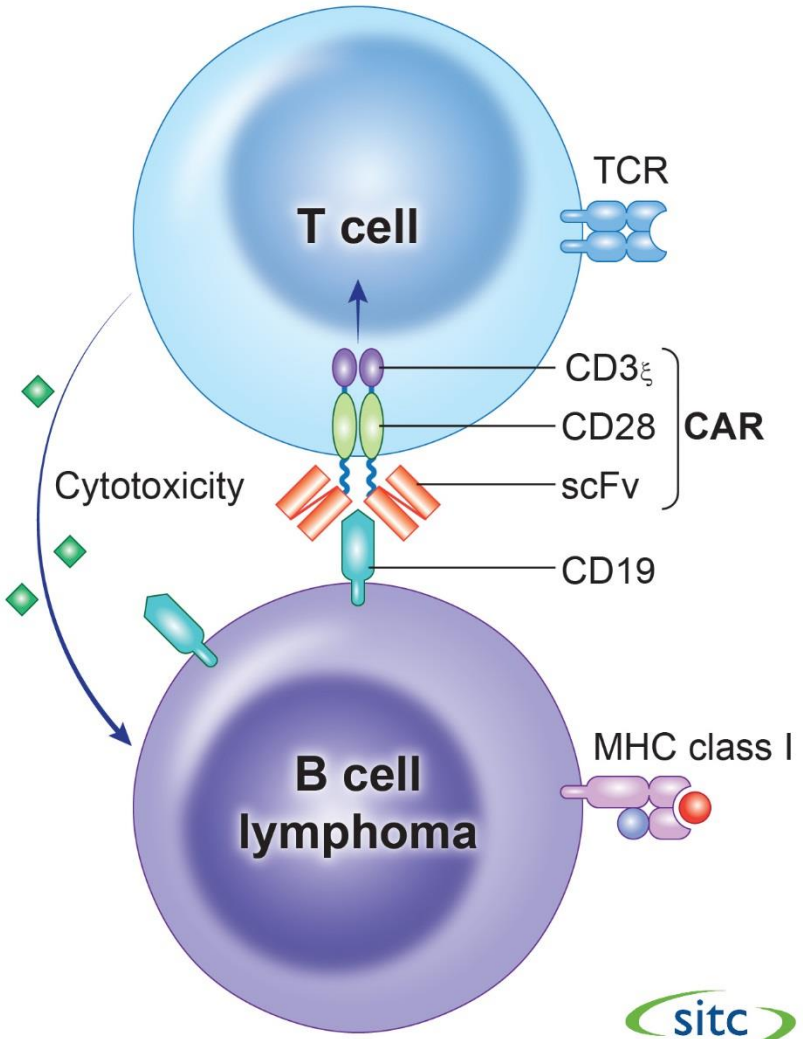
The goal of T cell adoptive transfer is to win the numbers game and overwhelm the tumor with tumor-specific T cells

Adoptive T cell therapy can involve engineered (CAR, TCR) or patient-derived (TIL, PBMC) T cells



Effective treatment of relapsed B cell ALL with CD19 CAR T cell therapy





Maude S, Frey N, Shaw P, Aplenc R, Barrett D, Bunin N, Chew A, Gonzalez V, Zheng Z, Lacey S, et al. 2016.
Chimeric antigen receptor T cells for sustained remissions in leukemia.
The New England Journal of Medicine. 374(10): 998.

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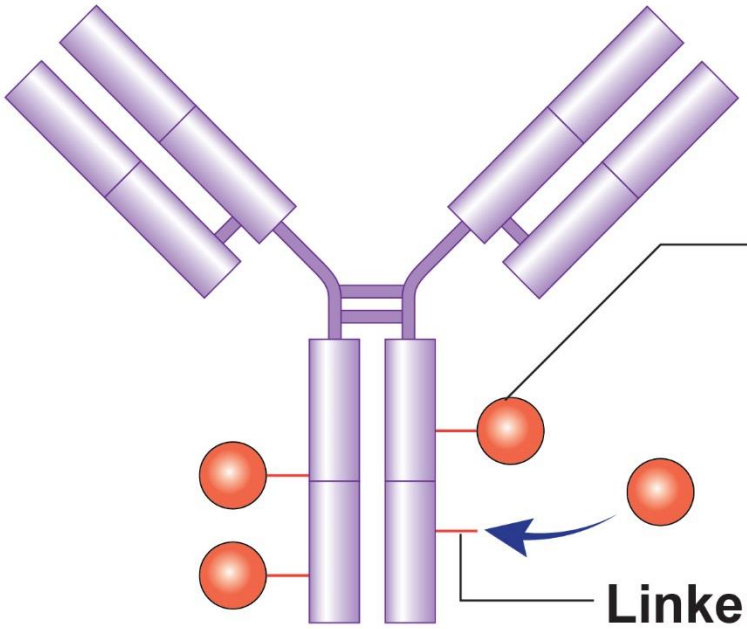
To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

The goal of effector antibodies is to specifically target and kill tumors cells using mechanisms which are difficult to evade of suppress

Effector antibodies and antibody-drug conjugates (ADCs)

Antibody
Specific to tumor-associated antigen



Cytotoxic agent
Designed to kill target cells when internalized and released or activated

Linker
Attaches cytotoxic agent to the antibody

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Key ADC/antibody principles

- **Specificity:** The more tumor specific the target antigen is, the higher the agent can be dosed without limiting toxicity

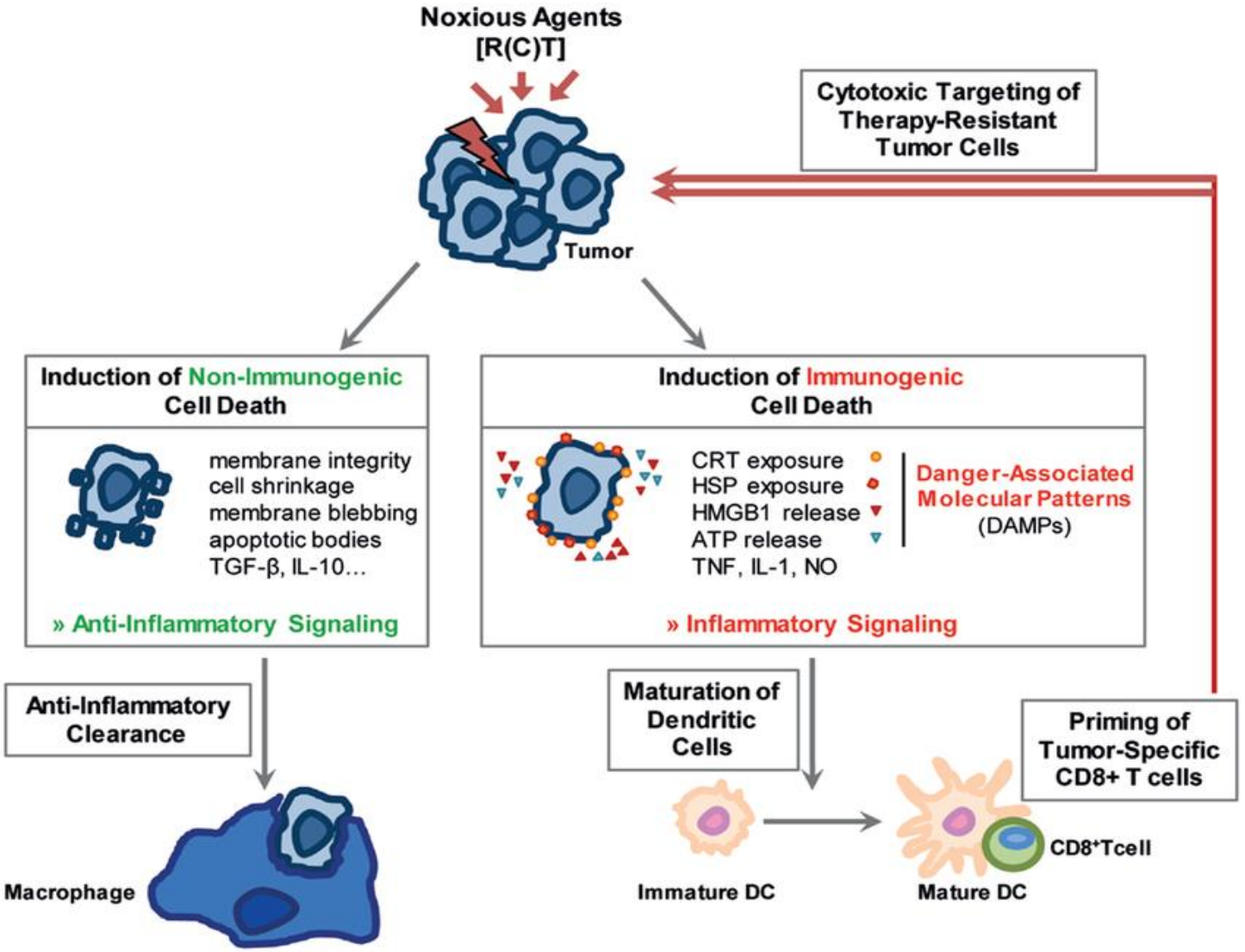
- **Internalization:** The target tumor surface protein must internalize to deliver the toxin - it should do so frequently and to a suitable endosomal compartment.

- **Stability:** The toxin must remain inert and tethered to the antibody until it is delivered to its target cell.

Chemotherapy / Radiation to Improve Immunotherapy

Chemotherapy and radiation therapy can enhance anti-tumor immune responses.

A different perspective on chemotherapy: Immunogenic versus non-immunogenic cell death



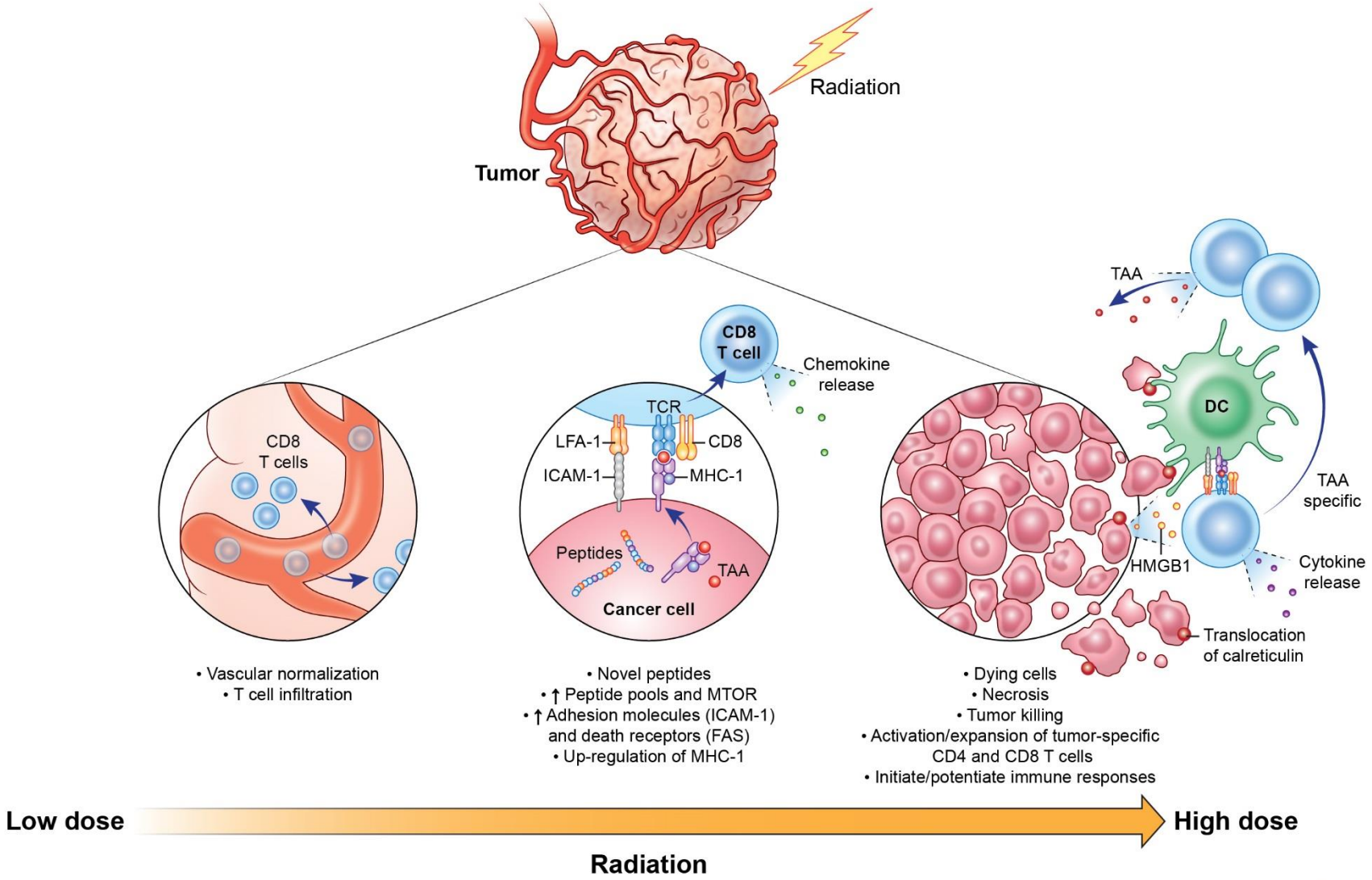
Derer A, Deloch L, Rubner Y, Fietkau R, Frey B and Gaipl US (2015) Front. Immunol. 6:505.

A different perspective on chemotherapy

Agent	Indications	Notes
Cyclophosphamide	Lymphoma, leukemia, solid tumors	• Immunosuppressive at high doses • Increases class I HLA expression on cancer cells • Selectively inhibits Treg cells and MDSCs, perhaps with a preferential activity on intratumoral populations • Favors the differentiation of IL-17-producing CD4+ cells • Stimulates the expansion of CD8α+ DCs • Restores T cell and NK cell functions • InhibitsIL-4, IL-10 and IL-13 production • Induces immunogenic cell death
Doxorubicin	Several solid and haematopoietic tumors	• Favors the proliferation of tumor-specific CD8+ T cells • Promotes tumor infiltration by IL-17-secreting $\gamma\delta$ T cells and activated IFNγ-secreting CD8+ T cells • Induces immunogenic cell death • Stimulates antigen presentation by DCs • Increases the permeability of tumor cells to granzyme B • Induces MCP1 expression on tumor cells, in turn driving the establishment of an immunosuppressive stroma
Gemcitabine	NSCLC, pancreatic cancer, bladder cancer, breast cancer	• Increases class I HLA expression • Enhances tumor antigen cross-presentation • Selectively kills MDSCs
Oxaliplatin	Colorectal cancer	• Increases class I HLA expression • Inhibits PDL2 expression • Induces immunogenic cell death

Galluzzi L, Senovill L, Zitvogel L, Kromer G. 2012.
The secret ally: immunostimulation by anticancer drugs.
Nature Reviews Drug Discovery. 11: 215-333

Radiation therapy: A potent adjuvant for tumor immunity



Exploiting the untapped potential of immunogenic modulation by radiation in combination with immunotherapy for the treatment of cancer

http://www.ncbi.nlm.nih.gov/pubmed/18777956

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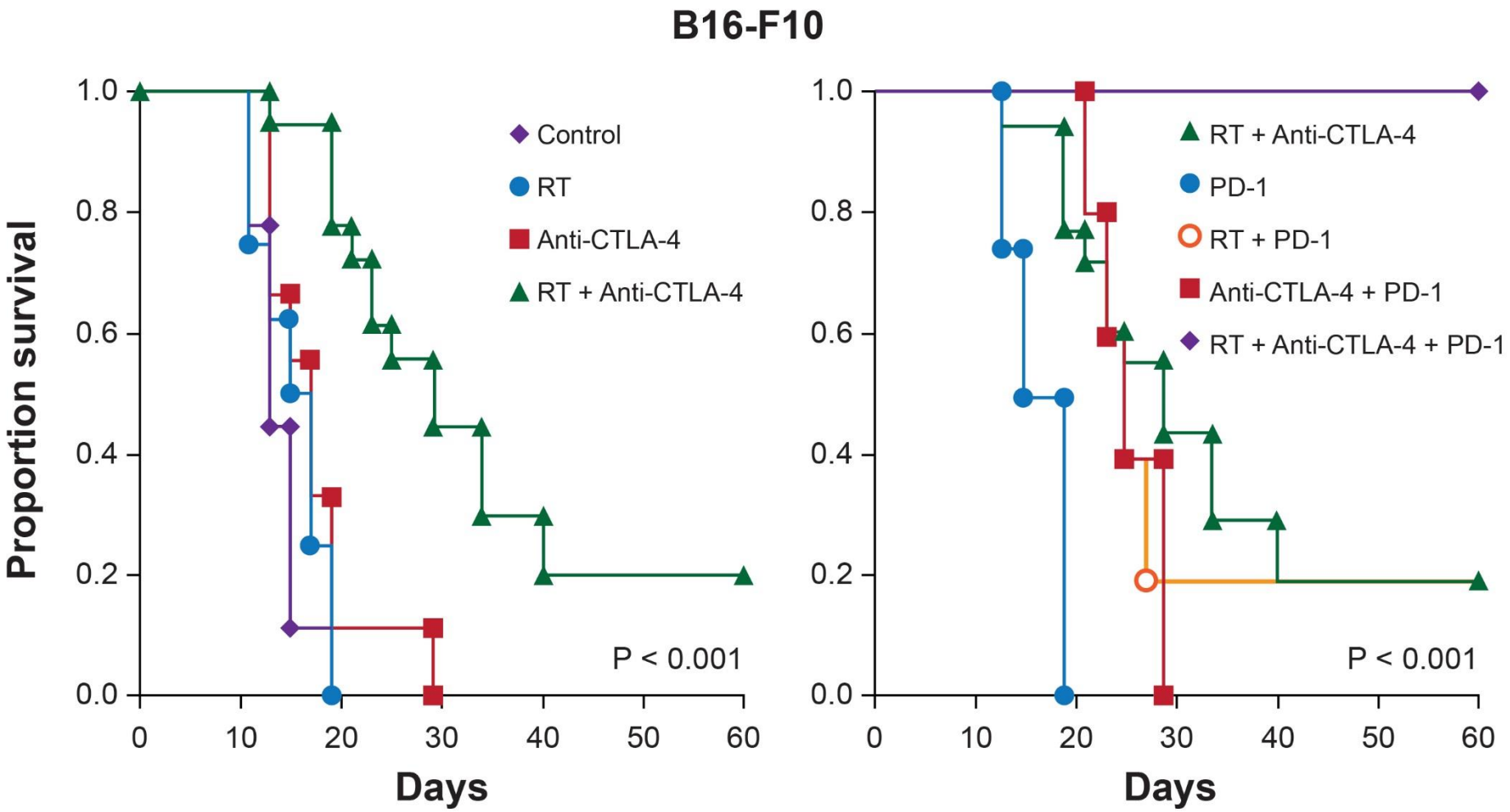
Radiotherapy synergizes with blockade of CTLA-4 and PD-1 to cure melanoma lung metastases



Victor CT, Rech A, Maity A, Rengan R, Pauken K, Stelekati E, Benci J, Xu B, Dada H, Odorizzi P, et al. 2015. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 520: 373-377.

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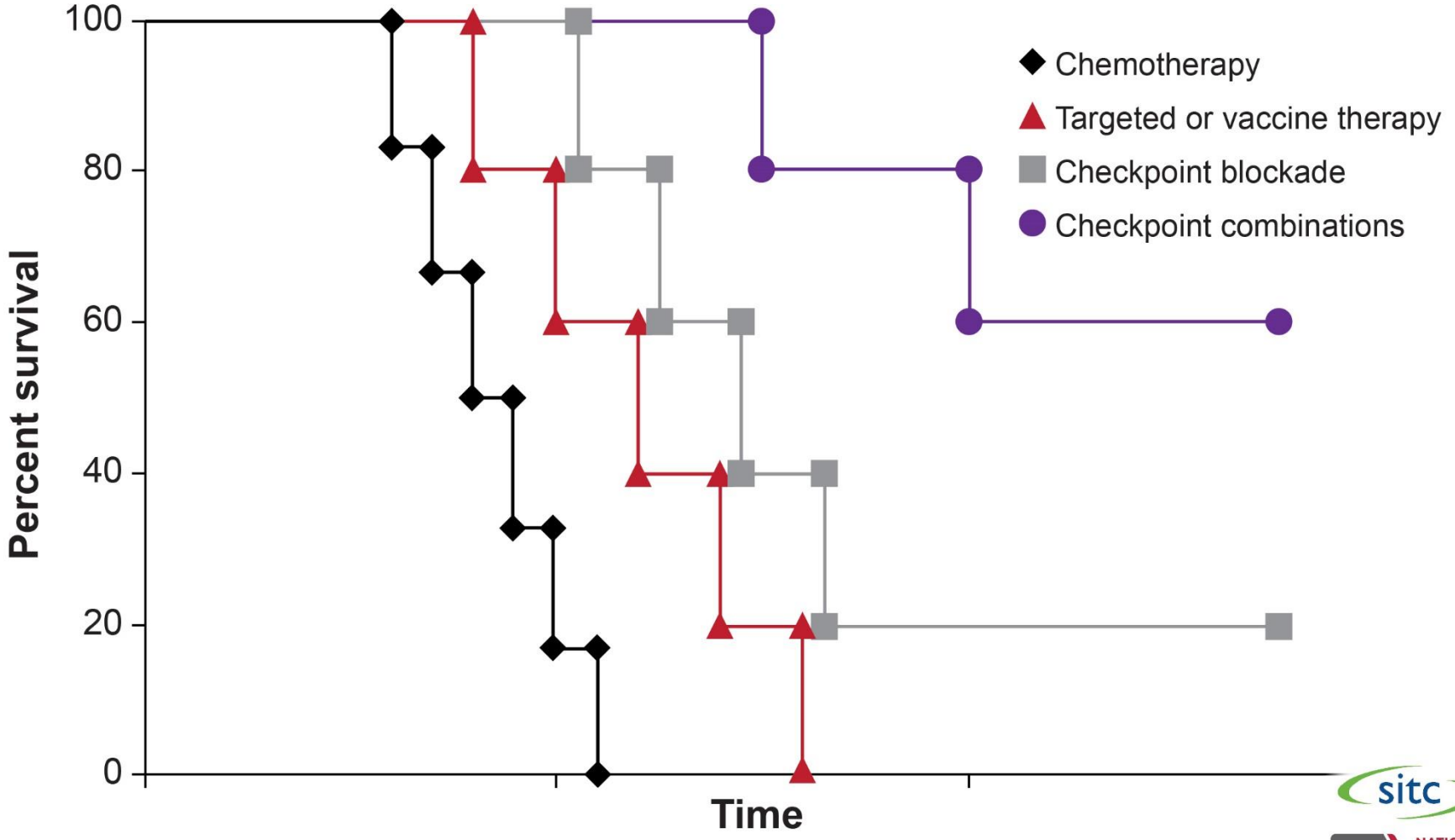
Why combination immunotherapy is the future? More consistent benefit for a larger percentage of patients with a wide range of cancer types



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