DANA-FARBER CANCER INSTITUTE

BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

Basic Principles of Tumor Immunotherapy

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Disclosures

Research grants:

- Bristol-Myers-Squibb; Merck; Celldex Therapeutics; ArmoBiosciences; Aztra-Zeneca/MedImmune

Consultant/advisor:

- Bristol-Myers-Squibb; Amgen; Alexion; Genentech, Celldex

I will not be discussing non-FDA approved uses of drugs

Cancer Immunotherapy: Timeline

1890s
1st cancer immunotherapy (Coley)

1973
Dendritic cell discovered (Steinman)

1976
1st Study of BCG in bladder cancer

1978
Tumor specific mAbs discovered

1985
1st study of adoptive T-cell transfer in cancer

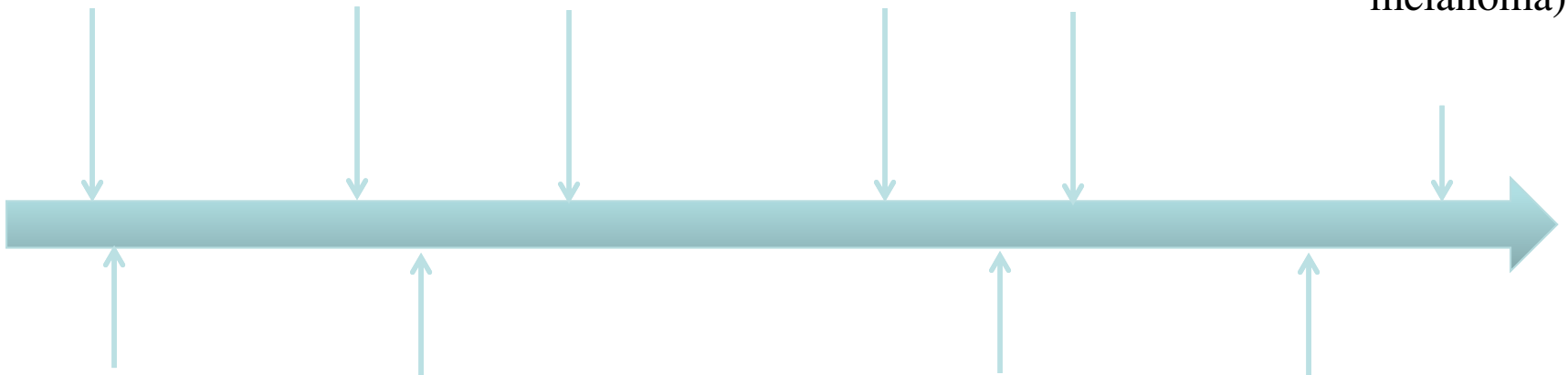
1990
CTLA-4 discovered (Allison)

1996
1st cytokine approved (IFN-alpha for hairy cell leukemia)

1998
IL-2 approved for melanoma

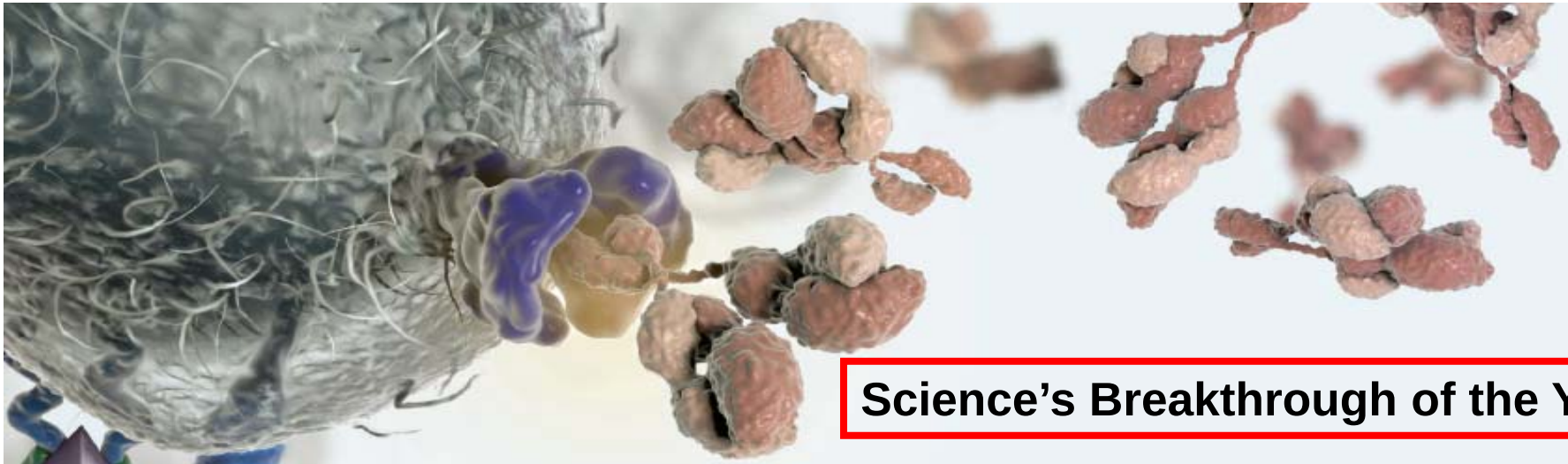
2010
1st vaccine approved (sipuleucel-T for prostate Ca)

2011
1st Checkpoint inhibitor approved (ipilimumab for melanoma)



Timeline of Cancer Immunotherapy

- 2014: Pembrolizumab and nivolumab(anti-PD-1 antibody) FDA approved for advanced melanoma
- 2014: "Breakthrough" designation to GVAX (GM-CSF based vaccine) for patients with metastatic pancreatic cancer
- 2014: "Breakthrough" designation to Nivolumab (anti-PD-1 antibody) for Hodgkin's Lymphoma
- 2014: "Breakthrough" designation to MPDL-3280A (anti-PD-L1 antibody) for bladder cancer
- 2015 Nivolumab approved in renal cell cancer
- 2015 Nivolumab and Pembrolizumab approved in NSCLC
- 2016: Ipilimumab plus Nivolumab approved in Melanoma



Science's Breakthrough of the Year

Cancer Immunotherapy

This year marks a turning point in cancer, as long-sought efforts to unleash the immune system against tumors are paying off—even if the future remains a question mark

History's path is unchartable when it's not yet past but present, when we are still standing in the middle of it. That's what made *Science*'s selection of this year's Breakthrough of the Year such a topic of internal debate, even anxiety. In celebrating cancer immunotherapy—harnessing the immune system to battle tumors—did we risk hyping an approach whose ultimate impact remains unknown? Were we irresponsible to label as a breakthrough a strategy that has touched a tiny fraction of cancer patients and helped only some of them? What do we mean when we call something a breakthrough, anyway?

Ultimately, we concluded, cancer immunotherapy passes the test. It does so because this year, clinical trials have cemented its potential in patients and swayed even the skeptics. The field hums with stories of lives extended: the woman with a grapefruit-size tumor in her lung from melanoma, alive and healthy 13 years later; the 6-year-old near death from leukemia, now in third grade and in remission; the man with metastatic kidney cancer whose disease continued fading away even after treatment stopped. a grounded-in-reality bunch, say a corner has been turned and we won't be going back.

With much pressure these days to transform biological insights into lifesaving drugs, there's a lesson to be learned from immunotherapy's successes: They emerged from a careful decoding of basic biology that spanned many years. The early steps were taken by cancer immunologist James Allison, now at the University of Texas MD Anderson Cancer Center in Houston. In the late 1980s, French researchers who weren't thinking about cancer at all identified a new protein receptor on the surface of T cells, called cytotoxic T-lymphocyte antigen 4, or CTLA-4. Allison found that CTLA-4 puts the brakes on T cells, preventing them from launching full-out immune attacks. He wondered whether blocking the blocker—the CTLA-4 molecule—would set the immune system free to destroy cancer.

Allison's rationale was untested.

Online
sciencemag.org
Podcasts, videos, and other extras (http://scim.ag/mcd_6165)

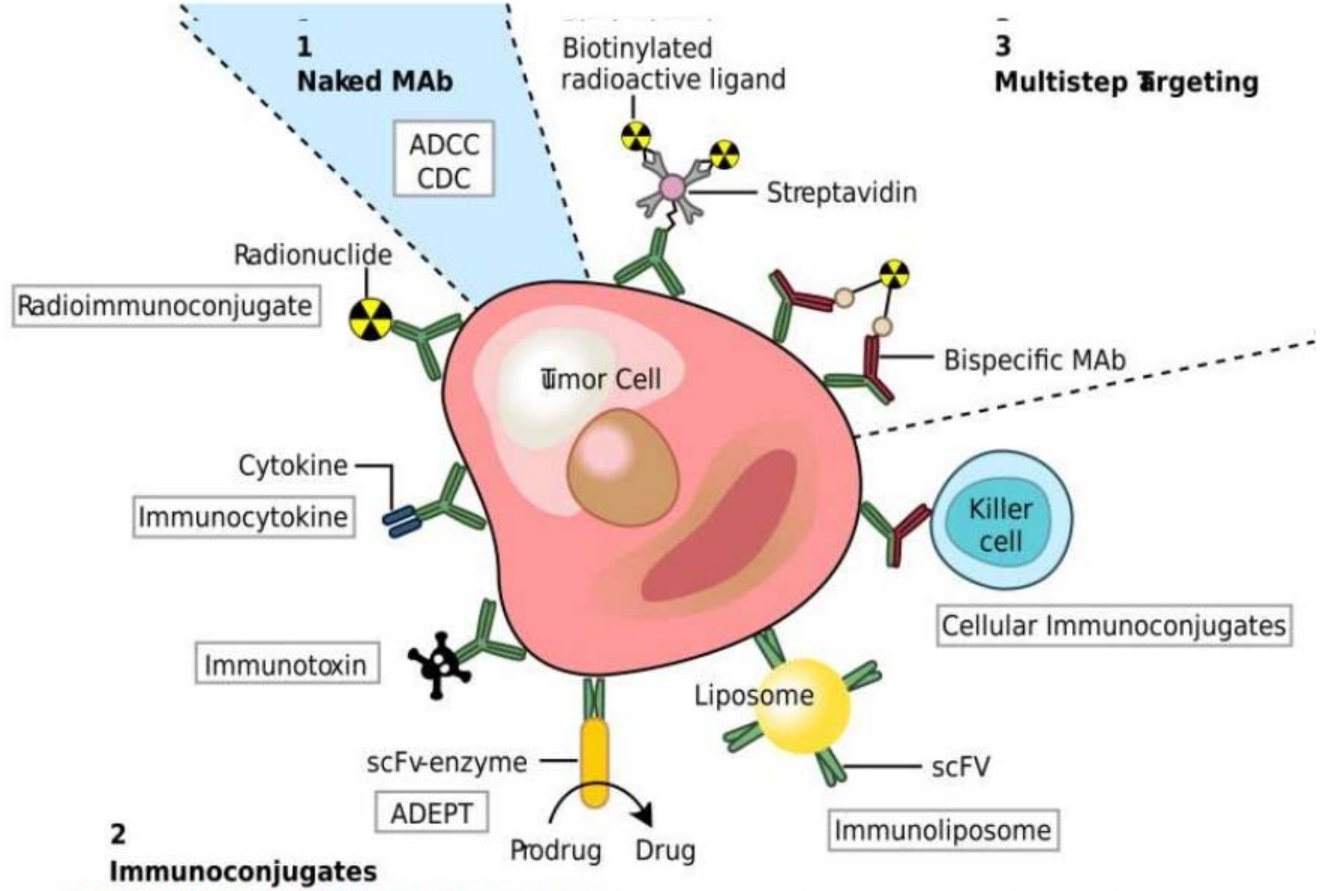
Features of Cancer Immunotherapy

Adaptable	**Ability to adapt the response beyond the initially targeted antigen**
Specific	**Ability to recognize and target only tumor cells**
Long Lasting	**Capacity for memory can result in durability of tumor responses**
Universal	**Potentially applicable to all cancers**

Cancer Immunotherapies: Different Approaches

Approach	Examples	Agents/Targets
Vaccines	Peptide, protein, DC, DNA, virus	
Immune Modulatory Antibodies	Checkpoint inhibitors	anti-CTLA-4 anti-PD-1/PD-L1
	Co-stimulatory Activators	anti-OX-40, anti-CD137, anti-GITR
Adoptive T cell therapy	T cells expanded from tumor infiltrating T cells (TIL) T cells expressing tumor antigen specific transgenic TCRs Chimeric antigen receptor (CAR) adoptive T cells	
Cytokines		IL-2, IFN-alpha, GM-CSF
Oncolytic Viruses		TVEC
Reversal of Immunosuppression	IDO- inhibitors	Epacadostat
	T-reg depletion	

Not all antibodies are immunotherapy



Monoclonal antibodies for cancer. ADEPT, antibody directed enzyme pro drug therapy; ADCC, antibody dependent cell-mediated cytotoxicity; CDC, complement dependent cytotoxicity; MAb, monoclonal antibody; scFv single-chain Fv fragment

Carter, *Nature Rev Cancer*, 2001

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What is a cancer vaccine?

"A preparation of a tumor antigen that upon administration stimulates antibody production or anti-tumor cellular immunity"

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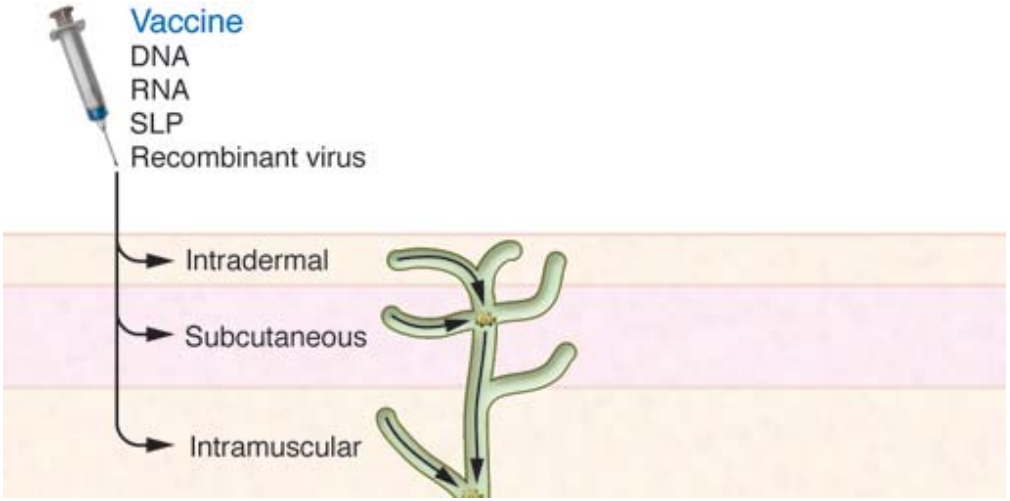
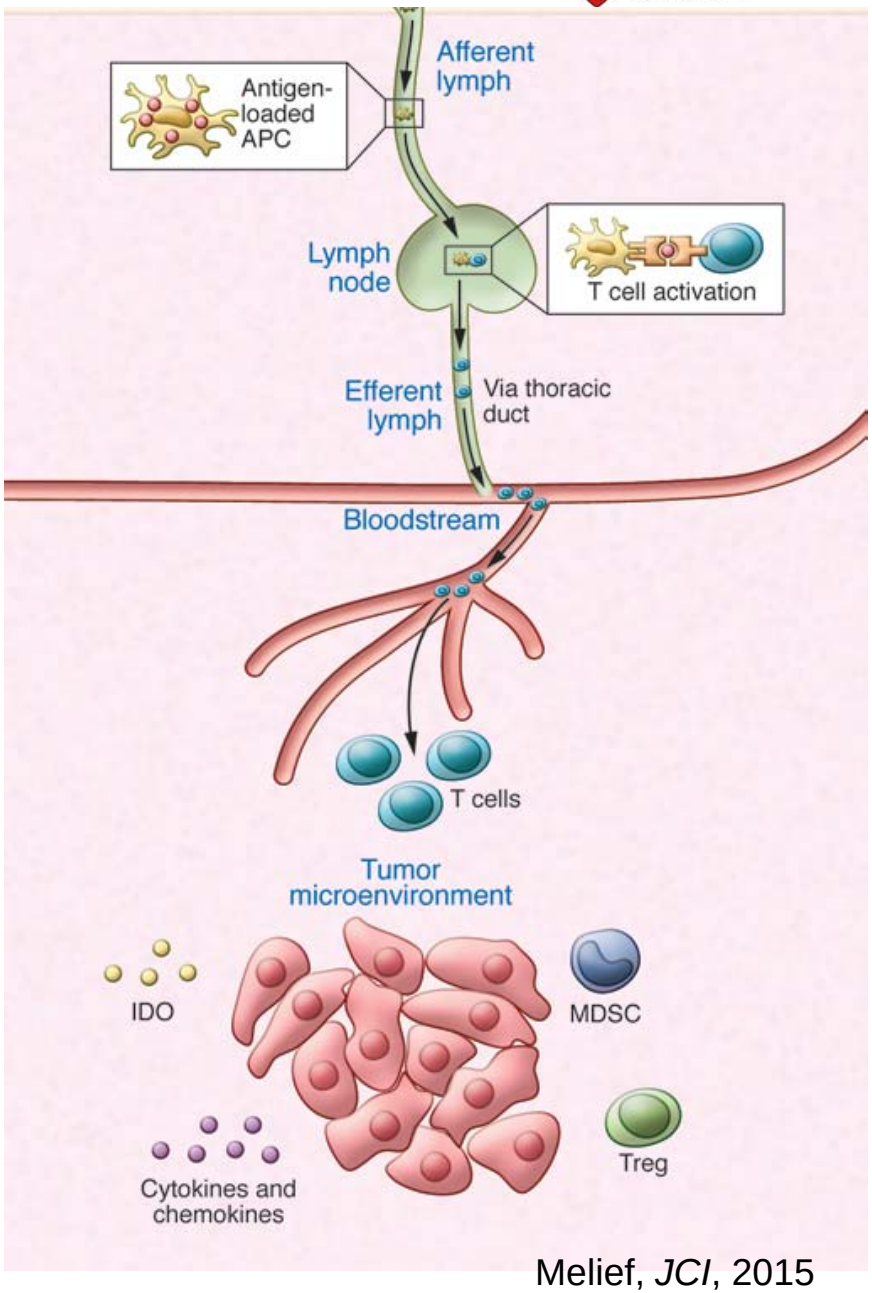
Routes of vaccine administration and migration of immune cells





Melief, *JCI*, 2015

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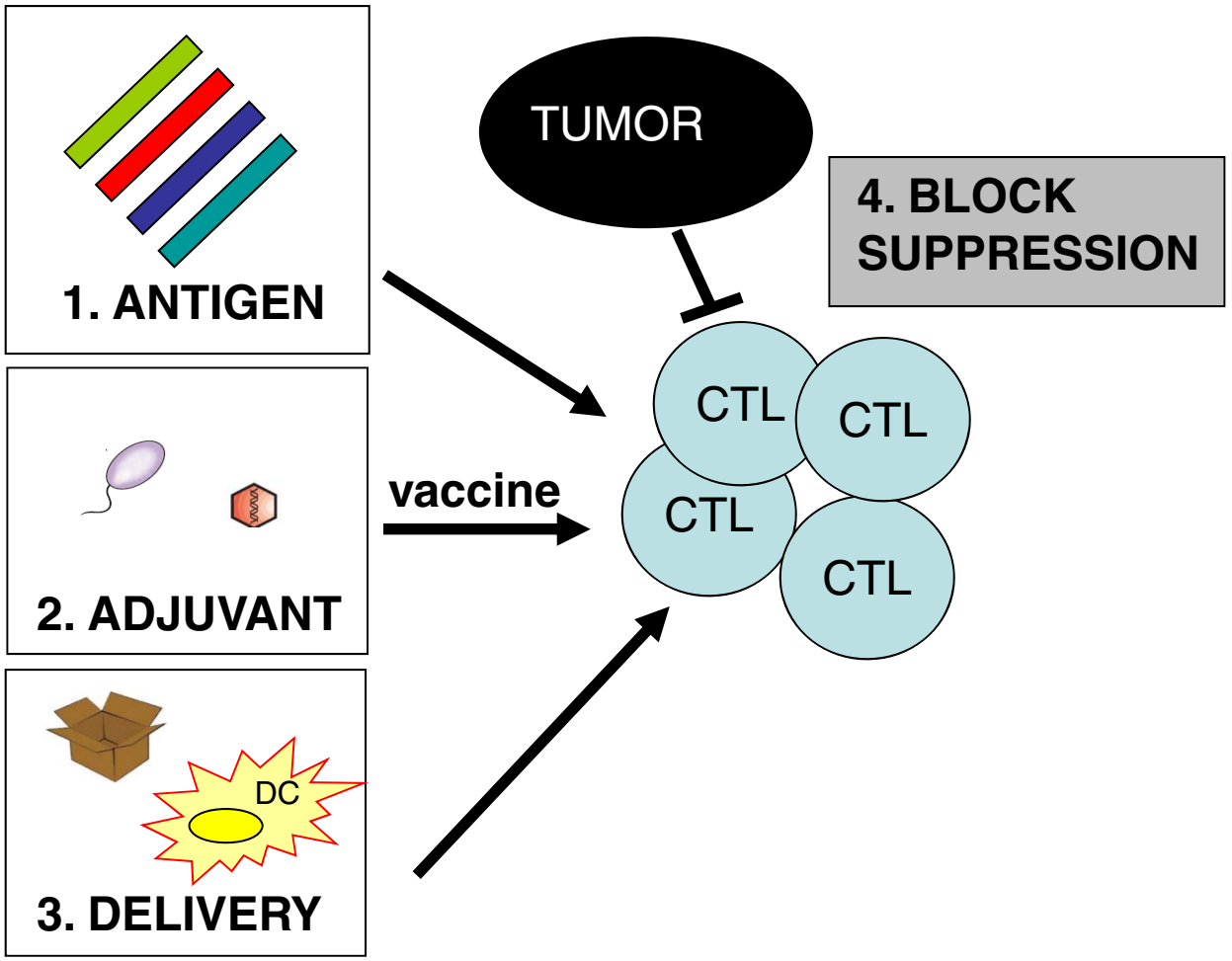
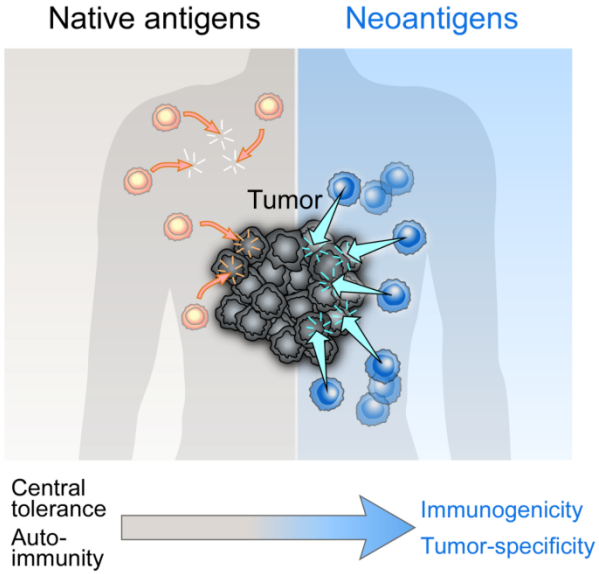
VACCINATION SITE

TUMOR SITE



Choice of Immunogen



- Choice of Antigen
  - Differentiation antigen (MART-1, gp100)
  - Cancer testis antigen (NY-ESO-1, MAGE)
  - Overexpressed in tumors (KIT, HER2)
  - Mutated antigen (Neoantigen)
- Choice of Format:
  - Protein (broader antigenic selection)
  - Peptide (more stable in vivo, lower cost, HLA restriction). Long versus short
  - Viral vector
  - DNA, RNA
  - Whole tumor cells
  - Dendritic cells pulsed with protein or peptide

Toll Like Receptor Agonists

Danger is represented by:

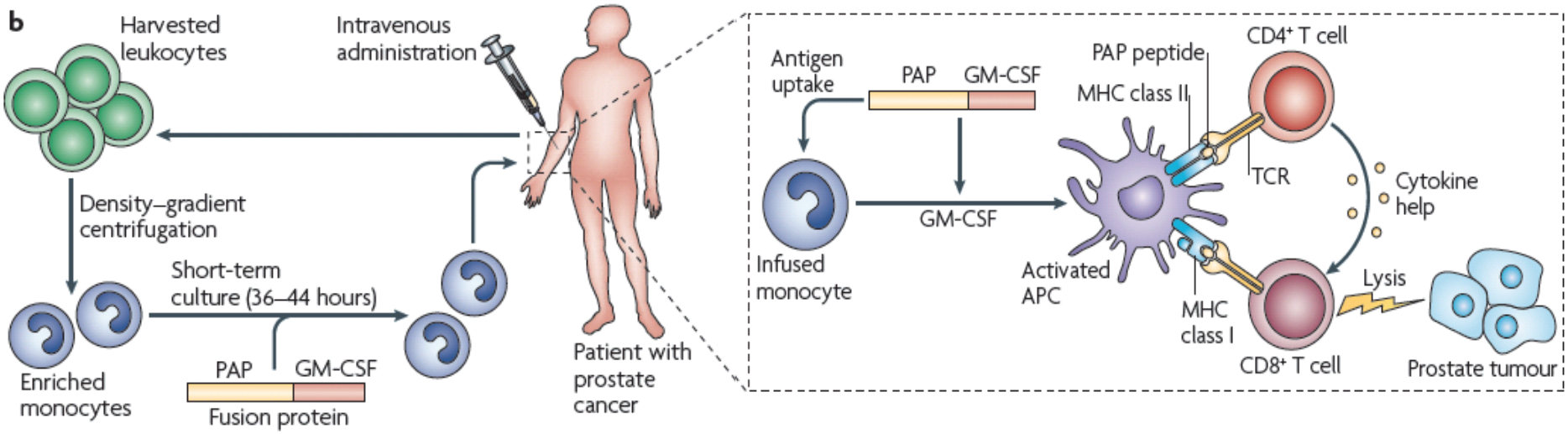
These have molecular features that distinguish them from our own cells:

endotoxin
DS RNA
HMGB1
binds RAGE, LPS; amplifies TLR signal
lipopeptides
CpG DNA
SS RNA
flagellin

Our immune systems have evolved to recognize them:

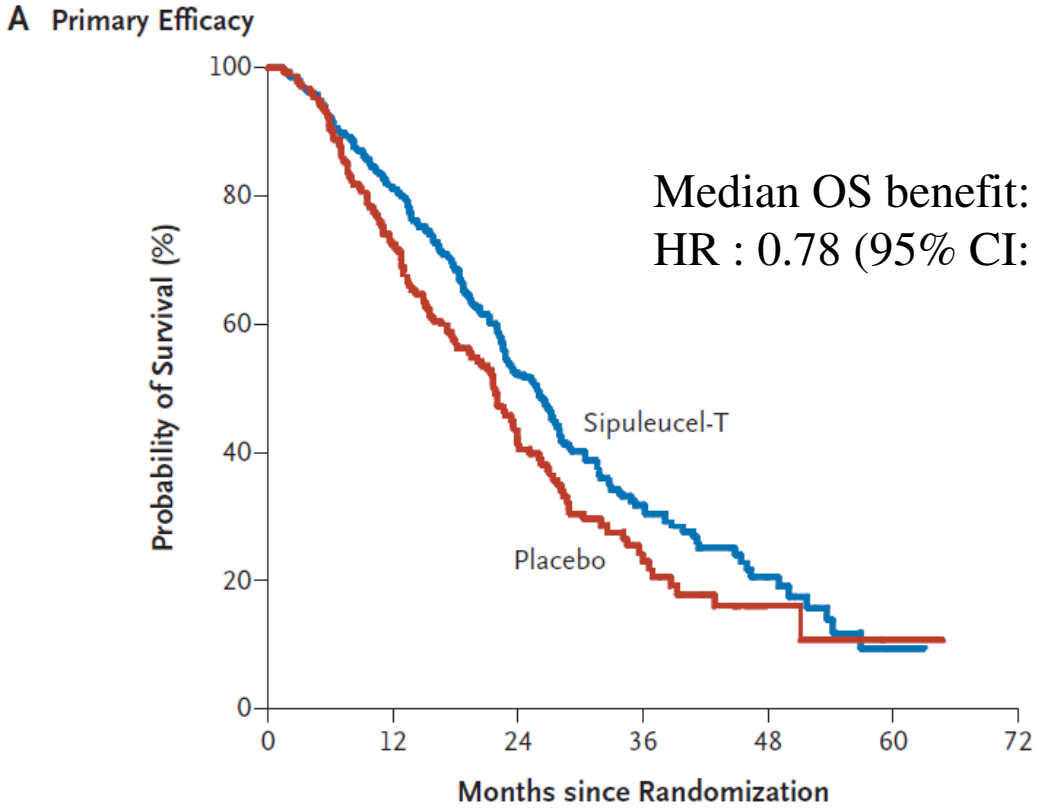
Obeid, *Sem. Oncol*, 2015

Sipuleucel-T: Vaccination With Fresh (Functional) APCs: Generate ex vivo and Reinfuse



Drake, Nat Rev Immunol. 2010.

Phase III Trial of Sipuleucel-T Immunotherapy in mCRPC (IMPACT): OS



Median OS benefit: 4.1 months
HR : 0.78 (95% CI: 0.61-0.98; P = .03)

Kantoff PW, et al. N Engl J Med. 2010

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Cancer Vaccines in Late Stage Development / approved

Name	Tumor	Antigen	Antigen Delivery	Immune Response	Clinical Activity
Siplileucel-T	Prostate Ca	PSA	Cell based - Monocytes	Yes	Yes – FDA approved
GVAX + CRS-207	Pancreatic Cancer	Mesothelin	Live attenuated listeria, prime - boost	Yes	Yes
IMA 901	Renal Cell Carcinoma	Tumor associated peptides (TUMAP)	Peptides with GM-CSF	Yes	Yes
Synthetic Long E6/7 Peptide vaccine HPV-01	HPV-induced malignancies (e.g vulvar neoplasia)	HPV E6 and E7	Mixture of 13 long peptides (25-35 AA)	Yes	Yes
Talimogene Laherparepvec (TVEC)	Melanoma	"Whole tumor" (in situ vaccination with onclytic virus)	Oncolytc virus (modified herpes virus encoding GM-CSF)	Yes	Yes - FDA approved
Rindopepimut	Glioblastoma	Mutated EGFRvIII	14-mer peptide, KLH	Yes	Yes
Fowlpox-PSA-TRICOM	Prostate Ca	PSA	Fowlpox expressing antigen + TRICOM (B7.1, ICAM-1, LFA-3)	Yes	Yes

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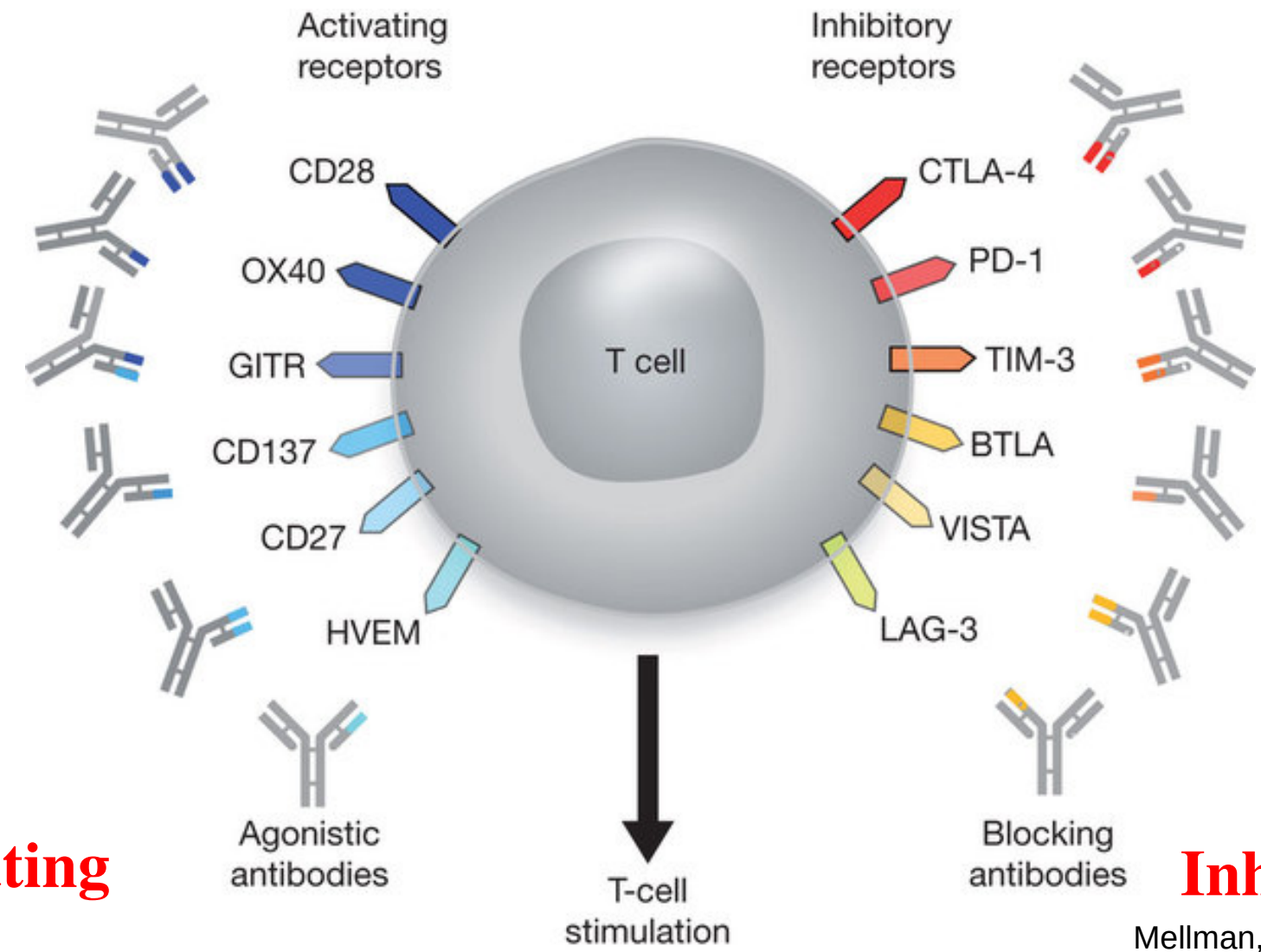
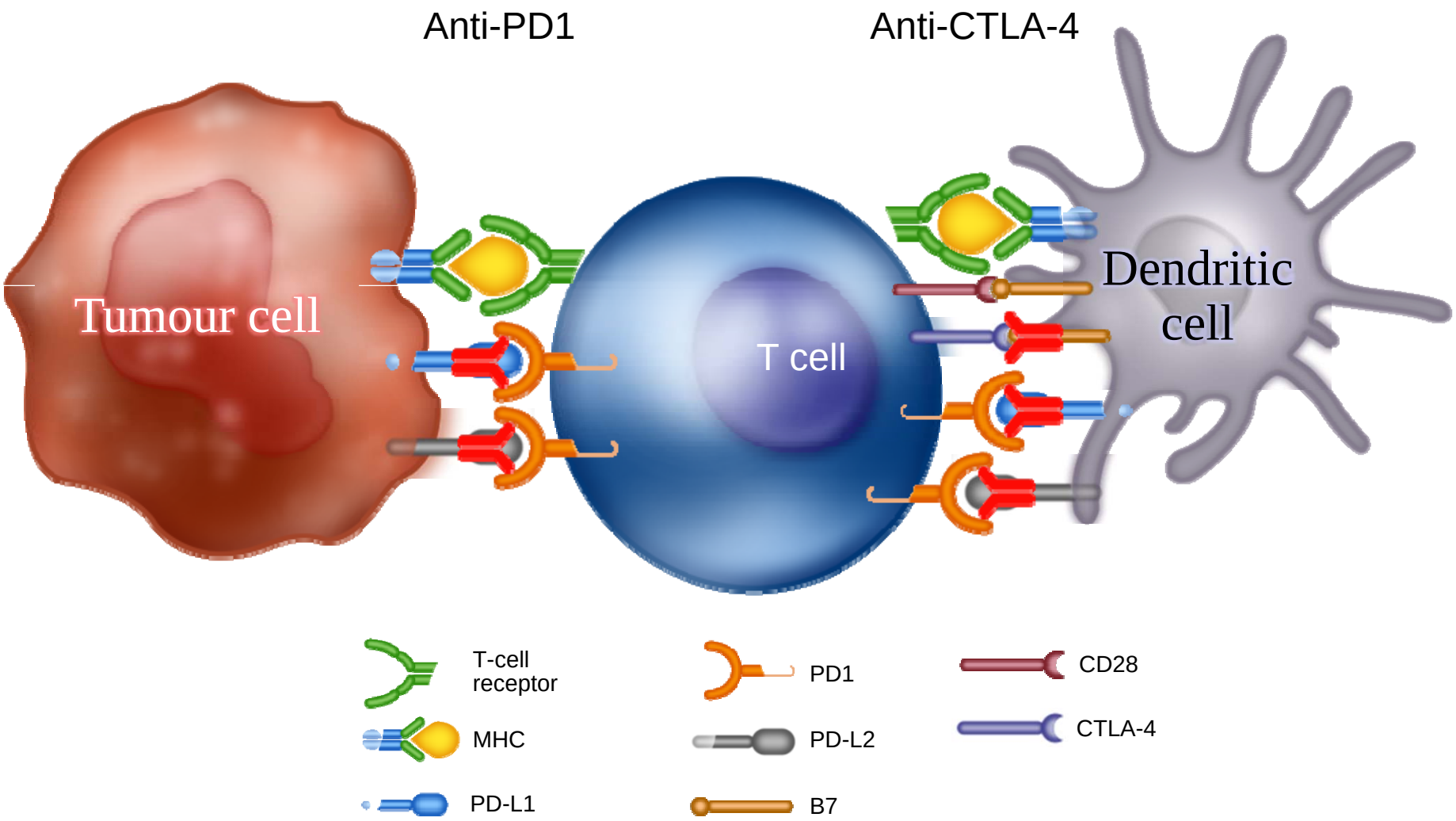
Immune Modulatory Receptors



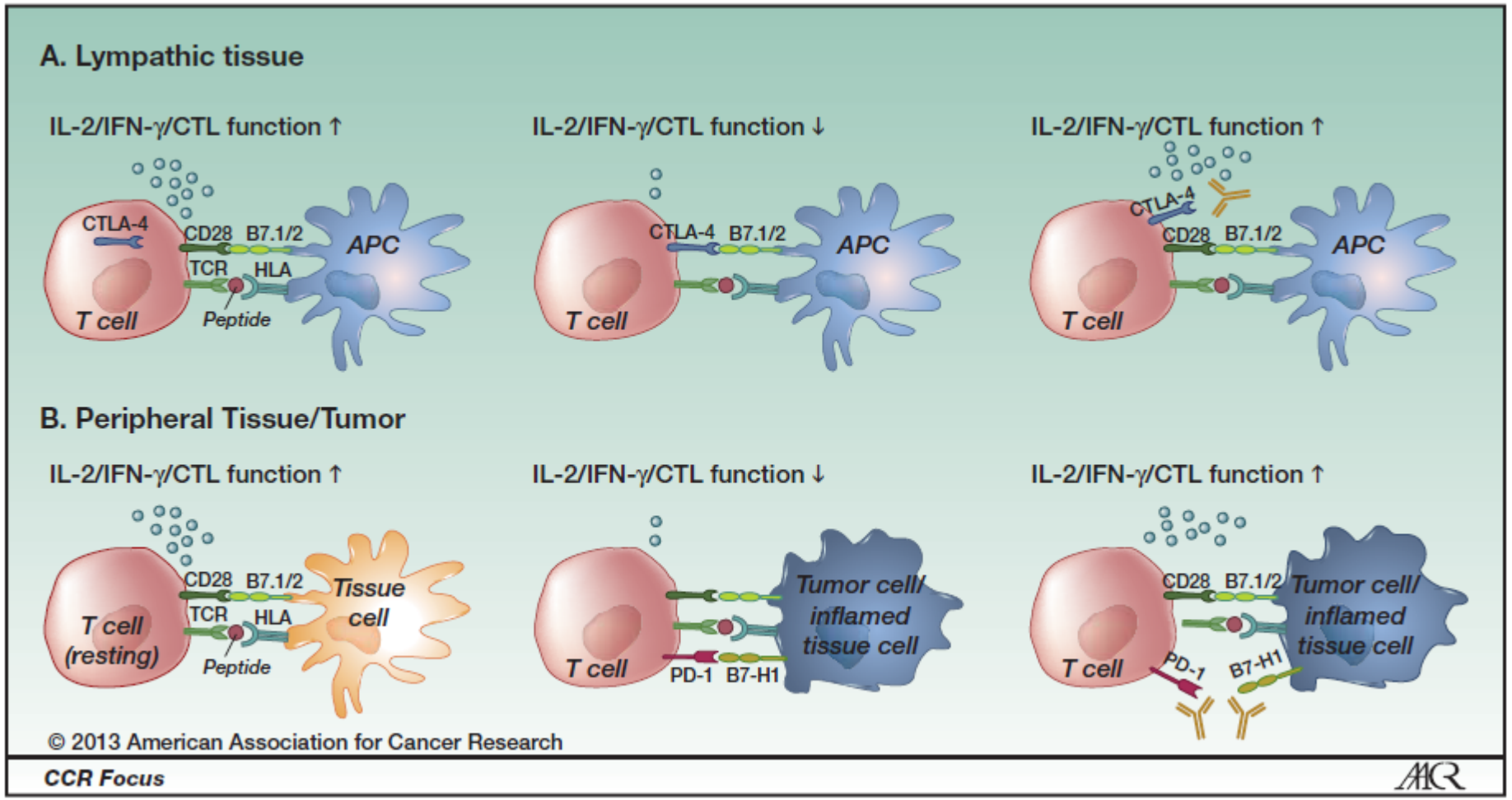
Activating **Inhibiting**

Mellman, *Nature*, 2011

Immune-checkpoint inhibition



Adapted from Sznol M, et al. Presented at ASCO 2013; oral presentation CRA9006



Ott, Hodi, Robert *Clin Cancer Res*; 19(19) October 1, 2013

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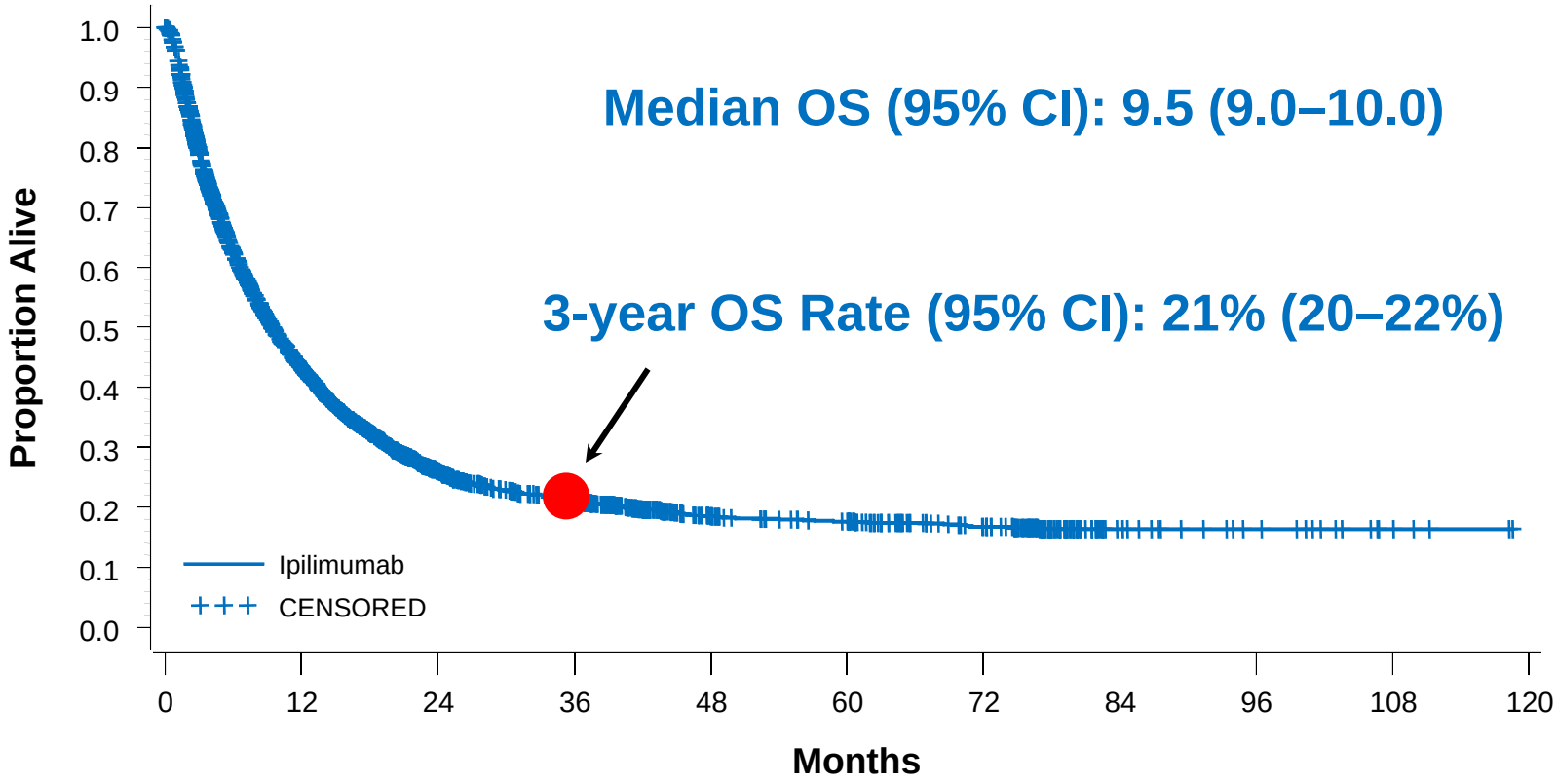
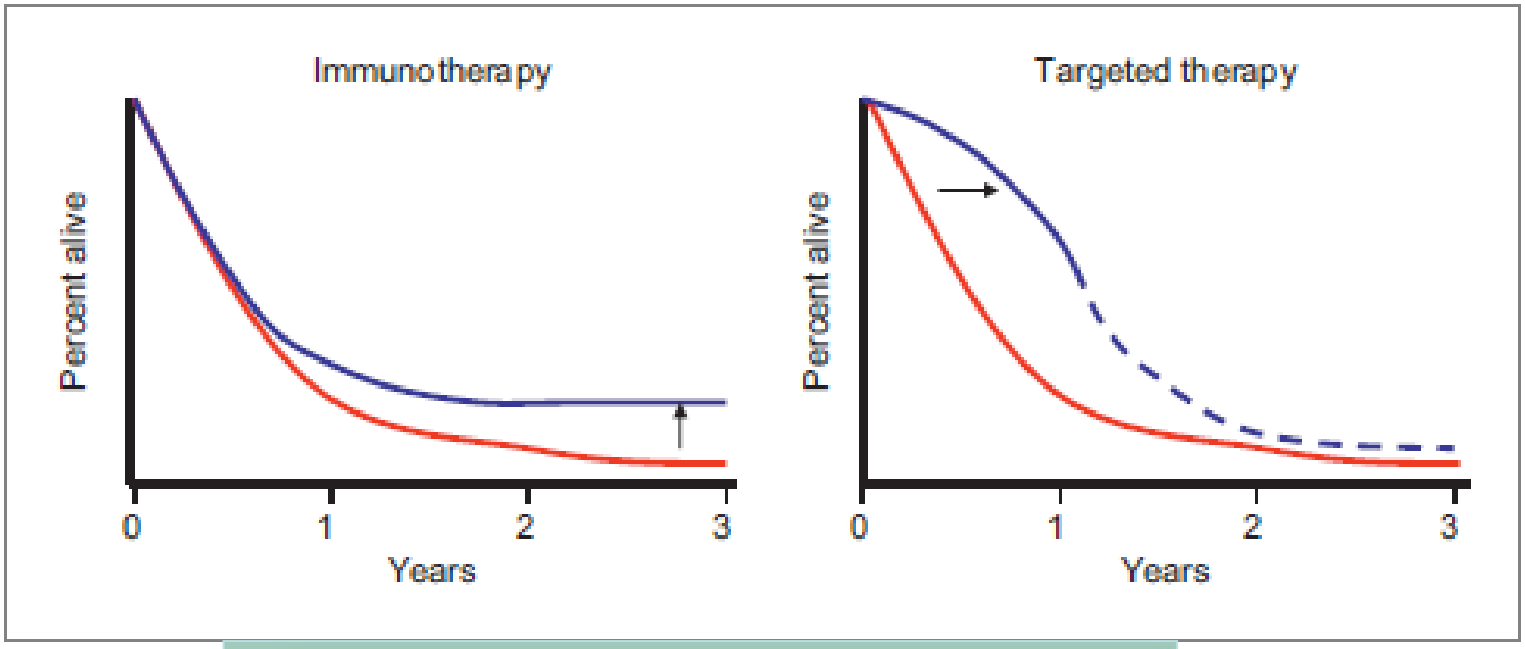
Pooled Overall Survival Analysis of 4846 Melanoma Patients Treated with Ipilimumab

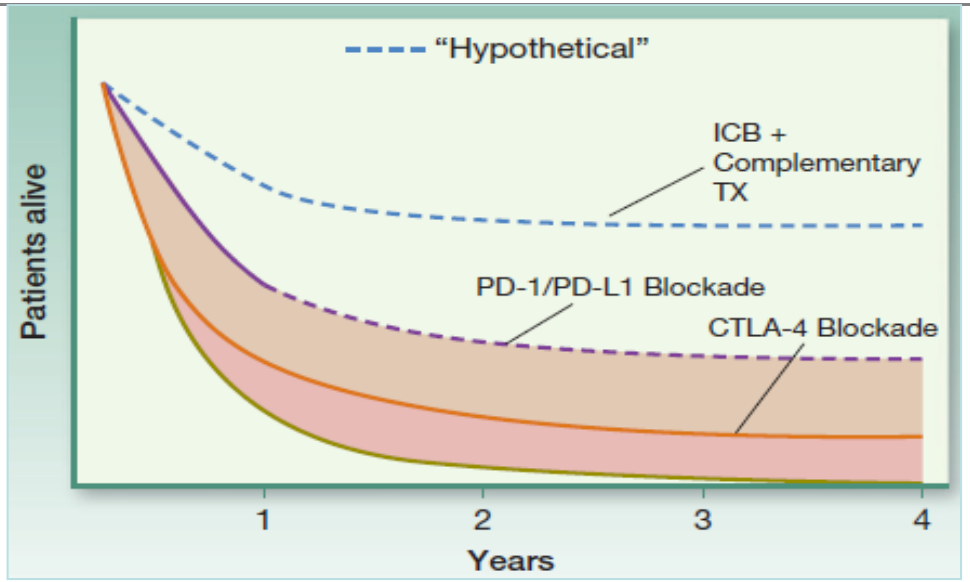


Patients at Risk

Ipilimumab	4846	1786	612	392	200	170	120	26	15	5	0

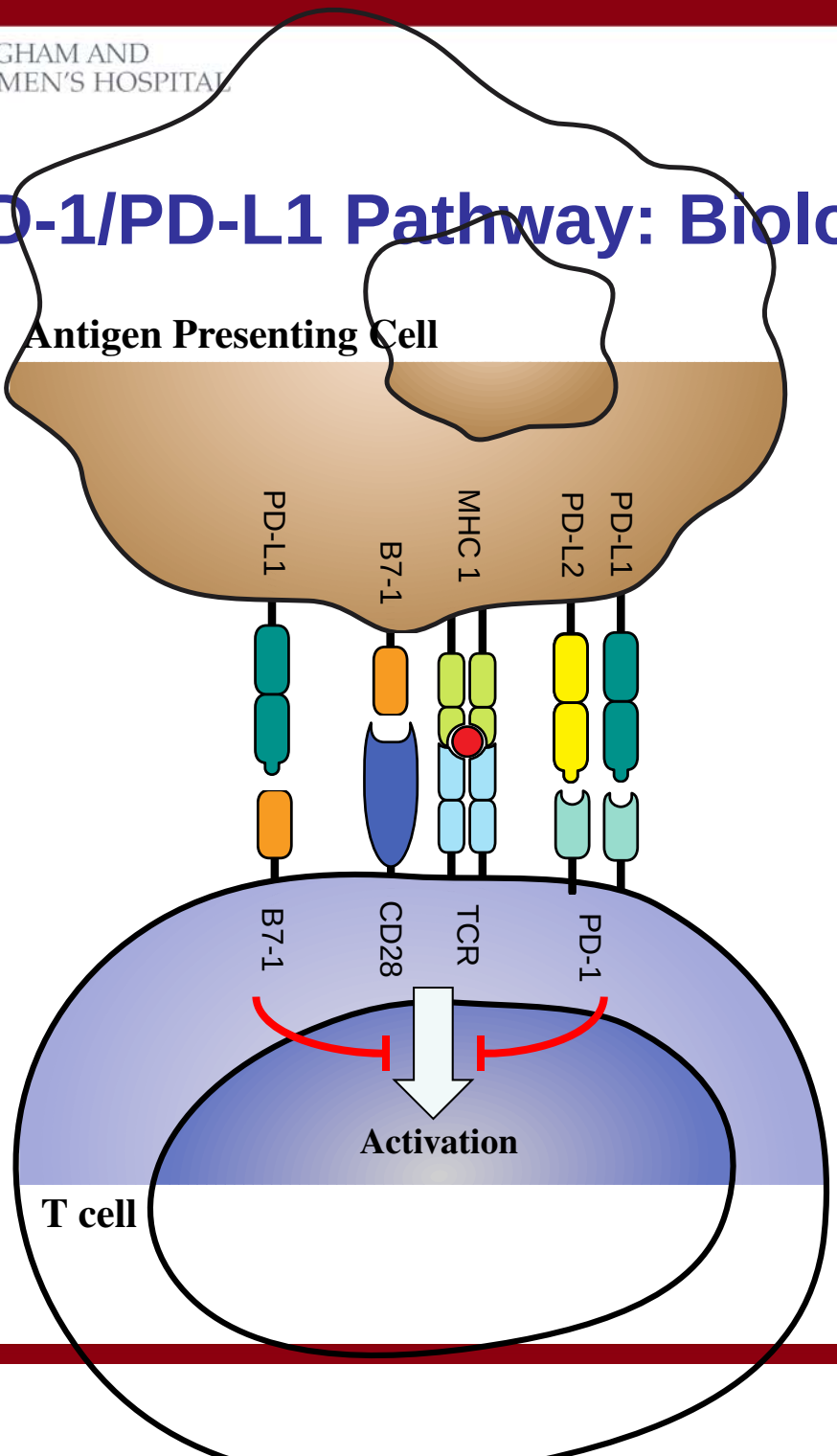
F-S. Hodi, MD – ECCO 2013





Ribas, Clin Can Res, 2012
Ott, Hodi, Robert, Clin Can Res, 2013

PD-1/PD-L1 Pathway: Biology



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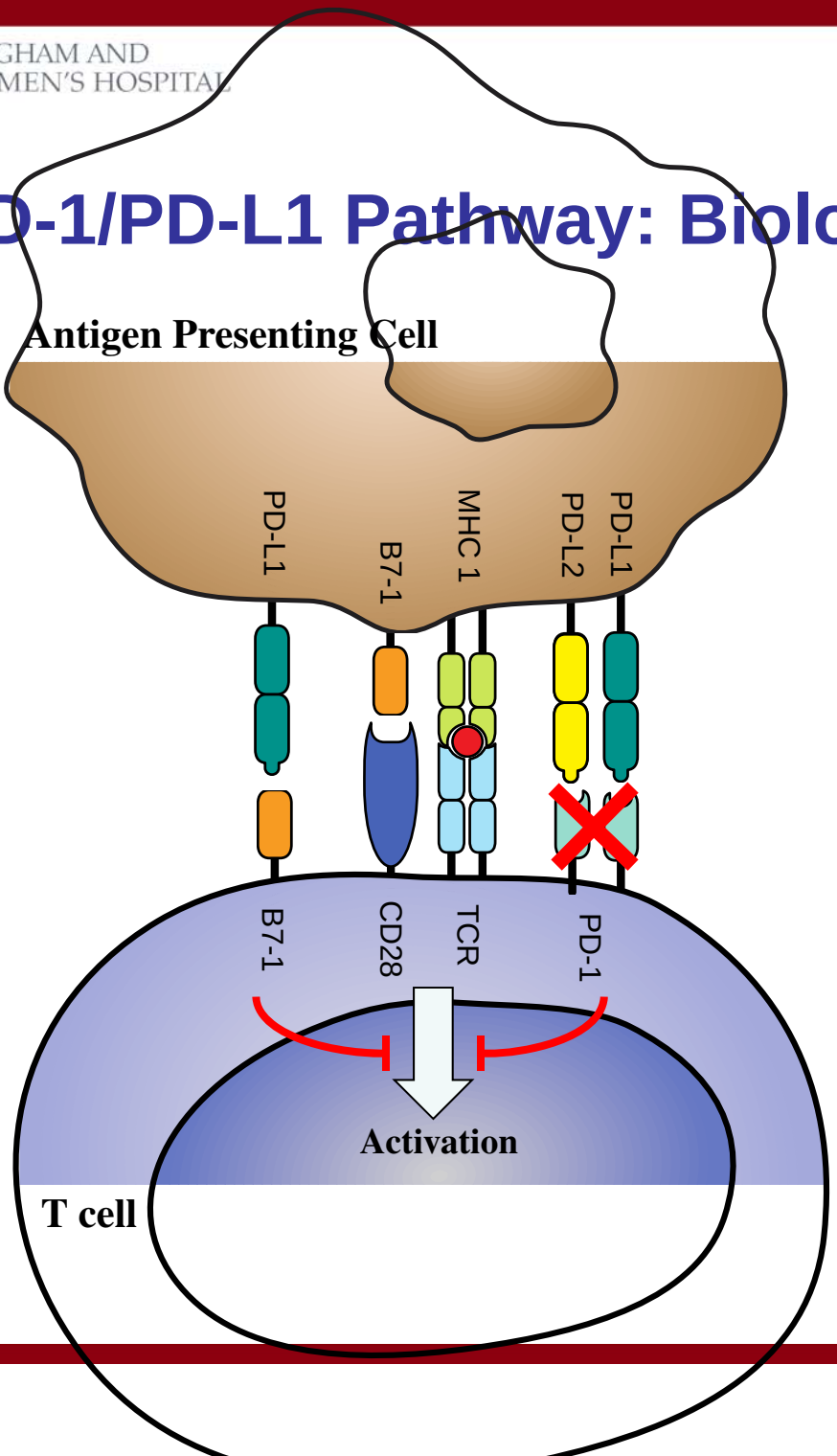

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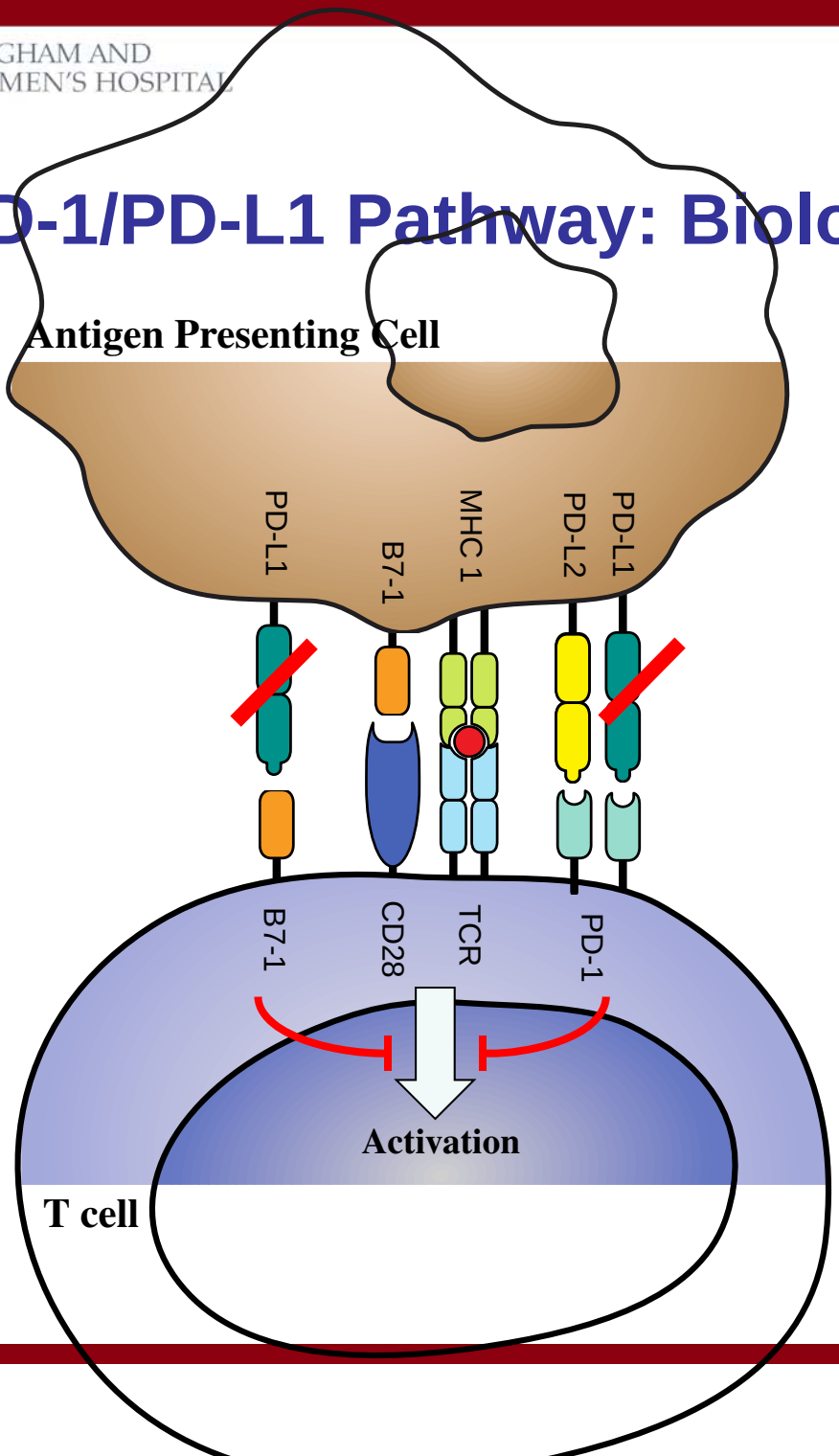

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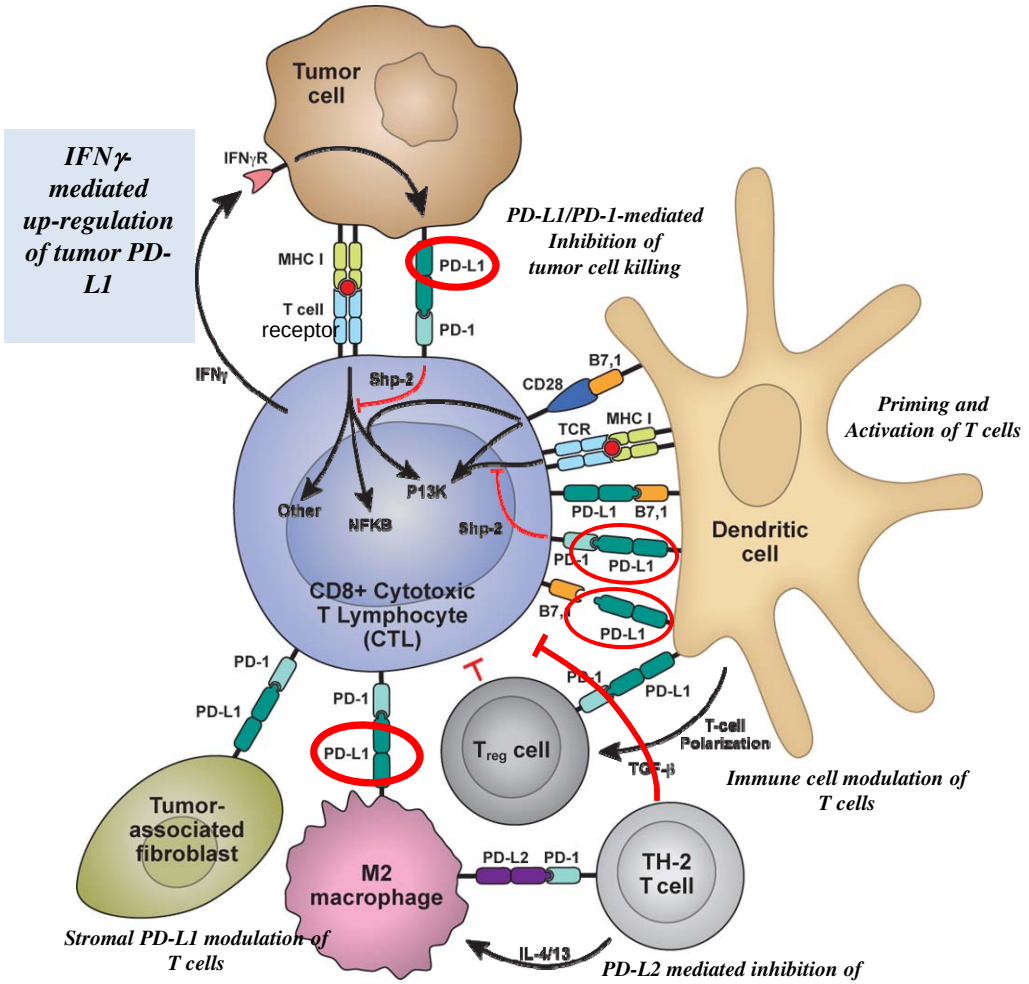
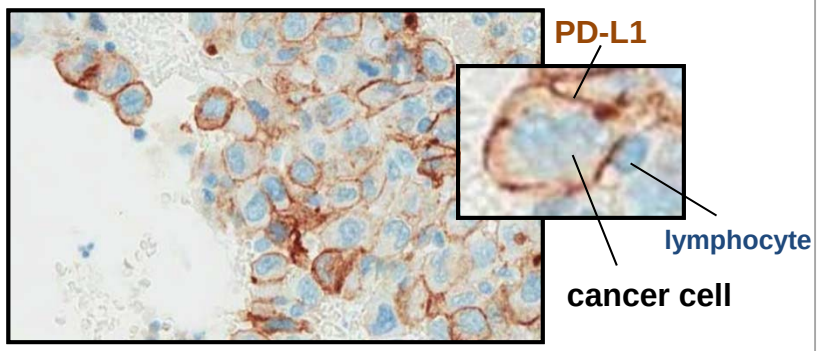
PD-L1 plays an important role in dampening the anti-tumor immune response



Chen DS, Irving BA, Hodi FS.
Clin Cancer Res. 2012;18:6580.



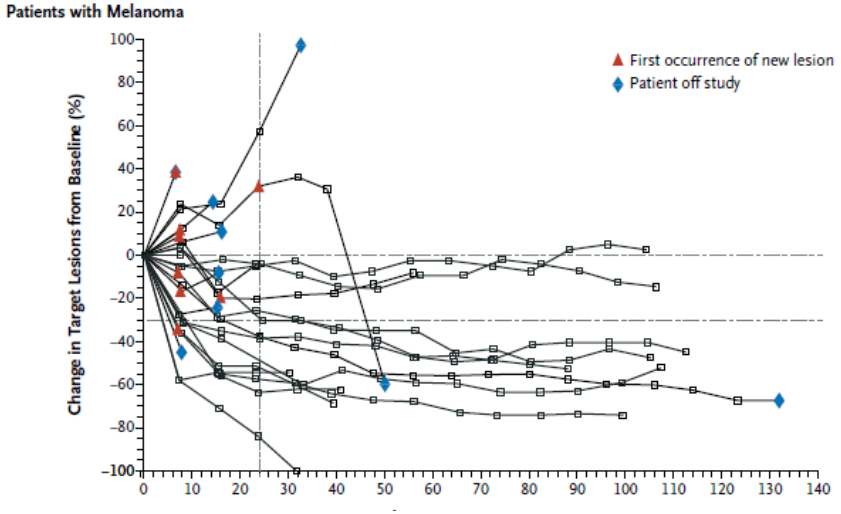
Presence of intratumoral T-cells may lead to adaptive immune resistance

PD-L1 expression in the tumor microenvironment can inhibit anti-tumor T cell activity:

1. PD-L1 expression by tumor infiltrating ***immune cells***
2. PD-L1 expression by ***cancer cells***

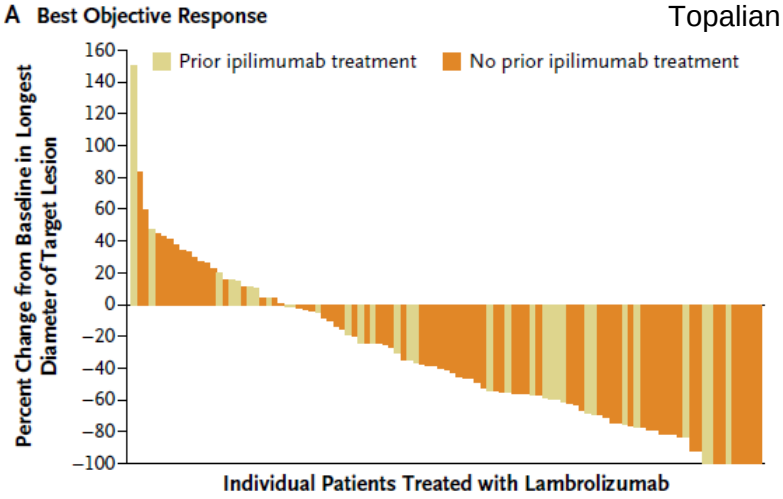
Anti-Tumor Activity of Anti-PD1 antibodies

- Nivolumab



Topalian et al, NEJM 2012

- Pembrolizumab



Hamid et al, NEJM 2013

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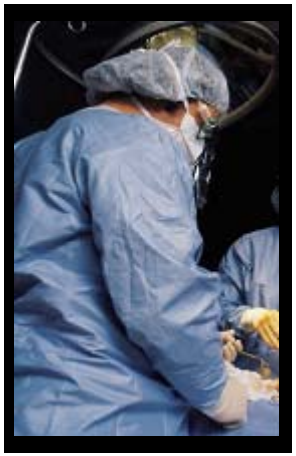
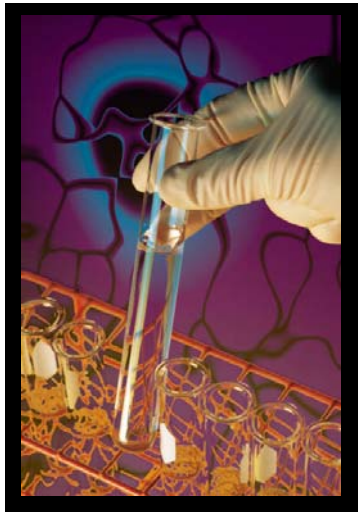
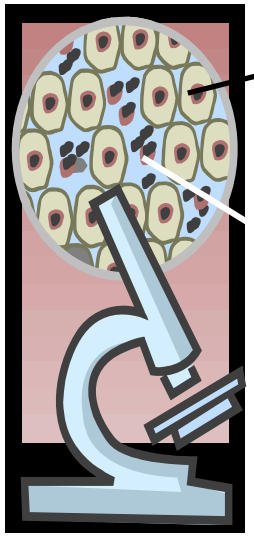
Adoptive Cell Therapy (ACT) with Antigen Specific T-cells



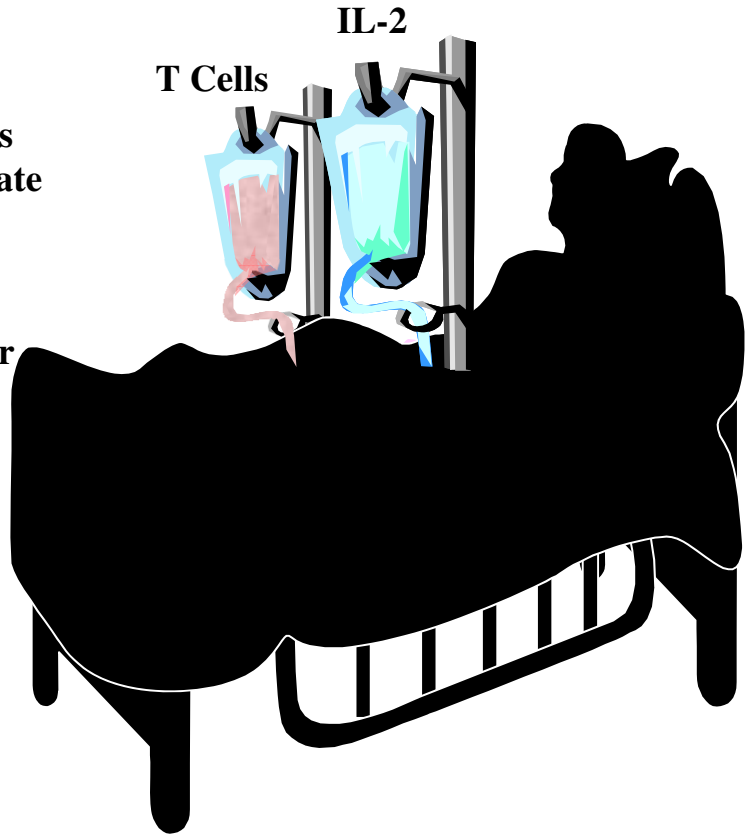
Single Cell Suspension Incubated with IL-2





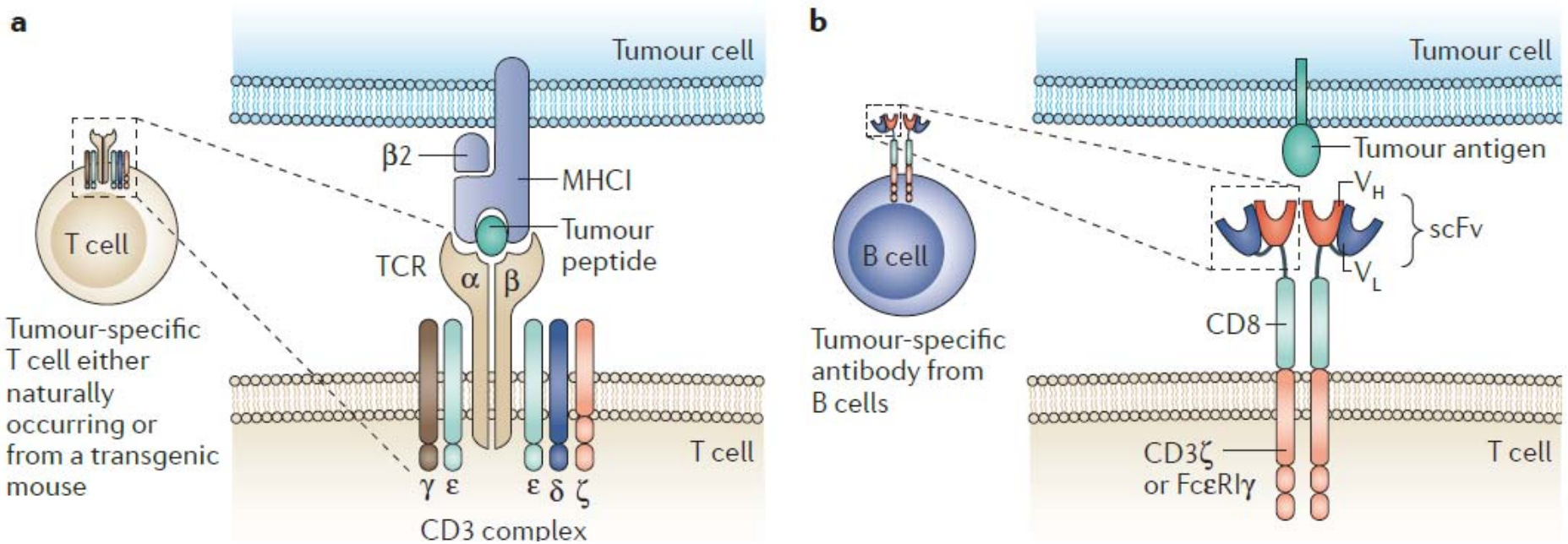
T Cells Proliferate

Cancer Cells Die



Courtesy of Patrick Hwu MD, PhD – MD Anderson Cancer Center

Derivation of TCRs and CARs for the genetic modification of T cells



Kershaw NATURE REVIEWS | **CANCER 2013**

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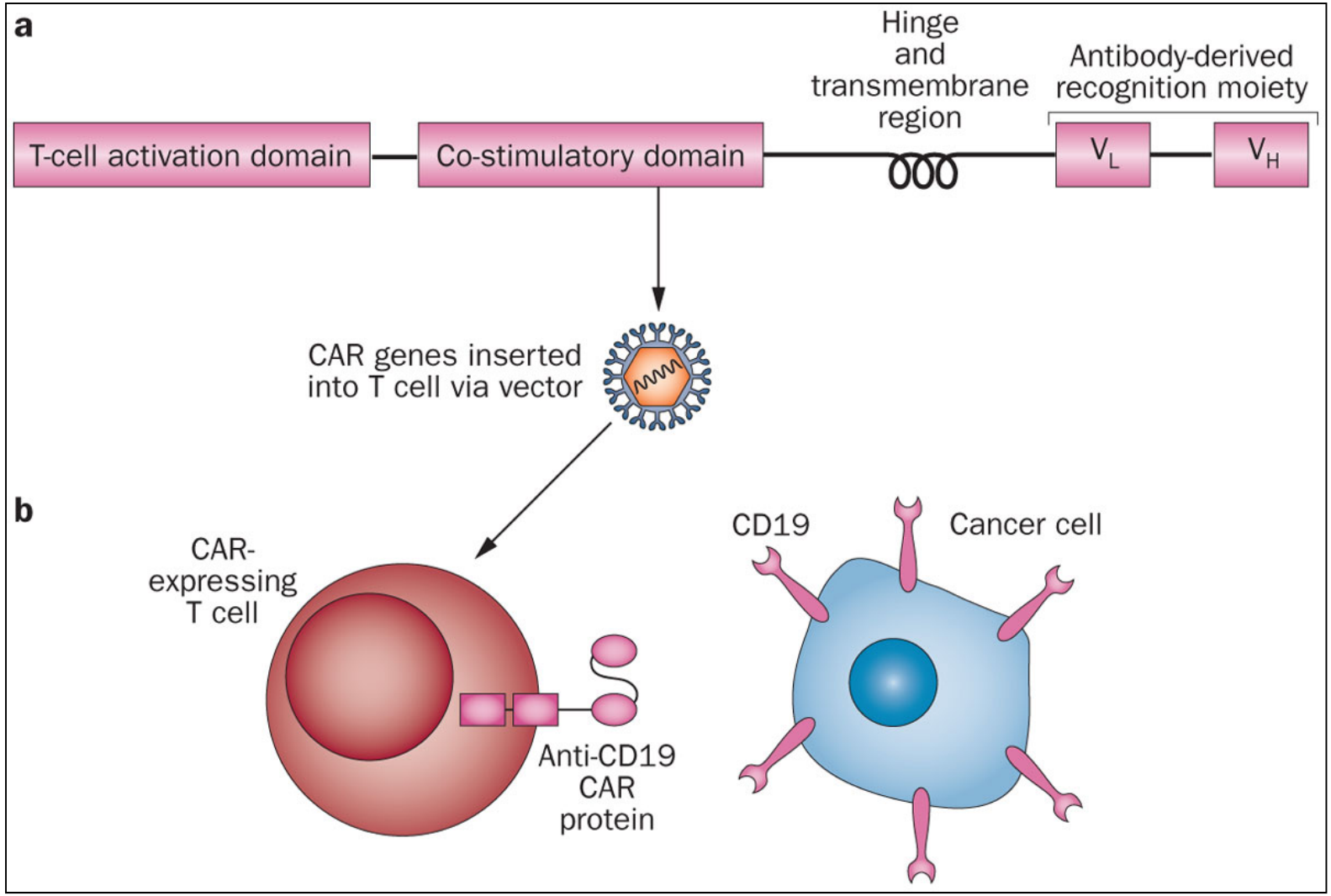
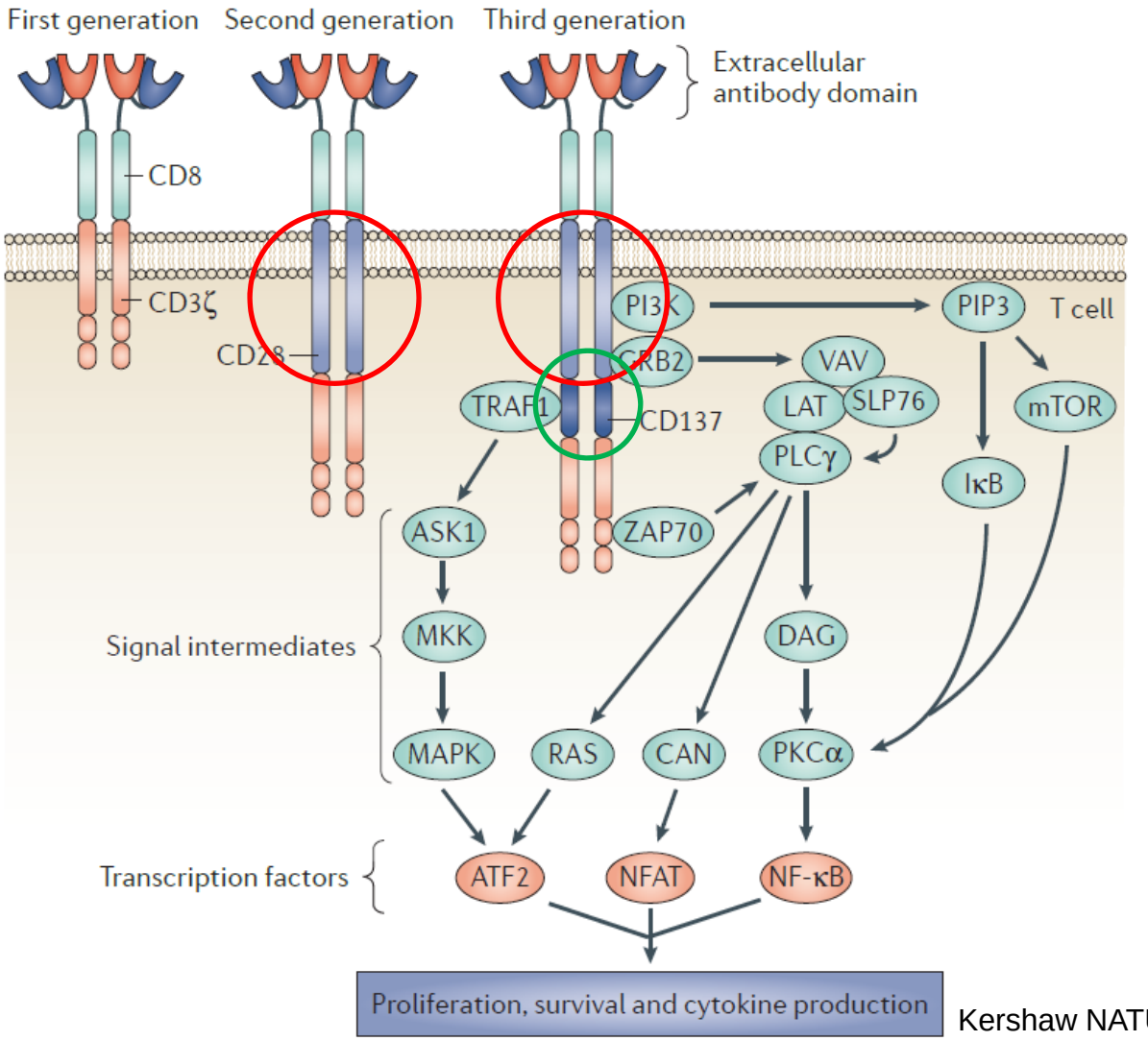
Chimeric Antigen Receptor (CAR) T cells Targeting CD19 in B Cell Cancers



Kochenderfer and Rosenberg. Nat Rev Clin Oncol. 2013

Successive Generations of CARs



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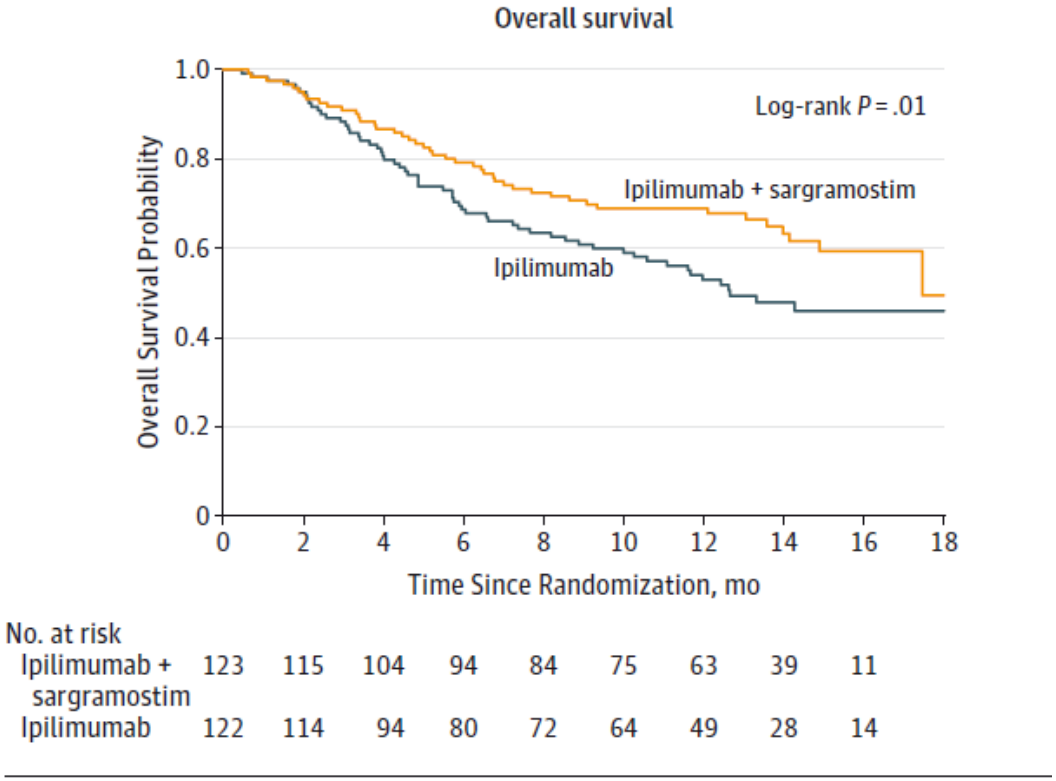
Ipilimumab + sargramostim in Advanced Melanoma



Treatment-Related Grades 3-5 Toxicity by Toxicity Category		
Gastrointestinal[b]	19 (16.1)	32 (26.7)
Investigations	17 (14.4)	18 (15.0)
Dermatology or other skin related	13 (11.0)	14 (11.7)
Metabolic	13 (11.0)	11 (9.2)
Constitutional symptoms	10 (8.5)	8 (6.7)
Musculoskeletal	8 (6.8)	8 (6.7)
Endocrine	4 (3.4)	9 (7.5)
Neurology	4 (3.4)	0
Vascular disorders	3 (2.5)	5 (4.2)
Infection or febrile neutropenia	2 (1.7)	4 (3.3)
Blood or bone marrow	1 (0.8)	1 (0.8)
Cardiac disorders	1 (0.8)	1 (0.8)
Hepatobiliary disorders	1 (0.8)	1 (0.8)
Immune system disorders	1 (0.8)	5 (4.2)
Injury, poisoning, and procedure complications	1 (0.8)	0
Neutrophil count	0	1 (0.8)
Pulmonary[b]	0	9 (7.5)
Renal or genitourinary	0	1 (0.8)
Any toxicity (with worst)[b]	53 (44.9)	70 (58.3)

Hodi, *JAMA*, 2014

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Cancer Immunotherapies: Different Approaches

Approach	Examples	Agents/Targets
Vaccines	Peptide, protein, DC, DNA, virus	
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Reversal of Immunosuppression	IDO- inhibitors	Epacadostat
	T-reg depletion	

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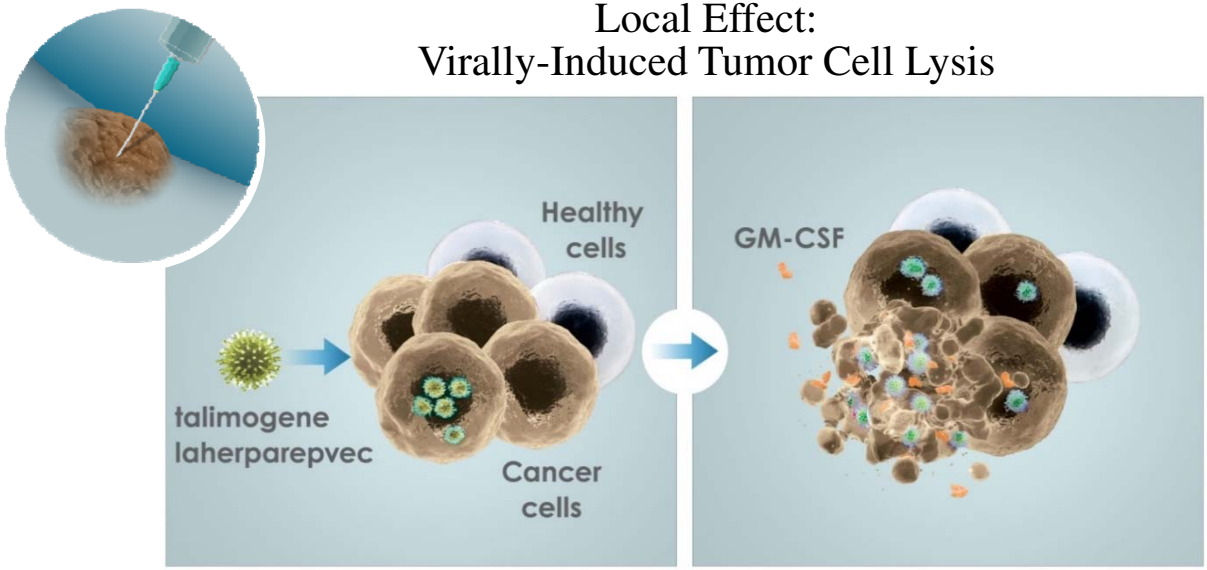
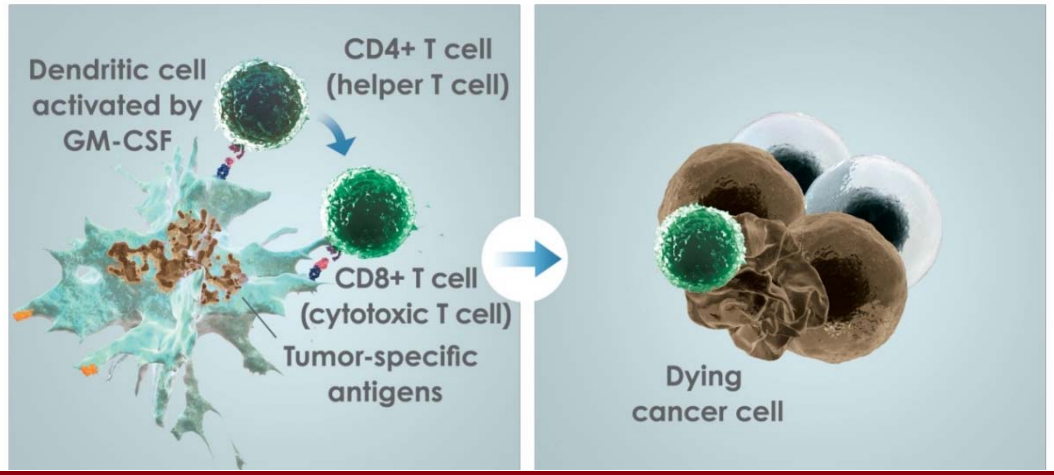
T-VEC: An HSV-1-Derived Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects

Local Effect:
Virally-Induced Tumor Cell Lysis



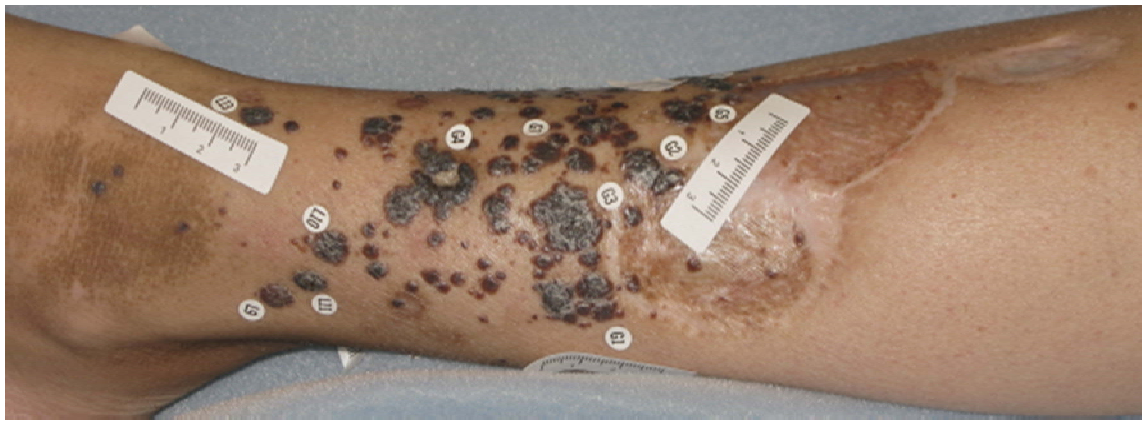
Systemic Effect:
Tumor-Specific Immune Response



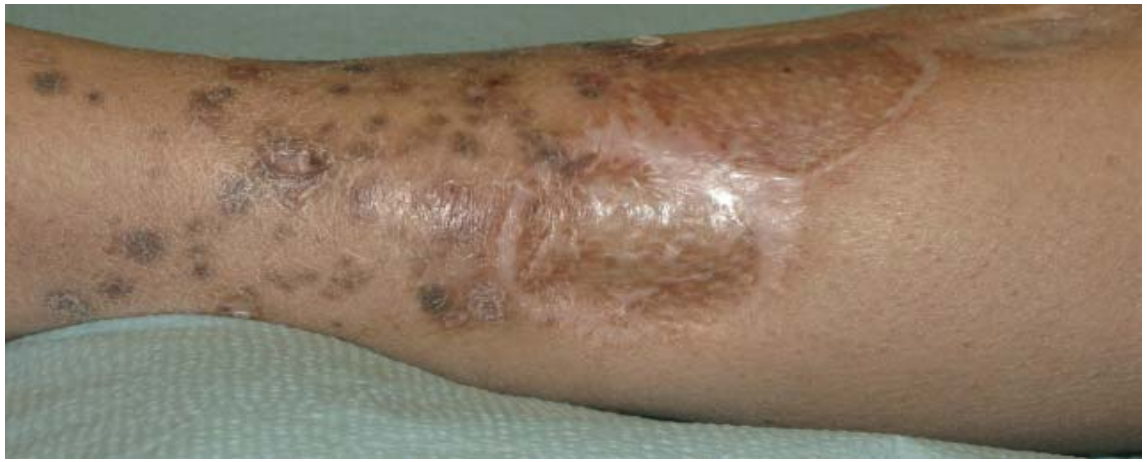
Kaufman et al. ASCO 2014

T-VEC Responses in Injected And Uninjected Lesions

Cycle 1



Cycle 13



Kaufman et al. ASCO 2014, J Clin Oncol 31, 2013 (suppl; abstr LBA9008)

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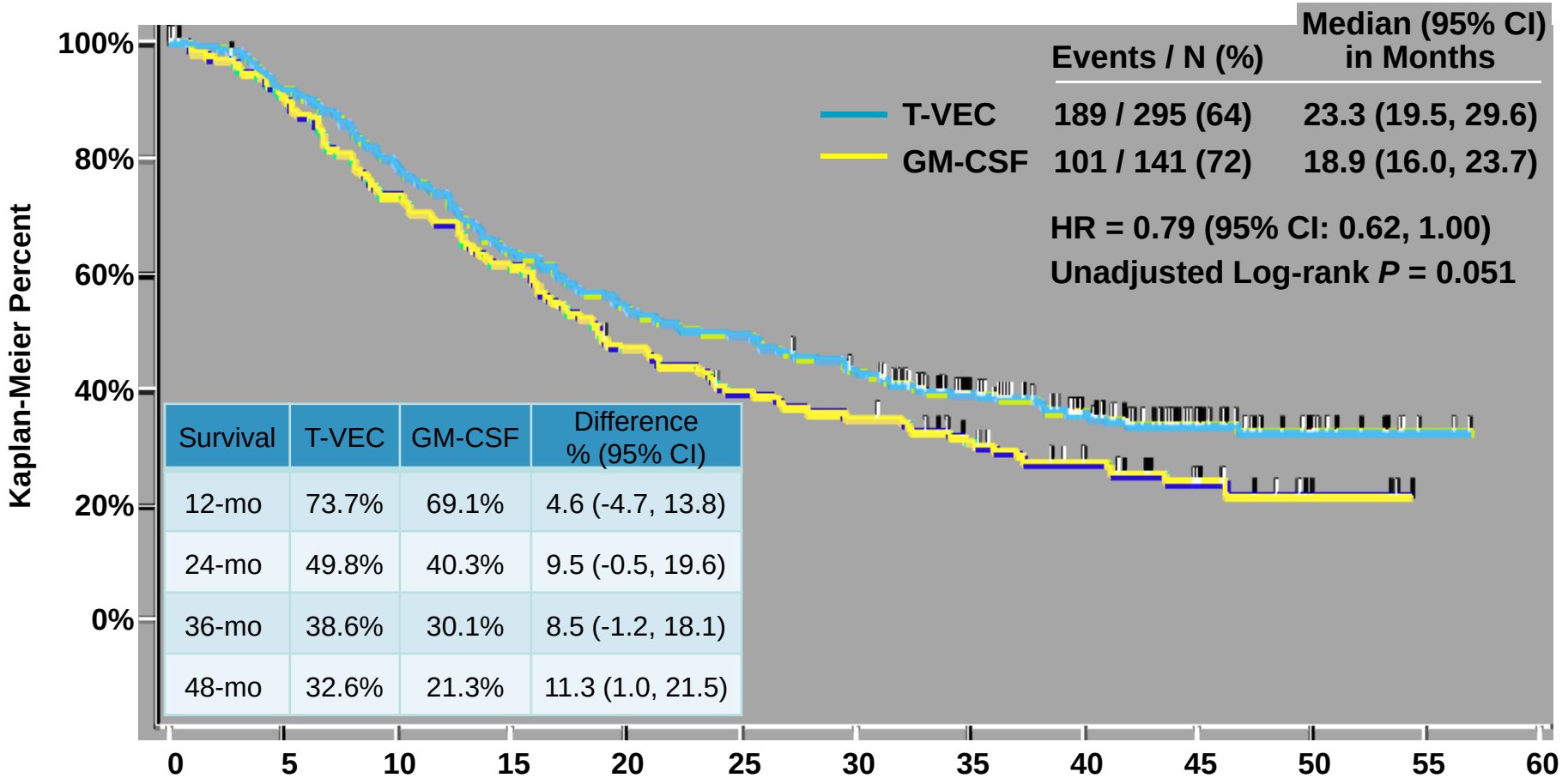
Primary Overall Survival



Survival	T-VEC	GM-CSF	Difference % (95% CI)
12-mo	73.7%	69.1%	4.6 (-4.7, 13.8)
24-mo	49.8%	40.3%	9.5 (-0.5, 19.6)
36-mo	38.6%	30.1%	8.5 (-1.2, 18.1)
48-mo	32.6%	21.3%	11.3 (1.0, 21.5)

Patients at risk:

T-VEC	**295**	**269**	**230**	**187**	**159**	**145**	**125**	**95**	**66**	**36**	**16**	**2**	**0**
GM-CSF	**141**	**124**	**100**	**83**	**63**	**52**	**46**	**36**	**27**	**15**	**5**	**0**	**0**

Kaufman et al. ASCO 2014, J Clin Oncol 31, 2013 (suppl; abstr LBA9008)

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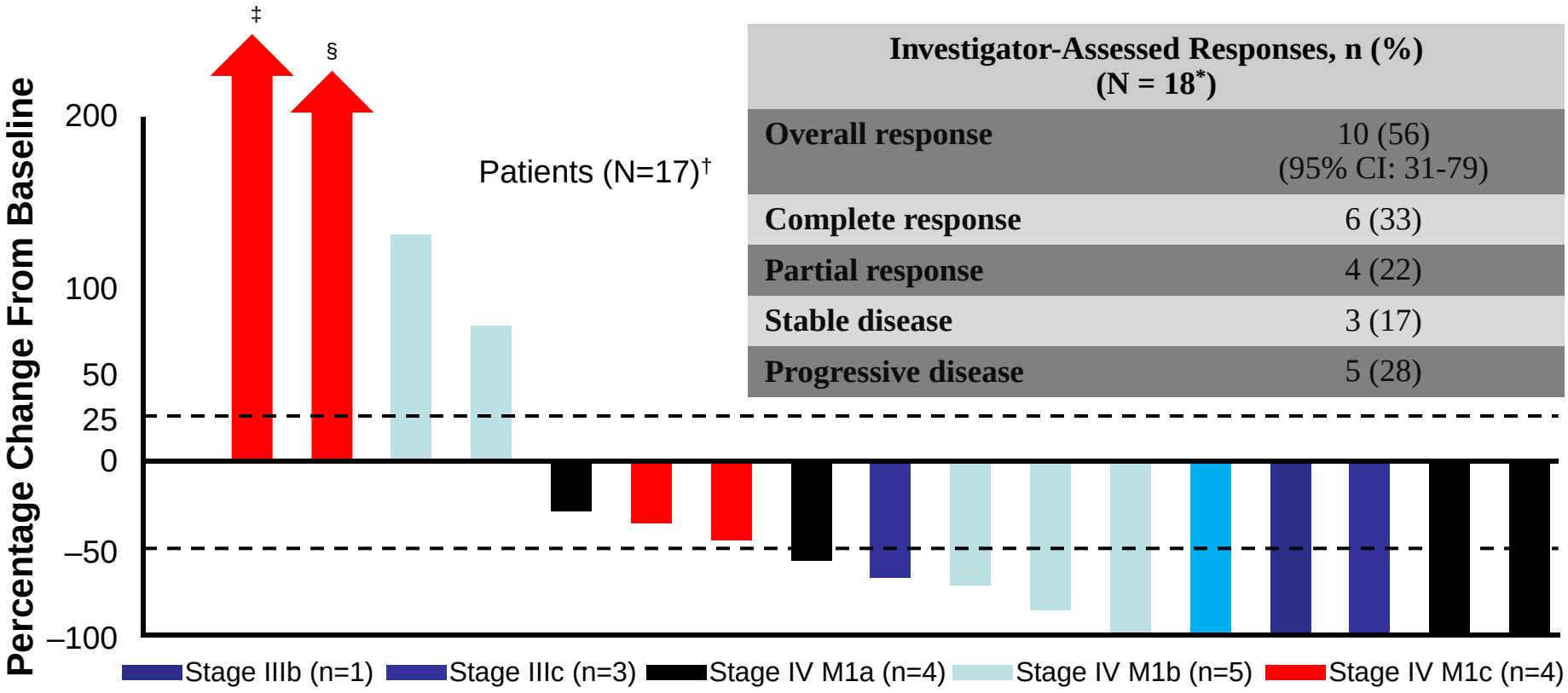
T-Vec + Ipi in Unresected Stage IIIB-IV Melanoma: Max Change in Tumor Burden



Investigator-Assessed Responses, n (%) (N = 18*)	
Overall response	10 (56) (95% CI: 31-79)
Complete response	6 (33)
Partial response	4 (22)
Stable disease	3 (17)
Progressive disease	5 (28)

*Only patients who received both T-Vec and ipilimumab. CR, CRu, and PD included.
† One patient with PD not shown in the plot because tumor burden could not be accurately calculated (missing post-baseline data)
‡ Percentage change from baseline: 538
§ Percentage change from baseline: 265

Puzanov I, et al. ASCO 2014

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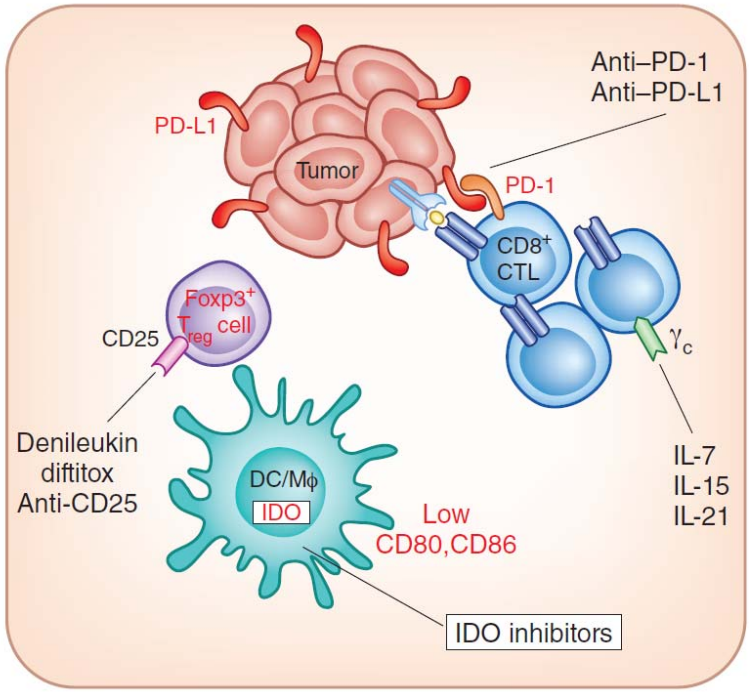
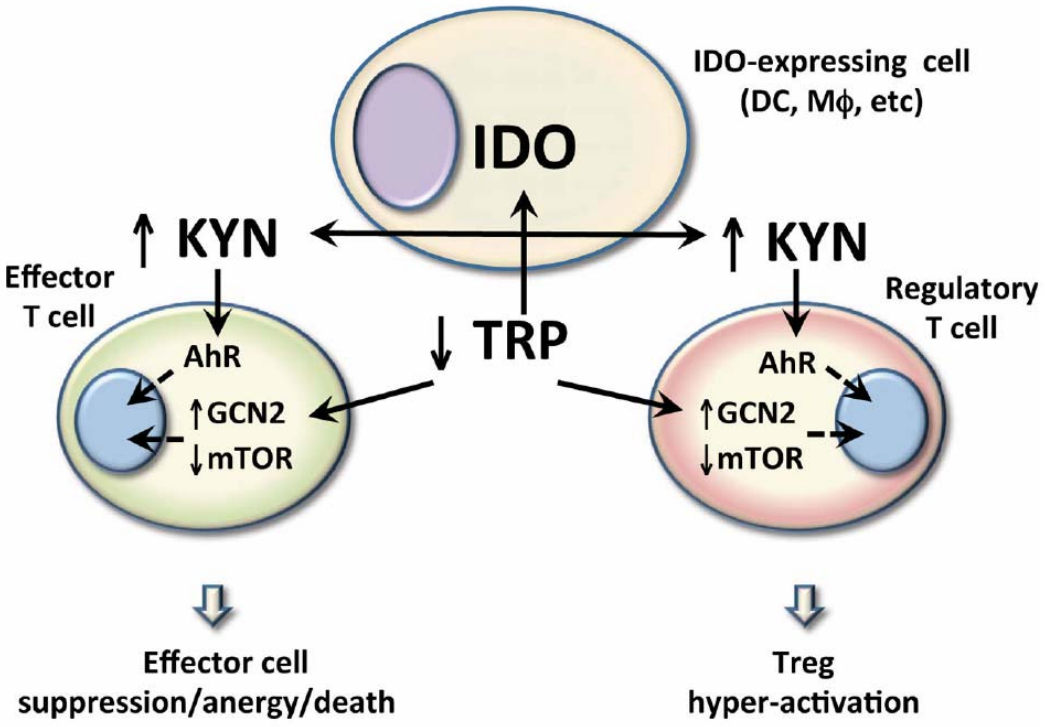
Reversal of Immunosuppression

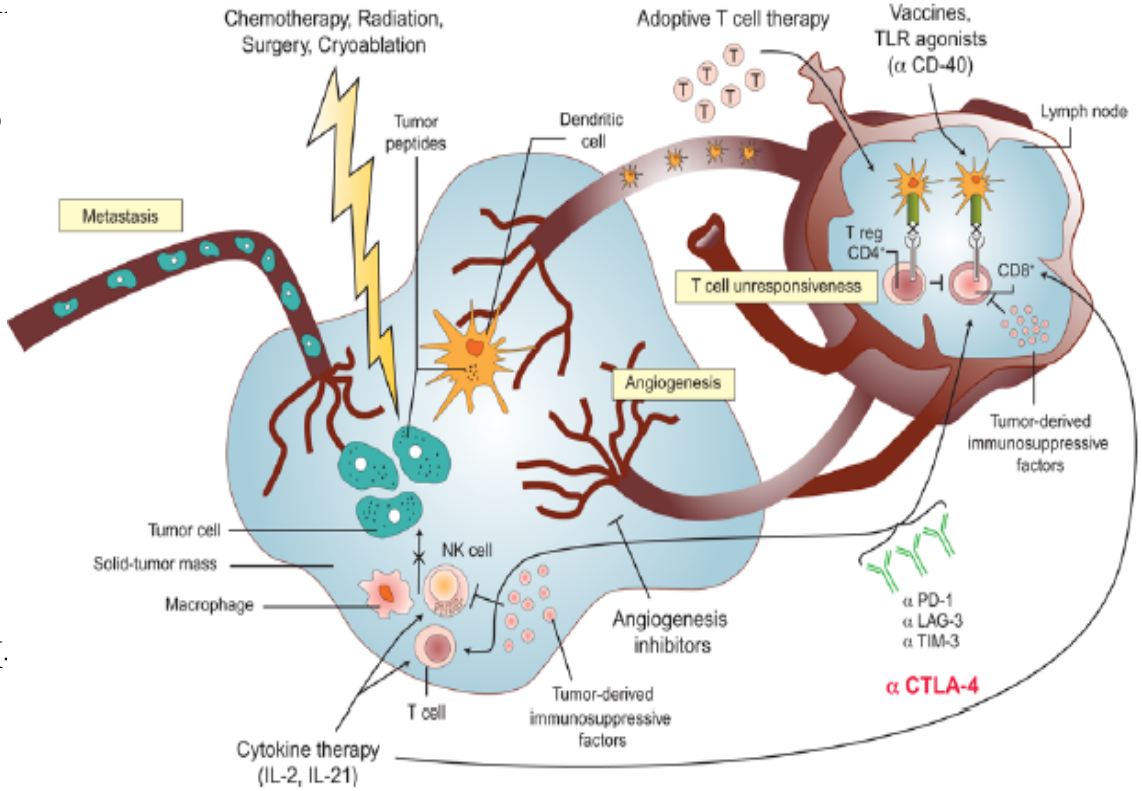




Sheridan *Nature Biotechnol*. 2015

Potential immunotherapy combinations

- Future is likely in combination
  - **Multiple checkpoints**
    - (PD-1 + CTLA-4, LAG3 etc.)
  - **Small Molecules Inhibitors**
    - (VEGFi or iNOS modulation + PD-L1)
  - **Radiation**
  - **Chemotherapy**
    - (Cyclophosphamide to deplete T_{reg} prior to checkpoint blockade)
  - **Costimulatory receptors** (OX-40, CD137, GITR, CD40)
  - **Novel Vaccines**
  - **Adoptive Cell Therapy**



Grosso and Jure-Kunkel, Cancer Immunity, 2013

Questions?