BASIC PRINCIPLES OF IMMUNOTHERAPY

Ivan Borrello, M.D.

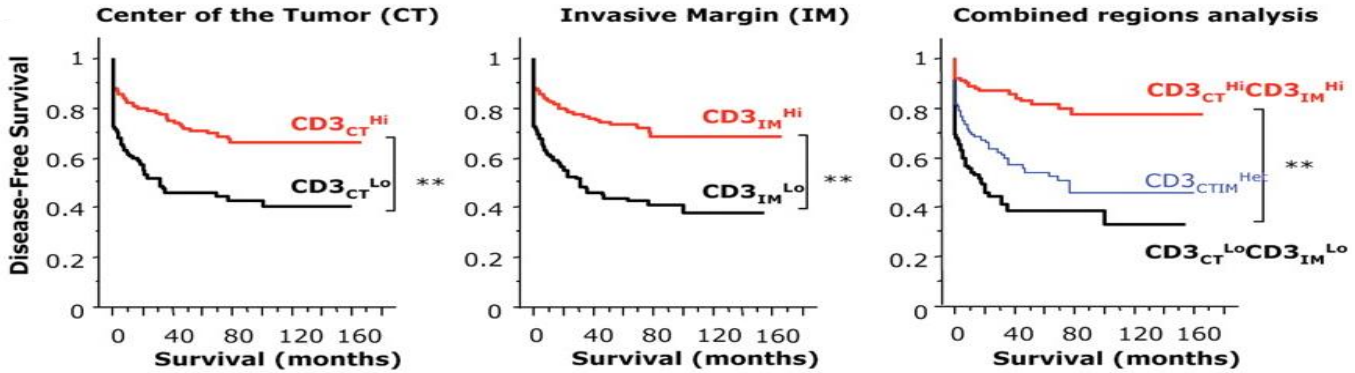
Sidney Kimmel Cancer Center at Johns Hopkins

DISCLOSURES

- WindMIL Therapeutics - Receipt of Intellectual Property Rights/Patent Holder
- Bristol-Myers Squibb, Celgene Corporation - Contracted Research
- I will be discussing non-FDA approved treatments during my presentation.

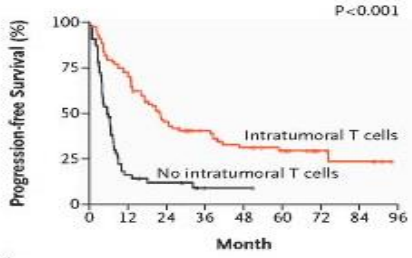
Effect of Immune Infiltration on Overall Survival

Colon Cancer

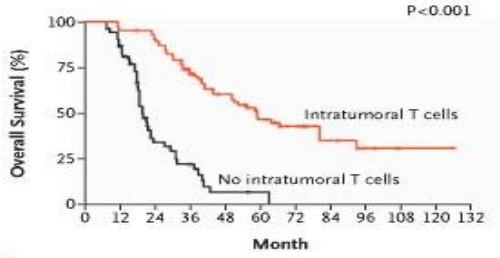


Galon Science 2006

Ovarian Cancer



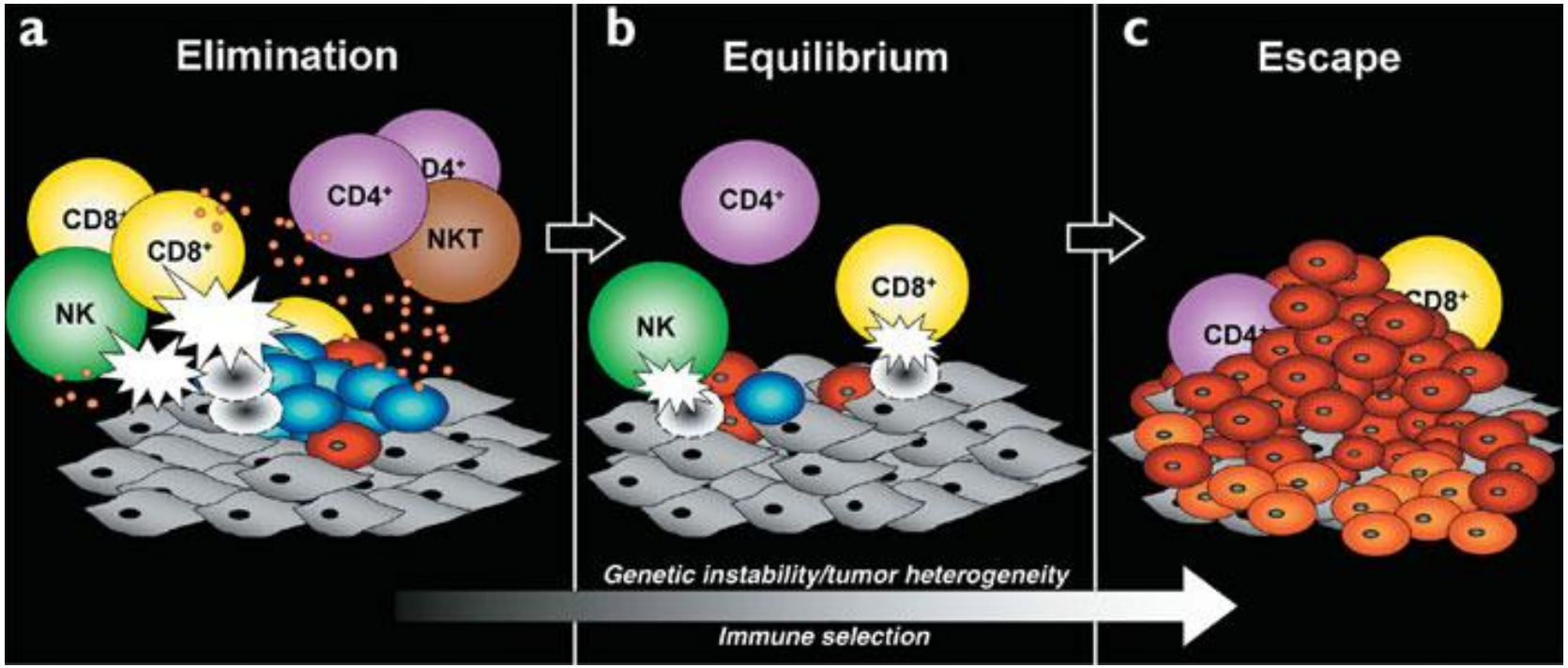
Intratumoral T Cells								
At risk	87	63	37	27	19	15	6	4
Events	24	23	4	6	1	0	1	0
Censored data	0	3	6	2	3	9	1	4
No Intratumoral T Cells								
At risk	55	8	5	1	1			
Events	44	2	2	0	0			
Censored data	3	1	2	0	1			



Intratumoral T Cells											
At risk	102	90	78	57	42	27	17	9	4	1	1
Events	12	10	16	8	11	2	2	1	0	0	0
Censored data	0	2	5	7	4	8	6	4	3	0	1
No Intratumoral T Cells											
At risk	72	48	14	8	2						
Events	21	29	5	5	1						
Censored data	3	5	1	1	1						

Zhang et al NEJM 2003

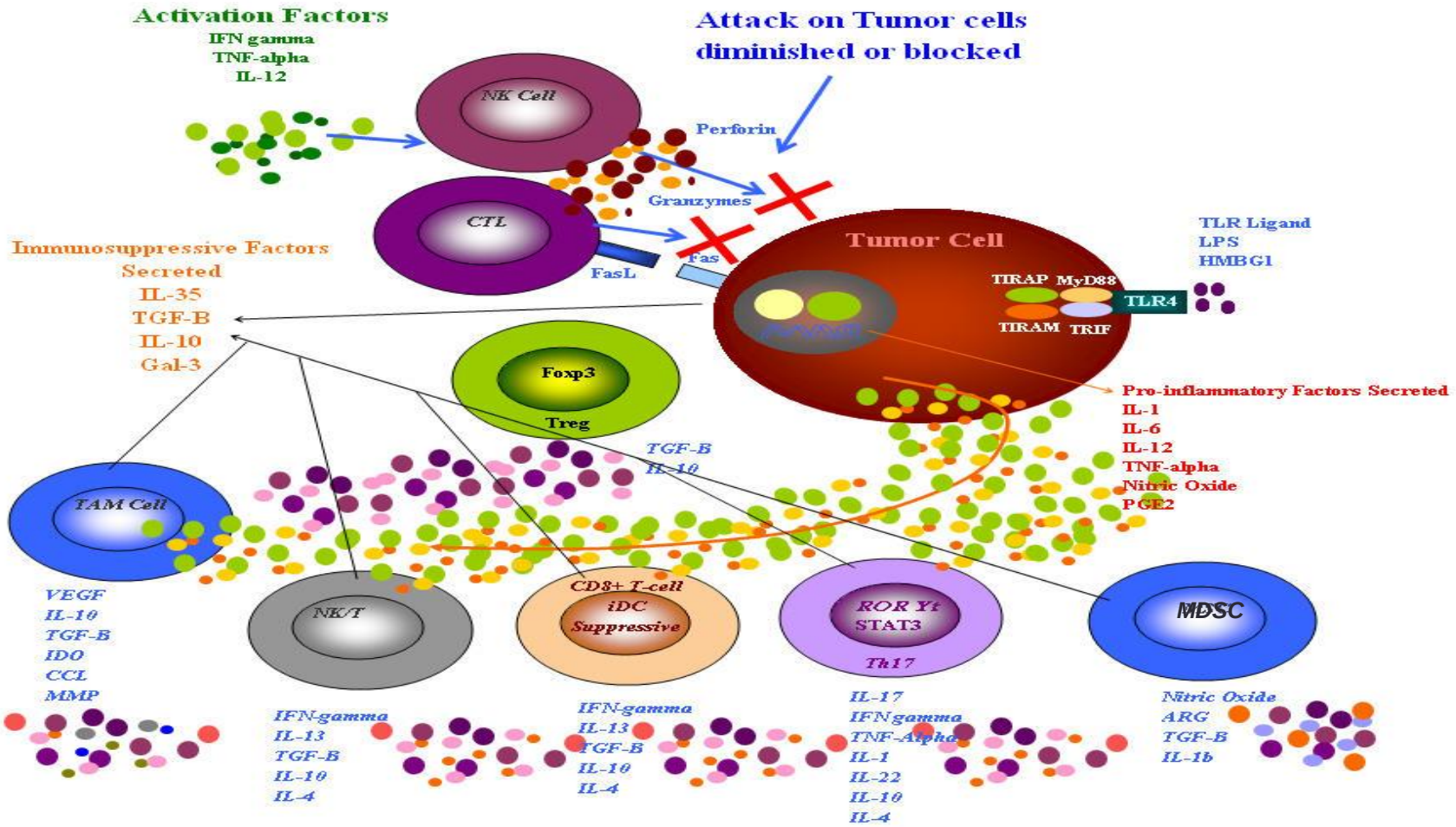
The Immune Editing Hypothesis (3E's)

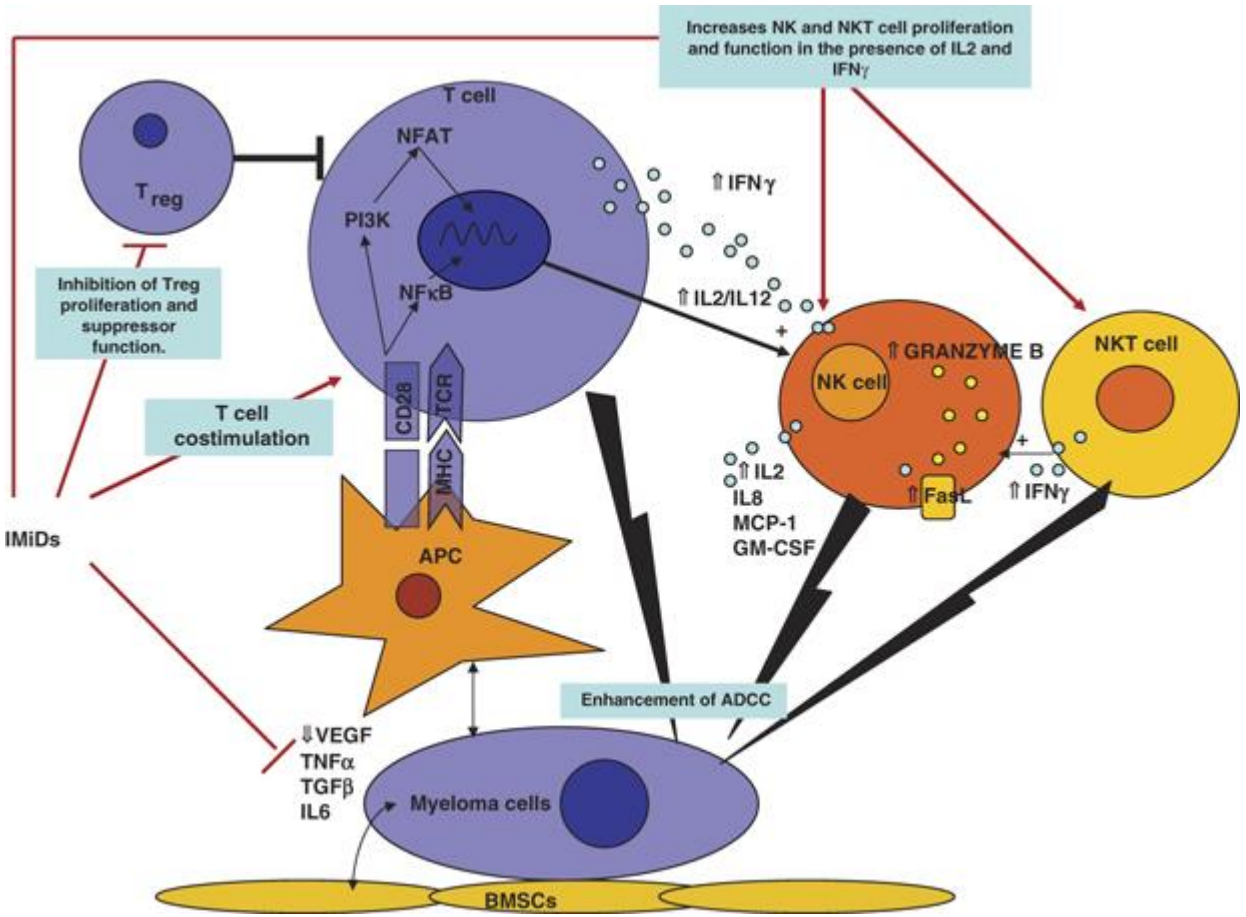


Types of Anti-Tumor Immunotherapy

- Cancer Vaccines – educate T cells to better recognize and kill the pre-existing tumor
- Adoptive Immunotherapy – activate and increase T cell numbers to better kill tumor
- Immunomodulation – use drugs or antibodies to either:
  - increase immune stimulation
  - overcome immune inhibition

Mechanisms of Tumor-induced Immune Tolerance





Quach et al Leukemia (2010) **24,** 22–32

CANCER VACCINES

Normal Host:

Cancer Patient:

Cancer Vaccine Design

Vaccine Requirements

- Contain a desired antigen(s)
- Possess an adjuvant capable of stimulating/generating an immune response

Vaccine Antigens

Single Antigen Approaches

- Nucleic Acids: RNA or DNA
  - generally targets a single antigen
- Peptides
- Proteins

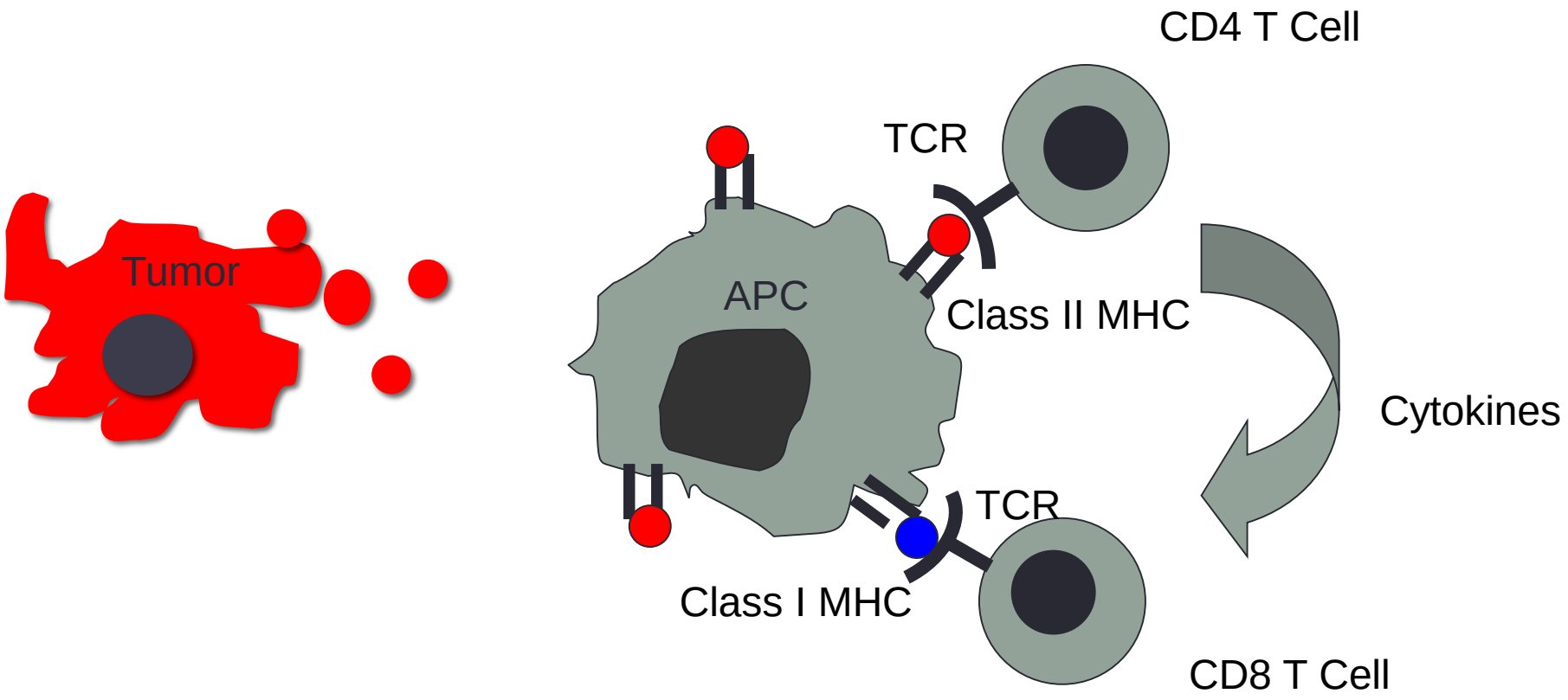
Multiple Antigen Approaches

- Pulsed Dendritic Cells
- Tumor cell – Dendriitc Cell Fusions
- Whole cell vaccines

Cancer Vaccine Goal ….

Dendritic Cells Traffic and Present Antigen To Specific CD4 and CD8 T Cells in the Draining Lymph node through a process known as

<u>Cross Presentation</u>



Issues Around Tumor Vaccines

Benefits:

- Capable of generating a durable, long-lived response
- Delivered with minimal toxicity
- May be an “off-the-shelf” product
- Can be combined with additional immunotherapies to enhance overall efficacy.

Disadvantages:

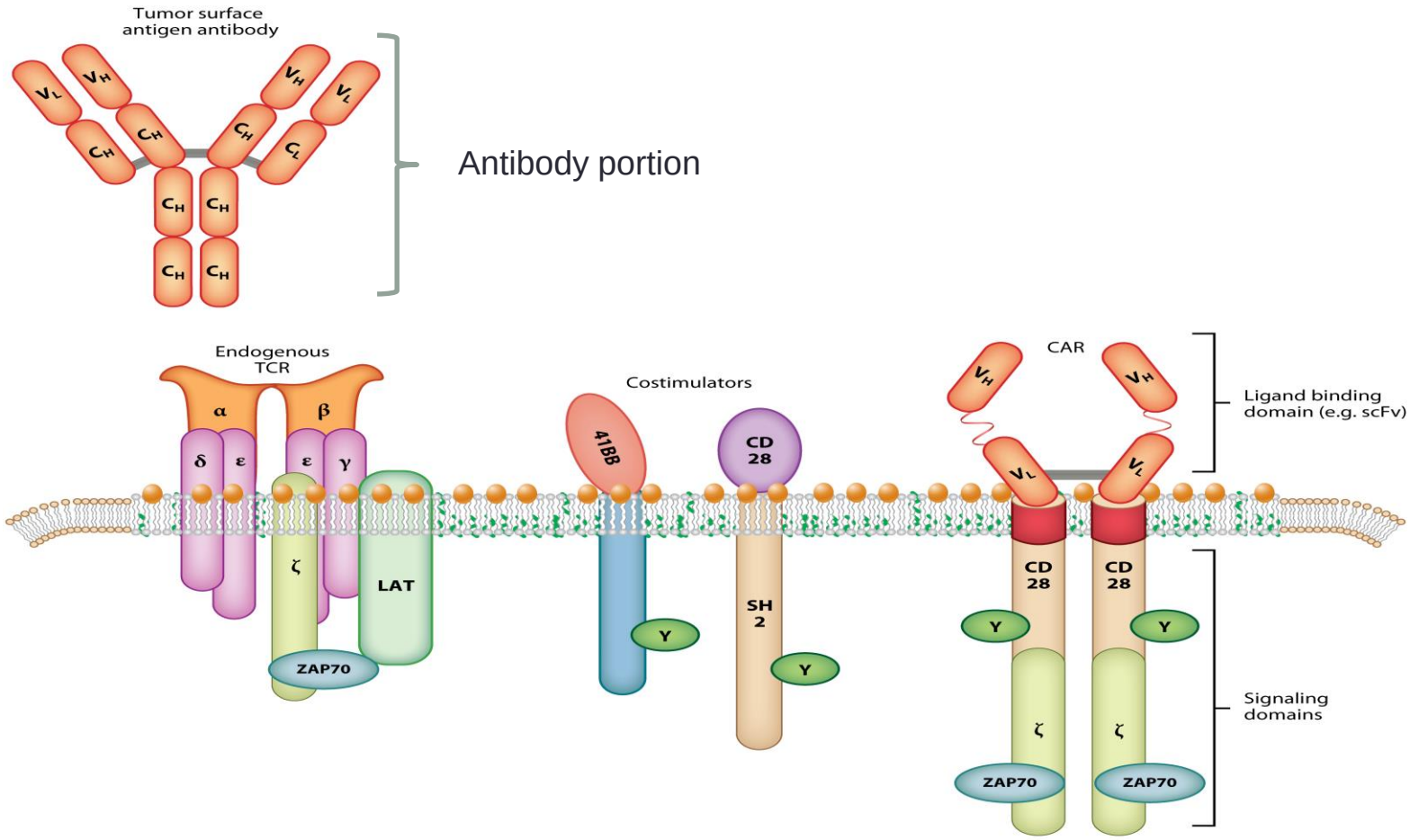
- Can take several weeks to generate a meaningful systemic response
- Likely works best in a setting of minimal disease or a slow growing tumor
- Relapses of antigen-specific vaccines may be with the generation of antigen escape variants

T CELL THERAPIES

T Cell Therapy

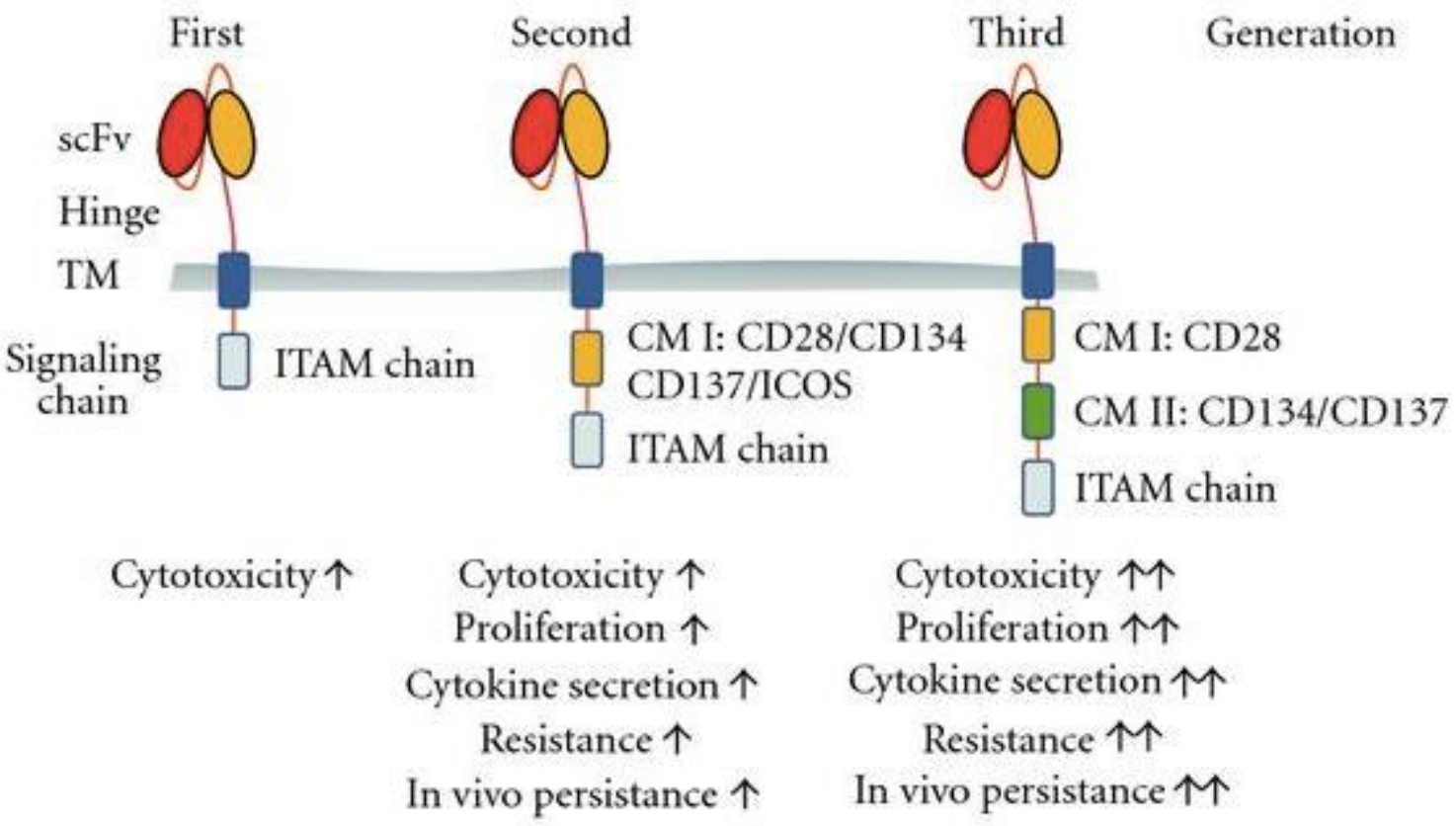
- CARs – chimeric antigen receptors
- TCRs – T cell receptors
- TILs – Tumor infiltrating lymphocytes
- MILs – Marrow infiltrating lymphocytes
- Allogeneic BMT

Composition of a CAR



Barrett DM, et al. 2014.
Annu. Rev. Med. 65:333–47

CAR's



http://www.hindawi.com/journals/bmri/2010/956304/fig3/

TCR Engineered T cells

- TCR cloned for a specific CD8 restricted antigen-specific peptide
- T cells genetically engineered to express this TCR
- T cells are HLA-restricted for the specific peptide

Non-gene modified T cells

- TILs
  - obtained surgically from metastatic lesions
  - present in 40-60% of patients
  - able to be expanded in 50% of those patients
  - expansion takes 2-4 weeks
  - available as therapy to ~25% of patients
  - shown efficacy in metastatic melanoma

Non-gene modified T cells

- MILs
  - found in 100% of the bone marrow of patients
  - expanded in virtually all patients
  - expansion in 7-10 days
  - has broad antigenic specificity
  - potentially beneficial in solid tumors

ANTIBODY APPROACHES

Immune Checkpoint Modulators

a

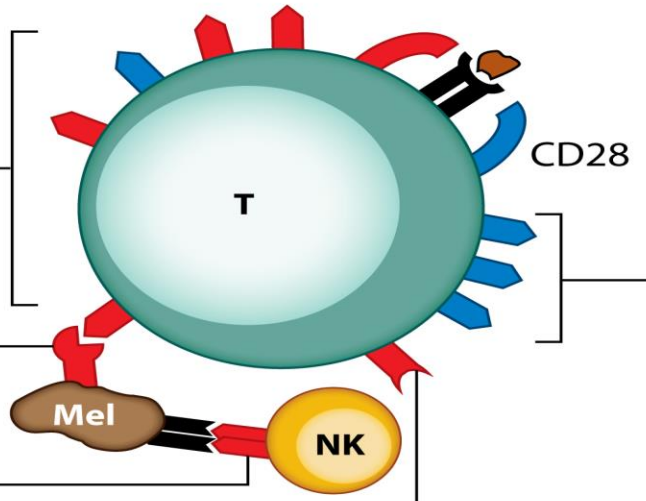
CD28/CTLA-4 Ig family	
Target	**Status**
CTLA-4	Approved
PD-1	Ph III accruing
BTLA	Preclinical
LAG3	Preclinical
ICOS	Preclinical

c

PD-L1	Ph II accruing

d

KIR	Ph II accruing



b

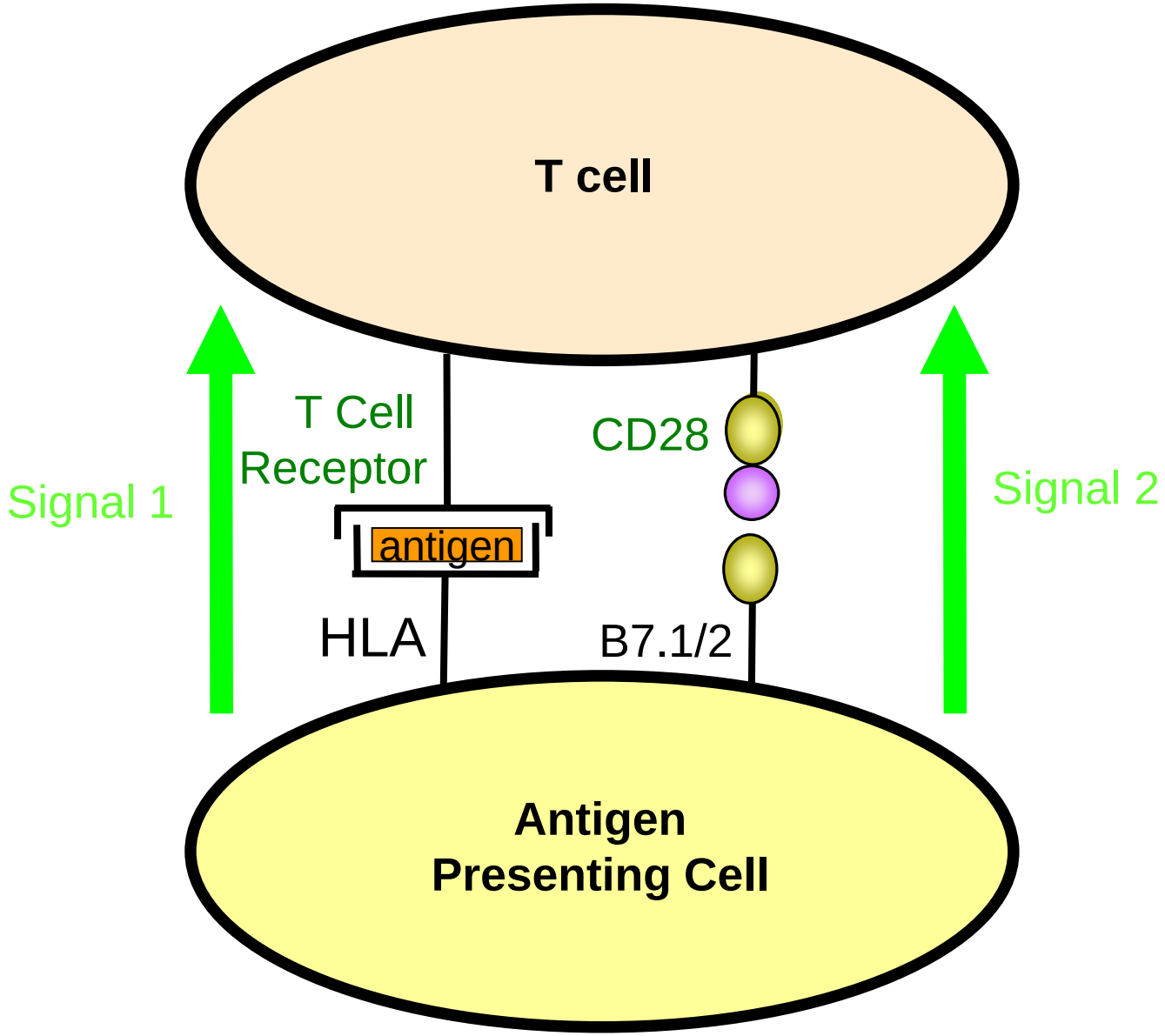
TNF superfamily	
Target	**Status**
CD40	Ph I
OX40	Ph I accruing
CD137	Ph II
GITR	Ph I accruing
CD27	Ph I accruing

e

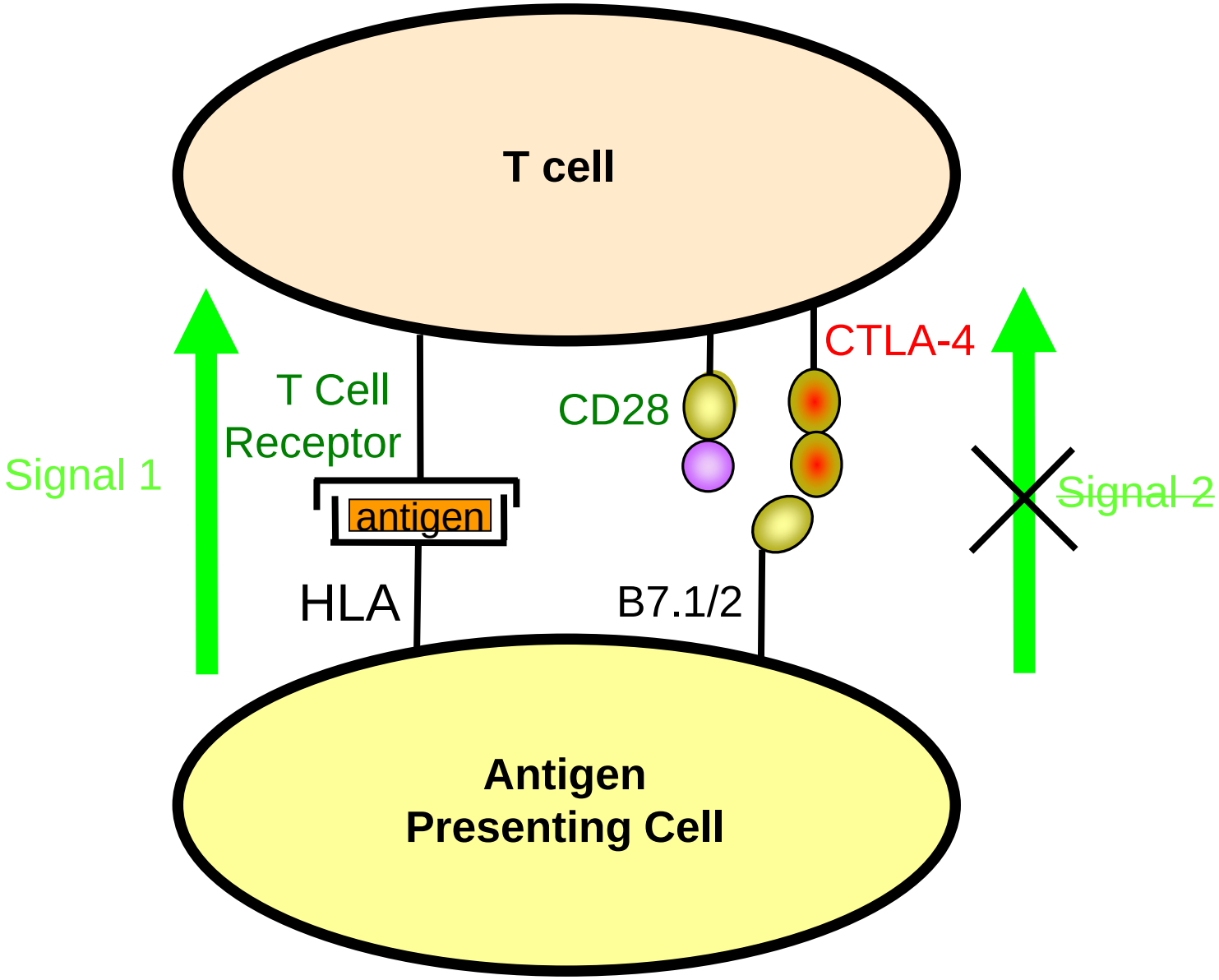
TIM-3	Preclinical

Page DB, et al. 2014.
Annu. Rev. Med. 65:185–202

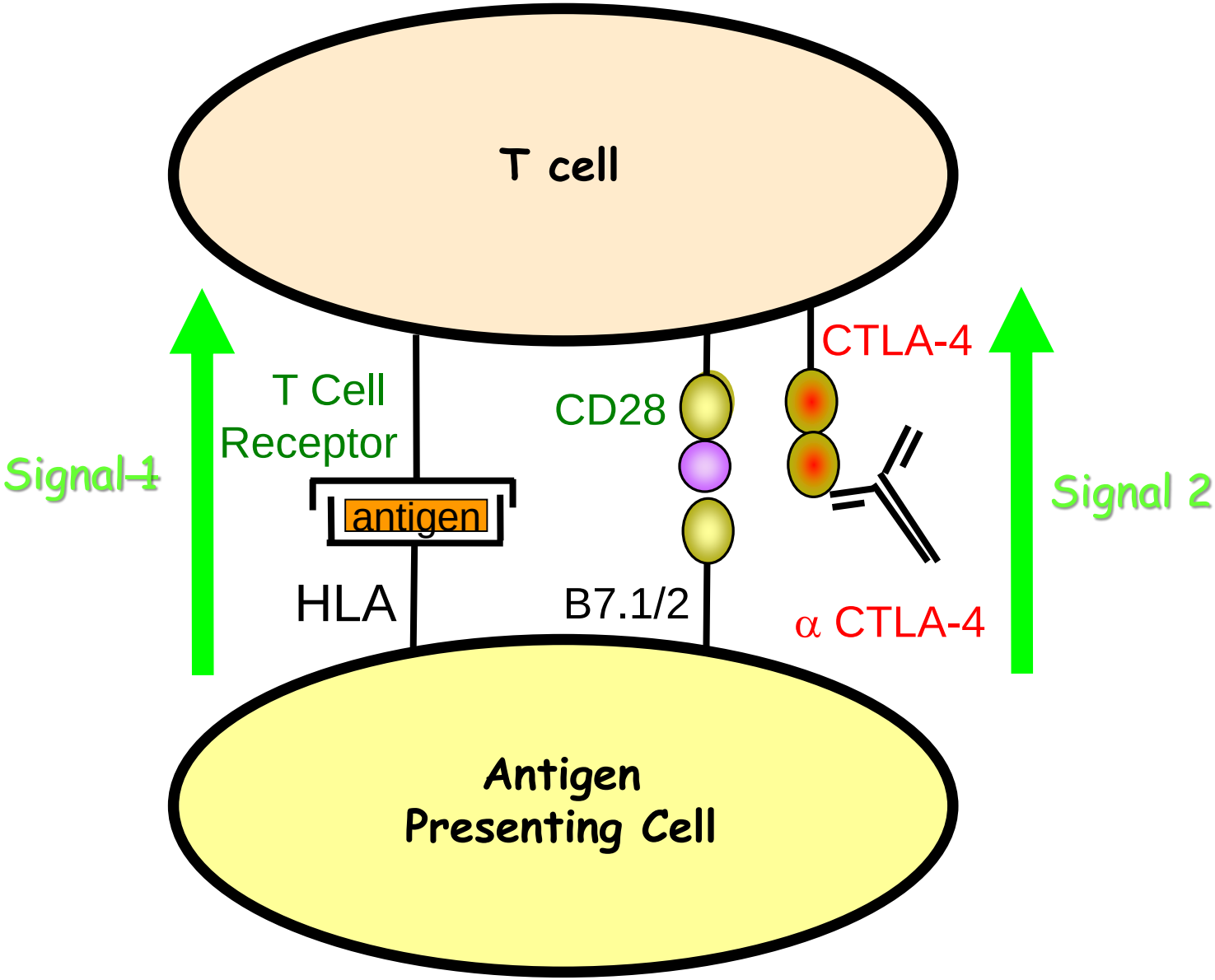
Anti-CTLA-4


T cell
T Cell
Receptor
CD28
Signal 1
Signal 2
antigen
HLA
B7.1/2
Antigen
Presenting Cell

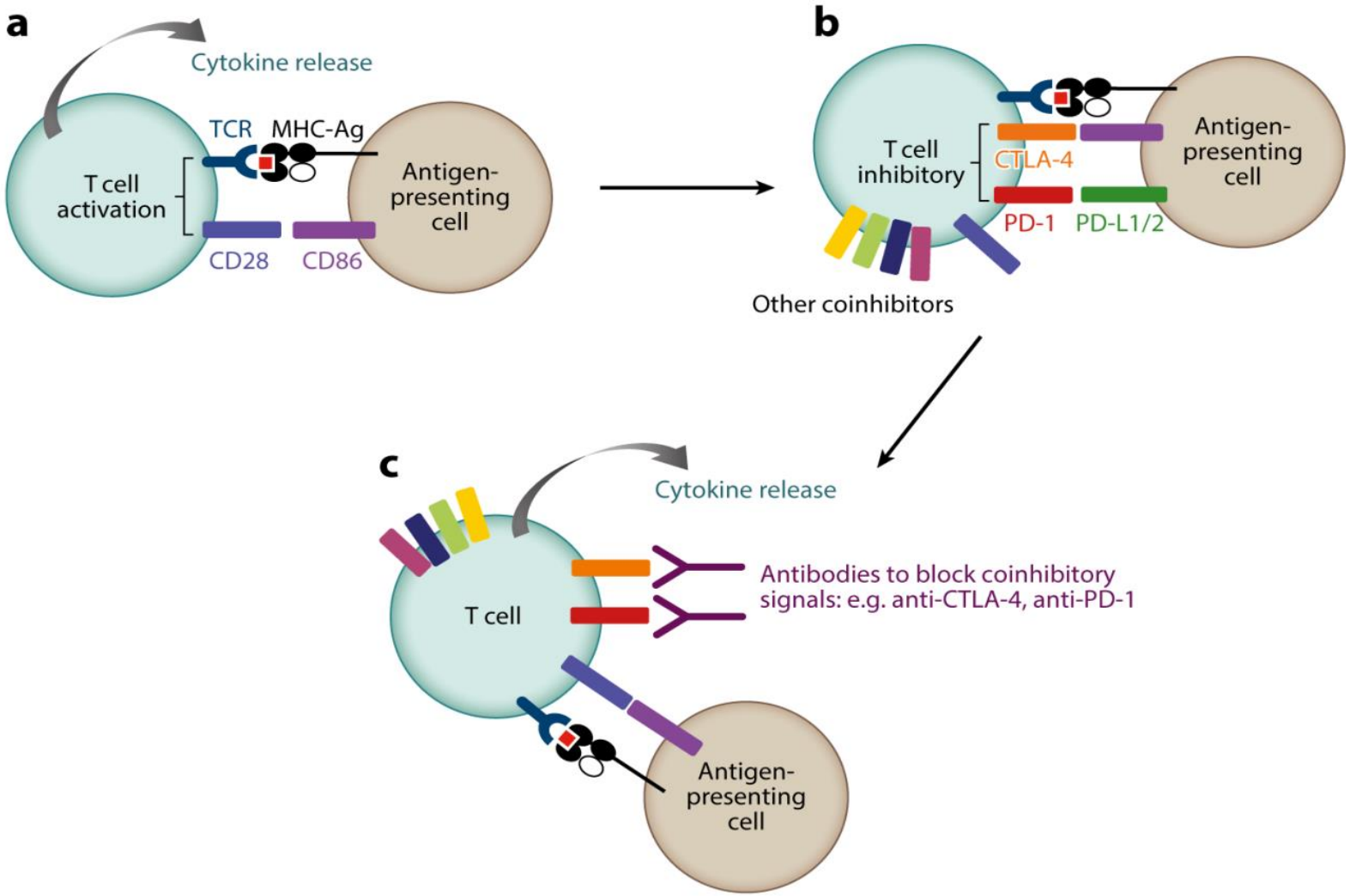
CTLA-4 Prevents Normal T Cell Activation



Ipilimumab (Anti-CTLA-4) Blocks the CTLA-4 Checkpoint, RestoringT Cell Activation

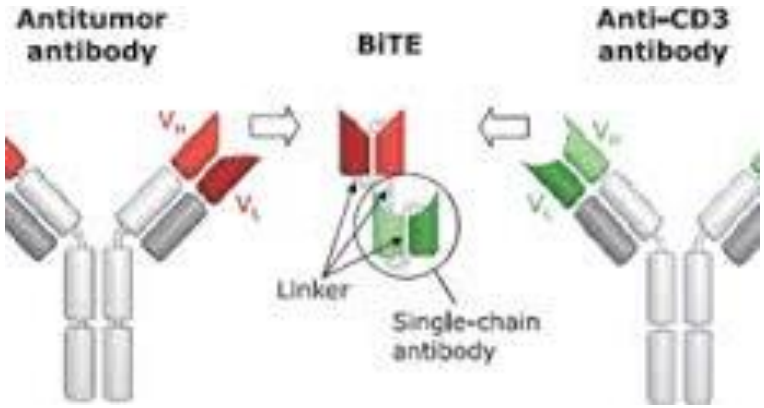


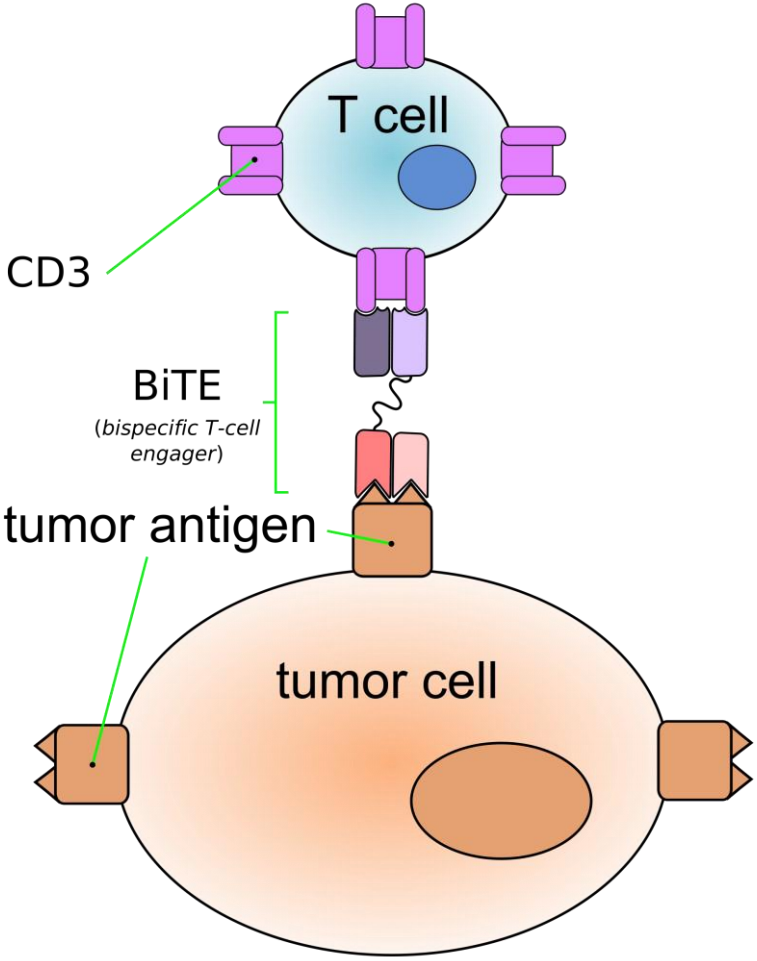
Role of Checkpoint Inhibitors



Lizée G, et al. 2013.
Annu. Rev. Med. 64:71–90

BiTE

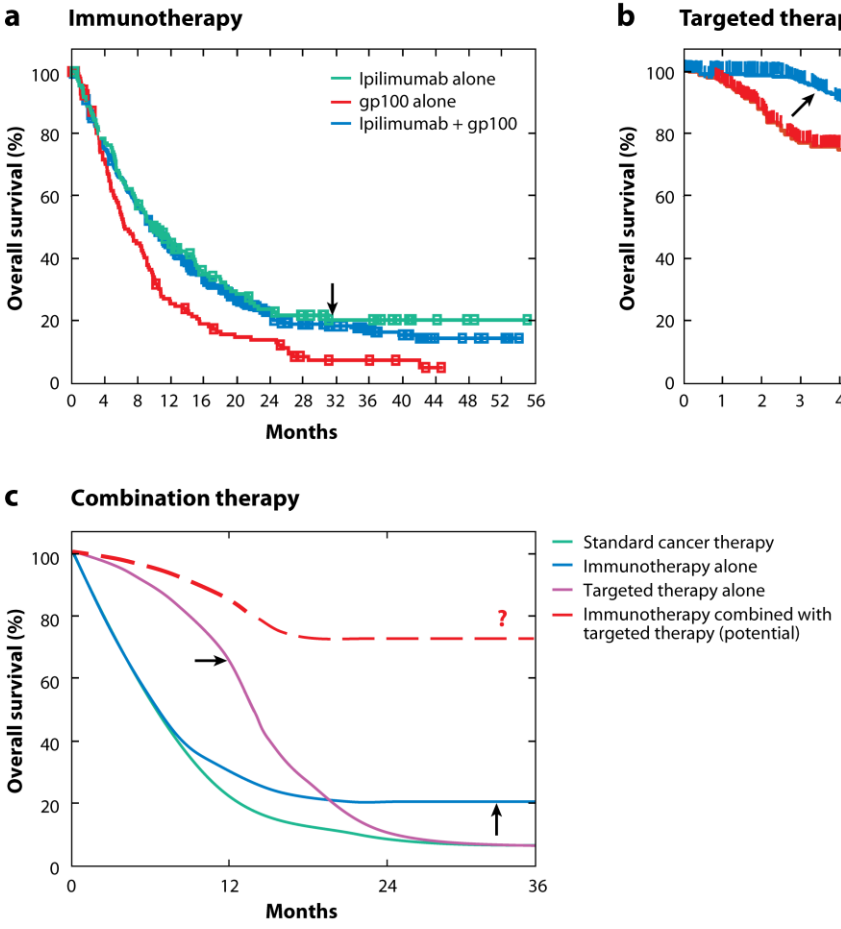

Antitumor antibody
BiTE
Anti-CD3 antibody
Linker
Single-chain antibody


T cell
CD3
BiTE
(bispecific T-cell engager)
tumor antigen
tumor cell

Limitation of Current BiTEs

- Absence of an Fc responsible for short half-life
- Act through engagement of CD3+ cells
- Combines the benefit of antibody targeting with a T cell response
- Require a continuous infusion because of their short half-life

Rationale for Combination Chemo-Immunotherapy



Maus MV, et al. 2014.
Annu. Rev. Immunol. 32:189–225