Disclosure Information

Basic Principles of Tumor Immunology

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I have the following financial relationships to disclose:

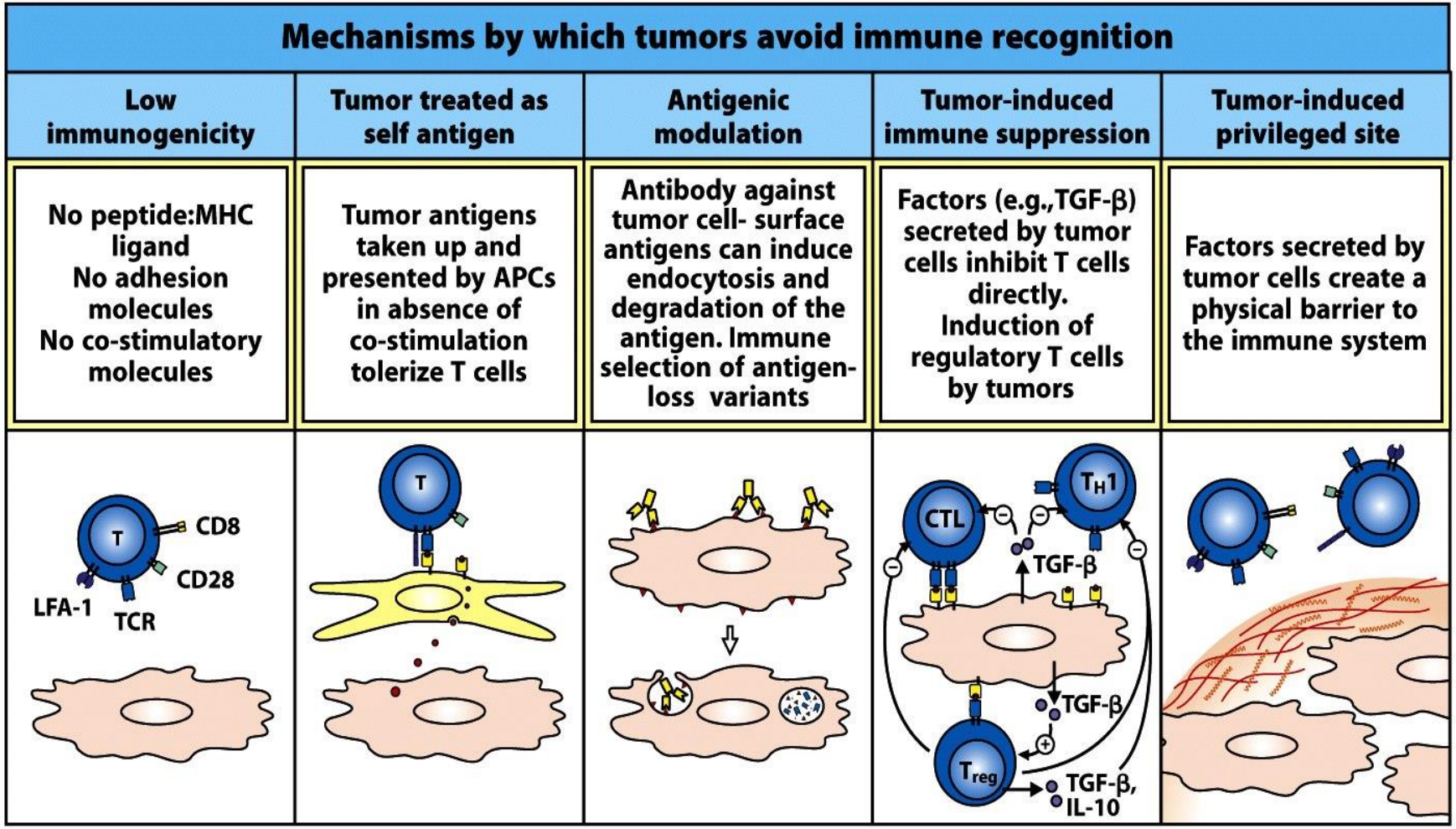
- Consultant: VentiRx
- Speaker's Bureau: N/A
- Grant/Research support from: Seattle Genetics, EMD Serono, Celgene, Jannsen
- Stockholder in: VentiRx, EpiThany
- Honoraria from: N/A
- Employee of: University of Washington (inventor named on patents)
- I will not be discussing non-FDA approved treatments

Basic Principles of Tumor Immunology

I. How tumors escape from the immune system

II. What we can do about it

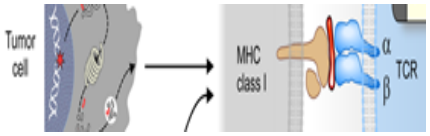
Many ways cancer evades the immune system



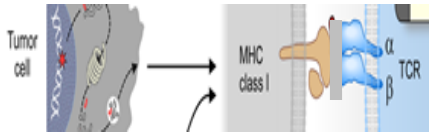
Murphy et al. Immunobiology, 7ed Garland Science 2008

Interplay of innate and adaptive immunity

Mutated antigens

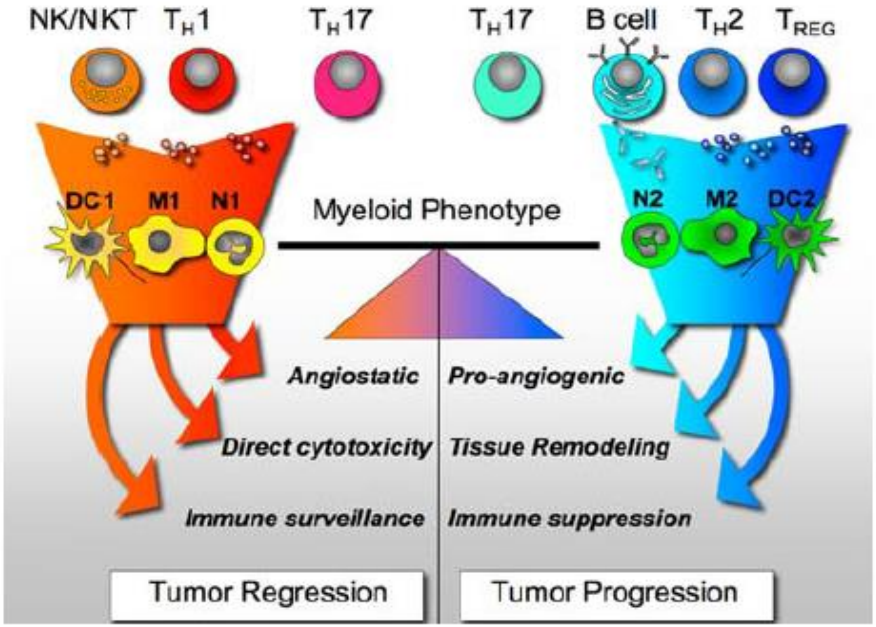


Self antigens



Viral response

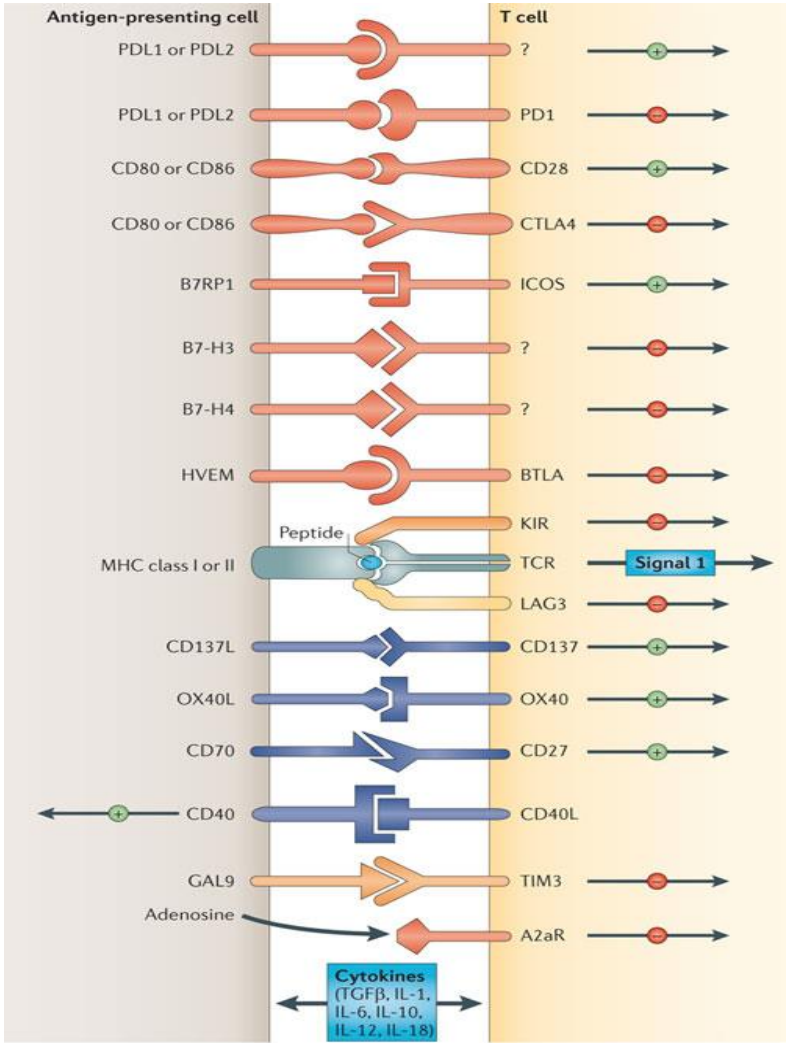
Wound healing response

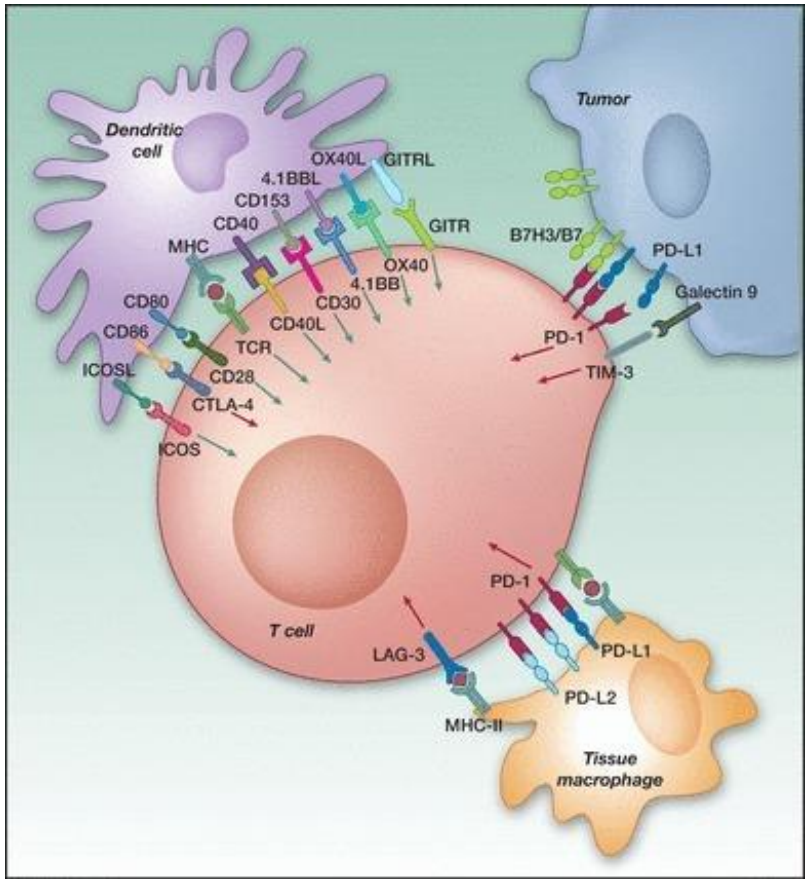


Type 1 **Type 2**

DeNardo et al, Cancer Metastasis Rev, 2010

T-cell function is orchestrated by stimulatory and inhibitory signals

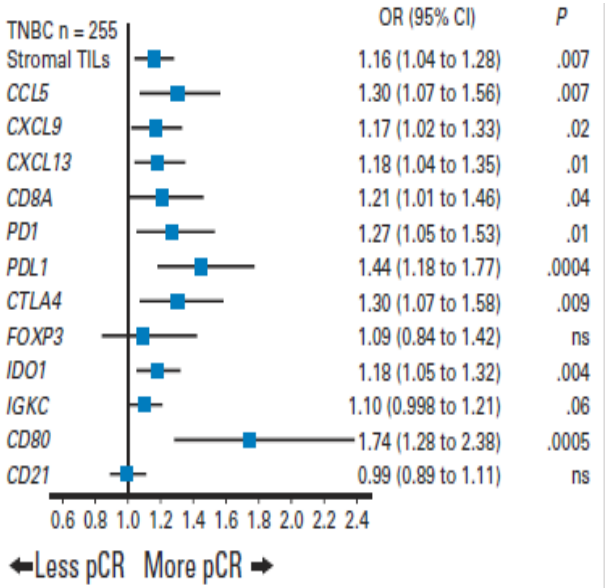




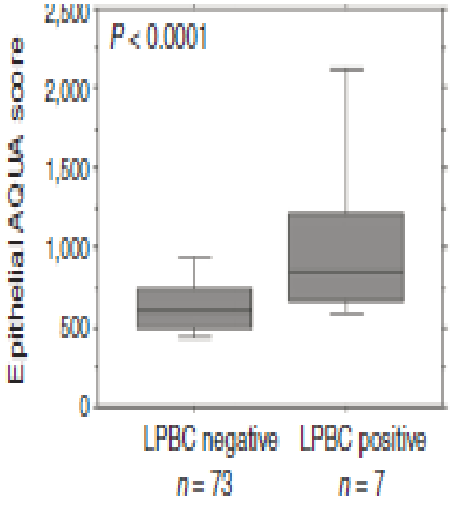
Pardoll, Nat Rev Ca, 2012; Ott et al, Clin Ca Res, 2013

High TIL is associated with increased PD-1 expression

TNBC

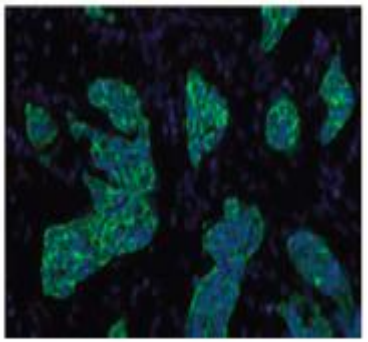


Denkert C et al, JCO, 2015

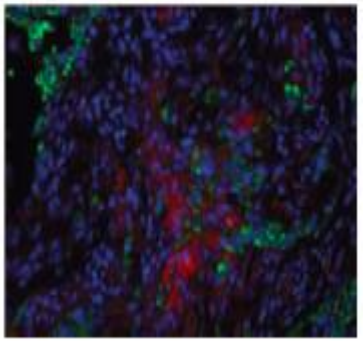


Wimberly H et al, JCO, 2015

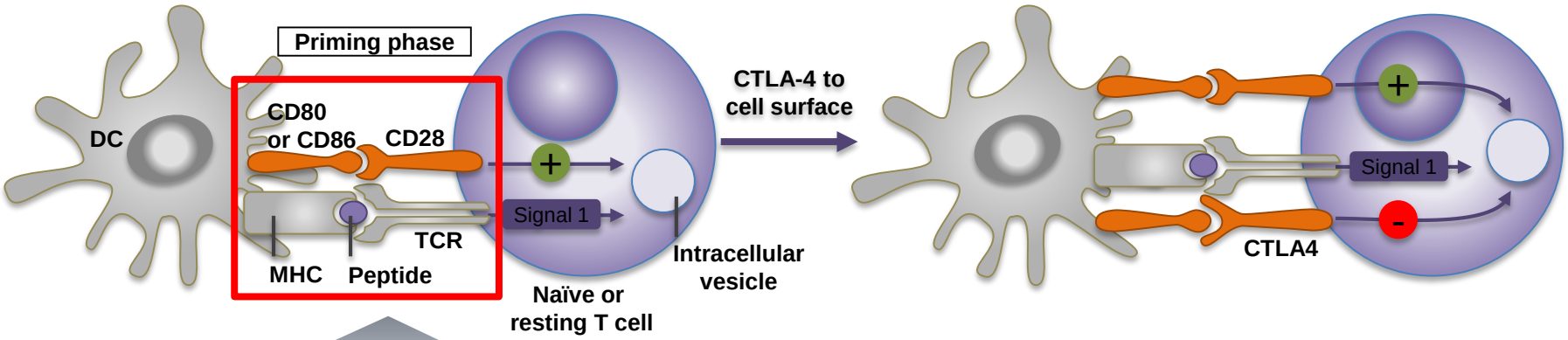
High PD-1

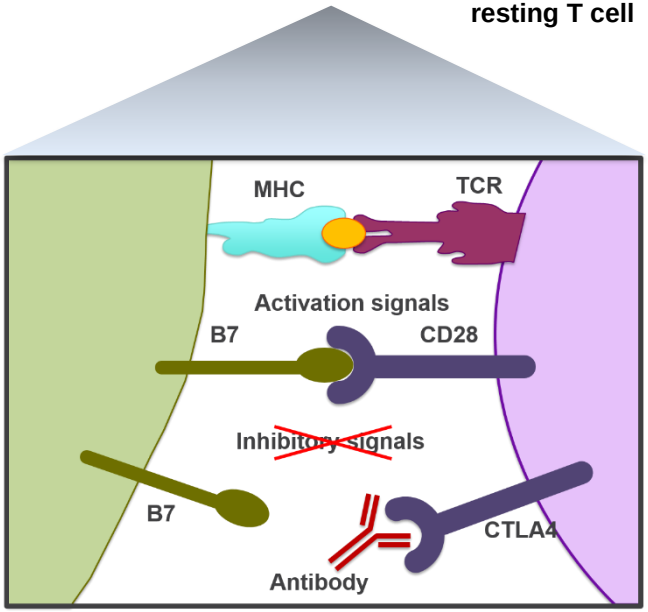


Low PD-1



CTLA-4 pathway regulates T-cell activation

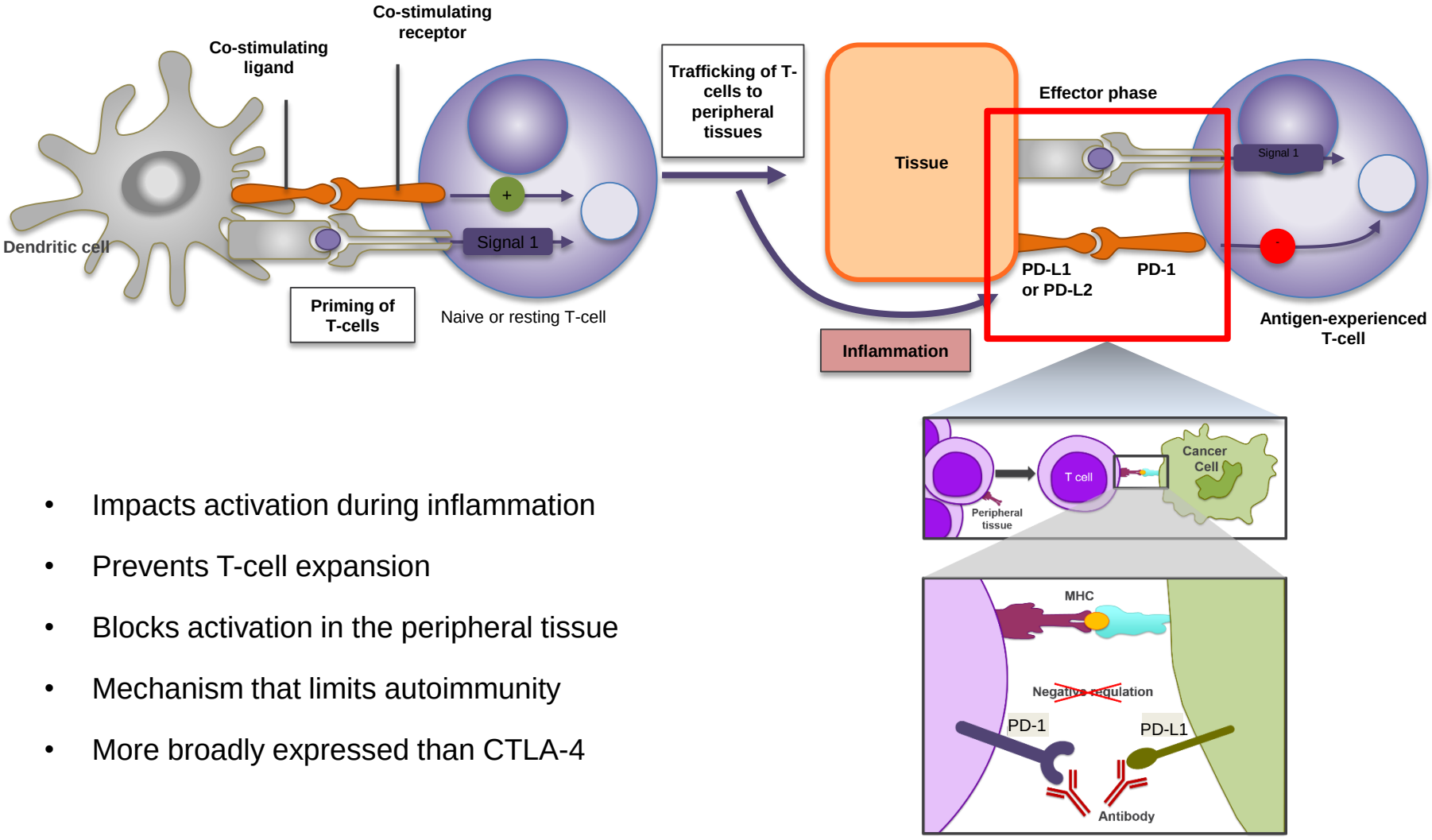




- Impacts T-cell priming
- Occurs during initial interaction of T-cells with APC
- Blocks activation in the lymph nodes
- Regulates amplitude of early activation of naïve and memory T-cells
- Antibodies targeting CTLA-4

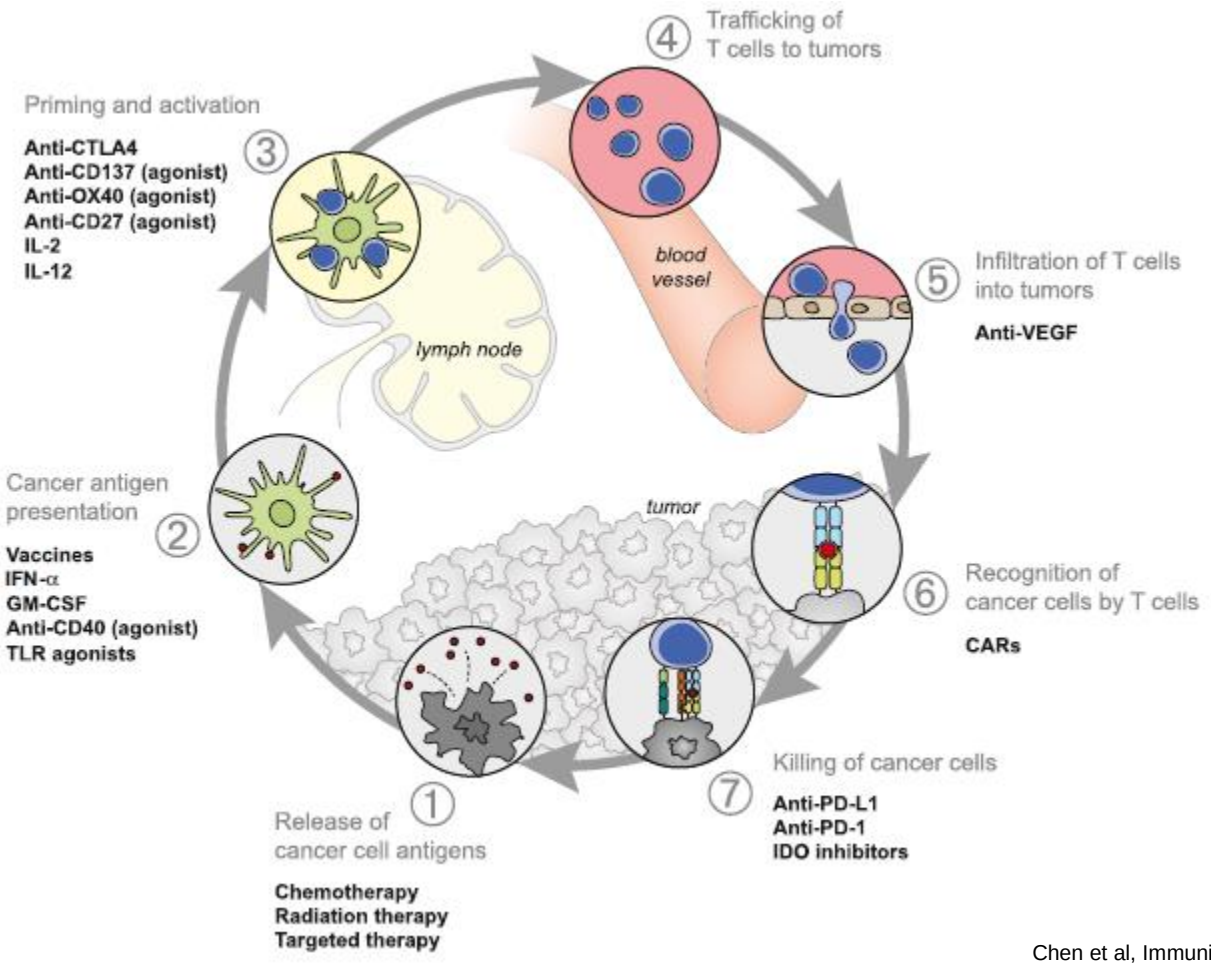
Pardoll, Nat Rev Ca, 2012; Ribas et al, NEJM, 2012

PD-1/PD-L1 limits the activity of activated T-cells



- Impacts activation during inflammation
- Prevents T-cell expansion
- Blocks activation in the peripheral tissue
- Mechanism that limits autoimmunity
- More broadly expressed than CTLA-4

Immuno-oncology drugs focus on escape mechanisms



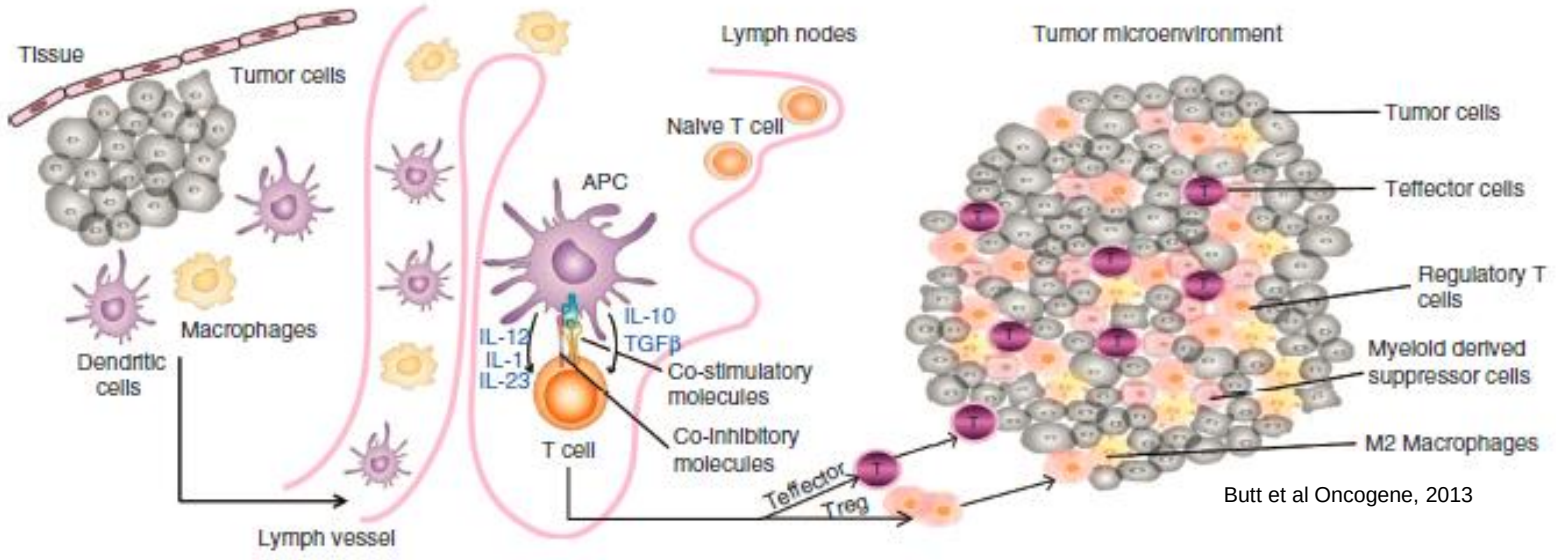
Chen et al, Immunity, 2013

Basic Principles of Tumor Immunology

I. How tumors escape from the immune system

II. What we can do about it

Approaches to immunotherapy

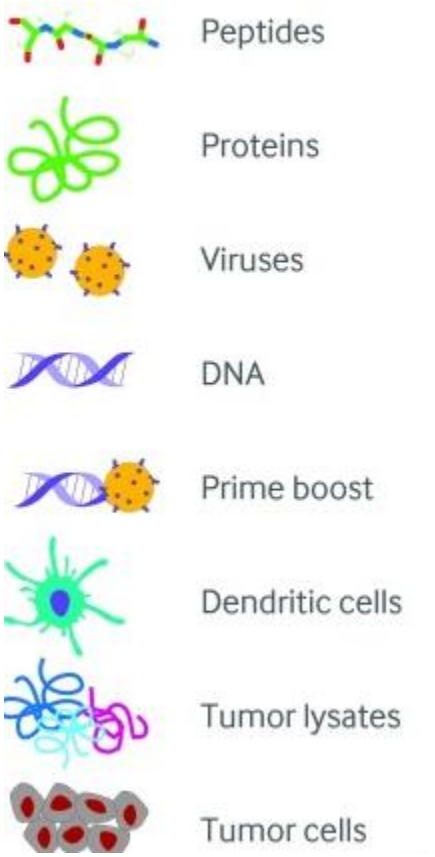


Butt et al Oncogene, 2013

Increase effector T-cells — Enhance existing immunity → Modulate the tumor microenvironment

Vaccines and adjuvants

Delivery systems



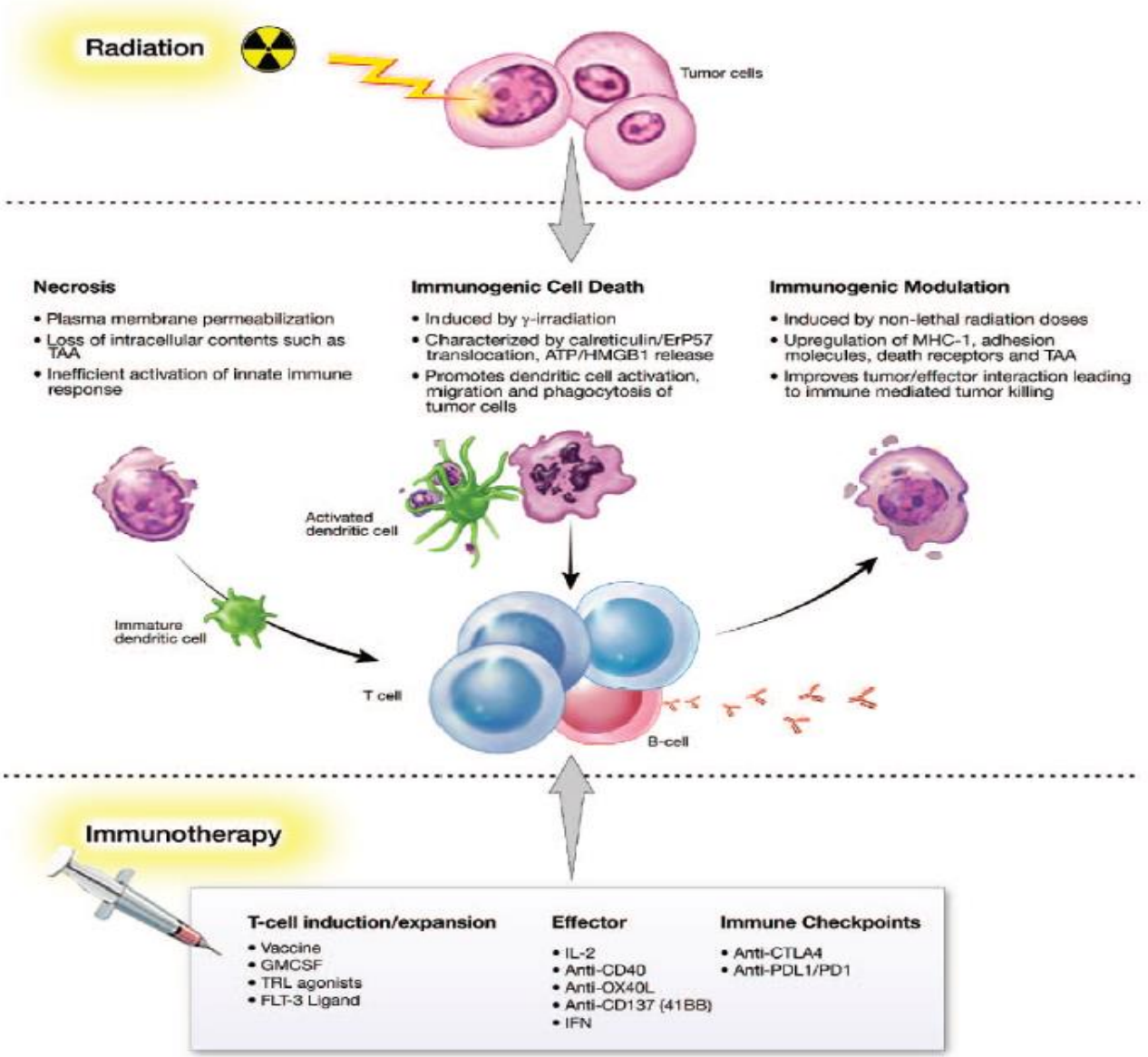
Butterfield, BMJ, 2014

Adjuvant in Clinical Trials

Adjuvant name	Class	Mechanism or receptor	Type of immune response	Clinical phase or licensed product name
dsRNA analogues (for example, poly(I:C))	IM	TLR3	Ab, T_H1, $CD8^+$ T cells	Phase 1
Lipid A analogues (for example, MPL, RC529, GLA, E6020)	IM	TLR4	Ab, T_H1	Cervarix, Supervax, Pollinex Quattro, Melacine
Flagellin	IM	TLR5	Ab, T_H1,T_H2	Phase 1
Imidazoquinolines (for example, Imiquimod, R848)	IM	TLR7 and TLR8	Ab, T_H1	Aldara
CpG ODN	IM	TLR9	Ab, T_H1, $CD8^+$ T cells	Phase 3
Saponins (for example, QS21)	IM	Unknown	Ab, T_H1,T_H2, $CD8^+$ T cells	Phase 3
C-type lectin ligands (for example, TDB)	IM	Mincle, Nalp3	Ab, T_H1, T_H17	Phase 1
CD1d ligands (for example, α- galactosylceramide)	IM	CD1d	Ab, T_H1, T_H2, $CD8^+$ NKT cells	Phase 1
Aluminum salts (for example, aluminum oxyhydroxide, aluminum phosphate)	PF	Nalp3, ITAM, Ag delivery	Ab, T_H2	Numerous licensed products
Emulsions (for example, MF59, AS03, AF03, SE)	PF	Immune cell recruitment, ASC, Ag uptake	Ab, T_H1, T_H2	Fluad, Pandemrix
Virosomes	PF	Ag delivery	Ab, T_H1,T_H2	Epaxal, Inflexal V
AS01 (MPL,QS21, liposomes)	C	TLR4	Ab, T_H1, $CD8^+$ T cells	Phase 3
AS02 (MPL,QS21, emulsion)	C	TLR4	Ab, T_H1	Phase 3
AS04 (MPL, aluminum salt)	C	TLR4	Ab, T_H1	Cervarix
AS15 (MPL, QS21, CpG, liposomes)	C	TLR4 and TLR9	Ab, T_H1, $CD8^+$ T cells	Phase 3
GLA-SE (GLA, emulsion)	C	TLR4	Ab, T_H1	Phase 1
IC31 (CpG, cationic peptide)	C	TLR9	Ab, T_H1, T_H2, $CD8^+$ T cells	Phase 1
CAF01 (TDB, cationic liposomes)	C	Mincle, Ag delivery	Ab, T_H1, $CD8^+$ T cells	Phase 1
ISCOMs (saponin, phospholipid)	C	Unknown	Ab, T_H1,T_H2, $CD8^+$ T cells	Phase 2

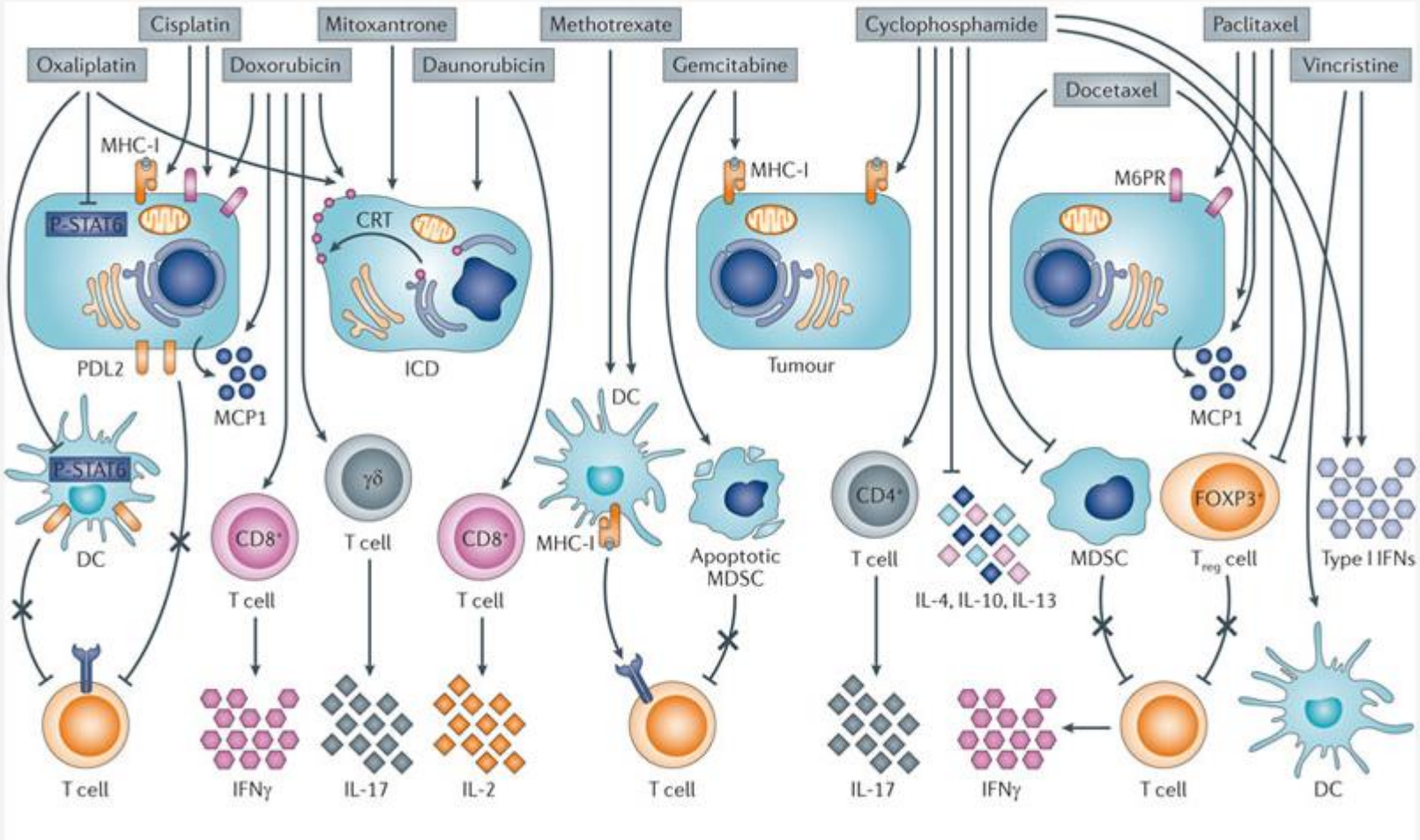
Reed et al, Nat Med, 2013

Radiation therapy and systemic immunity



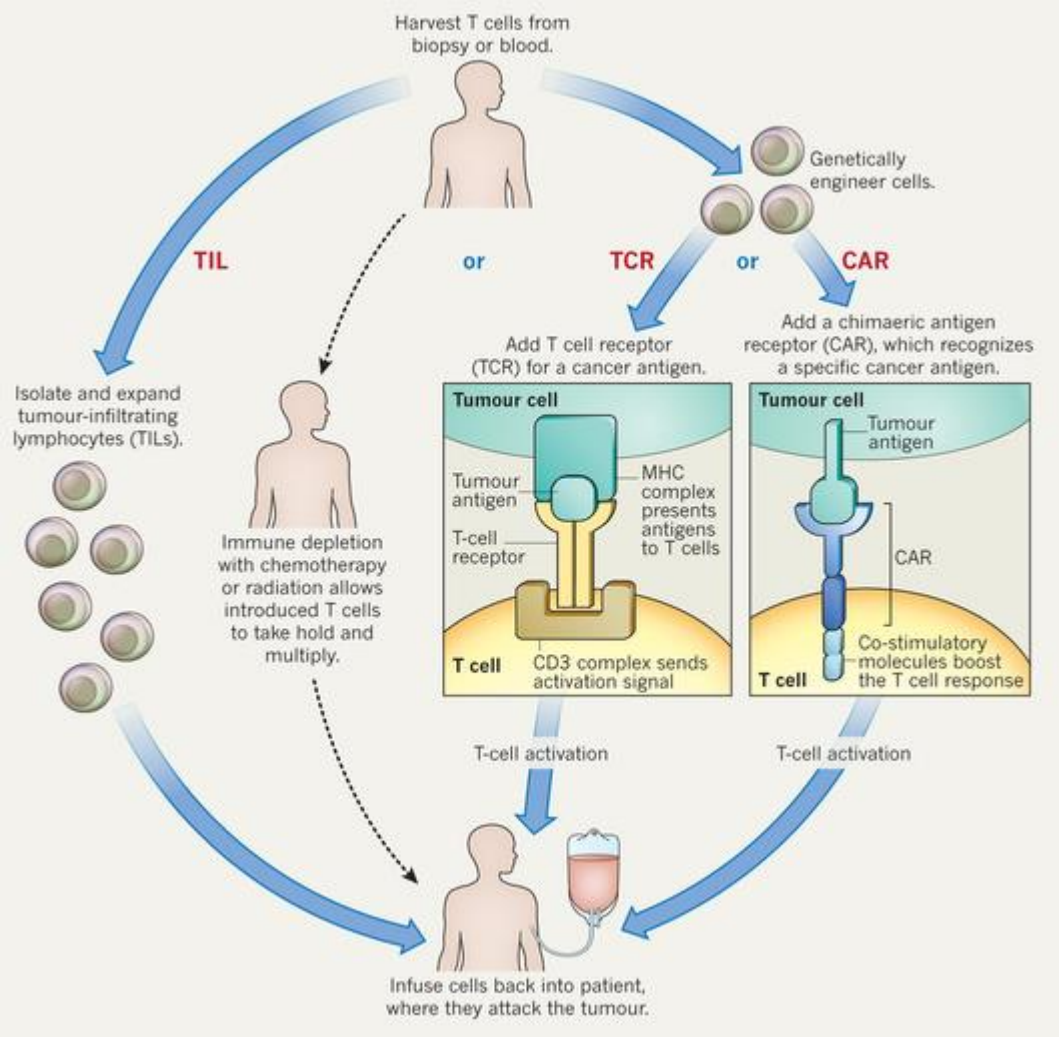
Wattenberg et al, Radiation Res, 2014

Immunologic effects of chemotherapy



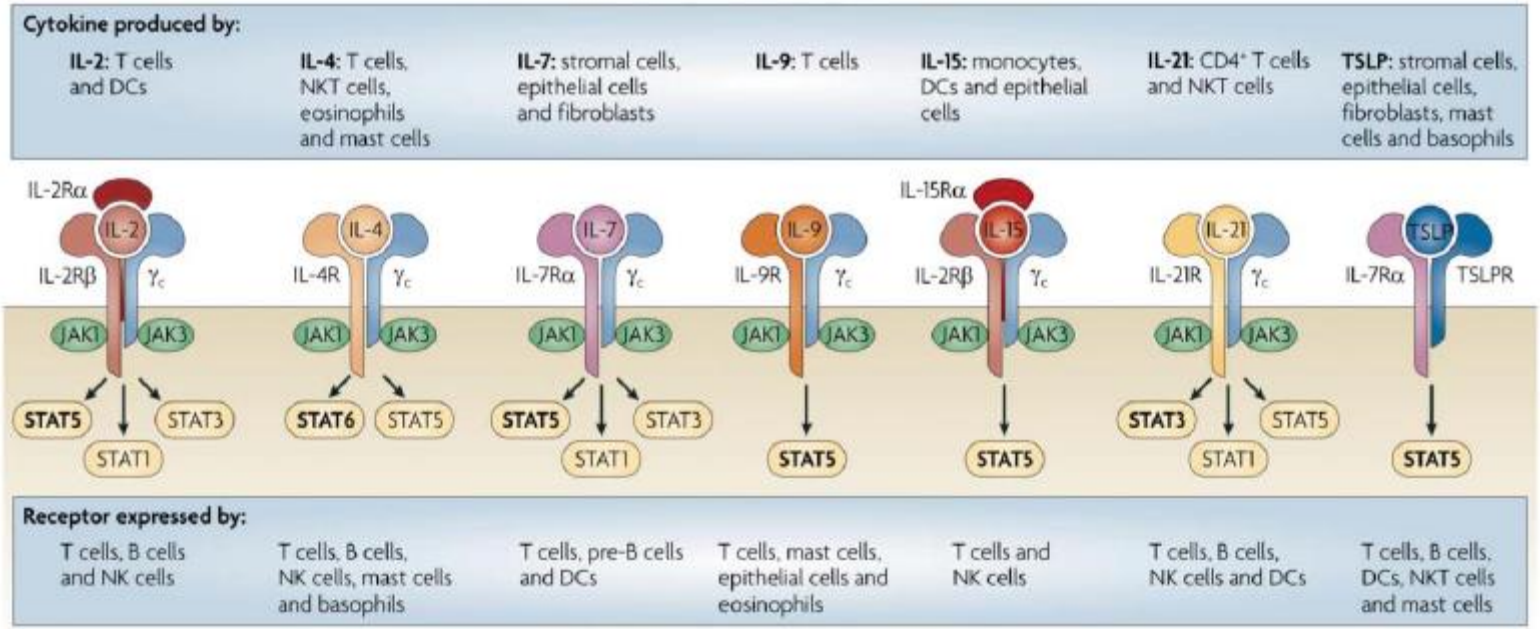
Galluzzi et al, Nat Rev Drug Disc, 2012

Adoptive T cell approaches



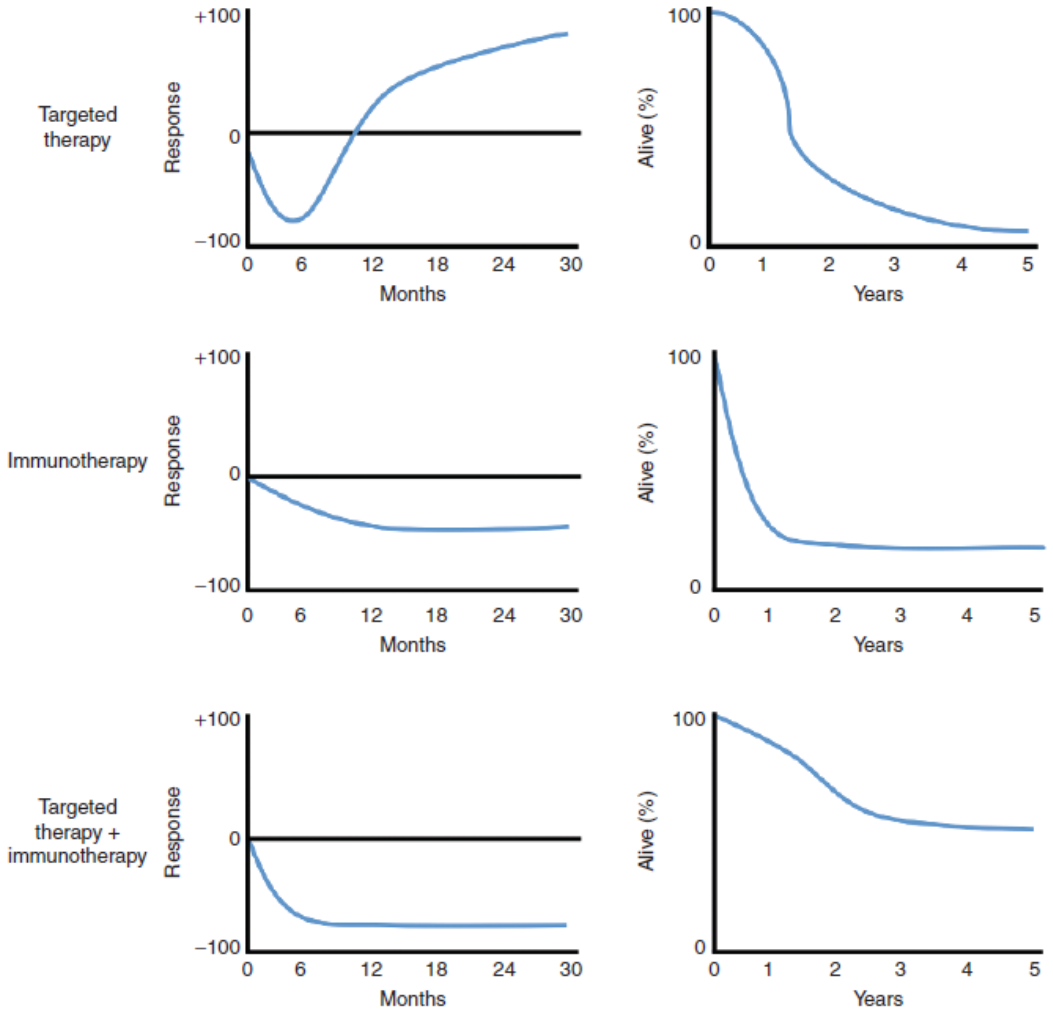
Humphries, Nature, 2013

Cytokines that act on T-cells



Lee et al, Cancers, 2011

Future is combination immunotherapy



Wargo et al, Ca Discovery, 2014