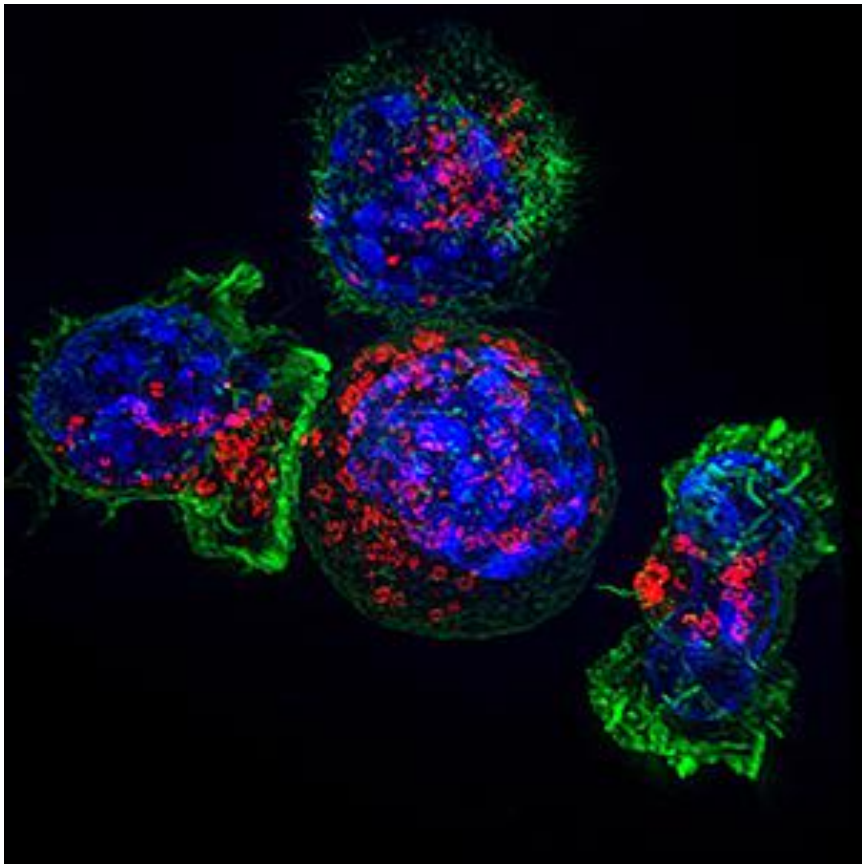
Advances in Cancer Immunotherapy

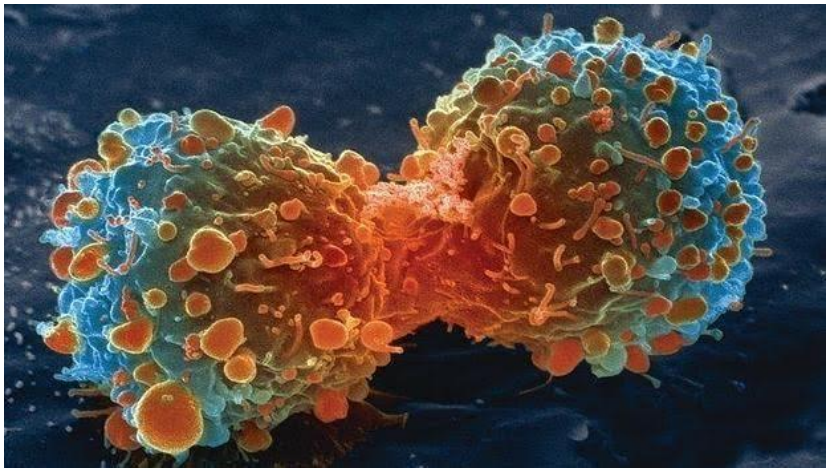


Tomer M. Faraggi

MacMillan Group Meeting

May 1st, 2018

The Impact of Cancer on Society



class of diseases arising from abnormal, rapid and uncontrolled growth of cells

malignant tumors are defined as those which can expand and invade other parts of the body

- Second leading casuse of death globally (1 in 6 of total deaths)
- 14 million newly reported cases annually, along with 8 million deaths
- Total global economic cost of approx 1.6 trillion USD annually

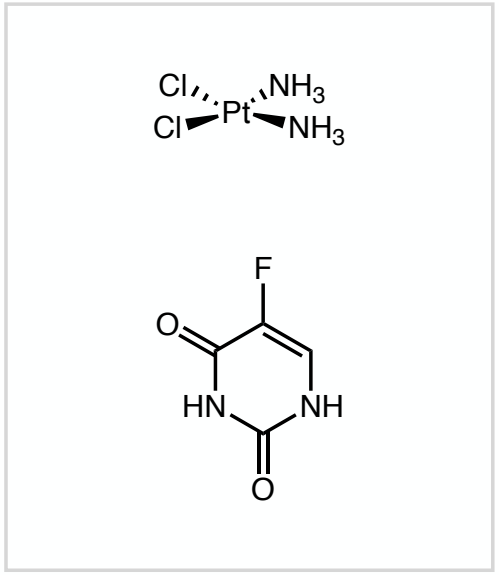
the challenge in developing new treatments is in how to differentiate cancer cells from healthy ones

http://www.who.int/en/news-room/fact-sheets/detail/cancer
Sudhakar, A., *J. Cancer Sci. Ther.* **2009**, *1*, 1.

Traditional Cancer Therapy

surgery

radiotherapy



chemotherapy

focus on factors such as anatomical location or unique features of tumor cells for targeting

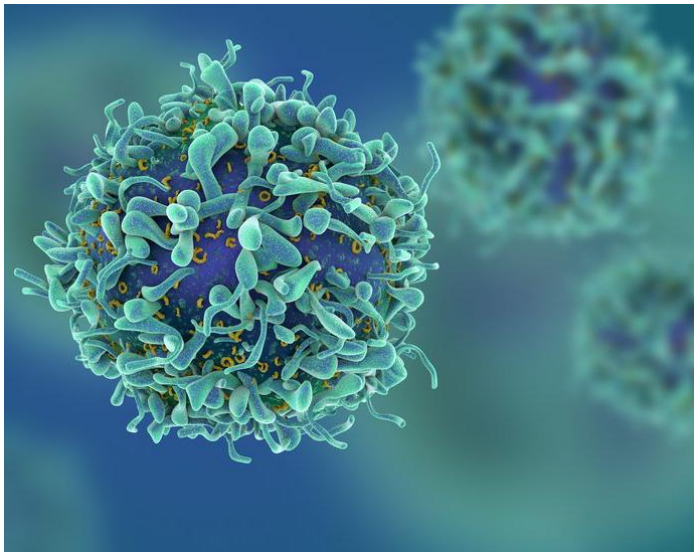
many cancers remain difficult to treat, particularly in advanced stages following significant metastesis

negative side effects and toxicity to healthy cells remain a challenge in development of new theraputics

http://www.who.int/en/news-room/fact-sheets/detail/cancer

Sudhakar, A., *J. Cancer Sci. Ther.* **2009**, *1*, 1.

Introduction to Immunotherapy

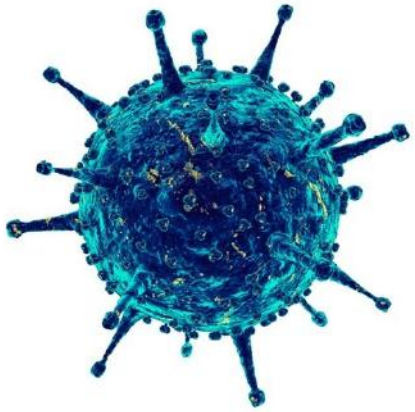


- Immunotherapy harnesses the ability of the immune system to identify and destroy tumors, as opposed to targeting them directly

- Potential advantages of this strategy include a high degree of selectivity for tumor cells and decreased toxicity to the patient

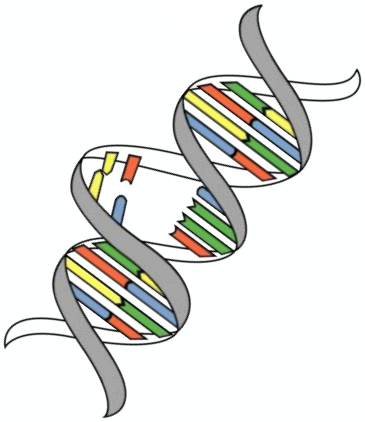
- However, tumors can develop a range of means to suppress the immune response, often exploiting the body's own regulation system

tumor cells present distinct antigens to healthy cells due to a range of genetic and epigenetic changes



oncogenic virus

eg HPV, HBV



mutated DNA

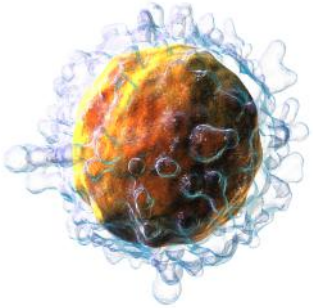
eg through UV exposure

Decker, W. K. *et al. Front. Immunol.*, **2017**, *8*, 829.
Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine,* **2016**, *14*, 73.

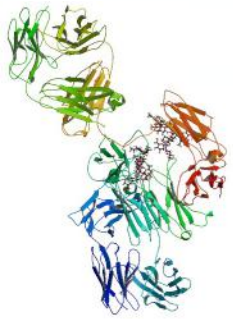
Introduction to Immunotherapy

William Coley

1893- utilized live bacteria to stimulate immune response



1967- T- cells first identified and characterized



2011- ipilimumab FDA approved

1998/2001- Evidence for T-cell mediated tumor immune surveillance

2017- FDA approves tisagenlecleucel

1987- CTLA-4 discovered

1890 — 1910 — 1970 — 1990 — 2010

1909- Paul Ehrlich proposes surveillance of cancer by immue system

1973- Discovery of dendridic cells

1995- Elucidation of CTLA-4's role as an immune checkpoint

2011- sipuleucel-T FDA approved

Decker, W. K. *et al. Front. Immunol.*, **2017**, *8*, 829.

Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine,* **2016**, *14*, 73.

A (Very) Brief Overview of the Immune System

The Immune System

innate immune system

- Component of the immune system that responds generically to all pathogens
- Does not confer immunological memory and generally provides immediate response

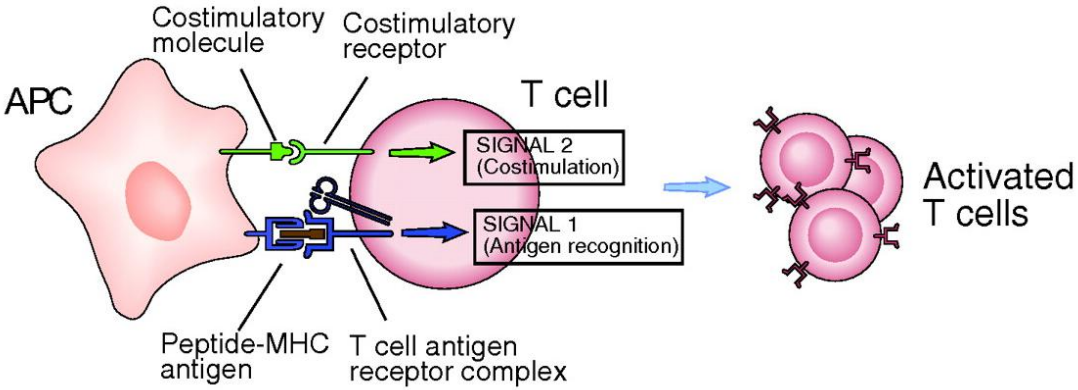
APCs

adaptive immune system

- Component of the immune system mediated by antigen-specific lymphocytes and antibodies
- Components include B and T cells, includes the development of immunological memory

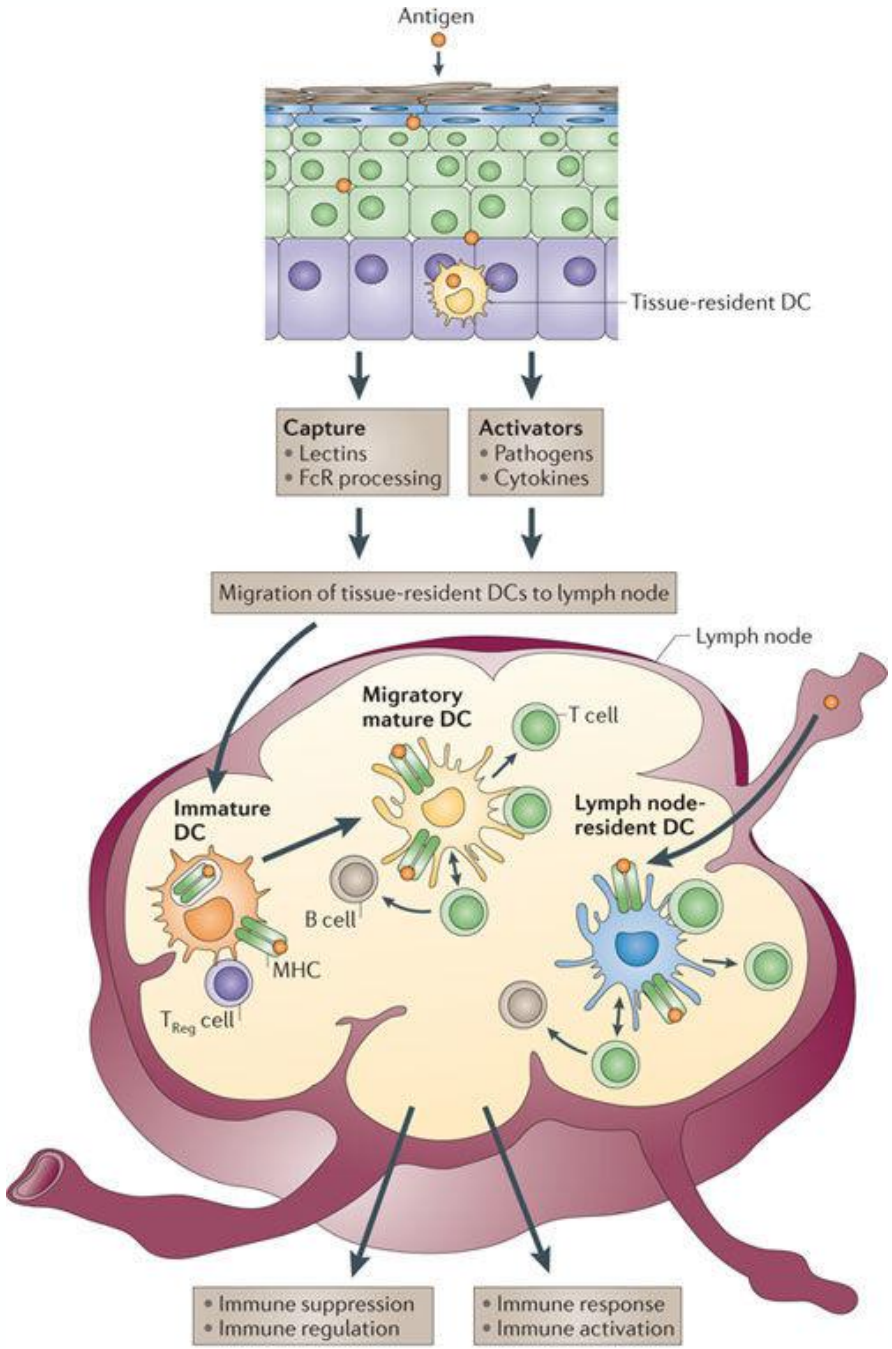
- Antigen-presenting cells (APCs) display foreign antigens in the form of complexes with MHCs to T-cells
- MHC= Major Histocompatibility Complex, a distinct protien which displays an antigen on a cell surface for recognition
- An important subcategory is dendridic cells (DCs), which are located throughout tissues and in lymph nodes
- Binding to foreign antigens causes DCs to mature and express costimulatory ligands on their surface

T-cell activation requires both antigen and co-stimulant



Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine,* **2016**, *14*, 73.

A (Very) Brief Overview of the Immune System



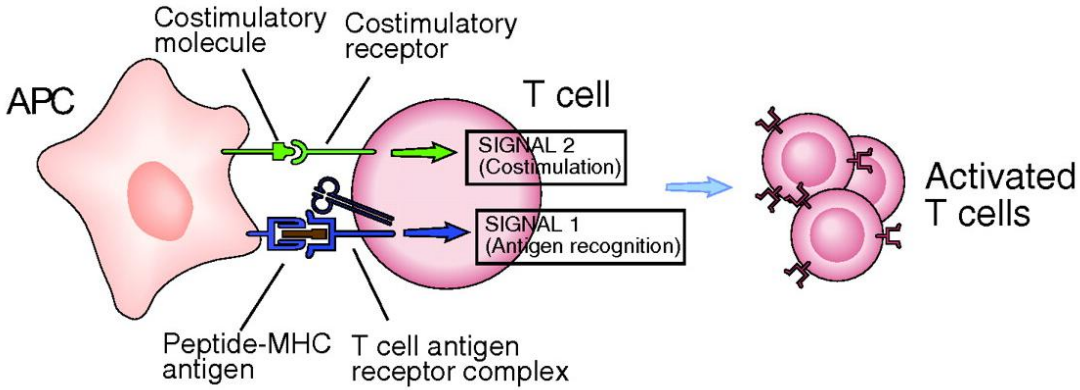
- Antigen-presenting cells (APCs) display foreign antigens in the form of complexes with MHCs to T-cells

- MHC= Major Histocompatibility Complex, a distinct protien which displays an antigen on a cell surface for recognition

- An important subcategory is dendridic cells (DCs), which are located throughout tissues and in lymph nodes

- Binding to foreign antigens causes DCs to mature and express co-stimulatory ligands on their surface

T-cell activation requires both antigen and co-stimulant



Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine,* **2016**, *14*, 73.

A (Very) Brief Overview of the Immune System

CD4+ (helper) T cells

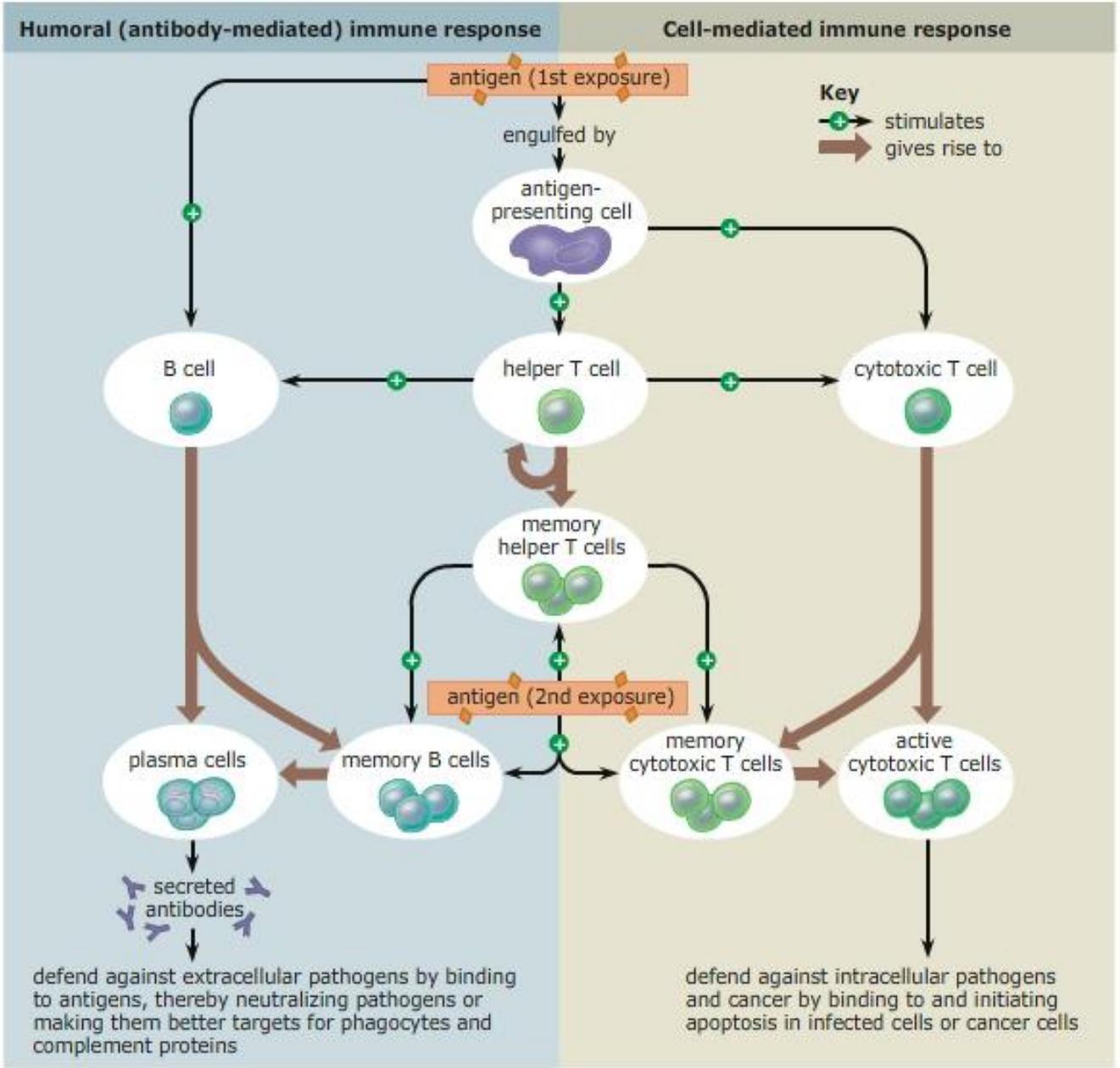
- Responsible for the activation and inhibition of other immune cells

CD8+ (killer) T cells

- Responsible for destroying virally infected and tumor cells

Regulatory T cells (T_{Reg})

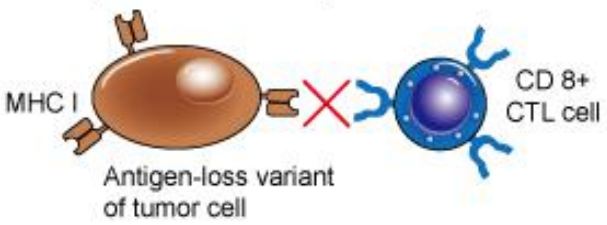
- Suppress the action of other activated cytotoxic T-cells



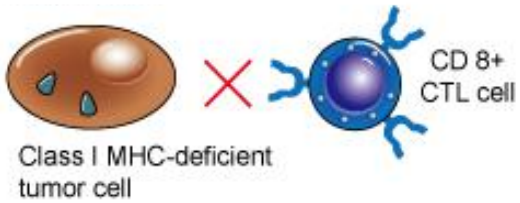
Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine,* **2016**, *14*, 73.

How Tumor Cells Evade the Immune Response

the immune response imposes a selection pressure on tumors, allowing resistant variants to proliferate

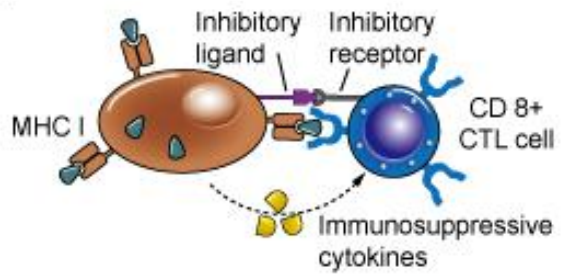


antigen deficient



MHC deficient

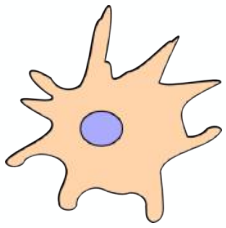
evades T-cell detection



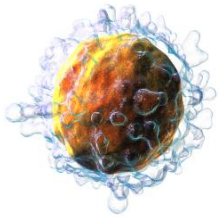
Suppression of immune response

Produces cytokines which promote formation of T_{reg} cells around tumor

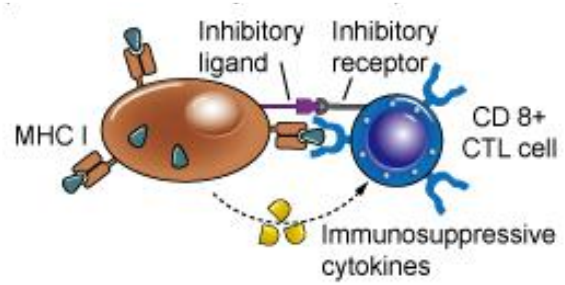
how can we stimulate an immune response to overcome these defence mechanisms?



mature DC



active T-cells



Suppression of immune response

Decker, W. K. *et al. Front. Immunol.*, **2017**, *8*, 829.

Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine* **2016**, *14*, 73.

Immunotherapy Strategies

theraputic cancer vaccines

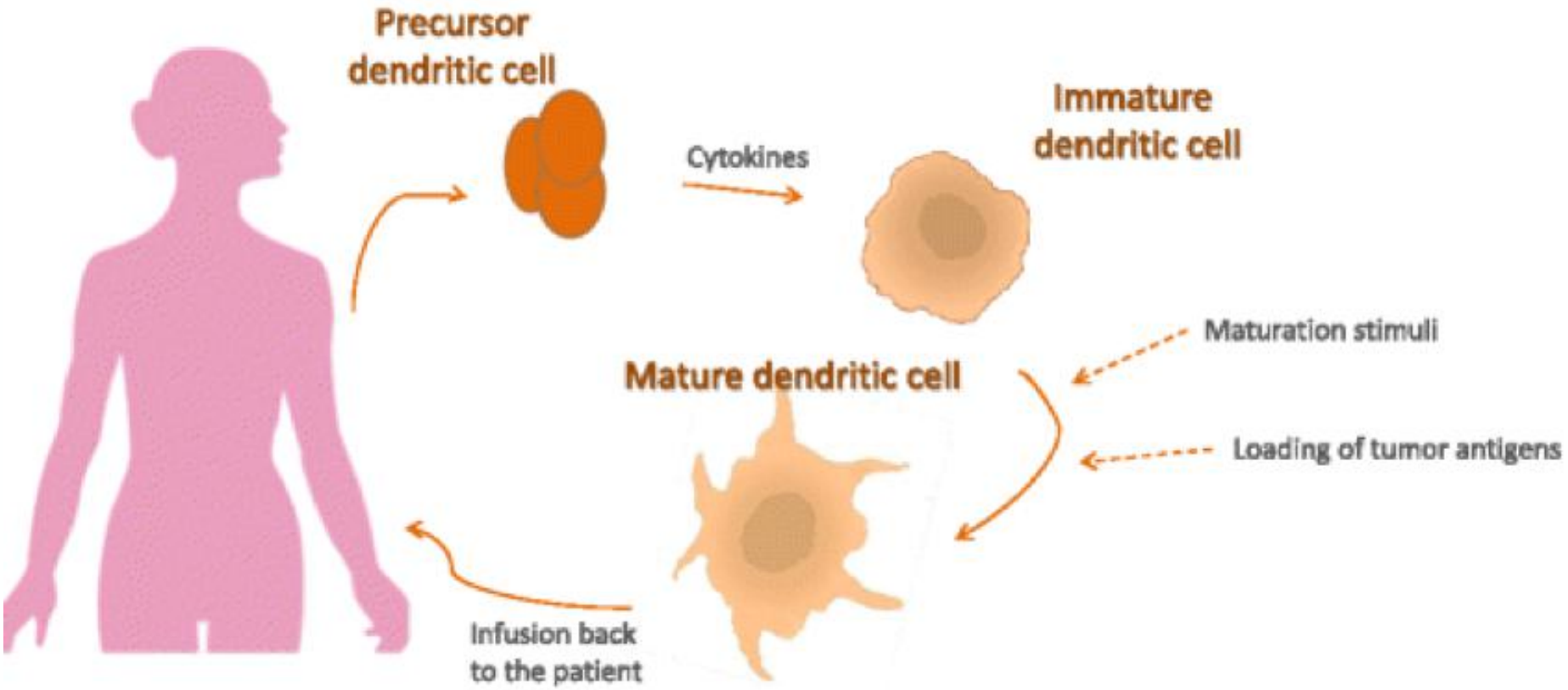
immune checkpoint blockade therapy

adoptive cell transfer therapy

Cancer Vaccines via Antigen Stimulated Dendridic Cells

cancer vaccines attempt to stimulate T cell activation pathways by APCs

early attempts to use peptides based on tumor antigens were largely unsuccessful

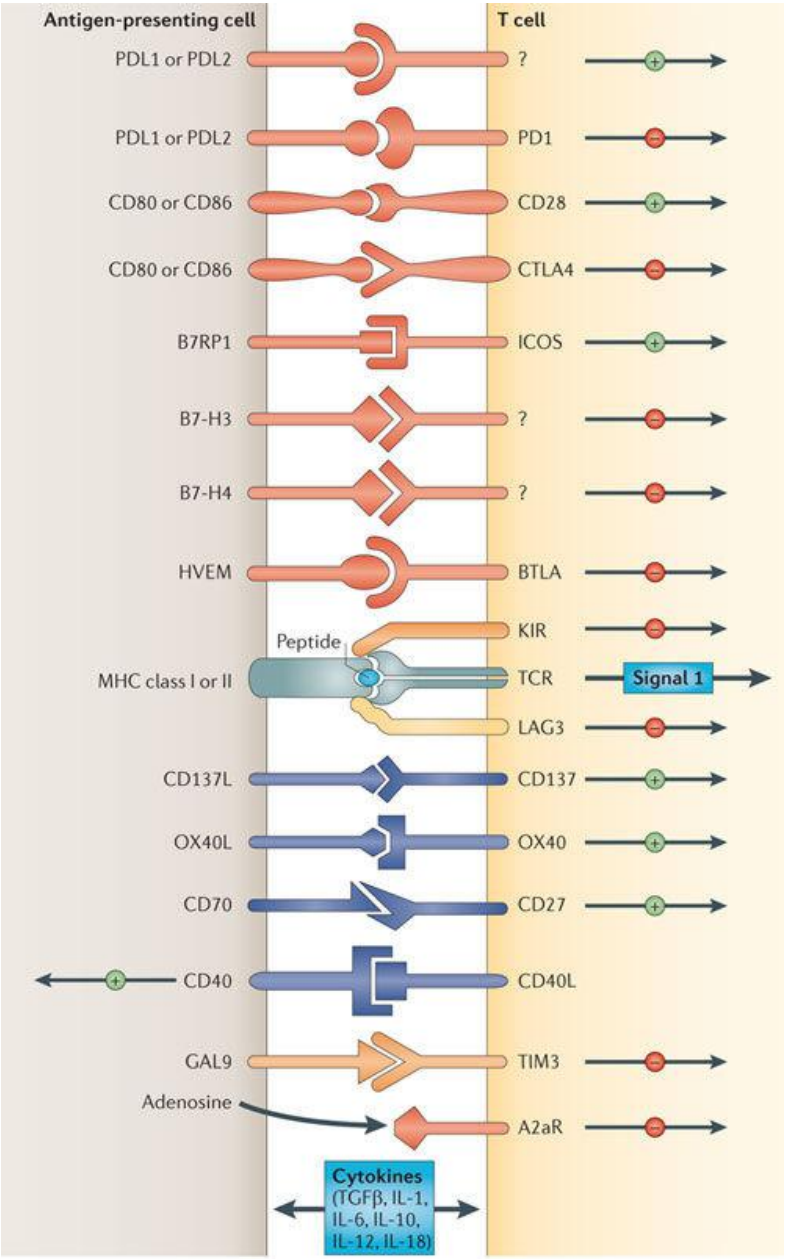


- Only one approved drug to date (Spileucel T) for castration resistant protate cancer patients
- Shows 4 month improvement in median surviaval, but no meaningful decrease in tumor volume

Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine,* **2016**, *14*, 73.

Immune Stimulation via Checkpoint Blockade

the amplitude of T-cell response is mediated by a balance of stimulatory and inhibitory signals



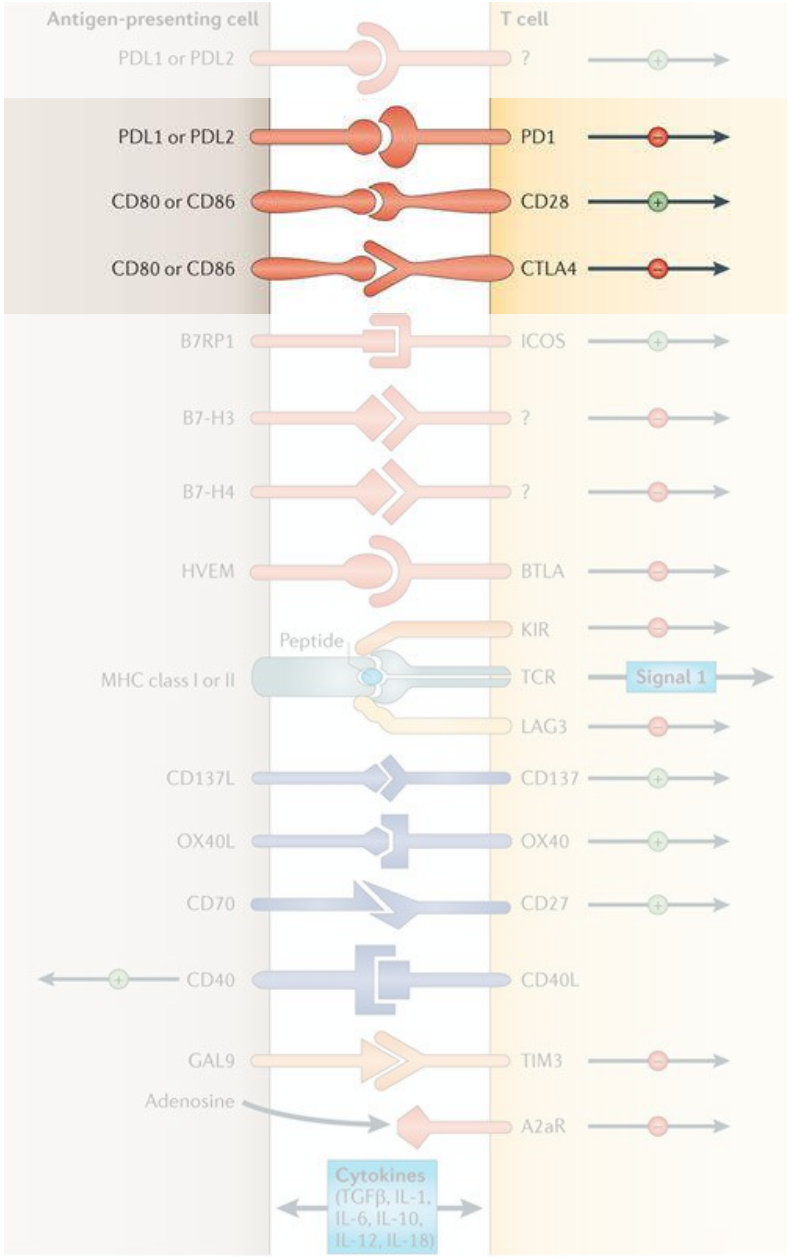
- Inhibitory ligands and receptors which regulate T-cell functions in tissues are often overexpressed by tumors, leading to immune supression in the tumor environment

Pardoll, D. M. *Nature Reviews Cancer*, **2012**, *8*, 252.

Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine,* **2016**, *14*, 73.

Immune Stimulation via Checkpoint Blockade

the amplitude of T-cell response is mediated by a balance of stimulatory and inhibitory signals



- Inhibitory ligands and receptors which regulate T-cell functions in tissues are often overexpressed by tumors, leading to immune supression in the tumor environment

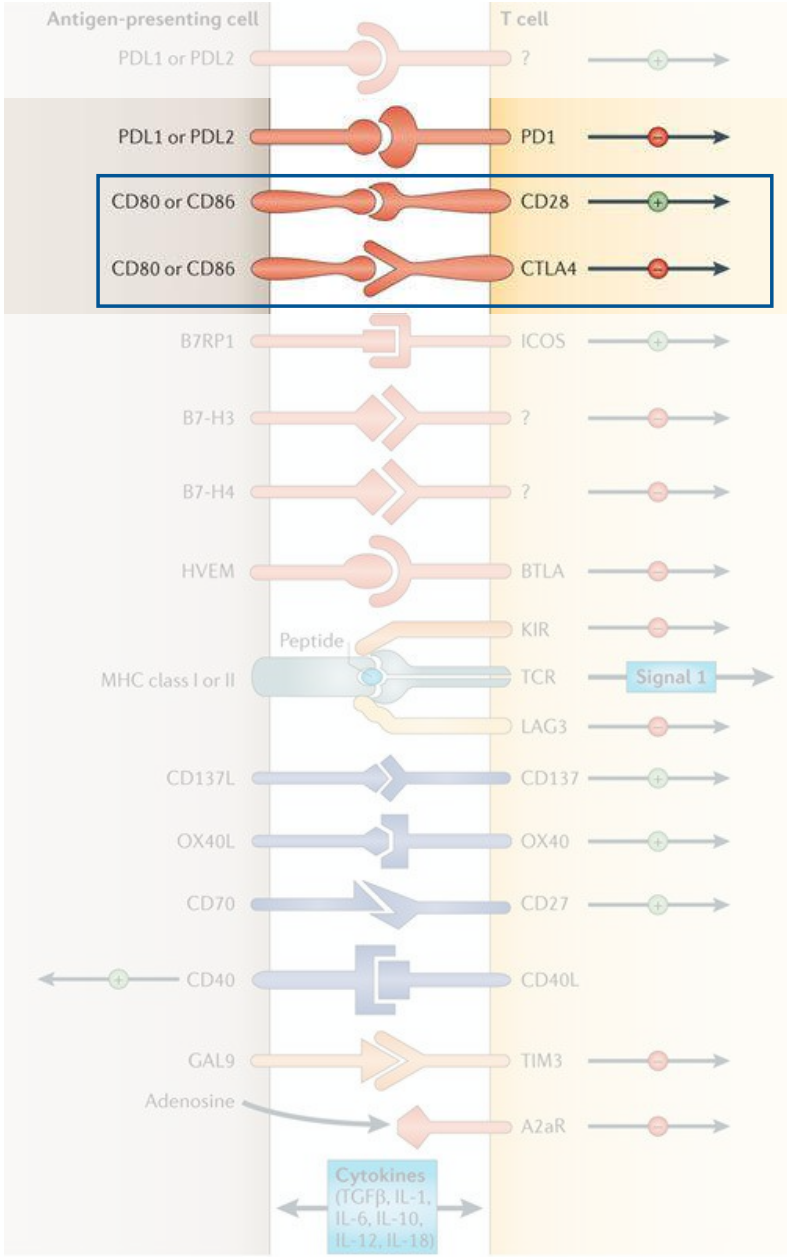
- **CTLA-4** is an inhibitory receptor which is expressed exclusively on T- cells and is responsible for down-regulating the initial stages of naive T-cell activation

- **PD-1** is a receptor expressed on activated T-cells, limiting T-cell functions in peripheral tissues and is often overexpressed by cancerous cells

Pardoll, D. M. *Nature Reviews Cancer*, **2012**, *8*, 252.
Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine,* **2016**, *14*, 73.

Immune Stimulation via Checkpoint Blockade

the amplitude of T-cell response is mediated by a balance of stimulatory and inhibitory signals



- Inhibitory ligands and receptors which regulate T-cell functions in tissues are often overexpressed by tumors, leading to immune supression in the tumor environment

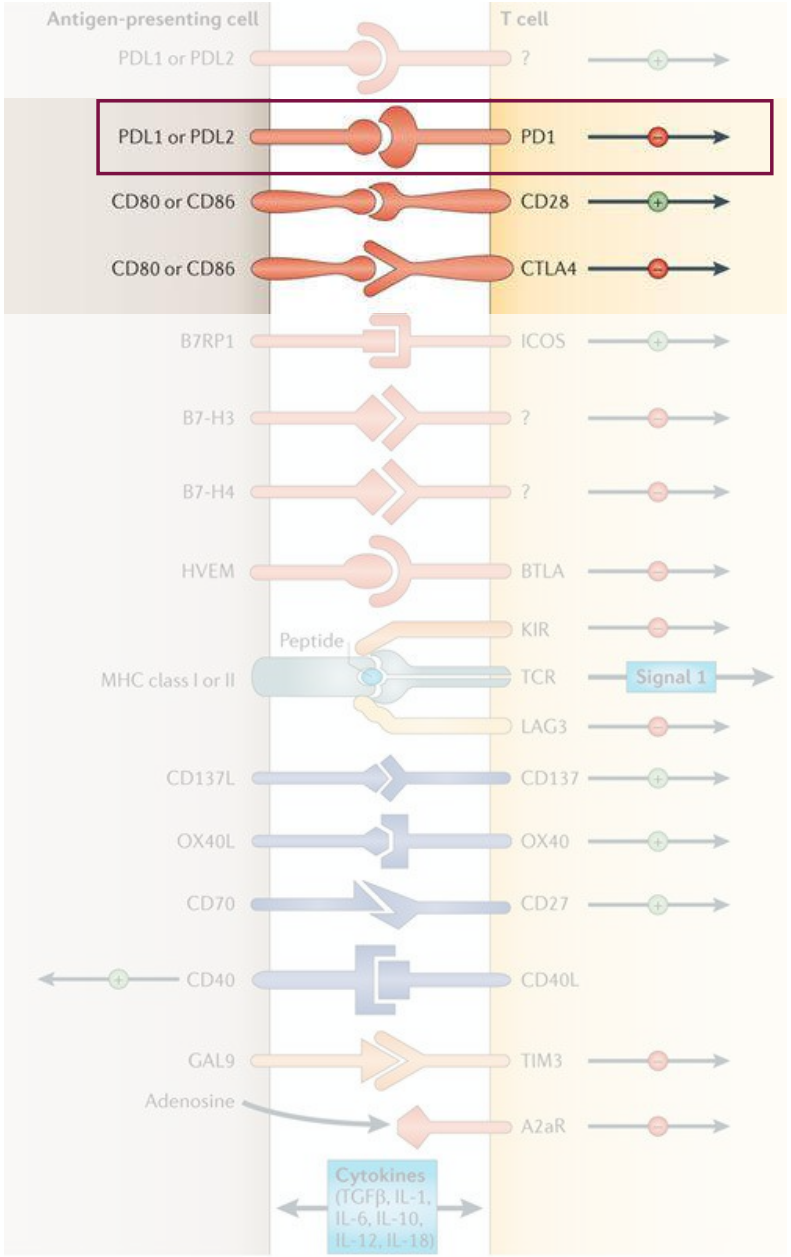
- **CTLA-4** is an inhibitory receptor which is expressed exclusively on T- cells and is responsible for down-regulating the initial stages of naive T-cell activation

Pardoll, D. M. *Nature Reviews Cancer*, **2012**, *8*, 252.

Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine,* **2016**, *14*, 73.

Immune Stimulation via Checkpoint Blockade

the amplitude of T-cell response is mediated by a balance of stimulatory and inhibitory signals



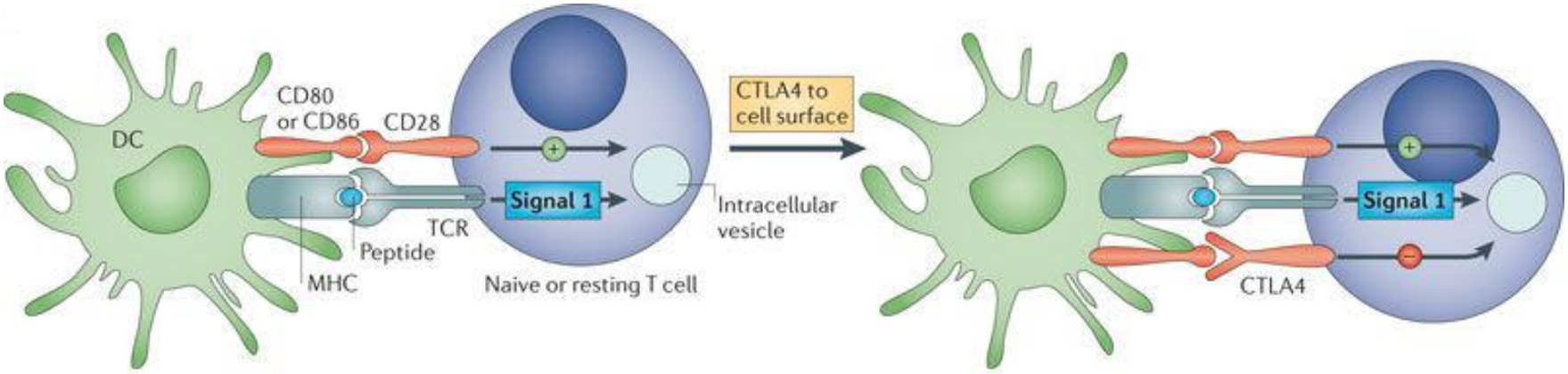
- Inhibitory ligands and receptors which regulate T-cell functions in tissues are often overexpressed by tumors, leading to immune supression in the tumor environment

- **CTLA-4** is an inhibitory receptor which is expressed exclusively on T- cells and is responsible for down-regulating the initial stages of naive T-cell activation

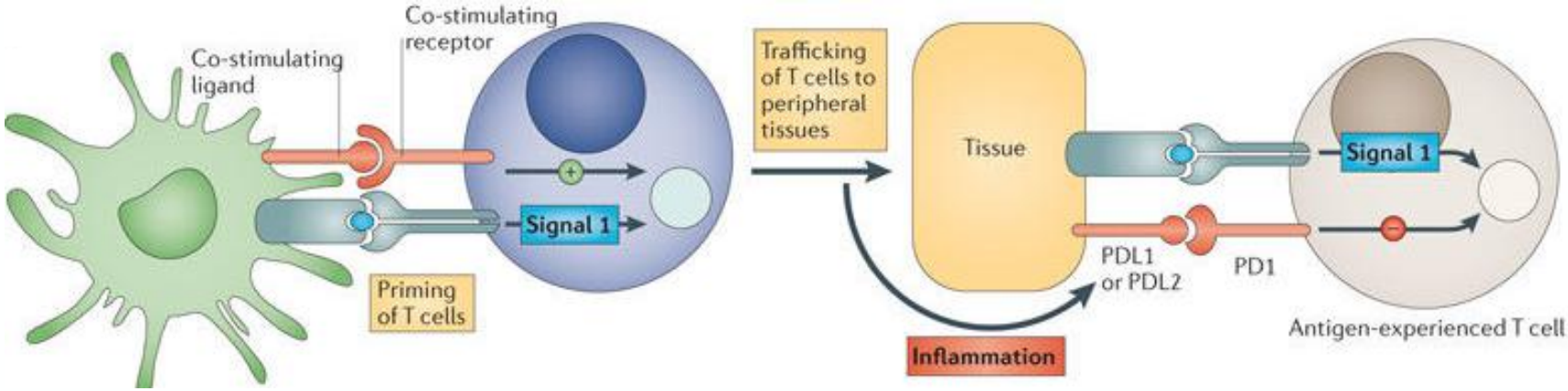
- **PD-1** is a receptor expressed on activated T-cells, limiting T-cell functions in peripheral tissues and is often overexpressed by cancerous cells

Pardoll, D. M. *Nature Reviews Cancer*, **2012**, *8*, 252.
Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine,* **2016**, *14*, 73.

CTLA-4 and PD-1 as Immune Checkpoints



- CTLA-4 has a considerably greater affinity for APC ligand, but is initially not present on cell surface
- Binding to CD28 receptor induces transport of CTLA-4 to the surface where it dampens the activation
- Concentration of CTLA-4 on cell surface is proportional to strength of original stimulation

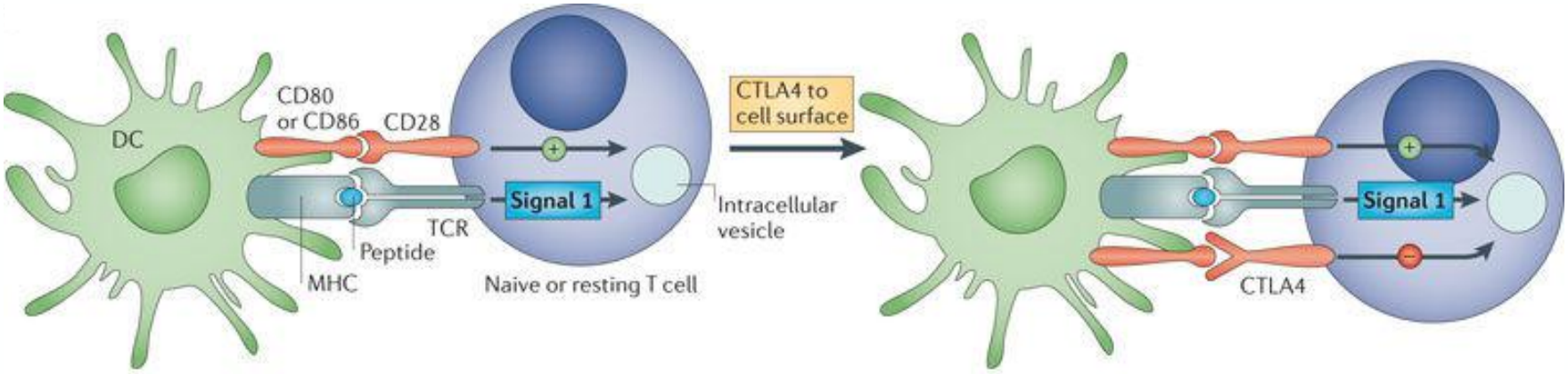


- Activated T-cells upregulate PD-1, which is activated by inflammatory signals in tissues
- This downregulates the effect of T-cells, preventing collateral damage to healthy tissues

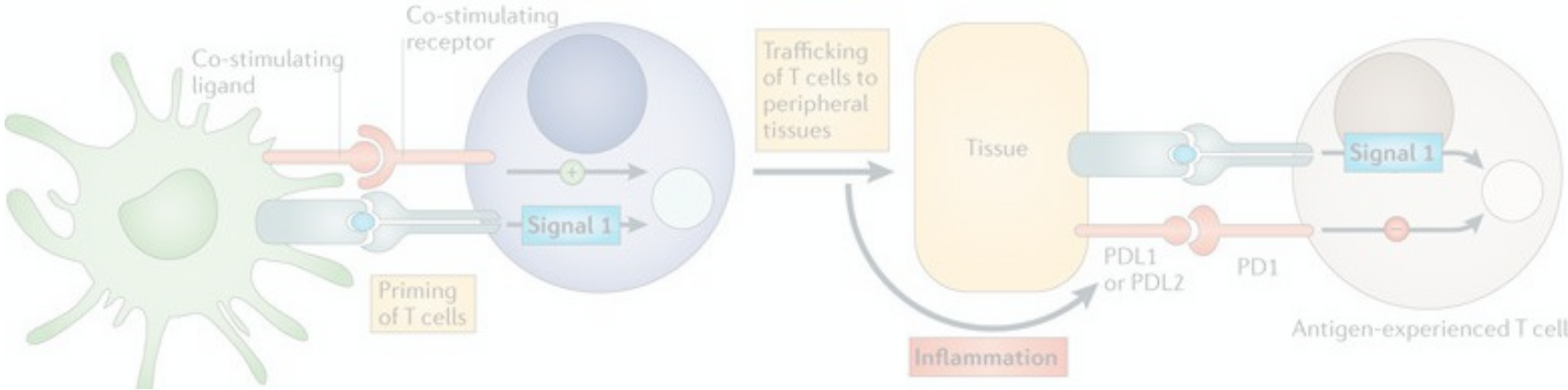
Pardoll, D. M. *Nature Reviews Cancer*, **2012**, *8*, 252.

Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine,* **2016**, *14*, 73.

CTLA-4 and PD-1 as Immune Checkpoints



- CTLA-4 has a considerably greater affinity for APC ligand, but is initially not present on cell surface
- Binding to CD28 receptor induces transport of CTLA-4 to the surface where it dampens the activation
- Concentration of CTLA-4 on cell surface is proportional to strength of original stimulation



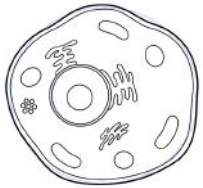
- Activated T-cells upregulate PD-1, which is activated by inflammatory signals in tissues
- This downregulates the effect of T-cells, preventing collateral damage to healthy tissues

Pardoll, D. M. *Nature Reviews Cancer*, **2012**, *8*, 252.

Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine,* **2016**, *14*, 73.

The Importance of CTLA-4

knockout of genes coding for CTLA-4 demonstrate its importance in immune regulation

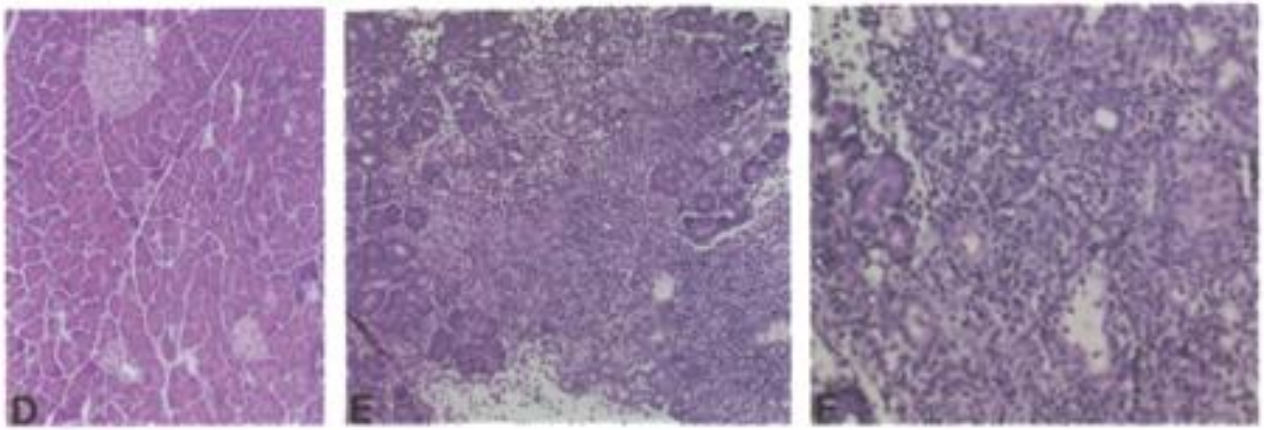


stem cells deficient in ***CTLA-4*** gene

CTLA-4 deficient mice

mice die within 3-4 weeks

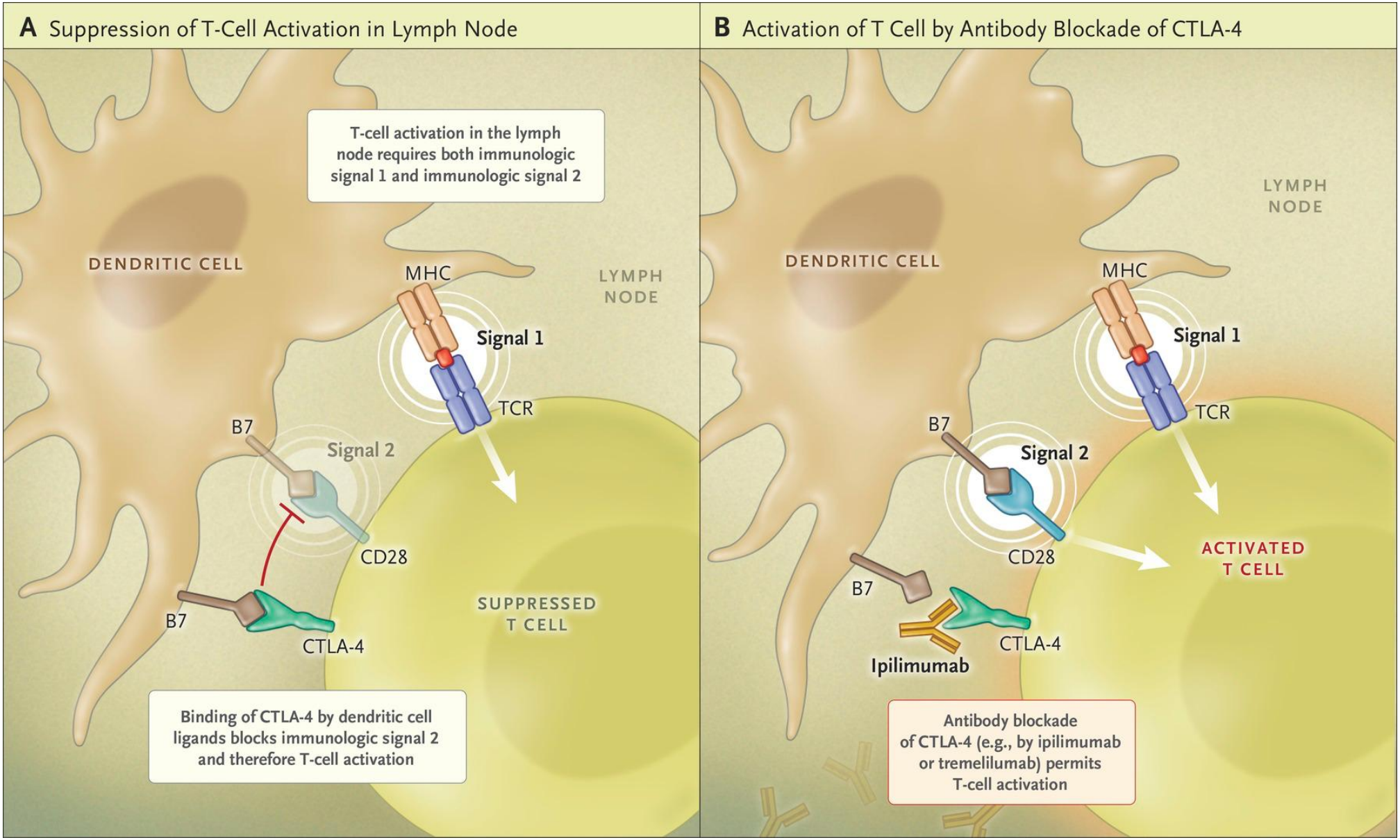
Geno-type	Wet weight (mg)		Lymphocytes (10^7)	
	Lymph nodes	Spleen	Lymph nodes	Spleen
Ctla-4$^{+/+}$	71	69	1.3	3.1
Ctla-4$^{+/-}$	97	77	1.7	3.1
Ctla-4$^{-/-}$	540	145	28.0	7.7
Ctla-4$^{-/-}$	380	501	12.0	16.5



Pancreatic tissue samples in unmodified (D) and modified (E / F) mice

Tivol, E. A. *et al. Immunity*, **1995**, *3*, 541.
Waterhouse, P. *Science,* **1995**, *270*, 985.

CTLA-4 Blockade as a Theraputic Strategy

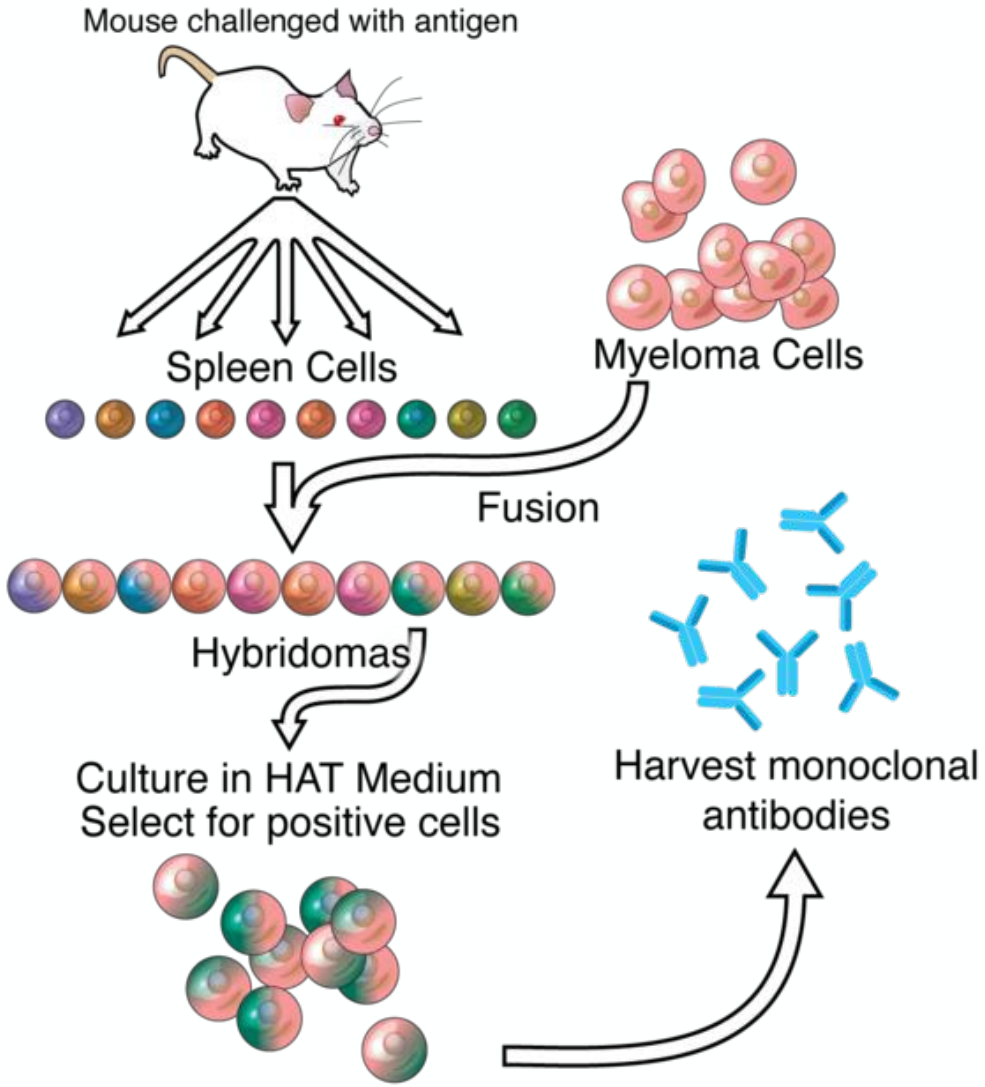


Ribas, A. *N. Engl. J. Med.,* **2015**, *373*, 1490.

Monoclonal Antibodies to Target Specific Sites

monoclonal antibodies are made by immune cells that are clones of an original parent cell

specific antibodies can be made for almost any substance, bind to substrate with a high level of specificity




Niels K. Jerne


Georges J.F. Köhler


César Milstein

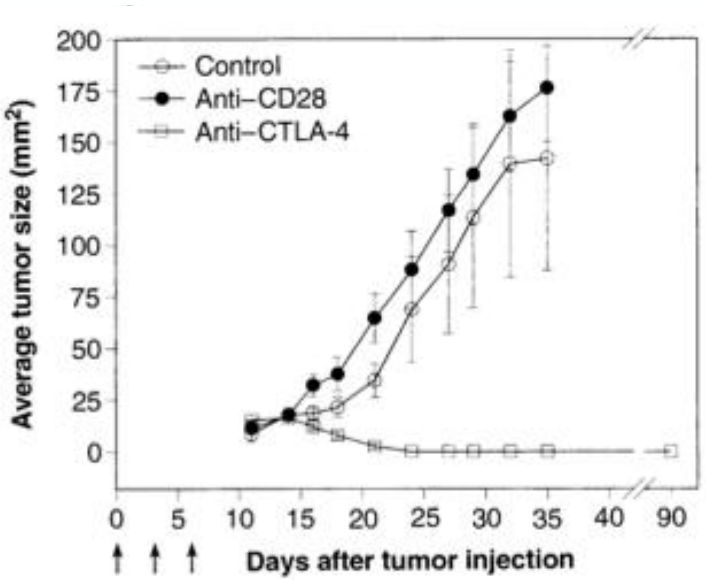
1984 Nobel Prize

"for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies"

Weiner, G. J. *Nat. Rev. Cancer,* **2015**, *15*, 361.

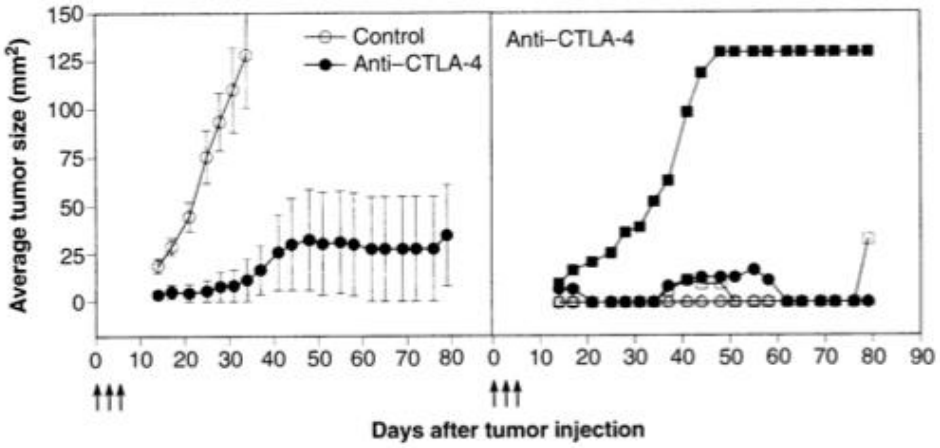
First in-vivo demonstration of anti-CTLA-4 antibody

mice injected with tumor cells (colon carcinoma) subsequently treated with an anti-CTLA-4 antibody



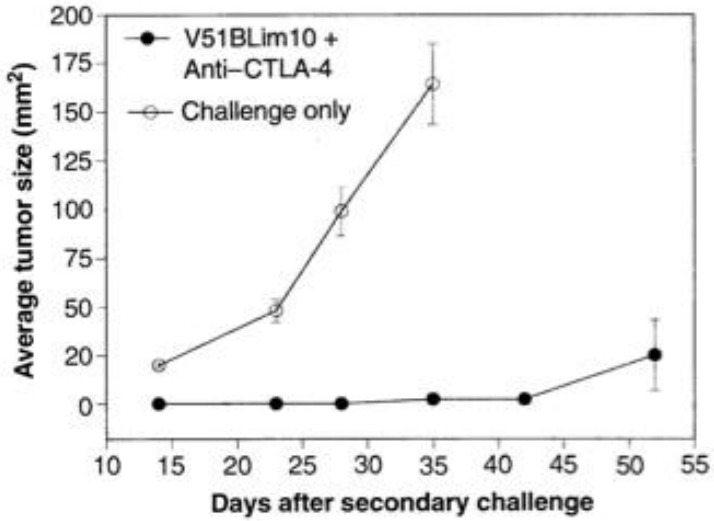
mice either injected with CDLA-4 or CD28 antibody or left untreated (control)

first in-vivo demonstration of the ability of CTLA-4 monoclonal antibodies to induce a theraputic antitumor immunity



control here is "irrelevant hamster antibody"

graph on right shows tumor growth in each mouse



recovered mice reinjected with new tumor after 70 days

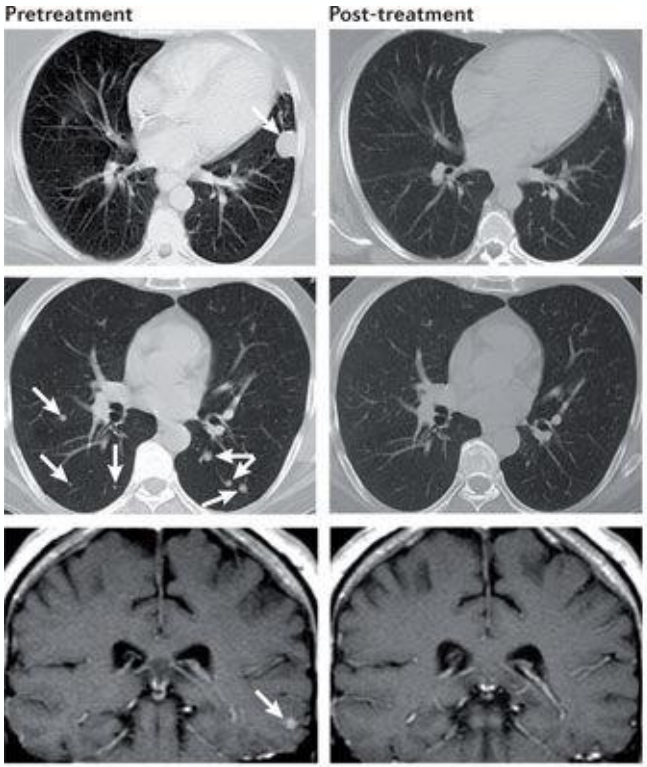
Leach, D. R.; Krummel, M. F.; Allison, J. P. *Science,* **1996**, *271*, 1734.

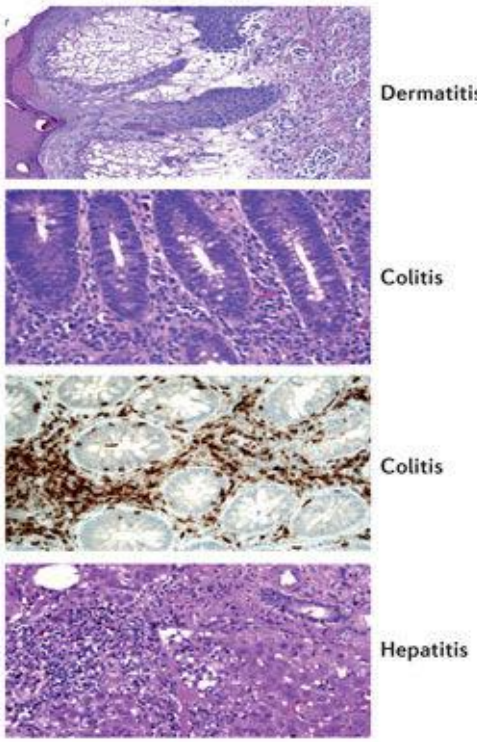
Clinical trial results for Ipilimumab

Clinical trials performed for anti-CTLA-4 monoclonal antibodies vs metastatic melanoma

Initial trials with Ipilimumab

- Objective clinical response in approx 10% of patients
- 25-30% of patients display immune related toxicities





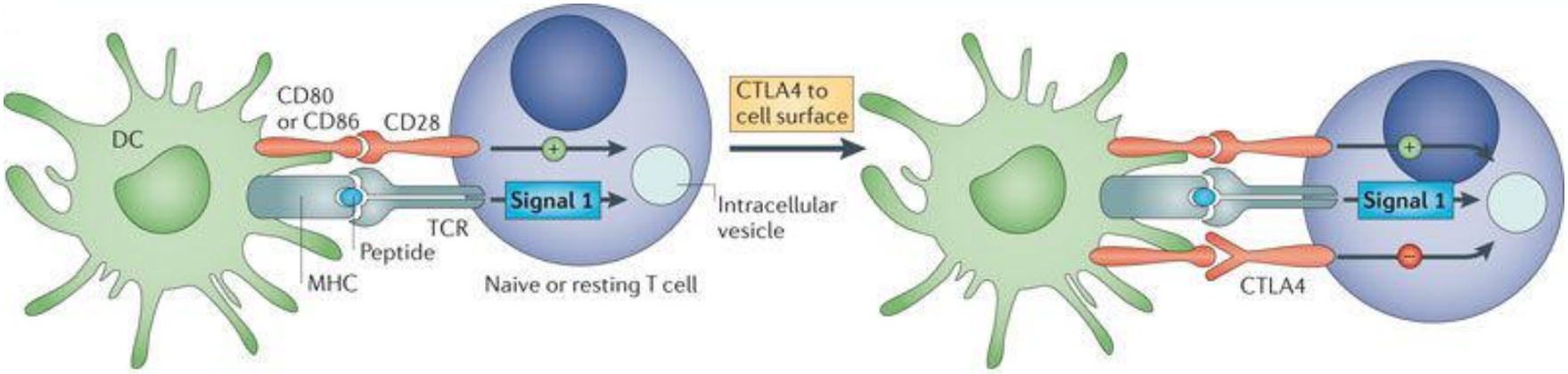
Phase III trials

- Tested using gp100 peptide vaccine specific to melanoma as a control
- Ipilimumab demonstrated a mean survival benefit of 3.5 months compared to control
- 18% of patients survived beyond two years compared to 5% in control group

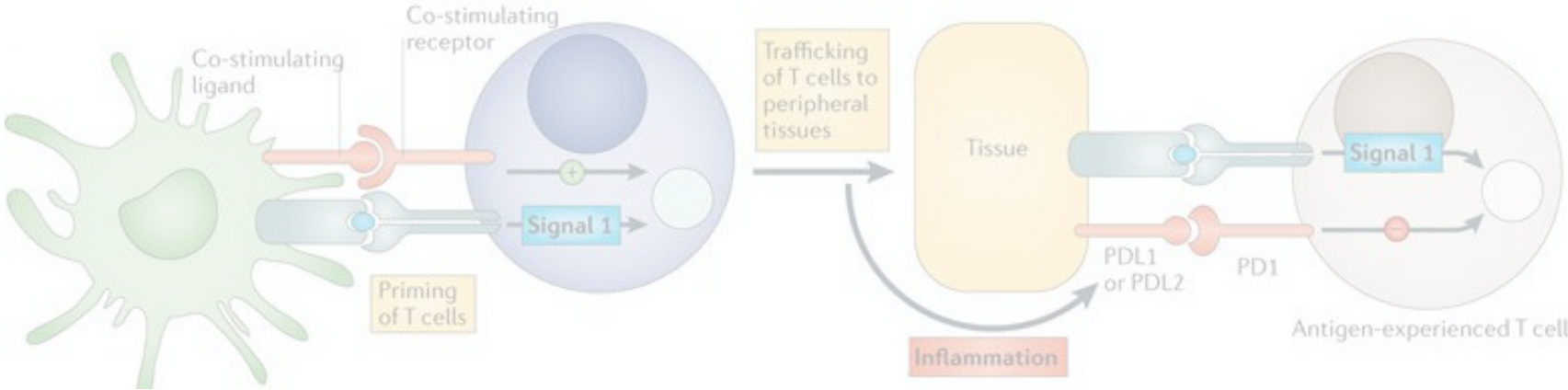
First therapy to demonstrate a survival benefit for metastatic melanoma

Phan, G. Q. *et al. PNAS*, **2003**, *100*, 8372.
Hodi, F. S. *et al. N. Engl. J. Med.*, **2010**, *363*, 8.

CTLA-4 and PD-1 as Immune Checkpoints



- CTLA-4 has a considerably greater affinity for APC ligand, but is initially not present on cell surface
- Binding to CD28 receptor induces transport of CTLA-4 to the surface where it dampens the activation
- Concentration of CTLA-4 on cell surface is proportional to strength of original stimulation

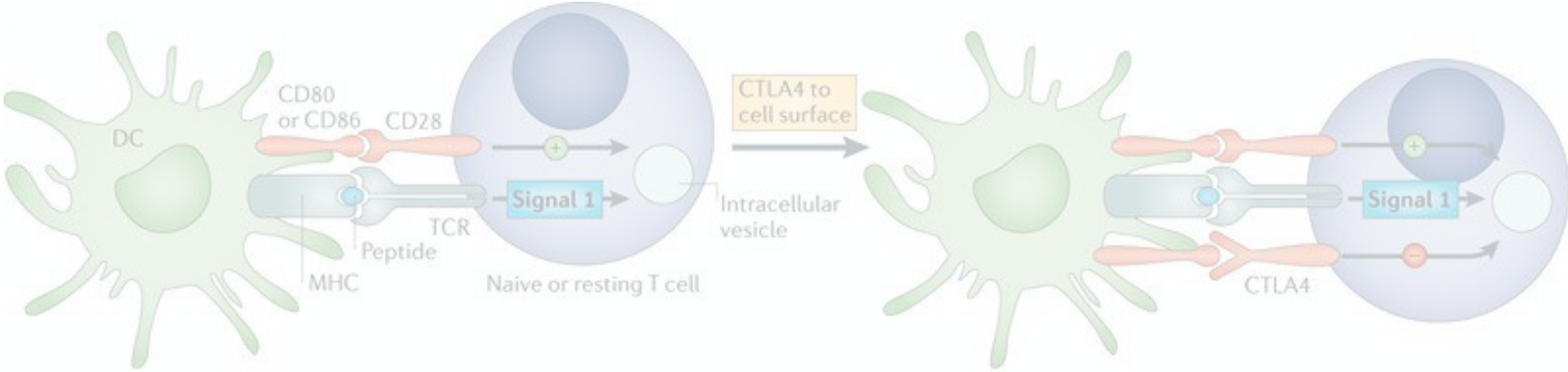


- Activated T-cells upregulate PD-1, which is activated by inflammatory signals in tissues
- This downregulates the effect of T-cells, preventing collateral damage to healthy tissues

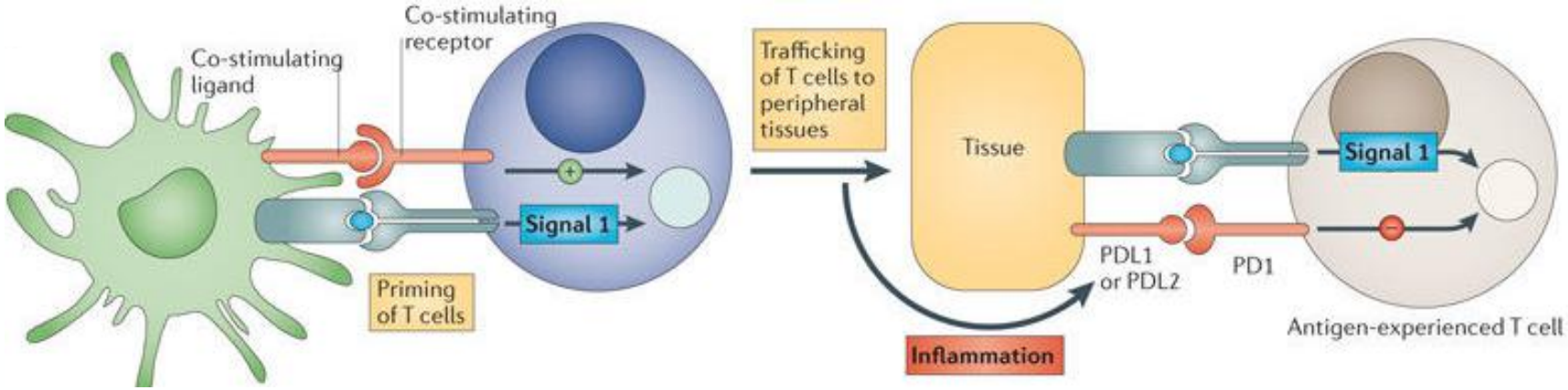
Pardoll, D. M. *Nature Reviews Cancer*, **2012**, *8*, 252.

Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine,* **2016**, *14*, 73.

CTLA-4 and PD-1 as Immune Checkpoints



- CTLA-4 has a considerably greater affinity for APC ligand, but is initially not present on cell surface
- Binding to CD28 receptor induces transport of CTLA-4 to the surface where it dampens the activation
- Concentration of CTLA-4 on cell surface is proportional to strength of original stimulation



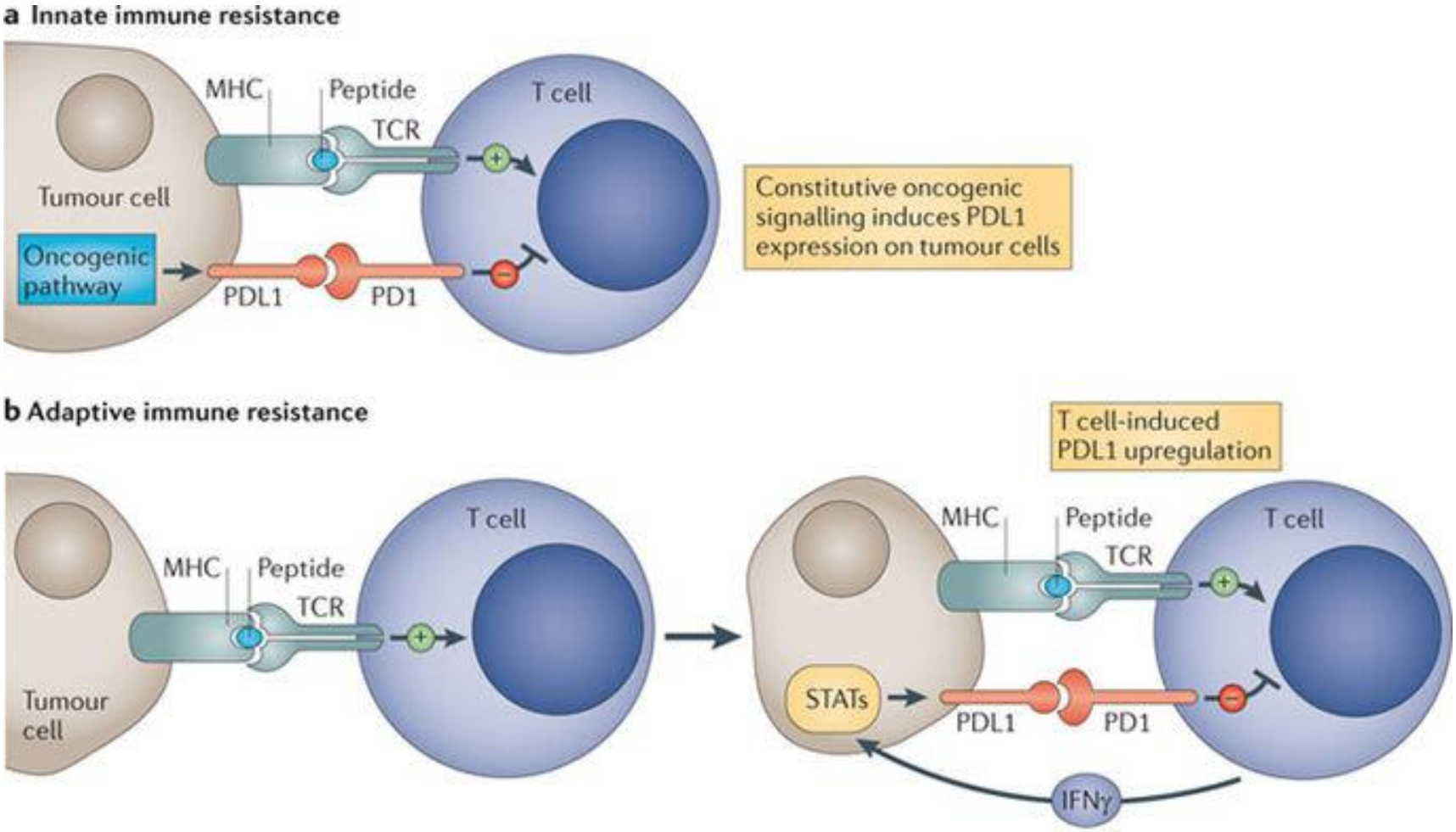
- Activated T-cells upregulate PD-1, which is activated by inflammatory signals in tissues
- This downregulates the effect of T-cells, preventing collateral damage to healthy tissues

Pardoll, D. M. *Nature Reviews Cancer*, **2012**, *8*, 252.

Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine,* **2016**, *14*, 73.

The Role of PD-1 in Immune Resistance

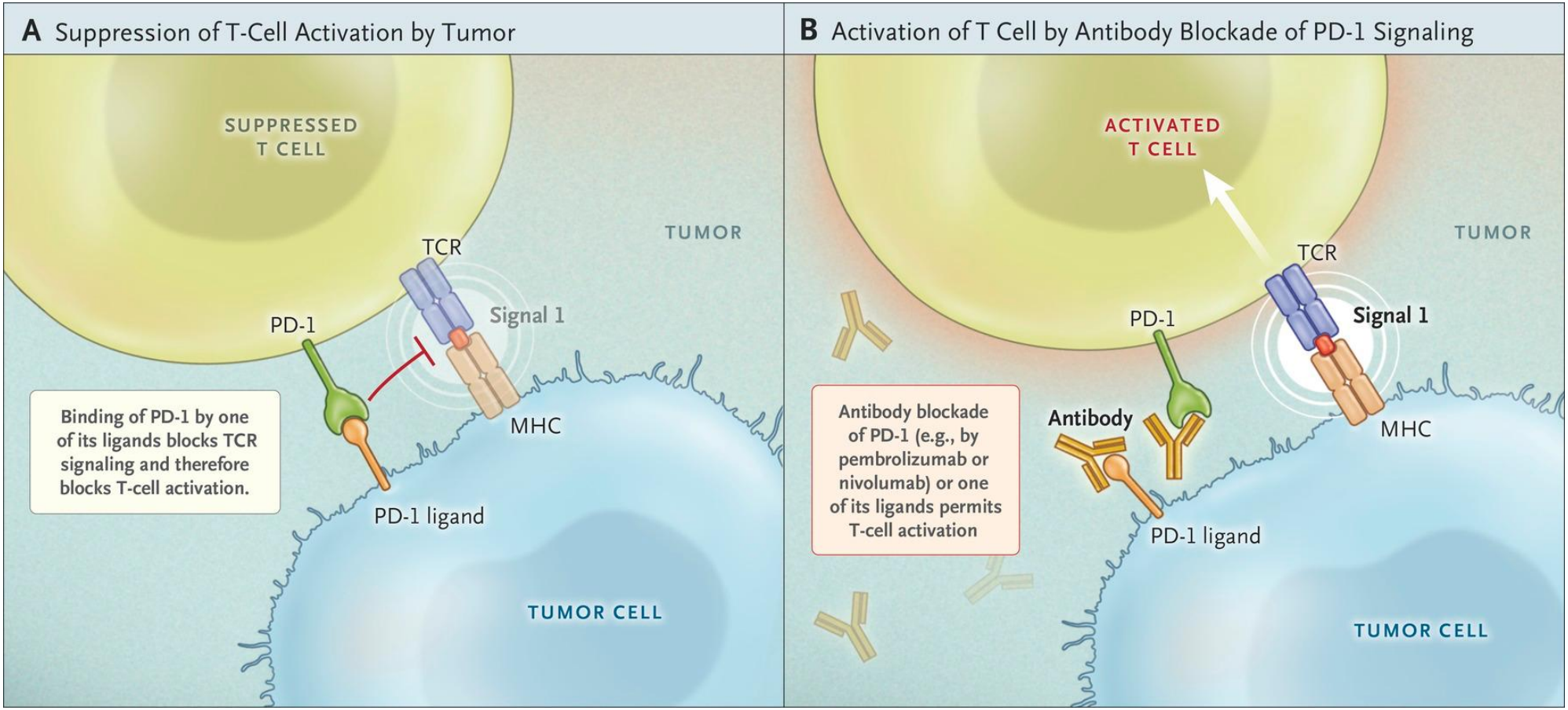
expression of PD-1 ligands is a known means by which tumors block T-cell response



PDL-1 enhanced tumors are found to be considerably less susceptible to T-cell attack

Pardoll, D. M. *Nature Reviews Cancer*, **2012**, *8*, 252.

CTLA-4 Blockade as a Theraputic Strategy



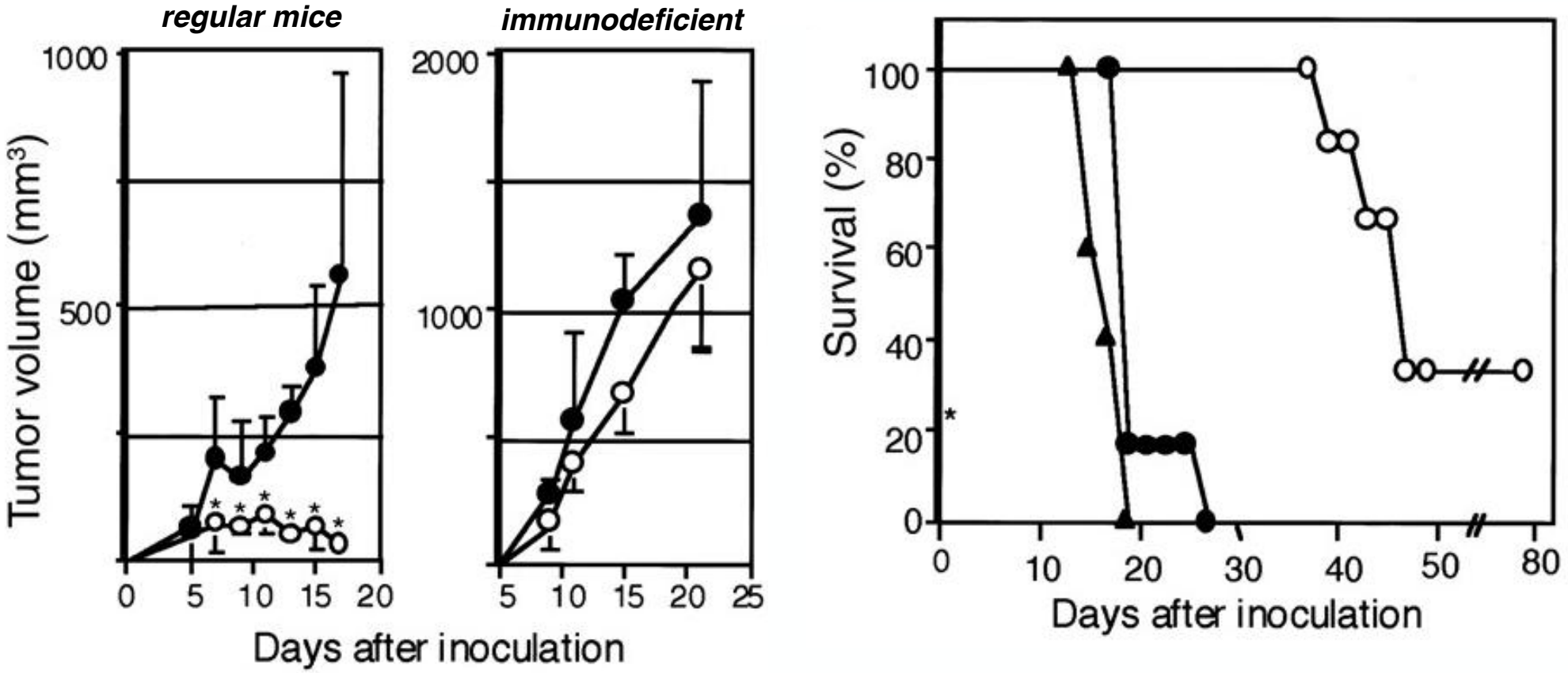
its role in the supression of immune response makes PD-1 an attractive target for checkpoint blockade

PD-1 blockade has been explored as an alternative to CTLA-4 with fewer autoimmune side effects

Ribas, A. *N. Engl. J. Med.*, **2015**, *373*, 1490.

The Role of PD-1 in Immune Resistance

studies on mice injected with PDL-1 enhanced tumors illustrates PDL-1's role in tumor immune resistance



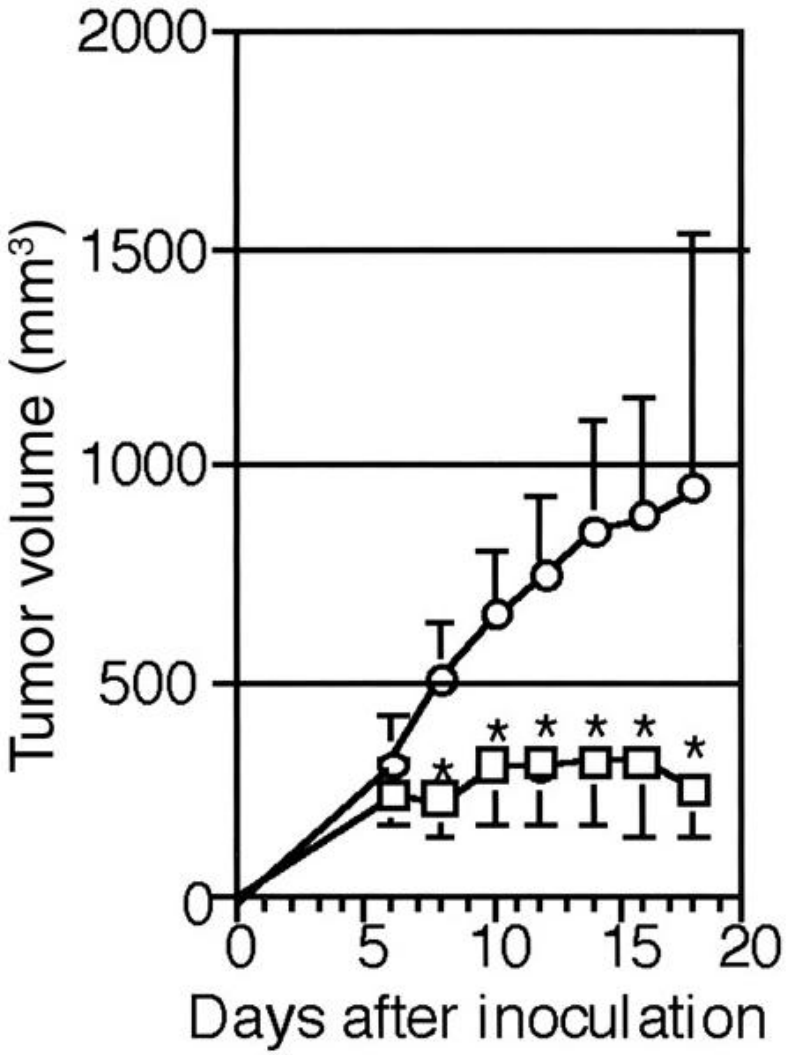
●-injected with PDL-1 enhanced tumor cells ○-injected with unmodified tumor cells

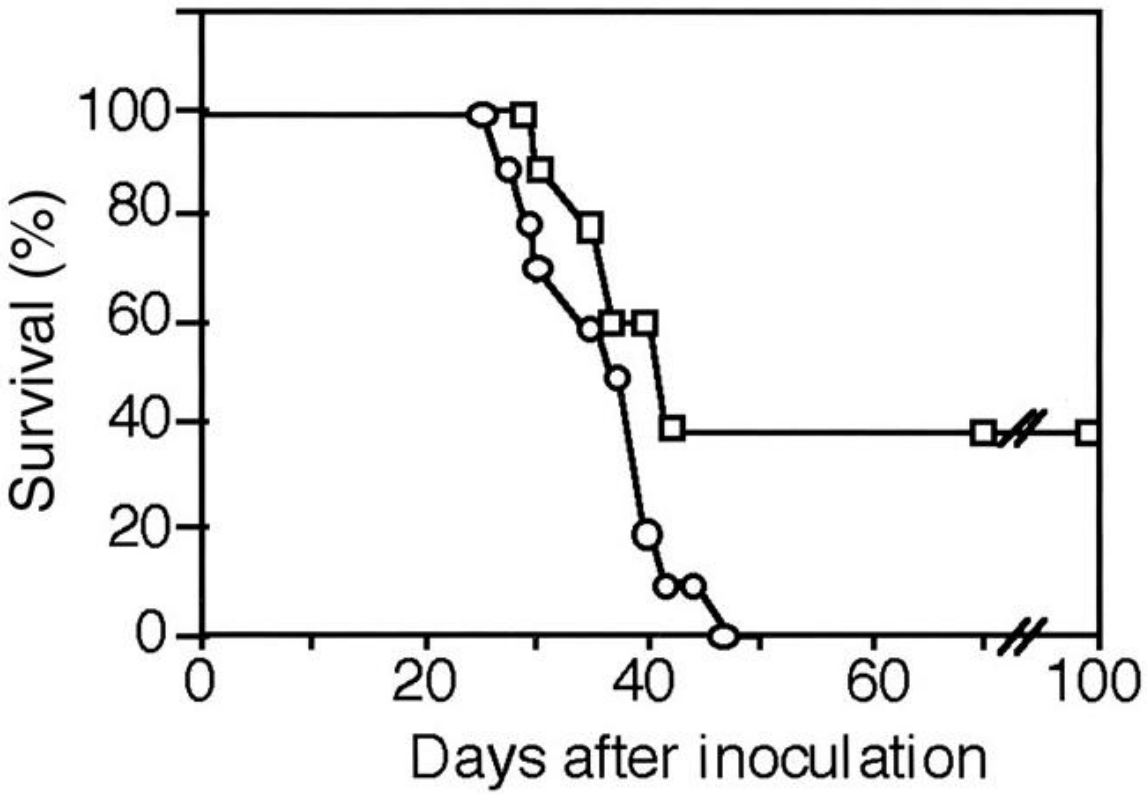
mice injected with PDL-1 enhanced tumors exhibit increased tumor volume and decreased life expectancy

Iwai, Y.; Ishida, M.; Tanaka Y.; Okazaki, T.; Honjo, T.; Minato, N. *PNAS*, **2002**, *99*, 12293.

The Role of PD-1 in Immune Resistance

injection of mice with anti-PDL-1 monoclonal antibody allows for immune response to tumors





□-injected with PDL-1 enhanced tumor cells and anti-PDL-1 antibody

○-injected with PDL-1 enhanced tumor cells and unrelated antibody

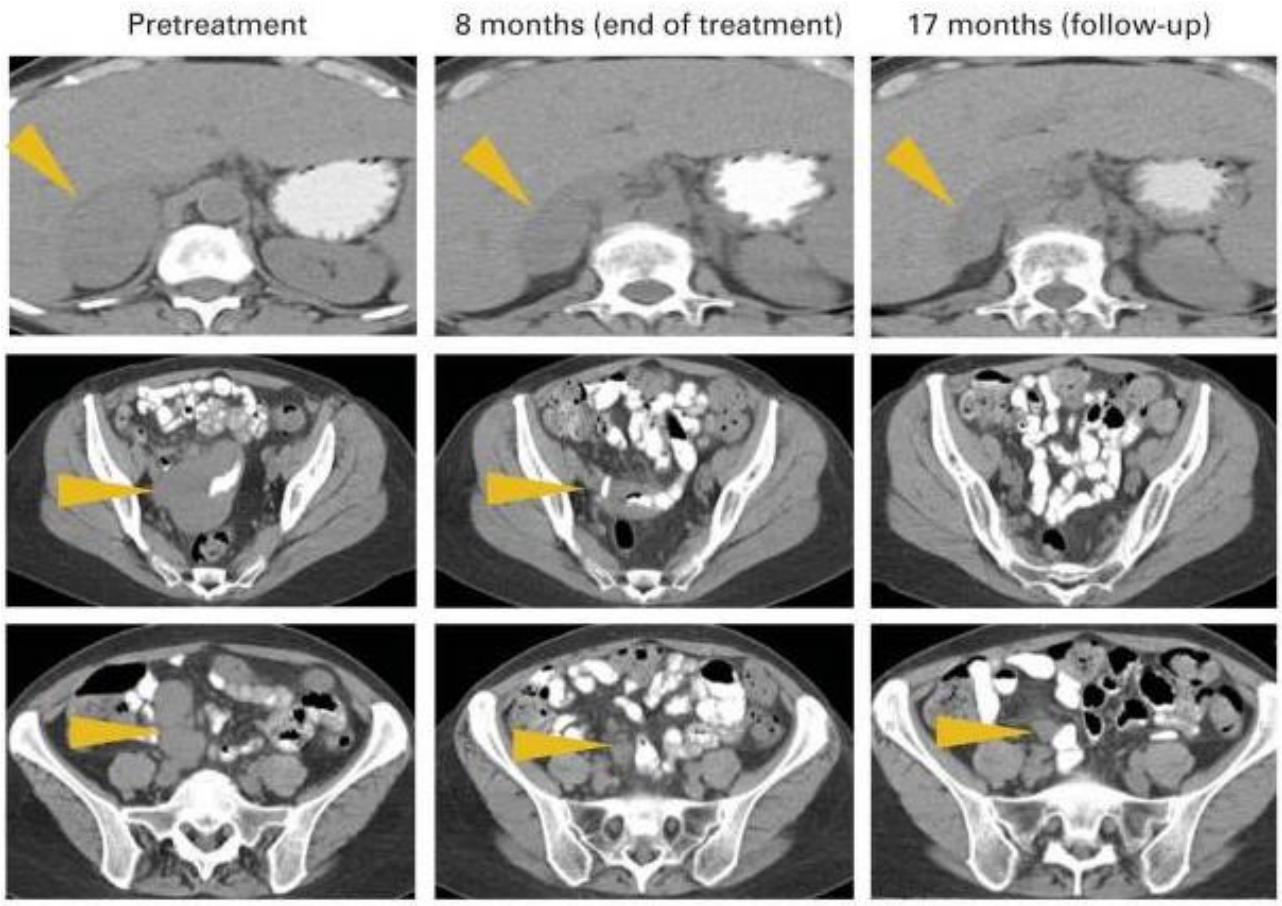
mice injected with anti-PDL-1 antibodies exhibit decreased tumor volume and increased life expectancy

Iwai, Y.; Ishida, M.; Tanaka Y.; Okazaki, T.; Honjo, T.; Minato, N. *PNAS*, **2002**, *99*, 12293.

Clinical Results with anti-PD-1 Antibodies

trials of anti-PD-1 antibodies investigated activity against several cancers (melanoma, lung, prostate)

nivolumab initially tested against late stage melanoma, gaining FDA approval in 2014



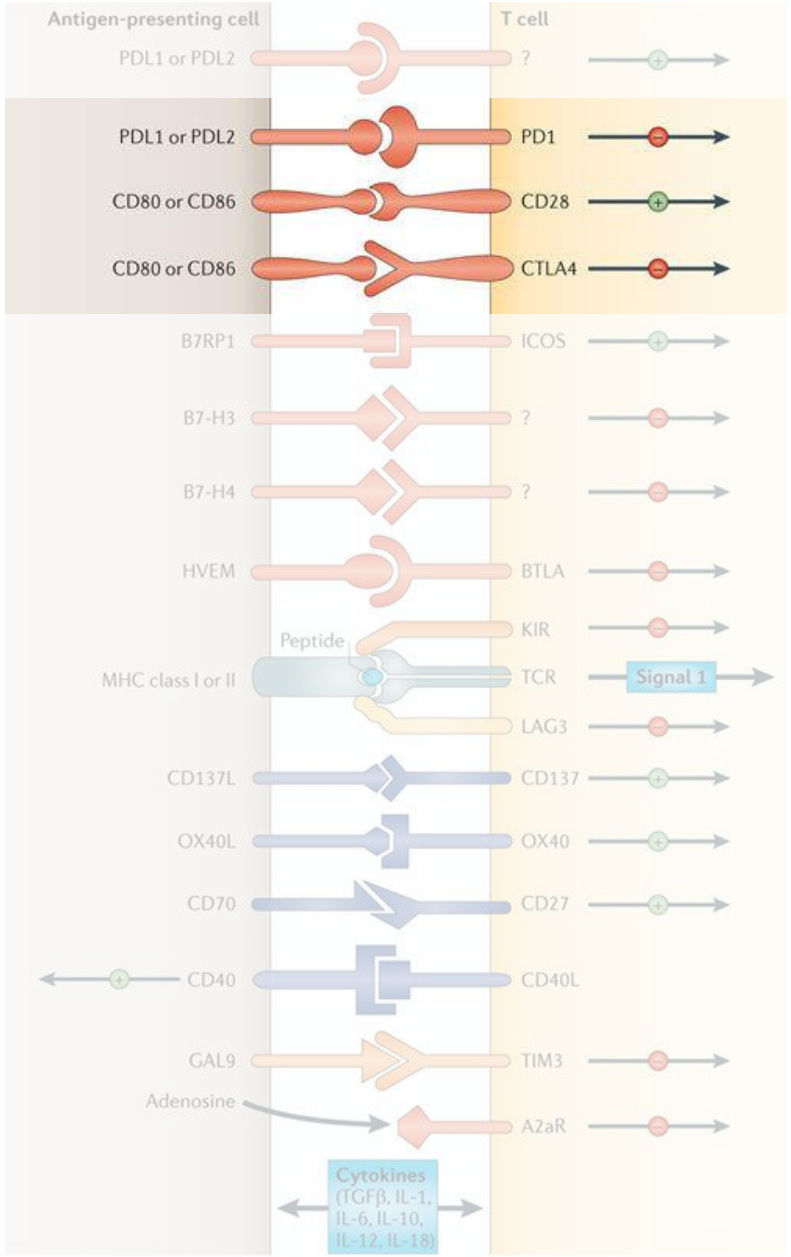
- Median survival - 16.8 months
- 1 year survival rate - 62%
- 2 year survival rate - 43%
- Tumor regression continued even after treatment was discontinued
- Automimmune symptoms observed, did not persist after treatment was discontinued

approved vs lung and renal cancer in 2015, Hodgkin lymphoma in 2016

Topalian, S. L. *et al. N. Engl. J. Med.,* **2012**, *366*, 2443.
Topalian, S. L. *et al. J. Clin. Oncol.,* **2014**, *32*, 1020.

Immune Stimulation via Checkpoint Blockade

identification of new immune checkpoints provides new theraputic avenues

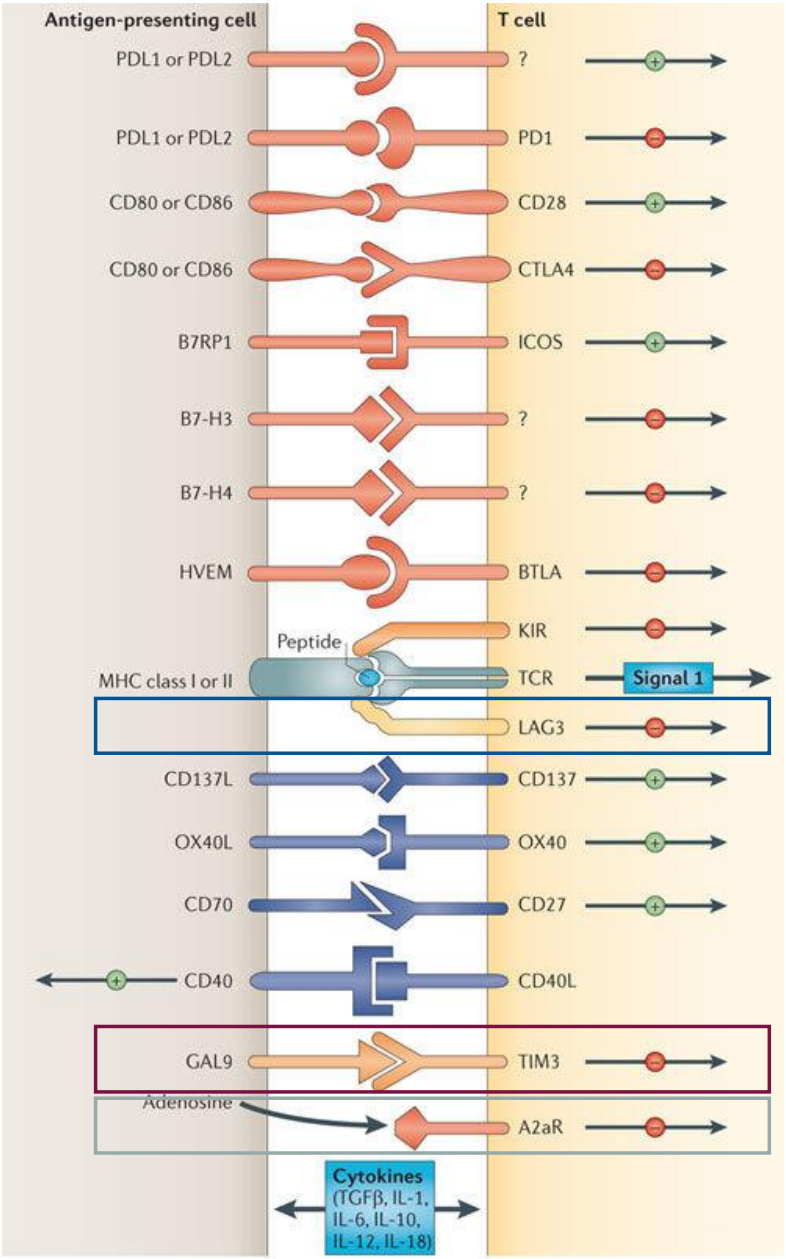


Pardoll, D. M. *Nature Reviews Cancer*, **2012**, *8*, 252.

Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine,* **2016**, *14*, 73.

Immune Stimulation via Checkpoint Blockade

identification of new immune checkpoints provides new theraputic avenues



- **LAG-3** (Lymphocyte activation gene 3)

Enhances function of T_{reg} cells and inhibits CD8+ cells

- **TIM3** (T-cell membrane protein 3)

Inhibits activity of helper T cells

- **A2aR** (Adenosine A2a receptor)

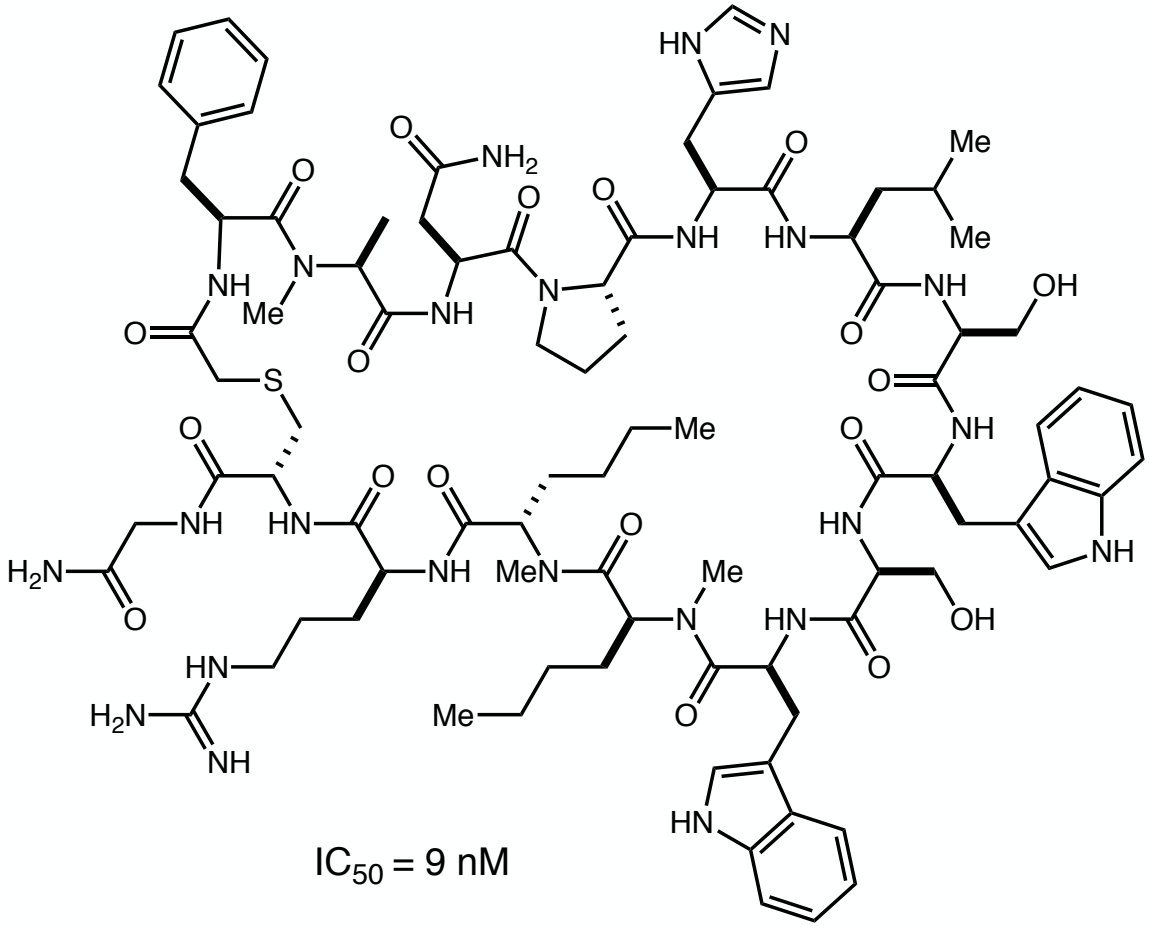
Drives T cells to become T_{reg} cells

- Due to release of adenosine by dying cells and high cell turnover within tumors, this is a potentially potent route for tumor immunity

Pardoll, D. M. *Nature Reviews Cancer*, **2012**, *8*, 252.

Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine,* **2016**, *14*, 73.

Small Molecule Checkpoint Inhibitors

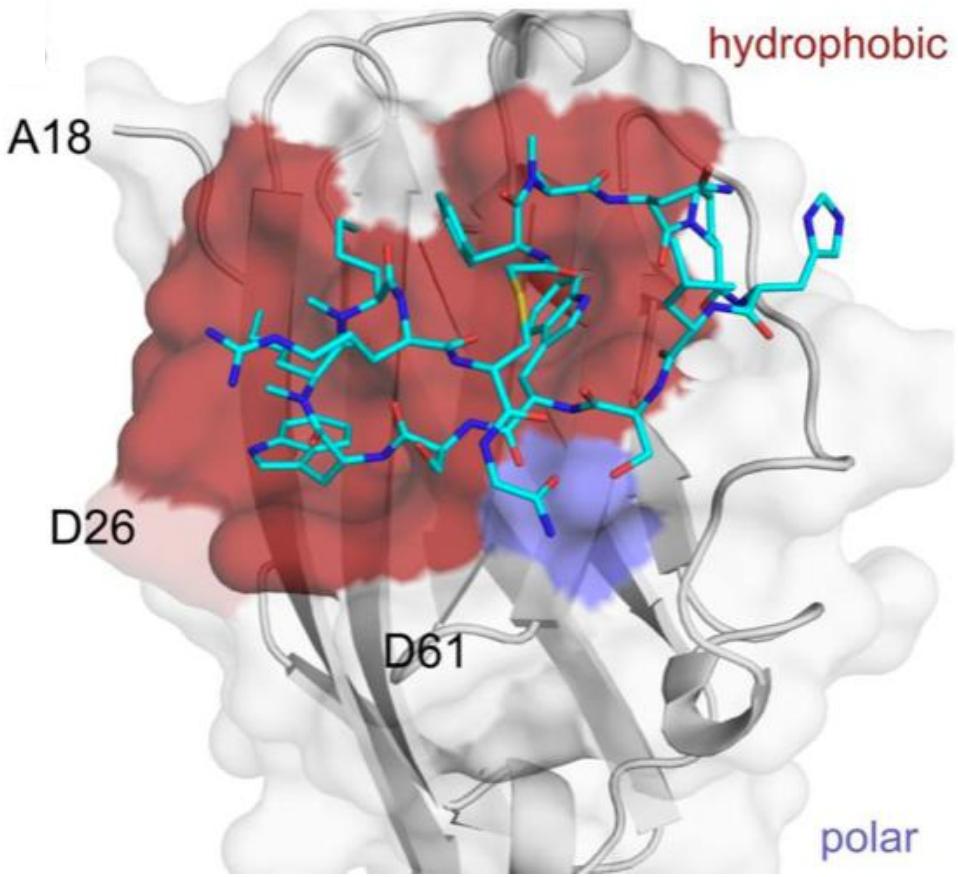


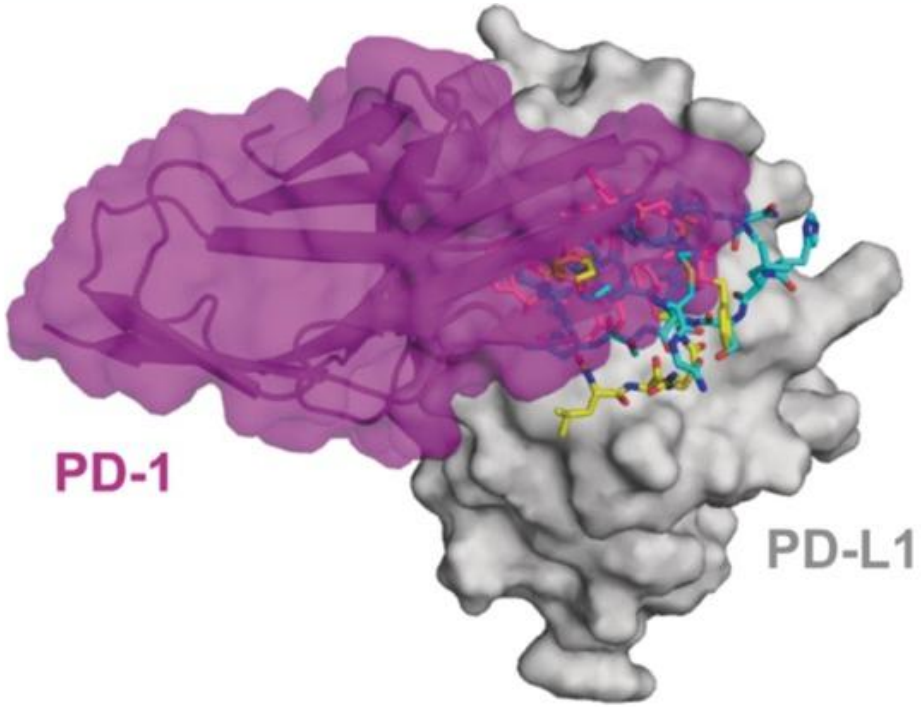
IC_{50} = 9 nM

- To date, the majority of immune checkpoint inhibitors have been focused on monoclonal antibodies
- Small molecule drugs have a number of advantages, such as lower cost as well as no immunogenicity
- The most extensive research thus far has been into blocking the PD-1/PDL-1 interaction

Weinmann, H. *ChemMedChem*, **2016**, *11*, 450.

Small Molecule Checkpoint Inhibitors

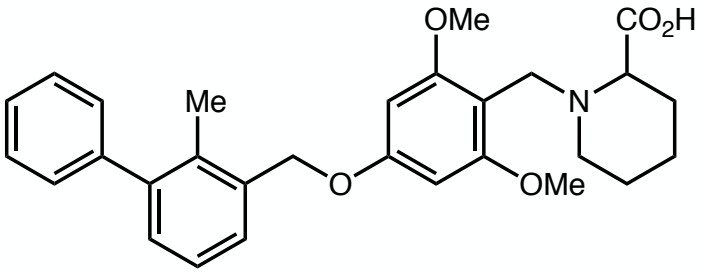




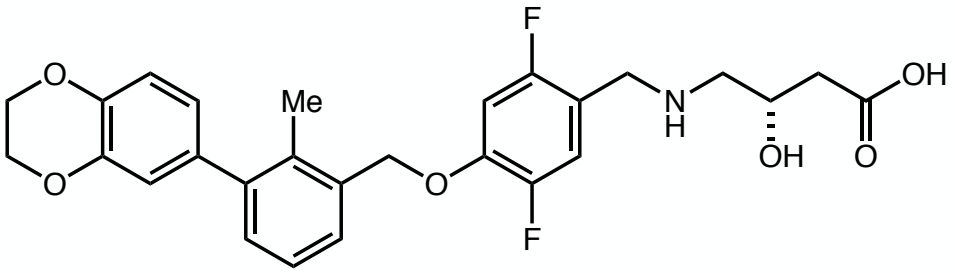
- To date, the majority of immune checkpoint inhibitors have been focused on monoclonal antibodies
- Small molecule drugs have a number of advantages, such as lower cost as well as no immunogenicity
- The most extensive research thus far has been into blocking the PD-1/PDL-1 interaction

Weinmann, H. *ChemMedChem*, **2016**, *11*, 450.

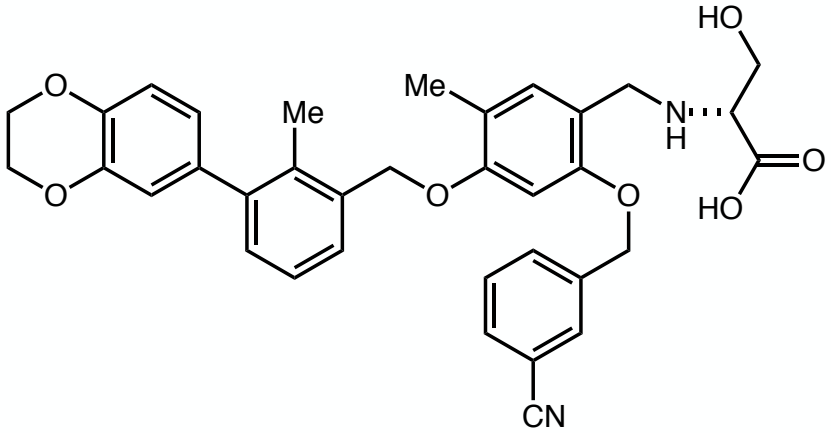
Small Molecule Checkpoint Inhibitors



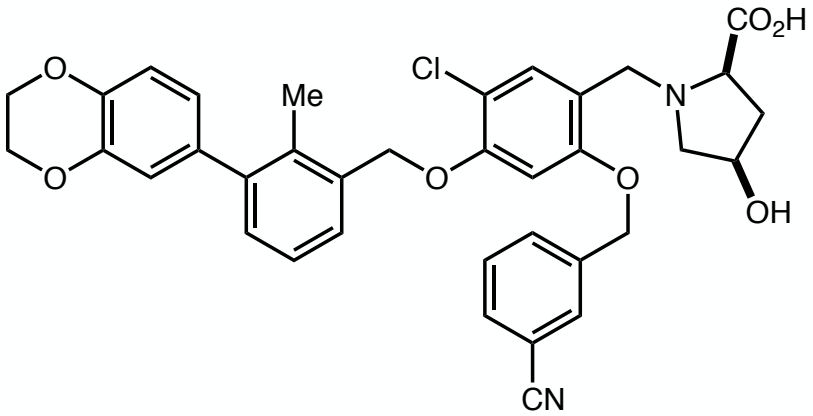
IC_{50} = 146 nM



IC_{50} = 80 nM



IC_{50} = 2.5 nM



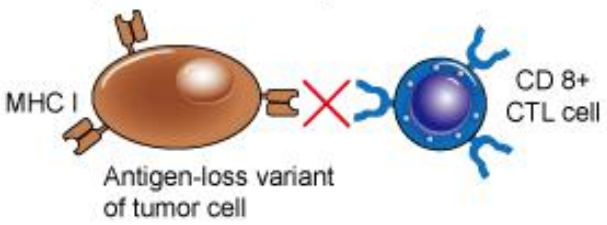
IC_{50} = 1.4 nM

- To date, the majority of immune checkpoint inhibitors have been focused on monoclonal antibodies
- Small molecule drugs have a number of advantages, such as lower cost as well as no immunogenicity
- The most extensive research thus far has been into blocking the PD-1/PDL-1 interaction

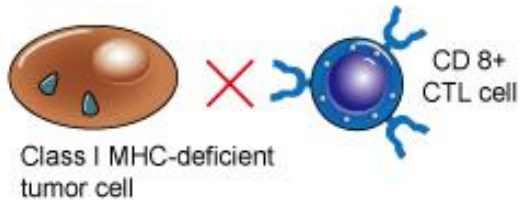
Weinmann, H. *ChemMedChem*, **2016**, *11*, 450.

How Tumor Cells Evade the Immune Response

the immune response imposes a selection pressure on tumors, allowing resistant variants to proliferate

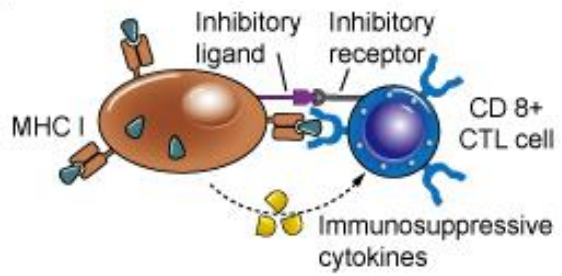


antigen deficient



MHC deficient

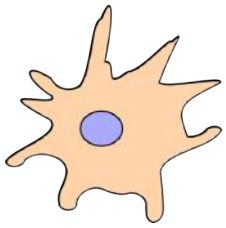
evades T-cell detection



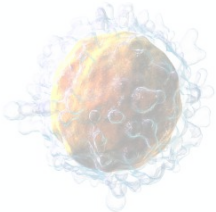
Suppression of immune response

Produces cytokines which promote formation of T_{reg} cells around tumor

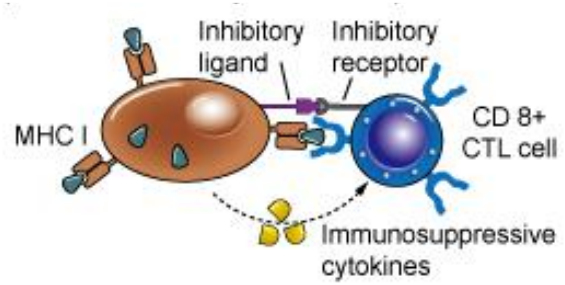
how can we stimulate an immune response to overcome these defence mechanisms?



mature DC



active T-cells



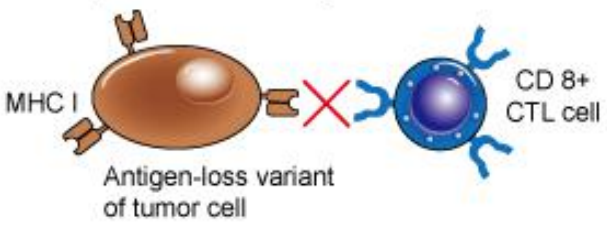
Suppression of immune response

Decker, W. K. *et al. Front. Immunol.*, **2017**, *8*, 829.

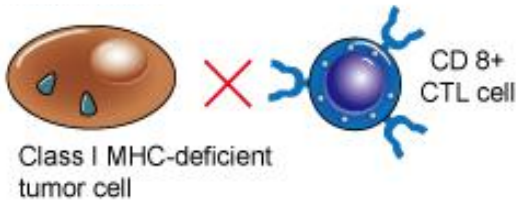
Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine* **2016**, *14*, 73.

How Tumor Cells Evade the Immune Response

the immune response imposes a selection pressure on tumors, allowing resistant variants to proliferate

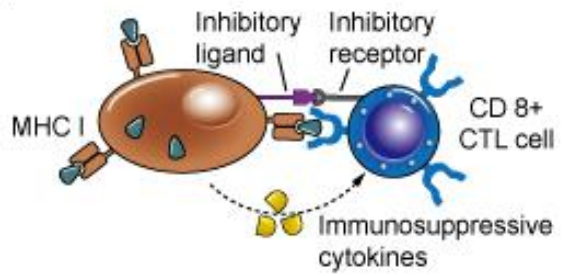


antigen deficient



MHC deficient

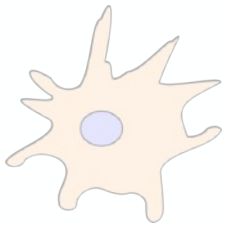
evades T-cell detection



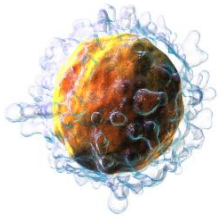
Suppression of immune response

Produces cytokines which promote formation of T_{reg} cells around tumor

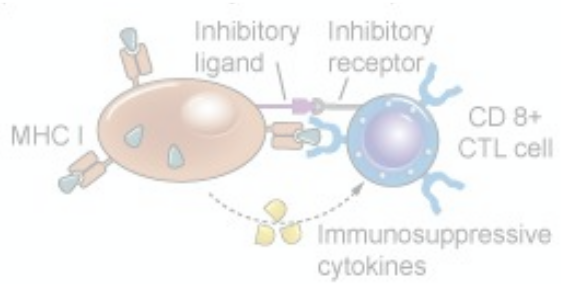
how can we stimulate an immune response to overcome these defence mechanisms?



mature DC



active T-cells



Suppression of immune response

Decker, W. K. *et al. Front. Immunol.*, **2017**, *8*, 829.

Farkona, S.; Diamandis, E. P.; Blasutig, I .M. *BMC Medicine* **2016**, *14*, 73.

Immunotherapy Strategies

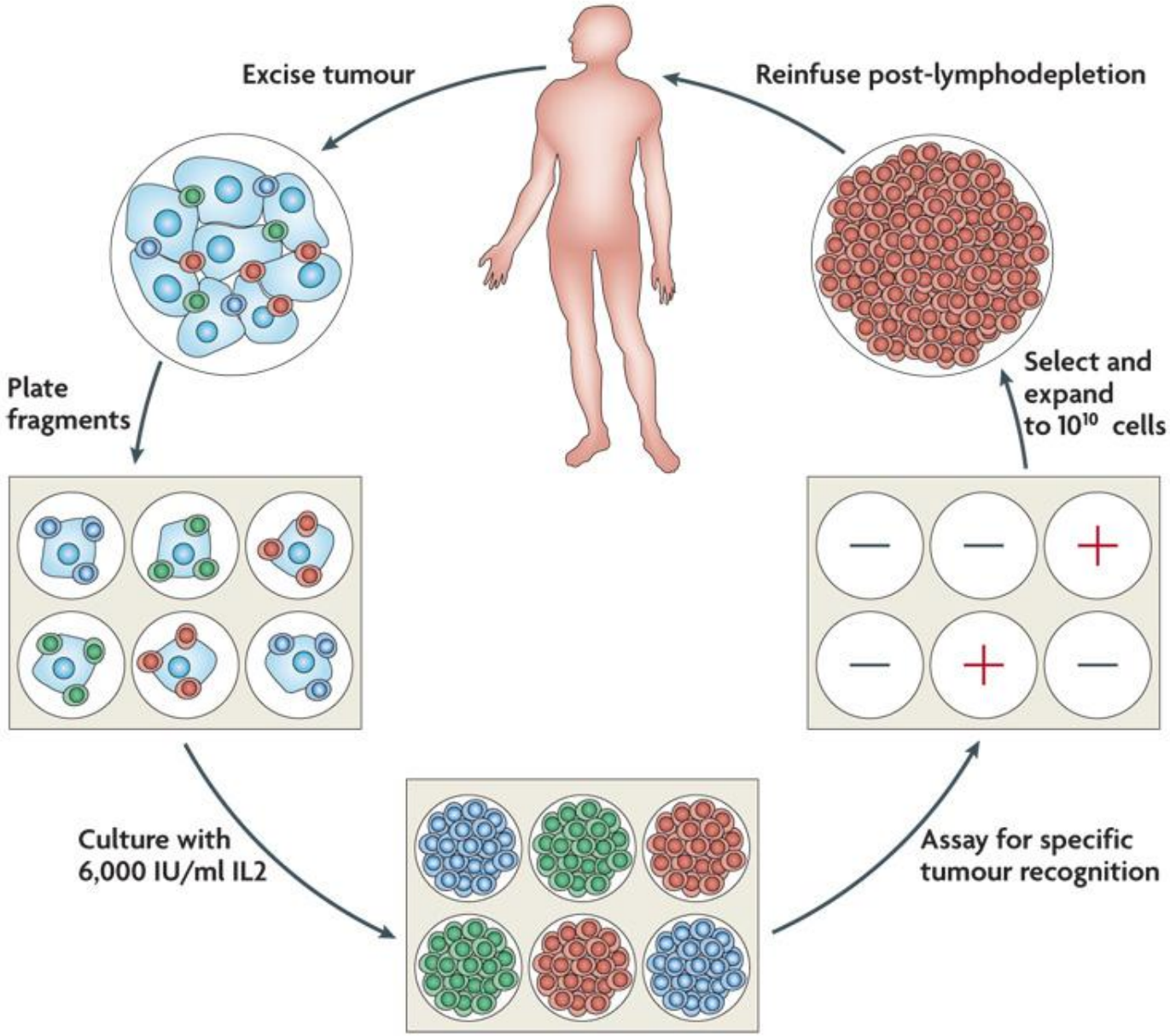
theraputic cancer vaccines

immune checkpoint blockade therapy

adoptive cell transfer therapy

Adoptive T-cell transfer

involves extraction of T-cells from tumors, enrichment for an antigen specific variant then re-infusion

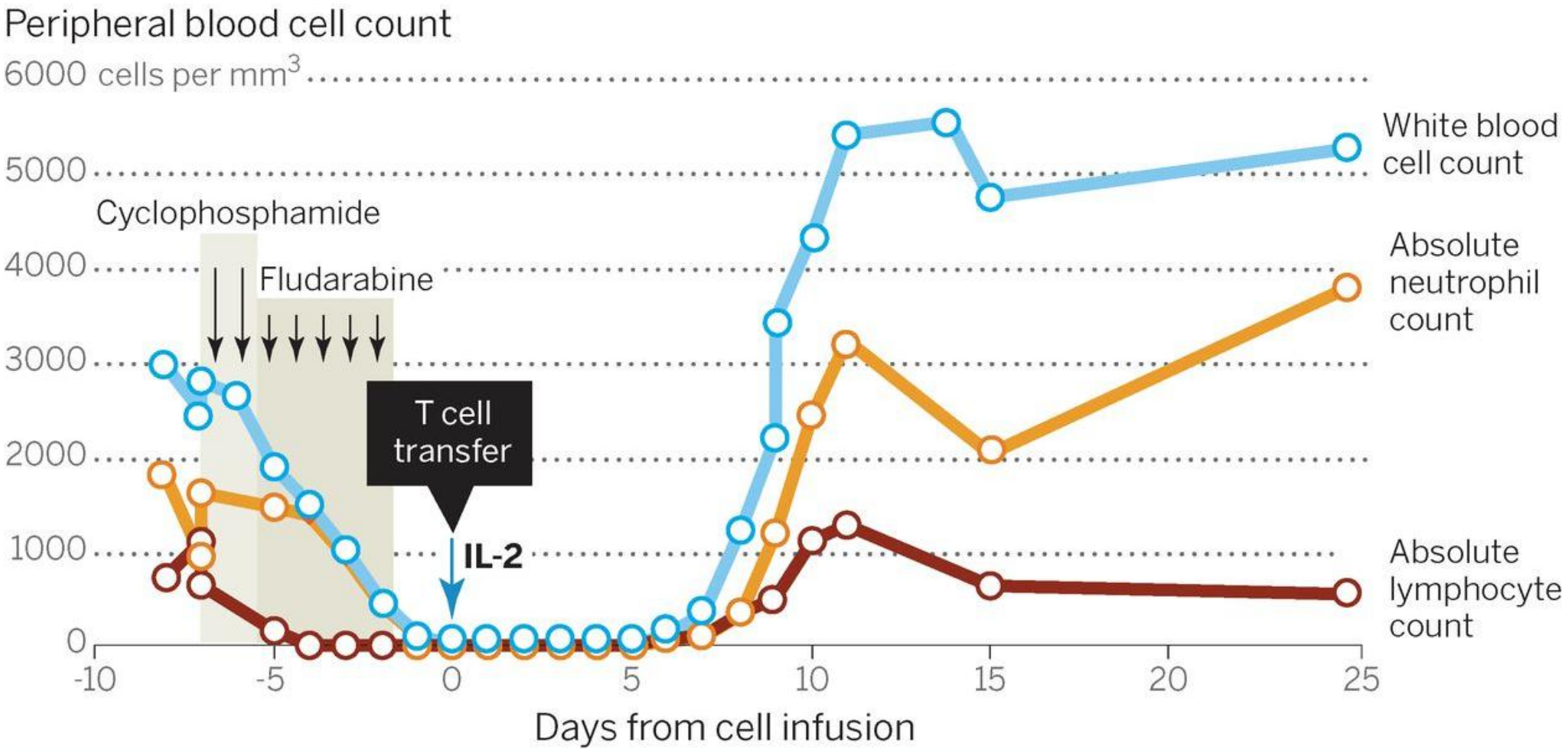


in theory circumvents the need to break the tolerance of tumor antigens to T-cell response

Rosenberg S. A. *et al. Nat. Rev. Cancer,* **2008**, *8*, 229.

Adoptive T-cell transfer

lymphodepletion of target was found to be important to the success of ACT (in mice, 10x more effective)



thought to be needed in order to deplete T_{reg} popuations, as well as to promote production of growth factors

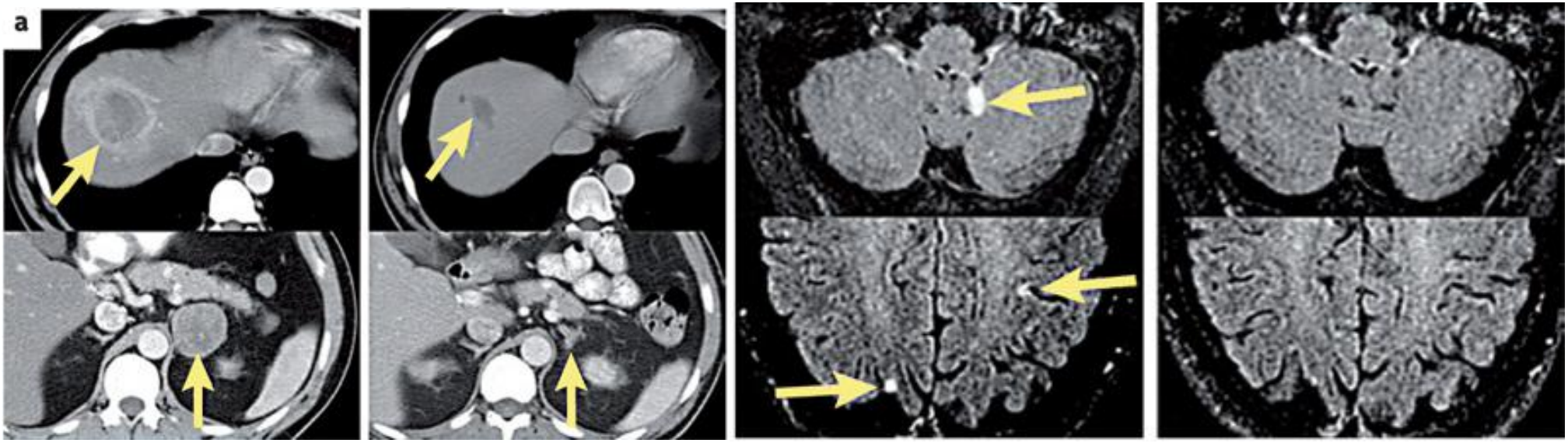
Rosenberg, S. A.; Restifo, N. P. *Science,* **2015**, *348*, 62.

Adoptive T-cell Transfer- Initial Attepts

initial human trials of ACT only had significant success against melanoma- likely due to its high mutation rate

CELLS USED FOR ACT	YEAR	CANCER HISTOLOGY	MOLECULAR TARGET	PATIENTS	NUMBER OF ORS
Tumor-inflitrating lymphocytes*	1998	Melanoma (*12*)		20	55%
	1994	Melanoma (*88*)		86	34%
	2002	Melanoma (*13*)		13	46%
	2011	Melanoma (*17*)		93	56%
	2012	Melanoma (*19*)		31	48%
	2012	Melanoma (*18*)		13	38%

before treatment after treatment before treatment after treatment

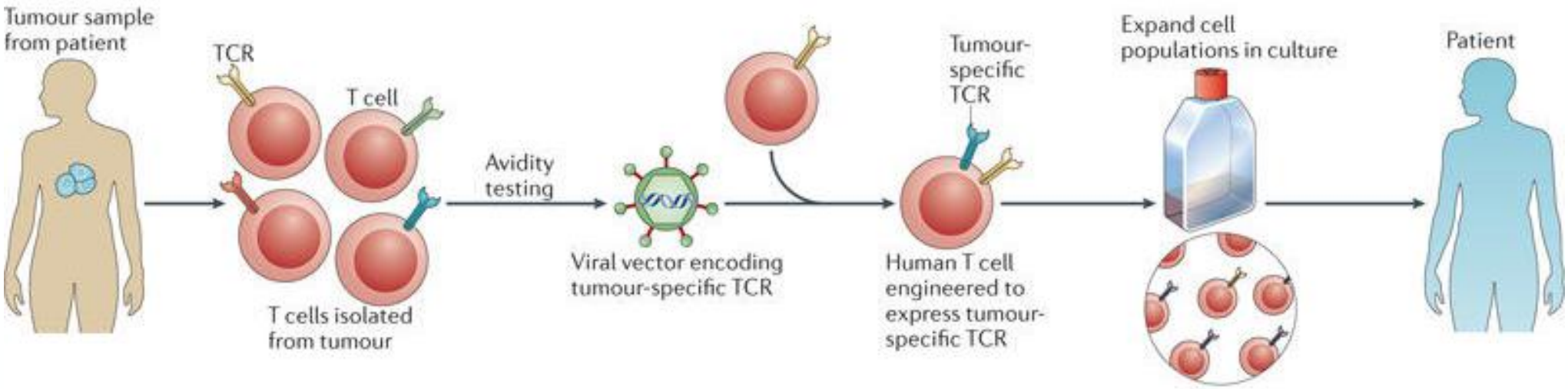


a number of efforts have been made to modify T-cells to allow for expansion to cancers other than melanoma

Rosenberg, S. A.; Restifo, N. P. *Science,* **2015**, *348*, 62.

Strategies for Genetic Engineering of T-Cells

isolation of high affinity T-cell receptors

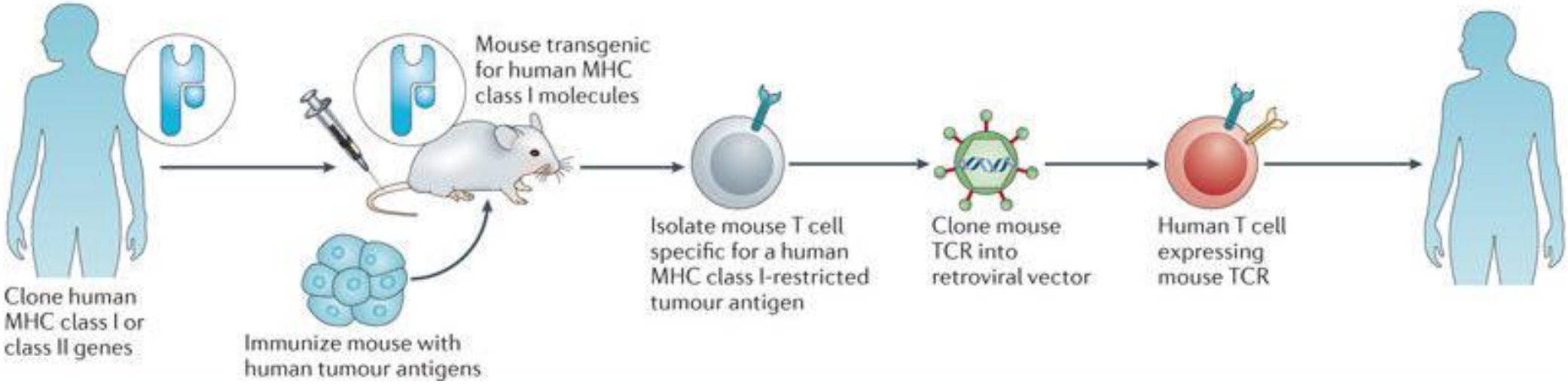


- Some patients naturally express T-cells bearing high affinity T-cell receptors for specific tumor types
- Genes encoding the receptor can be extracted and cloned into a virus to make analogous T-cells
- The affinity of such engineered receptors can be increased through directed evolution

Restifo, N. P.; Dudley, M. E.; Rosenberg, S. A. *Nat. Rev. Immunology,* **2012**, *12*, 269.

Strategies for Genetic Engineering of T-Cells

isolation of high affinity T-cell receptors

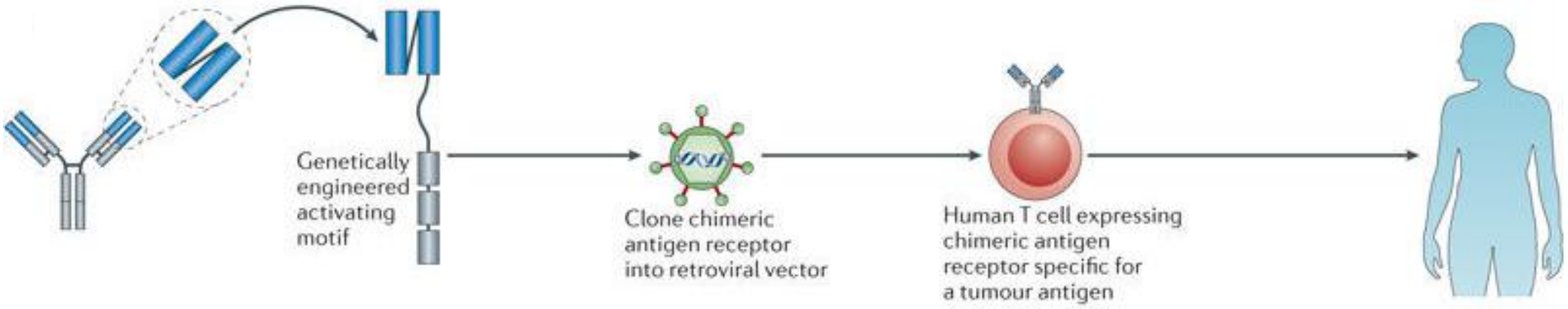


- Humanized mice can be used to produce specific human TCR genes upon infection with tumor
- Genes encoding the receptor can be extracted and cloned into a virus to make analogous T-cells
- The affinity of such engineered receptors can be increased through directed evolution

Restifo, N. P.; Dudley, M. E.; Rosenberg, S. A. *Nat. Rev. Immunology,* **2012**, *12*, 269.

Strategies for Genetic Engineering of T-Cells

isolation of high affinity T-cell receptors



- Genetic code from antibodies engineered to encode singe chain structure fused to T-cell receptor
- Allows T-cells to recognize structures on cell surface with the specificity of a monoclonal antibody
- First drug using this technology, tisagenlecleucel approved by the FDA in 2017

Restifo, N. P.; Dudley, M. E.; Rosenberg, S. A. *Nat. Rev. Immunology,* **2012**, *12*, 269.

Conclusions

theraputic cancer vaccines

immune checkpoint blockade therapy

adoptive cell transfer therapy

- Cancer immunotherapy has emerged as a distinct approach to longstanding cancer therapies
- Manipulation of the immune response shown to be a viable strategy for control of tumor growth
- Novel techniques such as immune checkpoint blockade have provided durable remission
- Studies are ongoing to determine which patients and which types of tumor will best respond
- Severe autoimmutity remains a complication with many successful therapies