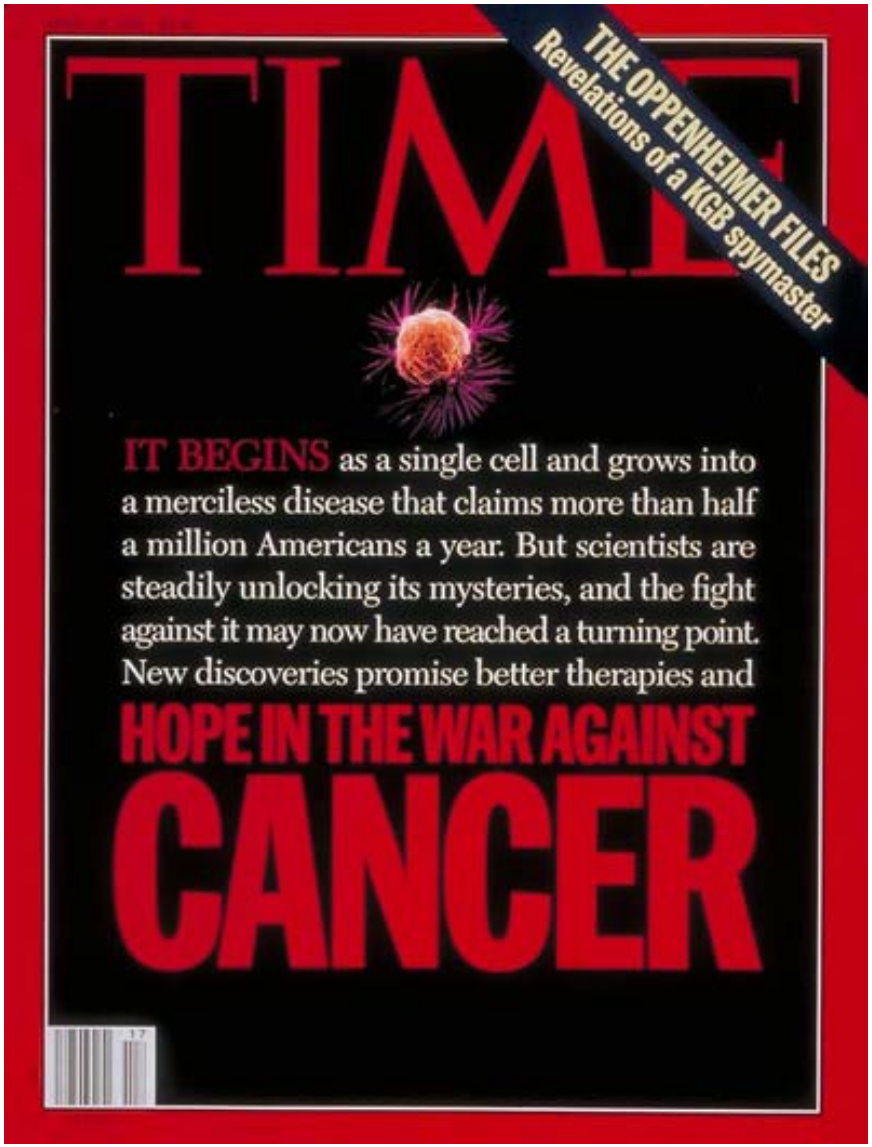
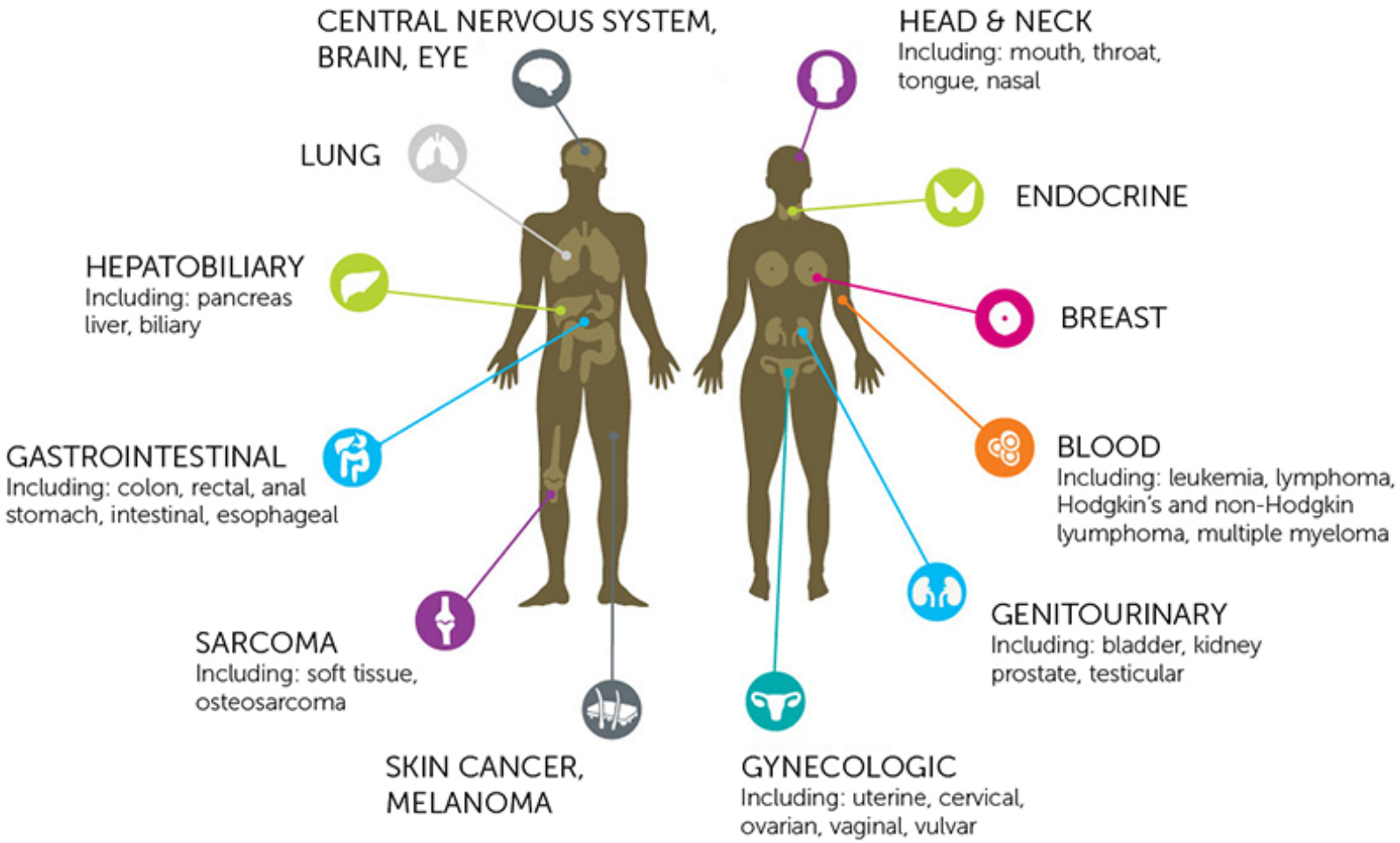
Tumor Immunobiology

- Tumor formation
- Tumor microenvironment
- Tumor Immune evasion
- Tumor Immune therapy

War Against Cancer



Cancer


CENTRAL NERVOUS SYSTEM, BRAIN, EYE
HEAD & NECK
Including: mouth, throat, tongue, nasal
LUNG
ENDOCRINE
HEPATOBILIARY
Including: pancreas liver, biliary
BREAST
GASTROINTESTINAL
Including: colon, rectal, anal stomach, intestinal, esophageal
BLOOD
Including: leukemia, lymphoma, Hodgkin's and non-Hodgkin lyumphoma, multiple myeloma
GENITOURINARY
Including: bladder, kidney prostate, testicular
SARCOMA
Including: soft tissue, osteosarcoma
SKIN CANCER, MELANOMA
GYNECOLOGIC
Including: uterine, cervical, ovarian, vaginal, vulvar

Cancers of the blood system

- Leukemias:
  - Develop in the bone marrow and moves to periphery
    - Acute: the bone marrow cells cannot mature properly
    - Chronic: the bone marrow cells can mature partly but not completely

- Lymphomas:
  - Develop in the lymph nodes
    - Non Hodgkin: B and T cells
    - Hodgekin: abnormal B cells (very large, Reed-Sternber cell)

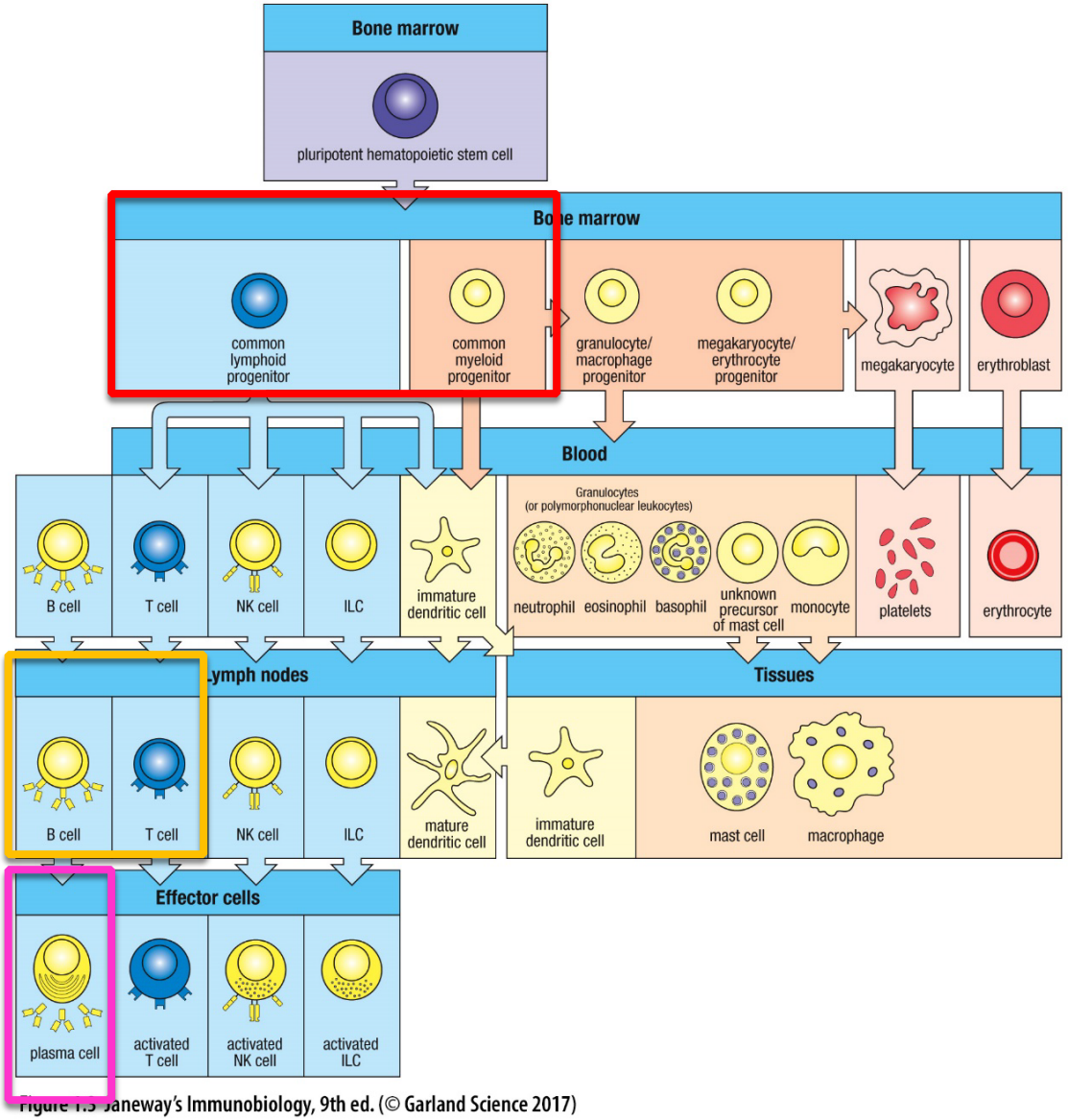
- Multiple Myeloma
  - Plasma cells in the bone marrow

Cancers of the blood system

Leukemias

Lymphomas

Multiple Myeloma

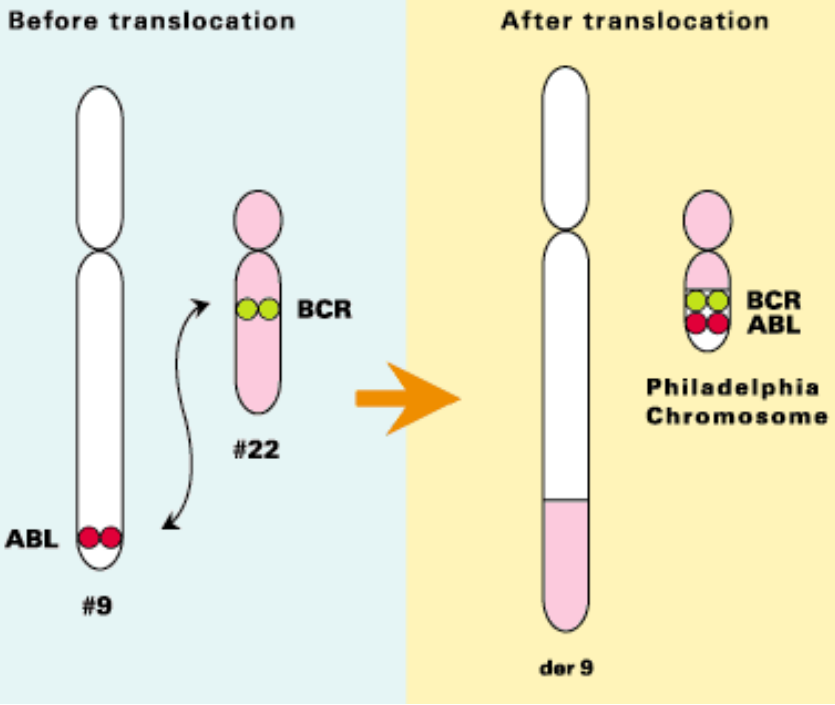


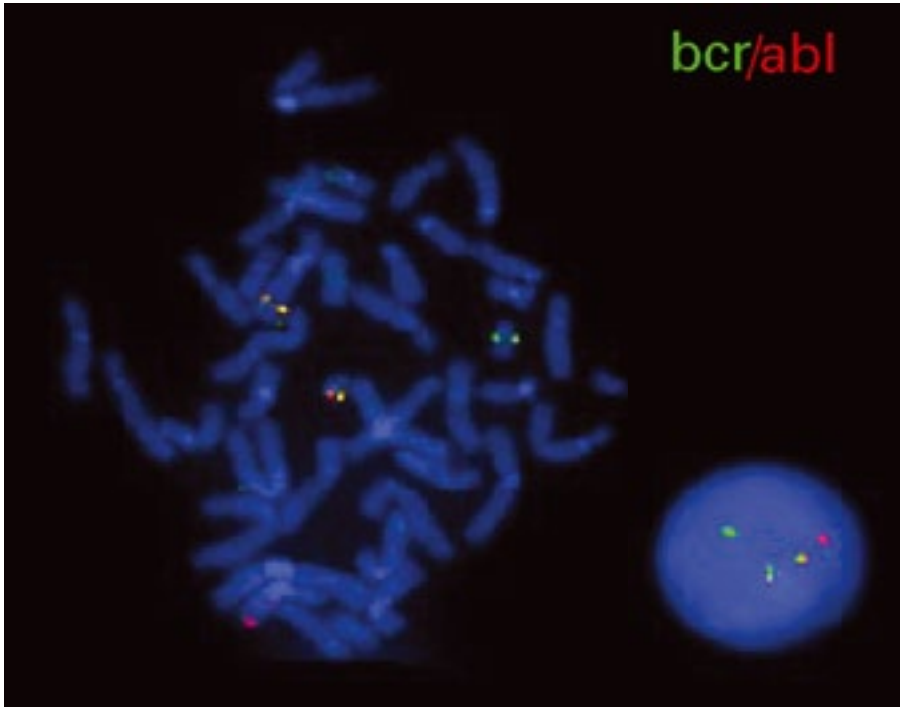
Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Chronic Myelogenous Leukemia (CML) Is Characterized by a Translocated Chromosome

Philadelphia chromosome:

- reciprocal translocation between chromosome 9 and 22 [t(9;22)(q34;q11)]
- occurs in 95% of CML cases



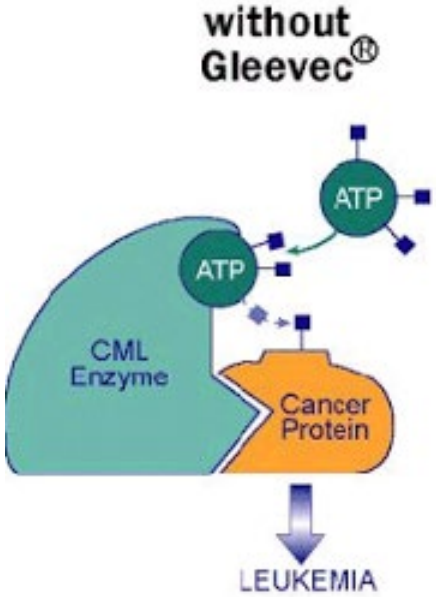


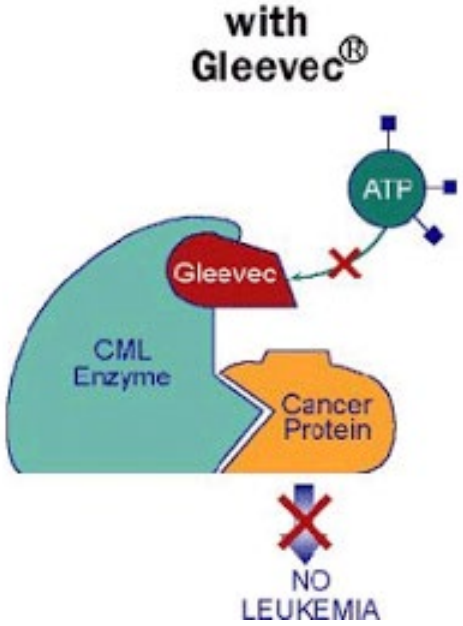
http://en.wikipedia.org/wiki/Philadelphia_chromosome

Bone Marrow Transplantation (2004) 33, 247–249.

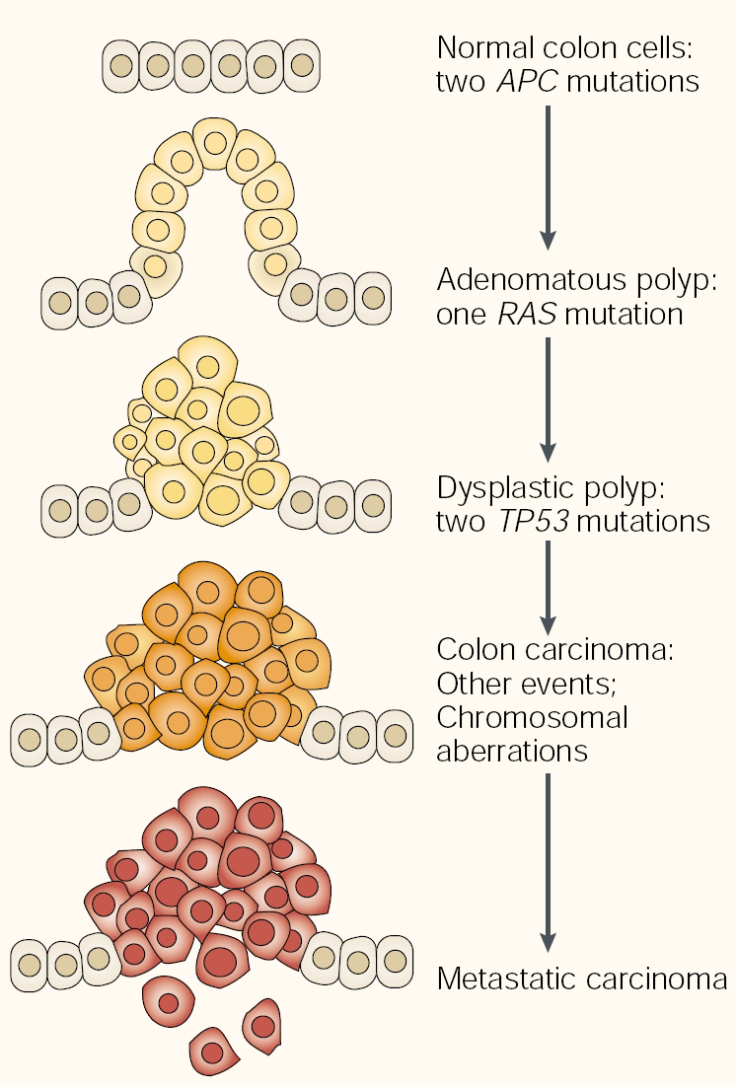
Gleevec


MAY 28, 2001
www.time.com AOL Keyword: TIME
TIME
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER.
THESE ARE THE BULLETS.
Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?


without Gleevec®
ATP
ATP
CML Enzyme
Cancer Protein
LEUKEMIA


with Gleevec®
ATP
Gleevec
CML Enzyme
Cancer Protein
NO LEUKEMIA

It is Hard to Grow A Tumor



Cells accumulate multiple mutations
Abnormal chromosomes
Epigenetic changes

Uncontrolled growth of progeny of transformed cells

Cancer is unique in each person

Spread to unconnected parts

http://www.nature.com/scitable/topicpage/cell-division-and-cancer-14046590

Tumor Associated Antigens

Point mutation
Gene fusion
Increase of expression level

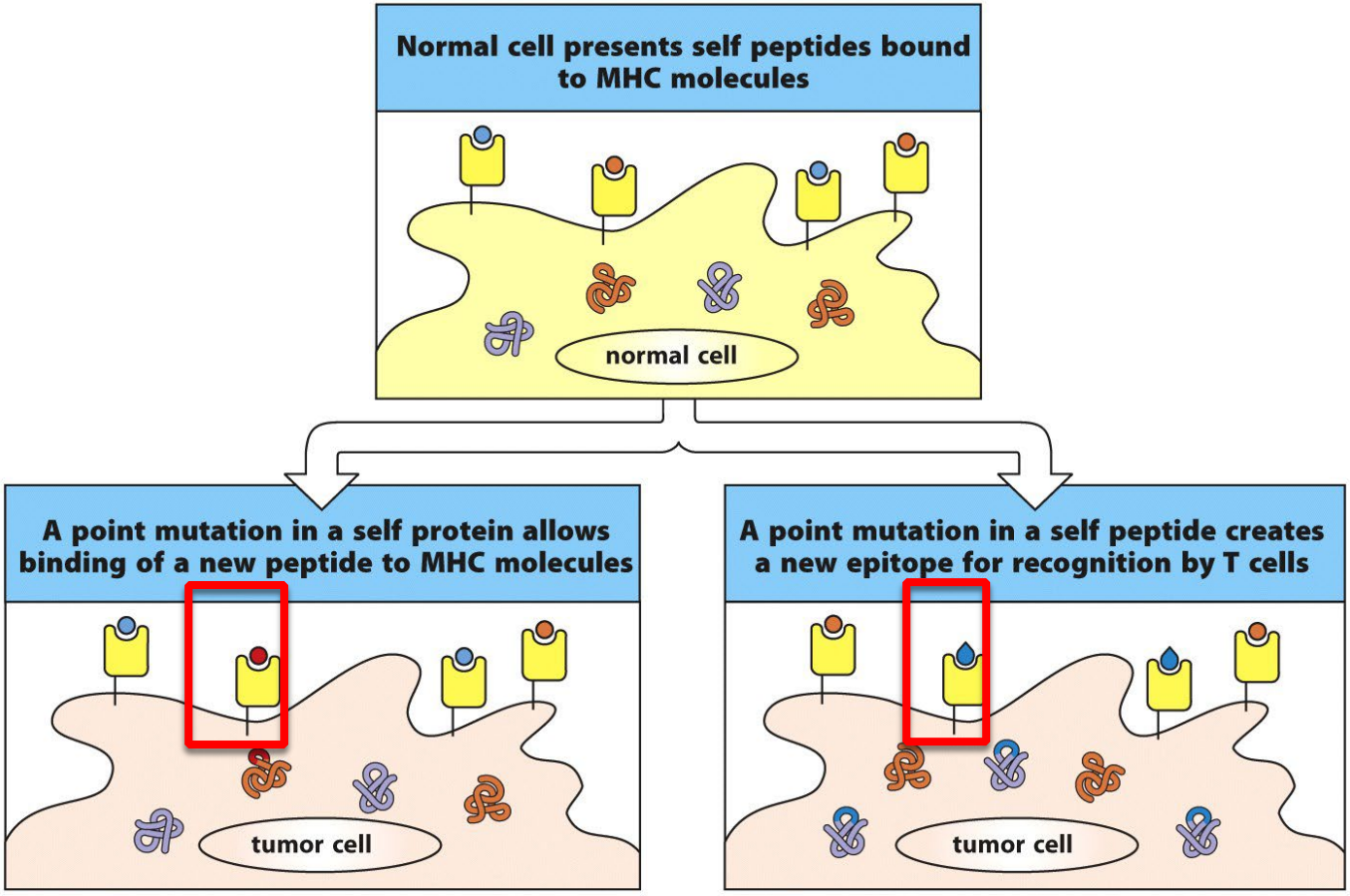
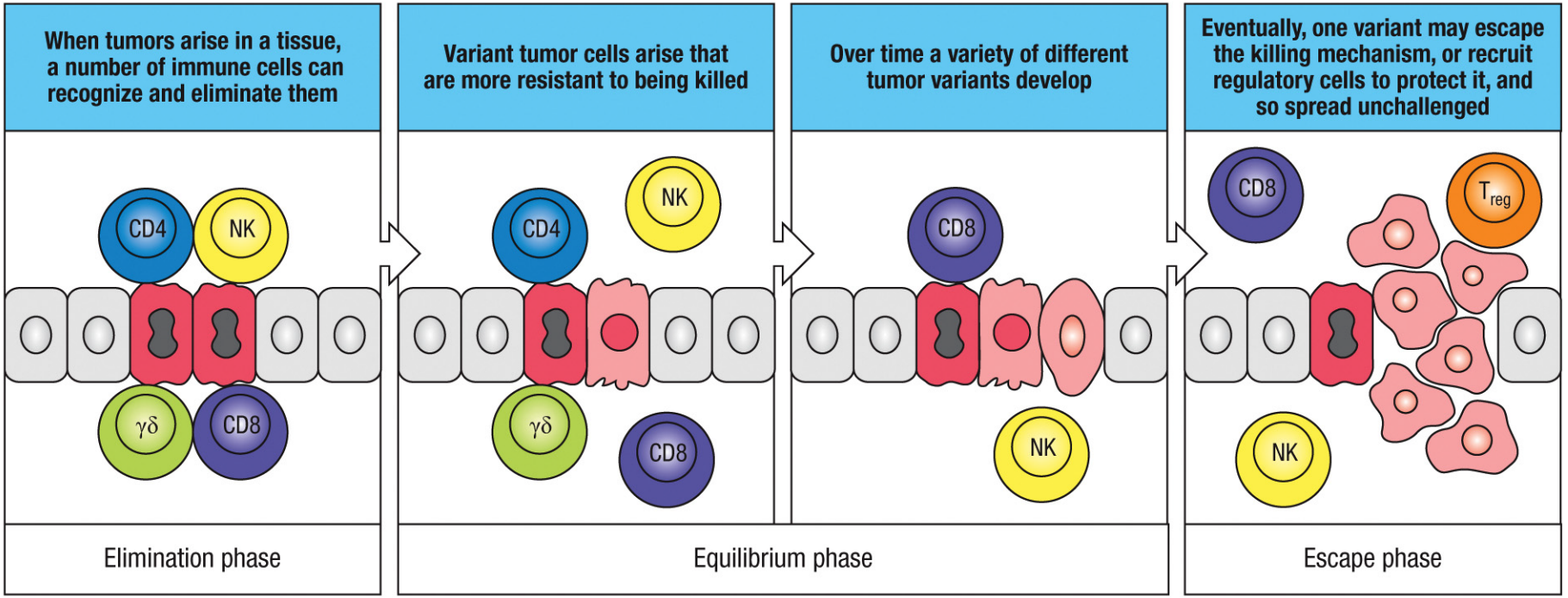


Figure 16.17 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

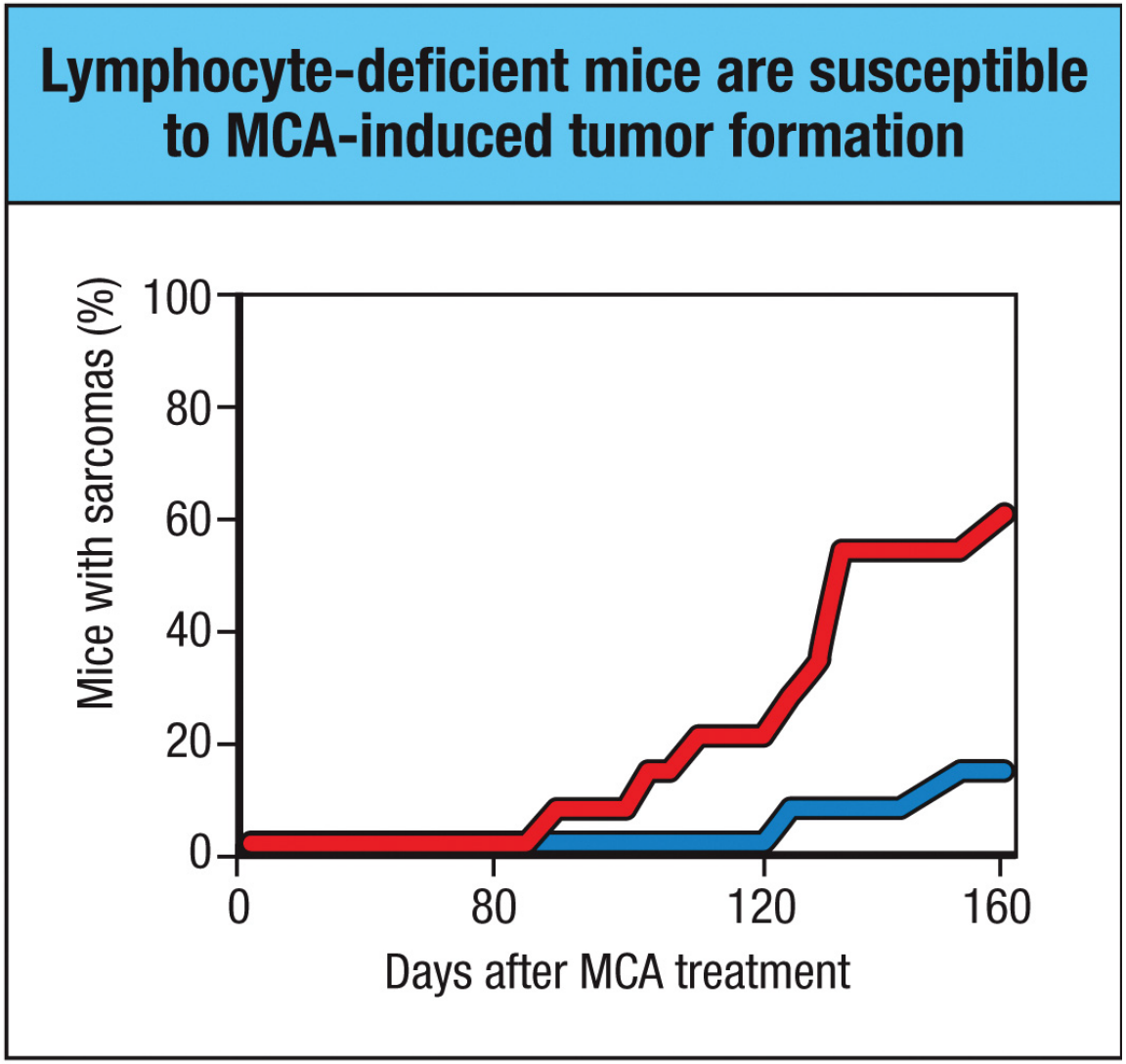
Immune surveillance

Cancer Immunoediting



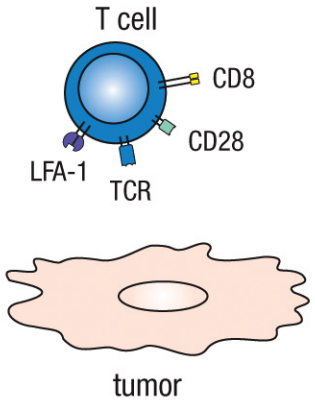
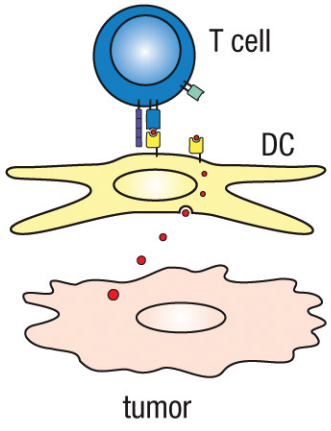
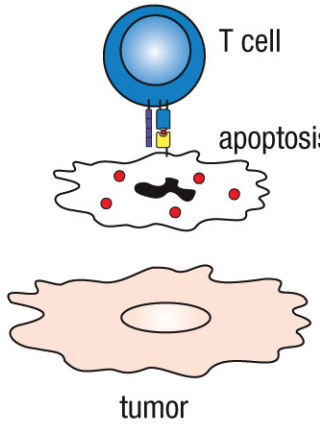
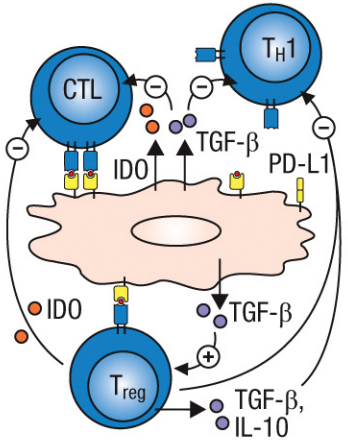
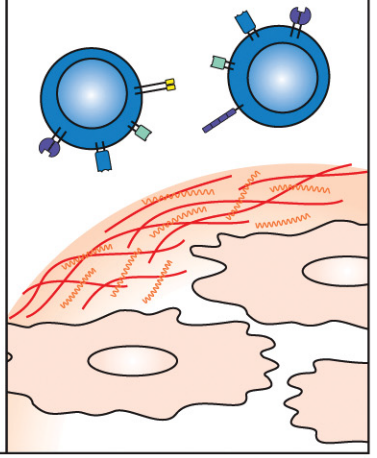
Those mutated cells escape immune detection develop into tumors
That is why cancer is so hard to treat once they develop

Immune surveillance

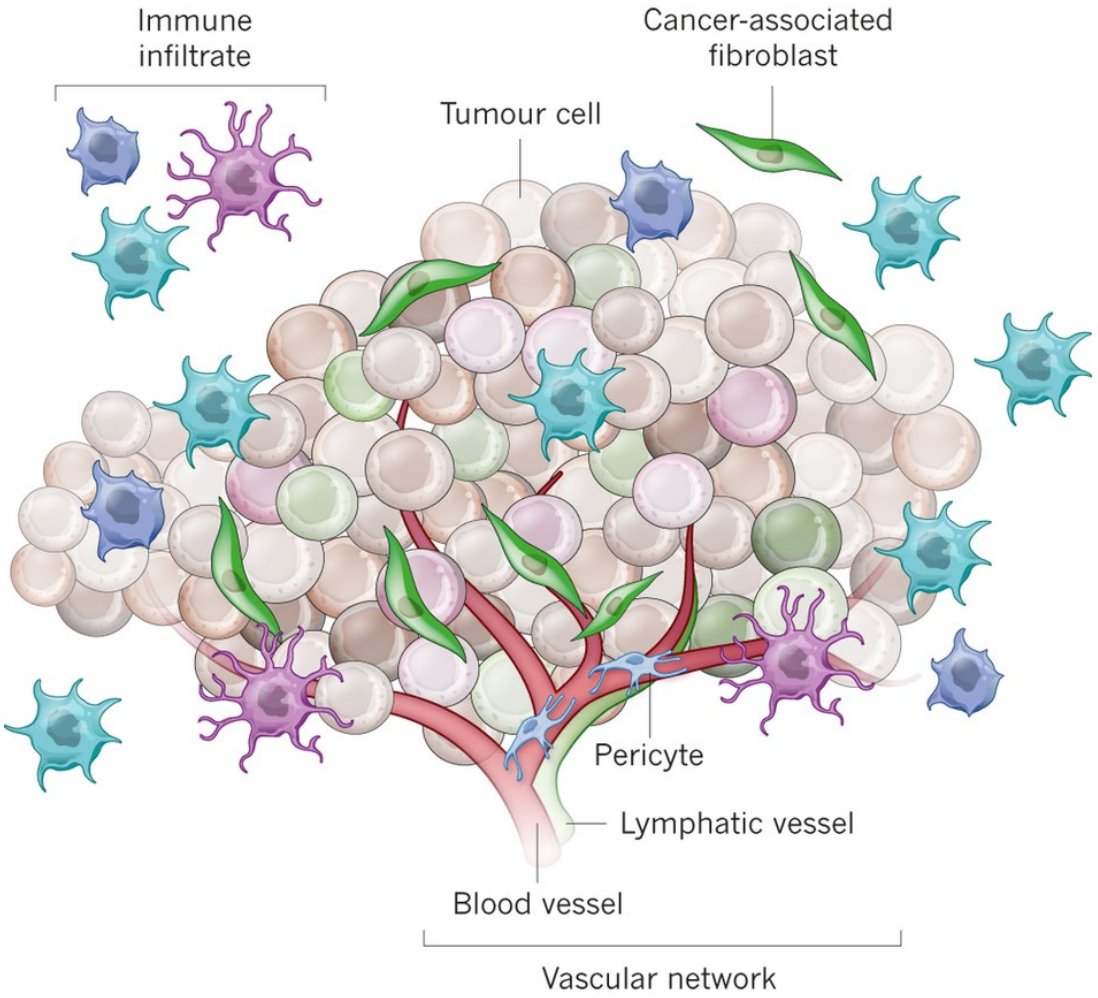


Rag2 -/- (red line)
WT (blue line)

Tumor Immune Evasion

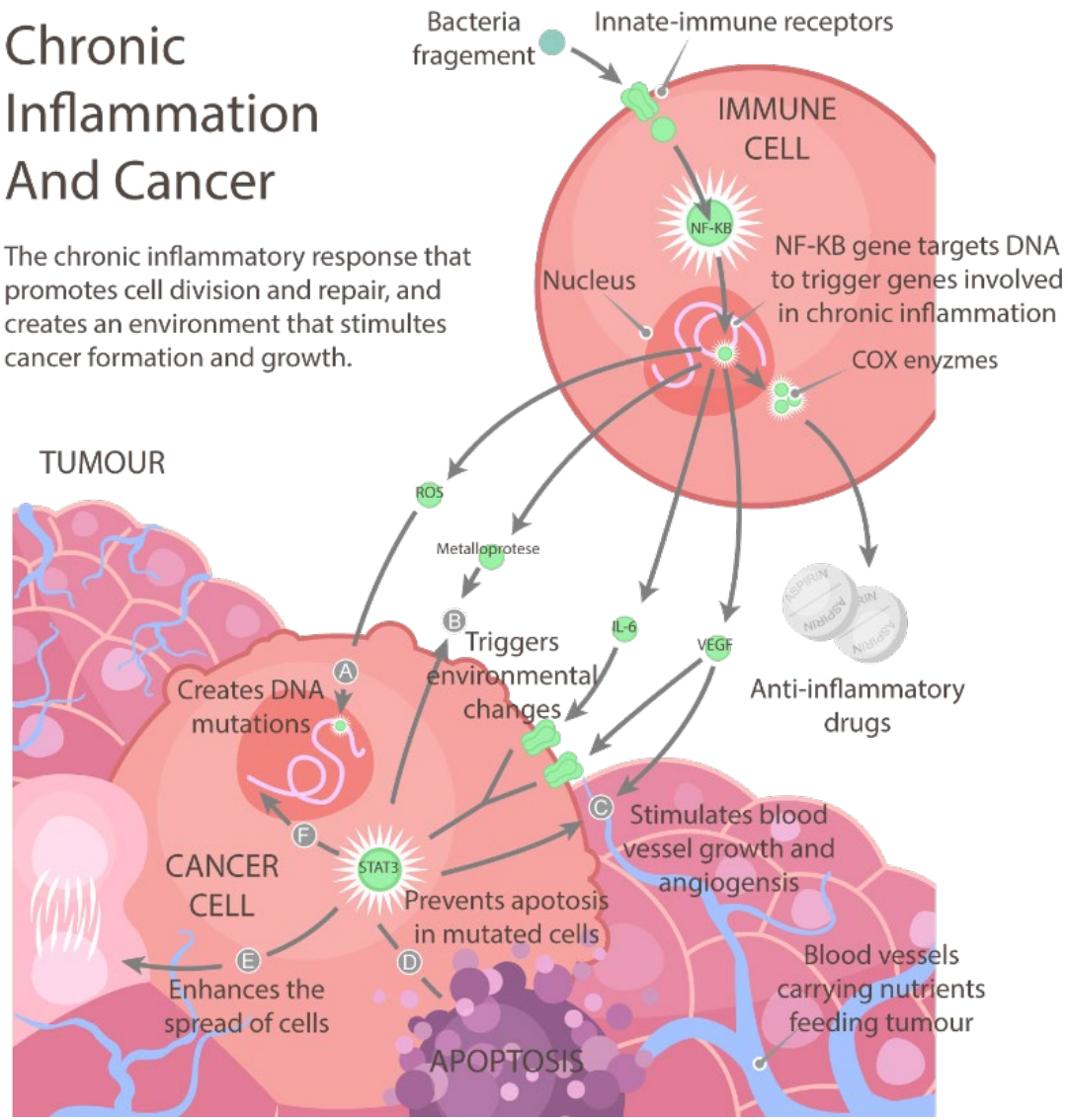
Mechanisms by which tumors avoid immune recognition				
Low immunogenicity	**Tumor treated as self antigen**	**Antigenic modulation**	**Tumor-induced immune suppression**	**Tumor-induced privileged site**
No peptide:MHC ligand No adhesion molecules No co-stimulatory molecules	Tumor antigens taken up and presented by APCs in absence of co-stimulation tolerize T cells	T cells may eliminate tumors expressing immunogenic antigens, but not tumors that have lost such antigens	Factors (e.g.,TGF-β, IL-10, IDO) secreted by tumor cells inhibit T cells directly. Expression of PD-L1 by tumors	Factors secreted by tumor cells create a physical barrier to the immune system
				

Cancer Microenviroment



http://www.nature.com/nature/journal/v501/n7467/full/nature12626.html

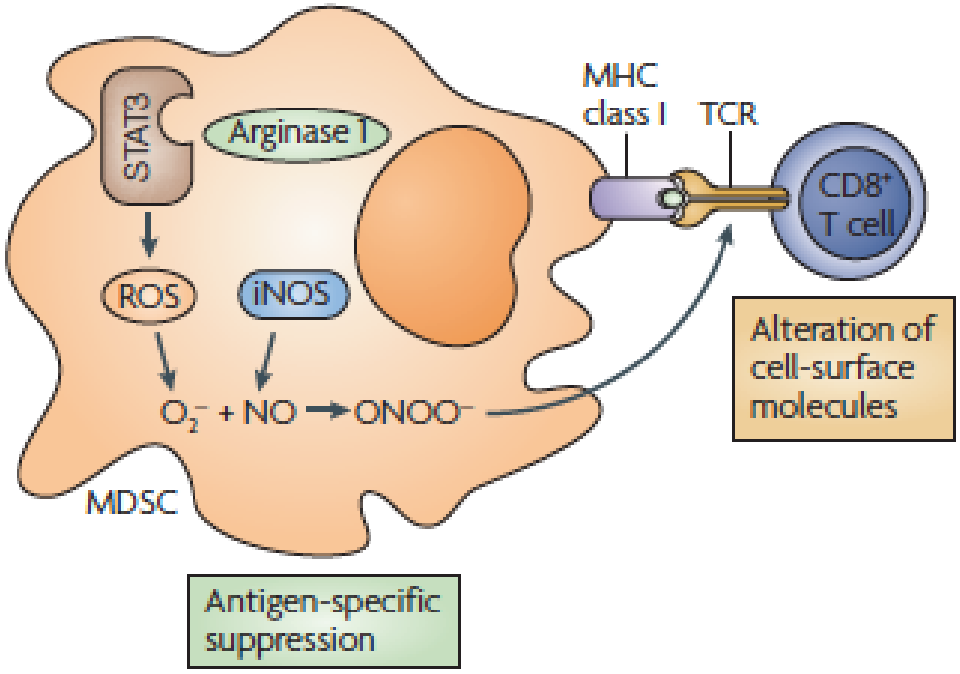
Cancers are Wounds that Never Heal



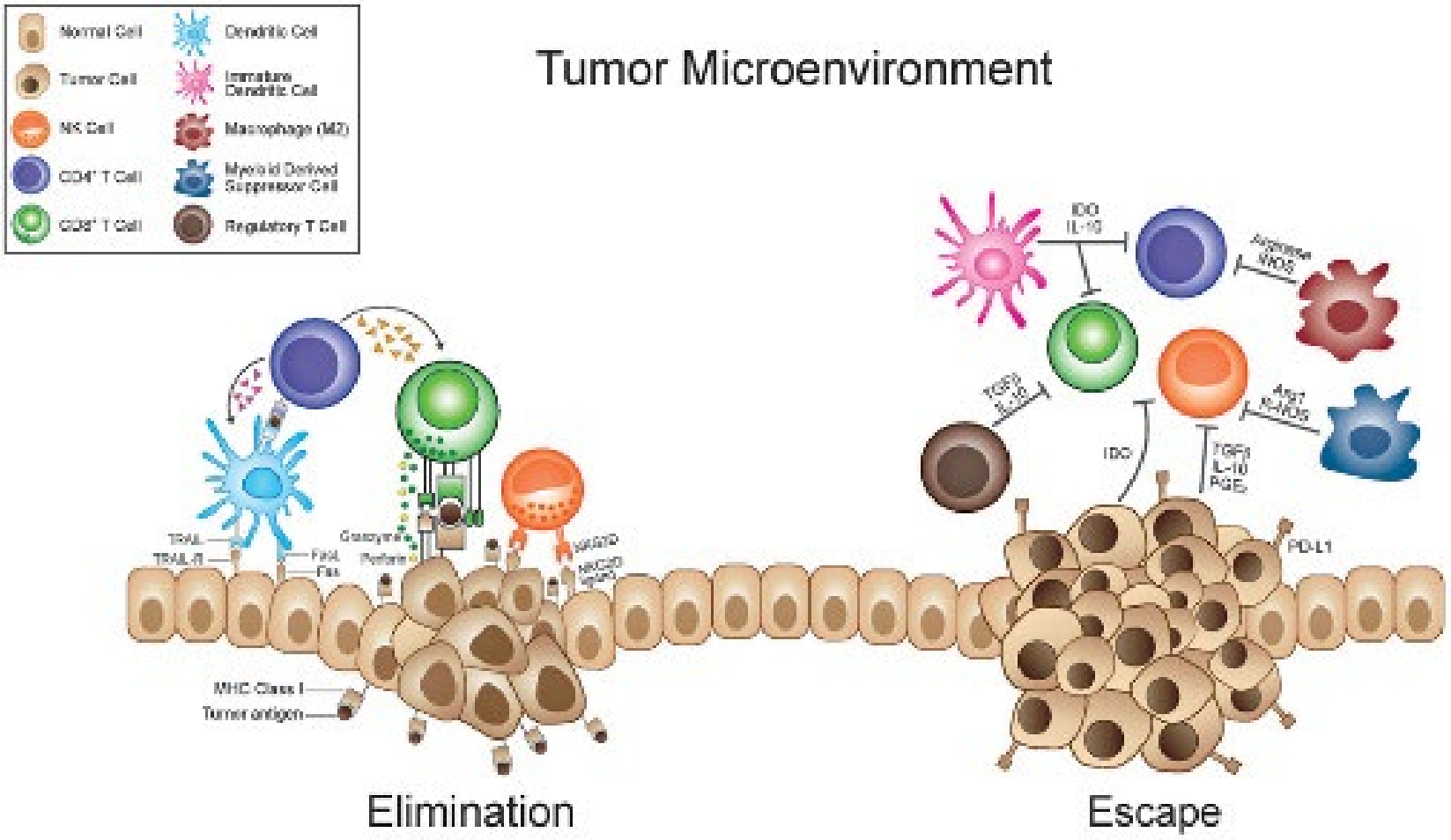
http://earthingcanada.ca/chronic-inflammation-and-cancer/

Myeloid Derived Suppressor Cells

MDSC act as a T cell target by presenting antigen to them and then disabling the TCR upon engagement of the MHC complex through production of reactive nitrogen species



Tumor Microenviroment



http://commons.wikimedia.org/wiki/File:Tumor_microenvironment.jpg

Tumor Immunobiology

- Tumor formation
- Tumor microenvironment
- Tumor Immune evasion
- Tumor Immune therapy

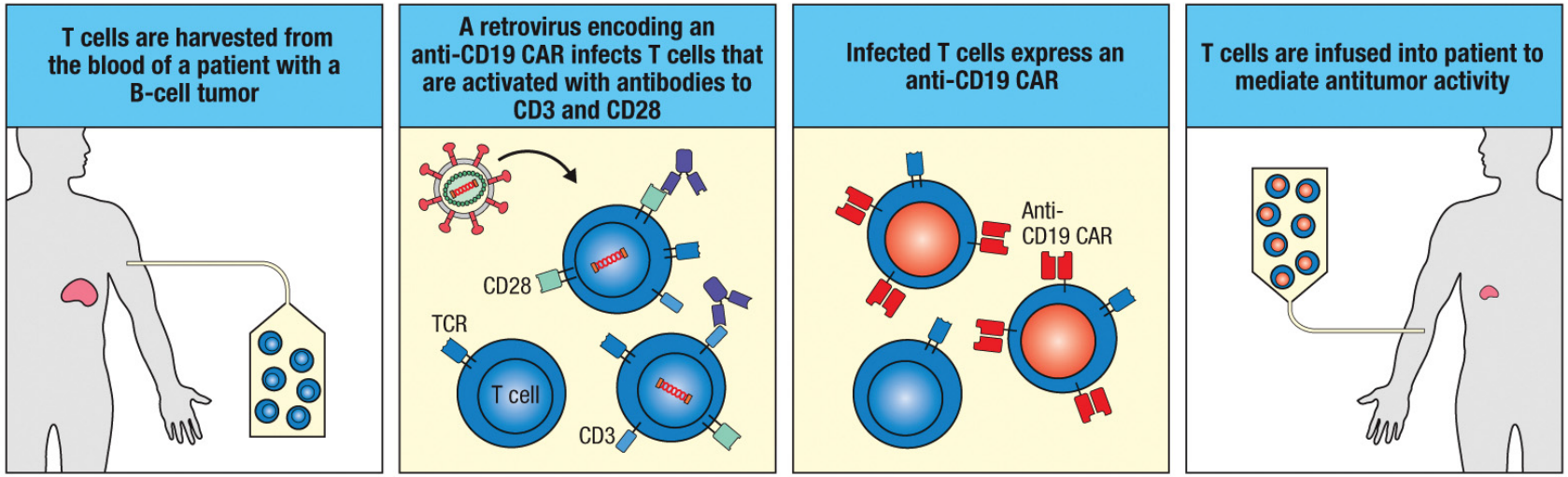
How Do We Break the Tolerance?

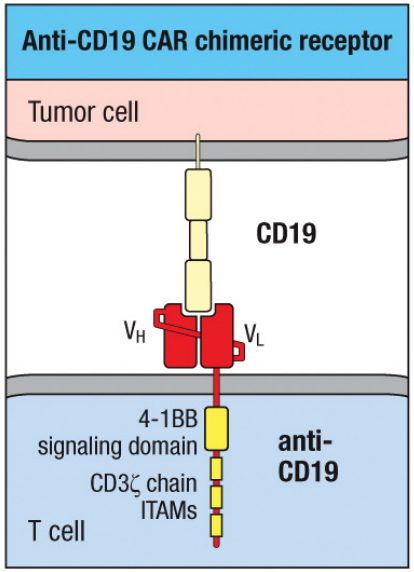
- Target Tumor associated myeloid cells
- How to use tumor specific antigens?
  - Adoptive T-cell therapy
    - Expanded tumor specific T cells in vitro
  - Monoclonal antibodies
    - Tagged with toxin or radionuclide
  - Vaccination
    - Infections that induce cancer-prevention
    - Tumor rejection antigen unknown
    - Dendritic cells loaded with tumor antigen
  - Make tumors immunogenic (using patient cells)
    - Transfect patient tumor cells with B7, cytokine
    - Virus to lyse tumor cells
    - CTLA-4 and PD-1 inhibition

Tumor Rejection Antigens: Basis of Immunotherapies

Potential tumor-rejection antigens have a variety of origins			
Class of antigen	**Antigen**	**Nature of antigen**	**Tumor type**
Tumor-specific mutated oncogene or tumor suppressor gene	Cyclin-dependent kinase 4	Cell-cycle regulator	Melanoma
	β-Catenin	Relay in signal transduction pathway	Melanoma
	Caspase 8	Regulator of apoptosis	Squamous-cell carcinoma
	Surface Ig/ idiotype	Specific antibody after gene rearrangements in B-cell clone	Lymphoma
Cancer-testis antigens	MAGE-1 MAGE-3 NY-ESO-1	Normal testicular proteins	Melanoma Breast Glioma
Differentiation	Tyrosinase	Enzyme in pathway of melanin synthesis	Melanoma
Abnormal gene expression	HER-2/neu	Receptor tyrosine kinase	Breast Ovary
	WT1	Transcription factor	Leukemia
Abnormal post-translational modification	MUC-1	Underglycosylated mucin	Breast Pancreas
Abnormal post-transcriptional modification	NA17	Retention of introns in the mRNA	Melanoma
Oncoviral protein	HPV type 16, E6 and E7 proteins	Viral transforming gene products	Cervical carcinoma

T Cells Expressing Chimeric Antigen Receptors





Kill transformed B cells

Long lasting T cell response

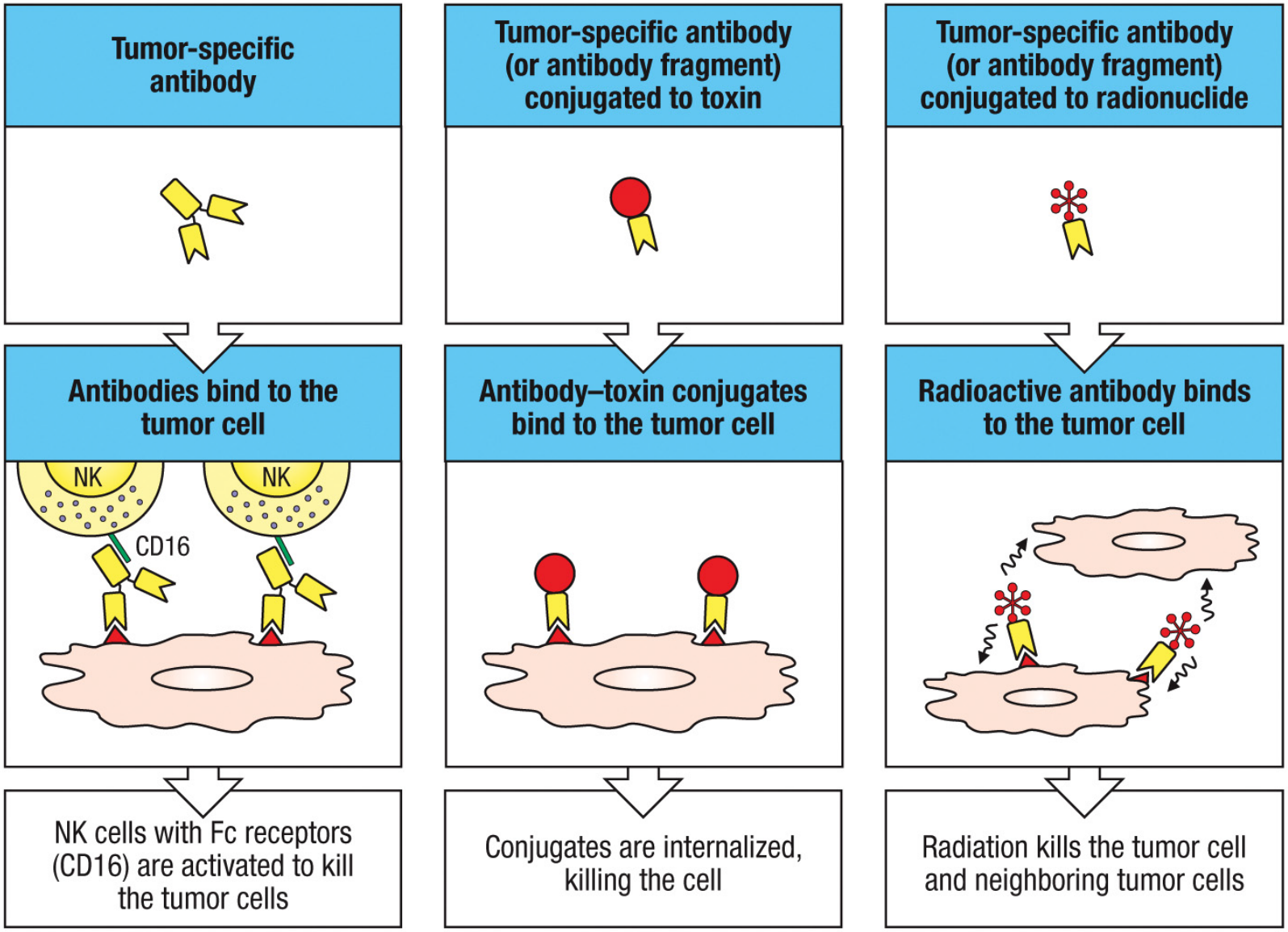
Memory?

Limitation

- Potency
- Specific tumor surface antigen
  - CD19 mutation

- Safety
- Self reactive T cells
  - Artificial amplification
- Cytokine storm

Antibody Therapy



Monoclonal Antibodies Against Tumor Antigens

Tumor tissue origin	Type of antigen	Antigen	Tumor type
Lymphoma/ leukemia	Differentiation antigen	CD5 Idiotype CD52 (Campath-1H)	T-cell lymphoma B-cell lymphoma T- and B-cell lymphoma/ leukemia
	B-cell signaling receptor	CD20	Non-Hodgkin's B-cell lymphoma
Solid tumors	Cell-surface antigens Glycoprotein Carbohydrate	 CEA, mucin-1 $Lewis^Y$ CA-125	 Epithelial tumors (breast, colon, lung) Epithelial tumors Ovarian carcinoma
	Growth factor receptors	Epidermal growth factor receptor HER-2/neu IL-2 receptor Vascular endothelial growth factor (VEGF)	Lung, breast, and head and neck tumors Breast, ovarian tumors T- and B-cell tumors Colon cancer Lung, prostate, breast
	Stromal extracellular antigen	FAP-α Tenascin Metalloproteinases	Epithelial tumors Glioblastoma multiforme Epithelial tumors

Limitation

- Antibody itself does not kill
- Penetration
  - Single chain Fv molecule
- Soluble target Protein
  - Competition
- Drugs that require internalization

How Do We Break the Tolerance?

- Target Tumor associated myeloid cells

- How to use tumor specific antigens?
  - Adoptive T-cell therapy
    - Expanded tumor specific T cells in vitro
  - Monoclonal antibodies
    - Tagged with toxin or radionuclide
  - Vaccination
    - Infections that induce cancer-prevention
    - Tumor rejection antigen unknown
    - Dendritic cells loaded with tumor antigen
  - Make tumors immunogenic (using patient cells)
    - Transfect patient tumor cells with B7, cytokine
    - CTLA-4 and PD-1 inhibition

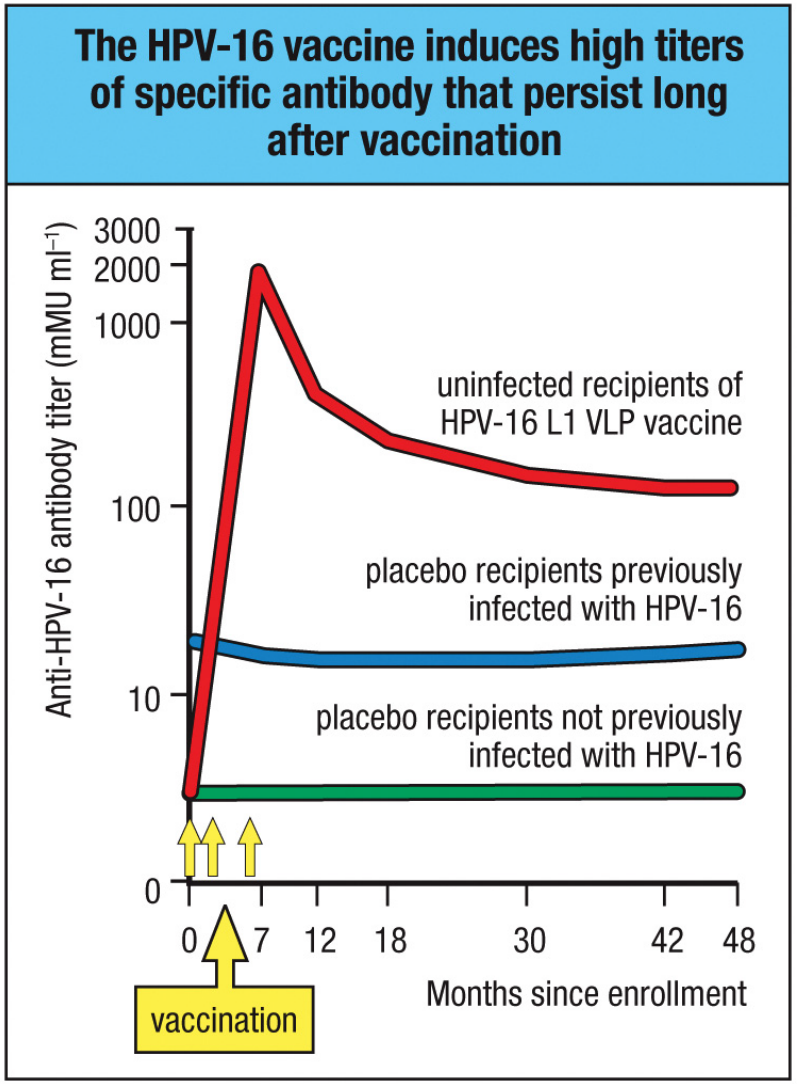
Prevention

•**Cervical cancer:**
•Virtually all cases caused by HPV,
- HPV types, 16 and 18, are responsible for about 70% of all cases.

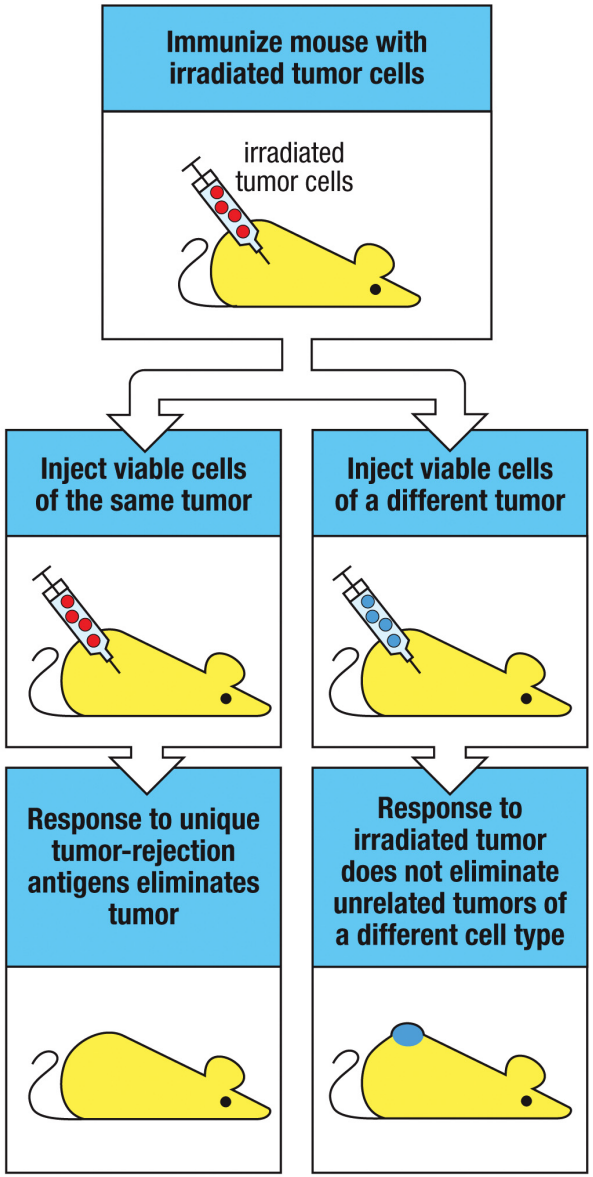
•**Anal cancer:**
•About 95% caused by HPV.
- Most caused by HPV type 16.

•**Oropharyngeal cancers:**
•About 70% caused by HPV.
•more than half of cancers diagnosed linked to HPV type 16.

•**Rarer cancers:**
•HPV causes about 65% of vaginal cancers, 50% of vulvar cancers, and 35% of penile cancers.
• Most of these are caused by HPV type 16.

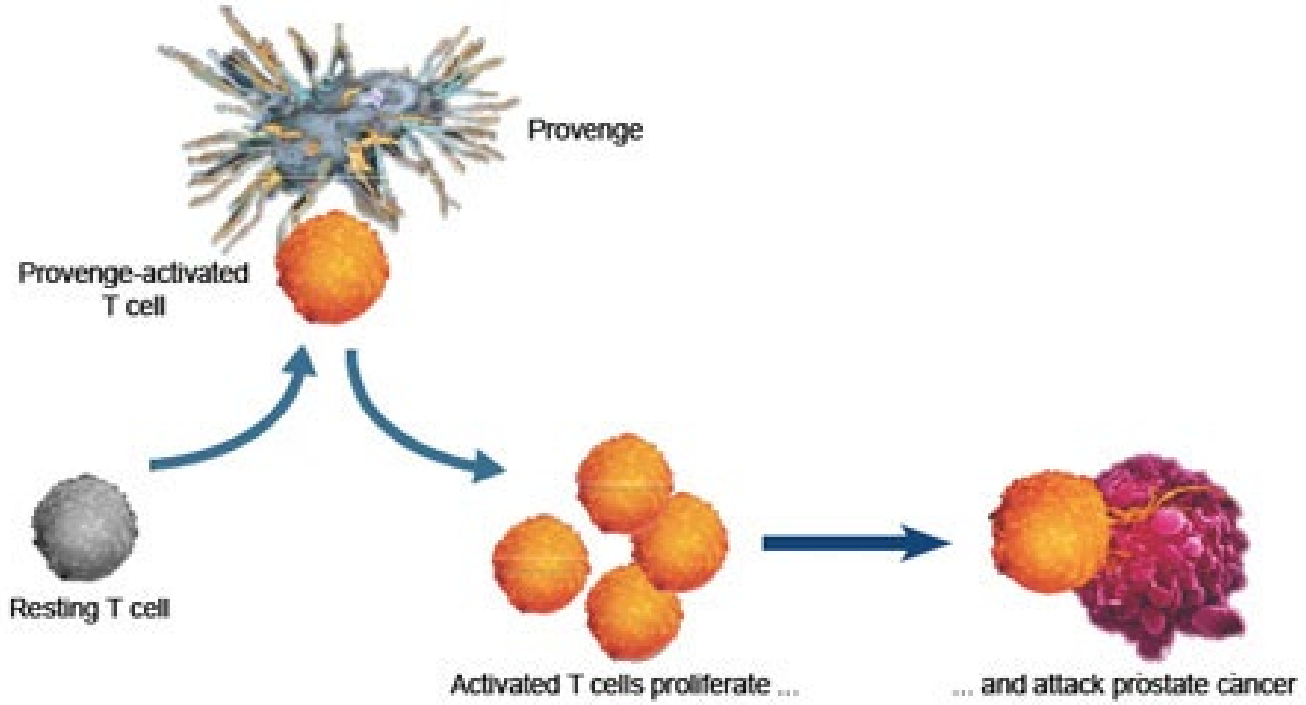


Cancer Vaccine as Treatment?



Options

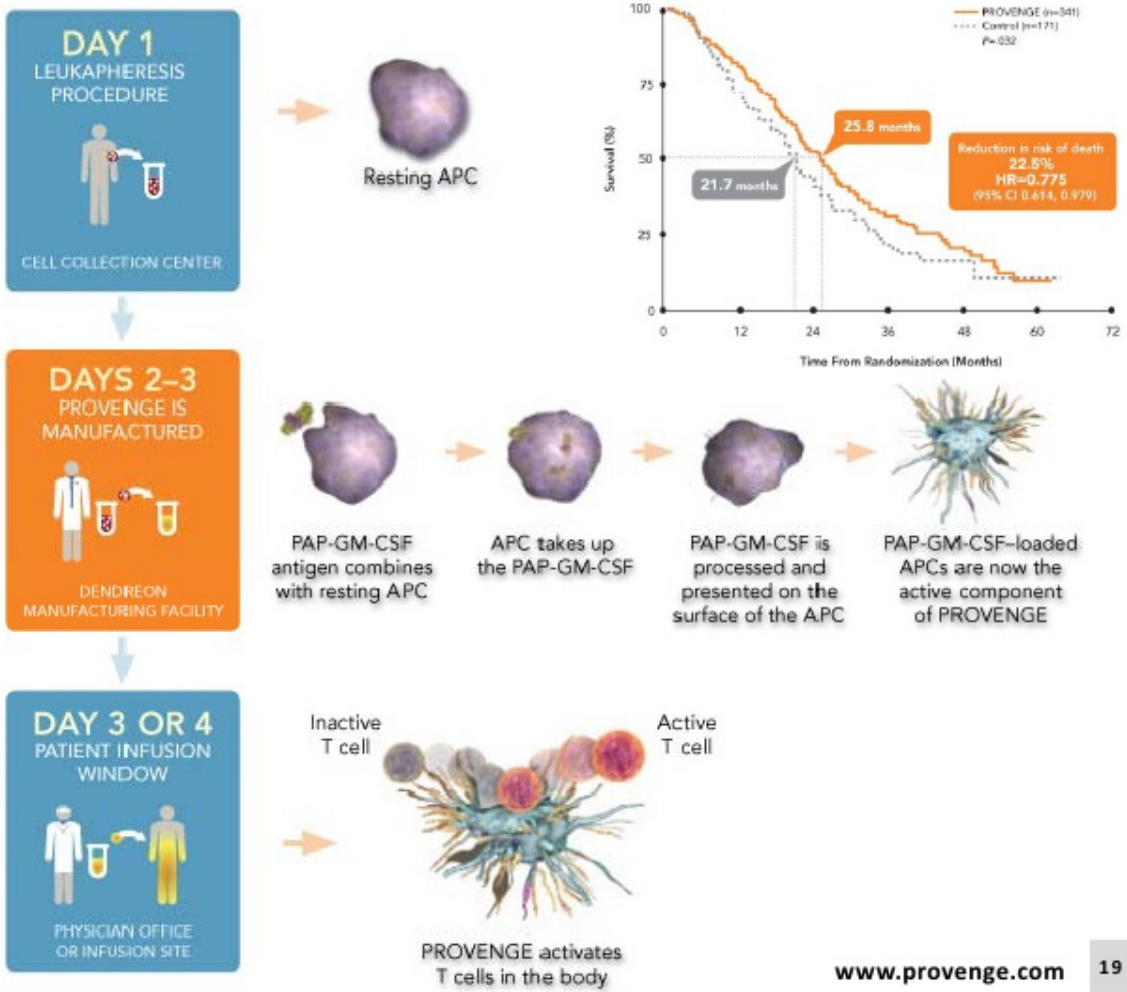
- Provenge (sipuleucel-T treatment)
- metastatic castrate-resistant (mCRPC)
- Antigen loaded Dendritic Cells



Provenge

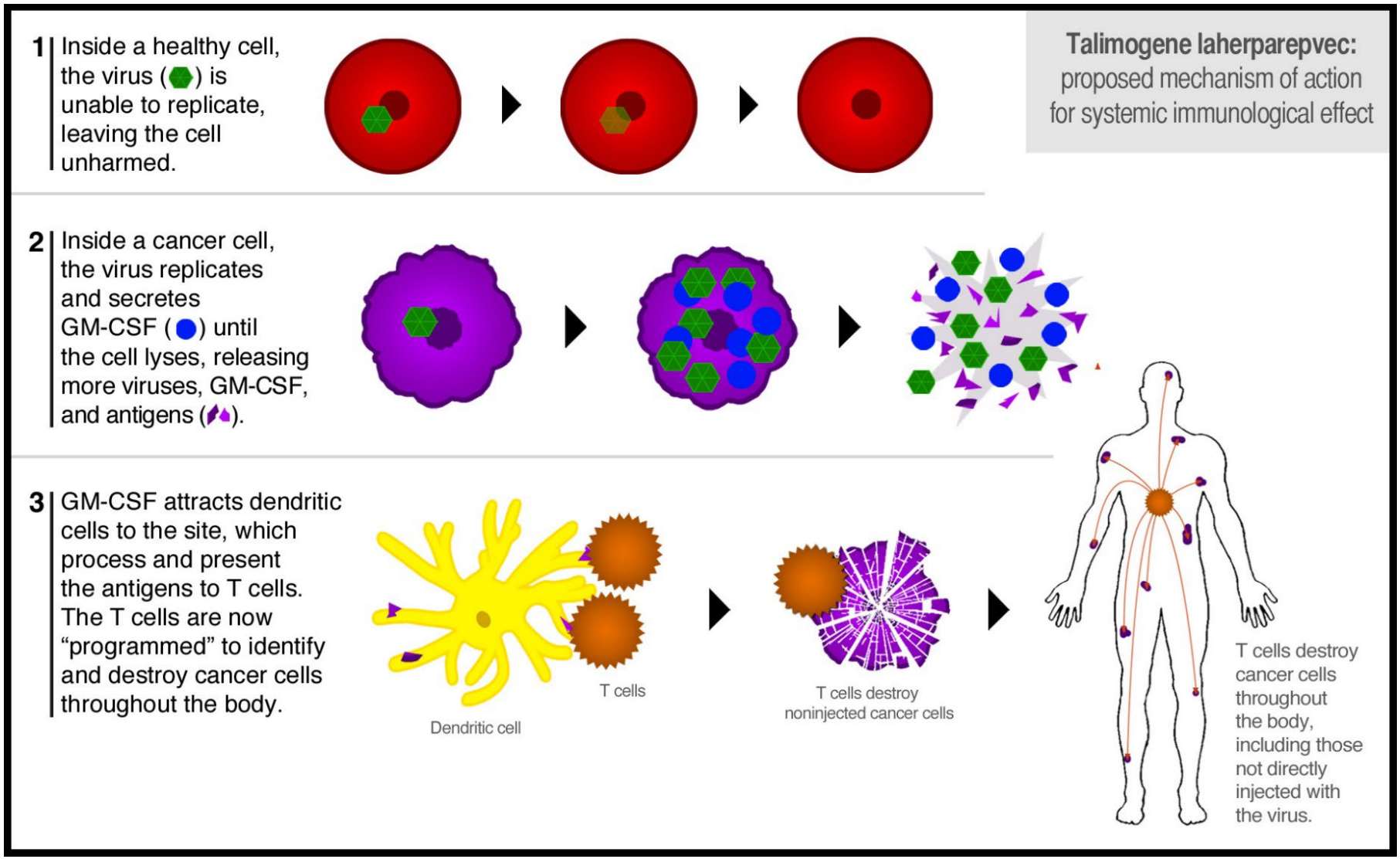
First immunotherapy product approved 29 Apr 2010: Provenge

- Hormone refactory prostate cancer
- Collection of white blood cells
- Transduction w/ PAP & GMCSF to activate antigen presenting cells
- Return cells into patient
- First immunotherapy product !
  - PAP = prostatic acid phosphatase
  - GMCSF = granulocyte macrophage colony stimulating factor



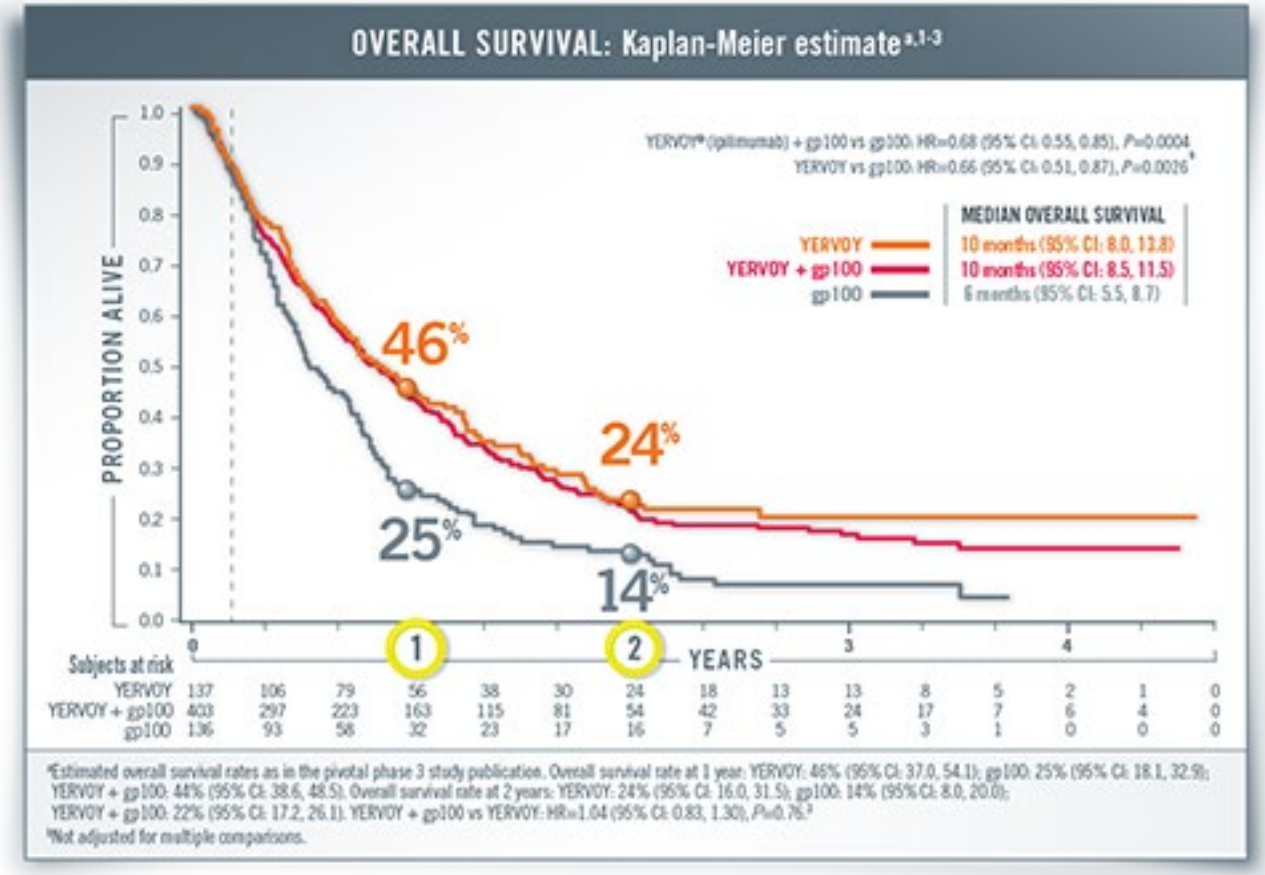
T-VEC (Imlygic™)

FDA approved in 2015, however failed in clinical trials



Checkpoint Blockade: CTLA-4

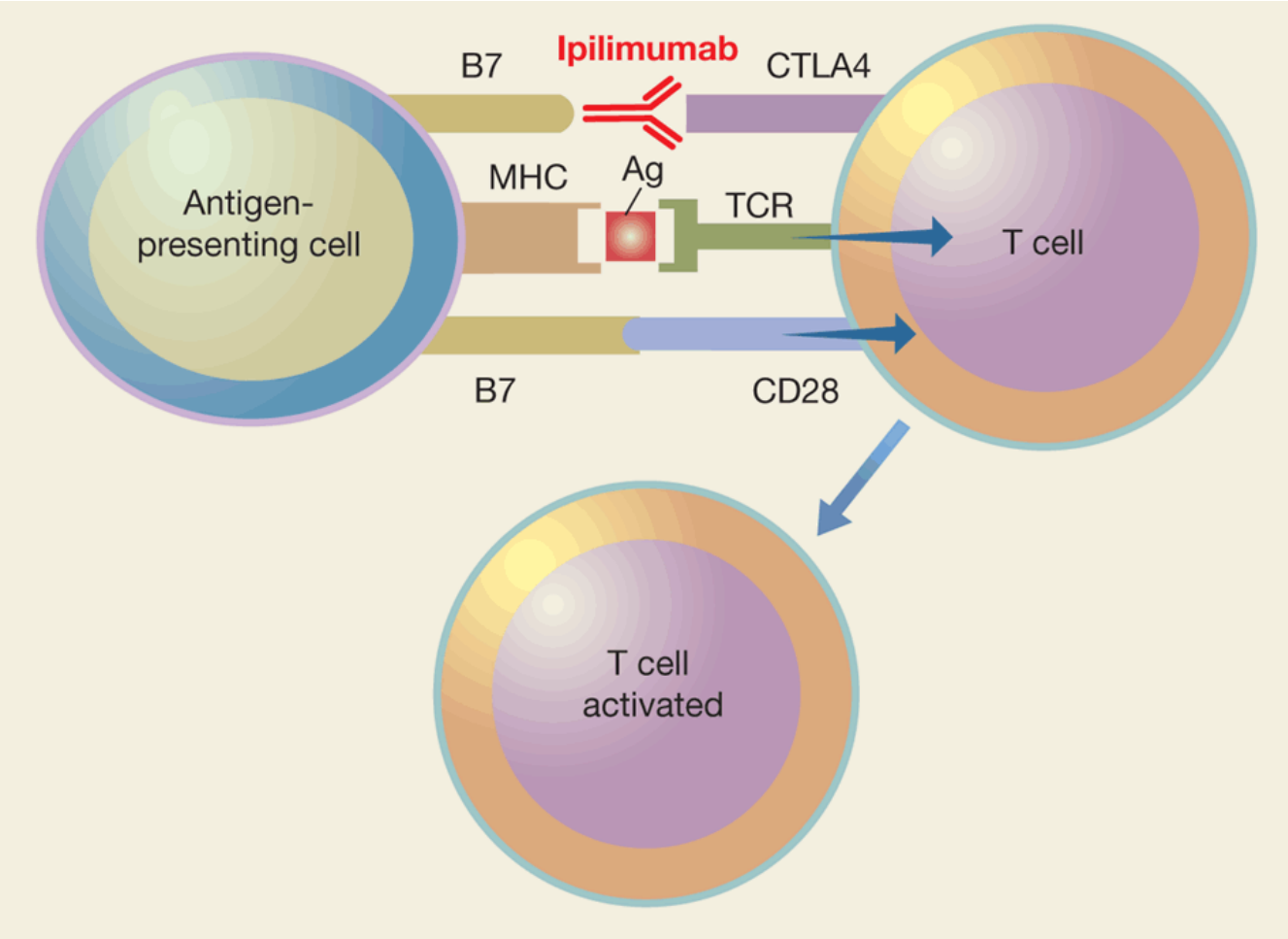
- Ipilimumab: approved in 2011 for the treatment of melanoma, undergoing clinical trials for lung, bladder, prostate and other cancer.
- Gp100:peptide vaccine



24% 2-YEAR survival rate*

Some patients were alive up to 4.5 YEARS*

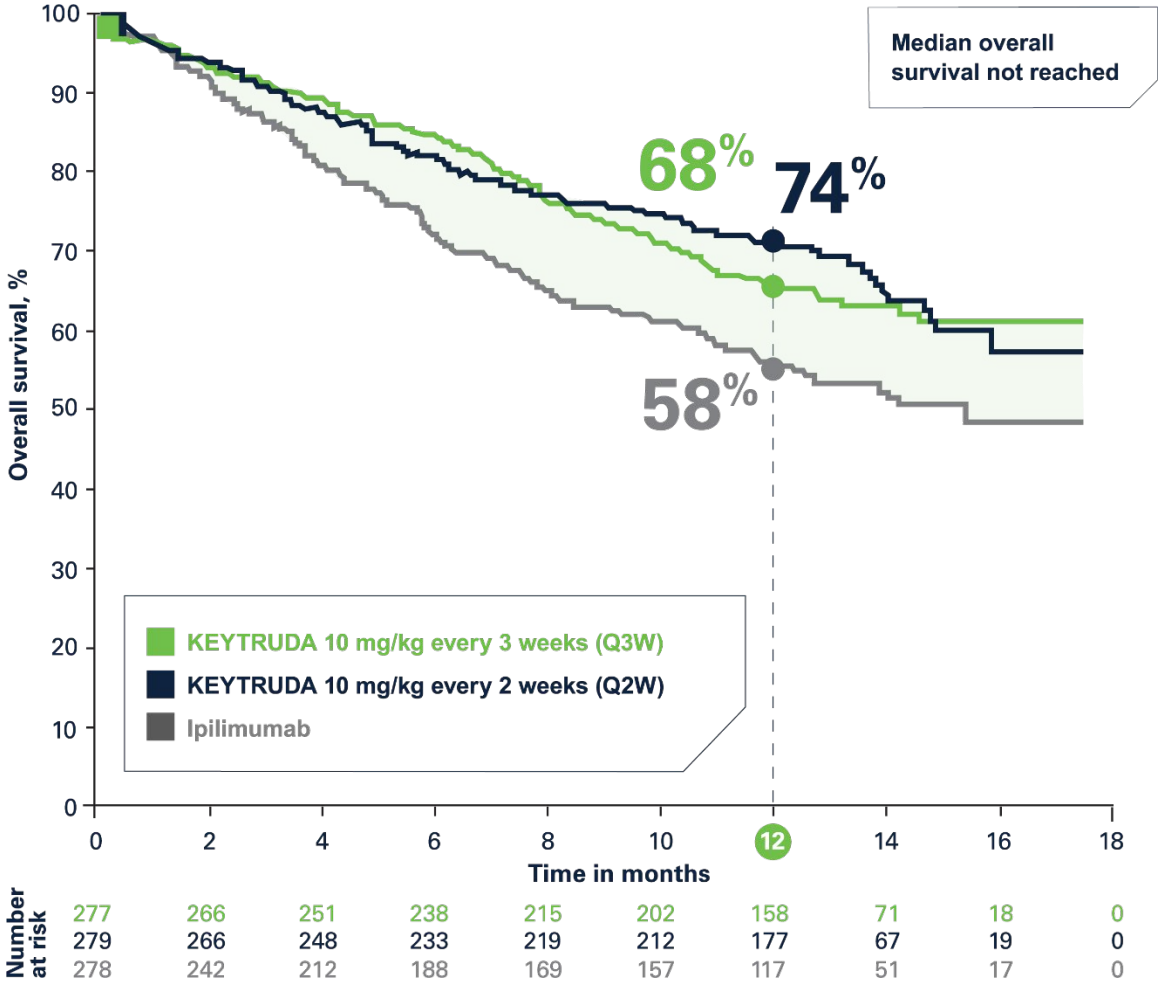
Checkpoint Blockade: CTLA-4



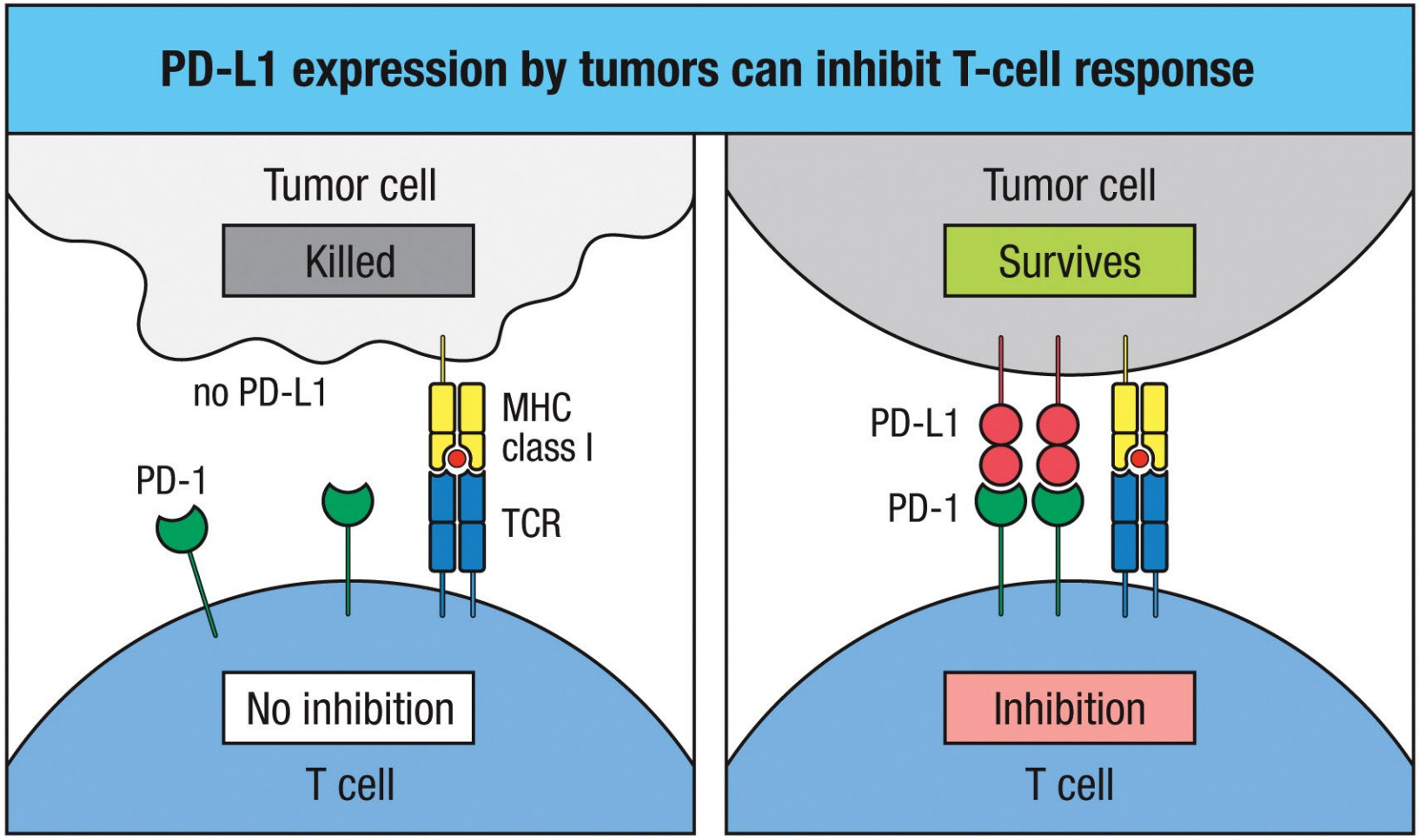
Potential auto-immune problems

Checkpoint Blockade: PD-L1

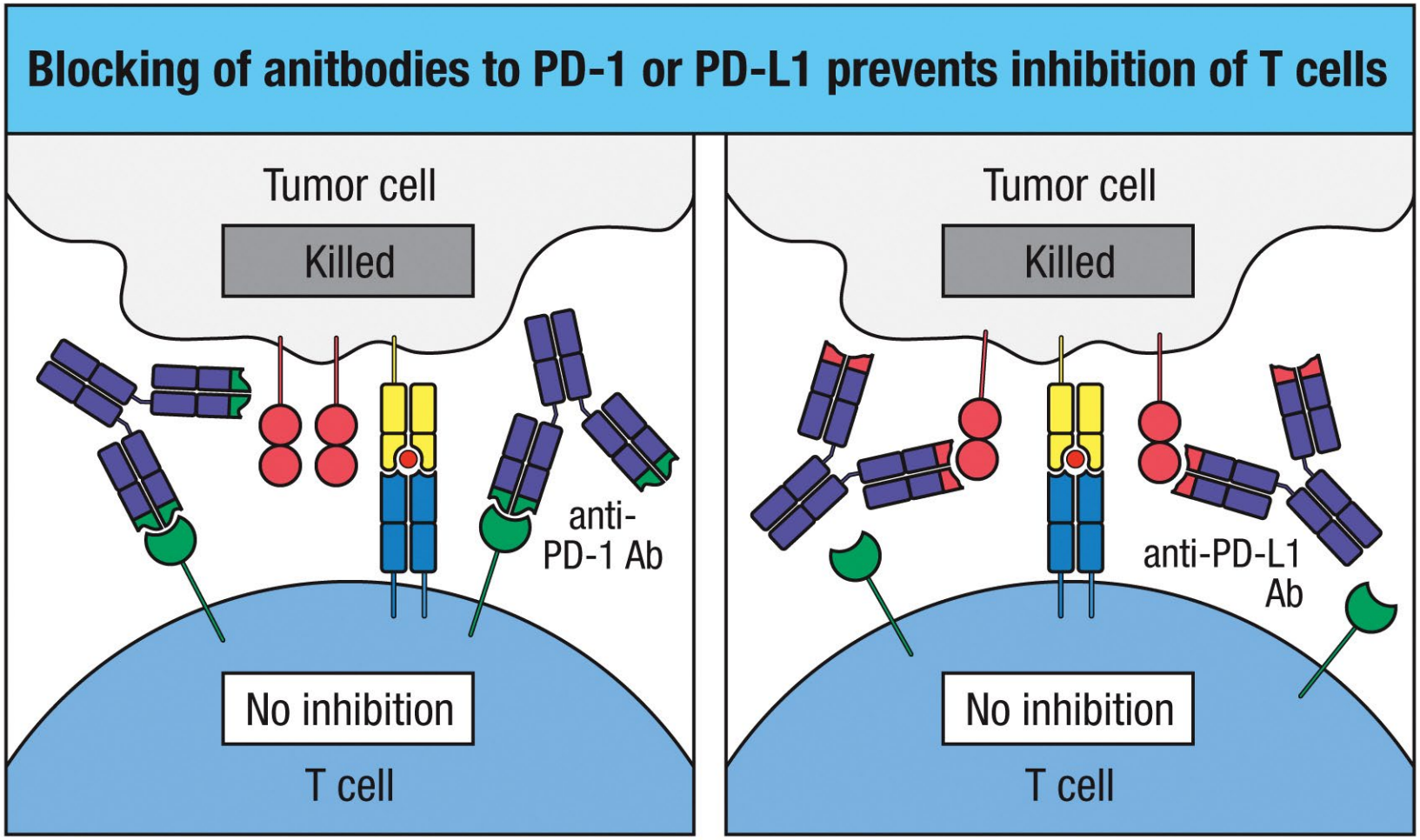
- Pembrolizumab: In 2017 the FDA approved it for any unresectable or metastatic solid tumor with certain genetic anomalies (mismatch repair deficiency or microsatellite instability).



Checkpoint Blockade: PD-L1



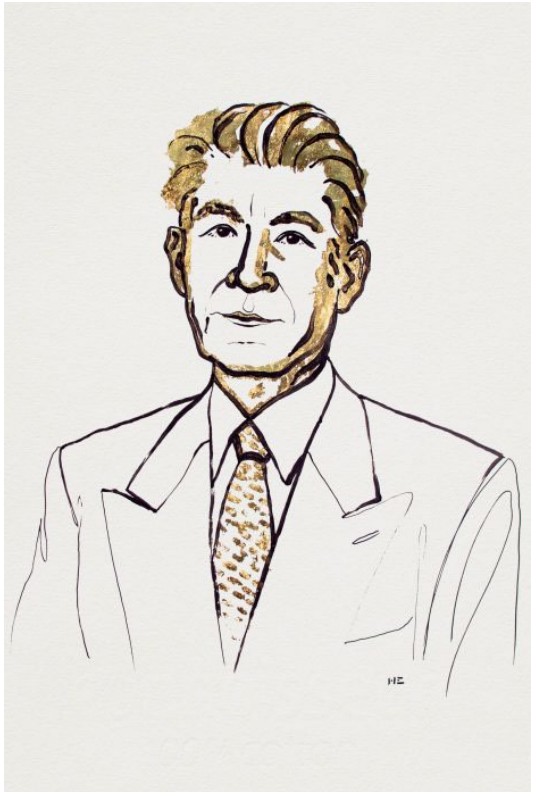
Checkpoint Blockade: PD-L1



The Nobel Prize in Physiology or Medicine 2018

their discovery of cancer therapy by inhibition of negative immune regulation

James P. Allison



Tasuku Honjo

Checkpoint Blockade: PD-L1

nature International weekly journal of science

NATURE | NEWS

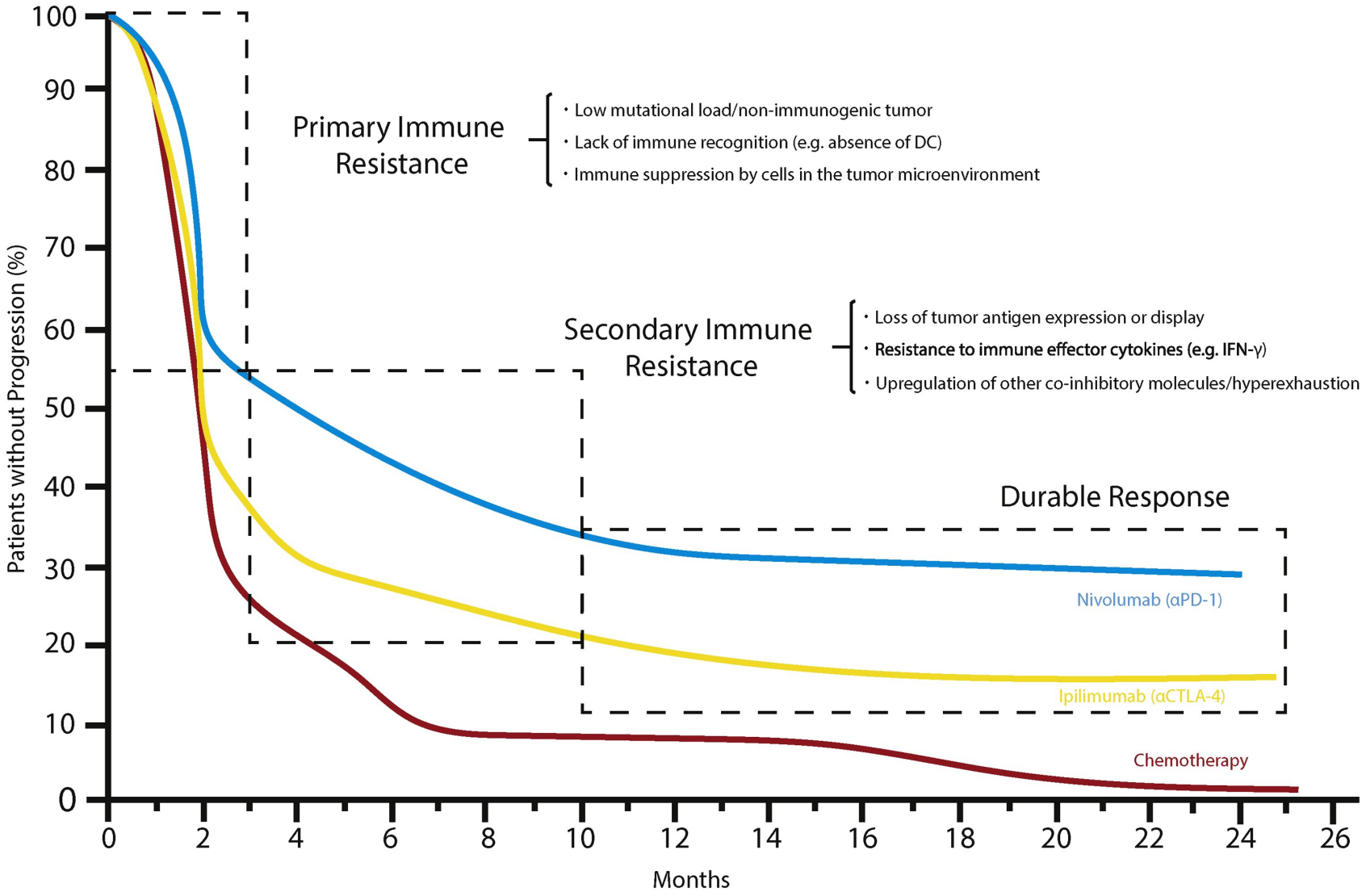
Promising cancer drugs may speed tumours in some patients

Early studies fuel scientists' determination to understand how immunotherapy may sometimes make disease worse.

Heidi Ledford

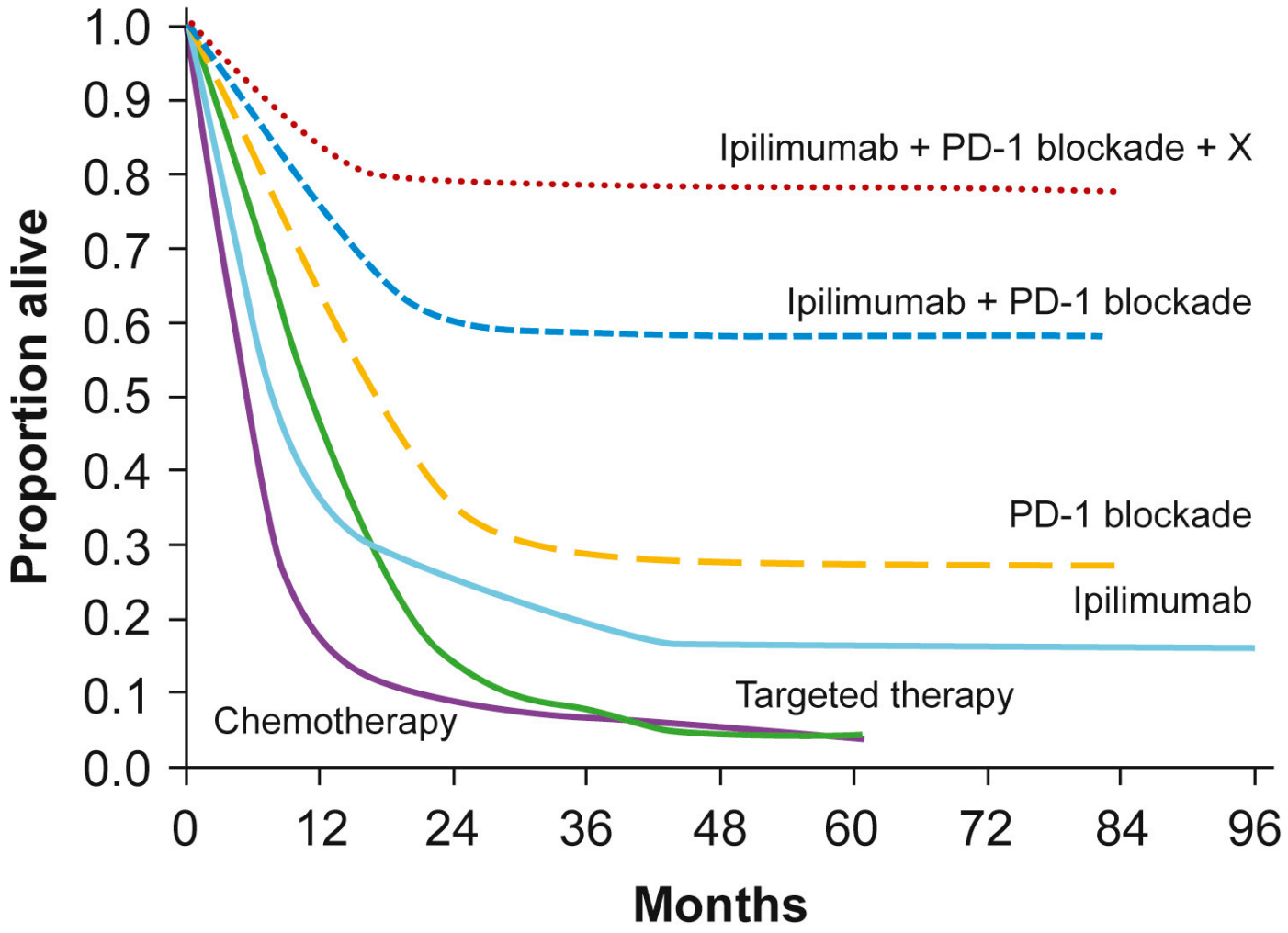
31 March 2017

Immune Checkpoint Blockade Therapy



https://www.sciencedirect.com/science/article/pii/S1359610117300758#fig0005

Model: Combinatorial Therapy



https://www.sciencedirect.com/science/article/pii/S0959804917309188

Future Direction

- Combinatorial Therapy
  - Anti PD-1
  - Anti CTLA-4
  - Vaccine
  - IL-2
- Cell Therapy
  - CAR-T, CAR-NK, CAR-Neutrophil
- Personalized Treatment