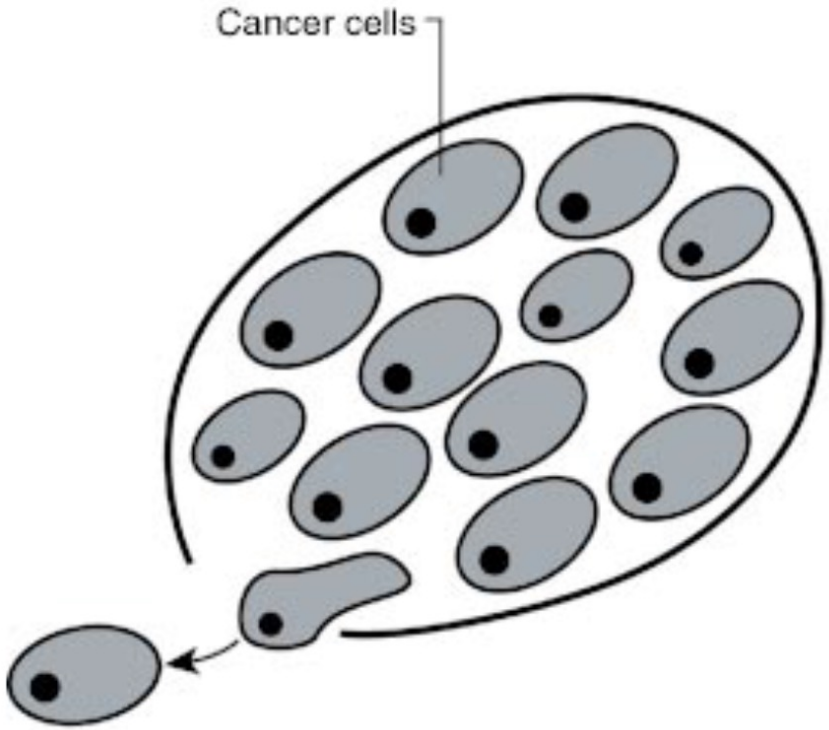
Tumor Immunology: Basic Concepts

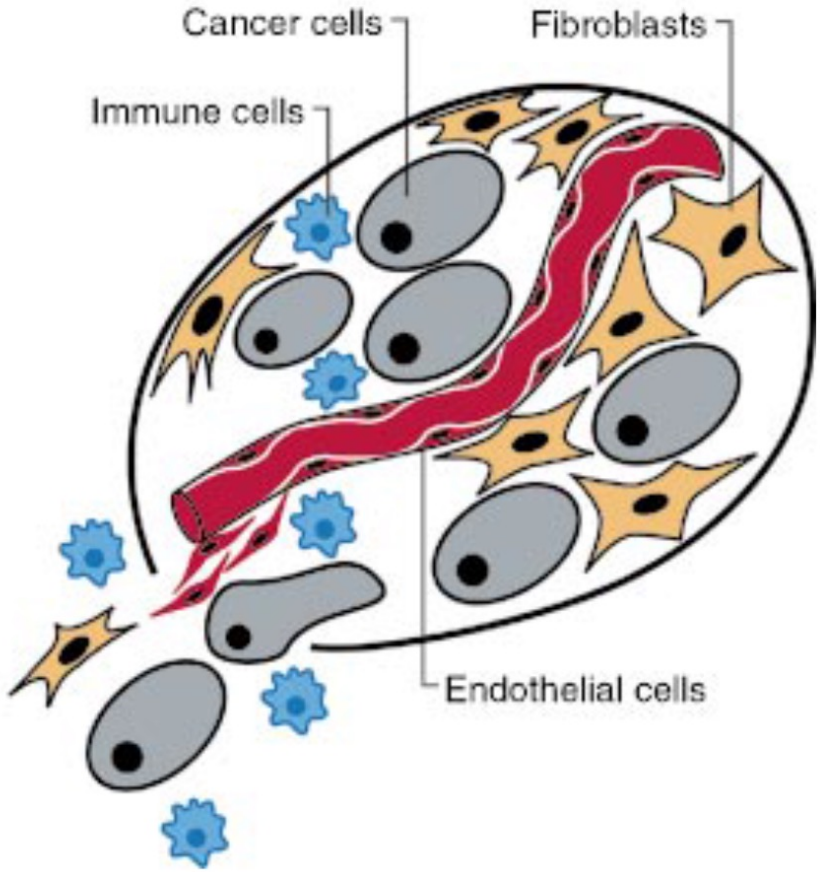
Ming Li

Tumors as Complex Tissues

The Reductionist View



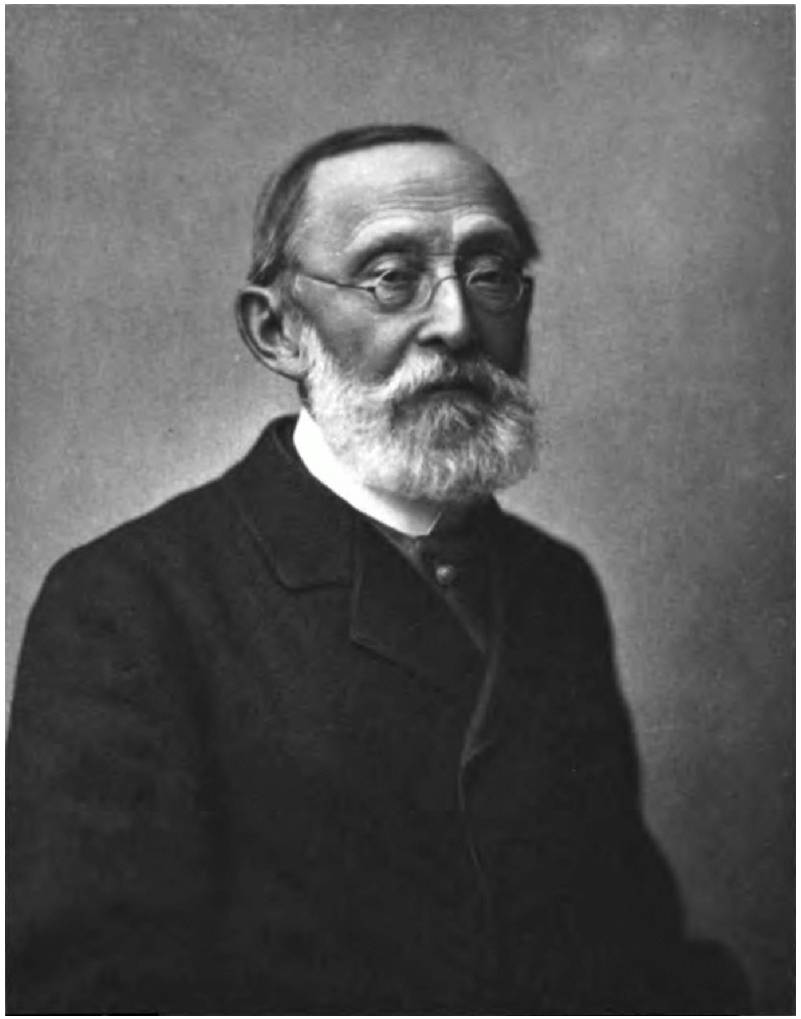
A Heterotypic Cell Biology



Hanahan D & Weinberg RA *Cell* 2000 100: 57-70.

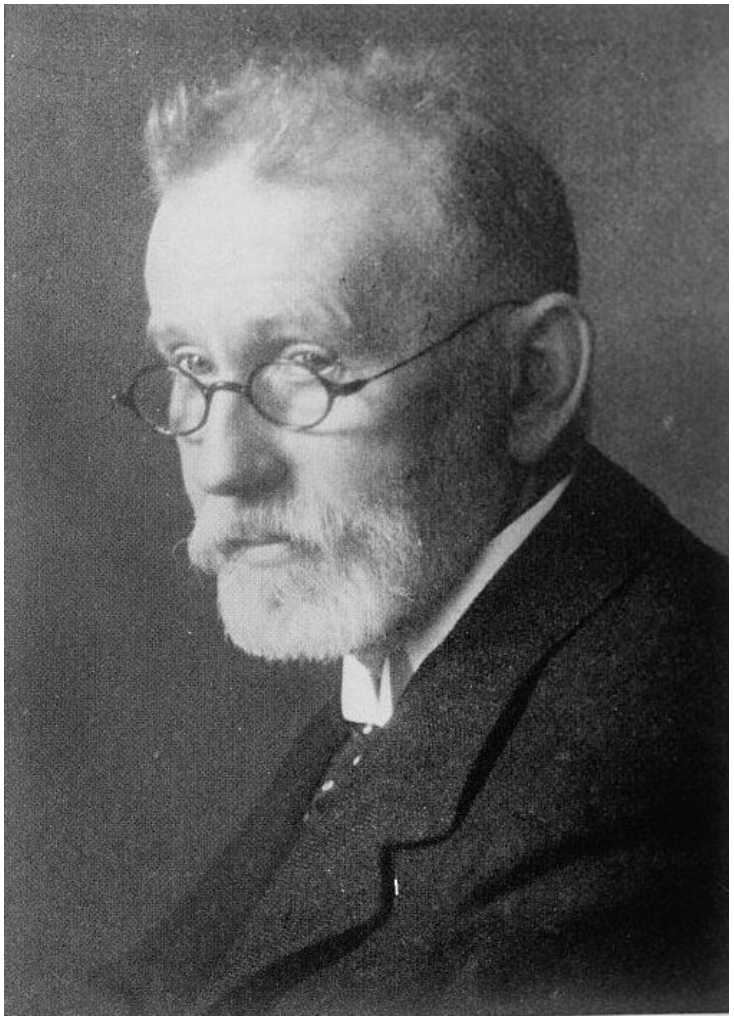
Cancer-Associated Immune Response --- Friend or Foe?

Theory of Chronic Irritation



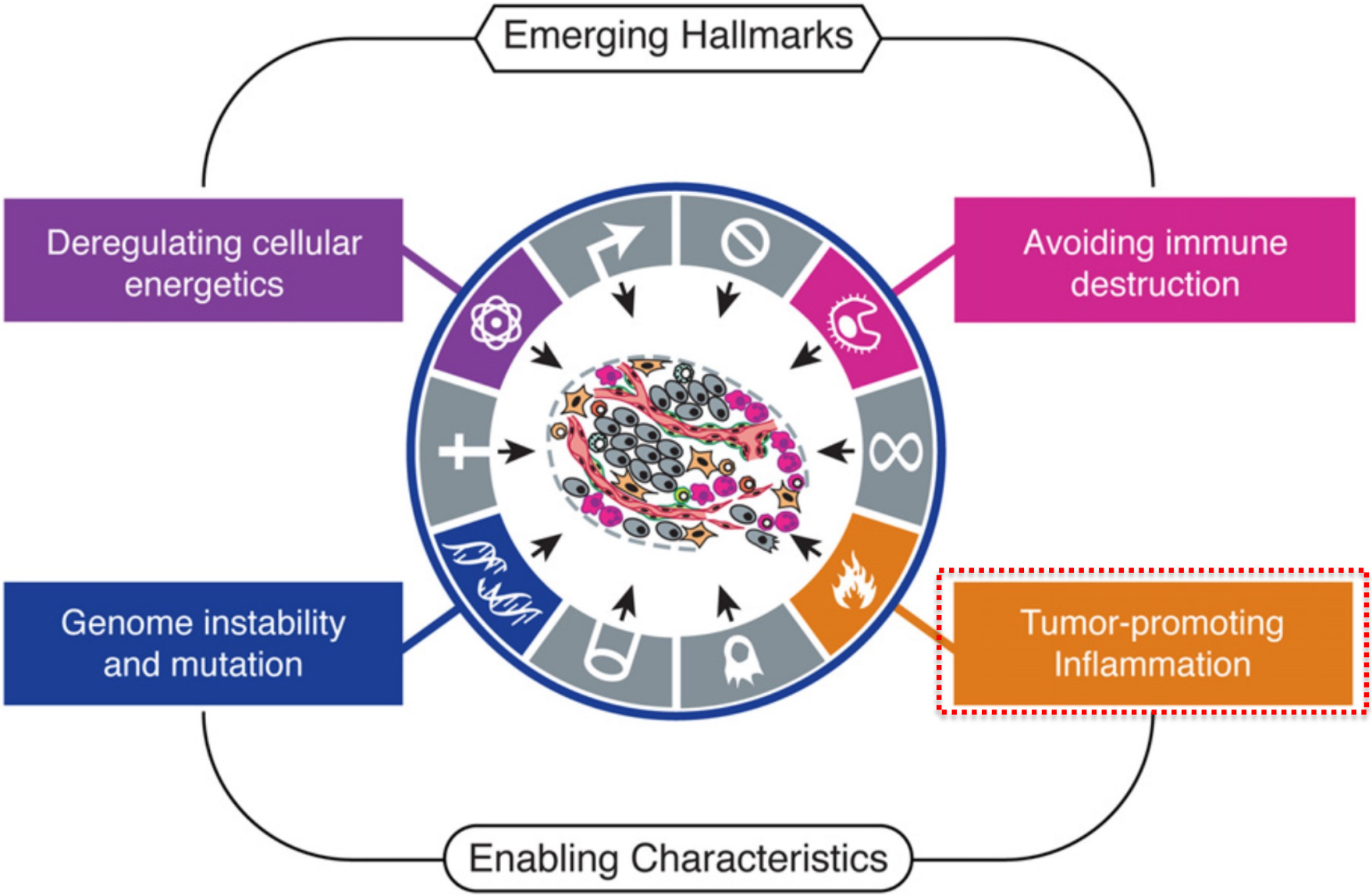
Rudolf Virchow (1850s)

Concept of Immunosurveillance



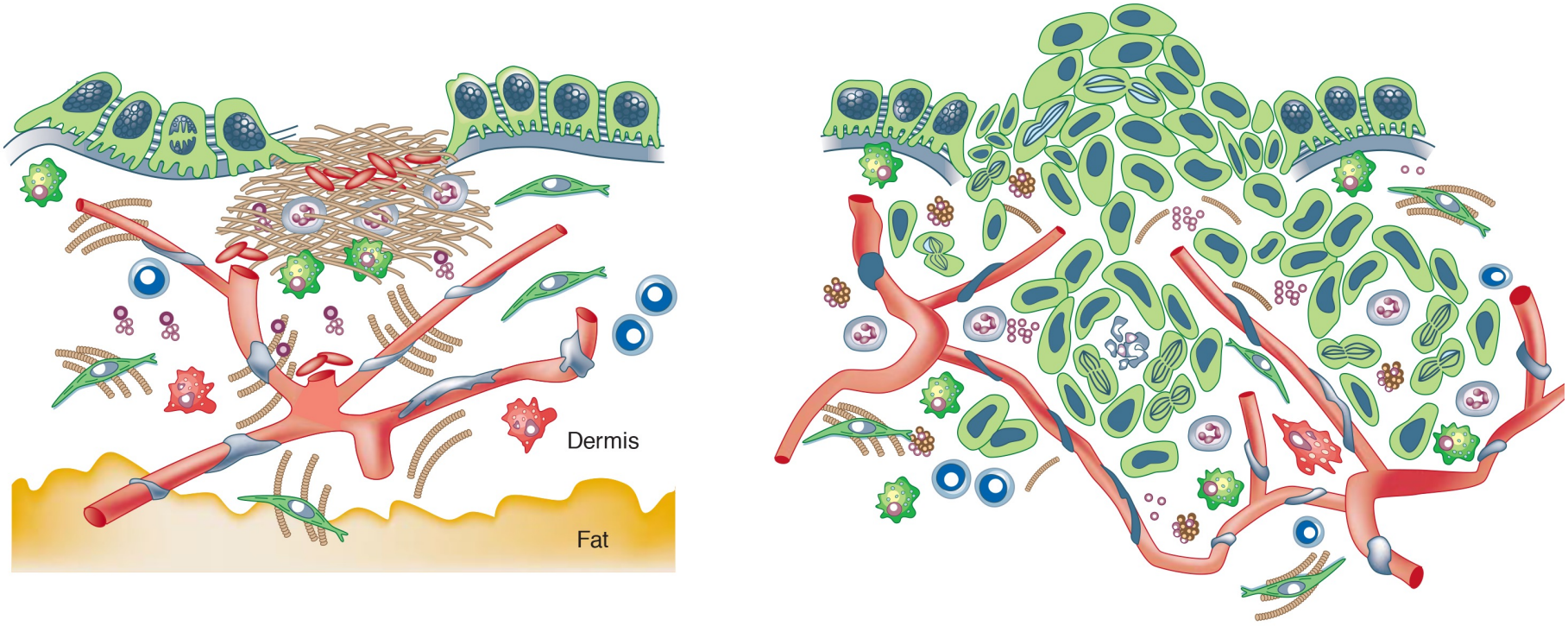
Paul Ehrlich (1900s)

Tumor Immune Adaptation



Hanahan D & Weinberg RA *Cell* 2011 144: 646-674.

Wound Healing and Invasive Tumor Growth



"Tumors: wounds that do not heal."

--- Harold Dvorak *N. Engl. J. Med.* 1986 315: 1650-9.

Chronic Inflammation Promotes Cancer

Table 1 **Chronic inflammatory conditions associated with neoplasms**

Pathologic condition	Associated neoplasm(s)	Aetiologic agent
Asbestosis, silicosis	Mesothelioma, lung carcinoma	Asbestos fibres, silica particles
Bronchitis	Lung carcinoma	Silica, asbestos, smoking (nitrosamines, peroxides)
Cystitis, bladder inflammation	Bladder carcinoma	Chronic indwelling, urinary catheters
Gingivitis, lichen planus	Oral squamous cell carcinoma	
Inflammatory bowel disease, Crohn's disease, chronic ulcerative colitis	Colorectal carcinoma	
Lichen sclerosus	Vulvar squamous cell carcinoma	
Chronic pancreatitis, hereditary pancreatitis	Pancreatic carcinoma	Alcholism, mutation in trypsinogen gene on Ch. 7
Reflux oesophagitis, Barrett's oesophagus	Oesophageal carcinoma	Gastric acids
Sialadenitis	Salivary gland carcinoma	
Sjögren syndrome, Hashimoto's thyroiditis	MALT lymphoma	
Skin inflammation	Melanoma	Ultraviolet light
Cancers associated with infectious agents		
Opisthorchis, *Cholangitis*	Cholangiosarcoma, colon carcnoma	Liver flukes (*Opisthorchis viverrini*), bile acids
Chronic cholecystitis	Gall bladder cancer	Bacteria, gall bladder stones
Gastritis/ulcers	Gastric adenocarcinoma, MALT	*Helicobacter pylori*
Hepatitis	Hepatocellular carcinoma	Hepatitis B and/or C virus
Mononucleosis	B-cell non-Hodgkin's lymphoma, Burkitts lymphoma,	Epstein-Barr Virus
AIDS	Non-Hodgkin's lymphoma, squamous cell carcinomas, Kaposi's sarcoma	Human immunodeficiency virus, human herpesvirus type 8
Osteomyelitis	Skin carcinoma in draining sinuses	Bacterial infection
Pelvic inflammatory disease, chronic cervicitis	Ovarian carcinoma, cervical/anal carcinoma	Gonnorrhoea, chlamydia, human papillomavirus
Chronic cystitis	Bladder, liver, rectal carcinoma, follicular lymphoma of the spleen	Schistosomiasis

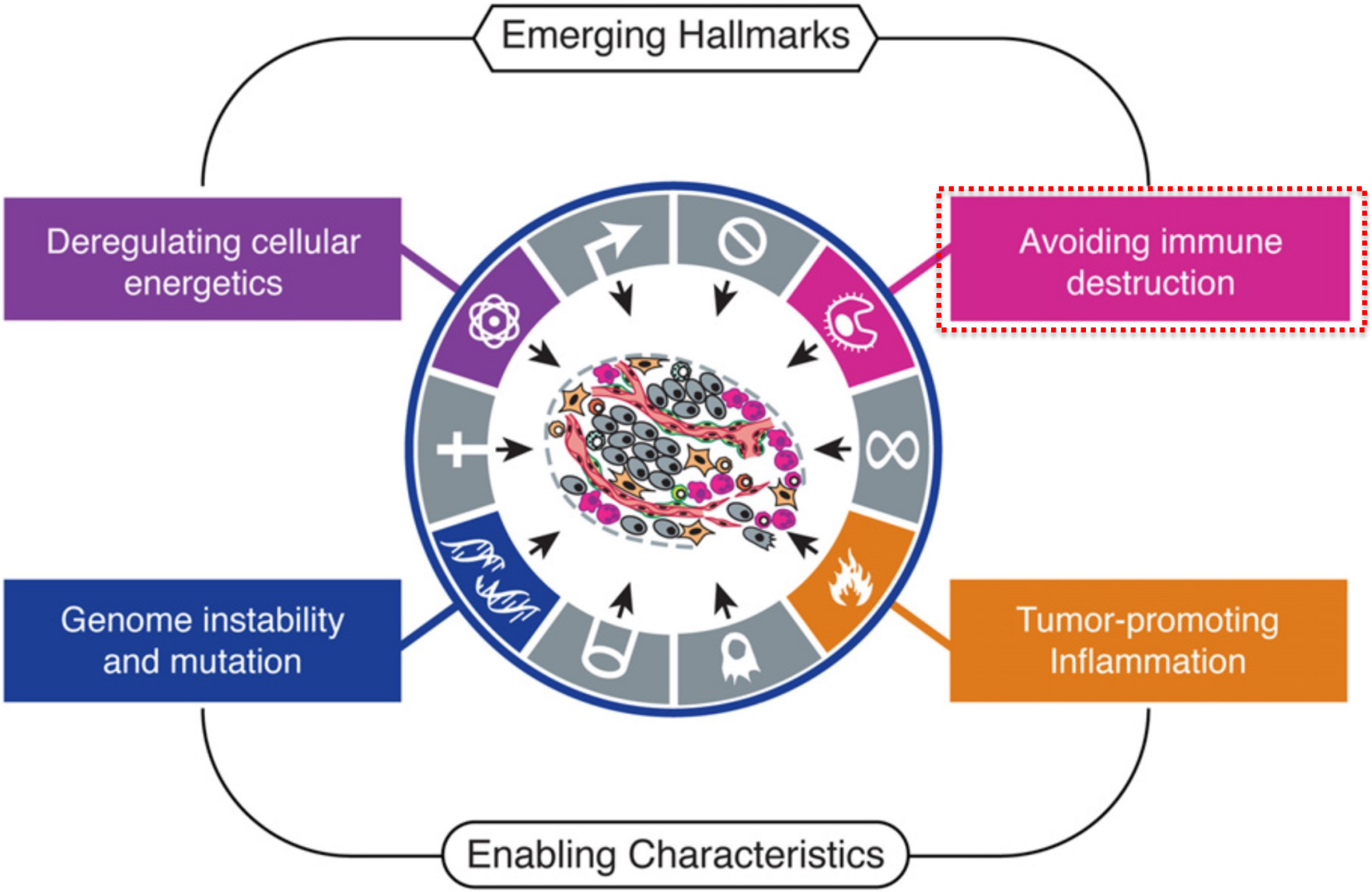
Modified from refs 29, 67. MALT, mucosa-associated lymphoid tissue.

Sterile insults

Chronic infection

Coussens LM & Werb Z *Nature* 2002 420: 860-7.

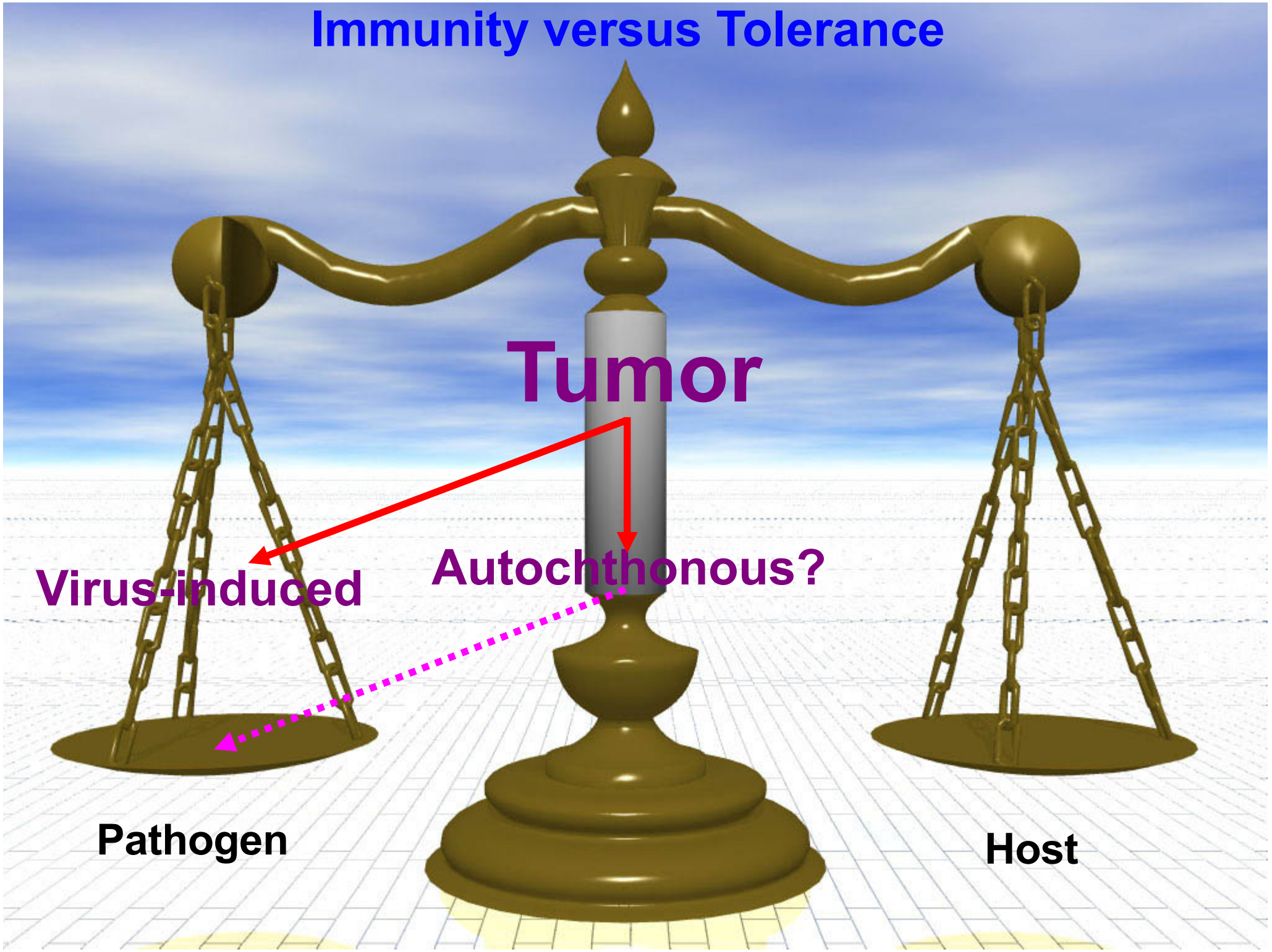
Tumor Immune Adaptation



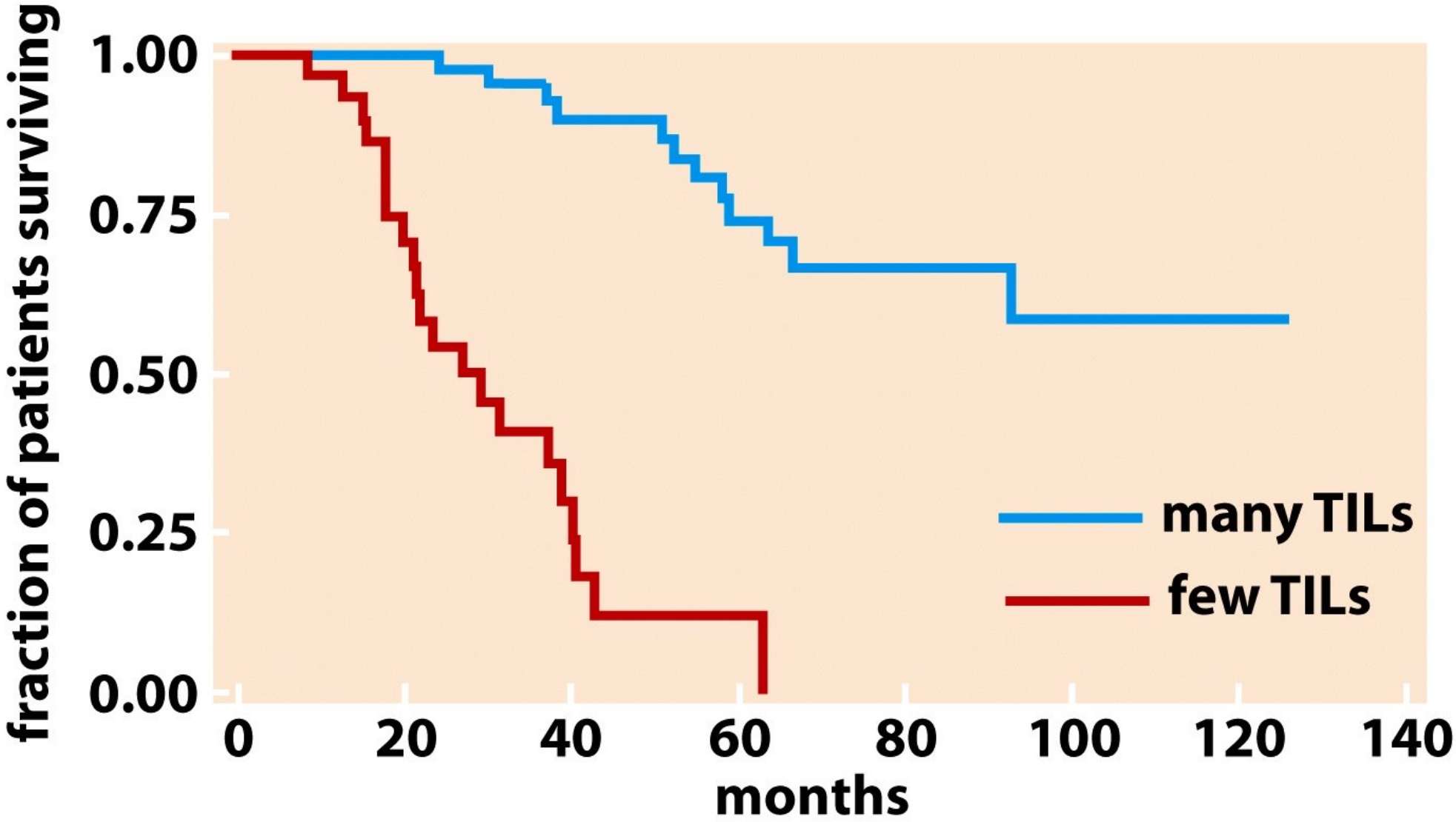
Hanahan D & Weinberg RA *Cell* 2011 144: 646-674.

Cancer Immunosurveillance

Spontaneous tumoricidal immune responses


Immunity versus Tolerance
Tumor
Virus-induced
Autochthonous?
Pathogen
Host

TIL as a Marker for Positive Prognosis



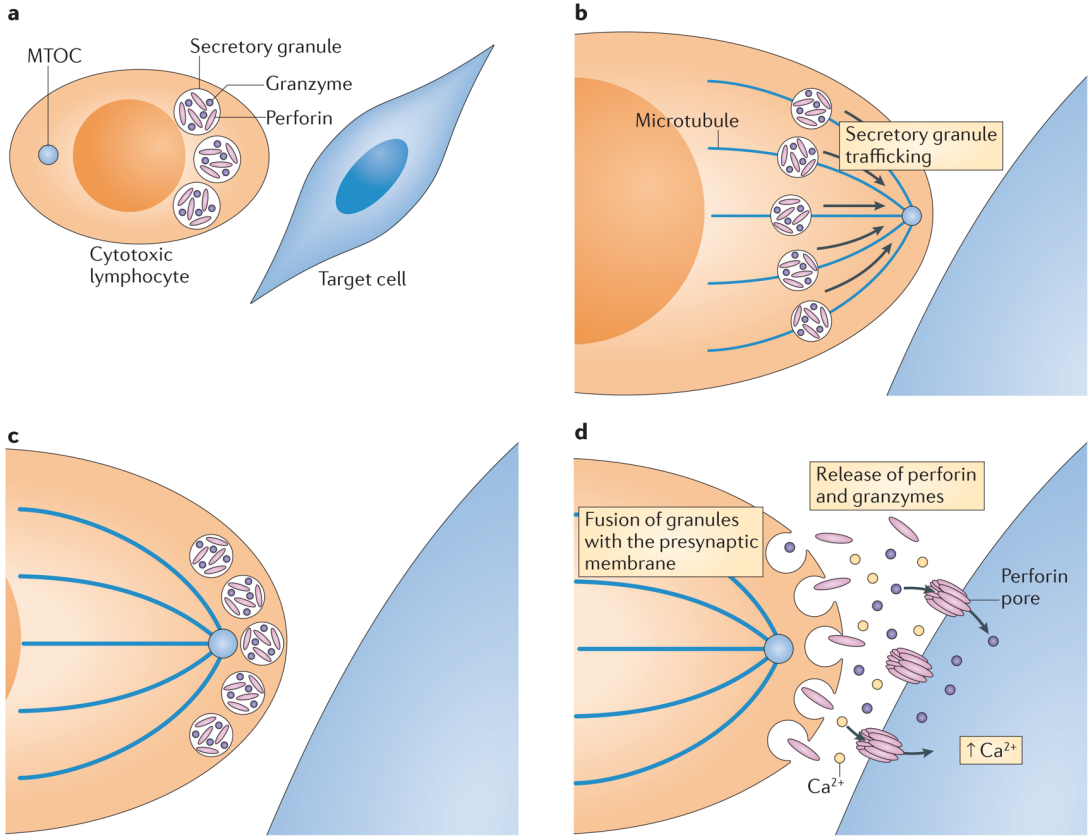
Zhang L *N Engl J Med* 2003 348: 203-13.

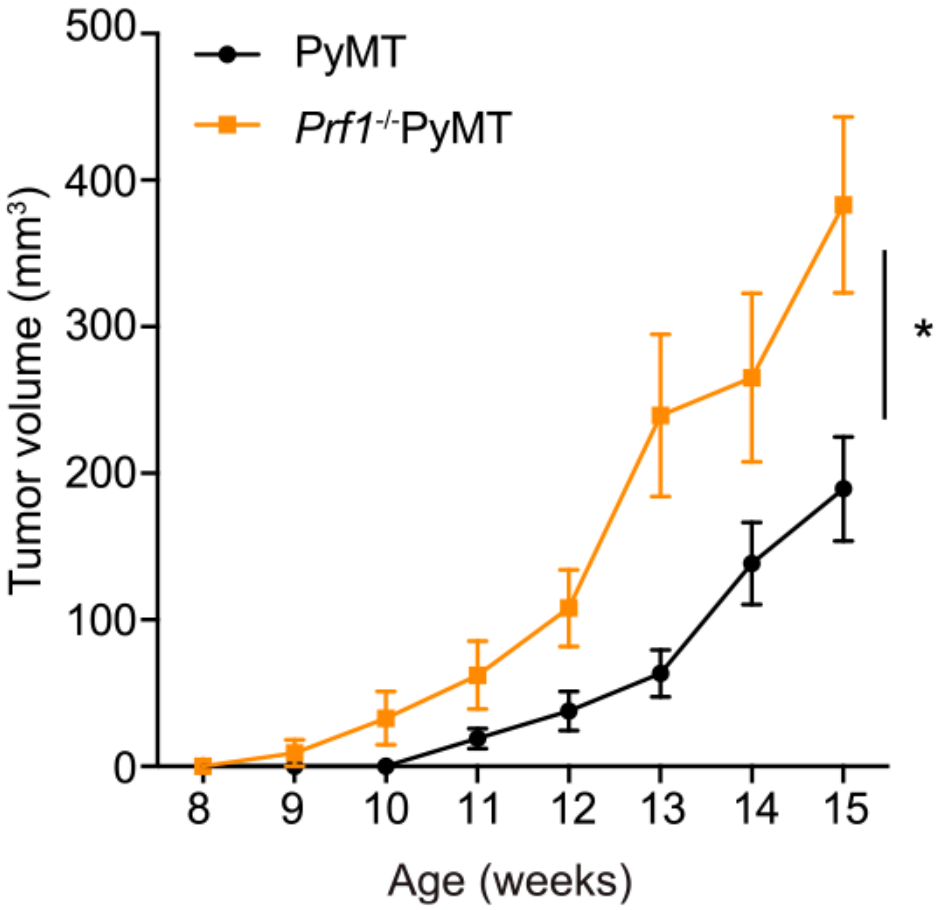
Enhanced Tumor Development in Immunodeficient Mouse Strains

Strain	Description	Phenotype	Reference
SCID	Lack T and B cells	Mice develop T cell lymphomas (15% of mice)	118
Rag2$^{-/-}$	Lack T and B cells	Mice develop intestinal adenomas (~50%), or adenocarcinoma of the intestine (~35%) or lung (~15%); tumors detected at 15–16 months of age	3
Rag2$^{-/-}$*Stat1*$^{-/-}$	Lack T and B cells, deficient for type I and II IFN signaling	Mice develop intestinal adenomas like *Rag2*$^{-/-}$ mice (~20%), but also develop adenocarcinoma of the breast (~40%), colon (~10%), or breast and colon (~20%); tumors detected at 12–18 months of age	3
Perforin$^{-/-}$	Lack perforin	Mice develop B cell lymphomas at 14–21 months of age	4
Ifng$^{-/-}$	Lack IFN-γ	Mice develop lymphomas (predominantly T cell) at 13–19 months of age; effect is strain dependent (C57BL/6 are susceptible, BALB/c are resistant)	5
Perforin$^{-/-}$*Ifng*$^{-/-}$	Lack both perforin and IFN-γ	Mice develop B cell lymphomas similar to those observed in perforin-deficient mice, but with earlier onset and increased frequency	5
Perforin$^{-/-}$*B2m*$^{-/-}$	Lack both perforin and MHC class I expression	Mice develop B cell lymphomas similar to those observed in perforin-deficient mice, but with earlier onset and increased frequency	6
Lmp2$^{-/-}$	Defective MHC class I antigen presentation	Mice develop uterine neoplasms (36%) by 12 months of age	119
Trail$^{-/-}$	Lack TRAIL	About 25% of mice develop lymphomas late in life (>400 days)	8
Gmcsf$^{-/-}$*Ifng*$^{-/-}$	Lack GM-CSF and IFN-γ	Mice develop a range of malignancies, including lymphomas and solid tumors (predominantly ovarian choriocarcinoma, luteomas, or teratomas)	11
Il12rb2$^{-/-}$	Lack IL-12Rβ2	Mice develop plasmacytomas, lung carcinomas, or both (50%)	10

Swann JB & Smyth MJ *J Clin Invest* 2007 117: 1137-46.

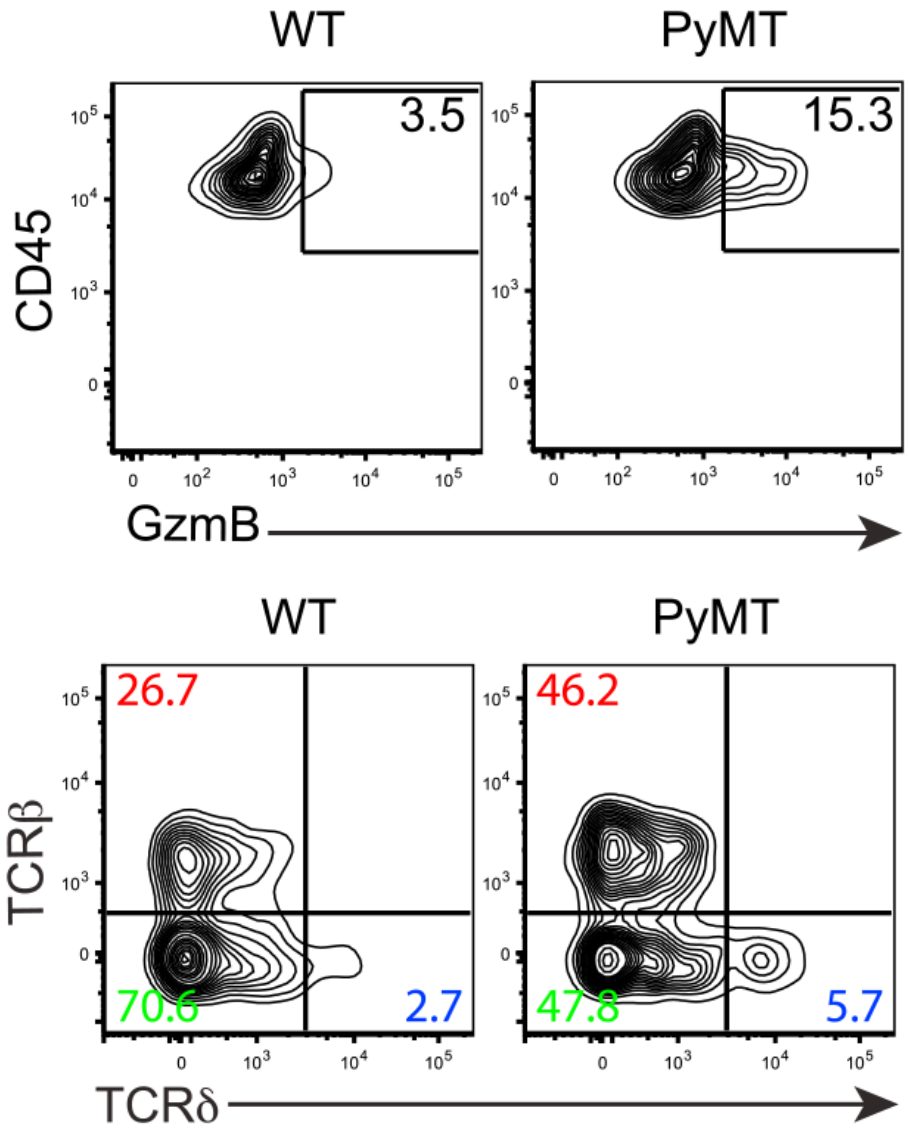
Perforin Deficiency Results in Accelerated Tumor Growth in a Mouse Model of Breast Cancer

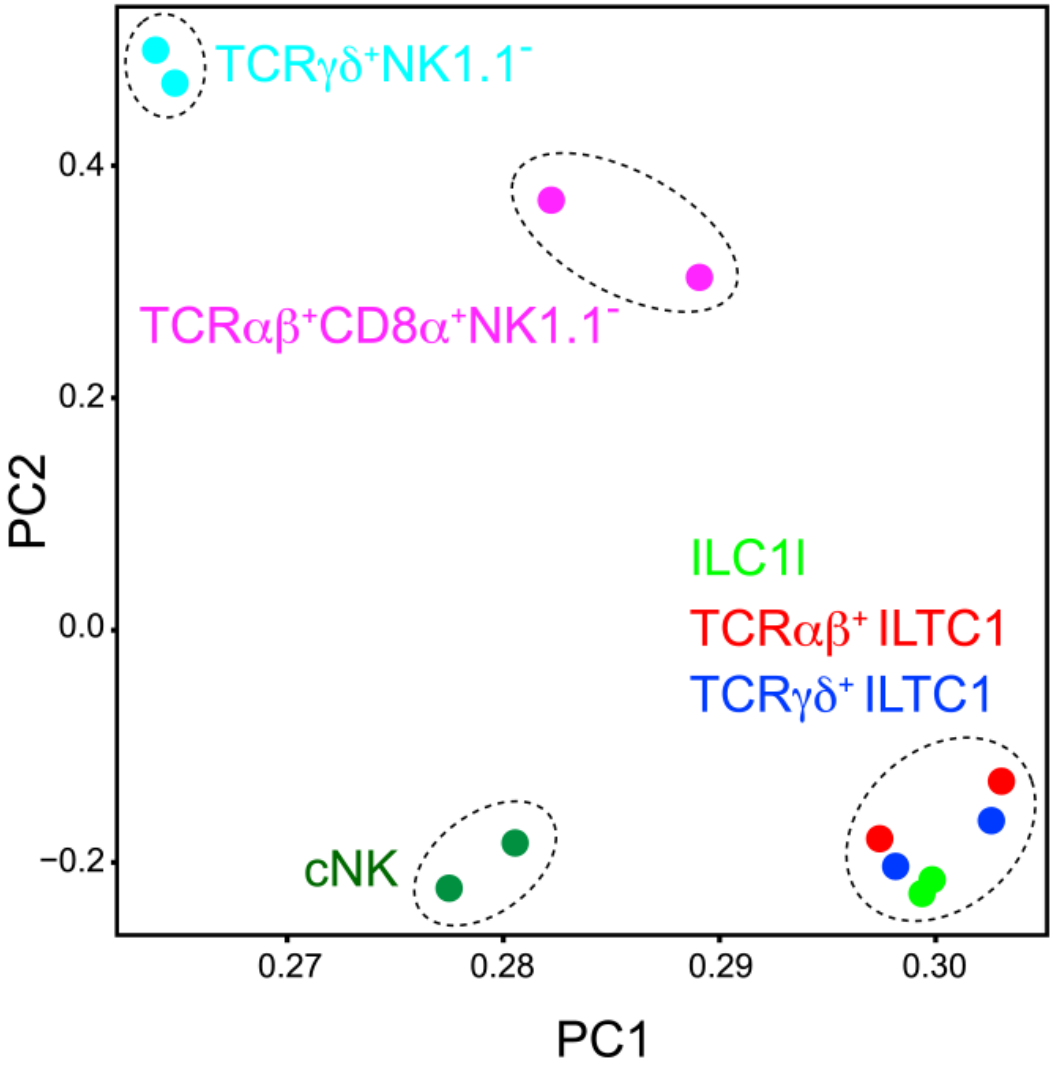




Dadi S. et al. *Cell* 2016 164: 365-77.

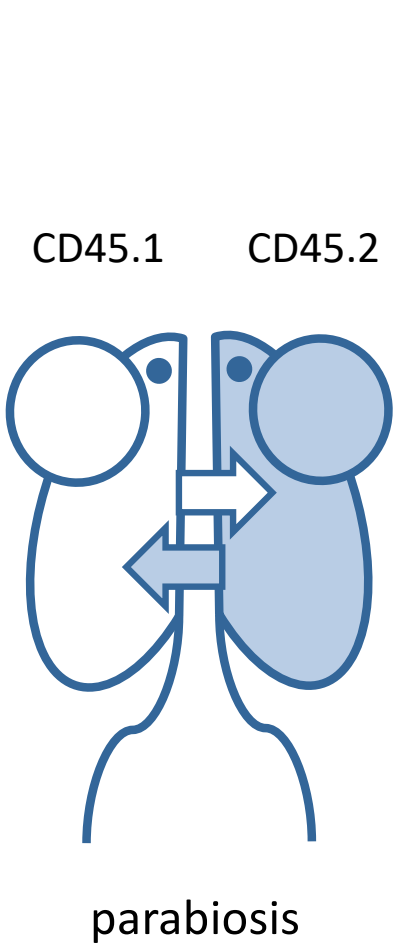
Tumor-Induced Unconventional Innate Lymphoid Cells and Innate-like T Cells

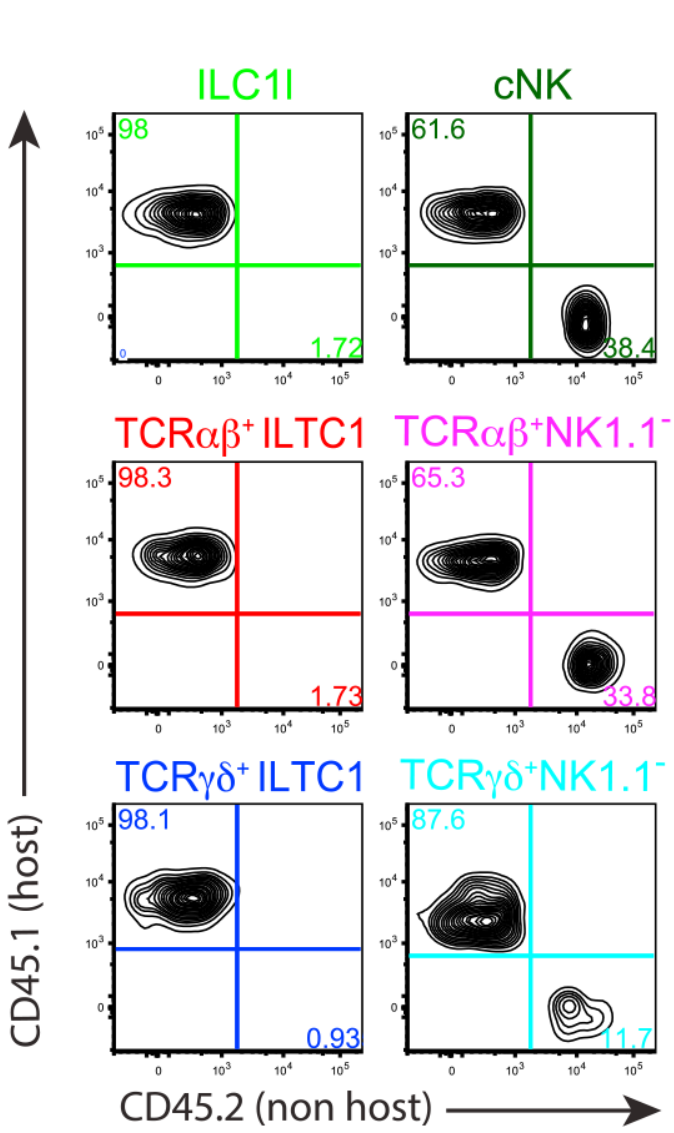


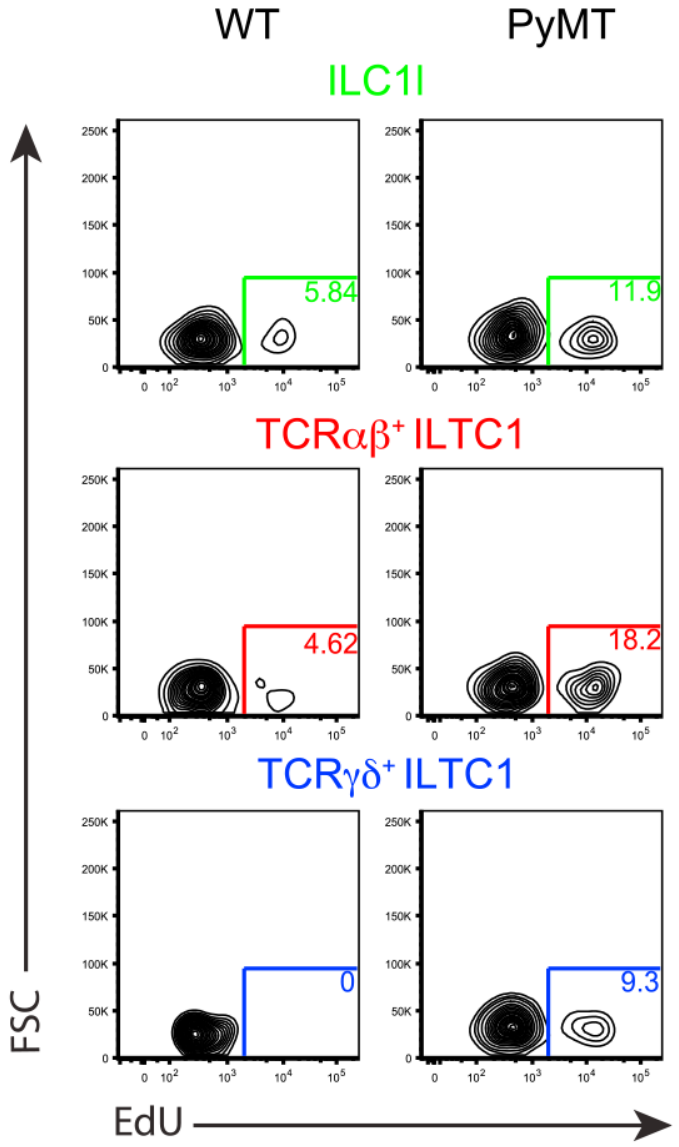


Dadi S. et al. *Cell* 2016 164: 365-77.

ILC1Is and ILTC1s are Tissue-Resident Lymphocytes and Expand in Cancerous Lesions

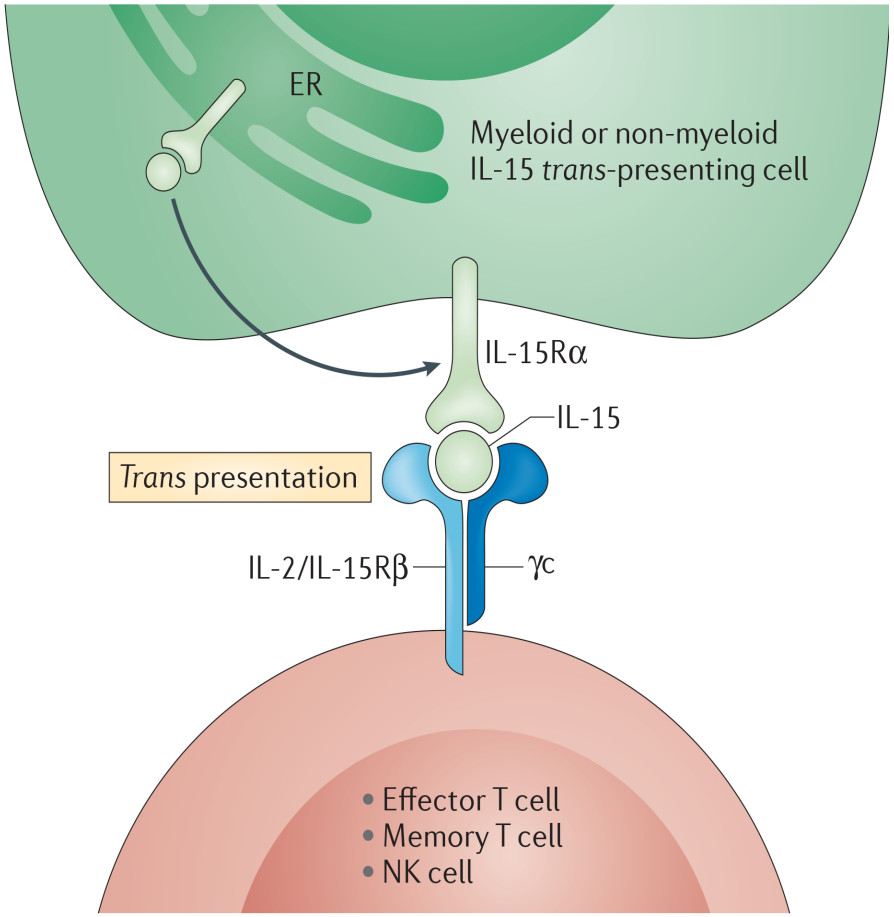


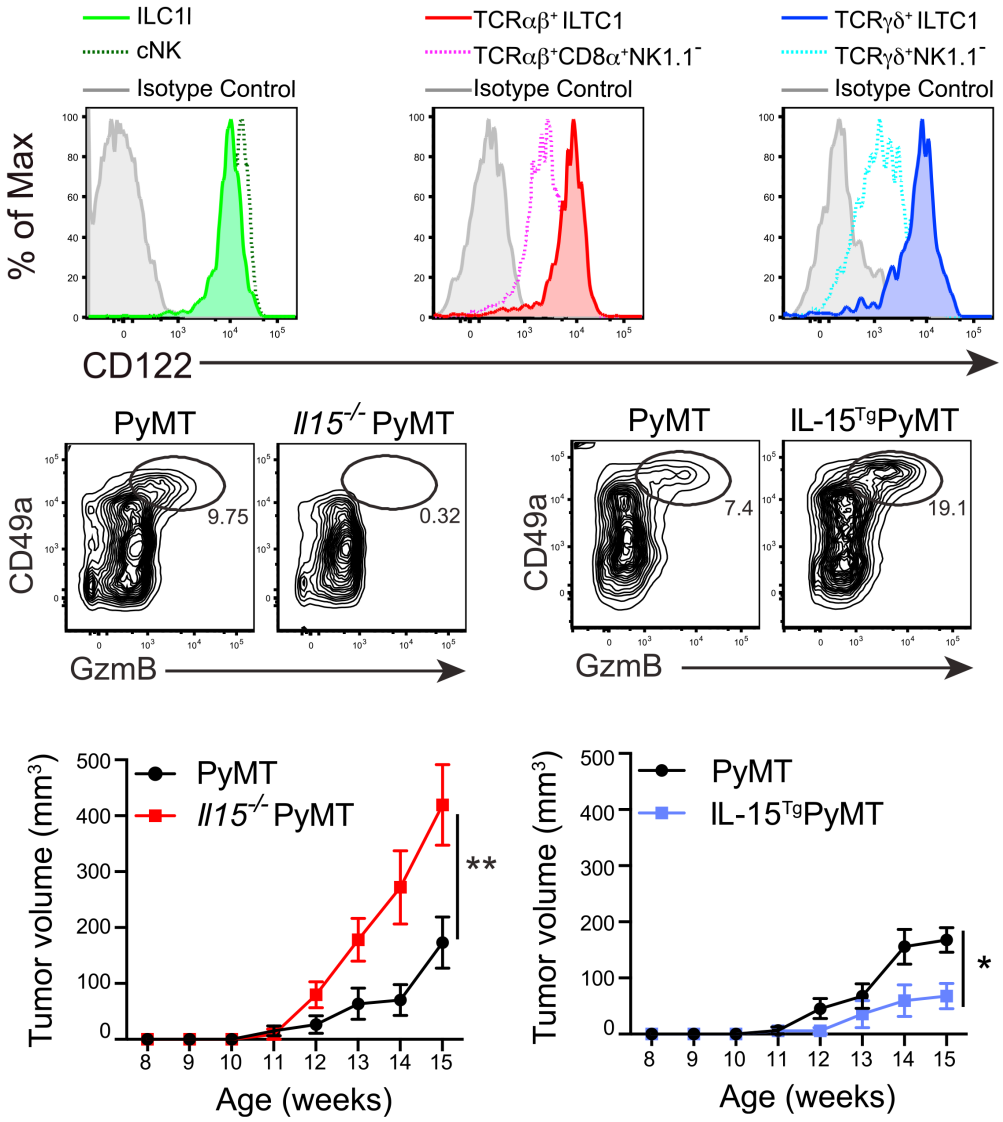




Dadi S. et al. *Cell* 2016 164: 365-77.

IL-15 Regulates ILC1I and ILTC1 Generation and Tumor Growth





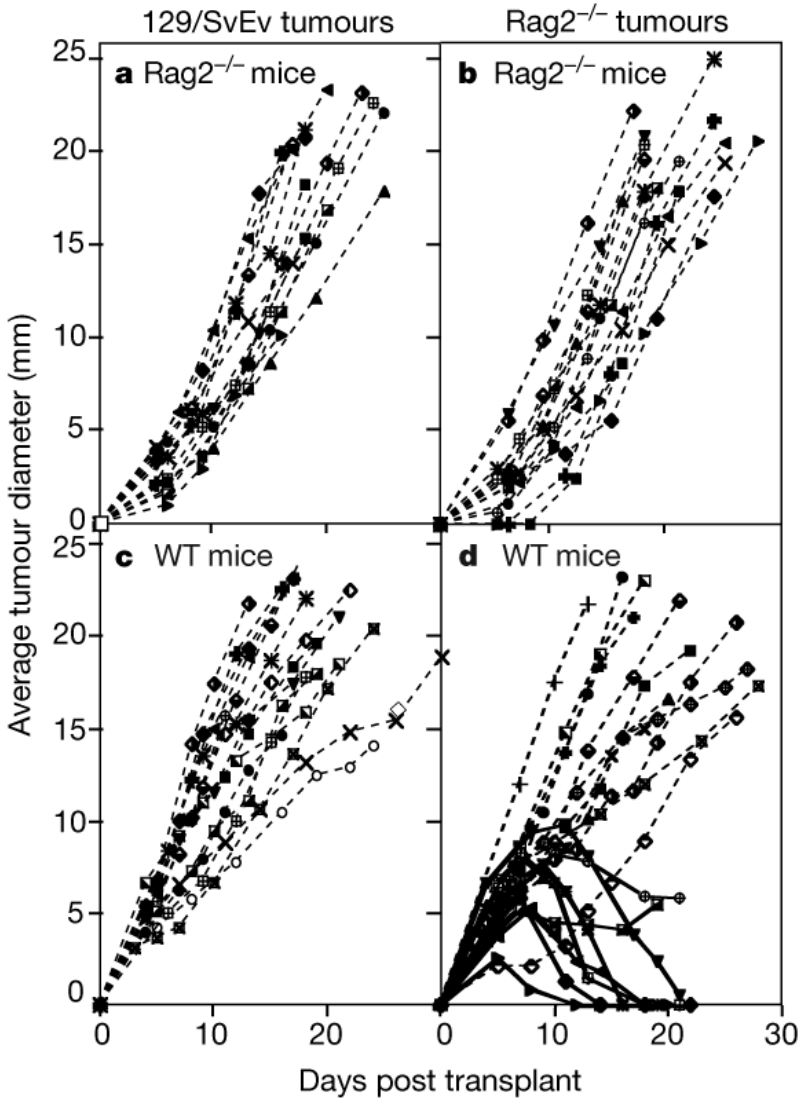
Dadi S. et al. *Cell* 2016 164: 365-77.

Carcinogen-Induced Tumor in Immunodeficient Mice

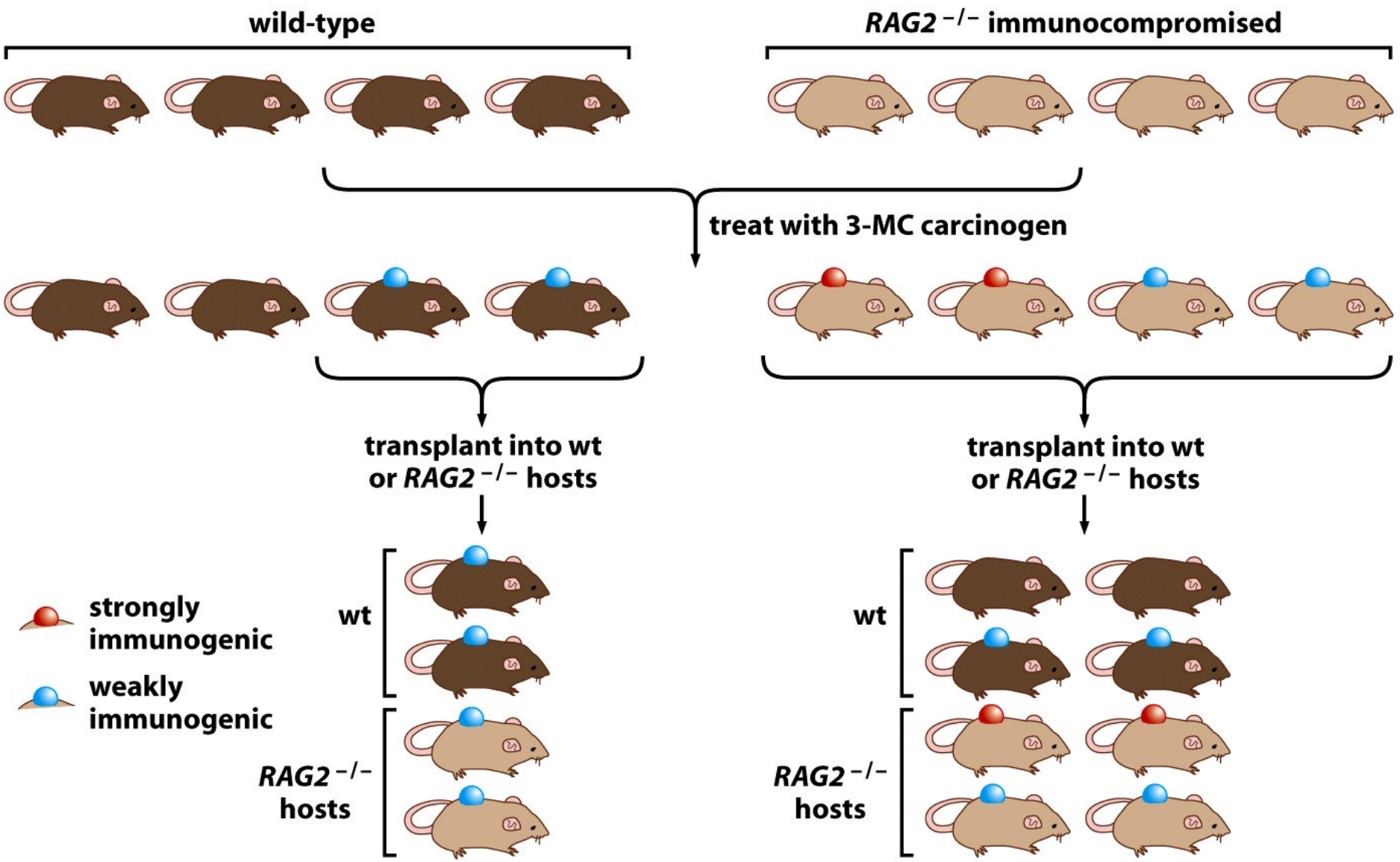
Strain	Description	Phenotype	Reference
Rag2$^{-/-}$	Lack T and B cells	Increased susceptibility to MCA-induced sarcomas, about 40% of sarcomas rejected following transplantation into WT recipients	3
Nude	Lack most T cells due to lack of thymus	Increased susceptibility to MCA-induced sarcomas, but dependent on strain; compared with sarcomas derived from WT mice, sarcomas from nude mice express higher levels of MHC class I and grow less aggressively when transplanted into WT hosts	14, 120
SCID	Lack T and B cells	Increased susceptibility to MCA-induced sarcomas	13
Tcrb$^{-/-}$	Lack $\alpha\beta$ T cells	Increased susceptibility to MCA-induced sarcomas	15
Tcrd$^{-/-}$	Lack $\gamma\delta$ T cells	Increased susceptibility to MCA-induced sarcomas and DMBA/TPA-induced skin carcinogenesis	15
Cd1d$^{-/-}$	Lack CD1d-restricted T cells	Increased susceptibility to MCA-induced sarcomas, some sarcomas rejected on transplantation into WT recipients	16
Ja18$^{-/-}$	Lack semi-invariant NKT cells	Increased susceptibility to MCA-induced sarcomas, some sarcomas rejected on transplantation into WT recipients	16, 17
RAE1 transgenic	Defective killing through the NKG2D pathway	Increased susceptibility to DMBA/TPA-induced skin carcinogenesis	27
Perforin$^{-/-}$	Lack perforin	Increased susceptibility to MCA-induced sarcomas	19, 121
Trail$^{-/-}$	Lack TRAIL	Increased susceptibility to MCA-induced sarcomas	122
Ifngr1$^{-/-}$	Lack IFN-γR1	Increased susceptibility to MCA-induced sarcomas, reconstituting sarcomas with IFNGR1 facilitates their rejection by WT mice	21
Ifng$^{-/-}$	Lack IFN-γ	Increased susceptibility to MCA-induced sarcomas and N-methyl-N-nitrosourea–induced lymphomas	25, 121
Stat1$^{-/-}$	Deficient for type I and type II IFN signaling	Increased susceptibility to MCA-induced sarcomas	3
Perforin$^{-/-}$*Ifng*$^{-/-}$	Lack both perforin and IFN-γ	Increased susceptibility to MCA-induced sarcomas	121
Il-12p35$^{-/-}$	Lack IL-12	Increased susceptibility to MCA-induced sarcomas and N-methyl-N-nitrosourea–induced lymphomas	25
Il-23p19$^{-/-}$	Lack IL-23	Decreased susceptibility to DMBA/TPA-induced skin carcinogenesis	28
Il-12p40$^{-/-}$	Lack IL-12 and IL-23	Increased susceptibility to MCA-induced sarcomas, decreased susceptibility to DMBA/TPA-induced skin carcinogenesis	16
Ifnar1$^{-/-}$	Lack type I IFN signalling	Increased susceptibility to MCA-induced sarcomas	22
Cd80$^{-/-}$*Cd86*$^{-/-}$	Lack costimulatory molecules CD80 and CD86	Increased susceptibility to UV-induced skin carcinogenesis	123

Swann JB & Smyth MJ *J Clin Invest* 2007 117: 1137-46.

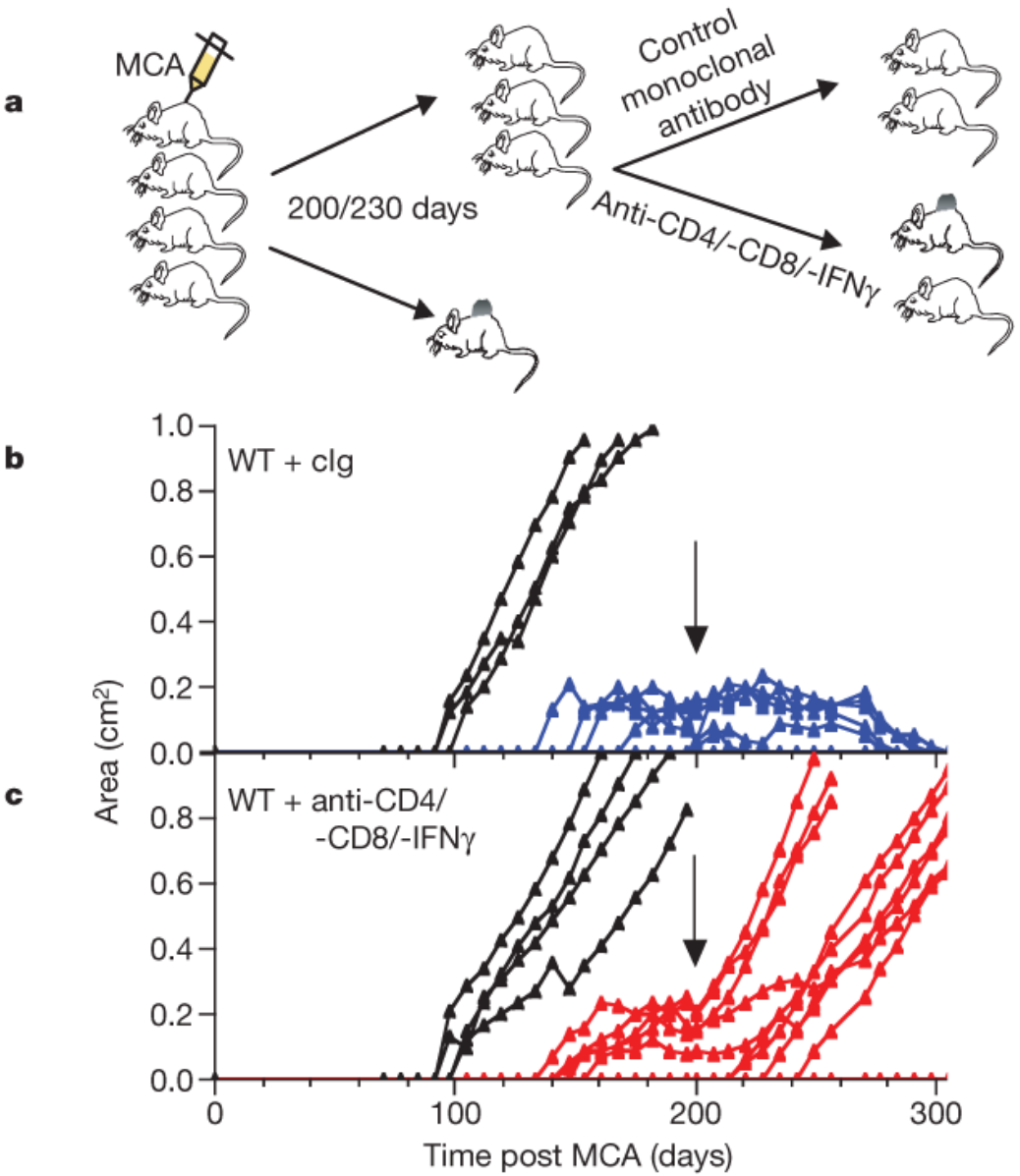
Increased Immunogenicity of Carcinogen-Induced Tumor Derived from Immunodeficient Mice



Shankaran V et al. *Nature* 2001 410: 1107-11.


wild-type
RAG2 −/− immunocompromised
treat with 3-MC carcinogen
transplant into wt or RAG2 −/− hosts
transplant into wt or RAG2 −/− hosts
strongly immunogenic
weakly immunogenic
wt
RAG2 −/− hosts
wt
RAG2 −/− hosts

Adaptive Immune System Promotes an Equilibrium State in Carcinogen-Induced Sarcomas



Koebel CM et al. *Nature* 2007 450: 903-7.

Tumor-Specific Rejection Antigens

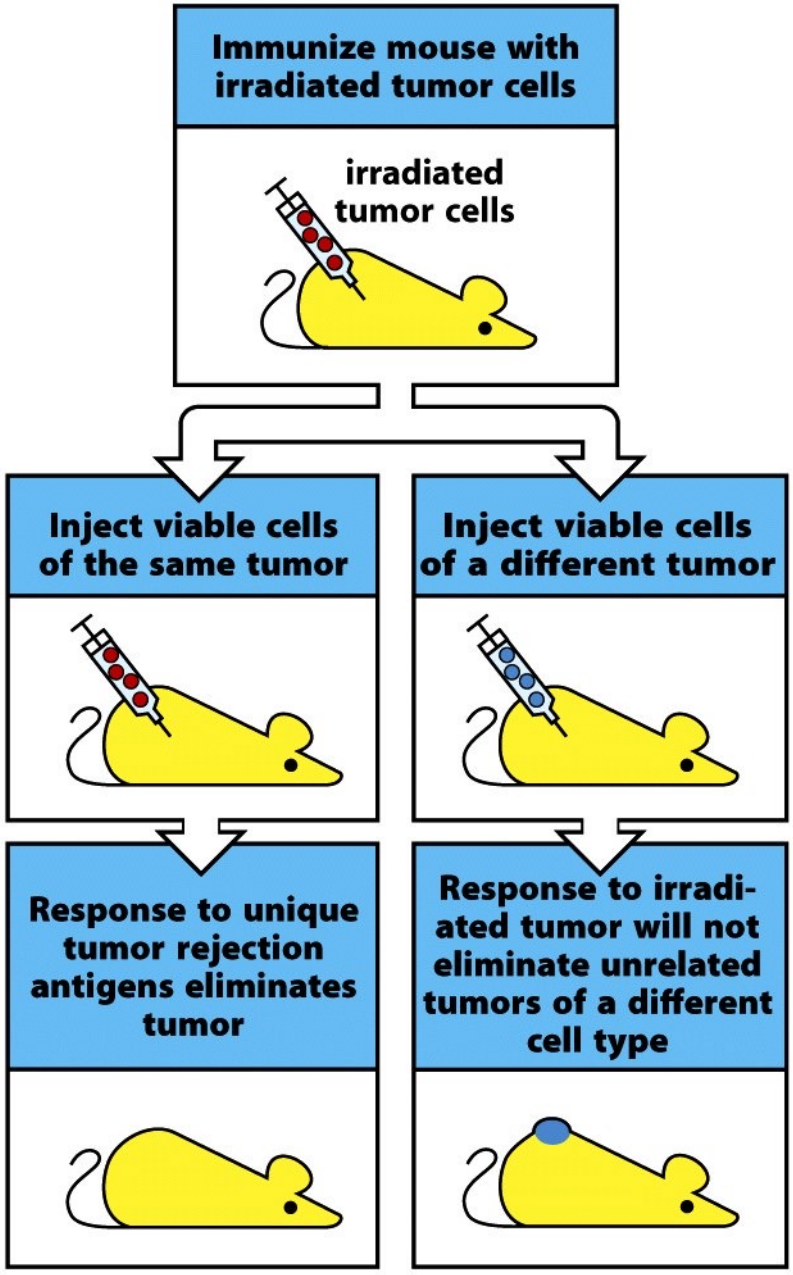


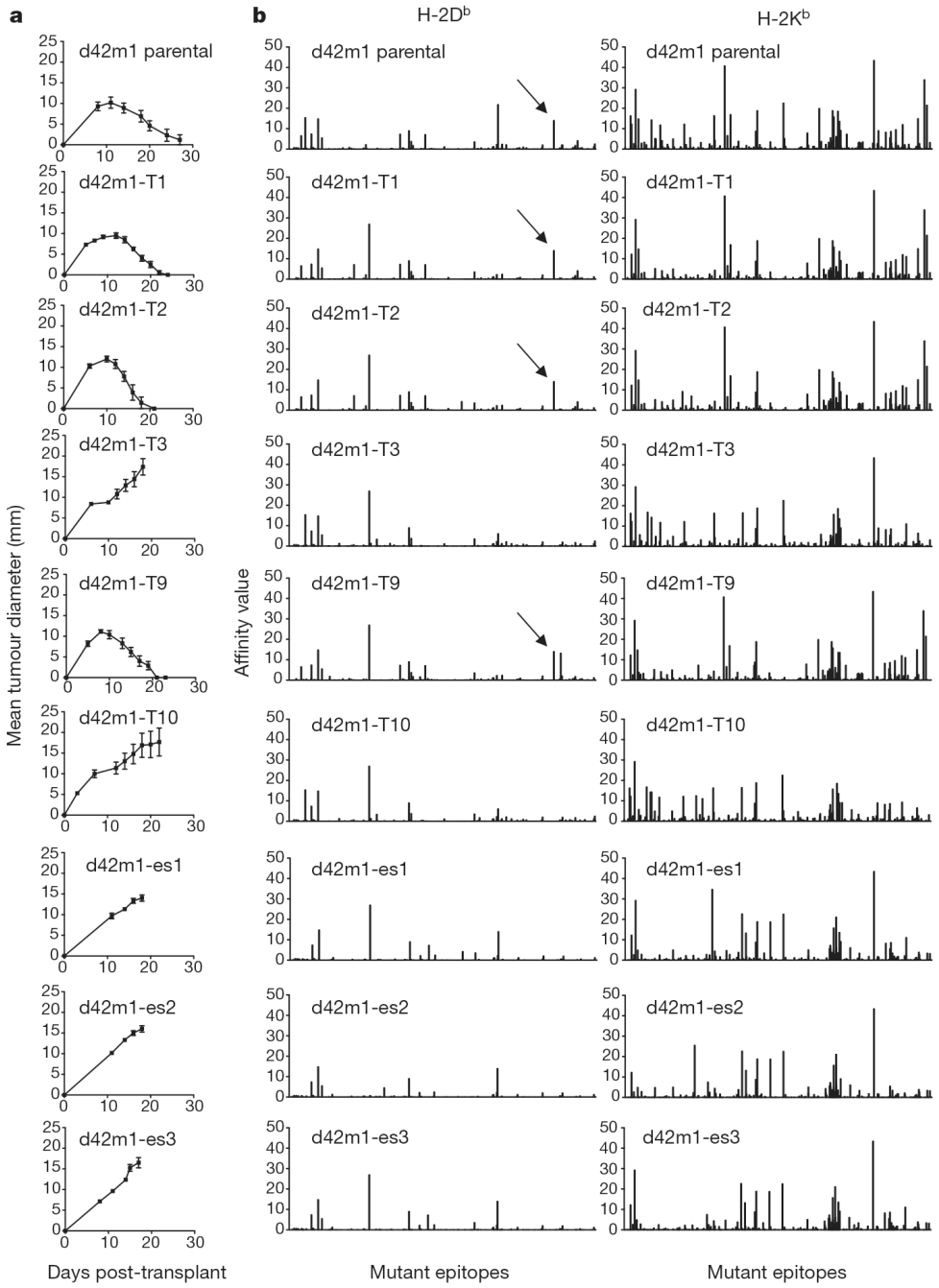
Figure 15-12 Immunobiology, 7ed. (© Garland Science 2008)

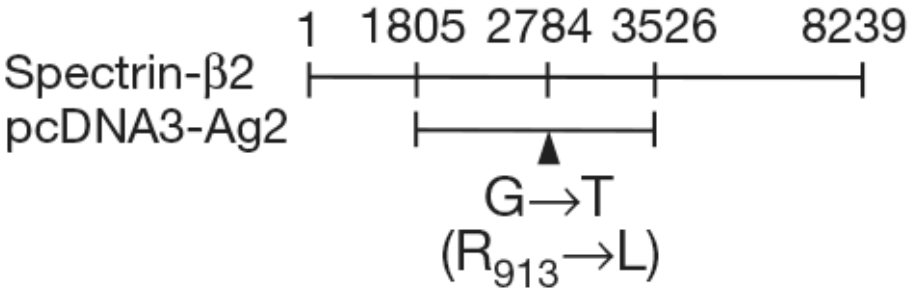
Tumor-Specific Antigens Come with Different Flavors

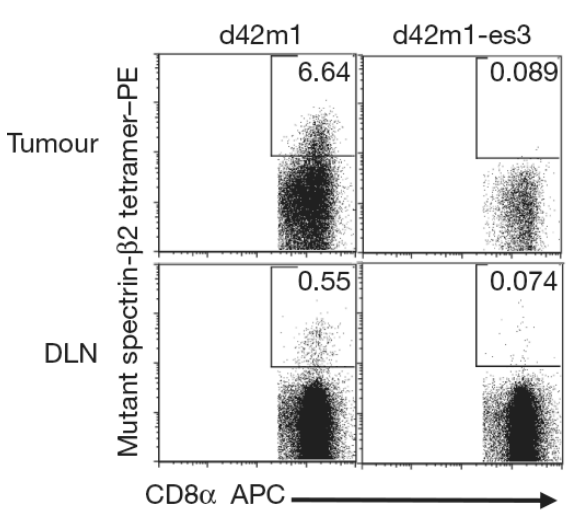
Potential tumor rejection antigens have a variety of origins			
Class of antigen	**Antigen**	**Nature of antigen**	**Tumor type**
Tumor-specific mutated oncogene or tumor suppressor	Cyclin-dependent kinase 4	Cell-cycle regulator	Melanoma
	β-Catenin	Relay in signal transduction pathway	Melanoma
	Caspase-8	Regulator of apoptosis	Squamous cell carcinoma
	Surface Ig/ Idiotype	Specific antibody after gene rearrangements in B-cell clone	Lymphoma
Germ cell	MAGE-1 MAGE-3	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
	Wilms' tumor	Transcription factor	Leukemia
Abnormal post-translational modification	MUC-1	Underglycosylated mucin	Breast Pancreas
Abnormal post-transcriptional modification	GP100 TRP2	Retention of introns in the mRNA	Melanoma
Oncoviral protein	HPV type 16, E6 and E7 proteins	Viral transforming gene products	Cervical carcinoma

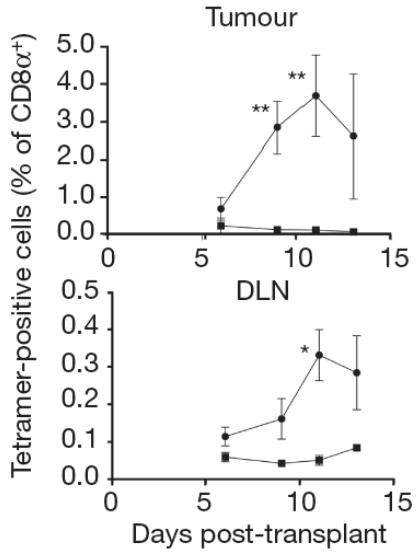
Figure 15-17 Immunobiology, 7ed. (© Garland Science 2008)

Exome Sequencing Reveals Tumor Rejection Antigen



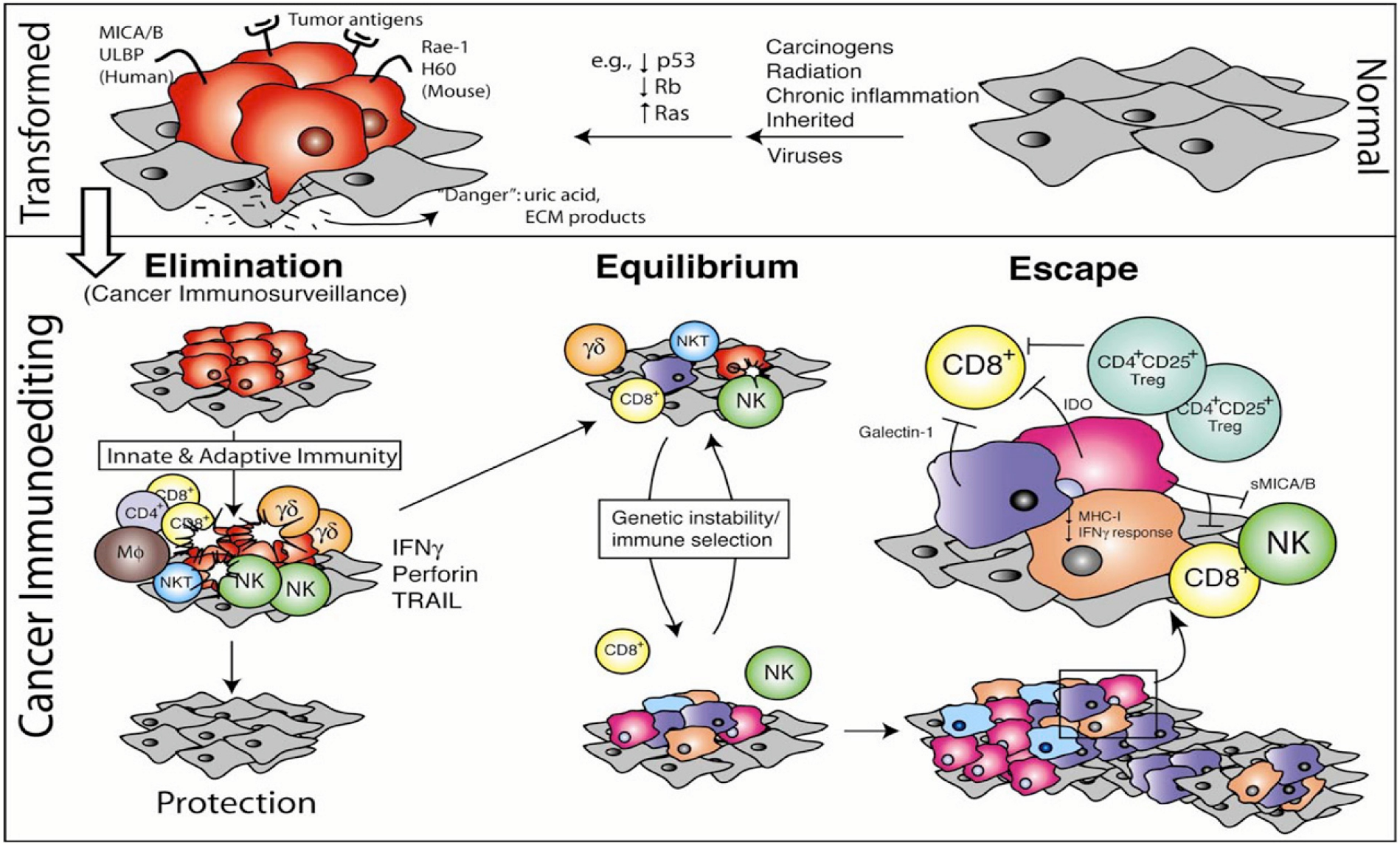




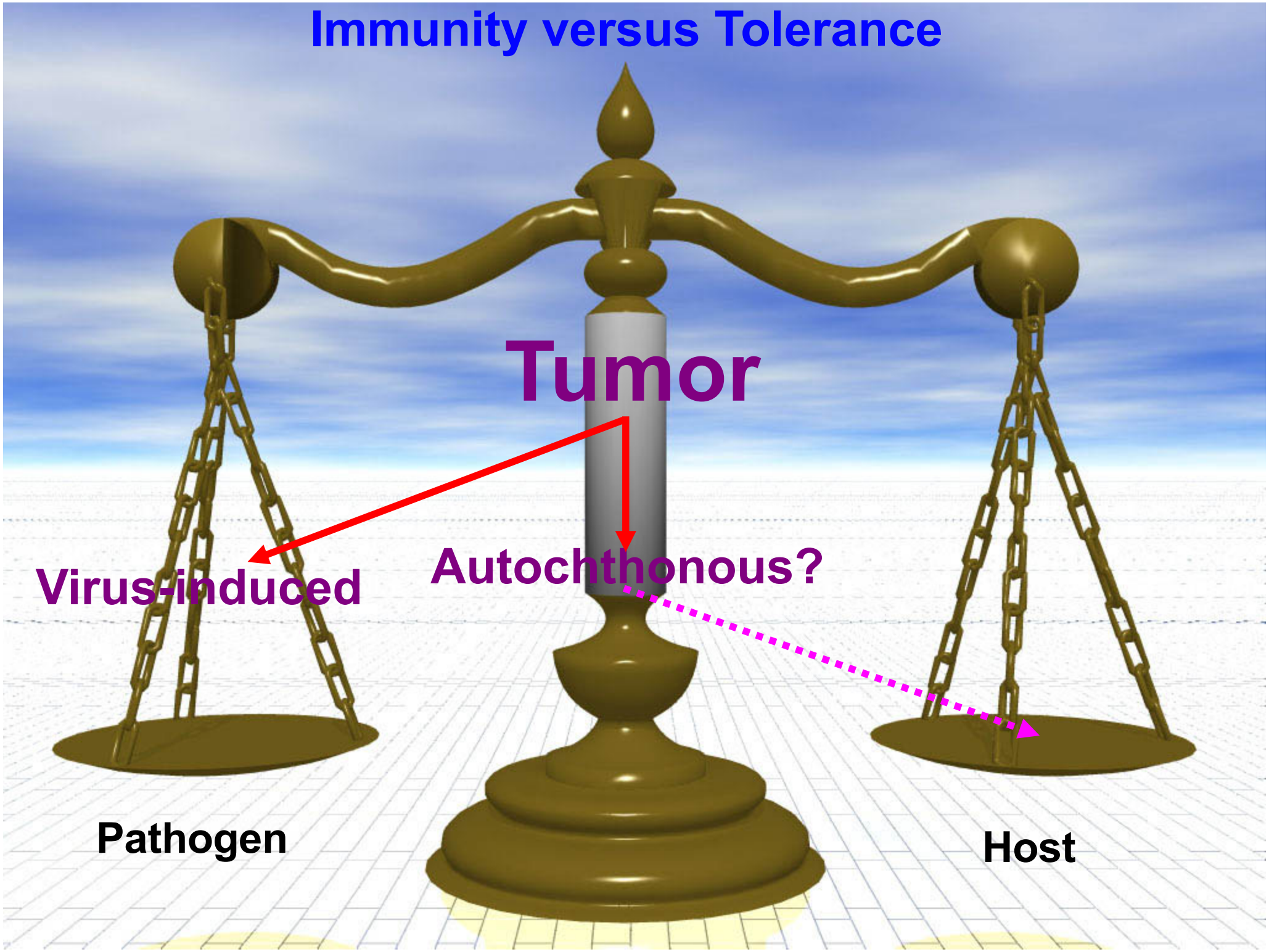


Matsushita H et al. *Nature* 2012 482: 400-4.

Cancer Immunoediting



Dunn GP et al. *Immunity* 2004 21: 137-48.


Immunity versus Tolerance
Tumor
Virus-induced
Autochthonous?
Pathogen
Host

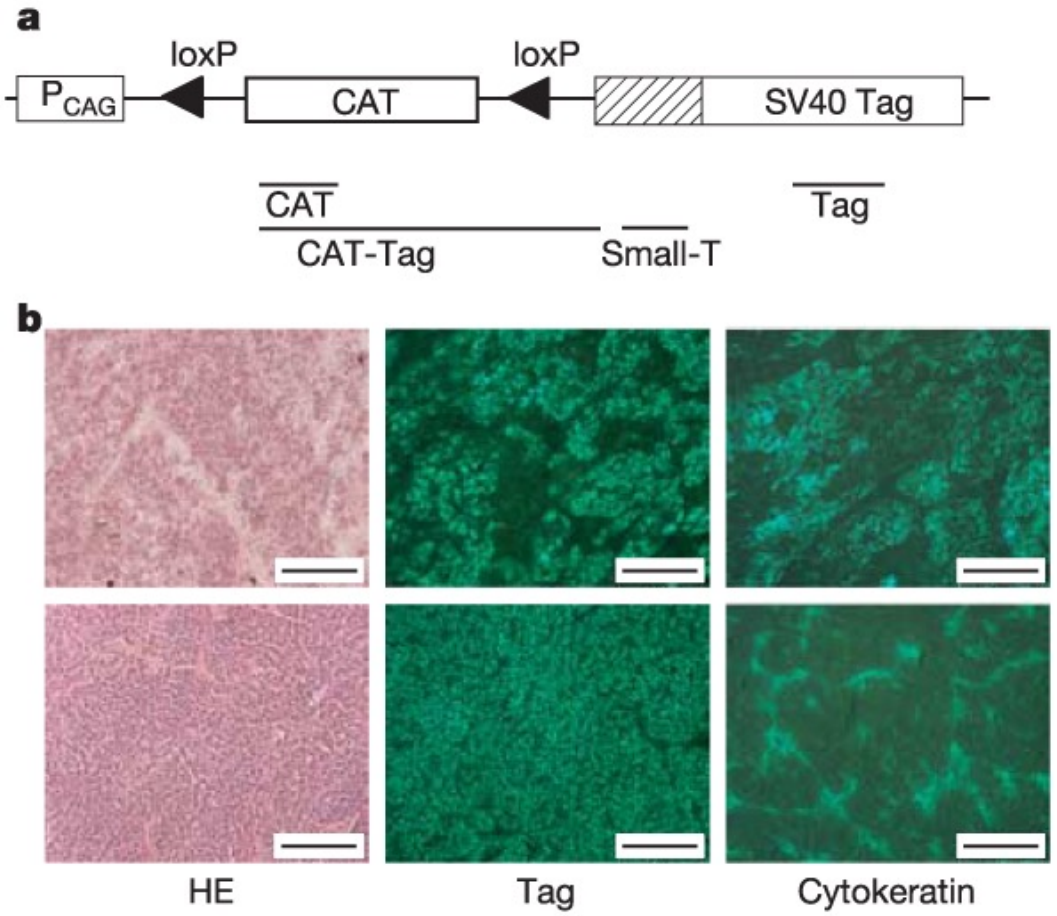
Immune Deficiency and Cancer Risk

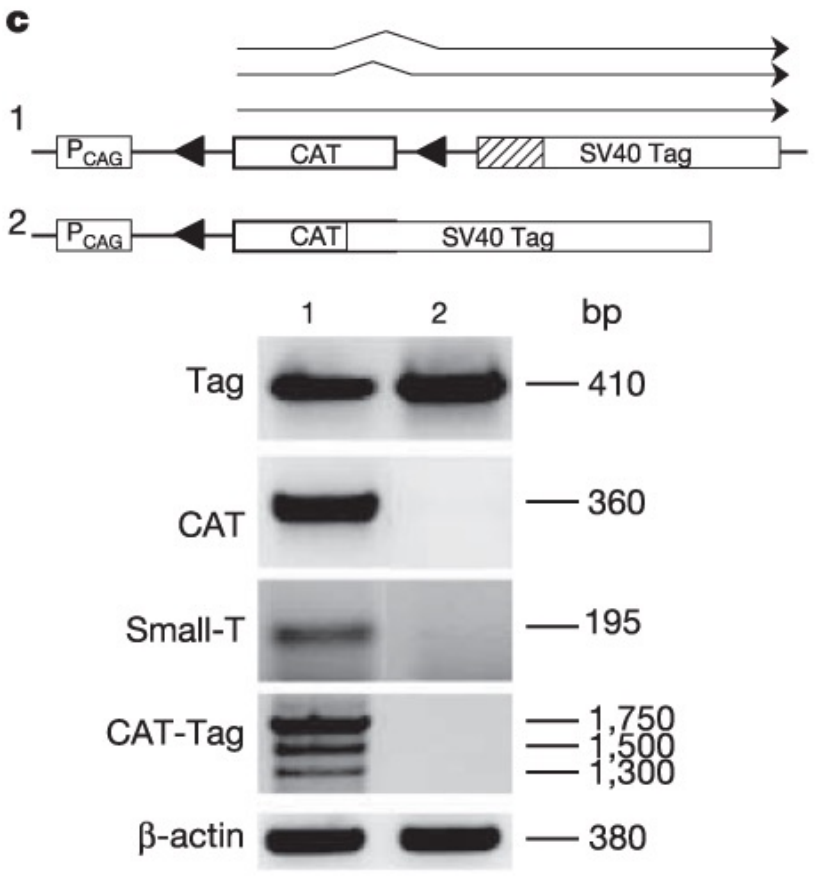
Table 2 | **Human immune-deficient status and cancer risk**

Immune deficiency	Cohort size	Cancer type	Relative risk	References
AIDS-defining cancers/viral-associated cancers				
AIDS	122,993	Kaposi sarcoma	97.5 (male) 202.7 (female)	102
		Non-Hodgkin lymphoma	37.4 (male) 54.6 (female)	
		Skin (excluding Kaposi sarcoma)	20.9 (male) 7.5 (female)	
		Cervical	9.1	
AIDS	8,828	Kaposi sarcoma	545	103
		Non-Hodgkin lymphoma	24.6	
AIDS	302,834	Kaposi sarcoma	177.7	104
		Non-Hodgkin lymphoma	72.8	
		Cervical	5.2	
Liver transplant	187	Cutaneous	16.9	66
Liver transplant	174	Skin (non-melanoma)	70	105
Non-AIDS-defining cancers (with reduced RR)				
AIDS	302,834	Breast	0.5	104
		Prostate	0.5	
AIDS	122,993	Prostate	0.7	102
		Bladder	0.5	
		Breast	0.8 (HIV positive) 0.2 (post-AIDS onset)	
AIDS	8,828	Prostate	0.8	103
AIDS	62,157	Ovarian	0.58	106
		Breast	0.55	
		Uterine	0.28	
Kidney/heart transplant	25,914	Breast (year 1)	0.49	107
		Breast (year 2–11)	0.84	
Liver transplant	1,000	Breast, ovary, uterus and cervical	0.53	67
		Genitourinary	0.68	

De Visser KE *NRC* 2006 6: 24-37.

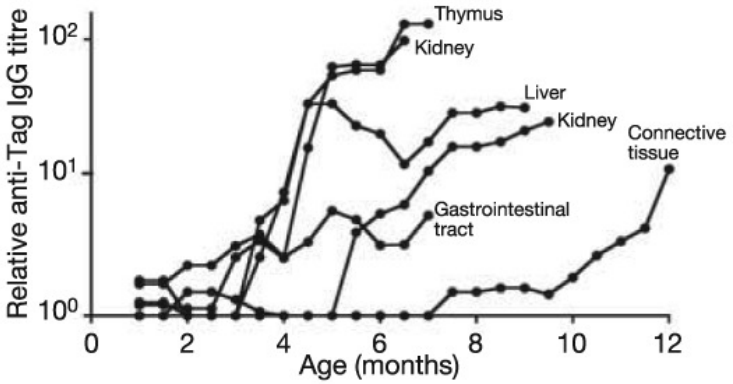
Sporadic Tumor Model with a Defined Antigen

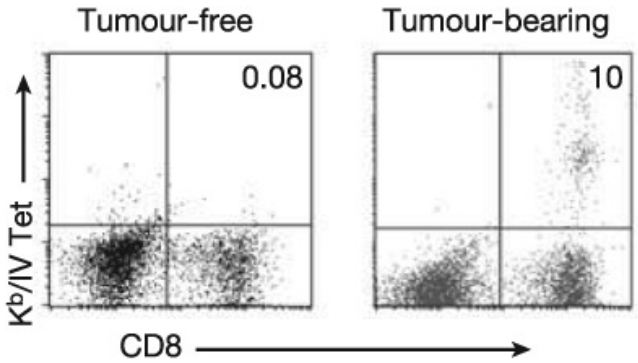


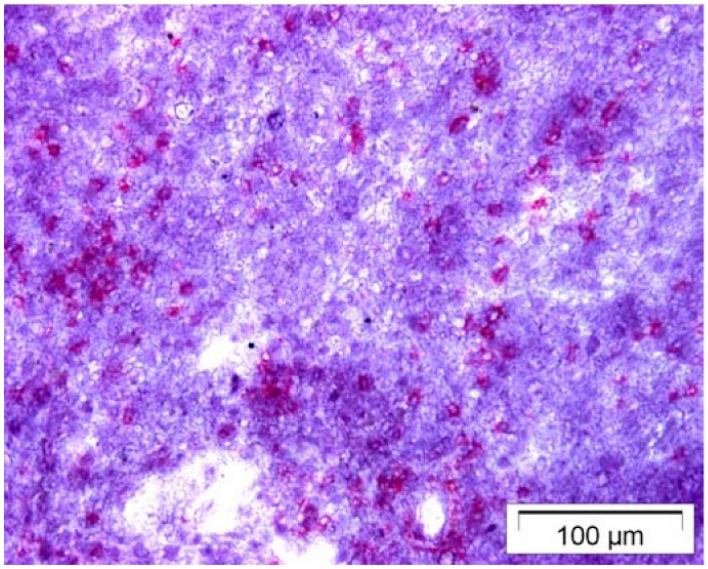


Williamsky G & Blankenstein T *Nature* 2005 437: 141-6.

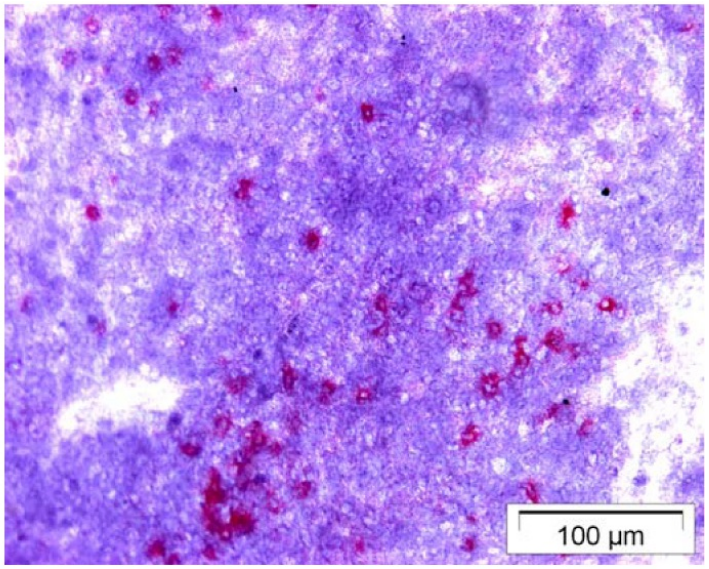
Tag-Specific Immune Responses







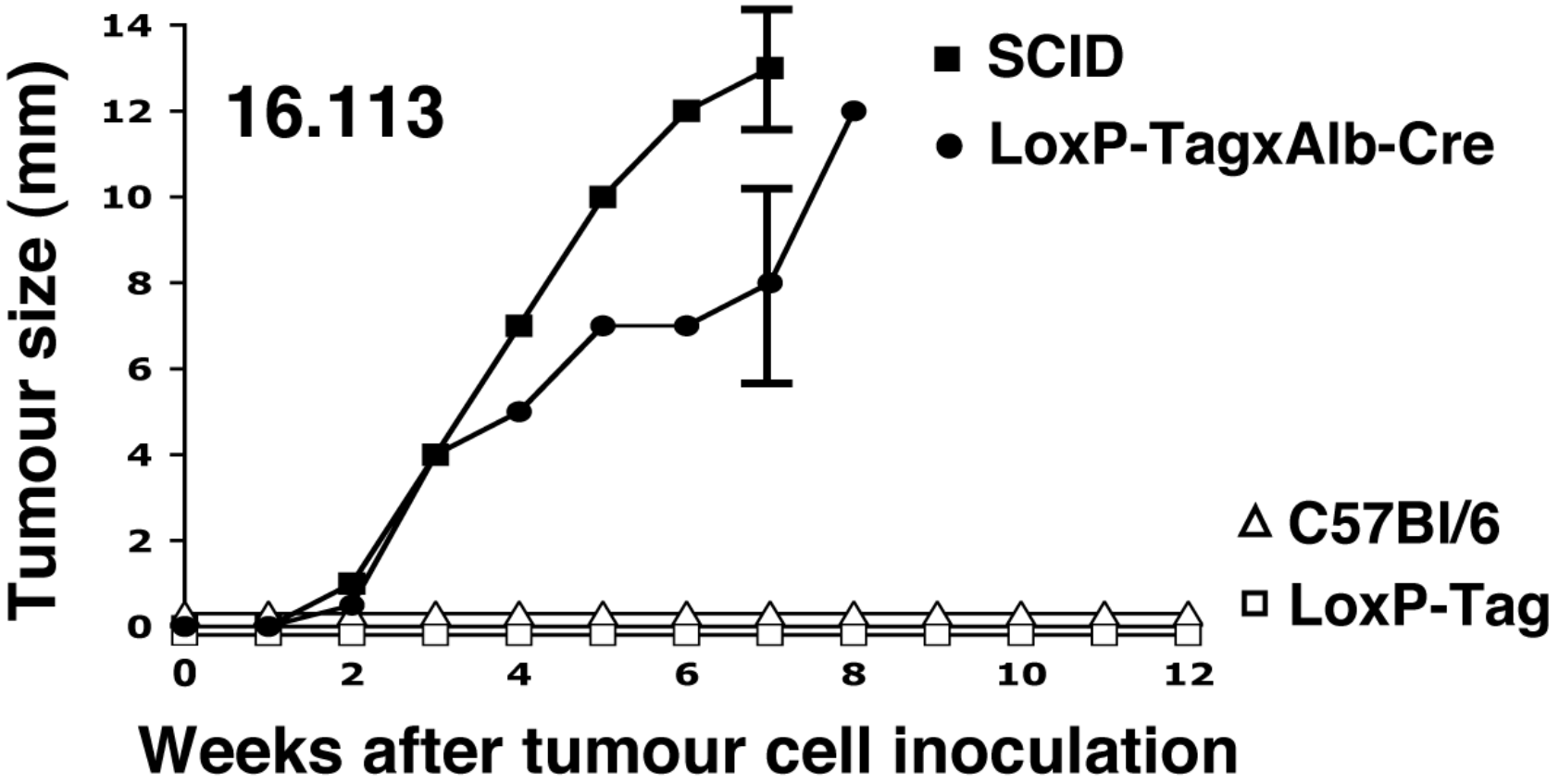
CD8



CD4

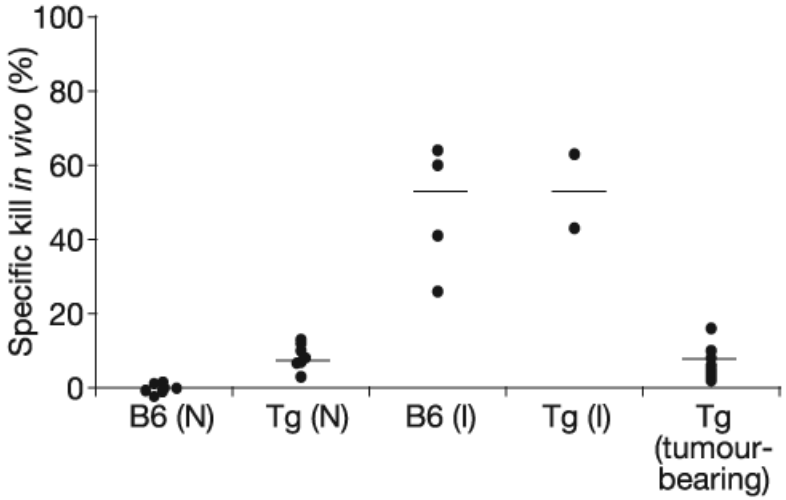
Williamsky G & Blankenstein T *Nature* 2005 437: 141-6.

Sporadic Tumors are Immunogenic due to Tag Expression

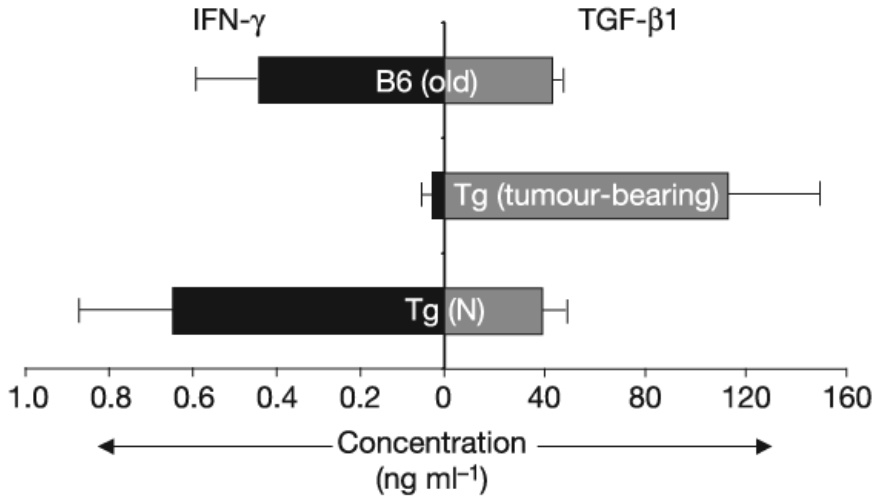


Williamsky G & Blankenstein T *Nature* 2005 437: 141-6.

Sporadic Immunogenic Tumors Induce T Cell Tolerance



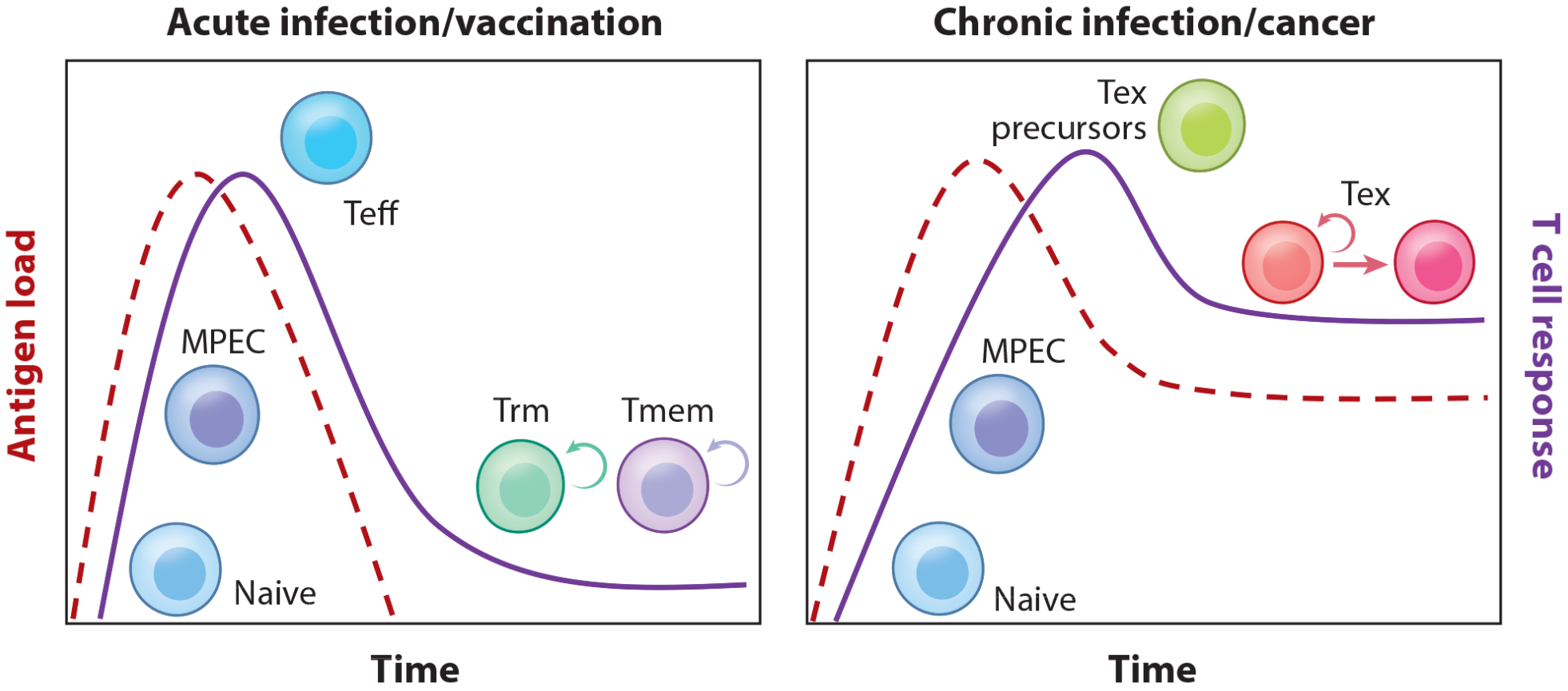
Tag-specific CTL Activity



Cytokine Serum Levels

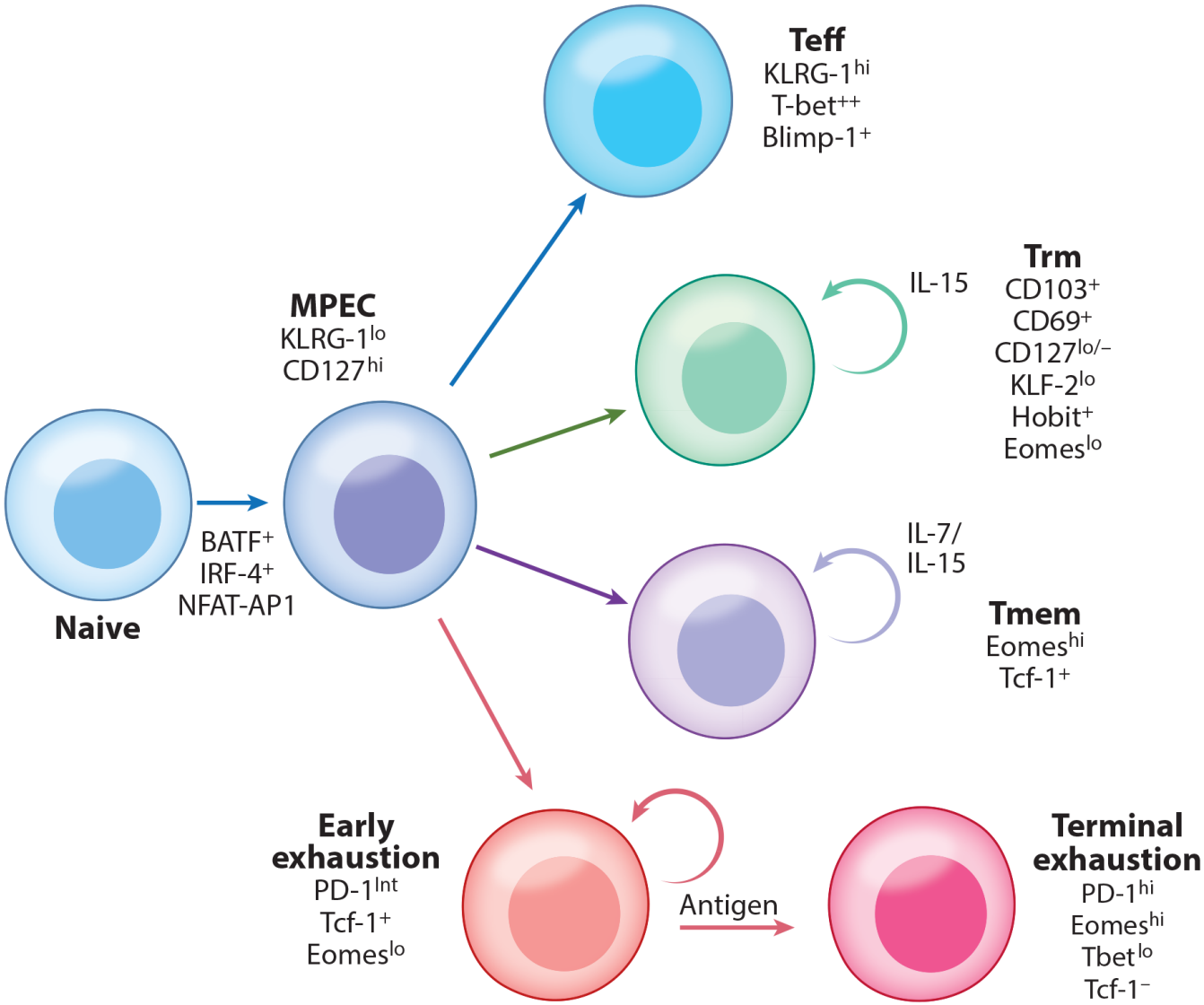
Williamsky G & Blankenstein T *Nature* 2005 437: 141-6.

Chronic Antigen Stimulation Triggers T Cell Exhaustion



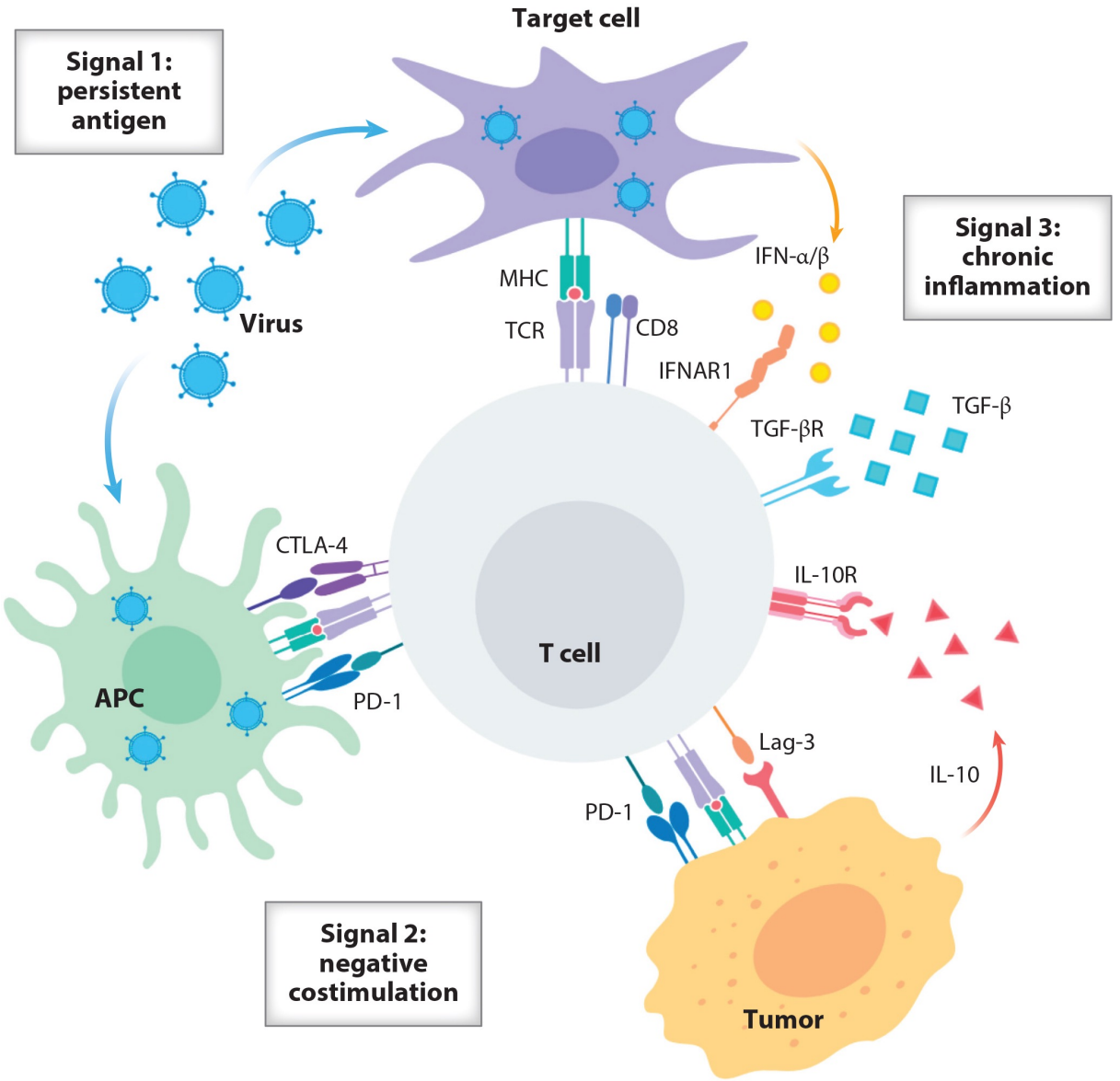
McLane LM et al. *Annu. Rev. Immunol.* 2019 37: 457-95.

T Cell Exhaustion Is Defined by Expression of Inhibitory Receptors



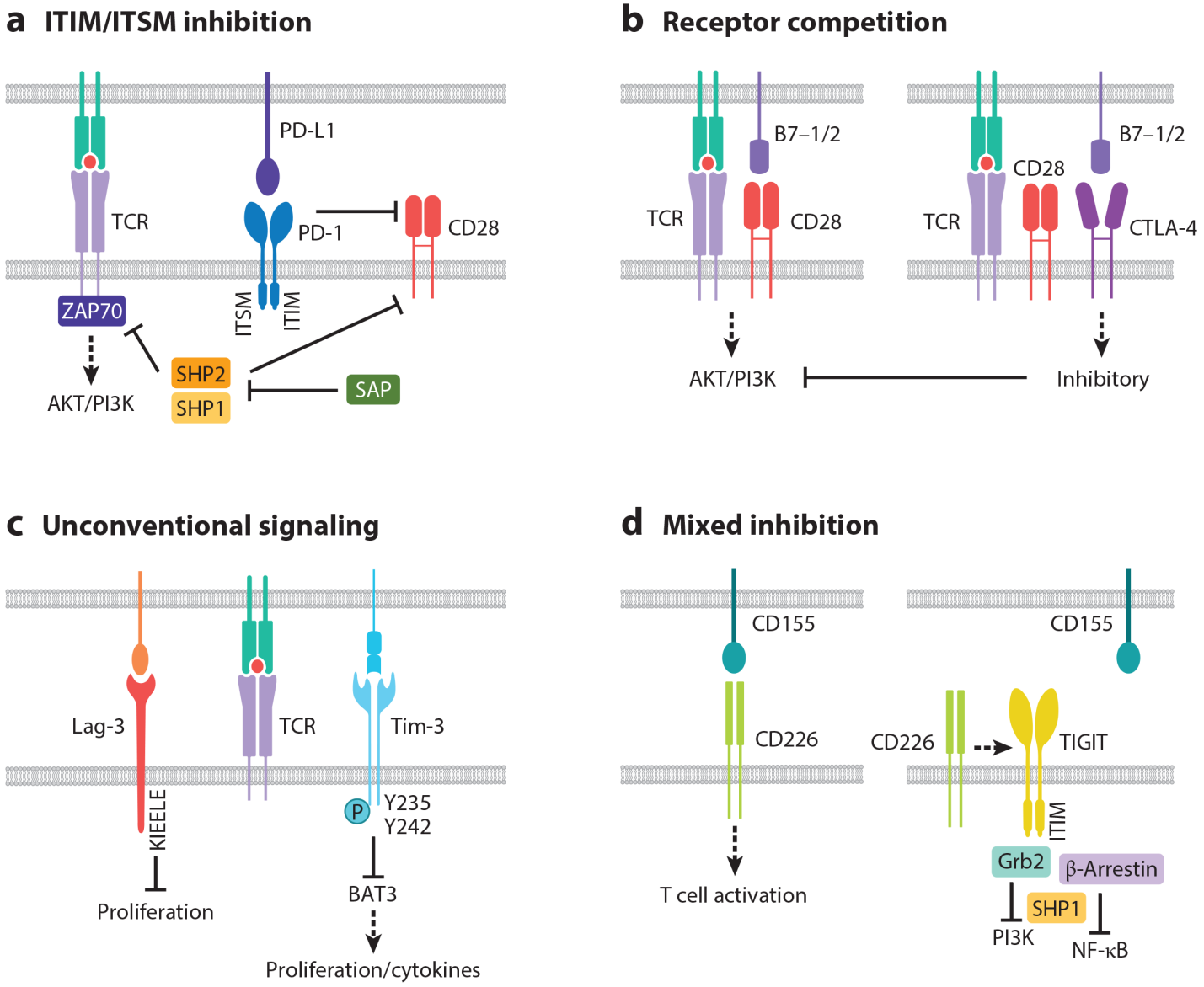
McLane LM et al. *Annu. Rev. Immunol.* 2019 37: 457-95.

Antigen, Co-stimulation and Inflammatory Signals In Control of T Cell Exhaustion



McLane LM et al. *Annu. Rev. Immunol.* 2019 37: 457-95.

Inhibitory Receptors Suppress T Cell Responses via Multiple Mechanisms

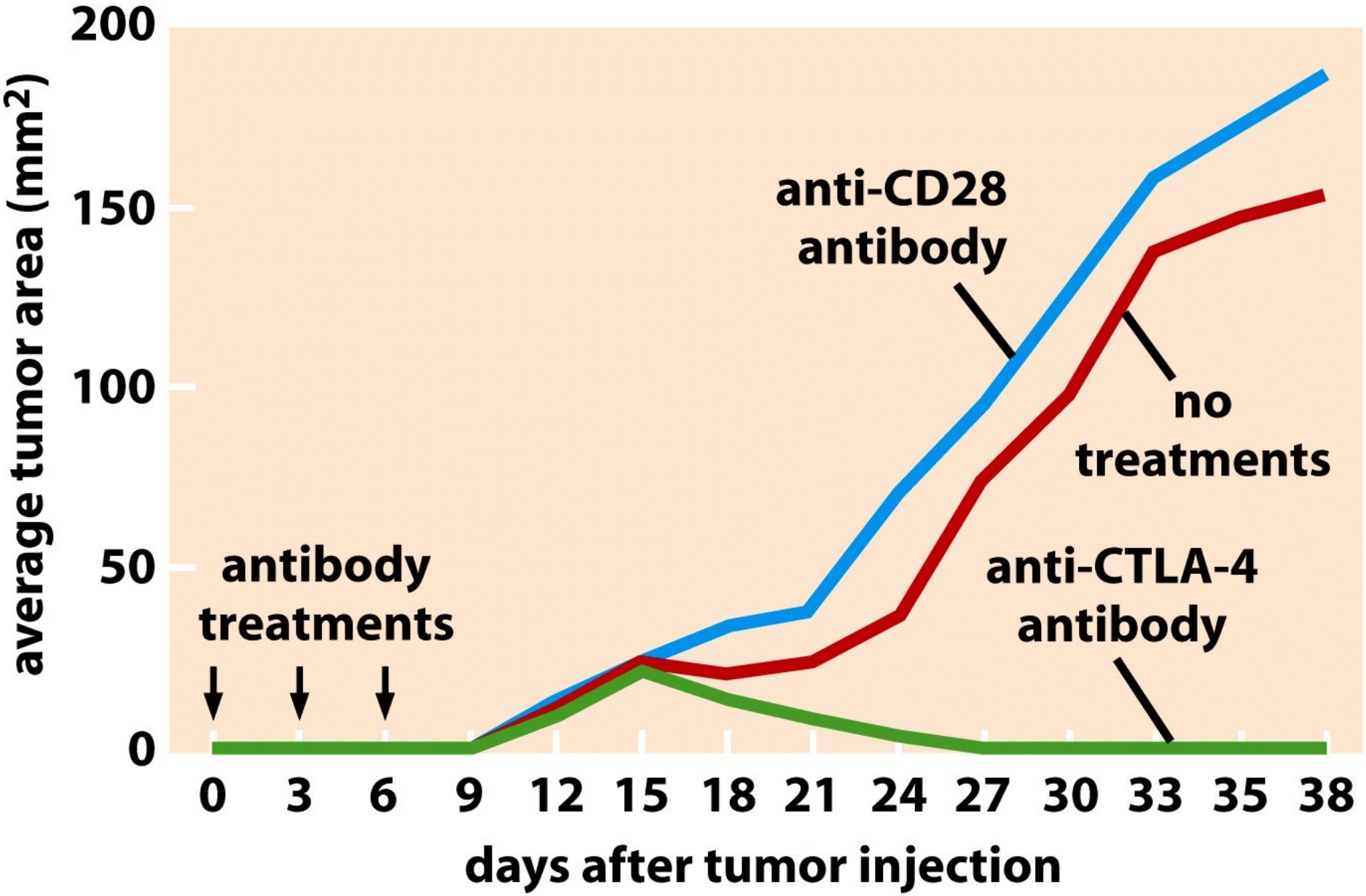


McLane LM et al. *Annu. Rev. Immunol.* 2019 37: 457-95.

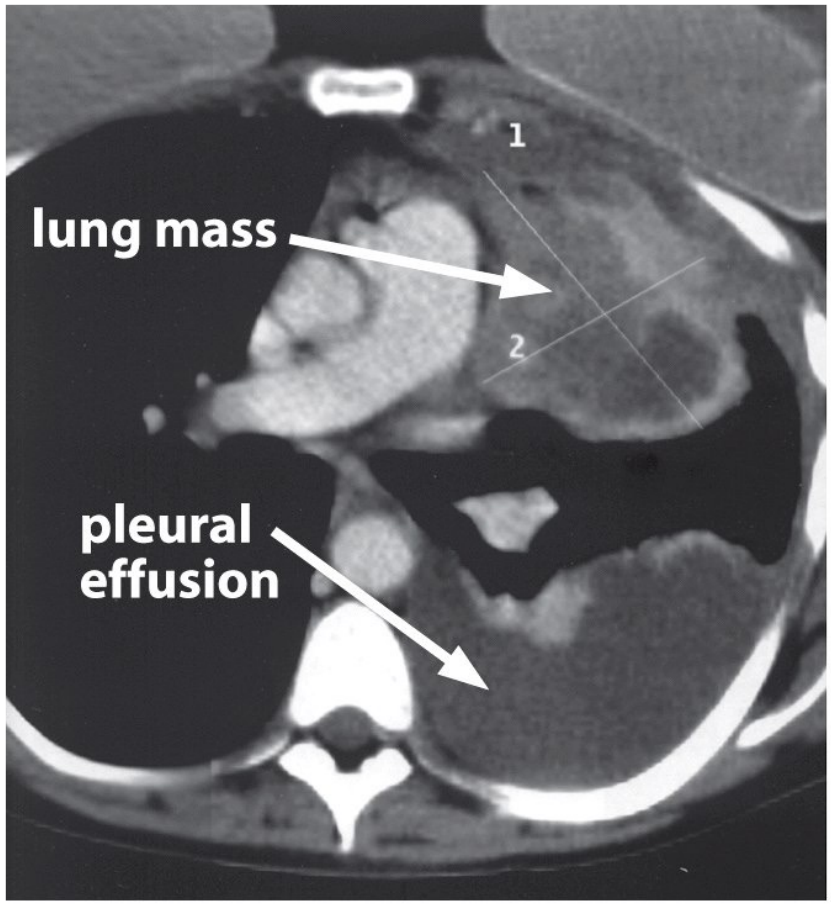
Immunotherapy of Cancer

Feasible
if there is insufficient immunosurveillance

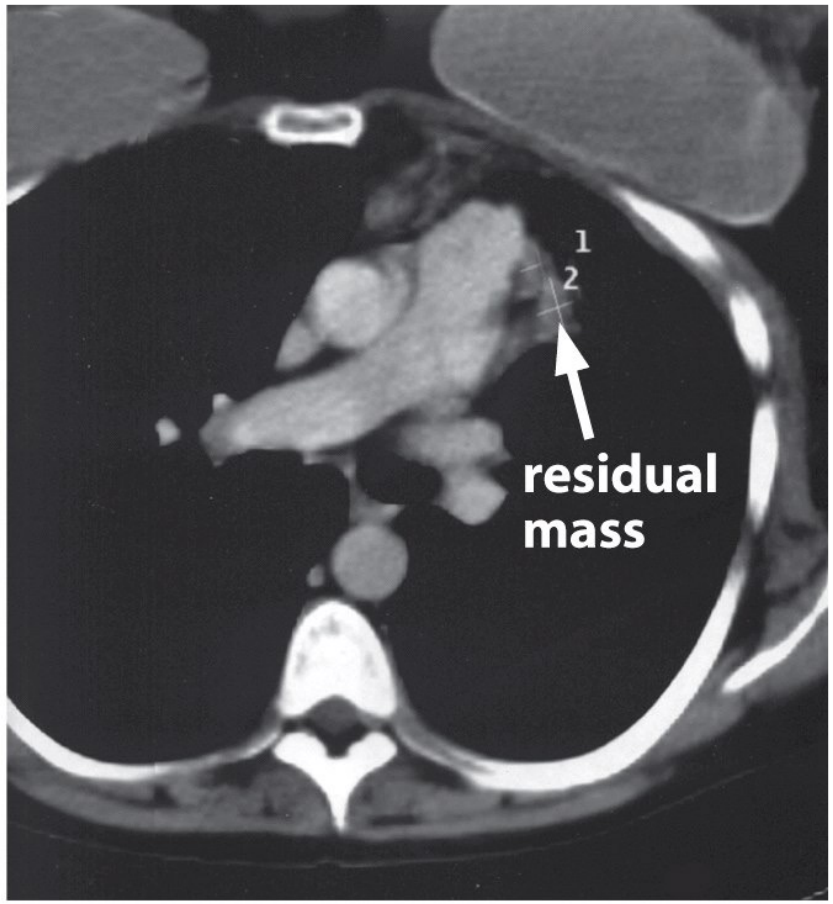
Induction of Tumor Immunity through the Blockade of CTLA-4 Signaling in T Cells



Immunotherapy via CTLA-4 mAb



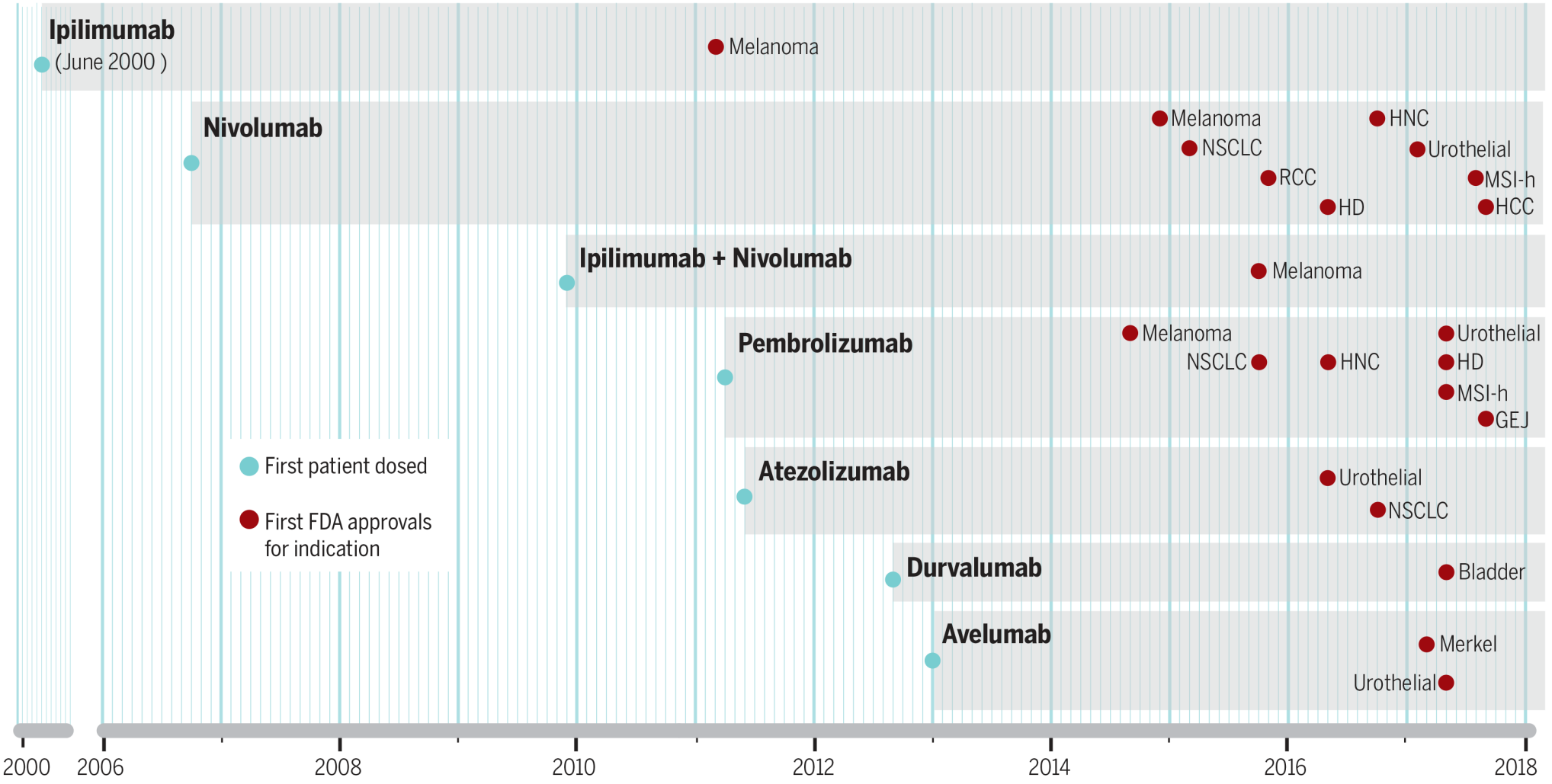
pre-treatment



5 months post-treatment

1st FDA Approved Immunotherapy Targeting a Tumor Immune Tolerance Pathway! (3/25/11)

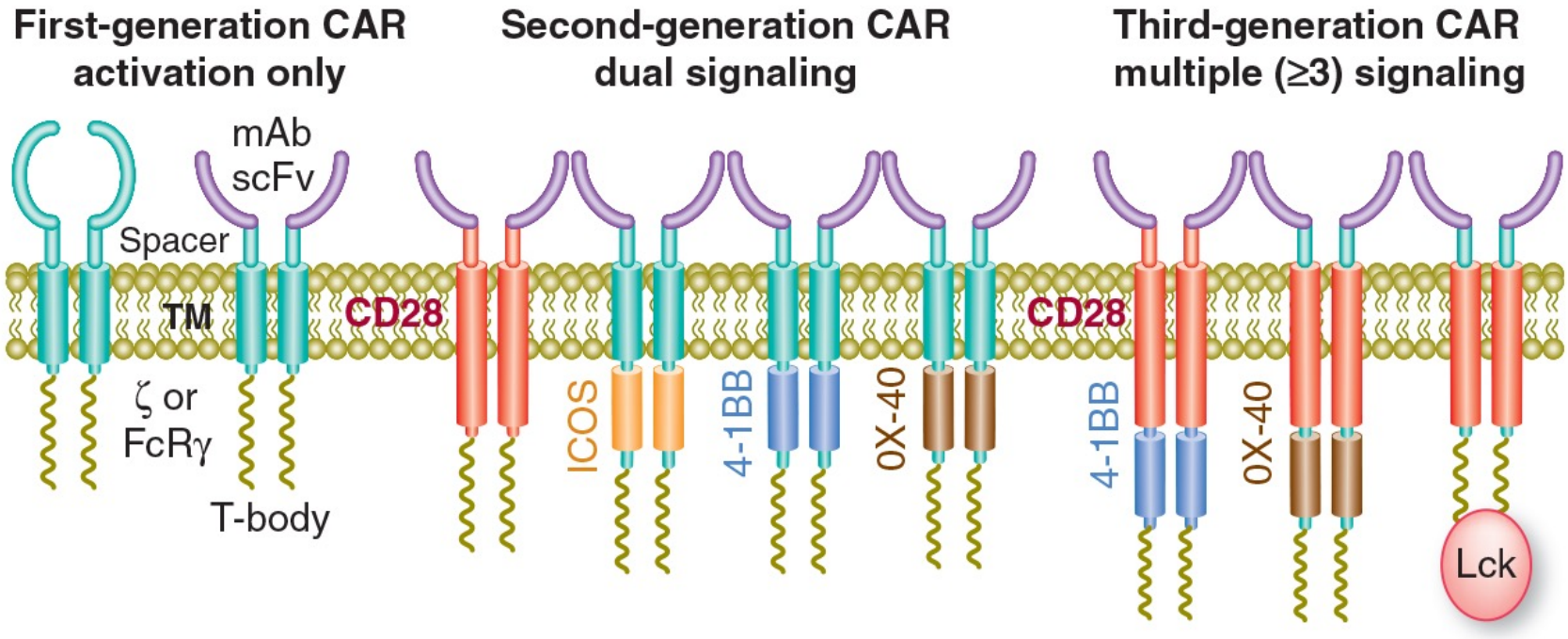
Clinical Development of anti-CTLA-4, anti-PD-1 and anti-PD-L1 for Cancer Immunotherapy



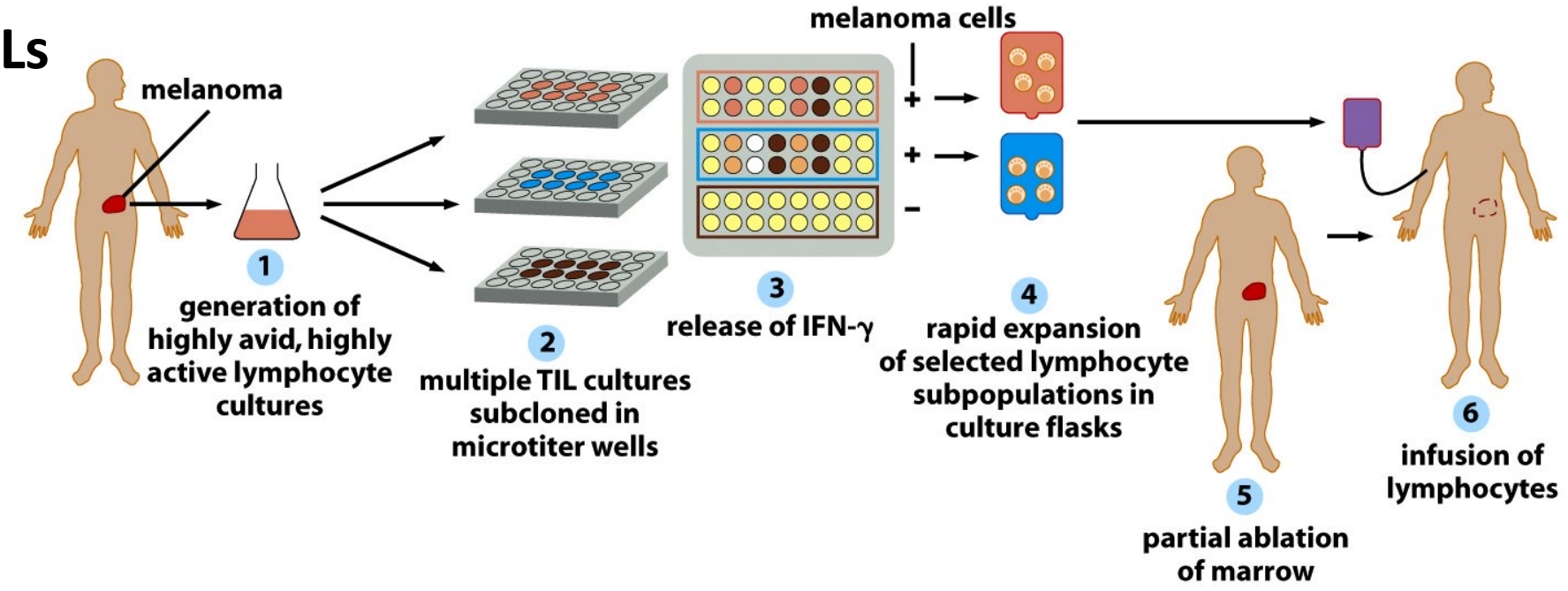
Ribas A & Wolchok JD *Science* 2018 359: 1350-5.

Adoptive T Cell Therapy

CARs



TILs



Summary

1) Leukocytes are a crucial component of the tumor microenvironment.

2) Chronic inflammation can promote cancer progression.

3) Innate and adaptive cytotoxic lymphocytes can repress cancer progression, and shape the immunogenicity of tumor cells.

4) Tumor-reactive lymphocytes can be rendered dysfunctional (e.g. induction of exhaustion), and are thus inconsequential for cancer progression.

5) Understanding the intricate interactions between tumors and the immune system provides new opportunities to conquer cancer.