Innate Immunity, Inflammation and Cancer

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Seminar BINGO!

To play, simply print out this bingo sheet and attend a departmental seminar.

Mark over each square that occurs throughout the course of the lecture.

The first one to form a straight line (or all four corners) must yell out BINGO!! to win!

SEMINAR BINGO

Speaker bashes previous work	Repeated use of "um…"	Speaker sucks up to host professor	Host Professor falls asleep	Speaker wastes 5 minutes explaining outline
Laptop malfunction	Work ties in to Cancer/HIV or War on Terror	"…et al."	You're the only one in your lab that bothered to show up	Blatant typo
Entire slide filled with equations	"The data *clearly* shows…"	FREE Speaker runs out of time	Use of Powerpoint template with blue background	References Advisor (past or present)
There's a Grad Student wearing same clothes as yesterday	Bitter Post-doc asks question	"That's an interesting question"	"Beyond the scope of this work"	Master's student bobs head fighting sleep
Speaker forgets to thank collaborators	Cell phone goes off	You've no idea what's going on	"Future work will…"	Results conveniently show improvement

title: "Seminar Bingo" - originally published 4/9/2007

Innate Immunity and Inflammation

- Definitions
- Cells and Molecules
- Innate Immunity and Inflammation in Cancer
- Bad Inflammation
- Good Inflammation
- Therapeutic Implications

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- Innate Immunity: Immunity that is naturally present and is not due to prior sensitization to an antigen; generally nonspecific. It is in contrast to acquired/adaptive immunity.

Adapted from *Merriam-Webster Medical Dictionary*

- **Innate Immunity:** Immunity that is naturally present and is not due to prior sensitization to an antigen; generally nonspecific. It is in contrast to acquired/adaptive immunity.

- **Inflammation:** a local response to tissue injury
  - Rubor (redness)
  - Calor (heat)
  - Dolor (pain)
  - Tumor (swelling)

Adapted from *Merriam-Webster Medical Dictionary*

“Innate Immunity” and “Inflammation” are vague terms

- Specific cell types and molecules orchestrate specific types of inflammation

“Innate Immunity” and “Inflammation” are vague terms

- Specific cell types and molecules orchestrate specific types of inflammation

- Innate Immunity A ≠ Innate Immunity B
- Inflammation A ≠ Inflammation B

“Innate Immunity” and “Inflammation” can mean many things

- Specific cell types and molecules orchestrate specific types of inflammation

- Innate Immunity A ≠ Innate Immunity B
- Inflammation A ≠ Inflammation B

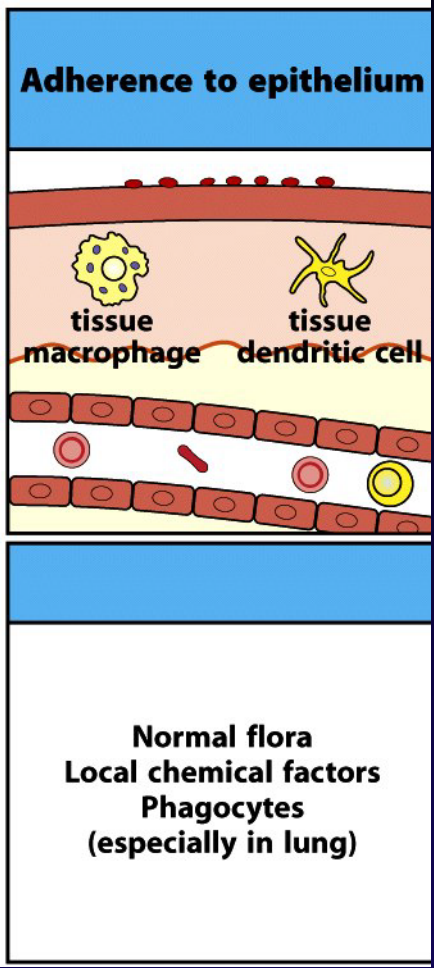
- Some immune responses promote cancer, others suppress it

Innate Immunity and Inflammation

Functions:

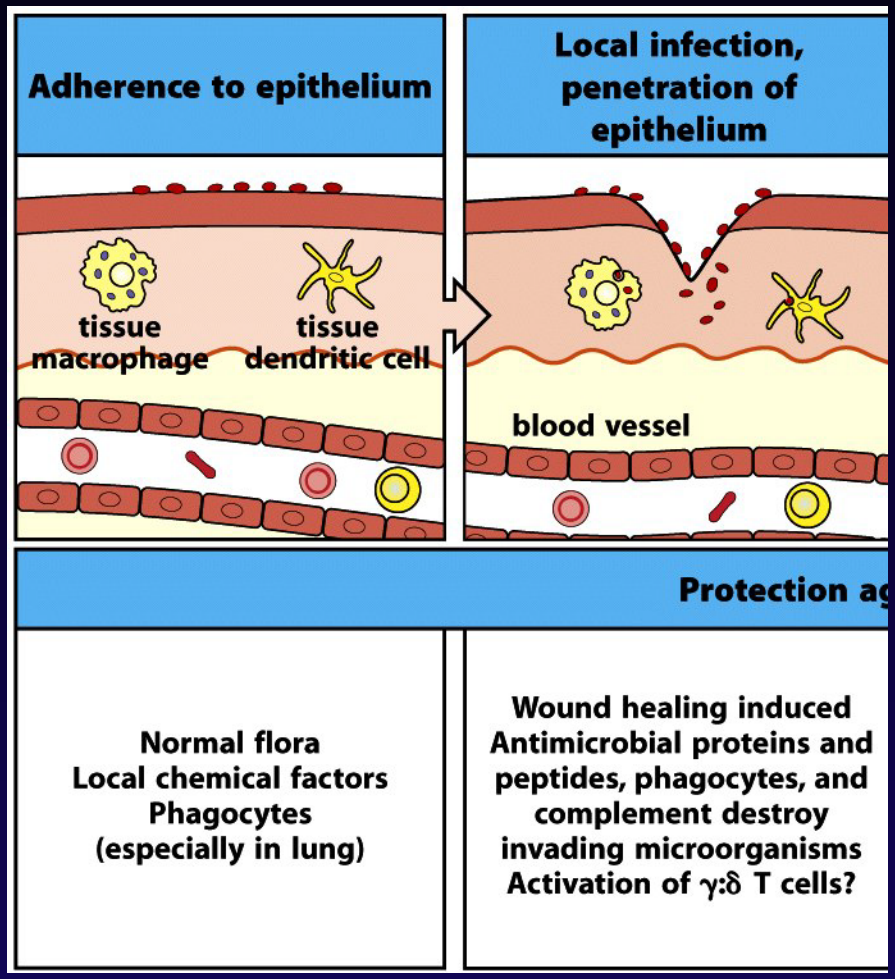
- Rapid response to tissue damage
- Limit spread of infection
- Initiate adaptive immune response (T, B)
- Initiate tissue repair

Innate Immunity and Inflammation: A Paper Cut



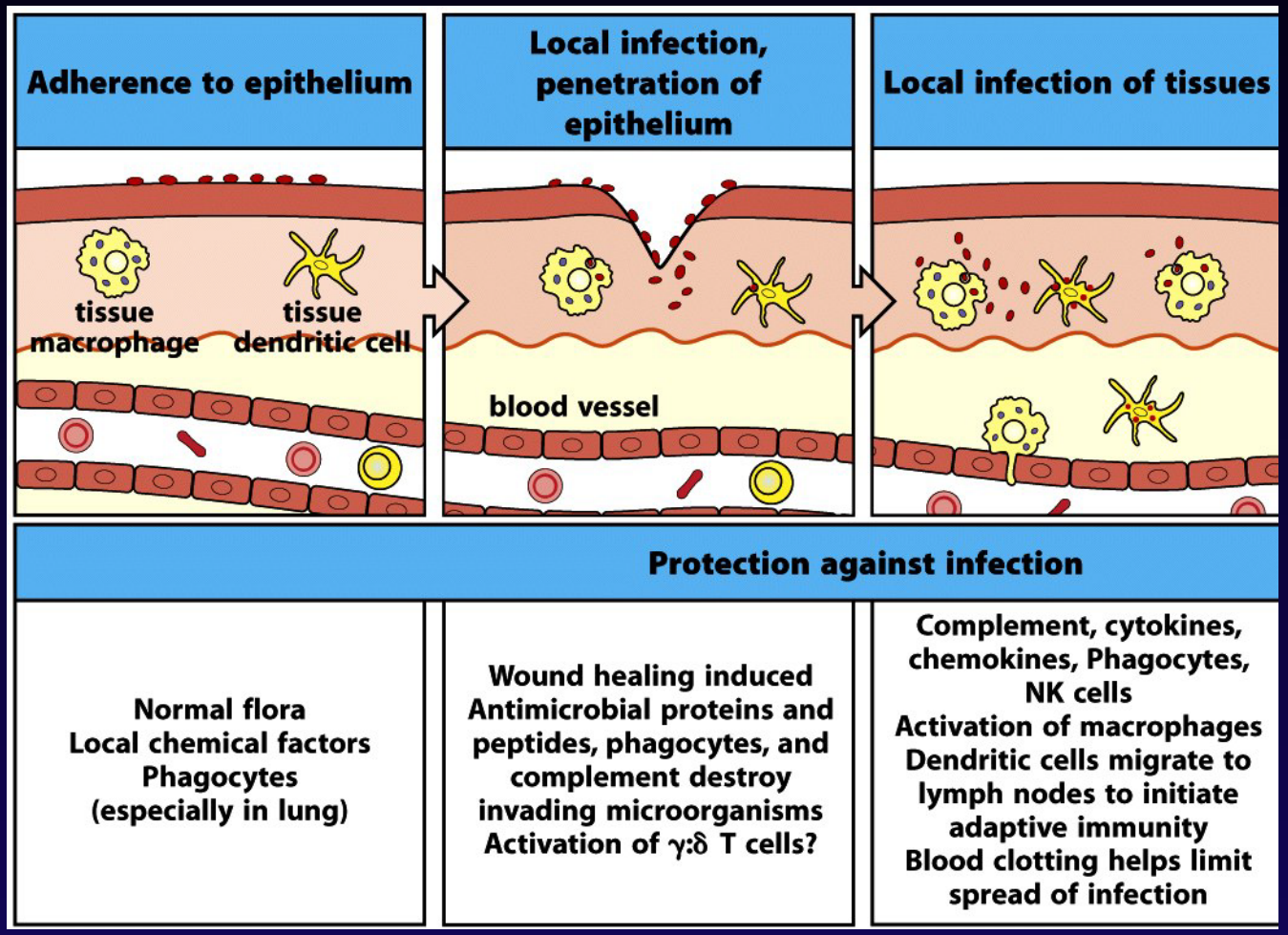
Janeway, *Immunobiology, 7th Ed.*

Innate Immunity and Inflammation: A Paper Cut



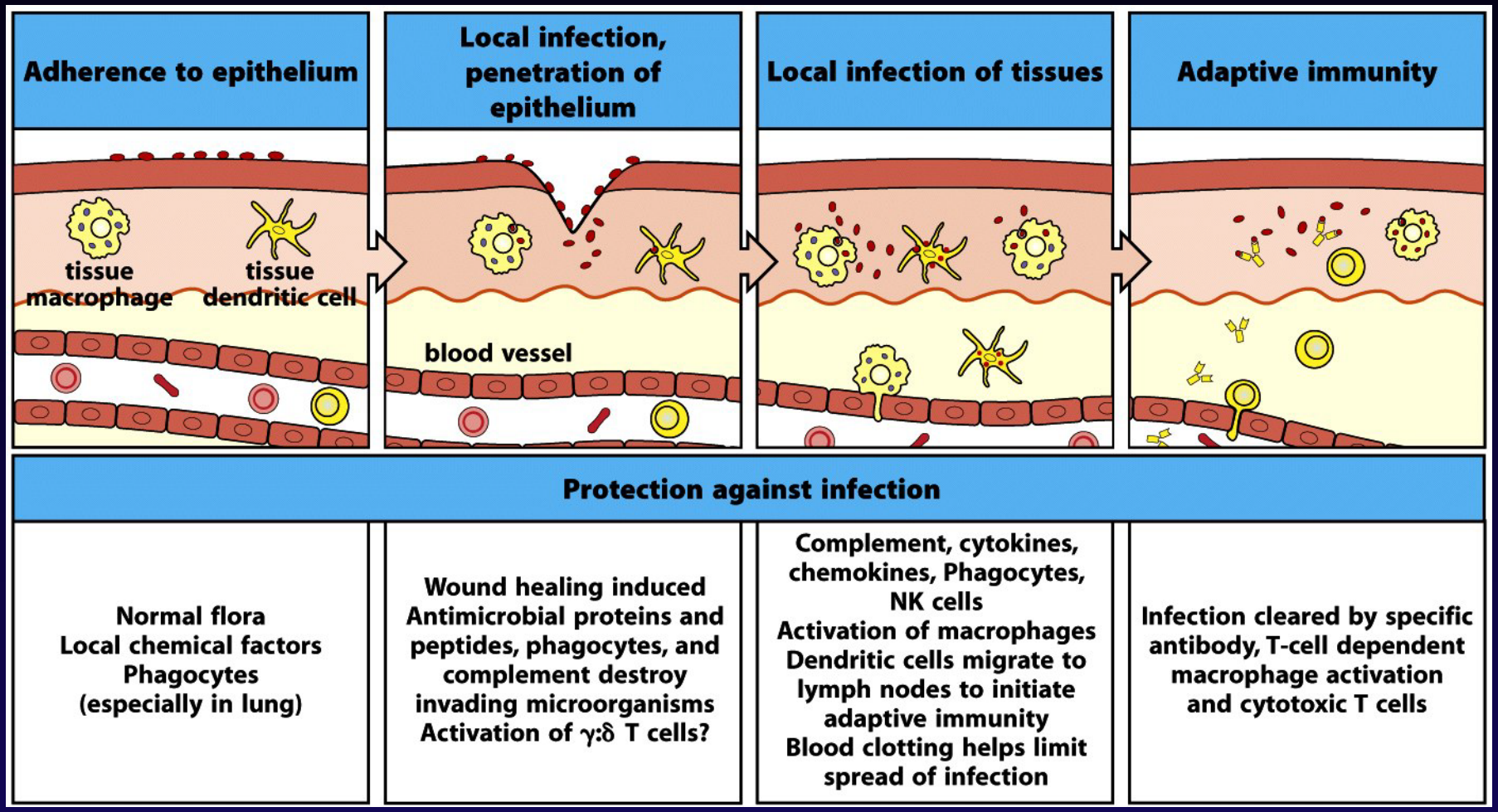
Janeway, *Immunobiology, 7th Ed.*

Innate Immunity and Inflammation: A Paper Cut



Janeway, *Immunobiology, 7th Ed.*

Innate Immunity and Inflammation: A Paper Cut



Janeway, *Immunobiology, 7th Ed.*

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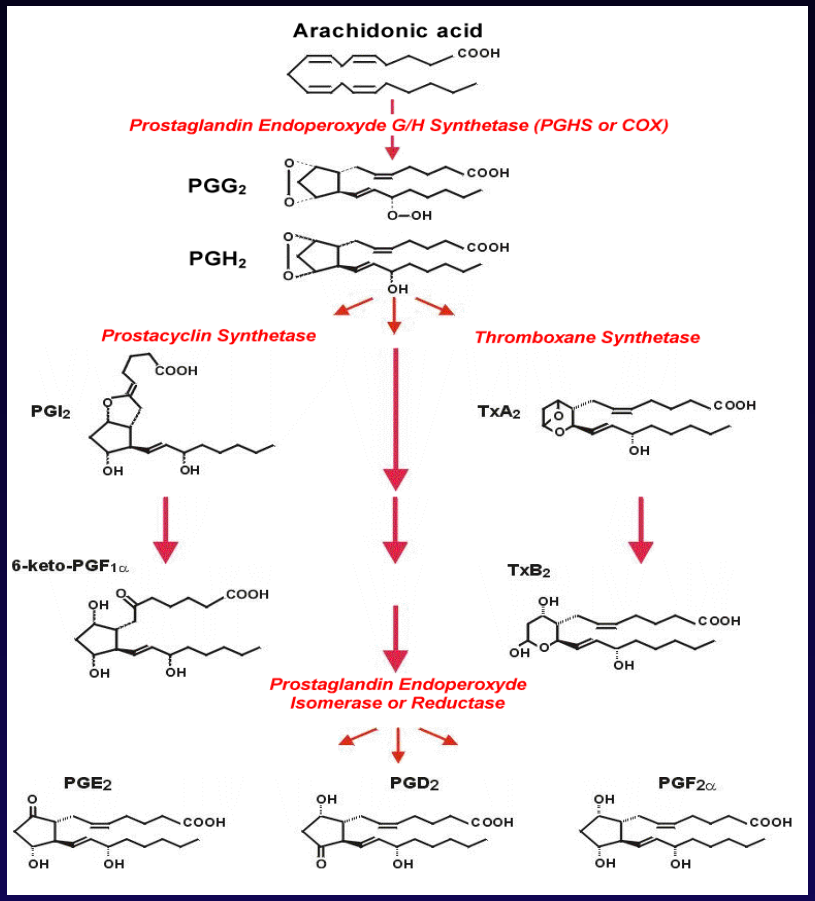
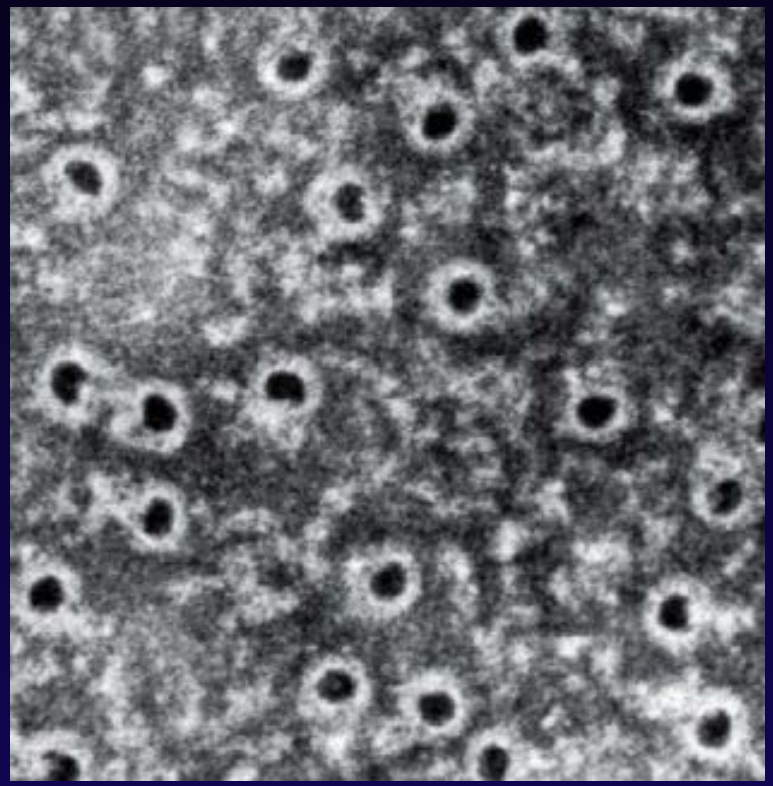
Innate Immune Molecules: Cyclooxygenase-2 (COX-2)



Recognize
- inflammation

Cause
- inflammation

Innate Immune Molecules: Complement System



Recognize
- pathogens
- antibodies
- lectins

Cause
- pathogen clearance
- chemotaxis
- inflammation

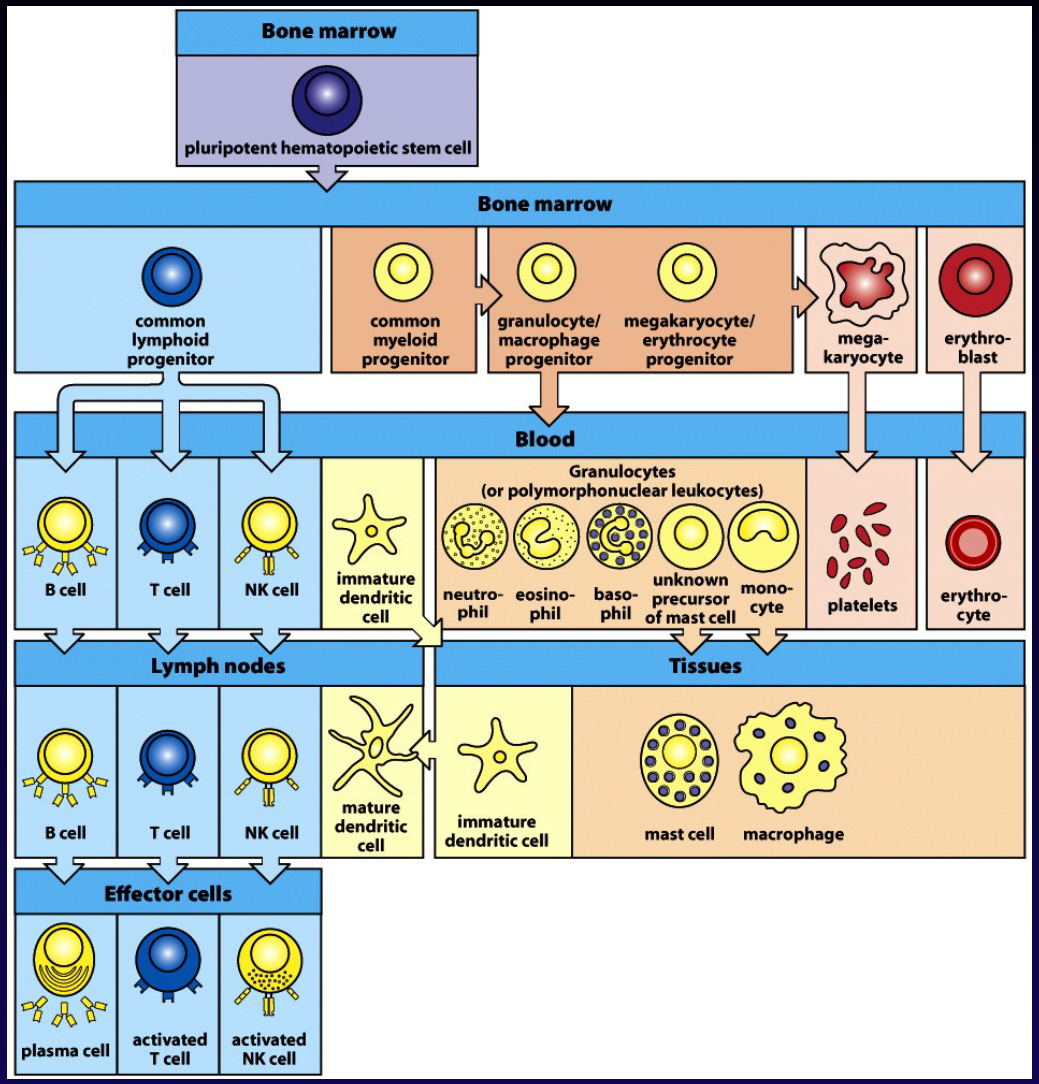
Janeway, *Immunobiology, 7th Ed.*

Innate Immune Molecules: type I IFN(-α, β)

- Induced by infection/damage
- Antiviral/Antiproliferative
- Increase innate and adaptive immunity

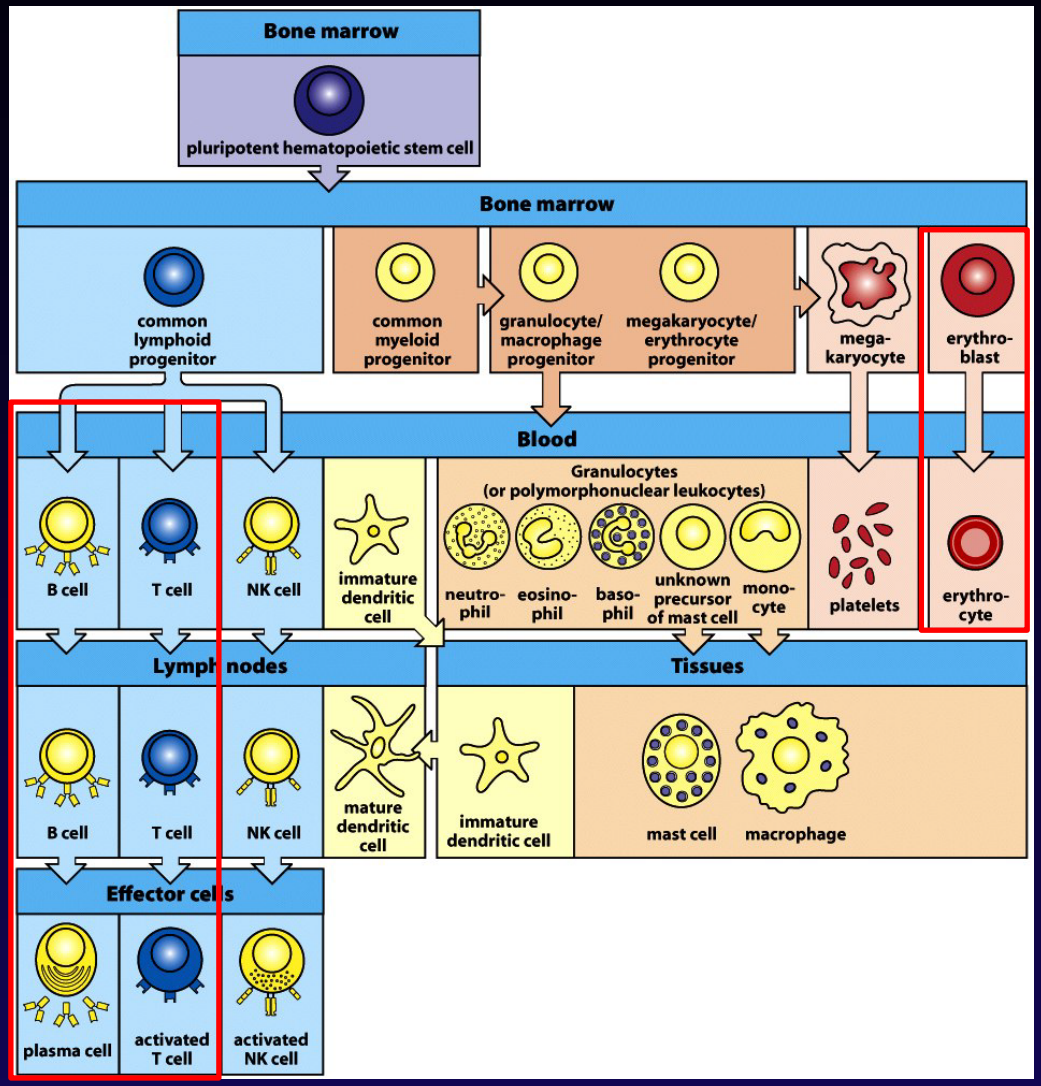
- Cause inflammation

Innate Immune Cells



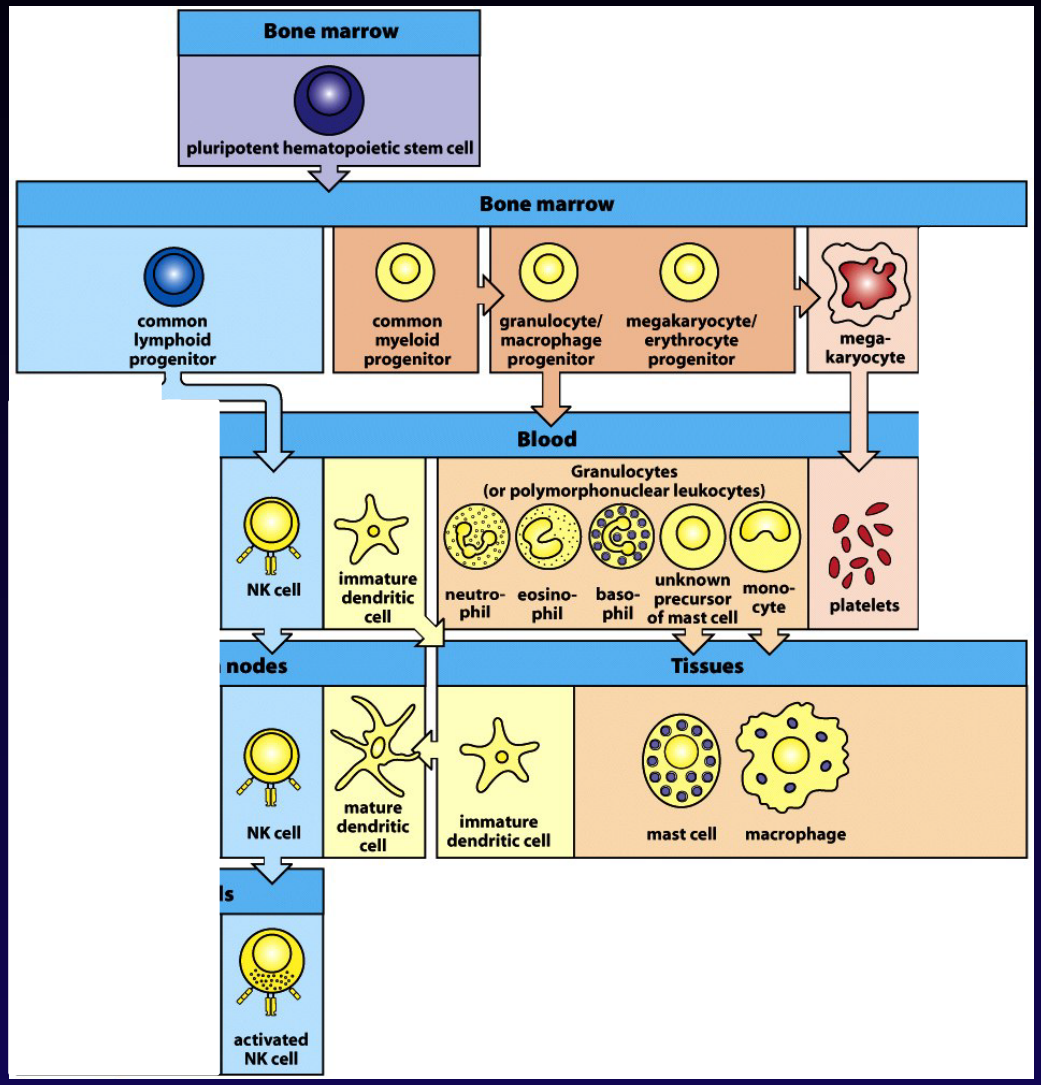
Janeway, *Immunobiology, 7th Ed.*

Innate Immune Cells



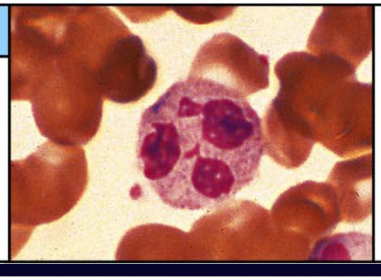
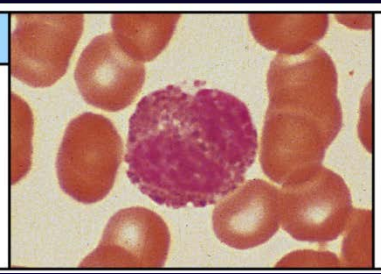
Janeway, *Immunobiology, 7th Ed.*

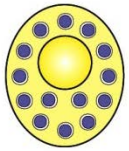
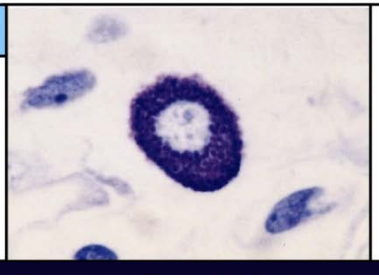
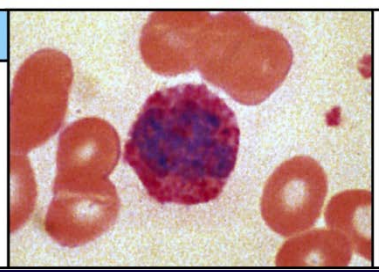
Innate Immune Cells



Janeway, *Immunobiology, 7th Ed.*

Innate Immune Cells: granulocytes

Cell		Activated function
Neutrophil 		Phagocytosis and activation of bactericidal mechanisms
Eosinophil 		Killing of antibody-coated parasites

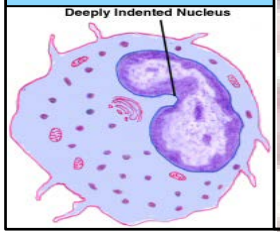
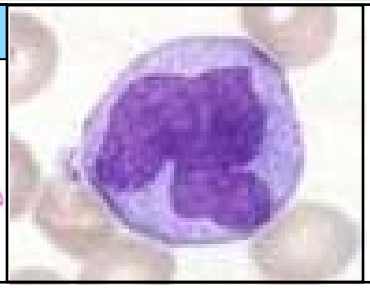
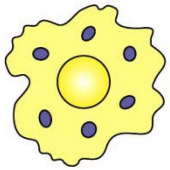
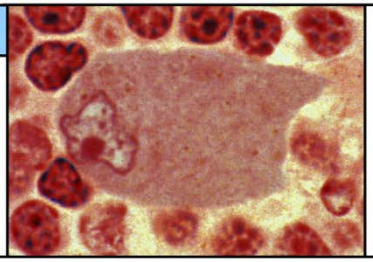
Cell		Activated function
Mast cell 		Release of granules containing histamine and active agents
Basophil 		(Unknown) Antigen Presentation

Recognize
- pathogens
- antibodies

Cause
- pathogen clearance
- inflammation

Janeway, *Immunobiology, 7th Ed.*

Innate Immune Cells: phagocytes

Cell		Activated function
Monocyte 		Blood precursor of tissue Macrophages and Dendritic Cells
Macrophage 		Phagocytosis and activation of bactericidal mechanisms Antigen presentation
Dendritic cell 		Antigen uptake in peripheral sites Antigen presentation

Recognize
- pathogens
- antibodies

Cause
- pathogen clearance
- adaptive immunity
- inflammation

Janeway, *Immunobiology, 7th Ed.*

Innate Immune Cells: NK, NKT and γδ T cells

Recognize

- pathogens
- stressed cells
- “altered self”

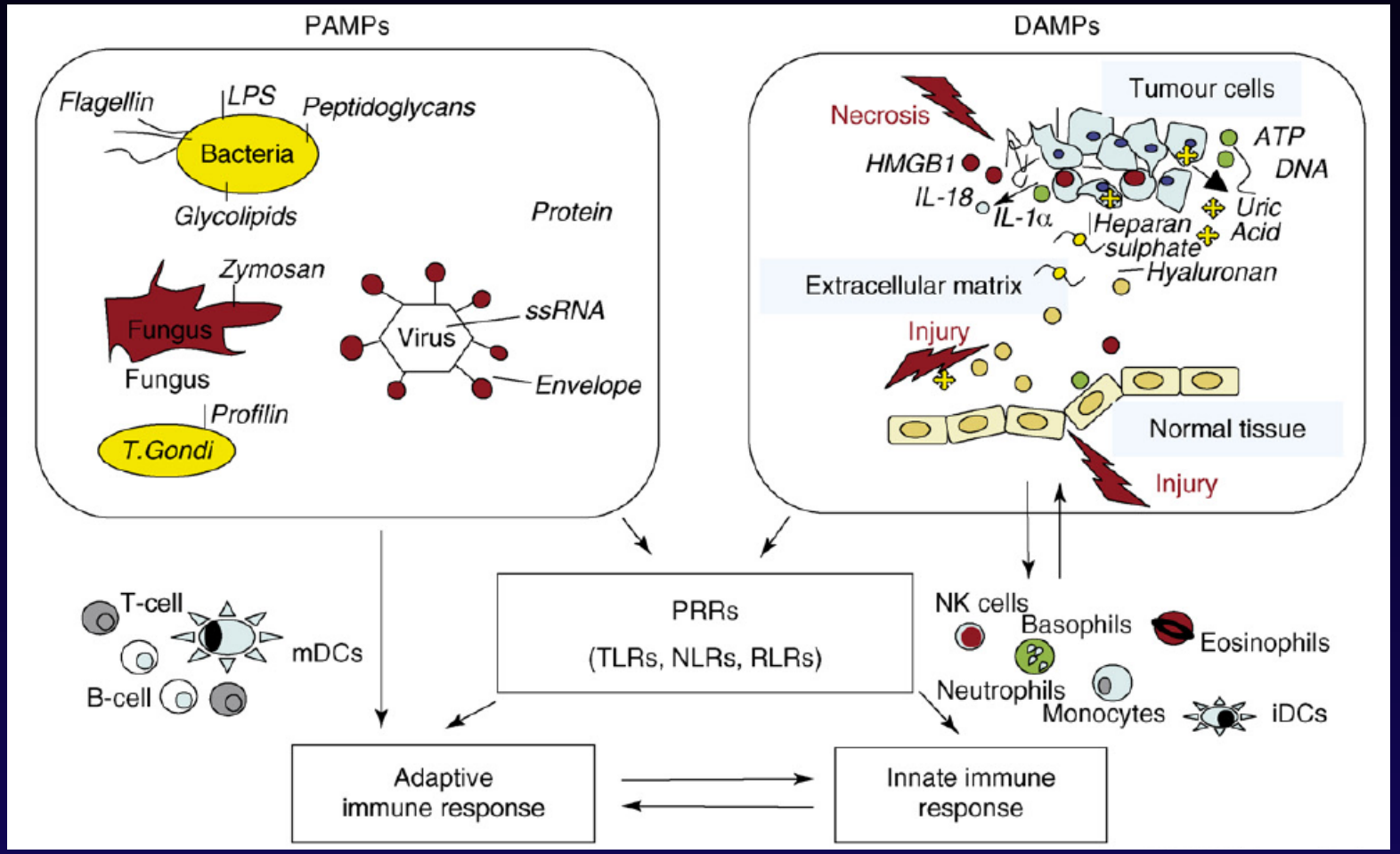
Cause

- pathogen clearance
- stressed/abnormal cell clearance
- inflammation

Danger signals start inflammation

PATHOGENS

DAMAGE

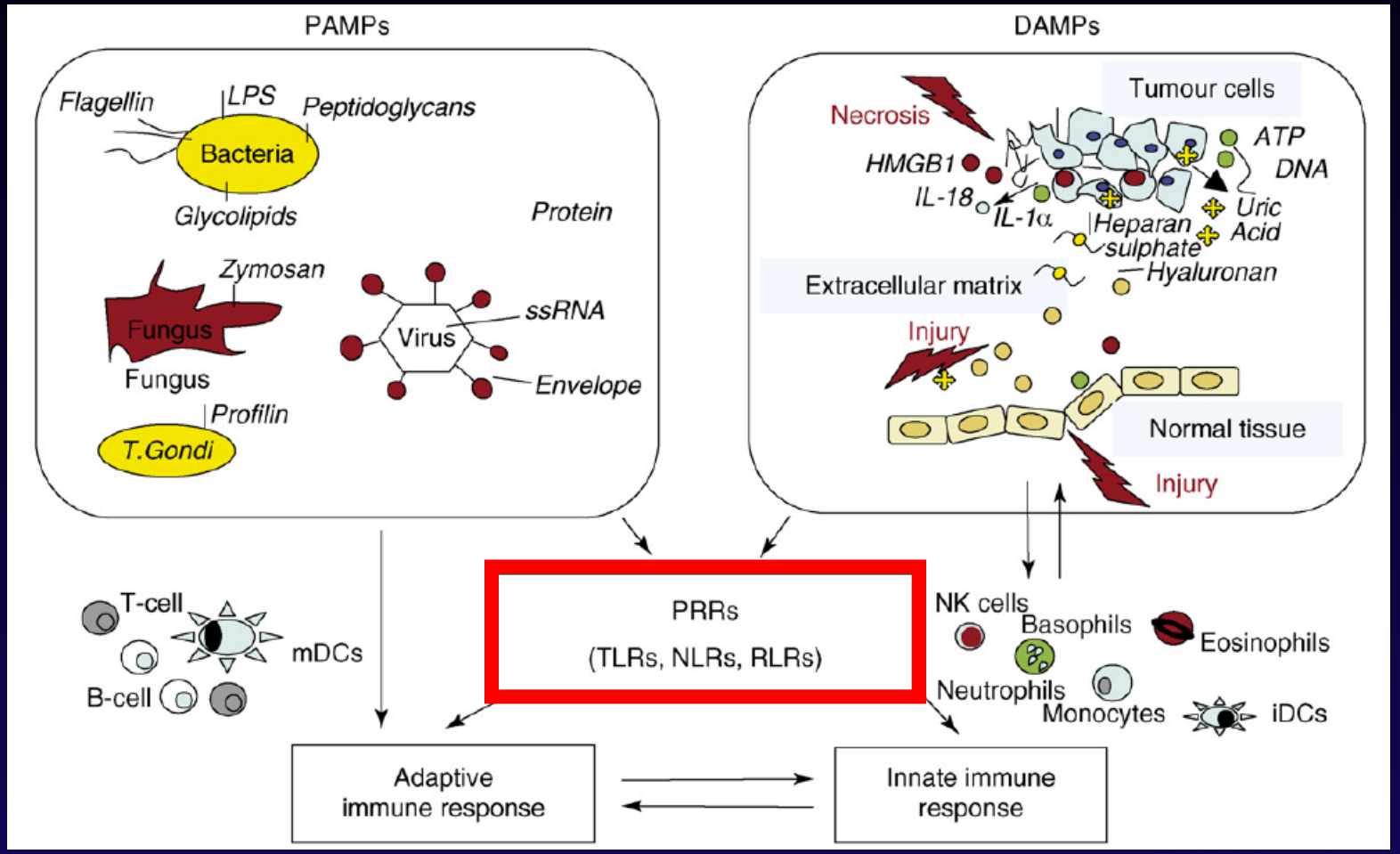


Rubartelli & Lotze, *Trends in Immunology 2007*

Danger signals start inflammation

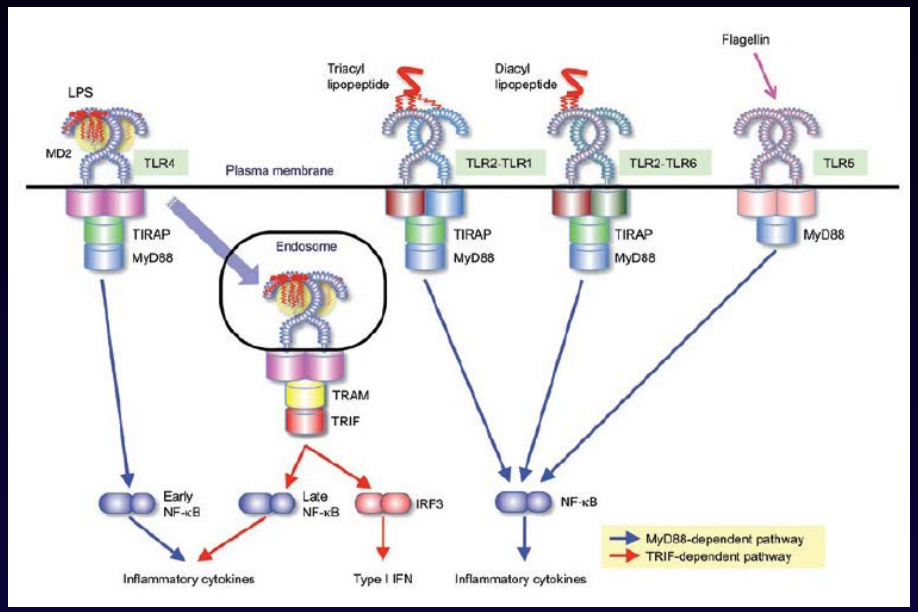
PATHOGENS

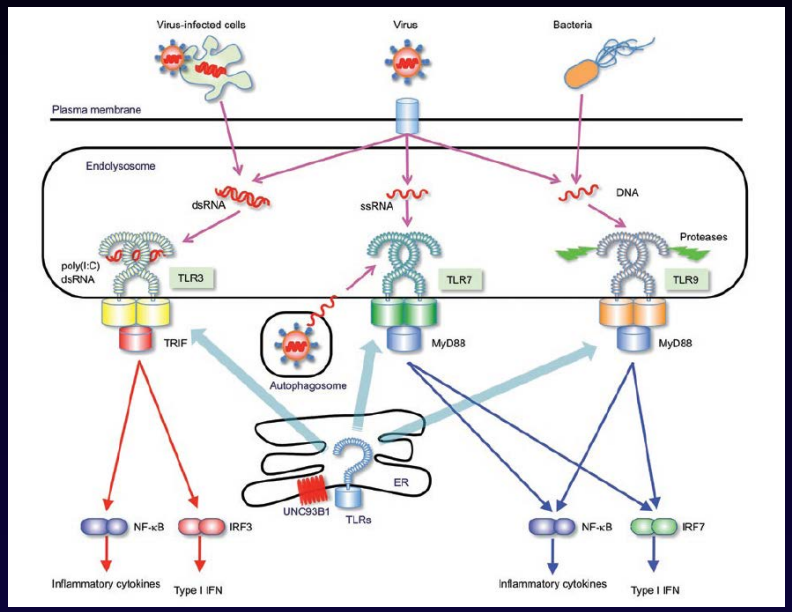
DAMAGE



Rubartelli & Lotze, *Trends in Immunology 2007*

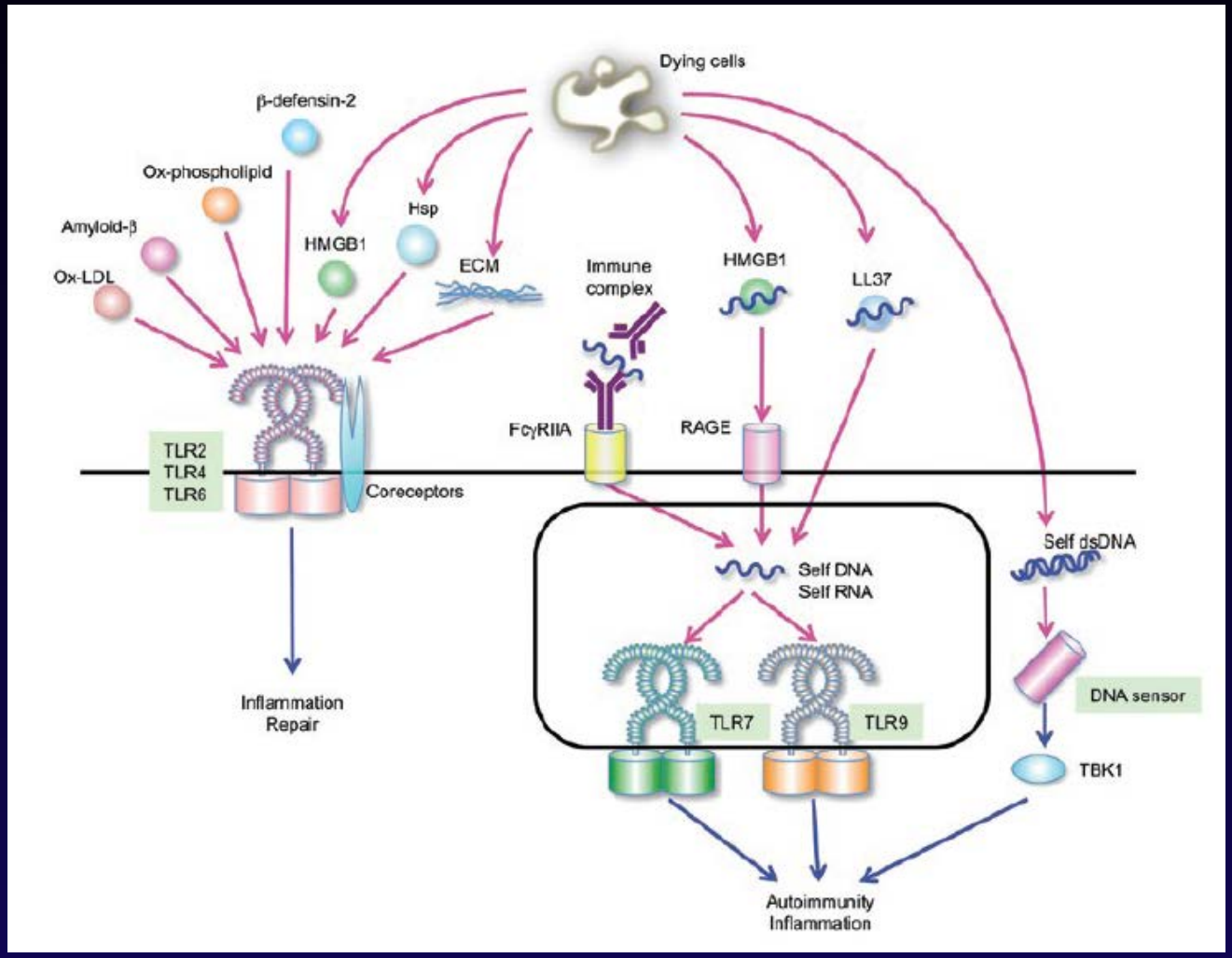
Receptors sense Danger: Pathogens





Kawai & Akira, *Nat. Immunol. 2010*

Receptors sense Danger: Damage



Kawai & Akira, *Nat. Immunol. 2010*

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- Therapeutic Implications

Innate Immunity and Inflammation in Cancer

- Outcomes vary:

  - Promote cancer (Bad inflammation)

  - Suppress cancer (Good inflammation)

Innate Immunity and Inflammation

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- Therapeutic Implications

Bad Inflammation Causes Cancer

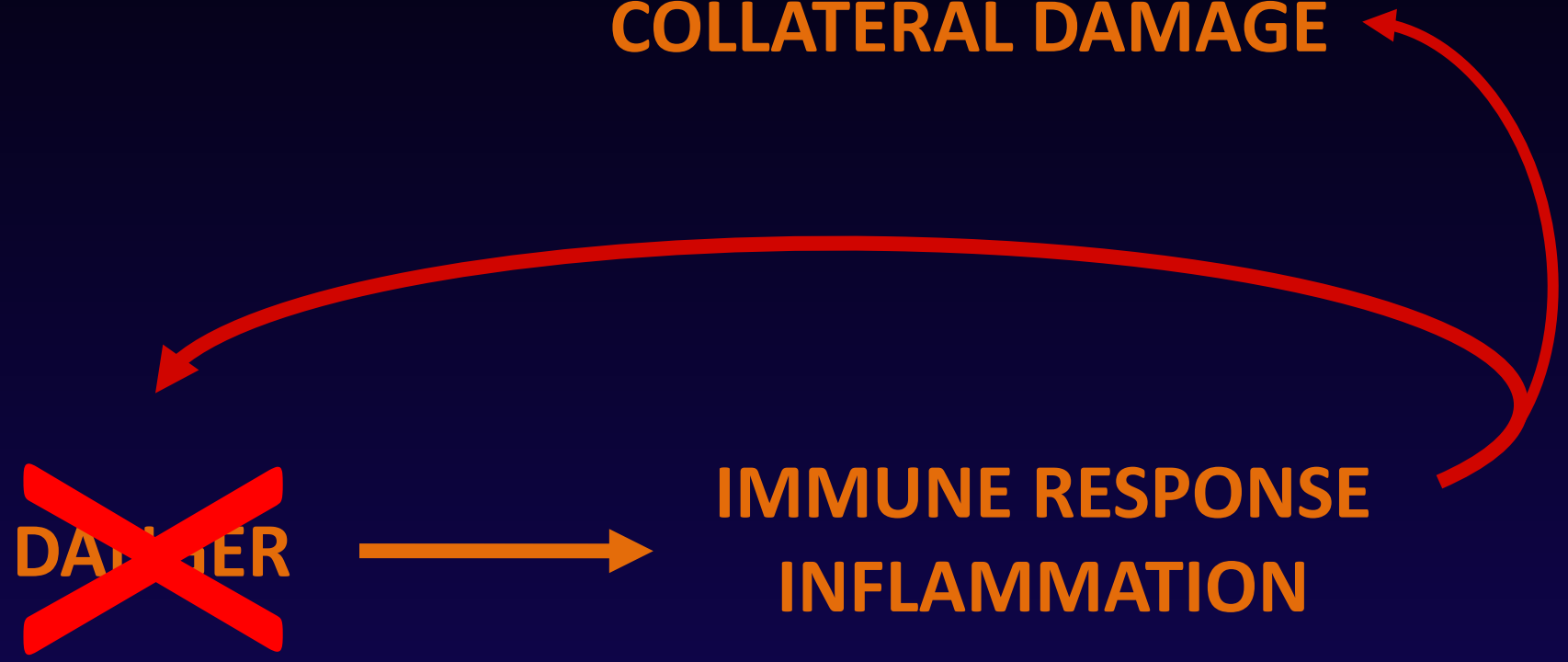
DANGER

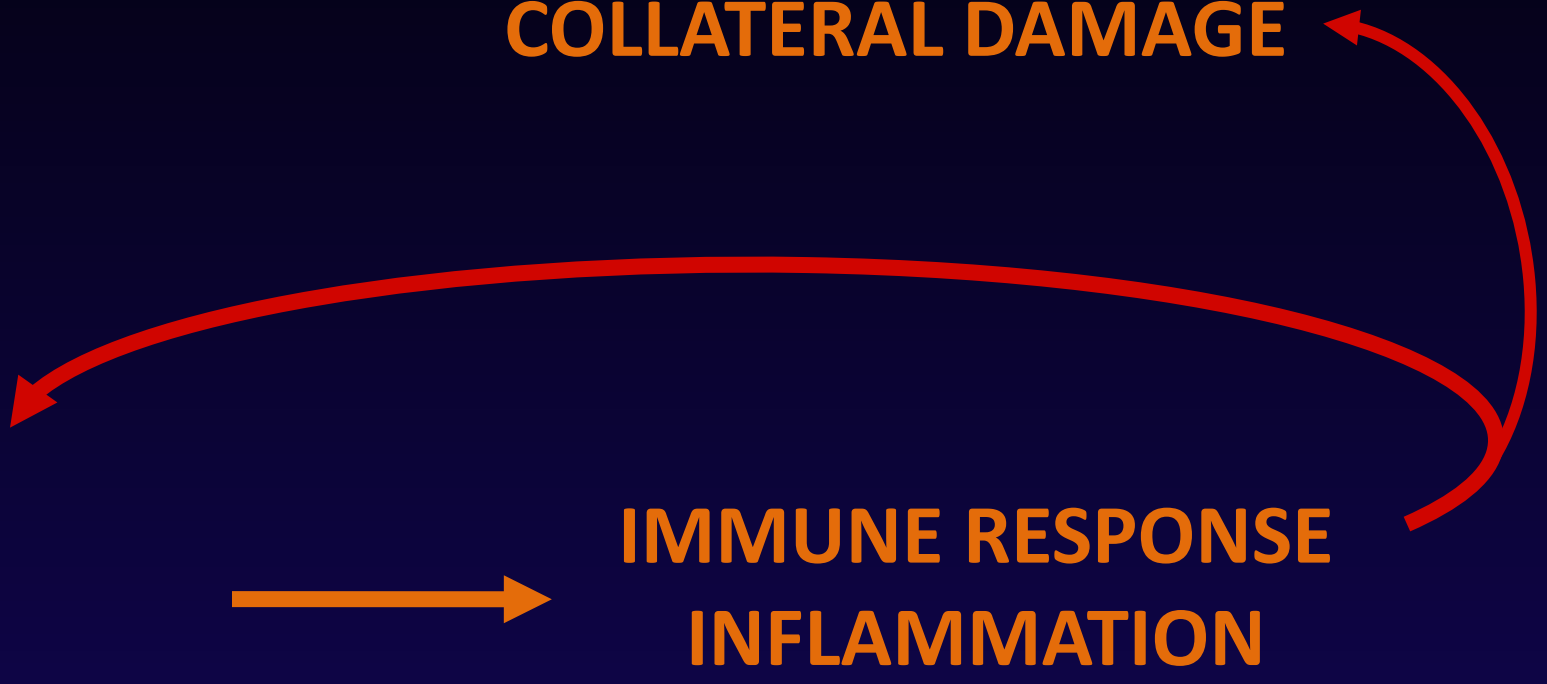
cellular damage caused by

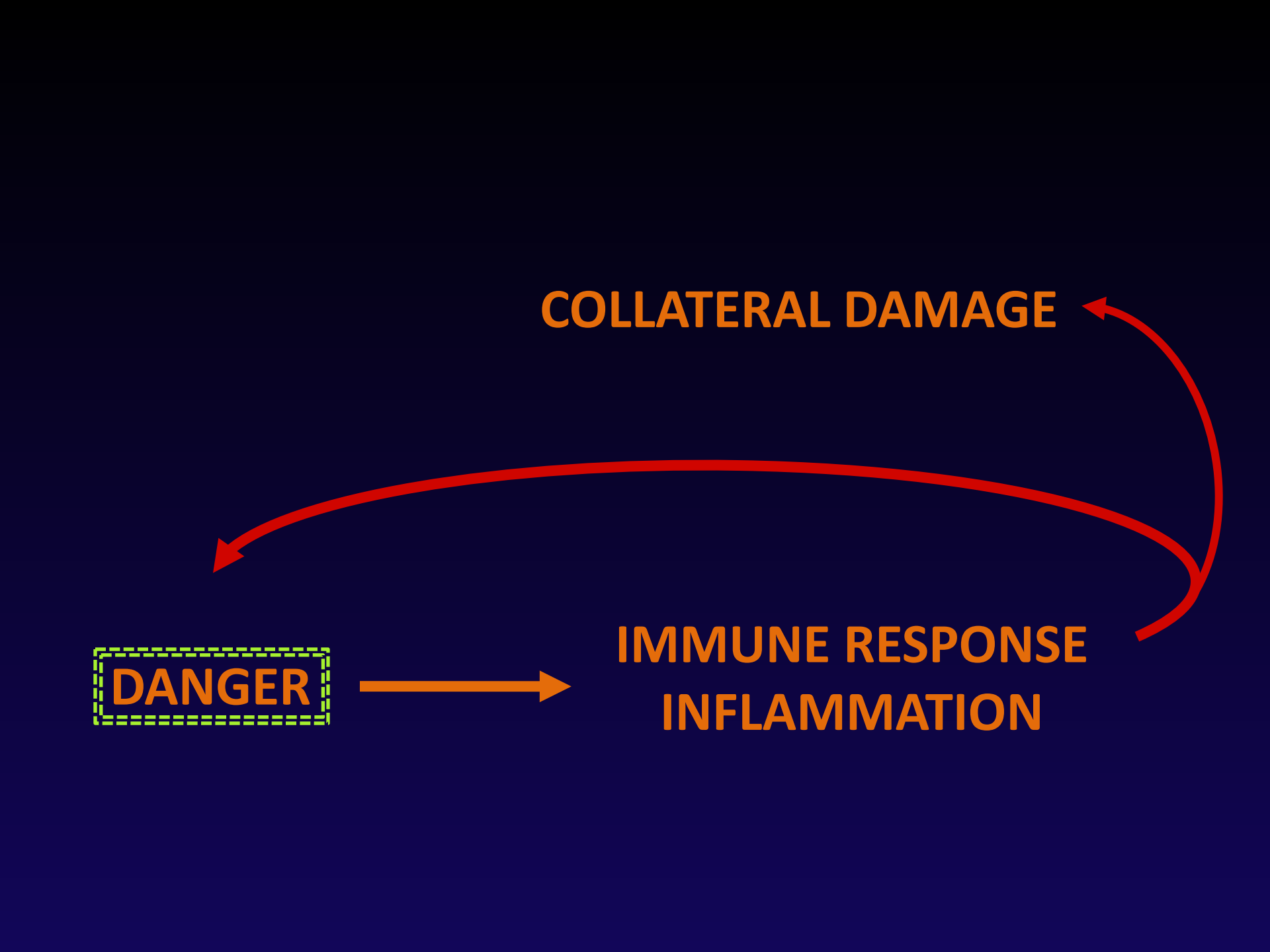
- **pathogens**
- **physical damage**
- **chemicals**
- **UV**
- **etc**

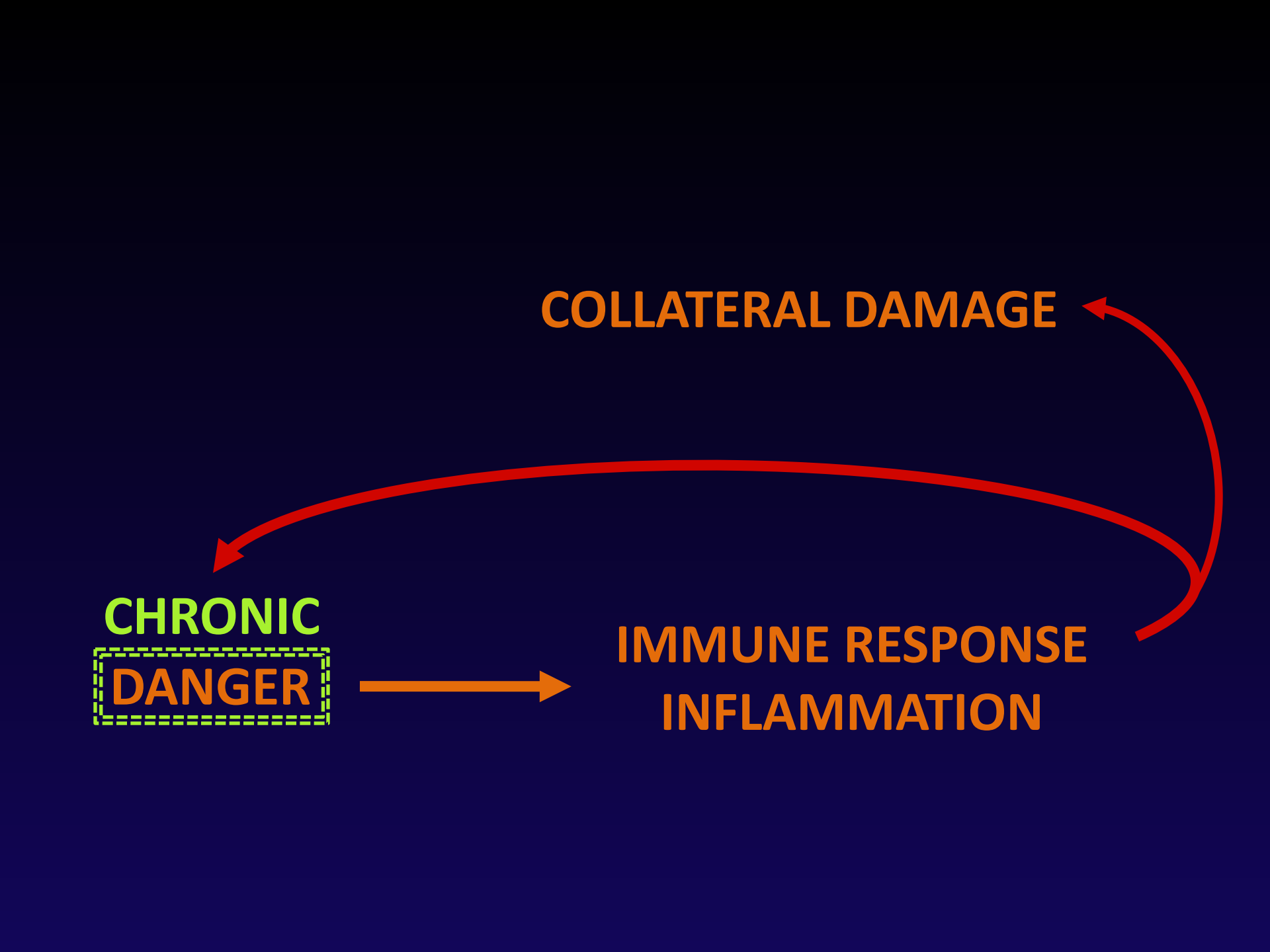
DANGER → IMMUNE RESPONSE
INFLAMMATION

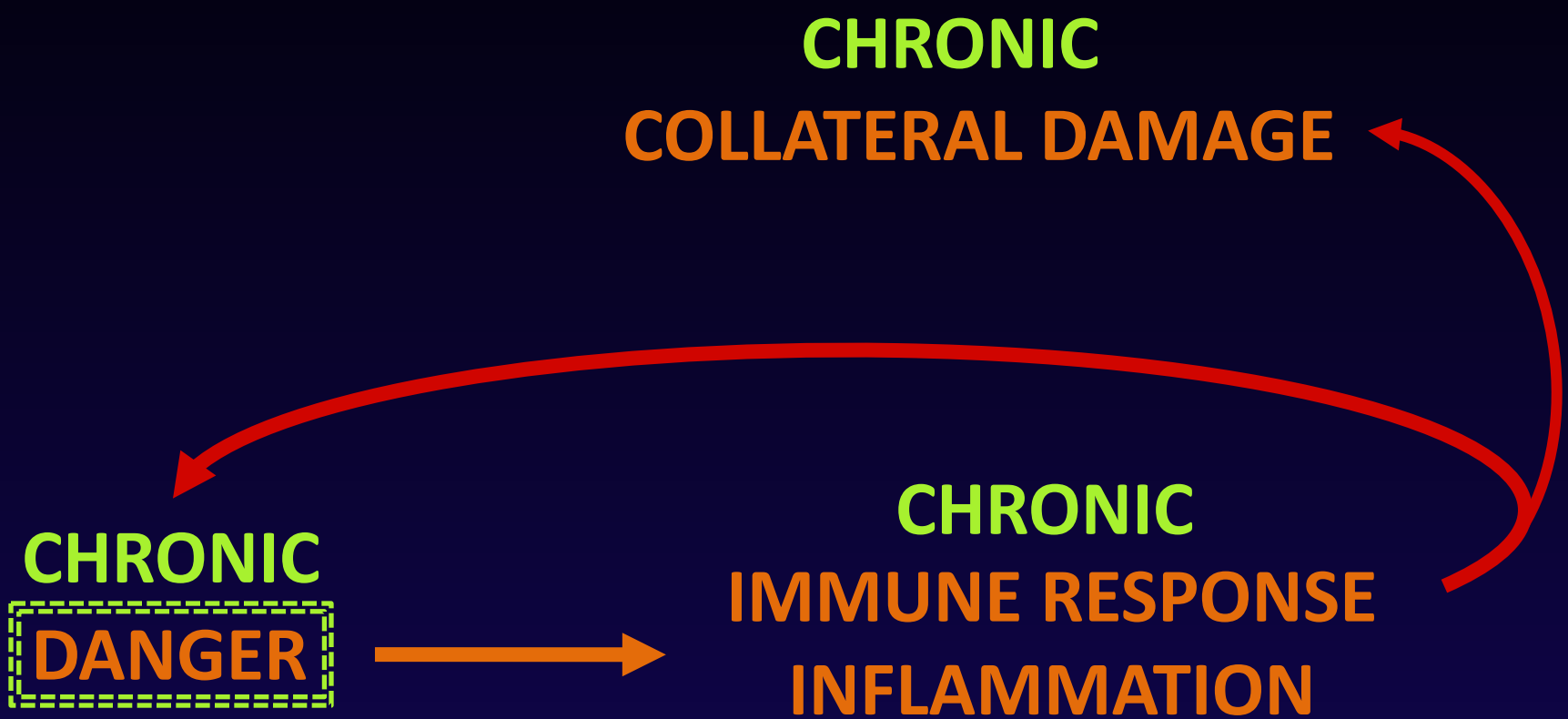

DANGER
IMMUNE RESPONSE
INFLAMMATION

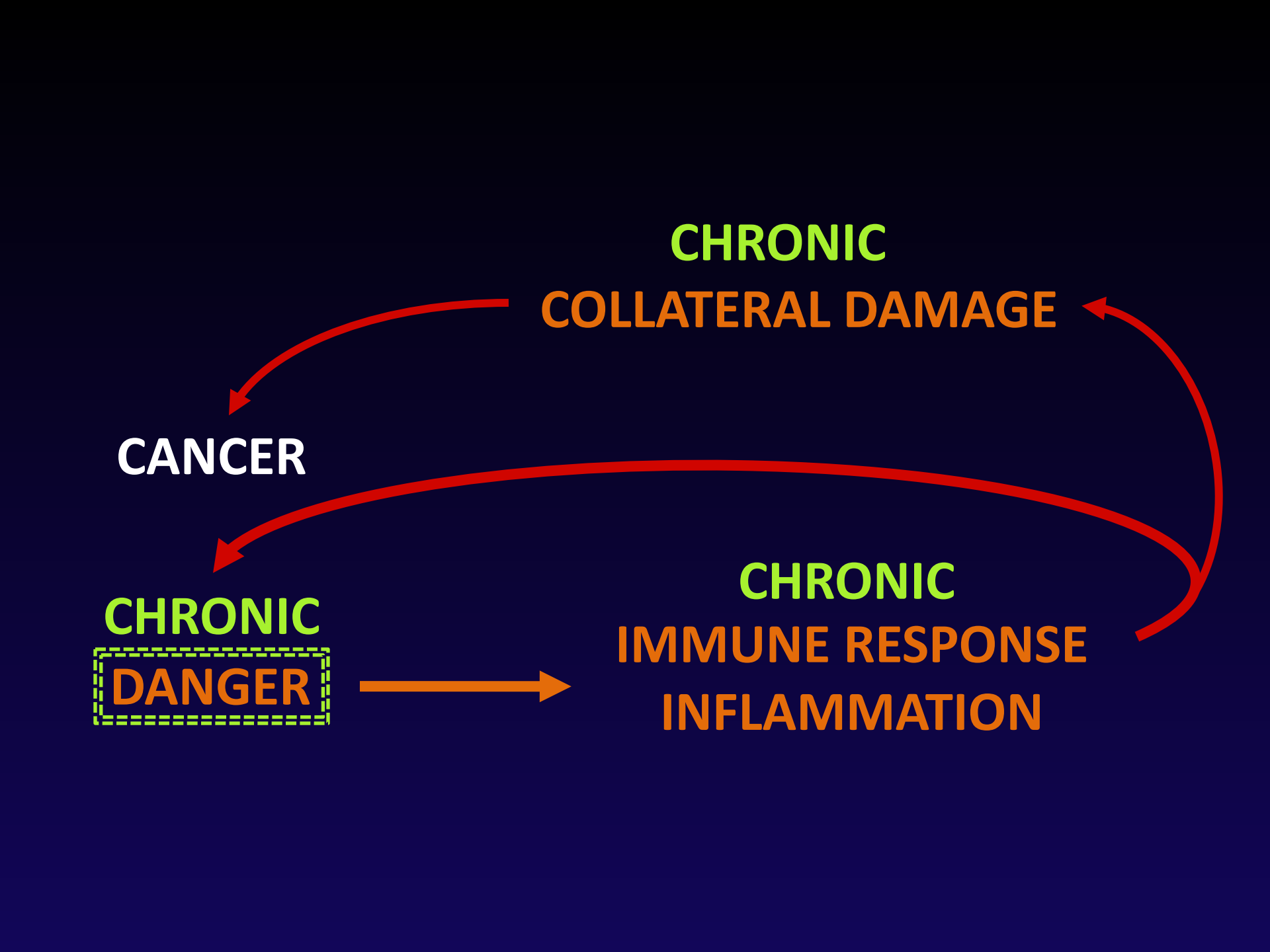

COLLATERAL DAMAGE
IMMUNE RESPONSE
INFLAMMATION

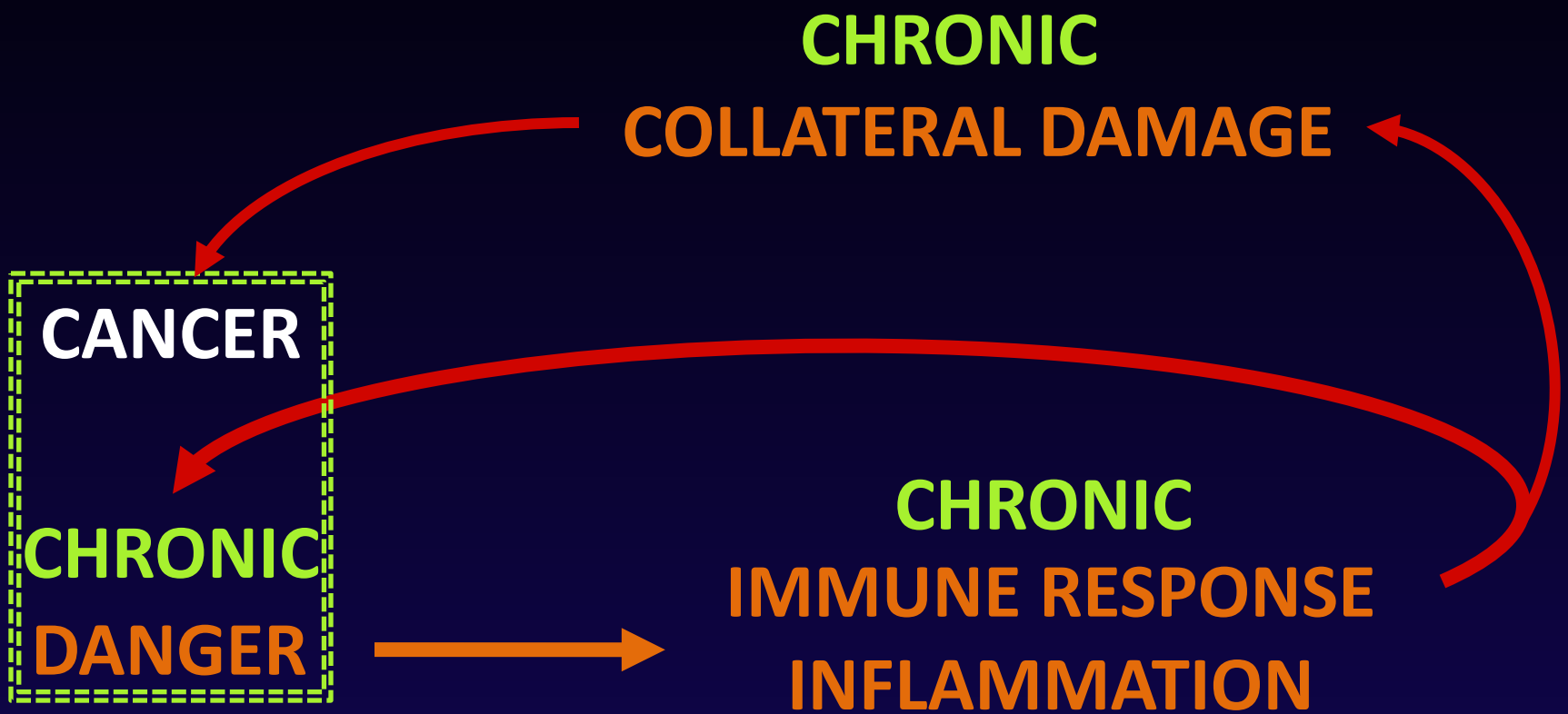

COLLATERAL DAMAGE
IMMUNE RESPONSE
INFLAMMATION

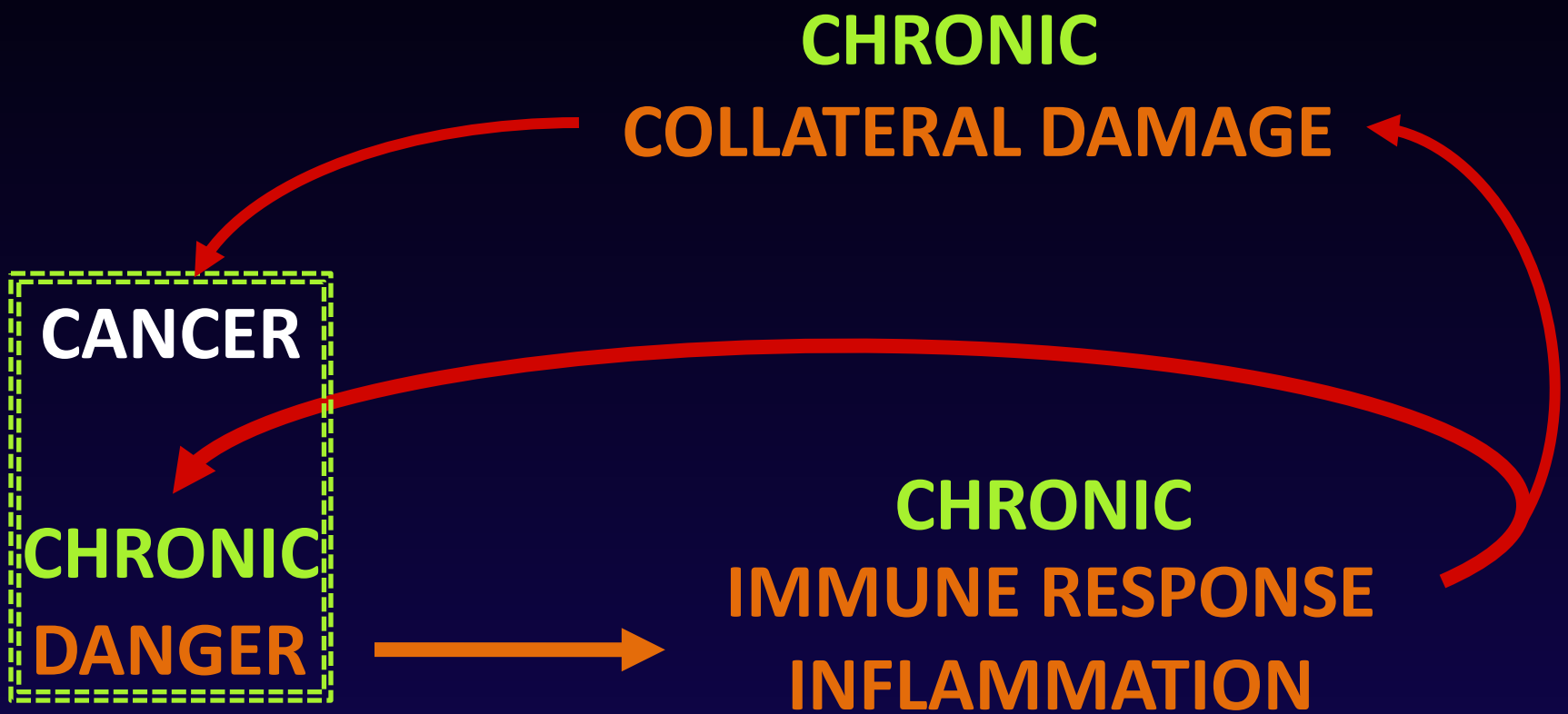

COLLATERAL DAMAGE
DANGER
IMMUNE RESPONSE
INFLAMMATION


COLLATERAL DAMAGE
CHRONIC
DANGER
IMMUNE RESPONSE
INFLAMMATION


CHRONIC
COLLATERAL DAMAGE
CHRONIC
IMMUNE RESPONSE
INFLAMMATION
CHRONIC
DANGER


CHRONIC
COLLATERAL DAMAGE
CANCER
CHRONIC
DANGER
CHRONIC
IMMUNE RESPONSE
INFLAMMATION


CHRONIC
COLLATERAL DAMAGE
CANCER
CHRONIC
DANGER
CHRONIC
IMMUNE RESPONSE
INFLAMMATION



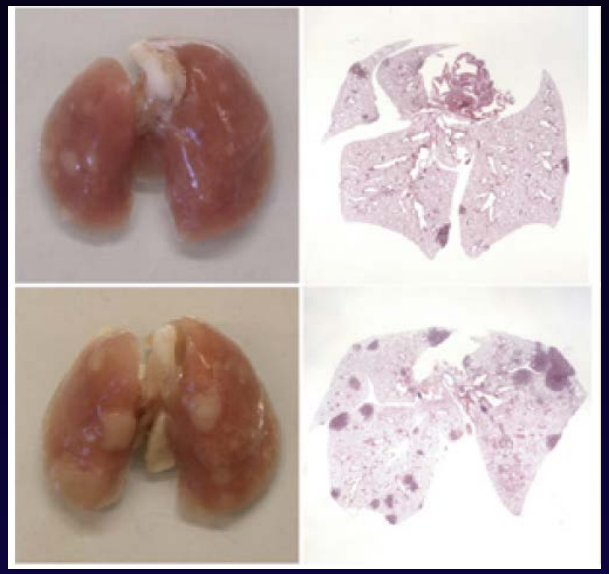
cancer: a “never-healing wound”

Dvorak , *NEJM* 1986

Inflammation can Promote Cancer: collaboration with K-ras mutation

no smoking

4 cigarettes per day



K-ras mutation
&
normal myeloid cells

Takahashi et al. , *Cancer Cell* 2010

Inflammation can Promote Cancer: collaboration with K-ras mutation

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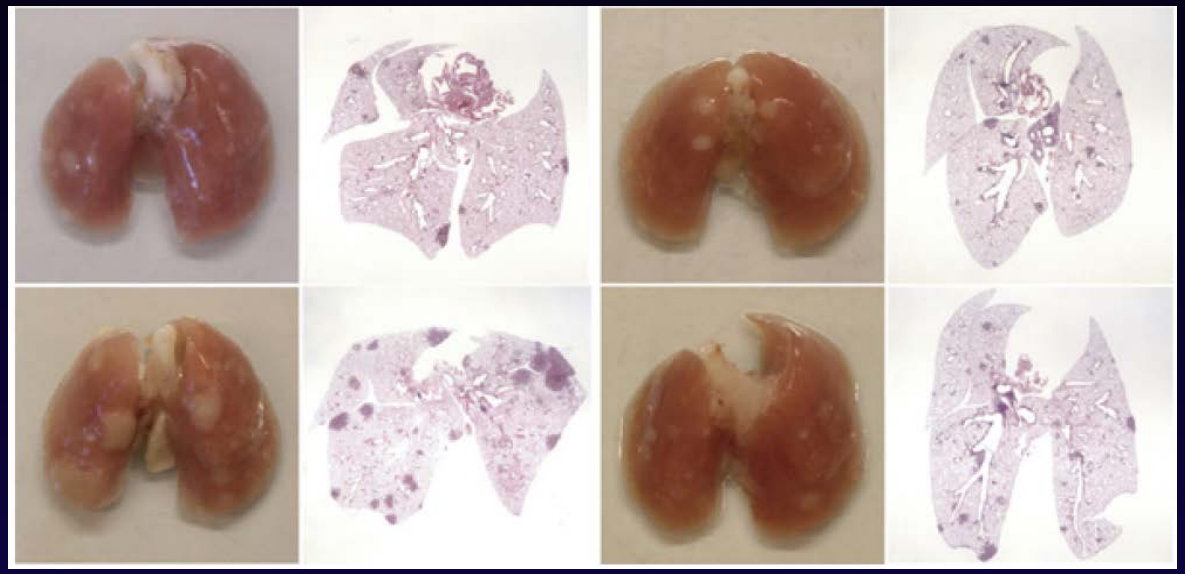

K-ras mutation & normal myeloid cells

K-ras mutation + $IKK^{-/-}$ myeloid cells

Takahashi et al. , *Cancer Cell* 2010

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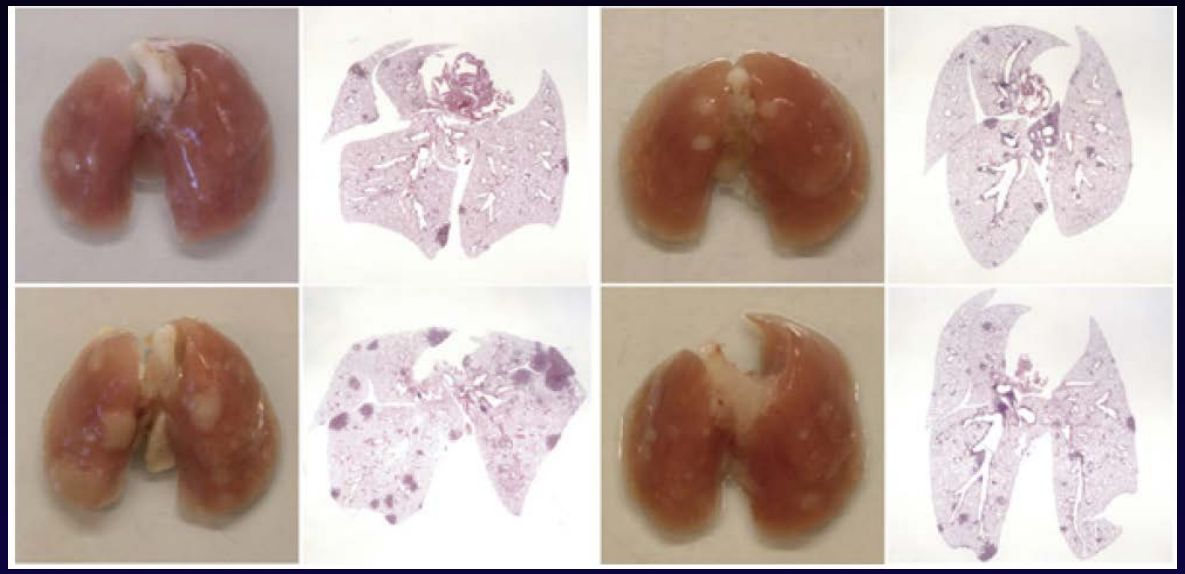


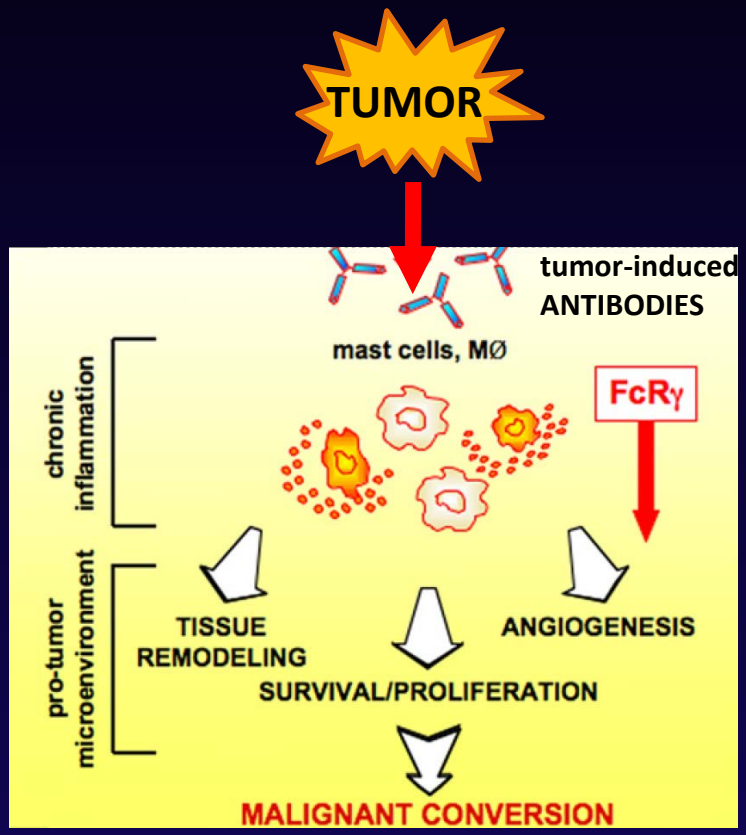
K-ras mutation & normal myeloid cells

K-ras mutation + $IKK^{-/-}$ myeloid cells

- ↓ NF-κB
- ↓ pSTAT3
- ↓ IL-6
- ↓ neutrophils
- ↓ angiogenesis

Takahashi et al. , *Cancer Cell* 2010

Inflammation can Promote Cancer: collaboration with HPV E6/E7 oncogene



De Visser et al., *Cancer Cell* 2005
Andreu et al., *Cancer Cell* 2010

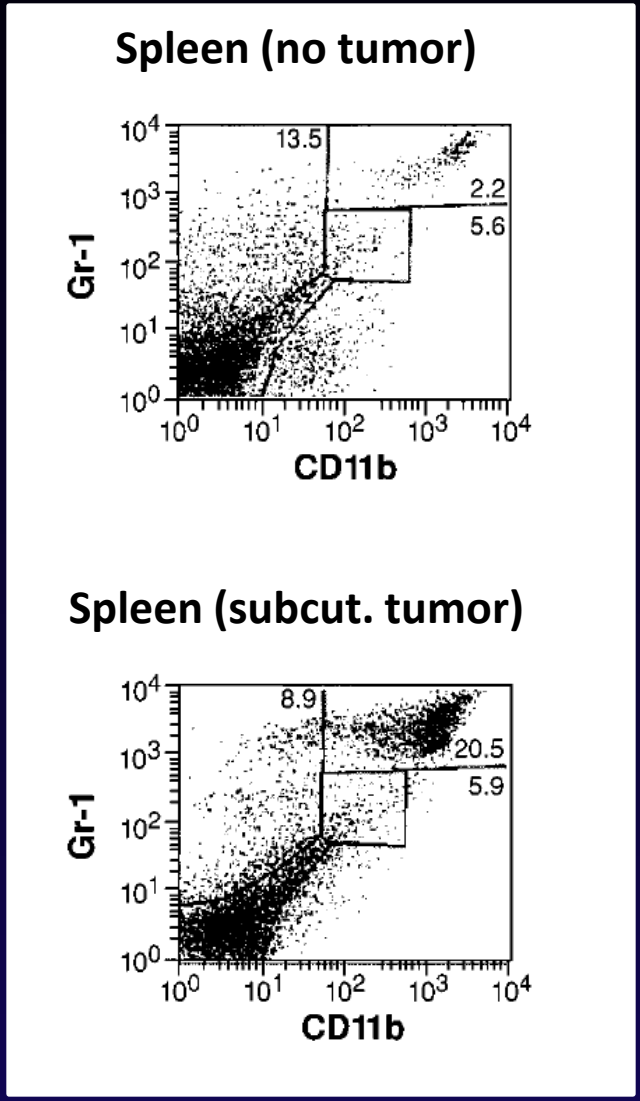
Tumors can induce bad inflammation

Apoptotic Death of CD8$^+$ T Lymphocytes After Immunization: Induction of a Suppressive Population of Mac-1$^+$/Gr-1$^+$ Cells[1]

Vincenzo Bronte,[2]* Michael Wang,† Willem W. Overwijk,* Deborah R. Surman,* Federica Pericle,‡ Steven A. Rosenberg,* and Nicholas P. Restifo[3]*

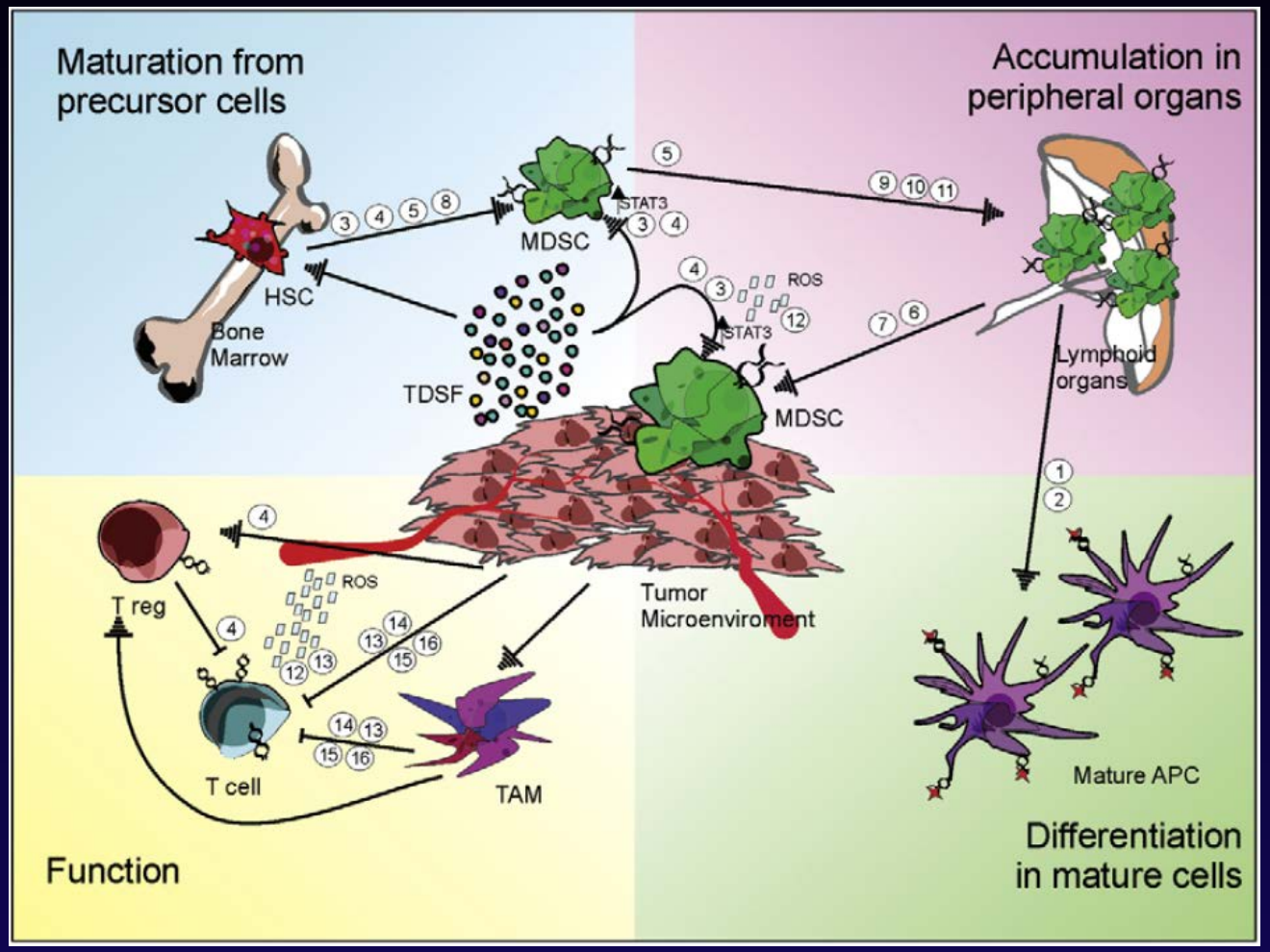
The Journal of Immunology, 1998, 161: 5313–5320.

Tumors can induce bad inflammation



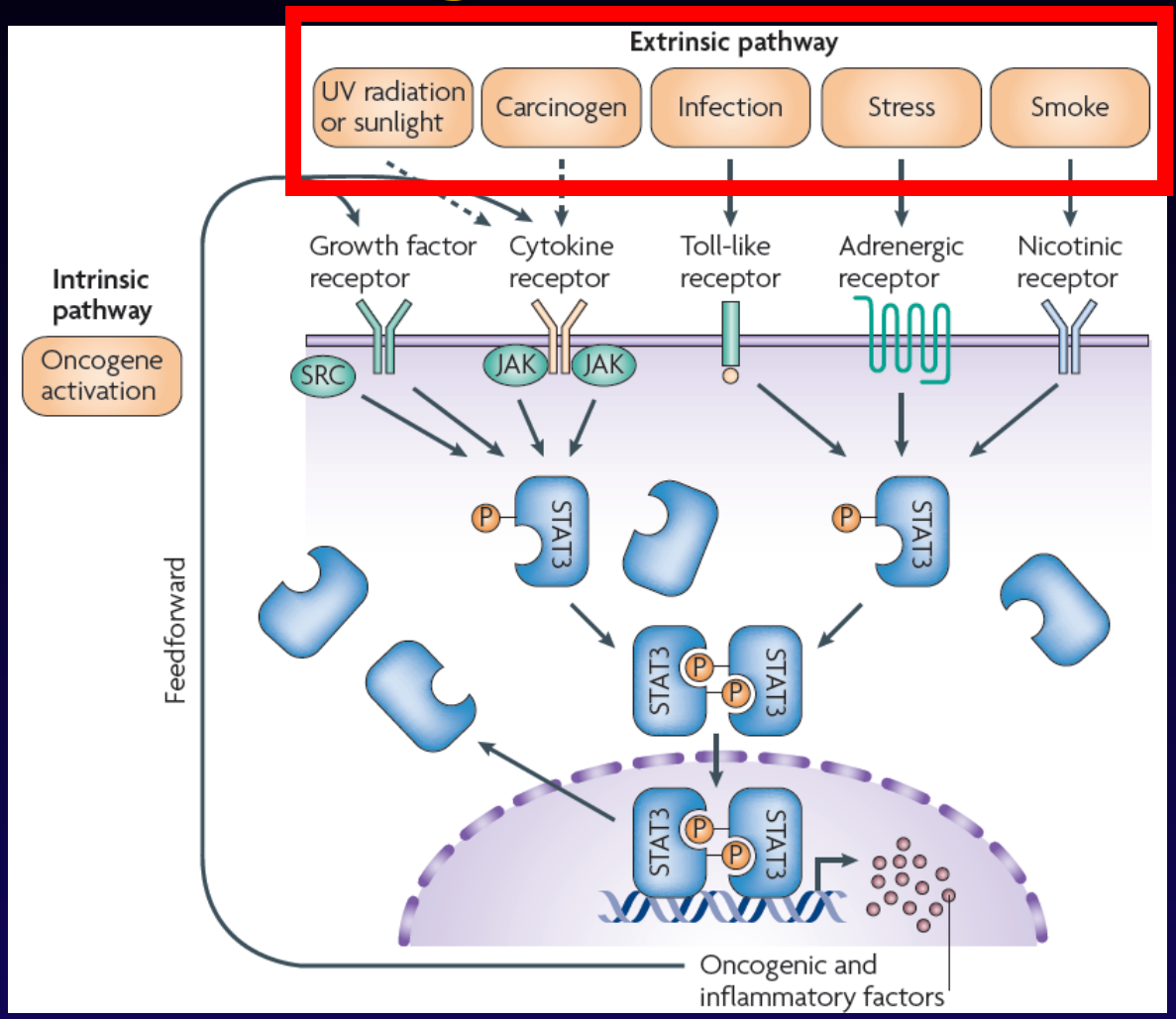
Bronte et al., *J. Immunol.* 1999

Tumors can induce bad inflammation



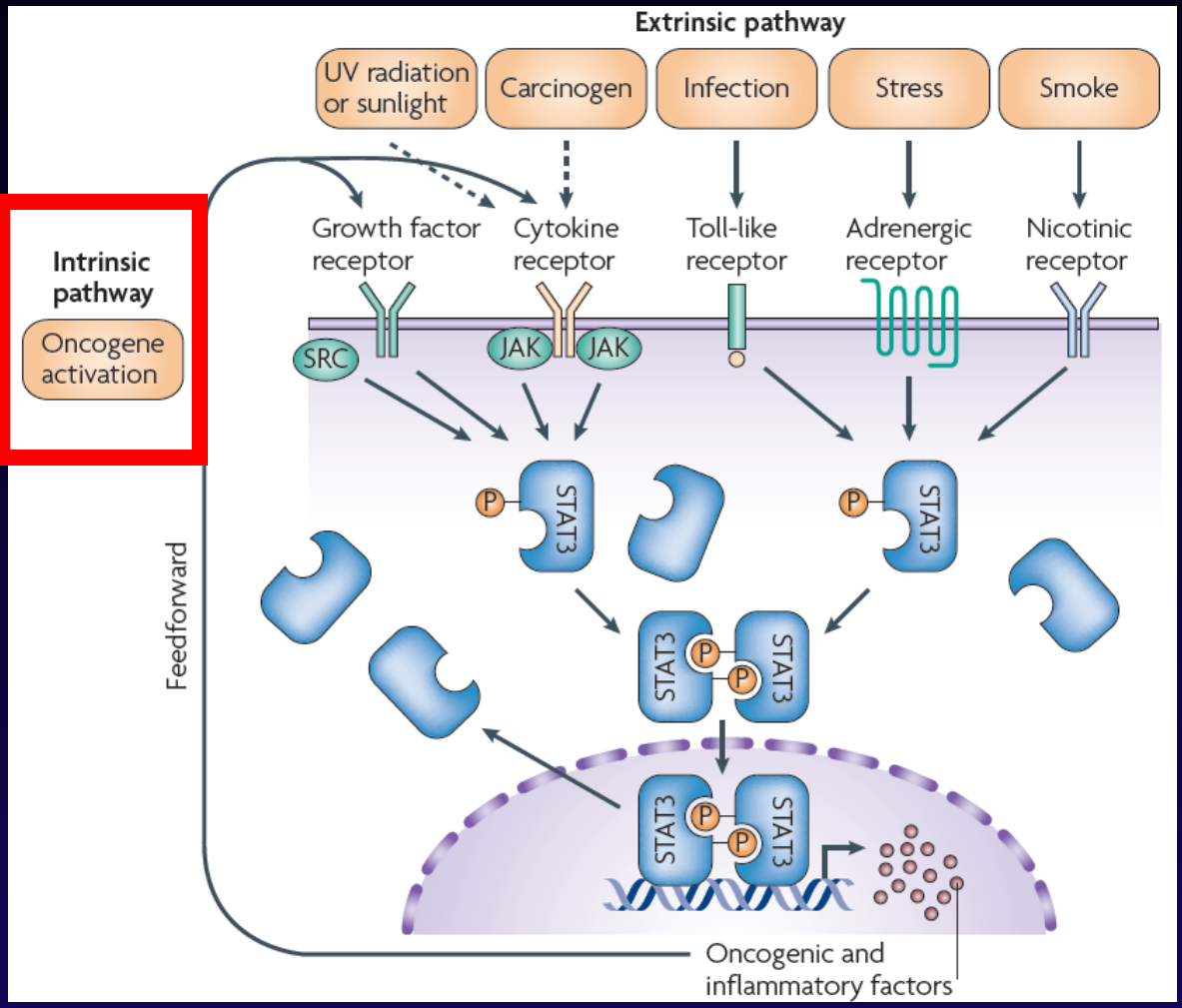
Ugel et al., *Curr. Opin. Pharmacol.* 2010

Tumors can induce bad inflammation
Oncogenic STAT3



Yu et al., *Nat. Rev. Cancer* 2009

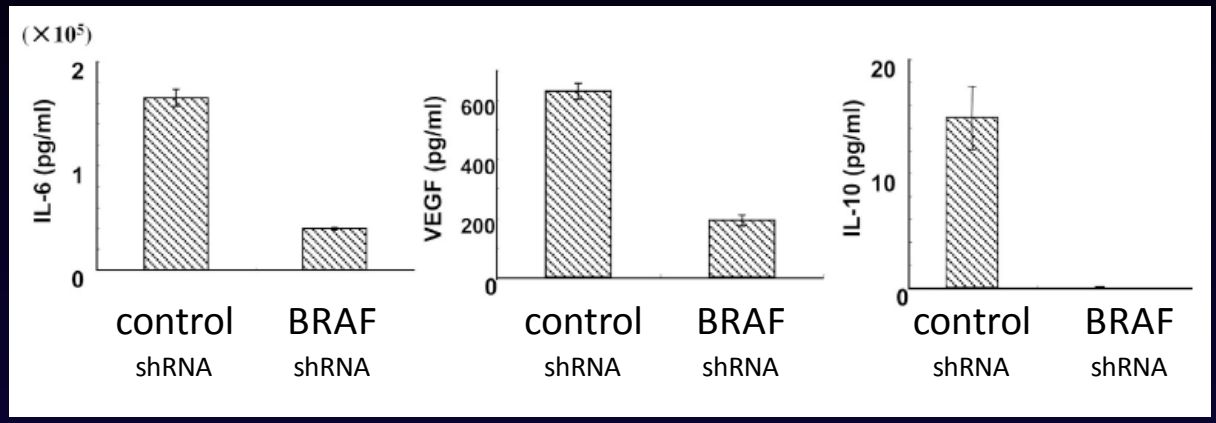
Tumors can induce bad inflammation
Oncogenic STAT3



Yu et al., *Nat. Rev. Cancer* 2009

Mutations can Drive Bad Inflammation

Mutated BRAF → tumor cells produce bad, imunosuppressive cytokines

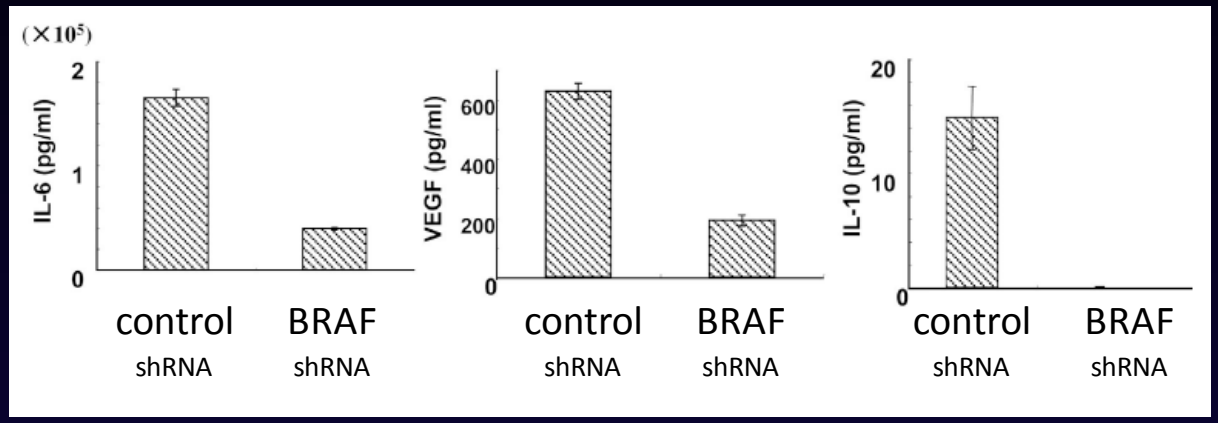


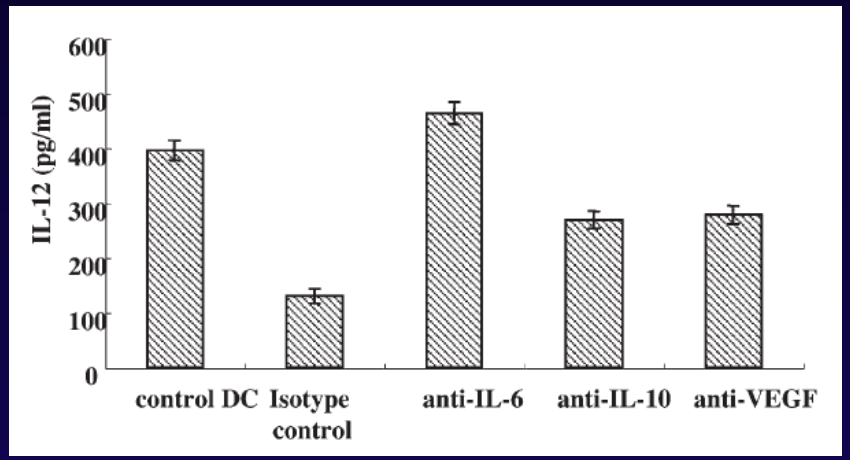
Sumimoto et al., *J. Exp. Med.* 2006

Mutations can Drive Bad Inflammation

Mutated BRAF → tumor cells produce bad, imunosuppressive cytokines

block production of good cytokines in DCs



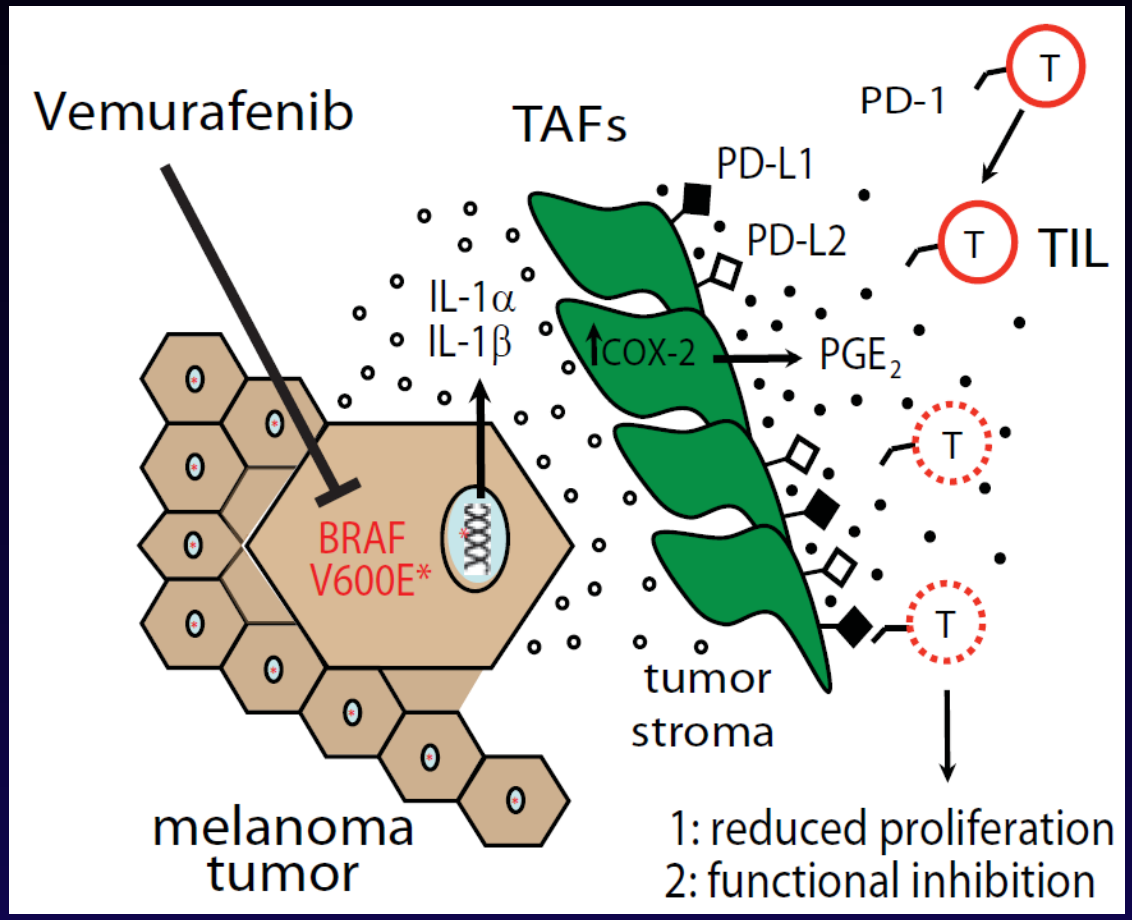


Sumimoto et al., *J. Exp. Med.* 2006

Mutations can Drive Bad Inflammation

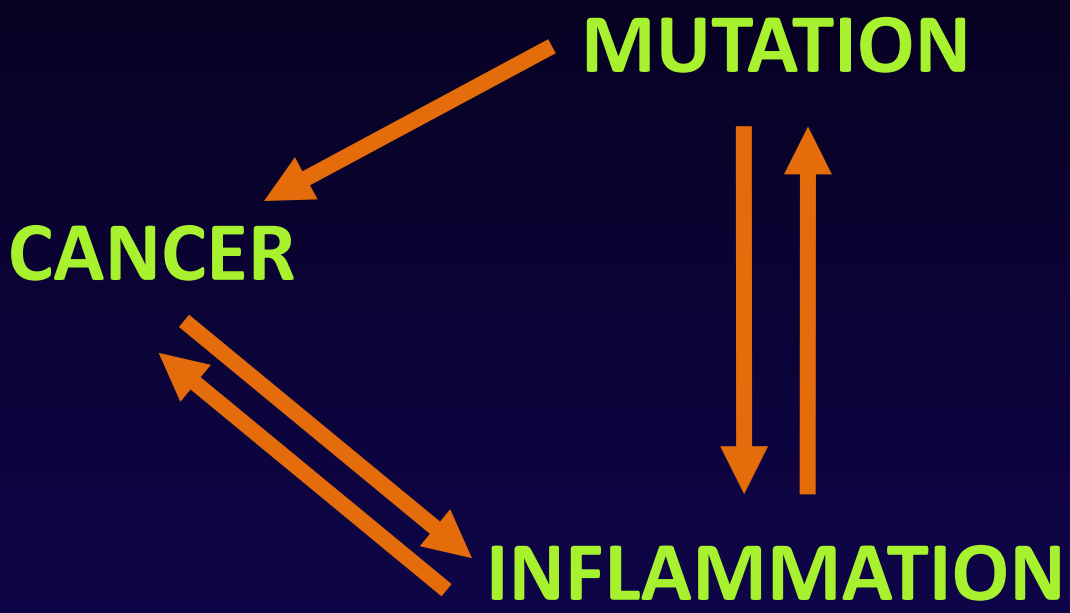
Mutated BRAF → tumor cells produce bad, imunosuppressive cytokines

promote expression of immunosuppressive molecules

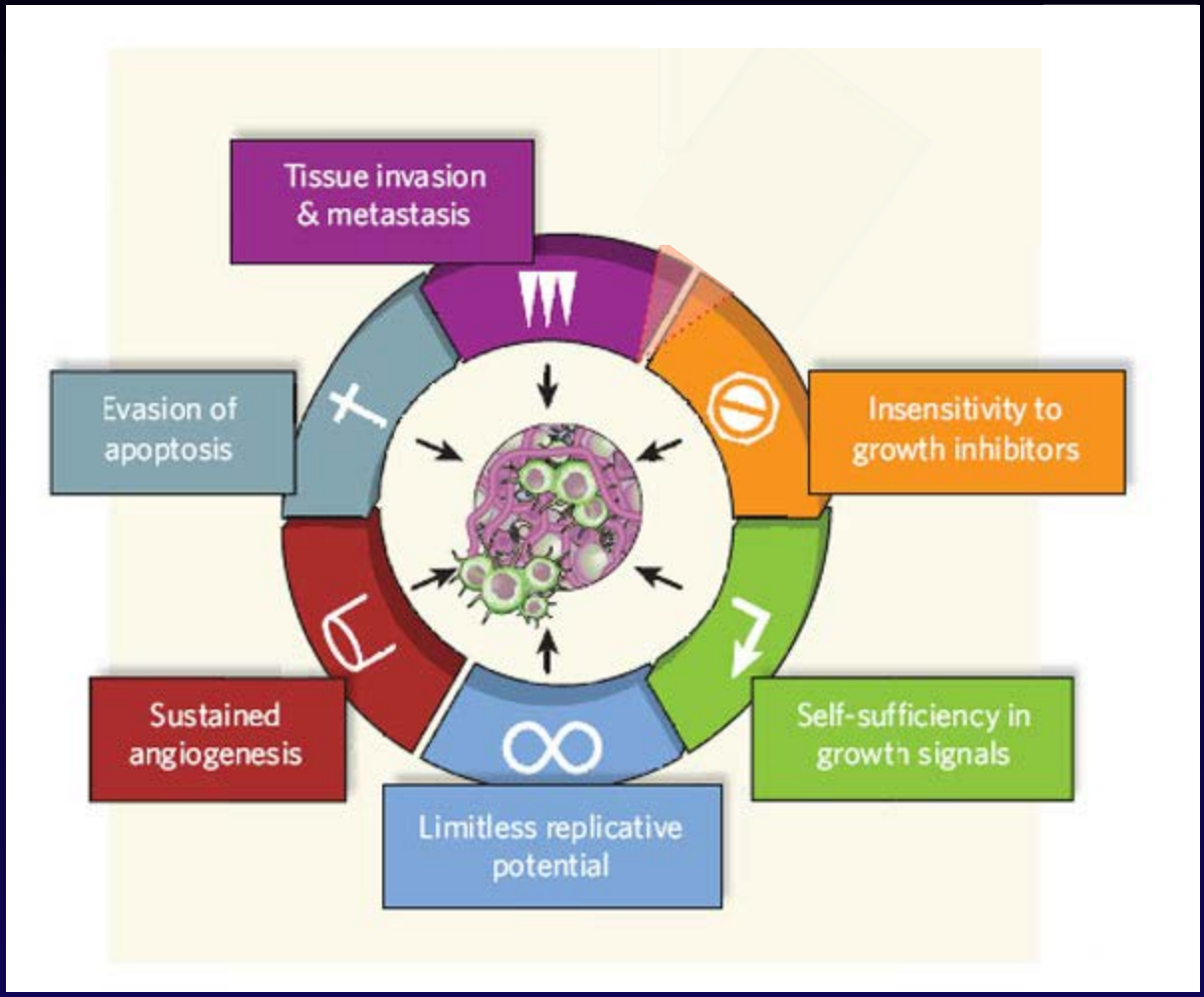


Khalili et al., *Clin. Cancer Res.* 2012

Inflammation and Cancer: A Vicious Cycle

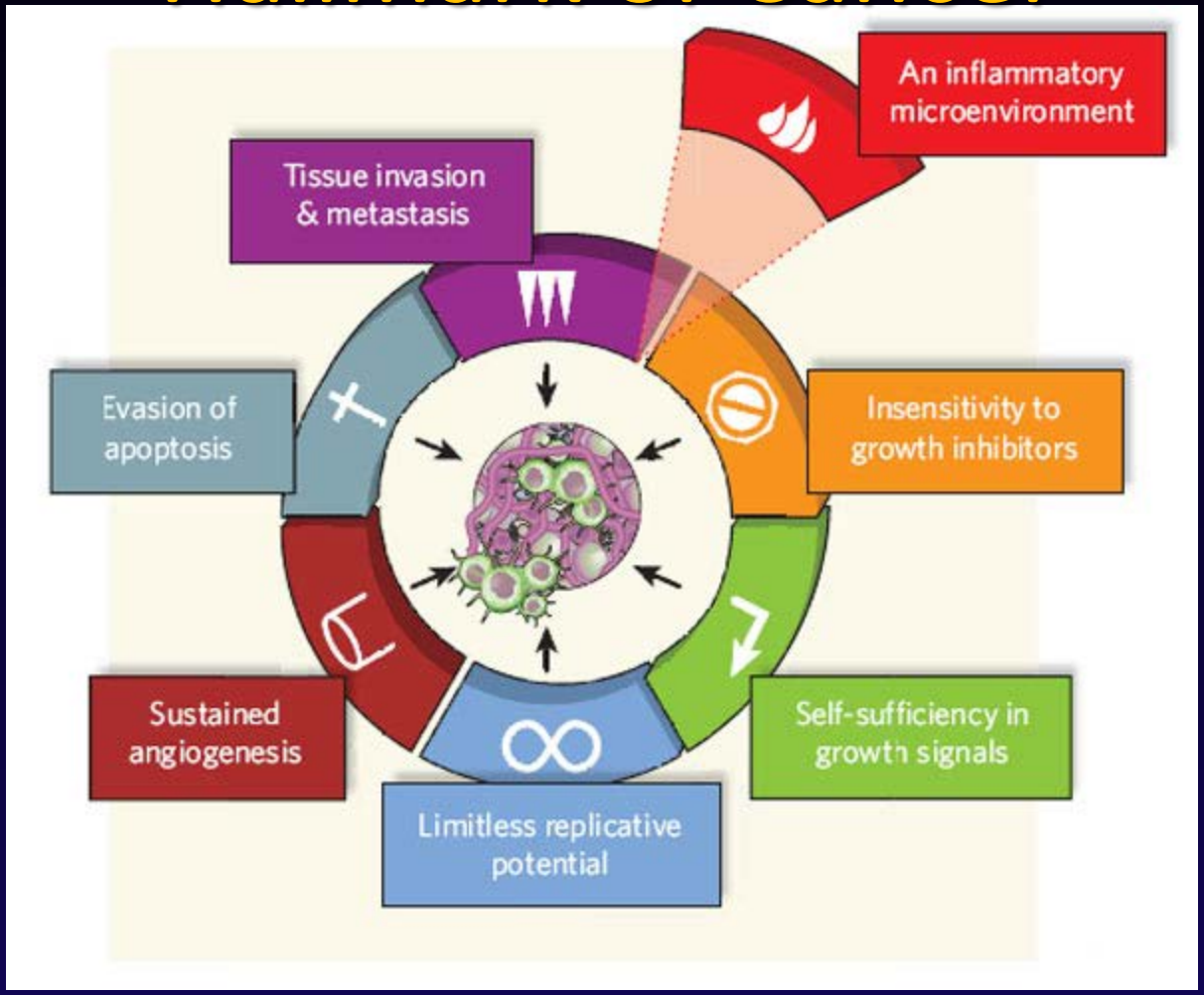


Classic Hallmarks of Cancer



Mantovani et al., *Nature* 2009
Hanahan & Weinberg, *Cell* 2000

Inflammation is (now) a Classic Hallmark of Cancer



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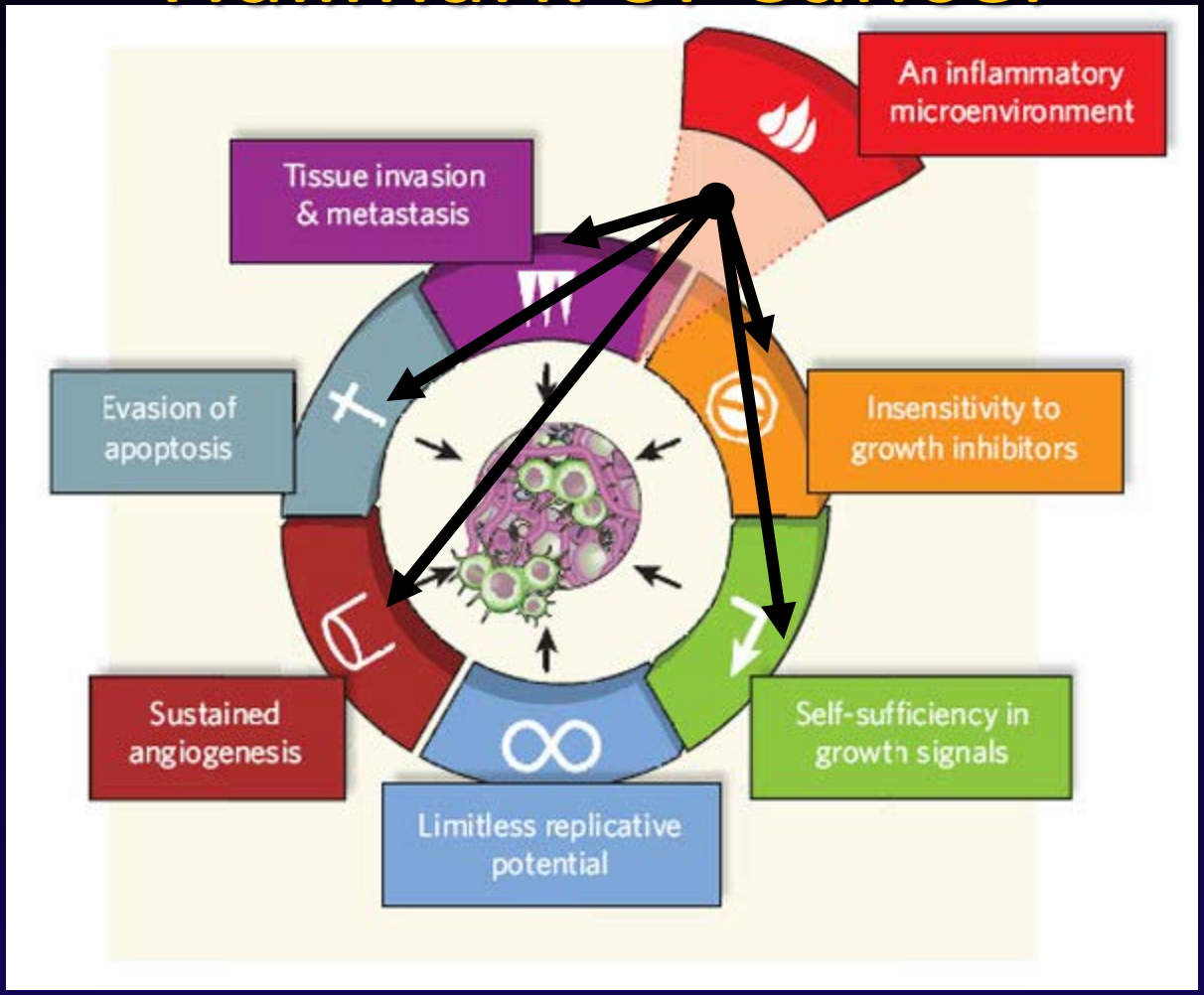

Mantovani et al., *Nature* 2009
Hanahan & Weinberg, *Cell* 2000

Innate Immunity and Inflammation

- Definitions
- Cells and Molecules
- Innate Immunity and Inflammation in Cancer
- Bad Inflammation
- Good Inflammation
- Therapeutic Implications

Good *vs.* Bad Inflammation in Cancer

Immunity, Inflammation, and Cancer

Sergei I. Grivennikov,[1] Florian R. Greten,[2] and Michael Karin[1,*]

Cell *140*, 883–899, March 19, 2010

Cancer and Inflammation: Promise for Biologic Therapy

Sandra Demaria, Eli Pikarsky,† Michael Karin,‡ Lisa M. Coussens,§ Yen-Ching Chen,‖ Emad M. El-Omar,¶ Giorgio Trinchieri,# Steven M. Dubinett,** Jenny T. Mao,†† Eva Szabo,‡‡ Arthur Krieg,§§ George J. Weiner,‖‖ Bernard A. Fox,¶¶ George Coukos,## Ena Wang,*** Robert T. Abraham,††† Michele Carbone,‡‡‡ and Michael T. Lotze§§§*

J Immunother • Volume 33, Number 4, May 2010

IFN-γ Suppresses Human Tumor Development

Multiple cutaneous squamous cell carcinomas in a patient with interferon γ receptor 2 (IFNγR2) deficiency

Toyoda et al., *J. Med. Genetics* 2010

IFN-γ Suppresses Human Tumor Development

Multiple cutaneous squamous cell carcinomas in a patient with interferon γ receptor 2 (IFNγR2) deficiency

At 17 years of age, the patient developed multifocal Squamous Cell Carcinomas on the face and both hands. Despite local tumour excision, multiple lesions occurred and the patient died at 20 years of age of disseminated SCC. Inherited disorders of IFN-γ–mediated immunity may predispose patients to SCC.

Toyoda et al., *J. Med. Genetics* 2010

Human Immune System can Suppress Existing Tumors for Years

1982: patient with primary, resected melanoma

1997: declared disease-free and “cured”

1998: died of brain hemorrhage, donated kidneys

2000: - kidney recipient 1 died of metastatic donor melanoma

- kidney recipient 2 taken off immunosuppression; start IFN-α

- kidney recipient 2 rejects kidney and melanoma

MacKie et al., *NEJM* 2003

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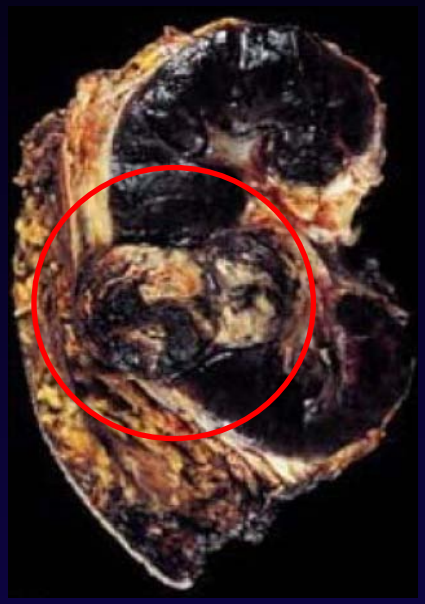

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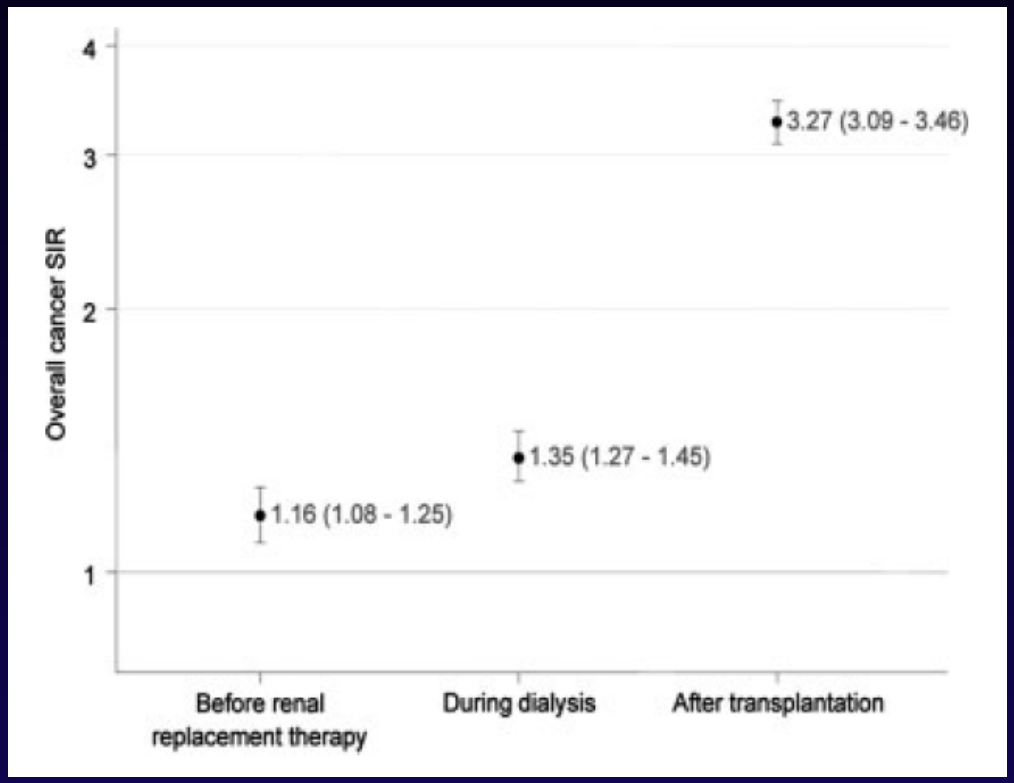
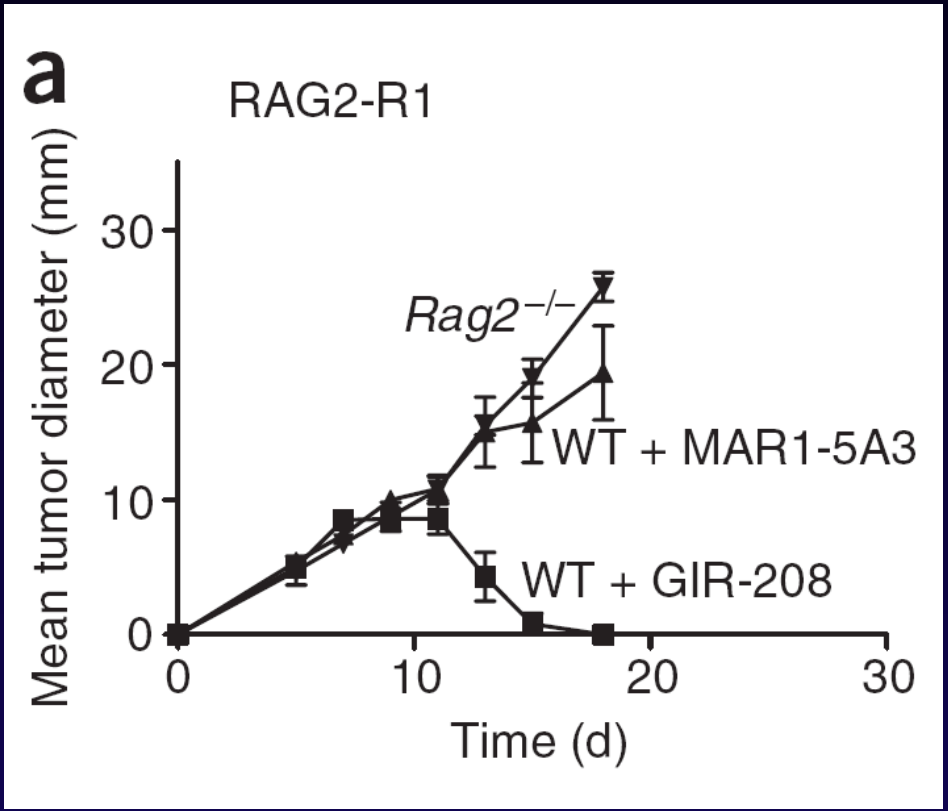
Post-transplant Immunosuppression Increases Cancer Incidence



Vajdic & Van Leeuwen , *Int. J. Cancer 2009*

Type I IFNs Suppress Growth of Transplanted Tumors

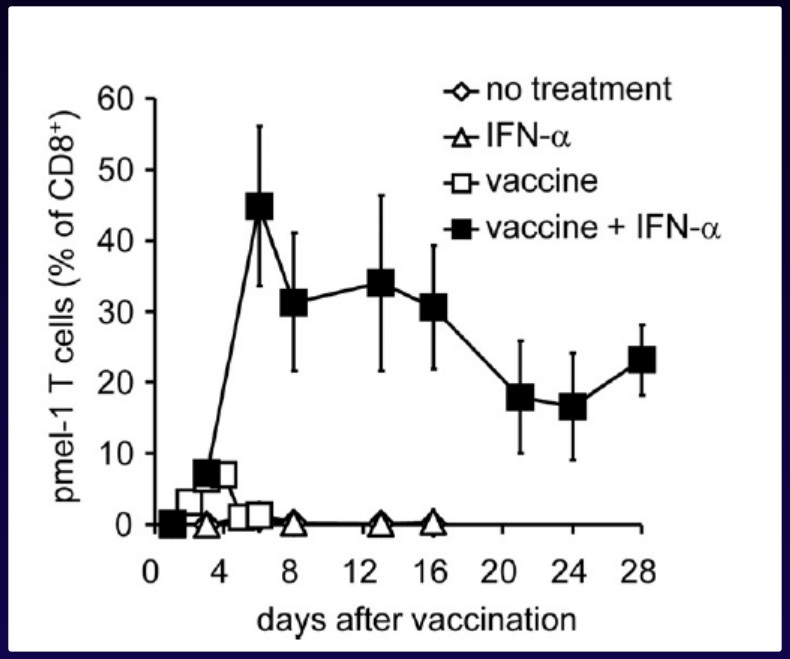


IFN-α receptor blocking mAb

control mAb

Dunn et al. *Nat. Immunol.* 2005

IFN-α treatment enhances anti-cancer vaccination



Sikora et al. *J. Immunol.* 2009

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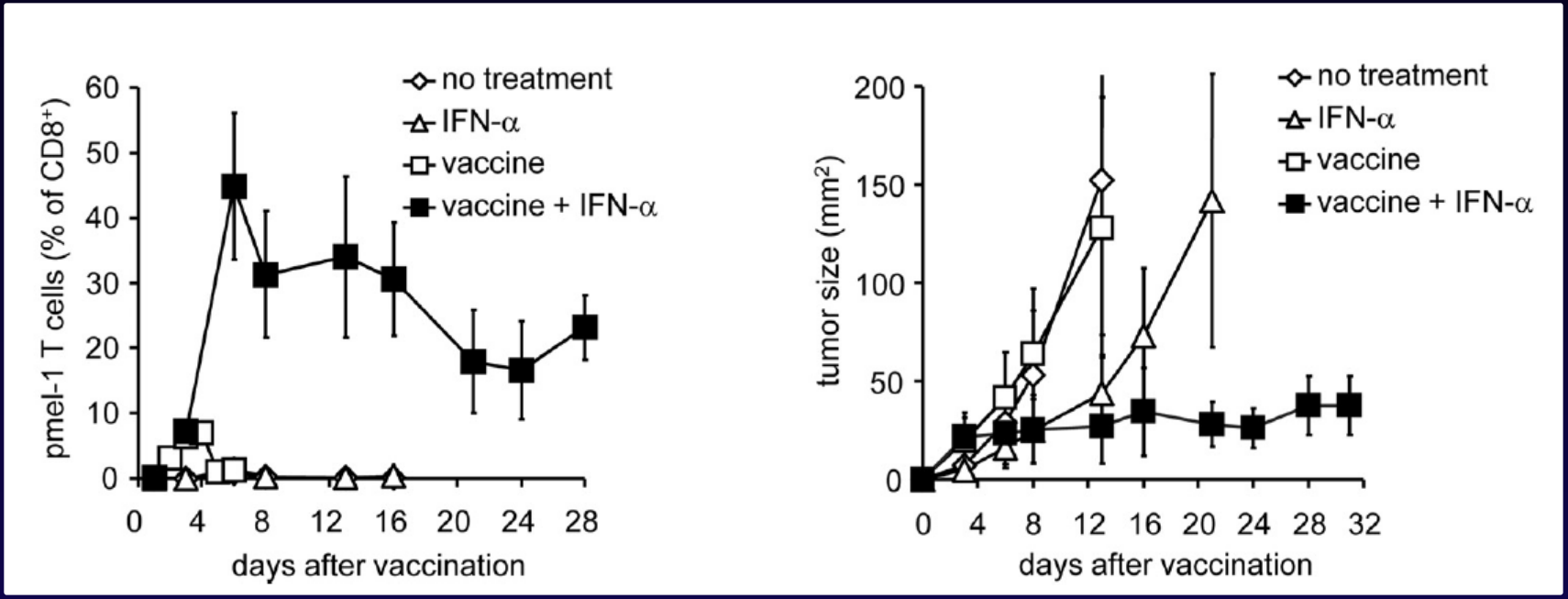
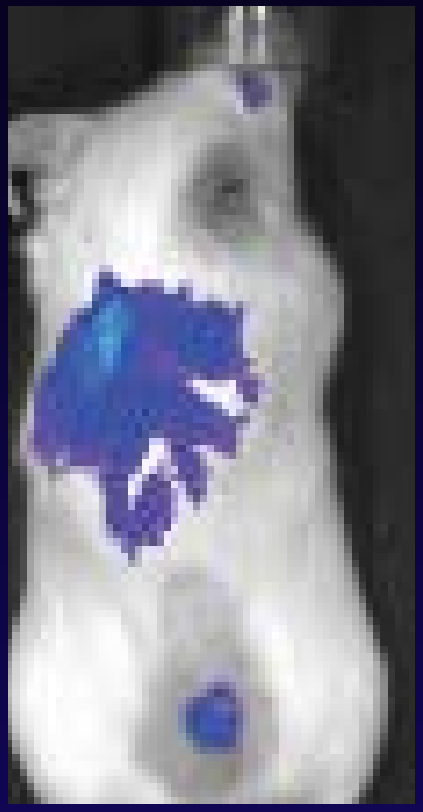


Sikora et al. *J. Immunol.* 2009

CpG Causes Tumor Inflammation and Intratumoral T cell Accumulation

Intratumoral PBS



Intratumoral CpG

Intravenous CpG

Lou et al. , *J. Immunother*. 2011

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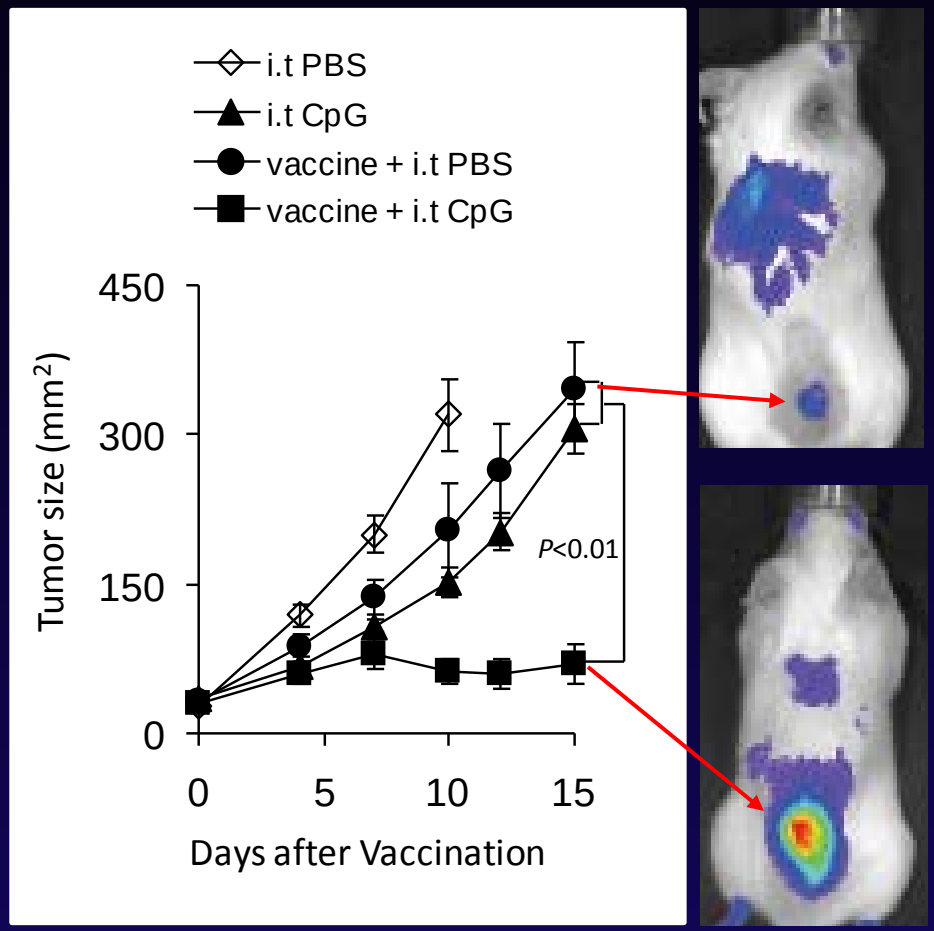
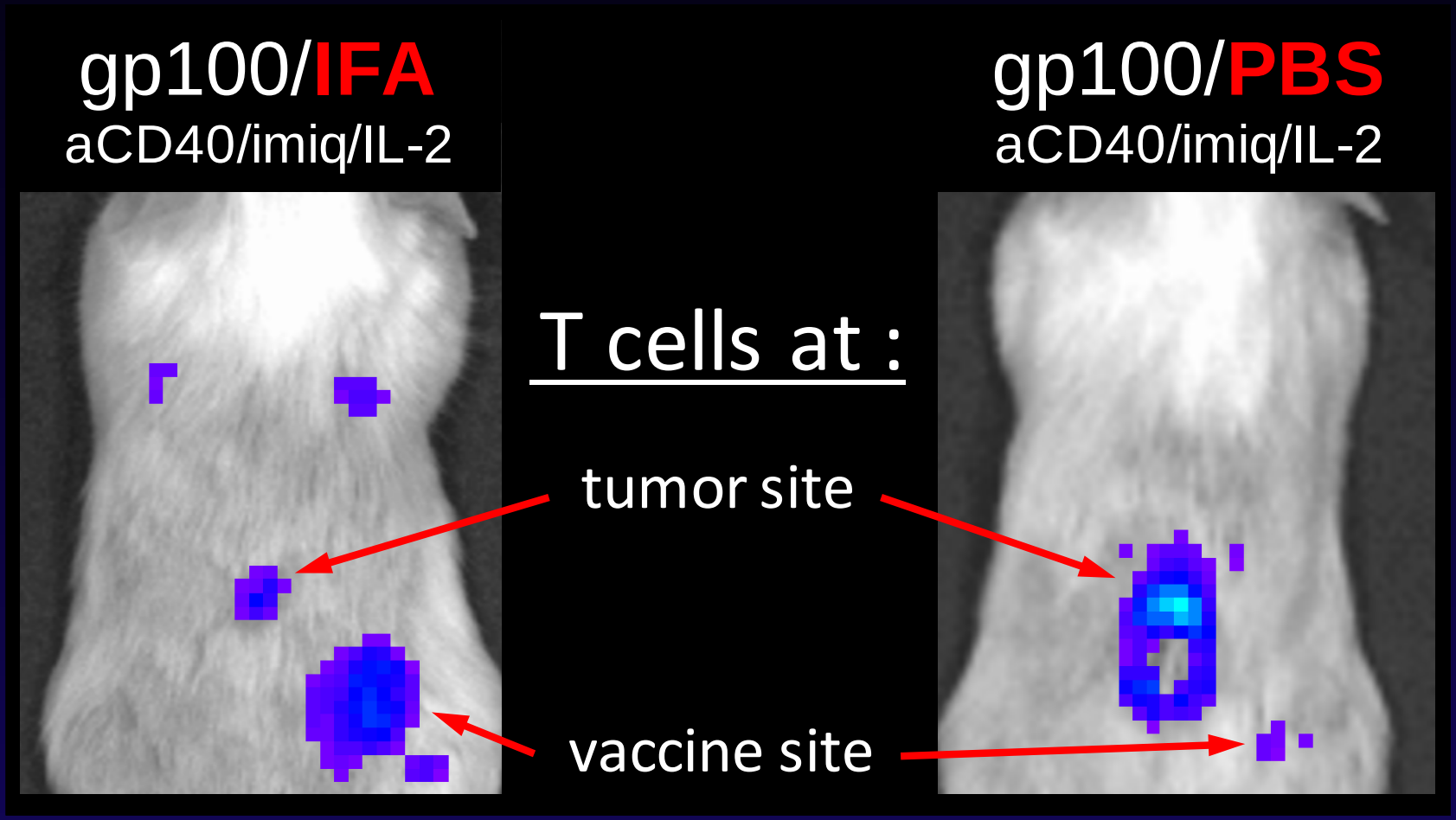
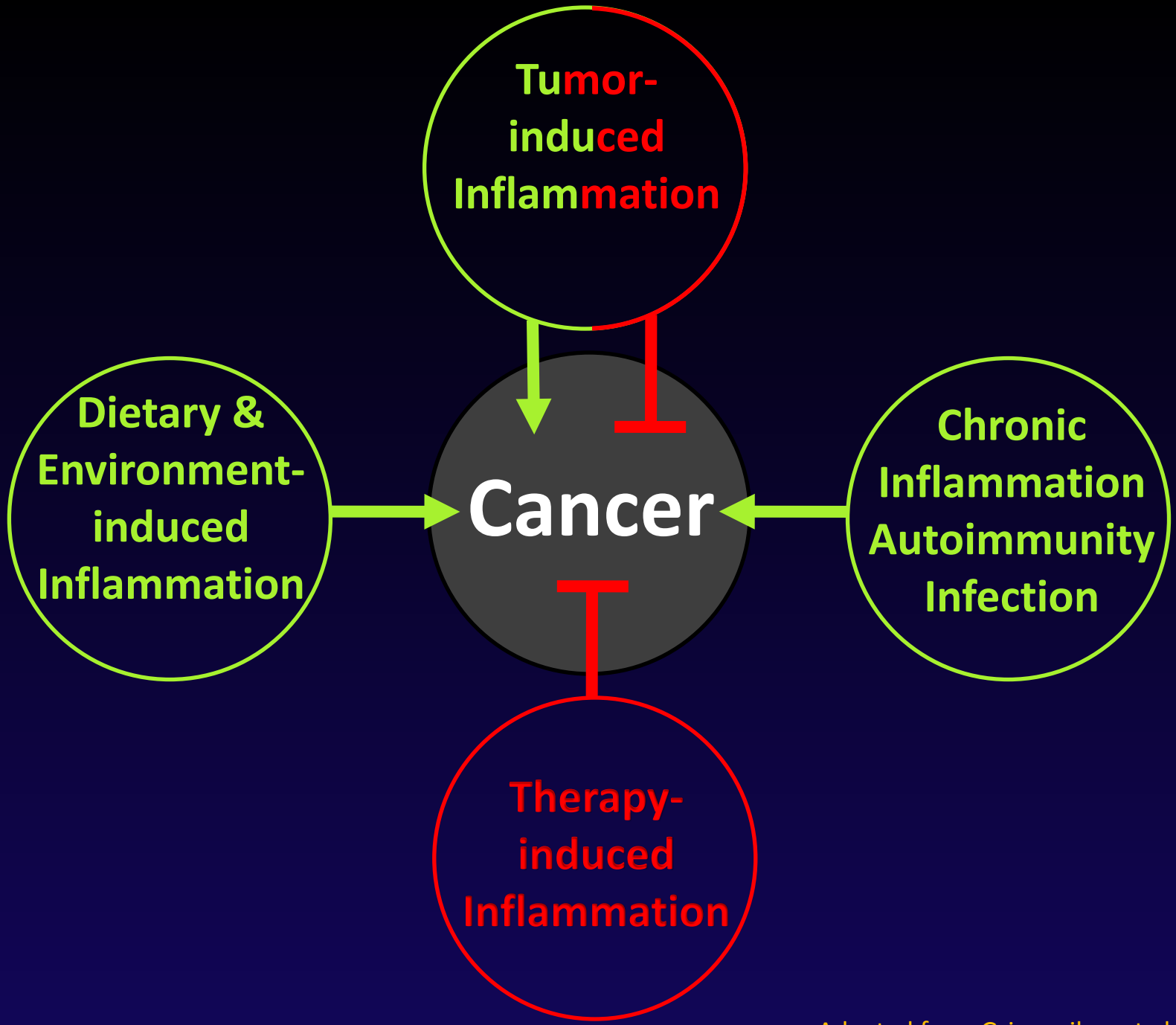


Lou et al. , *J. Immunother*. 2011

Choice of vaccine adjuvant controlsT cell trafficking to tumor



Hailemichael et al. , *Nat. Med.* 2013



Adapted from Grivennikov et al. *Cell* 2010

Bottom Line: Inflammation can be Good or Bad: Pro or Anti-Tumor

Table 1. Roles of Different Subtypes of Immune and Inflammatory Cells in Antitumor Immunity and Tumor-Promoting Inflammation

Cell Types	Antitumor	Tumor-Promoting
Macrophages, dendritic cells, myeloid-derived suppressor cells	Antigen presentation; production of cytokines (IL-12 and type I IFN)	Immunosuppression; production of cytokines, chemokines, proteases, growth factors, and angiogenic factors
Mast cells		Production of cytokines
B cells	Production of tumor-specific antibodies?	Production of cytokines and antibodies; activation of mast cells; immunosuppression
$CD8^+$ T cells	Direct lysis of cancer cells; production of cytotoxic cytokines	Production of cytokines?
$CD4^+$ Th2 cells		Education of macrophages; production of cytokines; B cell activation
$CD4^+$ Th1 cells	Help to cytotoxic T lymphocytes (CTLs) in tumor rejection; production of cytokines (IFNγ)	Production of cytokines
$CD4^+$ Th17 cells	Activation of CTLs	Production of cytokines
$CD4^+$ Treg cells	Suppression of inflammation (cytokines and other suppressive mechanisms)	Immunosuppression; production of cytokines
Natural killer cells	Direct cytotoxicity toward cancer cells; production of cytotoxic cytokines	
Natural killer T cells	Direct cytotoxicity toward cancer cells; production of cytotoxic cytokines	
Neutrophils	Direct cytotoxicity; regulation of CTL responses	Production of cytokines, proteases, and ROS

Grivennikov et al. *Cell* 2010

In the Clinic: Cancer Therapies that Block Bad Inflammation

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- COX-2 inhibitor — Aspirin, Celecoxib (colorectal)

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• Targeted Therapy?	TKI inhibitors (many cancers)

In the Clinic: Cancer Therapies that Induce Good Inflammation

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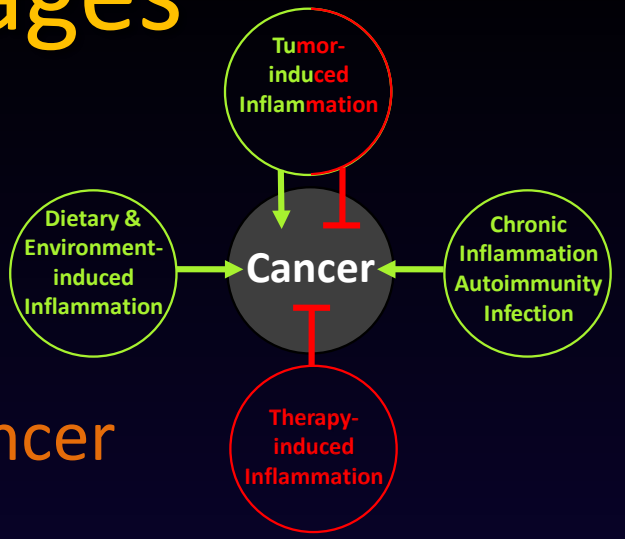
• T cells	Adoptive T cell Transfer (melanoma)
• Vaccine	PAP-loaded DCs (prostate)

How therapeutics may promote cancer

- induce mutation (chemotherapy)
- induce inflammation (cytokines, TLR agonists, agonistic antibodies)
- change the microbiome (antibiotics, foods)?
- **block cells/factors that suppress cancer**
  - $CD8^+$ T cells/NK cells
  - type I IFN, IFN-γ
  - TNF-α - lymphoma?
  - IL-15?
  - IL-12/IL-23
  - IL-17A?

Take Home Messages



- Inflammation is a classic hallmark of cancer
- Innate Immunity & Inflammation can promote or suppress cancer
- Manipulating immunity can promote or suppress cancer
- Understanding of inflammatory cells & molecules in cancer is limited but growing, allowing therapeutic intervention

Cancer Vaccines

Willem W. Overwijk, PhD

Department of Melanoma Medical Oncology

MD Anderson Cancer Center

Houston, TX, USA

University of Puerto Rico

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

What is a Cancer Vaccine?

A preparation of a tumor antigen (usually protein) that upon administration stimulates antibody production or cellular anti-tumor immunity.

When could cancer vaccines be useful?

- **Cancer Prevention**
- **Cancer therapy**

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What is a Cancer Vaccine?

peptide(s)

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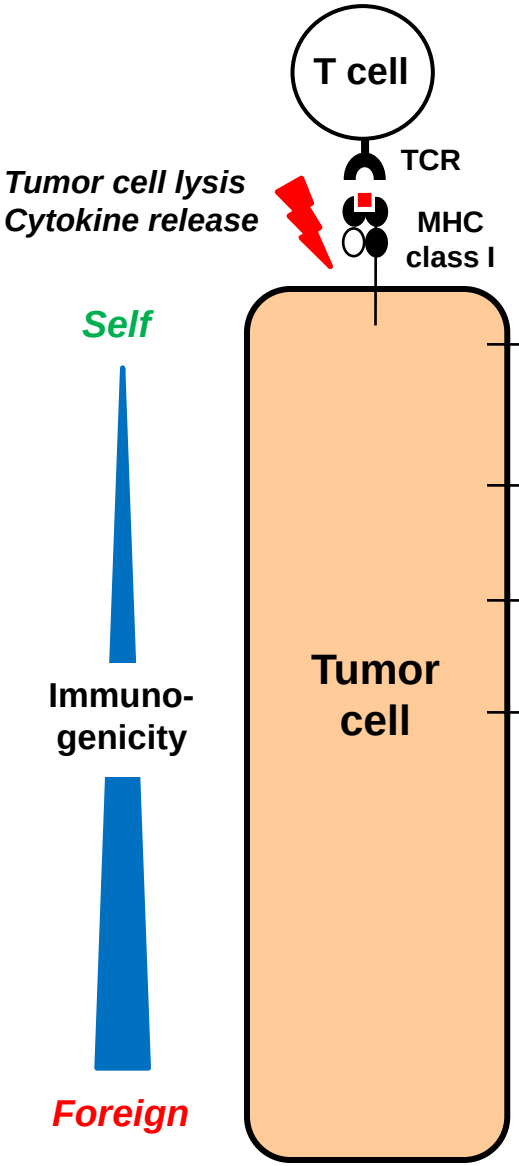
Tumor-Associated Antigens



Non-mutated antigens (normal)

- → **Self Ags - ubiquitous, not tumor-specific (eg. actin, vimentin) > *98%***
- → **Tissue differentiation Ags (eg. gp100, Tyrosinase, MART-1/Melan-A)**
- → **Cancer / testis Ags (eg. MAGE, GAGE, NY-ESO-1)**
- → **Over-expressed in tumors (eg. KIT, HER2, HERV)**

Adapted from Dr. Gregory Lizee, Melanoma Med. Oncol.

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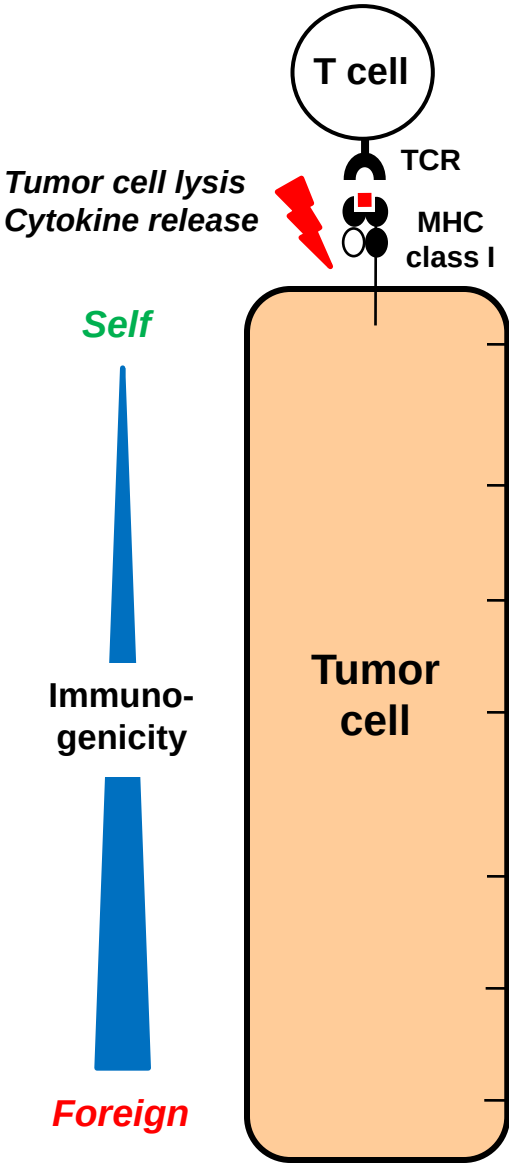

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→ **Cancer / testis Ags (eg. MAGE, GAGE, NY-ESO-1)**

→ **Over-expressed in tumors (eg. KIT, HER2, HERV)**

→ **Single point mutations**

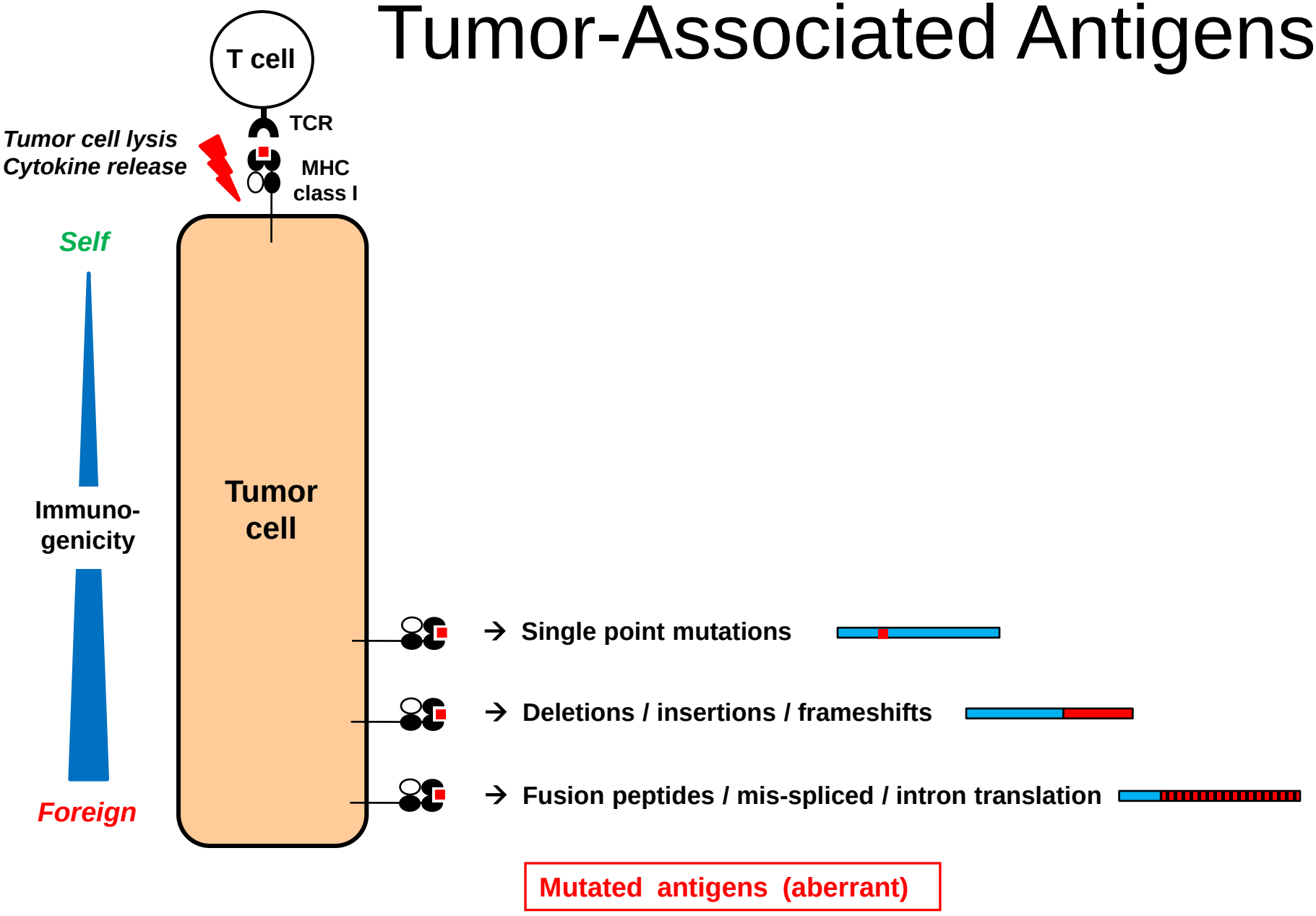
→ **Deletions / insertions / frameshifts**

→ **Fusion peptides / mis-spliced / intron translation**

Mutated antigens (aberrant)

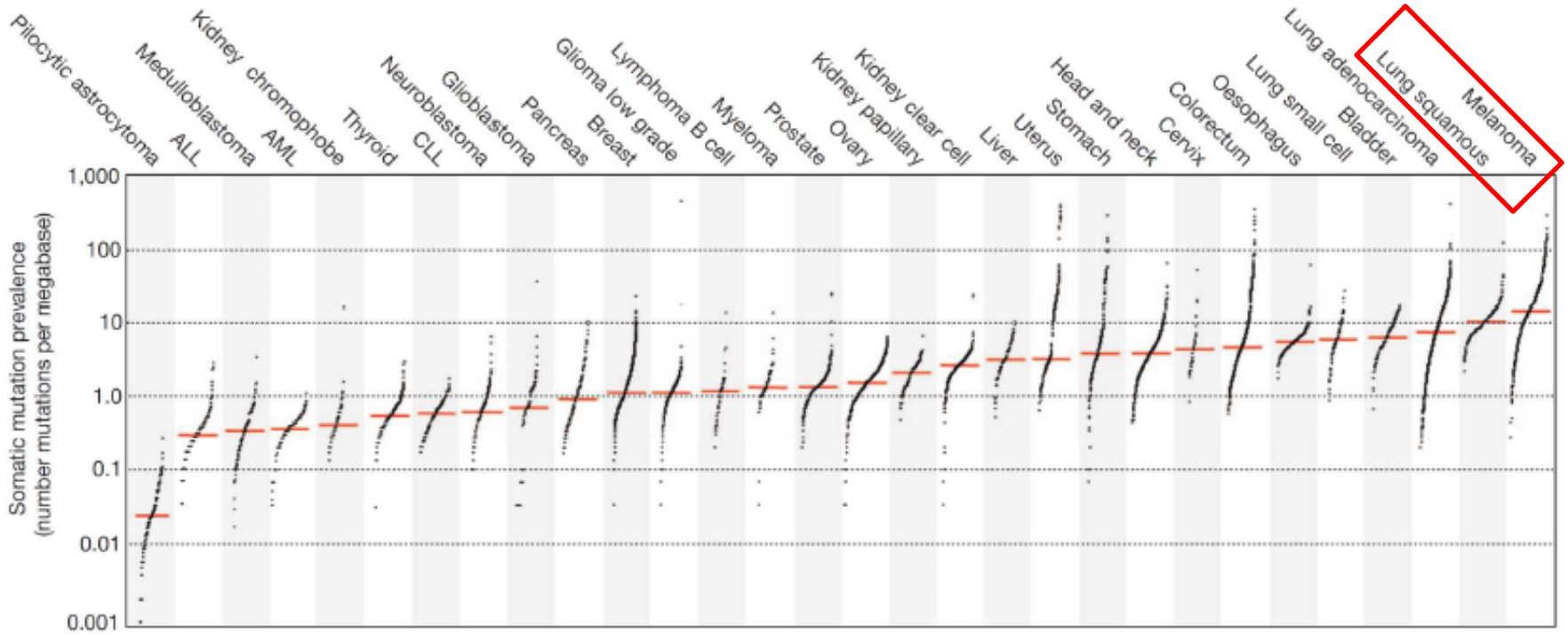
Adapted from Dr. Gregory Lizee, Melanoma Med. Oncol.

Tumor-Associated Antigens



Adapted from Dr. Gregory Lizee, Melanoma Med. Oncol.

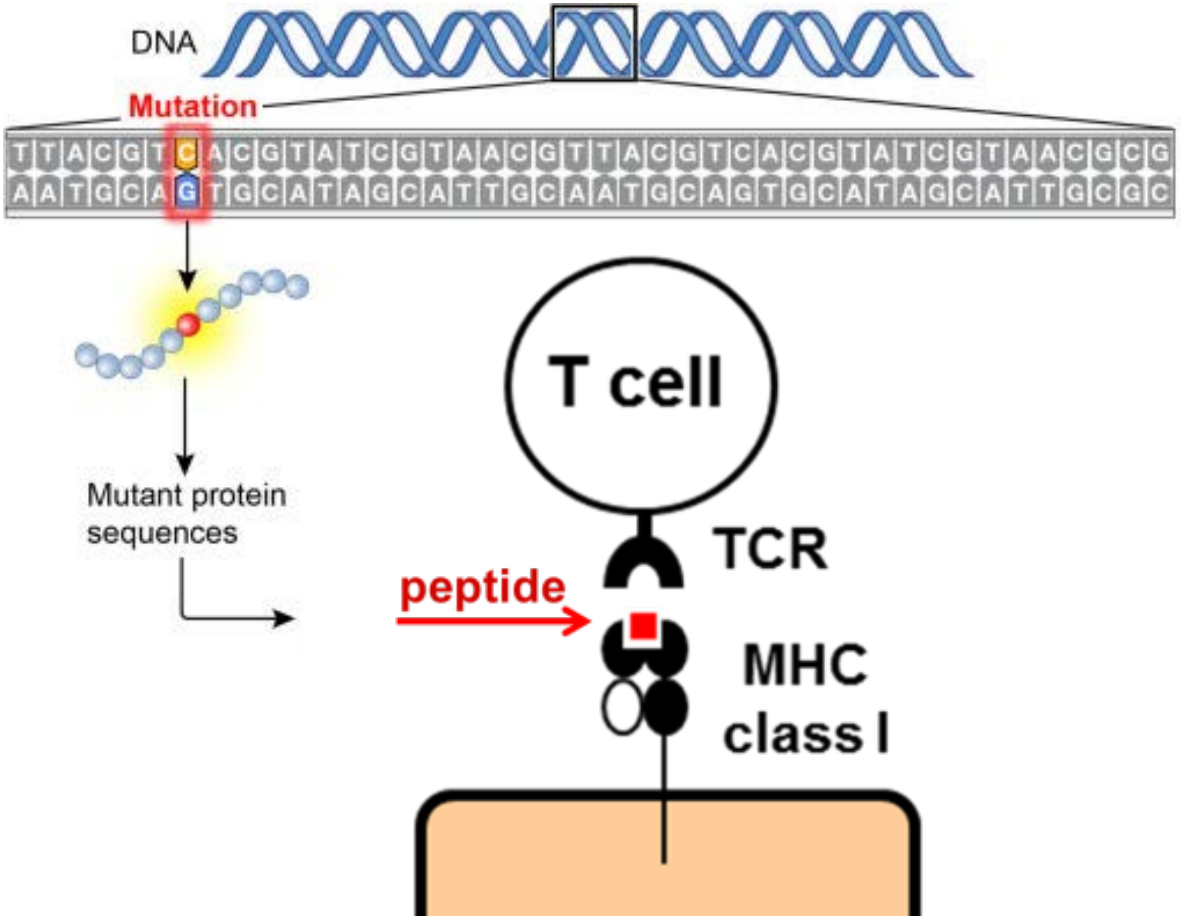
The prevalence of somatic mutations across human cancer types



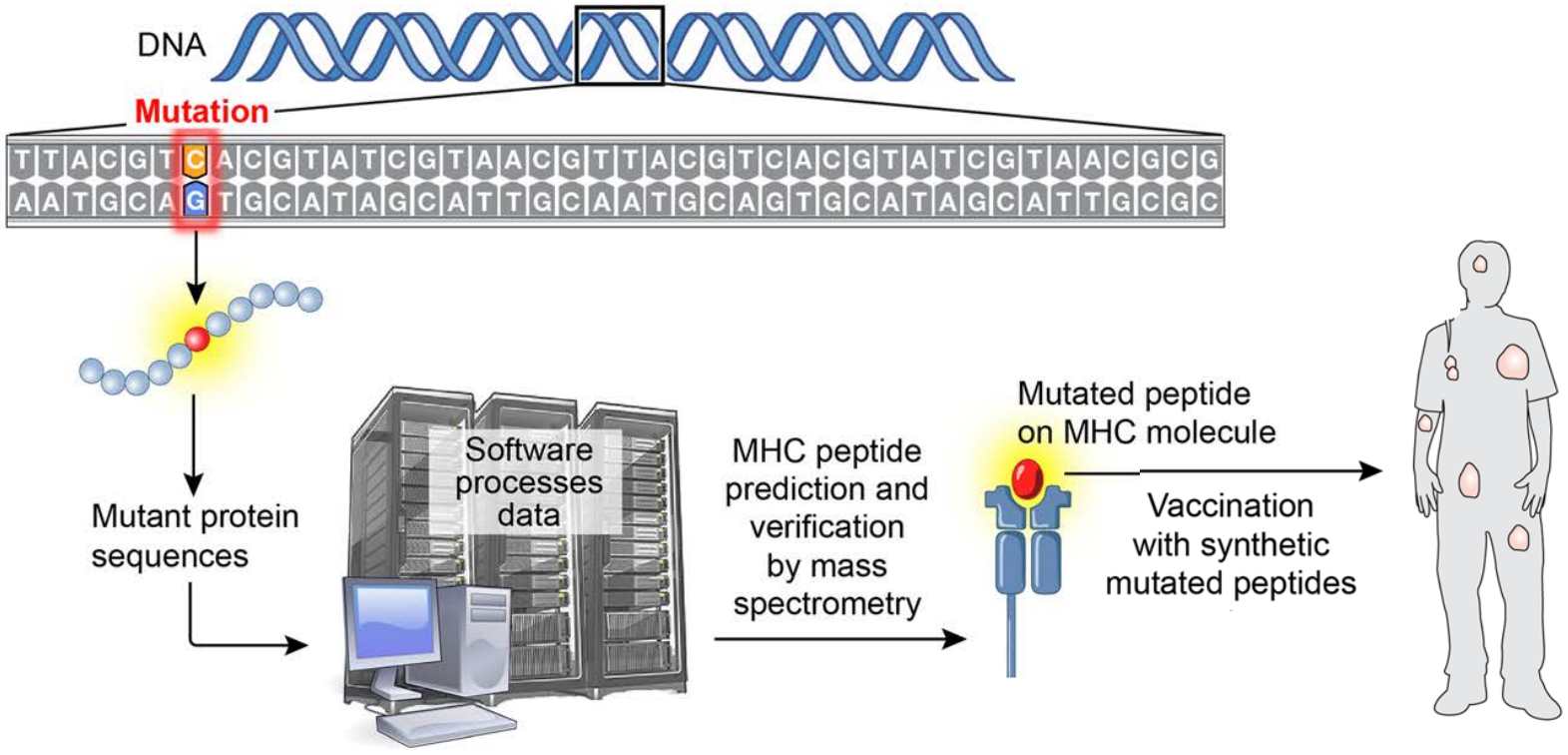
Signatures of mutational processes in human cancer Alexandrov et al.

Nature Volume: 500,Pages:415–421Date published:(22 August 2013)DOI:doi:10.1038/nature12477

Mutated Peptides as Cancer Antigens



From Mutation to Vaccine



adapted from Overwijk *et al.*, JITC, 2013

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vaccine adjuvant

A **preparation** of a **tumor antigen** (usually protein) that upon administration stimulates antibody production or cellular anti-tumor immunity.

Vaccine Adjuvants

- mechanisms of action:
    - antigen depot for prolonged release
    - protects antigen from degradation
    - increases antigen uptake by APCs
    - pro-inflammatory/pro-immunogenic milieu

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

gp100 Peptide Vaccine and Interleukin-2 in Patients with Advanced Melanoma

Douglas J. Schwartzentruber, M.D., David H. Lawson, M.D., Jon M. Richards, M.D., Ph.D., Robert M. Conry, M.D., Donald M. Miller, M.D., Ph.D., Jonathan Treisman, M.D., Fawaz Gailani, M.D., Lee Riley, M.D., Ph.D., Kevin Conlon, M.D., Barbara Pockaj, M.D., Kari L. Kendra, M.D., Ph.D., Richard L. White, M.D., Rene Gonzalez, M.D., Timothy M. Kuzel, M.D., Brendan Curti, M.D., Phillip D. Leming, M.D., Eric D. Whitman, M.D., Jai Balkissoon, M.D., Douglas S. Reintgen, M.D., Howard Kaufman, M.D., Francesco M. Marincola, M.D., Maria J. Merino, M.D., Steven A. Rosenberg, M.D., Ph.D., Peter Choyke, M.D., Don Vena, B.S., and Patrick Hwu, M.D.

gp100 peptide vaccine has activity in metastatic melanoma

Stage IV and locally advanced stage III melanoma patients

High-dose IL-2 +/- gp100 peptide in IFA (= water-in-oil emulsion)

	IL-2+gp100/IFA	IL-2	p-value
Overall response rate	22.1%	9.7%	0.022
Progression free survival	2.9 months	1.6 months	0.010
Median overall survival	17.6 months	12.8 months	0.096

Schwartzentruber *et al*., NEJM 2011

Clinical Trials of Cancer Vaccines

402 open studies (USA only) using cancer vaccines (www.clinicaltrial.gov)

1. Study of Peptide Vaccination With Tumor Associated Antigens Mixed With Montanide in Patients With **CNS Tumors**
2. CpG 7909/IFA With or Without Cyclophosphamide in Combination Either With NY-ESO-1-derived Peptides or the NY-ESO-1 Protein for **NY-ESO-1-expressing Tumors**
3. Vaccine Therapy in Treating Patients With **Non-Small Cell Lung Cancer** (NSCLC) Stages IIIB/IV
4. Randomized Study of Adjuvant WT-1 Analog Peptide Vaccine in Patients With Malignant Pleural **Mesothelioma** (MPM) After Completion of Combined Modality Therapy
5. Immunotherapy of Stage III/IV **Melanoma** Patients
6. A Clinical Trial of Autologous Oxidized Tumor Cell Lysate Vaccine For Recurrent **Ovarian, Fallopian Tube or Primary Peritoneal Cancer**
7. Vaccine Therapy and Monoclonal Antibody Therapy in Treating Patients With Stage III or Stage IV **Melanoma** That Cannot Be Removed by Surgery
8. Safety Study of Multiple-Vaccine to Treat **Metastatic Breast Cancer**
9. IDO Peptide Vaccination for Stage III-IV **Non Small-cell Lung Cancer** Patients.
10. Survivin Vaccine Therapy for Patients With **Malignant Gliomas**
11. Phase I Poly IC:LC and NY-ESO-1/gp100/MART **(Melanoma)**
12. A Phase I Study of WT1 Peptides to Induce Anti-Leukemia Immune Responses Following Autologous or Allogeneic Transplantation for **AML, CML, ALL, MDS, and B Cell Malignancies**
13. Vaccination of High Risk **Breast Cancer** Patients
14. MAGE-A3/HPV 16 Vaccine for **Squamous Cell Carcinoma of the Head and Neck**
15. Novel Adjuvants for Peptide-Based **Melanoma** Vaccines

Peptide-based Cancer Vaccines

The NEW ENGLAND JOURNAL of MEDICINE

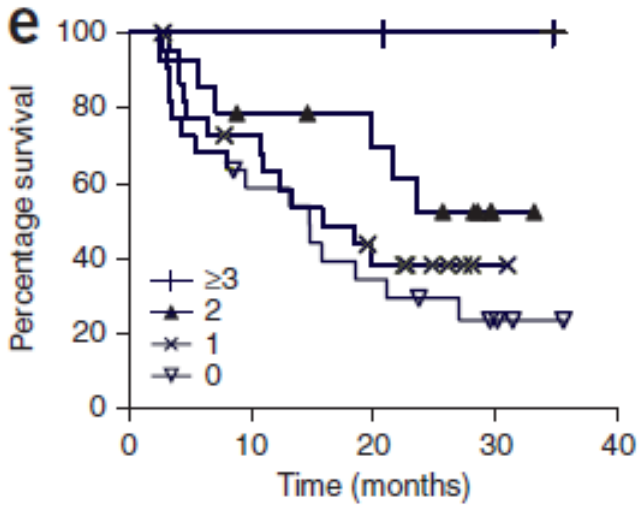
ORIGINAL ARTICLE

Vaccination against HPV-16 Oncoproteins for Vulvar Intraepithelial Neoplasia

Gemma G. Kenter, M.D., Ph.D., Marij J.P. Welters, Ph.D.,
A. Rob P.M. Valentijn, Ph.D., Margriet J.G. Lowik,
Dorien M.A. Berends-van der Meer, Annelies P.G. Vloon, Farah Essahsah,
Lorraine M. Fathers, Rienk Offringa, Ph.D., Jan Wouter Drijfhout, Ph.D.,
Amon R. Wafelman, Ph.D., Jaap Oostendorp, Ph.D., Gert Jan Fleuren, M.D., Ph.D.,
Sjoerd H. van der Burg, Ph.D., and Cornelis J.M. Melief, M.D., Ph.D.

79% clinical response
47% CR (>24 months)

Immune response can correlate with clinical outcome



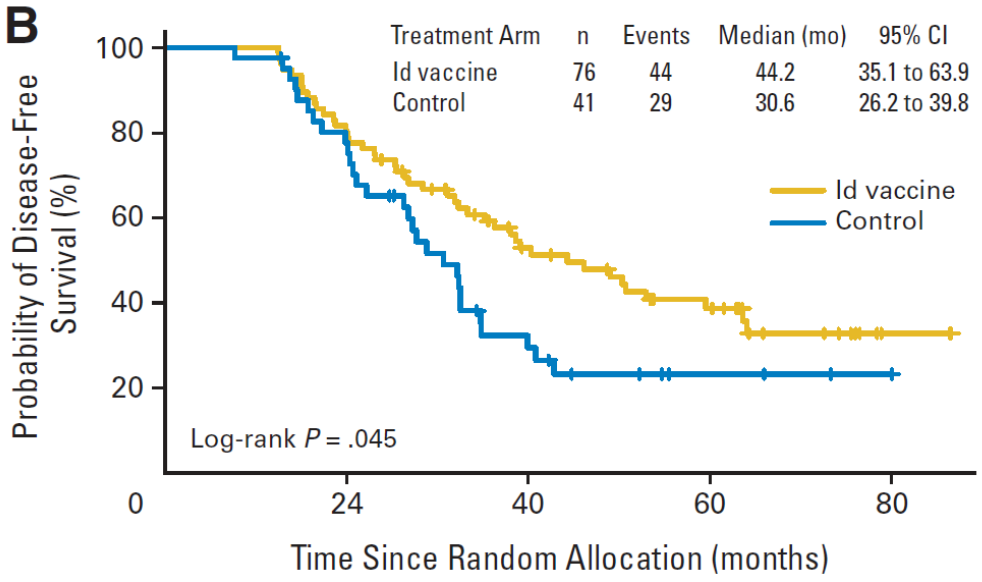
nature medicine AUGUST 2012

Multipeptide immune response to cancer vaccine IMA901 after single-dose cyclophosphamide associates with longer patient survival

Steffen Walter[1,21], Toni Weinschenk[1,21], Arnulf Stenzl[2], Romuald Zdrojowy[3], Anna Pluzanska[4], Cezary Szczylik[5], Michael Staehler[6], Wolfram Brugger[7], Pierre-Yves Dietrich[8], Regina Mendrzyk[1], Norbert Hilf[1], Oliver Schoor[1], Jens Fritsche[1], Andrea Mahr[1], Dominik Maurer[1], Verona Vass[1], Claudia Trautwein[1], Peter Lewandrowski[1], Christian Flohr[1], Heike Pohla[9,10], Janusz J Stanczak[11], Vincenzo Bronte[12], Susanna Mandruzzato[13,14], Tilo Biedermann[15], Graham Pawelec[16], Evelyna Derhovanessian[16], Hisakazu Yamagishi[17], Tsuneharu Miki[18], Fumiya Hongo[18], Natsuki Takaha[18], Kosei Hirakawa[19], Hiroaki Tanaka[19], Stefan Stevanovic[20], Jürgen Frisch[1], Andrea Mayer-Mokler[1], Alexandra Kirner[1], Hans-Georg Rammensee[20], Carsten Reinhardt[1,21] & Harpreet Singh-Jasuja[1,21]

Vaccination With Patient-Specific Tumor-Derived Antigen in First Remission Improves Disease-Free Survival in Follicular Lymphoma

Stephen J. Schuster, Sattva S. Neelapu, Barry L. Gause, John E. Janik, Franco M. Muggia, Jon P. Gockerman, Jane N. Winter, Christopher R. Flowers, Daniel A. Nikcevich, Eduardo M. Sotomayor, Dean S. McGaughey, Elaine S. Jaffe, Elise A. Chong, Craig W. Reynolds, Donald A. Berry, Carlos F. Santos, Mihaela A. Popa, Amy M. McCord, and Larry W. Kwak



Antigen: Lymphoma Idiotype (antibody) conjugates to KLH

Adjuvant: GM-CSF

VOLUME 29 · NUMBER 20 · JULY 10 2011

JOURNAL OF CLINICAL ONCOLOGY

Question

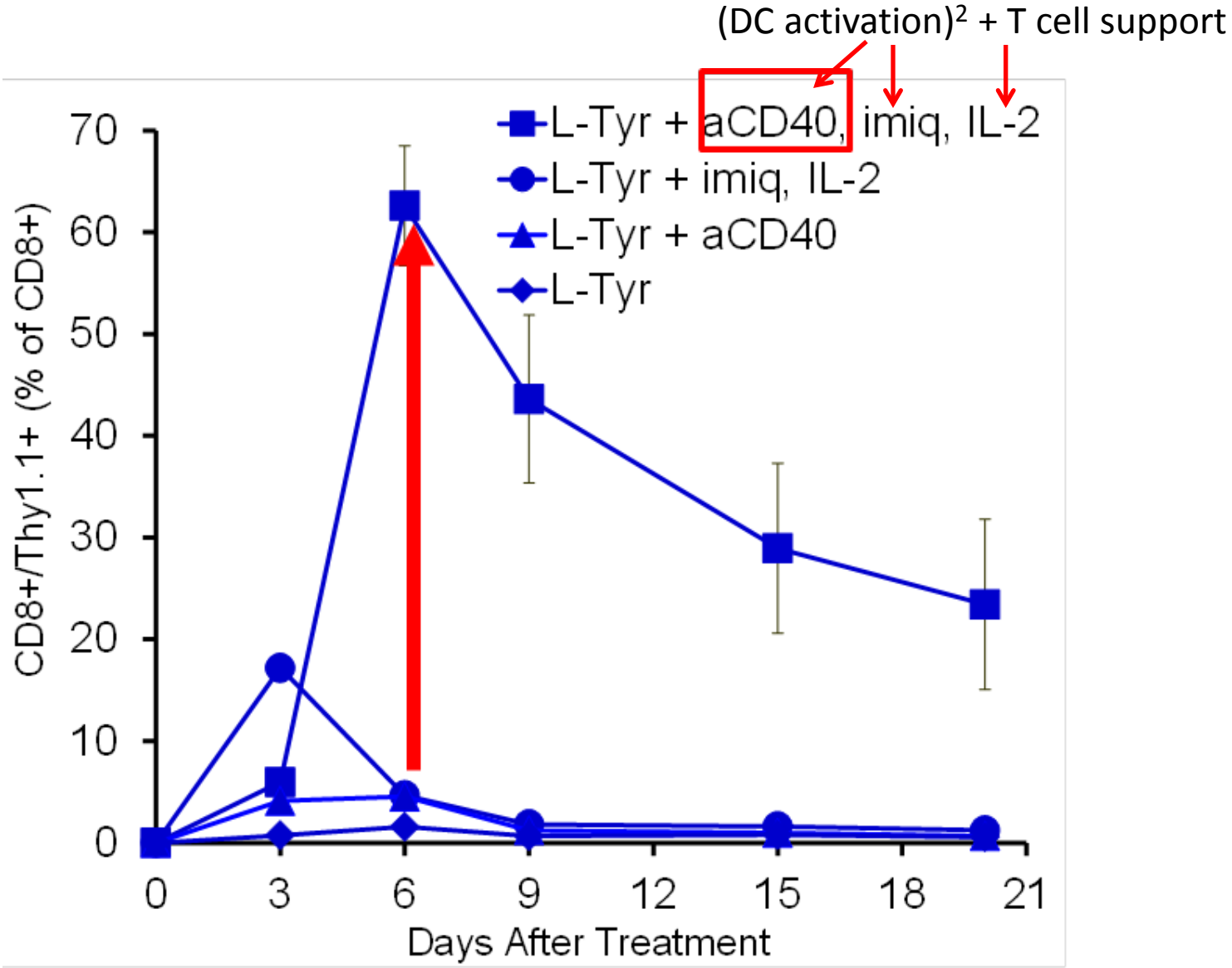
Why do many vaccinated cancer patients not experience tumor regression despite increased levels of cancer-specific T cells?

Question

Why do many vaccinated cancer patients not experience tumor regression despite increased levels of cancer-specific T cells?

- immunosuppressive tumor microenvironment
- too few T cells induced
- poor T cell effector function/wrong phenotype
- poor T cell trafficking to tumor

Combination Adjuvants are Key

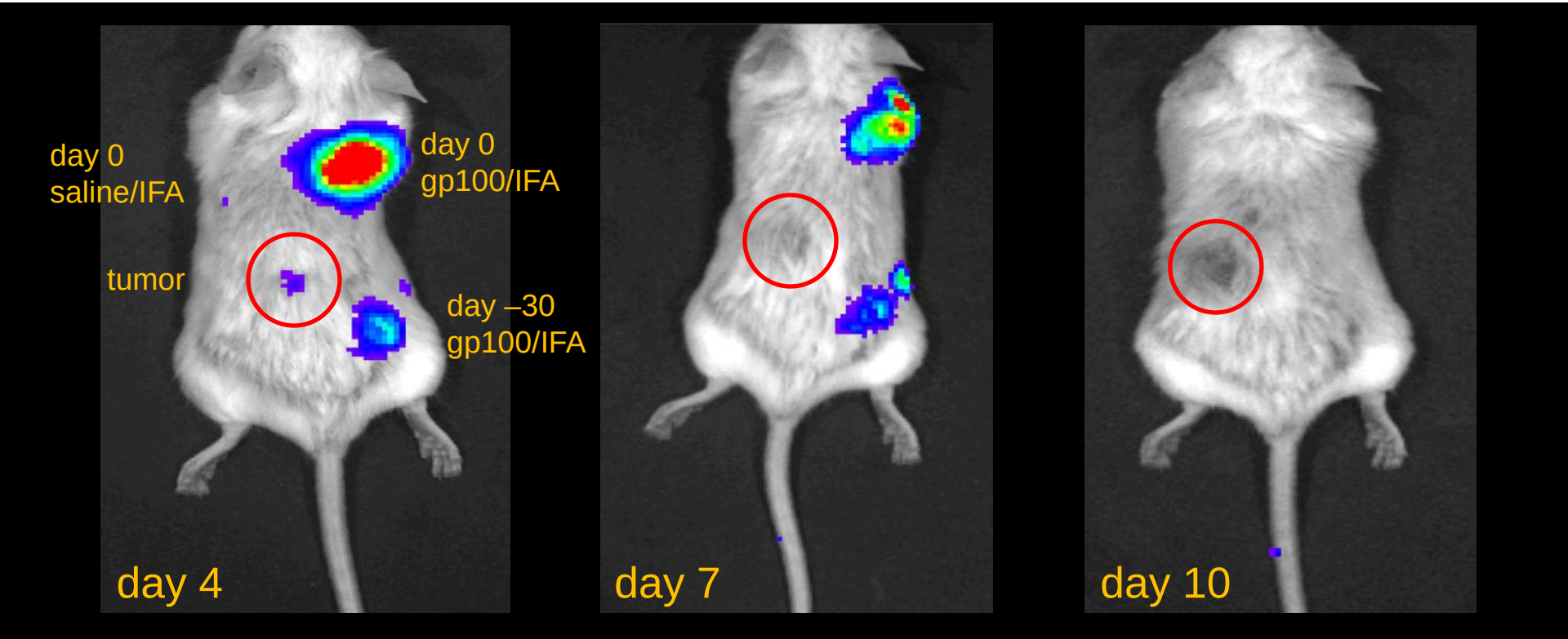


Hiep Khong

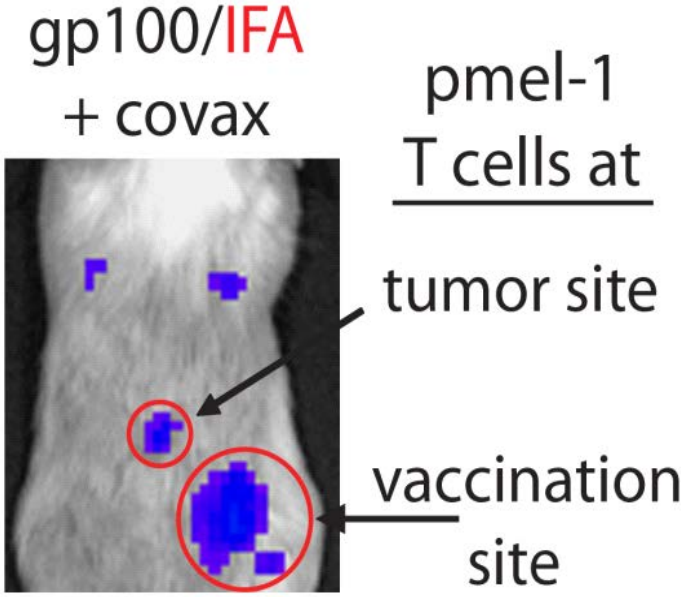
Where are the T cells?

gp100/IFA s.c. + *eLuc*-transduced pmel-1 T cells i.v.

Rabinovich *et al.*, PNAS 2008

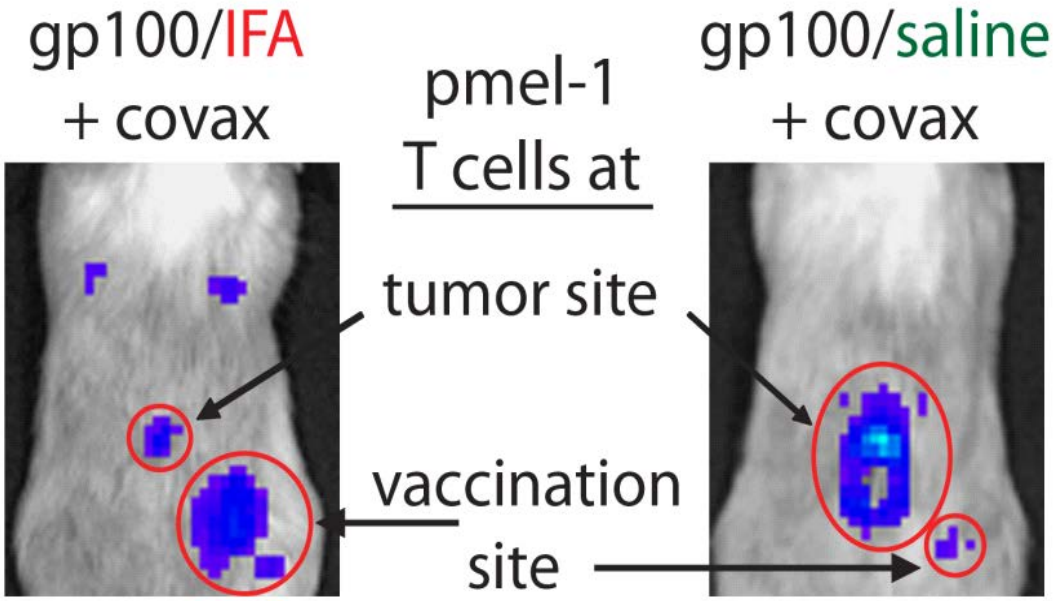


Oil-based vaccines sequester T cells at the vaccination site



Hailemichael *et al*., Nat. Med. 13, 2013

Water-based vaccines permit T cell accumulation in tumor



Hailemichael *et al*., Nat. Med. 13, 2013

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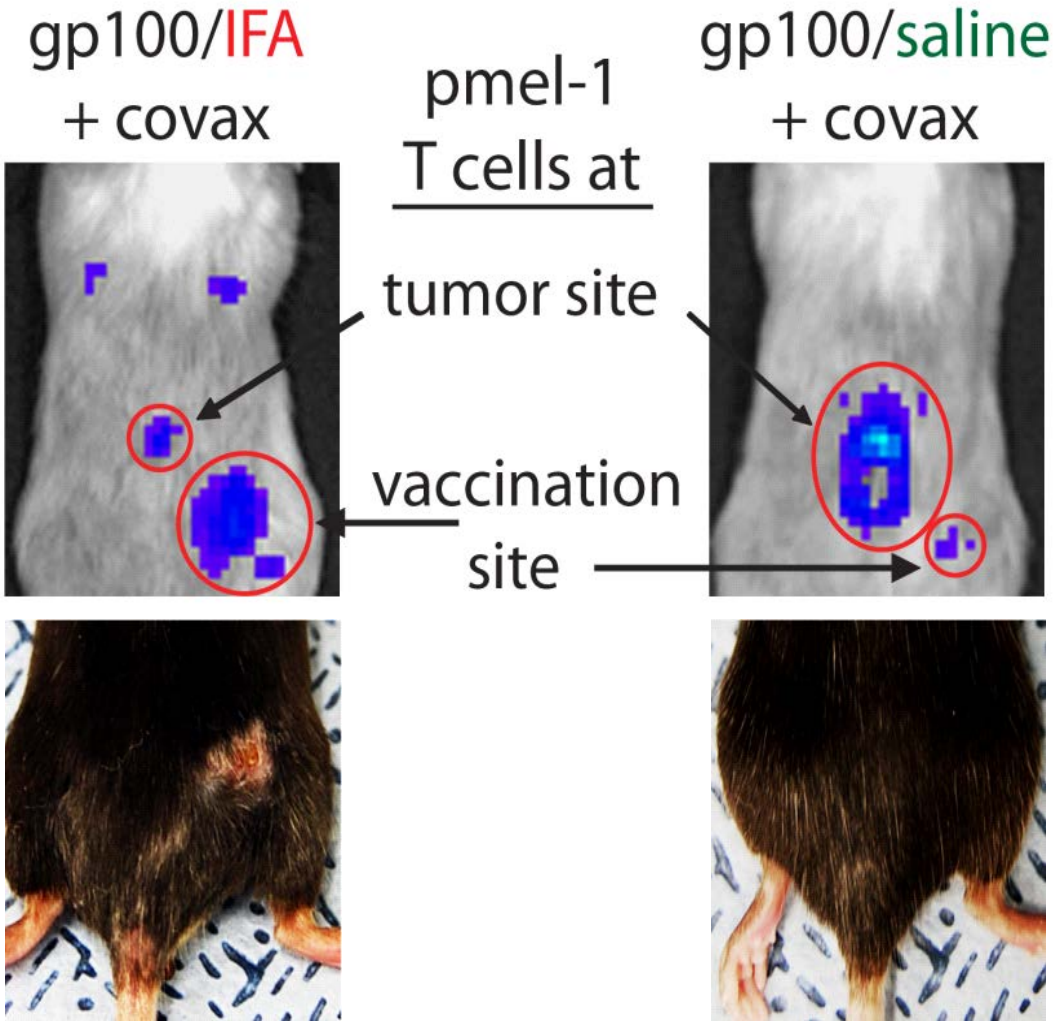
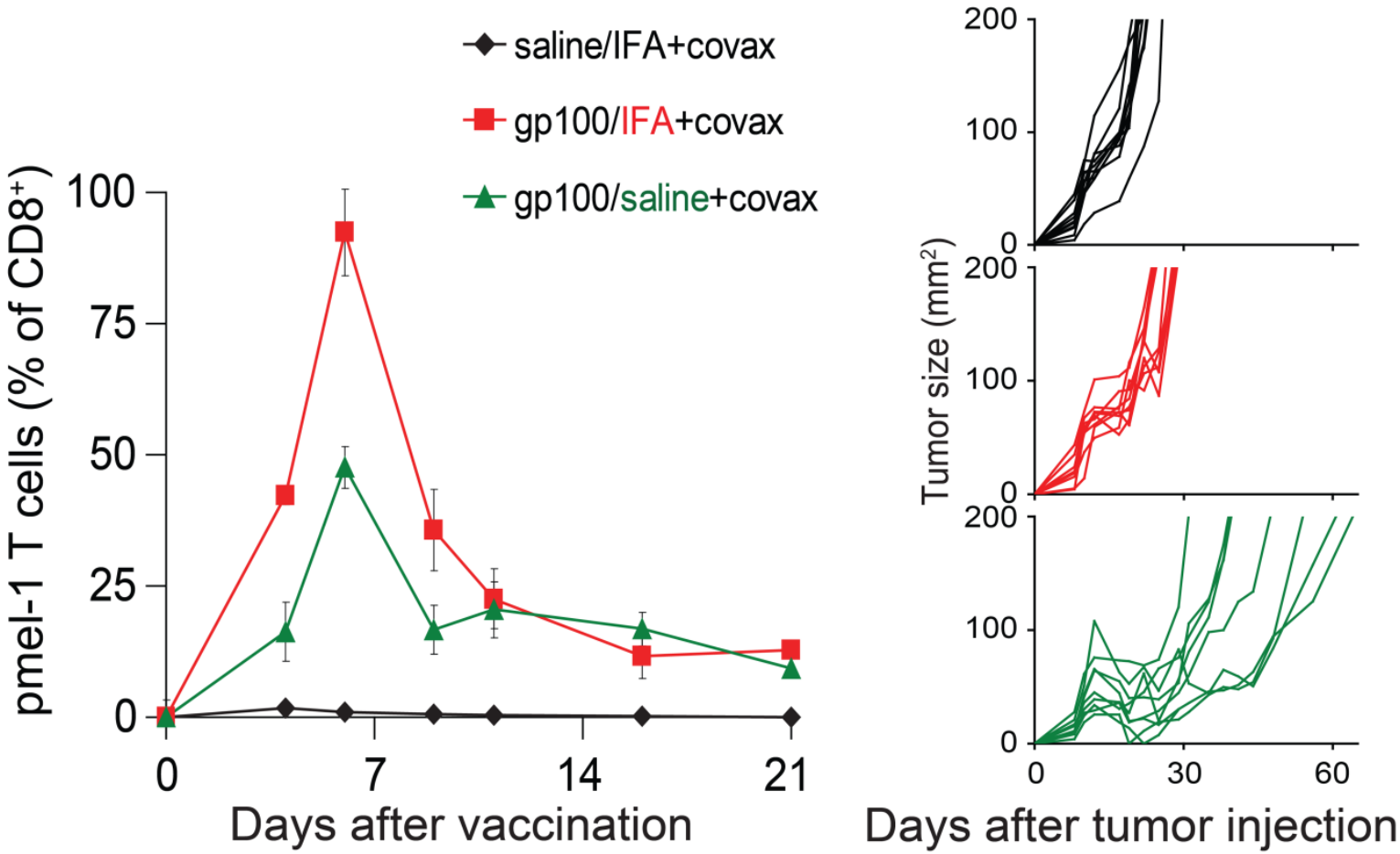


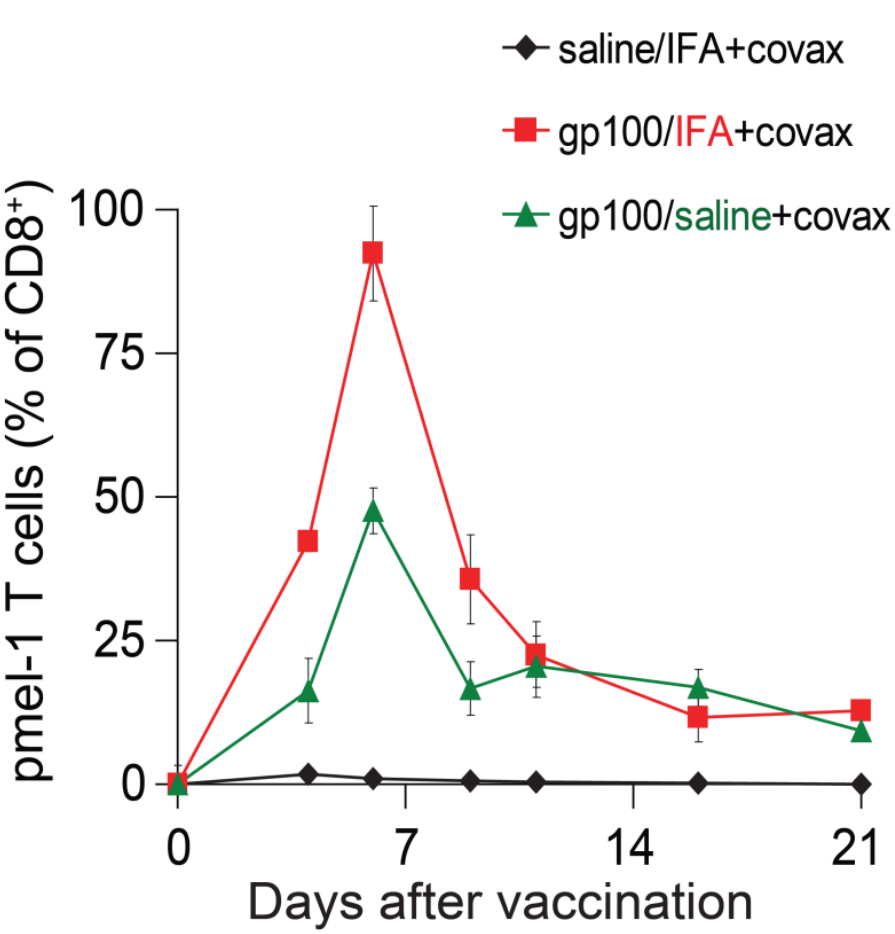
Hailemichael *et al*., Nat. Med. 13, 2013

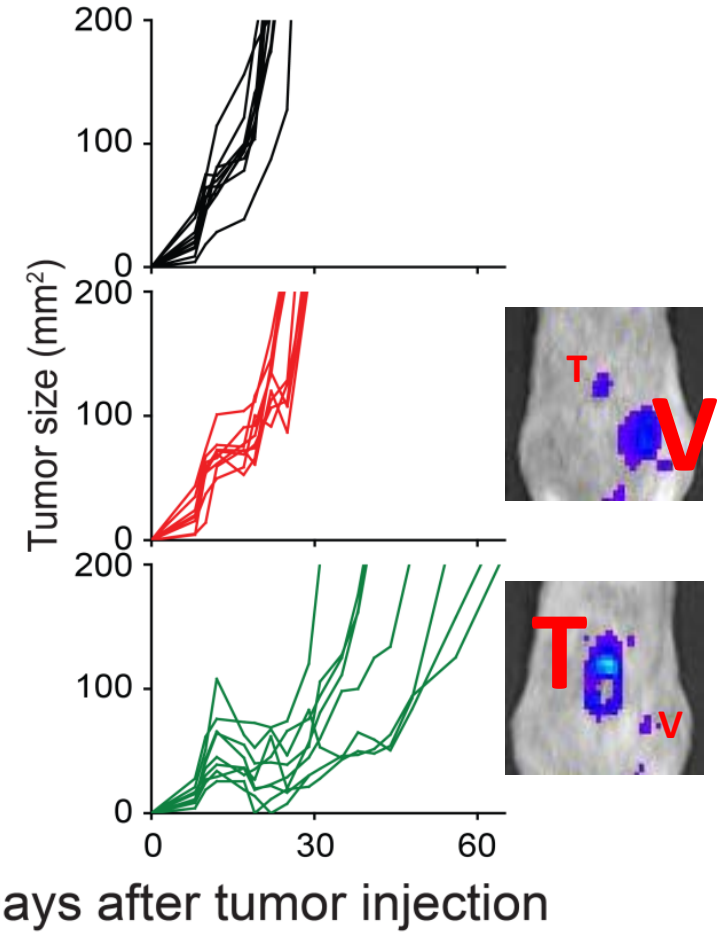
Tumor therapy with long-lived *vs.* short-lived vaccine



Hailemichael *et al*., Nat. Med. 13, 2013

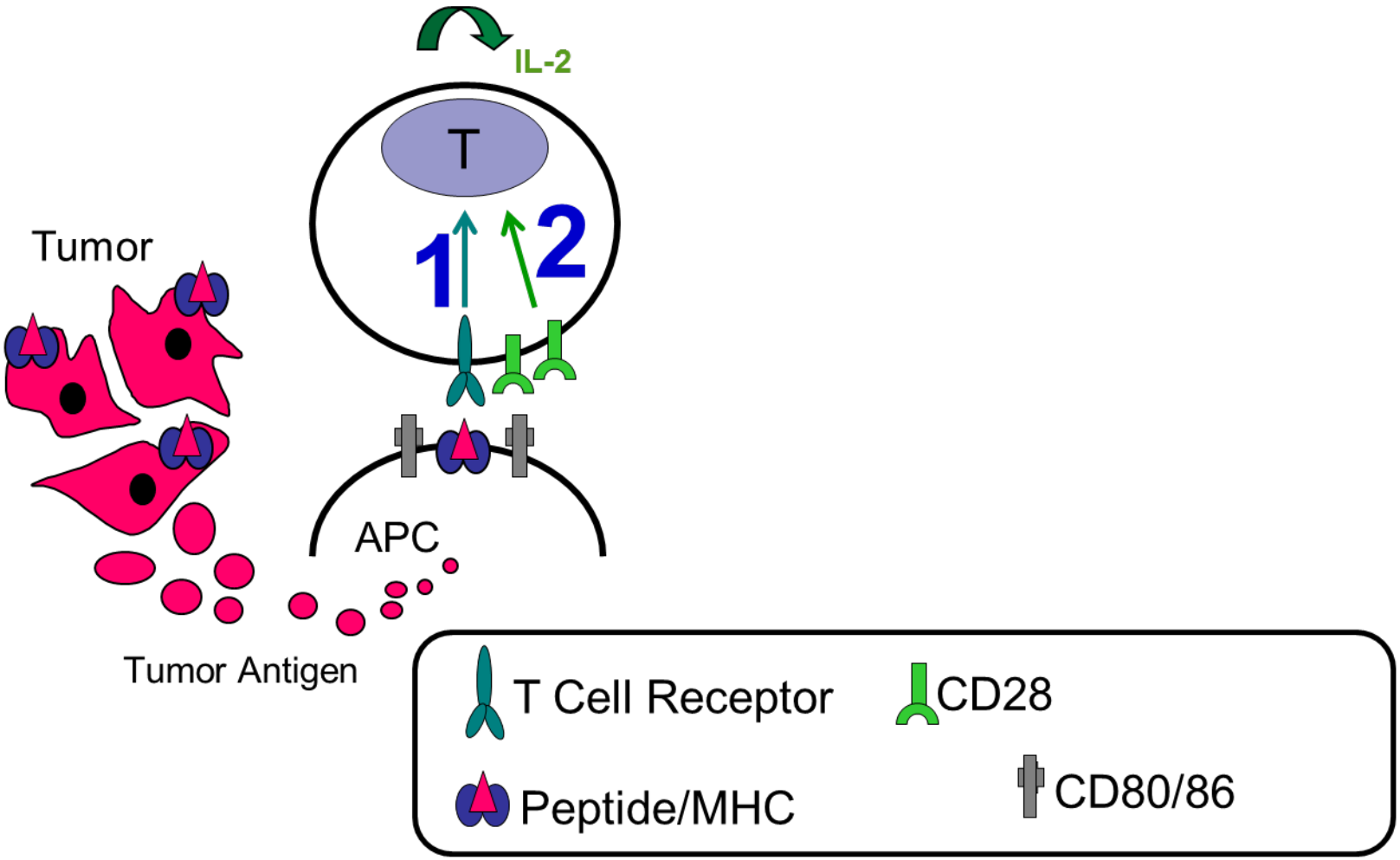
Tumor therapy with long-lived *vs.* short-lived vaccine





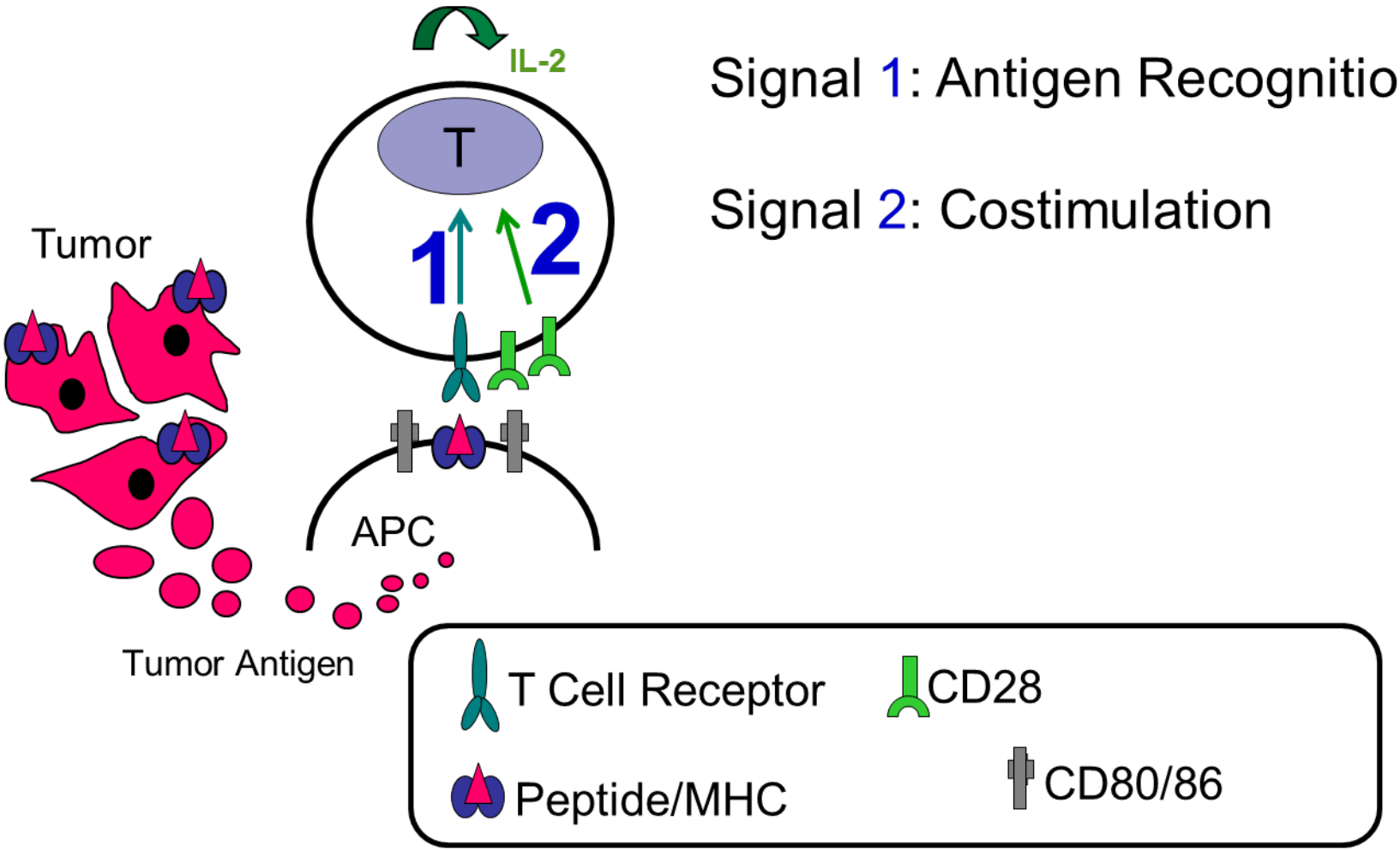
Hailemichael *et al*., Nat. Med. 13, 2013

T cell Activation: 2 signals



adapted from JP Allison

T cell Activation: 2 signals

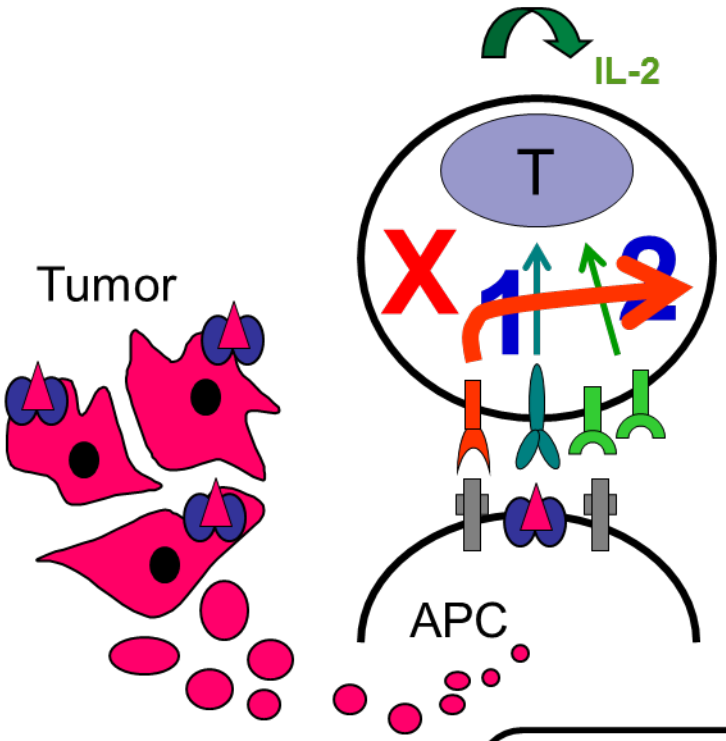


Signal 1: Antigen Recognition

Signal 2: Costimulation

adapted from JP Allison

T cell Activation: 2 signals



Signal 1: Antigen Recognition

Signal 2: Costimulation

Signal X: Checkpoint

T Cell Receptor

CD28

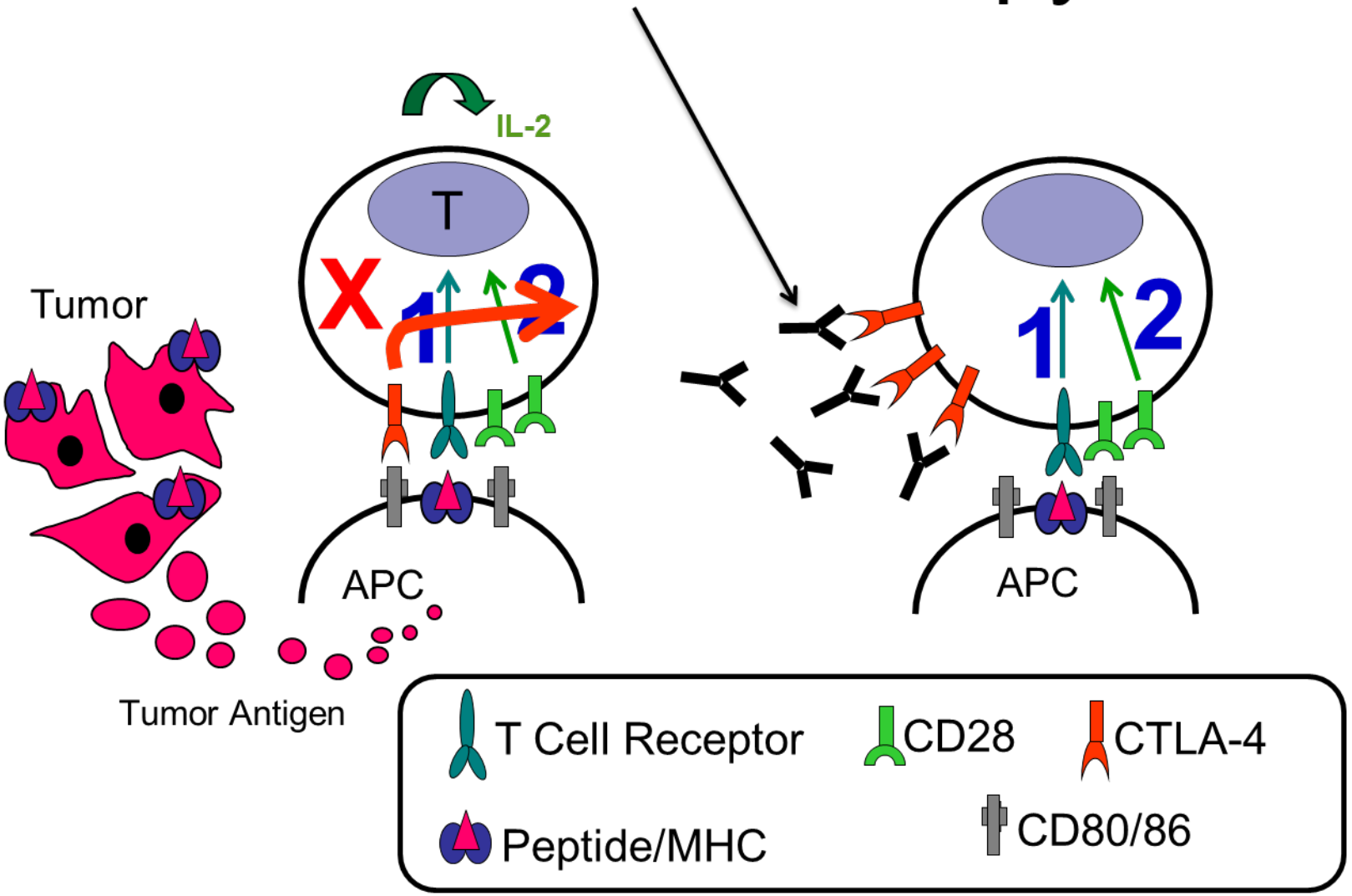
CTLA-4

Peptide/MHC

CD80/86

adapted from JP Allison

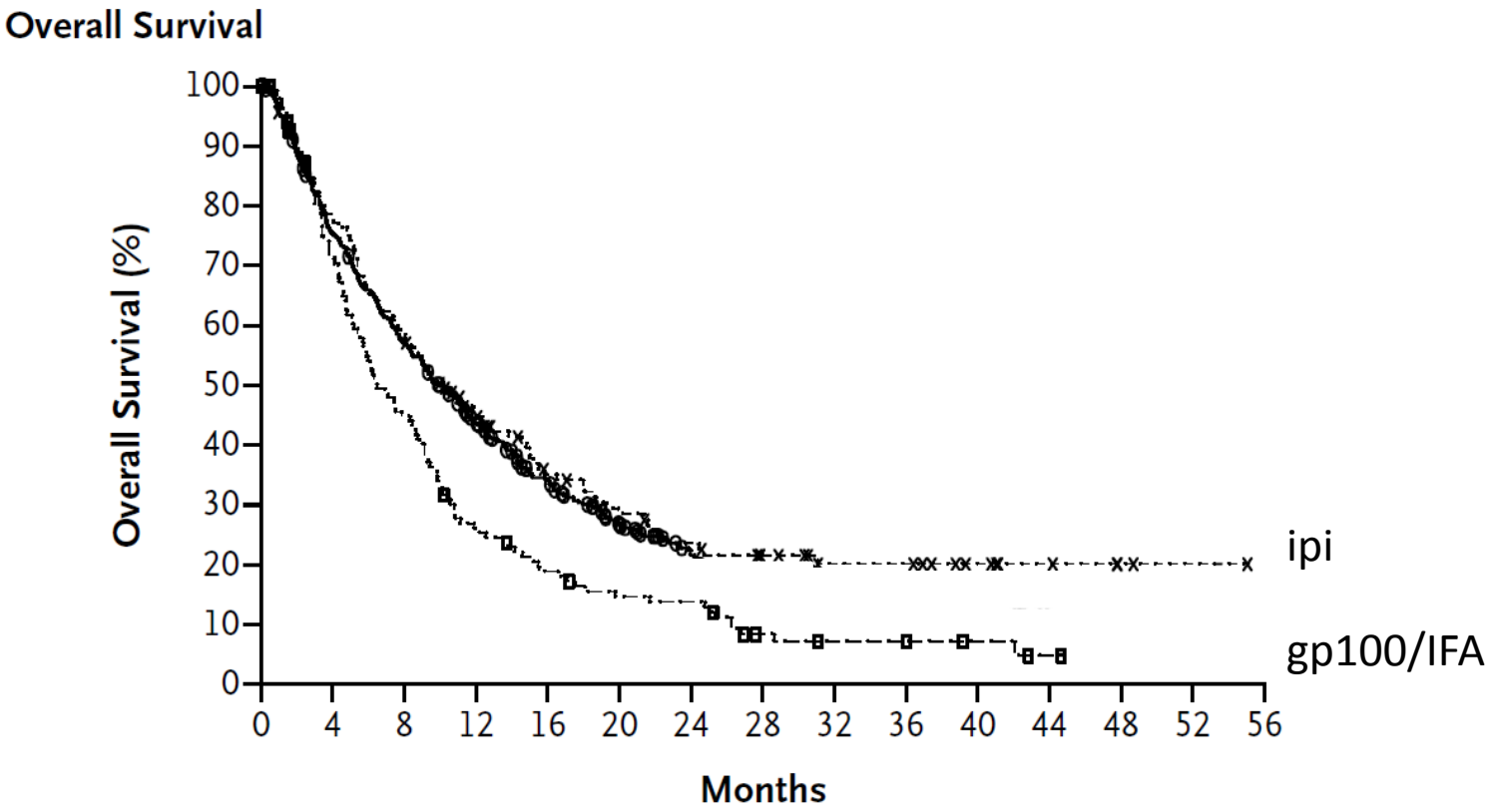
Anti-CTLA-4 therapy



adapted from JP Allison

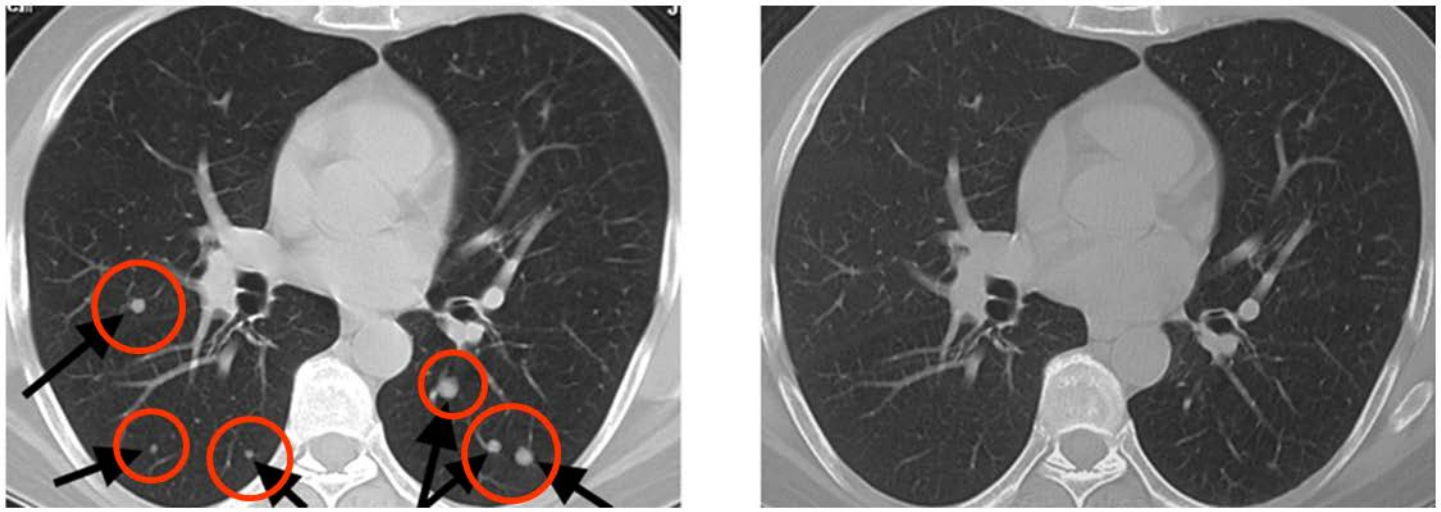
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.



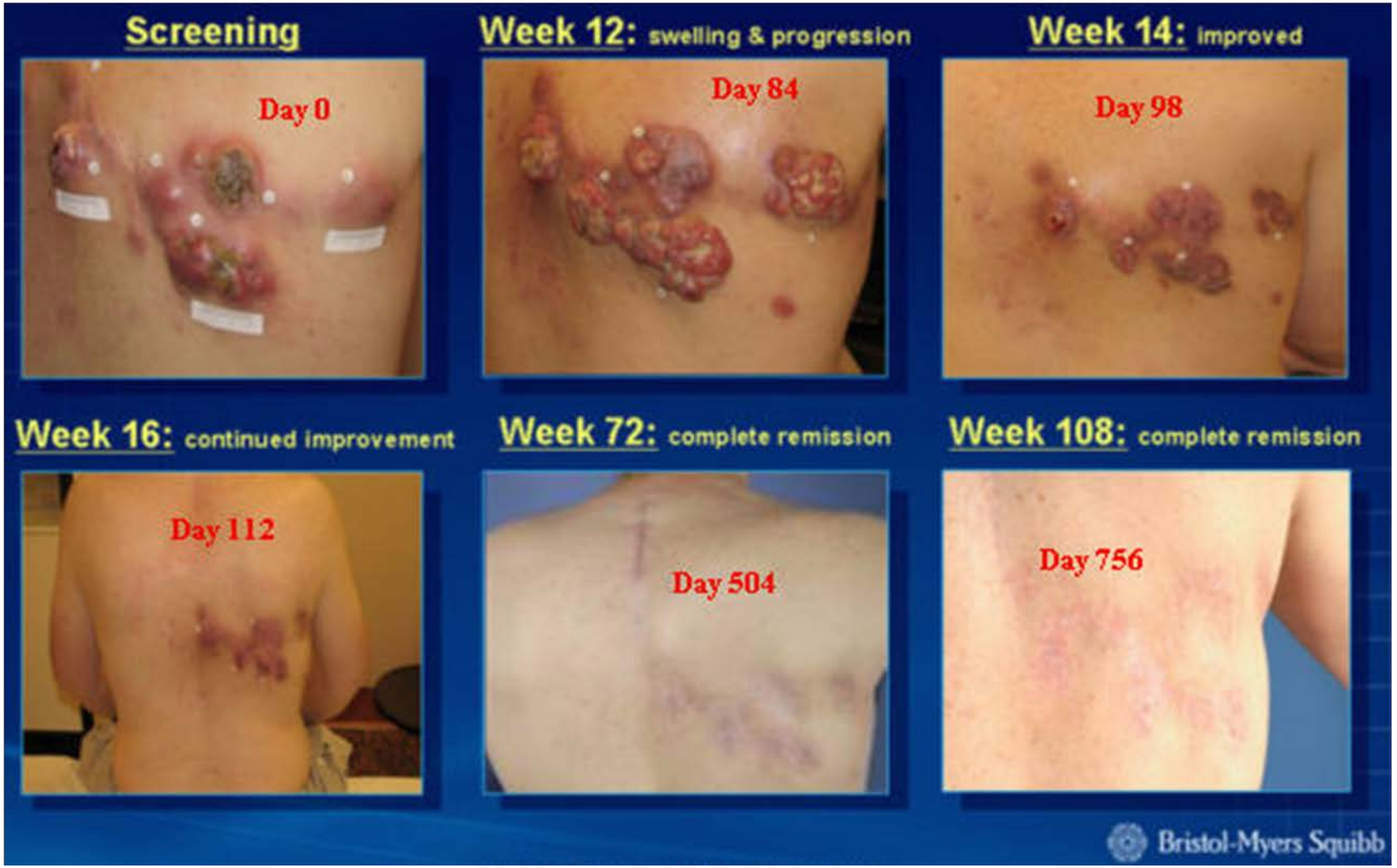
Complete Responder: Patient 11
Metastatic Melanoma

Experienced complete resolution of 2 subcutaneous nodules, 31 lung metastases and 0.5 cm brain metastasis.



BMS

Slow, prolonged tumor regression



Checkpoint Blockade + Vaccines

Vaccination and anti-CTLA-4/PD-1 both activate T cells, through different pathways, and could synergize.

However, this was not observed.

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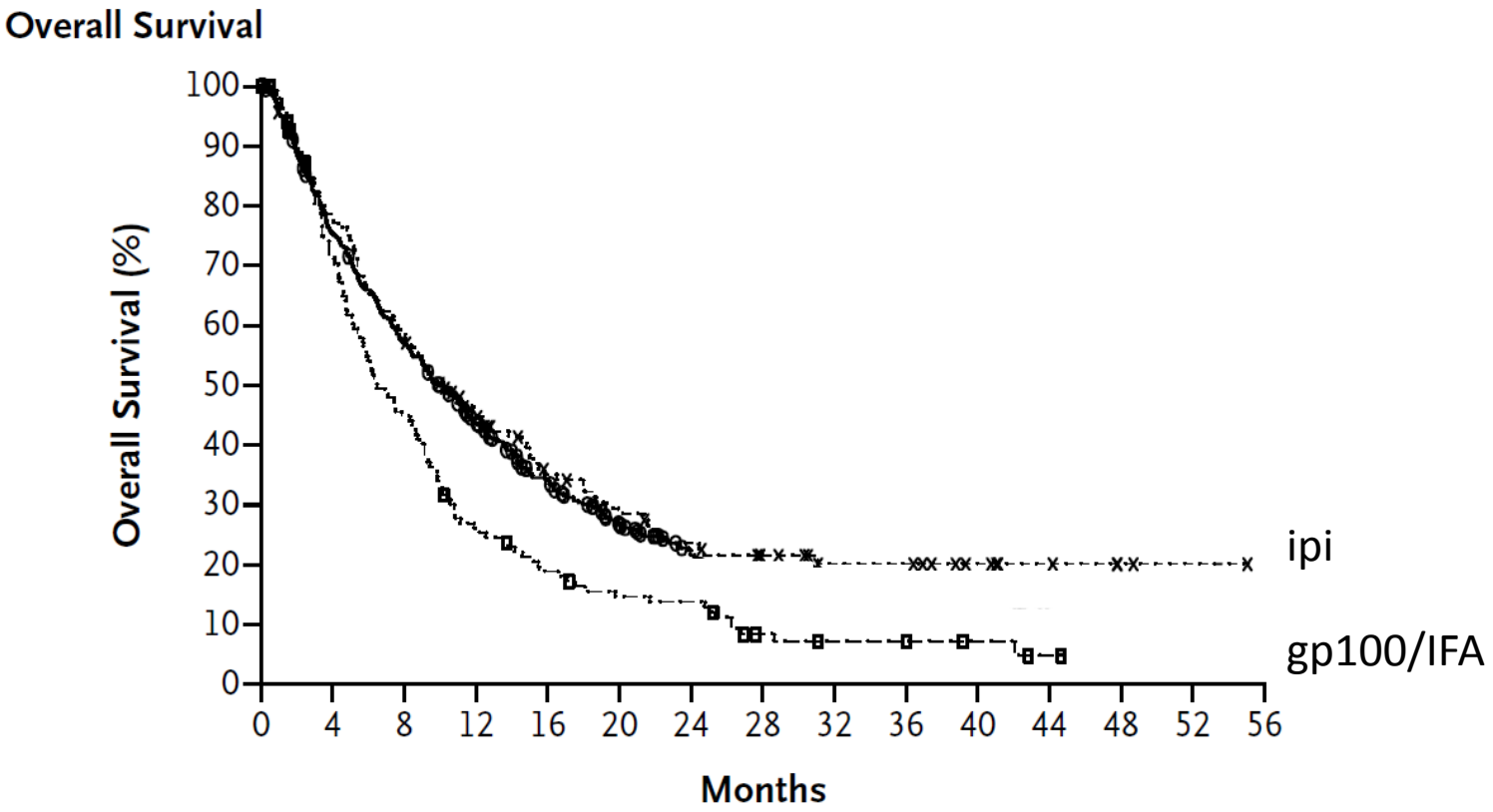

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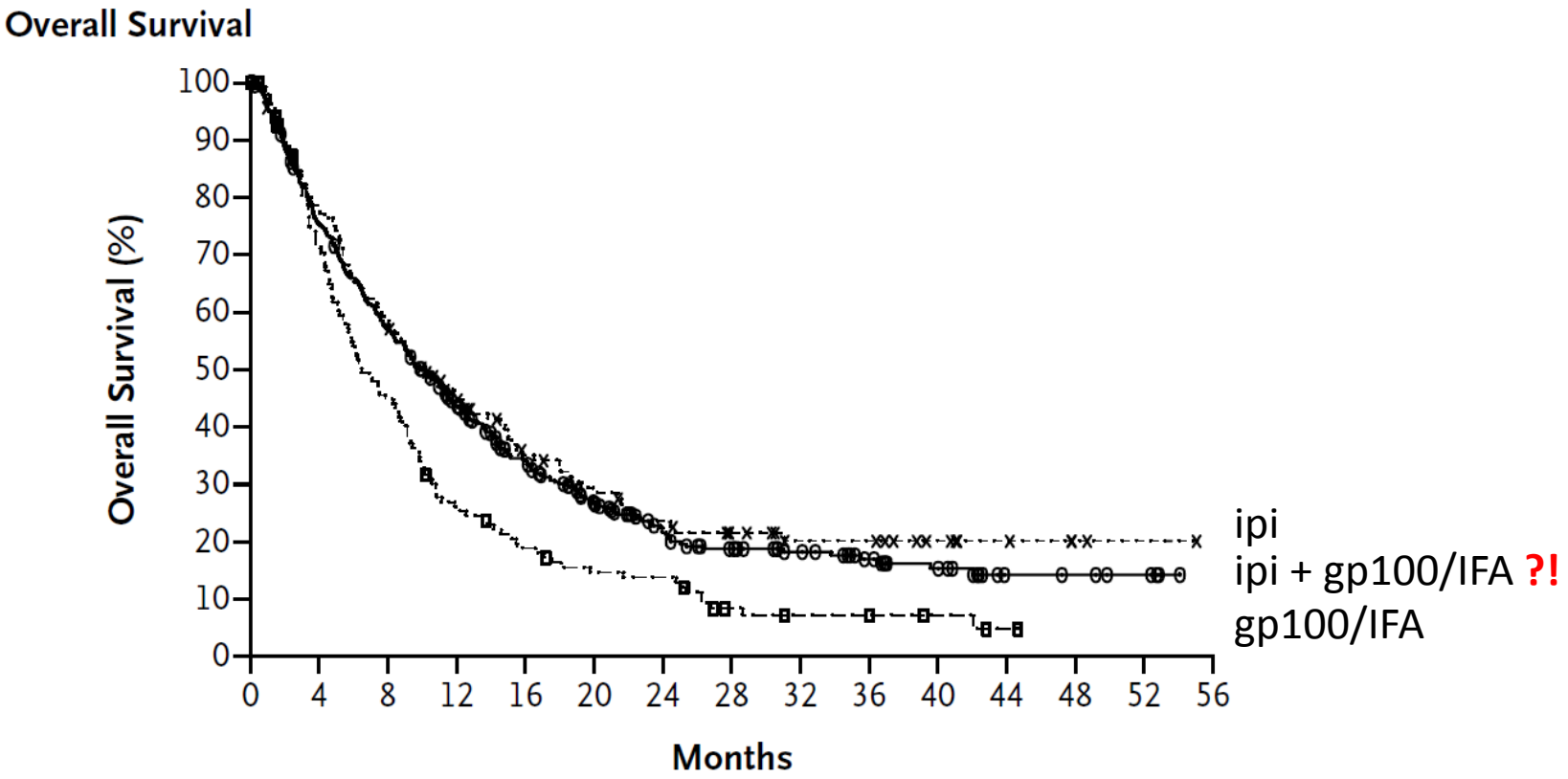
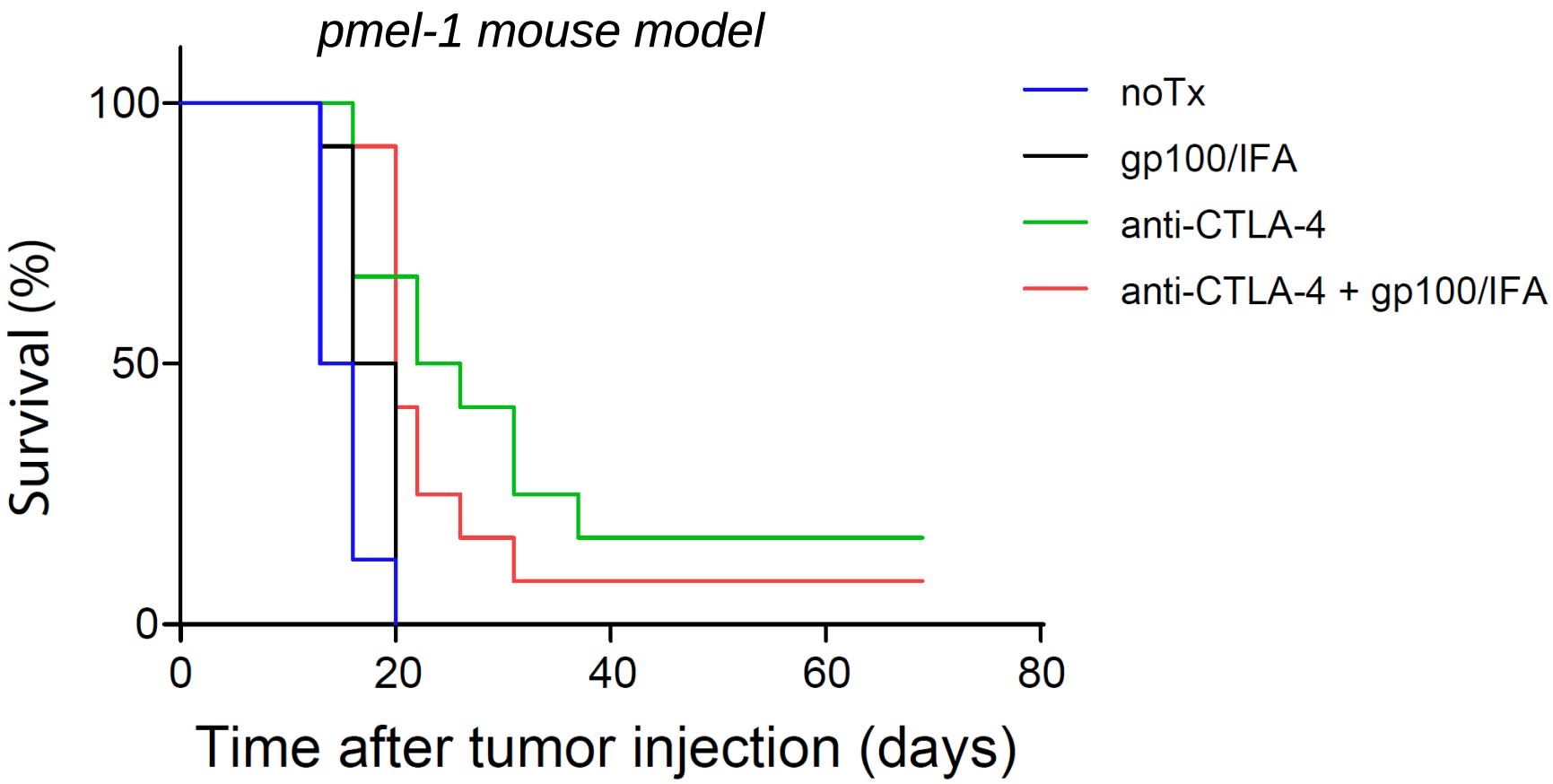
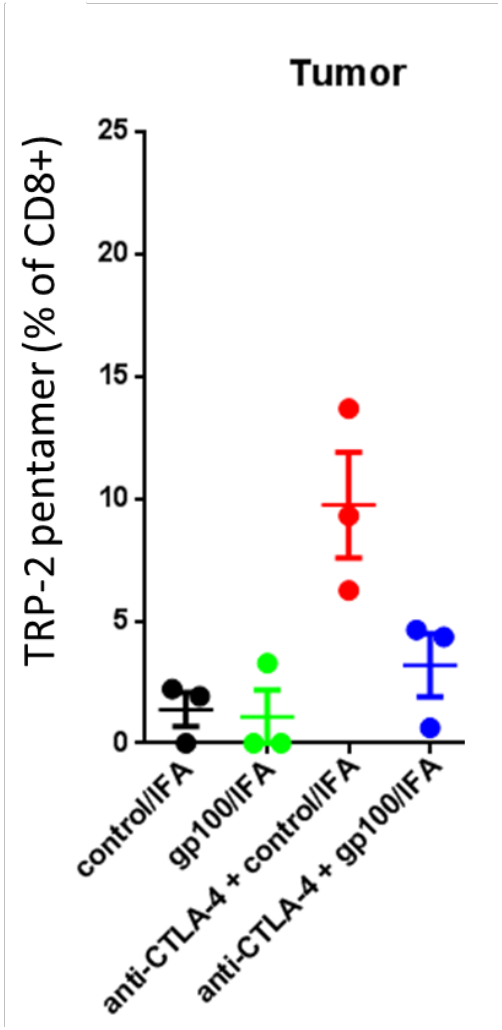


IFA-based vaccination does not synergize with anti-CTLA-4 therapy



Yared Hailemichael

IFA-based vaccination sequesters T cells induced by anti-CTLA-4 therapy



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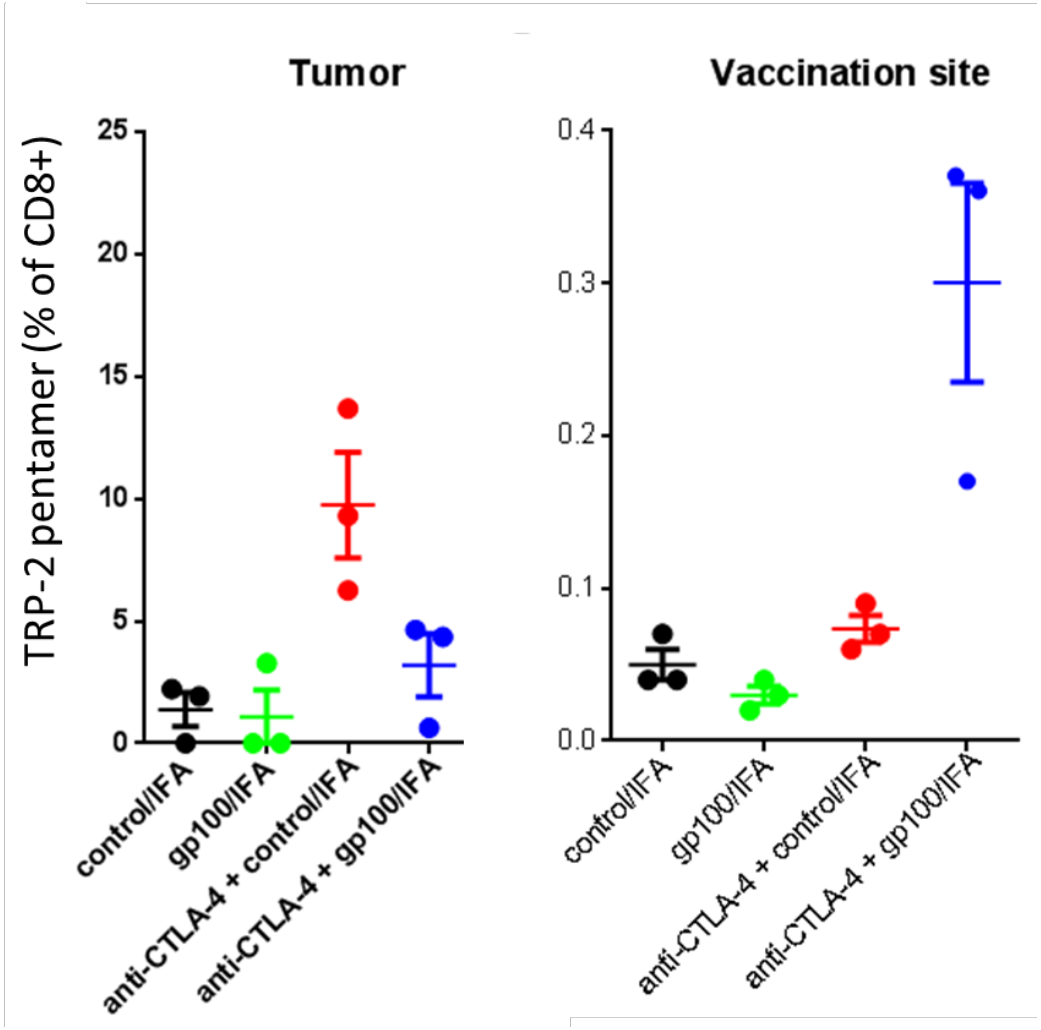

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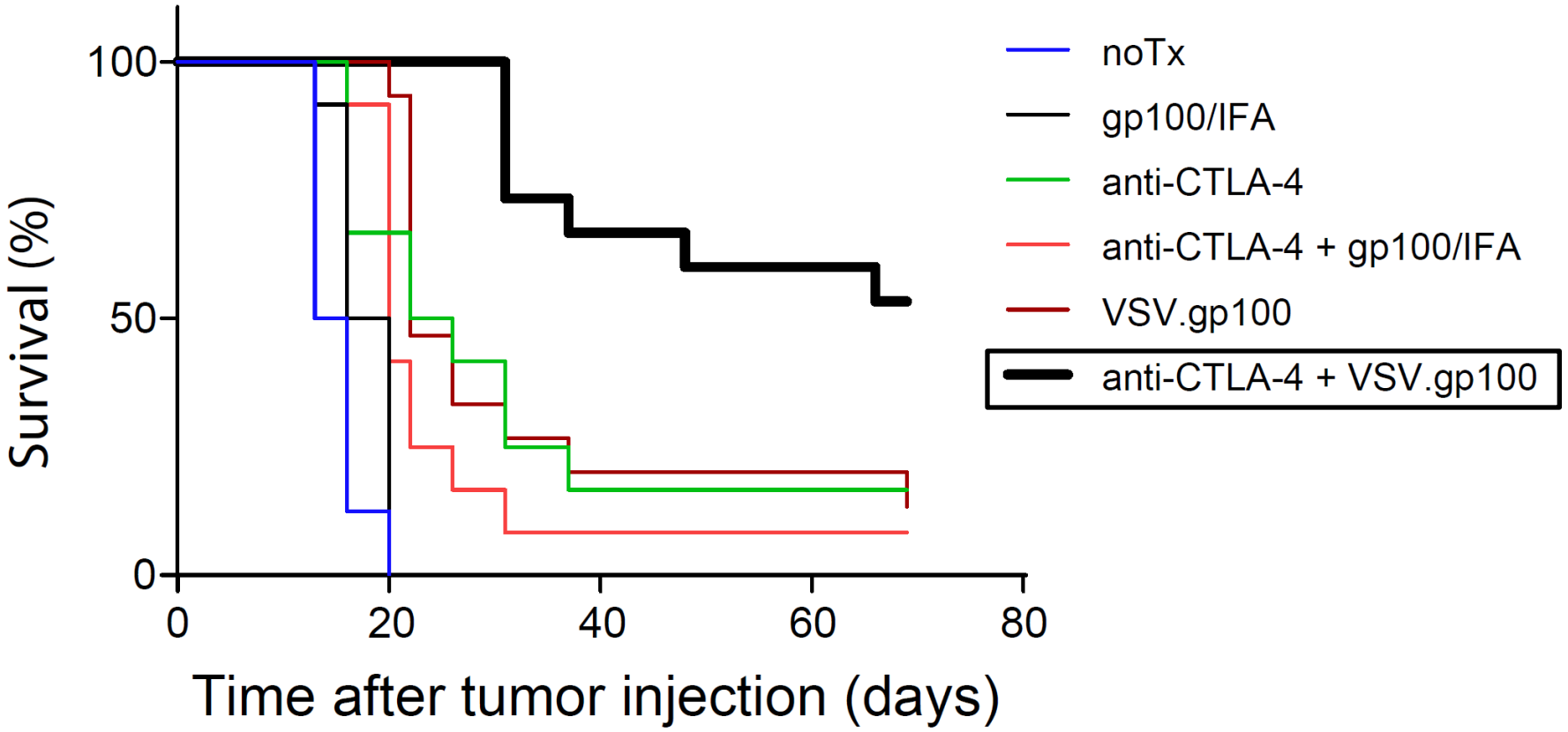
Virus-based vaccination synergizes with anti-CTLA-4 therapy



Yared Hailemichael

Conclusions

- Cancer vaccines can have clinical impact
- T cell responses tend to be (too) low or dysfunctional

To induce better T cell / clinical responses:

- Formulation matters: possible T cell sequestration
- Add immunomodulators (cytokines, TLR agonists)
- Combine with checkpoint blockade
- Combination Vaccines: Multiple Immunostimulatory Molecules

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John Carwile, D.V.M, and team

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Melanoma Research Alliance

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