Immunotherapy Patient Forum

for the Treatment of Melanoma, Leukemia, Lymphoma, Lung and Genitourinary Cancers - November 7, 2015

sitc
Society for Immunotherapy of Cancer

Melanoma
Research Alliance

Global Resource for Advancing Cancer Education

What is Immunotherapy & Its Mechanisms of Action

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@gulleyj1

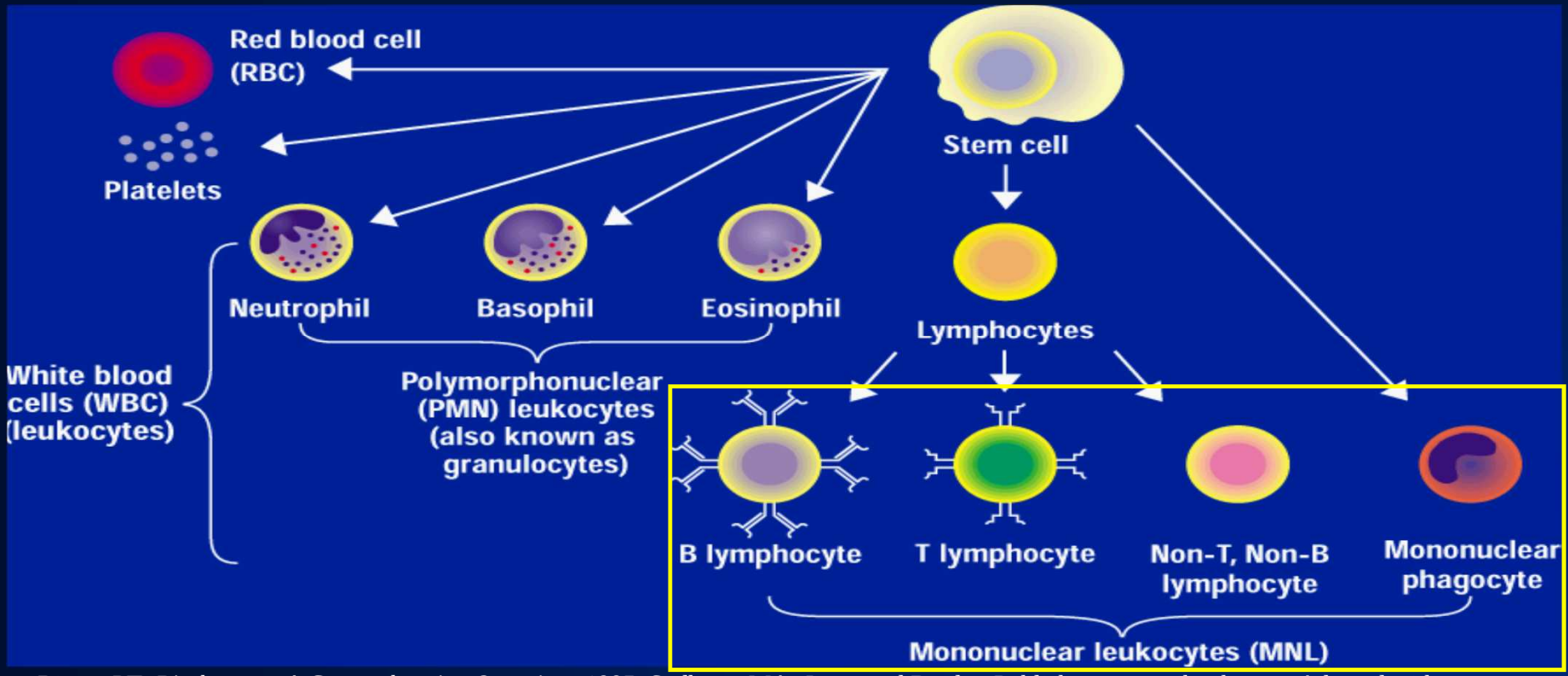
Disclosure

James Gulley has no relevant disclosures

The Immune System

- Adaptive defense system
  - protects against invading microorganisms and cancer
- Consists of two activities
  - *Recognition*
  - *Response*

Hematopoetic cell lineage

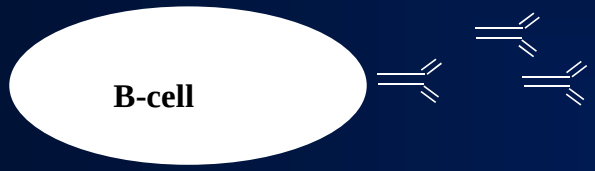


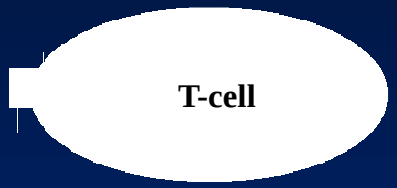
Rieger PT, *Biotherapy: A Comprehensive Overview*, 1995, Sudbury, MA: Jones and Bartlett Publishers. www.jbpub.com. Adapted with permission

Immune system

- It is made up of many cell types.
  - Trainers / Teachers
    - Antigen presenting cells (e.g., Dendritic Cells)
  - Soldiers
    - B-cells
    - T-cells

Immune system: selective targeting





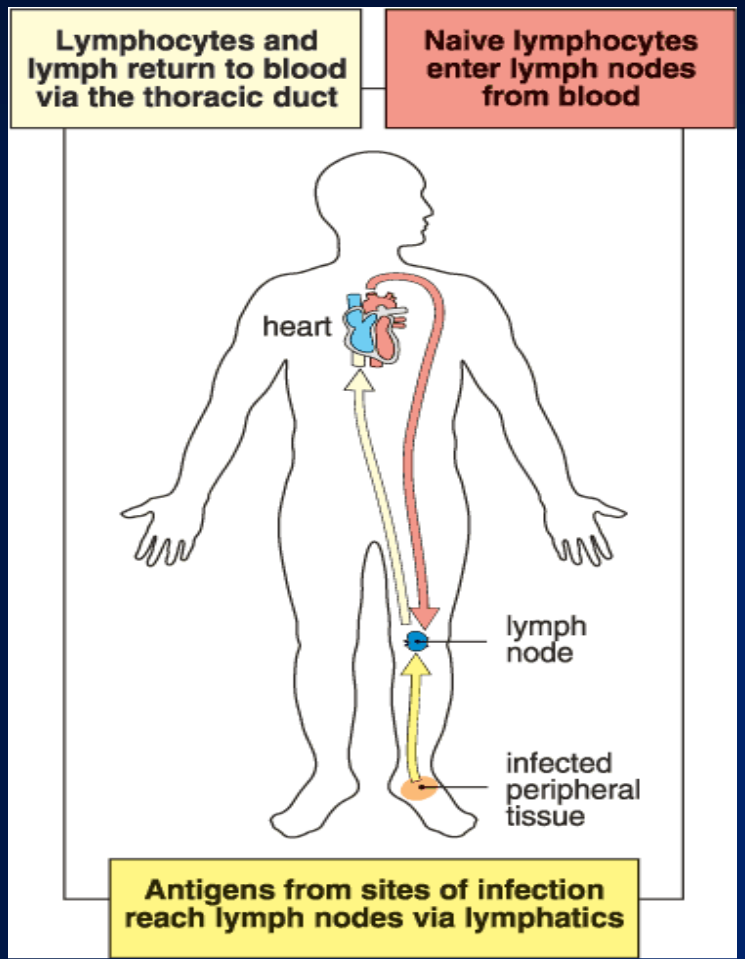
Can be trained to recognize proteins (targets) on cell surface

Make Antibodies (Cruise missiles)

Can be trained to recognize *any* protein (target) made by cell

Direct contact (Hand-to-hand) through T-cell receptor

Anatomy of the Lymphoid system



Immunotherapy: The Perfect Anti-cancer Therapy

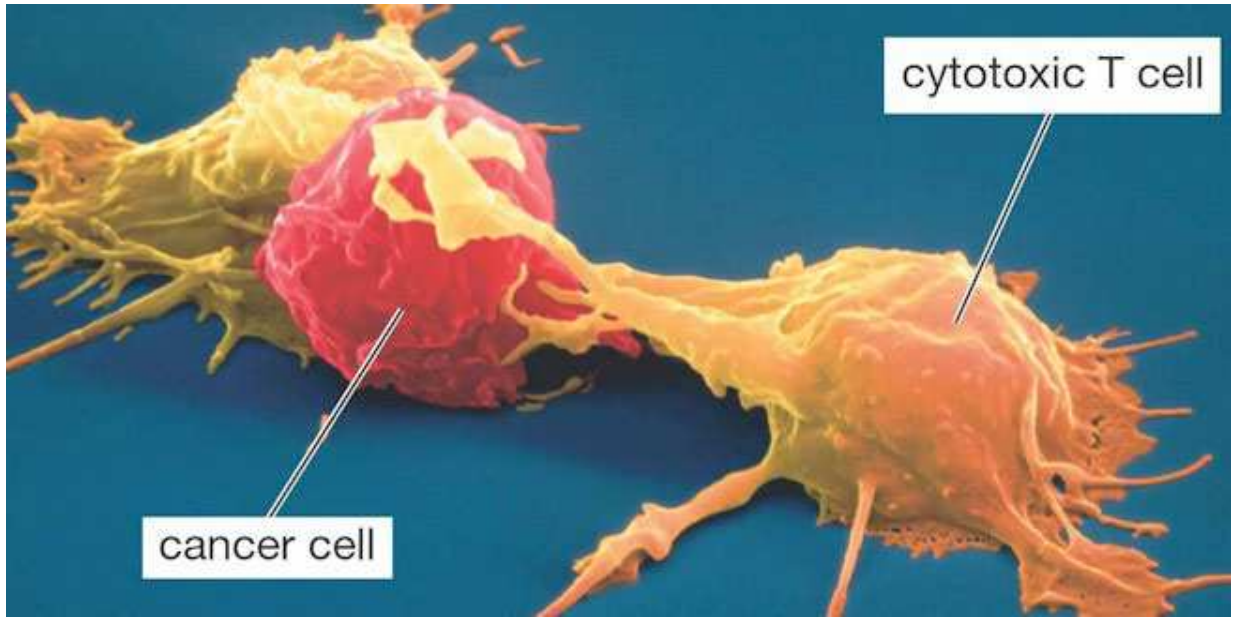
- **Ideal therapeutic should effect only on damaged / diseased cells with no impact on normal cells.**

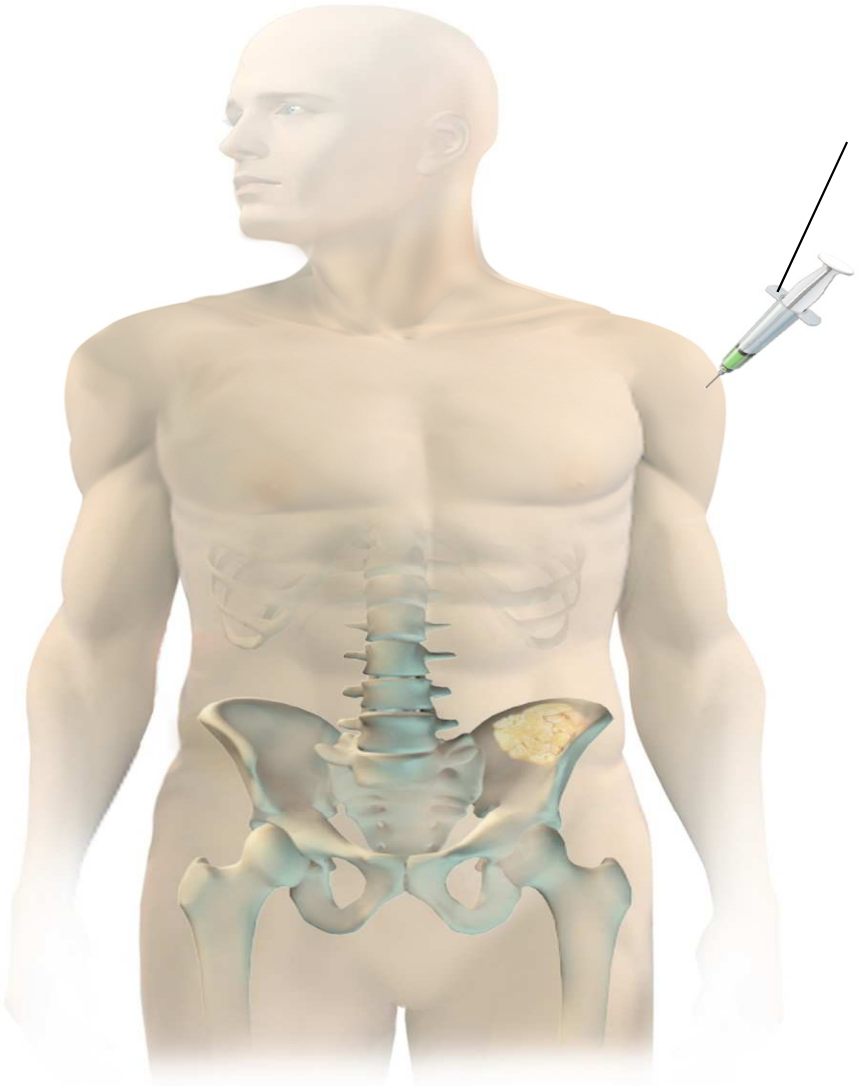
- **Recognition**
  - T-cells 10^{18} unique targets
  - B-cells 10^{22} unique targets

- **Multiple weapons systems**
  NO, H_2O_2, Superoxides, FasL
  Trail, Perforin, Granzyme,
  Phagocytosis, Compliment

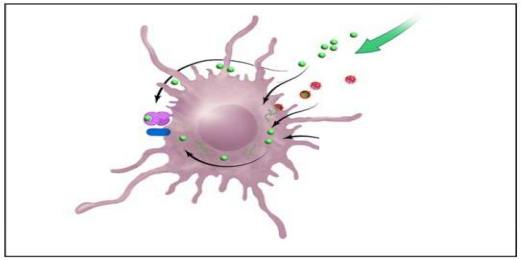
- **Mutations only add targets**

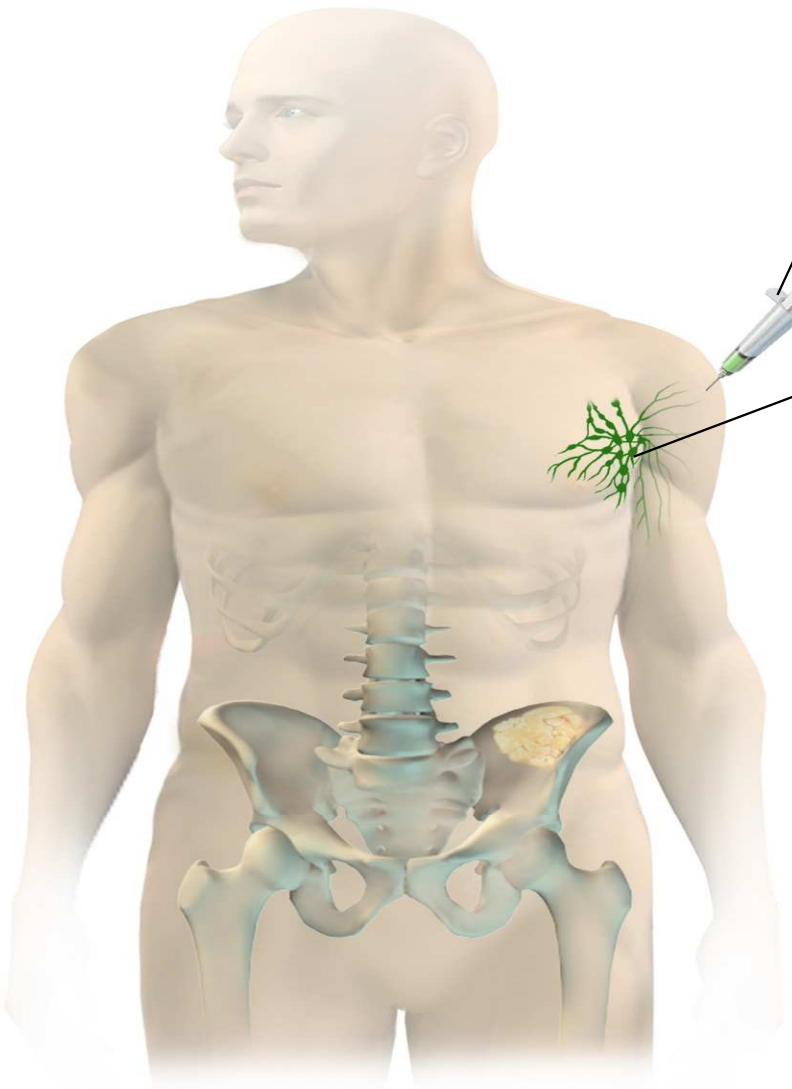
- **Memory response**





1. Antigen presenting cells in skin-Antigen uptake





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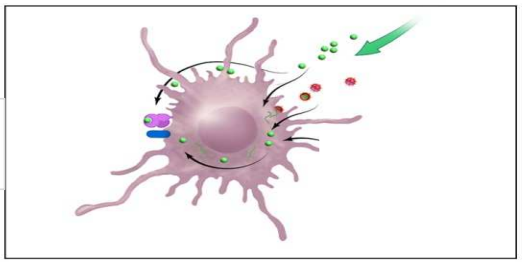
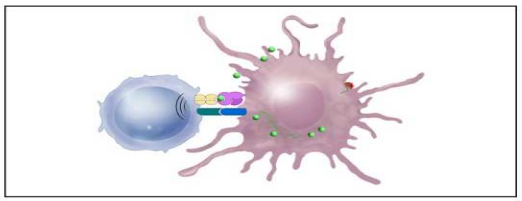
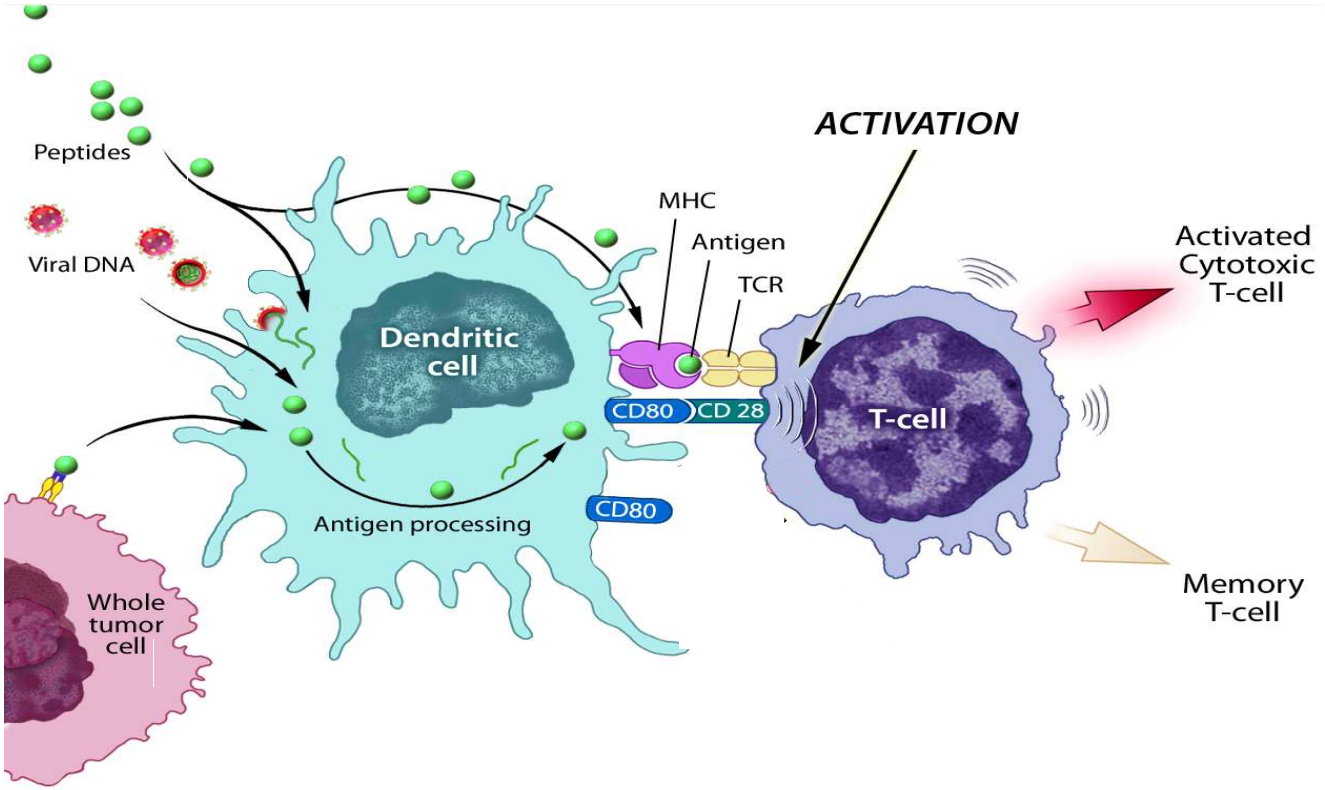


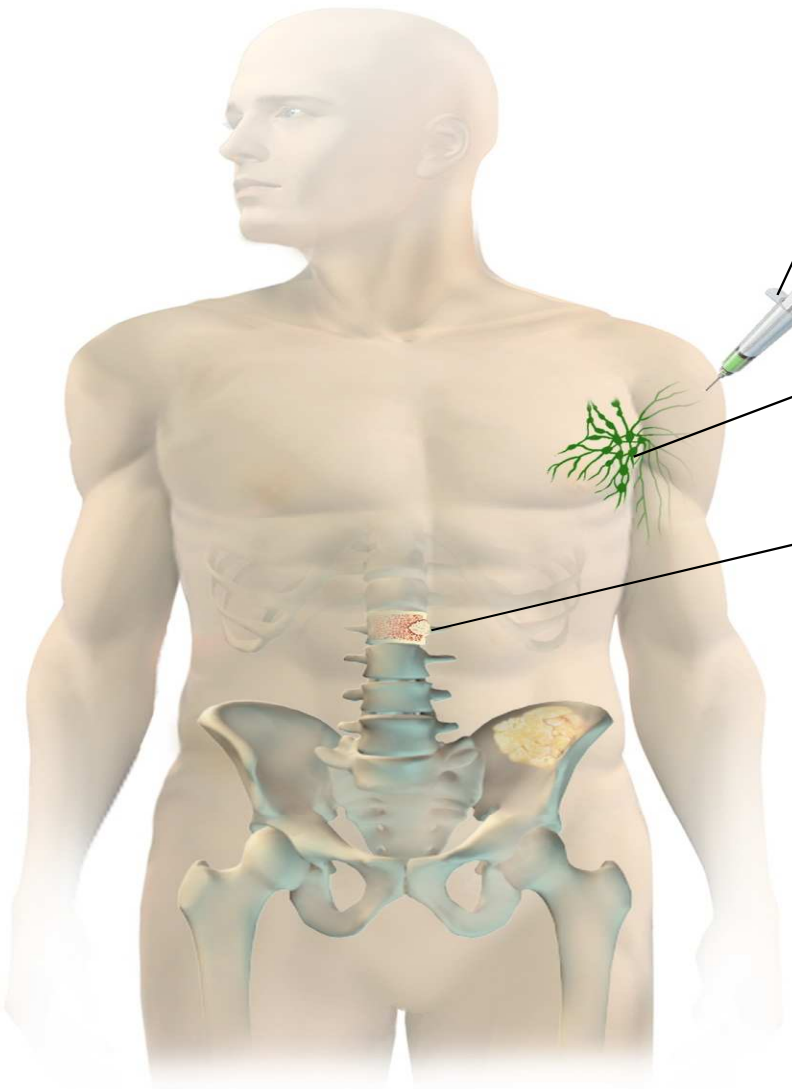
2. Antigen presentation
in lymph nodes



How vaccines activate TAA specific T-cells



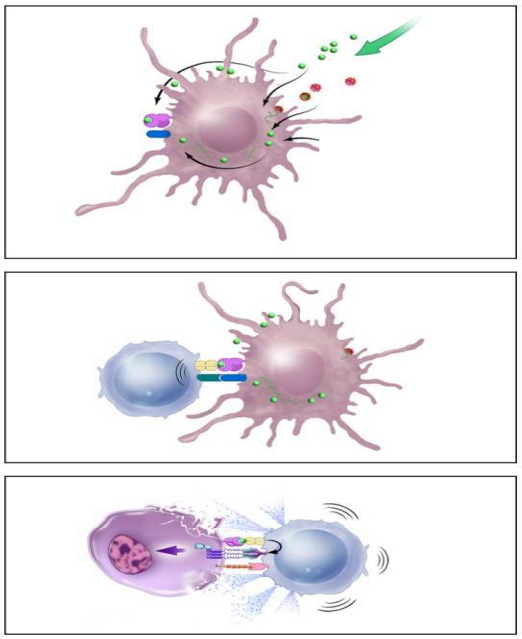
Tarassoff, …Gulley *The Oncologist*, 2006



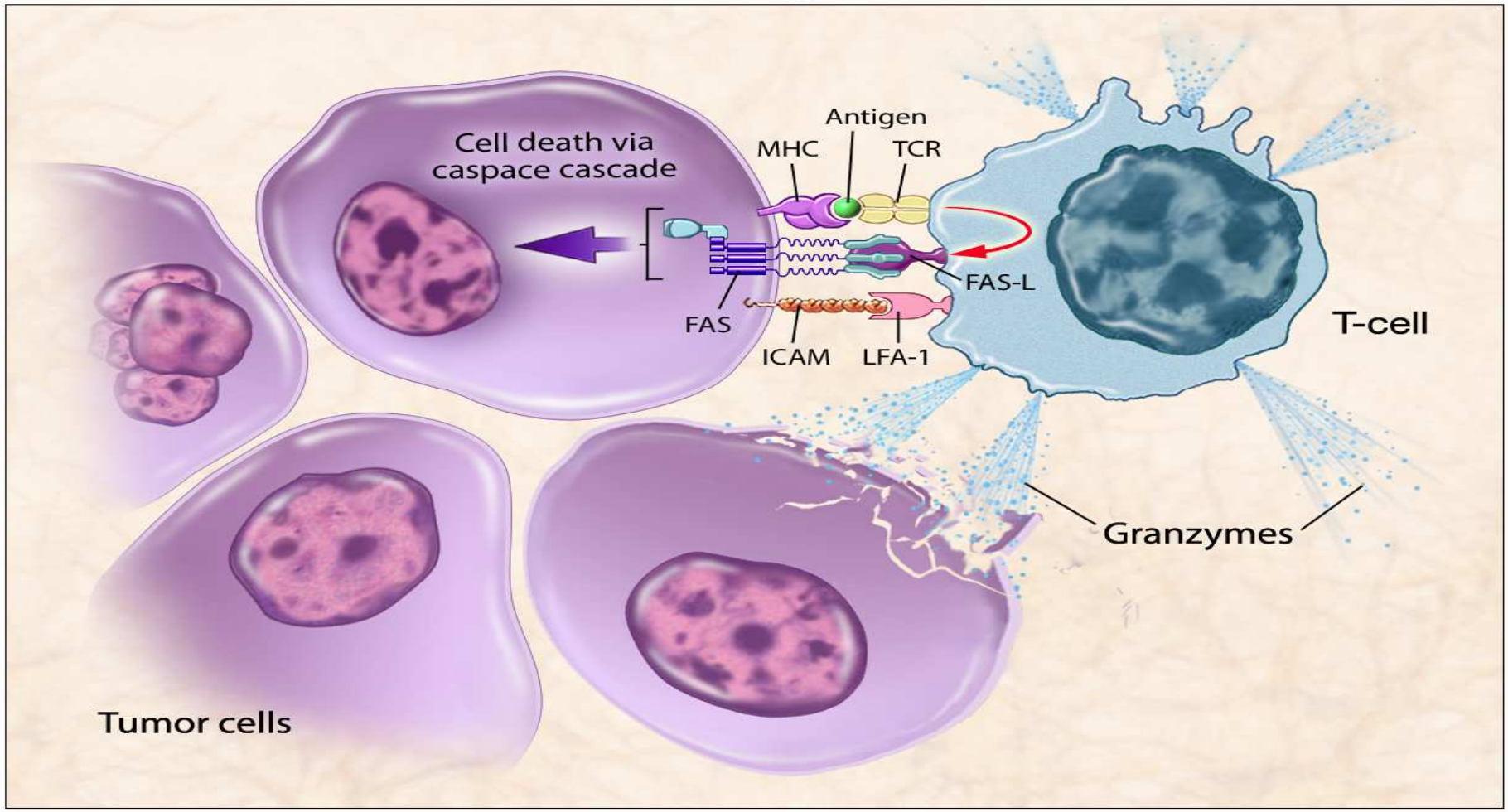
1. Antigen presenting cells in skin-Antigen uptake

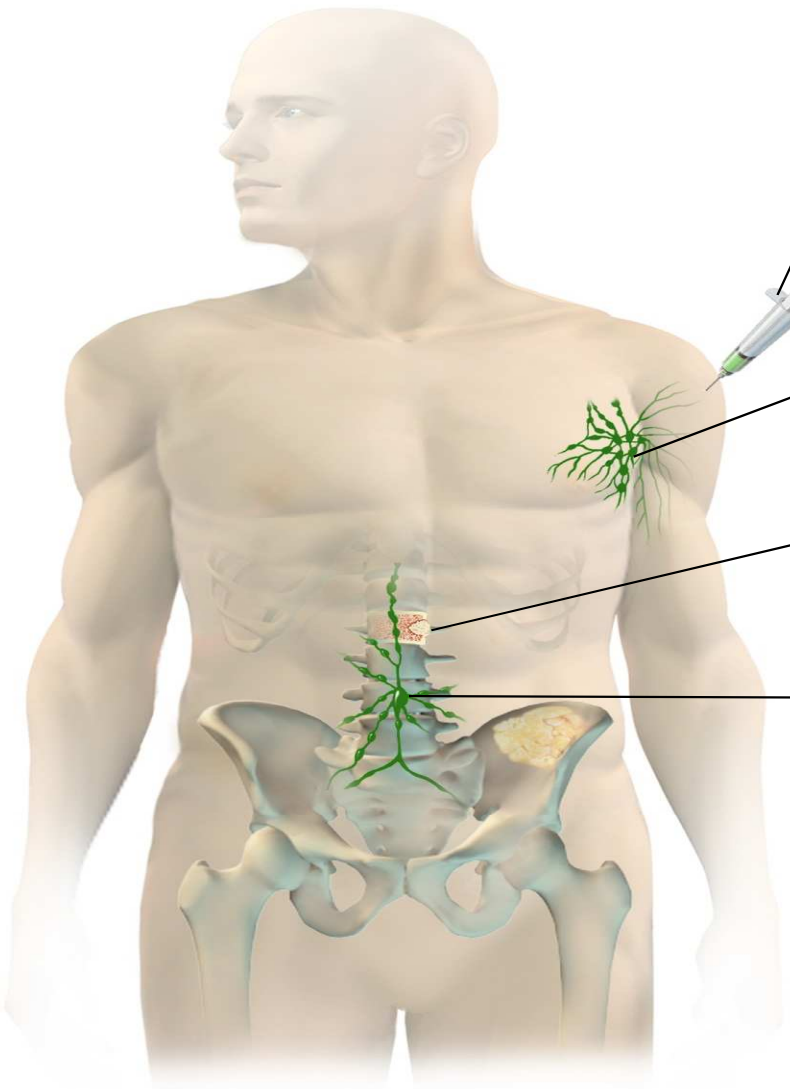
2. Antigen presentation in lymph nodes

3. Tumor attack



T- cell mediated killing of Tumor cells





1. Antigen presenting cells in skin-Antigen uptake

↓

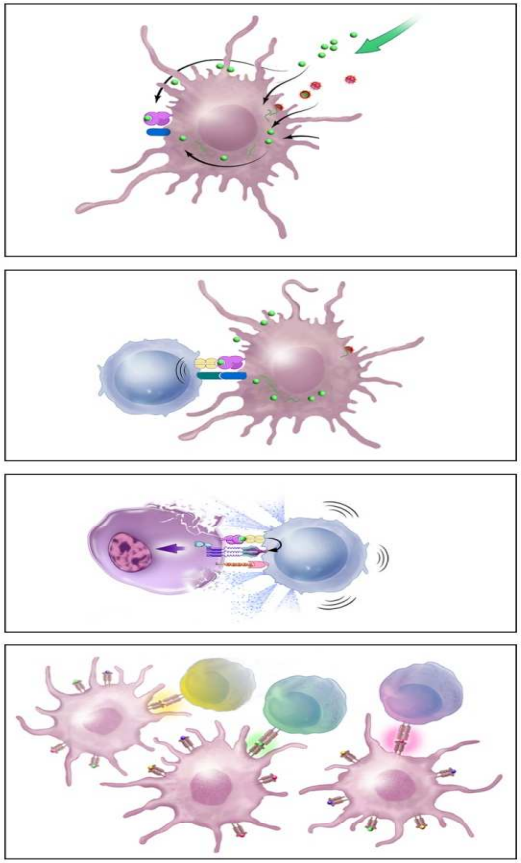
2. Antigen presentation in lymph nodes

↓

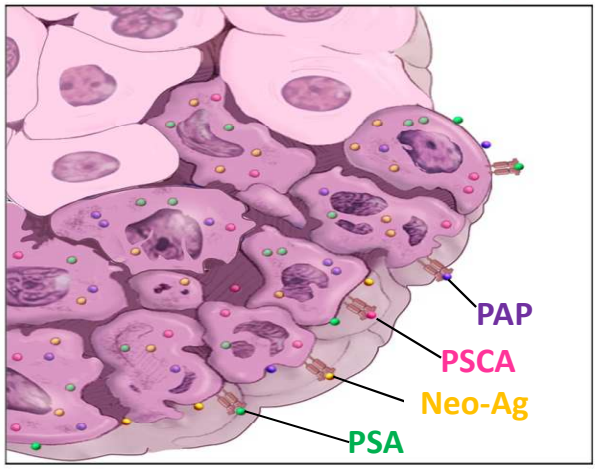
3. Tumor attack

↓

4. Cross-presentation of multiple tumor antigens in draining lymph nodes



A. Degenerating tumor expresses different immunogenic targets



- Spontaneous immune response
- Induced immune response (vaccine, adoptive therapy)

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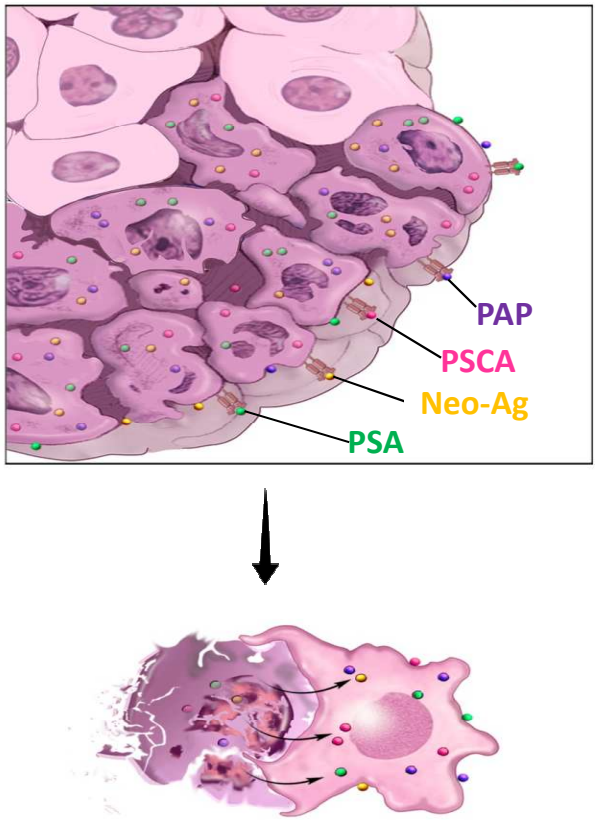

B. Immature dendritic cell phagocytoses dying tumor cell along with a transfer of tumor-specific antigens

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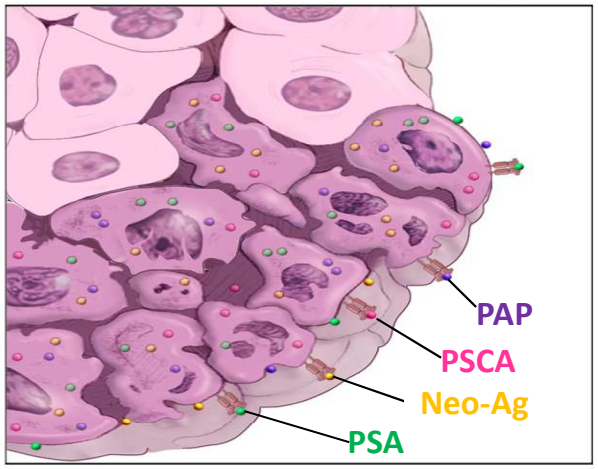

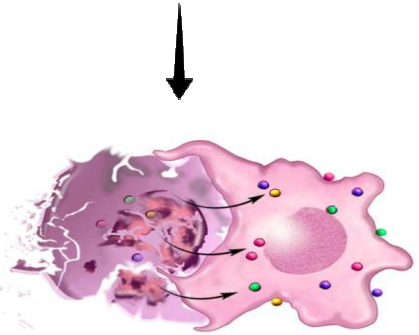

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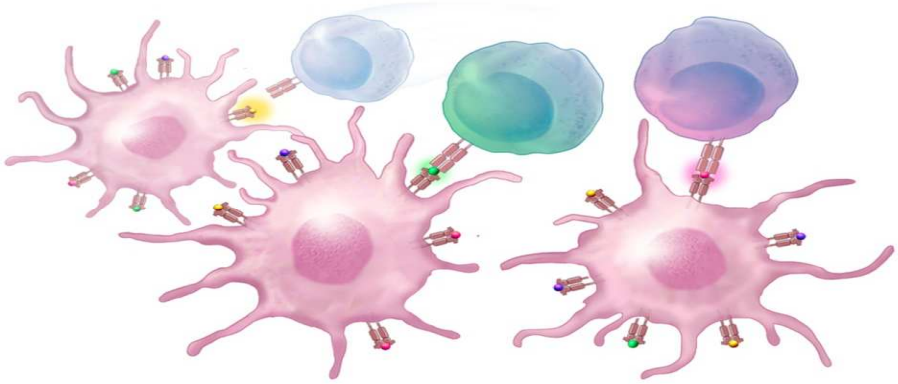

C. Mature dendritic cells present tumor-specific antigens to T-cells

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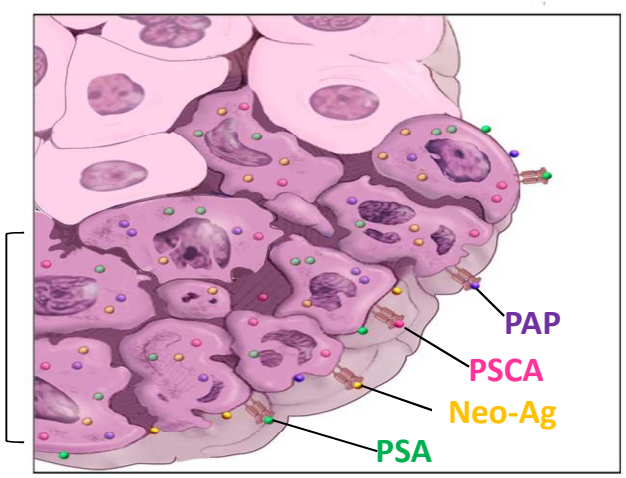

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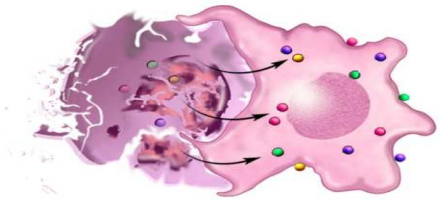

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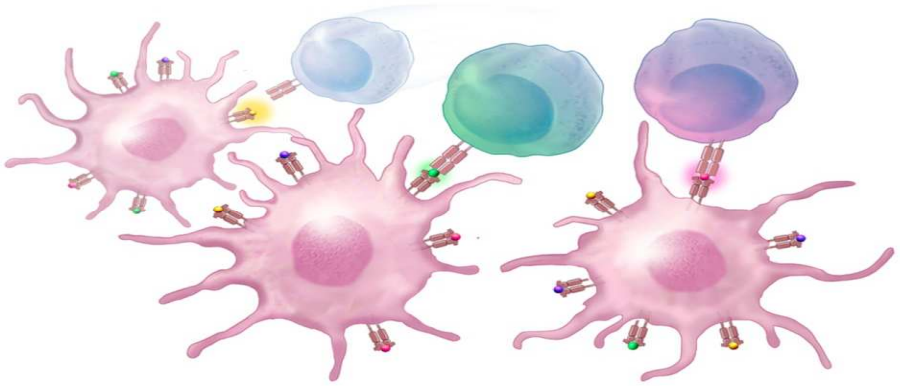
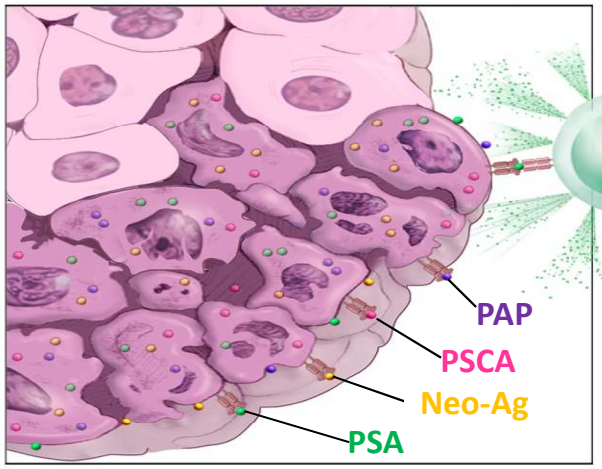


D. Newly activated tumor-specific T-cells form in greater concentration and variation

A. Degenerating tumor expresses different immunogenic targets



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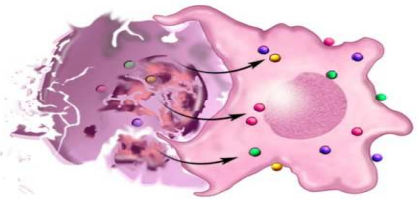

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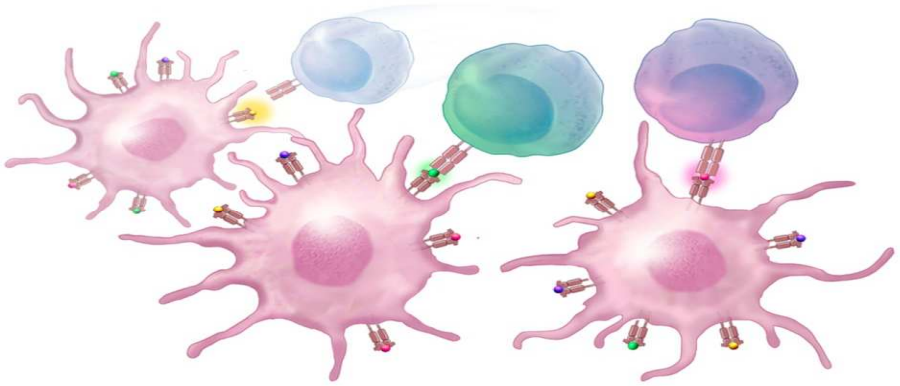
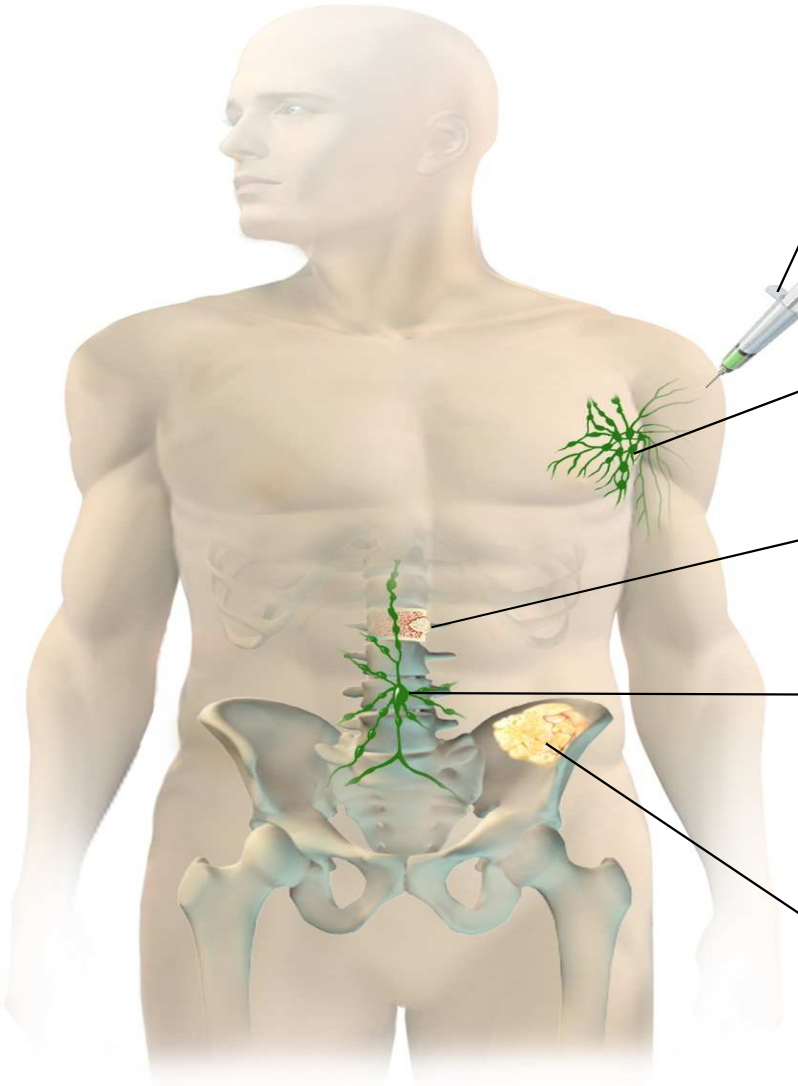


D. Newly activated tumor-specific T-cells form in greater concentration and variation

E. Fully activated T-cell destroys tumor cells



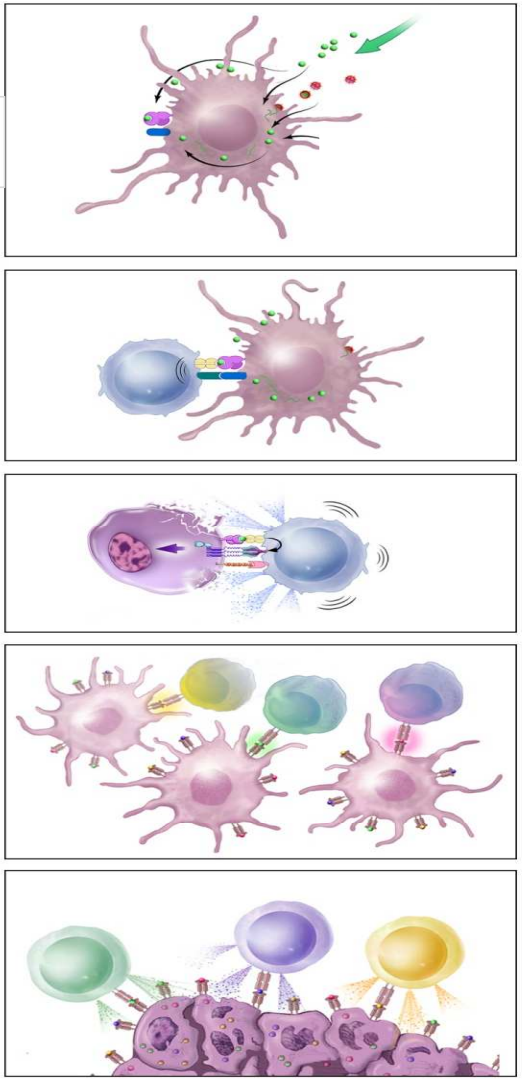
1. Antigen presenting cells in skin-Antigen uptake

2. Antigen presentation in lymph nodes

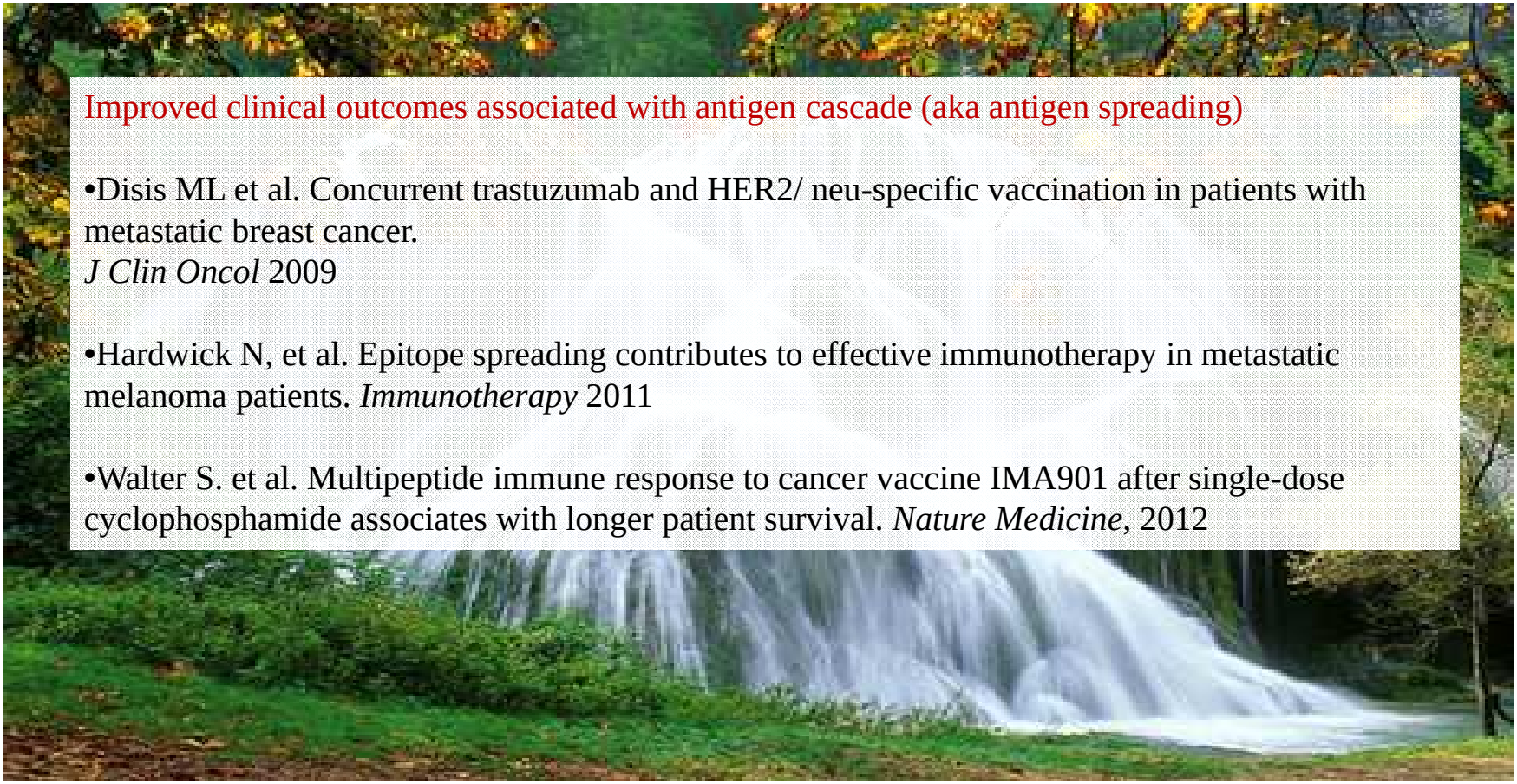
3. Tumor attack

4. Cross-presentation of multiple tumor antigens in draining lymph nodes

5. Broadened immune response/attack at secondary tumor site



Antigen Cascade



Improved clinical outcomes associated with antigen cascade (aka antigen spreading)

•Disis ML et al. Concurrent trastuzumab and HER2/ neu-specific vaccination in patients with metastatic breast cancer.
J Clin Oncol 2009

•Hardwick N, et al. Epitope spreading contributes to effective immunotherapy in metastatic melanoma patients. *Immunotherapy* 2011

•Walter S. et al. Multipeptide immune response to cancer vaccine IMA901 after single-dose cyclophosphamide associates with longer patient survival. *Nature Medicine*, 2012

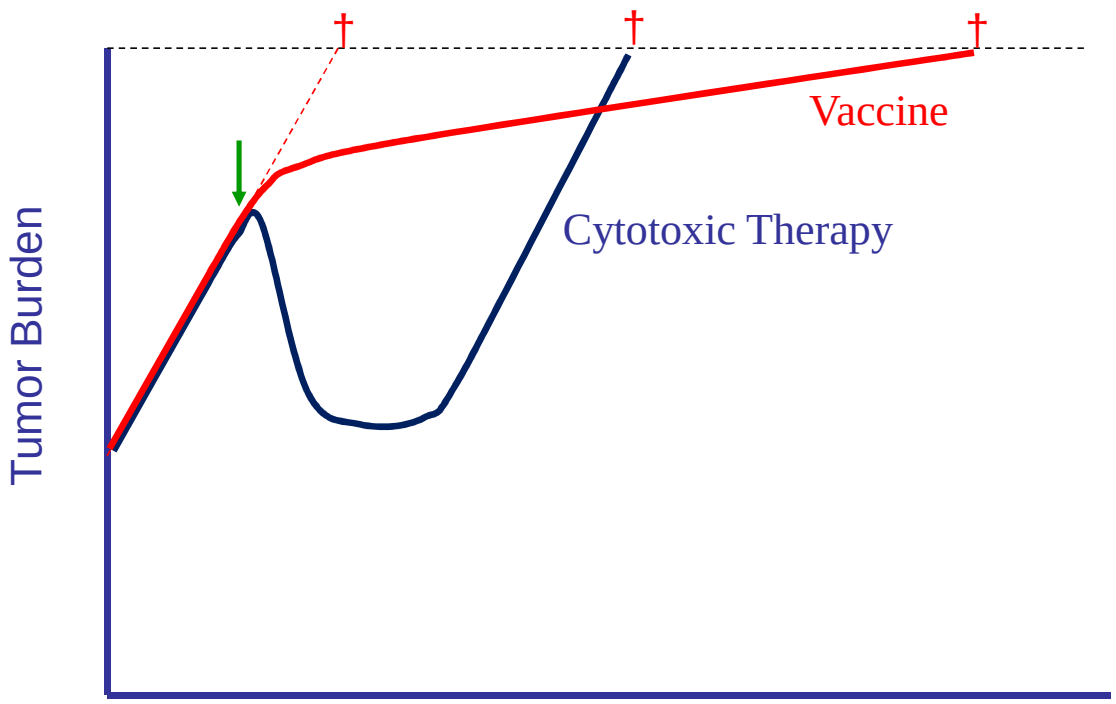
Gulley JL. Therapeutic vaccines: The ultimate personalized therapy? *Hum Vaccin Immunother,* 2012

Immunothearpy vs. Conventional therapy

	Conventional Therapy	Immunotherapy
Target	Tumor or its microenvironment	Immune system
Pharmacodynamics	Often immediate action	Delayed (adaptable, may get better over time)
Memory Response	No	Yes
Tumor Evolution / new mutations	Resistance to therapy	New immunogenic targets
Limitations	Toxicity	Requires adequate immune system function (both systemically and at tumor site)

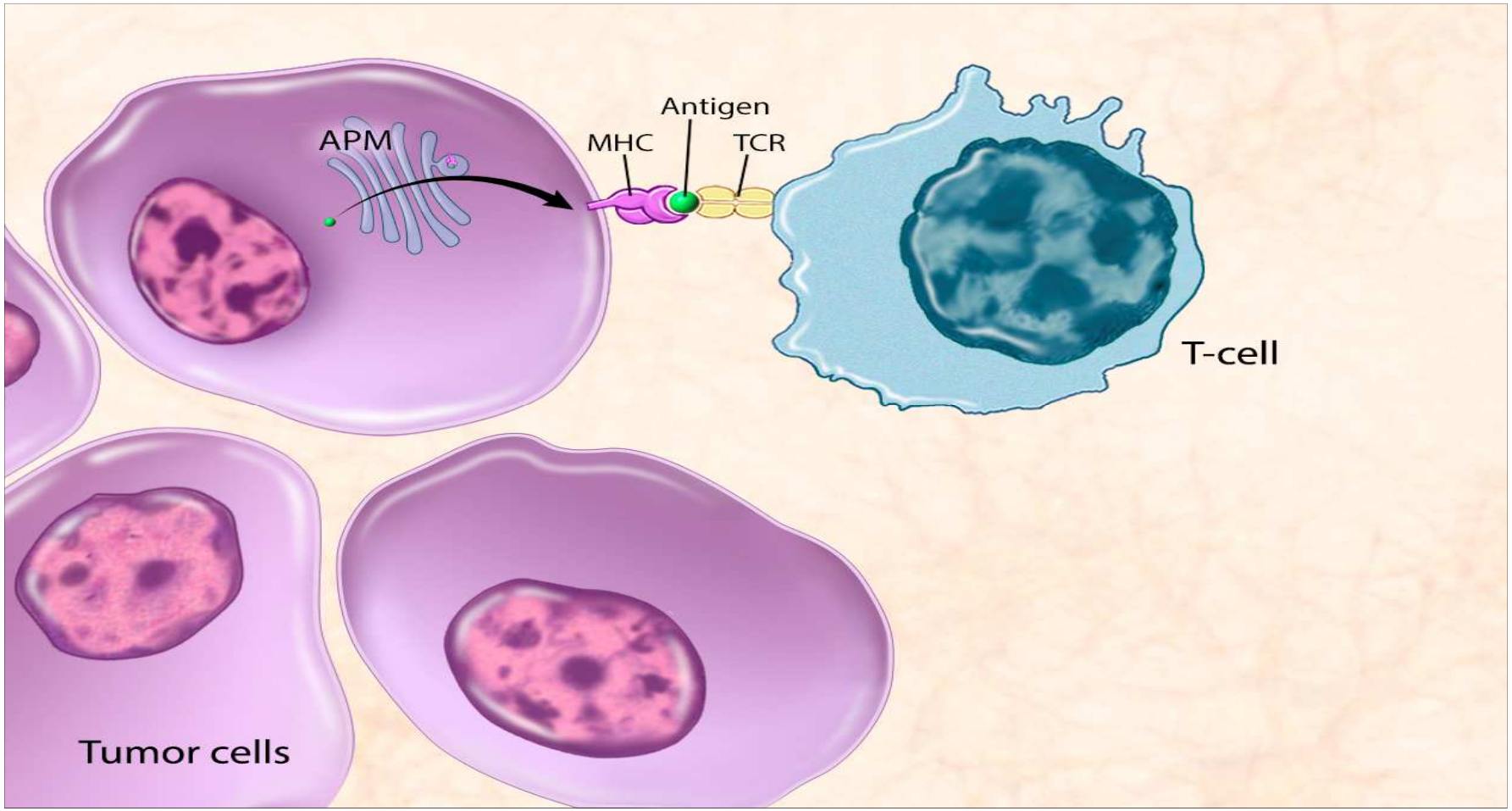
Gulley et al., ASCO Education Book, 2013

Tumor Growth Rate

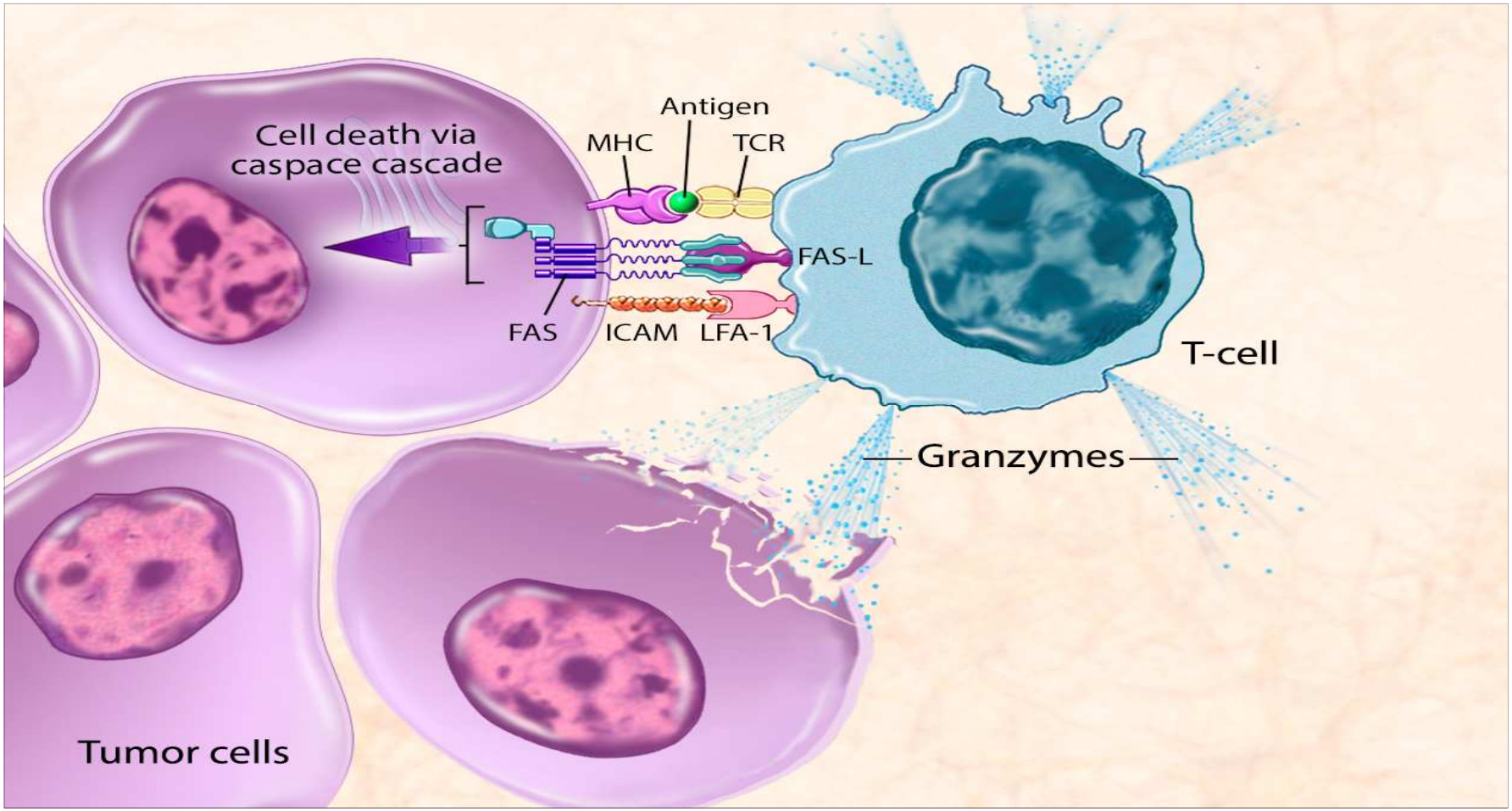


Stein W, et al. *Clin Ca Res*, 2011
Madan RA, *Oncologist*, 2011

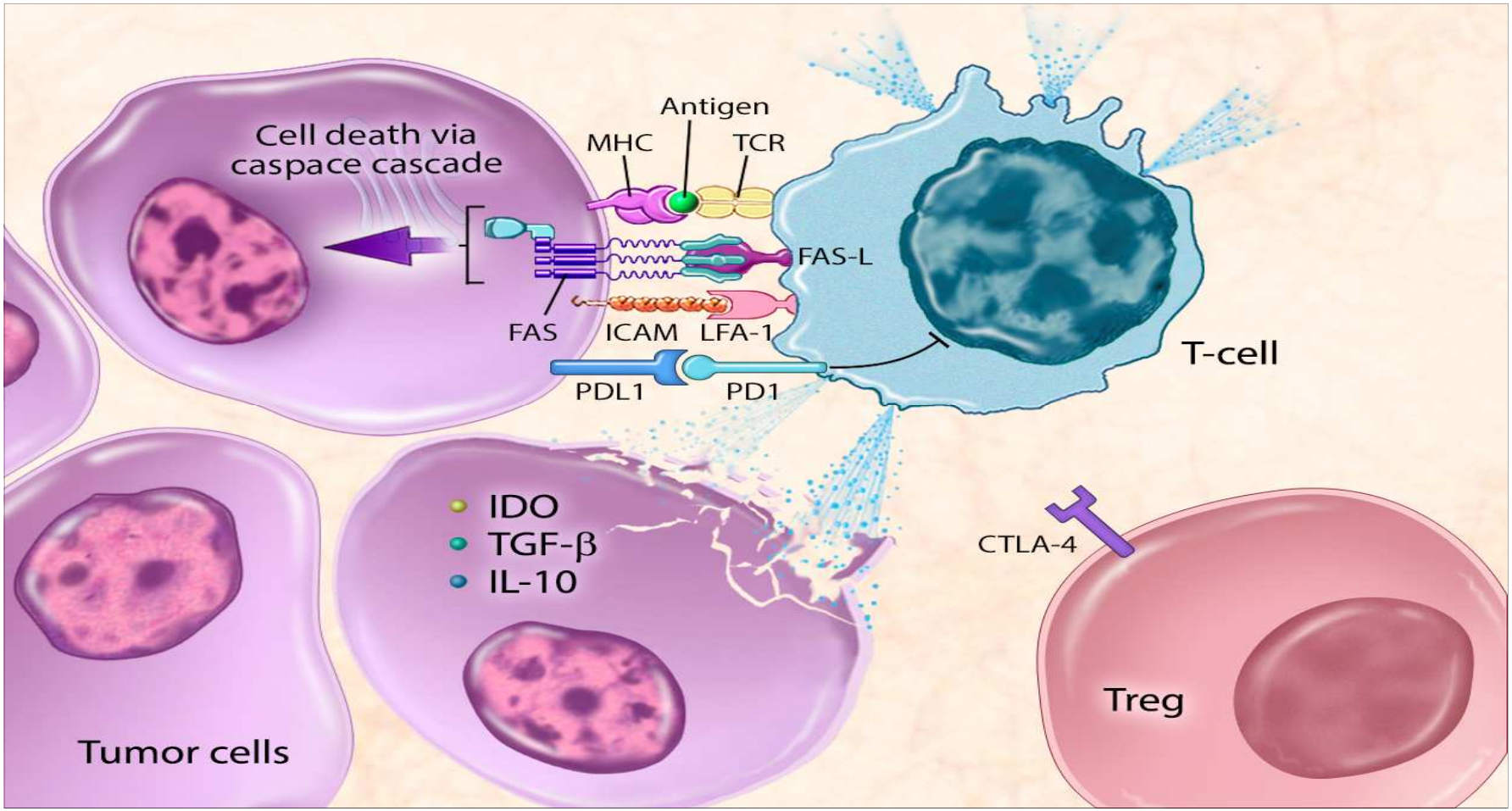
T cell recognition of tumor cell



T cell function at tumor cell: to kill

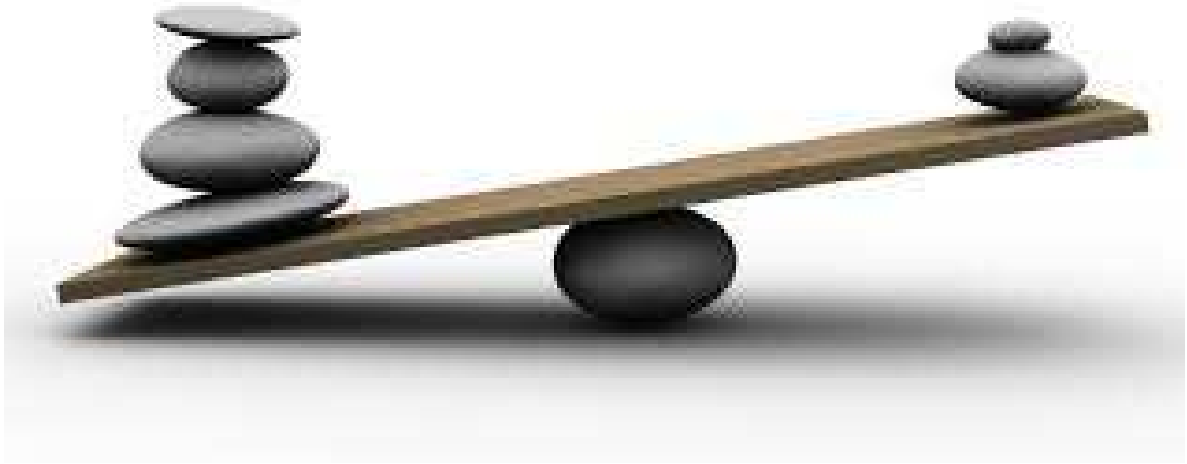


T cell function at tumor cell: or not to kill

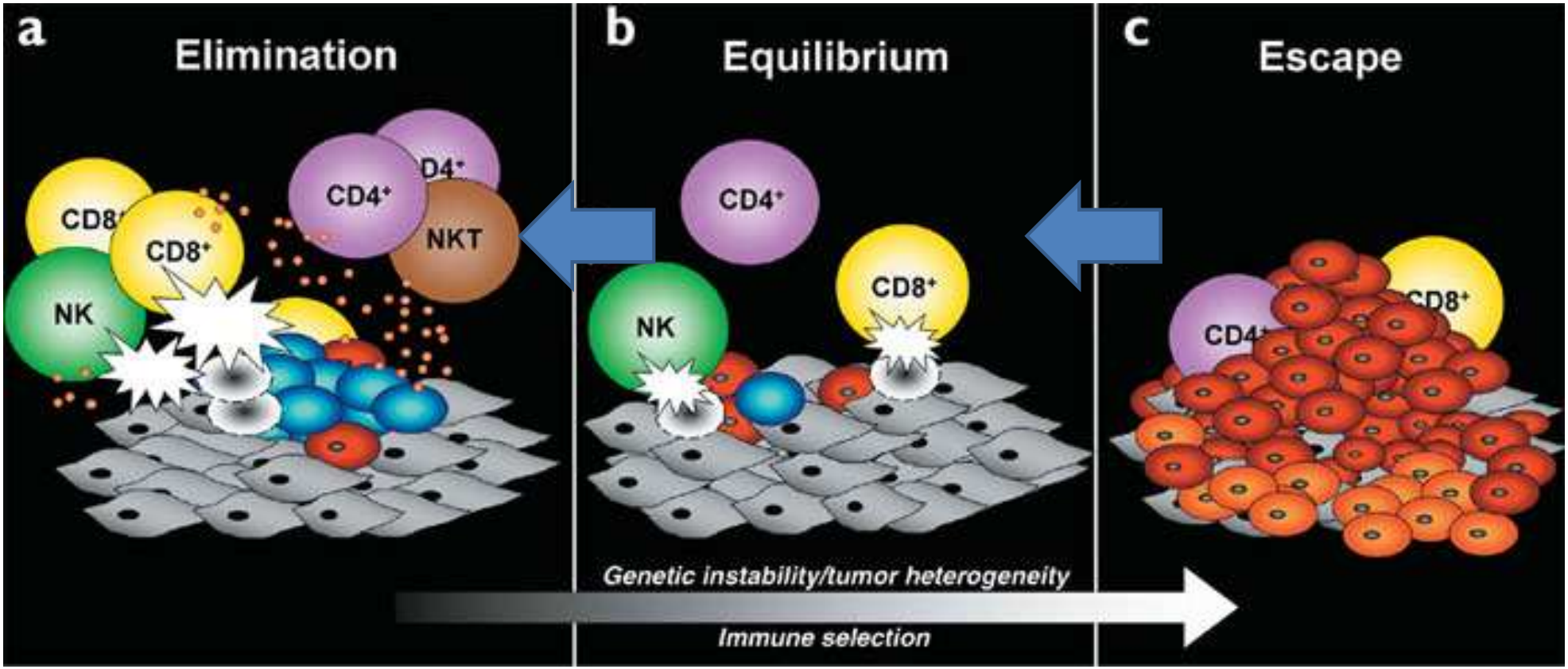


Balance in Immune System Activation

- Too little: cancer
- Too much: autoimmunity



3 E's

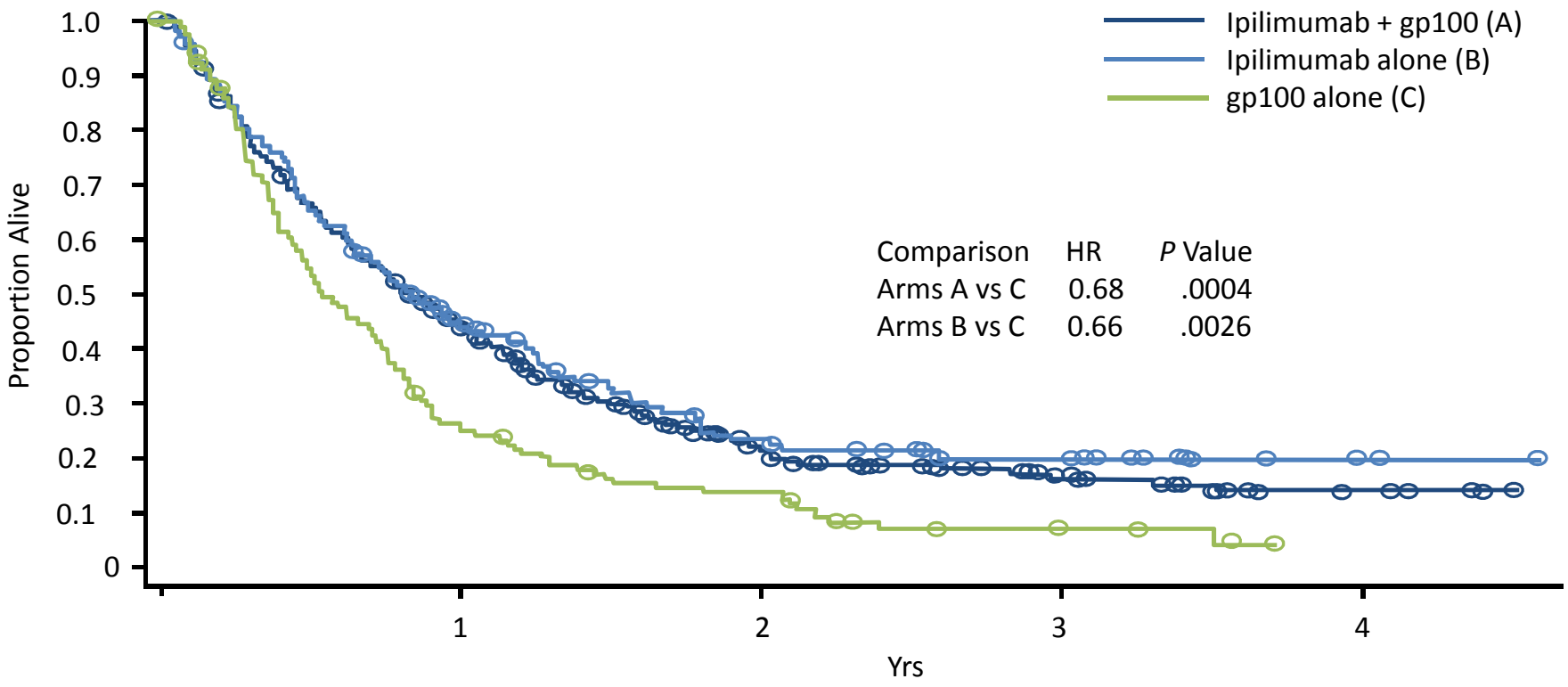

a
Elimination
CD4+
NKT
CD8+
NK
b
Equilibrium
CD4+
CD8+
NK
c
Escape
CD8+
Genetic instability/tumor heterogeneity
Immune selection

Therapies

- Steering
  - Therapeutic Vaccines (Sipuleucel-T TVEC)
  - Adoptive Cellular Therapy (CAR-T)
- Brakes / Gas
  - Cytokines (IL-2, GM-CSF, IFN)
  - Immune Checkpoint Modulators (Ipilimumab, nivolumab, pebrolizumab)

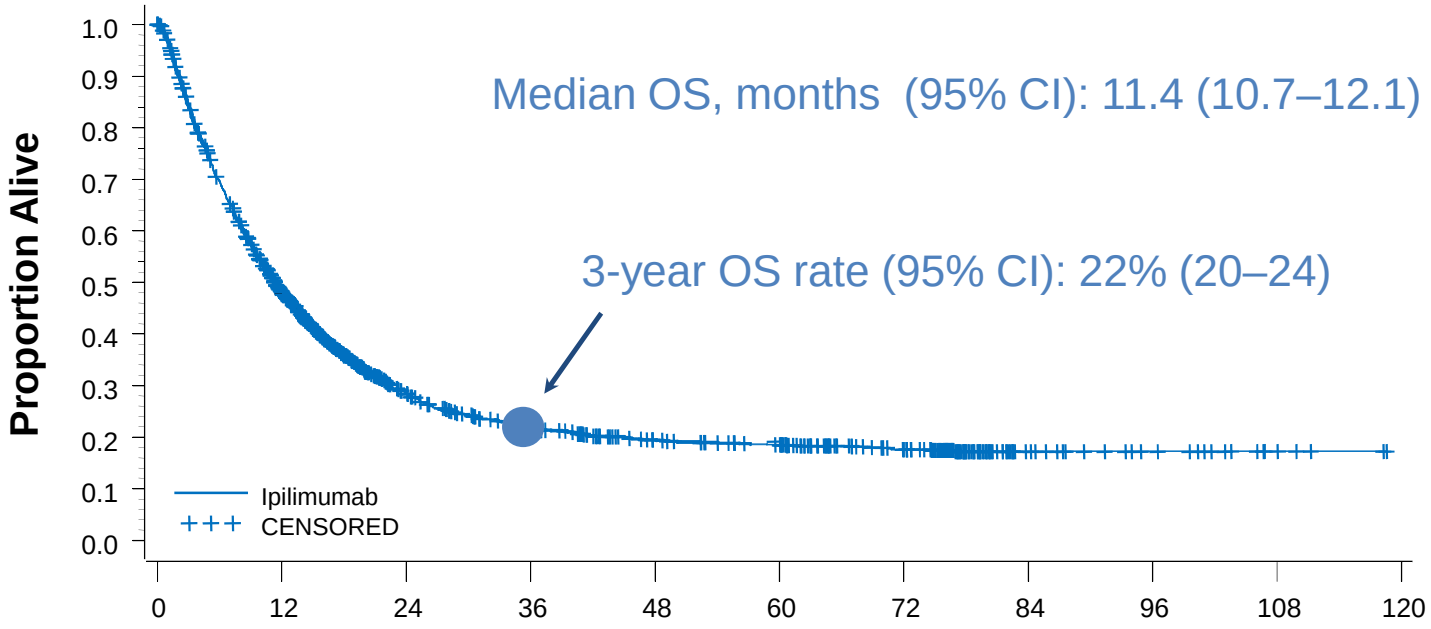
FDA approval

Ipilimumab in Advanced Melanoma: Overall Survival



Hodi FS, et al. N Engl J Med. 2010;363:711-723.

Pooled OS Data from PhII + PhIII Trials of Anti-CTLA4 in Metastatic Melanoma: 1861 Patients



Patients at Risk

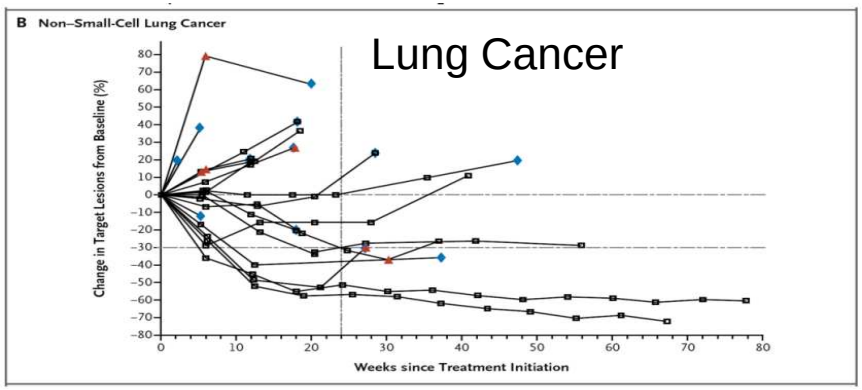
Ipilimumab	1861	839	370	254	192	170	120	26	15	5	0

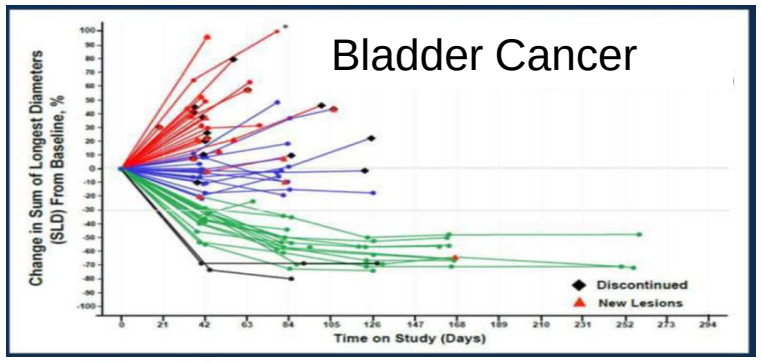
Schadendorf et al., ESMO 2013

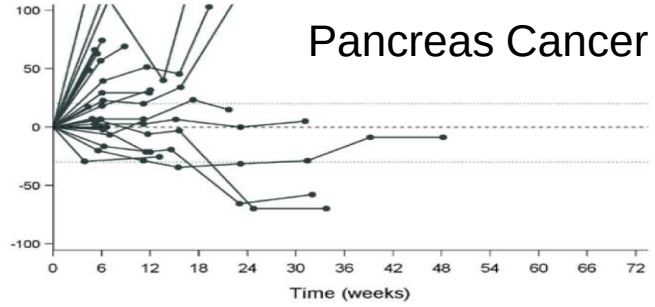
Immune response capable of being:

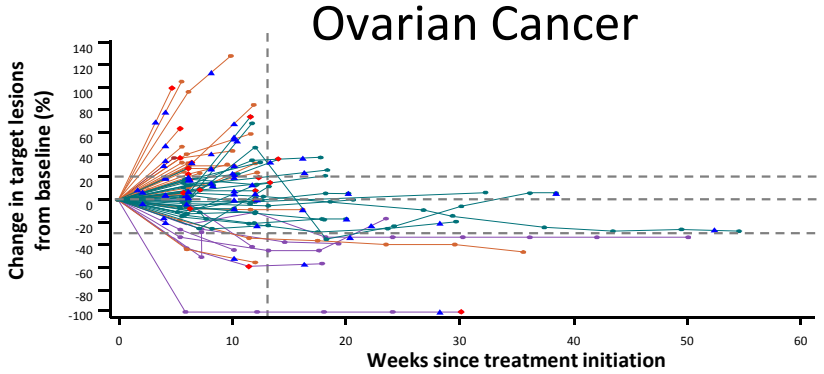
- Rapid
- Durable
- Self propagating
- Adaptable

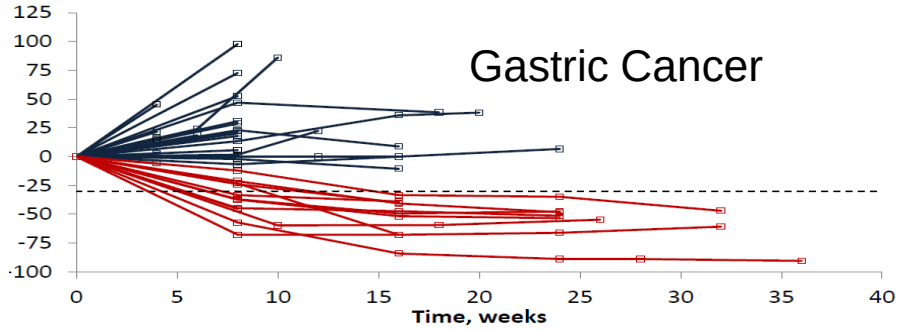
anti-PD1 or anti-PD-L1

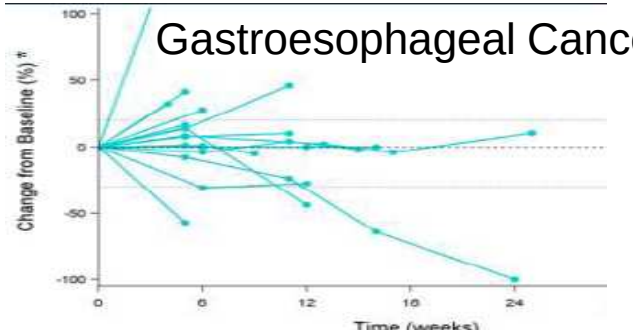












Modified from a Slide Courtesy of “Mac” Cheever

Avelumab, an anti-PDL1 antibody (EMD Serono / Pfizer)

PR in metastatic clear cell

Baseline: 69 mm RLL lesion

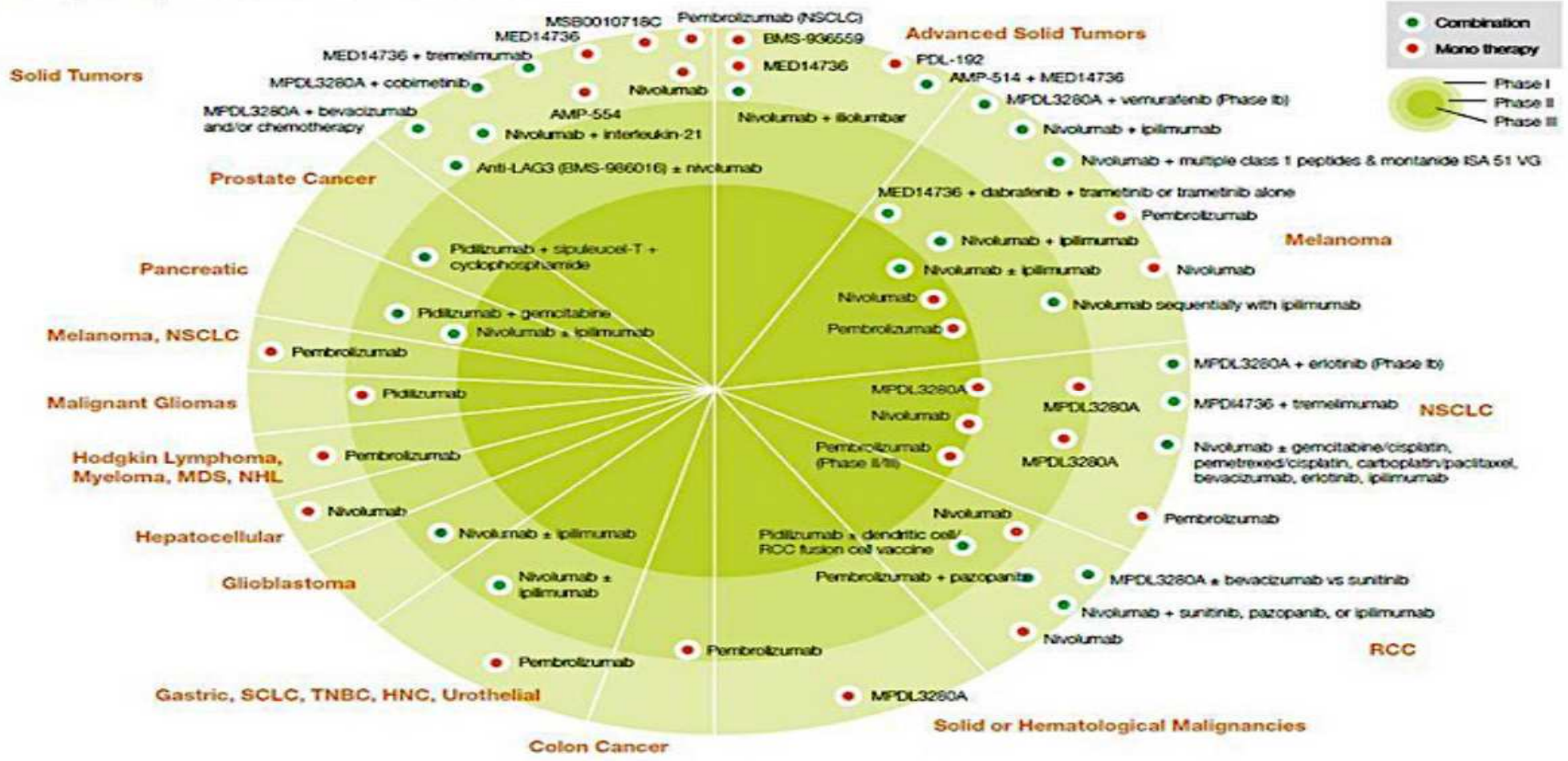
Week 25: 41 mm (-40.6%)

- 65 years old; 6 prior lines for metastatic disease
- 4th assessment cycle, still on treatment
- Safety: well tolerated (grade 1-2 rigors; grade 1 flu-like symptoms and fatigue)
- PR by RECIST ongoing at time of analysis

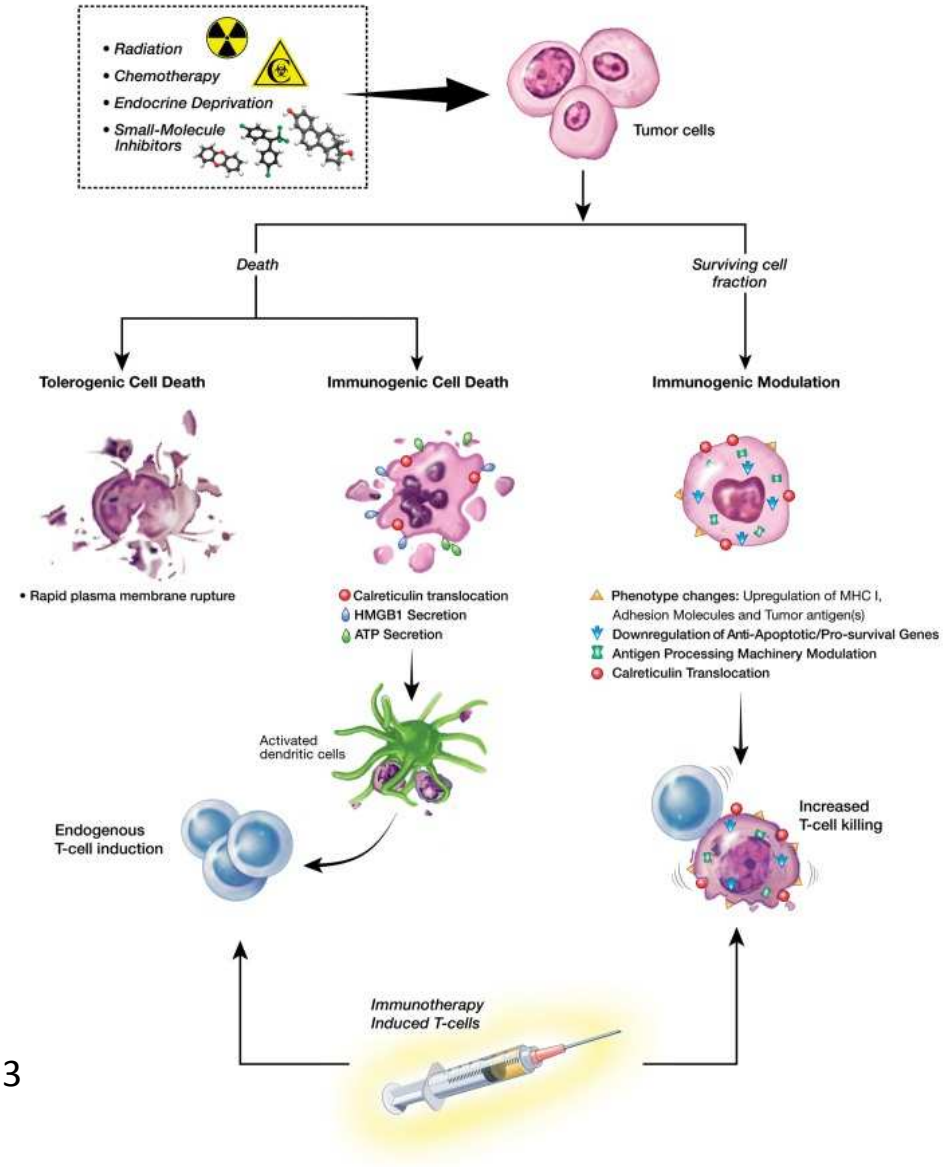
Courtesy of Dr. S. Ejadi, Scotsdale, AZ

Presented By Mary Disis at 2015 ASCO Annual Meeting

Summary: Pipeline radar chart

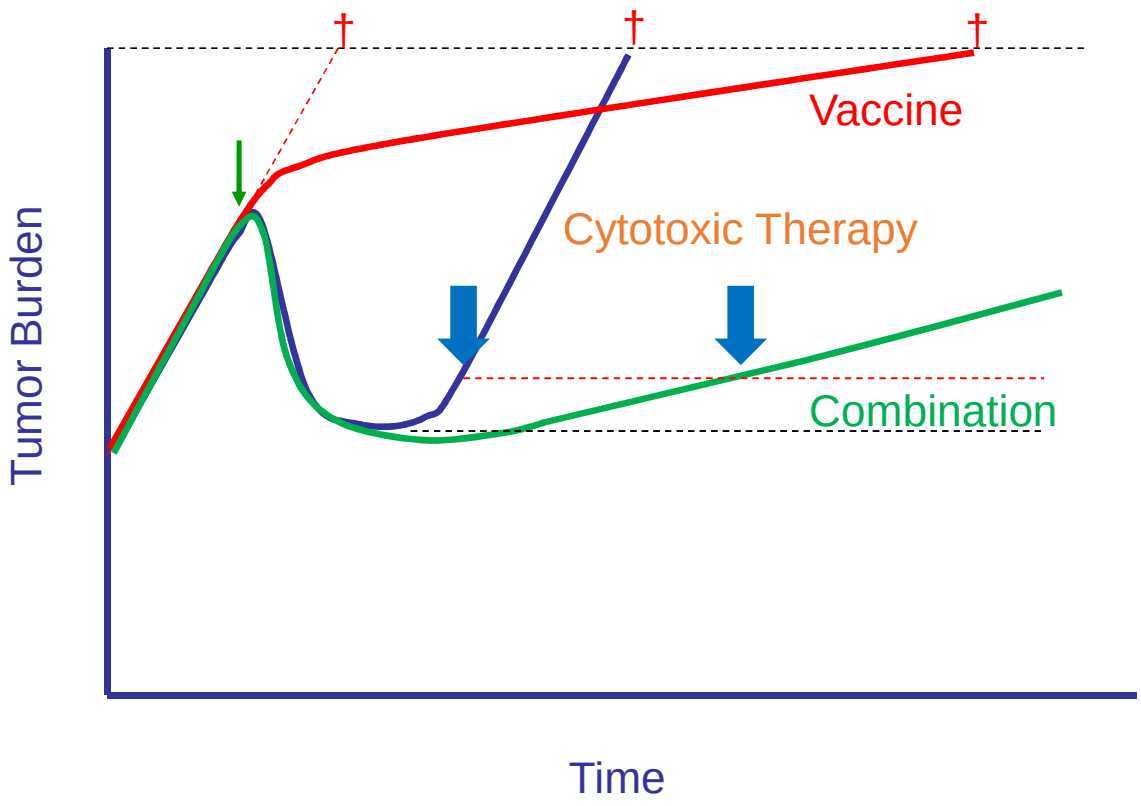


Source: @PDRennart, pic.twitter.com/pg9UtTNfHX June 2015

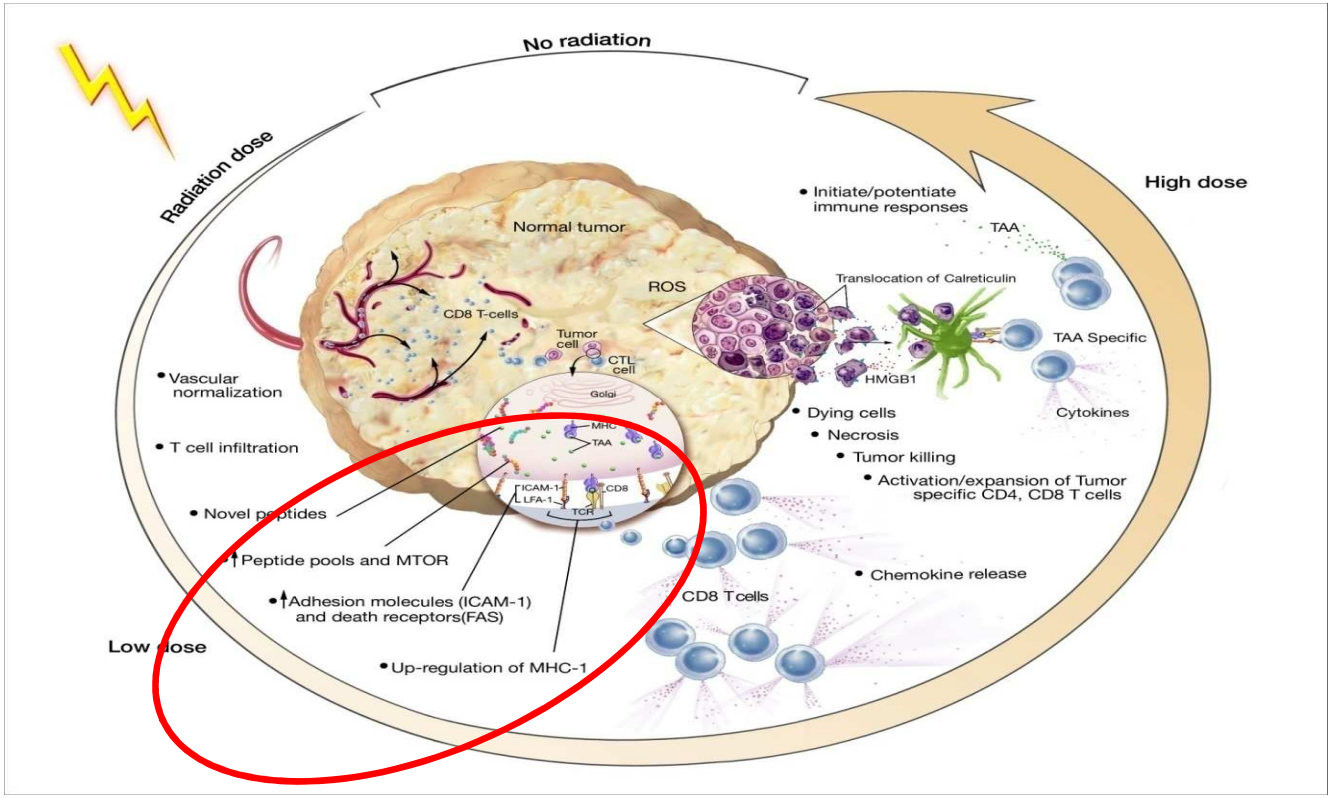


Hodge et al., OncoImmunology, 2013

Growth Rates with Combination Therapy

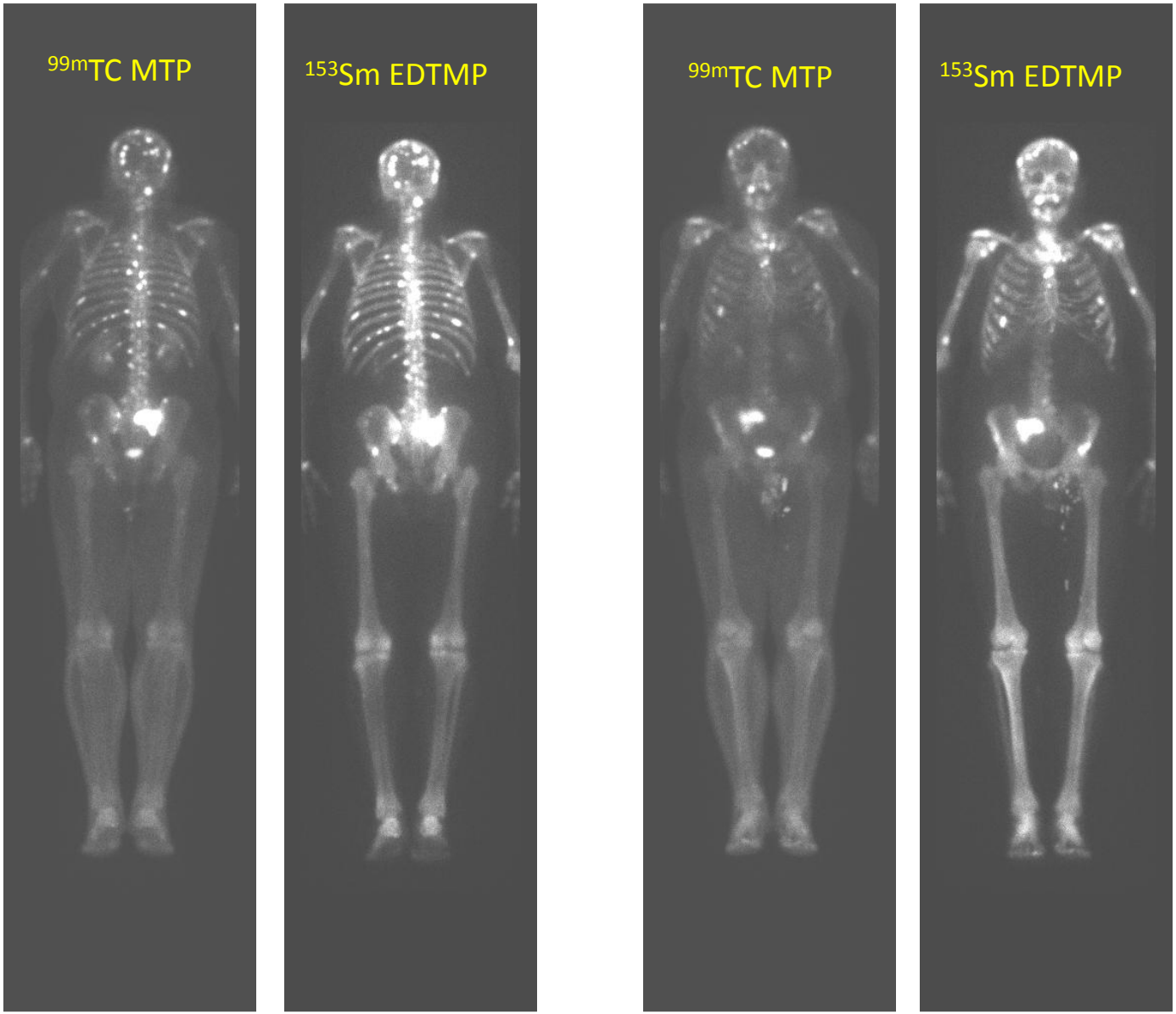


Potential Multiple Effects of Local Irradiation of Tumors



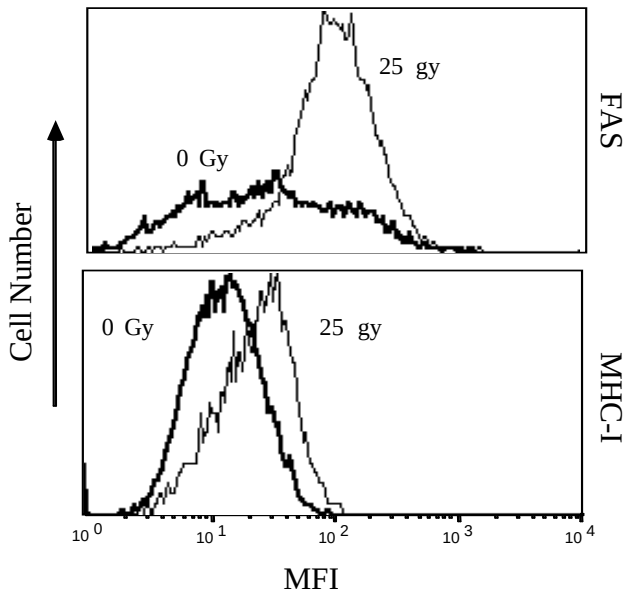
May facilitate broader immune response - antigen spreading

Hodge …Gulley et al., Oncology 22:1064-70.


^{99m}TC MTP
^{153}Sm EDTMP
^{99m}TC MTP
^{153}Sm EDTMP

Treatment of LnCaP Prostate Cells with Palliative Levels of ^{153}Sm (Quadramet) Modulates Phenotype, Upregulates TAA, and Increases Sensitivity to Antigen-specific CTL Killing

Treatment of LnCaP prostate cancer cells with palliative doses of ^{153}Sm results in the upregulation of MHC class I and Fas

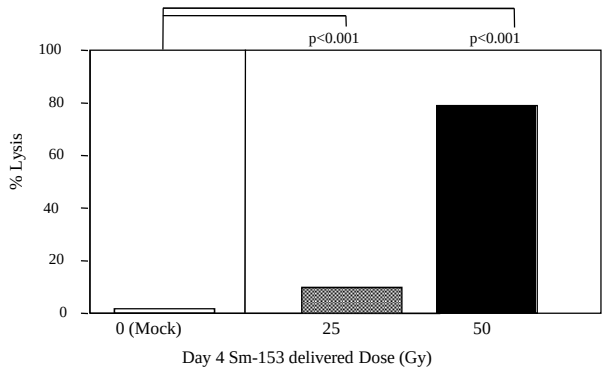


Chakraborty, Wansley…Schlom, Hodge, NCI. Clin Cancer Res. 2008
Collaboration with Nuclear Medicine Branch

Treatment of LnCaP prostate cancer cells with palliative doses of ^{153}Sm results in the upregulation of TAAs

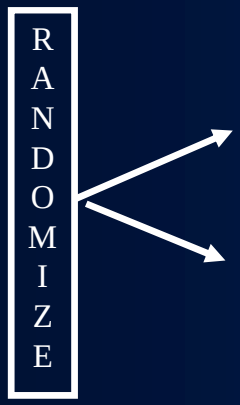
	0 G y	25 G y
PS A	1	2.7 9
PSM A	1	4.14
P A P	1	29.0
CE A	1	10.3
MUC -1	1	3.67

Treatment of LnCaP prostate cancer cells with palliative doses of ^{153}Sm results in increased sensitivity to multiple CTLs



^{153}Sm +/- PSA-TRICOM

Patient Population: CRPC Metastatic to bone



Arm A: PSA-TRICOM + ^{153}Sm (n=34)

Arm B: ^{153}Sm (n=34)

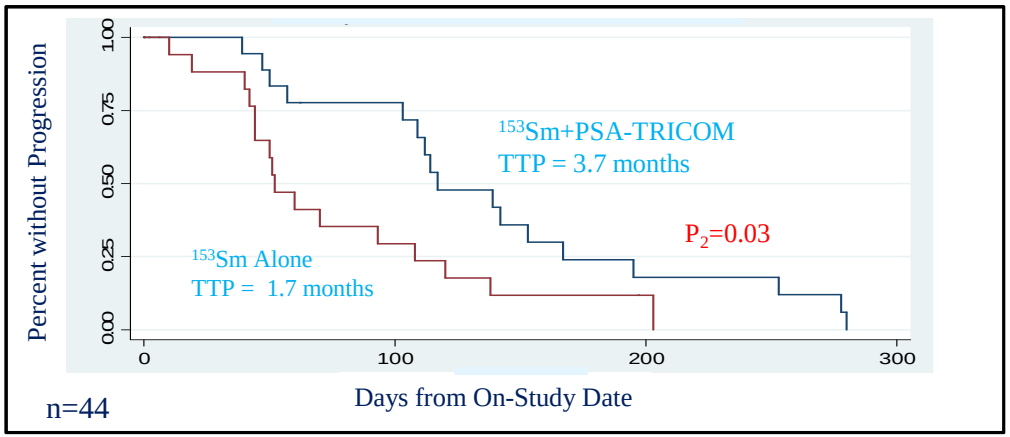
Vaccine: rV-PSA/TRICOM s.c. d 1
rF-PSA/TRICOM s.c. d 15, 29, q 4 wks

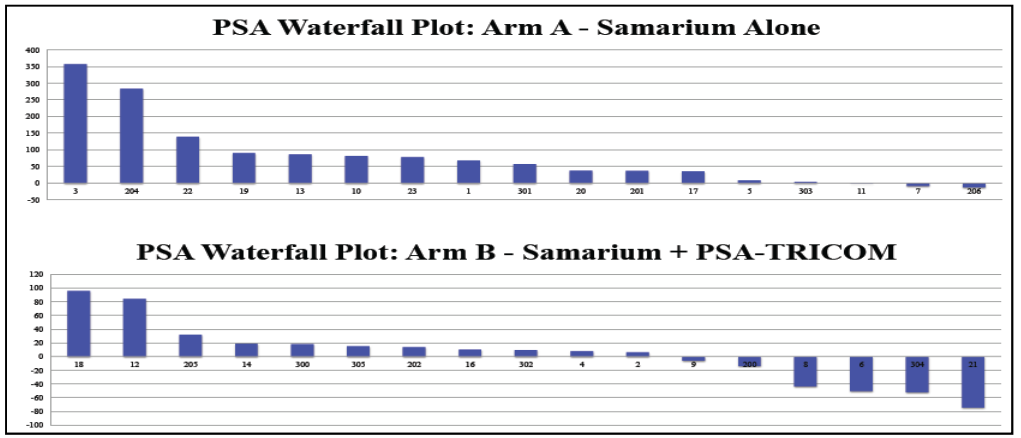
^{153}Sm: 1 mCi/kg d 8, may be repeated
q 12 wks upon hematologic recovery.

NCT00450619; PI Gulley
CINJ (DiPaola) and UC (Stadler)

^{153}Sm +/- PSA-TRICOM: Prolonged PFS and Favorable PSA Response Profile

- Final data of n = 44 patients with mCRPC
- 1° endpoint: PFS
- Progression defined by utilizing PCWG, but not PSA criteria

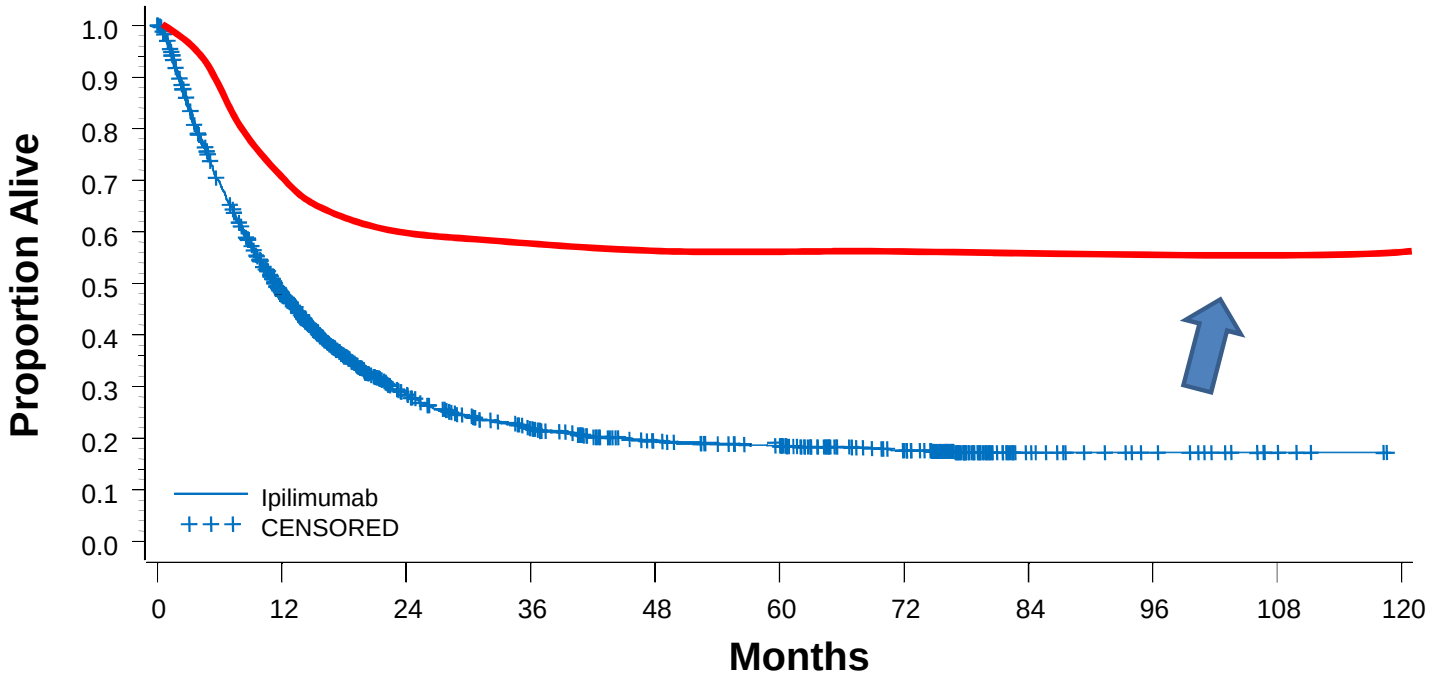




PCWG = Prostate Cancer Working Group response criteria

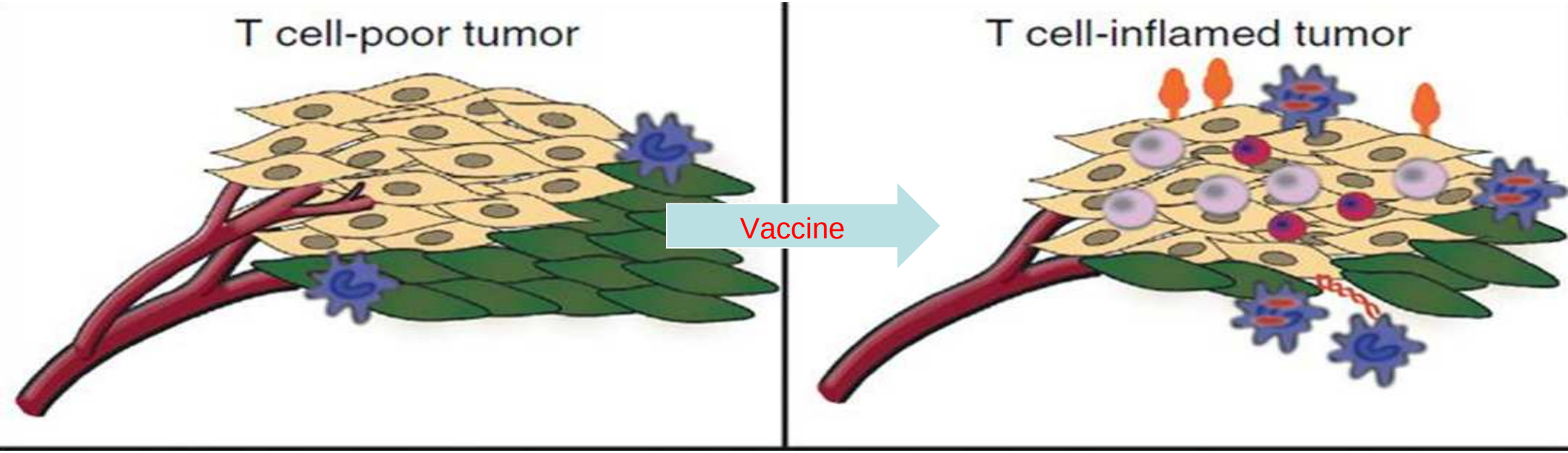
Heery…Gulley ASCO GU 2013

Immunogenic Intensification



Schadendorf et al., ESMO 2013

Effect of Vaccination on Tumor PD-L1 Expression

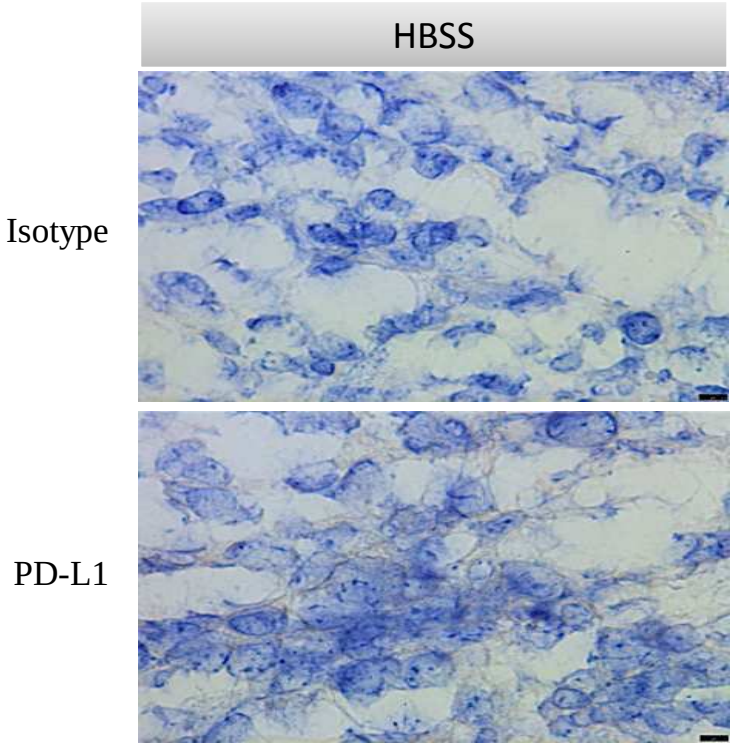


No anti-tumor immune response
for ICM to unleash

ICM can unlock / unleash ineffective
underlying immune response

Gajewski T et al. Current Opinion in Immunology, 25, 1-9 2013

Effect of Vaccination on Tumor PD-L1 Expression



Similar results with LLC lung carcinoma cells

Conclusions

Key Points

- Immunotherapy is powerful and can lead to durable, adaptable responses.
- Therapeutic Vaccines and Immune Checkpoint Modulators have been FDA approved for indications such as Prostate Cancer, Melanoma and Lung Cancer with multiple other indications under late stage investigation
- Immunotherapy can be combined with other therapies (vaccines with immune checkpoint inhibitors)

Lessons Learned

- Immunotherapy may take time to generate clinically meaningful responses
- Patients with an underlying immune response may benefit best from immune checkpoint modulators

Potential Impact on the Field

- Could be that in 10 years most cancers will be treated with immunotherapy

Examples of Therapeutic Vaccines*

- **APC based vaccine (Sipuleucel-T, Dendreon; NW Biotherapeutics)**
- **Antigen Based Vaccine**
  - Protein (HER2 Peoples)
  - Peptide (long vs. short)
  - DNA / RNA (VBIR Pfizer, RNActive CureVac)
  - Vector
    - Virus (Pox virus [Prostvac] BN, Adeno [ProstAtak] Advantagene, Adeno Etubics)
    - Bacteria (Listeria [CRS-207] Aduro)
    - Yeast (GI-6301, GlobeImmune / Celgene)
- **Whole Tumor Cell Vaccine (GVAX, Aduro)**
- **Oncolytic Vaccine (T-Vec, Amgen)**

*Selected partial list for brevity, 2 agents FDA approved to date