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COMPREHENSIVE CANCER CENTER

PATIENT CARE
RESEARCH
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Tumor Immunology 101
For the Non-Immunologist

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NCI CCC *A Comprehensive Cancer Center Designated by the National Cancer Institute*

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Disclosure

Consulting Fees

- Abbvie Pharmaceuticals
- Novartis
- Merck
- Genetech
- Symphogen
- Cytomax
- Immunovative Therapies, Ltd.

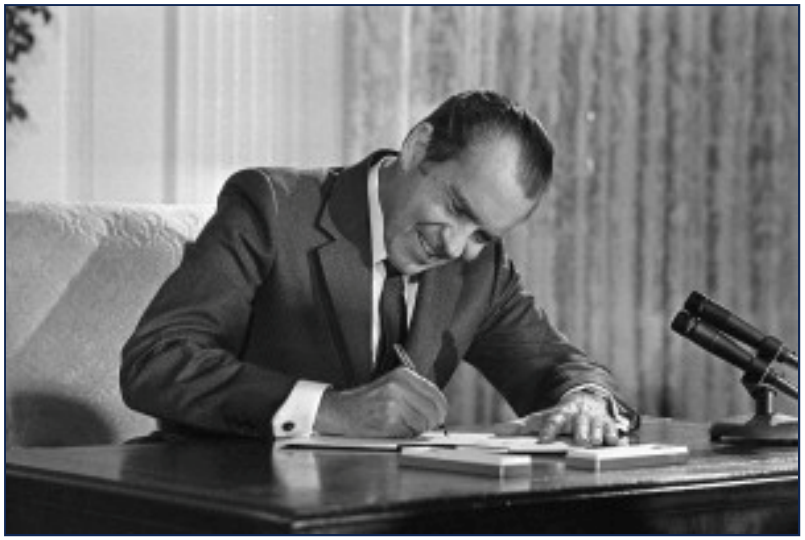
Contracted Research

- Symphogen

Ownership Interest

- Celldex
- Jounce
- Merrimack

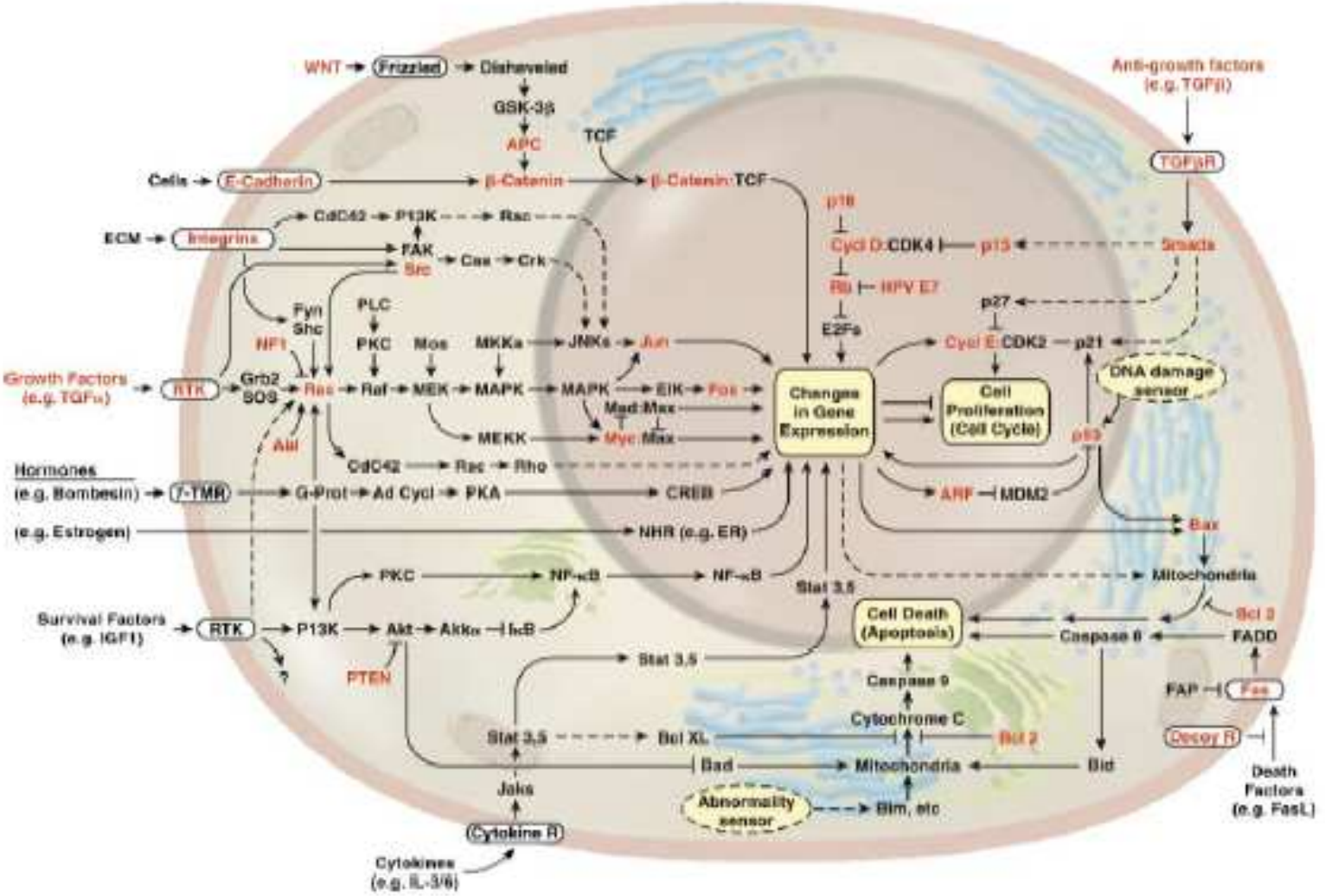
We Have Been at War Against Cancer Throughout Human History



President Nixon declares a “War on Cancer” in 1971

Medieval Saxon man with a large tumor of the left femur

Which Target?



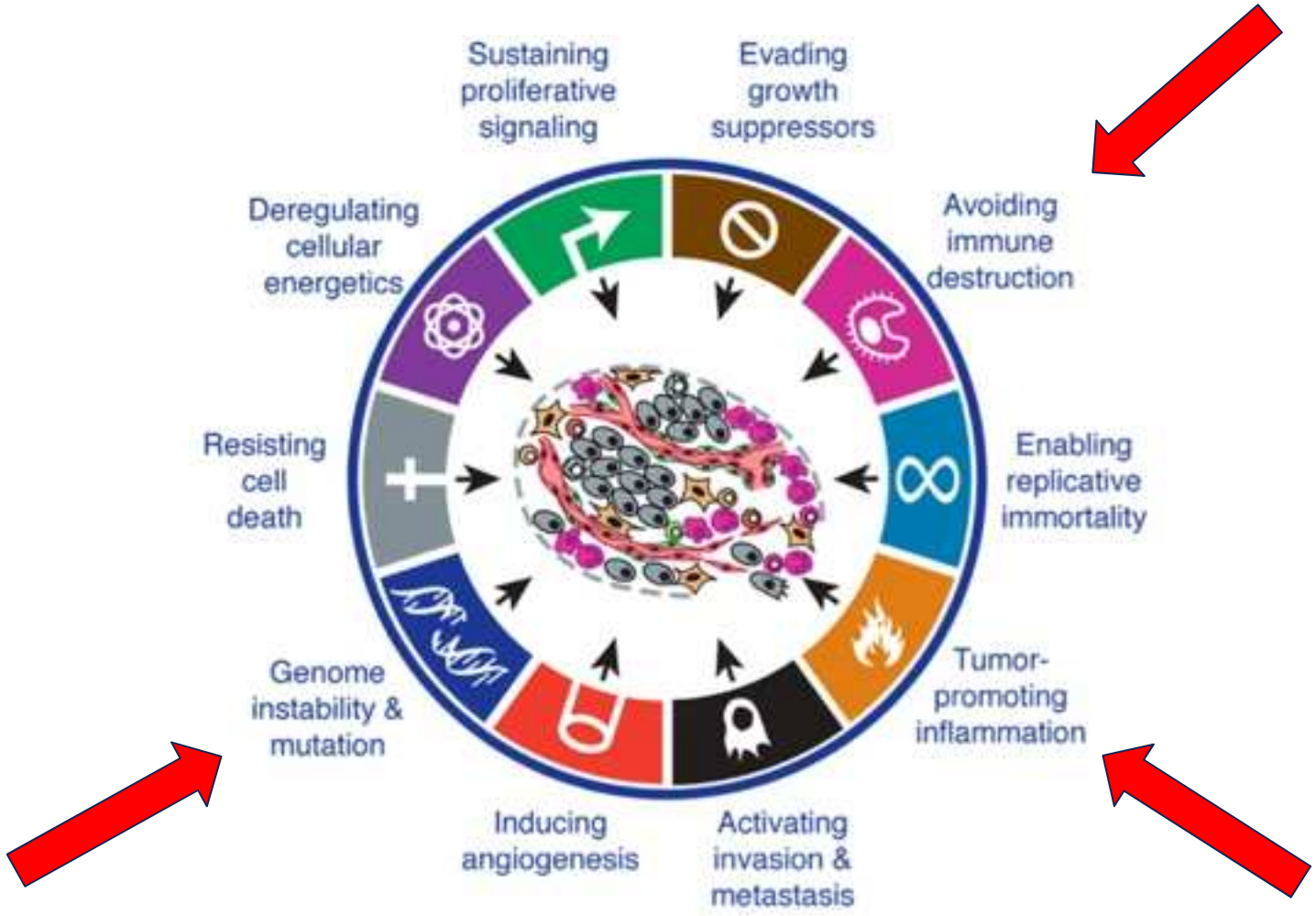
Hanahan, Weinberg, Cell 2000

The “War on Cancer”

is fought one person at a time…

- Primary Combatants:
  - Malignant cell population
  - Host immune system
- The host immune system is the dominant active enemy faced by a developing cancer
- All “successful” cancers must solve the challenges of overcoming defenses erected by host immune systems

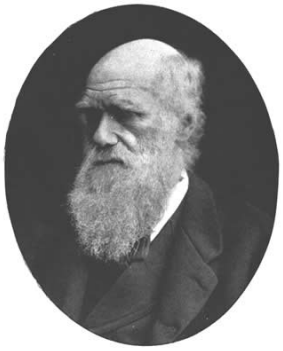
Which System?



Hanahan, Weinberg, Cell 2011

The Case for Cancer Immunotherapy

- Surprisingly few new truly curative anti-cancer cytotoxic drugs or targeted therapies in 20+ years
  - Tumor heterogeneity
  - Too many escape routes?



- The immune response is designed to identify and disable “escape routes” that cancers employ

- Immunotherapy can cure cancers

Immunotherapy

- Treatment of disease by inducing, enhancing, or suppressing an immune response

- “Treating the immune system so it can treat the cancer” (J. Wolchok)

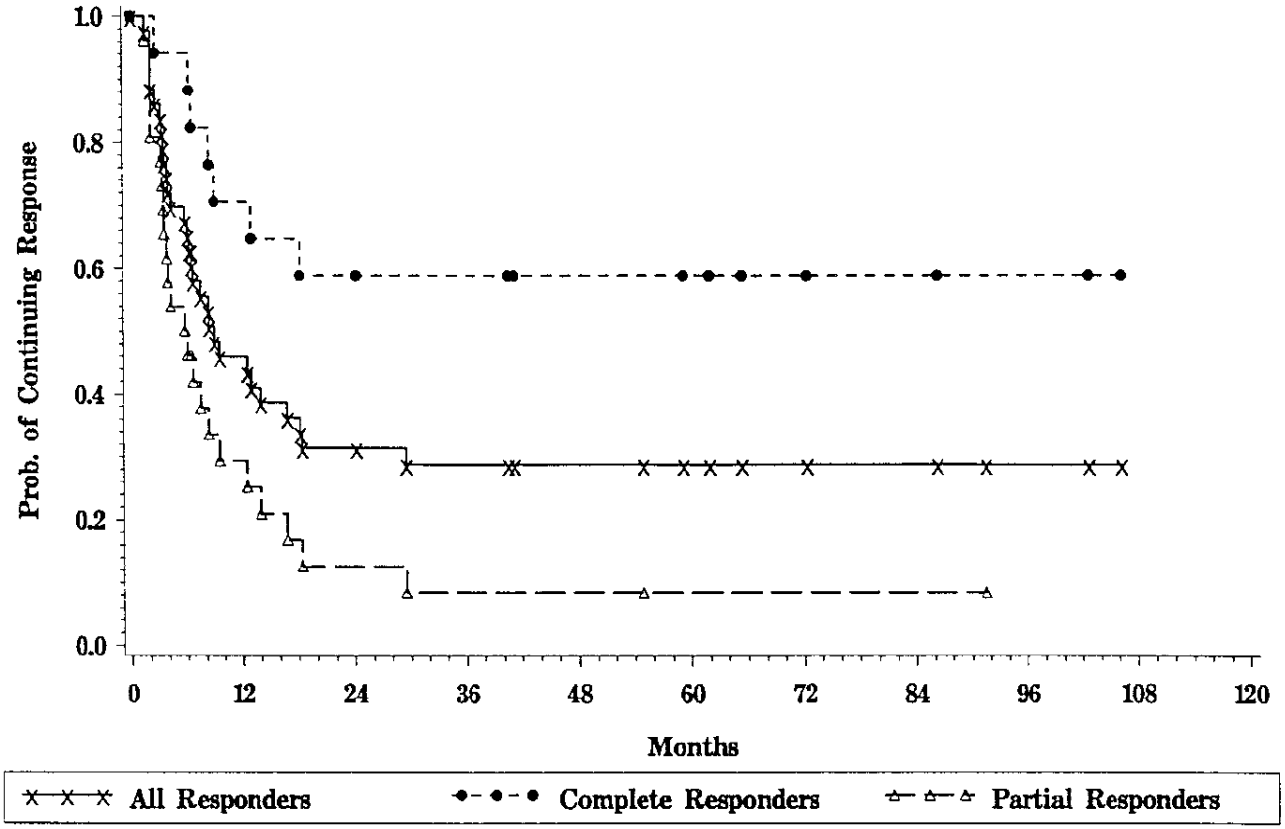
Some Examples of Successful Cancer Immunotherapy

- Type 1 interferons – bladder cancer*
- BCG – bladder cancer*
- High-dose IL-2 – kidney cancer*, melanoma*
- Ipilumumab** (anti-CTLA4 Ig) – melanoma
- Anti-PD1/PD-L1 antibodies** – melanoma, kidney, lung, Hodgkin's, bladder, HNC (n = 17+ cancers)
- Anti-tumor monoclonal antibodies – rituximab*** (lymphoma), trastuzumab*** (breast cancer), cetuximab (colorectal cancer)
- Provenge vaccine (prostate cancer)

* Curative as a single agent
** Long term remissions, too soon to know if cures
*** Curative in combination with chemotherapy

Immunotherapy Can Yield Durable Results

High Dose Recombinant Interleukin-2 Therapy for Patients with Metastatic Melanoma: Kaplan-Meier Plots of Response Duration for Patients who Achieved CR, PR or Any Response (Atkins MB et al, J Clin Onc 1999)



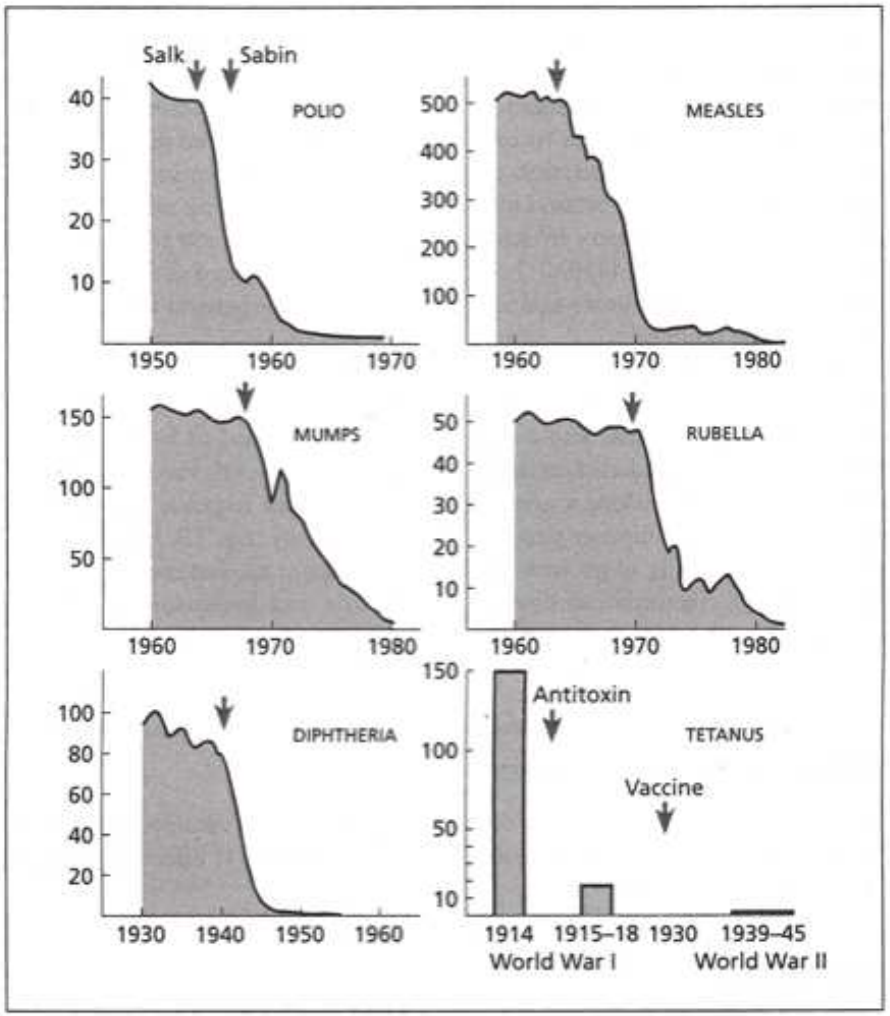
Edward Jenner- Late 18th Century

Figure 1-1 Immunobiology, 6/e. (© Garland Science 2005)

Observed that milkmaids who get a mild viral disease Cowpox (Vaccinia virus) do not get the deadly disease, Smallpox

Inoculation of Cowpox provided protection from Smallpox

Vaccinations Save Lives



Innate and Adaptive Immunity

- Innate Immunity
  - Neutrophils, Macrophages, NK cells
  - A primitive system conserved through evolution
  - Rapid Response – minutes to hours
    - Uses products of germline genes (no receptor rearrangements)
  - Not specifically directed against the invading microorganism
    - Low specificity
    - Recognizes patterns (leads to potential for collateral damage)
  - **NO IMMUNOLOGICAL MEMORY**

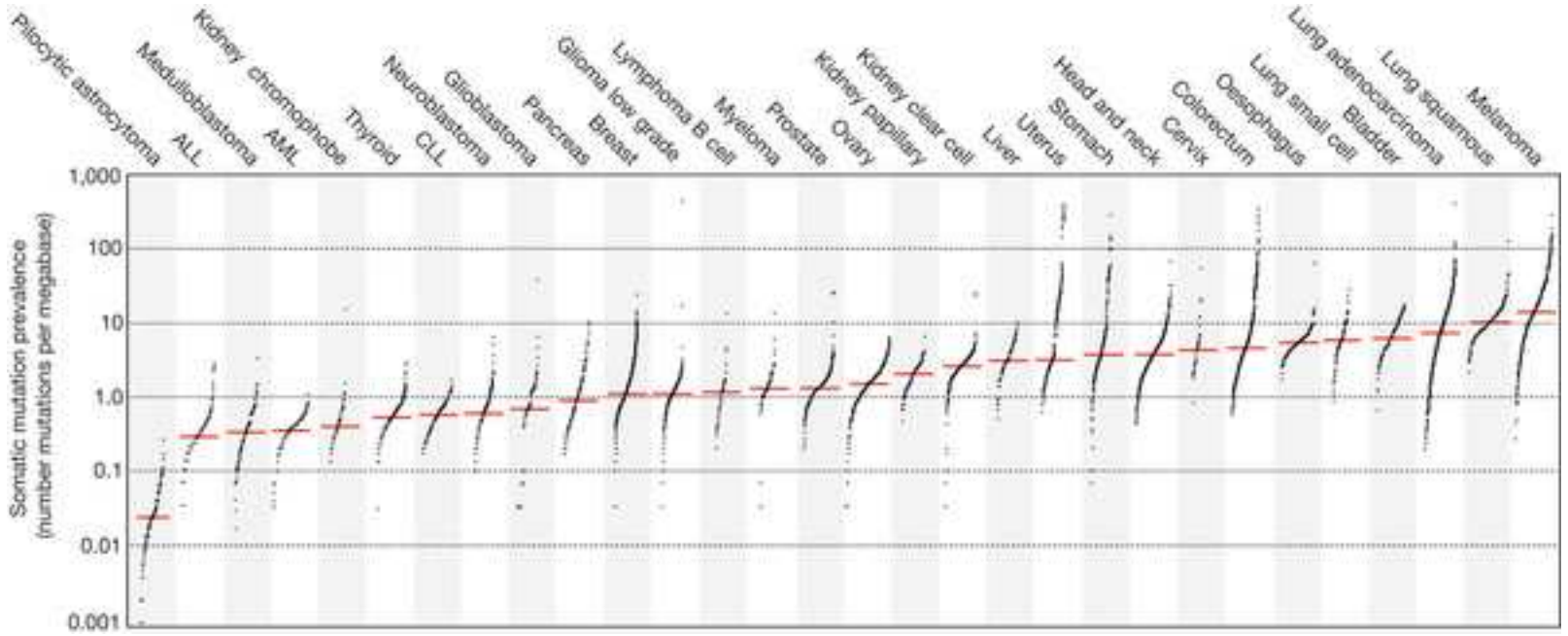
- Adaptive Immunity
  - T cells, B cells
  - Exquisite specificity
    - Minimizes collateral damage
  - **MEMORY CAN LAST A LIFETIME**

- Cytokines and chemokines regulate both types of immunity

The Immune System Recognizes and Eradicates Cancer by Targeting Antigens

- **Tumor-associated antigens (TAA)**: (e.g., CEA, PSMA)
- **Tumor-specific Ag**: mutated molecules (e.g., CDK4 and β-catenin)
- **Cancer-testis Ag**: expressed only in germ cells (e.g., NY-ESO)
- **Differentiation Ag**: expressed only in particular tissues (e.g., CD19)
- **Overexpressed tumor Ag**: (e.g., HER-2/neu, WT1)
- **Abnormal post-translational modification Ag** (e.g., MUC-1)
- **Abnormal post-transcriptional modification**: novel proteins generated when introns are retained in the mRNA (e.g., GP100)
- **Oncoviral protein Ag**: (e.g., HPV type 16, E6 and E7)

Most Cancers Have Mutations

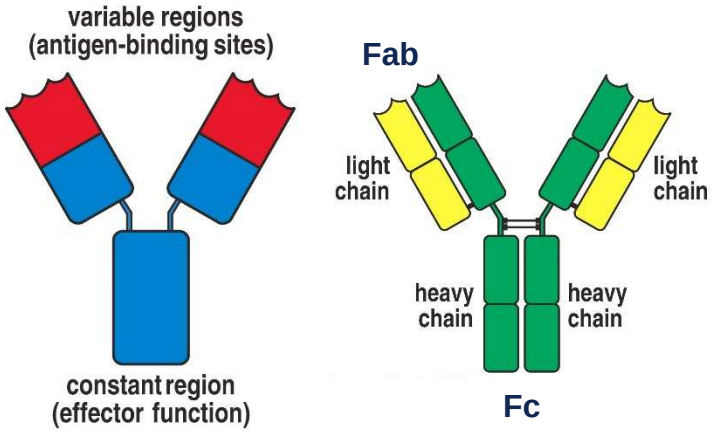


Mutated proteins represent potential antigens – targets for immune recognition and destruction

Lawrence, Nature 499:214 2013

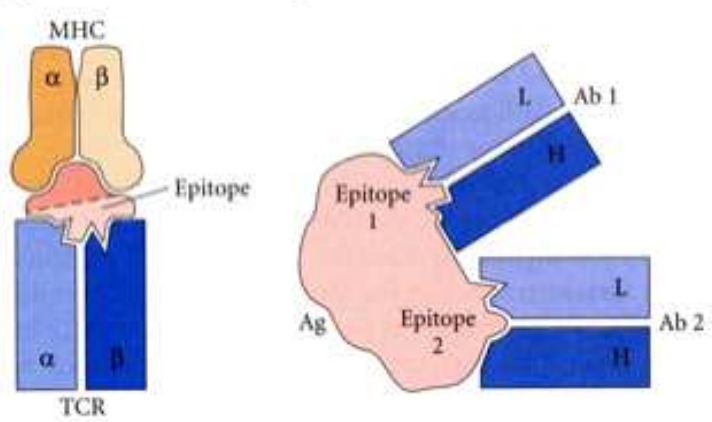
Antigen Receptors Underlie Specificity

Antibody



A protein produced by activated B lymphocytes that binds specifically to a particular substance – its antigen

T Cell Receptor



T cells bind to processed antigens via T cell receptor (TCR) recognition of peptides derived from proteins that were processed and presented by APC in the context of self-MHC

Antibodies bind to native antigens by recognizing protein conformations

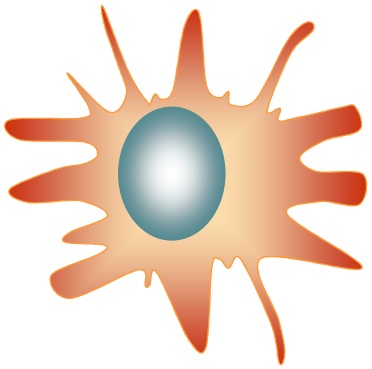
Portions of antigens = epitopes

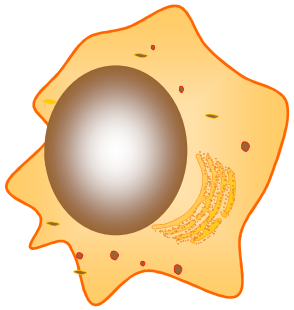
Antigen Presenting Cells (APCs)

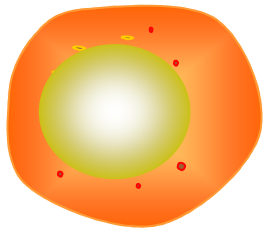
- The ability to process and present Ags on MHC class I molecules is a property of virtually all mammalian cells

- Professional APCs are highly specialized cells that can
  - Process and present an Ag associated with MHC class II
  - Provide a 2nd, co-stimulatory signal to T cells

Dendritic Cells Macrophages B Cells







Activation of naïve T cells requires two independent signals delivered by same APC

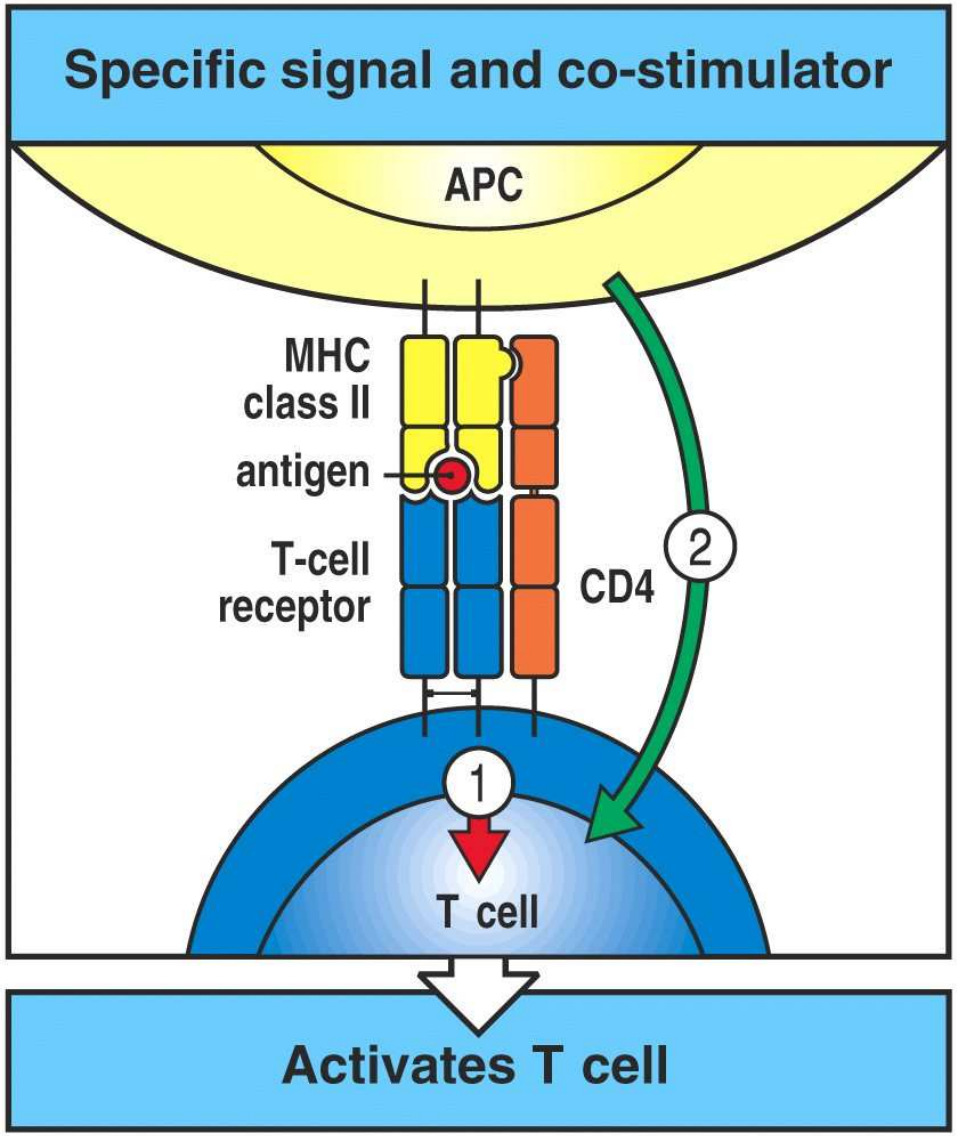


Figure 8-10 Immunobiology, 6/e. (© Garland Science 2005)

Only one signal - no activation or anergy

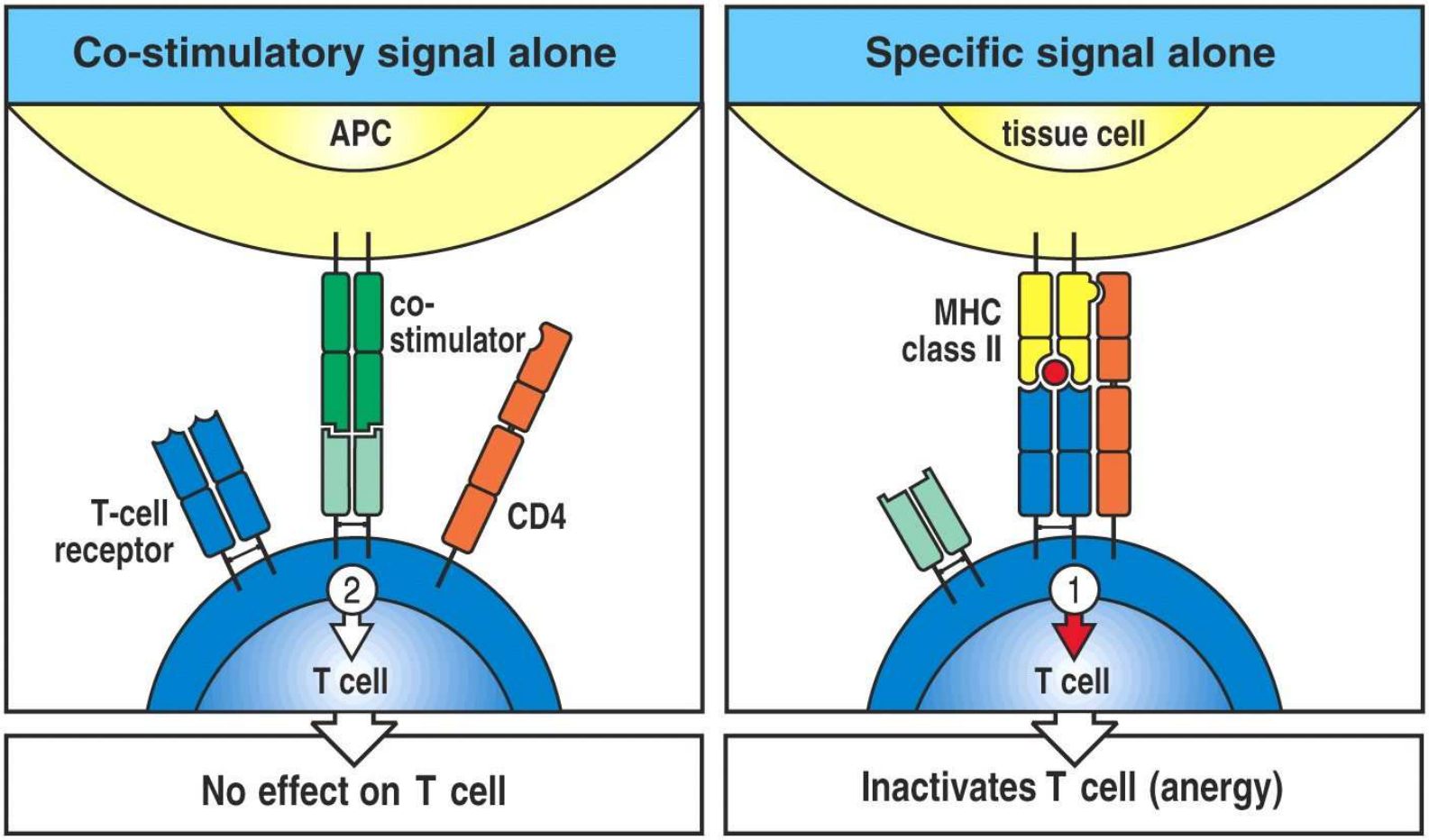


Figure 8-21 Immunobiology, 6/e. (© Garland Science 2005)

The principal co-stimulatory molecules expressed on APCs are B7 molecules that bind T cell protein CD28

TCR/CD3 activation provides “Signal 1”

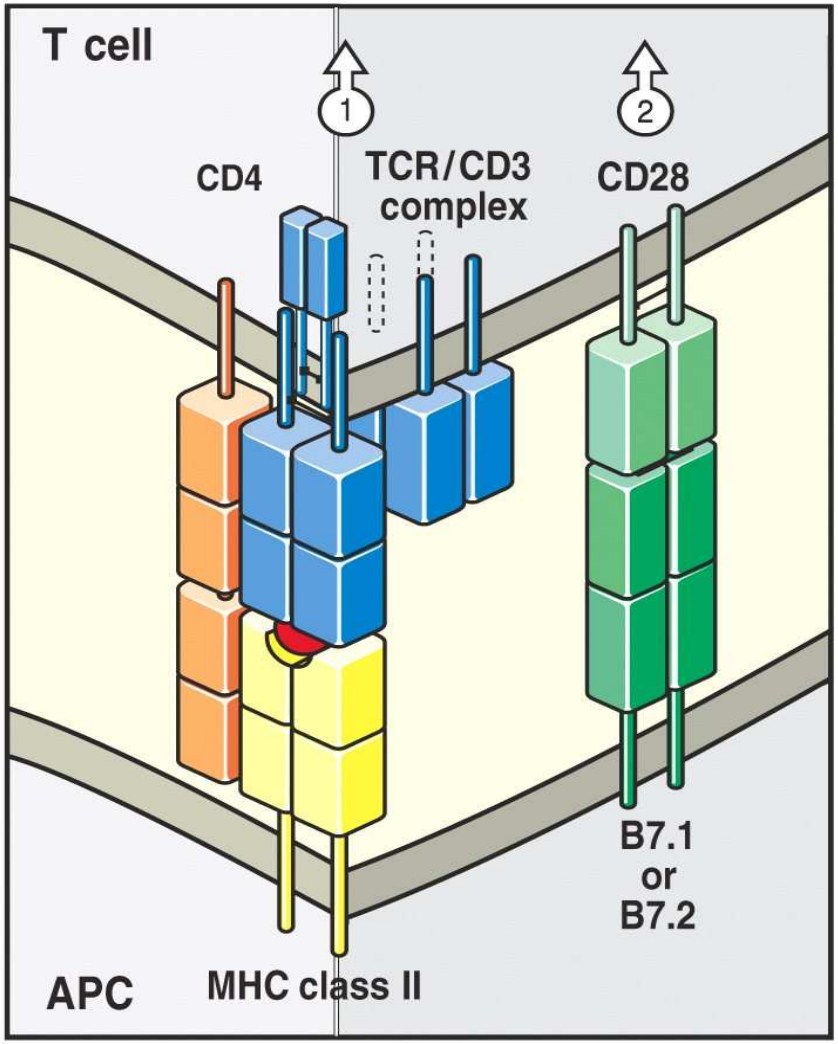


Figure 8-11 Immunobiology, 6/e. (© Garland Science 2005)

CD28 activation provides “Signal 2”

T cell activation through the TCR and CD28 leads to the increased expression of CTLA4

CTLA4 is an inhibitory receptor for B7 Molecules that shuts down Signal 2

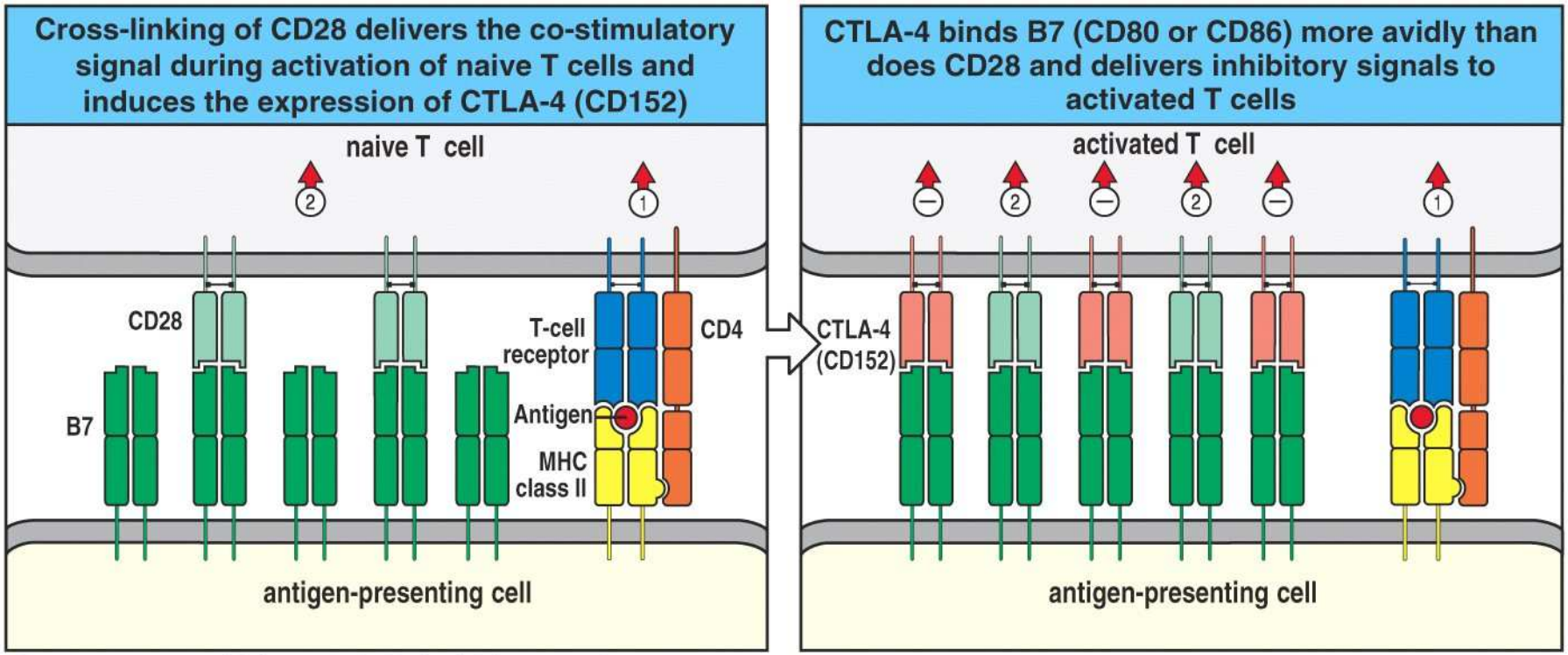


Figure 8-12 Immunobiology, 6/e. (© Garland Science 2005)

Armed effector T cells

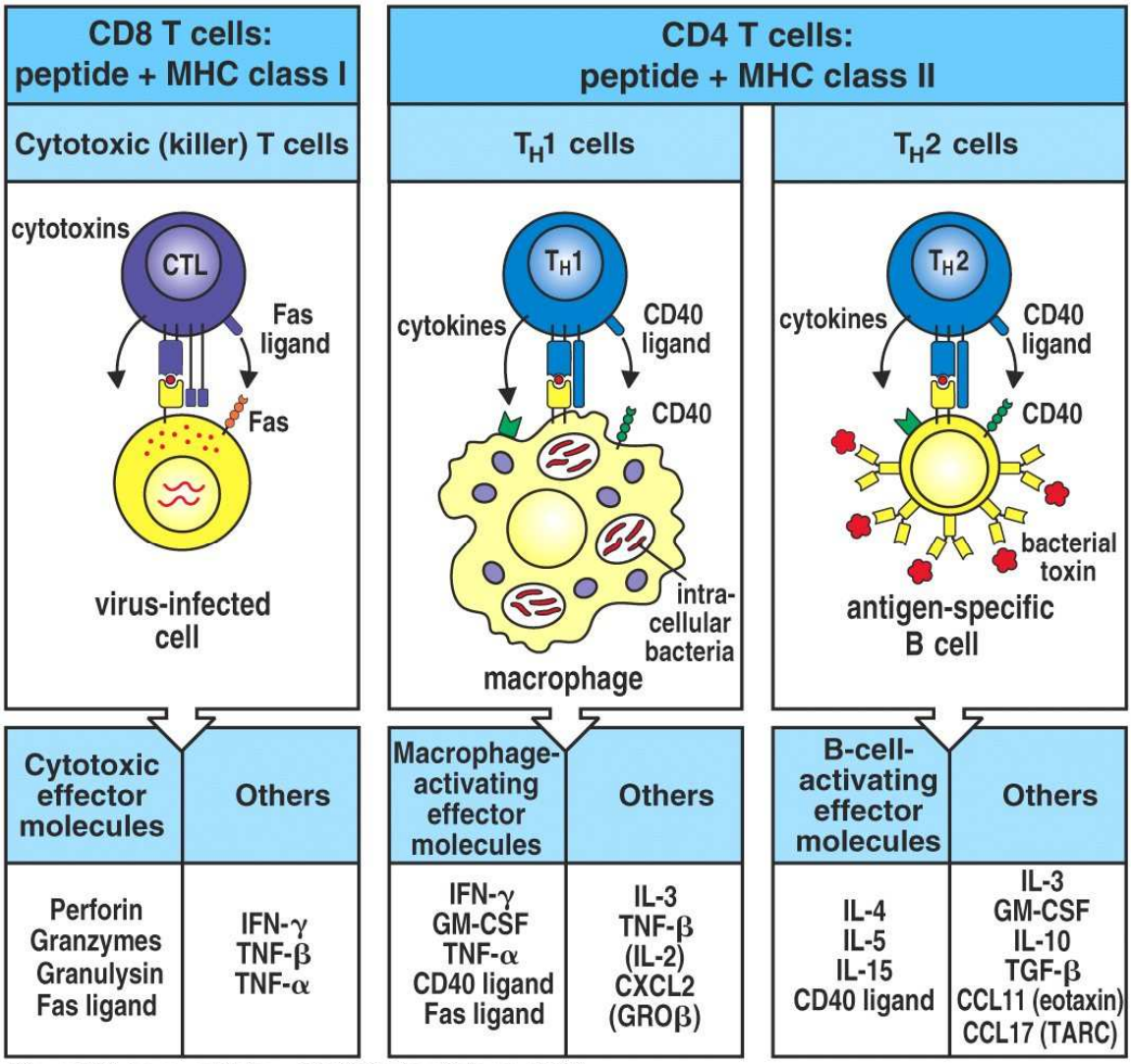


Figure 8-31 Immunobiology, 6/e. (© Garland Science 2005)

Immunosurveillance and Immunotherapy

- The cancer immunosurveillance hypothesis: initially proposed in 1909

- Burnet & Thomas, 1957: lymphocytes acting as sentinels in recognizing and eliminating continuously emerging transformed cells.

Schreiber, Smyth, 2001

Immunoediting: changes in the immunogenicity of tumors due to the anti-tumor response of the immune system, resulting in the emergence of immune-resistant variants.

In 2001…first real mechanistic evidence of immune-mediated protection against tumor development

IFNγ and lymphocytes prevent primary tumour development and shape tumour immunogenicity

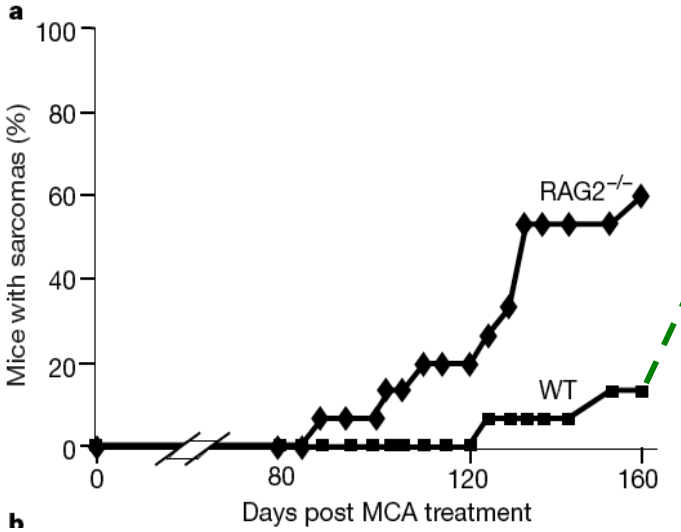
Vijay Shankaran*, Hiroaki Ikeda*, Allen T. Bruce*, J. Michael White*, Paul E. Swanson*, Lloyd J. Old† & Robert D. Schreiber*

** Department of Pathology and Immunology, Center for Immunology, Washington University School of Medicine, 660 South Euclid Avenue, St Louis, Missouri 63110, USA*
† Ludwig Institute for Cancer Research, New York Branch at Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA

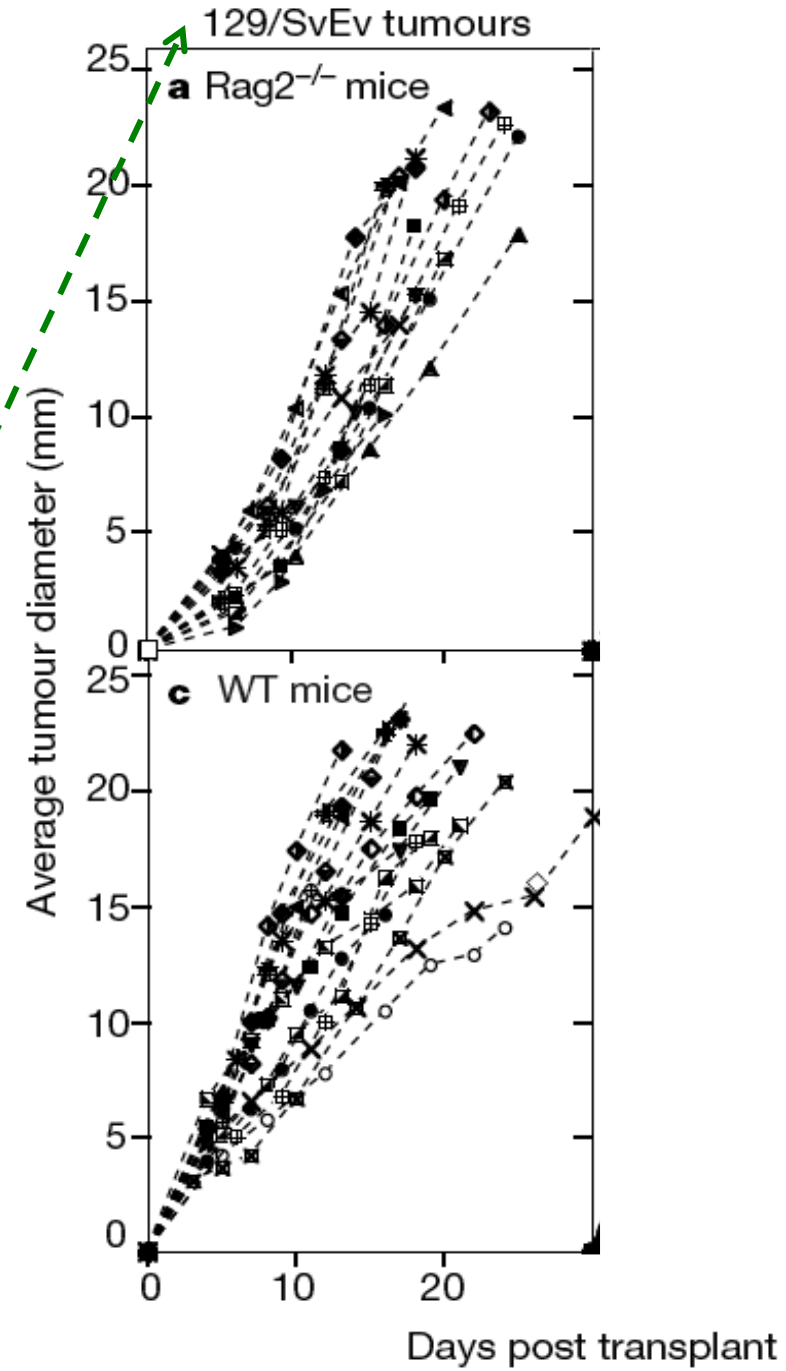
Nature 410:1107, 2001

- Lymphocytes and IFN-γ collaborate to protect against development of carcinogen-induced sarcomas and spontaneous epithelial carcinomas
- Explanation of the apparent paradox of tumor formation in immunologically intact individuals.

Increased immunogenicity of tumors derived from methylcholanthrene treated RAG2$^{-/-}$ mice.



RAG2$^{-/-}$ hosts inoculated on Day 0 with tumor cells derived from wild-type (a) or RAG2$^{-/-}$ (b) mice. WT mice were inoculated on day 0 tumor cells derived from WT mice (c) or RAG2$^{-/-}$ mice (d)



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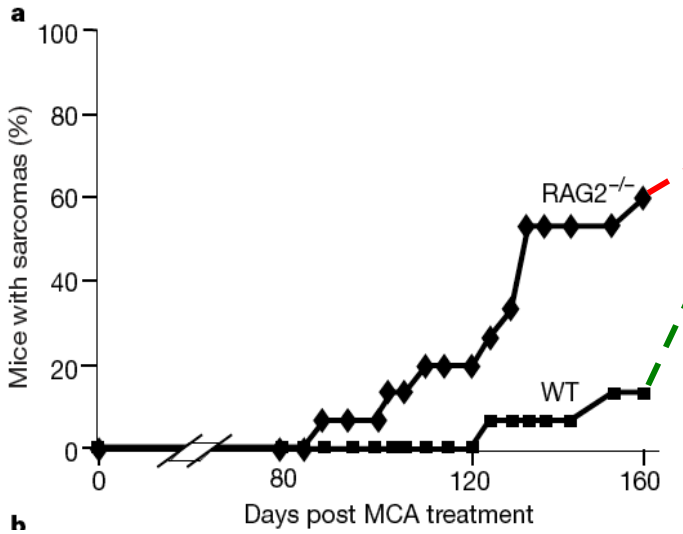

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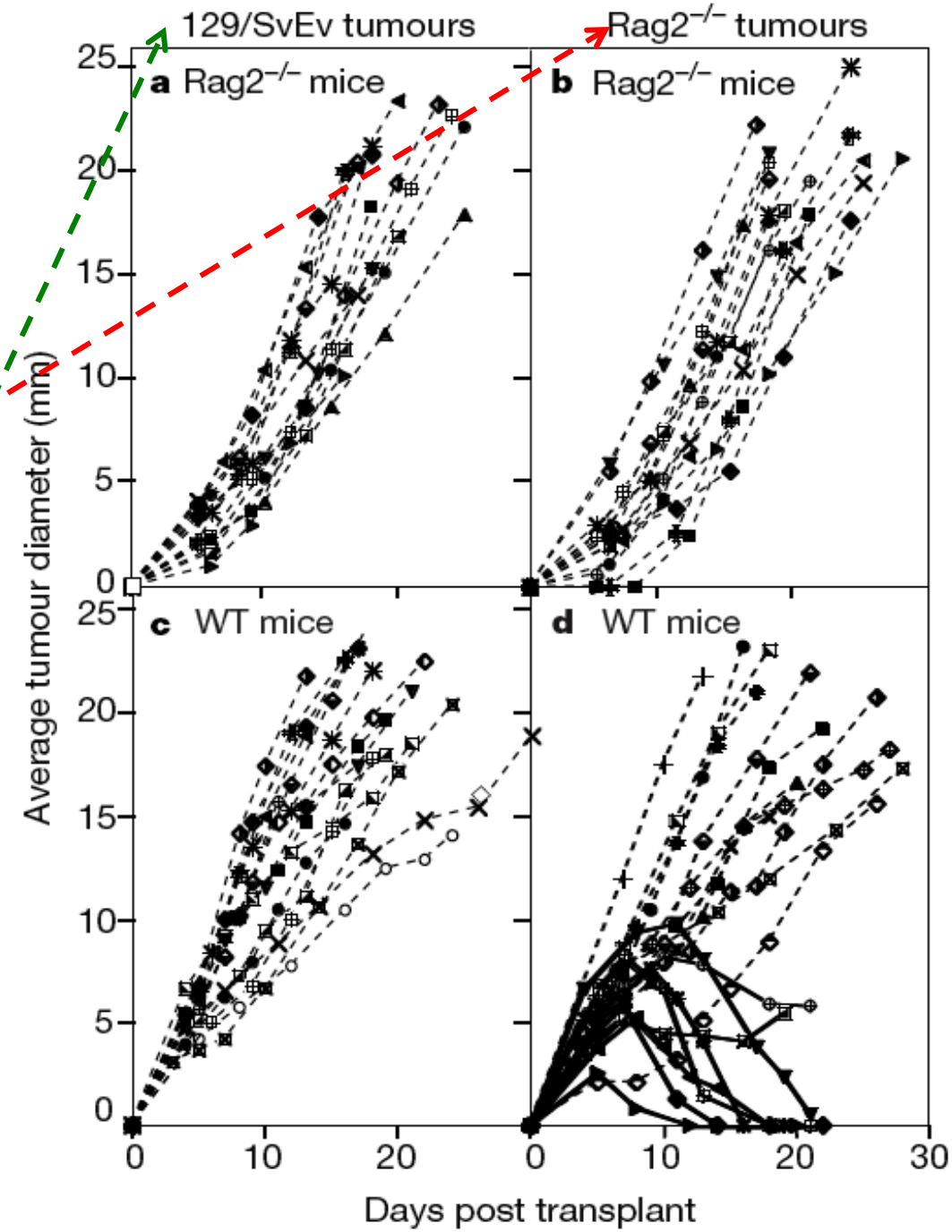
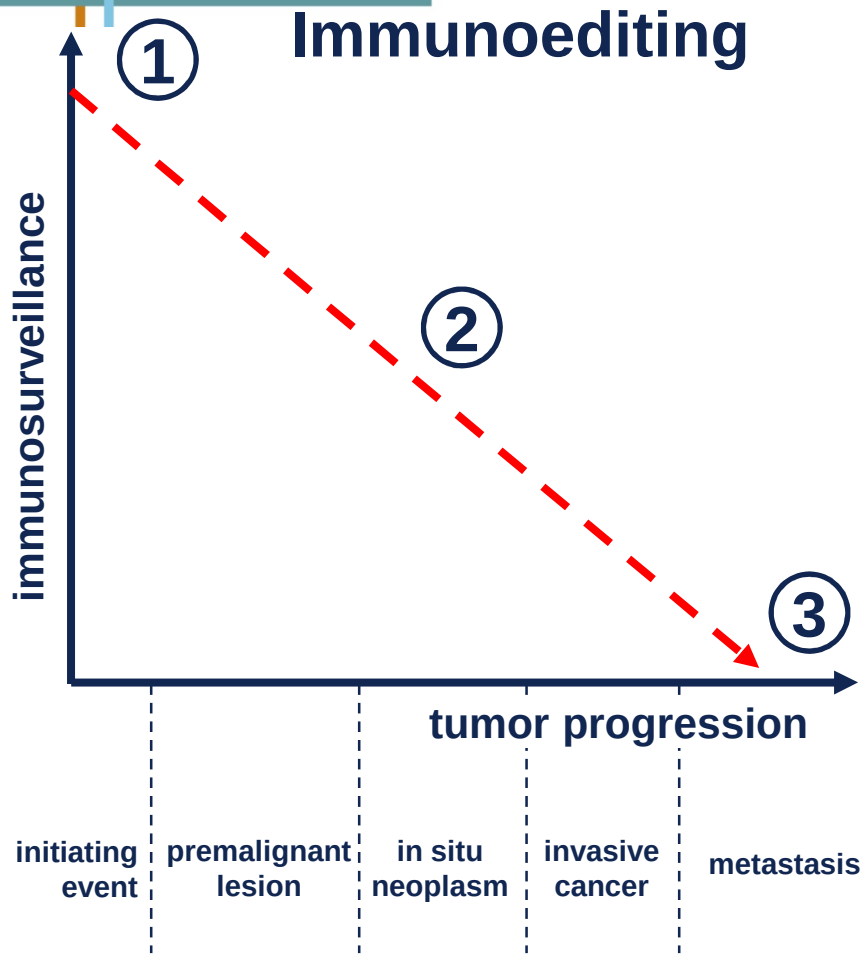


Immunosurveillance and Immunotherapy



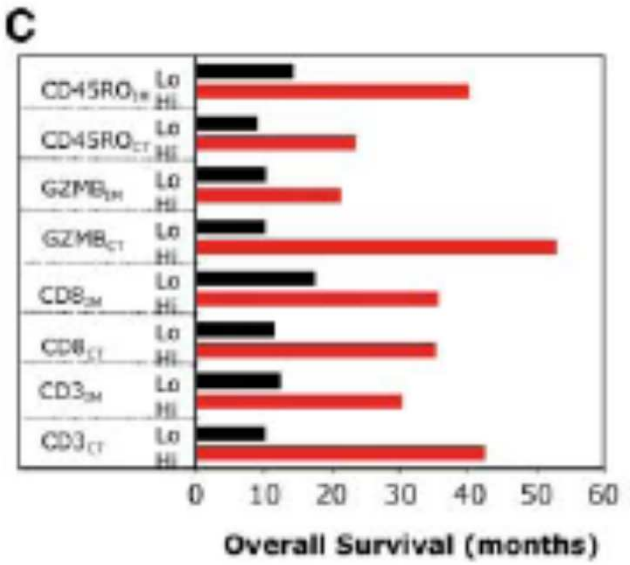
1. **Elimination:** immune system recognizes and destroys potential tumor cells.

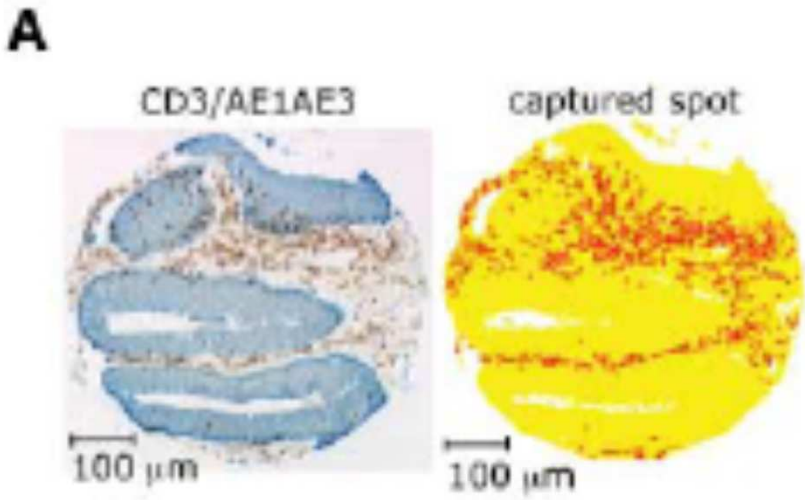
2. **Equilibrium:** elimination not complete successful, leading to a smoldering truce between the tumor and the host immune system

3. **Escape:** tumor or host are modified to permit malignant clones to escape immune control

Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome.

Galon et al, Science 313, 1960 (2006)





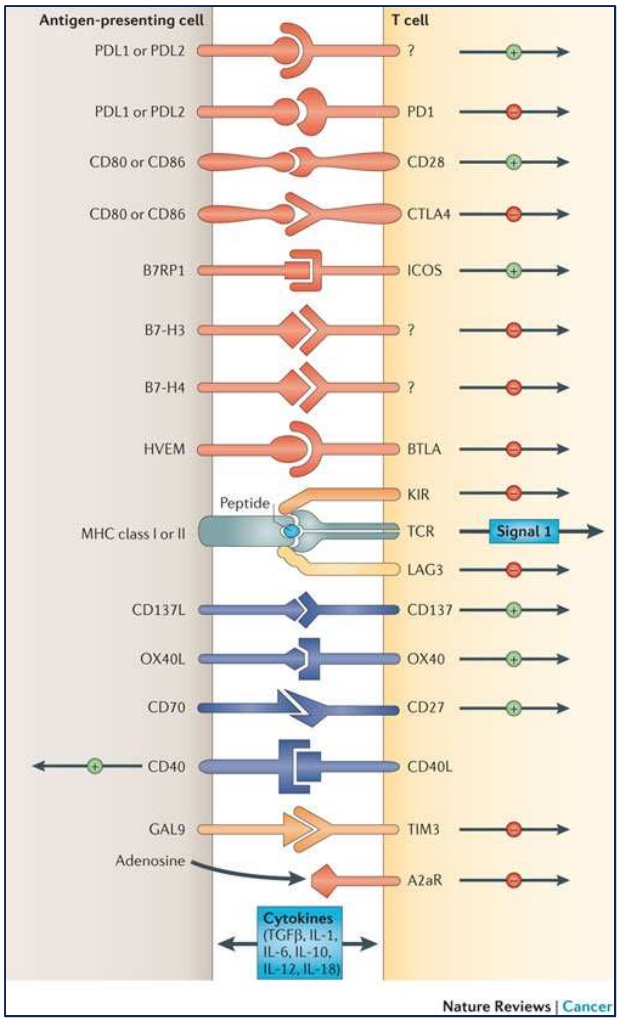
Also seen in breast and ovarian cancers

Even when the immune system cannot control the eventual development of a cancer it remains relevant

Successful Cancers Escape (Solve the Challenge of Host Immunity) in Different Ways

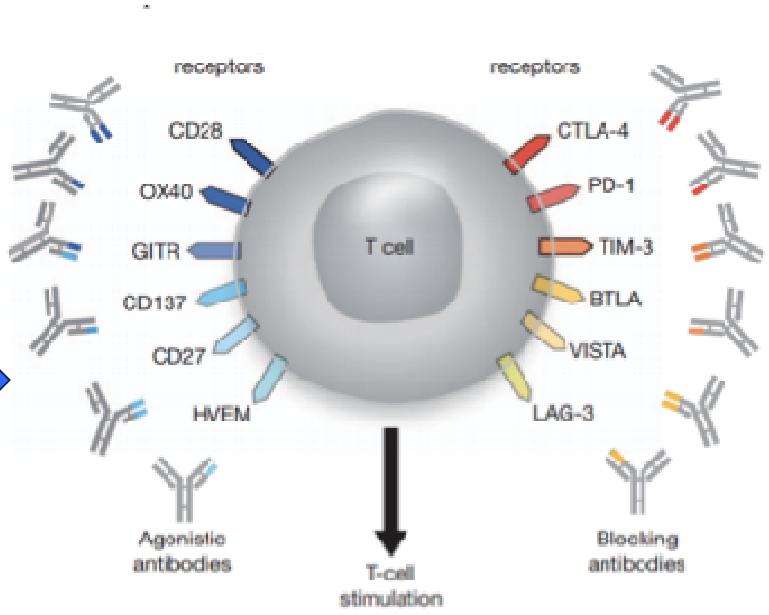
- ***Overwhelm*** – out-proliferate the immune response
- ***Hide*** – decreased antigen or MHC Class I or II expression
- ***Subvert*** – immunosuppressive chemokines, cytokines
- ***Shield*** – exclude infiltration by tumor antigen-reactive T cells
- ***Defend*** – deactivate tumor-targeting T cells that attack tumor cells

Immune Checkpoints Regulate Strength and Type of Anti-Tumor Immune Response



Science

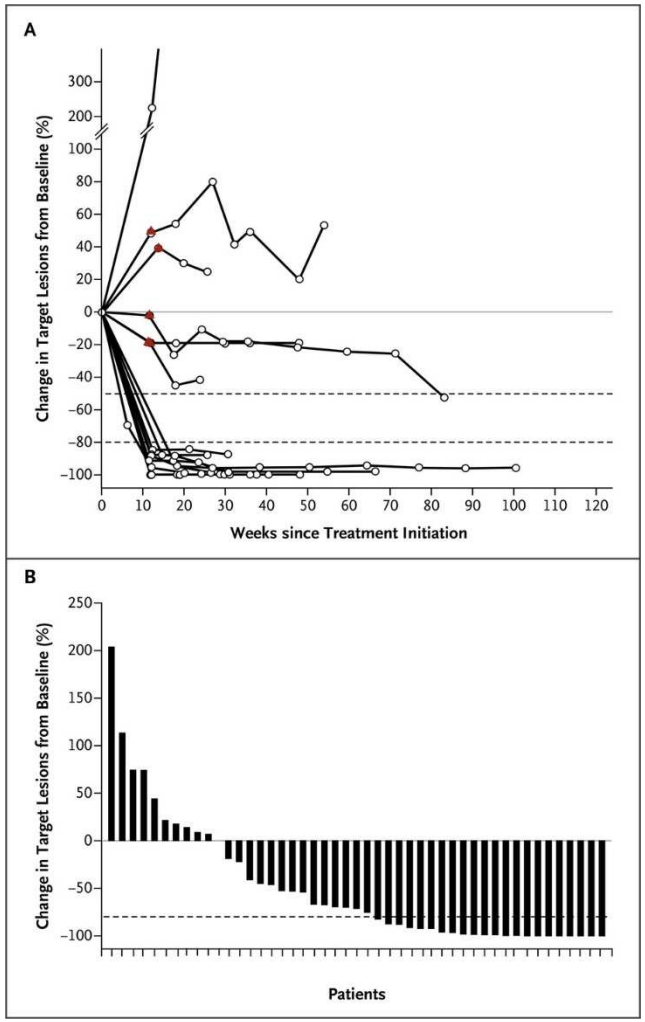
Business



Fink Z, Prop Think, Dec 2014

Pardoll, Nat Rev Cancer 2012

Clinical Activity of the Concurrent Regimen of Nivolumab and Ipilimumab in Advanced Melanoma



Wolchok JD et al. N Engl J Med 2013;369:122-133
Sznol M et al, Proc ASCO LBA9003 2014

Combination blockade of PDL1-PD1 and B7-CTLA4 interactions aiming to overcome “defensive” checkpoint inhibitors

Follow Up April 2015
(Proc AACR 2015)

Overall response rate ~ 60%
Complete response rate ~ 25%

Median survival > 40 mos
(expected survival ~ 7 mos)

Few relapses in responders

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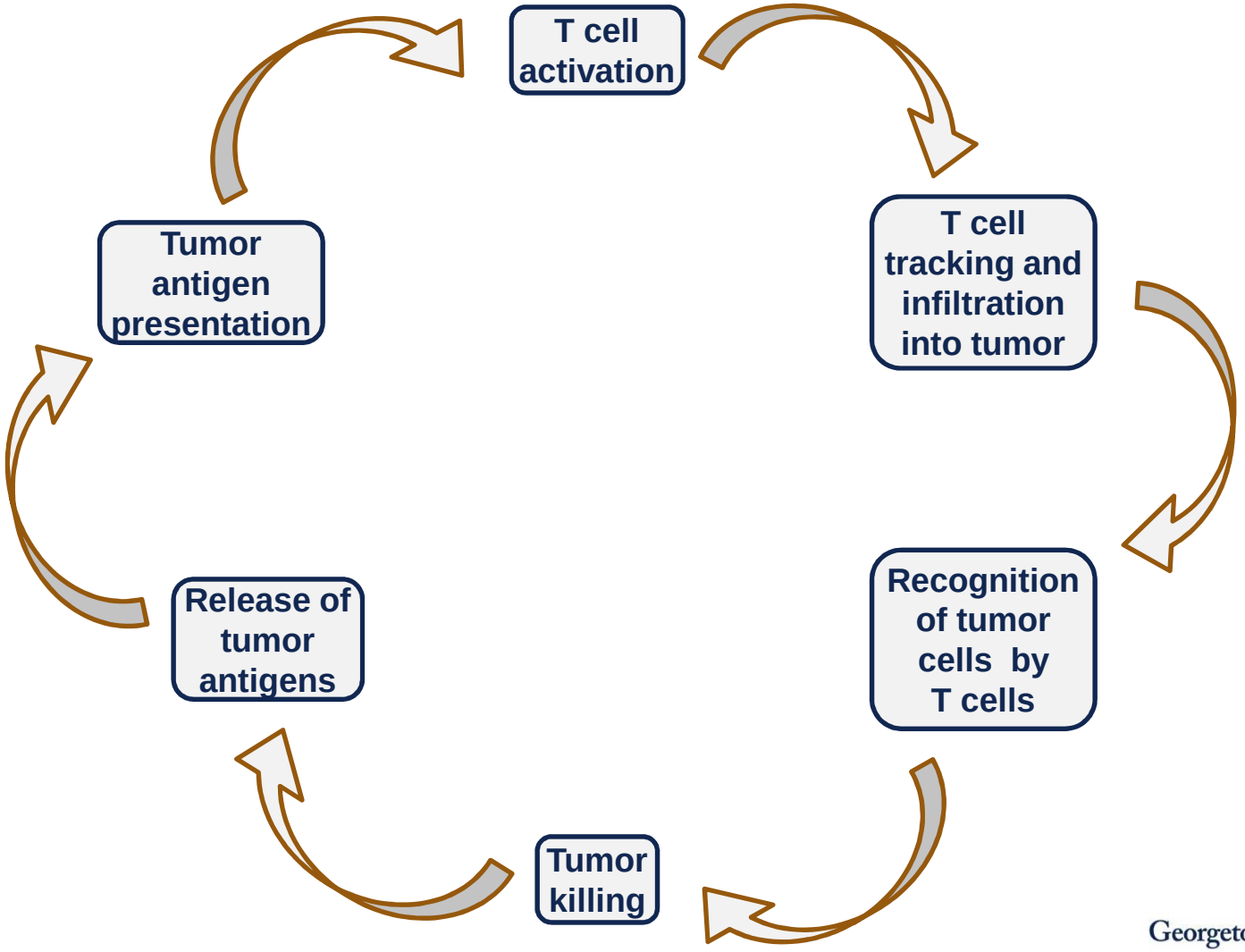
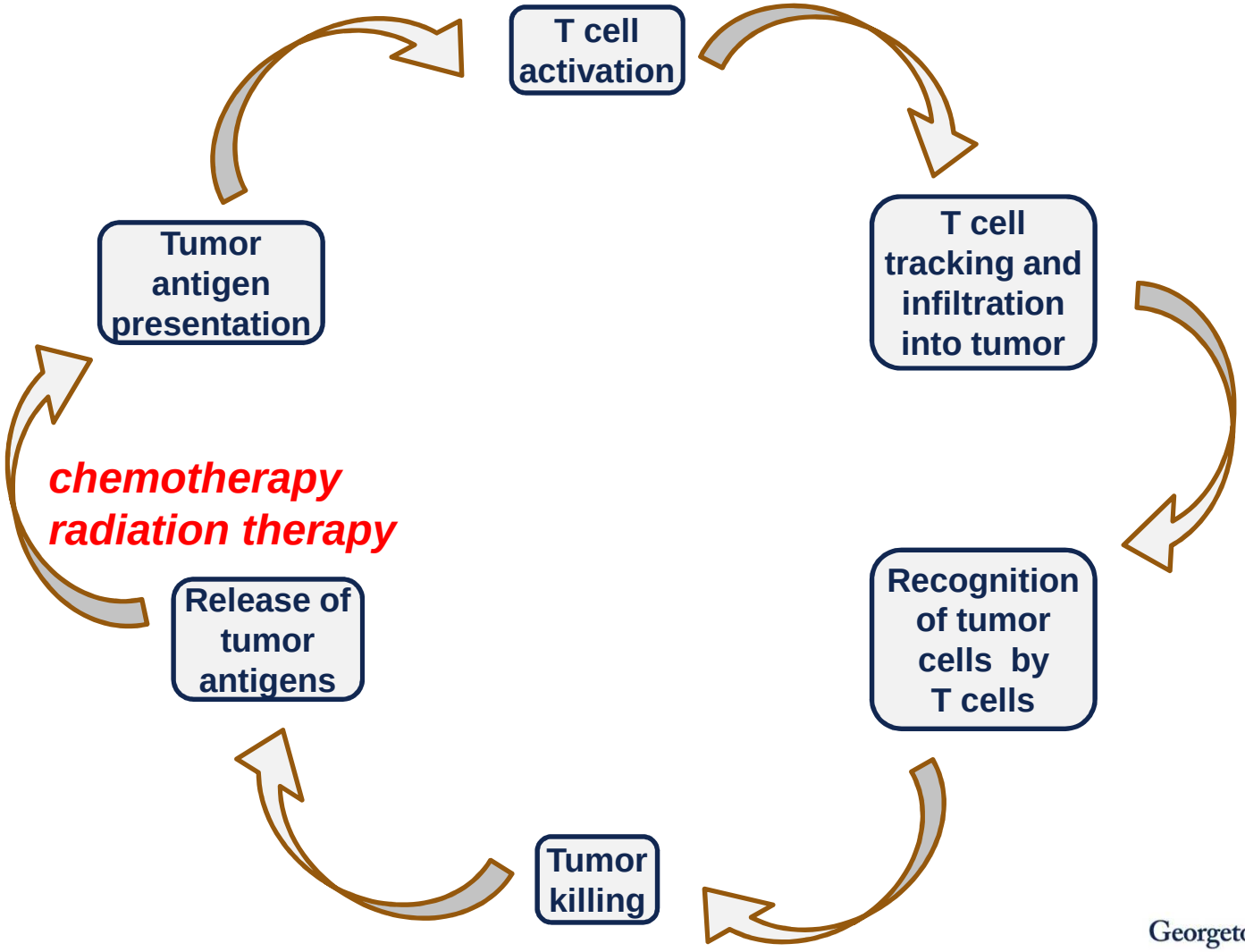
Approaches to Tumor Immunotherapy

The Cancer Immunity Cycle



Approaches to Tumor Immunotherapy



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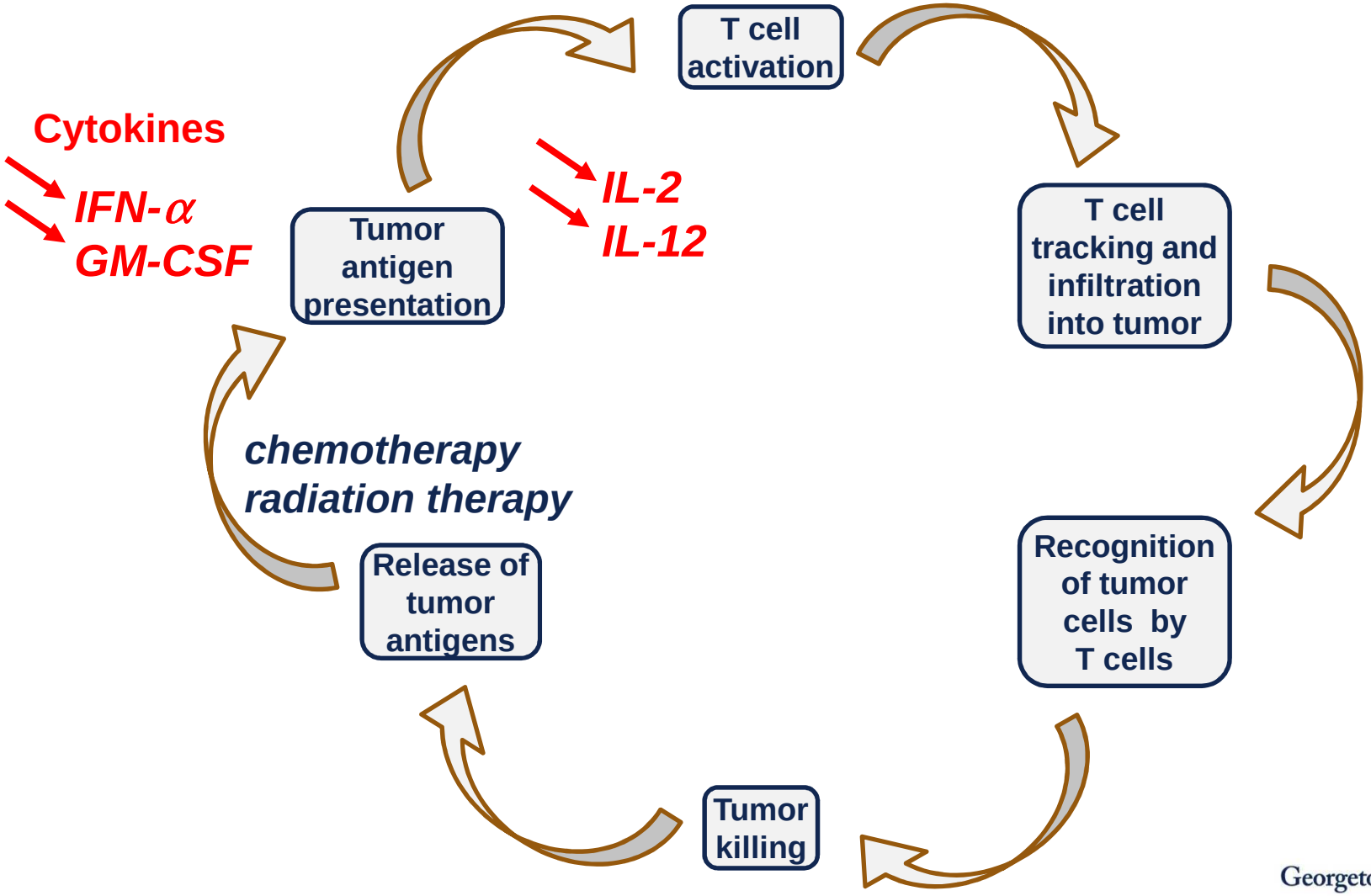

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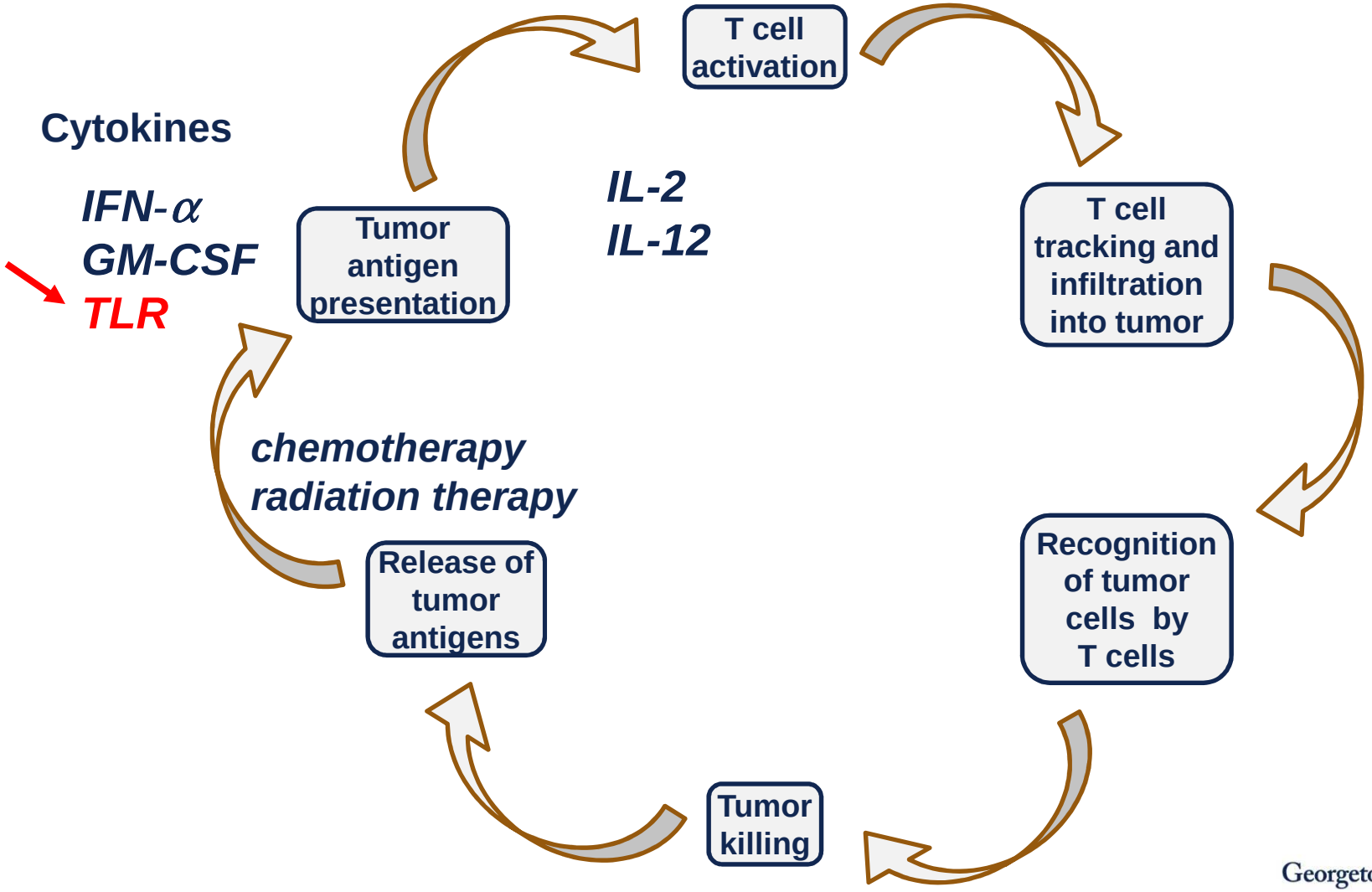

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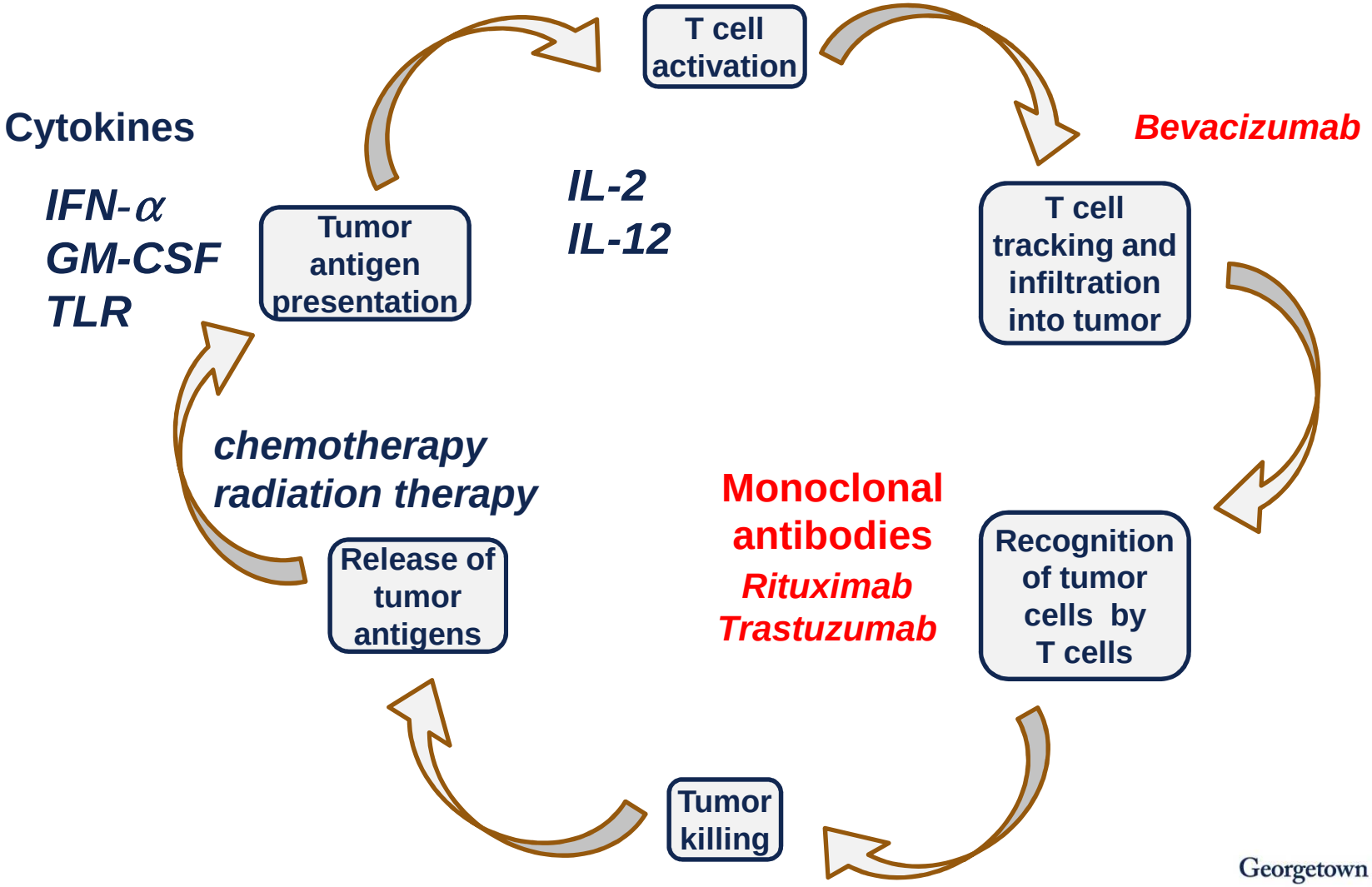

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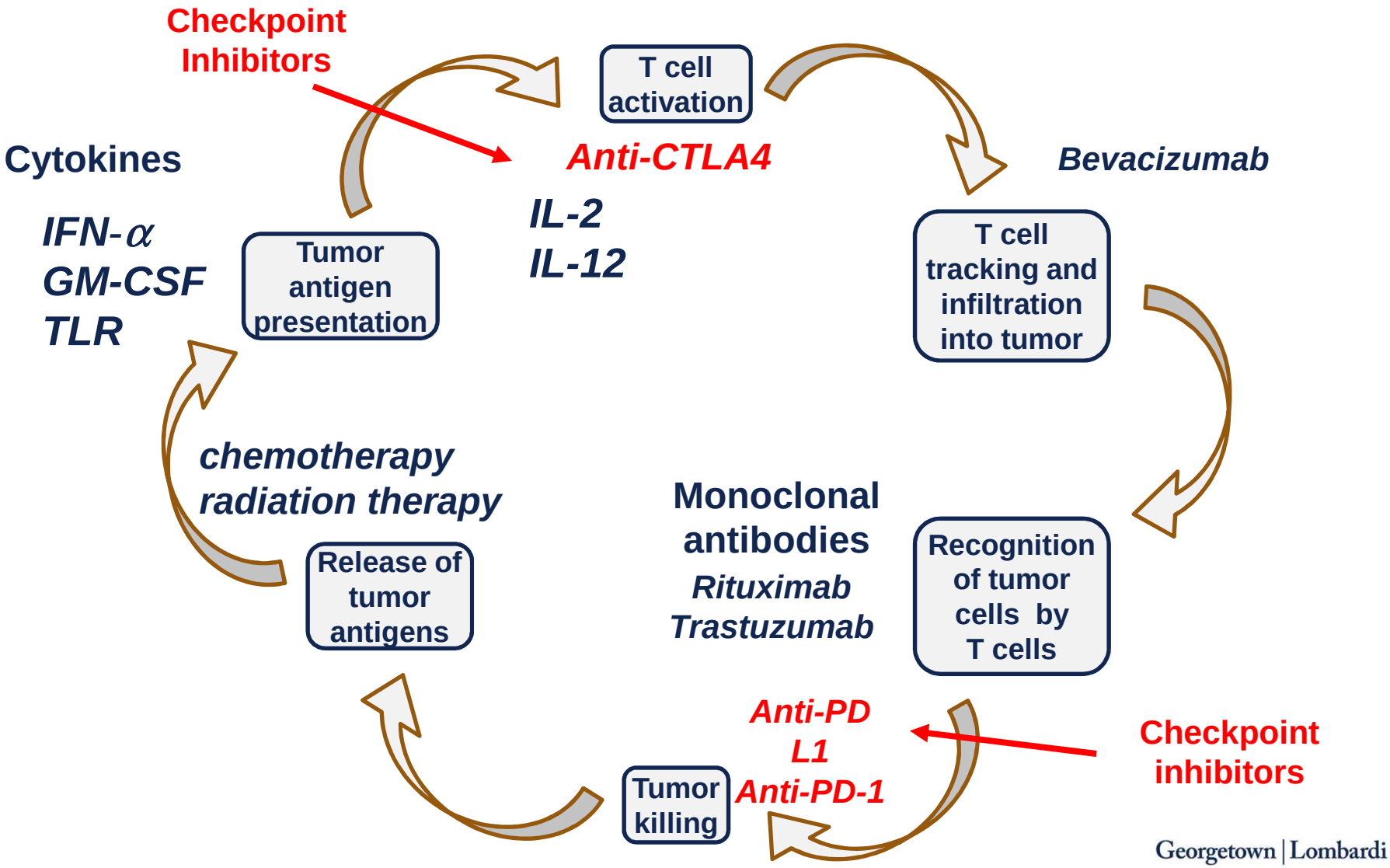
Approaches to Tumor Immunotherapy



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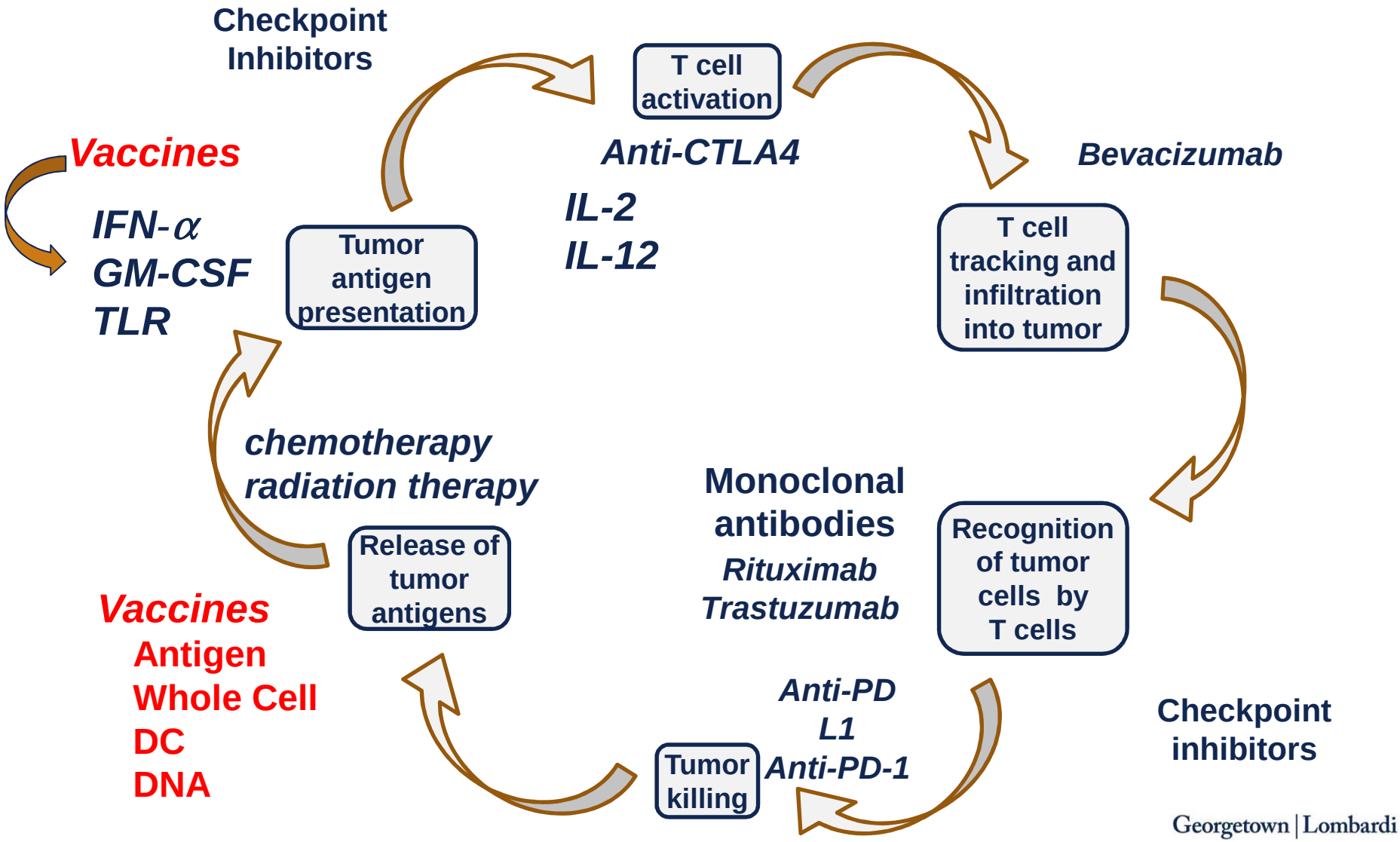
Approaches to Tumor Immunotherapy



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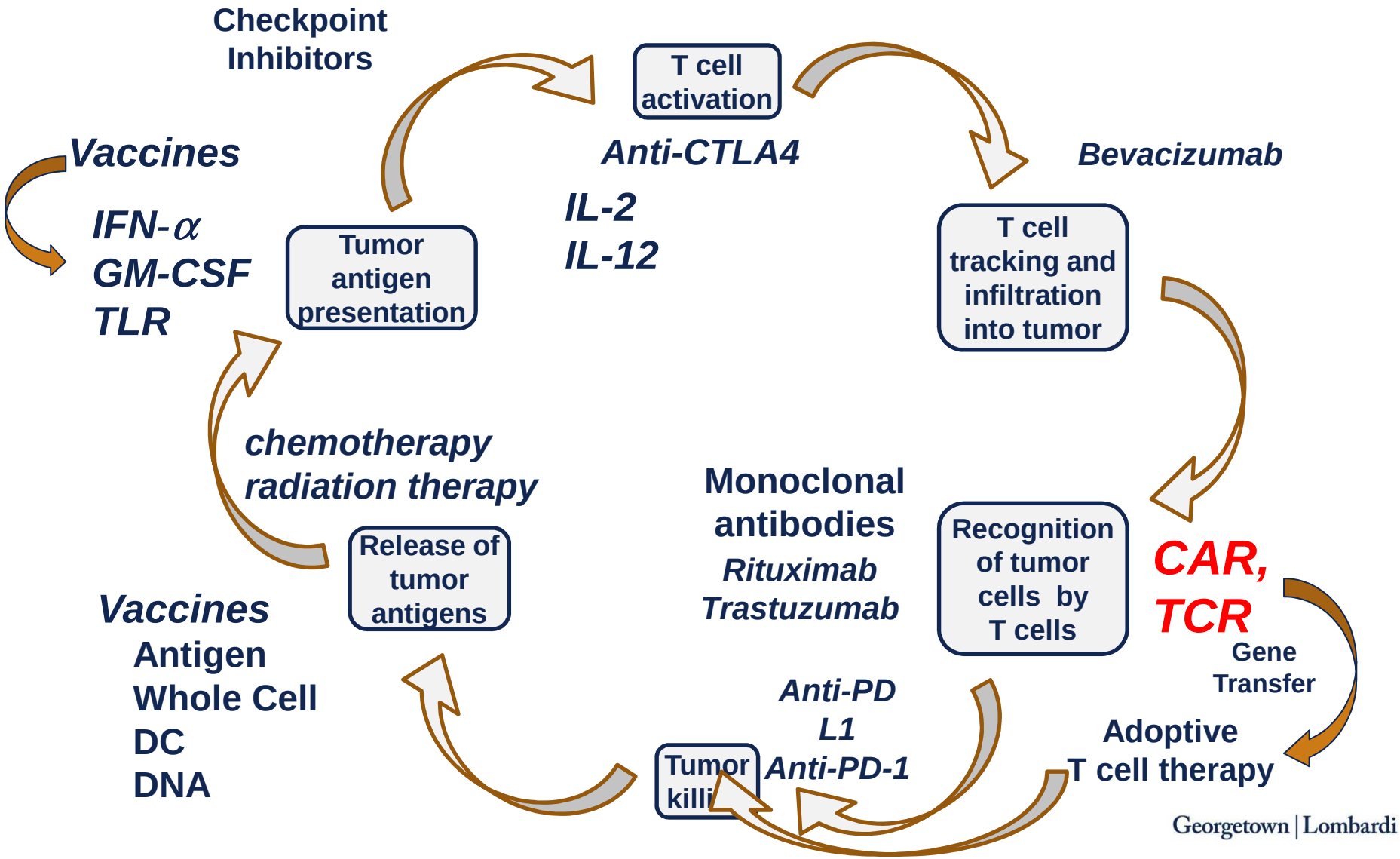

Summary

- We can win the war on cancer
- Understanding the mechanisms by which tumors respond to or resist immune recognition and attack is essential to developing new combinatorial therapy approaches
- Thanks to Dr. Satiro N. De Oliviera, UCLA for graciously providing slide content (the Cancer Immunity Cycle)