

# Presenter Disclosure Information

*Satiro De Oliveira, MD*

The following relationships exist related to this presentation:

*No Relationships to Disclose*

## Basic Principles of Tumor Immunotherapy

**Satiro De Oliveira, M.D.**

*Mattel Children's Hospital at UCLA  
Jonsson Comprehensive Cancer Center*

Tumor Immunology 101

11/12/16



Society for Immunotherapy of Cancer

# Outline

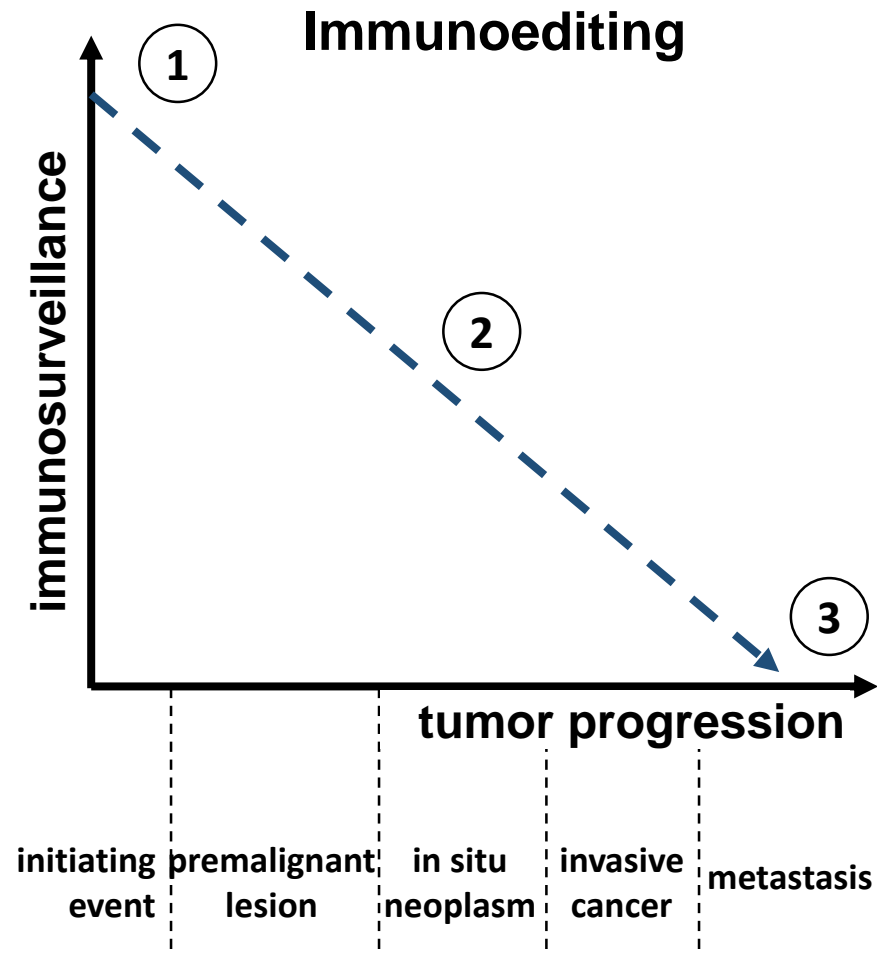
- 1. Immunosurveillance and Immunoediting*
- 2. Tumor-associated antigens*
- 3. Cancer Immunity Cycle*
- 4. Immunotherapy approaches*
- 5. Take Home Messages*

# Immunosurveillance and Immunoediting 1/3

- The cancer Immunosurveillance hypothesis: initial concept in 1909.
- Burnet & Thomas, 1957: lymphocytes acting as sentinels in recognizing and eliminating continuously emerging transformed cells.

**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.

# Immunosurveillance and Immunoediting 2/3



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

**2.Equilibrium:** elimination not complete successful, and tumor undergoes changes that aid survival facing selection pressure by the immune system

**3.Escape:** tumor cells accumulated sufficient mutations to escape the immune system, growing to become clinically detectable

# Immunosurveillance and Immunoediting 3/3

- **Immunotherapy:**

“treatment of disease by inducing, enhancing, or suppressing an immune response”

➤ to harness and augment antitumor responses to treat cancer more effectively

## ☐ **Passive immunotherapy:**

- does not engage adaptive immune response
- fast-acting
- transient
- cytokines, monoclonal antibodies, adoptive T cells

## ☐ **Active immunotherapy:**

- engages adaptive immune response
- delayed onset
- life-long generation of immunological memory
- cancer vaccines

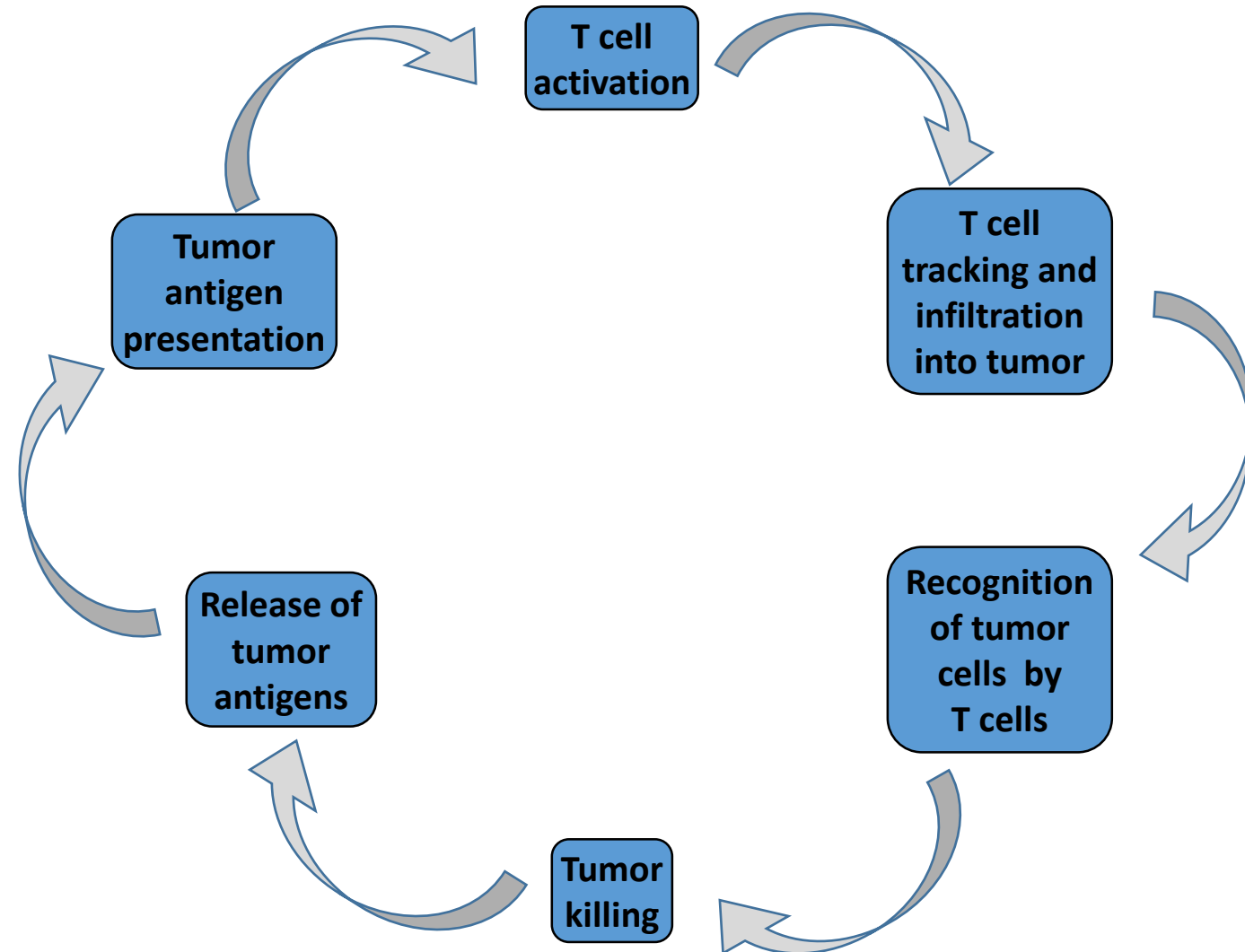
# How the Immune System Recognizes and Eradicates Cancer

## **Tumor-associated antigens (TAA):**

targets of a tumor-specific T-cell response that rejects the tumor; immunization with irradiated tumor cells protects from challenge with live cells from the same tumor.

1. Tumor-specific Ag: mutated molecules (CDK4 and  $\beta$ -catenin)
2. Cancer-testis Ag: expressed only in germ cells in testis (NY-ESO, MAGE-3)
3. Differentiation Ag: expressed only in particular tissues (tyrosinase, CD19)
4. Abnormal tumor expression Ag: overexpression in tumor compared to normal (HER-2/neu, WT1)
5. Abnormal post-translational modification Ag (underglycosylated MUC-1)
6. Abnormal post-transcriptional modification: novel proteins generated when introns are retained in the mRNA (GP100)
7. Oncoviral protein Ag: viral proteins expressed in virus-associated tumors (HPV type 16, E6 and E7 proteins)

# The Cancer Immunity Cycle



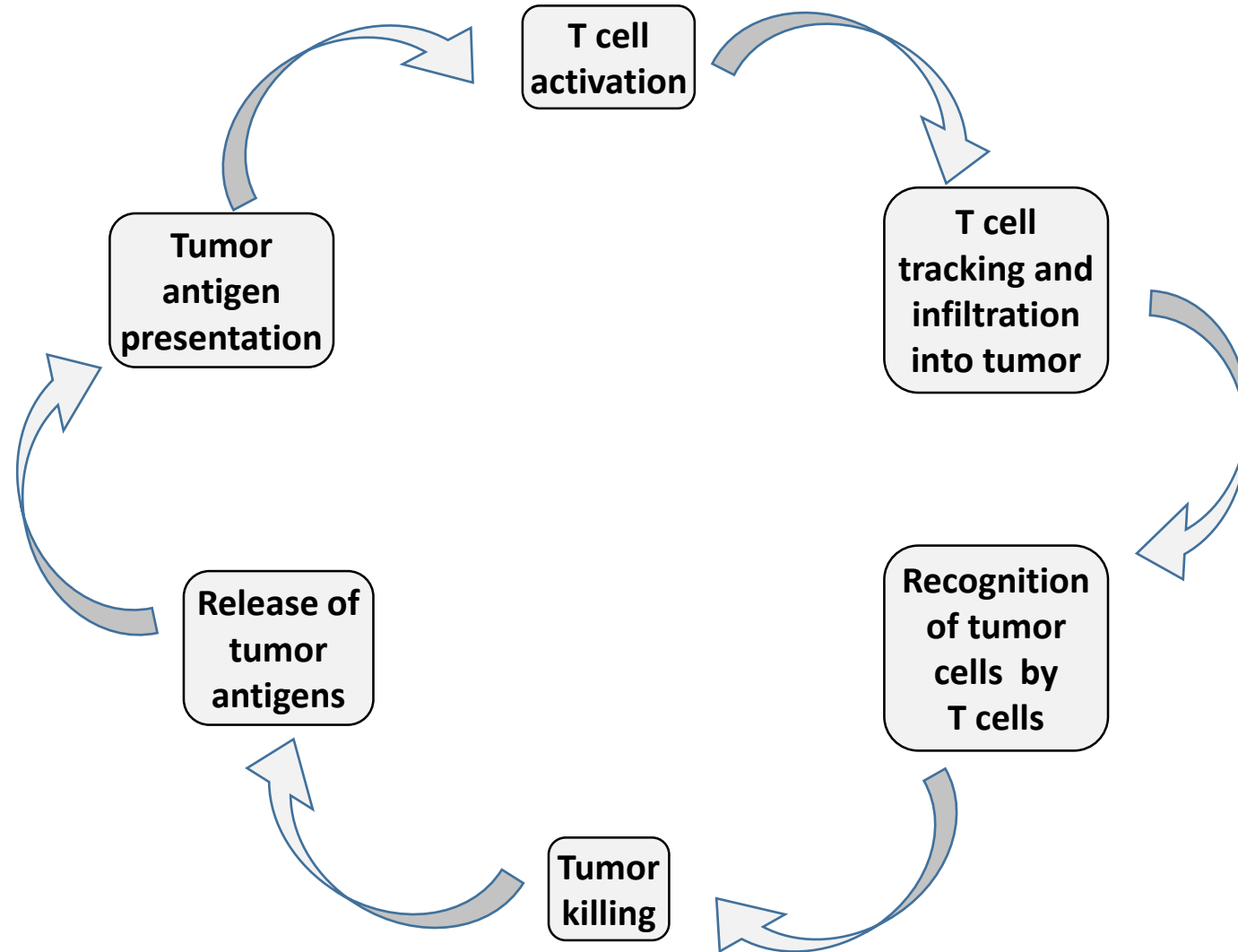
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Chen & Mellman, 2013



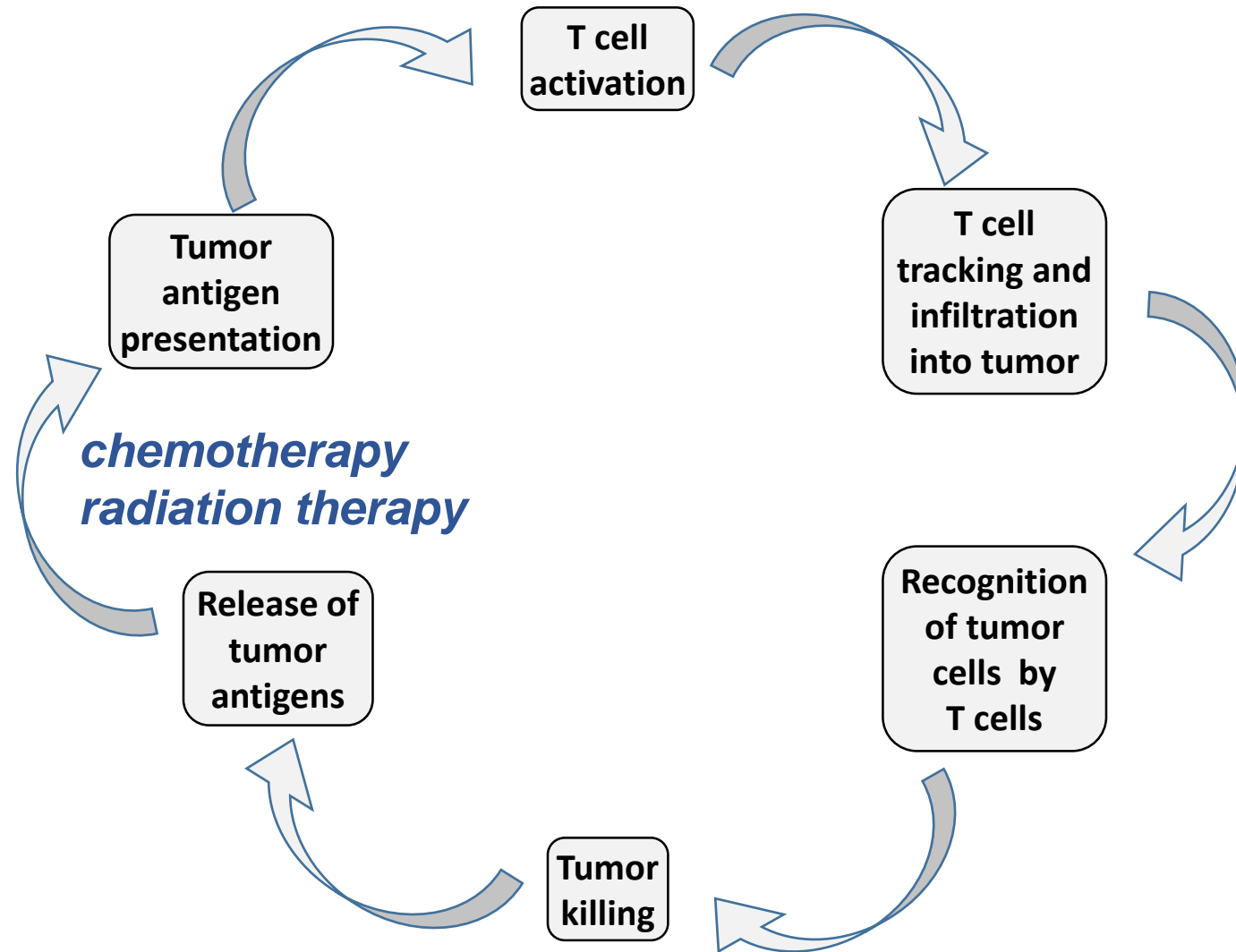
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- 2. Tumor-associated antigens*
- 3. Cancer Immunity Cycle*
- 4. Immunotherapy approaches**
- 5. Take Home Messages*

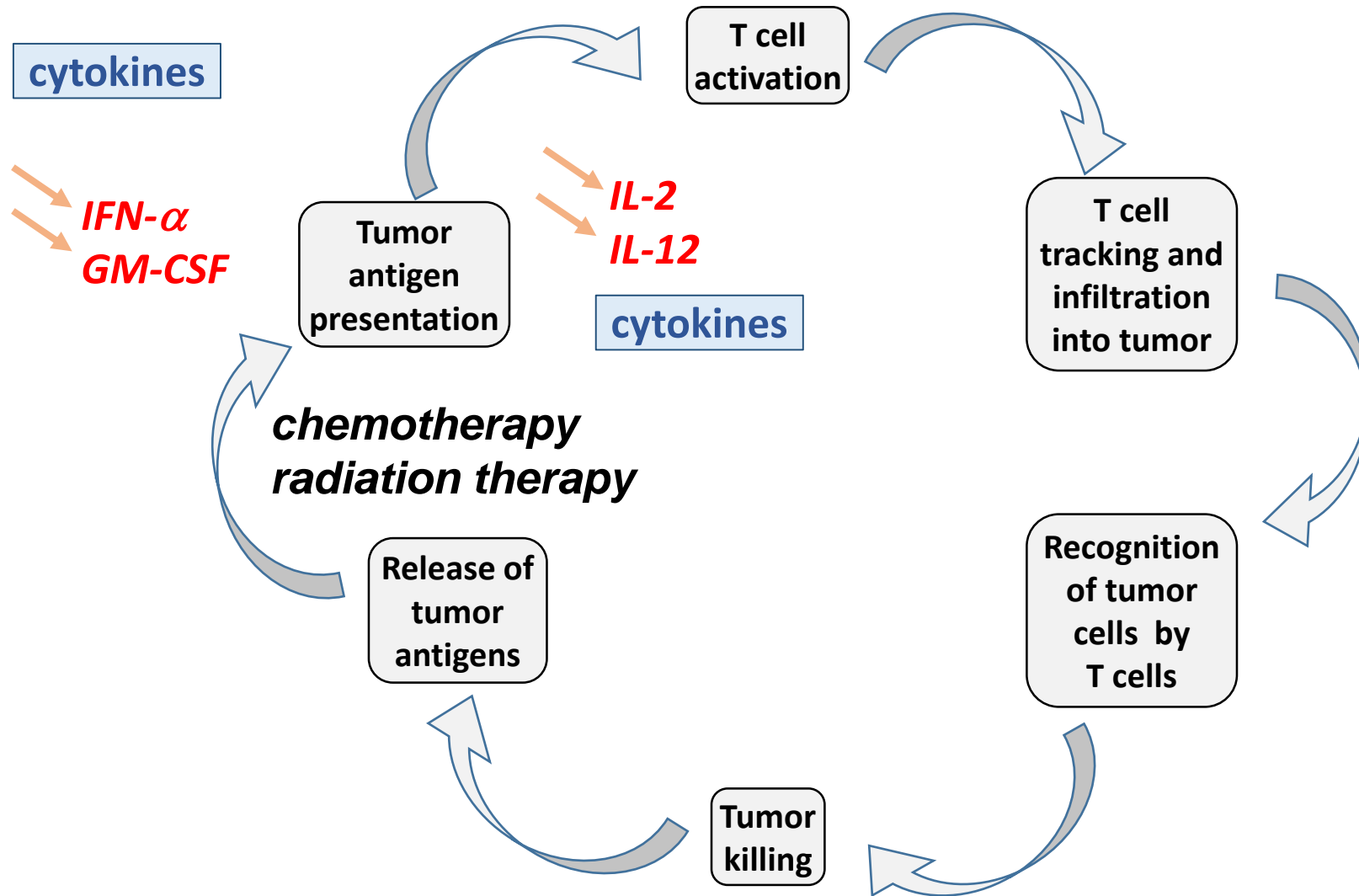
# Approaches to Tumor Immunotherapy



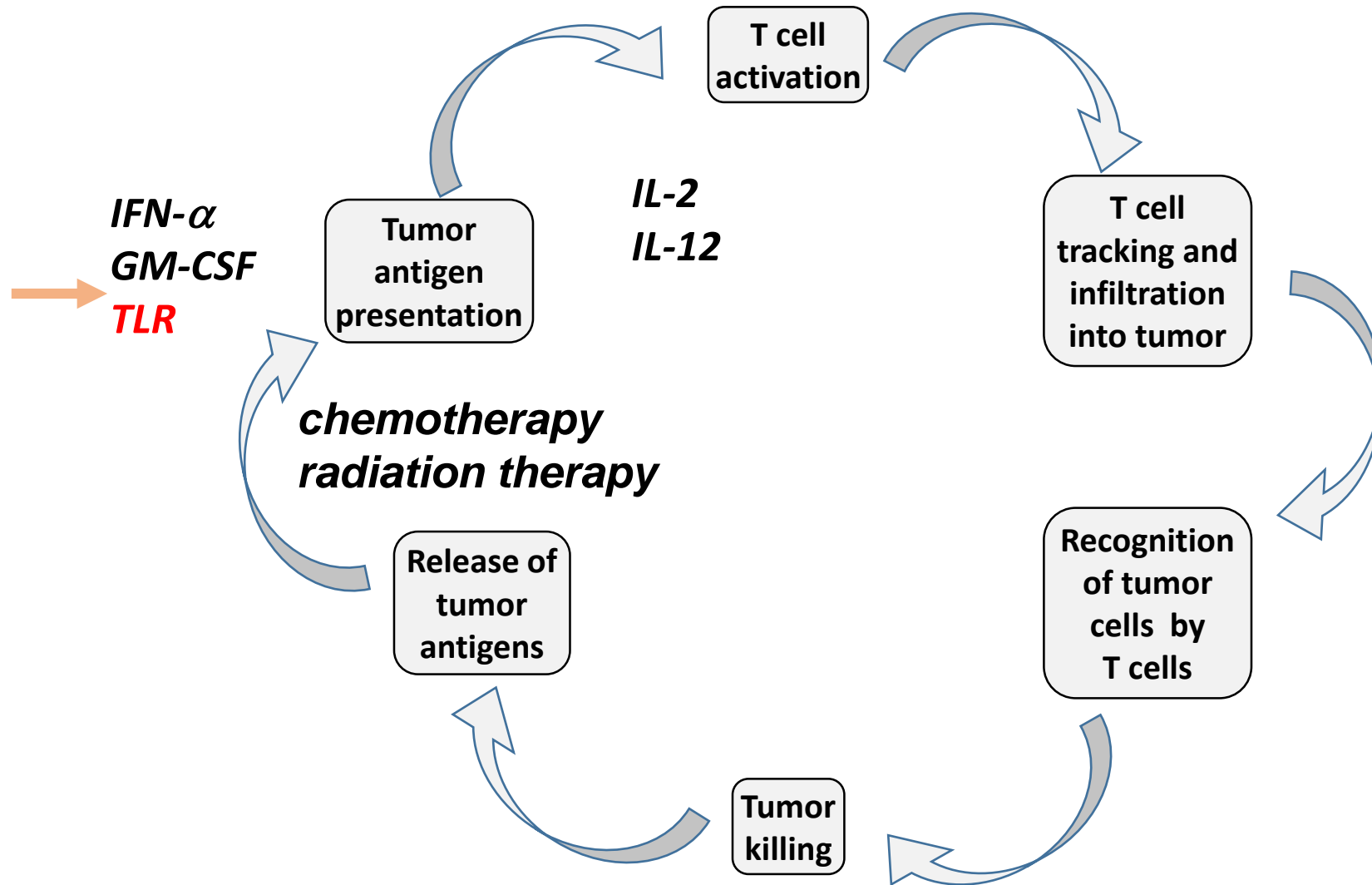
# Approaches to Tumor Immunotherapy



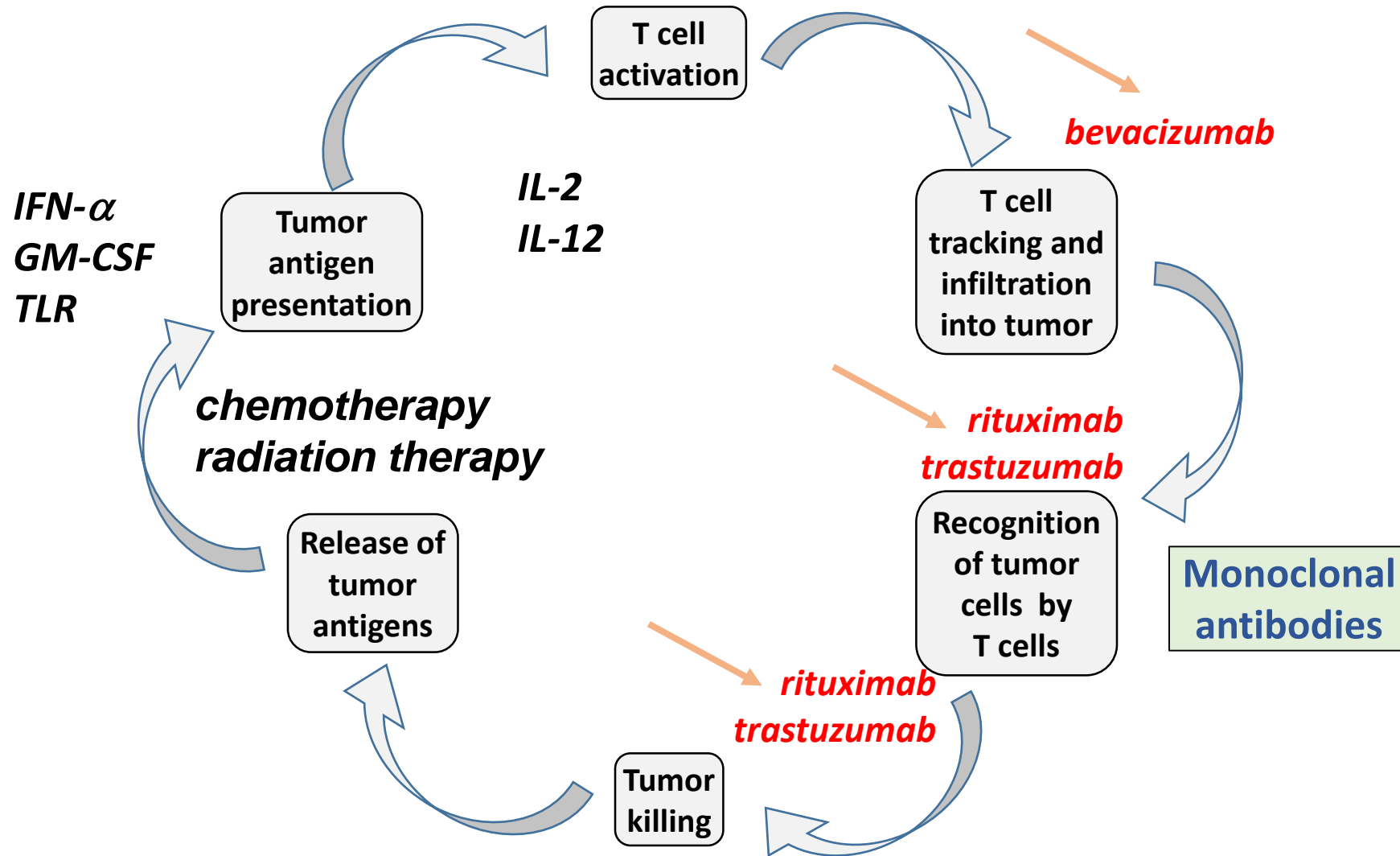
# Approaches to Tumor Immunotherapy



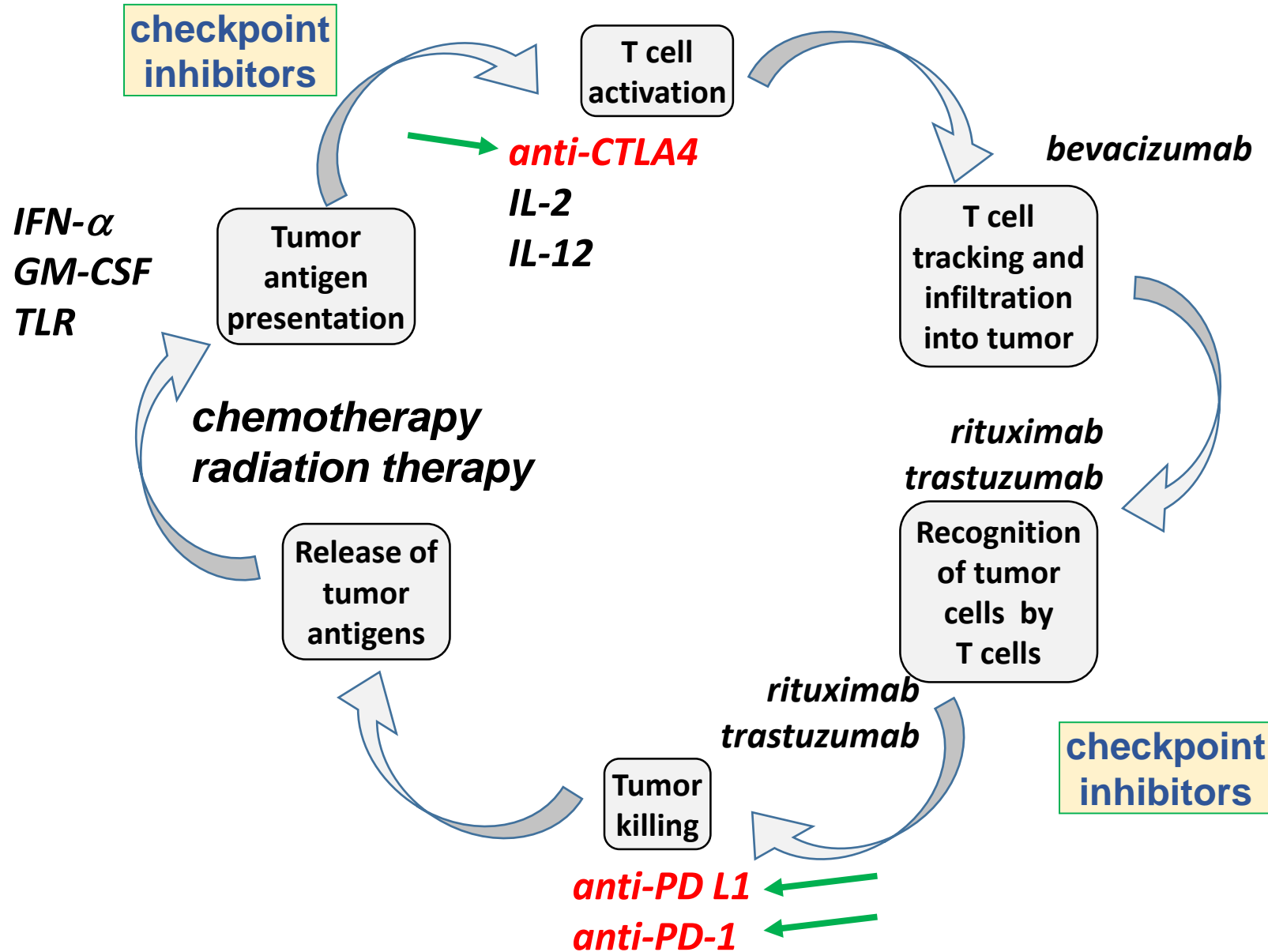
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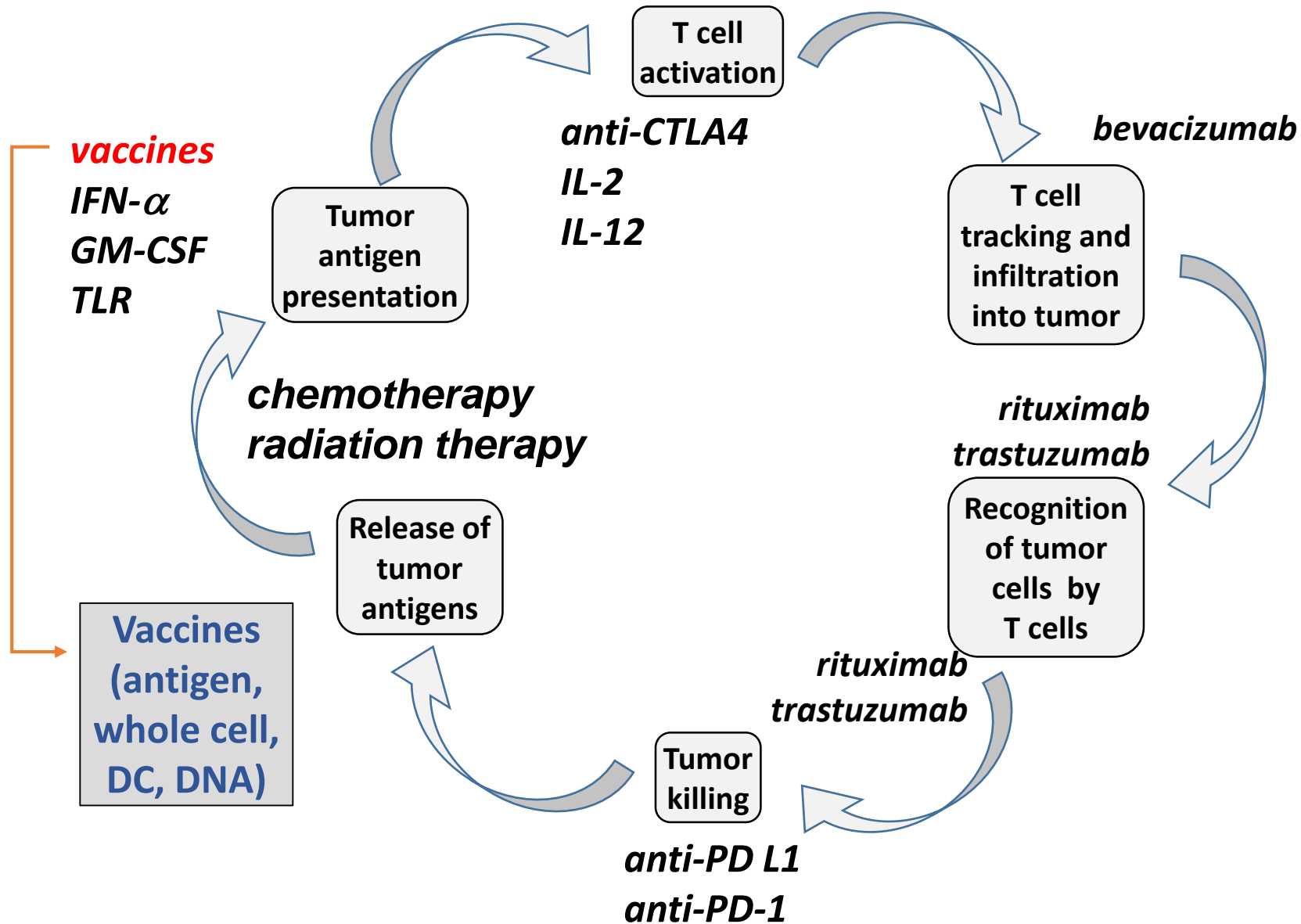
# Approaches to Tumor Immunotherapy



# Approaches to Tumor Immunotherapy

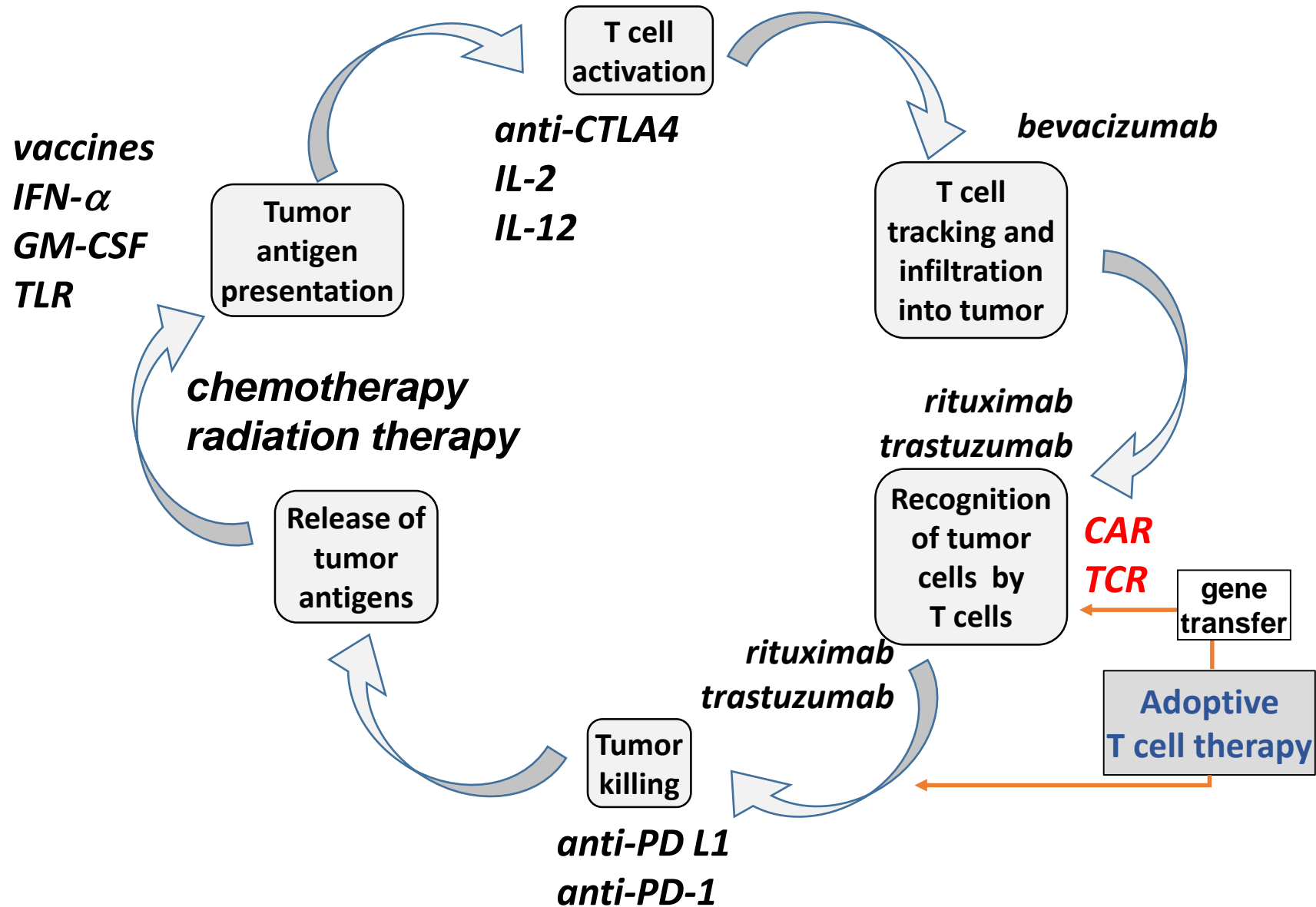


# Approaches to Tumor Immunotherapy

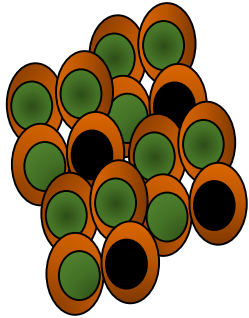




# Approaches to Tumor Immunotherapy



# Combinations

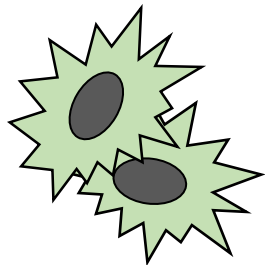
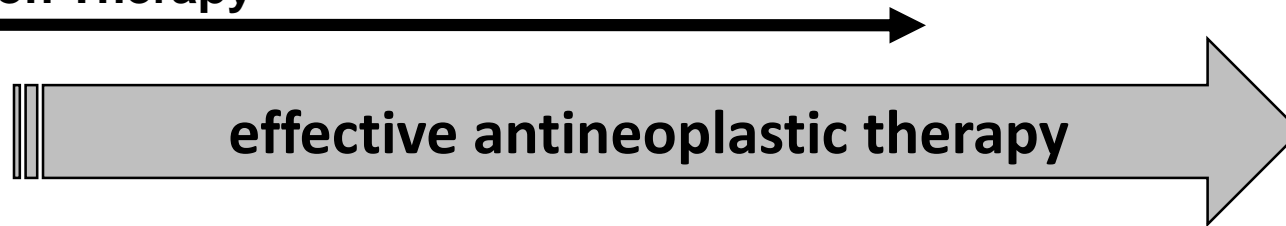


cancer  
cells

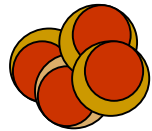
Surgery  
Chemotherapy  
Radiation Therapy

## Immunotherapy:

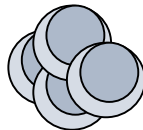
- Increase tumor antigenicity
- Increase tumor immunogenicity
- Increase tumor immune susceptibility



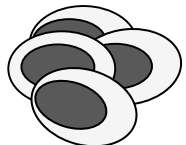
dendritic cells



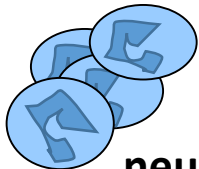
NK cells



T cells



monocytes



neutrophils

## Immunotherapy:

- Activation of innate immunity
- Activation of adaptive immunity
- Inactivation of suppressive factors

# Radiation therapy and the abscopal effect

- Abscopal effect (1953): “away from the target”
- Tumor regressions in renal cell carcinoma, lymphoma and leukemia, neuroblastoma, breast carcinoma and melanoma
- Immune-mediated mechanism

N Engl J Med 366 (2012) 925–931

Int J Radiat Oncol Biol Phys. 85 (2013) 293-295

Am J Clin Oncol. 38 (2015) 119-125

Cancer Letters 356 (2015) 82–90

# Chemotherapy has stimulatory and inhibitory effects on the immune system

## Immune-Suppression

- lymphopenia
- non-immunogenic cell death (apoptosis)

## Immune-Stimulation

- enhanced antigenicity and immunogenicity
- homeostatic proliferation
- inhibition of Tregs and MDSC

# Lessons and Take Home Messages

- Immunosurveillance has a key role in preventing and fighting cancer.
- Immunotherapy as a pillar of cancer therapy.
- Integration of immunotherapy concepts into cancer therapies will lead to improved outcomes.