

Society for Immunotherapy of Cancer (SITC)

Basic Principles of Tumor Immunotherapy

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Society for Immunotherapy of Cancer

Disclosures

No relevant financial relationships to disclose

Outline

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

Outline

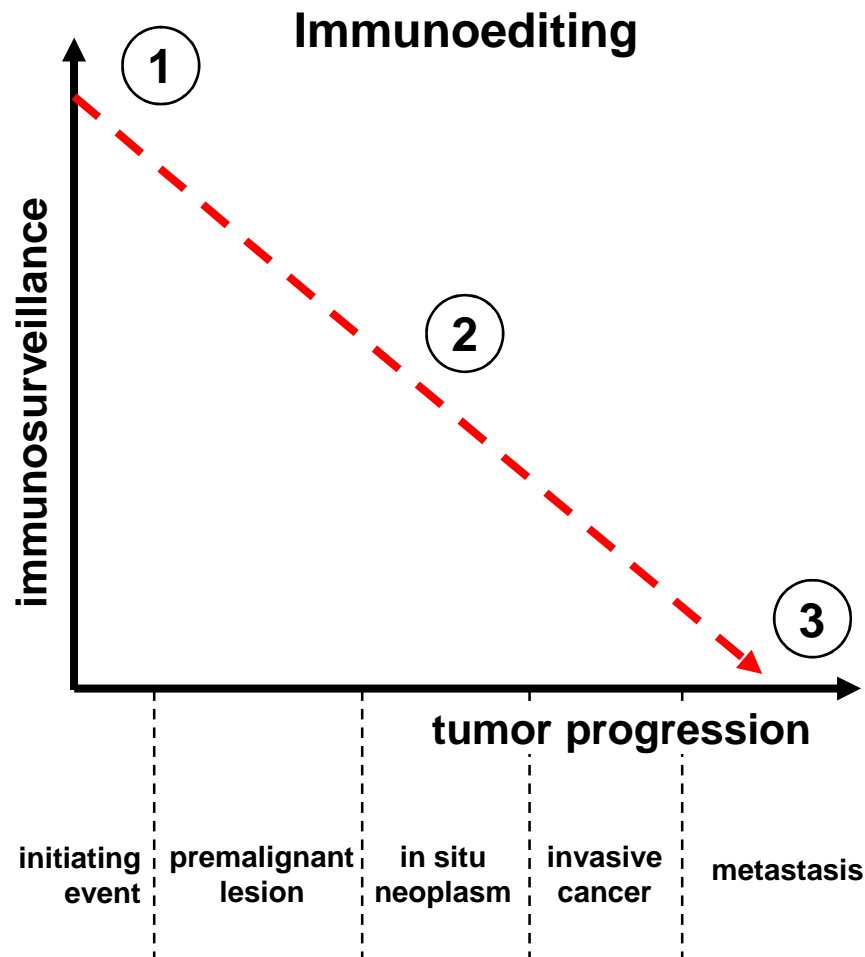
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Immunosurveillance and Immunotherapy

- 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 Immunotherapy ^{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 Immunotherapy

- **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

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How the Immune System Recognizes and Eradicates Cancer

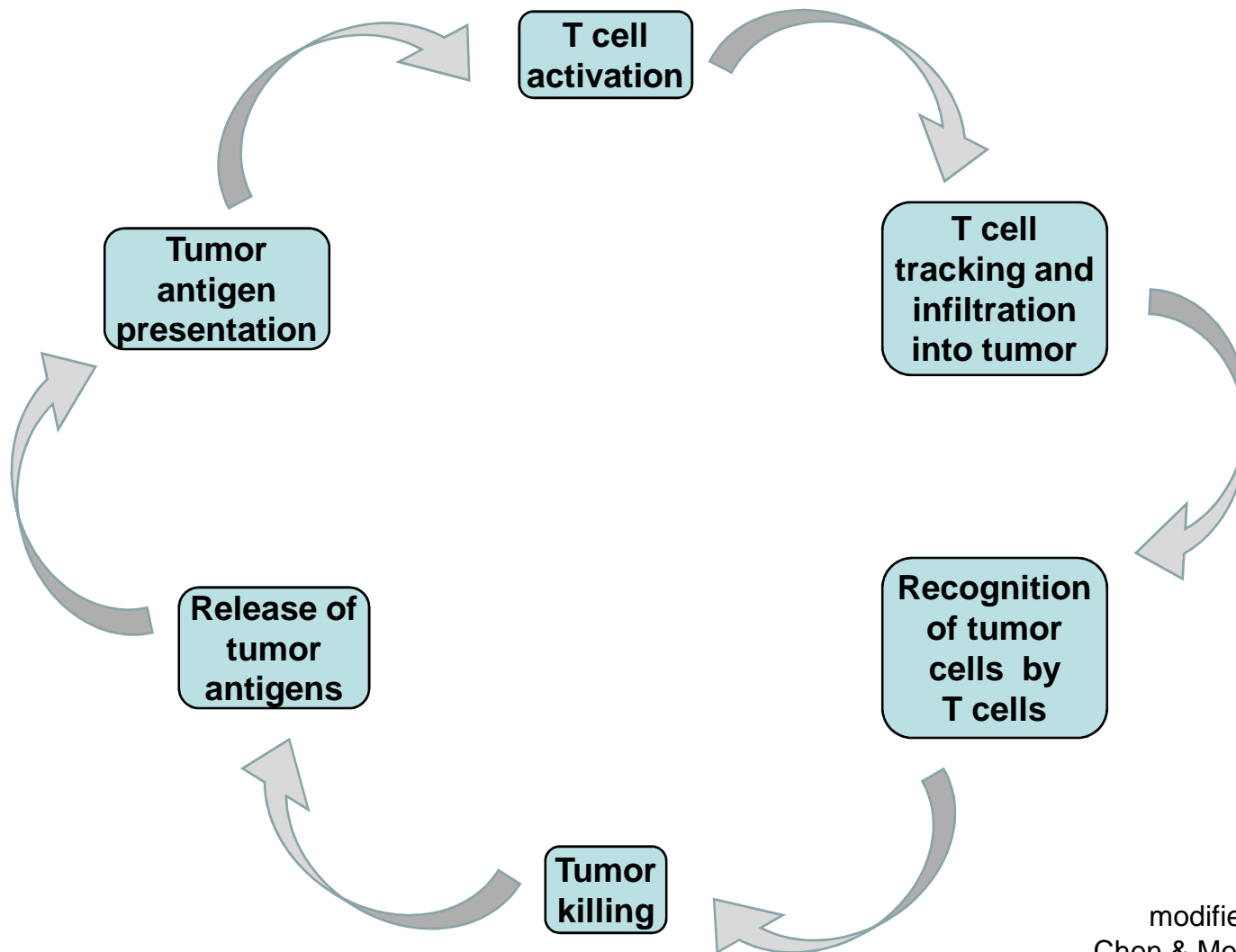
Tumor-associated antigens (TAA): targets of a tumor-specific T-cell response that rejects the tumor; immunization with irradiated tumor cells protects from challenge with live cells from the same tumor.

1. Tumor-specific Ag: mutated molecules (CDK4 and β -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 cells compared to normal counterparts (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)

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The cancer immunity cycle

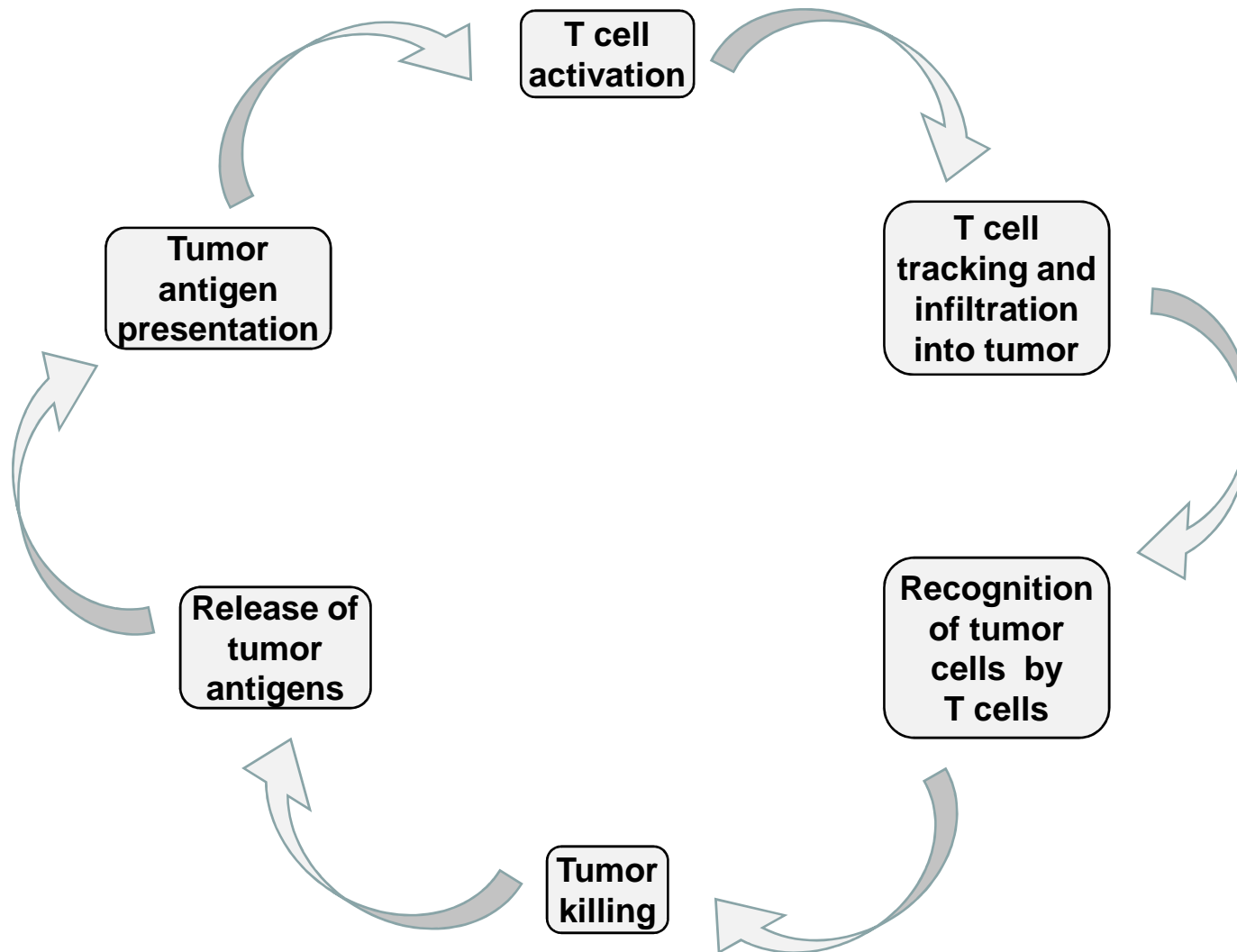


modified from
Chen & Mellman, 2013

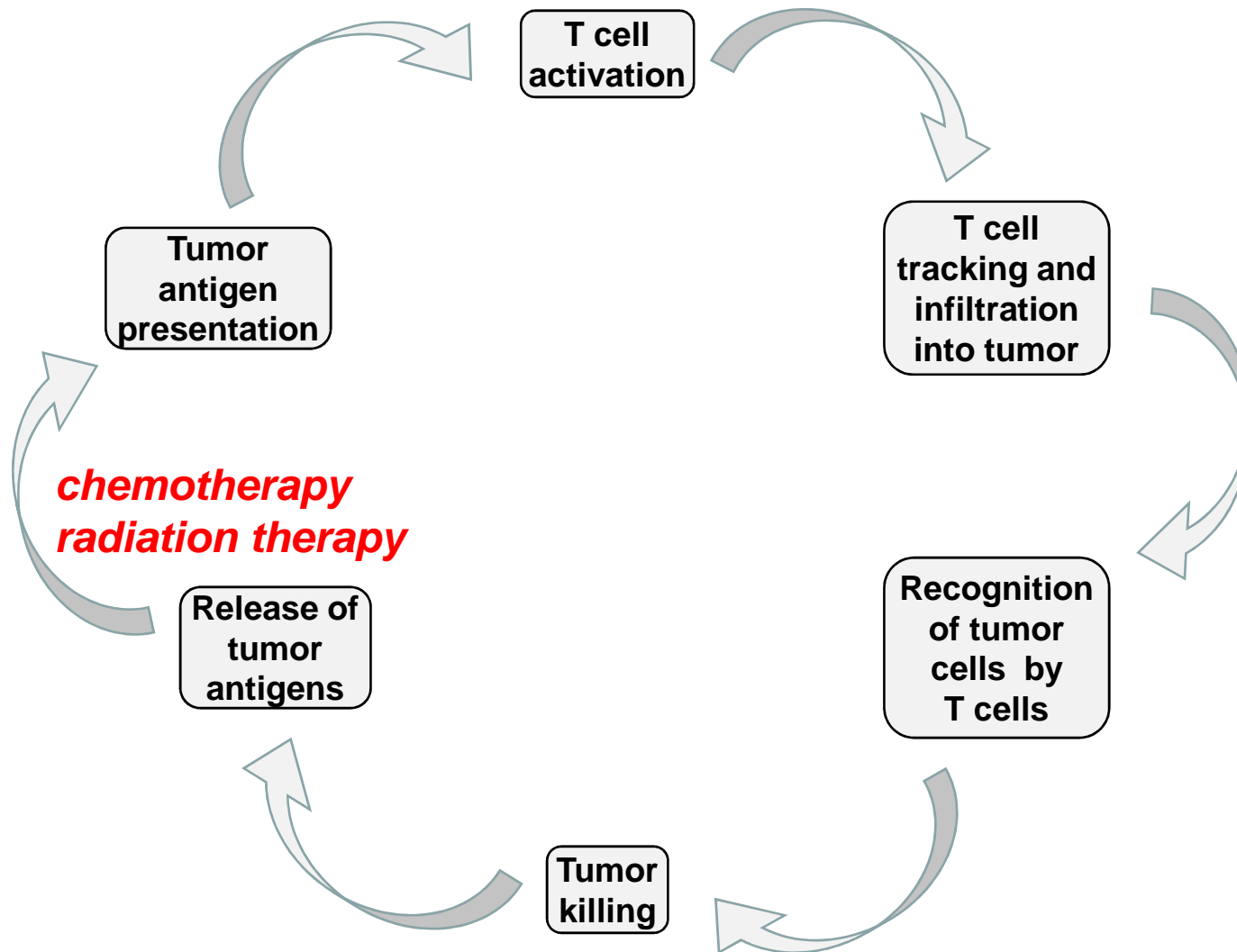
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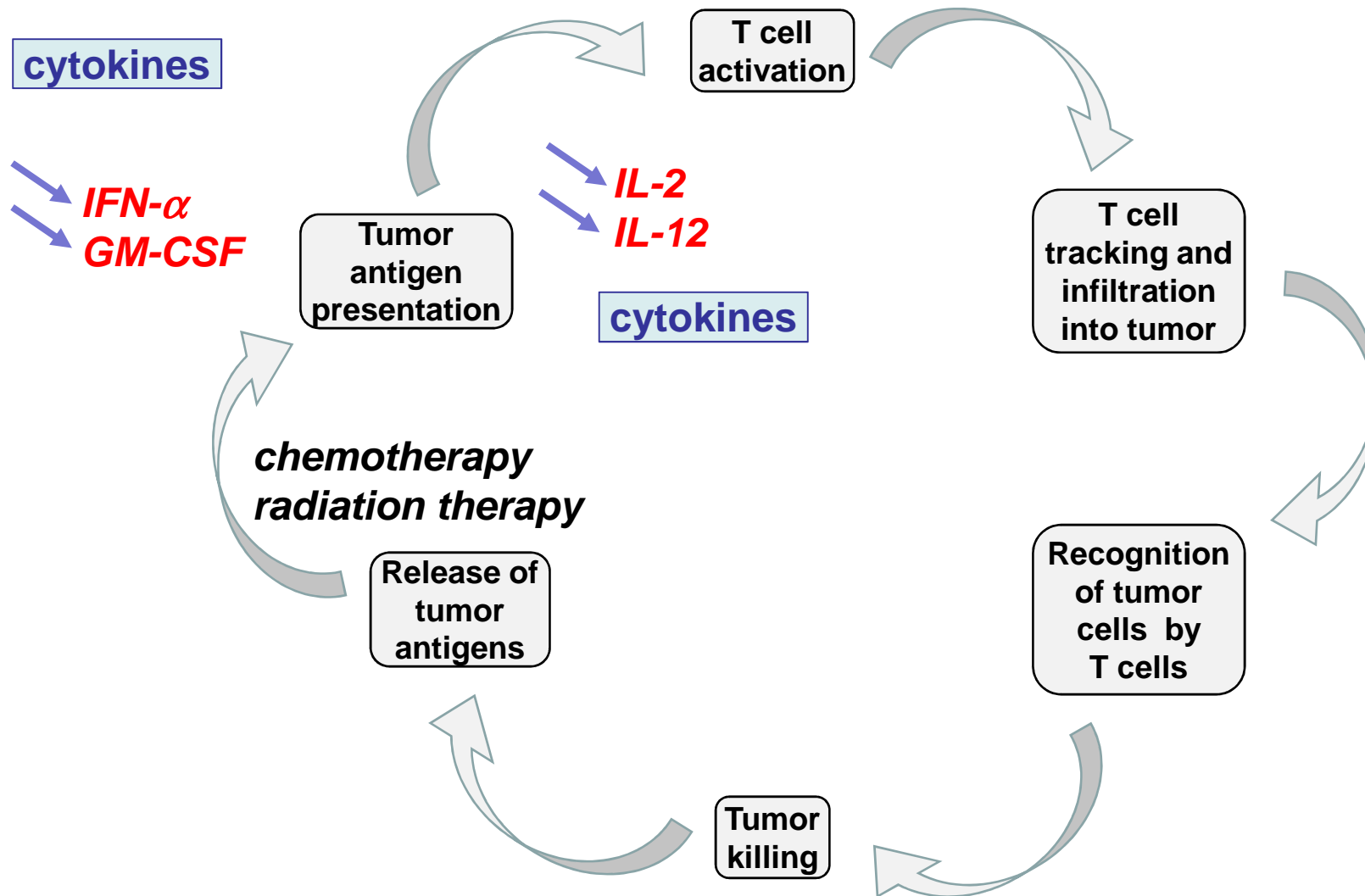
Approaches to Tumor Immunotherapy



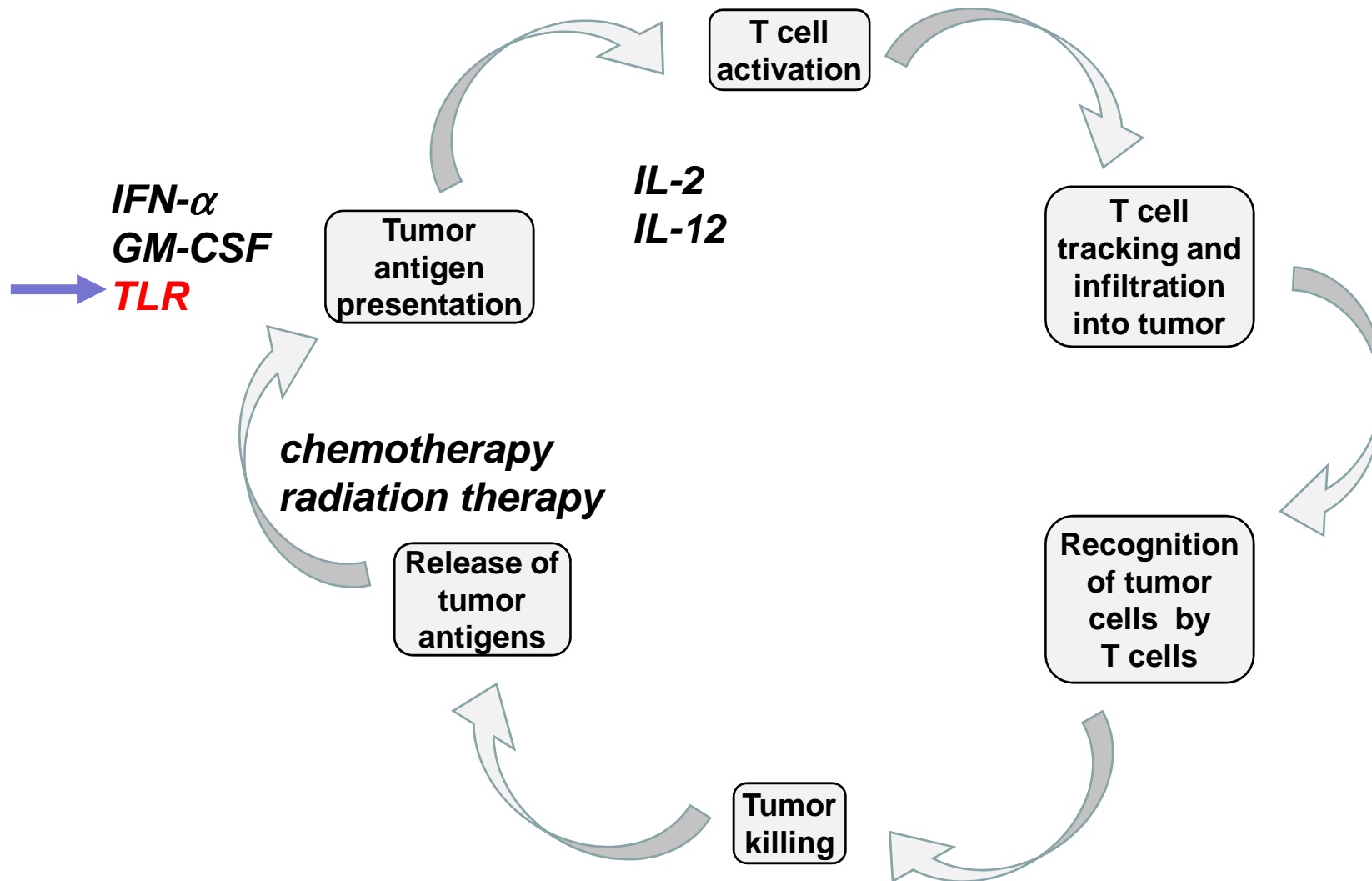
Approaches to Tumor Immunotherapy



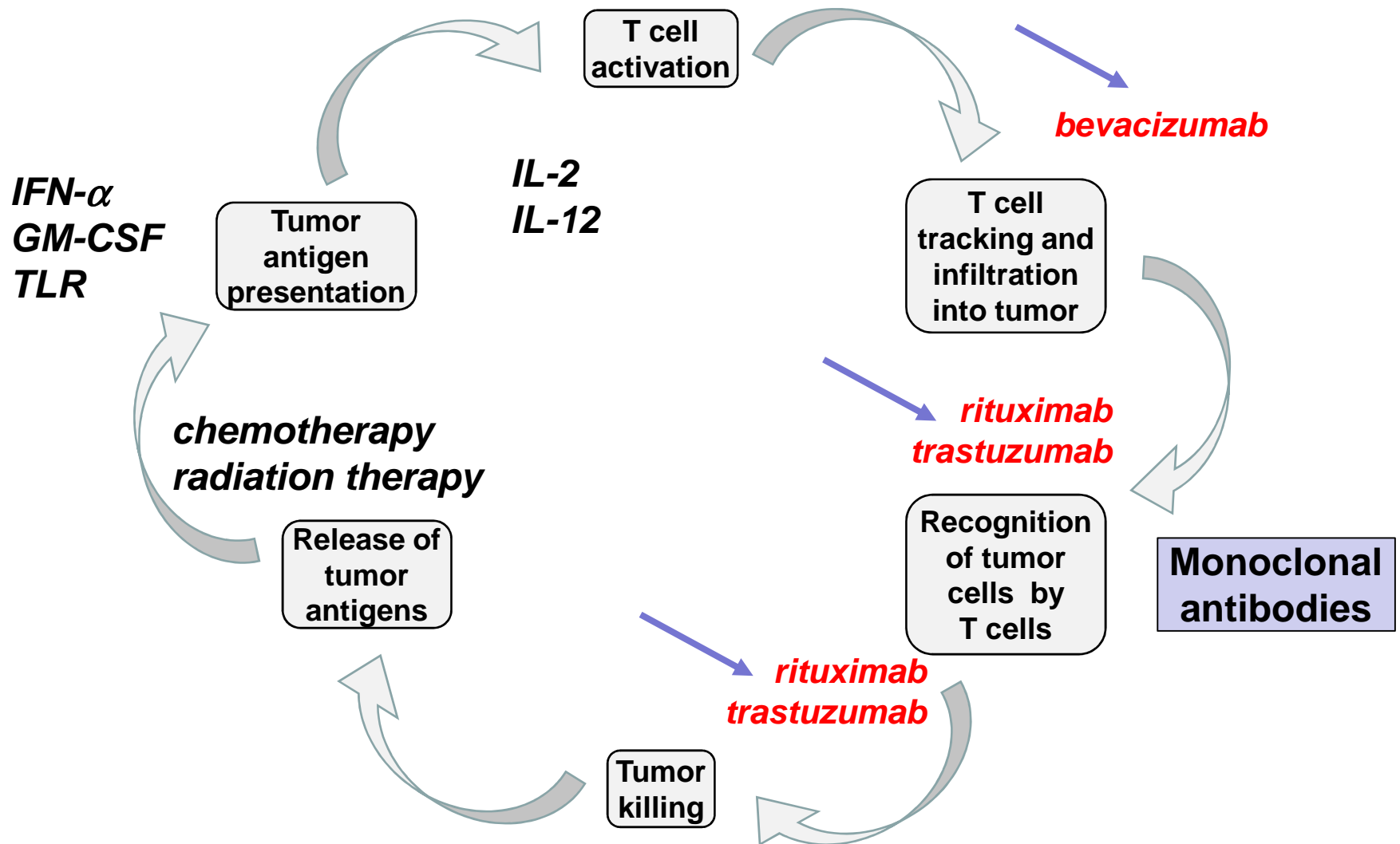
Approaches to Tumor Immunotherapy



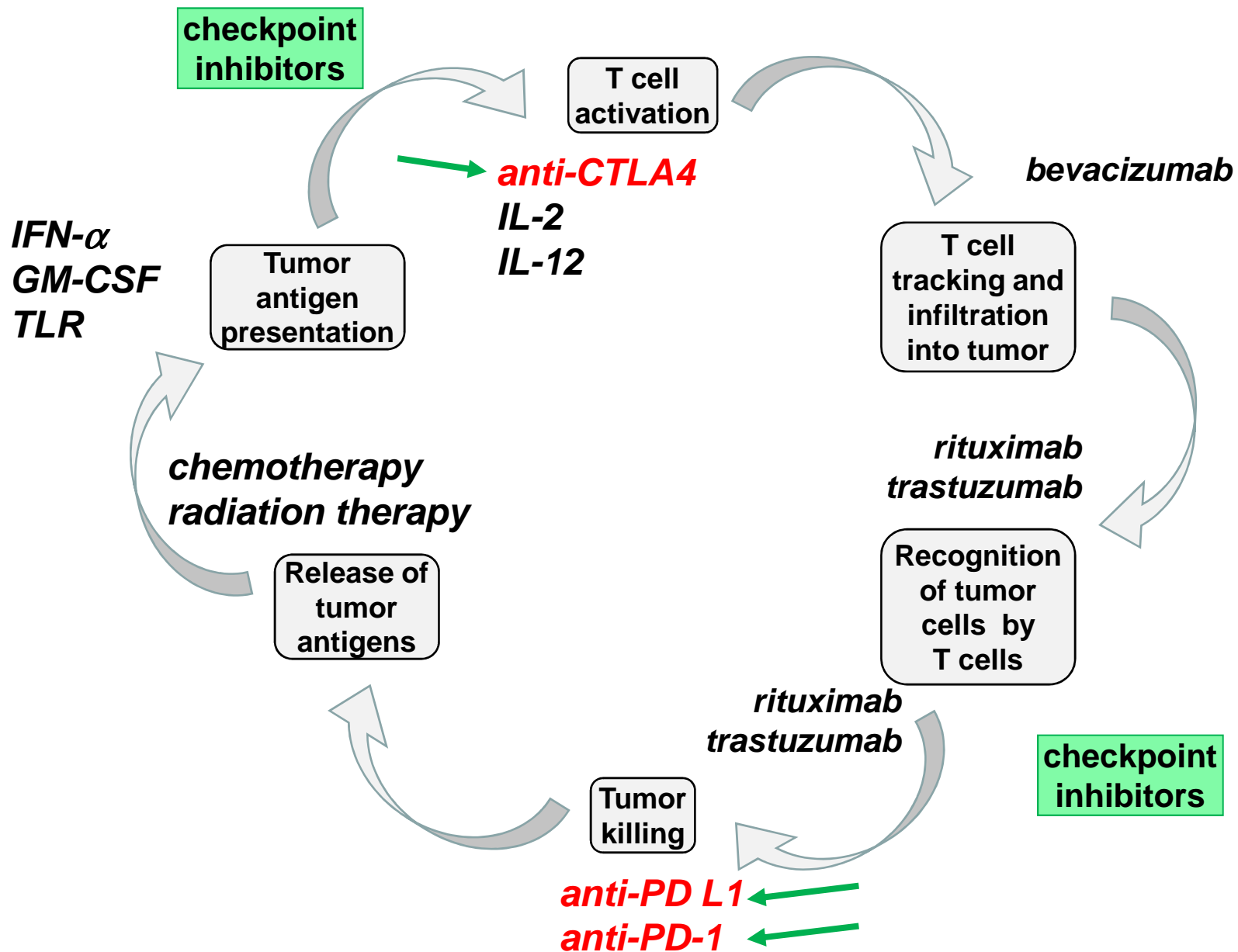
Approaches to Tumor Immunotherapy



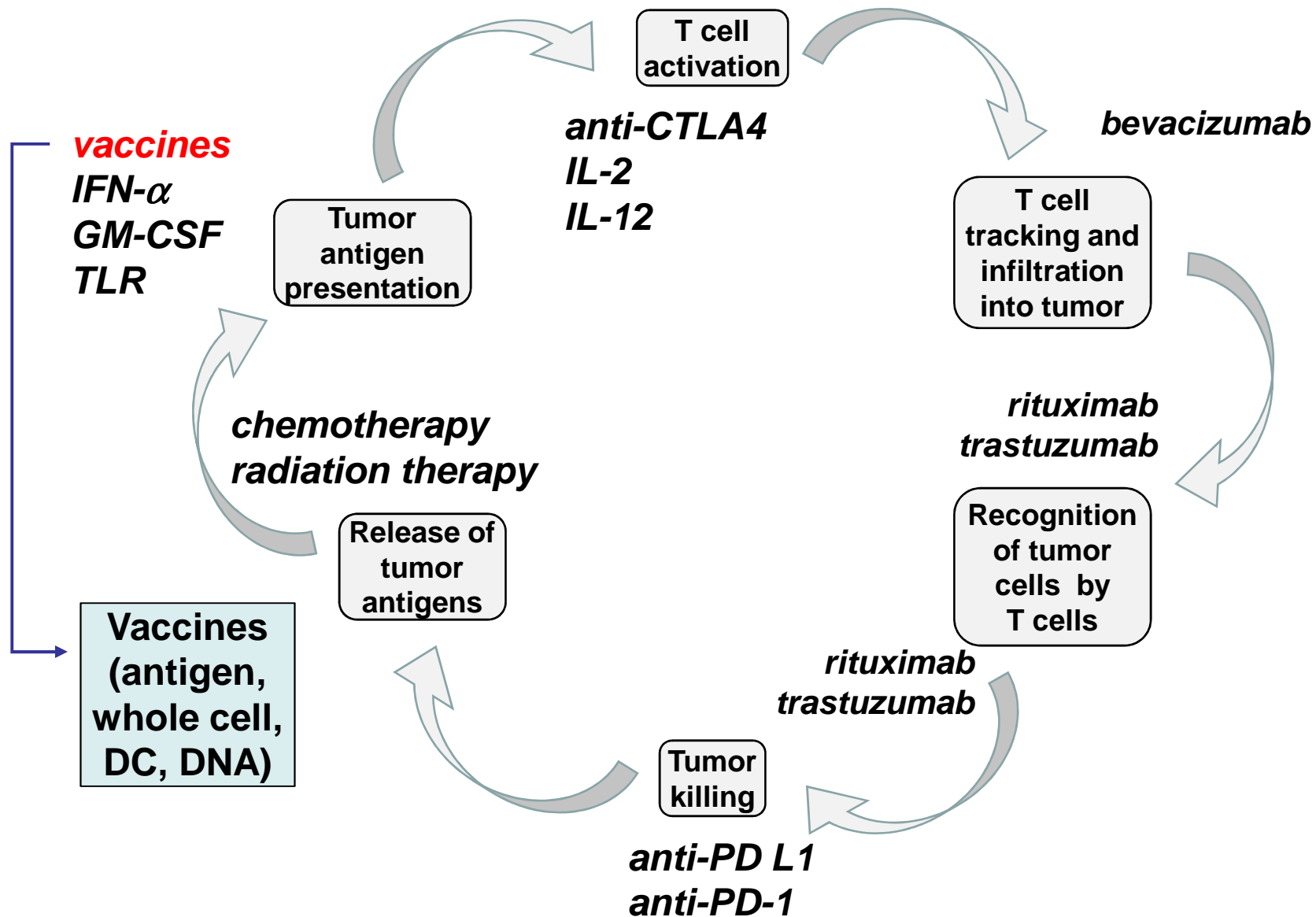
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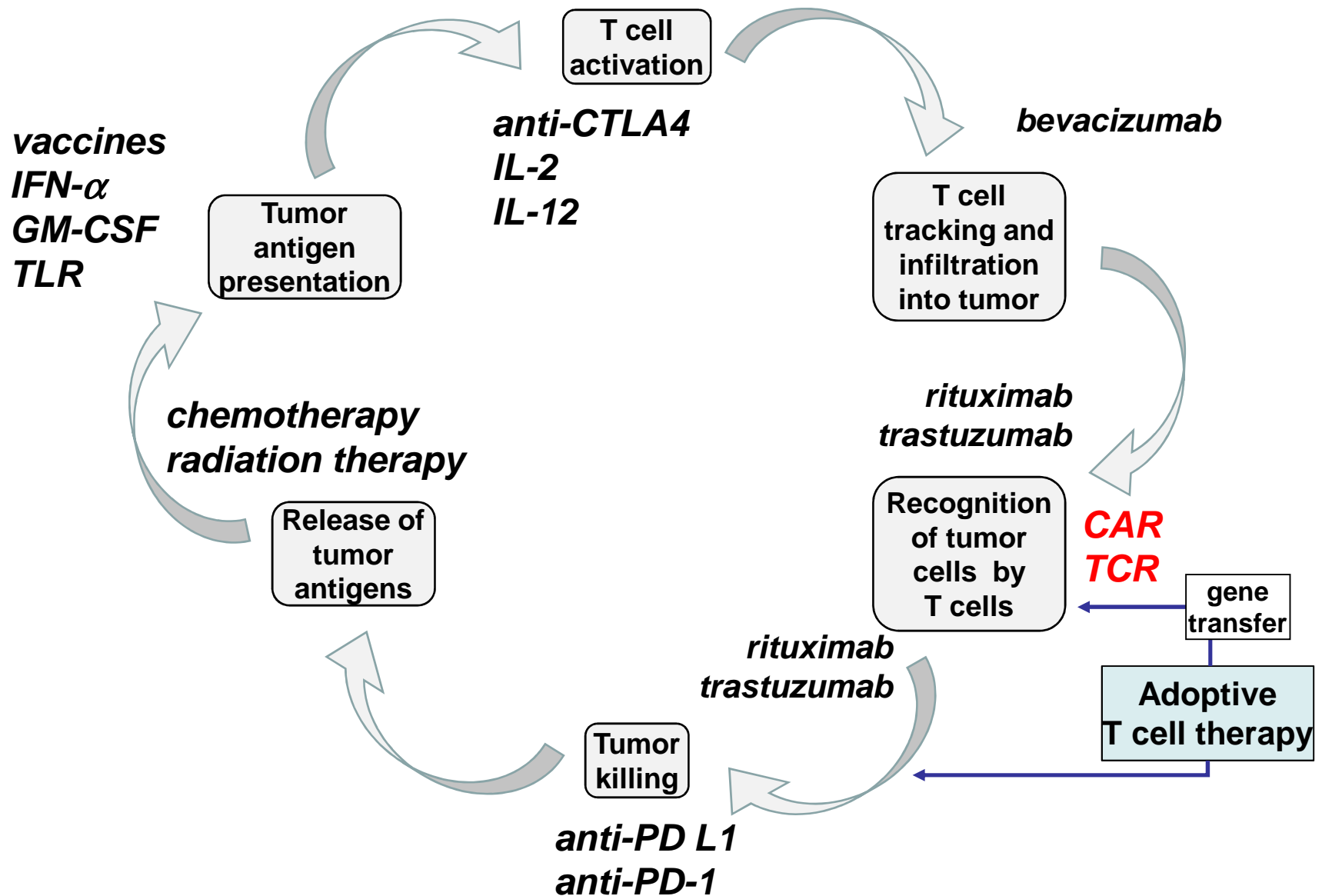
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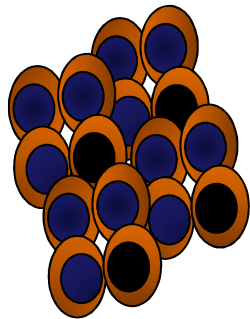
Approaches to Tumor Immunotherapy



Approaches to Tumor Immunotherapy



Combinations



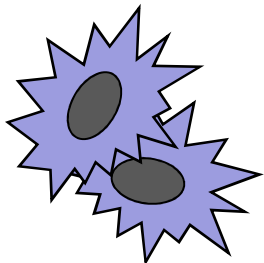
cancer cells

Surgery
Chemotherapy
Radiation Therapy

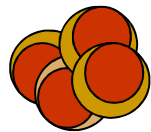
Immunotherapy:

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

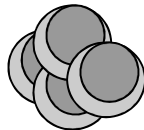
effective antineoplastic therapy



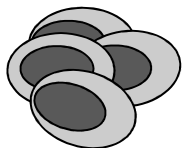
dendritic cells



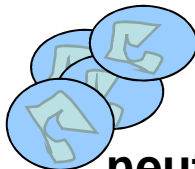
NK cells



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	Immune-Stimulation
<ul style="list-style-type: none">• lymphopenia• non-immunogenic cell death (apoptosis)	<ul style="list-style-type: none">• 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.



12/20/2013