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The Cancer Immunotherapy Armamentarium: Assessing Applications, Ambitions, and Amplitude

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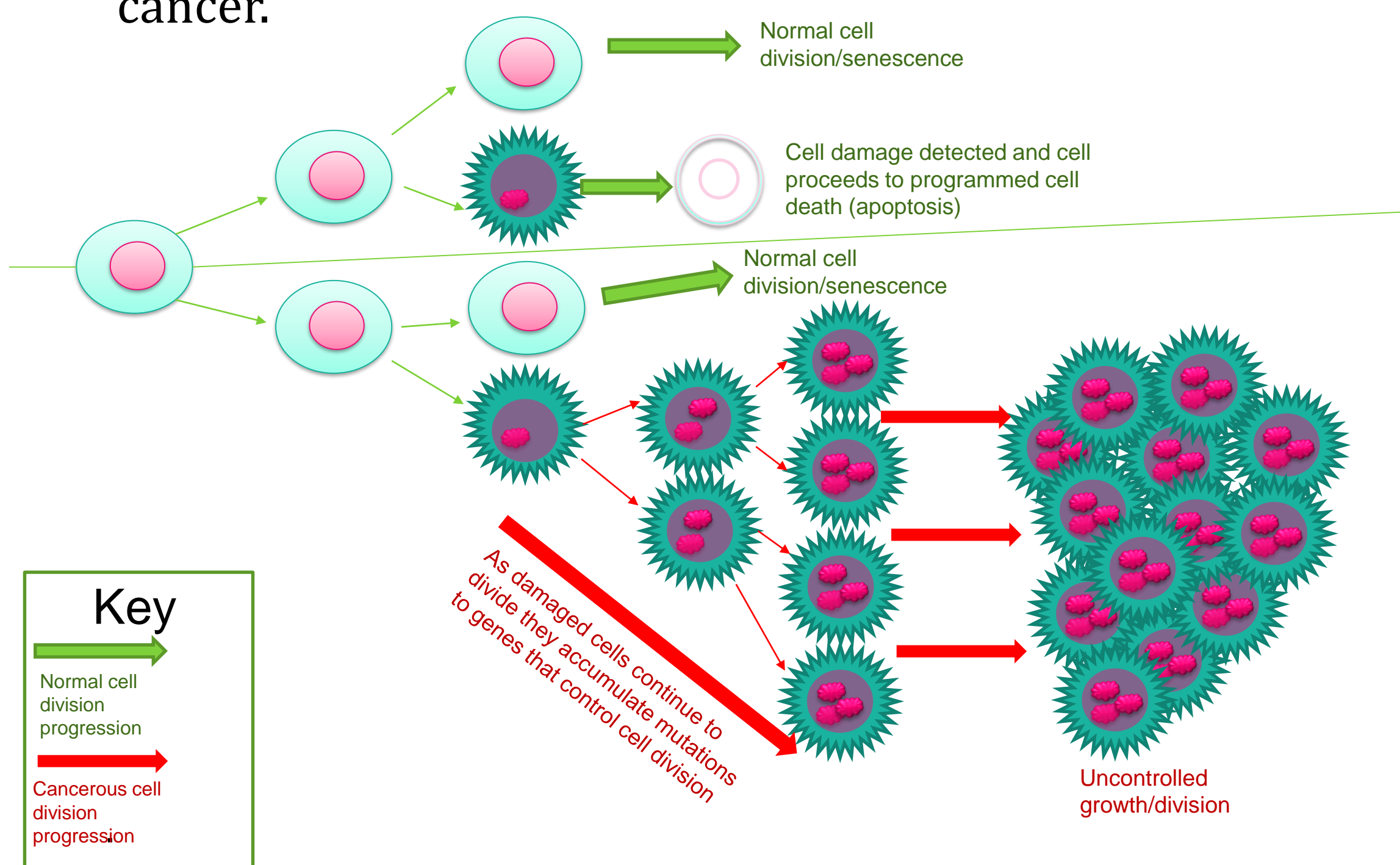
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-----Introduction-----

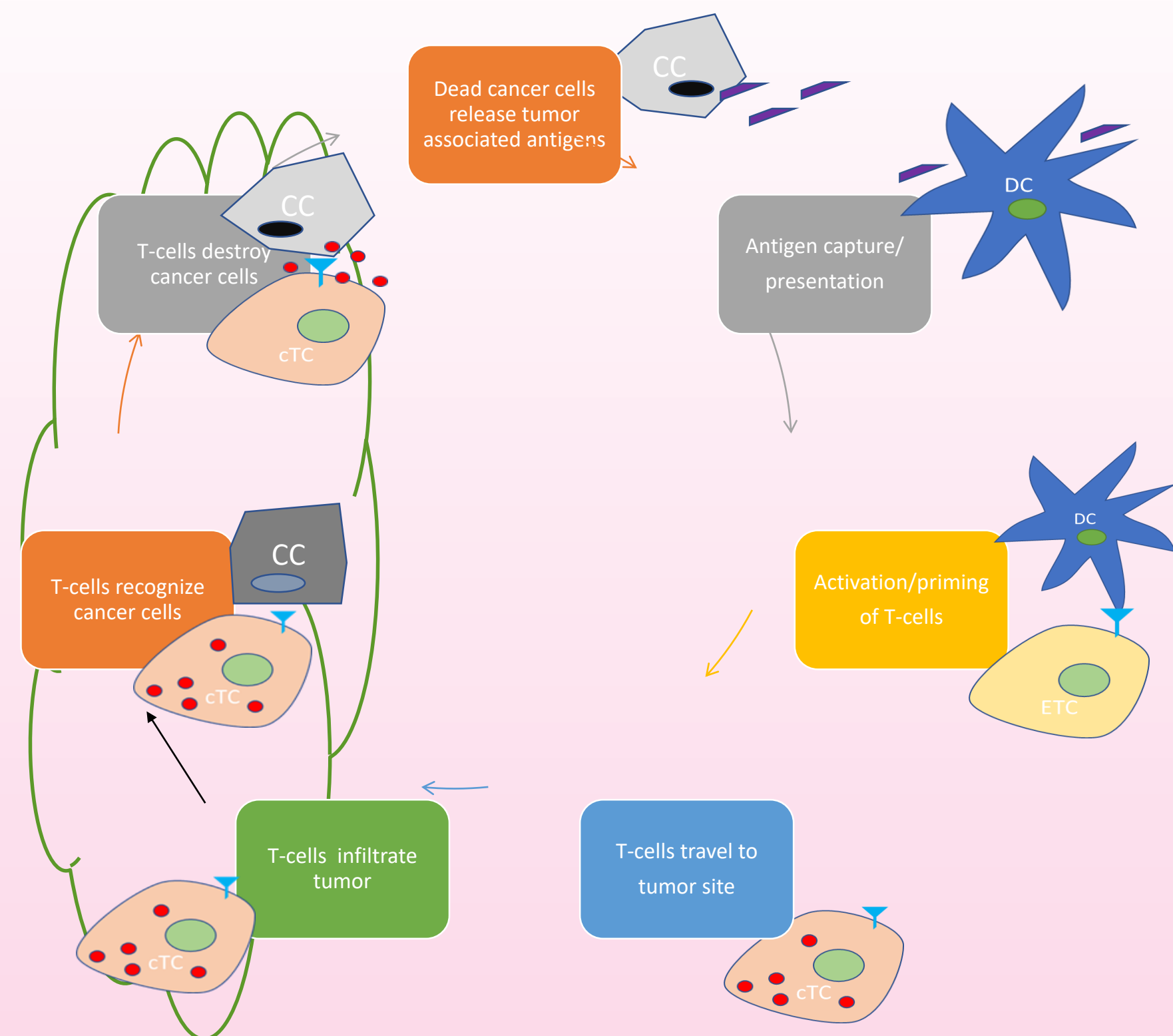
- ☉ Cancer is the second leading cause of death worldwide with a 70% increase in cases is expected over the next 20 years.¹
- ☉ Immunotherapy was recognized as advancement of the year in both 2016 and 2017.²
- ☉ Positive initial findings and clinical results of recent immunotherapies has precipitated a wave of attention and interest into the field, both in the general public and within the biomedical community.
- ☉ Some experts have speculated that this influx of attention and focus on immunotherapies has gone too far.³
- ☉ Others within the field think all the attention and support focused on immunotherapy can only be a good thing, and cultivates a landscape in which inquisition and competition leads to the best advances.⁴
- ☉ The aspect agreed upon by both sides: more funding and support of cancer research is needed.
- ☉ The importance of allocating funds and support sensibly is then critical.
- ☉ To achieve this, it is imperative that research areas and therapeutic modalities are assessed for current and prospective functionality, applicability, and amplitude.

-----Background-----

- ☉ Etiology, progression, and prognosis varies from one cancer type to another, the commonality is the abnormal proliferation of cells leading to malignant neoplasia (Fig. 1)
- ☉ A hallmark of cancers is their ability to suppress and/or evade the anti-tumor defenses of the immune system.⁵
- ☉ Restoration and enhancement of immune function within the neoplastic microenvironment is thereby a logical and promising path to continue pursuing in the fight against cancer.



- ☉ Essentially there are seven steps or points that must occur for the immune system to effectively kill cancer cells. (Fig. 2)



-----Current Approaches-----

Checkpoint Inhibitors

- ☉ Two common targets: PD-L1 and CTLA4
- ☉ Only approved for treating 10 of over 100 cancer types⁶
- ☉ Side effects/complications: autoimmune hepatitis, pneumonitis, pulmonary toxicity⁶
- ☉ Oversaturation in clinical trials: currently over 1100 active trials³

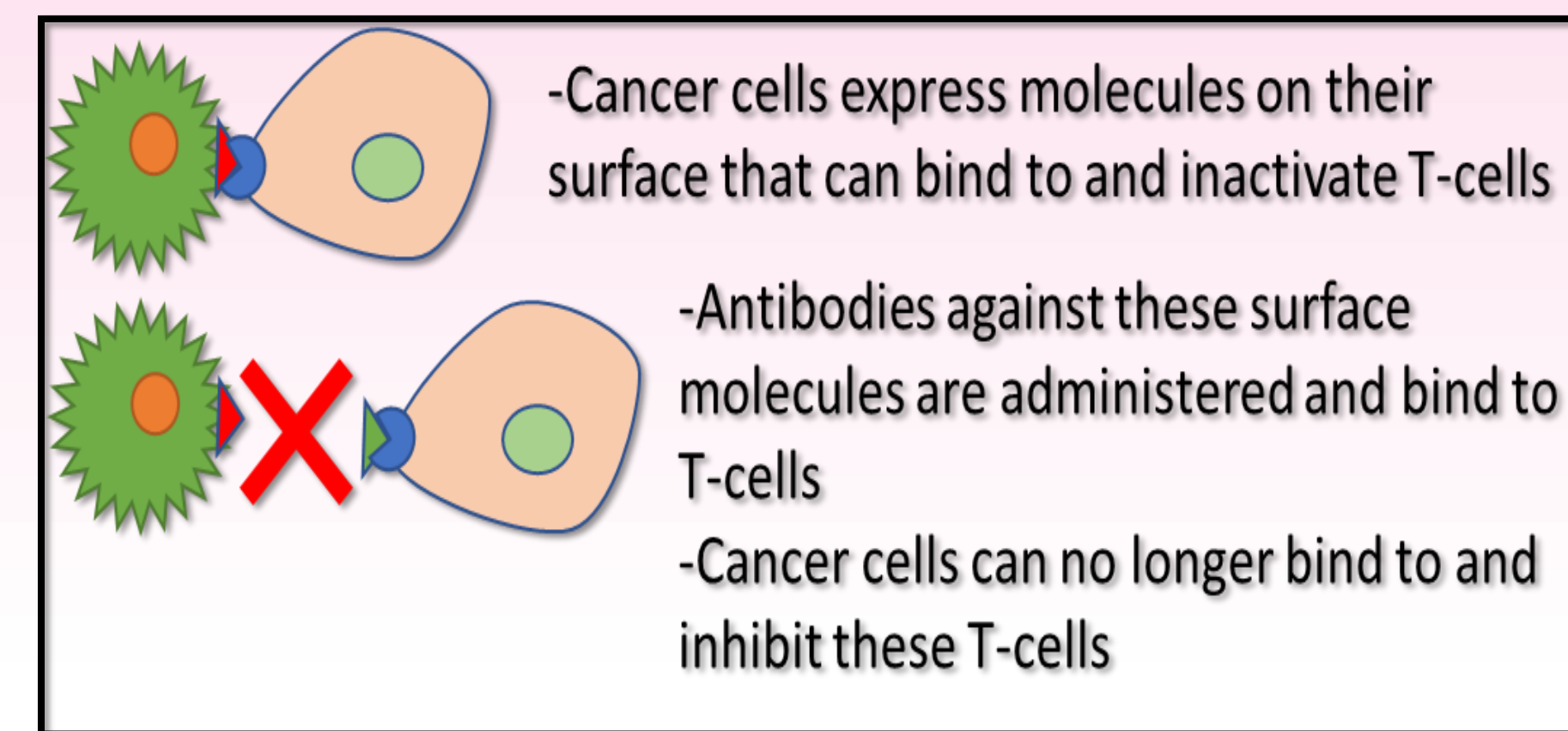


Figure 3. Checkpoint inhibitors reinvigorates the immune system by preventing the binding and inhibition by cancer cells at specific surface targets.¹⁴

Anticancer vaccines

- ☉ Anticancer vaccines use tumor antigen information, delivered via dendritic cell, peptide, or genetic vaccine to activate the patient's immune system to fight cancer⁷
- ☉ Relatively safe, lower incidence of serious side effects⁷
- ☉ Problems: low affinity, response maintenance, mismatching, degradation, insertional mutagenesis⁷

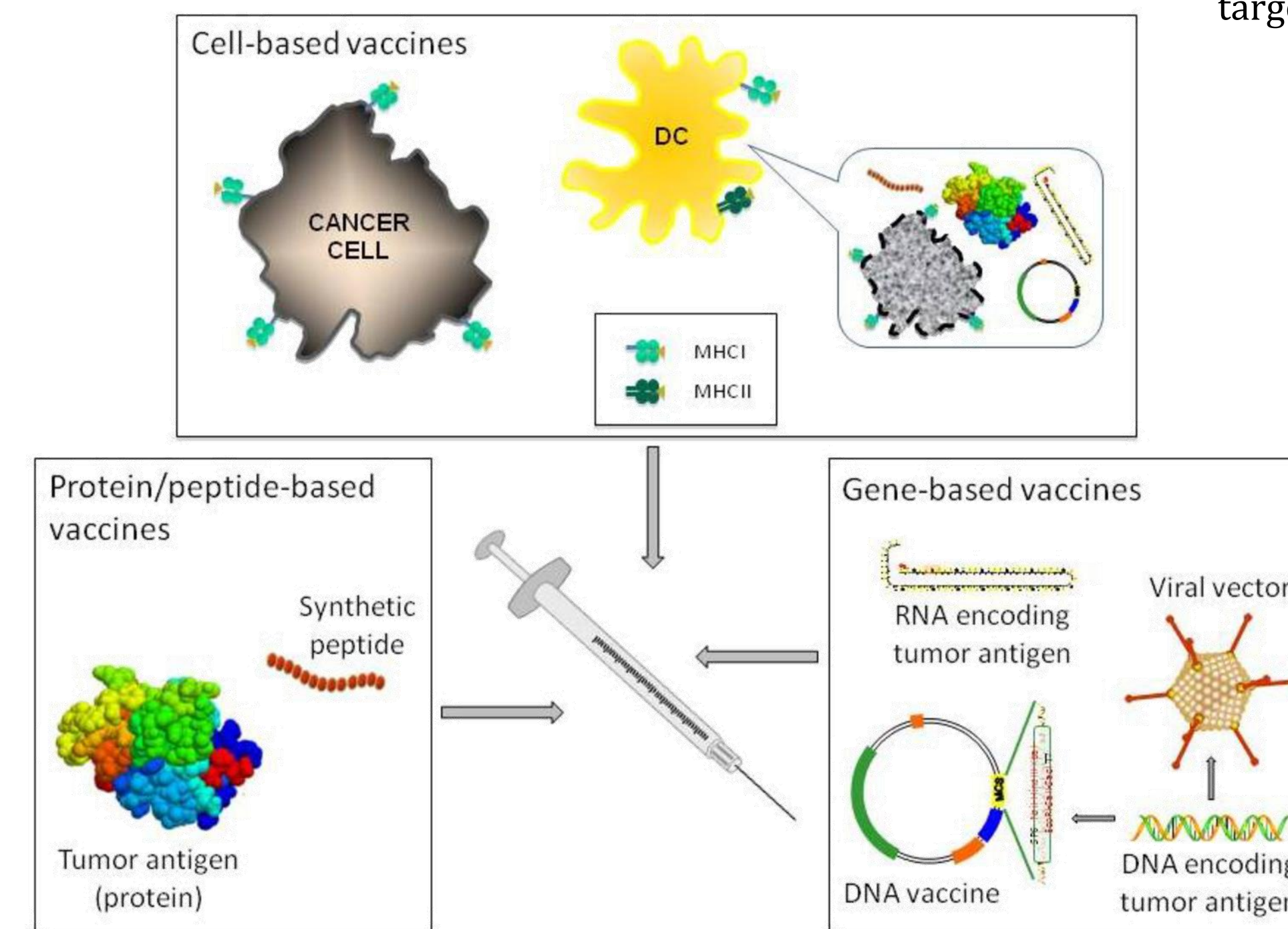


Figure 4. Anticancer vaccine formats.⁸

Adoptive Cell Transfer (ACT)

- ☉ Tumor infiltrating lymphocyte (TIL), T cell receptor (TCR), and chimeric antigen receptor (CAR) are three most common ACT therapies. (Fig. 5)
- ☉ In TIL, lymphocytes are harvested from patient, the most effective are isolated, stimulated for growth to achieve therapeutic numbers, and then reinfused.⁹
- ☉ In TCR and CAR, T-cells are harvested from the patient, engineered to highly express either a ligand binding receptor or chimeric antigen receptor, expanded, and reintroduced to the patient.¹⁰
- ☉ Challenges/limitations: immuno-depletion of already ill patients from cell harvesting, lack of persistence, antigen escape, and are difficult to produce with efficiency.¹⁰

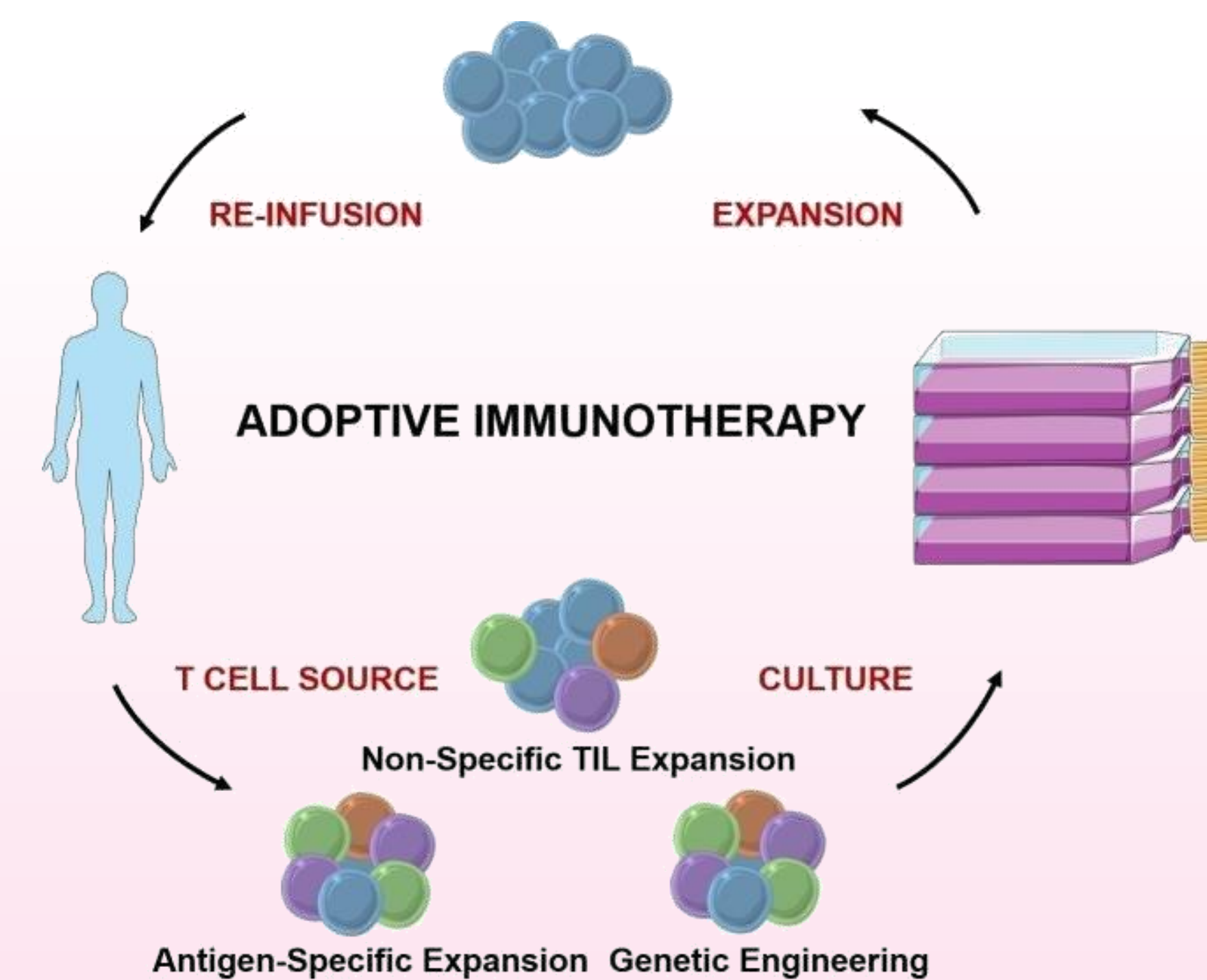


Figure 5. Schematic of adoptive cell transfer based immunotherapies.⁹

- ☉ Potential adverse effects: hyper immune response triggered toxicity including cytokine release syndrome, renal failure, neurotoxicity, and other on-target but off-tumor toxicity.¹¹

The cancer immunotherapy armamentarium: assessing applications, ambitions, and amplitude

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-----Future Directions-----

Nanocarriers

- ☉ Nanocarriers (NCs) have the potential to be a targeted delivery system for cancer therapies.
- ☉ Can be targeted passively, or for specific proteins or pH levels.
- ☉ A new form is coated with specific cancer cell proteins chosen for their physiological effects.¹¹

Mechanogenetics

- ☉ Mechanogenetics involves bioengineering cells that directly affect the transcriptional activity of target cells and can be activated remotely within a confined tissue space such in/around a tumor.¹²
- ☉ Advantages of mechanogenetics are its non-invasiveness and reversibility.
- ☉ Control genetic activity via chemical, radio, magnetic wave, or ultrasound activation of elements coupled with cellular channels which ultimately propagate nuclear signaling pathways.¹²

Epigenetic modulation

- ☉ Many of the mechanisms by which cancer evades the immune response are epigenetically regulated.
- ☉ These are like tags added to DNA that can affect how much of areas are available for transcription.
- ☉ This tagging/untagging is carried out by two specific protein enzyme families.
- ☉ Pre-clinical studies have shown inhibitors of these enzymes can both reverse the modifications as well as improve the anti-tumor immune response in models of some cancer types.¹³

-----Conclusion-----

- ☉ Immunotherapy is a promising field in cancer research and treatment, but could likely never be an all-encompassing savior in the fight against cancer.
- ☉ The challenge faced will be to work towards rational synergistic approaches with attainable applications and intelligent clinical designs.
- ☉ Interdisciplinary coordination and cooperation to appropriately allocate attention, funding, and further research will remain imperative to be most successful in elucidating and developing the best arsenal against cancer.

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¹⁴Figure 1, Figure 2, and Figure 3 created by poster author.