

How do cancer immunoengineering approaches that augment or stimulate the APC and T cell response compared to conventional cancer therapies that aim to kill cancer cells directly? Do you think one approach has more potential than the other?

Conventional cancer therapies, such as chemotherapies, targeted drugs or radiation primarily work by directly killing cancer cells or inhibiting their proliferation.

In contrast, immunotherapies, are designed to engage and strengthen the immune system's response to cancer.

Although, each method has its own side effects and potential for off-target effects, Research has indicated that chemotherapy can modify the tumor microenvironment to promote an effective antitumor response [1]:

- 1) The process of cancer cell death can release tumor antigens
- 2) Enhancing the infiltration of immune cells into the tumor microenvironment
- 3) Improving antigen presentation
- 4) Increase expression of costimulatory molecules that promote activation and effectiveness of immune cells.

Additionally, studies have shown that chemotherapy modulates tumor immunity by mechanisms distinct from immunogenic death. Combinations, with carefully calibrated drug dosage, frequency and the specific immunotherapies used, are an active area of research and have shown promising results [2].

We can envision future treatments involving multi-agent drugs and a variety of treatment regimens that align with the different stages of the Cancer Immunity Cycle.

However, the complexity of combining these treatments introduces significant challenges in clinical validation due to the intricate interactions between drugs and the cancer's biology. A promising strategy to manage this complexity is the development of targeted combination therapies for distinct molecular subtypes of cancer.

For example, therapies specifically designed for molecular subtypes of breast cancer, such as luminal A, luminal B, and HER2+ cancers in combination of chemotherapy, plus radiation, have already achieved significant success rates.

[1] Lesha A. Emens, "Chemotherapy and tumor immunity: an unexpected collaboration". PMC, 2011, doi:10.1158/2326-6066.CIR-15-0064

[2] L. A. Emens and G. Middleton, "The Interplay of Immunotherapy and Chemotherapy: Harnessing Potential Synergies," *Cancer Immunol. Res.*, vol. 3, no. 5, pp. 436–443, 2015, doi: 10.1158/2326-6066.cir-15-0064