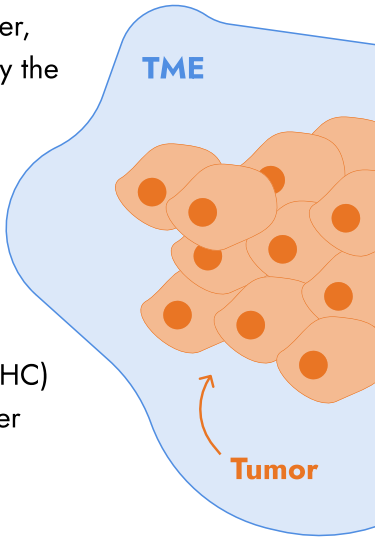
Tumor microenvironment considerations in tumor vaccine development

The development of effective tumor vaccines—particularly those targeting neoantigens—requires a deep understanding of the **tumor microenvironment (TME)**, a complex and dynamic milieu composed of immune cells, stromal components, blood vessels, and signaling molecules. **The TME plays a crucial role in dictating the immunogenicity of tumors and can significantly influence the success of neoantigen-based immunotherapies.**

Neoantigens offer a highly specific target for cancer immunotherapy. However, their recognition and subsequent immune activation are heavily modulated by the TME.



Immunosuppressive factors such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and checkpoint molecules (e.g., PD-L1) can inhibit dendritic cell (DC) function and T cell activation, dampening responses to neoantigens.

Additionally, the **low expression of major histocompatibility complex** (MHC) molecules **and poor antigen presentation** within the TME can further hinder neoantigen recognition by cytotoxic T lymphocytes (CTLs).

Strategies to enhance neoantigen presentation:

To improve the efficacy of tumor vaccines, several strategies are being explored **to modify the TME and boost neoantigen presentation.**

Some of these are:

- **Adjuvant therapies** such as toll-like receptor (TLR) agonists to activate innate immune responses and enhance DC maturation and antigen presentation.
- **Checkpoint blockade** using antibodies against PD-1/PD-L1 or CTLA-4, to relieve T cell suppression and rejuvenate effector function.
- **Modulation of stromal barriers** through enzymes like hyaluronidase or inhibitors of CAF (cancer-associated fibroblasts), to improve immune cell infiltration.
- **Cytokine therapy** particularly IL-12 or GM-CSF, to support antigen presentation and T cell activation.
- **Oncolytic viruses and in situ vaccination**, which can lyse tumor cells and release neoantigens in an immunostimulatory context.

These approaches aim to **reshape the immunogenic TME** being mainly immunosuppressive in cancer. Therefore, it is important to change the immunosuppressive situation of the surrounding cancer lesions to a more favorable immunopermissive state. **The goal is to enhance the visibility of neoantigens to the patient immune system and optimizing the therapeutic potential of tumor vaccines** especially in the context of personalized treatments.