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An improved CD206 binder for targeted immune checkpoint blockade and delivery to tumor-associated macrophages

Stanford scientists have developed a new, better binder for the tumor-associated macrophage marker CD206. This binder can be conjugated to a variety of payloads, including an anti-immune checkpoint protein antibody for more selective immune checkpoint blockade.

Immune checkpoint proteins expressed on the surface of immune cells inhibit their activity and prevent excessive immune responses. In cancer, the overactivation of these proteins can prevent the immune system from killing cancer cells. Antibodies that re-activate the immune system by blocking checkpoint proteins ("checkpoint blockade") can therefore treat a wide variety of cancers. However, these drugs can cause dangerous side effects by also activating healthy immune cells, causing the immune system to attack both cancer and healthy tissues.

Stanford researchers therefore invented a new class of checkpoint inhibitors that selectively act on immune cells involved in cancer. These molecules comprise a novel binder for CD206, a marker expressed on tumor-associated macrophages ("TAMs," immune cells that contribute to cancer progression) conjugated to an antibody that binds but does not inhibit a checkpoint protein. When this molecule binds to a TAM, the cell internalizes and destroys the immune checkpoint proteins on its surface, allowing it to kill cancer cells. These molecules can also destroy soluble immune cell signaling proteins such as cytokines involved in cancer progression. The CD206 binder can also be conjugated to other payloads, such as siRNA, cytotoxic drugs, or imaging agents.

Stage of Development
In vitro: selective binding to TAMs and depletion of immune checkpoint proteins and cytokines in macrophage cell lines

Applications

- Targeted cancer immunotherapy
- Antibodies for imaging tumor-associated macrophages
- siRNA conjugates for delivery to tumor-associated macrophages
- ADCs for delivery of cytotoxic drugs to tumor-associated macrophages

Advantages

- Better binding and easier to synthesize than prior, polymeric CD206 binders
- CD206 binder can be conjugated to a variety of payloads
- More selective and less toxic than traditional checkpoint inhibitors
- Platform technology for targeted cancer immunotherapy
- Degradation of both cell-surface (i.e., ICAM-1) and soluble (i.e., IL-4) proteins involved in cancer progression
- More selective and easier to synthesize than prior tumor-associated macrophage binders

Publications

- Mariko Morimoto, Nicholas A. Till, Carolyn R. Bertozzi (2023). Tumor Immune Cell Targeting Chimeras (TICTACs) For Targeted Depletion of Macrophage-Associated Checkpoint Receptors. BioRxiv.

Patents

- Published Application: WO2025096664

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