Platform for Locally Assembling Antibody Drug Conjugates (ADCs) With Enhanced Specificity

Next-generation ADC platforms with high specificity and reduced systemic toxicity

Technology

The Neel Lab has improved upon traditional Antibody Drug Conjugate (ADC) technology by incorporating biorthogonal click chemistry to conceptualize a new paradigm for enhancing the specificity and reducing the toxicity of standard ADCs. Instead of designing a single antibody to carry the entire toxic payload, this innovation splits the drug into two non-toxic parts, each attached to a different antibody targeting distinct epitopes on the same or different molecules (e.g., proteins) present in cis or trans on the surface of pathogenic cells. When the antigens pairs are in spatial proximity, each antibody pair will also be in spatial proximity, and the complementary portions of each payload will react and assemble into the active cytotoxic drug when endocytosed, thereby reducing the off-target effects of traditional ADCs. For example, in the context of cancer, one antibody in the pair could target HER2 and the other EPCAM (for the treatment of breast cancer, gastric cancer, or other HER2 amplified or low epithelial cancers), or one antibody in the pair could target EGFR and the other MET (for the treatment of non-small cell lung cancer).

In all, this interdependent, bivalent drug delivery system increases the specificity of drug targeting due to the requirement of proximal antigens for drug assembly and activation, resulting in a more efficacious and less toxic therapeutic for diseases characterized by more than one cell-surface protein marker.

Background

Traditional ADCs face challenges with off-target toxicity because many targeted antigens are also expressed on healthy cells (i.e., not tumor-specific), which causes unintended drug leakage to sites outside the tumor. Best-in-class ADCs, such as trastuzumab emtansine (T-DM1) for HER2-positive breast cancer and brentuximab vedotin for Hodgkin lymphoma, have demonstrated significant efficacy but are associated with off-target toxicities like hepatotoxicity, peripheral neuropathy, and myelosuppression. In autoimmune diseases, ADCs are still in development but could lead to similar toxicities due to antigen expression in healthy tissues. Promising ADCs for viral infections, such as 3B3-PE38 for HIV, face comparable challenges with off-target effects. There is an ongoing need for precision medicines that can reduce off-target effects and limit systemic toxicity. This approach addresses this unmet need by increasing the threshold of specificity required for drug delivery.

Applications

Category

Life Sciences/Therapeutics/Oncology
Autoimmune Disease
Life Sciences/Drug Delivery Systems
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Treatment of diseases that express two or more cell-surface markers, including but not limited to:

- Cancer (e.g., HER2 and EPCAM in breast cancer, or EGFR and MET in non-small cell lung cancer)
- Autoimmune disease (e.g., in systemic lupus erythematosus [SLE] or rheumatoid arthritis)
- Viral infections (e.g., in HIV, hepatitis B)

Advantages

- **Precision medicine:** The drug assembles and activates only within cancer cells expressing both target antigens
- **Reduced off-target effects:** By enhancing drug specificity, systemic toxicity is reduced.
- **Customizable platform:** Adaptable to target different antigen combinations, making it versatile for various cancers and diseases.

Development Stage and Next Steps

The innovation has been fully conceptualized but is not published. NYU TOV is seeking a commercial partner to further develop this innovative, selective, bivalent antibody approach in the context of diseases with high unmet need.

Intellectual Property

NYU has filed a U.S. provisional patent application covering the methodology and its applications in treating different human diseases.