Docket #: S23-430

Lectin-Drug Conjugates Enable Selective Cytotoxicity to Treat Cancer or other Diseases

Selective cytotoxicity, or the ability to selectively remove certain cell types from a population, is a vital technology that is often applied to various therapeutic applications. The most obvious application of these technologies is cancer treatment by eliminating malignant cells while sparing healthy ones, but other applications include treatments for infectious disease or elimination of specific immune cells. Outside of the clinic, researchers rely on selective cytotoxicity to conduct functional genomic screens or directed evolution campaigns.

The gold standard approach today is the antibody-drug conjugate (ADC). ADCs are comprised of antibodies, which can bind a target antigen with exquisitely high affinity and selectivity. Cells that lack the antigen have much lower exposure to the delivered drug, which reduces side-effects and increases the therapeutic window of these molecules. While a significant advancement, ADCs are far from perfect. Numerous suitable antigens to target with ADC therapy have proven exceptionally difficult to identify. As such, there is a need to develop additional methods of selection that can better distinguish the subtle differences between target and bystander cells.

The Bertozzi group at Stanford University has created a lectin-drug conjugate (LDC) as an alternative strategy for selective cytotoxicity. Lectins are proteins that selectively interact with glycoproteins or glycolipids, proving to be useful to distinguish cancer cells that have altered glycosylation from healthy ones. Although they lack the affinity and selectivity of antibodies, they can differentiate between glycoforms in ways that antibodies cannot. The inventors successfully leverage lectin galectin-1 (Gal1) to increase targeting specificity and cytotoxicity in the K562 cancer cell line. They further demonstrated the technique's utility as a functional genomic research tool by isolating a cell-surface receptor that was key to the

toxicity of the LDC.

Applications

- Targeted therapeutics, such as for cancer
- Research tool, such as for functional genomic screens

Advantages

- Target versus bystander differentiation. Unlike the gold standard of antibody-drug conjugates (ADCs), the invention has both protein and glycan specificity for increased cytotoxicity to target cells
- Improve selectivity due to ability to differentiate between glycoforms in ways that antibodies cannot
- Increased cytotoxicity for target cells

Publications

- Donnelly, J., Kamber, R. A., Wisnovsky, S., Roberts, D. S., Peltan, E. L., Bassik, M. C., & Bertozzi, C. R. (2024). "A Genome-Wide CRISPR Screen Identifies Sortilin as the Receptor Responsible for Galectin-1 Lysosomal Trafficking". bioRxiv, 2024-01.

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