Docket #: S21-461

Cell-type specific enzymatic degradation of pathological mucins

Targeted protein degradation is an emerging strategy for the elimination of classically undruggable proteins. Mucins are known to be involved in tumor-progressive pathways but are difficult to target using small molecules and antibodies. To overcome this issue, Nobel laureate Carolyn Bertozzi and her research team have engineered a cancer antigen-targeting mucin-specific protease (novel composition of matter) to degrade cell surface mucins on cancer cells and other cells in which aberrant mucin expression drives pathology. Fusion of the engineered mucinase variant to a cancer antigen-binding nanobody resulted in selective demucination of cancer cells,

Mucins have remained canonically undruggable. Therapeutic interventions face the challenge that mucin signaling occurs through the cooperative action of hundreds of arrayed epitopes and a unique, scaffolding secondary structure. There is no catalytic site to inhibit with a small molecule, nor is there a single binding site to block with an antibody. By bringing a protease directly to disease-driving mucins, we bypass these challenges via targeted protein degradation (TPD) of these unwanted molecules. This invention will further the development of biologics which degrade specific glycoforms of cell surface targets.

These enzyme conjugates can be a platform technology for a new class of cell type- and target-specific TPD therapeutics.

Stage of Development

- ***In vivo*** data - Cell line models and mouse models of breast cancer
- **Continued research** - Engineering of enzymes in the human proteome that are capable of digesting mucins.

Applications

- **Cancer therapeutics**, including common carcinomas such as breast, ovarian, and intestinal cancers which have mucinous forms wherein tumor cells present as individual colonies suspended in a matrix of secreted mucin.
- Other therapeutic applications include the **range of human diseases which are characterized by aberrant mucin phenotypes, including but not limited to gut dysbiosis, cystic fibrosis, and bacterial endocarditis**.

Advantages

- **Novel composition of matter**
- **Addresses key challenge of undruggable mucins**
- **Potential new platform technology** - Extracellular proteins are nearly all glycosylated, and glycosylation status is commonly altered in disease. This invention establishes a blueprint for the development of biologics which degrade cell surface proteins with specific glycosylation patterns, creating a general opportunity for increasing on-target specificity for disease-driving extracellular proteins.
- **First-in-class approach** - To our knowledge, this is the first application of injectable proteases to digest and clear disease-relevant mucins

Publications

- Pedram, Kayvon, D. Judy Shon, Gabrielle S. Tender, Natalia R. Mantuano, Jason J. Northey, Kevin J. Metcalf, Simon P. Wisnovsky et al. "Design of a mucin-selective protease for targeted degradation of cancer-associated mucins." Nature Biotechnology (2023): 1-11.
- MacCormick, Holly Alyssa. A bioengineered enzyme-based scissors cuts off cancer cells' defenses. *Stanford News* (2023).

Patents

- Published Application: WO2023212733

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