Docket #: S23-091

Small-molecule control of membrane and secreted proteins via human proteases

Researchers at Stanford have created a translational platform capable of controlling protein activity in cellular therapeutics using a human protease. Current tools in synthetic biology that offer control over protein level and activity are sourced from foreign species such as bacteria and viruses. This presents an immunogenic risk for translational applications in human medicine such as cell and gene therapies. This invention alleviates that risk and addresses other key cell therapy challenges by offering small-molecule control over protein level and activity using human-derived components.The platform takes advantage of extracellular human proteases that have high substrate specificity, such as Renin, paired with FDA-approved inhibitors. Proteases can be modified to be secreted, tethered to the cellular membrane, or retained within the endoplasmic reticulum (ER), depending on the desired application. Proteins of interest (POIs) are then modified with appropriate protease cleavage sites to control their activity and localization. POIs can be engineered to have their activity reconstituted, abrogated, or released from the ER or cellular membrane upon cleavage. Overall, this platform technology allows proteases to be exogenously expressed to control genetically modified proteins of interest, which can be used in cell therapies for multiple indications.

Stage of Development:
Proof of Concept

Applications

- Can be used in cellular therapeutics to control protein secretion, activity, and membrane expression using human components:
    - Cancer

    - Autoimmune diseases
    - Muscle regeneration
- Can be used in cellular therapeutics to reduce or eliminate immunogenic risk

Advantages

- Protein circuits can be compactly expressed in single transcripts for engineering of cells.
- Allows user control via dosage of a small-molecule inhibitor.
- Eliminates the immunogenic risk of foreign bodies used in current therapies.

Publications

- Carlos A. Aldrete, Alexander E. Vlahos, Jimin Pei, Qian Cong, Xiaojing J. Gao. Orthogonalized human protease control of secreted signals. bioRxiv 2024.01.18.576308 (Preprint).

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