487 S18-179: Lysosome targeting chimeras

Asset Overview

Product Type	Gene therapy
Indication	Various diseases
Current Stage	Discovery
Target(MoA)	Mannose-6-phosphate receptor (CIM6PR, also called IGF2R)
Brief Description	Researchers at Stanford have developed a platform for targeted degradation of extracellular or cell surface proteins via the lysosomal pathway. Many protein-directed therapeutics act by obstructing target function or recruiting immune effectors. However, these mechanisms do not work for many potential therapeutic targets. Thus, new methods are needed for these "undruggable" targets. New protein degradation technologies have been developed to try and meet this need, but they only work on proteins with intracellular domains. Many secreted and membrane proteins play key roles in a variety of diseases. Thus, additional methods are needed to target extracellular and membrane proteins for degradation. To help meet this need the inventors have developed the lysosome targeting chimera (LYTAC) platform. LYTACs are conjugates capable of binding to the cell surface lysosome targeting receptor and the extracellular domain of a target protein.
Organization	Stanford University

Differentiation

□ **Targeted protein degradation**

- Targeted protein degradation is a powerful strategy to address the canonically undruggable proteome
- Current technologies are limited to targets with cytosolically accessible and ligandable domains
- Unlike the proteasomal pathway, the lysosomal pathway for protein degradation is not limited to proteins with intracellular domains

□ **Lysosome Targeting Chimeras (LYTACs)**

- LYTACs can be used as biochemical probes to study receptor trafficking and protein degradation, and are capable of degrading both secreted and membrane proteins of therapeutic interest
- The inventors demonstrated that LYTACs mediate efficient degradation of apolipoprotein-E4, epidermal growth factor receptor (EGFR), CD71, and programmed death-ligand 1 (PD-L1)

□ **Advantages of LYTACs**

- LYTACs enable targeted degradation of secreted and membrane proteins
- Chemical tunability and modularity offer new opportunities in targeted protein degradation
- Potential to develop therapeutics directed towards "undruggable" targets

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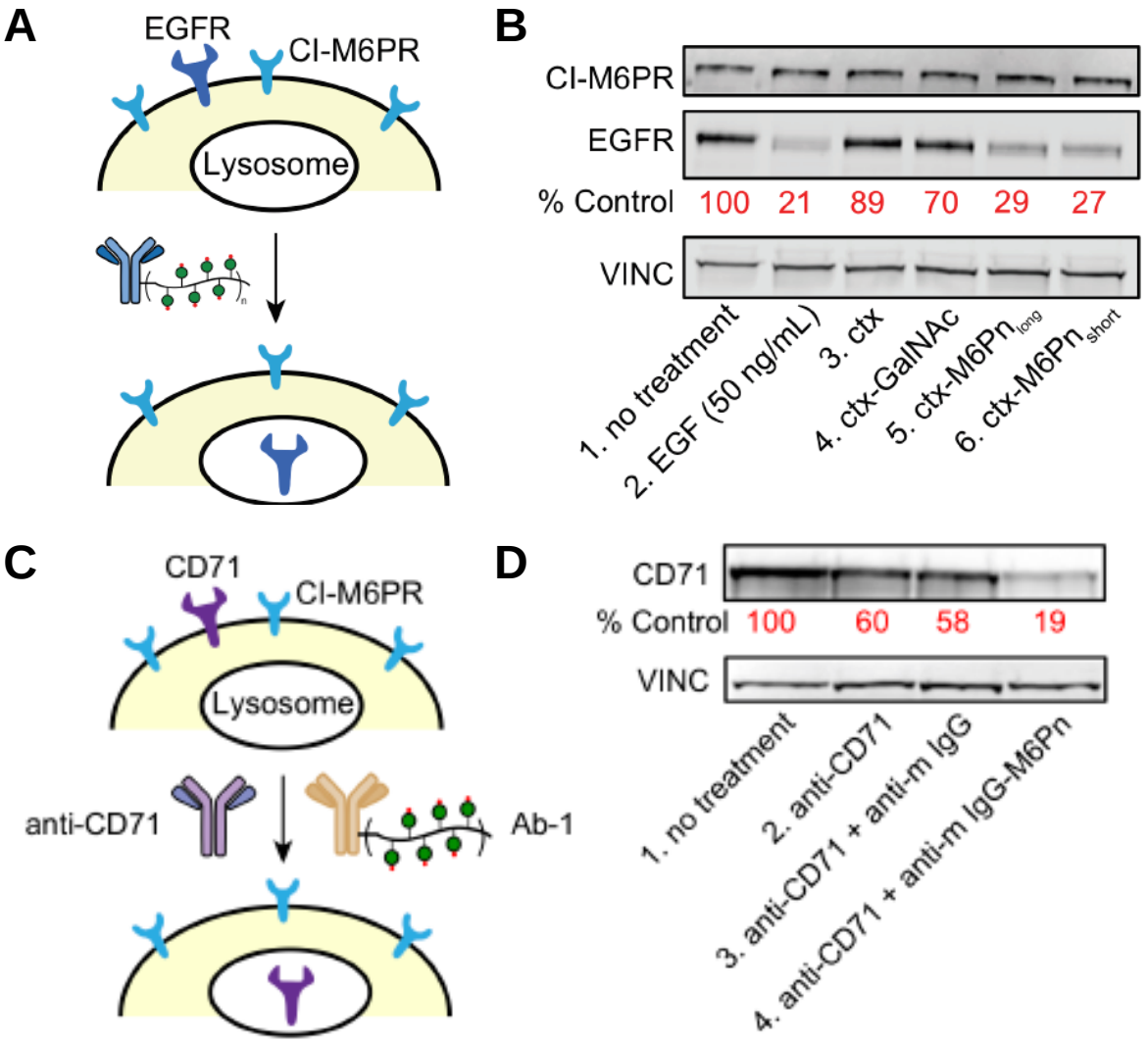
Key Data

LYTACs accelerate degradation of membrane proteins



(A) EGFR degradation using antibody LYTACs. (B) Western blot of HeLa cells treated with 100 nM ctx (lane 3), ctx-GalNAc (lane 4), ctx-M6Pnlong (lane 5) or ctx-M6Pnshort (lane 6) for 24 hours in complete growth media. EGF stimulation is a positive control for EGFR downregulation. (C) Degradation of CD71 mediated by a primary antibody and Ab-1 (LYTAC conjugated form). (D) Western blot analysis of CD71 degradation in Jurkat cells after 24 hours.

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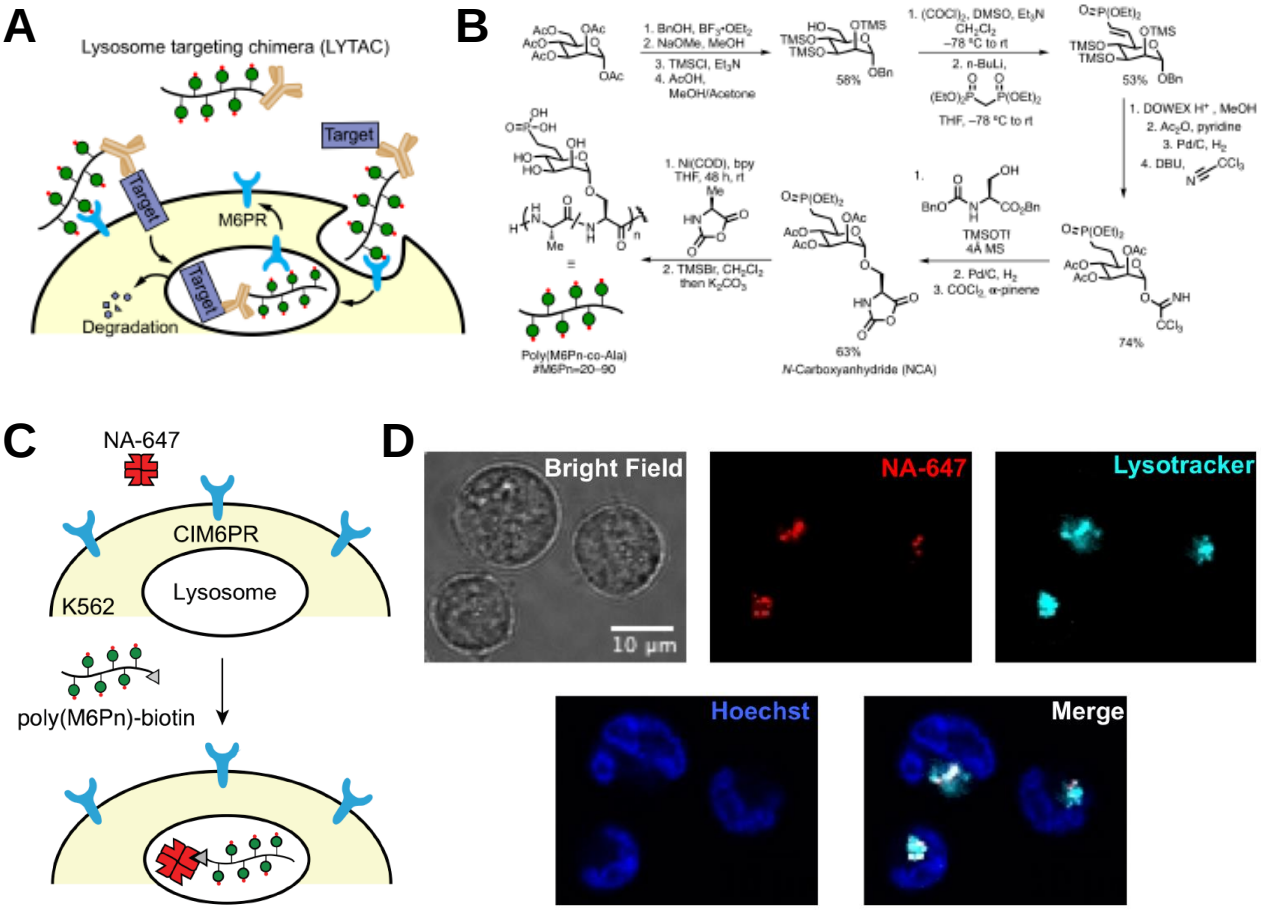
Lysosomal targeting chimeras (LYTACs)



Lysosomal targeting chimeras (LYTACs) utilizing the cation-independent mannose-6-phosphate receptor (CI-M6PR) traffic proteins to lysosomes. (A) LYTAC concept where a glycopolypeptide ligand for CI-M6PR is conjugated to an antibody to traffic secreted and membrane proteins to lysosomes. (B) Synthesis of mannose-6-phosphonate (M6Pn) glycopolypeptide agonists for CI-M6PR. (C) NeutrAvidin-647 (NA-647) internalization assay for biotin-based LYTACs. (D) Live cell confocal microscopy images of K562 cells.

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Intellectual Property

Patent No.	
Application Date	
Status	
Country	

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