Aquaporin-Enabled Degraders

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BACKGROUND

Extracellular proteins are central regulators of numerous intercellular signaling networks, playing vital roles in both health and disease. These proteins include receptors, ligands, cytokines, growth factors, adhesion molecules, and other signaling mediators that coordinate communication between cells and tissues. Dysregulation of extracellular signaling contributes to a wide range of pathological conditions, including cancer, fibrotic disease, inflammatory and immune disorders, neurodegenerative disease, infectious disease, and more. Nearly 40% of the human genome encodes extracellular and membrane-associated proteins, making them promising targets for modern therapeutics.

Current therapeutic strategies remain predominantly blockade- or occupancy-based: small molecules or biologics operate by temporarily blocking or occupying a protein's functional site or ligand interaction site. To achieve a sustained therapeutic effect, a stoichiometric occupancy-based blockade demands continuous, high doses of drugs or repeated dosing. Consequently, pharmacological blockades may provide incomplete and/ortransient inhibition rather than durable elimination of protein function. These limitations are particularly evident in complex chronic disease settings where the sustained removal of pathogenic proteins is desirable. To this end, targeted protein degradation using PROteolysis TArgeting Chimeras (PROTACs) and molecular glues has demonstrated significant advantages over conventional blockade-based strategies; however, these approaches are primarily directed to intracellular targets.

DESCRIPTION

Researchers at the University of California, Santa Barbara have taken advantage of naturally occurring aquaporin cell membrane proteins and engineered a targeted extracellular protein degradation platform known as Aquaporin-Enabled Degraders (AEDs). The AEDs are genetically encoded, fully modular, and selective and are designed for sustained lysosomal degradation of extracellular disease-causing proteins via engineered aquaporin fusion proteins and bispecific molecular binders. This breakthrough therapeutic platform genetically encodes a two-component system to selectively remove extracellular and membrane proteins causing disease. The core innovation is an engineered human aquaporin-1 fused to a destabilizing domain that is rapidly internalized and traffics cargo to lysosomes independent of native lysosome-targeting receptors, overcoming significant safety and functional limitations of prior innovations. Combined with customizable bispecific binder proteins that link specific extracellular targets to theaquaporin-1 based degradation effector, AEDs enable programmable, sustained, and cell-type selective

CONTACT

Donna M. Cyr
cyr@tia.ucsb.edu
tel: .

INVENTORS

- Mukherjee, Arnab
- Wan, Jinyang
- Xu, Binzhi

OTHER INFORMATION

KEYWORDS

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- **Medical**
  - Therapeutics

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degradation of pathological proteins – capabilities that are beyond the reach of existing (non-genetic) degradation tools.

The AED platform can be effectively deployed in the context of gene therapy or engineered cell therapies and monitored noninvasively using MRI via the aquaporin-1 scaffold, which can also serve as an MRI reporter gene. To our knowledge, this system is the first fully genetic, LTR (Lysosome-Targeting Receptor)-orthogonal platform for extracellular targeted protein degradation. The AED platform ensures robust function across virtually all cell types, achieving a level of portability, genetic programmability, and specificity that was previously unattainable and unpredictable based on existing methodologies.

ADVANTAGES

- ▶ Fully genetically encoded and modular platform allowing easy target swapping
- ▶ Orthogonal to native LTRs ensuring broad cell-type functionality without disrupting physiological functions of LTRs
- ▶ Sustained protein degradation through continuous gene expression reducing dosing frequency
- ▶ Programmable and cell-type selective action via gene delivery and synthetic gene circuits
- ▶ Noninvasive in vivo monitoring of therapeutic delivery and expression by MRI using the aquaporin-1 reporter
- ▶ Applicable to extracellular targets previously deemed undruggable by conventional drugs
- ▶ Flexible deployment in gene therapy vectors or engineered cell therapies like CAR-T cells

APPLICATIONS

- ▶ Next-generation gene therapies targeting extracellular oncogenic receptors, immune checkpoint proteins, and secreted factors
- ▶ Engineered cell therapies (e.g., CAR-T cells) with integrated extracellular protein degradation functionality
- ▶ Treatment of cancer, fibrotic diseases, immune disorders, neurodegeneration, and infectious diseases driven by extracellular proteins
- ▶ Therapeutic platform for degradation of “undruggable” extracellular targets with ligand-independent functions
- ▶ Companion diagnostic development leveraging MRI-based tracking of gene expression
- ▶ Drug development pipelines leveraging modular binder swaps to rapidly generate disease-specific degraders
- ▶ Research tools for modulating extracellular protein levels in vivo with genetic precision and temporal control

PATENT STATUS

Patent Pending

University of California, Santa Barbara
Office of Technology & Industry Alliances
342 Lagoon Road, ,Santa Barbara,CA 93106-2055 |
https://www.tia.ucsb.edu
Tel: 805-893-2073 | Fax: 805.893.5236 | padilla@tia.ucsb.edu