DESIGN RULES FOR ENDOSOMAL ESCAPE

Tech ID: 33322 / UC Case 2024-032-0

PATENT STATUS

Patent Pending

BRIEF DESCRIPTION

The efficient delivery of protein-based therapeutics into the cytosol is a significant hurdle in drug development, as most internalized proteins remain trapped and degraded within endosomal compartments. To address this challenge, UC Berkeley researchers have identified a set of biophysical "design rules" that promote the successful escape of proteins from these vesicles. The researchers found that selecting or engineering proteins with high intrinsic disorder or a specific thermal stability (T_m)—specifically the tendency to unfold at physiological temperatures—greatly enhances their ability to penetrate the endosomal membrane. This discovery provides a rational engineering framework for creating next-generation intracellular biologics, including enzymes and gene-editing tools, that can effectively reach their target sites within the cell.

SUGGESTED USES

- Cytosolic Delivery of Biologics: Optimizing the design of therapeutic proteins, such as antibodies or enzymes, to ensure they reach the cytoplasm of target cells rather than being degraded.
- Enhanced Gene Editing: Improving the intracellular transport and endosomal escape of CRISPR-Cas complexes for more effective genome modification in therapeutic applications.
- Targeted Cancer Therapy: Designing pro-apoptotic or signaling-modulatory proteins that can bypass endosomal entrapment to induce cell death specifically in malignant tissues.
- Protein-Based Vaccines: Engineering antigens to escape the endosome and enter the cytosol, facilitating more efficient cross-presentation and a stronger T-cell immune response.
- Intracellular Diagnostic Probes: Developing protein-based sensors that can enter the cytosol to provide real-time reporting on cellular health, metabolism, or drug response.

ADVANTAGES

- Rational Design Platform: Replaces inefficient trial-and-error screening with a predictive framework based on quantifiable biophysical properties like intrinsic disorder and thermal stability.
- Increased Bioavailability: Significantly boosts the functional concentration of therapeutic proteins at their intracellular site of action by preventing entrapment.
- Versatile Applicability: These design rules can be applied across a diverse range of protein scaffolds and therapeutic classes without requiring complex chemical modifications.
- Reduced Toxicity: Leverages the intrinsic physical properties of the protein for escape, potentially reducing the need for harsh membrane-disrupting delivery agents.
- Strategic Thermal Tuning: Balances the requirements for structural integrity with the thermal flexibility needed for effective membrane transition at physiological temperatures.

RELATED MATERIALS

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- Improved Vehicles For Endosomal Escape
- Ribosomal Synthesis Of Ketone-Containing Peptide Backbone Via O To C Acyl Shift
- Methods For The Synthesis Of Peptide Macrocycles With Embedded Heterocycles

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OTHER INFORMATION

CATEGORIZED AS

- **Biotechnology**
- Health
- Proteomics
- **Medical**
- Therapeutics
- **Research Tools**
- Protein Synthesis

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