Docket #: S17-025

Non-immunogenic Destabilizing Domains

Stanford researchers have developed methods of regulating protein stability using destabilizing domains (DDs) optimized for use in humans. The ability to control the abundance of a specific protein in cells is a powerful tool for investigating biological behavior and for gene therapy.
Well-established methods of modulating protein activity involve knocking down the corresponding gene-of-interest. Among the many challenges of these methods is the inability to directly regulate the protein-of-interest.
To overcome these limitations the inventors have developed methods using DDs to directly control the protein level. The DDs are engineered to be unstable in the absence of their stabilizing ligand. The DD is fused to a gene-of-interest and upon expression the instability is conferred to the fused protein partner resulting in degradation of the entire protein. The stabilizing ligand can bind to and stabilize the DD thereby restoring function to the protein-of-interest. This technology provides tools to directly interrogate protein function in living cells and animals and because this DD is derived from an endogenous human protein and is regulated by FDA-approved drugs, this technology holds promise for clinical use in gene therapy.

Stage of Development - Proof of Concept
DDs based on human proteins have been created and validated. These DDs show great promise.

Related technology
The Wandless lab has also developed additional conditional protein stability systems, see Stanford Docket S06-024 and Stanford Docket S07-252.

Applications

- Regulate gene expression for:

    - Research
    - Gene Therapy

Advantages

- DD system optimized for human use and based on human proteins:
    - Minimally immunogenic
    - Stabilized by FDA approved drugs
- Specific-stabilizing ligand binds to fusion protein with no effect on other cell functions and allows direct control of protein level
- Rapid
- Reversable
- Tunable - protein function can be turned on or off in a dose dependent manner

Publications

- Wandless, T. J., Chen, L. C., & Miyamae, Y. (2024). *U.S. Patent No. 11,891,634*. Washington, DC: U.S. Patent and Trademark Office. https://patents.google.com/patent/US11891634B2/en

Patents

- Published Application: 20200123514
- Published Application: 20240158770
- Issued: 11,891,634 (USA)

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