PHOTACS: Photo-Activatable PROTACS

Spatial and temporal control over protein target degradation in diseased tissue

Technology

This invention pertains to the development of novel PHOtoactivatable proTACS (PHOTACS) for precision protein degradation in multiple disease types. The developed PHOTACS were designed with a light-responsive photoswitch engineered into the linker region between the two ligands. In proof-of-concept studies (*Reynders et al. Sci Advs 2020*), these synthesized PHOTACS show little or no proteolytic activity in the dark, but can trigger protein degradation in a light-responsive manner. Further, these PHOTACS were demonstrated to induce targeted, light-controlled degradation of BET family proteins BRD2-4, as well as, FKBP12.

Background

PROteolysis TArgeting Chimeras (PROTACs) have emerged as new drug modalities for the treatment of diseases caused by aberrant protein expression and function. These heterobifunctional drugs are composed of two oppositely-opposed ligands, one which targets and binds a protein of interest (POI) and one which recruits an E3 ubiquitin ligase for proteasomal degradation of the POI. PROTACS have been successfully used to degrade many different types of protein targets, including the androgen and estrogen receptors, BET family epigenetic readers (BRD2-4), and various kinases (CDK9, BCR-ABL, RTKs). One fundamental limitation of PROTACS, however, hurting the gained therapeutic benefit, is the lack of precise spatiotemporal control over protein degradation.

Applications

Disease indications where precise protein targeting is needed to avoid systemic toxicity (i.e., protein targets with pleiotropic functions across different tissues)

Advantages

- Precision protein degradation: PHOTACS allow for spatial and temporal control of proteolytic degradation activity
- Minimized systemic toxicity: Optical control over protein-target degradation minimizes off-target toxicity
- Optical control: Light is a cheap, convenient, and optimizable means of modulation

IP Status

A U.S. non-provisional patent application has been filed for this technology.

References

1. Dirk Trauner, PhD, et al. , PHOTACs enable optical control of protein degradation

Category

Life Sciences/Imaging
Life Sciences/Diagnostics
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