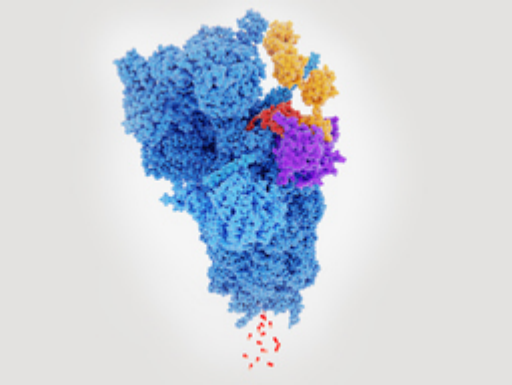
INNOVATION PARTNERSHIPS
UNIVERSITY OF MICHIGAN

Small-Molecule Inhibitors of DCN1

TECHNOLOGY NUMBER: 7301



OVERVIEW

A small molecule inhibitor that helps correct dysregulation of normal protein homeostasis

- The molecule DI-591 binds to an important enzyme in the ubiquitin-proteasome system
- Permits future research and treatment of cellular disorders and treatments

BACKGROUND

The maintenance of cellular homeostasis is tightly regulated by the balance of protein synthesis and degradation. Cullin RING ligases (CRLS) are responsible for maintenance of about 20% of intracellular proteins, and CRLS dysregulation has been implicated in a variety of diseases including cancer, cardiovascular diseases, neurodegenerative disorders, and viral infections. Inappropriately decreased CRLs functioning can lead to overaccumulation of those proteins that are intended for destruction by pathway. Normal activation of the intracellular proteins responsible for the timely destruction of proteins relies on a cascade of enzyme reactions which are controlled by the ubiquitin-proteasome system (UPS) via tagging the ubiquitin on targeted proteins. One important interaction required for the successful progression of this cascade involves the binding of enzymes DCN1 and UBC12. The potential benefits of modulating this interaction have led to a need for agents which can influence the UBC12-DCN1 binding site.

INNOVATION

Researchers at the University of Michigan have discovered a small molecule inhibitor of the UBC12-DCN1 interaction named DI-591. The effects of this inhibition can help treat diseases caused by dysregulation of the cellular forces that provide protein homeostasis. The DI-591 discovery is highly potent and cell-permeable small molecule inhibitor that selectively binds to

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Category

Therapeutics and Vaccines
Life Sciences

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DCN1 while leaving other enzymes along the ubiquitin-proteasome system pathway unaffected. Previous attempts to define small molecule molecules in the UPS pathway have been limited by the relatively large and flat physical shapes of the protein interfaces. While most of the existing inhibitors have relied on chemically reactive groups for successful binding, DI-591 physically complexes with a well-defined binding groove in DCN1. This selectivity stands out favorably when compared to existing agents that modify this pathway for protein breakdown. DI-591 therefore serves as a selective, small molecular inhibitor of the UBC12-DCN1 interaction and facilitates the future investigation of its role in different cellular processes and a wide variety of human diseases.