TRIM21: New opportunities for targeted protein degradation of aggregated CNS proteins

Marc A. Scemama de Gialluly[1,2,3], Anthony R. Allen,[1,2] Elijah H. Hayes,[4] Patrick Zhuang,[4] Ralston B. Goldfarb,[1,2] Amanda N. Farrar,[1,2] Yuriy Fedorov,[1,2] Drew J. Adams[1,2,4]

[1] Department of Genetics and Genome Sciences, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106, USA.
[2] Chemical Biology Program, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106, USA
[3] Department of Pathology, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106, USA
[4] Department of Pharmacology, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106, USA.

Neurodegenerative diseases such as Alzheimer's and Huntington's are characterized by the accumulation of pathogenic protein aggregates, which cannot be reversed by existing therapies. While targeted protein degradation has rapidly emerged as an innovative pharmacological approach, the identification of small molecules that degrade disease-causing protein aggregates remains challenging. Promising genetic therapy strategies have redirected TRIM21, an E3 ubiquitin ligase specialized in the ubiquitination of large protein complexes, to pathological protein aggregates such as Tau. Recently we established that two clinically-evaluated anticancer agents function as molecular glues that redirect TRIM21 to the nuclear pore. Elucidation of this mechanism has enabled medicinal chemistry efforts that have elaborated these molecular glues to TRIM21-targeting PROTACs that degrade an aggregated protein. Ongoing studies seek are evaluating the ability of TRIM21-targeting molecules to degrade pathological protein aggregates. These findings establish TRIM21 as a versatile platform for targeted protein degradation and open new avenues for the treatment of neurodegenerative disorders using both small molecule and genetic approaches.

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Presenter Name and contact information:
Drew Adams, Ph.D., Associate Professor
Department of Genetics and Genome Sciences
Case Western Reserve University School of Medicine
Cleveland, Ohio, USA
Email: drew.adams@case.edu