BRIAN CLARK BIOTECH LECTURE

Wednesday 29 November 2023 at 15:15

NUCLEUS (1871-120)

Hosted by Søren Lykke-Andersen

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Extracellular targeted protein degradation with small molecules

Targeted protein degradation (TPD) using PROteolysis TArgeting Chimeras (PROTACs) is a rapidly emerging therapeutic strategy for difficult-to-drug cytosolic proteins. PROTACs are heterobifunctional small molecules that bridge their target with an E3 ubiquitin ligase, destining it for degradation by the proteasome. They have the potential to be orally available and to act catalytically, switching their pharmacology from occupancy-driven to event-driven, but PROTACs are absolutely limited to cytosolic targets. Draupnir Bio has developed a unique strategy for targeted degradation of extracellular proteins by reshaping the interaction between a broadly expressed lysosome receptor and its natural ligand for engineering extracellular degraders. These induce ternary complex formation with their target and the receptor, followed by endocytosis and lysosomal degradation. Degrader activity can be genetically encoded as demonstrated by converting an IgG binding nanobody to an IgG degrading nanobody, or by chemical conjugation enabling single step conversion of therapeutic antibodies from binding their target to driving degradation. Importantly, using structure-based design, we generated small molecule degraders with picomolar activity against targets such as inflammatory cytokines and membrane-bound receptors, and with physicochemical properties in the range of PROTACs. Our results demonstrate that the technology constitutes a versatile and highly modular platform for rapid generation of degraders of in theory any extracellular target and with the potential to have wide impact in drug discovery.

The Brian Clark Lecture Series is organised by Dept. Molecular Biology and Genetics

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