Highly specific intracellular ubiquitination of a small molecule

Quan Yuan

2025.1.18

Introduction of the author

Corresponding author

Jonathan M.L. Ostrem

University of California, San Francisco: Assistant Professor

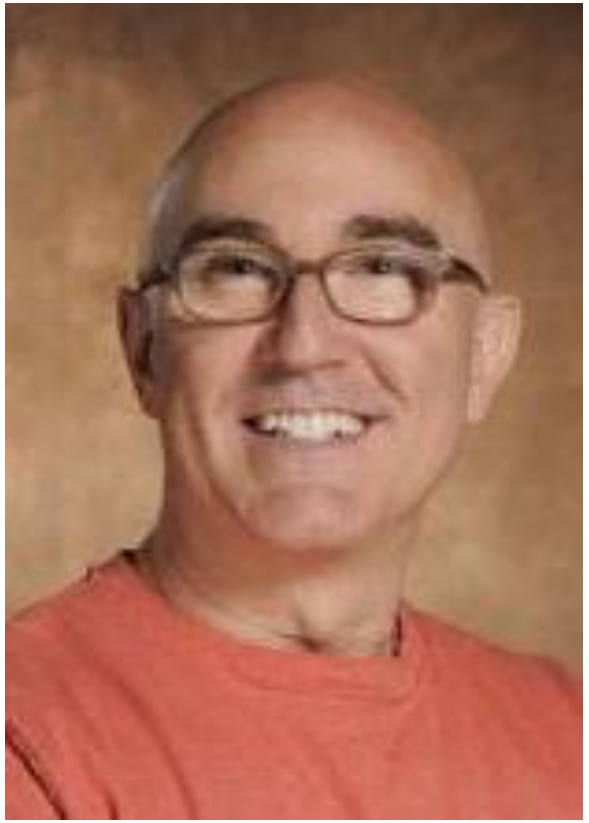
Educational Background

- University of California, San Francisco: PhD in Chemical Biology (2013).
- University of California, San Francisco: MD (2016).
- Brigham and Women's Hospital, Harvard Medical School: Completed Internal Medicine training (2018).
- Dana-Farber Cancer Institute, Harvard Medical School: Completed Medical Oncology training (2022).

Reasearch Focus

- Chemical biology approaches to develop new cancer treatment modalities.
- Design small molecules and antibody cancer therapeutics targeting oncogenic signaling pathways.

Introduction of the author



Stuart L. Schreiber

Morris Loeb Professor of Chemistry and Chemical Biology, Emeritus
Howard Hughes Medical Institute Investigator

Educational Backgroud

- University of Virginia: Bachelor of Science in Chemistry (1977).
- Harvard University: PhD in Chemistry, under the guidance of Robert Burns Woodward and Yoshito Kishi (1981).

Research Focus

- Chemical Biology
- Small Molecule Probes and Therapeutics
- Signal Transduction and Gene Regulation
- Diversity-Oriented Synthesis (DOS)
- Cancer Therapy

Introduction of the author

Cigall Kadoch

Associate Professor of Pediatric Oncology, Dana-Farber Cancer Institute
Affiliated Faculty, Biological Chemistry and Molecular Pharmacology, Harvard Medical School
Investigator, Howard Hughes Medical Institute
Institute Member and Epigenomics Program Co-Director, Broad Institute of MIT and Harvard

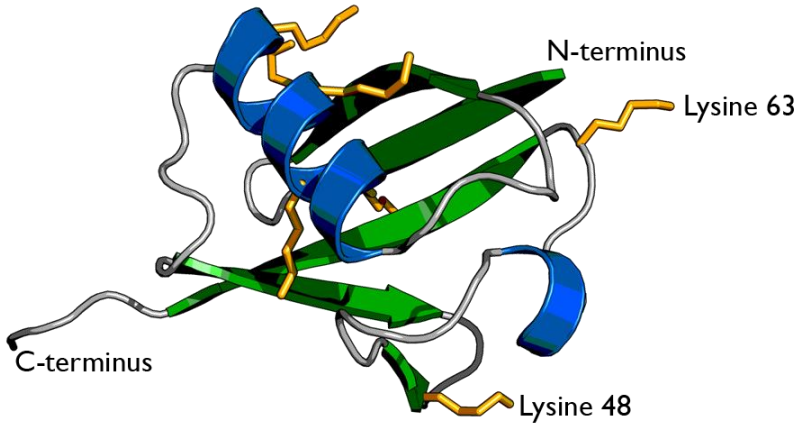
Educational Background

- University of California, Berkeley: Bachelor of Science in Molecular and Cell Biology.
- Stanford University School of Medicine: PhD in Cancer Biology, under the supervision of developmental biologist Gerald Crabtree.

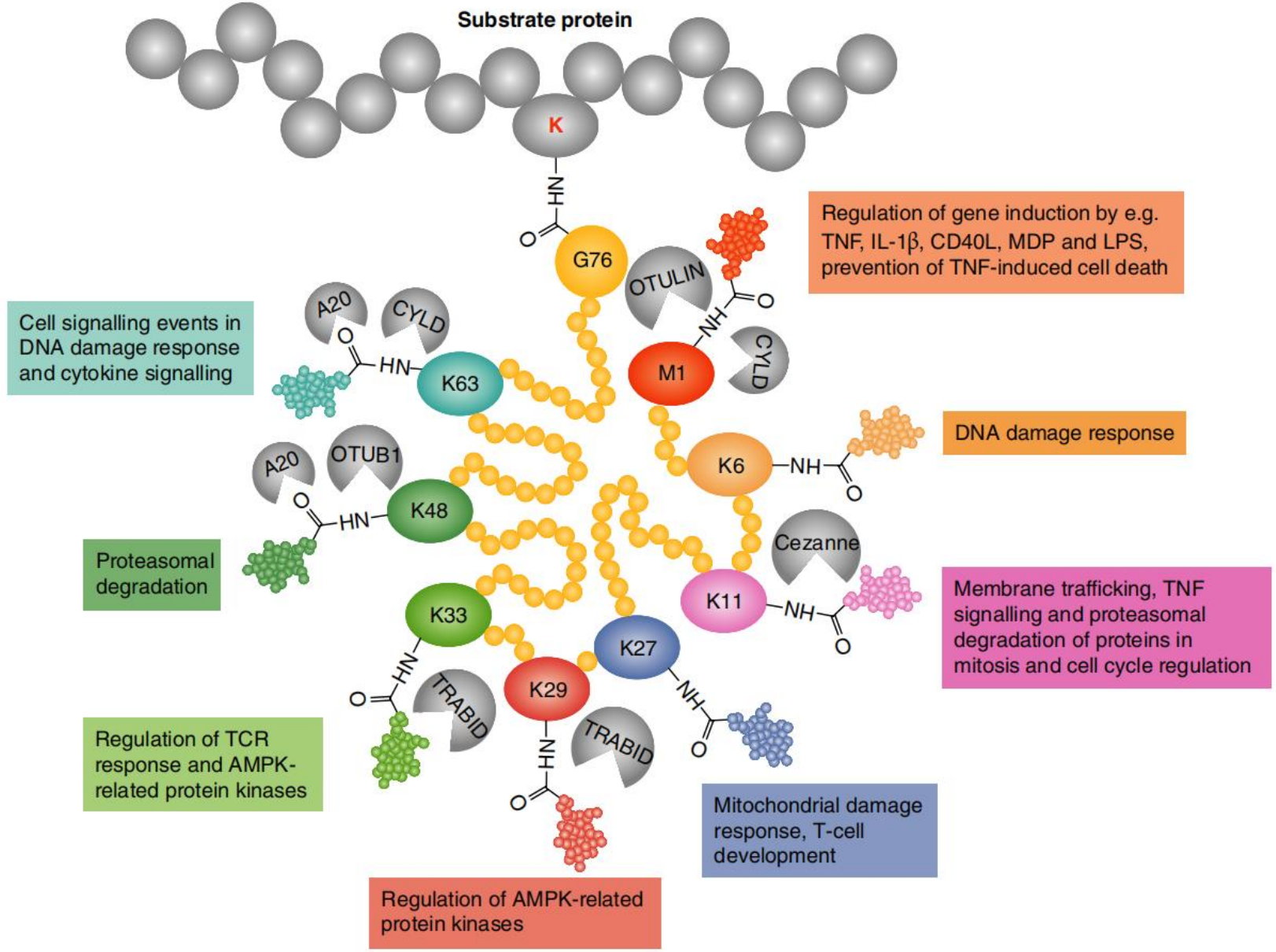
Research Focus

Chromatin Regulation; SWI/SNF Complex; Cancer Therapy

Ubiquitin（泛素）

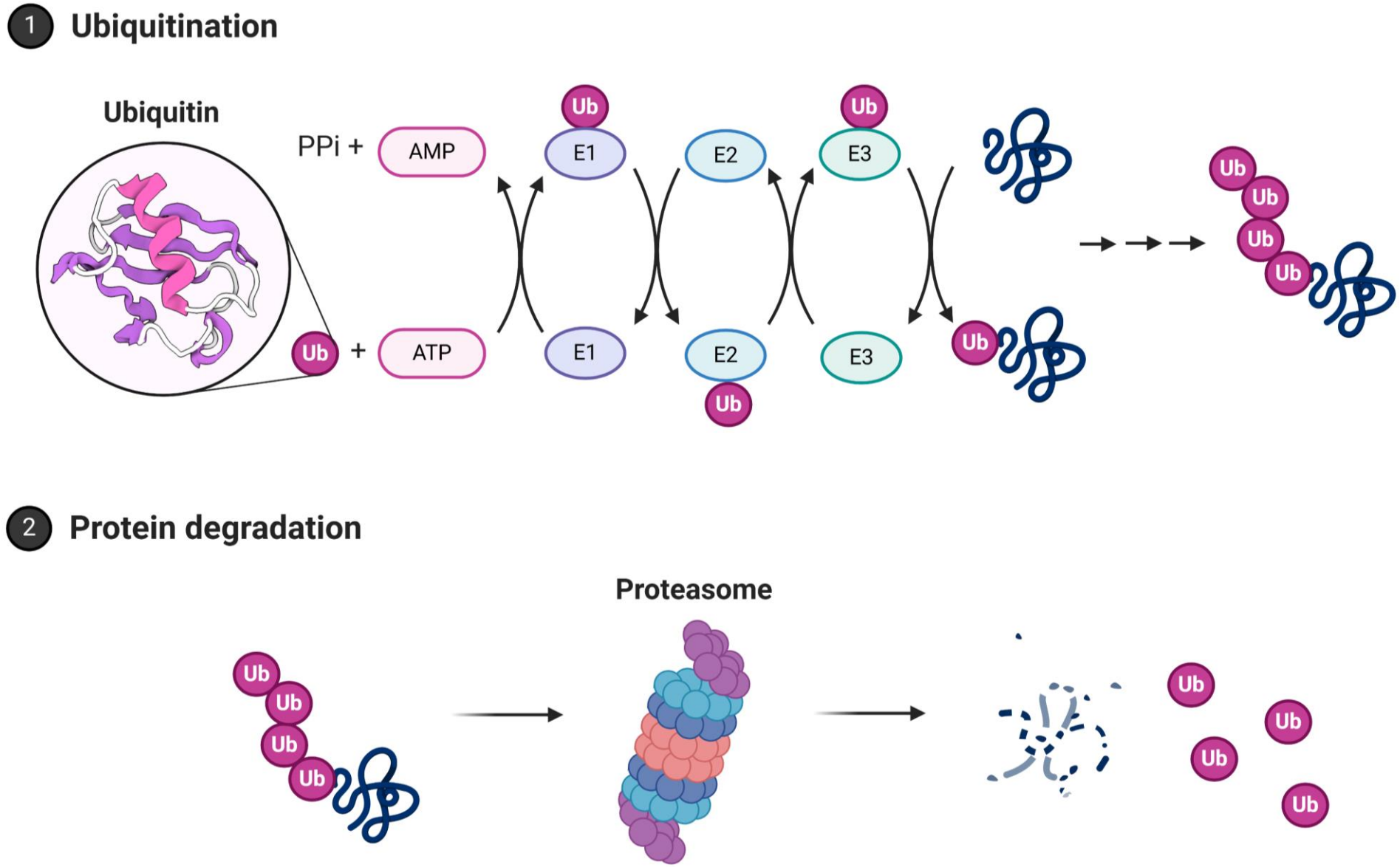


Ubiquitin
PDB: 1UBQ



Zinngrebe J. *et al.* EMBO Rep. 2014 Jan;15(1):28-45.

Ubiquitin-Proteasome System (UPS)



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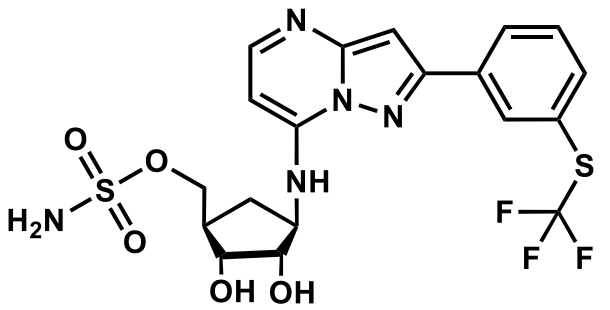
Small Molecule Inhibitors of UPS



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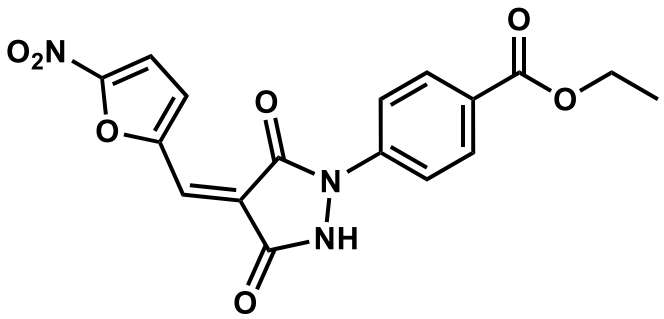

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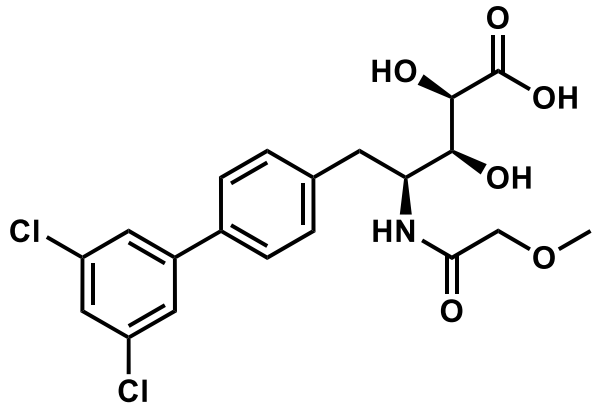

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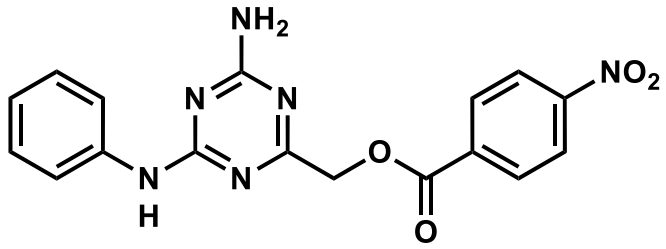

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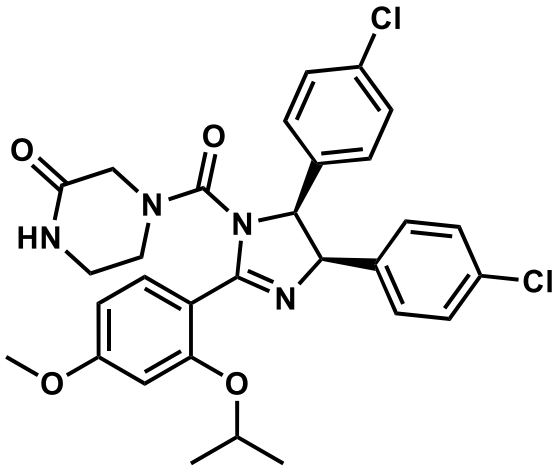
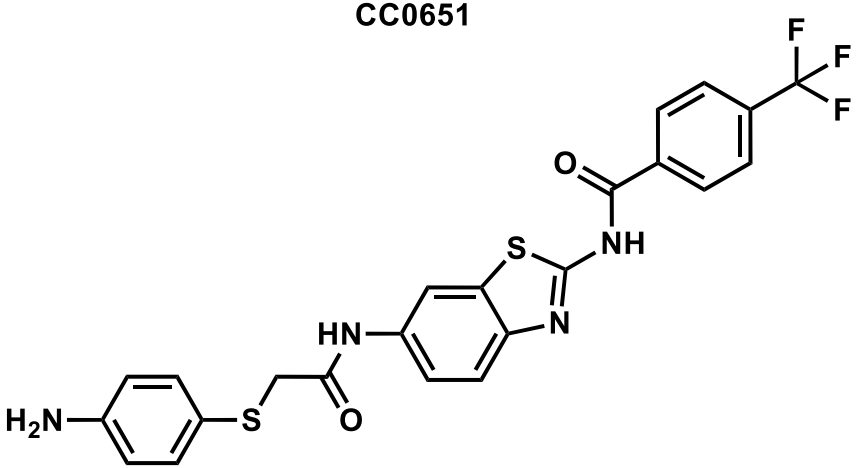


Nutlin-3a



ZM223

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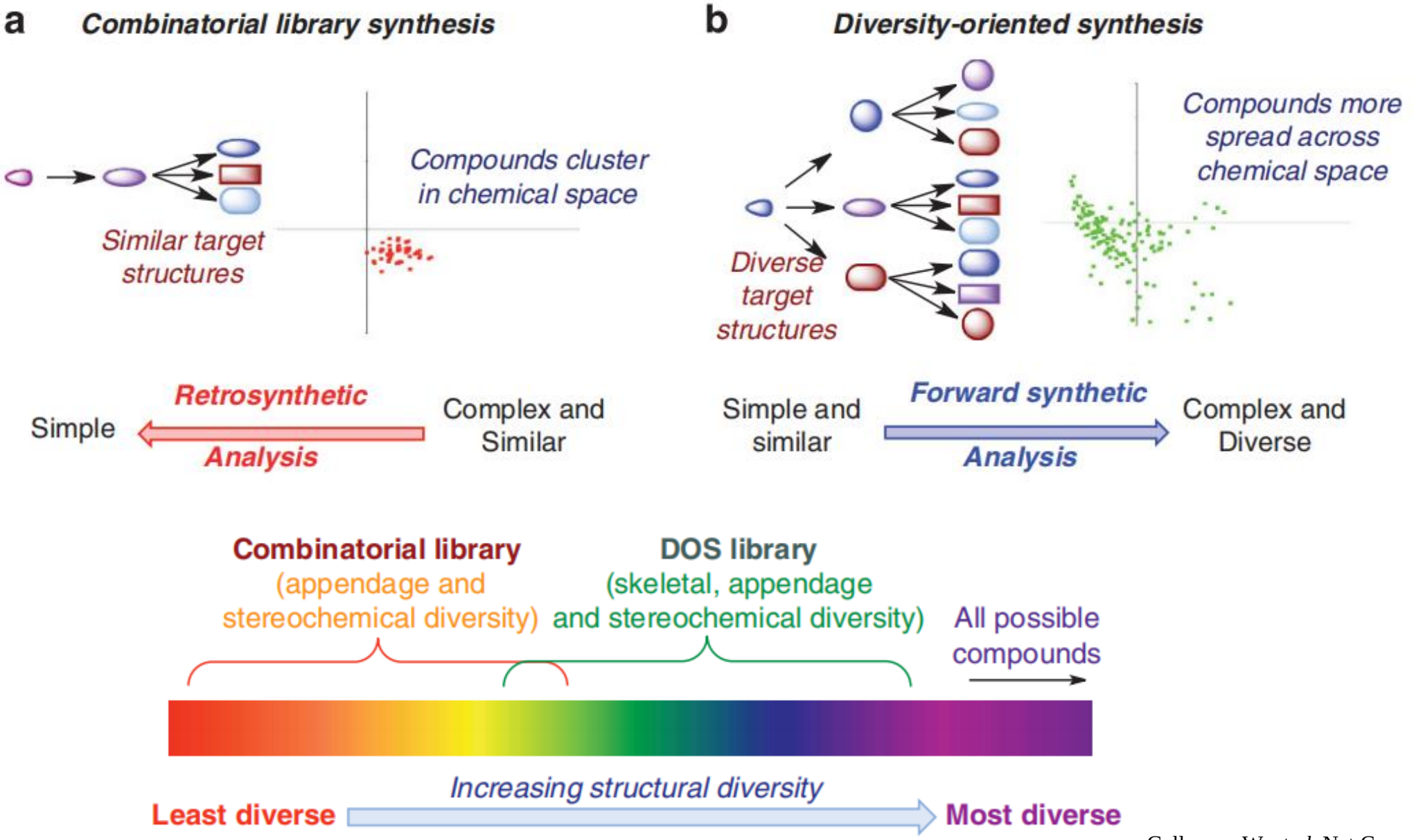
Diversity-Oriented Synthesis (DOS)



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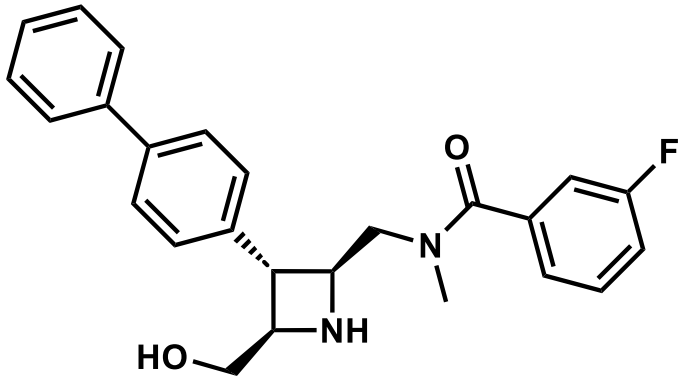
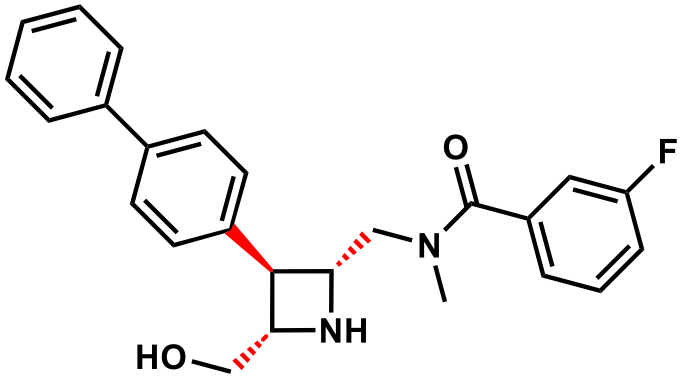
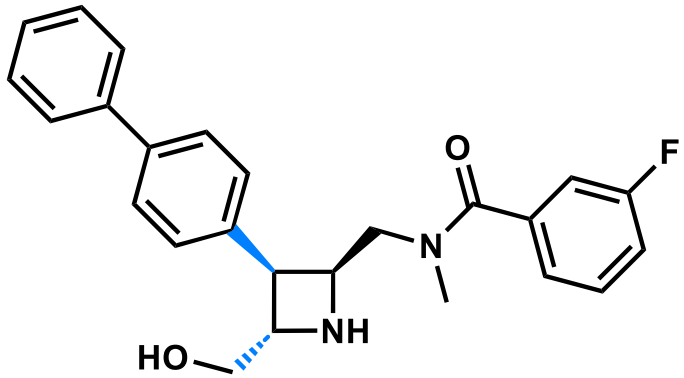
Screening of BDR1732



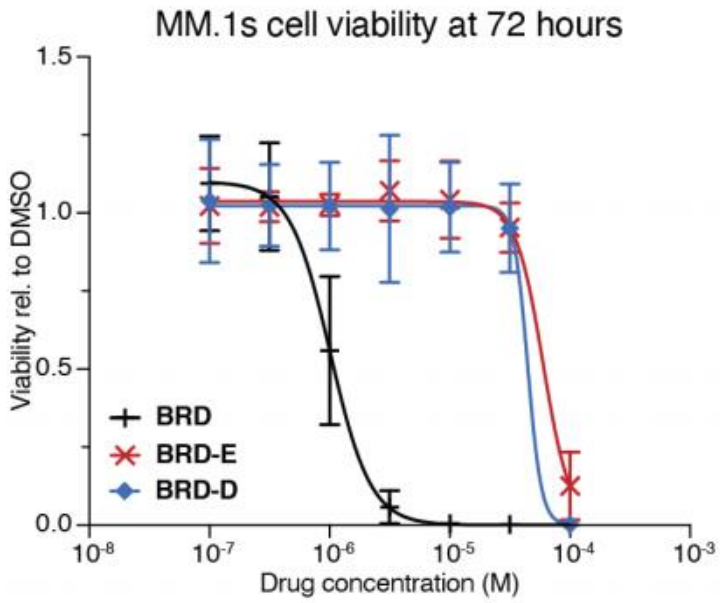
BRD
BRD1732
(2S,3R,4R)

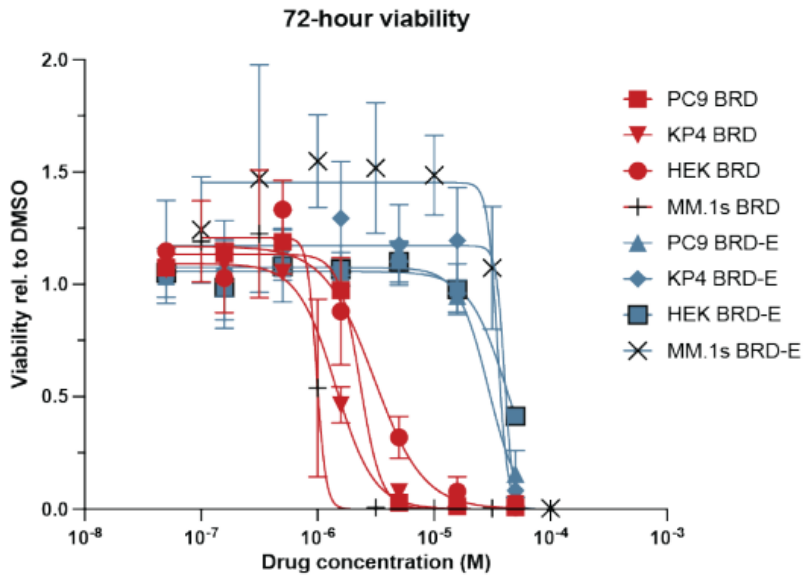


BRD-E
BRD1732 Enantiomer
(2R,3S,4S)

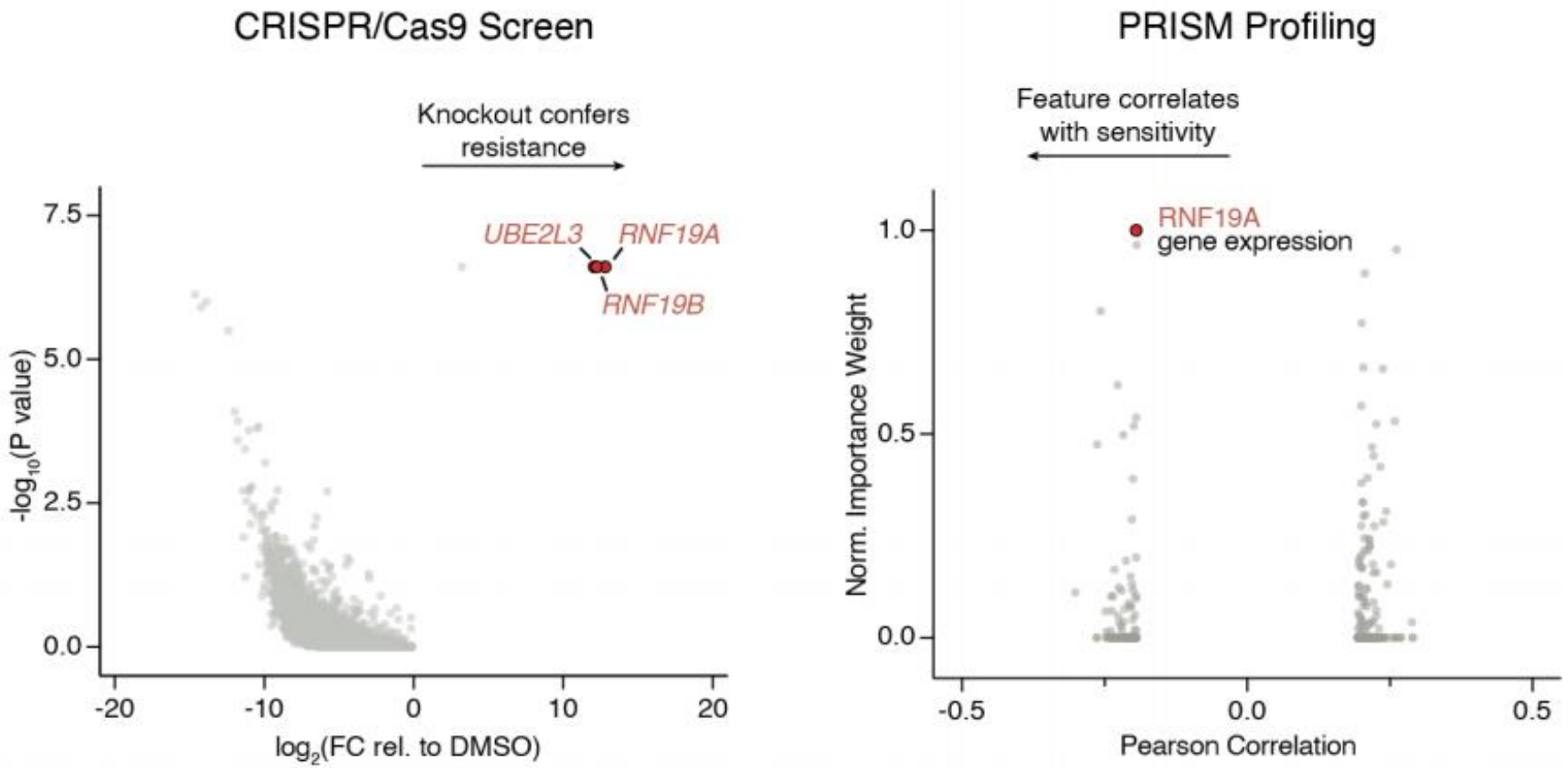


BRD-D
BRD1732 Diastereomer
(2R,3R,4S)





Molecular Mechanism of BDR1732 Cytotoxicity

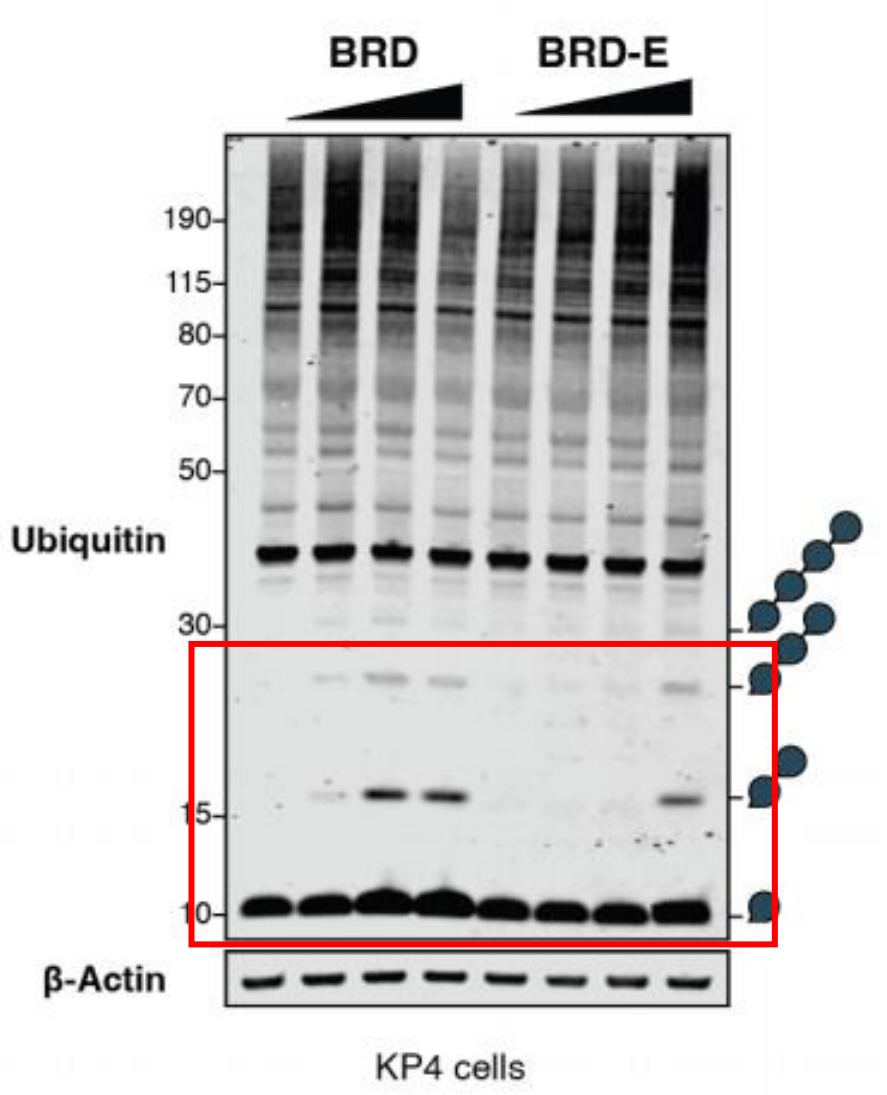


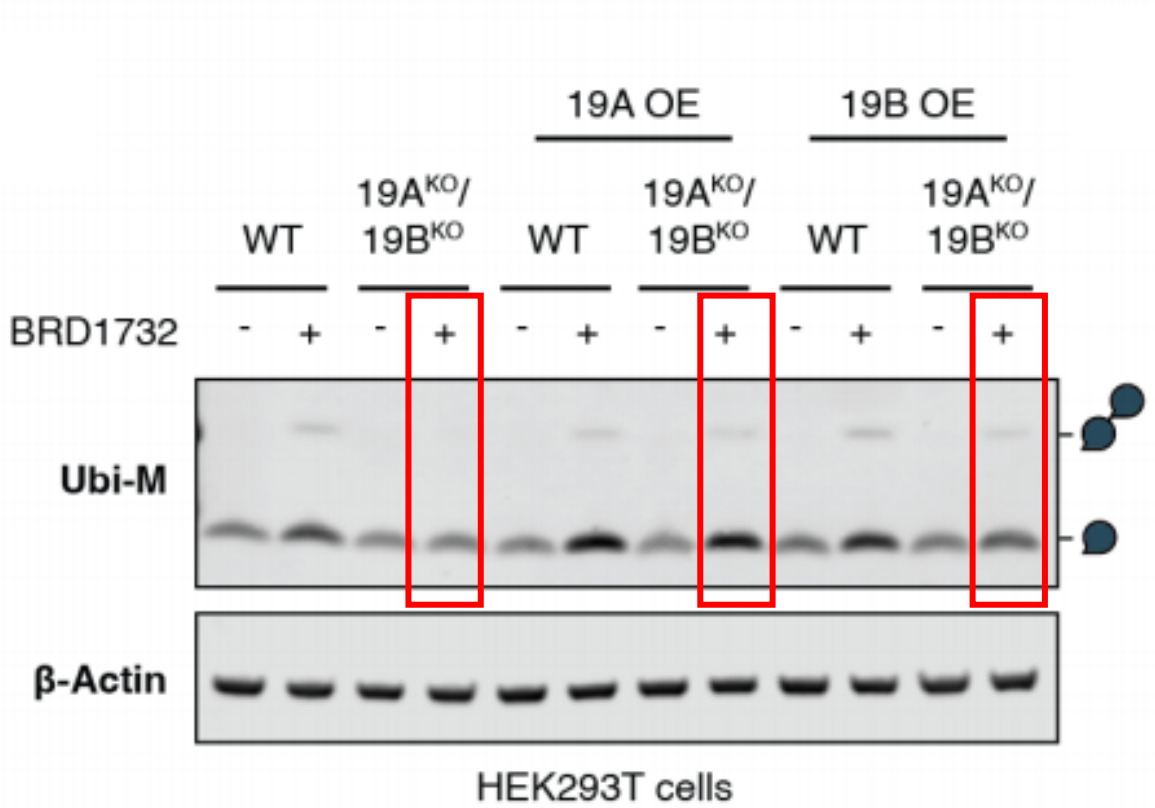
RNF19A(Dorfin): RING-in-between-RING (RBR) E3 ubiquitin ligase.

RNF19B(Parkin): RBR E3 ubiquitin ligase.

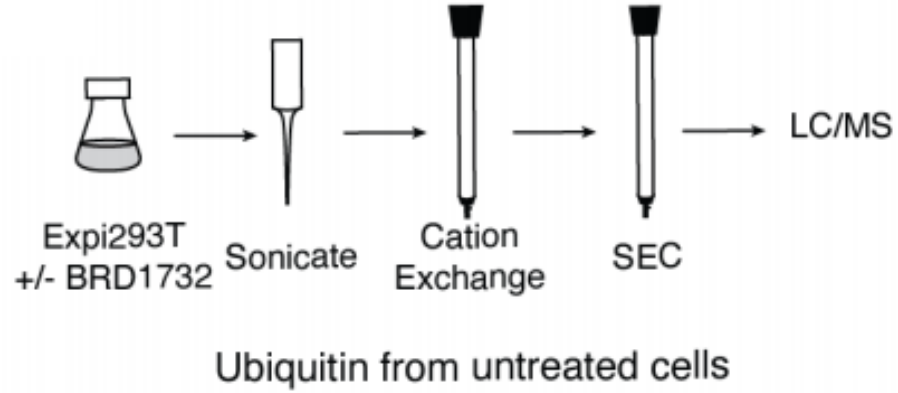
UBE2L3: E2 ubiquitin-conjugating enzyme

Molecular Mechanism of BDR1732 Cytotoxicity

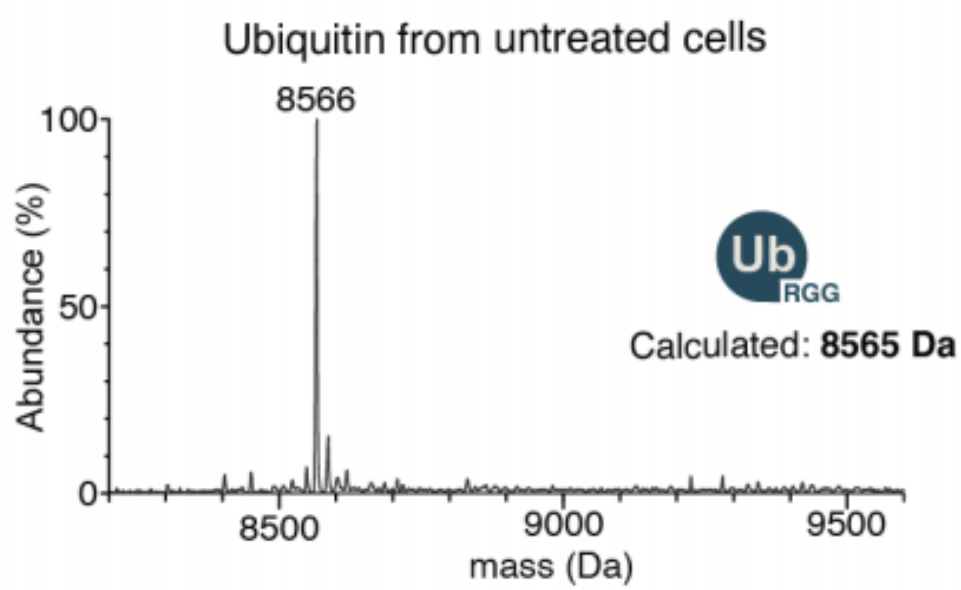


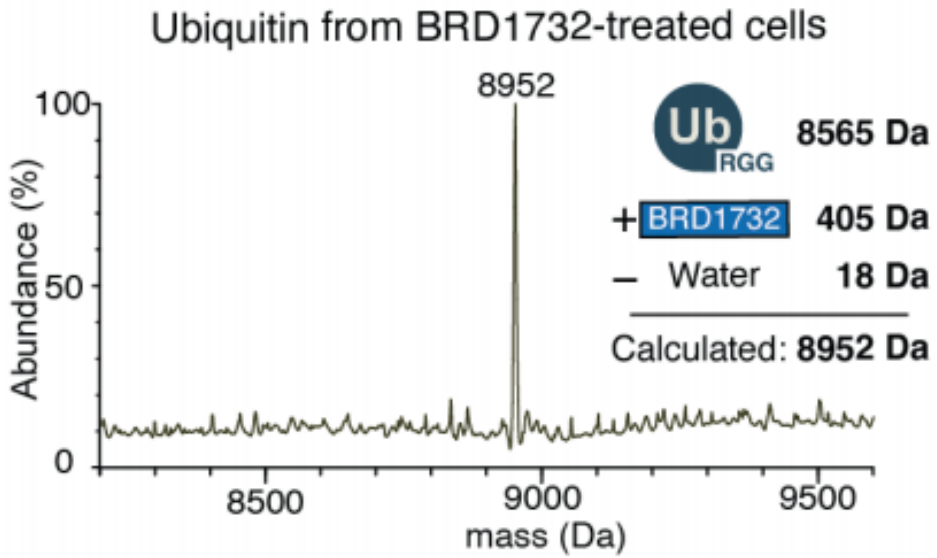


BRD1732 is Directly Ubiquitinated in Cells

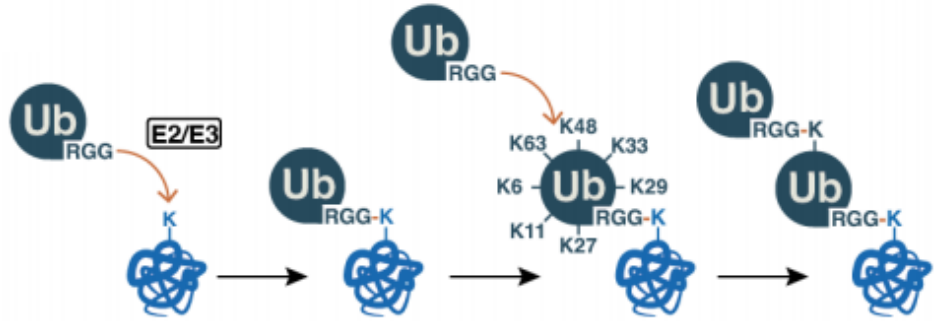


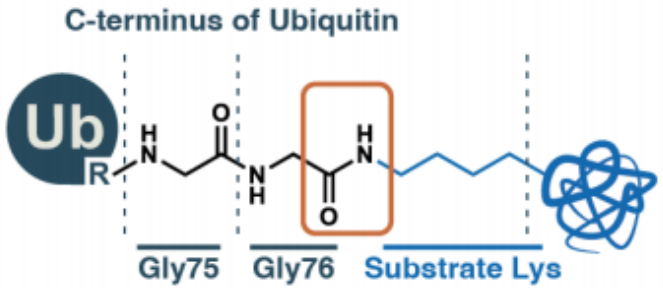
Ubiquitin from untreated cells

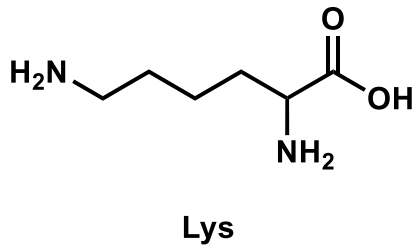


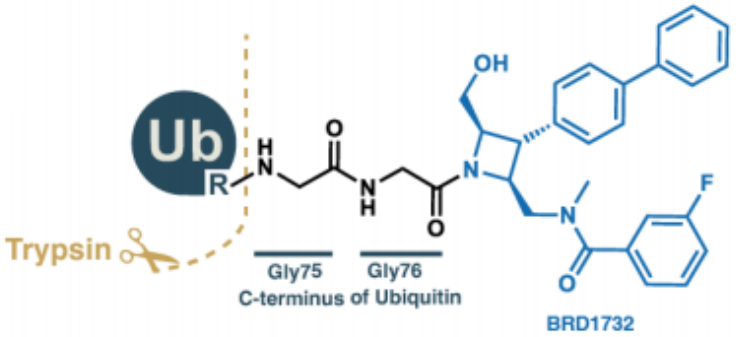


BRD1732 is Directly Ubiquitinated in Cells

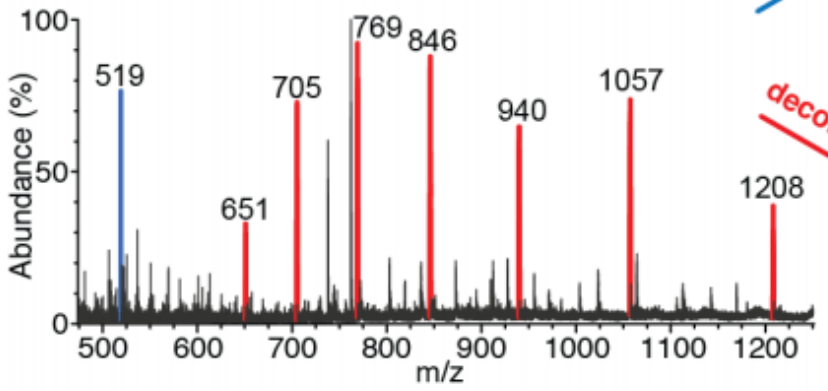




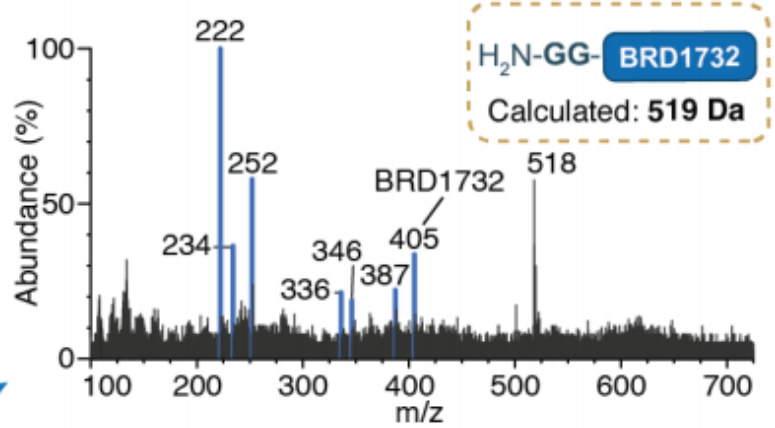




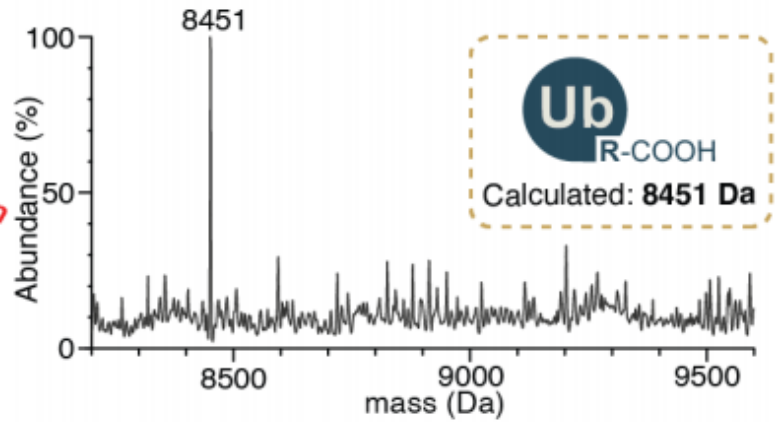
LC/MS



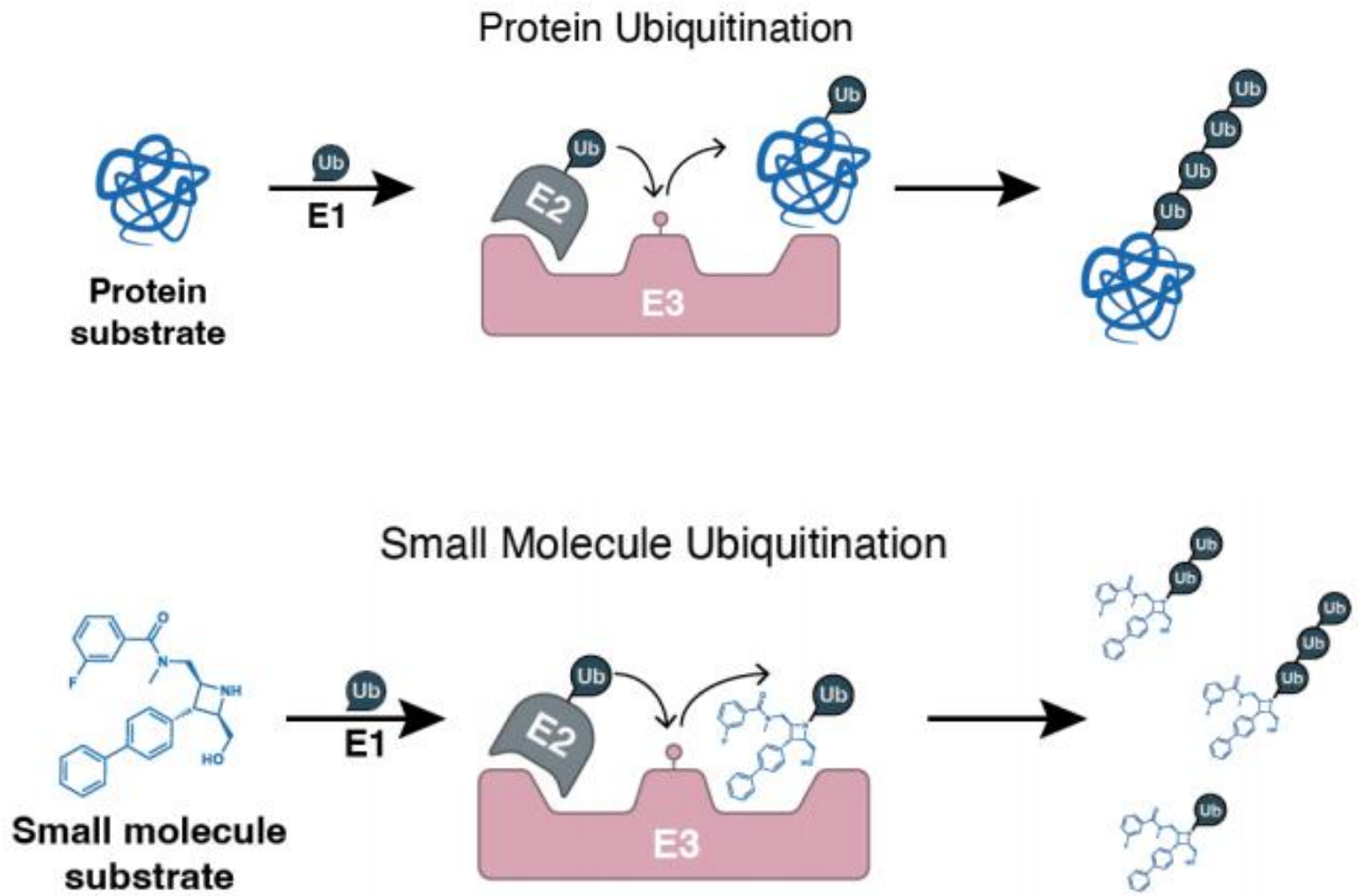
fragmentation



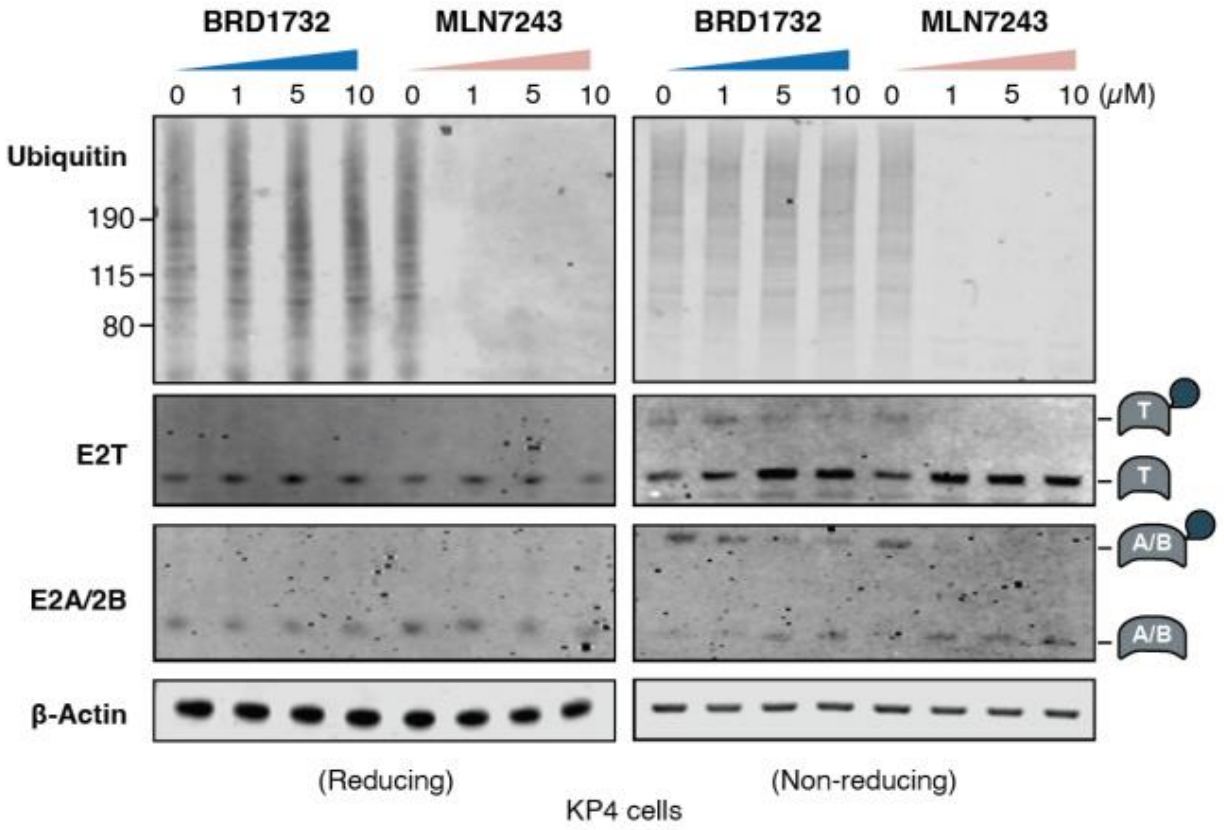
deconvolution

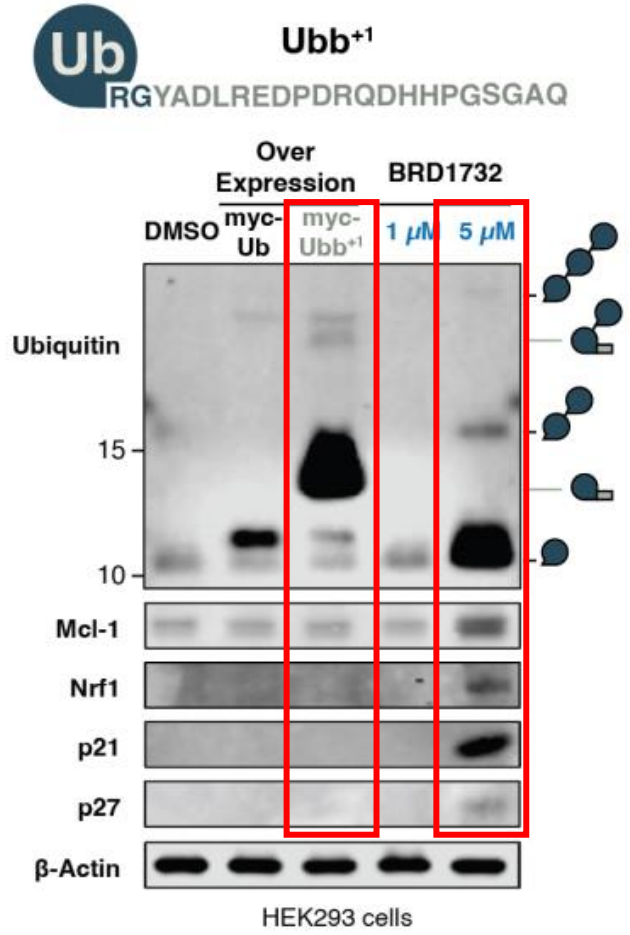


BRD1732 is Directly Ubiquitinated in Cells



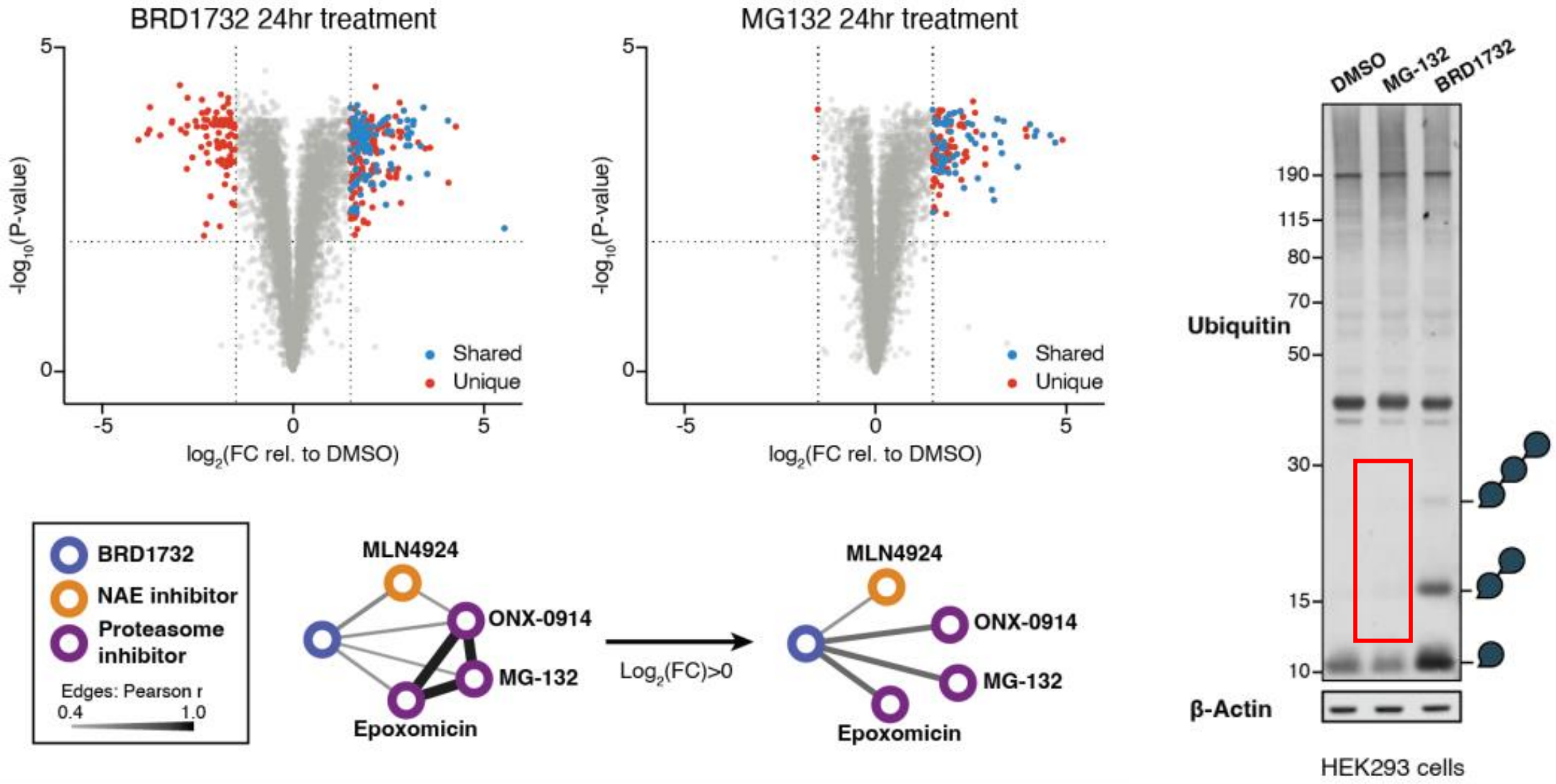
BRD1732 Disrupts the UPS at Multiple Pathway Nodes





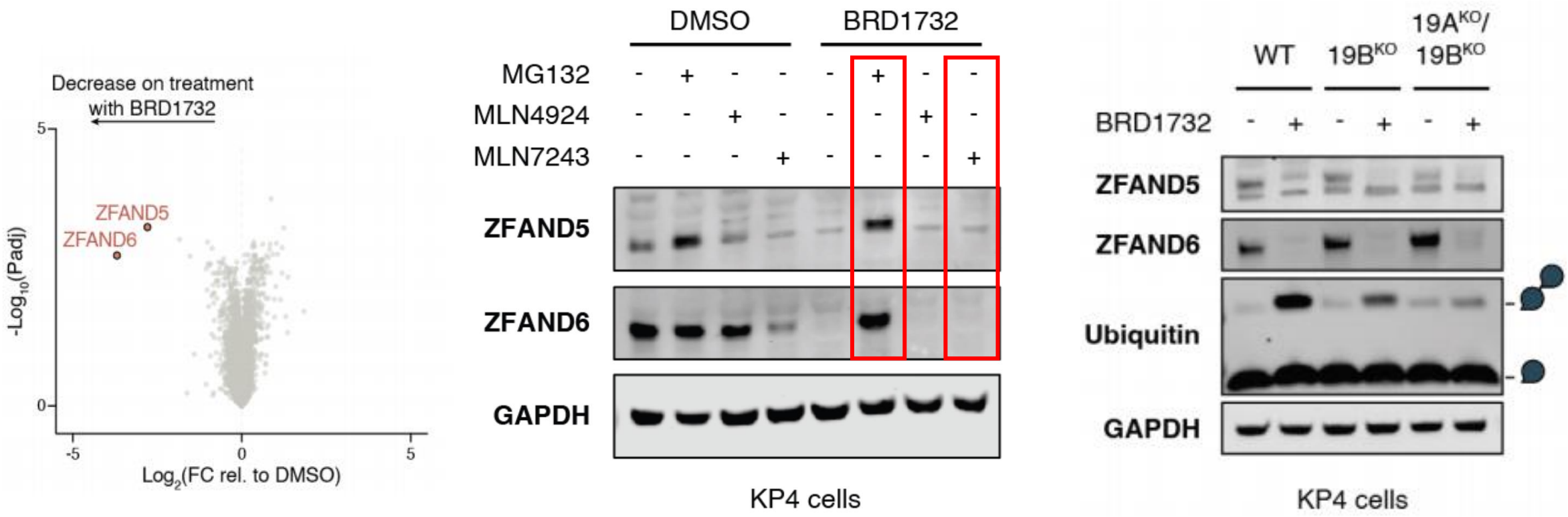
MLN7243：adenosine monophosphate (AMP) mimetic ubiquitin activating enzyme (UAE) inhibitor

BRD1732 Disrupts the UPS at Multiple Pathway Nodes



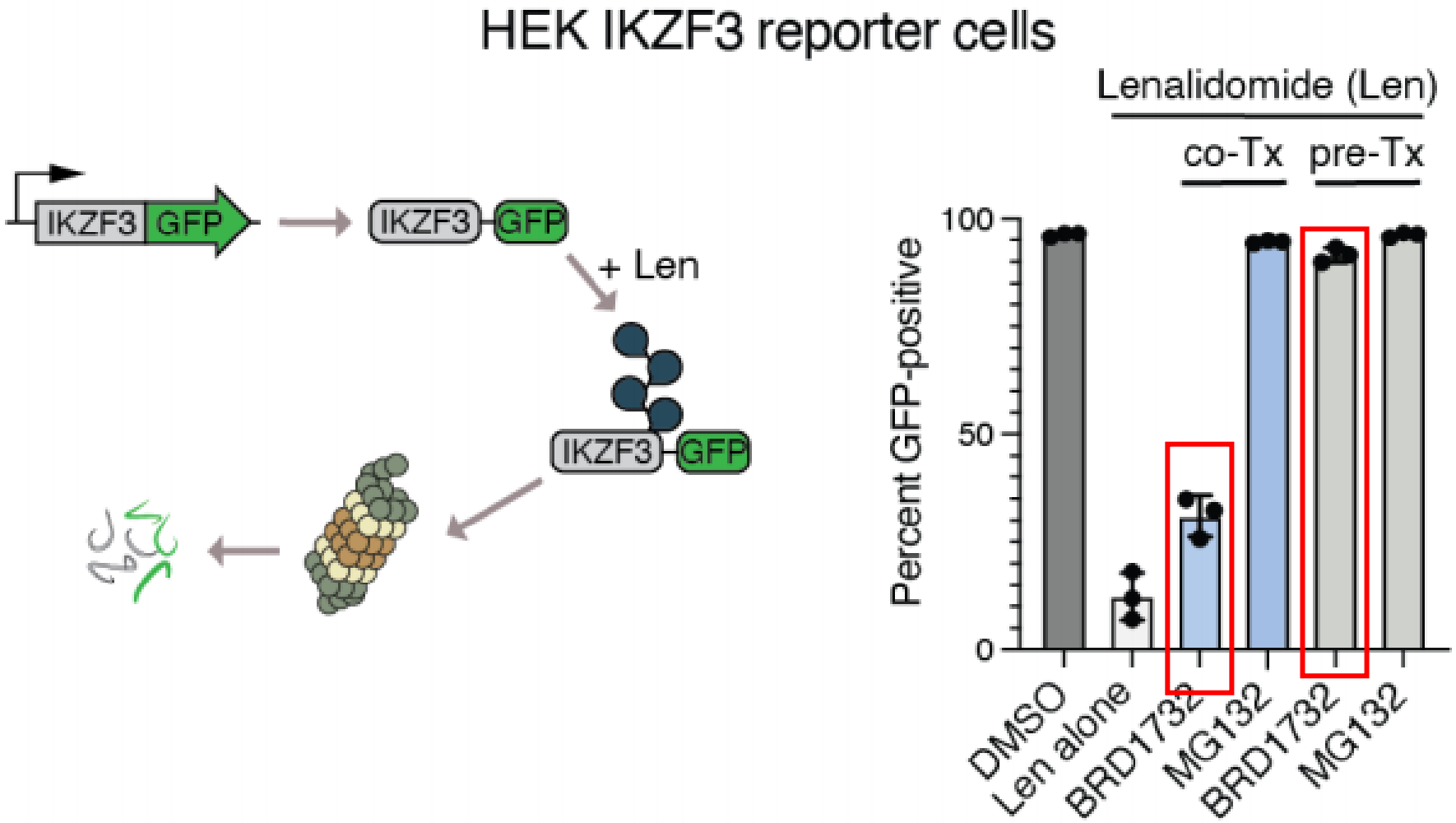
MG132：proteasome inhibitor

BRD1732 Disrupts Ubiquitin-Dependent Proteasomal Degradation



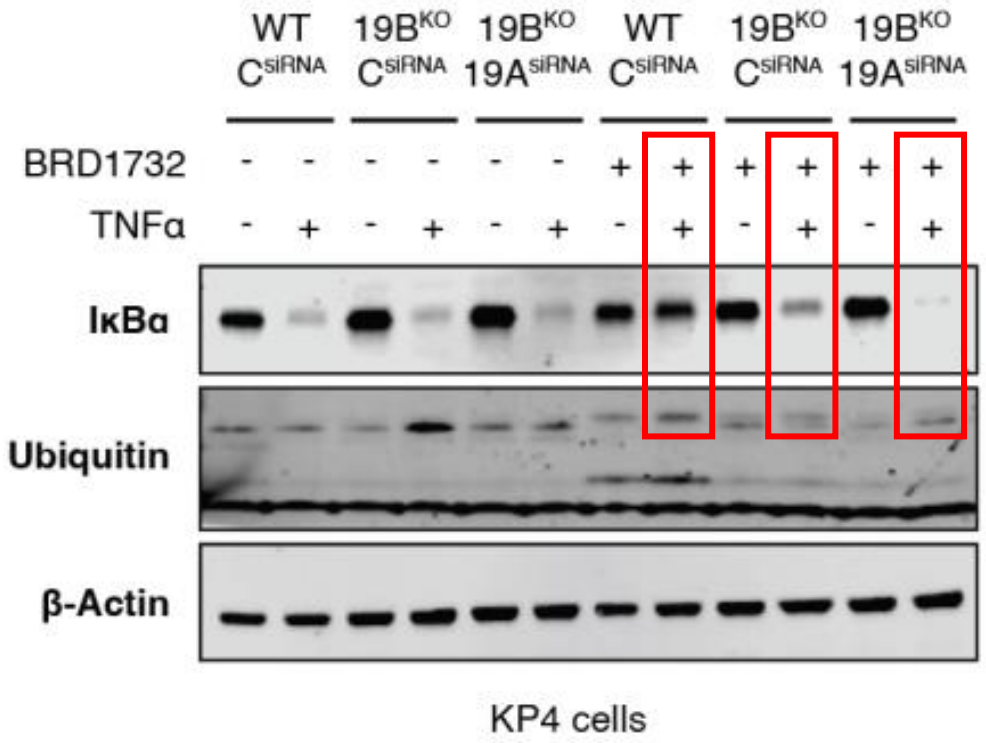
ZFAND5/6：two highly homologous zinc finger proteins

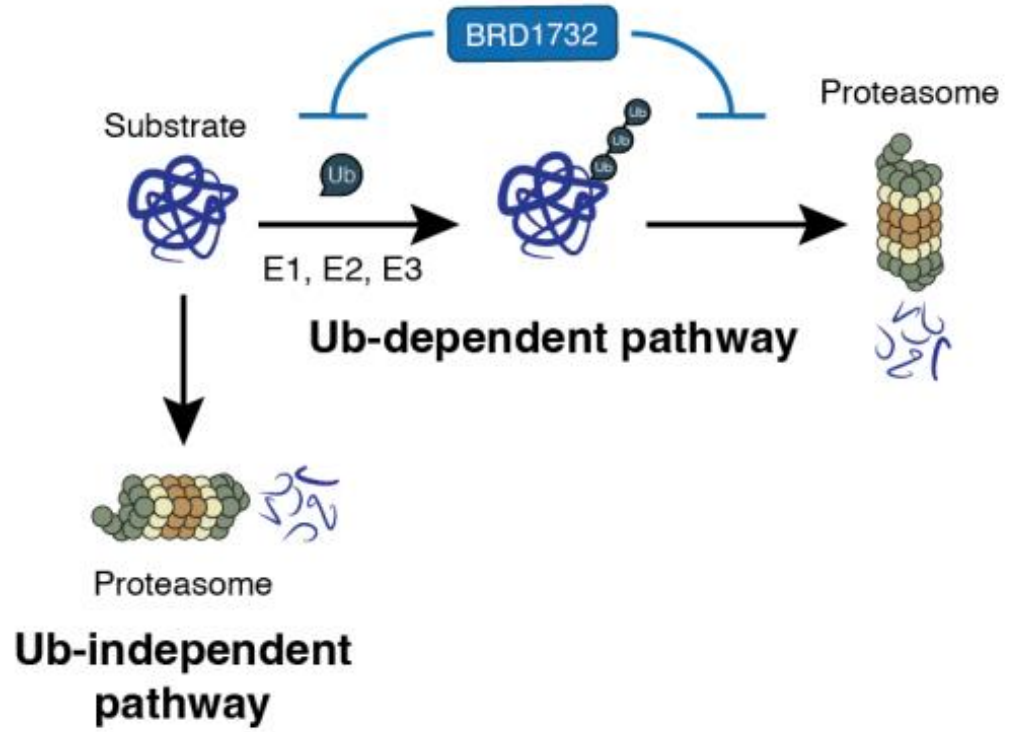
BRD1732 Disrupts Ubiquitin-Dependent Proteasomal Degradation



Lenalidomide： induces ubiquitination and degradation of IKZF3 by the E3 ubiquitin ligase cereblon

BRD1732 Disrupts Ubiquitin-Dependent Proteasomal Degradation

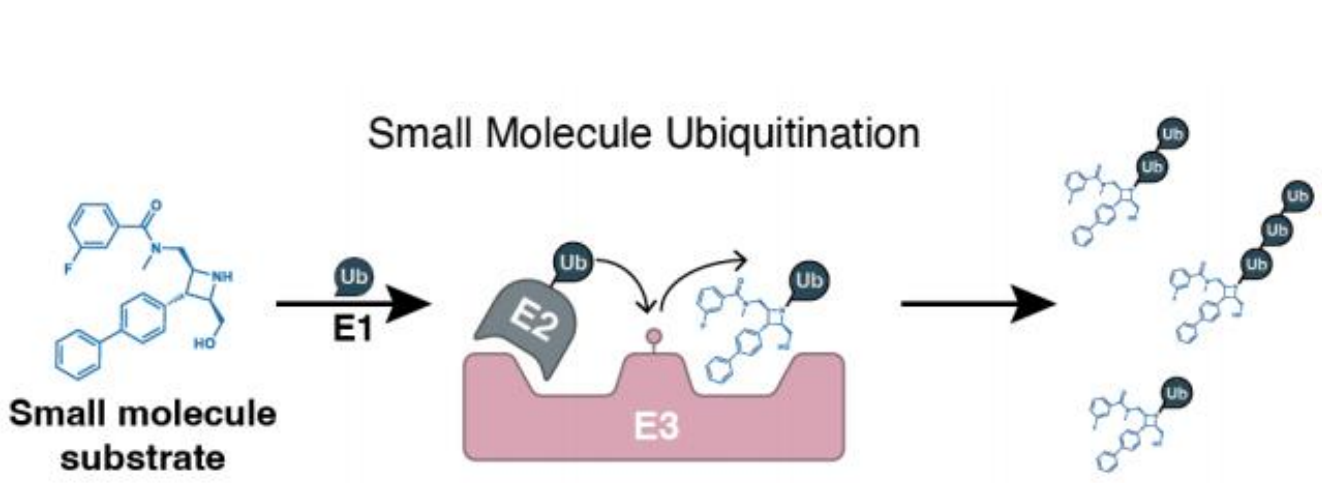


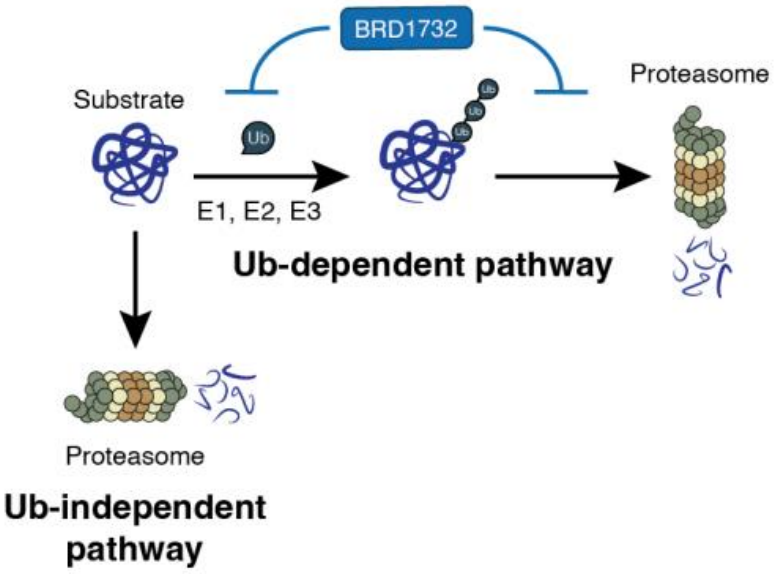


TNFα (tumor necrosis factor α): a major regulator of inflammatory responses

Summary and Discussion

- A small molecule that can be directly labeled by the ubiquitination system in cells was discovered.
- BRD1732 can achieve multi-node interference of the ubiquitin-proteasome system (UPS).
- Reveals the new potential of trans modification mediated by small molecules in drug development.





Thanks for your attention!

Synthesis Route