2.1 The rise of molecular glues and bifunctional compounds

Stuart L. Schreiber1, 2
1Harvard University, 2Broad Institute

Efforts to translate novel biological findings have revealed a need for new approaches to drug discovery. The methods we are now pursuing trace back to the revelation that the cyclosporin and FK506 act in a way previously not seen — as “molecular glues” that induce protein–protein associations (Cell, 1991, 66, 807-815). The realization that additional medicines act as molecular glues has fueled the surge of interest in strategies for inducing functional protein–protein associations. I will discuss advances in the discovery of binders and molecular glues that alter their targets’ cellular lifetimes and localizations and may facilitate the translation to novel therapeutics having tissue and substrate selectivity. See also “The Rise of Molecular Glues”, Cell, 2021, 184, 3-9.

2.2 Mapping the Degradable Kinome: A Resource for Expedited Degrader Development

Katherine A. Donovan1, 2, Fleur M. Ferguson1, 2, Jonathan W. Bushman1, 2, Nicholas A. Eleuteri1, Debabrata Bhunia5, SeongShick Ryu7, Li Tan1, 2, 4, 5, Kun Shi4, 5, Hong Yue1, 2, Xiaoxi Liu1, 2, Dennis Dobrovolsky1, 2, Baishan Jiang1, 2, Jinhua Wang1, 2, Mingfeng Hao1, 2, Inchul You1, 2, Mingxing Teng1, 2, Yanke Liang1, 2, John Hatcher1, 2, Zhengnian Li1, 2, Theresa D. Manz1, 2, Brian Groendyke1, 2, Wanyi Hu1, Yunju Nam7, 8, Sandip Sengupta6, 8, Hanna Cho7, 8, Injae Shin7, Michael P. Agius6, Irene M. Ghobrial6, Michelle W. Ma1, 2, Jianwe Che1, 2, Sara J. Buhrlage1, 2, Taeb Sim6, 7, 8, Nathanael S. Gray1, 2, Eric S. Fischer1, 2

1Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, MA 02215, USA, 2Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA 02, 3Department of Pharmaceutical and Medicinal Chemistry, Saarland University, Saarbruecken, Germany, 4Interdisciplinary Research Center on Biology and Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Beijing 100049, China, 5Chemical Kinomics Research Center, Korea Institute of Science and Technology, 5 Hwarangro 14-gil, Se, 7KU-KIST Graduate School of Converging Science and Technology, Korea University, 145 Anam-ro, Seongbuk, 8Severance Biomedical Science Institute, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaem, 9Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA

Small molecules that induce protein degradation through ligase-mediated ubiquitination have shown considerable promise as a new pharmacological modality. We and others have demonstrated that efficacious degradation of kinases and other targets can be achieved in vitro and in vivo, however, many targets remain recalcitrant to degradation. In this presentation, I will discuss the use of large-scale chemical-proteomics approaches to map kinase degradability and accelerate the development of degraders as novel chemical probes for kinases.

100300, https://doi.org/10.1016/j.mcpro.2022.100302