



Grand Prize
winner

Zuzanna Kozicka

Category: Molecular Medicine

Essay title: *Gluing the pieces together: Illuminating the path to degrading troublesome proteins*

Biography

Dr. Zuzanna Kozicka grew up in Kraków, Poland. She moved to the UK for an undergraduate degree in Medicinal and Biological Chemistry at the University of Edinburgh. Inspired by a year-long internship with Prof. Nenad Ban at the ETH Zürich and a summer project with Prof. Alessio Ciulli in Dundee during her studies, Zuzanna relocated to Switzerland to pursue a PhD with Dr. Nicolas Thomä with a focus on targeted protein degradation. She worked on molecular glue degraders, which are compounds able to inactivate disease-causing proteins through sending them to the cellular waste disposal system. Her research identified a novel class of glues and yielded insights into how such drugs could be designed.

Zuzanna recently began her postdoctoral work at the Dana Farber Cancer Institute and MIT with Prof. Benjamin Ebert and Prof. Angela Koehler, continuing to explore how compounds can bring together seemingly unrelated proteins.

Abstract

Molecular glue degraders hold great therapeutic promise, yet because their discoveries have been serendipitous, their design principles remain unclear. We developed new approaches to systematically identify such degraders and discovered a diverse class of compounds that deplete cyclin K. To investigate how chemically dissimilar small molecules can all trigger cyclin K degradation, we evaluated 91 putative degraders in structural, biophysical, and cellular assays.

We discovered that they function by simultaneously binding to CDK12-cyclin K and the ubiquitin ligase adaptor DDB1 and solved 29 crystal structures of compound-induced complexes. This systematic study of the relationships between the glue's structure and activity provides a framework for designing and optimizing molecular glue degraders. We further demonstrate cyclin K degraders have distinct transcriptional signatures, thereby offering unique therapeutic opportunities.