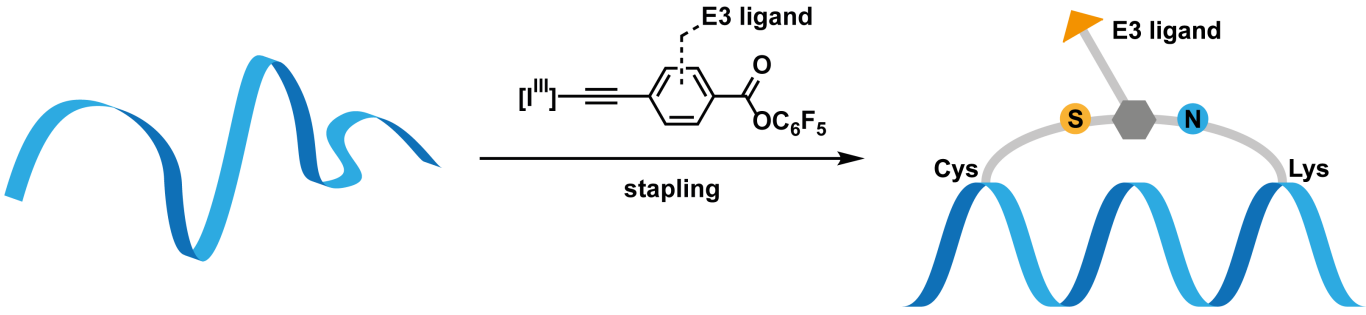
Stapled-Peptide PROTACs by Hypervalent Iodine Staples

Yuji Kamei[1,2], Beat Fierz[1], Jerome Waser[2]

[1]Laboratory of Biophysical Chemistry of Macromolecules, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland
[2]Laboratory of Catalysis and Organic Synthesis, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland
yuji.kamei@epfl.ch

Protein–protein interactions (PPIs) are deemed undruggable due to the lack of well-defined binding pockets on corresponding proteins. Peptides can target undruggable proteins by mimicking PPIs. Indeed, development of peptide-based inhibitors of PPIs is one of the major topics in current medicinal chemistry. PROTAC (proteolysis targeting chimera) technology is an emerging modality to degrade pathological proteins.[1] Most of the PROTACs are synthesized by linking two small-molecule ligands: a POI (protein of interest) ligand and an E3 ligand. However, the development of small-molecule ligands for undruggable proteins is in itself challenging. Thus, the availability of POI ligands is hampering the development of PROTACs for undruggable proteins.

We developed E3 ligand-loaded hypervalent iodine staples based on our previous report,[2] which readily transformed peptides into stapled-peptide PROTACs for degradation of undruggable proteins. Peptide stapling is known to stabilize α-helices and improve inappropriate properties for in vivo efficacy of peptides, namely low membrane permeability and low proteolytic stability. These staples modify peptides to have degradation activity as well as good physicochemical properties targeting intracellular environment at the same time. Thus, this tool would pave the way for rapid drugging of currently untouched proteins, even if small-molecule ligands are not available. We first chose to target the steroid receptor coactivator-1 (SRC-1) which interacts with transcription factors, with a reported SRC-1 degrader as a benchmark.[3]



[1] K. T. G. Samarasinghe, C. M. Crews, *Cell Chem. Biol.* **2021**, *28*, 934-951.
[2] J. Ceballos, E. Grinhagena, G. Sangouard, C. Heinis, J. Waser, *Angew. Chem., Int. Ed.* **2021**, *60*, 9022-9031.
[3] Y. Lee, J. Heo, H. Jeong, K. T. Hong, D. H. Kwon, M. H. Shin, M. Oh, G. A. Sable, G-O. Ahn, J.-S. Lee, H. K. Song, H.-S. Lim, *Angew. Chem., Int. Ed.* **2020**, *59*, 17548–17555.