PROTACS as tools for the modulation of pharmacological targets

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The proteolysis targeting chimera (PROTAC) concept is currently receiving major attention in drug discovery field as it holds tremendous potential in the therapy of different human diseases (Scudelari, M (2019) Nature 567, 298-300). PROTAC strategy uses a heterobifunctional molecule comprised of a small-molecule ligand (binding to a protein of interest), another small molecule ligand (binding to an endogenous E3 ligase), and a linker moiety connecting both compounds. If designed successfully, PROTAC molecules hijack the endogenous ligase and the ubiquitin proteasome system to degrade, rather than just inhibit, protein(s) of interest (Burslem, GM et al. (2020) Cell 181, 1-13).

Our work is focused on several important pharmacological targets, namely the O-GlcNAc transferase (OGT), B-cell lymphoma 2 (BCL-2), and cyclin-dependent kinase 6 (CDK6). The cellular levels of all three proteins are dysregulated in many diseases; therefore, development of their degraders is a viable strategy in the development of both possible therapeutics and useful chemical probes to study involvement of these proteins in various molecular pathways inside cells. During the development of PROTACs for these targets, we utilized their known inhibitors as starting points, i.e. OSMI-4 for OGT, venetoclax for BCL-2, and palbociclib for CDK6. Moreover, for the construction of chimeras we used ligands for at least three different E3 ligases, such as cereblon, von Hippel-Lindau, and Inhibitor of Apoptosis Protein. Such modularly assembled PROTACs did yield potent and selective degraders of CDK6 (Steinebach C et al. (2020) Chemical Science, doi: 10.1039/D0SC00167H), which represent extremely valuable tools for future development of anti-cancer therapeutics.