Making the Undruggable Druggable: Synthetic Prolin-Derived Modules (ProMs) as Building Blocks for Rational and Library-Based Drug Development

Slim Chiha, Peter ten Dijke, Ronald Kühne, Hans-Günther Schmalz

University of Cologne (Germany), Leiden University Medical Center (Netherlands), Leibniz Institute for Molecular Pharmacology in Berlin (Germany)

Protein domains specialized in the recognition of proline-rich segments (PRS) adopting a polyproline type II helix (PPII) conformation are particularly abundant, yet so far undruggable.[1] Moreover, these domains often play a key role in disease-related cellular malfunctions (e.g. the expansion of invasive cancer), making small-molecule competitors of PRS urgently needed.

We designed and established efficient syntheses of proline-derived modules (ProMs), i.e. polycyclic dipeptide units structurally rigidified in a PPII conformation.[2] These were then used as building blocks in the synthesis of tailored small molecule ligands, which selectively bind to the target domain with remarkable affinity.

As a proof of concept, we developed a highly selective, ProM-based inhibitor of protein-protein interactions involving Ena/VASP, a target of choice for the development of an antimetastatic drug. Furthermore, in vivo studies revealed that treating highly invasive breast cancer cells with this ProM-inhibitor caused a strong suppression of cell motility and chemotaxis, as reflected by an inhibition of cancer cell invasion by 66%.[3]