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RESEARCH AREA

Protein-protein interactions (PPIs) play key role in many cellular processes including pathological conditions such as cancer progression. PPIs mediated by intrinsically disordered proteins, which fold during protein binding, are especially challenging to target. Investigating the binding mechanism and structural changes of such proteins would lead to better understanding of their function and could serve as starting points for drug discovery.

One of our approaches includes the modification of a known ligand using non-natural amino acids, which influence their binding properties and stability. In our other approach we use libraries of non-natural peptides to find binding motifs that recognize the target protein surface. Our goal is to develop methods that can be used to create high affinity and selective ligands based on the identified binding motifs. One such method is dynamic covalent chemistry where the protein acts as a selection pressure to form the best binders. Another approach is to use DNA templated synthesis to connect the binding motifs which can be identified by their DNA code.

TECHNIQUES AVAILABLE IN THE LAB

Proteins are expressed using a bacterial expression system, peptides are synthesized using solid-phase peptide synthesis. Purification of the products are carried out using different chromatographic methods such as HPLC, affinity, size-exclusion or ion-exchange chromatography. Characterization can be carried out using mass spectrometry and gel electrophoresis methods. Binding to target protein is investigated using fluorescence anisotropy and isothermal titration calorimetry. For structure and binding site determination NMR spectroscopy can be used. Molecular modelling can be used for ligand design.

SELECTED PUBLICATIONS

Kupihár, Z., Ferenc, G., Petrovicz, V. L., Fáy, V. R., Kovács, L., Martinek, T. A., **Hegedüs, Z.** (2023) *Improved Metal-Free Approach for the Synthesis of Protected Thiol Containing Thymidine Nucleoside Phosphoramidite and Its Application for the Synthesis of Ligatable Oligonucleotide Conjugates.* **Pharmaceutics. 15:** 248.

Hóbor, F., **Hegedüs, Z.**, Ibarra, A. A., Petrovicz, V. L., Bartlett, G. J., Sessions, R. B., Wilson, A. J., Edwards, T. A. (2022) *Understanding p300-transcription factor interactions using sequence variation and hybridization.* **RSC Chem Biol. 3:** 592-603.

Hegedüs, Z., Hóbor, F., Shoemark, D. K., Celis, S., Lian, L. Y., Trinh, C. H., Sessions R.B., Edwards, T.A., Wilson, A. J. (2021) *Identification of β-strand mediated protein–protein interaction inhibitors using ligand-directed fragment ligation.* **Chem Sci. 12:** 2286-2293.

Hegedus, Z., Grison, C.M., Miles, J.A., Rodriguez-Marin, S, Warriner, S.L., Webb, M.E., Wilson, A.J. (2019) *A Catalytic Protein-Proteomimetic Complex: Using Aromatic Oligoamide Foldamers as Activators of RNase S.* **Chem Sci. 10:** 3956-3962.

Bartus, É., **Hegedüs, Z.**, Wéber, E., Csipak, B., Szakonyi, G., Martinek, T. A. (2017) *De Novo Modular Development of a Foldameric Protein–Protein Interaction Inhibitor for Separate Hot Spots: A Dynamic Covalent Assembly Approach.* **ChemistryOpen 6:** 236-241.