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## Increasing affinity and selectivity for target proteins by peptide conjugation to small molecule ligands – extending interactions just outside of the binding pocket

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Organic synthesis has reached a level of proficiency that allows the efficient preparation of molecules of high complexity but the design of small organic molecules and peptides with sufficient affinities and selectivities for proteins in biomedical applications lags behind. We have developed a technology where polypeptide conjugation to small organic molecules or peptides provides affinities increased by as much as four orders of magnitude in comparison to those of the small molecules. Selectivities between highly homologous proteins, measured as ratios of dissociation constants, have been shown to increase by between one and two orders of magnitude. The aspect of the technology that appears to be the most surprising, while it at the same time makes it the most attractive to use, is that a single sixteen membered set of polypeptides is enough to improve affinities and selectivities for essentially any protein. We have recently begun to focus our attention on problems related to in vivo applications, addressing a) the risk of elicitation of immune responses and b) the problem of fast renal clearance. To this end, chemical modifications were introduced that allowed us to reduce the size of the polypeptides from the original 42-residue scaffolds to 11-mers without loss of affinity. We have identified a small molecule ligand that will provide tight binding of peptides to human serum albumin, a carrier protein present in human blood at a concentration of 0.6 mM. HSA binding will keep peptides in circulation thus reducing the problem of fast renal clearance and, in addition, the rate of proteolytic degradation. The peptide conjugates to be discussed may be used e.g. in clinical imaging or as radiotherapeutic agents, but also as guides for the redesign of small molecule drugs or for target validation purposes.

Illustration of concept. Conjugate formed from small molecule ligand and 42-residue polypeptide binds target protein due to small molecule-protein interactions supplemented by those between peptide and protein in close proximity to the small molecule binding site. Protein is human Carbonic Anhydrase II and small molecule ligand is benzenesulphonamide.

### Biography

Lars Baltzer is Professor in Organic chemistry at Uppsala University since 2004. He has a well-documented and longstanding interest in research topics related to catalysis and molecular recognition based on fundamental principles of physical-organic chemistry. He has introduced catalytic sites, demonstrated rate enhancements of several orders of magnitude and proven the formation of enzyme-substrate complexes in proteins he has designed from scratch. More recently he has become engaged in research on the molecular recognition of proteins by polypeptide conjugates, for the purpose of increasing affinities and selectivities for proteins of biomedical interest. Affinity enhancements due to peptide conjugation of four orders of magnitude, increased selectivities as well as improved pharmacokinetic and pharmacodynamic properties have been demonstrated. He has expertise in molecular design and the quantitative evaluation of structure and activity relationships especially those related to protein recognition. Aleksandra Balliu obtained her Ph D in the laboratory of Lars Baltzer, working on aspects of the polypeptide conjugate technology.

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