Peptide chemical engineering: from substrate-derived inhibitors to bioconjugation techniques

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Peptide chemical engineering gained substantial relevance in the field of diagnostics and therapeutics. The rapid development of drug-resistant bacteria is a serious healthcare threat that prompted the exploration of new antibacterial targets. Targeting bacterial virulence, instead of developing bactericidal compounds, became a promising strategy to block pathogenicity by disarming pathogens without affecting bacterial viability. Resulting in less selective pressure on the development of antibiotic resistance. Recently, we have reached a milestone in targeting an essential virulence factor of Gram-positive pathogenic bacteria, i.e. *S. aureus* Sortase A (SrtA), which has remained an unmet challenge for many years. In our studies we have developed the first non-covalent peptidomimetic inhibitors of SrtA, already showing promising *in vitro* activity towards growth and biofilm inhibition in pathogenic *S. aureus*. Our results outline the strategy to successfully turn a peptide substrate into an inhibitor, which is of great importance and interest in the strongly emerging field of new modalities and drug discovery. Combined with our computational studies, we have established a pharmacophore model, allowing us to pinpoint the important interactions for activity.

Another important emerging field is the development of site-specific conjugation approaches, notably for the synthesis of biochemical probes or molecular conjugates for targeted delivery. We report a mild ionic liquid (IL)-mediated thiolation technique that relies on the use of IL as a solvent and precursor to generate activated IL, as well as a solvent for the conjugation reaction. First, a focused library of active ILs was prepared for functionalizing/conjugating cysteine-containing small molecules and unprotected peptides. Interestingly, a bifunctional active IL could also be successfully employed as a linker for the conjugation of peptides lacking Cys. This study sets the ground for further investigation of the use of active ILs for modifying, labeling, or conjugating of larger and more complex therapeutic modalities such as proteins and antibodies.