

## Peptide conjugates for biological applications

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## Peptide Conjugates for Biological Applications

Peptide and protein conjugates hold a prominent position in the area of bioconjugate chemistry. They have been the subject of intensive studies over the years, because of their high potential in, for example, the biomedical field. Furthermore, their functional richness and structural vulnerability makes efficient and selective conjugation of these biomolecules often a real endeavor. I have been involved in this highly active research field for a number of years already, and have seen it mature into an area where highly complex hybrid structures can be created. Still, with regard to both toolbox development and application of bioconjugation strategies much research is required.

In this special issue, we would like to highlight some important new activities in the field. We start off with advances in conjugation chemistry. Although many approaches have been reported, varying from traditional activated ester chemistries and thiol-maleimide conjugation reactions to bio-orthogonal click methods, creative scientists are able to find new and improved pathways to functionalize peptides and proteins. A clear example is the review by Deming, describing modification strategies for methionine, which has until recently been an overlooked site of attachment. An up to date overview of how the conjugation toolbox can be used for the selective modification of therapeutic peptides and proteins is provided by Ozer and Chilkoti, who describe how the combined expertise from molecular biology, organic, and polymer chemistry is required to achieve the desired level of control over conjugation. The importance of site selective control is furthermore demonstrated by the research paper of Klok and co-workers, who conjugate different PEG architectures to a peptide heptad repeat fusion inhibitor against HIV-1. As they are able to obtain full control over the site of attachment, they could perform a systematic structure–activity relationship study to explain the diminished biological activity of the pegylated peptide. The Heilshorn group utilizes tyrosine modification as a site selective tool to install bio-orthogonal cross-linking sites in protein engineered polypeptides, which are subsequently successfully applied in cell culturing. This paper again demonstrates the level of involvement of bioconjugation chemistry in materials design for biomedical applications.

The second section covers peptide conjugates with supra-molecular features, in particular, peptide-based amphiphiles, which self-assemble into well-defined and functional structures. This field is introduced by a topical review by Hamley and Castelletto. Guler and co-workers show how the modular assembly of different peptide amphiphiles can lead to a fiber-based hydrogel which allows stem cell differentiation. The composition and spatial organization of the exposed functional units thereby determines the fate of the cells. Tovar et al. furthermore demonstrate the versatility of the peptide amphiphile approach, by incorporating a tetrathiophene unit in between two signaling peptides, which leads to assembly into functional fibers via  $\pi$ – $\pi$  stacking. The formed fibers are used to support human neural stem cell differentiation.

The third part of this special issue is dedicated to the use of peptide conjugates in drug delivery. In a number of research articles different approaches are described. Börner and colleagues report on the usage of peptide conjugates as solubilizing agents for poorly water-soluble drugs. Using a combinatorial approach, they are able to detect appropriate sequences for a range of photosensitizers. The groups of Lehto and Astakhova both describe peptide-mediated oligonucleotide delivery to cells. The former paper presents a cell penetrating peptide modified with a fatty acid tail that allows complexation with the oligonucleotide to be delivered. In the latter example, an oligonucleotide–peptide conjugate is made via click chemistry, and the effect of this conjugation on the properties of the antisense oligonucleotides is systematically investigated. Peptide motifs are also very useful for targeted drug delivery approaches. One such example is given by Lu et al. in which a peptide with binding affinity for a receptor overexpressed on glioma cells is used to target drug-loaded micelles. Certain peptides display antibiotic activity. Kasko and co-workers have prepared hybrids which can cross the bacterial cell membrane with high efficiency.

The final section of this special issue is dedicated to protein conjugates. Site-selective modification is in this case even more challenging than for peptides. Protein conjugation can lead to improved properties, such as more effective stealth behavior, but at the same time hamper others, like efficacy in binding. Maynard and co-workers have investigated a polymer conjugated with trehalose side chains that is capable of improving multiple features, such as the external stability and the in vivo plasma half-life of a therapeutic protein. In the reviews by Ovaa et al. on ubiquitin and Kiick et al. on collagen-based systems, special attention is paid to the controlled synthesis of these important proteins. The biological relevance of how ubiquitin is attached to target proteins requires full control over structural modifications, which can be best achieved by a chemical synthesis of this small protein. Chemical synthesis is also highly relevant for the preparation of collagen-like peptides. The difficulty of introducing hydroxyprolines into the collagen sequence via standard protein engineering often requires creative solutions, such as the preparation of short collagen-like sequences that self-assemble into fiber-like structures. These difficulties are not encountered when elastin-like polypeptides (ELPs) are used, as described by Rodriguez Cabello et al. They have developed a facile protein engineering approach to construct ELPs with FRET properties that are able to form stimulus-responsive hydrogels. The final paper of this section entails a review by Brock and co-workers on the three-dimensional tissue models that are currently available to study the behavior of peptide and protein conjugates in a biomimetic environment.

With this special issue we show you the level of sophistication and the broad variety of the activities in the

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field of peptide and protein conjugation. We hope this will inspire you to implement bioconjugation strategies in your own line of research, and of course, *Bioconjugate Chemistry* is interested to publish your own exciting results in this flourishing field of research.

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## ■ AUTHOR INFORMATION

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