COMBATING DISEASES WITH PEPTIDE – POLYMER CONJUGATES

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ABSTRACT

Peptides and proteins often combine unique self-assembly properties with very specific biological activities. From a therapeutic point of view, peptides and proteins are of interest, not only because of the possibilities to act as inhibitors or antagonists of biological processes (i.e. to act as therapeutics), but also because they provide opportunities e.g. for targeted delivery or to guide intracellular trafficking. Judiciously combining biologically active peptides or proteins with synthetic polymers provides opportunities to overcome problems related to the limited stability and plasma half life of peptides and proteins, to enhance the efficacy of polymer-drug conjugates and to augment the activity of peptide based therapeutics.[1-4] This presentation will consist of three parts which will successively discuss: (i) non-covalent polymer – drug conjugates in which the peptide-based linker not only acts to bind and release cargo but is also involved in directing intracellular trafficking;[5,6] (ii) polymer-modified HIV fusion inhibitors that show increased stabilities as compared to the unmodified peptides while maintaining activity[7] and (iii) multivalent HIV entry inhibitors based on side-chain peptide – polymer conjugates which allow to augment the activity of the peptide.[8] In all three cases, precision polymer synthesis is essential in the successful design of the final conjugates. Amongst others, the examples will highlight the importance of controlling molecular weight, the site of polymer – peptide conjugation as well as polymer architecture on the final properties and activities of the peptide – polymer conjugates.

References:

[1] M. A. Gauthier, H.-A. Klok, Peptide/protein – polymer conjugates: synthetic strategies and design concepts, Chem. Commun. (2008) 2591 – 2611.
[2] H.-A. Klok, Peptide/protein – synthetic polymer conjugates – Quo vadis, Macromolecules 42 (2009) 7990 – 8000.
[3] B. Apostolovic, M. Danial, H.-A. Klok, Coiled coils: attractive protein folding motifs for the fabrication of self-assembled, responsive and bioactive materials, Chem. Soc. Rev. 39 (2010) 3541 – 3575.
[4] M. A. Gauthier, H.-A. Klok, Polymer-protein conjugates: an enzymatic activity perspective, Polym. Chem. 1 (2010) 1352 – 1373.
[5] B. Apostolovic, S. P. E. Deacon, R. Duncan, H.-A. Klok, Hybrid polymer therapeutics incorporating bioresponsive, coiled coil peptide linkers, Biomacromolecules 11 (2010) 1187 - 1195.
[6] B. Apostolovic, S. P. E. Deacon, R. Duncan, H.-A. Klok, Cell uptake and trafficking behavior of non-covalent, coiled-coil based polymer-drug conjugates, Macromol. Rapid Commun. 32 (2011) 11 – 18.
[7] M. Danial, T. H. H. van Dulmen, J. Aleksandrowicz, A. J. G. Pötgens, H.-A. Klok, Site-specific PEGylation of HR2 peptides: effects of PEG conjugation position and chain length on HIV-1 membrane fusion inhibition and proteolytic degradation, Bioconjugate Chem. submitted.
[8] M. Danial, M. J. Root, H.-A. Klok, Polyvalent side chain peptide – synthetic polymer conjugates as HIV-1 entry inhibitors, Biomacromolecules 13 (2012) 1438 – 1447.