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Cover story

# PK modulation of peptides by hapten-mediated antibody complexation

One major hurdle that needs to be overcome for effective therapeutic application of peptides and peptide derivatives is the limited *in vivo* stability and unfavorable pharmacokinetic (PK) properties. Peptides, in most cases, are smaller than the exclusion limit for renal filtration. This feature translates into short serum half-life and fast *in vivo* clearance. Various technologies are currently being applied to address this issue, including the fusion to serum albumin or to IgGs [1,2]. These approaches work frequently for linear peptides composed of natural amino acids which tolerate fusion at either their C- or N-terminal without loss of activity. On the other hand, those peptides that are cyclized or stapled cannot be produced as antibody fusions. Other established approaches to improve PK/stability and biophysical behavior of peptides are conjugation of polymers, such as poly(ethylene glycol) (PEG) or hydroxyethyl starch [3,4], chemical conjugation to proteins, and covalent coupling to catalytic antibodies [5]. These approaches, however, may reduce the activity, and may also raise safety or potential toxicity issues under certain circumstances. Furthermore, in most cases, covalent linkage does not permit the release of a bioactive peptide from the PK-modulating entity.

In this issue, Eike Hoffmann and colleagues present a novel approach towards PK-modulation of therapeutic peptides [6]. They combined hapten-binding antibodies with haptenylated peptides to generate defined antibody–peptide complexes. As an example for this technology, noncovalent complexes of digoxigenin (Dig)-binding antibodies (IgGs) and a digoxigeninylated PYY(3-36) peptide derivative were generated. The PYY(3-36) peptide derivative which activates the Y2R receptor was selectively mono-digoxigeninylated by reacting a NHS-Dig derivative with an ε-amino group of lysine 2. This position tolerates modifications without destroying receptor binding and functionality of the peptide. Dig-peptide derivatives can be loaded onto Dig-binding IgGs in a simple and robust reaction, thereby generating peptide-IgG complexes in a defined two to one molar ratio. *In vitro* receptor binding and signaling assays showed that Dig-peptides as well as the peptide–antibody complexes retain better potency than the corresponding PEGylated peptides. *In vivo* analyses revealed prolonged serum half-life of antibody-complexed peptides as compared with unmodified peptides. Complexes possess sufficient stability for PK modulation. As a result, a prolonged weight reduction was observed in a murine diet-induced obesity (DIO) model with antibody-complexed peptides compared to unmodified peptides. The results of the work by the Hoffman group [6] indicate that antibody–hapten complexation can be applied to modulate the PK of haptenylated peptides for improved therapeutic efficacy.

There is one very interesting property of hapten-mediated antibody complexation. If an antibody releases its peptidic payload, it becomes free to re-bind available haptenylated peptides. This reversible binding property may provide a sustained release property that cannot be obtained by conventional sustained release formulations. The reversible binding property of an antibody may serve as a "PK-buffer" for therapeutic peptides. This approach can be universal, as various therapeutic peptides can be haptenylated.

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