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PK modulation of haptenylated peptides via non-covalent antibody complexation

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Abstract

We applied noncovalent complexes of Digoxigenin (Dig) binding antibodies with digoxigeninylated peptide derivatives to modulate their pharmacokinetic properties. A 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. Rationally designed 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. This indicates that each antibody arm becomes occupied by one haptenylated peptide. 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 compared to unmodified peptides. Thus, complexes are of sufficient stability for PK modulation. We observed more prolonged weight reduction in a murine DIO model with antibody-complexed peptides compared to unmodified peptides. We conclude that antibody–hapten complexation can be applied to modulate the PK of haptenylated peptides and in consequence improve the therapeutic efficacy of therapeutic peptides.

Biography

Dr. Stefan Dengl has completed his PhD in 2009 in the laboratory of Prof. Dr. Patrick Cramer at the Genecenter of the Ludwig-Maximilians-University in Munich. He then joined Roche in Penzberg, Germany as a postdoctoral fellow working in the field of antibody stability and antibody engineering. Since 2012 he is working as a scientist and expert for biostructure & protein design in Pharma Research and Early Development at Roche in Penzberg.