PEPTIDE BIOCONJUGATES FOR INTRACELLULAR TARGETING*

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For intracellular targeting there is need to design, prepare and properly characterize compounds with typically two (or even more) components possessing distinct functional properties. In our research we aimed at constructing oligo- or polypeptide conjugates for three different purposes. First, for specific elimination of (i) cells infected by intracellular microbes (e.g. L. donovani *parasites, M. tuberculosis, or (ii) tumour cells by delivery of chemotherapeutic drugs to targets present inside the cell. For these we developed different groups of bioconjugates in which antimicrobial/antitumor compound (e.g. methotrexate [MTX], daunomycin [Dau], vinblastine, antitubelculars), enzyme inhibitors/activators (e.g. calpain) are attached covalently to oligo/polypeptide with capability to enter the target cells. We have invented new groups of branched polypeptides taken up by endocytosis, cell penetrating peptides (e.g. penetratin, oligoarginine) or specific cell surface protein binding ligands (e.g. ErbB2 receptor). Secondly, we aimed at delivery "reporter" molecules (e. g. radioligand, chelators, fluorophore) to identify intracellular (or occasionally cell surface) targets and study the relevant mechanism of action. In this contribution there is an attempt to provide an overview of selected results obtained in our laboratories during the last decades concerning the preparation, structural and functional characterization of peptide based bioconjugates and highlight the major findings applicable perhaps for the development of more efficient therapies, diagnostics and/or for studying the mechanism of action of relevant intracellular events.*

Introduction

During the last two decades cellular targeting by peptide-based bioconjugates resulted in novel approaches for which various drugs, reporter entities or even epitopes were attached to appropriate structures[1-4]. These two- or three-component constructs are widely utilized for biomedical research studying their potential to eliminate selectively tumour cells, intracellular microbes or to study uptake mechanisms or changes in protein expression profiles. The partner molecules are attached by covalent bond and preserve relevant functional properties (like biological activity or "reporter properties") after conjugation (Figure 1.)

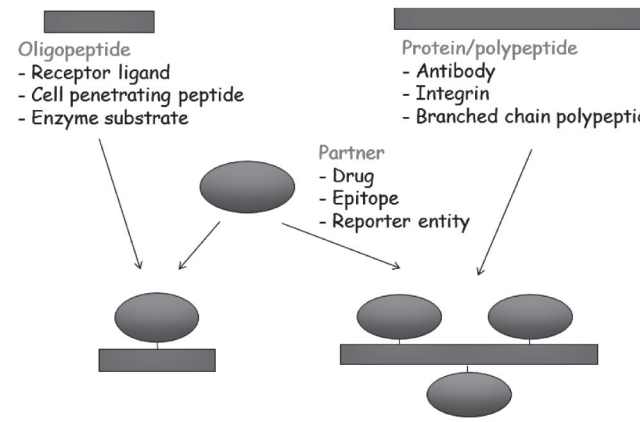

Fig. 1: Peptide/polypeptide/protein based bioconjugates.

The rationale of research in the group was to design and synthesis of biologically active peptides, peptide chimera and peptide conjugates for structure-function studies of therapeutically relevant applications including the

* Dedicated to the memory of Professor Parimal C. Sen

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