Pharmaceutica-2013
3rd International Conference and Exhibition on
Pharmaceutics & Novel Drug Delivery Systems
April 8-10, 2013 Hilton Chicago/Northbrook, USA

Recombinant fusion constructs of cell-penetrating peptides for targeted drug delivery to mildly acidic environment in solid tumors

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Abstract

Cell penetrating peptides (CPPs) are short sequences of amino acids that are able efficiently shuttle bioactive macromolecular cargo to the cytosolic, vesicular and/or nuclear compartments of cells. There are two main types of cationic CPPs: (1) amphipathic peptides, e.g., Model Amphipathic Peptide (MAP, KLALKLALKALKAALKLA), and (2) arginine-rich peptides, e.g., HIV Tat peptide (YGRKKRRQRRR) and oligoarginine (R_n). These two types of CPPs differ in both their internalization pathway and intracellular localization. Arginine-rich CPPs are internalized primarily through an endocytosis-independent pathway and are localized predominately in cytosol. On the other hand, amphipathic CPPs are taken up exclusively via endocytosis and accumulate in endosomal and nuclear compartments. Both types of CPPs have high non-specific absorption and accumulation in mammalian cells, which limit their application as effective carriers in drug delivery. To overcome this limitation, we have recently designed a recombinant construct containing the CPP sequence for MAP or TAT linked to a highly pH-sensitive histidine-glutamic acid (HE) sequence. The 10-mer HE sequence masks the cationic charges in the CPP sequences at neutral pH to prevent non-specific binding and internalization of the construct in non-target cells. In a mildly acidic environment with pH ranging 6.5 to 7.0 the protonation of histidine residues in the HE sequence will unmask the CPP moiety to reactivate its cellular uptake properties. The pH-sensitive model can be utilized in several different areas including the exploitation of the acidic microenvironment in diagnosis and targeting tumors or inflammation, and in the application of CPPs for receptor-mediated targeted delivery via endocytosis.

Biography

Jennica Zaro received her PhD in pharmaceutical sciences from the University of Southern California in 2005. She has worked for several years in the pharmaceutical industry in formulations and manufacturing of aerosol drug products, and in analytical method development and validation for protein drugs. She is currently a Research Assistant Professor of Pharmacology and Pharmaceutical Sciences at USC, focusing on targeted delivery of macromolecular drugs and recombinant bifunctional fusion proteins as therapeutics