Designing Cartilage Targeting and Drug Depot-Forming Cationic Fusion Protein of Insulin-Like Growth Factor 1

Bill Hakimi1, Timothy L. Boyer1, Ambika G. Bajpayee1

1Department of Bioengineering, Northeastern University, Boston, MA
hakimi.bi@northeastern.edu

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INTRODUCTION: Drug delivery into cartilage is challenging due to rapid clearance by synovial fluid (SF) and hindrance from the dense cartilage matrix comprised of sulfated glycosaminoglycan (CS-GAG) and collagen II. We recently designed an arginine-rich short-length cationic peptide carrier (CPC) with a distributed net charge of +14 that exhibited a superior transport into cartilage [1]. CPC transport relies on electrostatic interaction with GAG that showed ~300x greater cartilage uptake compared to its neutral counterpart yet localized only in anionic tissue, offering the potential of optimized targeted drug delivery [2]. Although the effect of net charge and hydrophobicity on cartilage transport has been studied, the effect of their different arrangement has not been elucidated yet. Thus, we investigated the contribution of charged and hydrophobic residue arrangement on CPC cartilage transport to optimize it. The optimized CPC is fused into IGF-1, a pro-anabolic drug candidate for osteoarthritic treatment, forming a cationic fusion protein called CPC-IGF-1.

METHODS: Peptide synthesis. Six configurations of labeled CPC with a net charge of +14 were synthesized with varying numbers of charge clusters (alternating (C-AL), end (C-EN), and block (H-BL); Fig. 1A). Table 1 lists the peptides with their number of charge clusters and hydrophobic clusters, respectively. These peptides were labeled with fluorophores or dark beads to observe time-lapse imaging using confocal microscopy.

RESULTS: The authors have no conflict of interest.

Figure 1 Results on peptide with different charged residue arrangement. A. List of peptides with their # of charge cluster. B. 24h uptake into healthy and OA cartilage in PBS. C. Diffusivity data. D. 1D penetration after 4h. E. Binding properties into CS-GAG. Figure 2 Results on peptide with different hydrophobic residue arrangement. A. List of peptides with their # of hydrophobic cluster. B. 24h uptake into healthy and OA cartilage in PBS. C. Diffusivity data. D. Binding properties into CS-GAG. E. 1D penetration after 4h. F. 24h uptake into healthy and OA cartilage in PBS. Figure 3 CPC-IGF1 fusion protein. Black bead represents Glu3→Arg3 substitution and yellow beads represent cysteine residues. Scale bar = 500 μm. *p<0.05

Fig. 1 Results on peptide with different charged residue arrangement. A. List of peptides with their # of charge cluster. B. 24h uptake into healthy and OA cartilage in PBS. C. Diffusivity data. D. 1D penetration after 4h. E. Binding properties into CS-GAG. Fig. 2 Results on peptide with different hydrophobic residue arrangement. A. List of peptides with their # of hydrophobic cluster. B. 24h uptake into healthy and OA cartilage in PBS. C. Diffusivity data. D. Binding properties into CS-GAG. E. 1D penetration after 4h. F. 24h uptake into healthy and OA cartilage in PBS. Fig. 3 CPC-IGF1 fusion protein. Black bead represents Glu3→Arg3 substitution and yellow beads represent cysteine residues. Scale bar = 500 μm. *p<0.05

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