

Accepted Manuscript

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PII: S0939-6411(18)30400-4
DOI: <https://doi.org/10.1016/j.ejpb.2018.06.026>
Reference: EJPB 12819

To appear in: *European Journal of Pharmaceutics and Biopharmaceutics*

Received Date: 23 March 2018
Revised Date: 22 May 2018
Accepted Date: 25 June 2018

Please cite this article as: S. Deyev, G. Proshkina, O. Baryshnikova, A. Ryabova, G. Avishai, L. Katrivas, C. Giannini, Y. Levi-Kalisman, A. Kotlyar, Selective staining and eradication of cancer cells by protein-carrying DARPin-functionalized liposomes, *European Journal of Pharmaceutics and Biopharmaceutics* (2018), doi: <https://doi.org/10.1016/j.ejpb.2018.06.026>

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Selective staining and eradication of cancer cells by protein-carrying DARPin-functionalized liposomes

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ABSTRACT

Since their discovery, liposomes have been widely employed in biomedical research. These nano-size spherical vesicles consisting one or few phospholipid bilayers surrounding an aqueous core are capable of carrying a wide variety of bioactive compounds, including drugs, peptides, nucleic acids, proteins and others. Despite considerable success achieved in synthesis of liposome constructs containing bioactive compounds, preparation of ligand-targeted liposomes comprising large quantities of encapsulated proteins and capable of affecting pathological cell still remains a big challenge. Here we described a novel method for preparation of small (80-90 nm in diameter) unilamellar liposomes containing very large quantities (thousands of protein molecules per liposome) of heme-containing cytochrome c, highly fluorescent mCherry and highly toxic PE40 (the fragment of *Pseudomonas aeruginosa* exotoxin A). Efficient encapsulation of the proteins was achieved through electrostatic interaction between positively charged proteins (at pH lower than pI) and negatively charged liposome membrane. The proteoliposomes containing large quantities of mCherry or PE40 and functionalized with designed ankyrin repeat protein (DARPin)₉₋₂₉, which targets human epidermal growth factor receptor 2 (HER2) were shown to specifically stain and kill in sub-nanomolar concentrations HER2-positive cells, overexpressing HER2, respectively. Specific staining and eradication of the receptor-positive cells demonstrated here makes the DARPin-functionalized liposomes carrying large quantities of fluorescent and/or toxic proteins a promising candidate for tumor detection and therapy.

Keywords: Cancer, liposomes, DARPin, mCherry, exotoxin A, apoptosis, cryo-TEM.

1. Introduction

Since their discovery [1] liposomes have been widely used in biomedical research (for reviews, see [2-4]). The ability to encapsulate a wide variety of small molecules,

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