NANYANG TECHNOLOGICAL UNIVERSITY
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OPTIMUS PHOTONICS
OPTIMUS – Centre for OptoElectronics and Biophotonics

Biodegradable Nanoparticle-Mediated K-ras Down Regulation For Pancreatic Cancer Gene Therapy

Abstract

RNA interference (RNAi) targeting the K-ras oncogene mutation in pancreatic cancer mediated by small interfering RNA (siRNA) transfection is a very promising treatment. However, the rapid degradation and negative charge of naked siRNAs restrict the direct delivery of them into cells. In this contribution, we propose a safe and effective transmembrane transport nanocarrier formulation based on a newly developed biodegradable charged polyester-based vector (BCPV) for K-ras siRNA delivery into pancreatic cancer cells. Our results have shown that these biocompatible vectors are able to transfect mutant K-ras siRNAs into the MiaPaCa-2 cells with high transfection efficiency. More importantly, the RNAi process has initiated a cascade gene regulation of the downstream proteins of K-ras associated with cell proliferation and apoptosis. Although in vivo testing data are limited, we propose that the BCPV based nanoparticle formulation could be a promising candidate as non-viral vectors for gene therapy in clinical settings.

Experimental Results

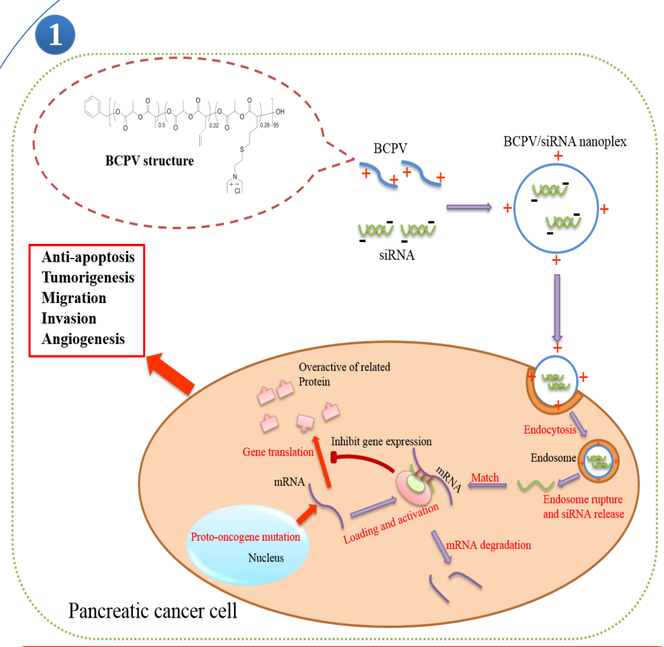

Fig 1. An overview of the BCPV/siRNA nanoplex formation and the gene knockdown process followed by siRNA transfection

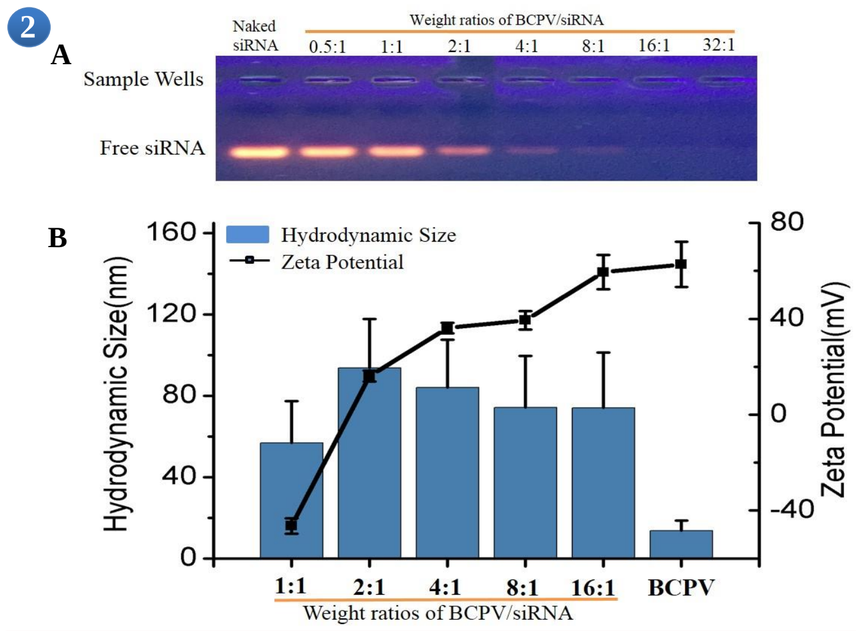

Fig 2. A. Agarose gel electrophoresis of BCPV/siRNA nanoplexes; B. The changes in particle hydrodynamic size and zeta potential with different weigh ratios of BCPV/siRNA

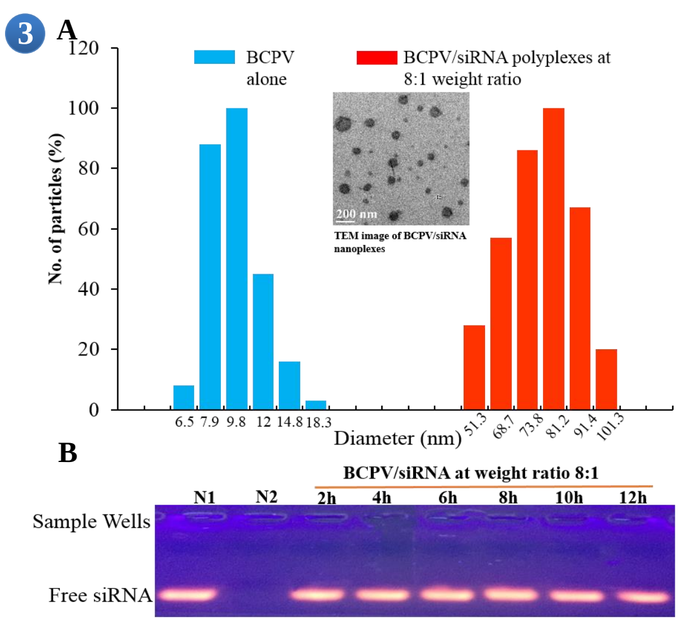

Fig 3. A. Hydrodynamic size distribution of BCPV and BCPV/siRNA. B. The ability of BCPV to protect siRNA from nuclease digestion

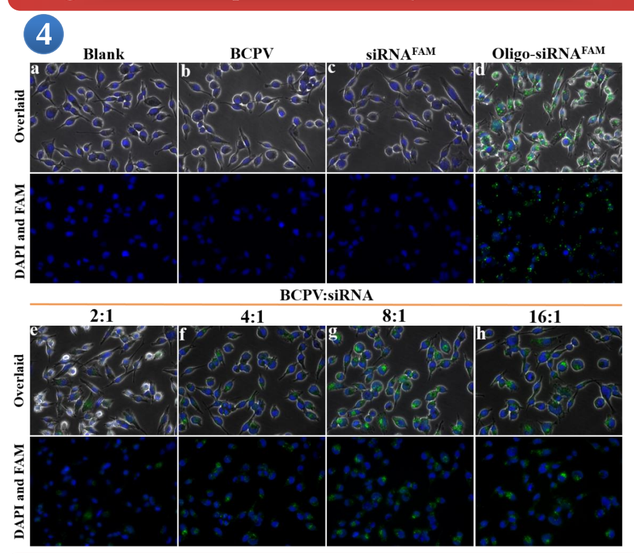

Fig 4. Fluorescence microscopy images of MiaPaCa-2 cells treated with different weight ratios of BCPV/siRNA^{FAM}

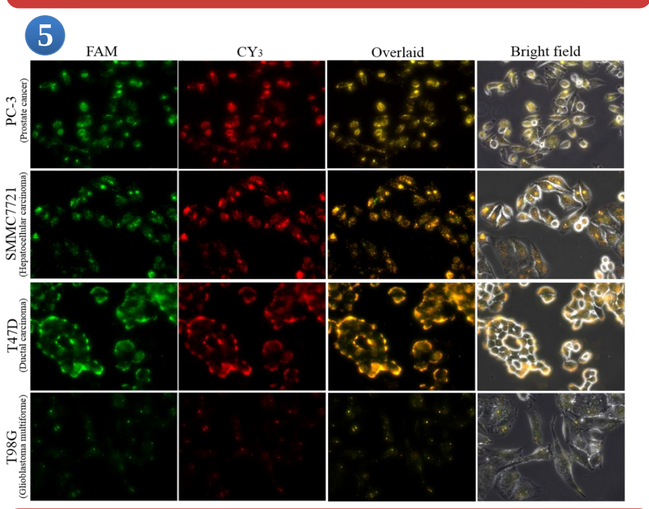

Fig 5. Various of adherent cancer cells were transfected by BCPV-siRNA^{FAM}-siRNA^{CY3} at 8:1 weight ratio

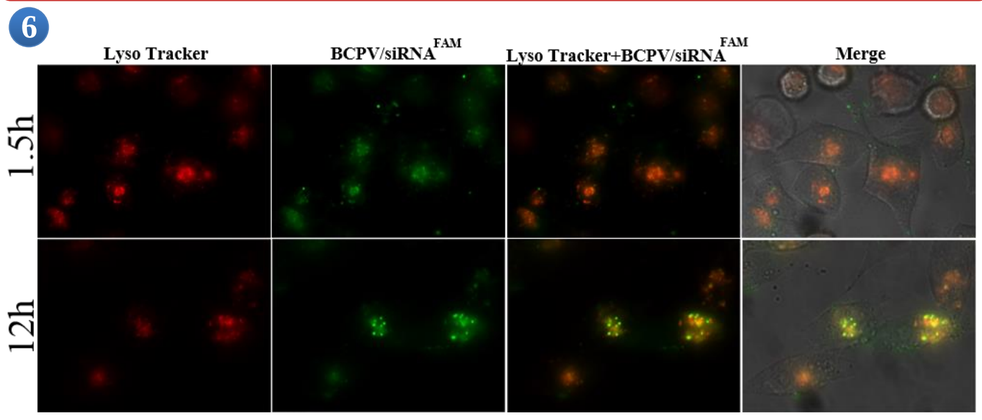

Fig 6. Cell uptake BCPV/siRNA^{FAM} process by MiaPaCa-2 cells, and siRNA^{FAM} was released from endosome (red color) after 12h incubation culture.

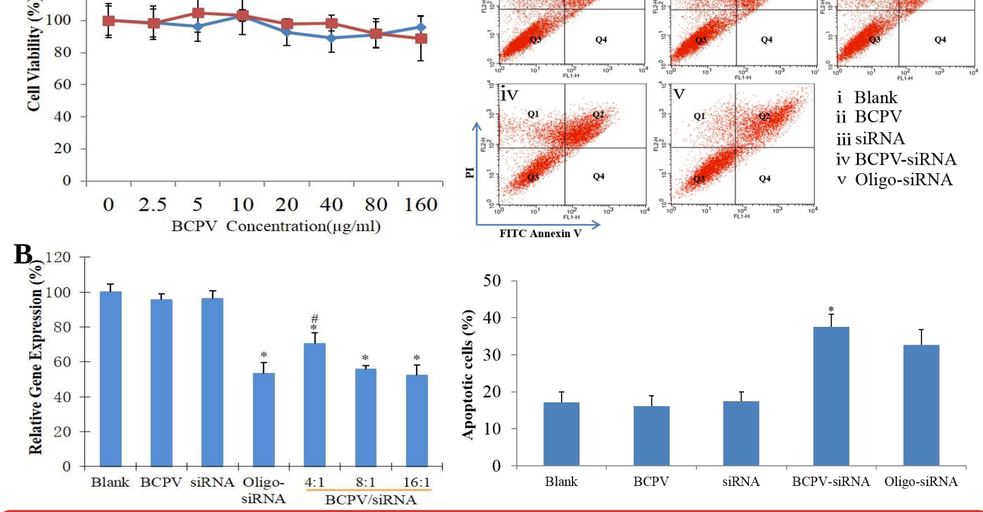

Fig 7. A. Cytotoxicity of BCPV on the MiaPaCa-2 cells. B. Gene expression of K-ras in MiaPaCa-2 cells of different complexes; C. Apoptosis assay on MiaPaCa-2 cells treated by BCPV/K-ras siRNA.

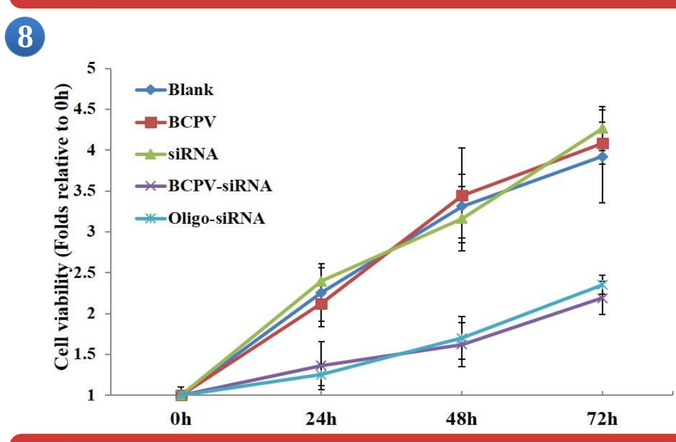

Fig 8. Proliferation of MiaPaCa-2 cells after treatment with BCPV/K-ras siRNA.

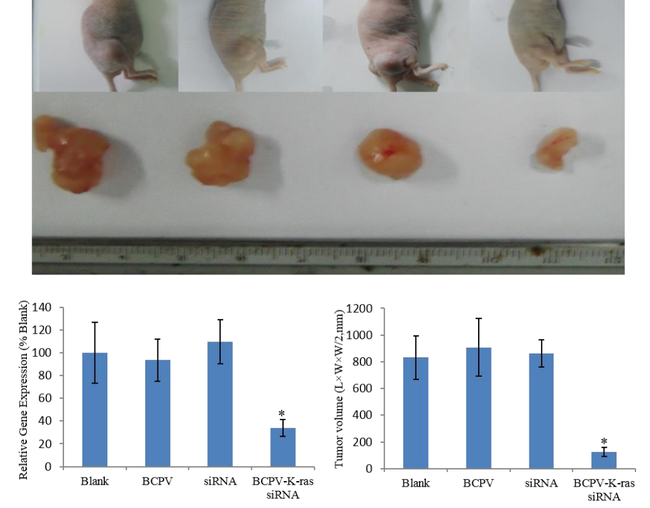

Fig 9. Antitumor activity of BCPV/K-Ras siRNA in MiaPaCa-2 xenograft animal model

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