ABT 737-loaded Upconversion Nanophotosensitizer for enhancement of photodynamic therapy efficacy through inhibition of survival pathway

Xiaomin Liu[1], Xianggui Kong[2], Hong Zhang[1,2]

[1] State Key Laboratory of Luminescence and Applications. Changchun Institute of Optics, Fine Mechanics and Physics, Chinese Academy of Sciences.

[2]Van't Hoff Institute for Molecular Sciences. University of Amsterdam

E-mail:xmliu@ciomp.ac.cn

Similar to many other anticancer therapies, photodynamic therapy (PDT) is also subject to intrinsic cancer resistance mediated by cell survival pathways. The reactive oxygen species (ROS) produced by PDT not only culminates the tumor, but also triggers a stress response that, as part of a cell survival mechanism, helps cancer cells to escape from the PDT-induced oxidative stress and cell damage, resulting in poor PDT effect[1-2]. These survival pathways are mediated by many different proteins, among which Bcl-2 protein, played an important role in regulation of programmed cell death, has been proved to involve in protecting against oxidative stimuli[3]. Here we reported, for the first time, that ABT737 molecules, an inhibitor of Bcl-2 proteins, combined with Zinc phthalocyanine (ZnPc) loaded upconversion nanophotosensitizer (ABT737@ZnPc-UCNPs), can significant enhance PDT efficacy through inhibition of survival pathway. The susceptibility to oxidants, mechanism of tumor cell apoptosis, tumor angiogenesis as well as the levels of antioxidant enzymes in PDT mediated by ZnPc-upconversion nanophotosensitizer (ZnPc-UCNPs) alone, and in combination with ABT 737 (ABT737@ZnPc-UCNPs) were studied in vitro and in vivo. With these experiments we verified that the ABT737@ZnPc-UCNPs could serve as an effective photosensitizer for significantly enhancement of PDT efficiency, which offers a potential new therapeutic option of applying survival pathway inhibitors as adjuvant agents in PDT.

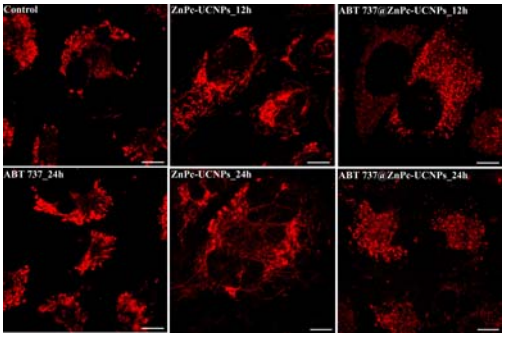

Figure 1. Cells may adapt to ZnPc-UCNPs mediated PDT through changes of mitochondrial morphology, resulting in PDT resistance to a certain extent, and inhibition of this process by ABT737 might recover the cytotoxic effects of ZnPc-UCNPs mediated PDT.

Acknowledgement: This work was financially supported by NSF of China (11374297, 11474278, 61275202, 21304084), Joint research program between CAS of China and KNAW of the Netherlands, the IOP program of The Netherlands, and John van Geuns foundation.

References:

[1] Z. Huang, L. B. Li, H. W. Wang, X. L. Wang, K. H. Yuan, A. Meyers, L. H. Yang, F. W. Hetzel, *J. Innov. Opt. Health Sci.* **2009**, 2, 73.
[2] M. Broekgaarden, R. Weijer, T. M. Van Gulik, M. R. Hamblin, M. Heger, *Cancer Metastasis Rev.* **2015**, 34, 643.
[3] A. Davies,*Trends Neuro, sci.* **1995**, 18, 355.