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Nuclear-uptake nanodrug delivery system for drug-resistant cancer therapy

The development of multidrug resistance (MDR) has become an increasingly serious problem in cancer therapy, making the long-term survival of patients with MDR-associated cancers extremely challenging. The cell-membrane overexpression of P-glycoprotein (P-gp), which can actively efflux various anticancer drugs from the cell, is a major mechanism of MDR. Nuclear-uptake nanodrug delivery systems, which enable intranuclear release of anticancer drugs, are expected to address this challenge by bypassing P-gp. However, before entering the nucleus, the nanocarrier must pass through the cell membrane, necessitating the coordination between intracellular and intranuclear delivery. To accommodate this requirement, Professor Weihong Tan's group at Hunan University has succeeded in developing a size-photocontrollable nuclear-uptake nanodrug system based on DNA hybridization and the near-infrared (NIR)-induced photothermal effect of the goldsilver nanorod (NR) [1].

In this work, Tan *et al*. assembled multiple small gold nanoparticles (NPs) onto the side face of the NR based on DNA hybridization (Figure 1). A cell-specific aptamer for cancer targeting was modified on the ends of the NR. A model anticancer drug doxorubicin (Dox) was chosen and loaded on the NPs through DNA intercalation. The nanocomplex entered tumor cells through the aptamer targeting, and subsequent NIR laser excitation released the Dox-loaded NPs from the NR through thermal denaturing of the DNA duplex. Then the released Dox-loaded NPs would diffuse into the cell nucleus to execute the killing effect.

Tan *et al.* carried out a series of *in vitro* validation experiments, and demonstrated that nanodrugs, through this photocontrolled and size-transformable nanosystem, could be efficiently transported across the cell membrane and entered the nucleus in a coordinated and harmonious manner. Furthermore, this DNA-based nanoassembly platform could accumulate chemotherapeutic drugs in the nuclei, thus greatly enhancing their therapeutic efficacy against drug-resistant cancer cells by effectively bypassing P-gp. The report by Prof. Tan *et al*. represents an exciting new step forward in the area of drug delivery against multidrug resistance for cancer therapy. This proof-of-concept structure opens a new door in the use of nanoassemblies for the design of drug delivery systems for biological and clinical research.

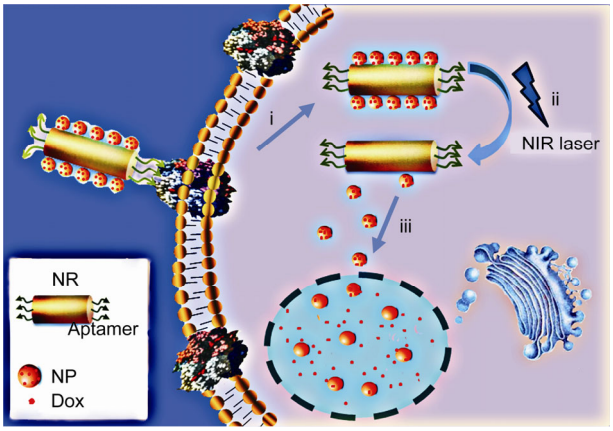

Figure 1 Schematic illustration of the cell-targeted photocontrolled nuclear-uptake nanodrug delivery system for cancer therapy. Reprinted with permission from Ref. [1]. Copyright (2015) American Chemical Society.

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1 Qiu LP, Chen T, Öcsoy I, Yasun E, Wu CC, Zhu GZ, You MX, Han D, Jiang JH, Yu RQ, Tan WH. A cell-targeted, size-photocontrollable, nuclear-uptake nanodrug delivery system for drug-resistant cancer therapy. *Nano Lett*, 2015,15: 457–463