

## Cancer Cell and Mitochondria Sequential Targeting Polyprodrug Micelle to Overcome Drug Resistance via Oxidative Stress Amplification and Responsive Drug

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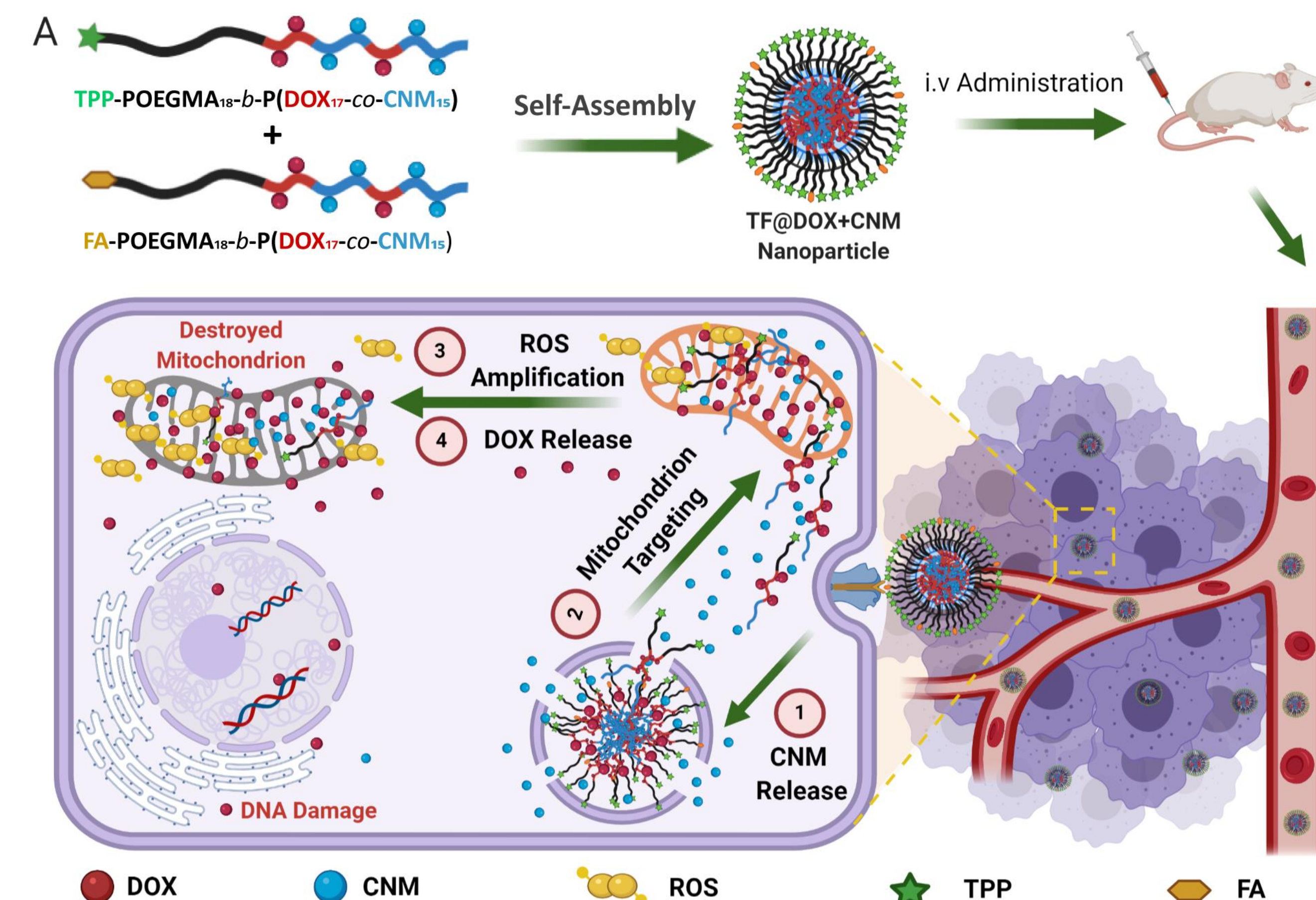
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### 1. Abstract

- Multi-drug resistance (MDR) remains the major menace that obstruct chemotherapy success in clinics.<sup>1</sup>
- In addition to the reported other factors that induce MDR during cancer treatment, the role of mitochondria to mediate pathways that generate cancer cell survival mechanisms under various stress is critical.<sup>2</sup>
- Therefore, targeting mitochondria metabolism should be an effective approach to diverse MDR and achieve enhanced cancer treatment effect.

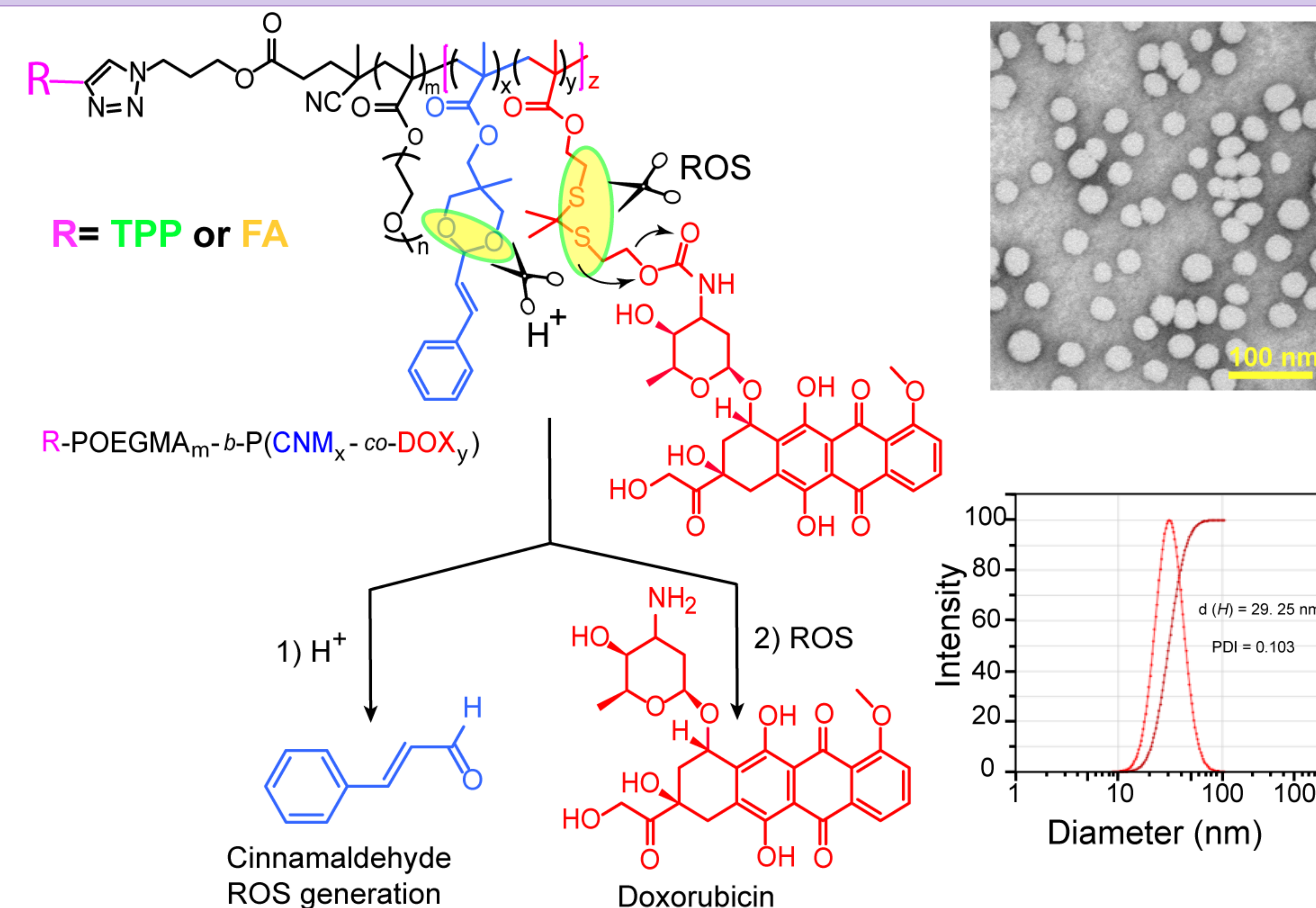
### 2. Introduction

- Herein, a novel dual targeting polyprodrug nanoparticle that can simultaneously target cancer cells and mitochondria by **folic acid (FA)** and **tetraphenylphosphonium (TPP)** targeting moiety, respectively, is rationally designed to overcome MDR in cancer treatment.



**Proposed mechanism of action**

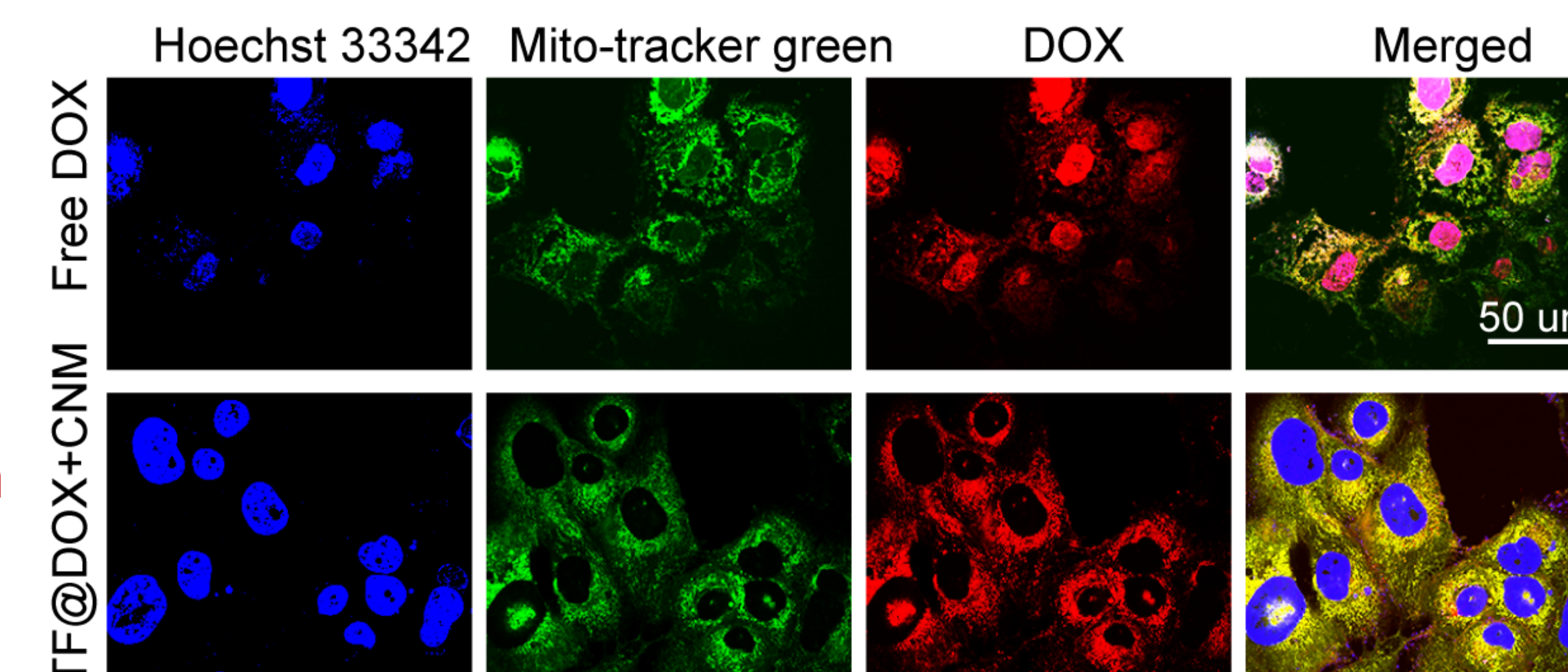
### 3. Methodology



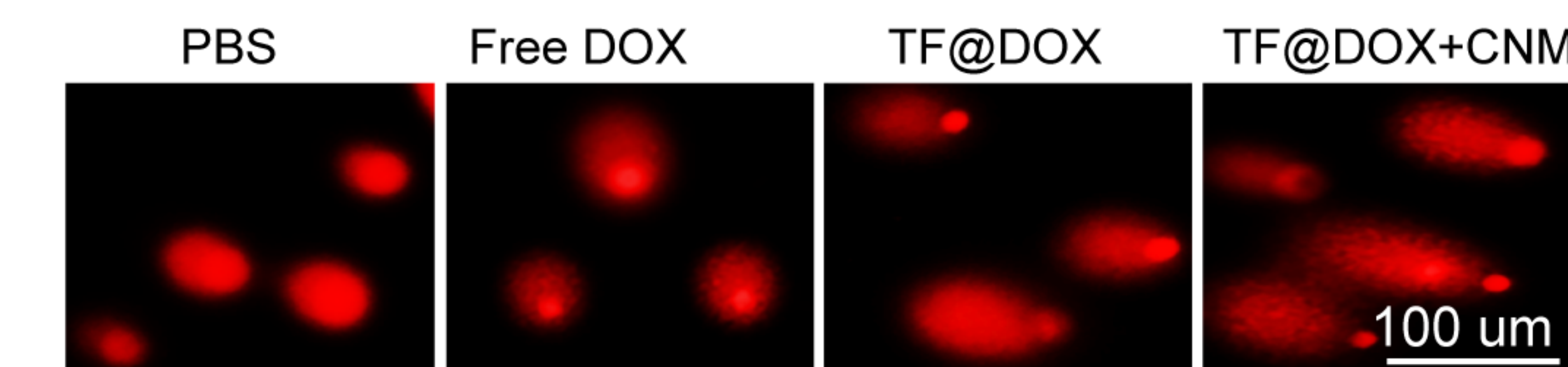
- An amphiphilic block copolymer named **FA&TPP-POEGMA<sub>18</sub>-b-P(DOX<sub>17</sub>-co-CNM<sub>15</sub>)** was prepared and self assembled into TF@DOX+CNM nanoparticles (micelles).
- The **TF@DOX+CNM nanoparticles** are designed to target and be accumulated into the cancer cells through folate receptor-mediated cellular internalization to induce excessive ROS generation by **cinnamaldehyde (CNM)** and subsequently trigger the release of anticancer drug that is **doxorubicin (DOX)**.

### 4. Results

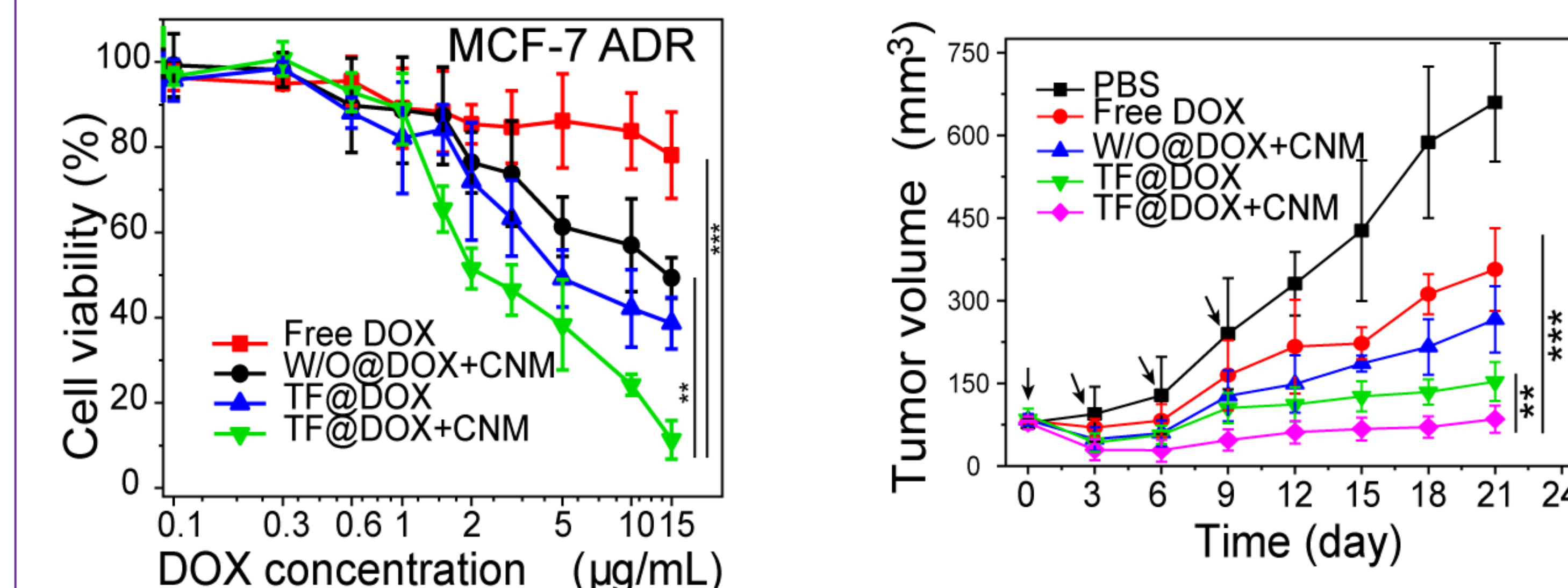
**Mitochondrial targeting and Internalization capacity**



### Cellular DNA damage evaluation



### In vitro and in vivo cytotoxicity evaluation



### 5. Conclusion

- TF@DOX+CNM nanoparticles** can target the tumor cells and mitochondria, amplify mitochondria ROS level and release DOX drug locally.
- This cancer treatment strategy showed potential to reverse MDR in cancer treatment and achieve enhanced therapeutic effect both *in vitro* and *in vivo*.

### 6. Acknowledgements



### 7. Reference

- H. Wang *et al.* Nat. Commun. 9 (2018) 562.
- P. Tsvetkov *et al.* Nat. Chem. Biol. 15 (2019) 681-689.