Enhanced Doxorubicin Transport to Multidrug Resistant Breast Cancer Cells via TiO_2 Nanocarriers

Wenzhi Ren[a], Leyong Zeng[a], Zheyu Shen[a], Lingchao Xiang[a], An Gong[a], Jichao Zhang[b], Chengwen Mao[b], Aiguo Li[b], Tatjana Paunesku[c], Gayle E.Woloschak[c], Narayan S. Hosmane[d], Aiguo Wu[a*]

*Corresponding Author. Aiguo Wu

Tel.: +86 574 86685039, fax: +86 574 86685163, E-mail address: aiguo@nimte.ac.cn

1. TEM images of as-prepared TiO_2 nanoparticles

Figure S 1A showed that the size of TiO_2 without heat treatment was 3-6 nm, but the yield was very low. The TiO_2 with 3-6 nm diameter was then heated in a vessel at 200℃ for 10 hours. Size of TiO_2 with heat treatment was 20-30 nm, and the yield was enhanced as shown in **Figure S 1B**. The TiO_2 with heat treatment was used as nanocarriers in this study. **Figure S 1C** showed the high resolution TEM and selected area electron diffraction of the nanocarriers. **Figure S 1D** showed that the size of TiO_2/DOX was also 20-30 nm.

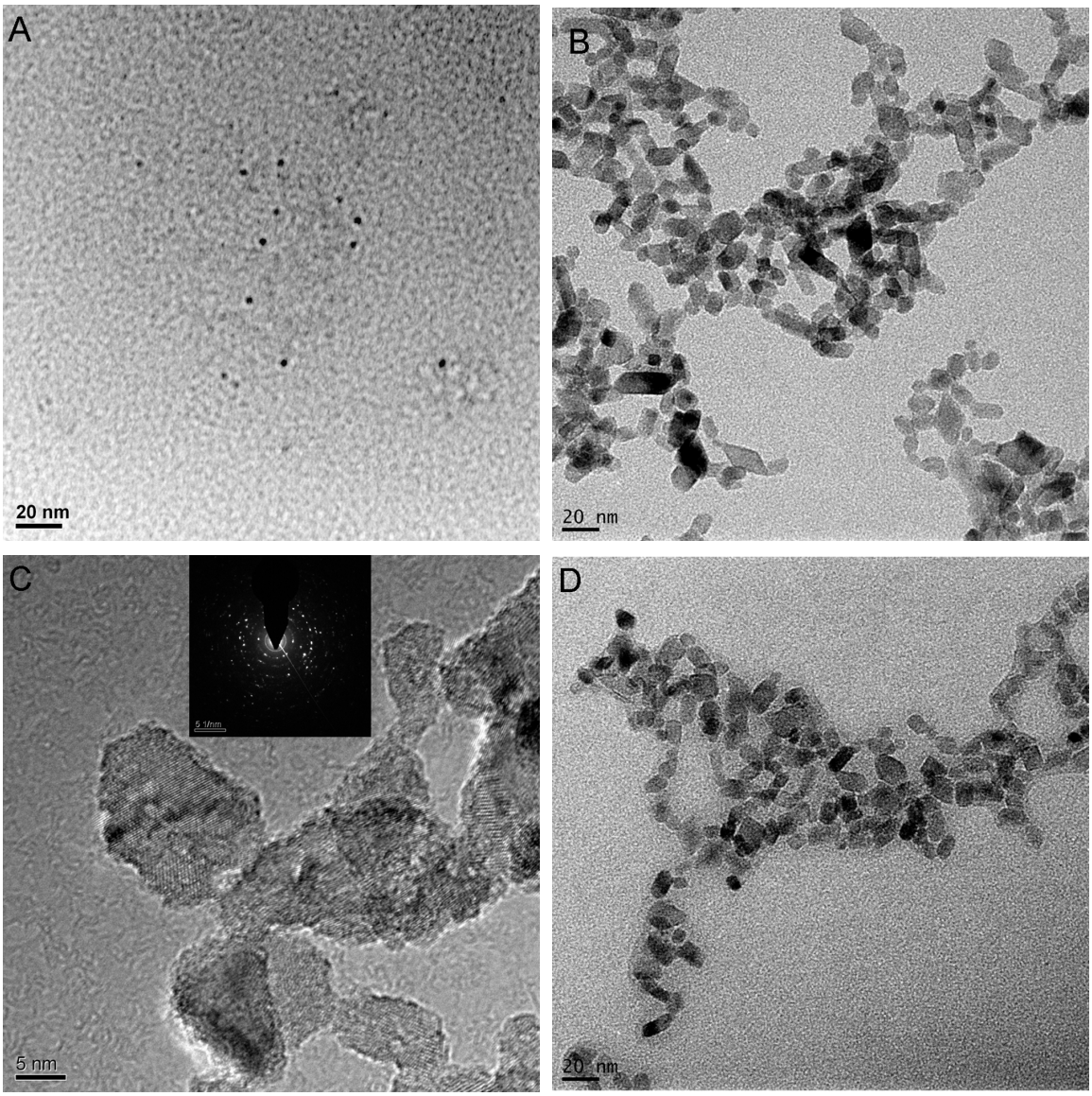


Figure S1 TEM images of TiO_2. TiO_2 without heat treatment (**A**), TiO_2 nanocarriers with heat treatment (**B**), high resolution TEM and selected area electron diffraction of TiO_2 (**C**), and TiO_2 /DOX (**D**).

2. XRD of TiO_2 nanoparticles

Figure S 2A showed that crystallinity of TiO_2 without heat treatment was not good.

Figure S 2B showed that crystallinity of TiO_2 with heat treatment was better.

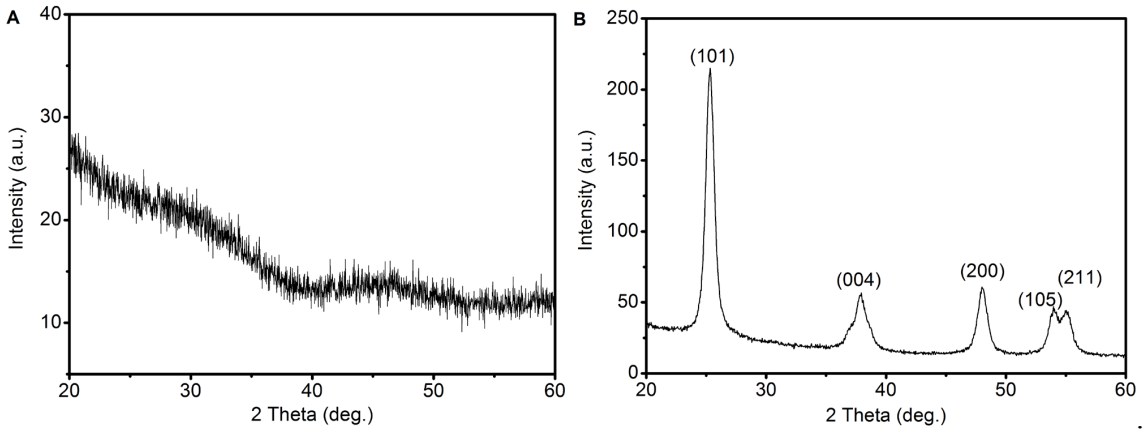


Figure S2 XRD of TiO_2. TiO_2 without heat treatment (**A**), TiO_2 nanocarriers with heat treatment (**B**).

3. Size distributions of TiO_2 or TiO_2/DOX for long time storage

Figure S 3 showed that size of TiO_2 nanocarriers (**Figure S 3A**) or TiO_2/DOX (**Figure S 3B**) could grow up slowly as time went on from 1 to 25 week(s).

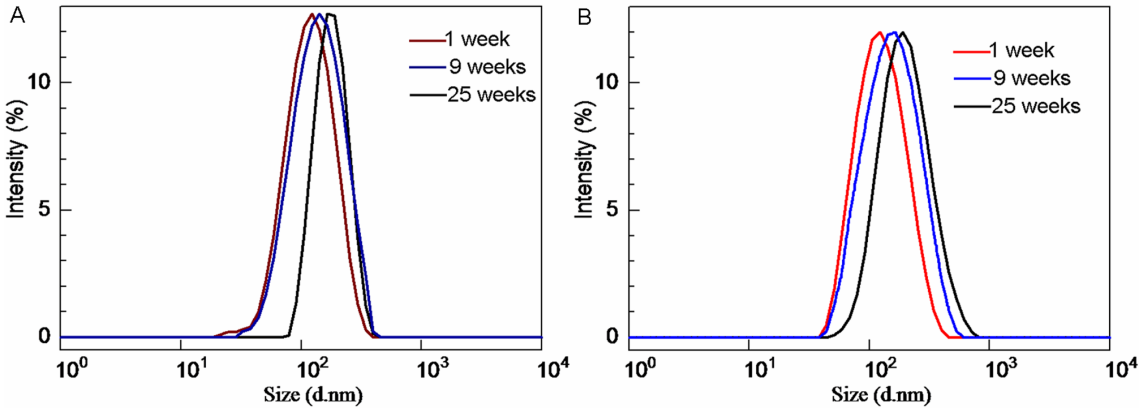
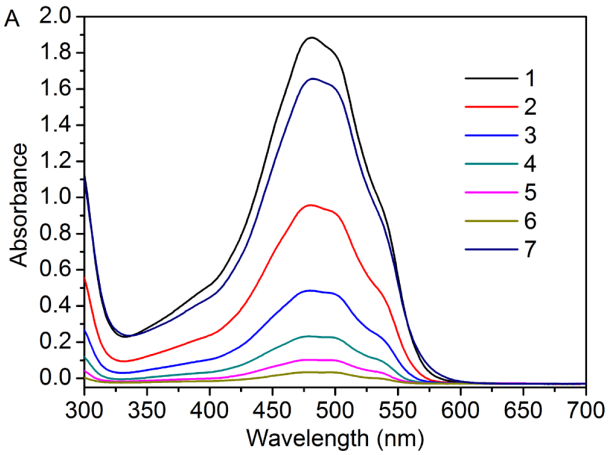


Figure S3 Size distribution of TiO_2 nanocarriers (**A**) and TiO_2/DOX (**B**) with different storage time.

4. Loading efficiency of DOX onto TiO_2 surface

In the first time to prepare TiO_2/DOX nanocomposites, 20mL DOX (0.5 mM) were drop-wise added into 5 mL TiO_2 (75mM) colloidal solution and stirred for 24 h. After stirring, the solution was centrifuged, and free DOX was collected (25mL). As shown in **Figure S 4A**, line 1 to 6 were absorptions of DOX at different concentration gradients from 0.25 to 0.0036

mM. **Figure S 4B** showed concentration-absorption cure of DOX which was calculated through absorptions of line 1 to 6. In **Figure S4C**, black line named "Supernatant-1" was absorption of the collected free DOX mentioned above. According to the cure of DOX, concentration of free DOX was 0.235 mM. Therefore, loading efficiency of DOX onto TiO_2 surface = (0.5 mM×20 mL - 0.235 mM×25 mL) ÷ (75 mM×5 mL)×100%, and the loading efficiency was 1.1%. In our manuscript, in order to keep stable of TiO_2/DOX, half amount of loaded DOX was used to prepare TiO_2/DOX in the following experiments. Briefly, 20mL DOX (0.103 mM) were stirred with 5 mL TiO_2 (75mM) for 24 h. After stirring, the solution was centrifuged; supernatant liquid was collected and characterized by UV-Visible spectra. As shown in **Figure S4 C**, it was difficult to measure the peak of free DOX from the red line named "Supernatant-2" which was absorption of the supernatant liquid mentioned above. Therefore, the DOX was loaded by TiO_2 completely, and the loading efficiency = (0.103 mM×20 mL) ÷ (75 mM×5 mL) ×100%=0.55%.



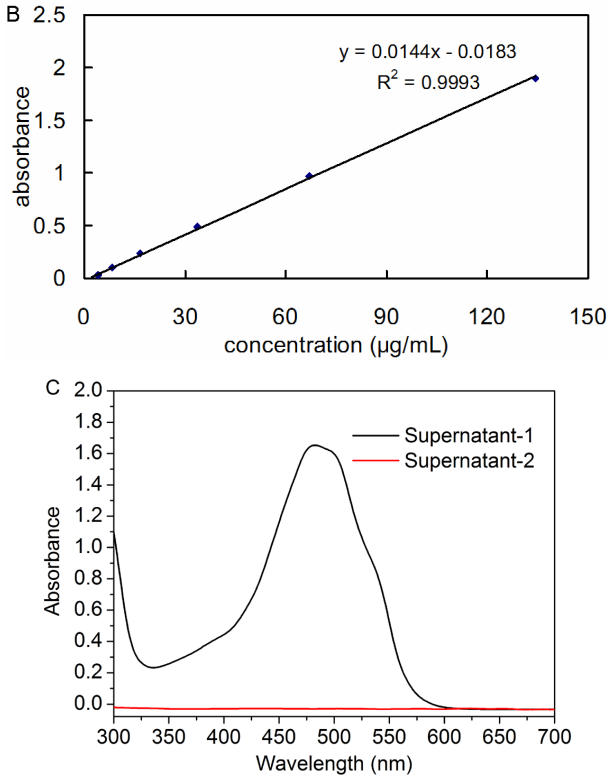


Figure S4 UV-Visible absorption of DOX at different concentration (**A**), concentration - absorption curve of DOX (**B**), and UV-Visible absorption of collected supernatant liquid after centrifugation(**C**).