Supporting Information

Schiff base interactions tuned mesoporous organosilica nanoplatforms with pH-responsive degradability for efficient anticancer drug delivery \textit{in vivo}

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1. SUPPORTING FIGURES AND TABLES

Table 1. The size and porous characters of S-SNPs prepared with different R_{T/S}.

<table>
<thead>
<tr>
<th>Sample</th>
<th>R_{T/S}</th>
<th>Diameter (nm)\textsuperscript{a)}</th>
<th>d-spacing (nm)\textsuperscript{b)}</th>
<th>S\textsubscript{BET} (m\textsuperscript{2}/g)\textsuperscript{c)}</th>
<th>P\textsubscript{BET} (nm)\textsuperscript{c)}</th>
<th>V\textsubscript{TOTAL} (cm\textsuperscript{3}/g)\textsuperscript{c)}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.0</td>
<td>88.5</td>
<td>3.14</td>
<td>1095</td>
<td>3.10</td>
<td>0.99</td>
</tr>
<tr>
<td>2</td>
<td>6.0</td>
<td>78.2</td>
<td>3.08</td>
<td>1009</td>
<td>3.02</td>
<td>0.93</td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>57.8</td>
<td>2.86</td>
<td>916</td>
<td>2.77</td>
<td>0.89</td>
</tr>
<tr>
<td>4</td>
<td>4.0</td>
<td>49.2</td>
<td>2.30</td>
<td>653</td>
<td>2.21</td>
<td>0.50</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>37.9</td>
<td>N/A</td>
<td>376</td>
<td>1.69</td>
<td>0.23</td>
</tr>
<tr>
<td>6</td>
<td>1.0</td>
<td>22.1</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

\textsuperscript{a)} Hydrodynamic diameters of CTAB stablized S-SNPs (1.0 mg mL\textsuperscript{-1} in water); \textsuperscript{b)} d-spacing of S-SNPs after removal of CTAB, calculated by SAXS; \textsuperscript{c)} S\textsubscript{BET}, the BET specific surface area; P\textsubscript{BET}, average mesopore diameter; V\textsubscript{TOTAL}, total pore volume.

Fig. S1 TEM images of S-SNPs prepared with different R_{T/S}.
Table S2. Elemental Analysis of S-SNPs with different R\textsubscript{T/S}.

<table>
<thead>
<tr>
<th>Sample/R\textsubscript{T/S}</th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (6:1)</td>
<td>23.72</td>
<td>3.804</td>
<td>3.705</td>
</tr>
<tr>
<td>3 (5:1)</td>
<td>25.06</td>
<td>3.952</td>
<td>3.812</td>
</tr>
<tr>
<td>4 (4:1)</td>
<td>27.46</td>
<td>4.118</td>
<td>3.937</td>
</tr>
<tr>
<td>5 (2:1)</td>
<td>34.02</td>
<td>4.515</td>
<td>4.523</td>
</tr>
</tbody>
</table>

Fig. S2 Porosity characters of S-SNPs analyzed by BET.

Fig. S3 SAXS spectra of S-SNPs.

The d-spacing of S-SNPs was calculated from Bragg equation as the following:

\[ n\lambda = 2d\sin\theta \]

\(\theta\) was obtained from SAXS data as shown in Figure S3, where \(n=1, \lambda = 0.15418\) nm.

For S-SNPs, with the increasing of feed ratio of S-SP, the \(2\theta\) increased from 2.62° (R\textsubscript{T/S}=8/1) to 3.5° (R\textsubscript{T/S}=4/1), demonstrating d-spacing changing of S-SNPs.
Fig. S4 SEM image of S-MON ($R_{1/2}$=5.0).

Fig. S5. FT-IR spectra of S-MON, Ad@S-MON and BzI@S-MON.

As shown in Fig. S5, the resonance of C=N bonds at 1640 cm$^{-1}$, phenyl groups at 794 cm$^{-1}$ of embedding Schiff bases in S-MON are depicted, these results demonstrate the existence of Schiff base groups in S-MON frameworks. In addition, the surface modified S-MONs were also characterized. Ad and CH$_2$SCH$_2$ of BzI groups were grasped at 2870 cm$^{-1}$ and 1350 cm$^{-1}$, respectively, proving a successful surface modification of S-MON.
Fig. S6 (a) DLS spectra and (b) TEM images of S-MON after being treated in PBS pH 7.4 for 24 h, 1.0 mg mL\(^{-1}\) in PBS, (c) DLS spectra and (d) TEM images of S-MON incubated in cell medium+10% FBS for 24h, 1.0 mg mL\(^{-1}\) in cell medium+10% FBS.

Fig. S7 Adsorption changes of degradable S-MON in PBS pH 5.4 for 12 h.

Fig. S8 XPS spectra of S-MON, Bzl@S-MON and Ad@S-MON.
Table S3. Atomic contents of surface modified S-MON calculated from XPS.

<table>
<thead>
<tr>
<th>Sample</th>
<th>C1s</th>
<th>N1s</th>
<th>O1s</th>
<th>Si2p</th>
<th>S2p</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-MON</td>
<td>62.83</td>
<td>2.69</td>
<td>26.21</td>
<td>8.17</td>
<td>--</td>
</tr>
<tr>
<td>Ad@S-MON</td>
<td>65.53</td>
<td>4.59</td>
<td>22.10</td>
<td>7.68</td>
<td>--</td>
</tr>
<tr>
<td>BzI@S-MON</td>
<td>65.49</td>
<td>4.44</td>
<td>21.08</td>
<td>7.42</td>
<td>1.66</td>
</tr>
</tbody>
</table>

XPS was used to quantify the grafting ratio of TESAd and TESBzl onto S-MON. And the peaks at 398, 162 ev are attributed to N1s (intensity increment due to the TESAd) and S2p (from TESBzl), respectively. This result proves that S-MON was successfully surface modified.

Fig. S9 DLS spectra (a) CTAB@S-MON in PBS 7.4 for 24 h. (b) DOX-loaded Ad@S-MON and BzI@S-MON, DSPs in PBS 7.4.

Fig. S10 TGA curves of DOX loaded S-MON based nanocarriers.
Fig. S11 (a) Nitrogen adsorption–desorption isotherms and (b) Zeta potentials of particles before and after drug loading.

Fig. S12 (a) TEM images and (b) DLS spectra of DSP-2 treated in PBS pH 5.4 for 8 h.
Viability of MIA PaCa-2 cells after incubation with different concentrations of DOX, Ad@S-MON, Bzl@S-MON, Doxil, DSP-1 and DSP-2 for 72 h. For Ad@S-MON and Bzl@S-MON, the amount of carrier was equal to the amount for the DSPs.

2. EXPERIMENTAL SECTION

Chemicals and Agents. 3-Aminopropyl triethoxysilane (APTES) (98%), tetraethyl orthosilicate (TEOS) (99%) were products of Tokyo Chemical Industry Co., Ltd. (Shanghai). Poly (ethylene glycol) methyl ether (PEG-OH) (Mw = 2,000 Da) was purchased from Aldrich. Allyl bromide (98%), benzimidazole (99%), terephthaldehyde (TPAL) (99%), 3-mercaptopropyl triethoxysilane (MPTES) (98%), 3-isocyanatopropyl triethoxysilane (iPTES) (99%), amantadine hydrochloride (99%) (Ad-NH$_2$·HCl), N,N’-dicyclohexylcarbodiimide (DCC) (99%), 4-dimethylaminopyridine (DMAP) (99%) were purchased from J&K. Doxorubicin hydrochloride (DOX·HCl) was a product of Beijing Ouhe Technology Co., Ltd. (98%) (Beijing, China). Doxorubincin Hydrochloride Liposome Injection (Doxil) was purchased from CSPC Ouyi Pharmaceutical Co., Ltd. (Shijiazhuang, China), a generic product that is therapeutically equivalent to Janssen’s Doxil®. DAPI and CCK-8 kit were purchased from Beyotime Institute of Biotechnology (Shanghai, China). LysoTracker™ Deep Red were purchased from Invitrogen (California, USA). Fetal bovine serum (FBS) was purchased from Corning (Manassas, VA, USA). DMEM, trypsin-EDTA, PBS and streptomycin/penicillin (S/P) were purchased from Life technologies (Shanghai, China). Paraformaldehyde (PFA) was purchased from Solarbio (Beijing, China). MIA PaCa-2 cells were purchased from American Type Culture Collection (Rockville, MD) and cultured in DMEM medium containing 10.0% FBS and 1.0% S/P. All cell studies were cultured at 37 °C, 5.0% CO$_2$ and 95.0% humidity.

Characterizations. All the solid state MAS NMR spectra were recorded using a 600 MHz JEOL JNM-ECZ 600R/M1. FT-IR spectrum were obtained using a PerkinElmer Spotlight 400. UV-vis spectroscopy was recorded using a PerkinElmer with a Lambda 35 spectrometer. Elemental analysis was measured by a Vario EL III. N$_2$ sorption (BET)
measurement was performed using an ASAP 2020. BJH model were used to analyze the particles porosity characters. Small-angle X-ray scattering (SAXS) measurement of the silica particles in dry state were performed on a Rigaku Smartlab diffractometer with Cu Kα radiation (λ = 0.15406 nm). X-ray Photoelectron Spectroscopy (XPS) was performed using a PHI Quantera SKM™. A Marven Zetasizer Nano ZS90 equipped with a 633 nm He-Ne laser and an avalanche photodiode detector (DLS) was used to characterize the hydrodynamic sizes and zeta potentials of the particles. The morphologies of the particles were characterized by an 80 kV Hitachi H-7650B transmission electron microscope and a 120 kV JEM-2010 microscope (TEM), corresponding element mapping/EDS spectrum were acquired on an Oxford X-Ray energy dispersion spectrometer. Inductively Coupled Plasma-Atomic Emission Spectrometry (ICP-AES) was performed using a IRIS Intrepid II produced from Thermo. The dispersions with proper concentration were dropped onto carbon coated copper grids and were blotted up after 1 min. This process was repeated for three times. The copper grids were air-dried before observation. Scanning electron microscopy (SEM) images were recorded on a Hitachi SU-8010 field emission scanning electron microscope at 5 kV. Thermal gravity analysis (TGA) was performed on a TA-Q2000 instrument at a scanning rate of 10 °C/min at N₂ atmosphere. The particles were vacuum-dried at ambient temperature and saved in dryer oven before using. CLSM images were taken using a Nikon Ti-E. All the animal experiments were approved by the by the Institutional Animal Care and Use Committee (IACUC) of Tsinghua University and carried out in compliance with guidelines.

**Synthesis of Schiff Base Bridged Silane Precursor (S-SP).** As shown in Scheme 1, S-SP was synthesized according to the reported method. ¹ Into a 250 mL double-necked round-bottom flask, 0.02 mol of TPAL and 35 mL ethanol were added. After stirring for 10 min, 0.04 mol of APTES in 25 mL ethanol was added into the reactor dropwise, and refluxed for 2 h at 80 °C. The reaction was allowed to cool. Anhydrous sodium sulfate was added to the mixture and was vigorously stirred for 15 min in order to make it free from moisture and filtered quickly. A yellow colored liquid was obtained. Then, the crude product was purified by flash silica gel column chromatography using methanol as eluent. Finally, the collected solvent was evaporated under low pressure, a yellow colored precursor was obtained and saved under Ar atmosphere.

**Synthesis of Schiff-base Embedded Silica Nanoparticles (S-SNPs).** To synthesize S-SNPs, varying molar ratio of TEOS/S-SP (R<sub>T/S</sub>) was performed as shown in Scheme 1. In order to study the effect of S-SP to porous structures of S-SNPs, it should be mentioned that the total amount of reacted precursors was quantified as 5.0 mmol, and all the hydrolysis reactions were performed in the same condition as the following: In a typical reaction, the molar ratio of R<sub>T/S</sub> was selected as 5.0 to illustrate the synthesis route of S-SNPs. 0.20 g of CTAB, 100 mL DI water and 0.70 mL of 2.0 M aq. NaOH were mixed at 70 °C for 1 h. Followed, the reaction temperature was increased to 80 °C. 4.16 mmol of TEOS (0.864 g) and 0.84 mmol of S-SP (0.46 g) were fully mixed, the transparent yellow liquid was added into the reactor syringe pump
(40.0 mL/min). After intense stirred for another 4 h, the solution was cooled to room temperature. White product was collected by centrifugation and washed using water and ethanol for several times, CTAB filled S-SNP was obtained (CTAB@S-SNP). Finally, the template CTAB was removed under reflux in 6.0 g/L of NH₄NO₃/ethanol solution to obtain yellow product (S-SNP).

**Synthesis of Surface Modified Agents (TESAd and TESBzl).** TESAd was synthesized according to the reported work.² TESAd was synthesized via a reaction of IPTES with Ad-NH₂·HCl in the presence of triethylamine (TEA). 0.85 g of Ad-NH₂·HCl was added into the mixture of TEA (1.0 mL) and anhydrous THF (40.0 mL), and the solution was stirred at room temperature for 1 h. Then, 1.2 mL of IPTES was added. After stirred for another 24 h, the solution was filtrated and evaporated under low pressure. The residue was extracted using cold diethyl ether, and dried under vacuum overnight, then saved under Ar atmosphere.

TESBzl was synthesized in two steps. First, 1-allyl benzimidazole was synthesized as the reported method.³ A THF solution of benzimidazole (50.0 mmol) was added to a suspension of oil-free sodium hydride (50.0 mmol) in 100 mL of THF and stirred for 1 h at 60 °C. Then 25.0 mL THF solution of 1-allyl bromide (55.0 mmol) was added dropwise to above solution. The mixture was continued to stir for 48 h at 60 °C and a yellow solution was obtained. The solvent was removed with a rotary evaporator and 50.0 mL of H₂O was added to the residue. Then the solution was extracted with 100 mL of chloroform, and the extracted solution was dried with anhydrous MgSO₄. After removing chloroform, a pale yellow liquid was obtained. Then, a typical thiol-ene “click” reaction was performed to obtain TESBzl. 20.0 mmol of 1-allyl benzimidazole and 20.0 mmol of MPTES were mixed in 25.0 mL of anhydrous ethanol, followed 0.04 mmol of benzophenone was added into the reactor. After irradiating under 326 nm UV lamp for 15 min, the solution was evaporated under low pressure to remove solvent. The residue was dried under vacuum overnight. Finally, TESBzl was obtained as yellow liquid and saved under Ar atmosphere.

**Surface Modification of S-MON.** The surface modification of S-MON involves two steps as shown in Scheme 1b. CTAB@S-MON (1.0 g) and 2.0 g of TESAd or TESBzl were dispersed in 20.0 mL of anhydrous toluene, then 1.0 mL of TEA was added into the reactor. After being heated under reflux for 16 h at N₂ atmosphere, the particles were collected by centrifugation at 8000 rpm and washed three times with ethanol. Secondly, these particles were refluxed in 6.0 g/L of NH₄NO₃/ethanol solution for 24 h to remove CTAB. Then, the particles were collected by centrifugation at 8000 rpm and washed using ethanol and DI water for several times. Finally, the yellow powder was lyophilized overnight to obtain Ad-functionalized S-MON (Ad@S-MON) and Bzl-functionalized S-MON (Bzl@S-MON).

**Synthesis of β-CD Ended PEG (β-CD-PEG).** β-CD-PEG was synthesized via a copper-catalyzed “click” reaction with CD-N₃ and PEG-yn e. N₃-CD and PEG-yn e were separately prepared according to the reported work.⁴ β-CD (52.9 mmol) was
suspended into 500 mL of water, and NaOH (164.0 mmol) in 20.0 mL of water was added dropwise. The suspension became homogeneous and slightly yellow before the addition was complete. p-toluenesulfonyl chloride (52.9 mmol) in 30 mL of acetonitrile was added dropwise, causing immediate formation of a white precipitate. After 2 h of stirring at room temperature the precipitate was removed by suction filtration and the filtrate refrigerated overnight at 4 °C. The resulting white precipitate was recovered by suction filtration and lyophilized for a pure white solid β-CD-OTs. Powdered β-CD-OTs (3.88 mmol) was suspended in dry DMF (15.0 mL), after warmed to 65 °C, the mixture became homogeneous. NaN₃ (38.0 mmol) were added, and the reaction mixture was stirred at 65 °C for 24 h. The reaction mixture was cooled to room temperature and precipitated in cold acetone/water (V/V=10/1) for several times. Then, the white precipitate was recovered by centrifugation and drying overnight to yield a pure white solid CD-N₃. 4-pentynoic acid (20.0 mmol), EDC·HCl (24.0 mmol), and DMAP (2.4 mmol) were dissolved in 250 mL of anhydrous CH₂Cl₂. After stirring for 1 h at ambient temperature, PEG-OH (4.0 mmol, Mn = 2,000 Da) in 200 mL of dry CH₂Cl₂ was slowly added to the former mixture at 0 °C. After adding completely, the reaction was conducted for 48 h under stirring at ambient temperature. Then, the solution was precipitated into an excess amount of diethyl ether, and the precipitation process were repeated for three times. The final product was dried in vacuum to obtain a white powder PEG-yne. PEG-CD was synthesized as the following:[33] CD-N₃ (3.0 mmol), PEG-yne (15 mmol), and PMDETA (3.0 mmol) were first dissolved in 60.0 mL of DMF. The solution was bubbled with nitrogen for 15 min. CuBr (3.0 mmol) was added to the mixture. The mixture was bubbled with nitrogen again for 30 min and sealed under N₂ atmosphere. The reaction was conducted at 60 °C for 24 h. The mixture was dialyzed (molecular weight cut off: 3000 Da) against distilled water for 5 days. PEG-CD was obtained by lyophilization as white powder.

**Drug Loading, Capping and pH-Dependent Release Experiments.** Then Drug-loaded S-MONs (DSPs) were prepared in two steps. Firstly, DOX·HCl (500 mg) was dispersed in 100.0 mL DMSO, followed TEA (0.62 mL) was added dropwise. The mixture was stirred overnight in darkness. Then, 500 mg of Ad@S-MON or BzI@S-MON was added into the reactor and incubated at 37 °C for 24 h in darkness. Followed, 10.0 mL solution was extracted to be completely washed and dried for TGA analysis. Secondly, the outlets of the particles were capped with PEG-CD through host-guest interactions between Ad/β-CD and BzI/β-CD. The above mixture was added 6.0 g of PEG-CD to be stirred for another 24 h in darkness. After centrifugation at 10,000 rpm and washed using DMSO and DI water for several times, the DOX-loaded and PEGylated particles were collected and washed using DMSO and water, then dialyzed in DMSO/DI water (V/V = 1/9). Finally, DSP-1 and DSP-2 were lyophilized overnight to yield brown-red powders, respectively. To study the pH-responsive release properties, 30.0 mg of DSP-1 or DSP-2 were dispersed in 30.0 mL of phosphate buffer solutions at different pH values. The pH values were stepwise adjusted to 7.4, 5.9 and 5.4. While incubating in PBS solution in 37 °C, 4.0 mL of supernatant was taken from the tube at fixing time and analysed by measuring the UV-vis absorbance at 488 nm to study the drug release.
kinetics.
To quantify the DOX loading amount, a standard curve was drawn. $Y=16.150 \times X$, $R^2=0.994$ (Y is absorbance intensity, X is DOX content). The loading content (LC %) was calculated using the following Equation S1:

$$\text{LC \%} = \frac{M_e}{M_o} \times 100\%$$

Where $M_e$ is DOX content in DSPs, $M_o$ is the weight of DSPs. The DOX accumulation release amount was calculated as the following Equation S2:

$$\text{DOX accumulation amount} = \frac{V_o \sum_{i=1}^{n} C_i + V_e C_n}{m_{\text{drug}}} \times 100\%$$

Where $V_e = 2.0 \text{ mL}$; $V_o = 30.0 \text{ mL}$; $C_i$ is the release amount of DOX at fixing time. $m_{\text{drug}}$ is the amount of tested DSPs. And the DOX loading ratio was quantified as 14.2 wt% in 1 g of S-MON.

**pH-Responsive Degradability of S-MON and DSP-2.** Same to the study on drug release manners of DSPs, 30.0 mg of S-MON or DSP-2 was dispersed in 30.0 mL of phosphate buffer solutions at different pH values. The pH values were adjusted to 7.4 and 5.4 separately. While incubating in PBS solution in 37 °C, 4.0 mL of solutions were taken and lyophilized overnight at fixing time. An equal volume of PBS solution at corresponding pH values was compensated afterward. The lyophilized residue was dispersed in ethanol for DLS and UV-vis analysis.

**Quantitative analysis of S-MON in PBS pH 5.4.** For determining the element content changes in PBS, 6 mg of S-MON was separately saved in 6 dialysis tubes, then these bags were individually saved in 1.0 mL of PBS pH 5.4 under shaking. At different time, the degradable sample was standing for layer separation in 1 min, followed the upper clear liquid was characterized for dissolved silicon content by ICP-AES. And the degradable residues were lyophilized overnight for elemental analysis to characterize the carbon content changes.

**Cell Viability Assay.** MIA PaCa-2 cells were seeded in 96-well plates at a density of 4 x 103 cells/well. Relative cell viability of MIA PaCa-2 cells after incubation with free DOX, Ad@S-MON, BzI@S-MON, Doxil, DSP-1 and DSP-2 for 72h was detected by CCK-8 kit according to the manufacture’s instructions. Briefly, 10.0 μL of CCK-8 was added into each well and then incubated for 1 h before detection of absorbance (A) at 450 nm by a multimode plate reader (EnVision, PerkinElmer, USA). All experiments were performed in sextuplicate.

**Cell Uptake Study.** MIA PaCa-2 cells were seeded in 35 mm 4-well glass-bottom petri dishes at a density of 2.5 x 105 cells/well. After incubation with DOX, Doxil, DSP-1 and DSP-2 (with an equivalent DOX concentration of 10.0 μg/mL) for 1h, lysoTracker™ deep red was added 30 min before cell uptake finished. Cells were washed with ice-cold PBS for 5 times to remove the free drug or nanoparticles, fixed with 4.0% PFA for
20 min and stained with DAPI for 5 min, and then observed under confocal scanning laser microscope (CSLM, Nikon Ti-E, Japan). The DAPI, DOX and lysoTracker™ deep red (marked as green) were excited at 405, 488 and 647 nm, respectively.

**In Vivo Distribution of DSPs.** Tumor-bearing BALB/C nude mouse were randomly divided into several groups and intravenously administrated with a single dose of DOX, Doxil, DSP-1 and DSP-2 (with an equivalent DOX dose of 10.0 mg/kg), respectively. All mouse were sacrificed after 24 h, and the major organs and tumors were dissected for ex vivo fluorescence imaging using in vivo imaging system (Caliper Life Sciences, USA). The fluorescence intensity was quantified by the IVIS software (Living Image 4.0, USA).

**In Vivo Anti-tumor Effect.** MIA PaCa-2 cells (5×10^6 cells/mL) were injected subcutaneously in ventral subaxillary to form xenograft tumors. Anti-tumor effects were carried out when the tumor volume reached about 100 mm^3 and then randomly divided into several groups. The mouse were intravenous administrated with saline, DOX, Doxil, DSP-1 and DSP-2 (with an equivalent DOX dose of 10.0 mg/kg) every 3 days for 4 times. Body weights and tumor sizes were recorded until the end of the experiments when the mouse were sacrificed. Tumor volumes were calculated using the formula: tumor volume = 0.5 × length × width^2. Final tumor weights were also measured to evaluate the anti-tumor effect. All the animal experiments were approved by the Institutional Animal Care and Use Committee (IACUC) of Tsinghua University and carried out in compliance with guidelines. For the subcutaneous pancreatic cancer xenograft model, MIA PaCa-2 cells (5×10^6 cells) were injected subcutaneously in the flank of BALB/C nude mice to form subcutaneous xenograft tumors. Anti-tumor effects were carried out when the tumor volume reached about 100 mm^3 and then mice were randomly divided into several groups (n=5 mice per group). The mice were intravenous administrated with Saline, DOX, Doxil, DSP-1 and DSP-2 (with an equivalent 10.0 mg/kg dose of DOX) every 3 days for 2 times. The body weights and tumor sizes were recorded until the end of the experiments when the mice were sacrificed. Tumor volumes were calculated using the formula: tumor volume = 0.5 × length × width^2. Final tumor weights were also measured to evaluate the anti-tumor effect. For the orthotopic pancreatic cancer xenograft model, mice was anaesthetized and operated to expose pancreas, MIA PaCa-2-luc cells (2×10^6 cells) were injected into the head of pancreas of BALB/C nude mice. Ten days after the cell injection, the mice were randomly divided into several groups (n=3 per group) and intravenous administrated with a single dose of Saline, DOX, Doxil and DSP-2 (with an equivalent 5.0 mg/kg dose of DOX), and Bzl@S-MON (equivalent amount with DSP-2) taken as a control of DSP-2.

3. **REFERENCE**

