# Supporting Information

**Hierarchical integration of degradable mesoporous silica nanoreservoirs and supramolecular dendrimer complex as a general-purpose tumor-targeted biomimetic nanoplatform for gene/small-molecule anticancer drug co-delivery**

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# Materials

$N_3$-PEG600-COOH and isothiocyanate (FITC) were purchased from Sigma-Aldrich. Ammonium nitrate ($NH_4NO_3$), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride(EDC), n-hydroxysuccinimide (NHS), concentrated ammonia solution, copper sulfate pentahydrate ($CuSO_4 \cdot 5H2O$) were purchased from Aladdin China. Tetraethyl orthosilicate (TEOS), (3-aminopropyl)trimethoxysilane and (3-Mercaptopropyl) trimethoxysilane were purchased from J&K Scientific Ltd China. 7-Ethyl-10-hydroxycamptothecin(SN-38) were purchased from Sango biotech (China). 3-(4,5)-dimethylthiahiazo(-z-y1)-3,5-di-pheny tetrazoliumromide (MTT) was obtained from Solarbio Science & Technology Co. Ltd China.

# Experiment section

**Synthesis of the G3.0 polyamidomain (PAMAM) dendrimer:**

For the synthesis of the G3.0 PAMAM dendrimers, 0.7 g of propargylamine was firstly dissolved using methanol (8 mL) and then transferred to a 100 mL flask, which was capped with a gas valve. Meanwhile, 8 mL of methyl acrylate was mixed with 10 mL of methanol and slowly dropped into the above solution, which was then stirred at 30°C for 48h under nitrogen protection and dark environment, and the G0.5 dendrimer is thus obtained. 2g of the as-prepared G0.5 dendrimer was dissolved in 10mL of methanol and then added with 10mL of ethylenediamine, and eventually stirred at 30°C for 48h with nitrogen protection and excluded from light. The raw products were obtained by repetitive precipitation for three times with methanol/diethyl ether solution, which is the G1.0 dendrimer. 1.13 g of the G1.0 dendrimers was redispersed into methanol (10 mL) and 2.5 mL of methyl acrylate was added dropwise. The solution was stirred at 30°C for 72 h with nitrogen atmosphere and light excluded. The raw product was purified by silica gel column chromatography using the mixture solution of methanol and ethyl acetate (1/10), which yielded the G1.5 dendrimer. 1.35 g of the G1.5 dendrimer was dispersed into methanol (5 mL) and mixed with of ethylenediamine (2.8 mL), and then stirred at 30°C for 48 h with nitrogen atmosphere in dark environment. The product was extracted by precipitating for three times using methanol/ether mixture to yield the G2.0 dendrimer. 1.5 g of the G2.0 dendrimer was dispersed into methanol (10 mL), into which 2.5 mL of methyl acrylate was added dropwise. The mixture was stirred at 30°C for 72 h with nitrogen protection under dark environment, and purification was carried out by silica gel column chromatography using methanol/ethyl acetate mixture (1/4), which yielded the G2.5

dendrimer. 1.39g of G2.5 dendrimer was dispersed into the mixture solution of methanol (15mL) and ethylenediamine (2.6 mL), which was then stirred at 30°C and 72h under nitrogen protection in dark environment, and eventually purified by precipitating three times in methanol/ether solution, thus yielding the G3.0 PAMAM dendrimer.

**Synthesis of the β-cyclodextrin modified PAMAM dendrimer:**

For the conjugation of the β-CD onto the PAMAM dendrimers, 0.5 mmol of β-CD and 1 mmol of CDI were firstly dispersed into N, N-dimethylformamide (DMF, 15 mL) and transferred to a 100 mL flask, which has been capped with a gas valve. The reaction was carried out under nitrogen and dark environment for 1.5 h while being stirred at 300 rpm, and the intermediate product was obtained by precipitating for three times with acetone, which was denoted as product a. Then, 0.2 mmol of G3.0 dendrimer and 0.3 mL of triethylamine were mixed in DMSO (5 mL) and then slowly dropped to product a. The mixture of the reagents would be stirred continuously for 14 h under stirring and then dialyzed in deionized water for 48 hours to yield the PAMAM-β-CD.

**Synthesis of redox-responsive polyethylene glycol (PEG)-modified azide ligand ($N_3$-PEG600-S-S-pyridine):**

200 mg of $N_3$-PEG600-COOH was dissolved with DMF in a 100 mL flask capped using gas valve, followed by the addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 84 mg) and N-hydroxysuccinimide (NHS, 51 mg). The activation of the carboxylic groups would last 1 h at room temperature and 57 mg of aminodithiopyridine was subsequently added. The reaction was carried out at 500 rpm and 25°C for 24 h to yield the $N_3$-PEG600-S-S-pyridine.

**Synthesis of the 4-Nitrophenyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzyl carbonate:**

0.47 g of p-nitrophenyl chloroformate was dissolved in a 200 mL flask containing 15 mL of tetrahydrofuran (THF) and incubated in ice bath. Meanwhile, 0.5 g of 4-hydroxymethylphenylboronic acid pinacol and 0.6 mL of triethylamine were co-solubilized using THF (5 mL) and slowly poured into the above solution, which would first be stirred with ice bath for about 10 min and then without the ice bath for 3 more hours. The reaction solution was finally washed by saturated $NaHCO_3$ solution for 3-4 times, and finally purified by passing through a silica gel column using methanol/petroleum ether. The solvent was subsequently evaporated to yield yellow powder substances, which is the desired NBC linker.

**Synthesis of the degradable dendritic mesoporous silica nanoparticle:**

24 mL of CTAC aqueous solution (25 wt%) was added to a 250 mL three-necked flask, followed by the addition of triethanolamine (0.18 g) and deionized water (36 mL). The reaction solution was stirred at 60°C for 1 h, and then slowly added with 20 mL of cyclohexane supplemented with TEOS (10 v/v%). The mixture was incubated at 60°C for 14 hours while being continuously stirred at 150 rpm. The obtained product was dMSN@CTAC, which has a particle size of 100 nm and a pore size of 10 nm.

**Functionalization of the dMSN surface:**

1) Grafting of amine groups: 100 mg of the as-synthesized dMSN was dispersed into 30 mL of toluene in a 150 mL single-necked flask, and the dispersion was homogenized by ultrasonication. 200 μL of 3-aminotrimethoxysilane (APTES) was injected into the solution, which was then refluxed at 60°C while being stirred at 400 rpm. After 20 h, the samples were subjected to centrifugation and washed with ethanol for three times to obtain $NH_2$-dMSN@CTAC.

2) The CTAC template was firstly removed before the modification of the channel walls. Specifically, 100 mg of $NH_2$-dMSN@CTAC was dispersed into 30 mL (0.5 mg/mL) of $NH_4NO_3$/Ethanol mixture and stirred at 400 rpm under 60°C for 6 h. The CTAC-removed $NH_2$-dMSN was then extracted via centrifugation and washed with ethanol for 2-3 times before being redispersed in ethanol.
3) Conjugation of NBC moieties: 100 mg of aminated $NH_2$-dMSN was dispersed into 20 mL of DMSO and added with 15 mg of NBC. The reaction was carried out at 25°C and stirred at 600 rpm. After 14 h, the samples were centrifuged and washed with ethanol to obtain NBC-dMSN.

**Modification of the inner channel wall of dMSNs:**

Subsequently, 100 mg of the CTAC-depleted NBC-dMSN was dispersed into 30 mL of toluene and added with 200 μL of 3-mercaptopropyltrimethoxysilane. The mixture was refluxed under 60°C while being stirred at 400 rpm. Nanoparticle samples were collected by centrifugation after 20 h. The pellet was washed with ethanol for 3 times to afford NBC-dMSN-SH. 100 mg of NBC-dMSN-SH was dispersed into 30 mL of ethanol and mixed with 200 mg of $N_3$-PEG600-S-S-pyridine. The reaction was carried out at room temperature (25°C) and stirred for 14 hours. The nanoparticles were extracted by centrifugation and washed with ethanol for 2-3 times to obtain NBC-dMSN-S-S-PEG600-$N_3$.

For the click reaction-mediated immobilization of the dendrimers onto the inner channel walls, the catalyst was firstly prepared as follows: 1.4 mg of ascorbic acid and 1.59 mg of $CuSO_4$ were co-solubilized using deionized water (10 mL) and homogenized by ultrasonication. Meanwhile, NBC-dMSN-S-S-PEG600-$N_3$ (100 mg) was dispersed into deionized water (30 mL) and mixed with PAMAM-β-CD (150 mg), after which 30 μl of the prepared catalyst was injected to initiate the reaction, which would last 24 h under room temperature (25°C) while being stirred at 400 rpm. When the reaction was complete, the solution was centrifuged to extract the functionalized nanoparticles, for which the pellet was washed with ethanol for 2-3 times to obtain NBC-dMSN-S-S-PEG-PAMAM-β-CD.

**FITC labeling of the nanoparticles and the dendrimers:**

As there are still some amine groups left after the conjugation of NBC moieties, they could be exploited for the nanoparticle substrate. Specifically, 20 mg of NBC-dMSN-S-S-PEG-$N_3$ and 3 mg of FITC were first co-dissolved in of absolute ethanol (15 mL). The reaction was carried out at room temperature (25 ° C) while being stirred at 300 rpm. FITC-NBC-dMSN-S-S-PEG-$N_3$ was obtained after reacting for 24 h.

As for the FITC labeling of the dendrimers, PAMAM was dissolved in $NH_4OH/H_2O$ solution at a molar ratio of 20 μM and 42 μM of FITC was added, and the subsequent reaction was the same as above, through which the NBC-dMSN-S-S-PEG-PAMAM-Mimic was obtained.

**Drug loading procedures:**

Loading of SN-38: 20 mg of NBC-dMSN-S-S-PEG-PAMAM-β-CD was dispersed into 5 mL of deionized water and then mixed with 2 mg of SN-38 solubilized in ethanol (200 μL). The solvent was then slowly removed under low vacuum (300-400 mbar) by rotary evaporation for 12 h. The SN-38 complexed nanoparticles were then purified using deionized water for 2-3 times to obtain NBC-dMSN-S-S-PEG-PAMAM-β-CD@SN-38. The loading capacity was tested by the fluorescence of the SN-38 with RF6000 SHIMADAZU Spectrofluorophotometer. The loading capacity (%LC) was calculated by the following equation: %LC = (Drug loaded)/(nanoparticle weight) 100%

**Loading of the siRNA:**

The NBC-dMSN-S-S-PEG-PAMAM-β-CD@SN-38 was purified 3 times by sterile PBS and subsequently diluted to a

concentration of 250 μg/mL in sterile PBS. 15 μg of siRNA was added and the mixture was gently shaken several times. After standing at room temperature for 20 min, the siRNA loaded nanoparticles (NBC-dMSN-S-S-PEG-PAMAM-β-CD@SN-38+ siRNA) were obtained.

**Extraction of 4T1 cell membrane:**

$2\times10^7$ units of 4T1 cells were firstly centrifuged and the resultant cell pellet was repeatedly frozen and thawed three times. The pellet was again centrifuged at 4000 rpm for 5 min to separate the cancer cell membrane into the supernatant, which was further extracted through centrifugation at 15000 rpm for 30 min. The raw product was loaded into a HAMILTON gastight syringe and extruded 10 times to obtain the cell membrane for nanoparticle coating.

**Degradation of dMSN and CCM-dMSN:**

20mg dMSN and CCM-dMSN was separated in 20mL Tris Buffer and Krebs Buffer respectively. Take 1mL buffer at regular time for TEM detection.

Krebs Buffer: 118 mM NaCl, 4.7 mM KCl, 1.2 mM $MgSO_4$, 1.25 mM $CaCl_2$, 1.2 mM $KH_2PO_4$, 25 mM $NaHCO_3$, 11 mM glucose

Tris Buffer: 1M Tris (pH 7.0)

**Preparation of the CCM-NBC-dMSN-S-S-PEG-PAMAM-β-CD@SN-38+siRNA:**

The as-prepared NBC-dMSN-S-S-PEG-PAMAM-β-CD@SN-38+siRNA and the processed cell membrane were mixed and loaded into HAMILTON gastight syringe at a mass ratio of 1:1.5, and subsequently extruded 10 times to obtain the CCM-coated drug loaded nanosamples, which were denoted as CCM-NBC-dMSN- S-S-PEG-PAMAM-β-CD@SN-38+ siRNA.

**Evaluation on the redox-triggered drug release and siRNA release:**

To investigate the redox-responsive drug release feature of nanosamples in GSH-rich environment, the NBC-dMSN-S-S-PEG-PAMAM-Mimic and CCM-NBC-dMSN-S-S-PEG-PAMAM-Mimic were separately dispersed in Tris buffer at pH 7.4 and the nanoparticle concentration was maintained at 0.5 mg/mL. After 2.5 h, equal volume of GSH-supplemented Tris buffer was added to the NBC-dMSN-S-S-PEG-PAMAM-Mimic and CCM-NBC-dMSN-S-S-PEG-PAMAM-Mimic solutions. For the comparative analysis of the redox responsiveness, each group contained two sample series with a GSH concentration of

0 mM and 10 mM, respectively. 0.2 mL of the solution was taken from each group at pre-determined intervals, and the supernatant was centrifuged at 10,000 rpm for 5 minutes and then subjected to fluorescence analysis. The FITC fluorescence intensity in the supernatant was examined on a fluorescence spectrophotometer at an excitation wavelength of 520-530 nm. The total amount of loaded drug was determined by dissolving 5 mg of NBC-dMSN-S-S-PEG-PAMAM-Mimic in NaOH solution (0.1 M) while being shaken under ultrasound for 5 min. The FITC fluorescence intensity in the solution was measured similarly. Similar method was used in siRNA release except the mimic were changed to siRNA-Cy5

**Quantification of SN-38 loading:**

To obtain the standard curve for SN-38 quantification, the standardized SN-38 solutions were prepared by dissolving SN-38 in ethanol solution containing 0.1M NaOH at graded SN-38 concentrations of 0.05mg/mL, 0.1mg/mL, 0.2mg/mL, 0.4mg/mL and 0.8mg/mL, respectively. As for the samples, 5 mg of NBC-dMSN-S-S-PEG-PAMAM-β-CD@SN-38 was dissolved in 1 mL of ethanol containing 0.1M NaOH and shaken under ultrasound for 5min. The fluorescence intensity of the nanosamples solution at the emission wavelength of 560 nm was then recorded for calculation.

**siRNA degradation assay:**

To detect the protection of siRNA of the nanoplatform, 100μg dMSN-S-S-PEG-PAMAM@siRNA and CCM-dMSN-S-S-PEG-PAMAM@siRNA each were equally divided into two group-with RNase A (1mg/mL) treated and without. Five minutes after RNase A digestion, particles were collected by centrifuge, 10000rpm, 5min. Then particles of each group were dispersed into 20μL DEPC water. Finally, different groups were loaded into 1% agarose gel to test the protection of siRNA by electrophoresis. The pristine siRNA was tested in equally amount.

**MTT assays:**

4T1 breast cancer cell line is used for the in vitro experiment in this study, which is cultured in DMEM supplemented with 10% fetal bovine serum (FBS, Gibco), penicillin (100 U/mL) and streptomycin (100 μg/mL). The temperature was set at 37°C, the incubation atmosphere contained 5% carbon dioxide. The culture medium was refreshed every 24 hours. 4T1 cells were seeded onto 96-well plates at a density of 8000 cells per well and subsequently incubated overnight in an incubator. The incubation temperature was 37°C and the atmosphere contained 5% $CO_2$. The culture media were subsequently changed to

new ones containing CCM-NBC-dMSN-S-S-PEG-PAMAM-β-CD@SN-38+siRNA, NBC-dMSN-S-S-PEG-PAMAM-β-CD @SN-38+siRNA, dMSN@SN-38 and dMSN, while pristine medium was used as the control. The nanoparticle concentration was 220 μg/mL, and the equivalent SN-38 concentration was maintained at 10 μg/mL. Cells were incubation for 12 or 24 h and each sample group contained 6 replicates. When the incubation was complete, fresh medium containing 0.5 mg/mL of MTT agent was injected to the cell samples and incubated for 4 hours. The emerging formazan crystals were solubilized for the subsequent spectroscopic evaluation by added DMSO (100 μL). The optical density of the samples under the excitation wavelength of 490 nm was recorded on a SpectraMax i3x microplate reader.

**Evaluation on the nanoparticle uptake:**

For the cellular uptake analysis, 2 x $10^5$ units of 4T1 cells were seeded into every well of 6-well plates. The cells were allowed to grow to a confluence around 70%, after which the culture media were changed to new ones supplemented with CCM-NBC-dMSN-S-S-PEG-PAMAM-β-CD and NBC-dMSN-S-S-PEG-PAMAM-β-CD, while pristine medium was used as blank control. The nanoparticle concentration was maintained at 220 μg/mL, and the incubation would last 6, 12 or 24 h. After the incubation, the residual nanoparticles were removed by adding PBS and washing 3 times. Trypsin without EDTA-Na was employed to detach the cells. The cell samples were further washed with PBS for 2 times and collected by centrifugation. The intracellular FITC concentration was measured by flow cytometry on a CytoFLEX system (Beckman Coulter).

For the CLSM analysis of nanoparticle uptake, 2 × $10^5$ units of 4T1 cells were first inoculated into confocal dishes and grew overnight at 37°C in an incubator, in which the atmosphere contained 5% $CO_2$. The initial incubation lasted 24 h and the culture media were changed to new ones with CCM-NBC-dMSN-S-S-PEG-PAMAM-β-CD, NBC-dMSN-S-S-PEG-PAMAM-β-CD, and pristine culture medium was used as blank control. The nanoparticle concentration was 220 μg/mL among all sample groups, and the incubation duration was 6, 12 or 24 h, respectively. The residual nanoparticles were then removed by rinsing with serum-free medium for 3 times and cells were then incubated with media containing rhodamine-labelled wheat germ agglutinin (10 μg/mL) to stain the cell membrane. The stained samples were washed with PBS for 3 times and fixed by formaldehyde. The fixation was carried out at 4°C and lasted 30 minutes, and PBS was again used to wash the cells for another 3 times. Subsequently, H33258 (10 μg/mL) was added and incubated for 5 min to stain the cell nuclei.

The residual agents were removed by rinsing with PBS for 3 times and mounted using glycerol, and later observed on a Leica TCS SP8 confocal laser microscope.

**Tracking of lysosomal escape of the nanosystems:**

$2 \times 10^5$ units of 4T1 cells were inoculated to a confocal dish and then incubated using the condition described above. The initial incubation lasted 24 h, and then the culture medium was changed to new ones containing CCM-NBC-dMSN-S-S-PEG-PAMAM-β-CD, CCM-NBC-dMSN-S-S-PEG, pristine culture medium was used as blank control. The nanoparticle concentration was maintained at 220 μg/mL and the incubation lasted 12 h. Subsequently, the samples were purified by serum-free medium for 3 times and added with lyso-tracker red (60 nM) solubilized in serum-free medium. The incubation would continue for another 30 min to stain the lysosomes. All samples were washed with PBS for 3 times before the fixation with formaldehyde. The fixed cells were cleaned by rinsing with PBS for 3 times, and the nuclei were stained with H33258 (10 μg/mL) for 5 minutes. The double stained cells were thoroughly purified with PBS and mounted using glycerol. Cell images were captured on a Leica TCS SP8 confocal laser microscope.

**Flow cytometric analysis on cancer cell apoptosis:**

$2 \times 10^5$ units of 4T1 cells were inoculated in 6-well plates and grew to a confluence of 70%. The medium was replaced fresh ones supplemented with CCM-NBC-dMSN-S-S-PEG-PAMAM-β-CD@SN-38+siRNA, NBC-dMSN-S-S-PEG-PAMAM-β-CD@SN-38+siRNA, dMSN@SN-38, dMSN and PBS, and the incubation would last for 24 hours. All nanoparticle concentrations were maintained at 220 μg/mL and the equivalent SN-38 concentration was 10 μg/mL. The exhausted medium was drained after the incubation and all samples were thoroughly purified with PBS before the digestion by EDTA-Na-free trypsin. The cells were purified twice by repetitive washing and centrifugation, and finally the Annexin V/PI was added for cell staining using the assay kit (Invitrogen). Cell apoptosis rate was detected on a CytoFLEX system (Beckman Coulter).

**Cell live/dead assay:**

4T1 cells were seeded in the confocal dish using the same procedure above and the live/dead ratio was analyzed by CLSM. After the incubation, the cell samples were incubated with fresh medium containing fluorescein diacetate (50 μg/mL) for 20 min and then added with propidium iodide (400 μg/mL) for 5 min. The processed samples were finally observed on a Leica

TCS SP8 laser microscope.

**Western blot assay:**

To examine the gene silencing effect of Bcl-2 siRNA, the expression levels of Bcl-2 and Bax proteins were investigated using western blot assay. To start with, $2 \times 10^5$ units of 4T1 cells were seeded into 6-well plates and grew to a confluence of 70%. Subsequently, the medium was replaced with fresh ones containing CCM-NBC-dMSN-S-S-PEG-PAMAM-β-CD@SN-38+siRNA, NBC-dMSN-S-S-PEG-PAMAM-β-CD@SN-38+siRNA, dMSN @SN-38, dMSN and PBS, and the incubation would last 24 h. The nanoparticle concentration was fixed at 220 μg/mL and the equivalent SN-38 concentration was maintained at 10 μg/mL. The cells were then lysed by RIPA lysate (Beyontime Biotechnology) for 20 minutes under ice bath to collect the proteins. The extracted proteins were detected by BCA assay kit (Beyontime Biotechnology), and then total protein was extracted using polyacrylamide (SDS-PAGE) gel containing 12% SDS. The captured proteins were further to a PVDF membrane (Immobilon p, Millipore) and finally detected by primary antibody and HRP-labeled secondary antibody. The final result was visualized on the molecular imager Versa doc MP 4000 system (Bio-Rad).

**In vivo experiments**

**Construction of the tumor mouse models and in vivo therapy:**

The mice used in this study were provided by Xinqiao Hospital in Chongqing, China. All in vivo experiments were conducted following the Animal Management Rules of the Ministry of Health of the People's Republic of China (Document NO. 55, 2001) and approved by the Animal Ethics Committee of Army Medical University. To establish the 4T1 tumors, $1 \times 10^7$ units of 4T1 cells were dispersed in 100 μL of PBS and then injected into their subcutaneous tissue. The mice were incubated until the tumor volume grew to 40 $mm^3$ and the initial weight of all mice was maintained at 22 ± 0.2 g, 30 mice with established 4T1 tumor tissues were selected and randomly divided into 5 groups (each groups comprised 6 mice), which were treated by PBS, dMSN, dMSN@SN-38, NBC-dMSN-S-S-PEG-PAMAM-β-CD@SN-38+siRNA and CCM-NBC-dMSN-S-S-PEG-PAMAM-β-CD@SN-38+siRNA, respectively. All samples were injected via the tail vein with an equivalent SN-38 concentration of 5 mg/kg. The injection was repeated every other day, and the weight and tumor volume of the nude mice were recorded regularly. Tumor volume was determined using the following formula: $V_{tumor} = L \times W^2/2$ (L: longitudinal

diameter of the tumor, W: transverse diameter of the tumor, both were measured with digital vernier calipers). After 21 days of treatment, all mice were euthanized, and relevant tissues/organs were extracted and fixed in paraformaldehyde solution (4%) for subsequent analysis.

**In vivo evaluation of tumor apoptosis:**

To study the apoptosis induced by the treatment of the nanoformulation in vivo, the tumor tissue was embedded in paraffin and treated by 10% formalin at 4°C for 24 hours for fixation. Those fixed samples were subsequently sliced and dewaxed with xylene, and transferred onto a glass slide. The tumor slices were washed twice with PBS. Afterwards, 20 μg/mL of DNase-free proteinase K was added dropwise to rinse the samples, which were incubated at 37°C for 30 min and then washed thoroughly with PBS before the staining by a TUNEL staining kit (Beyontime Biotechnology). The stained tissue slices were left standing at 37°C in a dark room for 60 min, and then washed 3 times with PBS before being mounted with an anti-fluorescence quencher. The processed tumor samples were finally observed on an inverted fluorescence microscope (Leica DMi8). In addition, tumor tissue and organ sections were also stained with hematoxylin and eosin (H&E staining), and the severity of apoptosis for tumor tissues and the cytotoxic damage in various organs were also observed by inverted fluorescence microscopy (Leica DMi8).

**Blood Circulation Studies:**

To invest the blood circulation time of nanoplatform, nine BALB/c mice (6-8 weeks) were divided into three groups, three mice in every group. Then mice were injected intravenously into the tail vein with siRNA, dMSN-S-S-PEG-PAMAMA@siRNA and CCM-dMSN-S-S-PEG-PAMAM@siRNA corresponding to three groups. Blood samples were collected at 0.5h, 1h, 2h, 3h, 6h, 12h and 24h.

# Figures

## Inner channel fabrication

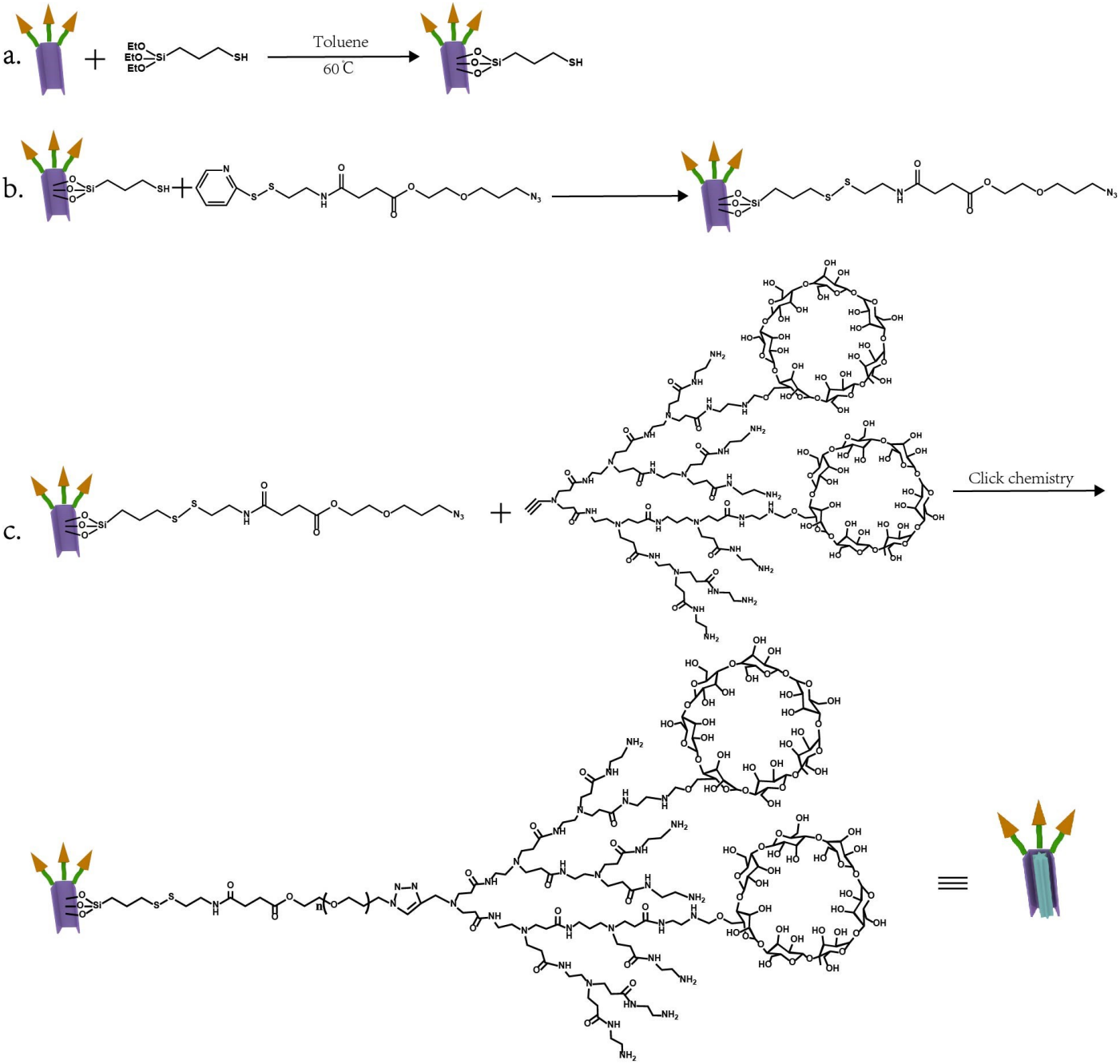
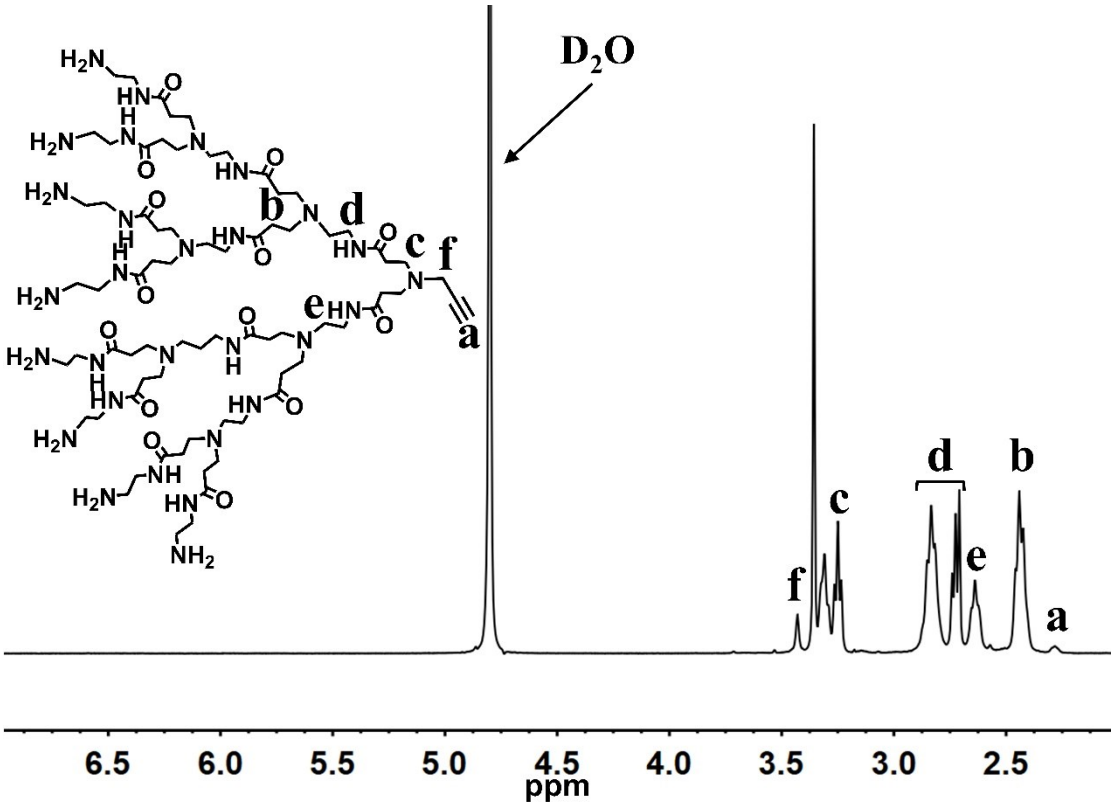



**Fig S1.** Modification procedure of the nanoplatform.

i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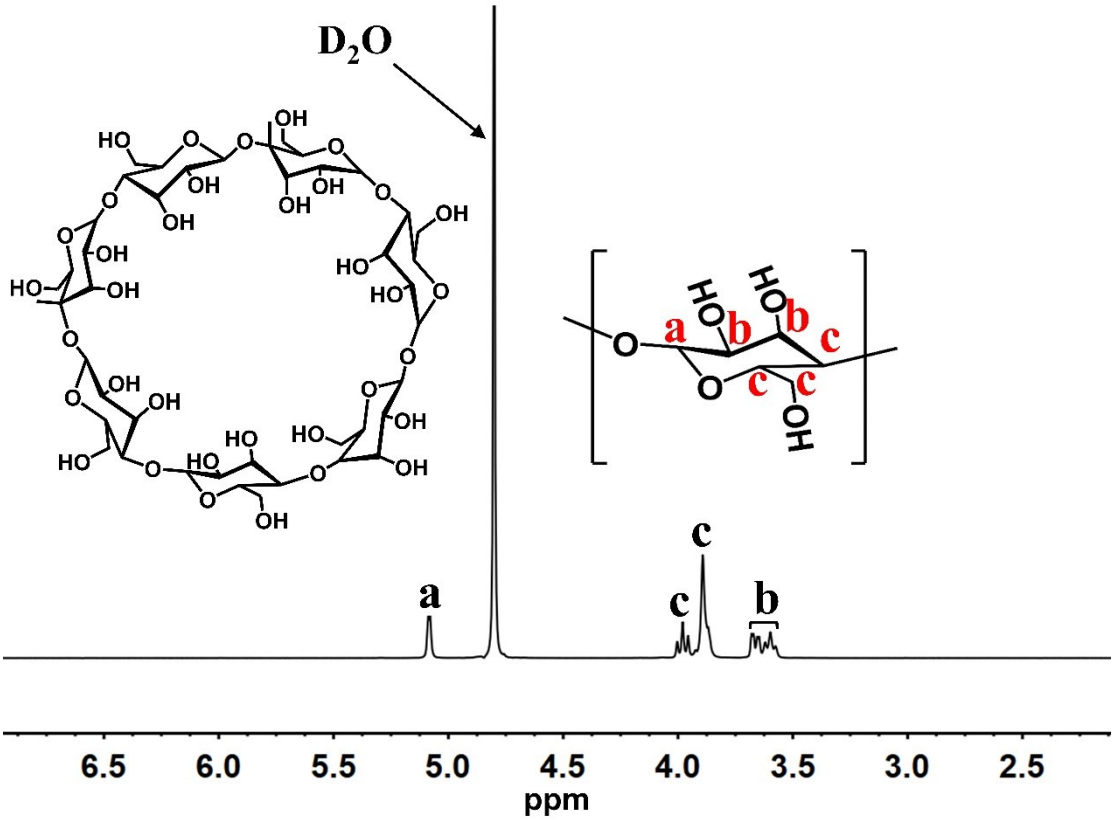
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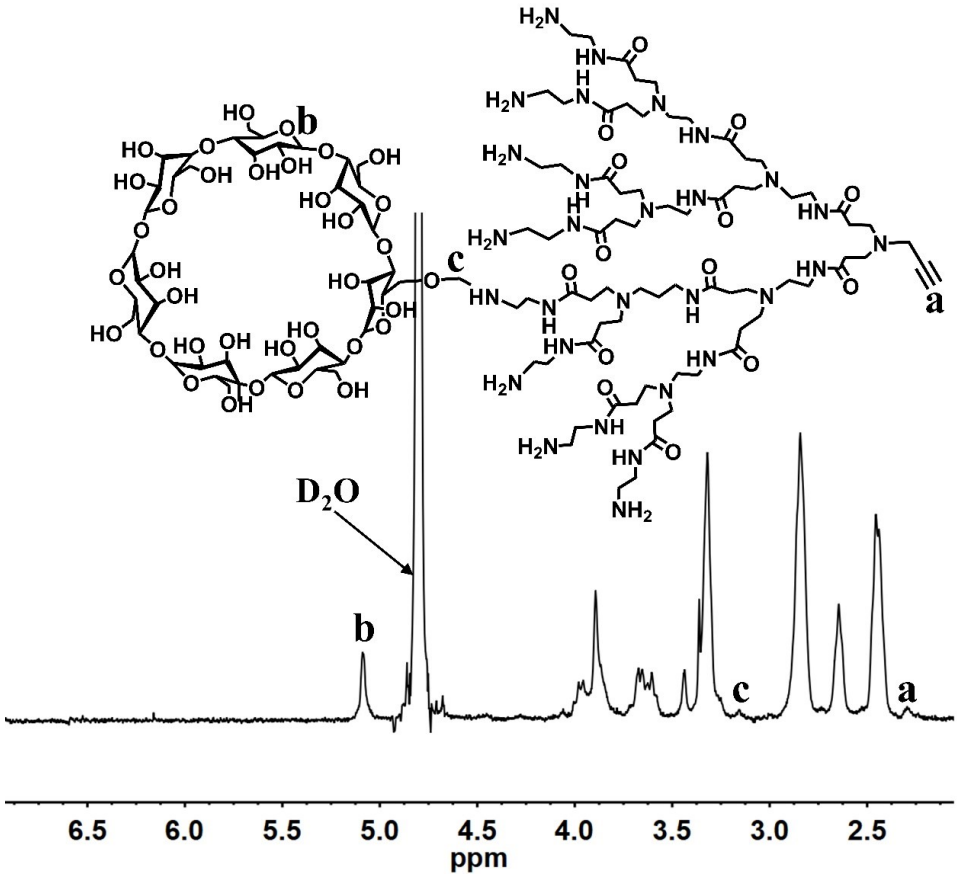
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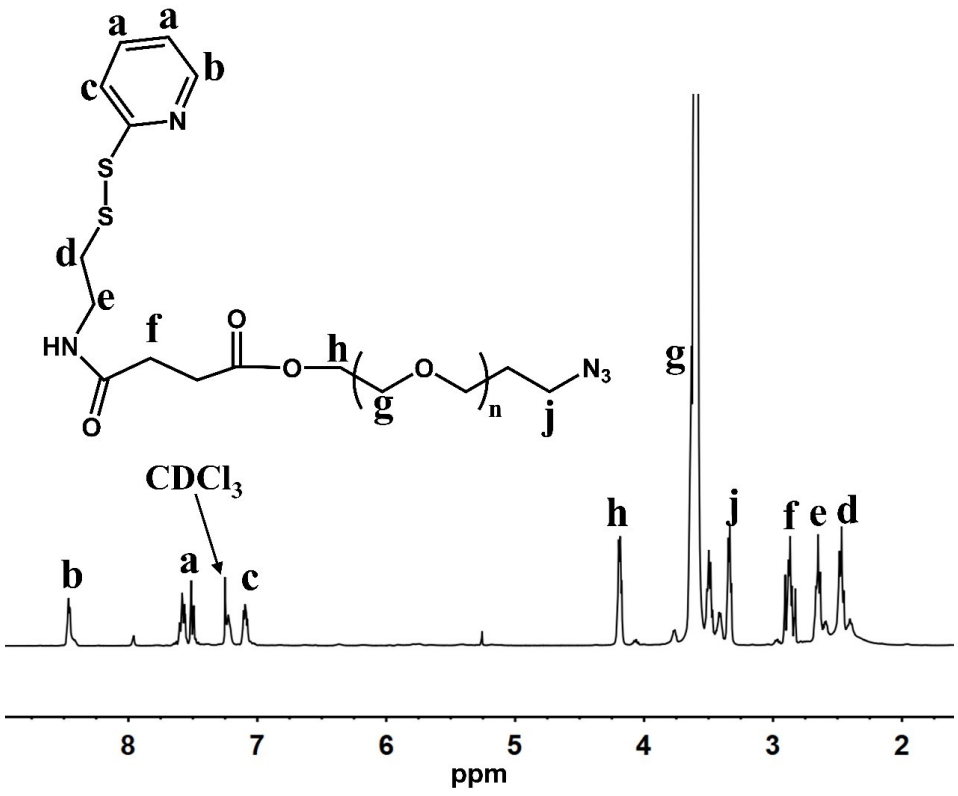
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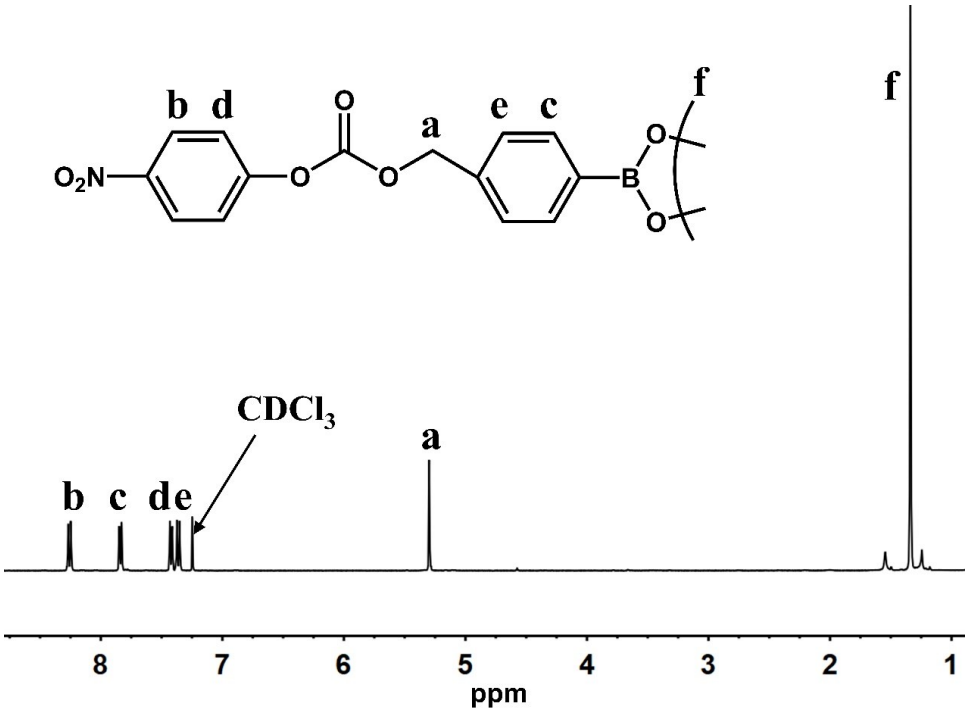


**Fig S2**. $^{1}H$ NMR spectra of (ⅰ) G3.0 PAMAM, (ⅱ) β-CD, (ⅲ) PAMAM-βCD, (ⅳ) Pyridine-S-S-$PEG_{600}$-$N_3$ and (ⅴ) NBC linker.

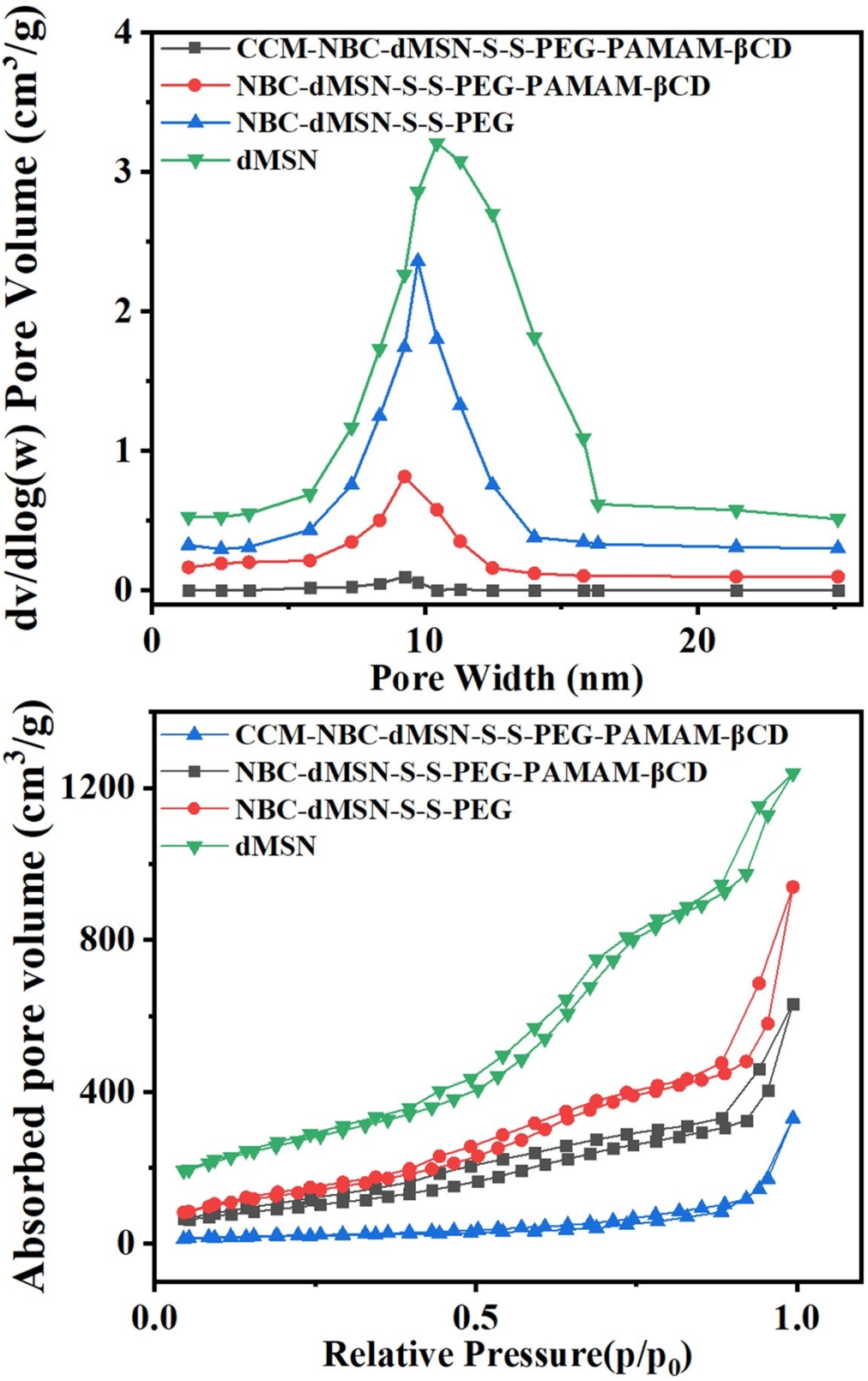


**Fig S3**. Nitrogen adsorption/desorption isotherms of the nanoparticle series showing their pore size distribution (A) and pore volumes (B).

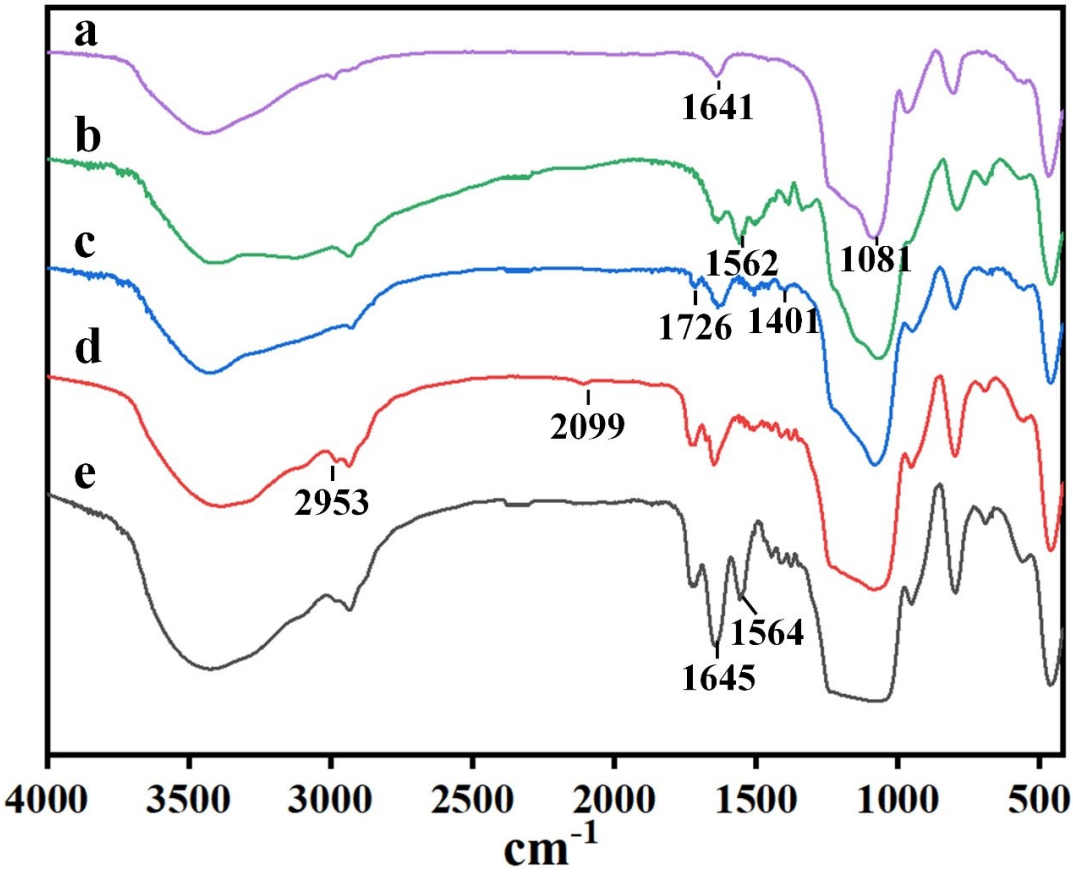


**Fig S4**. FTIR spectra of dMSNs through the stepwise modification. Samples include (a) dMSNs, (b) dMSNs-$NH_2$, (c)dMSNs-NH-NBC, (d)NBC-dMSNs-S-S-PEG-$N_3$, and (e) NBC-dMSNs-S-S-PEG-PAMAM-βCD.

It was observed that pristine dMSNs displayed a strong absorption signal at 1081 $cm^{-1}$, which was assigned to asymmetric stretching of Si-O-Si bridges. Peak at 1636 $cm^{-1}$ was attributed to physically adsorbed water molecules in dMSNs. As for the dMSNs-$NH_2$, a new peak emerged at 1562 $cm^{-1}$, which was caused by the amine group. The results indicate that amine groups have been successfully grafted onto dMSNs. After the modification with aryl boronic acid (NBC), the intensity of the peak at 1562 $cm^{-1}$ was reduced due to the consumption of the amine groups during reaction. Meanwhile, a new peak appeared at 1726 $cm^{-1}$, which was ascribed to the carbonyl group in NBC. The other peak at 1401 $cm^{-1}$ was caused by the stretching of benzyl groups from NBC. After reaction with MPTS and Pyridine-S-S-PEG-$N_3$, two new peaks appeared at 2099 $cm^{-1}$ and 2953 $cm^{-1}$ in the spectrum of dMSNs-S-S-PEG-$N_3$, each

representing the $N_3$ group and –CH2- units of Pyridine-S-S-PEG-$N_3$. Finally, the characteristic amine peak at 1562 $cm^{-1}$ appeared again in sample e, indicating that PAMAM-βCD were successfully conjugated to the particle.

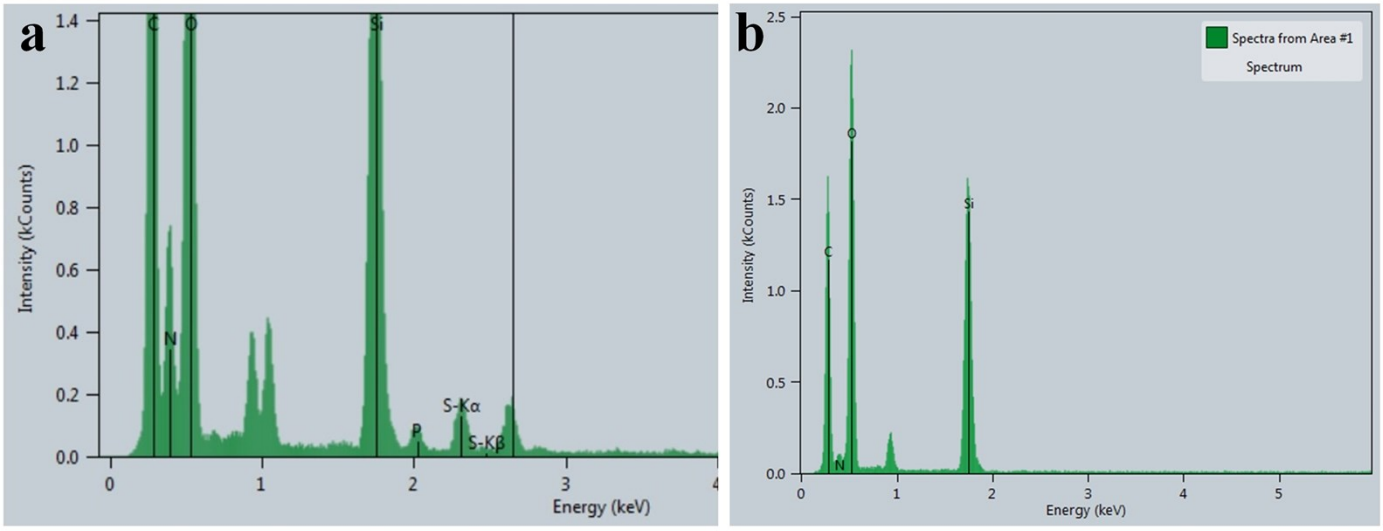


**Fig S5**. Energy dispersive X-ray analysis of a) CCM-dMSN and b) dMSN.

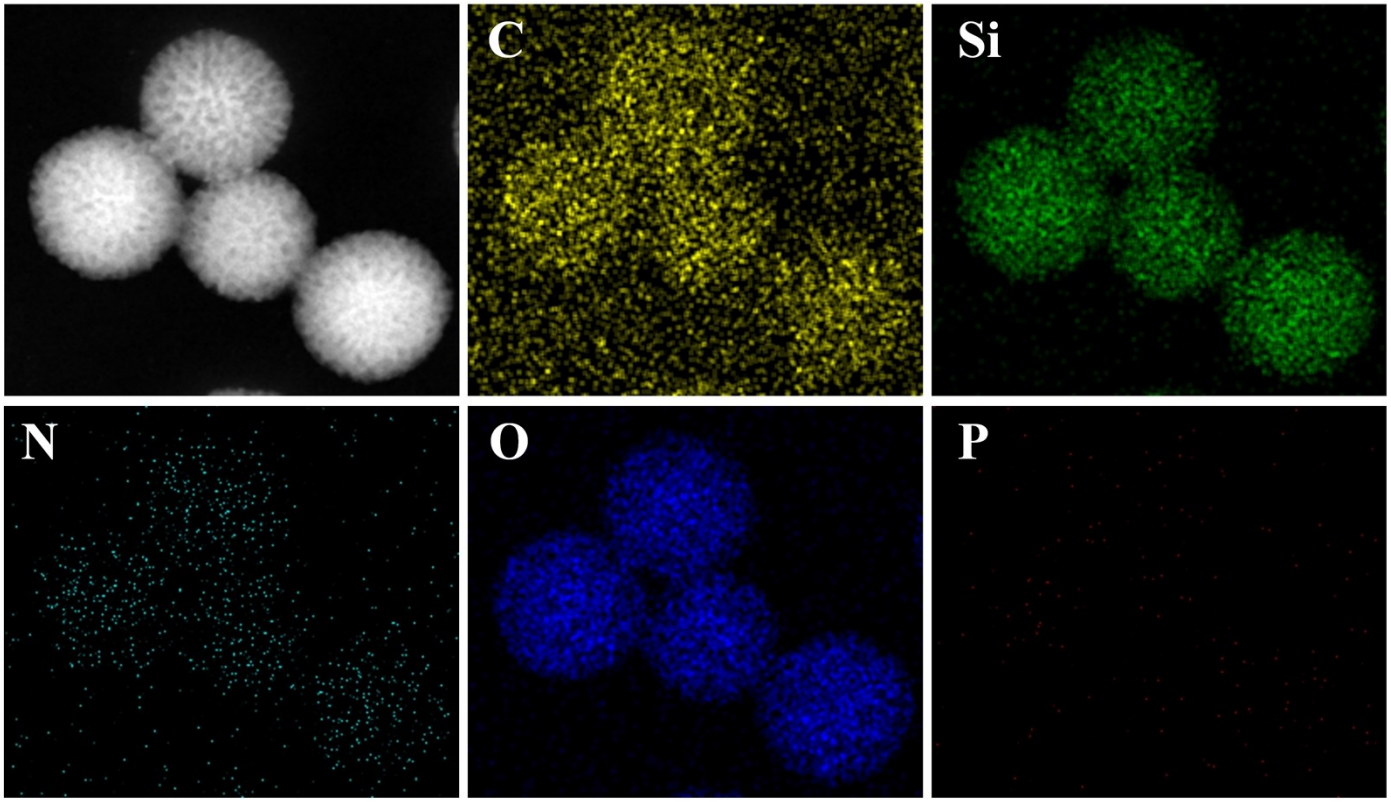


**Fig S6**. Elemental mapping results of dMSN.

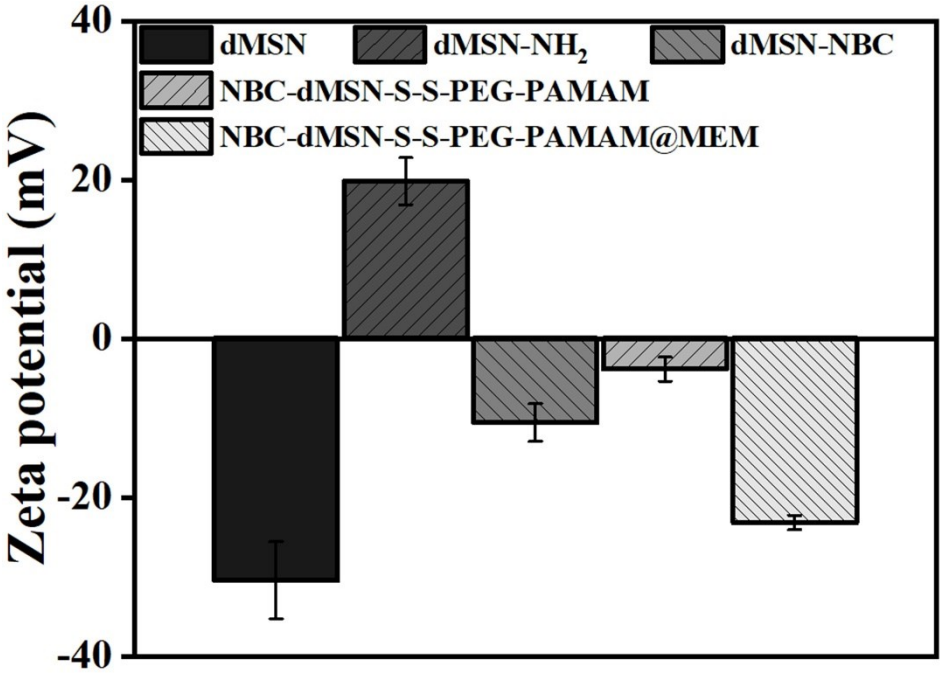


**Fig S7**. The changes in the zeta potentials of nanoparticles at different modification stages. Results are presented as means ± standard error.

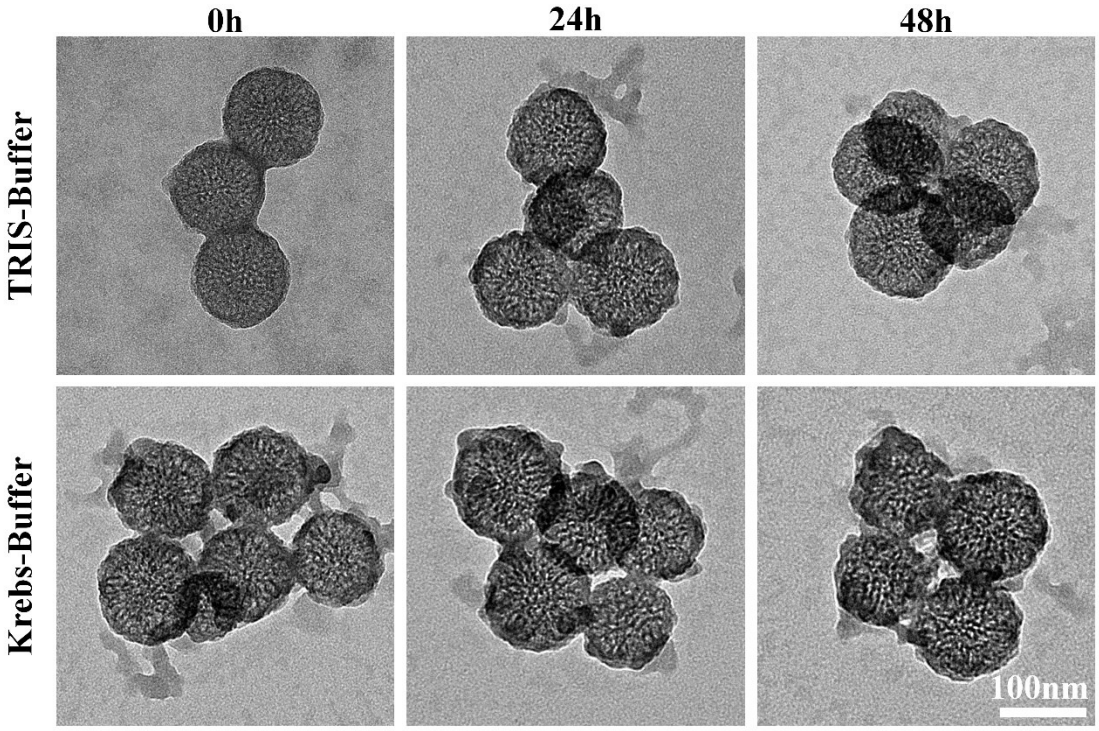


**Fig S8**. TEM images of CCM-dMSN-S-S-PEG-PAMAM-β-CD after incubation in Tris buffer and Krebs buffer, representing its adaptable degradability in tumor intracellular environment.

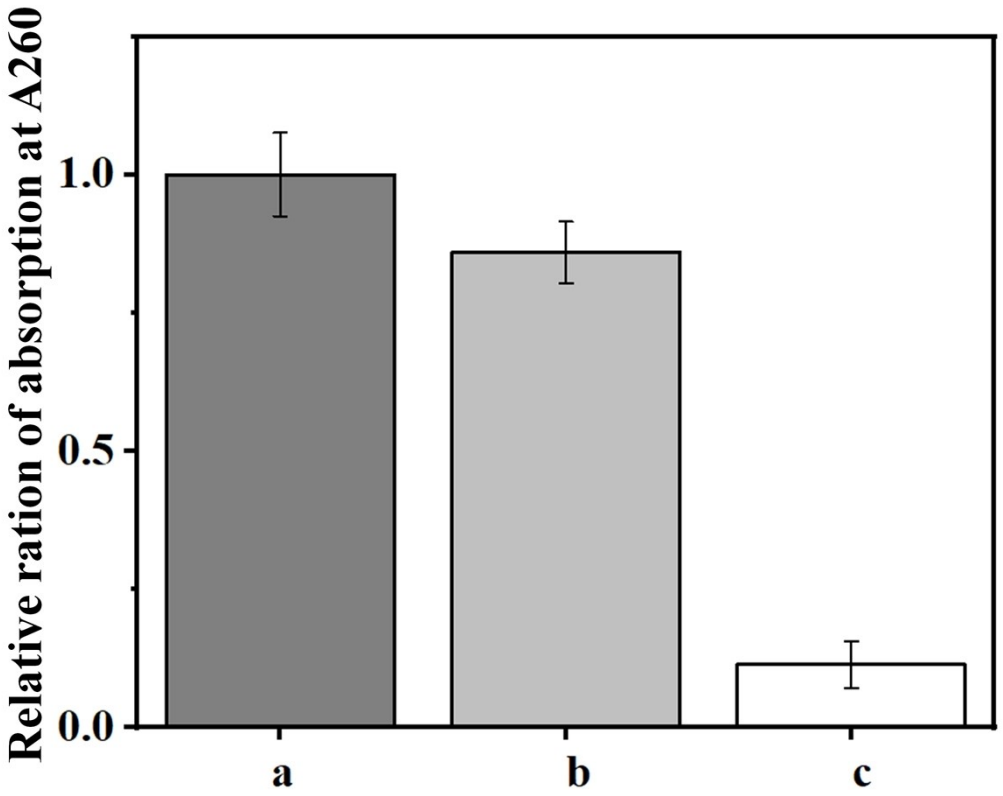


**Fig S9**. The Relative ratio of absorption at A260 of a) siRNA, b) dMSN-S-S-PEG-PAMAM@siRNA and c) dMSN@siRNA.

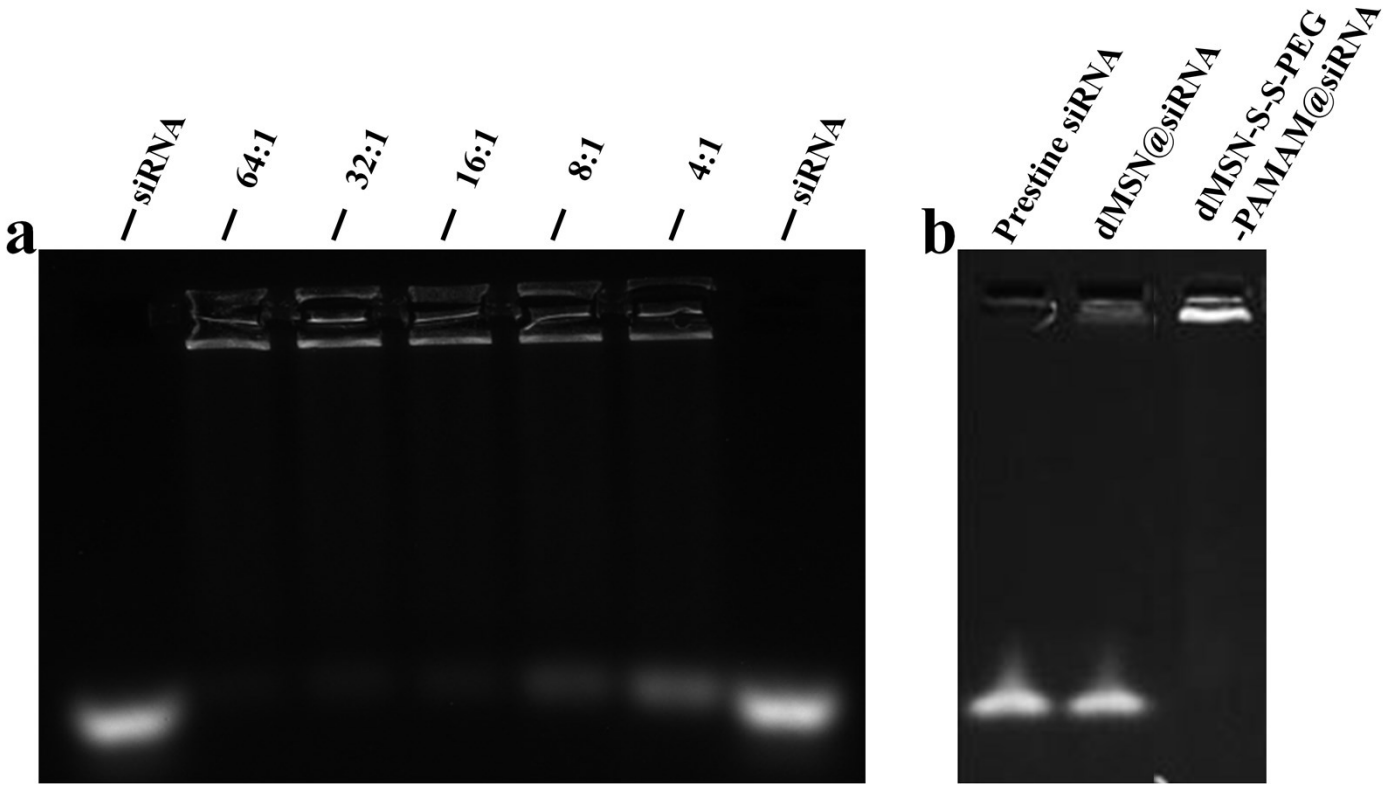


**Fig S10**. The RNA retardation assay of a) dMSN-S-S-PEG-PAMAM@siRNA in different mass ratio b) dMSN and dMSN-S-S-PEG-PAMAM@siRNA in mass ratio of 16:1.

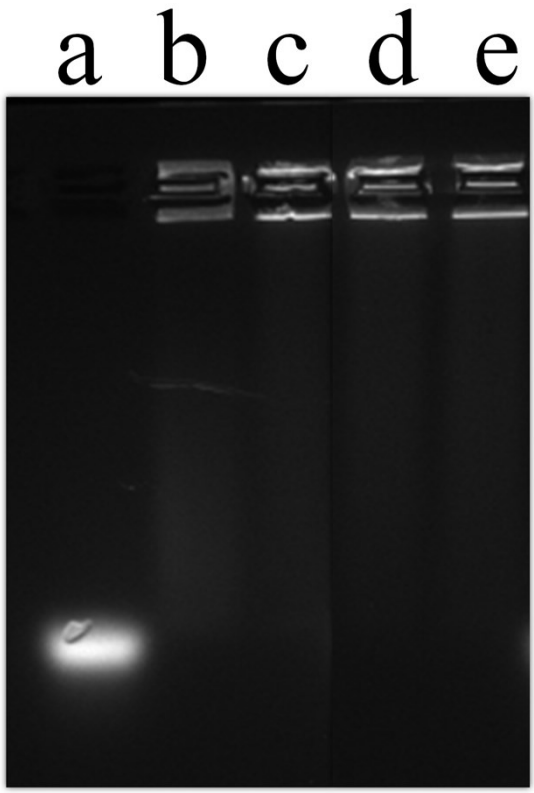


**Fig S11**. Agarose Gel Electrophoresis of a) siRNA, b) dMSN-S-S-PEG-PAMAM@siRNA/RNase A, c) dMSN-S-S-PEG-PAMAM@siRNA, d) CCM-dMSN-S-S-PEG-PAMAM@siRNA and e) CCM-dMSN-S-S-PEG-PAMAM@siRNA/RNase

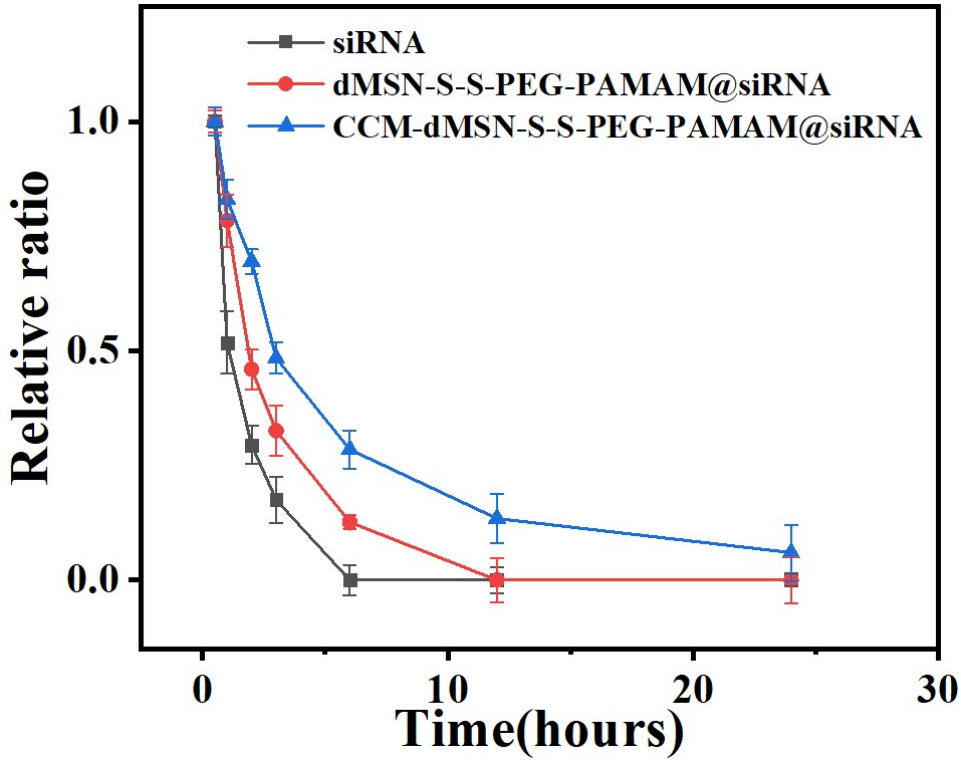


**Fig S12**. The blood circulation test of pristine siRNA-Cy5, dMSN-S-S-PEG-PAMAM@siRNA-Cy5 and CCM-dMSN-S-S-PEG-PAMAM@ siRNA-Cy5.

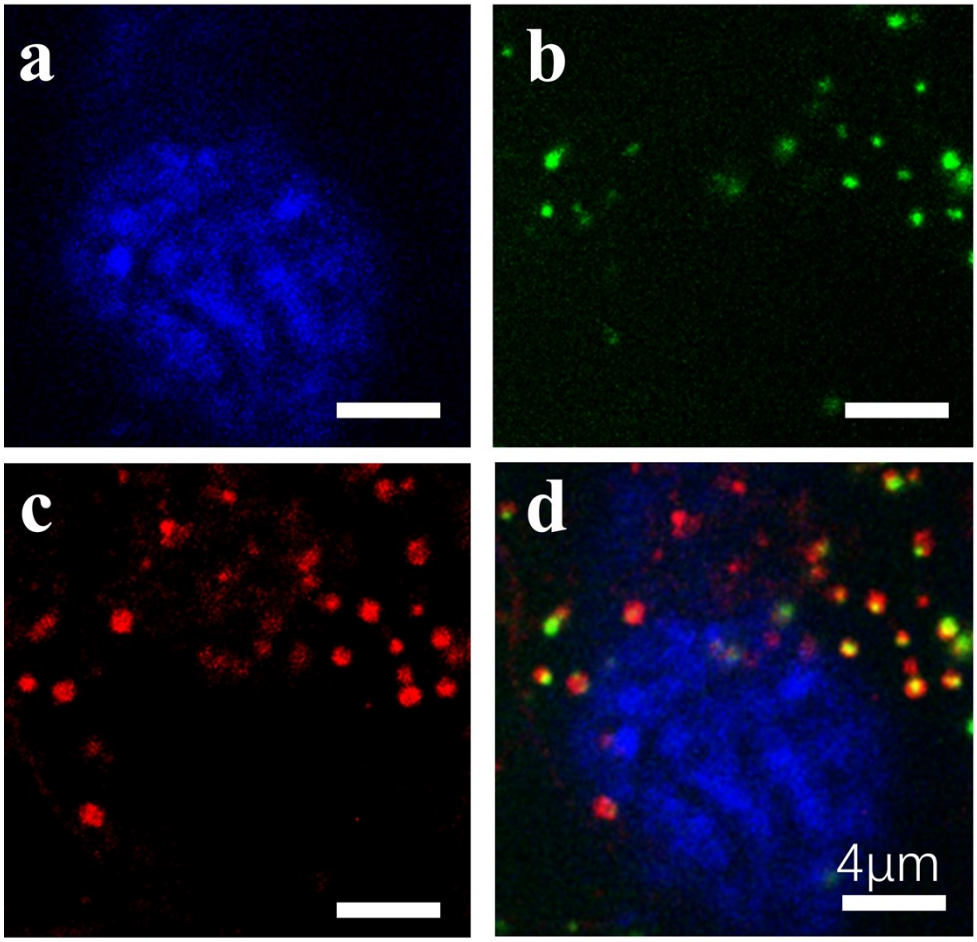


**Fig S13**. Confocal microscopic images of 4T1 cells treated with CCM-dMSN-S-S-PEG-PAMAM-βCD for 6h. a) DAPI-stained cell nucleus, b) FITC fluorescence of labeled nanoparticles, c) cancer cell membrane stained with Rhodamine Wheat Germ Agglutinin, d) merged channel

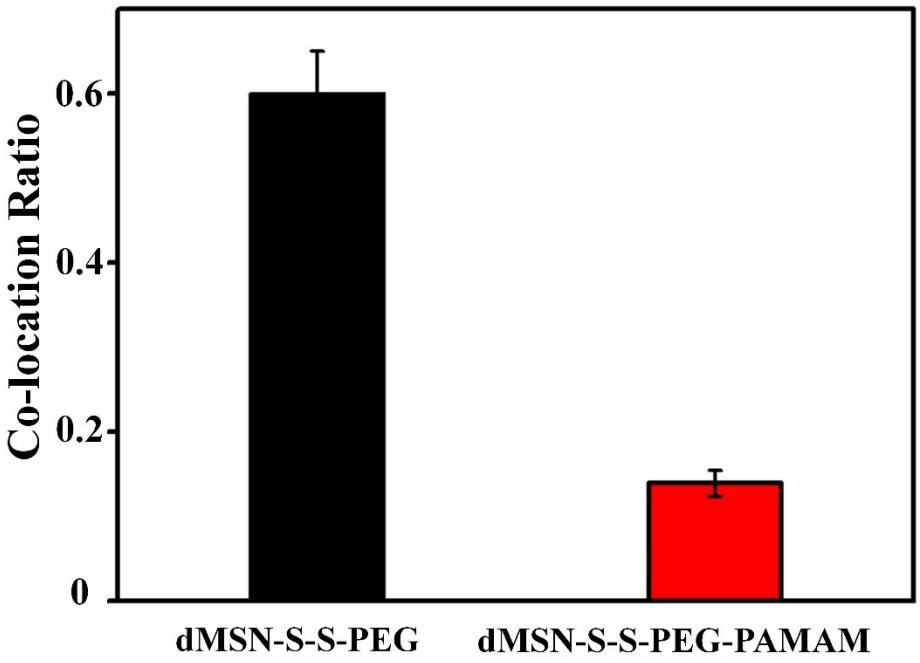


**Fig S14**. The Pearson's colocalization coefficients of dMSN-S-S-PEG and dMSN-S-S-PEG-PAMAM.

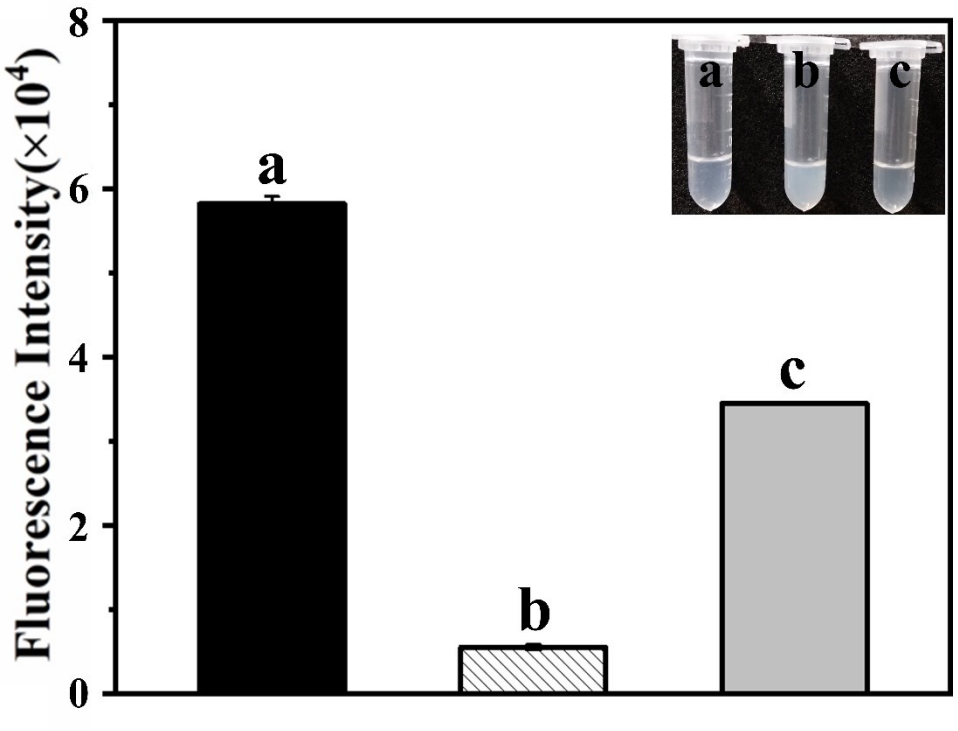


**Fig S15**. Analysis on the fluorescamine fluorescence intensity of (a) dMSN-$NH_2$, (b) dMSN-NH-NBC, (c)dMSN-NH-NBC (treated by 5mM $H_2O_2$)

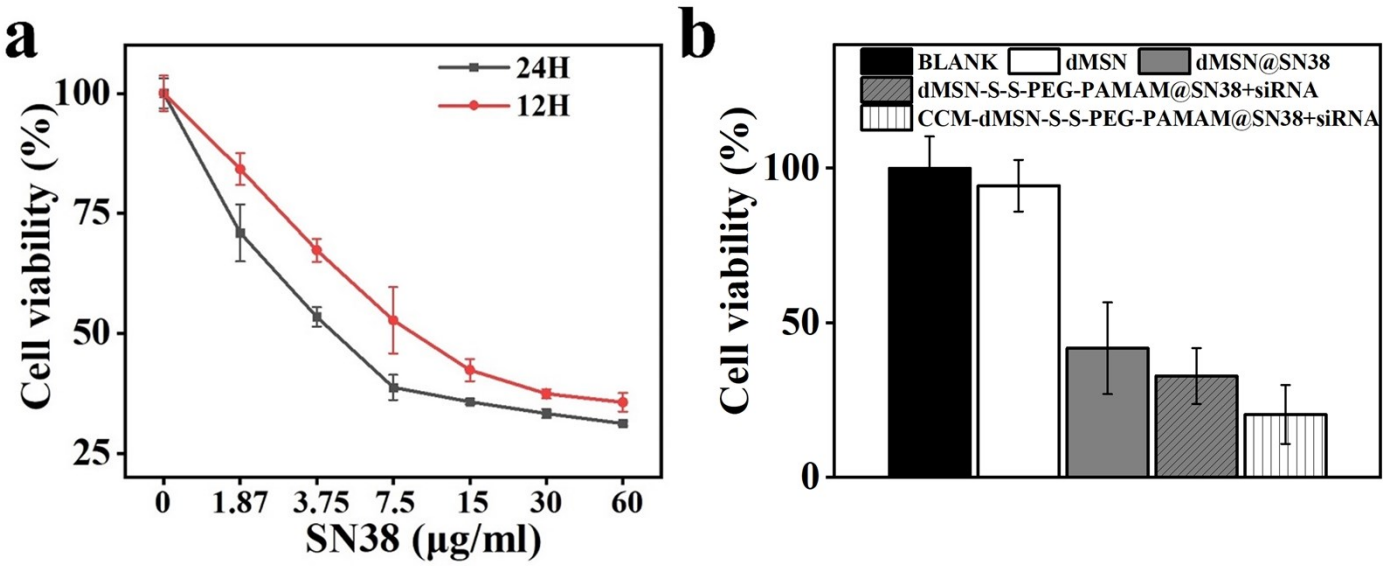


**Fig S16**. (a) Cytotoxicity assay of pristine SN-38 at different concentrations against 4T1 cells. Panel (b) showed the relative survival rates of 4T1 cells after treatment with blank (pristine culture medium), dMSN, dMSN@SN-38, dMSN-S-S-PEG-PAMAM@SN-38+siRNA and CCM-dMSN-S-S-PEG-PAMAM@SN-38+siRNA.

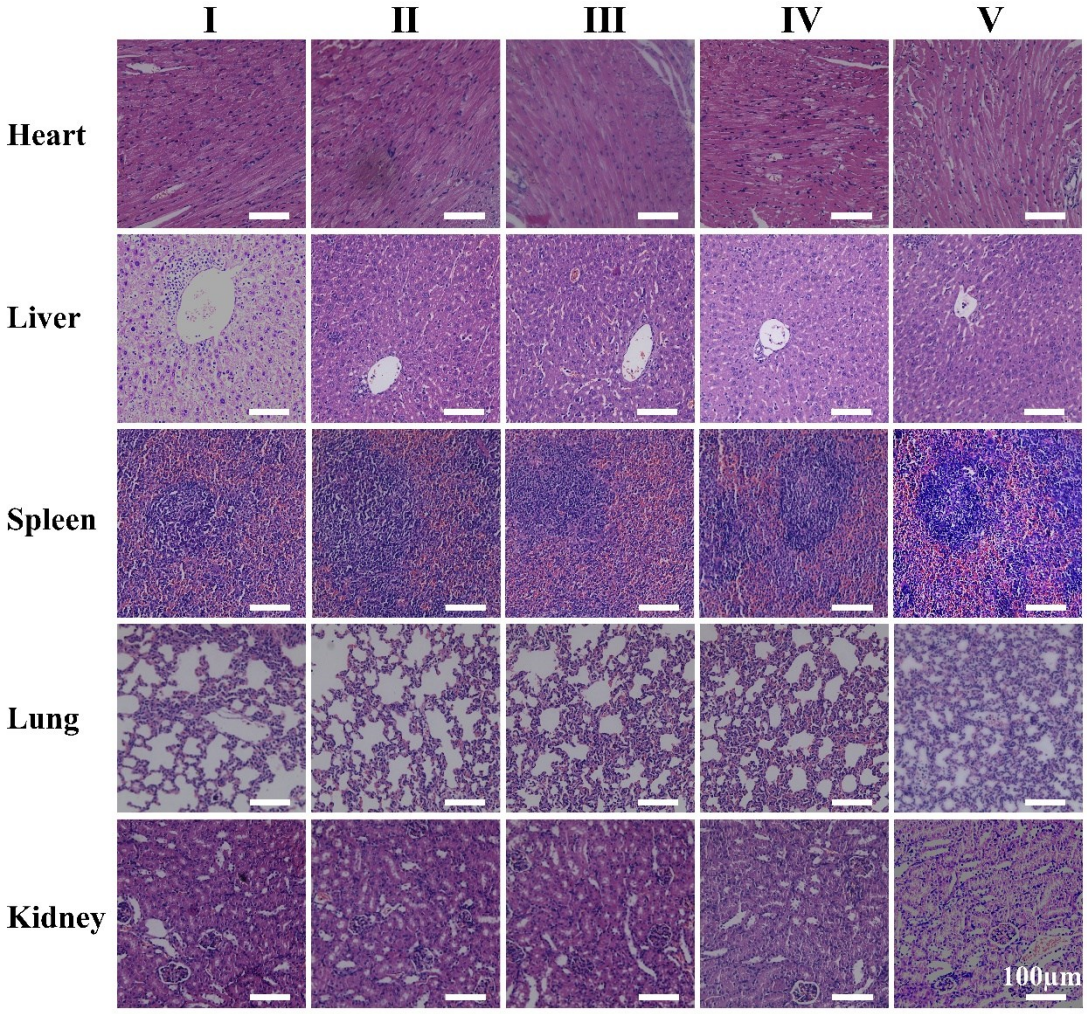


**Fig S17**. H&E staining images of major organs collected from different groups treated with (Ⅰ) Blank, (Ⅱ) dMSN, (Ⅲ) dMSN@SN-38, (Ⅳ) dMSN-S-S-PEG-PAMAM@SN-38+siRNA and (Ⅴ) CCM-dMSN-S-S-PEG-PAMAM@SN-38+siRNA.

**Table S1.** BET and BJH analysis for dMSNs at different modification stages.

| **Materials** | **BET surface area $S_{BET}$ ($m^2/g$)** | **BET pore volume $V_P$ ($cm^3/g$)** | **BJH pore diameter WBJH (nm)** |
|---|---|---|---|
| dMSNs | 944.03 | 1.34 | 10.441 |
| NBC-dMSN-S-S-PEG | 496.27 | 0.86 | 9.74 |
| NBC-dMSNs-S-S-PEG-PAMAM-βCD | 360.11 | 0.54 | 9.25 |
| CCM-NBC-dMSNs-S-S-PEG-PAMAM-βCD | 79.42 | 0.11 | / |

**Table S2.** Sequence of siRNA used in this work

| **siRNA** | **Sequence of siRNA** |
|---|---|
| *Bcl-2* | 5'-ACCUGCACACCUGGAUCCAGGAUAA-3' |