# Supplementary Information:

# Synthesis and Biological Response of Size-Specific, Monodisperse Drug-Silica Nanoconjugates

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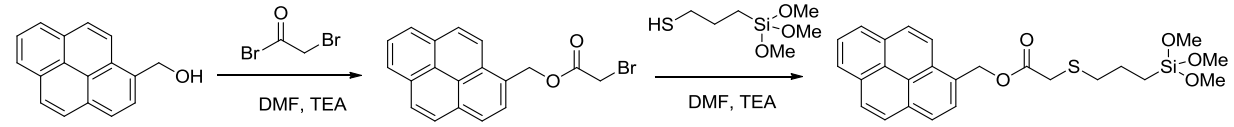
**General**

All chemicals including tetraethyl orthosilicate (TEOS, 99.999%), pyrenemethanol (Pyr-OH) and camptothecin (Cpt) were purchased from Sigma-Aldrich (St Louis, MO, USA) and used as received unless otherwise noted. $mPEG_{5k}$-triethoxysilane (mPEG-sil, **6**) (Scheme 1) was purchased from Laysan Bio (Arab, AL, USA) and used as received. All anhydrous solvents were purified by passing them through dry alumina columns and kept anhydrous by storing them in the presence of molecular sieves. The polyclonal rabbit anti-human Von Willebrand Factor (Factor VIII-related antigen) was purchased from Dako (Carpinteria, CA, USA). The FITC-conjugated goat polyclonal secondary antibody to rabbit IgG was purchased from Abcam (Cambridge, MA, USA). The low resolution electrospray ionization mass spectrometry (LR-ESI-MS) experiments were performed on a Waters Quattro II Mass Spectrometer. Matrix Assisted Laser Desorption/Ionization-Time Of Flight mass spectrometry (MALDI-TOF MS) spectra were collected on an Applied Biosystems Voyager-DE$^{TM}$ STR system. HPLC analyses were performed on a System Gold system (Beckman Coulter, Fullerton, CA, USA) equipped with a 126P solvent module, a System Gold 128 UV detector and a C18 analytical column (Luna C18, 250 × 4.6 mm, 5 $\mu$, Phenomenex, Torrance, CA, USA). The NMR experiments were conducted on a Varian U500, a VXR500 or on a UI500NB 500 MHz NMR spectrometer. The sizes and monodispersities of silica particles were determined on a Hitachi S4800 high resolution Scanning Electron Microscope (SEM). The real time monitoring of the drug(dye)-silica NC sizes and monodispersities were achieved via the use of ZetaPlus dynamic light-scattering (DLS) detector (15 mW laser, incident beam = 676 nm, Brookhaven Instruments, Holtsville, NY, USA). The solid forms of NCs were obtained by lyophilizing the NC/lyoprotectant solution using a Freezone benchtop lyophilizer (Fisher Scientific, Fairland, NJ, USA). The HeLa cells (ATCC,

Manassas, VA, USA) used for MTT assays and cellular internalization studies were cultured in MEM medium containing 10% Fetal Bovine Serum (FBS), 1000 units/mL aqueous Penicillin G and 100 μg/mL streptomycin (Invitrogen, Carlsbad, CA, USA). The absorbance wavelength on a microplate reader (Perkin Elmer, Victor$^3{}_{TM}$ V, Waltham, MA, USA) was set at 590 nm for the MTT assay. The Lewis lung carcinoma (LLC) cells (ATCC) were cultured in DMEM medium containing 10% FBS, 1000 units/mL aqueous Penicillin G and 100 μg/mL streptomycin. The confocal microscopy images for cell internalization studies were taken on a Zeiss LSM700 Confocal Microscope (Carl Zeiss, Thornwood, NY, USA) using a 63×1.4 oil lens with excitation wavelength set at 405 nm and 555 nm. The flow cytometry analysis of cells was conducted with a BD FACSCanto 6-color flow cytometry analyzer (BD, Franklin Lakes, NJ, USA). For the *ex vivo* study, the flash frozen tumor tissue embedded with optimum cutting temperature (O.C.T.) compound (Sakura Finetek, USA) was sectioned (thickness = 20 μm) with a Leica CM3050S cryostat and mounted on a glass slide. The tissue sections were observed on a fluorescence microscope (Zeiss Axiovert 200M) with 780 nm excitation wavelength. For the *in vivo* study, the formalin-fixed, paraffin-embedded 5 μm thick tumor sections were prepared by the Veterinary Diagnostic Laboratory histopathology service at the University of Illinois at Urbana-Champaign (Urbana, IL, USA). The tissue sections were analyzed on a Zeiss LSM700 confocal microscope for *in vivo* tumor penetration study. For biodistribution studies, the organs were fixed in 10% formalin; the fluorescence of the whole organ was measure *ex vivo* at 800 nm wavelength emission using Odyssey infrared mouse imaging system (LI-COR, Lincoln, NE, USA). The histopathological characterizations of tissues for mononuclear cell infiltrates (neutrophils and macrophages) were performed at College of Veterinary Medicine North Carolina State University. C57BL/6 mice (female) were purchased from Charles River Laboratories

(Wilmington, MA, USA). Feed and water were available *ad libitum*. The study protocol was reviewed and approved by the Illinois Institutional Animal Care and Use Committee (IACUC) of the University of Illinois at Urbana–Champaign. For both *ex vivo* and *in vivo* studies, C57BL/6 mice were injected subcutaneously in the right flank with $1 \times 10^6$ Lewis lung carcinoma (LLC) cells suspended in a 1:1 mixture of PBS buffer and matrigel (BD Biosciences, Franklin Lakes, NJ, USA).

**Synthesis of pyrenemethyl-2-((3-(trimethoxysilyl)propyl)thio)acetate** (Pyr-sil, **1**, Scheme 1)



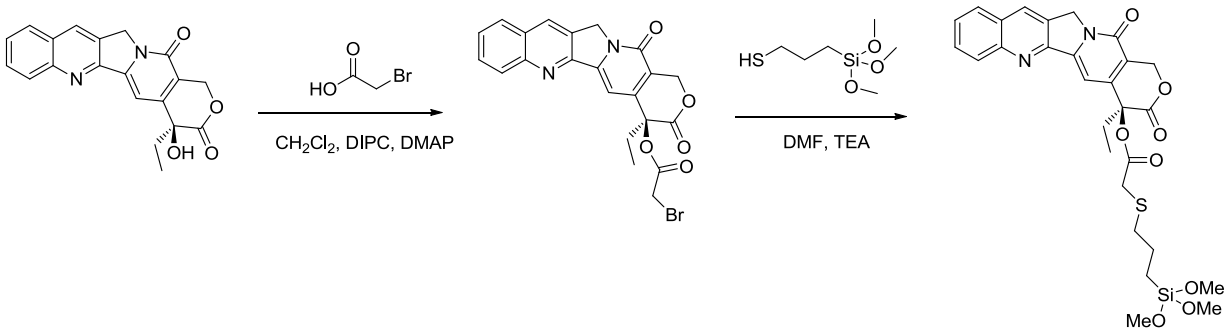

Pyr-OH Pyr-Br Pyr-sil

*Synthesis of pyrene-1-ylmethyl 2-bromoacetate (Pyr-Br)*: Pyrenemethanol (109.6 mg, 0.47 mmol) in anhydrous DMF (1.0 mL) was treated with anhydrous TEA (180 μL, 1.29 mmol) and 2-bromoacetyl bromide (132.2 μL, 1.50 mmol) in dichloromethane (1 mL). The mixture was stirred at rt for 17 h. After the solvent was evaporated, the crude product was purified by silica gel column (hexane/EtOAc = 2/1) to give final product as a yellow solid (167 mg, 90% yield). $^1$H NMR ($CDCl_3$, 500 MHz): δ 8.28-8.03 (m, 9H, ArH), 5.94 (s, 2H, $ArCH_2$), 3.90 (s, 2H, $CH_2Br$). MS (ESI): calcd. for $C_{19}H_{13}BrO_2Na$ $[M+Na]^+$ *m/z* 376.2, found 375.9.

*Synthesis of pyrenemethyl 2-((3-(trimethoxysilyl)propyl)thio)acetate (**1**, Scheme 1)*: Pyr-Br (40.2 mg, 0.11 mmol) in anhydrous DMF (0.5 mL) was treated with anhydrous TEA (180 μL, 1.29

mmol) and (3-mercaptopropyl)trimethoxysilane (210 μL, 1.10 mmol). The mixture was stirred at rt for 11 h. After the solvent was evaporated, the crude product was purified by silica gel column (hexane/EtOAc = 3/1) to give the final product **1**. HPLC purity: >95%. $^{1}$H NMR ($CDCl_3$, 500 MHz): δ 8.31-8.03 (m, 9H, ArH), 5.91 (s, 2H, $ArCH_2$), 3.51 (s, 9H, $(CH_3O)_3Si$), 3.29 (s, 2H, $CH_2Br$), 2.62 (t, 2H, $SCH_2$), 1.67 (m, 2H, $CH_2$), 0.65 (t, 2H, $CH_2Si$). $^{13}$C NMR ($CDCl_3$, 500 MHz): δ 171.0, 132.1-121.5, 65.8, 50.8, 42.0, 35.8, 33.7, 22.6. MS (ESI): calcd. for $C_{26}H_{28}O_5SSi$ $[M+H]^+$ *m*/*z* 469.6, found 469.2.

**Synthesis of camptothecin (Cpt) containing silane** (Cpt-S-sil, **2**, Scheme 1)



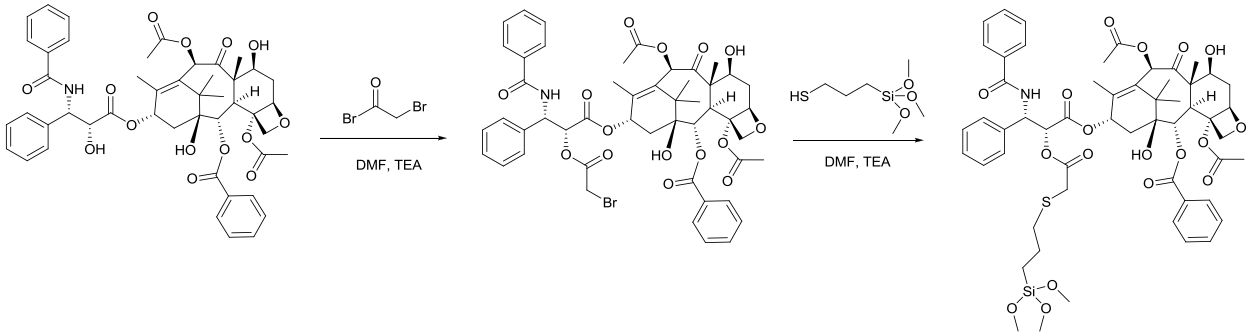

Cpt-OH Cpt-Br Cpt-S-sil

*Synthesis of Cpt-Br*: Cpt (10.4 mg, 0.030 mmol) was suspended in anhydrous dichloromethane (0.5 mL) followed by the addition of 4-dimethylaminopyridine (0.4 mg, 0.003 mmol), bromoacetic acid (30 mg, 0.18 mmol) and diisopropylcarbodiimide (26 μL, 0.18 mmol). The mixture was stirred at rt for 24 h. The reaction was monitored by HPLC. After the solvent was evaporated in vacuum, the crude product was purified by silica column ($CH_2Cl_2$/MeOH = 100/1). $^{1}$H NMR ($CDCl_3$, 500 MHz): δ 8.40 (s, H), 8.22 (d, H), 7.94 (d, H), 7.84 (t, H), 7.67 (t, H), 7.28 (s, H), 5.70 (d, H), 5.42 (d, H), 5.30 (s, 2H), 3.84 (m, 2H), 2.32 (q, H), 2.20 (q, H), 1.00 (t, 3H). $^{13}$C NMR ($CDCl_3$, 500 MHz): δ 167.1, 166.2, 157.5, 152.1, 149.2, 146.8, 145.1, 131.40, 130.9,

130.0, 128.7, 128.5, 128.4, 128.3, 120.6, 95.9, 88.6, 67.5, 50.2, 32.1, 25.2, 7.8. HPLC purity: >95%. MS (MALDI-TOF): calcd. for $C_{22}H_{18}BrN_2O_5$ $[M+H]^+$ *m*/*z* 470.3, found 470.1.

*Synthesis of Cpt-S-sil (**2**):* Cpt-Br (6.5 mg, 0.014 mmol) was dissolved in anhydrous DMF (0.5 mL). TEA (9 μL, 0.07 mmol) and (3-mercaptopropyl)trimethoxysilane (4 μL, 0.021 mmol) were added. The reaction mixture was stirred at rt for 3 h. After the solvent was evaporated in vacuum, the crude product was purified by preparative TLC ($CH_2Cl_2$/MeOH = 100/1). $^1$H NMR ($CDCl_3$, 500 MHz): δ 8.40 (s, H), 8.21 (d, H), 7.94 (d, H), 7.82 (t, H), 7.66 (t, H), 7.35(s, H), 5.68 (d, H), 5.40 (d, H), 5.29 (s, 2H), 3.47 (s, 9H), 3.84 (s, 2H), 2.65 (t, 2H), 2.28 (q, H), 2.17 (q, H), 1.68 (q, 2H), 0.99 (t, 3H), 0.75 (t, 2H). $^{13}$C NMR ($CDCl_3$, 500 MHz): δ 169.4, 167.5, 157.6, 152.6, 149.1, 146.57, 145.9, 131.4, 130.9, 130.0, 128.7, 128.4, 128.3, 120.4, 110.0, 96.2, 88.6, 67.3, 50.2, 46.3, 42.4, 35.5, 32.0, 23.7, 22.4, 7.9. HPLC purity: >95%. MS (ESI): calcd. for $C_{28}H_{33}N_2O_8SSi$ $[M+H]^+$ *m*/*z* 585.7, found 585.3.

**Synthesis of paclitaxel containing silane** (Ptxl-sil, **3**, Scheme 1)



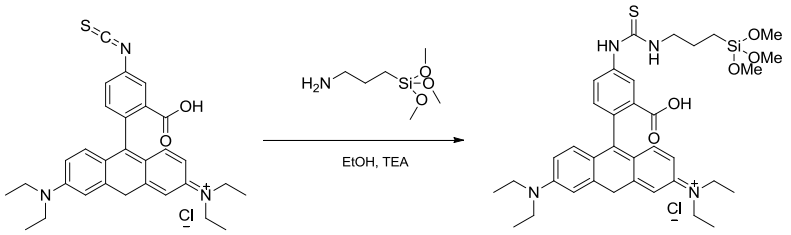

Ptxl Ptxl-Br Ptxl-sil

*Synthesis of Ptxl-Br:* Paclitaxel (Ptxl, 19.8 mg, 0.023 mmol) in anhydrous THF (1.0 mL) was treated with anhydrous TEA (16.1 μL, 5 eq.) and 2-bromoacetyl bromide (4.7 mg, 0.023 mmol)

in 0.1-mL dichloromethane at rt for 24 h. After the solvent was evaporated, the crude product was purified by preparative TLC (hexane/EtOAc = 1/2). HPLC purity: >95%. MS (MALDI-TOF): calcd. for $C_{49}H_{52}BrNO_{15}Na$ $[M+Na]^+$ *m*/*z*, 997.8, found 998.8.

*Synthesis of Ptxl-sil (**3**)*: Ptxl-Br (18.2 mg, 0.019 mmol) in anhydrous DMF (1 mL) was treated with TEA (anhydrous, 12 μL, 0.095 mmol, 5 eq.) and 3-mercaptopropyl)trimethoxysilane (10 μL, 0.057 mmol, 3 eq.) at rt for 12 h. After the solvent was evaporated, the crude product was purified by preparative TLC (hexane/EtOAc = 1:2) to give **3** in 62% yield. HPLC purity: >95%. MS (ESI): calcd. for $C_{55}H_{67}NO_{18}SSiNa$ $[M+Na]^+$ *m*/*z* 1113.3, found 1113.1.

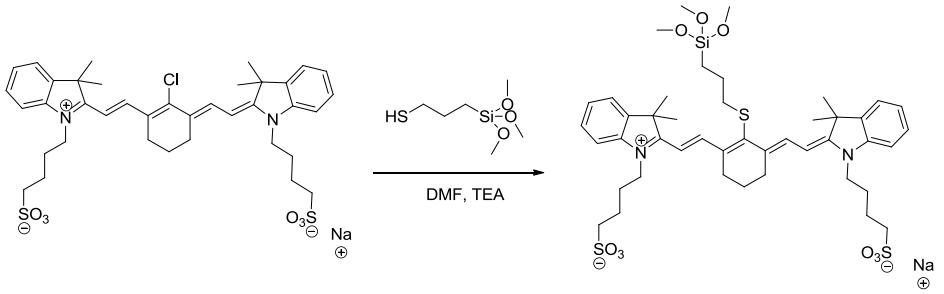
**Synthesis of rhodamine B isothiocyanate (RITC) containing silane** (RTIC-sil, **4**, Scheme 1)




RITC RITC-sil

In a reaction vial containing 3-aminopropyltrimethoxysilane (30 mg, 0.173 mmol) was added an anhydrous ethanol solution (1 mL) of RITC (17 mg, 0.032 mmol) and triethylamine (14.5 mg, 0.144 mmol). The reaction mixture was stirred for 12 h in nitrogen at 50 °C in dark. The solvent and unreacted triethylamine was removed by vacuum to give RITC-sil (**4**), which was used directly without further purification.

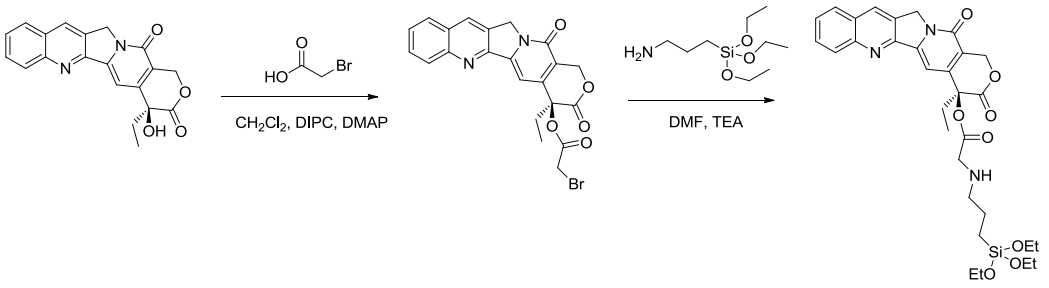
**Synthesis of infrared dye (IR783) containing silane group** (IR783-sil, **5**, Scheme 1)




IR783 IR783-sil

IR783 (23.5 mg, 0.031 mmol) in anhydrous DMF (1.0 mL) was treated with TEA (22 μL, 0.155 mmol, 5 eq.) and (3-mercaptopropyl)trimethoxysilane (30 μL, 0.155 mmol, 5 eq.) at 55°C for 12 h. After the solvent was evaporated, IR783-sil (**5**, 80% yield) was used directly for the fluorescent labeling of silica nanoconjugates. HPLC purity: >80%. MS (ESI): calcd. for $C_{44}H_{62}N_2O_9S_3Si$ $[M+H]^+$ *m/z* 885.0, found 886.0.

**Synthesis of Cpt-NH-sil** (**7**, Scheme 1)

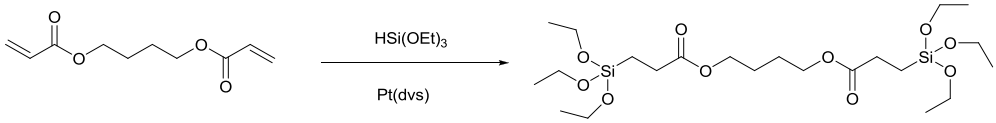



Cpt-OH Cpt-Br Cpt-NH-sil

Cpt-Br (6.5 mg, 0.014 mmol) (from the synthesis of Cpt-S-sil) was dissolved in anhydrous DMF (0.5 mL). TEA (9 μL, 0.07 mmol) and (3-aminopropyl)trimethoxysilane (4 μL, 0.021 mmol) were added. The reaction mixture was stirred at rt for 3 h. After the solvent was evaporated in vacuum, the crude product was purified by preparative TLC ($CH_2Cl_2$/MeOH = 100/1) to give **7** in 70% yield. $^1$H NMR ($CDCl_3$, 500 MHz): δ 8.40 (s, H), 8.20 (d, H), 7.94 (d, H), 7.82 (t, H), 7.65 (t, H), 7.20 (s, H), 5.66 (d, H), 5.40 (d, H), 5.28 (s, 2H), 3.73 (q, 6H), 3.58 (s, 2H), 2.66 (t,

2H), 2.28 (q, H), 2.16 (q, H), 1.63 (m, 2H), 1.20 (t, 9H), 0.96 (t, 3H), 0.63 (t, 2H). $^{13}$C NMR ($CDCl_3$, 500 MHz): δ 172.1, 167.6, 157.4, 152.5, 149.1, 146.6, 145.9, 131.4, 130.9, 129.9, 128.7, 128.4, 128.3, 120.5, 96.2, 76.4, 67.4, 58.9, 52.4, 50.4, 48.0, 31.7, 23.2, 18.5, 7.8. MS (ESI): calcd. for $C_{31}H_{40}N_3O_8Si$ $[M+H]^+$ *m/z* 610.8, found 610.3.

**Synthesis of ester bond bridged silane** (EBB-sil, **8**, Scheme 1)[57,58]




EBB-sil

To a solution of 1,4-butanediol diacrylate (1 g, 5.05 mmol) in anhydrous benzene (10 mL) was added triethoxysilane (2.4 ml, 13.2 mmol) followed by the addition of platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex solution (150 μL, in xylene, Pt ~2 %) under the protection of $N_2$. The resulting mixture was stirred at 50°C for 12h. After the reaction mixture was cooled to rt, benzene (10 mL) was added. The solution was then passed through silica gel packed filter. The solvent and low boiling point contaminates of the filtrate was removed under vacuum. The residue was dried to give the product **8** (2.4 g, 90%). $^1$H NMR ($CDCl_3$, 500 MHz): δ 4.08 (t, 4H, $OCH_2$), 3.86 (q, 12H, $SiOCH_2$), 2.31 (q, 4H, $CH_2C(O)$), 1.69 (m, 4H, $CH_2$), 1.22 (t, 18H, $CH_3$), 1.12 (t, 4H, $SiCH_2$). $^{13}$C NMR ($CDCl_3$, 500 MHz): δ 174.7, 64.3, 59.4, 27.8, 25.6, 18.2, 9.3. MS (ESI): calcd. for $C_{22}H_{46}O_{10}Si_2K$ $[M+K]^+$ *m/z* 565.9, found 566.0.

**Synthesis of acetal bond bridged silane** (ABB-sil, **9**, Scheme 1)[57,58]

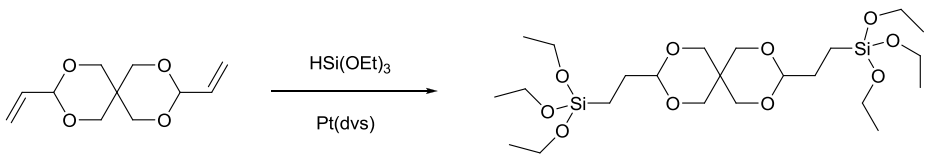
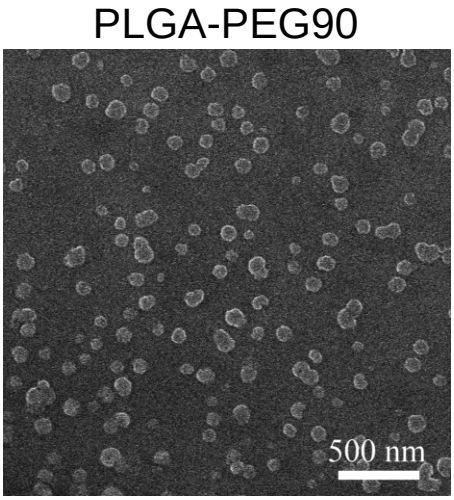


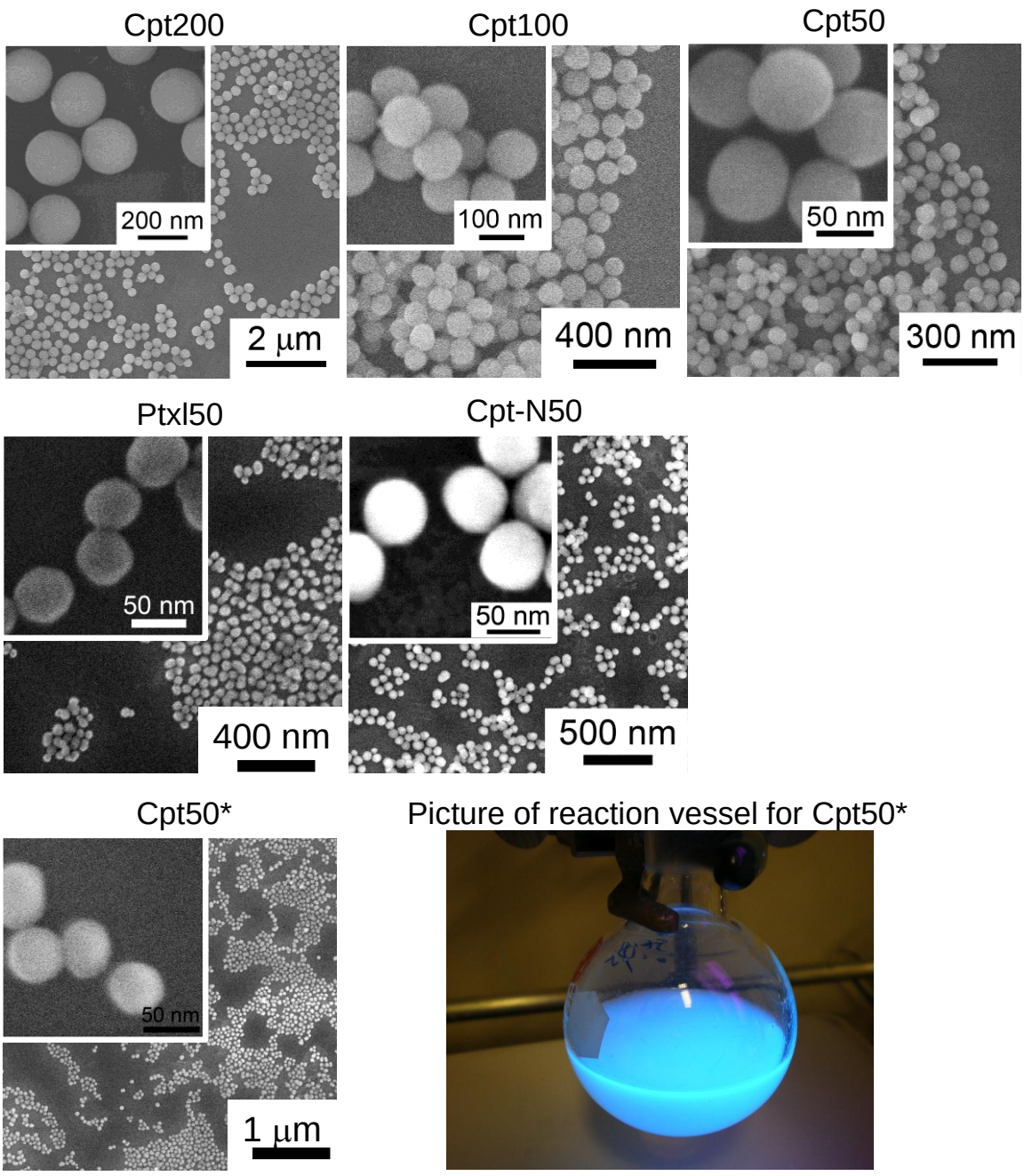

ABB-sil

To a solution of 3,9-divinyl-2,4,8,10-tetraoxaspiro[5.5] undecane (1 g, 4.7 mmol) in anhydrous benzene (10 mL), triethoxysilane (2.1 ml, 11.6 mmol) was added followed by the addition of platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex solution (150 μL, in xylene, Pt ~2 %) under $N_2$. The resulting mixture was stirred at 50°C for 12 h. After the reaction mixture was cooled to rt, benzene was added. The solution was then passed through a silica gel packed filter. The solvent and low boiling point contaminates of the filtrate was removed under vacuum. The residue was dried to give the product **9** (2.4 g, 93%). $^1$H NMR ($CDCl_3$, 500 MHz): δ 4.38 (t, 2H, OCH), 3.82 (q, 12H, $SiOCH_2$), 3.53 (q, 4H, $CH_2O$), 3.32 (d, 4H, $CH_2O$), 1.69 (m, 4H, $CH_2$), 1.20 (t, 18H, $CH_3$), 0.70 (t, 4H, $SiCH_2$). $^{13}$C NMR ($CDCl_3$, 500 MHz): δ 103.9, 70.8, 58.7, 32.6, 28.3, 18.5, 4.2. MS (ESI): calcd. for $C_{23}H_{49}O_{10}Si_2$ $[M+H]^+$ *m/z* 540.8, found 541.0.

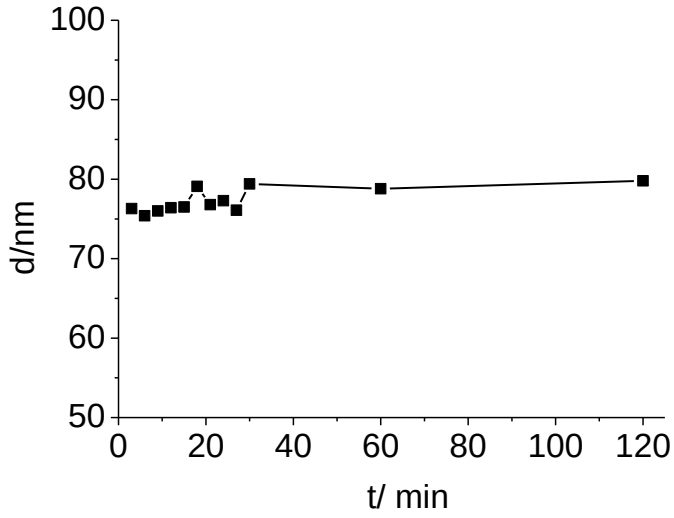
# Supplementary Figures and Tables



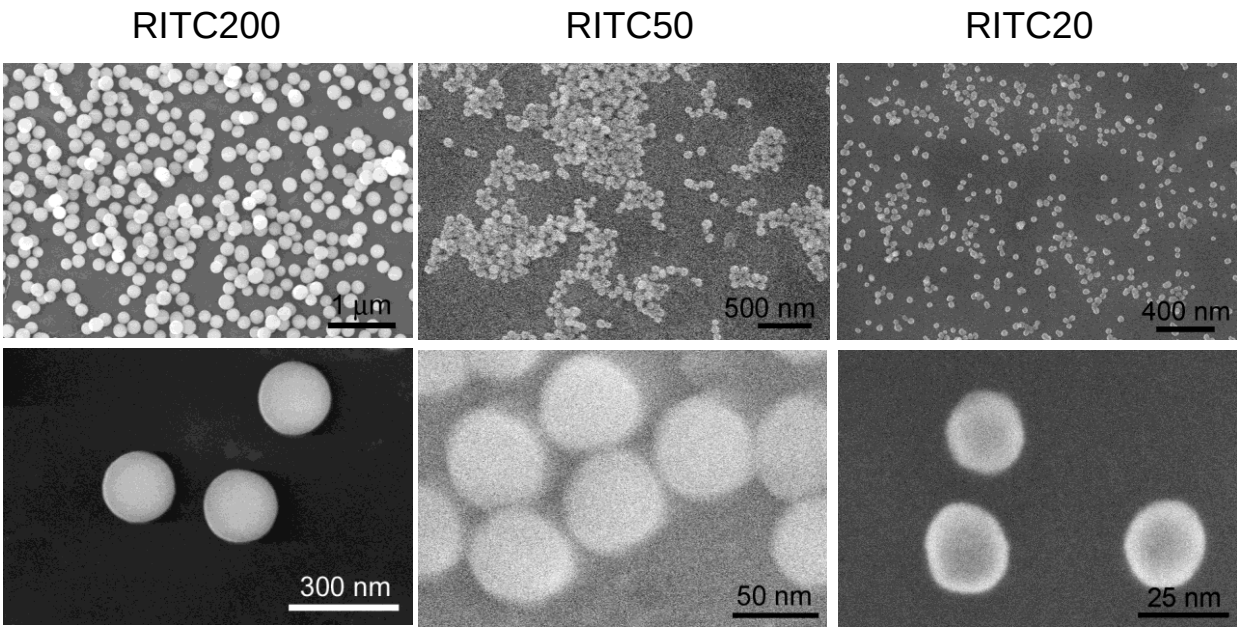

**Supplementary Figure S1.** SEM images of PLGA-PEG90 NP (entry 8, Table 1).



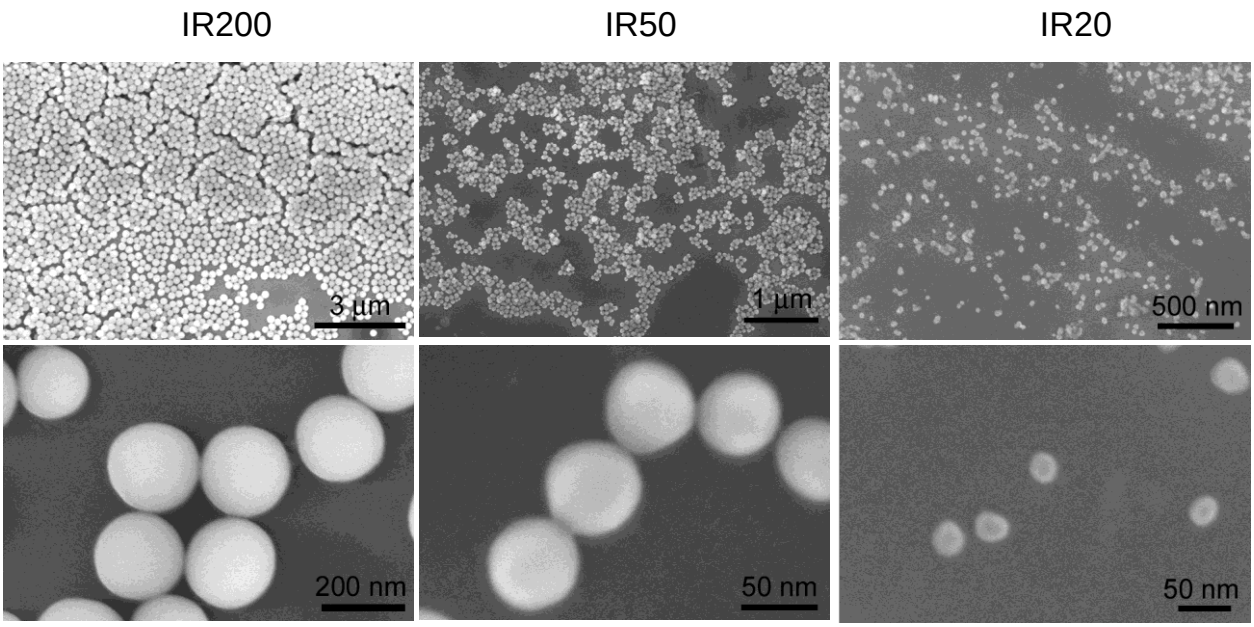

**Supplementary Figure S2.** SEM images of drug-NCs of various sizes and different drugs (entries 10-13, 21-22, Table 1). *The SEM image and the reaction vessel of Cpt50 prepared in gram-scale (entry 22, Table 1).



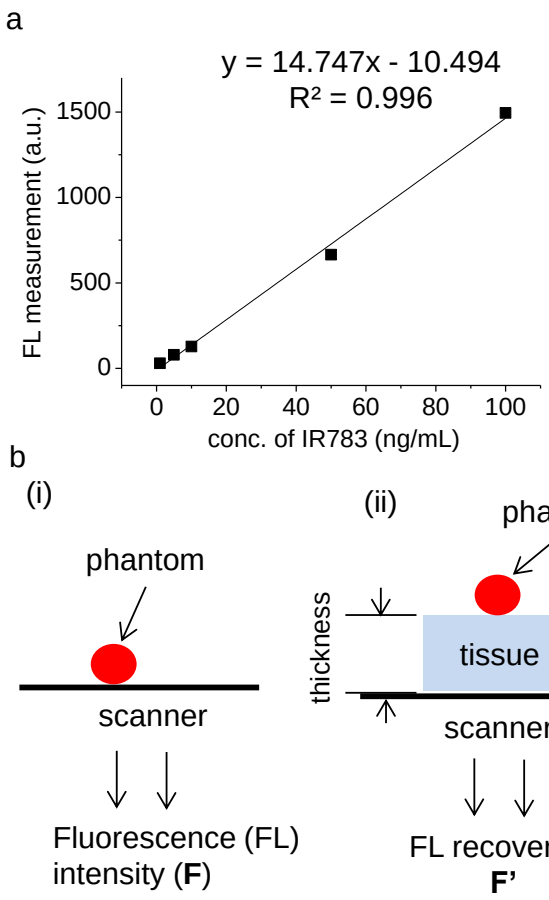

**Supplementary Figure S3.** Stability of PEGylated Pyr-NCs in cell medium containing 10% fetal bovine serum (FBS).




**Supplementary Figure S4.** SEM images of RITC-NCs of different sizes (entries 14-16, Table 1).




**Supplementary Figure S5.** SEM images of IR-NCs of different sizes (entries 17-19, Table 1).




(iii)

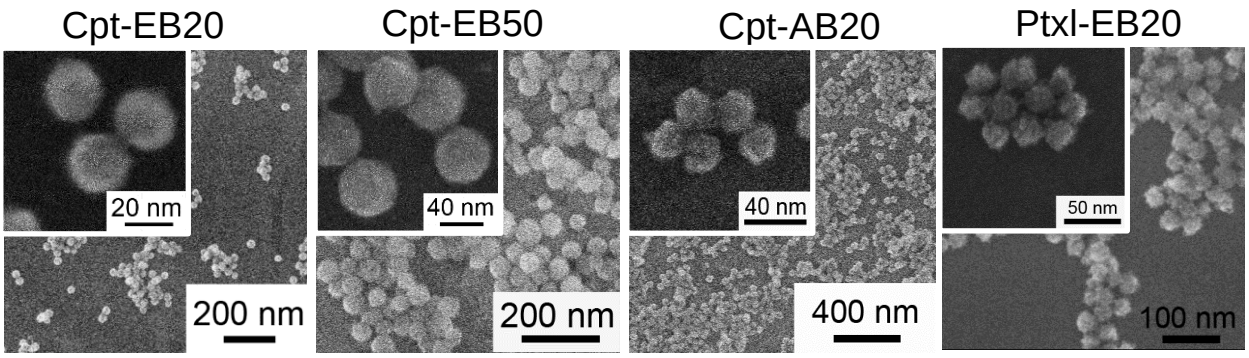
| Tissue | Thickness (mm) | **F'/F** (x 100)% |
|---|---|---|
| spleen | 1.5 | 96.3 |
| kidney | 2.5 | 100.0 |
| lung | 2 | 100.0 |
| heart | 3 | 64.4 |
| liver | 2 | 100.0 |
| | 4 | 80.0 |
| | 6 | 23.6 |
| tumor | 2 | 100.7 |
| | 4 | 75.0 |
| | 6 | 11.2 |

**Supplementary Figure S6.** **a**, Calibration curve of the fluorescence (FL) intensity determined by the Odyssey infrared mouse imaging system at 800 nm versus the concentration of IR783 placed in a phantom. **b**, **c,** Determination of the maximum thickness of tissues for complete FL recovery on the Odyssey imaging system at the 800-nm channel. (i) FL determined by placing a phantom containing known concentration of IR783 on top of the Odyssey imaging scanner (**F**), (ii) Recovered FL activity by placing the phantom used in (i) on top of the tissue (iii) with variable thickness (**F'**), (iii) Tissue thickness and correlation with the FL recovery.

**Discussion:**

IR783 (IR), a near inferred dye with excitation wavelength of 779-785 nm, was used in the biodistribution study in order to minimize the autofluorescence (from the tissues) for the accurate quantification IR-NCs. For each organ, the background fluorescence (FL) of a control tissue was subtracted from the FL of the tissue from the treated mice. As the thickness of the tissues has

significant effect on the accuracy of the FL measurement, we designed an experiment to determine the maximum thickness of the tissues that allows 100% recovery of the FL activity. We first measured the FL activity of the IR783 placed in a phantom and the FL intensity was denoted as **F**. Next, we placed a tissue with different thickness (as shown in (ii)) on the scanner and then put the same IR783-containing phantom on top of the tissue. The measured FL intensity was denoted at **F'**. The ratio of **F'**/**F** (see iii) is the FL recovery efficiency (i.e., FL penetration efficiency). As shown in (iii), only 10-25% of FL was recovered for FL allowed to penetrate a 6-mm thick tissue. However, when the tissue thickness is 2 mm or less, the FL recovery efficiency is essentially quantitative (iii). We thus measured the FL intensity of all tissues at thickness of 2 mm in Figure 3a-b.




**Supplementary Figure S7.** SEM images of Cpt/Ptxl-NCs with pH-sensitive, fast degradable domain (**8** or **9**) incorporated (entries 23-26, Table 1).

**Supplementary Table S1.** Reaction Conditions of Size-Controlled Pyr-NCs via Stöber Method.

| Method | MeOH (mL) | DI water (μL) | $NH_4OH$ (μL) | TEOS (μL) |
|---|---|---|---|---|
| St-A | 1.0 | 360 | 70 | 31.2 |
| St-B | 1.0 | 360 | 70 | 62.5 |
| St-C | 1.0 | 360 | 80 | 62.5 |
| St-D | 1.0 | 360 | 90 | 62.5 |
| St-E | 1.0 | 360 | 100 | 62.5 |
| St-F | 1.0 | 360 | 110 | 62.5 |
| St-G | 1.0 | 270 | 240 | 62.5 |
| St-H | 15.0 | 5400 | 1200 | 939 |

**Supplementary Table S2.** Reaction Conditions of Size-Controlled Silica NCs with Degradable Linkers via Reverse Microemulsion Method

| Method | Solvent | Triton X100 (mg) | TEOS (μL) | EBBsil (μL) | ABBsil (μL) | degrad. domain (wt%) |
|---|---|---|---|---|---|---|
| Trx-A | cyclohexane | 1.77 | 0 | 80 | 0 | 100% |
| Trx-B | decane | 1.77 | 0 | 80 | 0 | 100% |
| Trx-C | cyclohexane | 1.77 | 40 | 0 | 40 | 60.6% |

**Supplementary Table S3** Nanoparticle sizes determined by scanning electron microscopy (SEM) and dynamic light scattering (DLS).

| Name of NC | SEM [a] | DLS [b] | |
|---|---|---|---|
| | D ± SD [c] (nm) | D ± SD (nm) | PDI ± SD |
| Pyr20 | 26.6 ± 2.7 | 43.8 ± 0.3 | 0.126 ± 0.030 |
| Pyr50 | 43.4 ± 3.9 | 65.2 ± 0.4 | 0.110 ± 0.012 |
| Pyr65 | 64.1 ± 3.1 | 88.5 ± 1.1 | 0.045 ± 0.022 |
| Pyr80 | 84.4 ± 7.6 | 100.7 ± 0.8 | 0.028 ± 0.013 |
| Pyr100 | 104.4 ± 8.8 | 129.3 ± 1.5 | 0.033 ± 0.018 |
| Pyr200 | 195.3 ± 12.8 | 226.8 ± 5.0 | 0.055 ± 0.017 |

[a] The hard core sizes were measured by SEM. [b] The hydrodynamic sizes and polydispersity (PDI) were measured by dynamic light scattering (DLS). [c] D: diameter; SD: standard deviation.

**Supplementary Table S4** Cytotoxicity of Cpt NCs of different sizes.[a]

| Agent | $IC_{50}$ ( nM) |
|---|---|
| CPT | 1.5 |
| Cpt-N20 | 9.0 |
| Cpt-N50 | 17.0 |
| Cpt-N200 | 22.0 |
| Si-NP 50 nm | $>10^6$ |

[a] $IC_{50}$'s of Cpt-N20, Cpt-N50 and Cpt-N200 determined in HeLa cells by MTT assay. Cells were cultured with the agent for 72 h.