

Surface-displayed cholesterol enhances penetration and anti-tumor activity of a platinum nanodrug by targeting NPC1L1-expressing cancer associated fibroblasts

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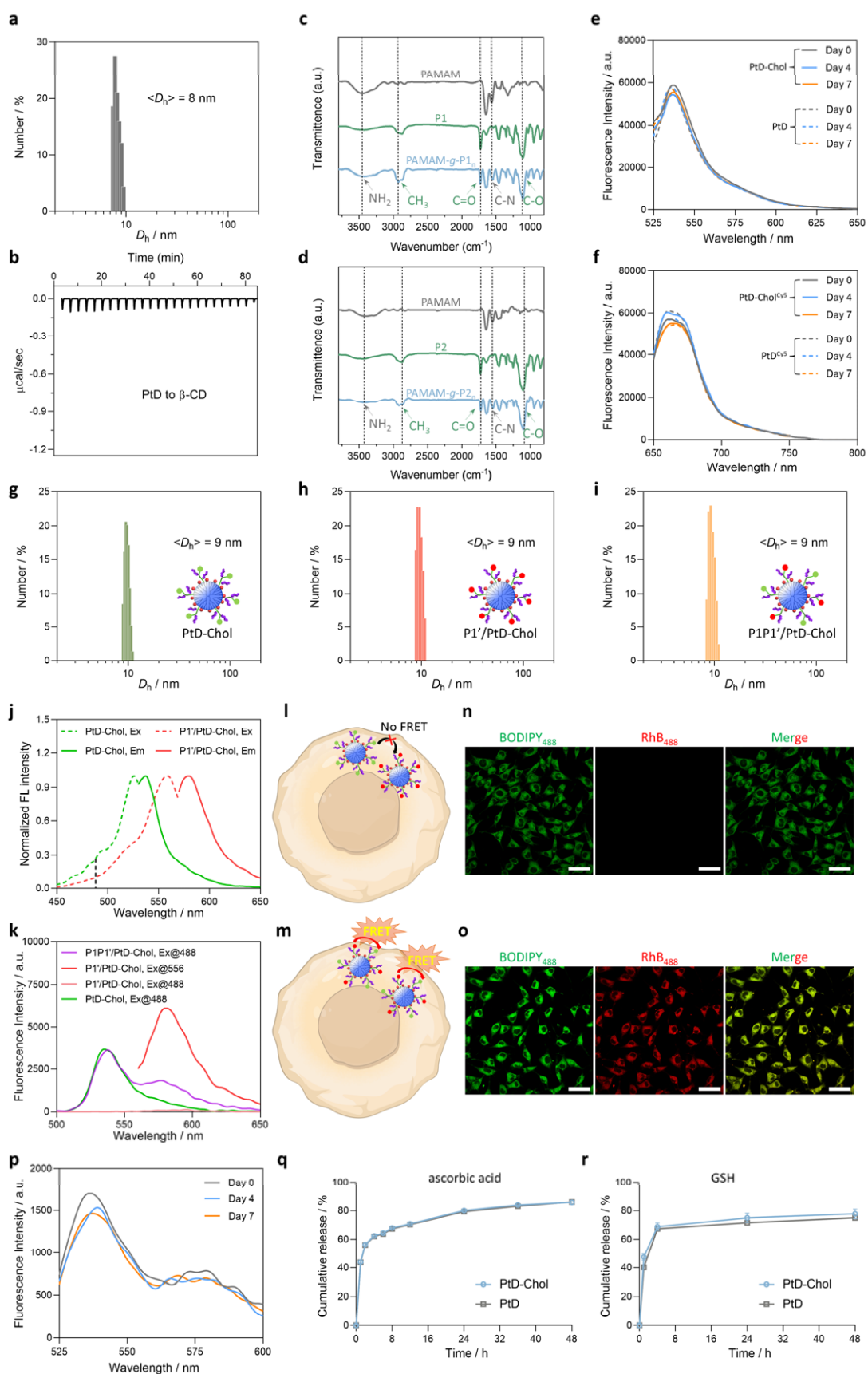
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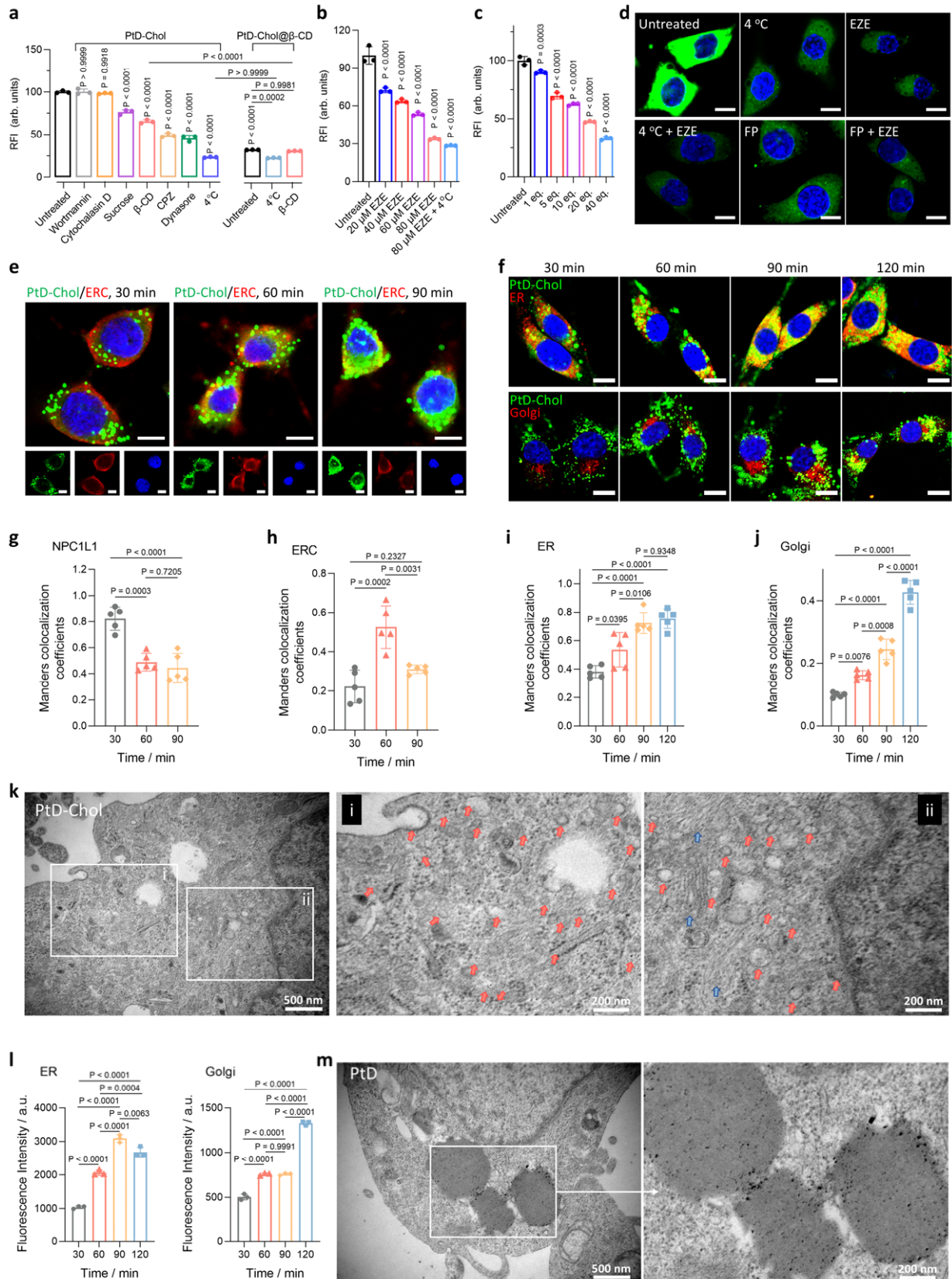
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Supplementary Figures

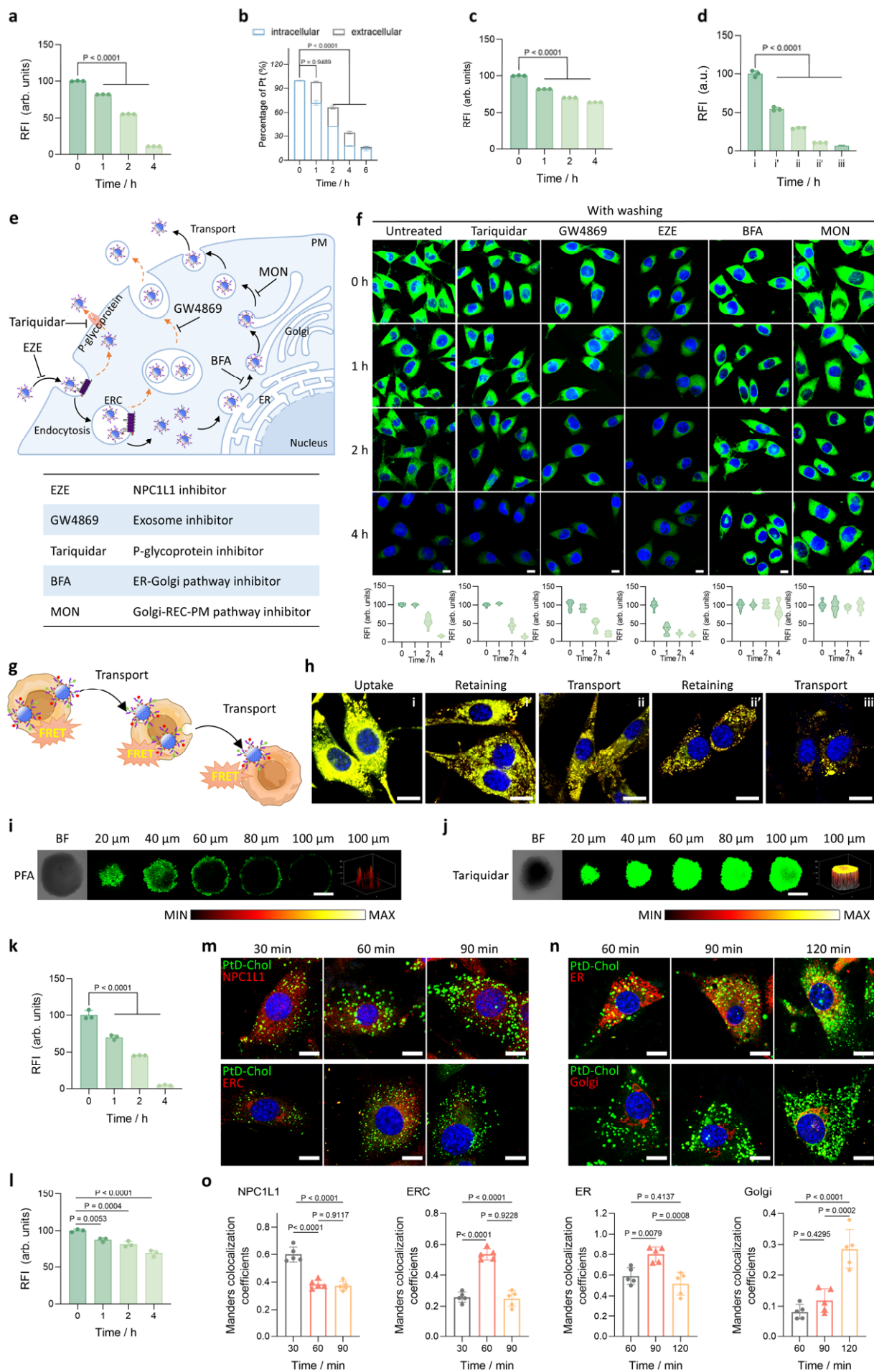


Supplementary Figure 1 | Characterization of the dendritic nanodrugs. **a**, Hydrodynamic size distribution of PtD. **b**, Representative ITC data for the binding of β -CD to PtD. **c**, FT-IR spectra of PAMAM, P1 (P(Chol-co-OEG-co-BODIPY)), and PAMAM-g-P1₁₀. **d**, FTIR spectra of PAMAM, P2 (P(OEG-co-BODIPY)), and PAMAM-g-P2₈. **e**, Fluorescent spectra of BODIPY labelled PtD-Chol and PtD, respectively. Excitation: 520 nm. **f**, Fluorescent spectra of Cy5 covalently labelled PtD-Chol and PtD, termed as PtD-Chol^{Cy5} and PtD^{Cy5}, respectively. Excitation: 640 nm. **g-i**, Hydrodynamic size distribution of PtD-Chol (**g**), P1'/PtD-Chol (**h**), and P1P1'/PtD-Chol (**i**). **j**, Fluorescence excitation spectrum and emission spectrum of PtD-Chol (Excitation: 525 nm, Emission: 536 nm) and P1'/PtD-Chol (Excitation: 556 nm, Emission: 560 nm). **k**, Fluorescent spectra of PtD-Chol (Excitation: 488 nm), P1'/PtD-Chol (Excitation: 488 or 556 nm), and P1P1'/PtD-Chol (Excitation: 488 nm). The results demonstrate that P1P1'/PtD-Chol was able to induce FRET. **l, m**, Schematic illustration for the FRET study of the PtD-Chol in tumor cells. PtD-Chol and P1'/PtD-Chol (labelled separately with BODIPY and RhB) were unable to elicit intracellular FRET (**l**). P1P1'/PtD-Chol, co-labelled with BODIPY and RhB, was capable of inducing intracellular FRET (**m**). **n, o**, CLSM images of 4T1 cells after incubation with P1/PtD-Chol + P1'/PtD-Chol (**n**) or P1P1'/PtD-Chol (**o**) for 1 h. Scale bars, 50 μ m. BODIPY was observed with a 488 nm laser and the emission was read from 500 to 550 nm, RhB was observed with a 488 nm laser, and the emission was read from 570 to 616 nm. **p**, Fluorescent spectra of P1P1'/PtD-Chol exhibited FRET, respectively. Excitation: 520 nm. **q, r**, Platinum drug release from PtD-Chol and PtD under ascorbic acid solution (5 mM, pH 7.4) or GSH solution (10 mM, pH 7.4) to mimic an intracellular redox environment. Platinum release was determined by ICP-MS. The nanodrugs were stored in PBS at 37 °C and detected on Day 0, Day 4, and Day 7 (**e-f, p**). In **a-k, p-r**, experiments were repeated three times independently; In **n-o**, n = 3 biologically independent samples; representative images are shown. In **a-k** and **p-r**, source data are provided as a Source Data file; **l** and **m** were created by Figdraw.com.

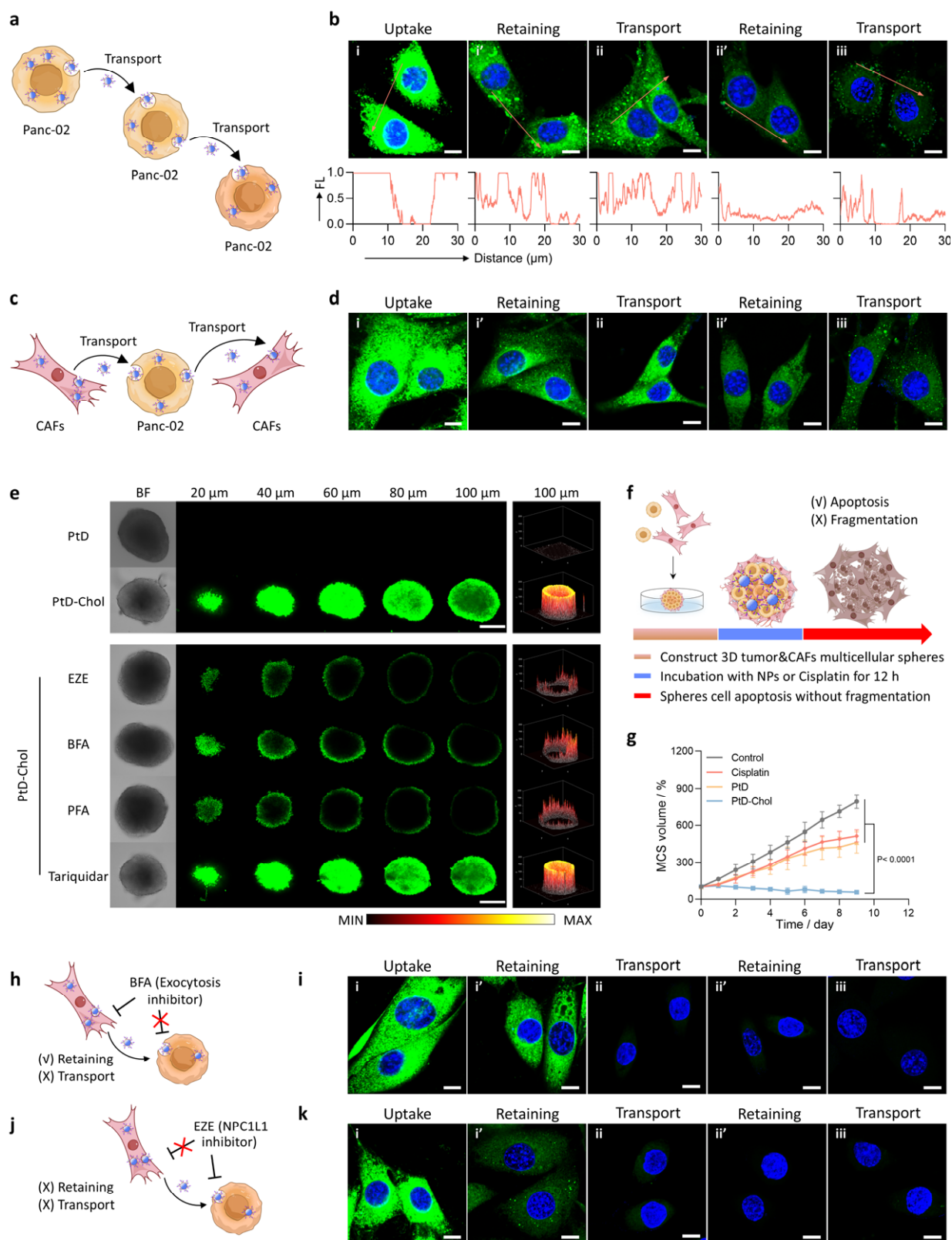


Supplementary Figure 2 | Uptake pathways and intracellular distribution of PtD-Chol. **a**, Effects of inhibitors on the cellular uptake of PtD-Chol into 4T1 cells measured by FC. **b**, Effects of EZE or 4 °C on the cellular uptake of PtD-Chol into 4T1 cells measured by FC. **c**, Effects of FP on the cellular uptake of PtD-Chol into 4T1 cells measured by FC. (FP, a hydrophilic polymer copolymerized from OEG-MA,

and Chol-MA). **d**, CLSM images of PtD-Chol in 4T1 cells pretreated with different inhibitors. **e**, CLSM images for observing the colocalization of PtD-Chol (green) with ERC (red) in 4T1 cells upon incubation for varying times. **f**, CLSM images for observing the colocalization of ER (PDI) or Golgi (GM130) with PtD-Chol in 4T1 cells upon incubation for varying times. (green: PtD-Chol; red: Golgi or ER) **g-j**, Manders correlation coefficients of PtD-Chol and NPC1L1 (**g**), ERC (**h**), ER (**i**), or Golgi (**j**) by pixel intensity using Image J software. **k**, TEM images show the microdistribution of PtD-Chol within tumor cells (4T1). The box shows the magnified area (i, ii) of the PtD-Chol distribution in the ER–Golgi apparatus. Arrows indicate PtD-Chol localization (blue: ER; red: Golgi). Scale bars, 500 nm or 200 nm. **l**, Fluorescence intensities of the ER and Golgi in 4T1 cells were measured after incubation with PtD-Chol for 30-120 minutes. **m**, TEM images show the microdistribution of PtD within tumor cells (4T1). Scale bars, 10 μ m (**d-f**), 500 nm (**k,m**) or 200 nm (**k,m**). In **a-d**, the concentration of PtD-Chol was 20 μ g/mL. In **e-m**, the concentration of PtD-Chol was 40 μ g/mL. In **a-d**, **k-m**, $n = 3$ biologically independent samples; representative images are shown in (**d**, **k**, **m**). In **e-j**, $n = 5$ biologically independent samples; representative images are shown in (**e-f**). In **a-c**, **g-j**, **l**, data are shown as the mean $\pm$ s.d.; source data are provided as a Source Data file; the statistical significance was calculated via one-way ANOVA with Tukey's multiple comparisons test (**a**, **g-j**, **l**) and one-way ANOVA with Dunnett's multiple-comparisons test (**b-c**), p-values are shown on the graphs, and p-values < 0.0001 are reported as such.

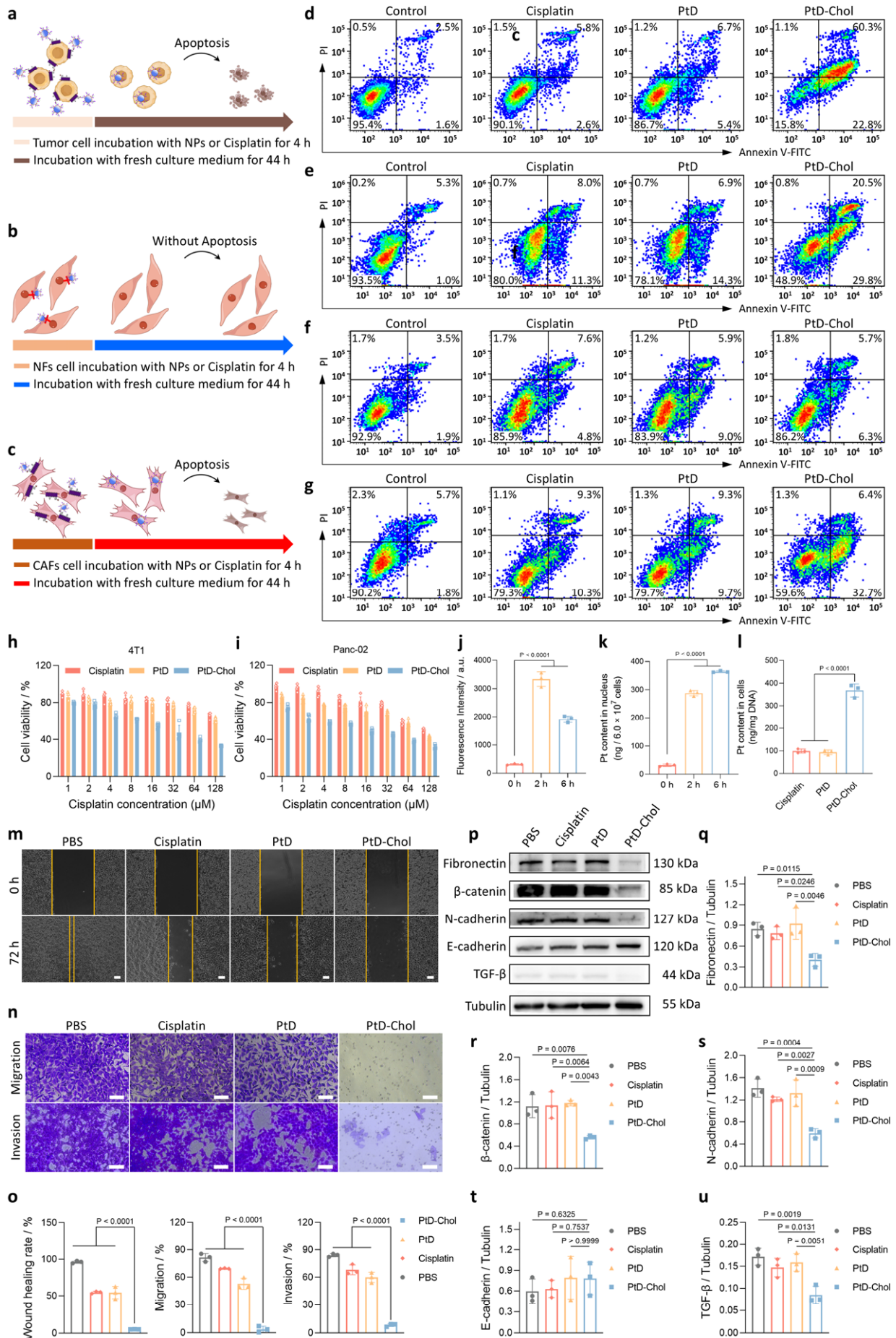


Supplementary Figure 3 | Cross-multicellular transport of PtD-Chol mediated by NPC1L1-ER-Golgi pathway. **a-b**, RFI (**a**), and intracellular/extracellular Pt content (**b**) for PtD-Chol exocytosis (experimental protocols as Figure 3a). **c-d**, RFI for PtD-Chol CMCT (experimental protocols as Figure 3d, **c**; Figure 3g, **d**). **e**, Schematic illustration of the potential transport pathways of PtD-Chol in tumor cells, examined using various inhibitors. Black solid lines, significantly affected processes; yellow dotted lines, no significant effect. EZE: ezetimibe; BFA: brefeldin A; MON: monensin; ER: endoplasmic reticulum; ERC: endocytic recycling compartment; REC: recycling endosome compartment; PM: plasma membrane. **f**, Effect of different inhibitors on PtD-Chol exocytosis in tumor cells (4T1). Representative CLSM images and whole-cell fluorescence quantification ($n = 30$ cells) after treatment with various inhibitors, with the medium replaced hourly over 0–4 h (with washing). **g, h**, Scheme (**g**) and representative CLSM images (**h**) of CMCT and FRET occurrence of P1P1'/PtD-Chol in 4T1 cells. **i, j**, Effect of 4 % Polyethylene glycol (PFA) (**i**) and Tariquidar (10 nM) (**j**) on the penetration of PtD-Chol in 4T1 tumor spheroids. **k**, RFI for PtD-Chol exocytosis in CAF (experimental protocols as Figure 3a). **l**, RFI for PtD-Chol CMCT in CAF (experimental protocols as Figure 3d). **m-o**, CLSM images (**m-n**) and Manders correlation coefficients (**o**) of PtD-Chol and NPC1L1, ERC, ER, or Golgi in CAFs. Scale bars, 10 μm (**f, h, m-n**), 200 μm (**i-j**). In **a-h, k-o**, the concentration of PtD-Chol or P1P1'/PtD-Chol was 40 $\mu\text{g/mL}$. In **i-j**, the concentration of PtD-Chol was 20 $\mu\text{g/mL}$. In **a-l**, $n = 3$ biologically independent samples; representative images are shown in **f and h-j**. In **m-o**, $n = 5$ biologically independent samples; representative images are shown in **m-n**. In **a-d, k-l, and o**, data are shown as the mean $\pm$ s.d.; the statistical significance was calculated via one-way ANOVA with Dunnett's multiple-comparisons test (**a-d, k-l**) and one-way ANOVA with Tukey's multiple-comparisons test (**o**). p-values are shown on the graphs, and p-values < 0.0001 are reported as such. In **a-d, f, k-l, and o**, source data are provided as a Source Data file. **e** and **g** were created by Figdraw.com.

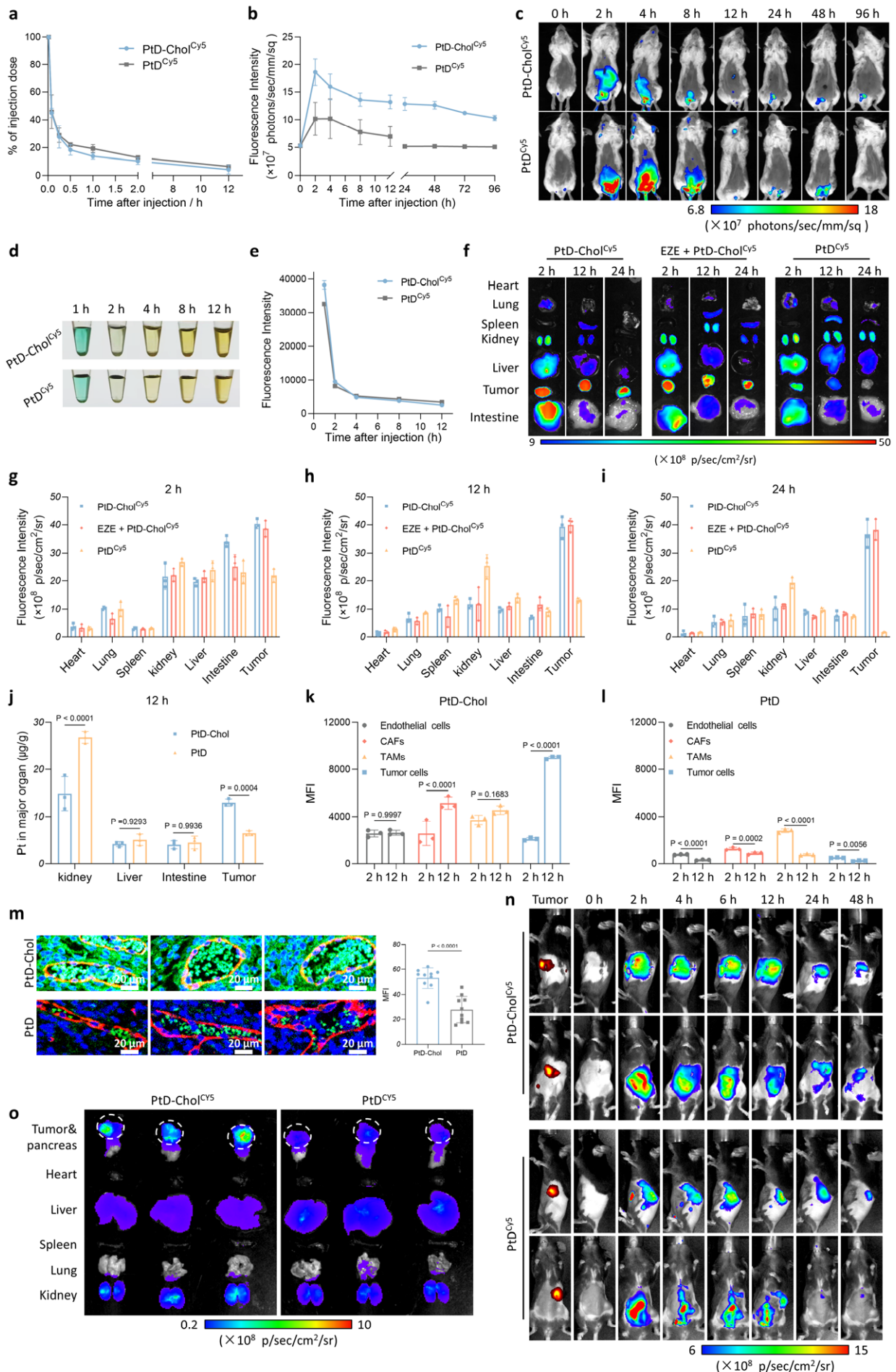


Supplementary Figure 4 | NPC1L1-mediated cross-multicellular transport enhances the inhibitory efficacy of PtD-Chol in hetero-spheroids composed of PDAC tumor cells and CAFs. **a**, **b**, Scheme of CMCT of PtD-Chol between PDAC tumor cells (Panc-02) (**a**), and representative CLSM images and variation of green fluorescence intensities across the representative region marked by red arrows (**b**). **c**, **d**, Scheme of CMCT of PtD-Chol between Panc-02 and CAFs (NIH-3T3^{TGF-β1}) (**c**), and representative CLSM images (**d**). **e**, In vitro

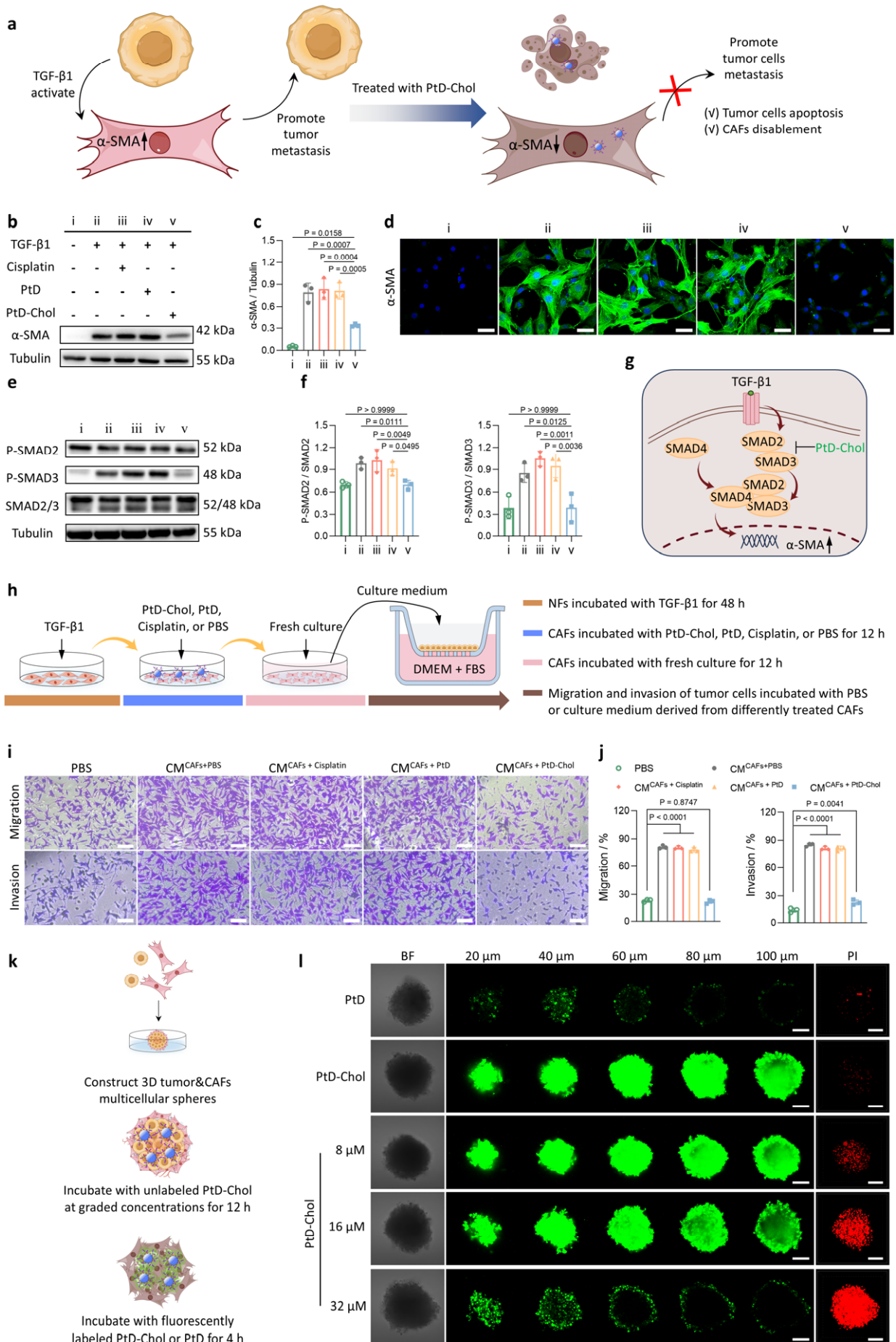
penetration of PtD-Chol and PtD in the hetero-spheroids composed of Panc-02 and CAFs (NIH-3T3) at a ratio of 1:5. To study the mechanism of CMCT, hetero-spheroids were pretreated with EZE, BFA, PFA (4% paraformaldehyde fix solution), or Tariquidar, respectively. Subsequently, the hetero-spheroids were cultured with PtD-Chol for 4 h. Green, (PtD-Chol or PtD). The concentration of nanoparticles was 20 µg/mL. **f, g**, Experimental protocols of tumor growth inhibition assay in Panc-02 hetero-spheroids (**f**). Panc-02 cells and NIH-3T3 cells, at a ratio of 1:5 to construct 3D hetero-spheroids. After incubation with PtD-Chol, PtD, or Cisplatin (16 µM), respectively, along with a control group treated with PBS, for 12 hours, the volume changes (MCS volume) of the cell spheres were measured (**g**). **h, i**, The blocking effect of BFA (20 µM) on the intercellular CMCT between CAFs and 4T1 cells was observed by CLSM. **j, k**, The blocking effect of EZE (80 µM) on the intercellular CMCT between CAFs and 4T1 cells was observed by CLSM. Scale bars, 10 µm (**b, d, i, k**), 200 µm (**e**). In **b, d, i, and, k**, the concentration of PtD-Chol was 40 µg/mL. In **e**, the concentration of PtD-Chol or PtD was 20 µg/mL. In **b-e and h-k**, n = 3 biologically independent samples; representative images are shown in (**b, d-e, i, k**). In **g**, n = 8 biologically independent samples; data are shown as the mean ± s.d.; the statistical significance was calculated via two-way ANOVA with Dunnett's multiple-comparisons test, p-values are shown on the graphs, and p-values < 0.0001 are reported as such. In **b, g**, source data are provided as a Source Data file. **a, c, f, and h-j** were created by Figdraw.com.



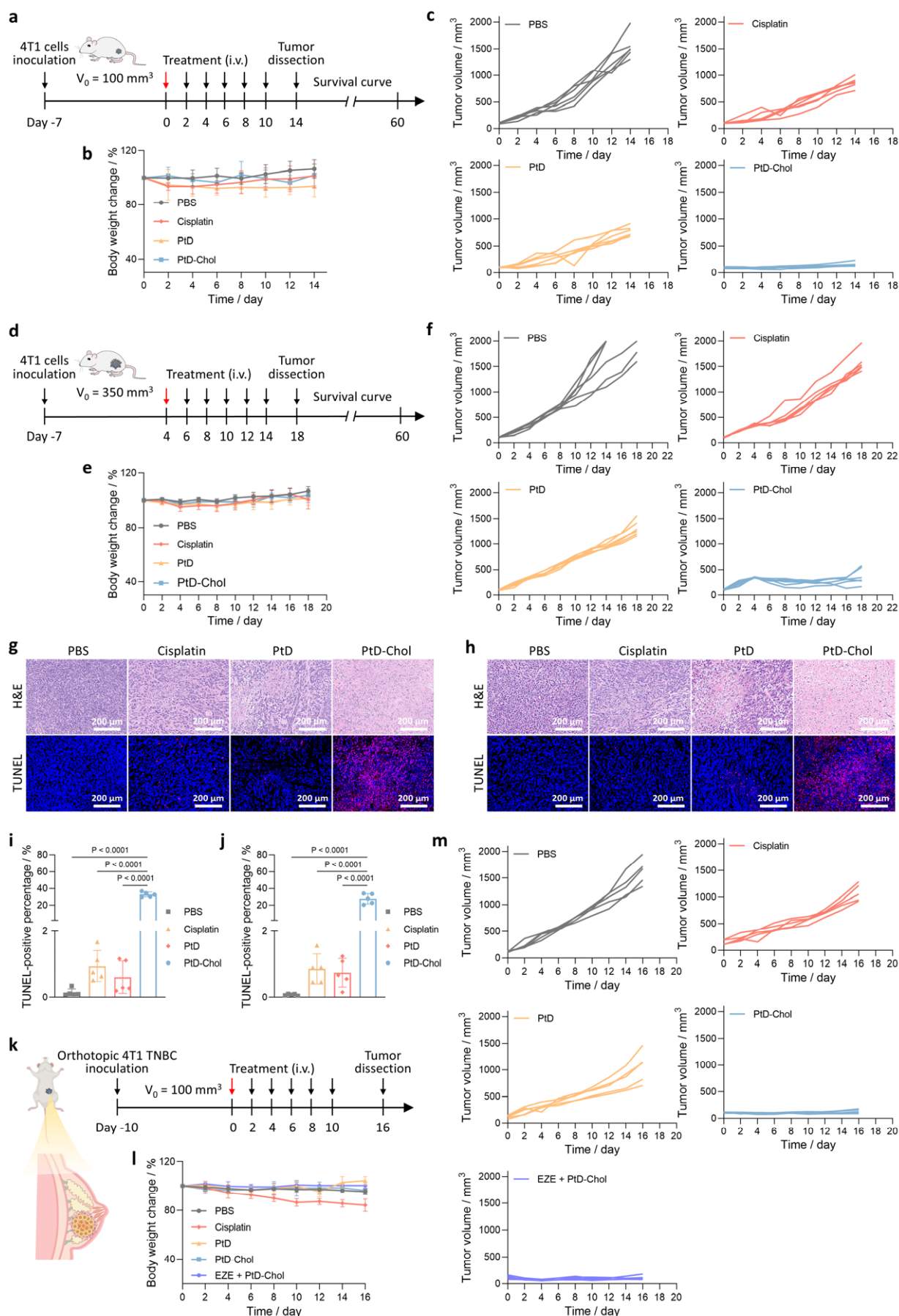
Supplementary Figure 5 | PtD-Chol inhibits tumor growth and metastasis in vitro. **a-c**, Experimental protocols of cell cytotoxicity study on tumor cells (**a**), NFs (**b**), and CAFs (**c**), respectively. After being treated with Cisplatin, PtD, or PtD-Chol for 4 hours, the cells were then incubated in fresh complete culture medium for an additional 44 hours. **d-g**, Cell apoptosis of 4T1 (**d**), Panc-02 (**e**), NIH-3T3 (**f**), and NIH-3T3^{TGF-β1} (**g**) analyzed by FC with Annexin V-FITC/PI double staining after being treated with PBS as a control, Cisplatin, PtD, and PtD-Chol, respectively. **h, i**, In vitro cytotoxicity determined by MTT assay against 4T1 (**h**) and Panc-02 (**i**). $n = 5$. **j, k**, Nuclear fluorescence (**j**) and Pt concentration (**k**) in 4T1 cells after PtD-Chol incubation (0, 2, 6 h). **l**, Quantification of Pt content in DNA of 4T1 cells after being treated with Cisplatin, PtD, or PtD-Chol for 4 hours. **m**, Representative microscopy images of 4T1 cells after a wound-healing assay, which were treated with PBS, Cisplatin, PtD, and PtD-Chol, respectively. **n**, Representative microscopy images of 4T1 cells after migration and invasion through a transwell treated with PBS, Cisplatin, PtD, and PtD-Chol, respectively. Cells only incubated with PBS were employed as the control. **m, n**, Quantification of the wound healing rate, migration, and invasion by counting three independent biological replicates. The cells only incubated with PBS were employed as the blank controls. **p-u**, Western blot analysis (**p**) and quantification results of Fibronectin (**q**), β -catenin (**r**), N-cadherin (**s**), E-cadherin (**t**), and TGF- β (**u**) expression in 4T1 cells being treated with Cisplatin, PtD, or PtD-Chol. Tubulin was used as a loading control. Scale bars, 100 μ m (**m-n**). Cisplatin-equiv. concentration: 32 μ M (**d-g**), 16 μ M (**m-n, p-u**). $n = 3$ (**d-g, j-u**), $n = 5$ (**h-i**), biologically independent samples; representative images are shown in (**m-n, p**). In **h-l, o, q-u**, data are shown as the mean $\pm$ s.d.; source data are provided as a Source Data file; the statistical significance was calculated via one-way ANOVA with Dunnett's multiple-comparisons test, p-values are shown on the graphs, and p-values < 0.0001 are reported as such. **a-c** were created by Figdraw.com.



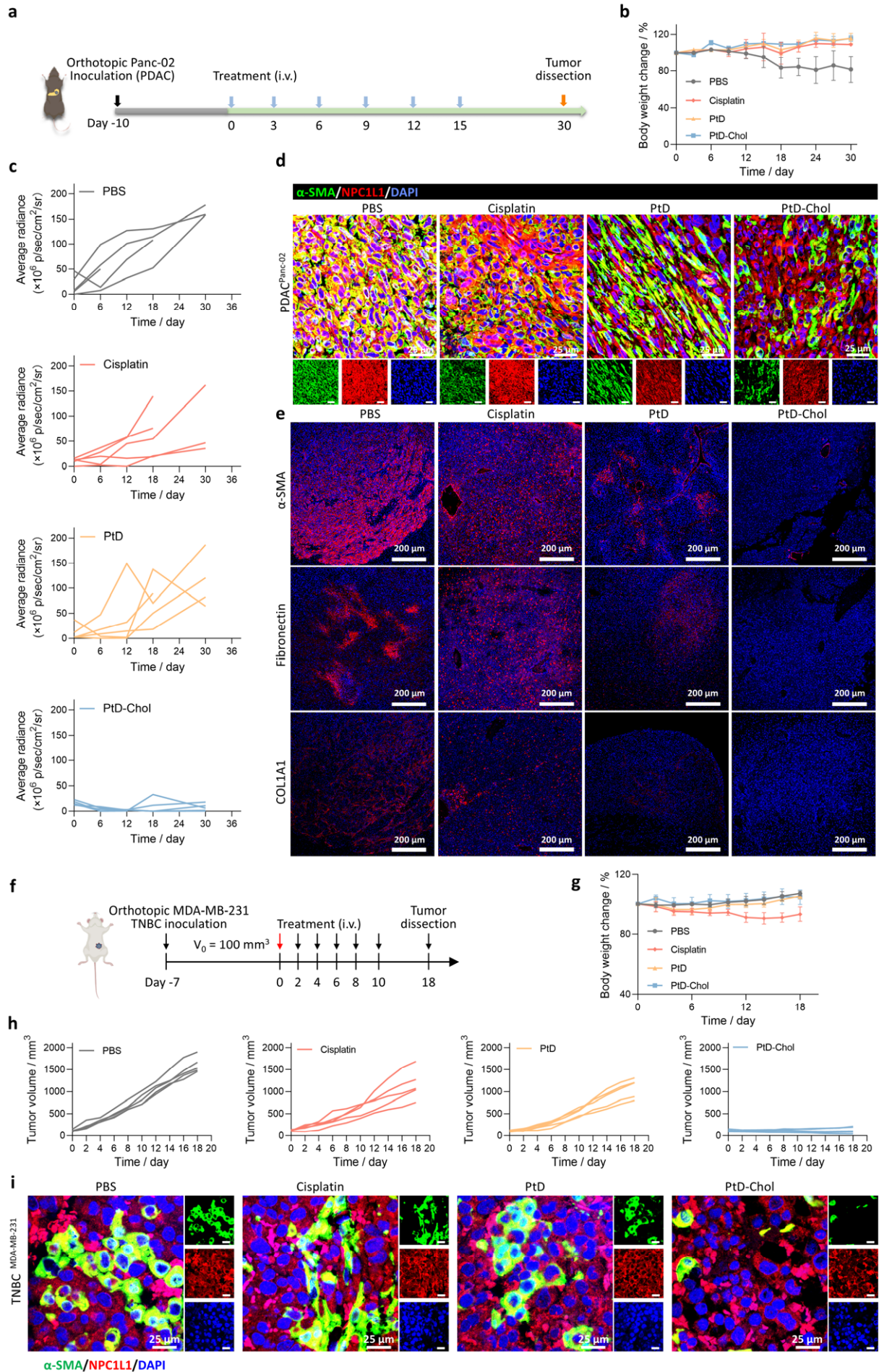
Supplementary Figure 6 | Pharmacokinetics, biodistribution and tumor accumulation of PtD-Chol in vivo. **a**, The blood circulation of PtD-Chol^{Cy5} and PtD^{Cy5} in BALB/c mice. The kinetics of blood circulation were determined over a 0-12 h period following intravenous administration of PtD-Chol^{Cy5} and PtD^{Cy5}, respectively. **b**, Fluorescence of tumors at different time points as shown in Figure 5b. **c**, In situ biodistribution of PtD-Chol^{Cy5} and PtD^{Cy5} in specific time points after intravenous injection into 4T1 tumor-bearing mice. **d, e**, Time-dependent images (**d**) and fluorescence intensity (**e**) of urine after i.v. treatment of PtD-Chol^{Cy5} and PtD^{Cy5}, respectively. **f-i**, Fluorescence images (**f**) and quantitative calculation (**g-i**) of tumor and major organs at 2 h, 12 h, and 24 h after intravenous administration in Orthotopic 4T1 tumor-bearing mice of PtD-Chol^{Cy5}, PtD^{Cy5}, and following oral EZE (5 mg/kg) given 12 hours before intravenous PtD-Chol^{Cy5} (EZE + PtD-Chol^{Cy5}), respectively. **j**, Quantification of Pt content in the kidney, liver, intestine, and tumor at 12 hours post-intravenous injection of PtD-Chol and PtD. **k-l**, Fluorescence intensities of vascular endothelial cells, CAFs, TAMs (tumor-associated macrophages), and tumor cells within 4T1 tumors at 2 and 12 hours after intravenous injection of PtD-Chol (**k**) and PtD (**l**). **m**, Magnified vascular field of Figure 3h and quantitative calculation. **n**, In situ biodistribution of PtD-Chol^{Cy5} and PtD^{Cy5} in specific time points after intravenous injection into Panc-02 tumor-bearing mice. **o**, Fluorescence images of tumor (indicated by a white dotted circle) and other major organs at 2 h after intravenous administration in Panc-02 tumor-bearing mice of PtD-Chol^{Cy5} and PtD^{Cy5}, respectively. In **a-l, n-o**, n = 3 mice for each group, (Cisplatin-equiv. dose, 3 mg/kg), representative images are shown in (**c, d, f, n-o**). In **m**, n = 10 independent fields (n = 3 mice); representative images are shown. In **j-m**, data are shown as the mean $\pm$ s.d., the statistical significance was calculated via two-way ANOVA with Šídák's multiple comparisons test (**j-l**) or unpaired two-tailed Student's t-test (**m**), p-values are shown on the graphs, and p-values < 0.0001 are reported as such. In **a-b, e**, and **g-m**, source data are provided as a Source Data file.



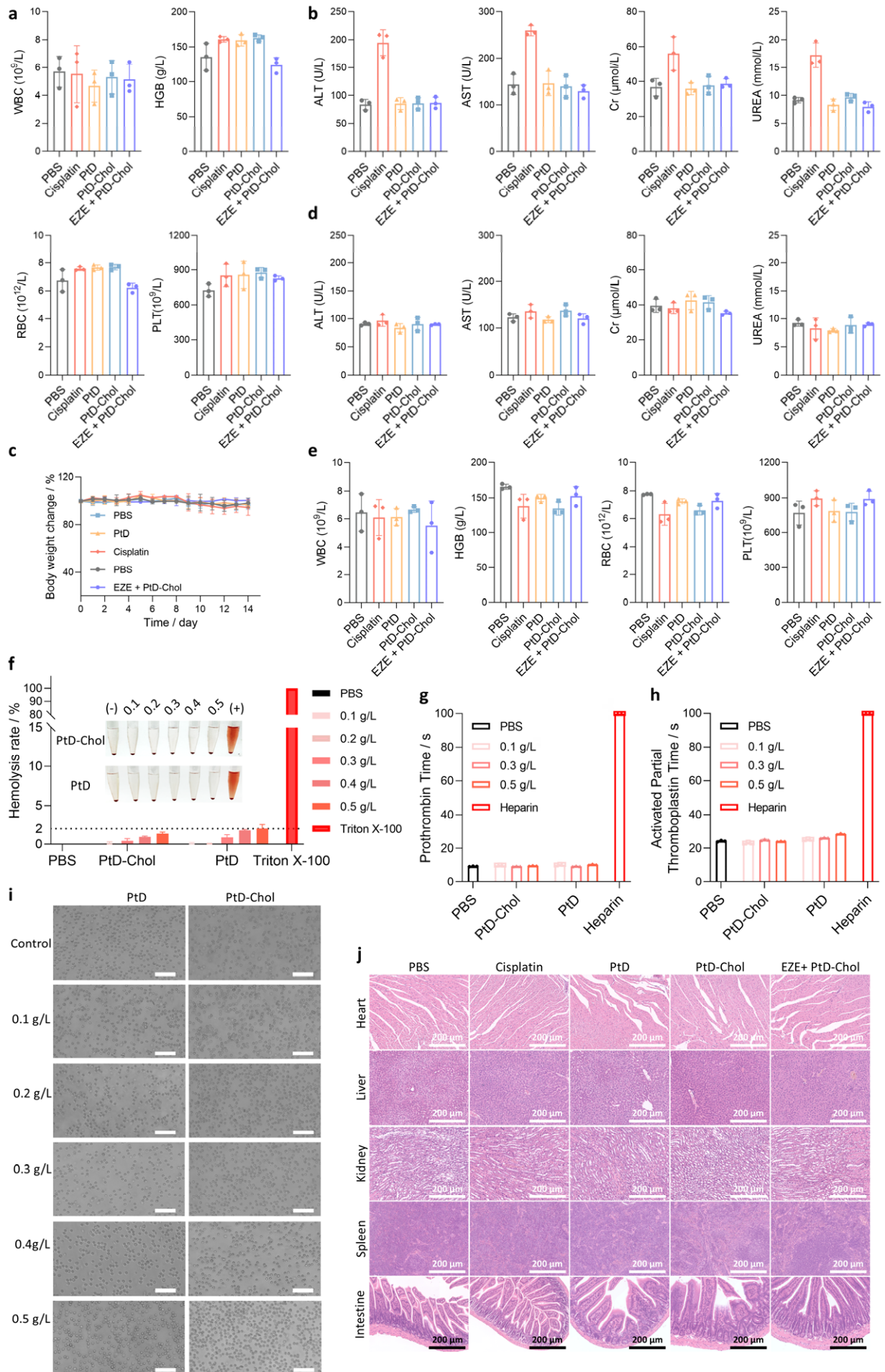
Supplementary Figure 7 | PtD-Chol blocks the function of CAFs in promoting tumor metastasis. **a**, The schematic diagram shows that CAFs promote tumor metastasis, which can be blocked by PtD-Chol treatment. **b, c**, Western blot analysis (**b**) and quantification results (**c**) of α -SMA expression in NFs or CAFs after the different treatments, including i (NFs, NIH-3T3), and ii (CAF, NIH-3T3^{TGF- β 1}), iii (CAF, NIH-3T3^{TGF- β 1} + Cisplatin), iv (CAF, NIH-3T3^{TGF- β 1} + PtD), v (CAF, NIH-3T3^{TGF- β 1} + PtD-Chol), respectively. Tubulin was used as a loading control. **d**, Representative CLSM image of α -SMA expression in NFs or CAFs after the different treatments, as shown in (**b**). Green, α -SMA; blue, cell nuclei. **e-f**, Western blot analysis (**e**) and quantification results (**f**) of P-SMAD2/SMAD2 and P-SMAD3/SMAD3 expression in NFs or CAFs after the different treatments, respectively. Tubulin was used as a loading control. **g**, The schematic diagram shows that PtD-Chol blocks the function of CAFs in promoting tumor metastasis by inhibiting the TGF- β /SMAD pathway. **h**, Schematic of the migration and invasion assay designed to assess CAF-induced tumor metastasis and its blockade by PtD-Chol. **i**, Representative microscopy images of 4T1 cells after undergoing migration and invasion through a transwell, which was treated with PBS, or with the culture medium of CAFs following incubation with Cisplatin, PtD-Chol, and PtD, respectively. Cells only incubated with PBS were employed as the control. **j**, Quantification of the migration and invasion by counting three independent biological replicates. **k, l**, Experimental protocols of for the penetration assay in 4T1 hetero-spheroid (**k**). CLSM images of PtD-Chol and PtD (20 μ g/mL) in relation to the apoptotic state of the hetero-spheroids (**l**). Scale bars, 50 μ m (**d**), 100 μ m (**i, l**). In **b-f, i-j, and, k-l**, n = 3 biologically independent samples; representative images are shown in (**b, d, e, i, l**). In **c, f, j**, data are shown as the mean $\pm$ s.d.; source data are provided as a Source Data file; the statistical significance was calculated via one-way ANOVA with Dunnett's multiple-comparisons test, p-values are shown on the graphs, and p-values < 0.0001 are reported as such. **a, g, h**, and **k** were created by Figdraw.com.



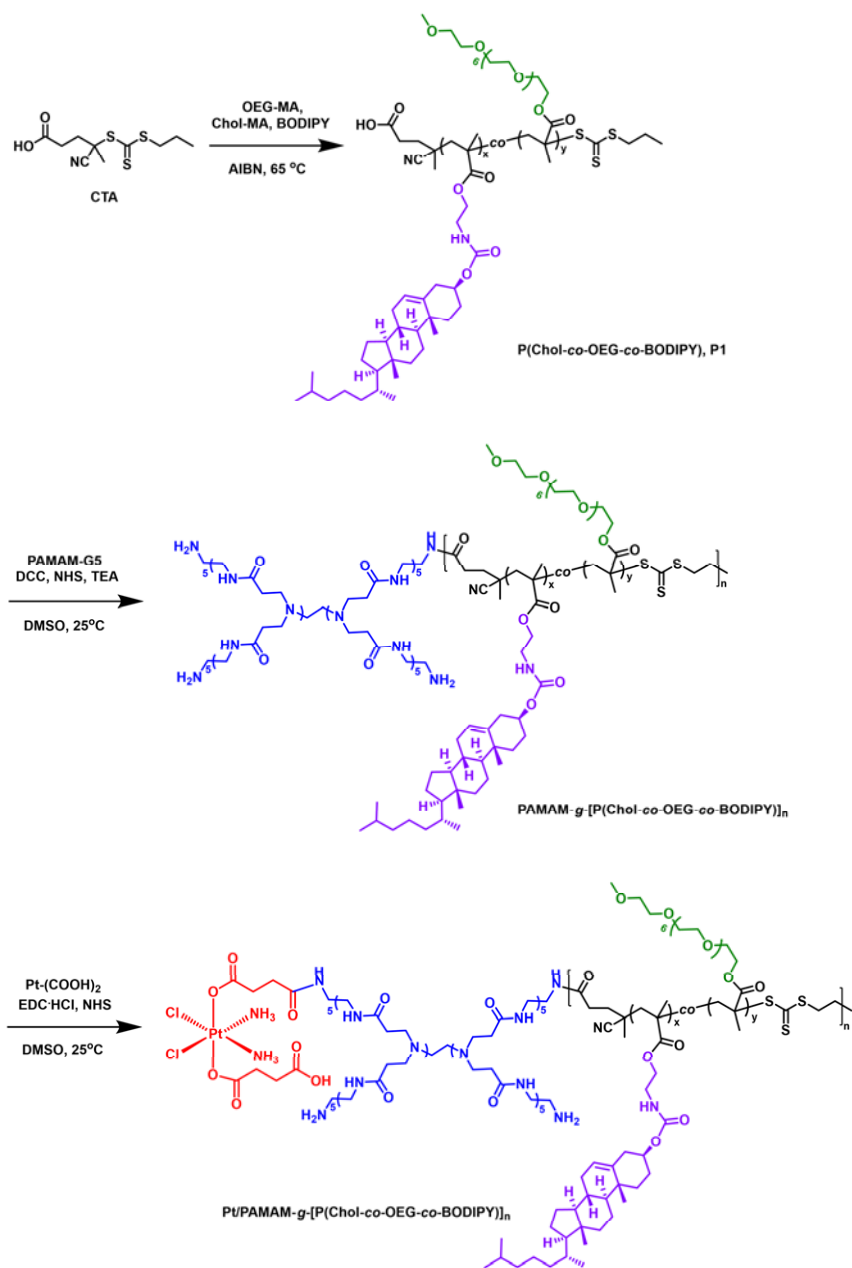
Supplementary Figure 8 | The anti-tumor efficacy of PtD-Chol in TNBC model. **a, d**, Schematic showing the establishment and treatment of 4T1 tumor-bearing mice with regular (V_0 of 100 mm³) (**a**) and large (V_0 of 350 mm³) (**d**) initial tumor volumes. **b, e**, Changes in the body weights of 4T1 tumor-bearing mice with regular (**b**) and large (**e**) initial tumor volumes during different treatments. **c, f**, Individual tumor growth curves of the 4T1 tumor-bearing mice with regular (**c**) and large (**f**) initial tumor volumes during different treatments. **g, h**, H&E and TUNEL assays of the excised tumor tissues from different groups in 4T1 regular (**g**) and large (**h**) tumor-bearing mice. Scale bars, 200 μ m. **i, j**, Quantification of the percentage of TUNEL-positive area in tumors with different treatments in 4T1 regular (**i**) and large (**j**) tumor-bearing mice. **k**, Schematic showing the establishment and treatment of orthotopic 4T1 tumor-bearing mice. **l**, Changes in the body weights of orthotopic 4T1 tumor-bearing mice during different treatments. **m**, Individual tumor growth curves of the orthotopic 4T1 tumor-bearing mice during different treatments. In **a-j**, The different treatment groups include PBS as control, and Cisplatin, PtD, PtD-Chol, each administered at a Cisplatin-equiv. dose of 3 mg/kg, respectively. In **k-m**, the different treatment groups include PBS as control, and Cisplatin, PtD, PtD-Chol, following oral EZE (5 mg/kg) given 12 hours before intravenous PtD-Chol (EZE + PtD-Chol), each administered at a Cisplatin-equiv. dose of 3 mg/kg, respectively. $n = 6$ (**a-f**), $n = 5$ (**g-j**, **l-m**) mice for each group. In **g-j**, Five random fields were observed for each group under the microscope; representative images are shown in **g, h**; the data are presented as the mean $\pm$ s.d.; the statistical significance was calculated via one-way ANOVA with Tukey's multiple-comparisons test (**i, j**), p-values are shown on the graphs, and p-values < 0.0001 are reported as such. **a, d**, and **k** were created by Figdraw.com. In **b-c**, **e-f**, **i-j**, and **l-m**, source data are provided as a Source Data file.



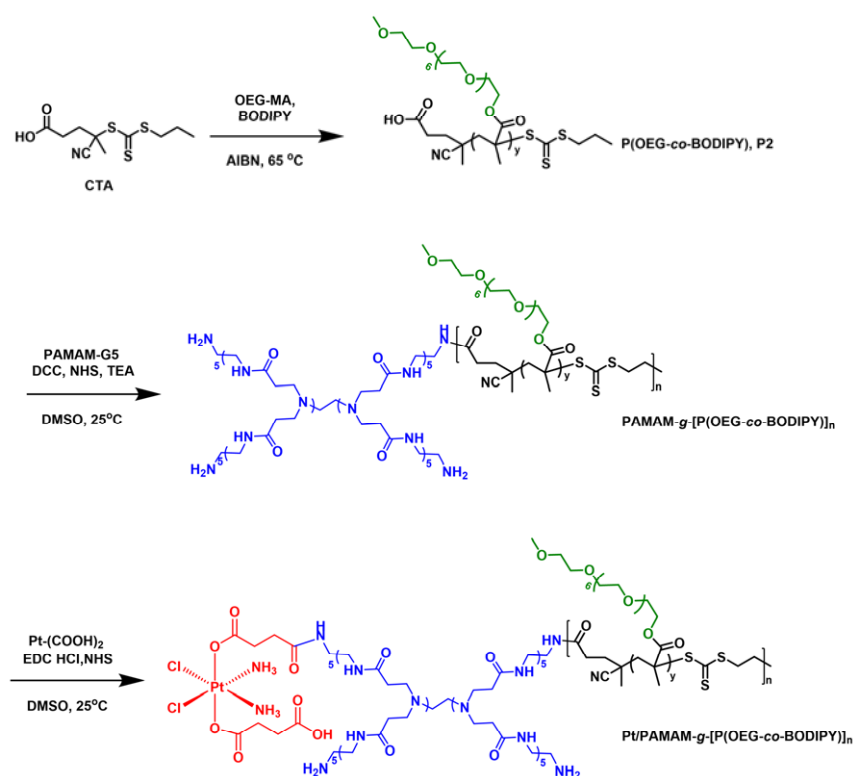
Supplementary Figure 9 | The anti-tumor efficacy of PtD-Chol and its ability to remodel the tumor stroma at both the primary site and metastatic sites in PDAC and CDX models. **a**, Schematic showing the establishment and treatment of orthotopic Panc-02 tumor-bearing mice. **b**, Changes in the body weights of orthotopic Panc-02 tumor-bearing mice during different treatments. **c**, Individual time-bioluminescence intensity curves of the orthotopic Panc-02 tumor-bearing mice during different treatments. **d**, Representative confocal microscopy images of the immunofluorescence showing the expression of α -SMA and NPC1L1 in orthotopic Panc-02 tumors with different treatments. Green, α -SMA; red, NPC1L1; blue, cell nuclei. Scale bars, 25 μ m. **e**, Representative confocal microscopy images of the immunofluorescence of extracellular matrix (ECM) proteins (α -SMA, Fibronectin, and COL1A1) in the liver of orthotopic Panc-02 tumor-bearing mice after different treatments. **f**, Schematic showing the establishment and treatment of orthotopic MDA-MB-231 tumor-bearing mice. **g**, Changes in the body weights of orthotopic MDA-MB-231 tumor-bearing mice receiving different treatments. **h**, Individual time-bioluminescence intensity curves of the orthotopic MDA-MB-231 tumor-bearing mice during different treatments. **i**, Representative CLSM images of the immunofluorescence showing the expression of α -SMA and NPC1L1 in MDA-MB-231 tumors with different treatments. Green, α -SMA; red, NPC1L1; blue, cell nuclei. Scale bars, 25 μ m. In **a-i**, the different treatment groups include PBS as control, and Cisplatin, PtD, PtD-Chol, each administered at a Cisplatin-equiv. dose of 3 mg/kg, respectively. In **a-e**, **g-i**, n = 5 mice for each group, representative images are shown in **d**, **e**, **i**. In **b-c**, and, **g-h**, source data are provided as a Source Data file. **a** and **f** were created by Figdraw.com.



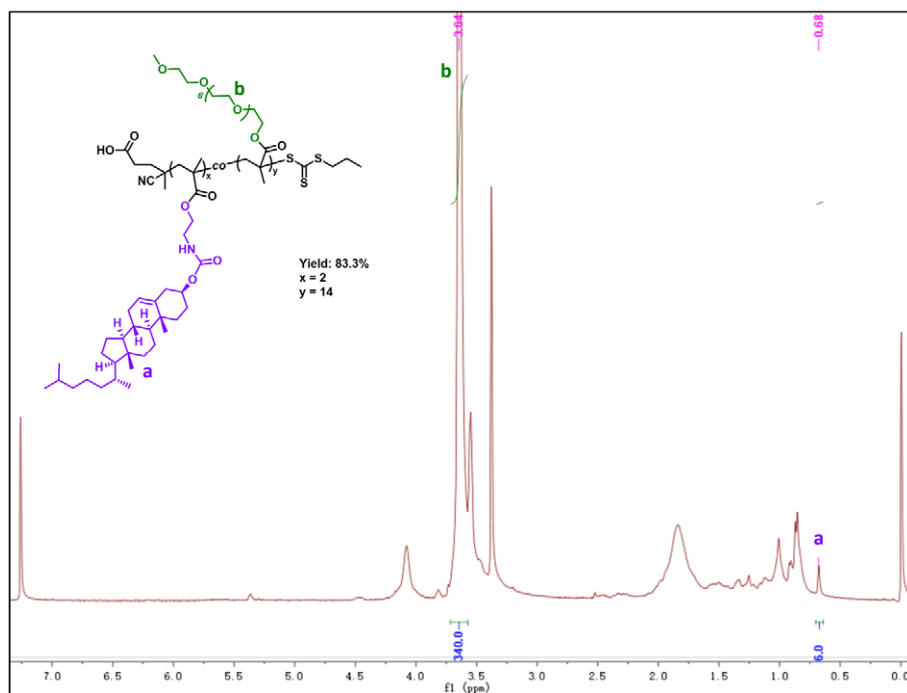
Supplementary Figure 10 | Biosafety evaluation of PtD and PtD-Chol. **a, b**, Hematological analysis of mice after the intravenous injection 24 hours of PBS, Cisplatin, PtD, PtD-Chol, or following oral EZE given 12 hours before intravenous PtD-Chol (EZE + PtD-Chol), at a dose of Cisplatin 3 mg/kg. **c-e**, Body weight change (**c**) and hematological analysis (**d-e**) of mice after the intravenous injection 14 days of PBS, Cisplatin, PtD, PtD-Chol, or following oral EZE given 12 hours before intravenous PtD-Chol, at a dose of Cisplatin 3 mg/kg. **f**, Hemolysis rate of red blood cells treated with PtD-Chol and PtD at concentrations ranging from 0.1 to 0.5 g/L for 2 h at 37 °C, using Triton X-100 as a positive control and PBS buffer as a negative control (n = 3). The hemolysis threshold is 2%. **g, h**, Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) of each group (n = 3); PT and APTT higher than 100 is represented as 100, using heparin as a positive control **i**, Hemagglutination assay of PtD and PtD-Chol at different concentrations. PBS was used as a control (n = 3), Scale bars, 50 µm. **j**, H&E staining images for histological analysis of major organs (heart, liver, kidney, spleen, and intestine) collected from orthotopic 4T1 tumor-bearing mice in different treatment groups. Scale bars, 200 µm. In **a-e, j**, n = 3 independent mice representative images are shown in **j**. In **f-i**, n = 3 biologically independent samples; representative images are shown in **i**. In **a-h**, source data are provided as a Source Data file.



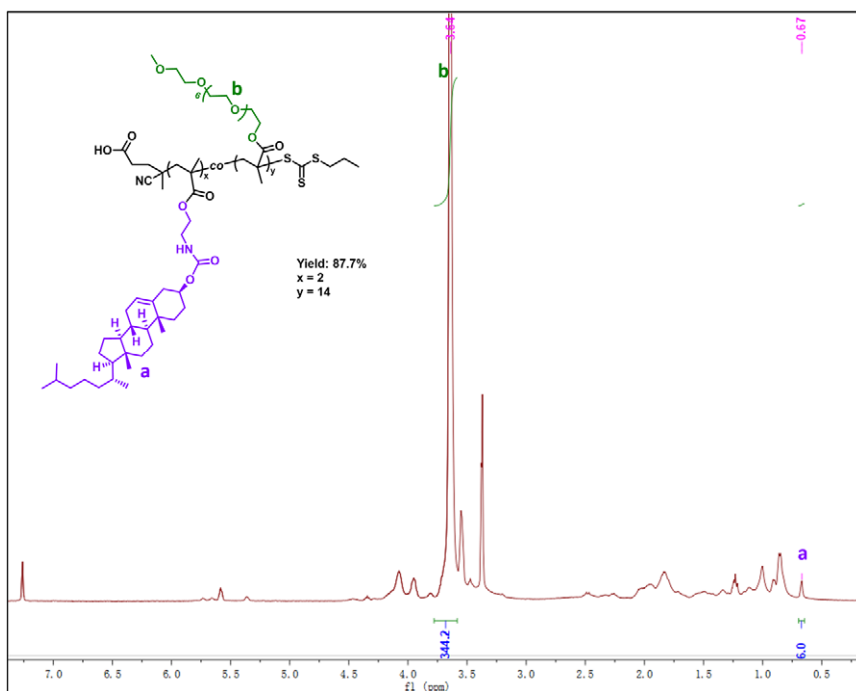
Supplementary Figure 11 | Synthetic routes employed for the preparation of cholesterol conjugated polymer P(Chol-co-OEG-co-BODIPY) (P1, labeled with 0.01 mol% BODIPY, not shown in the chemical structure), dendritic polymer PAMAM-g-P(Chol-co-OEG-co-BODIPY), and Cisplatin conjugated dendritic polymer Pt/PAMAM-g-P(Chol-co-OEG-co-BODIPY).



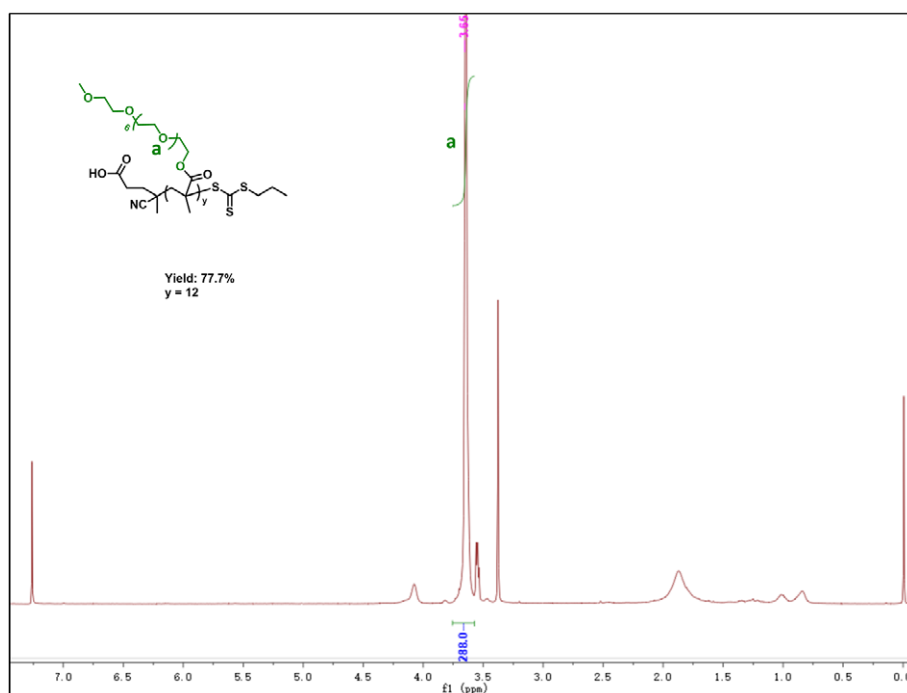
Supplementary Figure 12 | preparation of polymer P(OEG-co-BODIPY) (P2, without cholesterol conjugation, labeled with 0.01 mol% BODIPY, not shown in the chemical structure), dendritic polymer PAMAM-g-P(OEG-co-BODIPY), and Cisplatin conjugated dendritic polymer Pt/PAMAM-g-P(OEG-co-BODIPY).



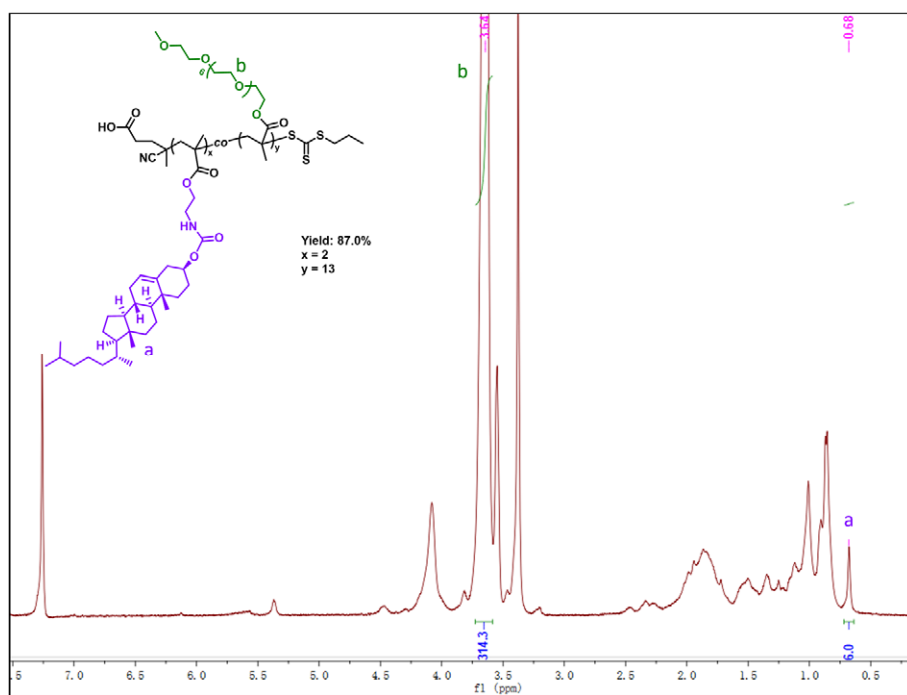
Supplementary Figure 13 | ^1H -NMR spectrum recorded for $\text{P}(\text{Chol}_{0.13}\text{-co-OEG}_{0.86}\text{-co-BODIPY}_{0.01})_{16}$ (P1) in CDCl_3 . ^1H NMR (400 MHz, CDCl_3) δ 3.64 (s, 340H), 0.68 (s, 6H). Source data are provided as a Source Data file.



Supplementary Figure 14 | ^1H -NMR spectrum recorded for $\text{P}(\text{Chol}_{0.13}\text{-co-OEG}_{0.86}\text{-co-RhB}_{0.01})_{16}$ ($\text{P1}'$) in CDCl_3 . ^1H NMR (400 MHz, CDCl_3) δ 3.64 (s, 344H), 0.68 (s, 6H). Source data are provided as a Source Data file.

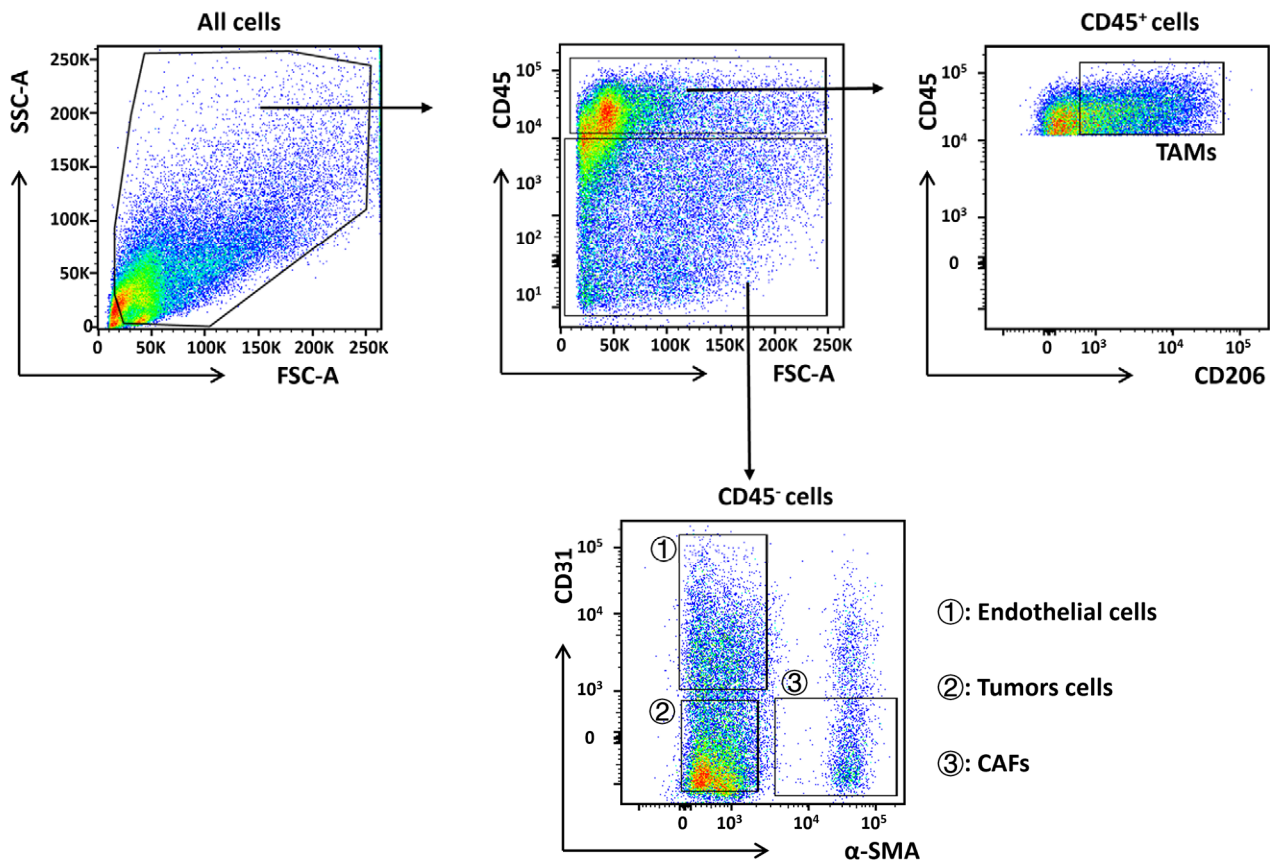


Supplementary Figure 15 | ^1H -NMR spectrum recorded for $\text{P}(\text{OEG}_{0.99}\text{-co-BODIPY}_{0.01})_{12}$ (P2) in CDCl_3 . ^1H NMR (400 MHz, CDCl_3) δ 3.65 (s, 288H). Source data are provided as a Source Data file.

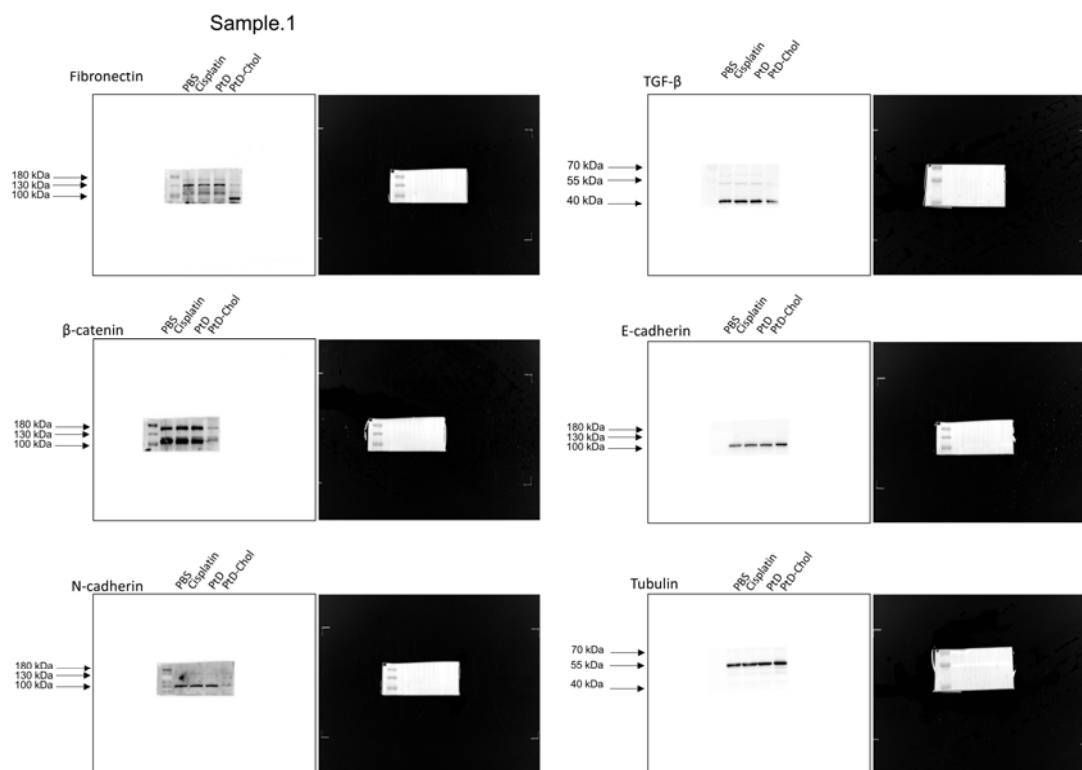


Supplementary Figure 16 | ^1H -NMR spectrum recorded for $\text{P}(\text{Chol}_{0.13}\text{-co-OEG}_{0.87})_{15}$ (free polymer, FP) in CDCl_3 . ^1H NMR (400 MHz, CDCl_3) δ 3.64 (s, 314H), 0.68 (s, 6H). Source data are provided as a Source Data file.

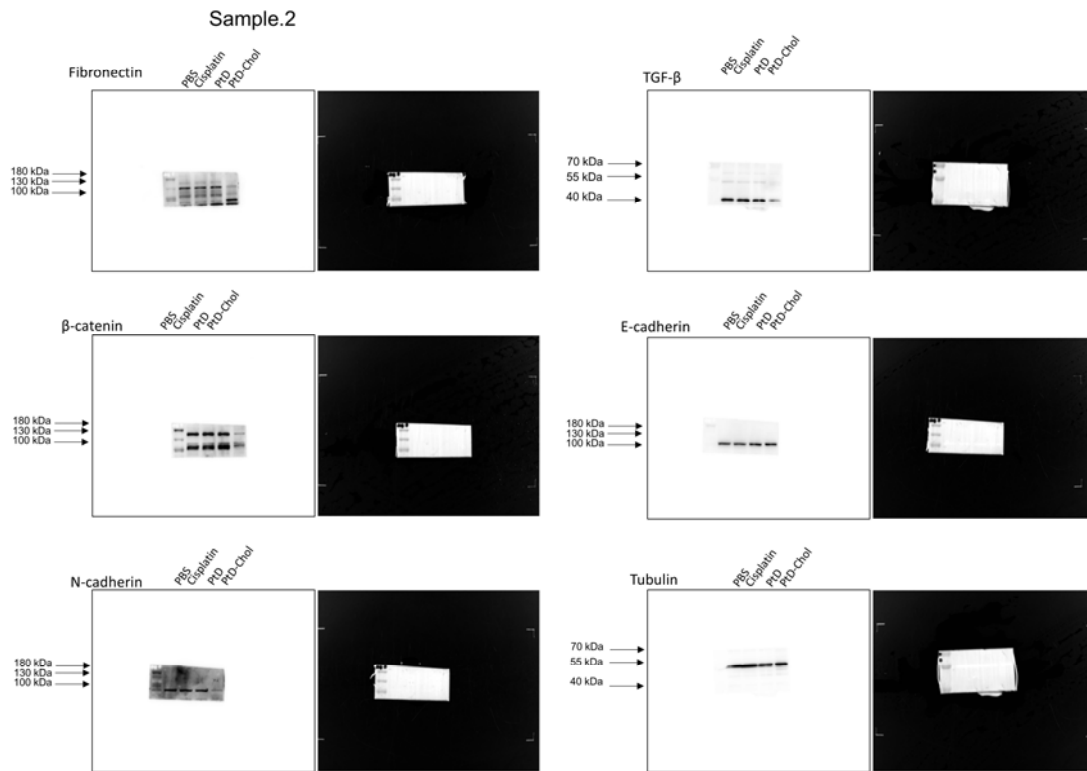
Flow cytometry gating strategy



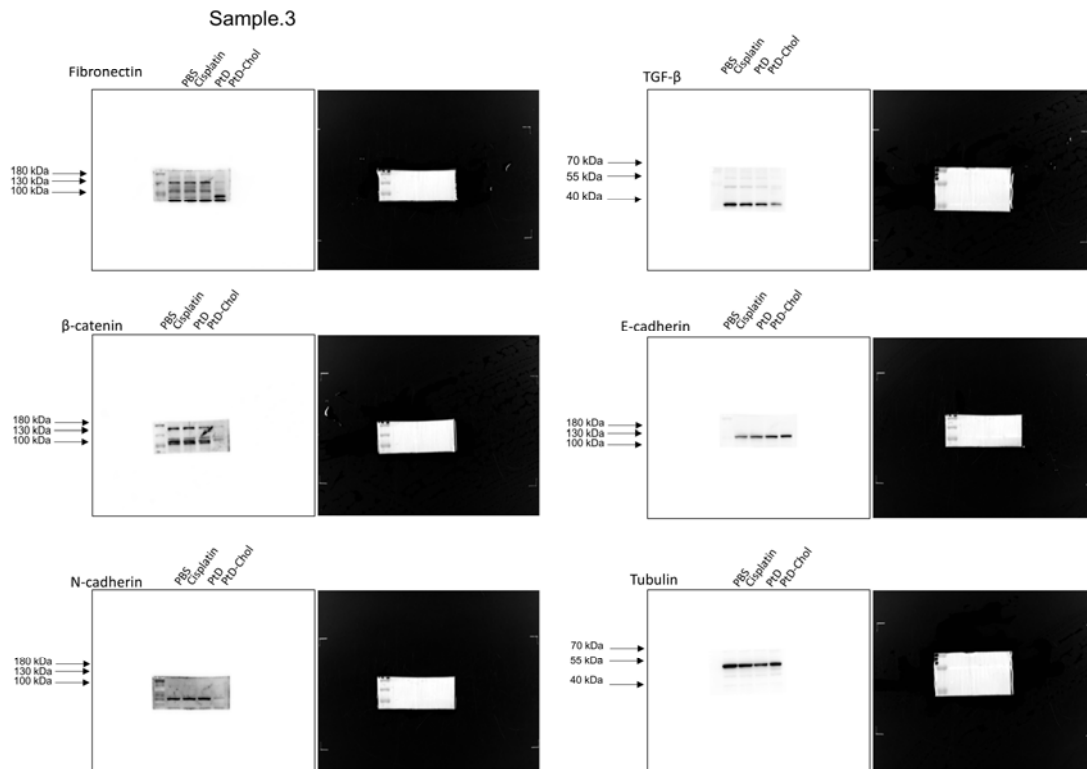
Supplementary Figure 17 | TAMs, Endothelial cells, CAFs, and tumor cells gating strategy of Supplementary Fig. 6k,l based on scatter of light and CD45/CD206/CD31/α-SMA staining.



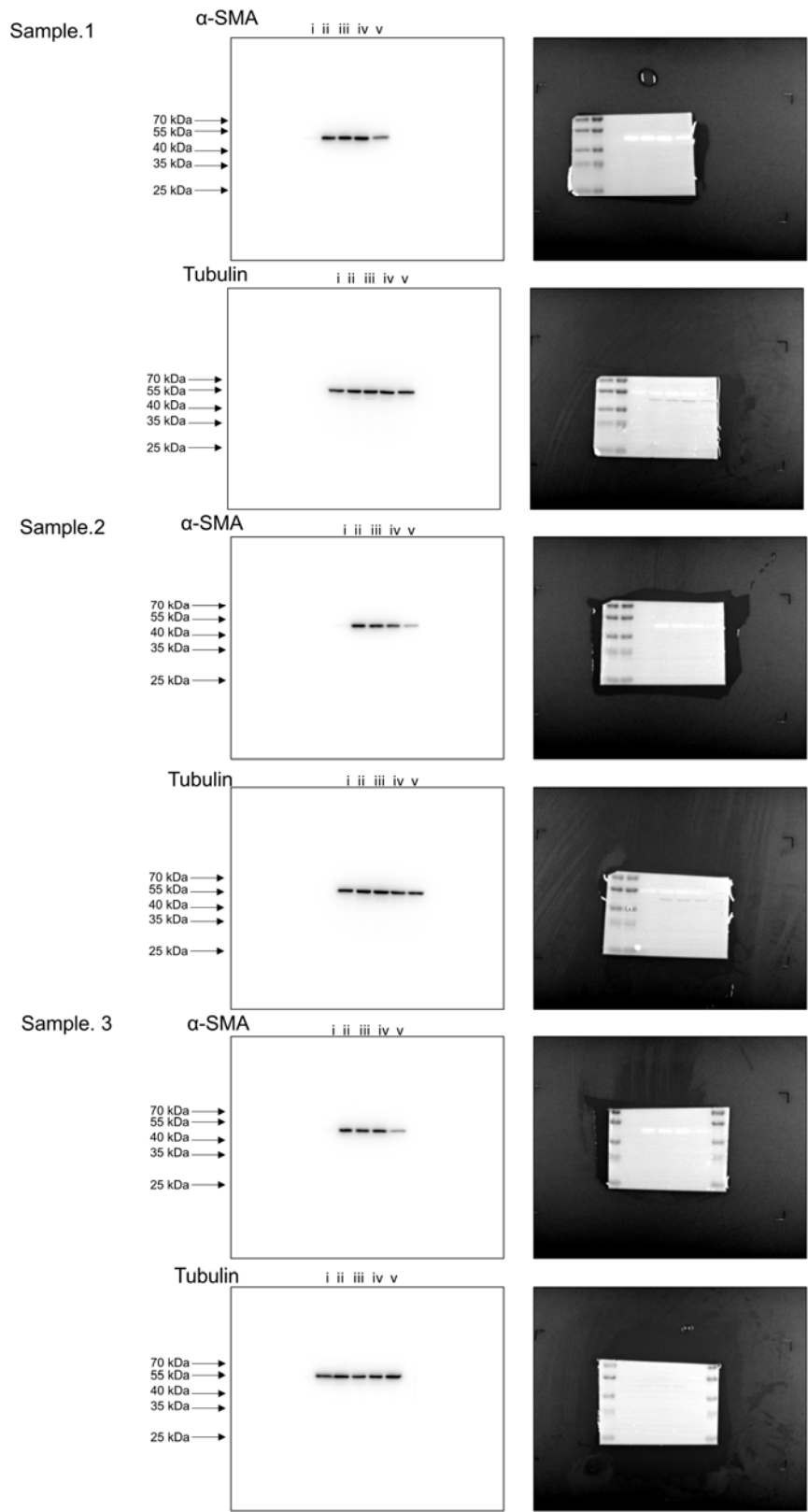
Supplementary Figure 18 | The uncropped scans blots of Supplementary Fig. 5p sample 1.



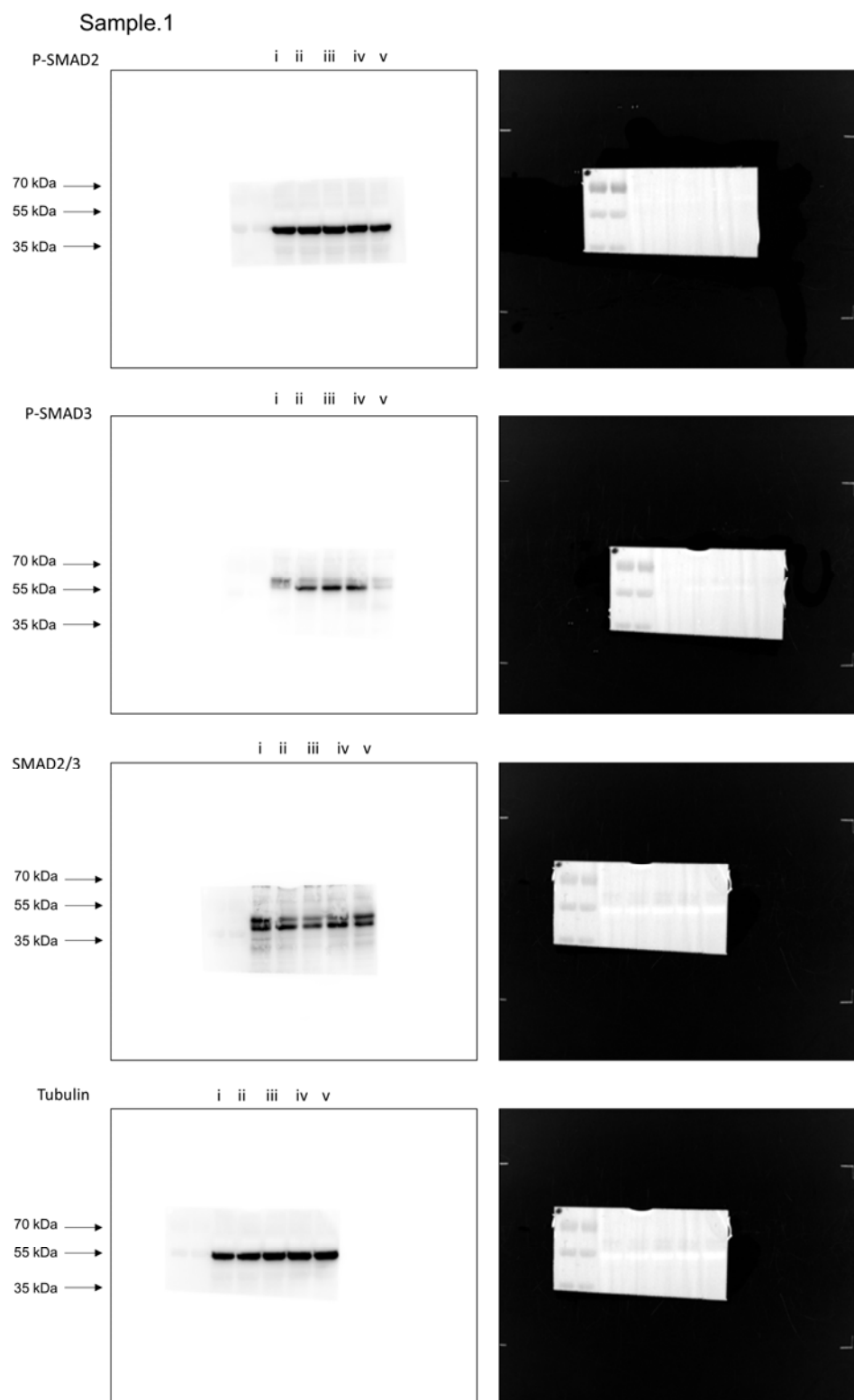
Supplementary Figure 19 | The uncropped scans blots of Supplementary Fig. 5p sample 2.



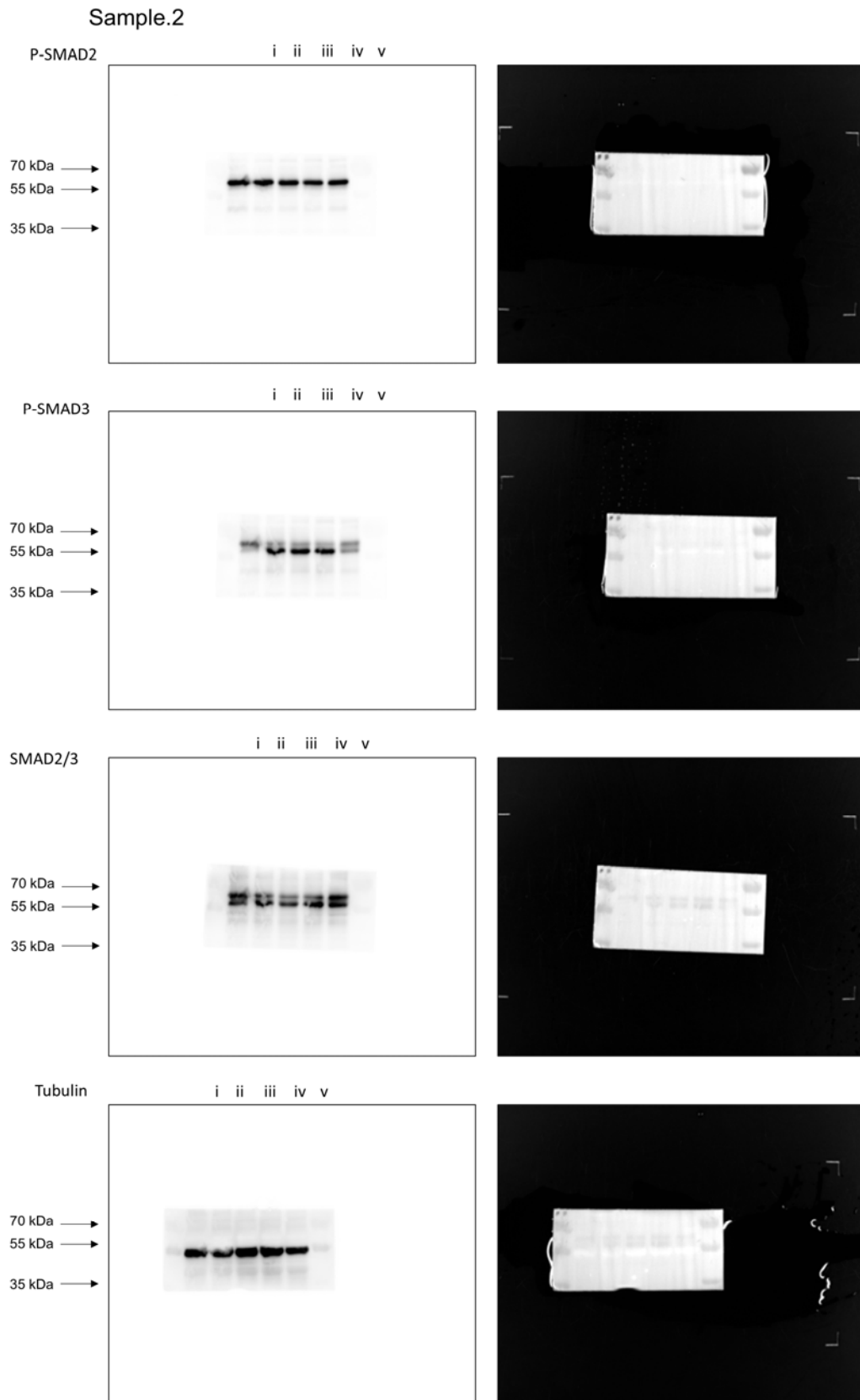
Supplementary Figure 20 | The uncropped scans blots of Supplementary Fig. 5p sample 3.



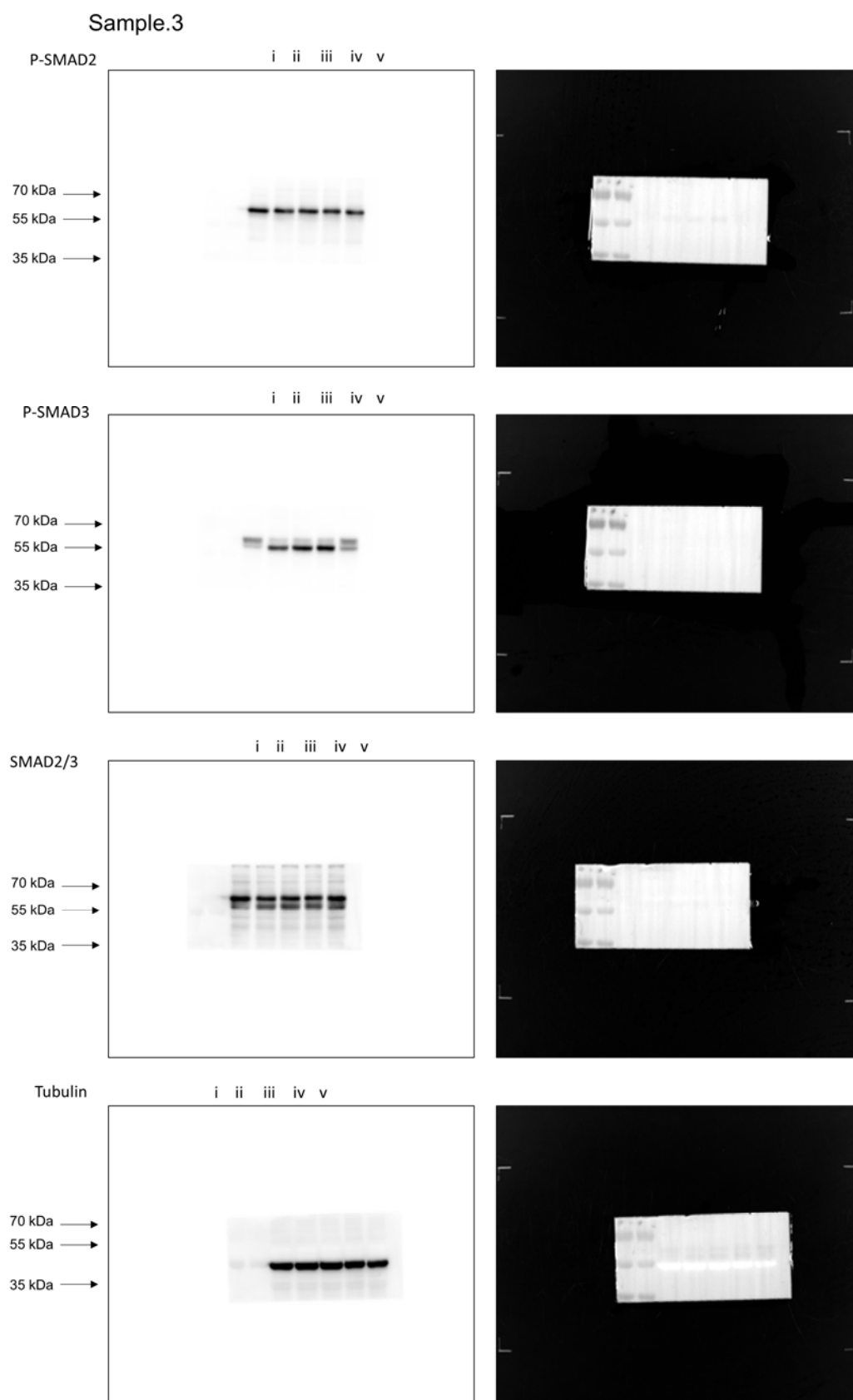
Supplementary Figure 21 | The uncropped scans blots of Supplementary Fig. 7b.



Supplementary Figure 22 | The uncropped scans blots of Supplementary Fig. 7e sample 1.



Supplementary Figure 23 | The uncropped scans blots of Supplementary Fig. 7e sample 2.



Supplementary Figure 24 | The uncropped scans blots of Supplementary Fig. 7e sample 3.

Supplementary Tables

Supplementary Table 1 | Overview of the chemical composition of polymers.

Polymers		Number of Chol per-chain
P1	$P(\text{Chol}_{0.13}\text{-}co\text{-OEG}_{0.86}\text{-}co\text{-BODIPY}_{0.01})_{16}$	2
P1'	$P(\text{Chol}_{0.13}\text{-}co\text{-OEG}_{0.86}\text{-}co\text{-RhB}_{0.01})_{16}$	2
P2	$P(\text{OEG}_{0.99}\text{-}co\text{-BODIPY}_{0.01})_{12}$	0
Free polymer (FP)	$P(\text{Chol}_{0.13}\text{-}co\text{-OEG}_{0.87})_{15}$	2

Supplementary Table 2 | Overview of the structure parameter of dendrimer nanoparticles. “Batch” represents different synthesis batches.

Dendrimer nanoparticles							
	Batch	Yield	Polymers	Number of Chol per-dendrimer	Pt wt%	$\langle D_h \rangle$ / nm	ζ -potential / mV
D-Chol	①	83%	PAMAM- <i>g</i> -P1 _{9,96}	19.92	0	8	15.0
	②	77%	PAMAM- <i>g</i> -P1 _{9,24}	18.84	0	8	18.9
	③	80%	PAMAM- <i>g</i> -P1 _{9,60}	19.20	0	9	16.4
PtD-Chol	①	69%	Pt/PAMAM- <i>g</i> -P1 _{9,96}	19.92	4.9%	8	-7.3
	②	65%	Pt/PAMAM- <i>g</i> -P1 _{9,24}	18.84	4.1%	8	-7.7
	③	67%	Pt/PAMAM- <i>g</i> -P1 _{9,60}	19.20	4.5%	9	-9.7
P1'/PtD-Chol	①	79%	Pt/PAMAM- <i>g</i> -P1' _{9,48}	18.96	5.1%	9	-7.4
P1P1'/PtD-Chol	①	77%	Pt/PAMAM- <i>g</i> -(P1P1') _{9,24}	18.48	5.4%	9	-8.4
D-NPs	①	70%	PAMAM- <i>g</i> -P2 _{8,40}	0	0	8	26.0
	②	76%	PAMAM- <i>g</i> -P2 _{9,12}	0	0	9	22.4
	③	75%	PAMAM- <i>g</i> -P2 _{9,00}	0	0	8	25.8
PtD	①	66%	PAMAM- <i>g</i> -P2 _{8,40}	0	6.1%	8	-2.6
	②	69%	PAMAM- <i>g</i> -P2 _{9,12}	0	7.0%	9	-3.7
	③	63%	PAMAM- <i>g</i> -P2 _{9,00}	0	6.7%	8	-4.1