Supplement Information

Personalized nanotherapy by specifically targeting cell organelles to improve vascular hypertension

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Figure S1. (a) UV-visible, (b) XRD and (c, d) XPS spectral patterns of both DAu and PLGA nanoparticles. Each spectrum represents the progression of native nanoparticles to active cilia-targeted nanoparticles. (e) FTIR-spectra represents the functional groups associated with the functionalized nanoparticles. (f) HPLC spectra of known fenoldopam (reference compound) concentrations to obtain a standard approach and fenoldopam retention time (top). An HPLC calibration curve of fenoldopam is also shown (bottom). (g) Fluorescence spectra of CT-DAu-NPs and CT-PLGA-NPs. n=3 for all experiments.

Figure S2. Representative images on the effects of CT-DAu-NPs (a) and CT-PLGA-NPs (b) on primary cilia of renal epithelia. Numbers indicate time in hour. ***$p < 0.001$, ****$p < 0.0001$ compared to time 0, prior to the treatment with CTNDDS. Statistical analysis was performed using ANOVA followed by a Bonferroni post hoc test.

Figure S3. Representative images on the effects of CT-DAu-NPs (a) and CT-PLGA-NPs (b) on primary cilia of vascular endothelia from *Pkd1* mice. Numbers indicate time in hour. ****$p < 0.0001$ compared to time 0, prior to the treatment with CTNDDS. Statistical analysis was performed using ANOVA followed by a Bonferroni post hoc test.

Figure S4. Representative images on the effects of CT-DAu-NPs (a) and CT-PLGA-NPs (b) on primary cilia of vascular endothelia from *Pkd2* mice. Numbers indicate time in hour. ****$p < 0.0001$ compared to time 0, prior to the treatment with CTNDDS. Statistical analysis was performed using ANOVA followed by a Bonferroni post hoc test.

Figure S5. Representative images on the effects of CT-DAu-NPs (a) and CT-PLGA-NPs (b) on primary cilia of vascular endothelia from *IFT88* mice. Numbers indicate time in hour. Statistical analysis was performed using ANOVA followed by a Bonferroni post hoc test, and there was no statistical significance within groups.

Figure S6. (a) Representative line and bar graphs showing the intracellular Ca^{2+} levels with different treatments. (b) Representative line and bar graphs showing the intracellular NO levels with different treatments. Arrows indicate the start of fluid-flow. n=5 for all experiments. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. Statistical analysis was performed using ANOVA followed by a Bonferroni post hoc test.

Figure S7. To measure the cytosolic and ciliary calcium, the DIC, mCherry and GFP images were captured after cells were treated with (a) PBS or (b) Fenoldopam under sub-minimal shear stress (0.5 dyn/cm^2). The colour bar indicates Ca^{2+} levels. n=3 for all experiments.

Figure S8. To measure the cellular and ciliary calcium, the DIC, mCherry and GFP images were captured after cells were treated with (a) cCT-DAu-NPs or (b) CT-DAu-NPs under sub-minimal shear stress (0.5 dyn/cm^2). The colour bar indicates Ca^{2+} levels. n=3 for all experiments.

Figure S9. To measure the cellular and ciliary calcium, the DIC, mCherry and GFP images were captured after cells were treated with (a) cCT-PLGA-NPs and (b) CT-PLGA-NPs under sub-minimal shear stress (0.5 dyn/cm^2). The colour bar indicates Ca^{2+} levels. n=3 for all experiments.

Figure S10. (a) Mean cytosolic (red) and cilioplasmic (blue) Ca^{2+} levels are shown in line graphs. The presence of shear stress is represented by the green background. (b) Kymograph analyses of Ca^{2+} signalling in the cell body and cilia in response to 0.5 dyn/cm^2 flow were performed. (c) Representative traces of changes in Ca^{2+} speed, acceleration, speed intensity and mean intensity within a single cilium are shown. The presence of shear stress is represented by the green background. n=3 for all experiments.

Figure S11. The cytotoxicity of CTNDDS (10 μg/mL for 48 hours) was analyzed with apoptotic (Annexin-V) and necrotic (propidium iodide, PI) markers. (a) Cells were analyzed with FACS. (b) Representative images were taken with microscope. DIC=differential interference contrast; negative control=phosphate saline treatment; positive control=30 minutes of methanol treatment.

Figure S12. Intracellular cGMP levels were quantified in cells treated with vehicle (PBS; control) or other treatments. Statistical analysis was performed using ANOVA followed by a Bonferroni post hoc test.

Figure S13. (a) Representative phase contrast images showing *Pkd2* zebrafish at 48 -hours post-fertilization. Fish were injected with vehicle (PBS), CT-DAu-NPs or CT-PLGA-NPs. Bar graphs showing the measurements of curly tail, which is an indication of disease phenotype. (b) H&E sections showing the *Pkd2* zebrafish treated with different treatments. Cystic kidneys are denoted by red asterisks, and the bar graph shows the percentage of zebrafish with cystic kidneys. (c) The quantitation of the artery diameters shown in the bar graph. (d) Representative line graphs show single-blood-cell speed and acceleration within the main dorsal artery. (e) Quantitations of blood

circulation characteristics and cardiac measurements are shown in the bar graphs to examine cardiovascular functions. n=3 for all experiments if not represented in dot plot. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$ compared to wild-type vehicle. #$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$, ####$p < 0.0001$ compared to *Pkd2* vehicle. Statistical analysis was performed using ANOVA followed by a Bonferroni post hoc test.

Figure S14. (a) Representative immunofluorescence images of primary cilia in arteries (A; white box) and veins (V; red box) are shown when the zebrafish treated with vehicle (PBS), CT-DAu-NPs or CT-PLGA-NPs. Average cilia length of the blood vessels is shown in the bar graphs. (b) Representative immunofluorescence images of primary cilia in the heart is shown. The square boxes show one cilium for visualization purposes. Average cilia length in the heart is shown in the bar graphs in zebrafish treated with vehicle (PBS), CT-DAu-NPs or CT-PLGA-NPs. For all immunofluorescence studies, green (acetylated-α-tubulin or cilia marker), red (NPs), and blue (DAPI or nucleus). n=50 for all experiments. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$ compared to wild-type vehicle. #$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$, ####$p < 0.0001$ compared to *Pkd2* vehicle. Statistical analysis was performed using ANOVA followed by a Bonferroni post hoc test.

Figure S15. (a) Pharmacokinetics profile of fenoldopam showing bolus injection (CT-DAu-NPs and CT-PLGA-NPs) and 30-minute infusion (fenoldopam-alone). (b) Area under the curve was calculated as an indication of total plasma concentration of fenoldopam in an hour. N=3 for each group. *$p < 0.05$ compared to fenoldopam-alone. Statistical analysis was performed using ANOVA followed by a Bonferroni post hoc test.

Figure S16. Representative immunofluorescence images of primary cilia from aortic endothelial cells showing red fluorescent CTNDDS (red arrows) and cilia (green arrows) at 24- or 72-hours after treatment. The insets show reduced views of the whole aorta and magnified views of cilia. White boxes indicated the magnified areas. Cilia length is shown in the bar graph. n=50 for all experiments. ****$p < 0.0001$ and ####$p < 0.0001$, compared to vehicle-treated wild-type and *Pkd2* mice, respectively. Statistical analysis was performed using ANOVA followed by a Bonferroni post hoc test.

Figure S17. Representative immunofluorescence images show the localization of CTNDDS and length of cilia in cardiac myocytes. Cilia length is presented in the bar graphs. For all immunofluorescence studies, green (acetylated-α-tubulin or cilia marker), red (CTNDDS), and blue (DAPI or nucleus). n=50 for all experiments. ****$p < 0.0001$ and ####$p < 0.0001$, compared to vehicle-treated wild-type and *Pkd2* mice, respectively. Statistical analysis was performed using ANOVA followed by a Bonferroni post hoc test.

Figure S18. Systolic blood pressure (SBP), mean arterial pressure (MAP) and heart rate (HR) measurement.

Figure S19. (a) Parameters of heart function were analysed. (b) NP fluorescence was quantified in major visceral organs to determine the NP bio-distribution at 24- and 72-hours after the intravenous injection. (c) A H&E histopathological analysis of major visceral organs from different treatments. n=5 mice for all experiments. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p <$

0.0001 compared to wild-type vehicle. #p < 0.05, ##p < 0.01, ###p < 0.001, ####p < 0.0001 compared to *Pkd2* vehicle. Statistical analysis was performed using ANOVA followed by a Bonferroni post hoc test.

Figure S20. (a) Line graphs showing the changes in systolic (SBP) and mean arterial (MAP) blood pressures when *IFT88* mice treated with different treatments for 8 weeks. (b) Representative left ventricular pressure-volume (P-V) loops from treatment with control (PBS), fenoldopam, CT-DAu-NPs or CT-PLGA-NPs. (c) The representative loop diagrams show the LVV and LVP relationship without (vehicle; PBS) and with stressors. Stress was achieved with either epinephrine (Epi) or diltiazem (Dlz). (d) Representative ECGs of the hearts over a 5-second duration. Arrows indicate uneven heart beats. ****p < 0.0001 compared to wild-type vehicle. Statistical analysis was performed using a second order quadratic polynomial Goodness of Fit followed with ANOVA using a Tukey's multiple comparisons test.

Table S1. Working heart analysis of wild-type (vehicle) and *Pkd2* mice.

Table S2. Working heart analysis of *Pkd2* mice treated with CT-DAu-NPs and CT-PLGA-NPs.

Table S3. Working heart analysis of *Pkd2* mice treated with fenoldopam.

Table S4. Safety evaluation of CTNDDS treatment *in vivo* was assessed by analyzing biochemistry parameters.

Figure S1

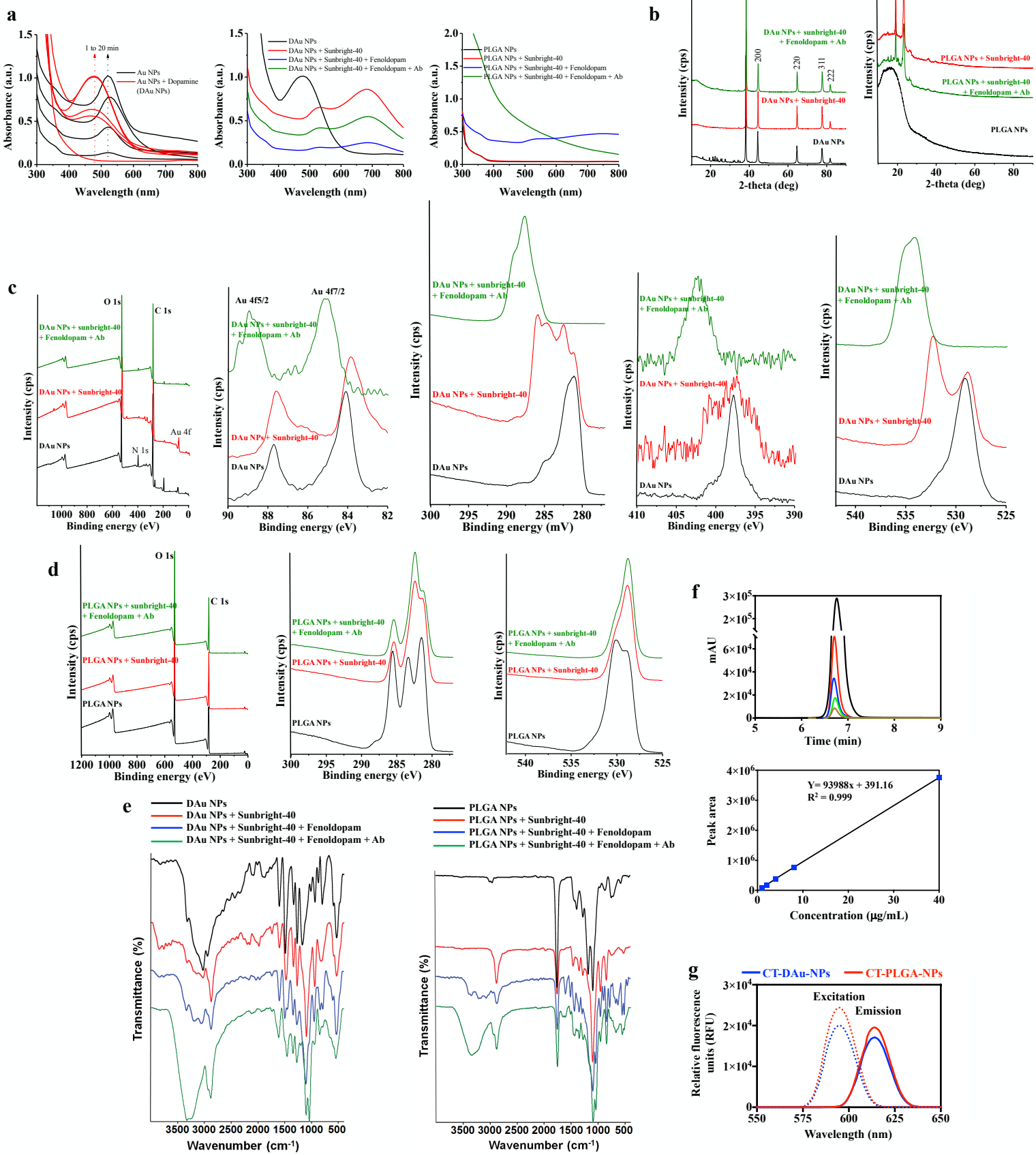

a
1 to 20 min
Au NPs
Au NPs + Dopamine (DAu NPs)
Absorbance (a.u.)
Wavelength (nm)
DAu NPs
DAu NPs + Sunbright-40
DAu NPs + Sunbright-40 + Fenoldopam
DAu NPs + Sunbright-40 + Fenoldopam + Ab
PLGA NPs
PLGA NPs + Sunbright-40
PLGA NPs + Sunbright-40 + Fenoldopam
PLGA NPs + Sunbright-40 + Fenoldopam + Ab
b
Intensity (cps)
2-theta (deg)
111
200
220
311
222
DAu NPs + sunbright-40 + Fenoldopam + Ab
DAu NPs + Sunbright-40
DAu NPs
PLGA NPs + Sunbright-40
PLGA NPs + sunbright-40 + Fenoldopam + Ab
PLGA NPs
c
O 1s
C 1s
Au 4f
N 1s
Au 4f5/2
Au 4f7/2
Binding energy (eV)
Binding energy (mV)
d
e
Transmittance (%)
Wavenumber (cm-1)
f
mAU
Time (min)
Peak area
Y= 93988x + 391.16
R2 = 0.999
Concentration (μg/mL)
g
CT-DAu-NPs
CT-PLGA-NPs
Excitation
Emission
Relative fluorescence units (RFU)
Wavelength (nm)

Figure S2

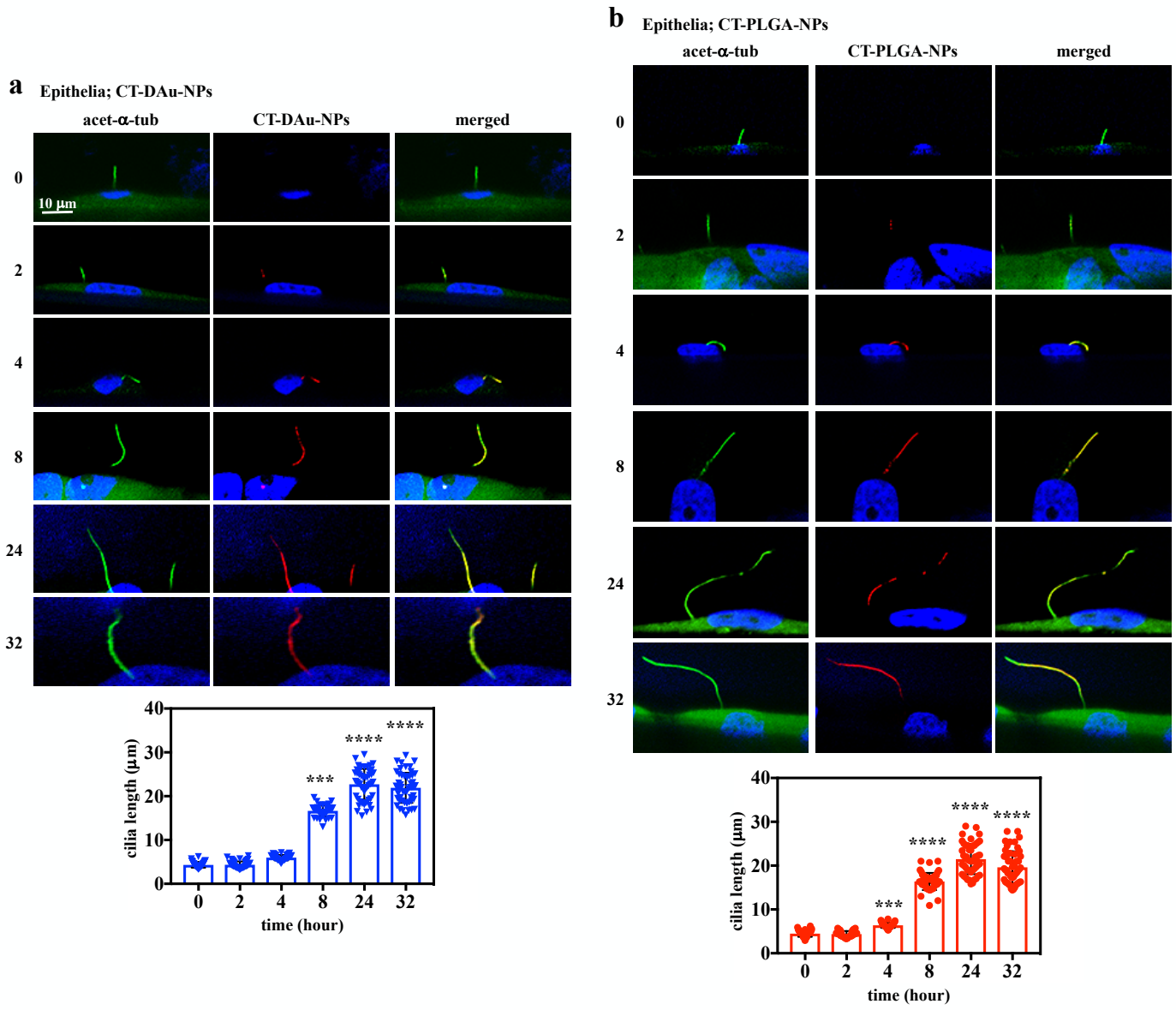

a
Epithelia; CT-DAu-NPs
acet-α-tub
CT-DAu-NPs
merged
0
2
4
8
24
32
10 µm
cilia length (µm)
time (hour)
***
****
****
b
Epithelia; CT-PLGA-NPs
acet-α-tub
CT-PLGA-NPs
merged
0
2
4
8
24
32
cilia length (µm)
time (hour)
***
****
****
****

Figure S3

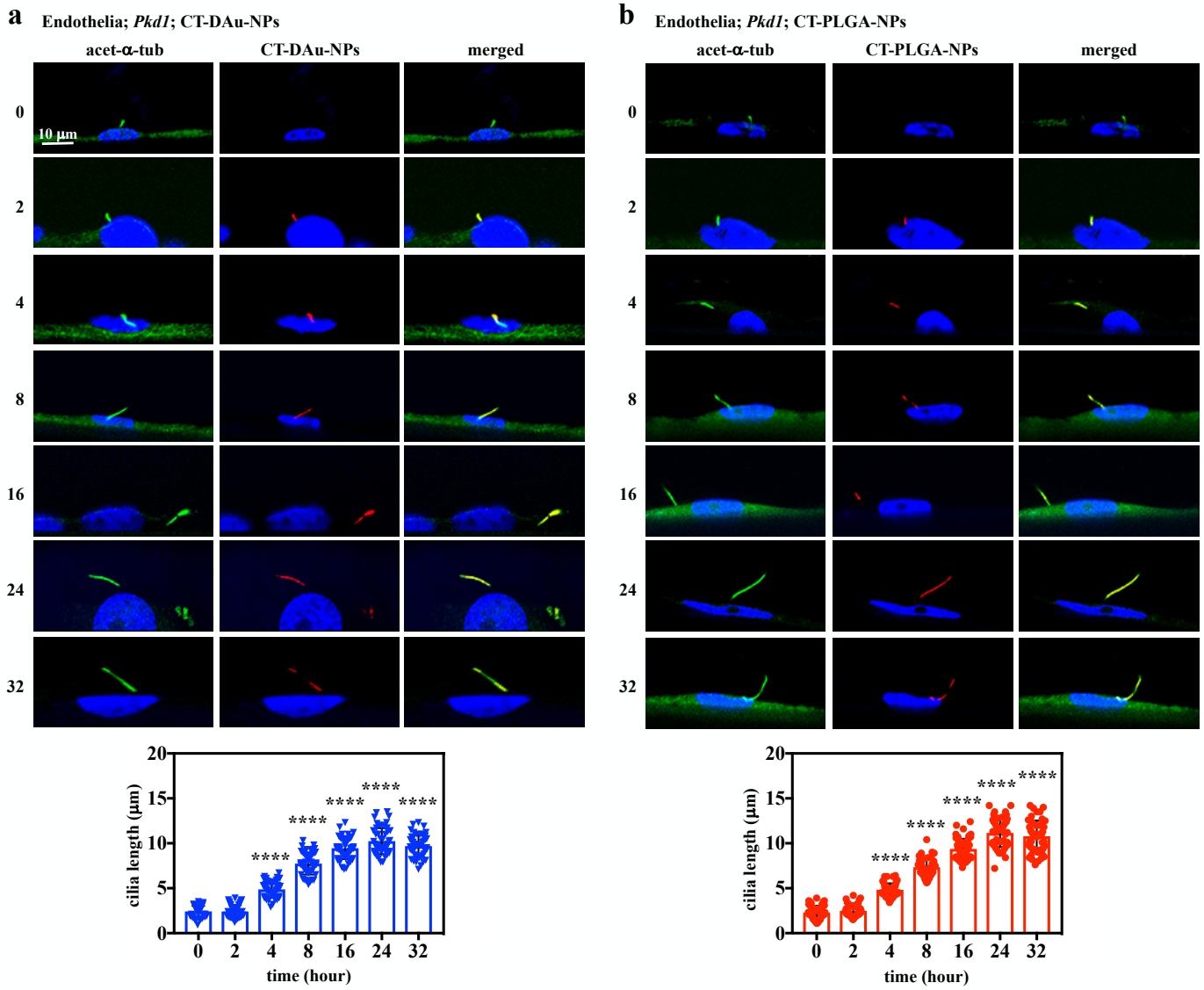

a
Endothelia; Pkd1; CT-DAu-NPs
acet-α-tub
CT-DAu-NPs
merged
0
2
4
8
16
24
32
10 μm
cilia length (μm)
time (hour)
b
Endothelia; Pkd1; CT-PLGA-NPs
acet-α-tub
CT-PLGA-NPs
merged
cilia length (μm)
time (hour)

Figure S4

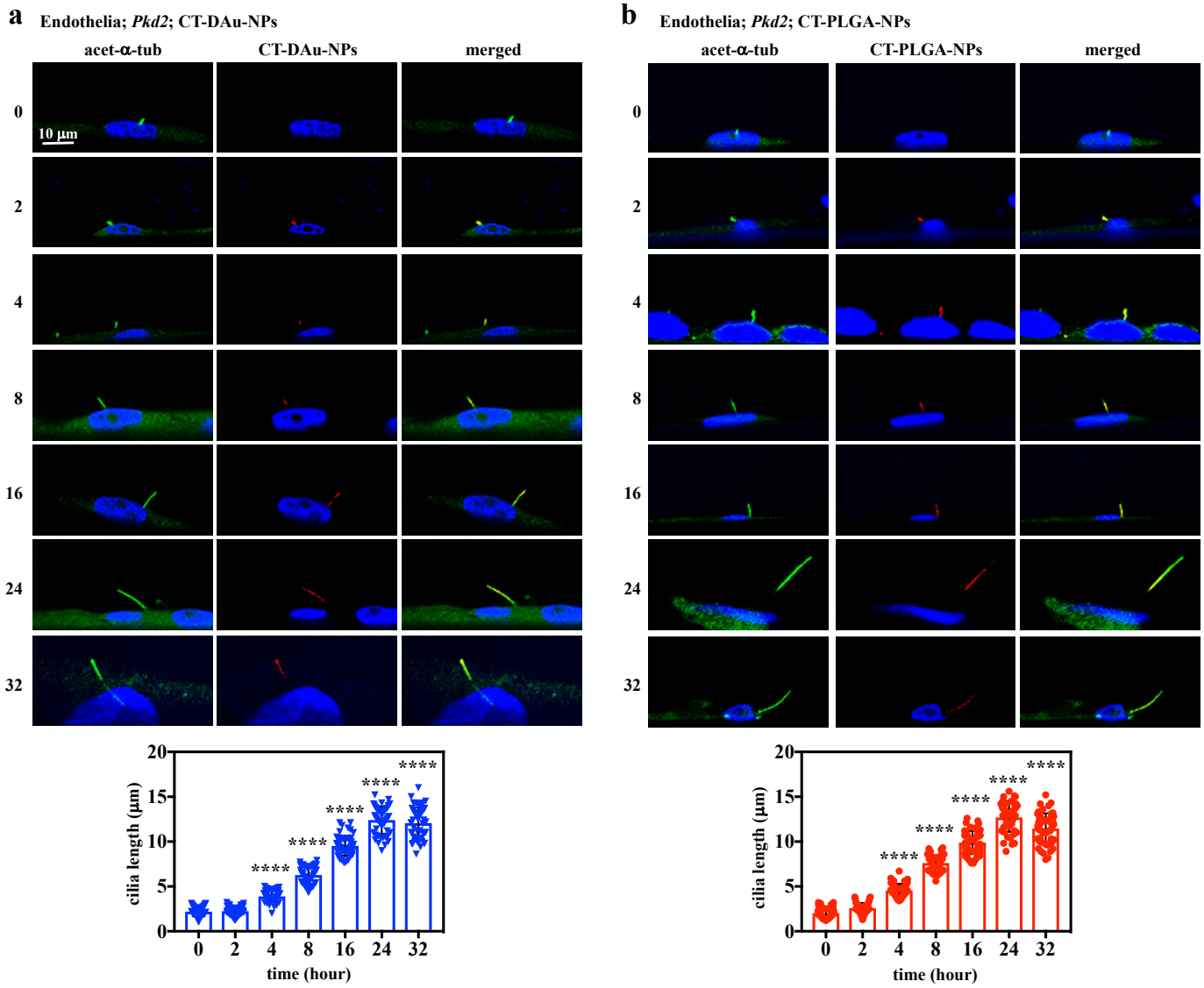

a
Endothelia; Pkd2; CT-DAu-NPs
acet-α-tub
CT-DAu-NPs
merged
0
2
4
8
16
24
32
10 μm
cilia length (μm)
time (hour)
****
b
Endothelia; Pkd2; CT-PLGA-NPs
acet-α-tub
CT-PLGA-NPs
merged
cilia length (μm)
time (hour)

Figure S5

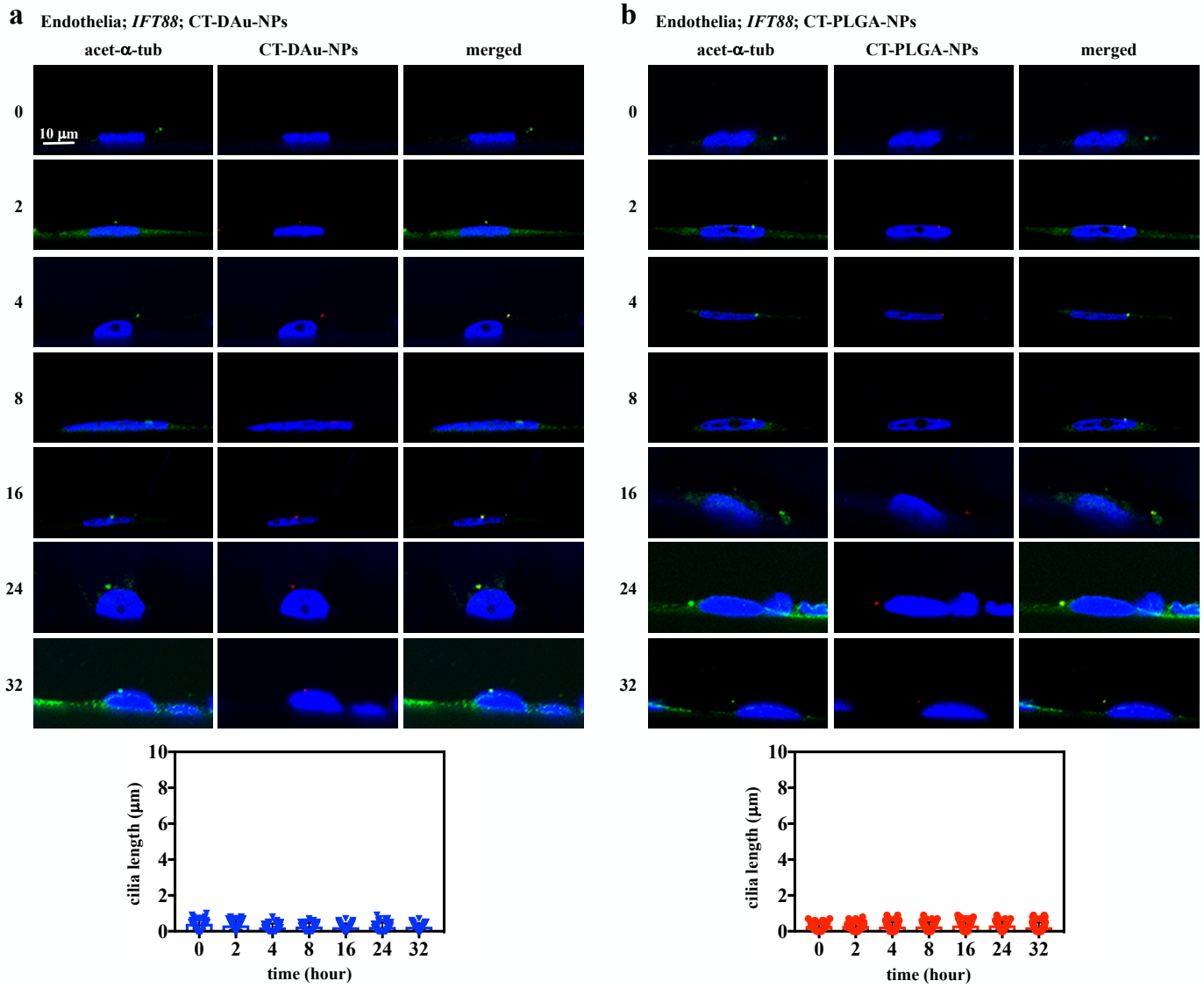

a
Endothelia; IFT88; CT-DAu-NPs
acet-α-tub
CT-DAu-NPs
merged
0
2
4
8
16
24
32
10 μm
cilia length (μm)
time (hour)
b
Endothelia; IFT88; CT-PLGA-NPs
acet-α-tub
CT-PLGA-NPs
merged
cilia length (μm)
time (hour)

Figure S6

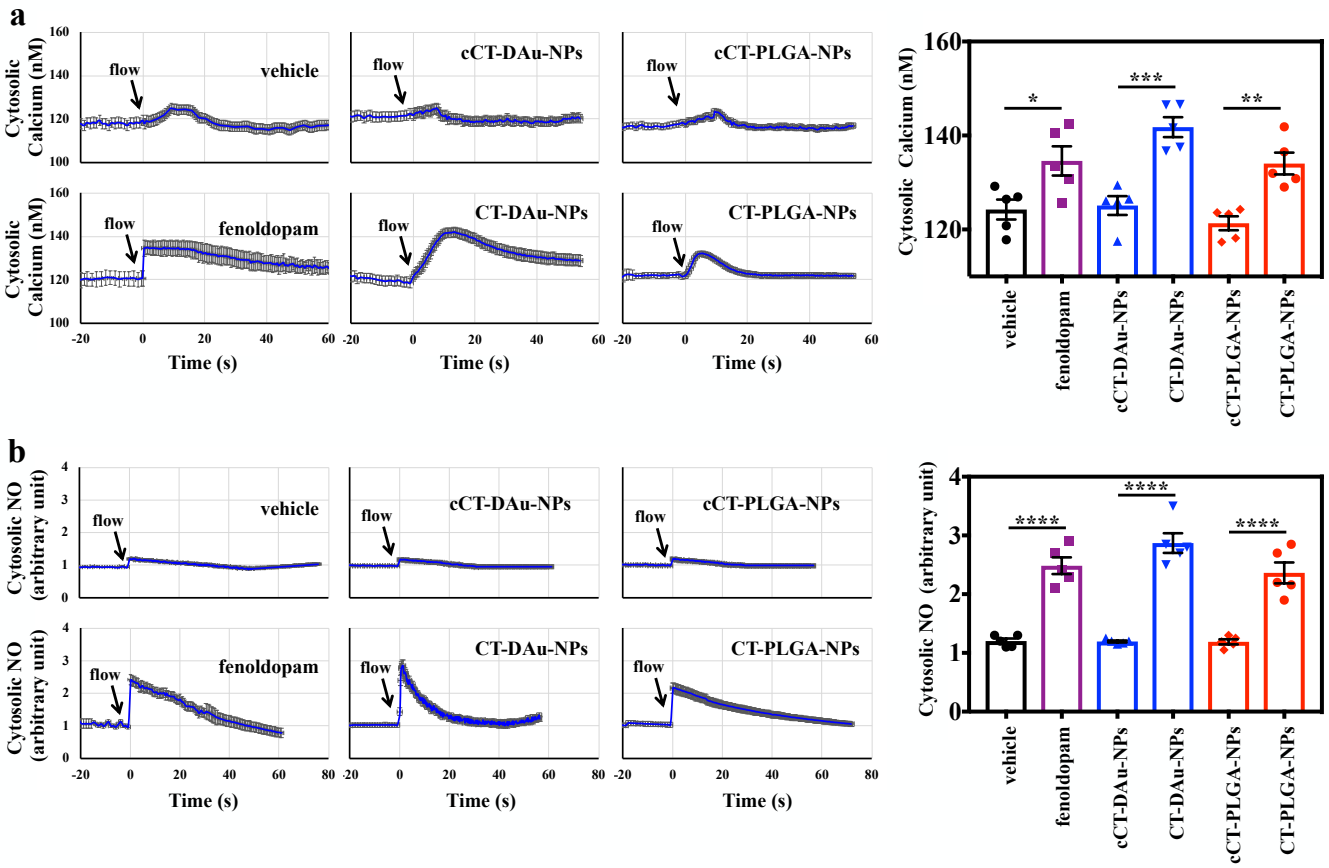
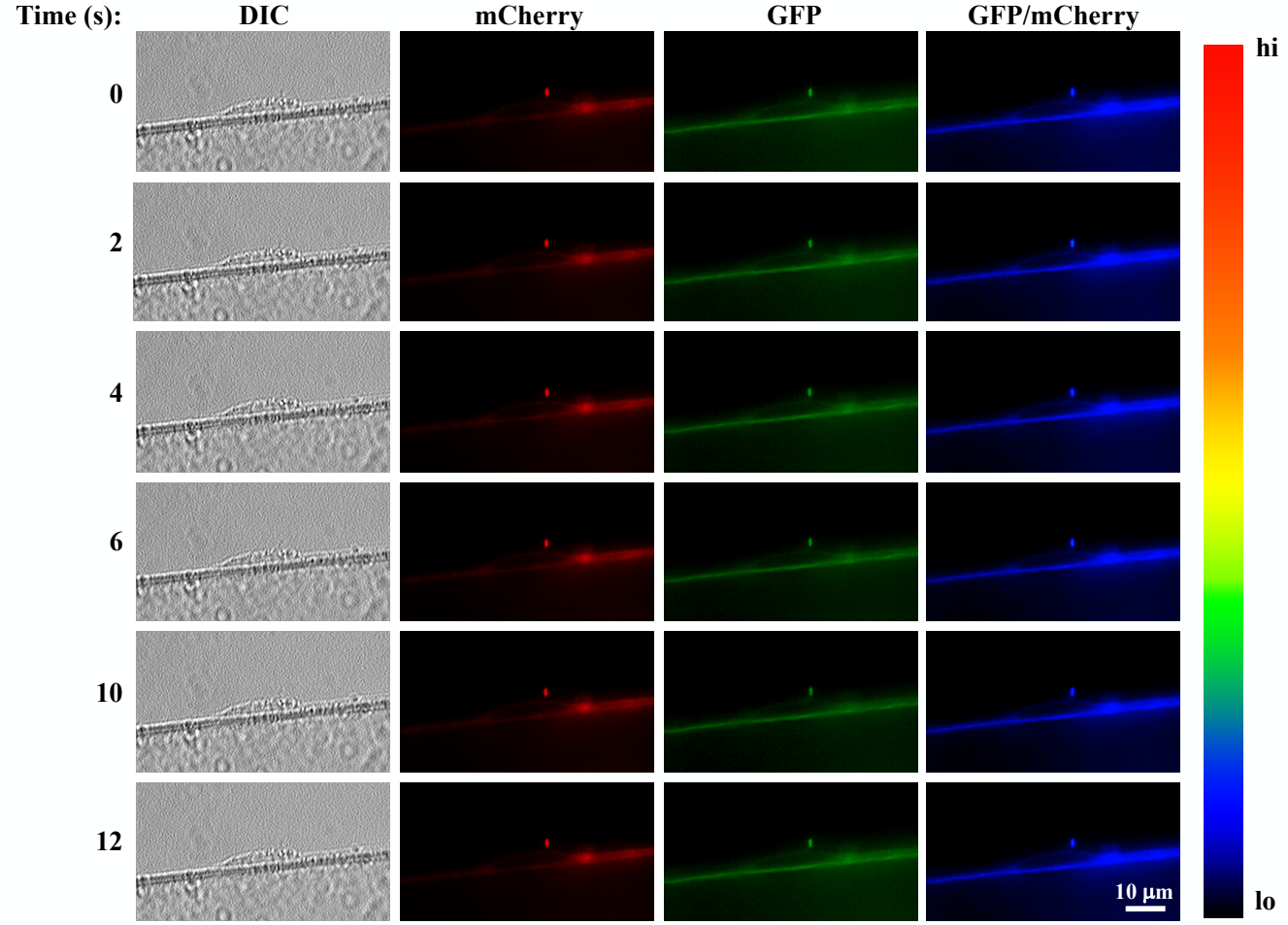

a
Cytosolic Calcium (nM)
flow
vehicle
cCT-DAu-NPs
cCT-PLGA-NPs
fenoldopam
CT-DAu-NPs
CT-PLGA-NPs
Time (s)
Cytosolic Calcium (nM)
vehicle
fenoldopam
cCT-DAu-NPs
CT-DAu-NPs
cCT-PLGA-NPs
CT-PLGA-NPs
b
Cytosolic NO (arbitrary unit)
Time (s)
Cytosolic NO (arbitrary unit)

Figure S7

a **Vehicle**



b **Fenoldopam**

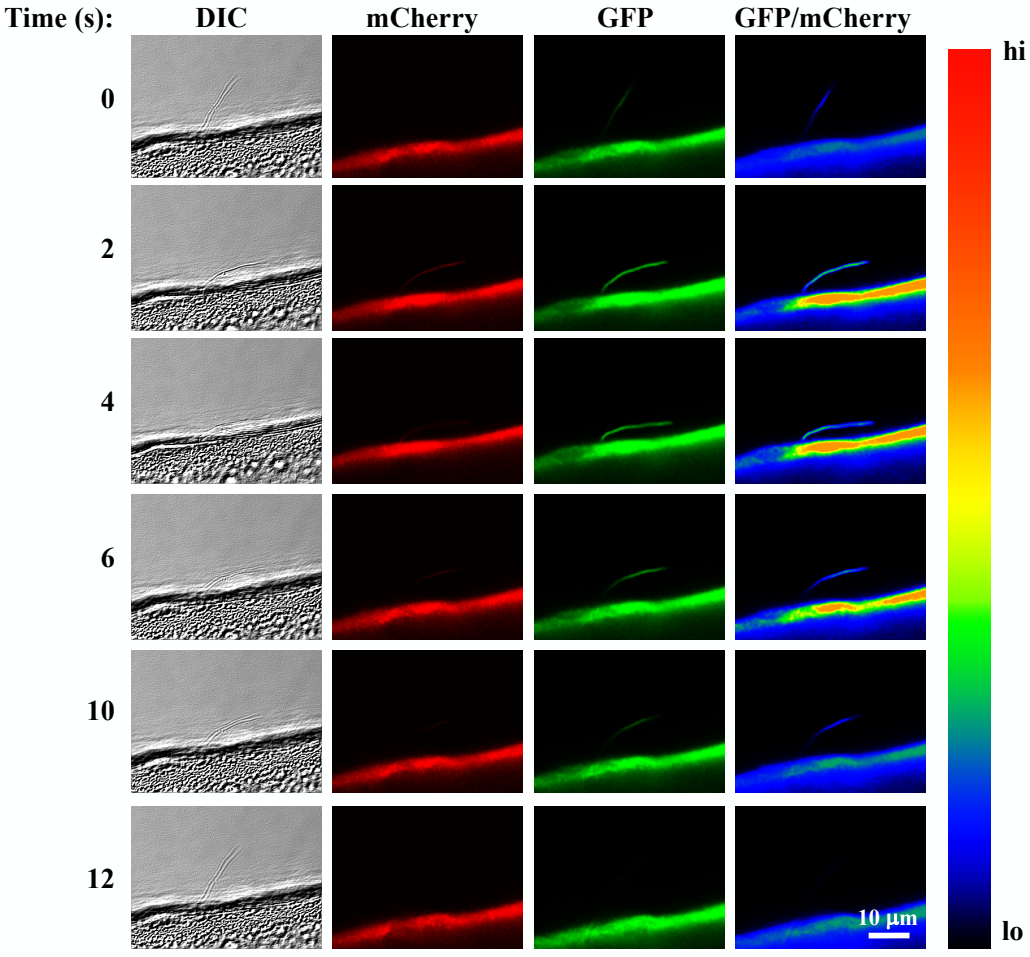
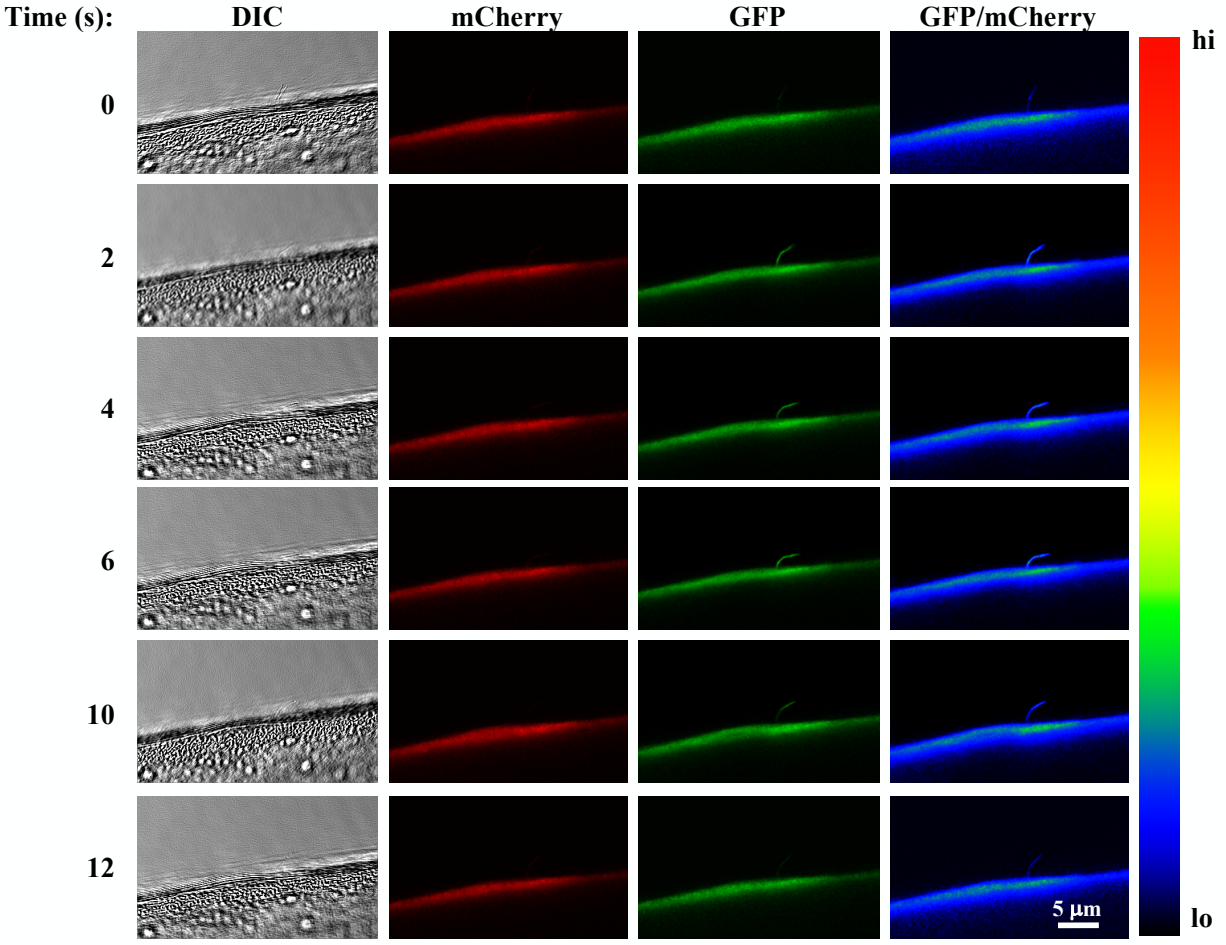


Figure S8

a **cCT-DAu-NPs**



b **CT-DAu-NPs**

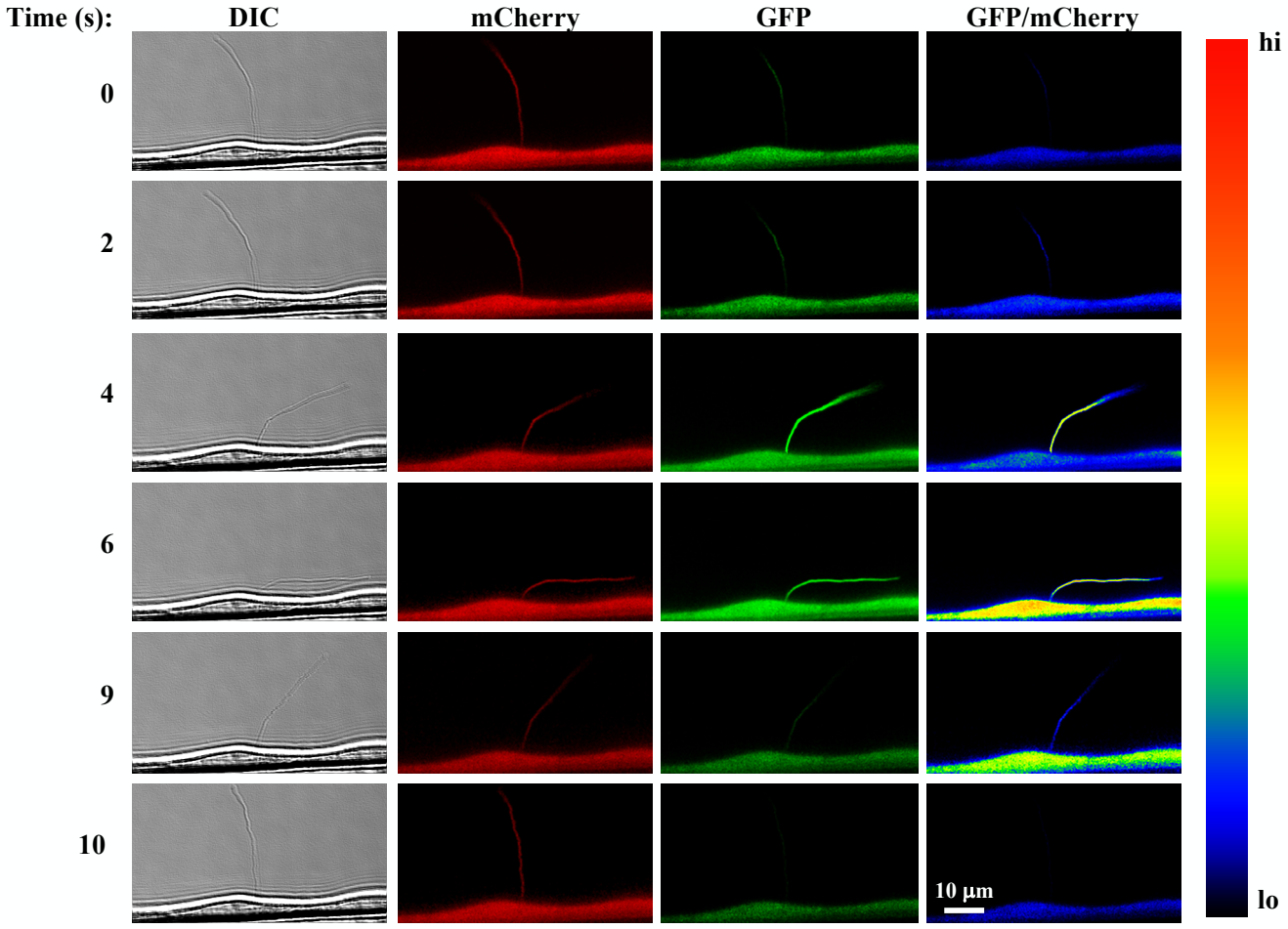
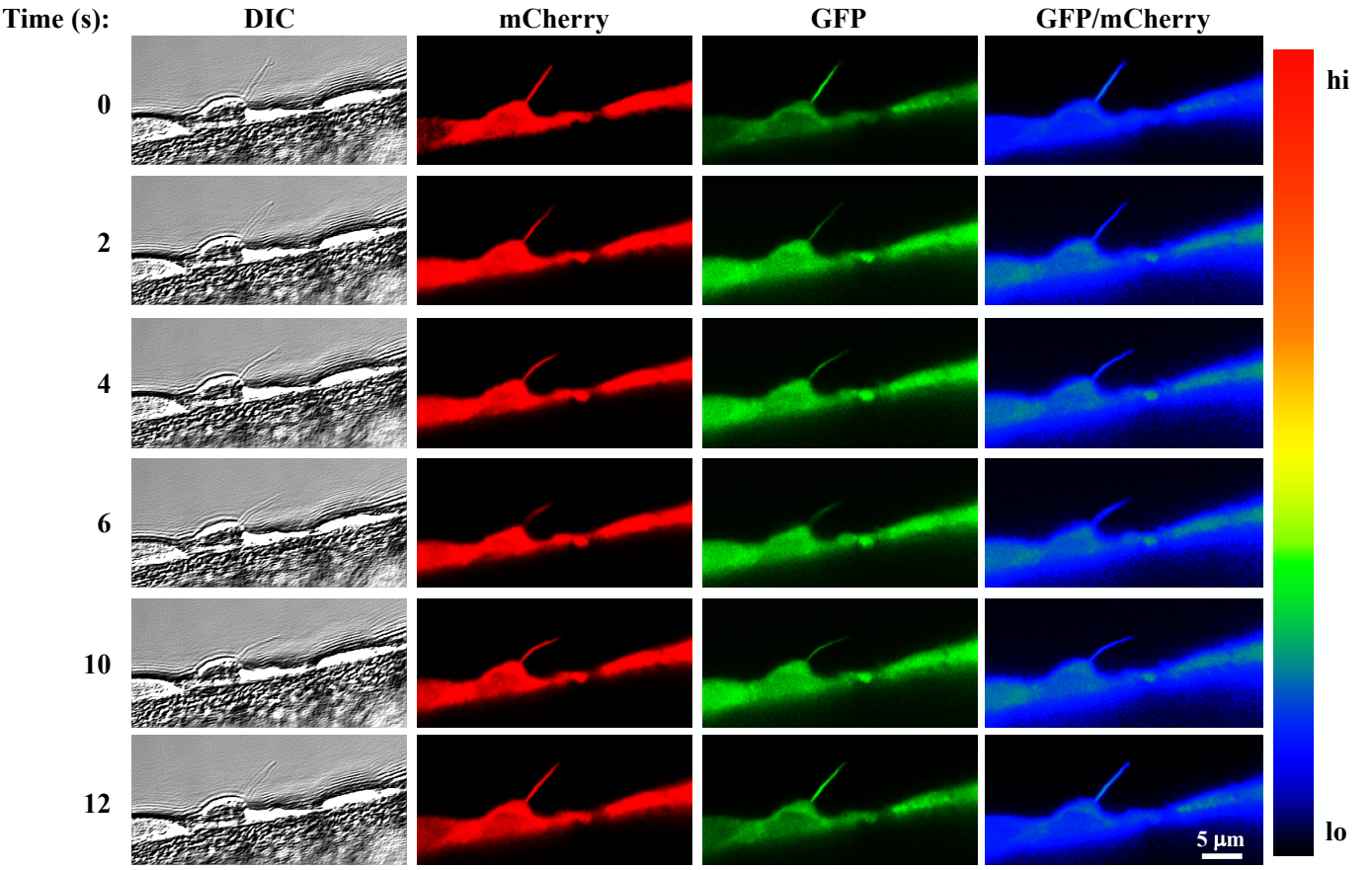


Figure S9

a **cCT-PLGA-NPs**



b **CT-PLGA-NPs**

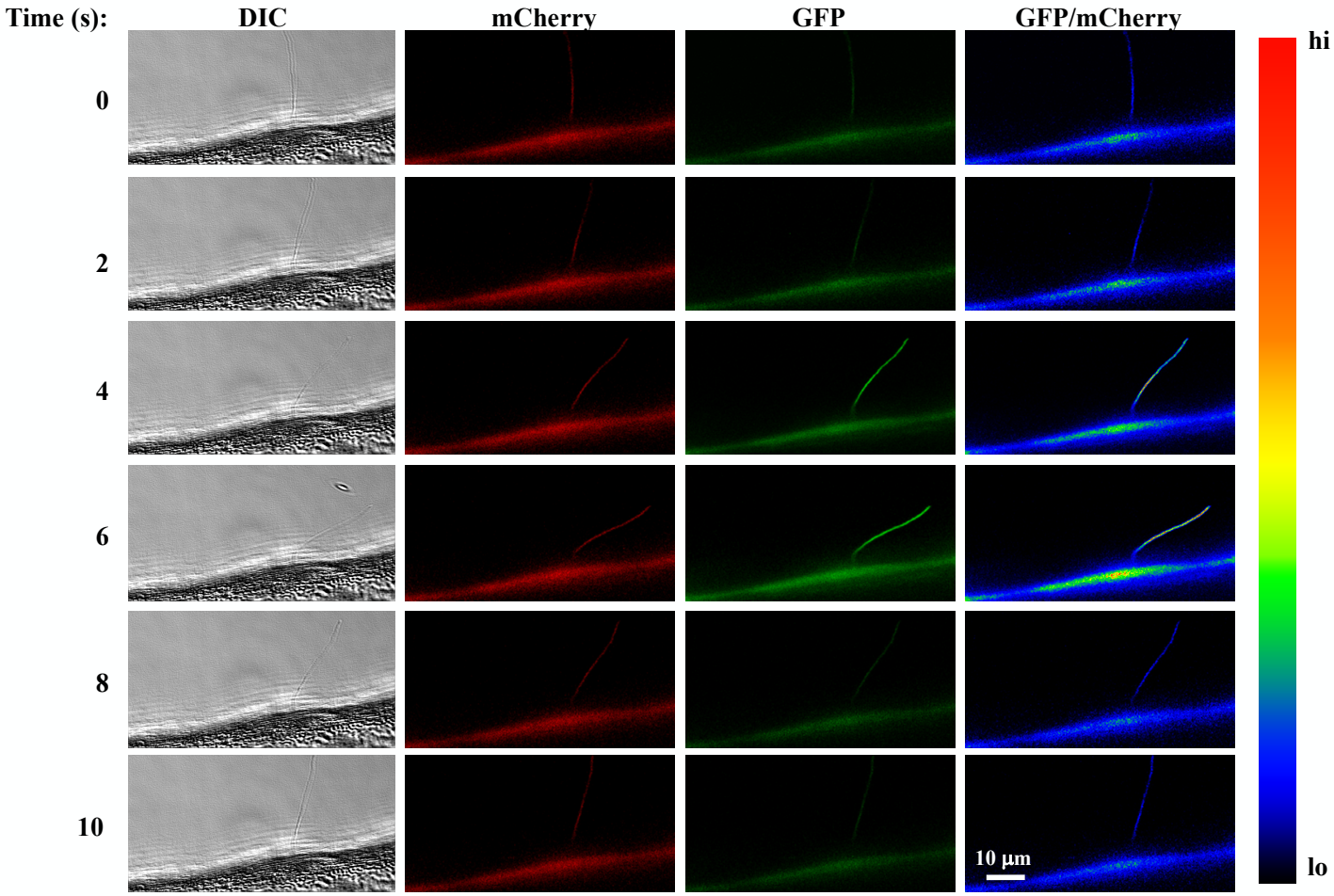


Figure S10

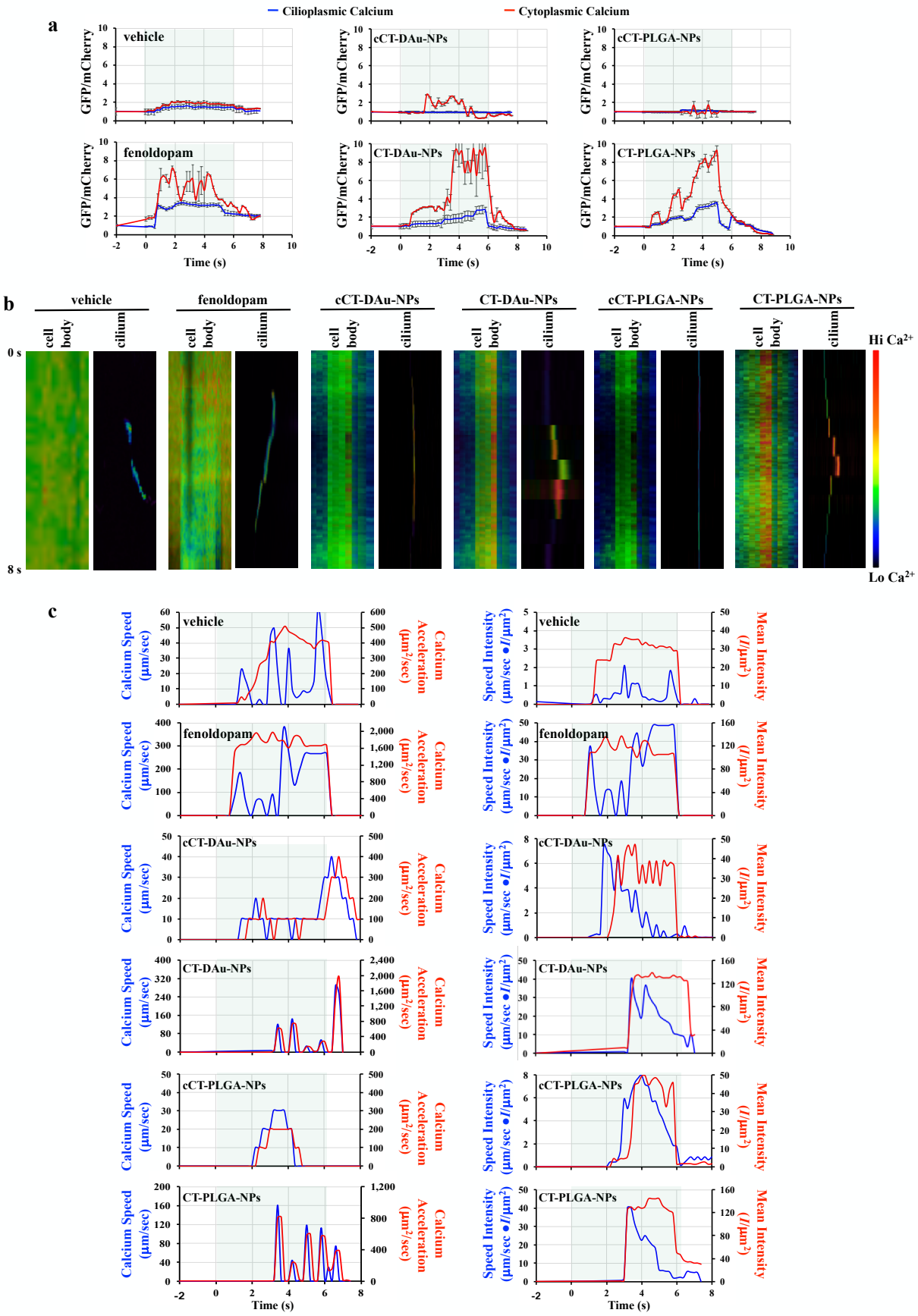

a
Cilioplasmic Calcium
Cytoplasmic Calcium
vehicle
cCT-DAu-NPs
cCT-PLGA-NPs
fenoldopam
CT-DAu-NPs
CT-PLGA-NPs
GFP/mCherry
Time (s)
b
vehicle
fenoldopam
cCT-DAu-NPs
CT-DAu-NPs
cCT-PLGA-NPs
CT-PLGA-NPs
cell body
cilium
0 s
8 s
Hi Ca2+
Lo Ca2+
c
Calcium Speed (µm/sec)
Calcium Acceleration (µm2/sec)
Speed Intensity (µm/sec •I/µm2)
Mean Intensity (I/µm2)
vehicle
fenoldopam
cCT-DAu-NPs
CT-DAu-NPs
cCT-PLGA-NPs
CT-PLGA-NPs
Time (s)

Figure S11

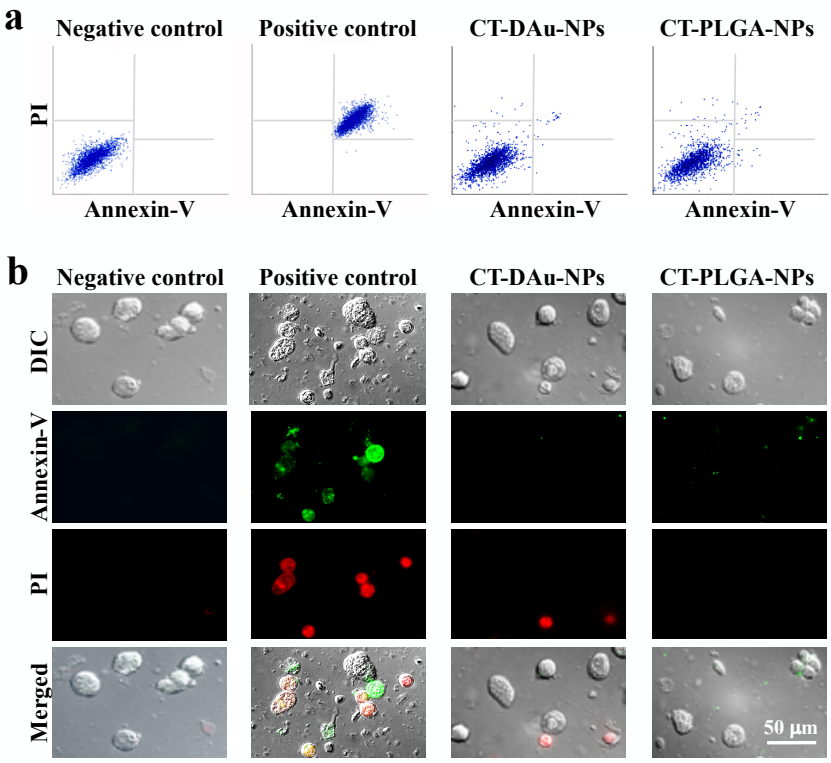

a
Negative control
Positive control
CT-DAu-NPs
CT-PLGA-NPs
PI
Annexin-V
Annexin-V
Annexin-V
Annexin-V
b
Negative control
Positive control
CT-DAu-NPs
CT-PLGA-NPs
DIC
Annexin-V
PI
Merged
50 μm

Figure S12

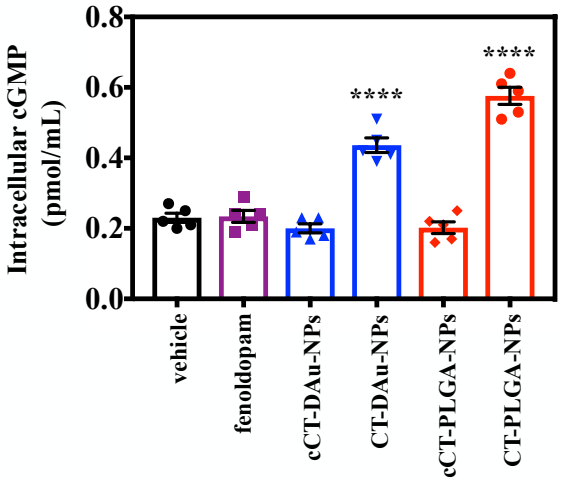

Intracellular cGMP
(pmol/mL)
0.8
0.6
0.4
0.2
0.0
****
****
vehicle
fenoldopam
cCT-DAu-NPs
CT-DAu-NPs
cCT-PLGA-NPs
CT-PLGA-NPs

Figure S13

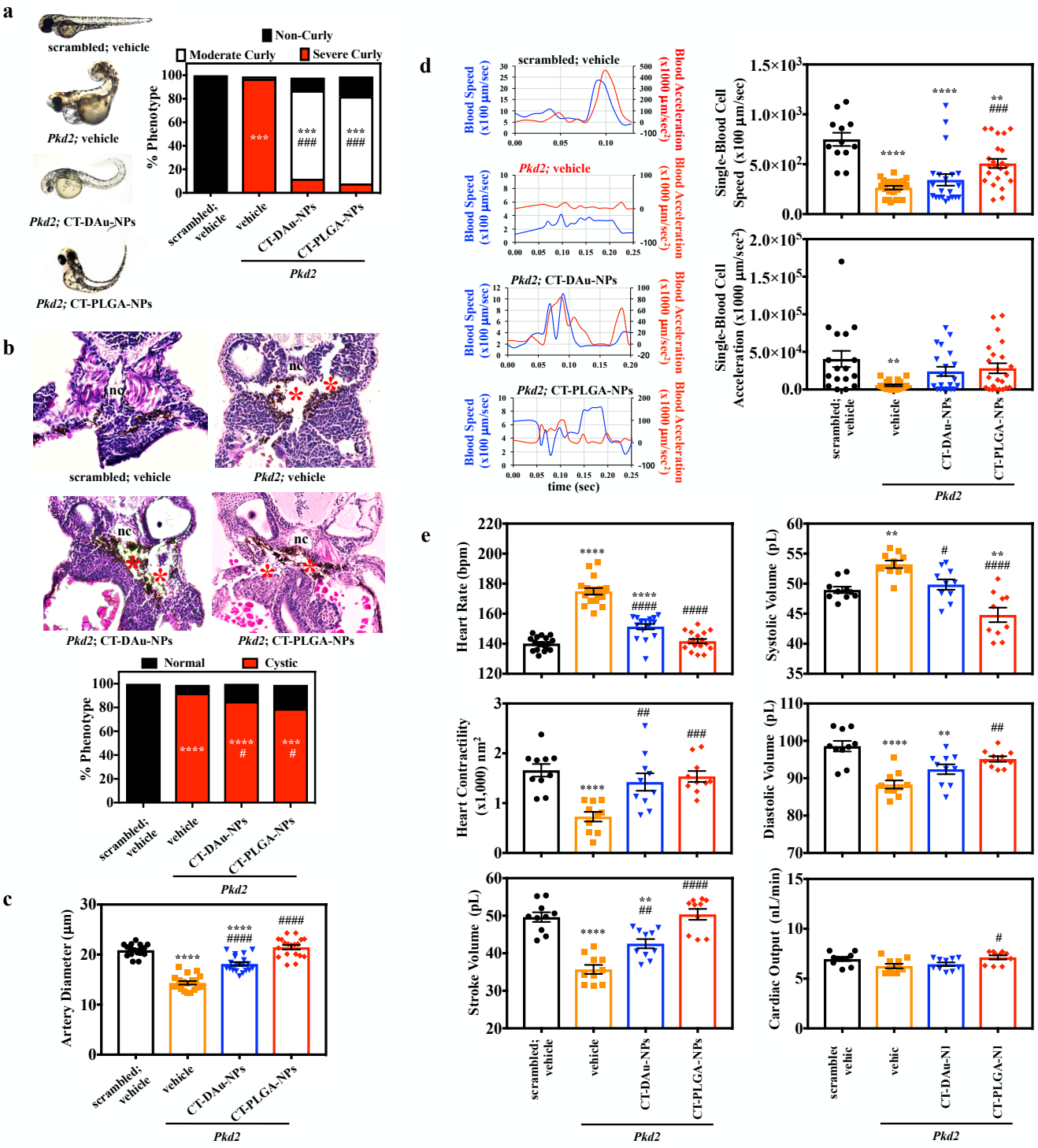

a
scrambled; vehicle
Pkd2; vehicle
Pkd2; CT-DAu-NPs
Pkd2; CT-PLGA-NPs
Non-Curly
Moderate Curly
Severe Curly
% Phenotype
scrambled; vehicle
vehicle
CT-DAu-NPs
CT-PLGA-NPs
Pkd2
b
nc
scrambled; vehicle
Pkd2; vehicle
Pkd2; CT-DAu-NPs
Pkd2; CT-PLGA-NPs
Normal
Cystic
% Phenotype
Pkd2
c
Artery Diameter (μm)
Pkd2
d
scrambled; vehicle
Pkd2; vehicle
Pkd2; CT-DAu-NPs
Pkd2; CT-PLGA-NPs
Blood Speed (x100 μm/sec)
Blood Acceleration (x1000 μm/sec²)
time (sec)
Single-Blood Cell Speed (x100 μm/sec)
Single-Blood Cell Acceleration (x1000 μm/sec²)
Pkd2
e
Heart Rate (bpm)
Systolic Volume (pL)
Heart Contractility (x1,000) nm²
Diastolic Volume (pL)
Stroke Volume (pL)
Cardiac Output (nL/min)
Pkd2

Figure S14

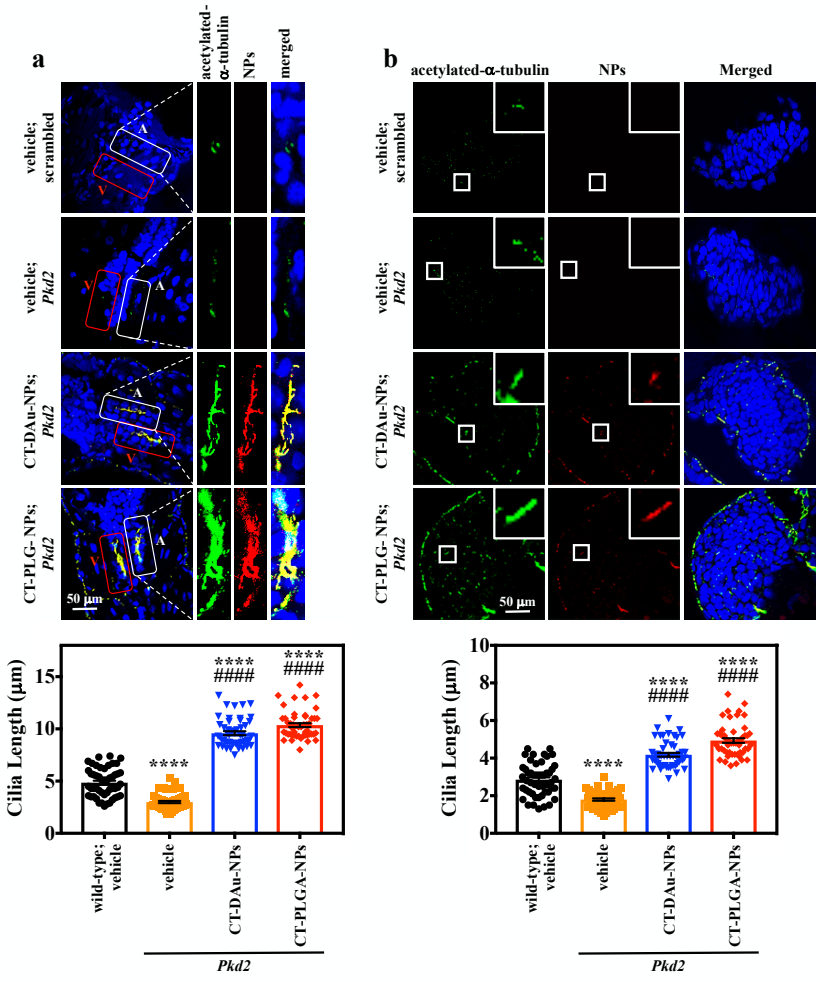

a
acetylated-α-tubulin
NPs
merged
vehicle; scrambled
vehicle; Pkd2
CT-DAu-NPs; Pkd2
CT-PLG- NPs; Pkd2
A
V
50 μm
b
acetylated-α-tubulin
NPs
Merged
vehicle; scrambled
vehicle; Pkd2
CT-DAu-NPs; Pkd2
CT-PLG- NPs; Pkd2
50 μm
Cilia Length (μm)
0
5
10
15
****
****
####
****
####
wild-type; vehicle
vehicle
CT-DAu-NPs
CT-PLGA-NPs
Pkd2
Cilia Length (μm)
0
2
4
6
8
10
****
****
####
****
####
wild-type; vehicle
vehicle
CT-DAu-NPs
CT-PLGA-NPs
Pkd2

Figure S15

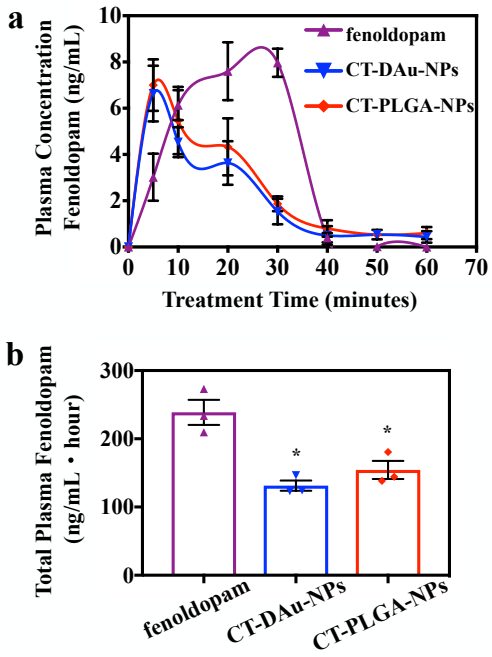
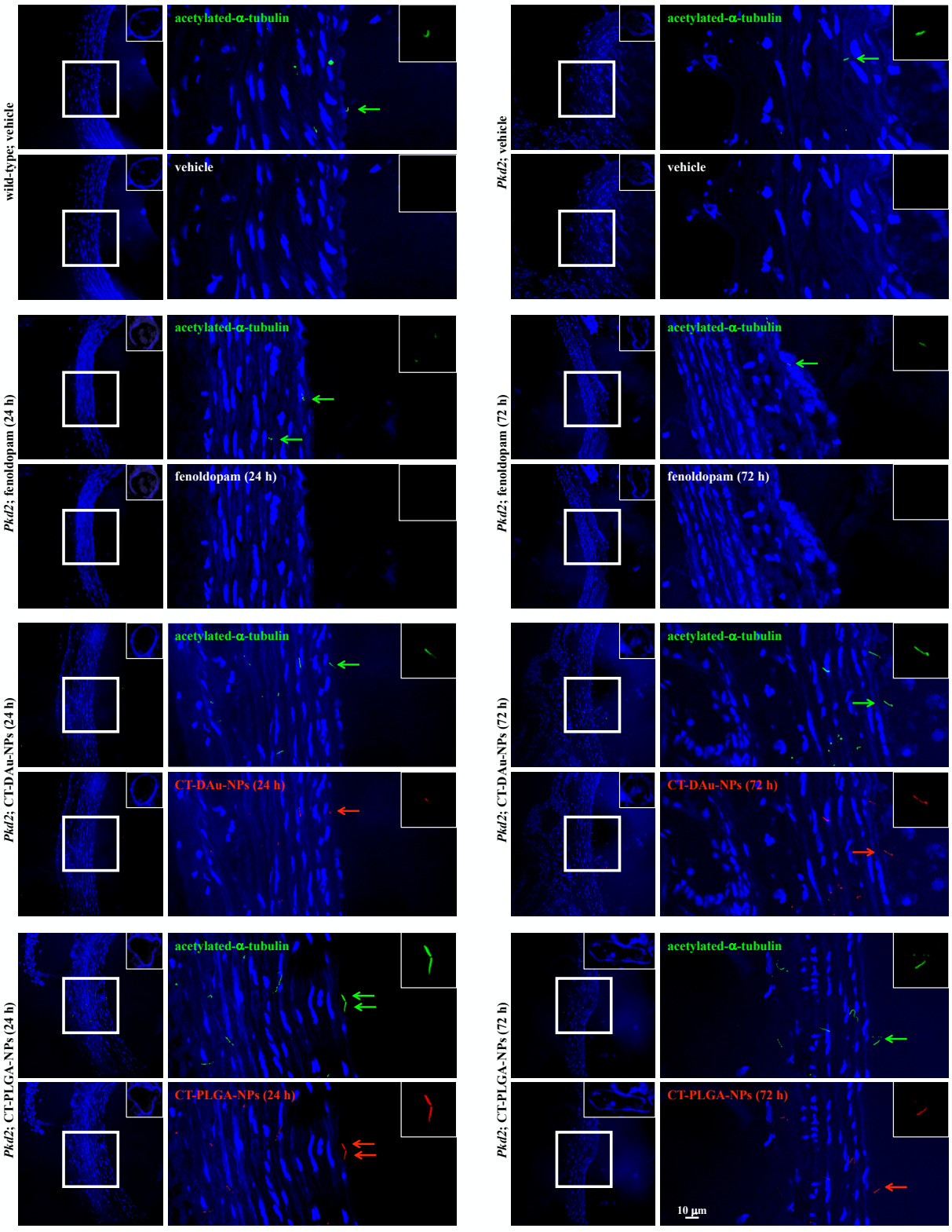

a
Plasma Concentration
Fenoldopam (ng/mL)
10
8
6
4
2
0
0
10
20
30
40
50
60
70
Treatment Time (minutes)
fenoldopam
CT-DAu-NPs
CT-PLGA-NPs
b
Total Plasma Fenoldopam
(ng/mL • hour)
300
200
100
0
*
*
fenoldopam
CT-DAu-NPs
CT-PLGA-NPs

Figure S16


wild-type; vehicle
acetylated-α-tubulin
vehicle
Pkd2; vehicle
acetylated-α-tubulin
vehicle
Pkd2; fenoldopam (24 h)
acetylated-α-tubulin
fenoldopam (24 h)
Pkd2; fenoldopam (72 h)
acetylated-α-tubulin
fenoldopam (72 h)
Pkd2; CT-DAu-NPs (24 h)
acetylated-α-tubulin
CT-DAu-NPs (24 h)
Pkd2; CT-DAu-NPs (72 h)
acetylated-α-tubulin
CT-DAu-NPs (72 h)
Pkd2; CT-PLGA-NPs (24 h)
acetylated-α-tubulin
CT-PLGA-NPs (24 h)
Pkd2; CT-PLGA-NPs (72 h)
acetylated-α-tubulin
CT-PLGA-NPs (72 h)
10 μm

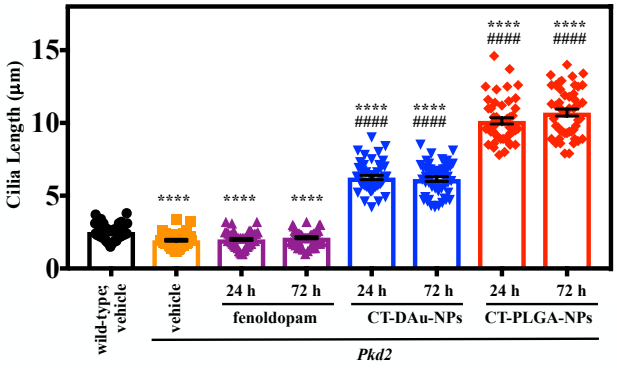

Cilia Length (μm)
15
10
5
0
****
****
****
****
####
****
####
****
####
****
####
wild-type; vehicle
vehicle
24 h
72 h
fenoldopam
24 h
72 h
CT-DAu-NPs
24 h
72 h
CT-PLGA-NPs
Pkd2

Figure S17

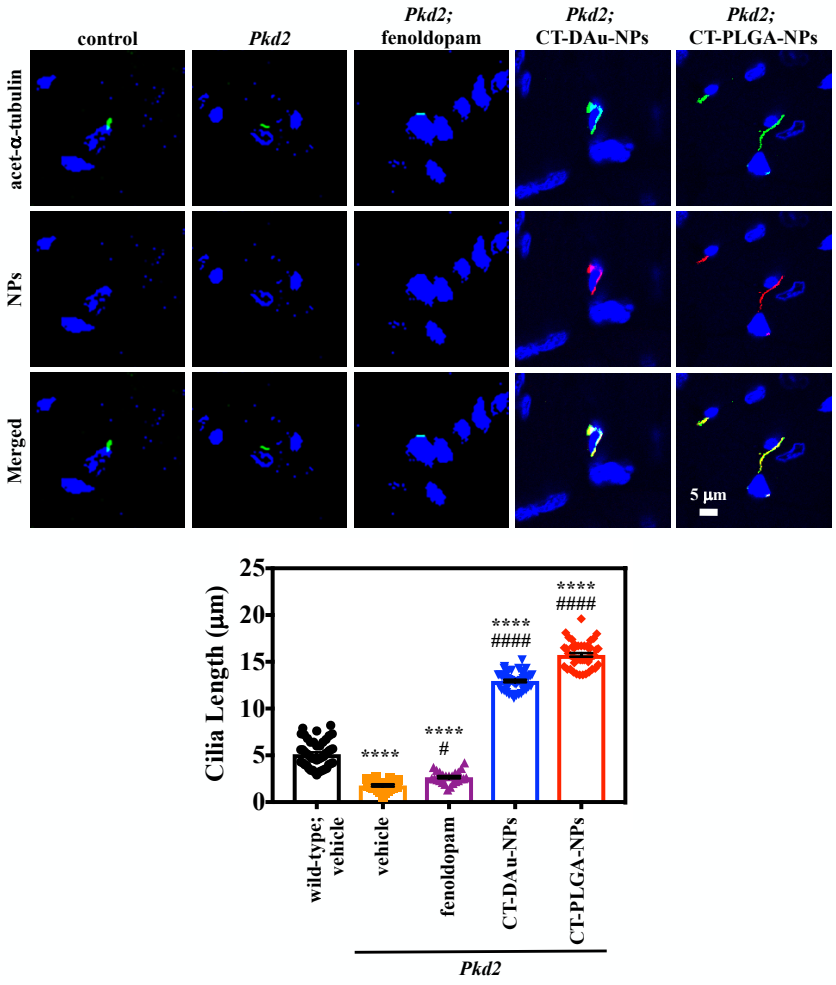

control
Pkd2
Pkd2; fenoldopam
Pkd2; CT-DAu-NPs
Pkd2; CT-PLGA-NPs
acet-α-tubulin
NPs
Merged
5 µm
Cilia Length (µm)
25
20
15
10
5
0
****
****
#
****
####
****
####
wild-type; vehicle
vehicle
fenoldopam
CT-DAu-NPs
CT-PLGA-NPs
Pkd2

Figure S18

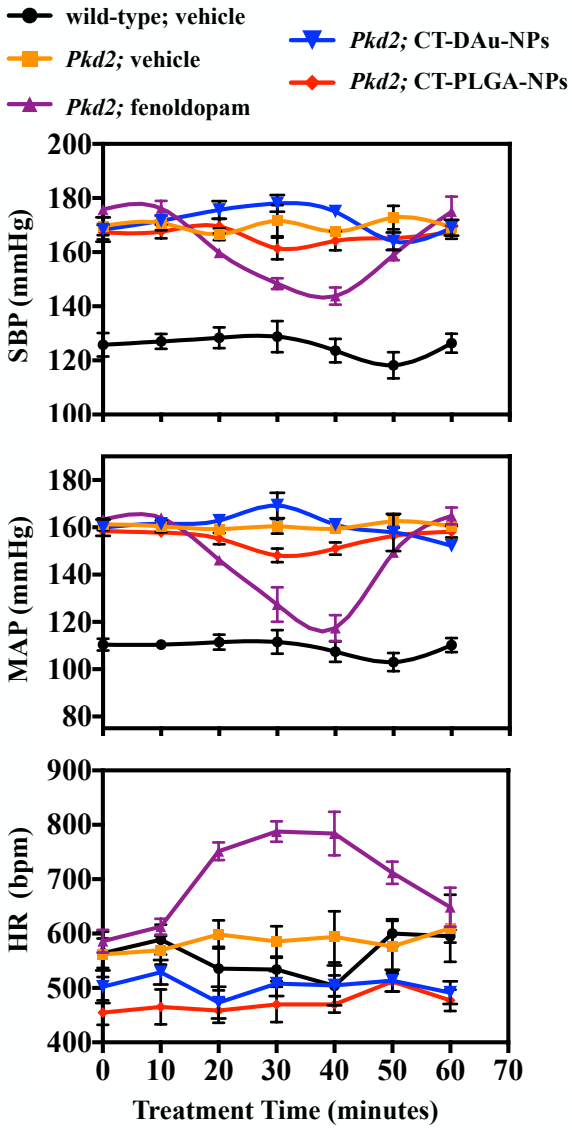

wild-type; vehicle
Pkd2; vehicle
Pkd2; fenoldopam
Pkd2; CT-DAu-NPs
Pkd2; CT-PLGA-NPs
SBP (mmHg)
MAP (mmHg)
HR (bpm)
Treatment Time (minutes)

Figure S19

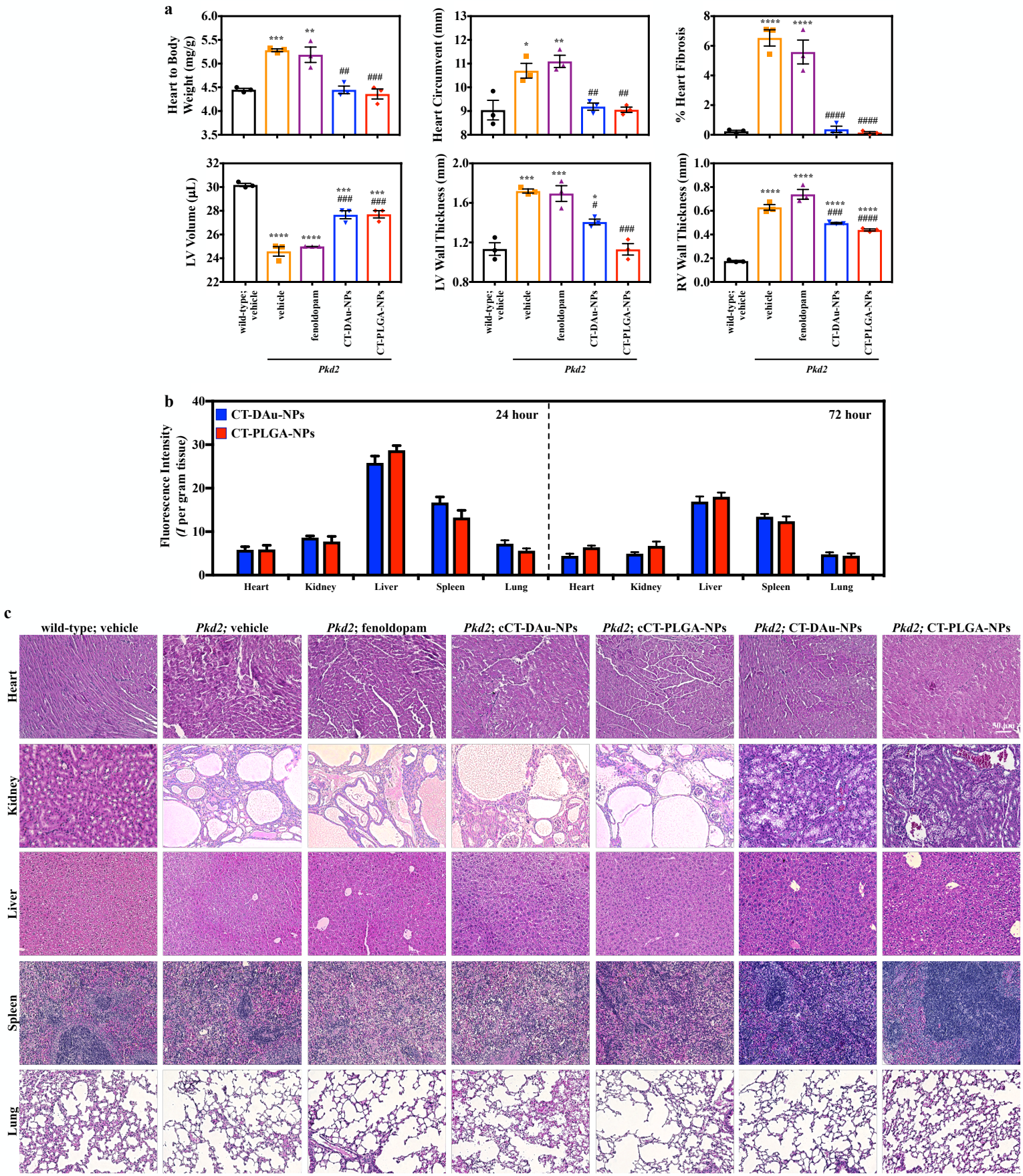

a
Heart to Body Weight (mg/g)
Heart Circumvent (mm)
% Heart Fibrosis
LV Volume (μL)
LV Wall Thickness (mm)
RV Wall Thickness (mm)
wild-type; vehicle
vehicle
fenoldopam
CT-DAu-NPs
CT-PLGA-NPs
Pkd2
b
CT-DAu-NPs
CT-PLGA-NPs
24 hour
72 hour
Fluorescence Intensity (I per gram tissue)
Heart
Kidney
Liver
Spleen
Lung
c
wild-type; vehicle
Pkd2; vehicle
Pkd2; fenoldopam
Pkd2; cCT-DAu-NPs
Pkd2; cCT-PLGA-NPs
Pkd2; CT-DAu-NPs
Pkd2; CT-PLGA-NPs
Heart
Kidney
Liver
Spleen
Lung

Figure S20

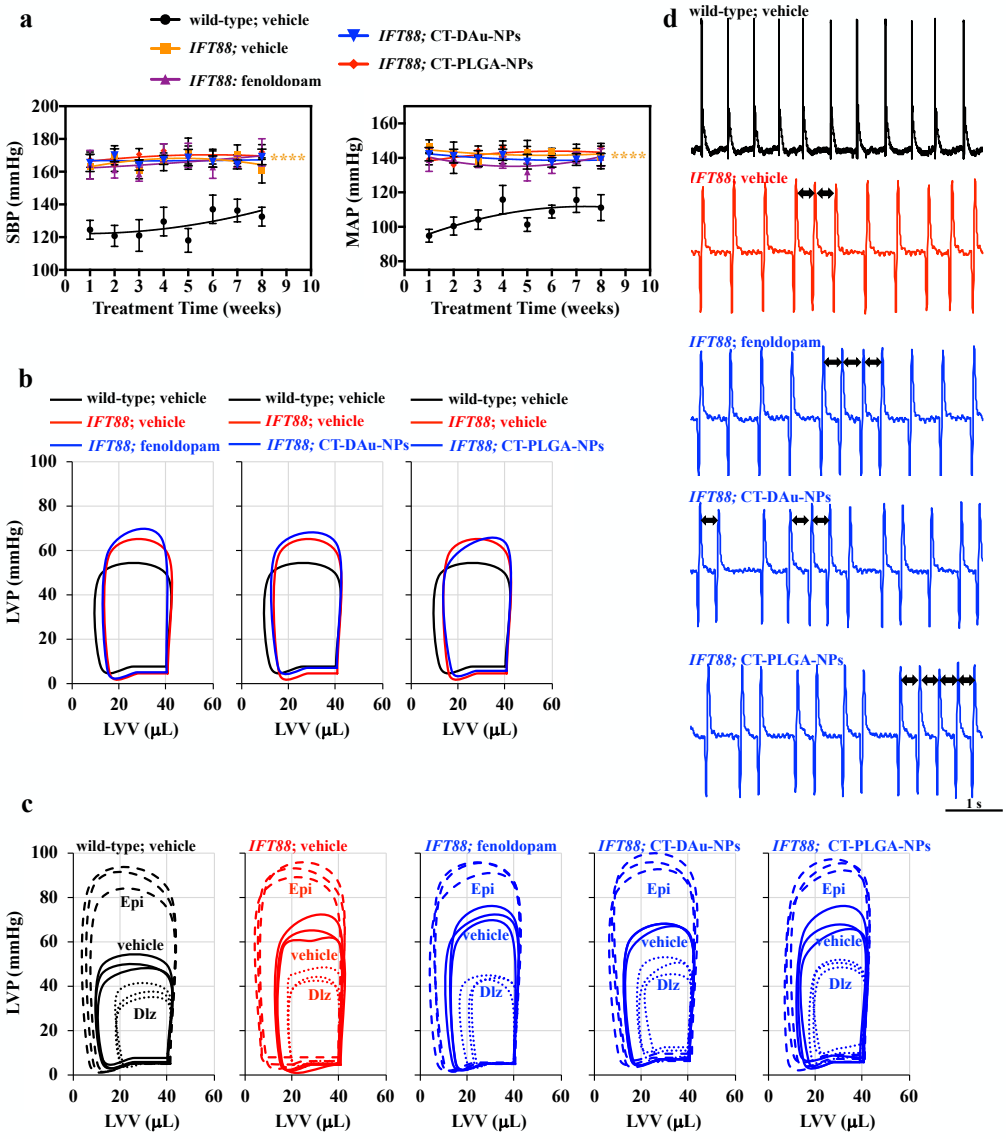

a
wild-type; vehicle
IFT88; vehicle
IFT88; fenoldopam
IFT88; CT-DAu-NPs
IFT88; CT-PLGA-NPs
SBP (mmHg)
MAP (mmHg)
Treatment Time (weeks)
****
b
wild-type; vehicle
IFT88; vehicle
IFT88; fenoldopam
IFT88; CT-DAu-NPs
IFT88; CT-PLGA-NPs
LVP (mmHg)
LVV (μL)
c
Epi
vehicle
Dlz
d
wild-type; vehicle
IFT88; vehicle
IFT88; fenoldopam
IFT88; CT-DAu-NPs
IFT88; CT-PLGA-NPs
1 s

Table S1

	wild-type			*Pkd2*		
	vehicle	**epinephrine**	**diltiazem**	**vehicle**	**epinephrine**	**diltiazem**
HR (beat/min)	144±15	209±16	72±20	134±17	230±15	76±9
ESPVR (mmHg/μL)	3.8±0.2	10.0±2.4	1.7±0.3	3.9±0.1	11.2±1.7	2.0±0.2
EDPVR (mmHg/μL)	0.15±0.02	0.12±0.01	0.13±0.01	0.13±0.01	0.13±0.01	0.13±0.01
dP/dtmax (mmHg/s)	5075±123	16222±808	3034±332	4711±157	16480±356	2845±954
dP/dtmin (mmHg/s)	-2008±200	-3048±114	-1401±59	-1297±144	-3096±81	-1071±358
LV Pmax (mmHg)	47.0±1.1	81.1±4.0	33.7±3.7	43.6±14.5	82.4±1.8	31.6±10.6
LV ESP (mmHg)	35.2±0.9	60.8±3.0	25.3±2.8	32.7±10.9	61.8±1.3	23.7±6.0
LV EDP (mmHg)	6.2±0.6	5.1±0.2	5.2±0.1	4.0±1.3	5.2±0.1	4.0±1.3
LV ESV (μL)	12.4±0.4	8.5±1.6	20.4±0.9	11.6±3.8	7.74±1.2	15.6±5.2
LV EDV (μL)	40.1±0.1	41.2±0.1	40.1±0.1	30.1±10.0	41.0±0.2	30.3±10.1
SV (μL)	27.7±0.3	32.7±1.7	19.7±1.0	18.4±6.1	16.6±7.4	14.7±5.0
SW (mmHg•μL)	1130±16	2486±292	562±152	1304±390	2283±114	407±23
EF (%)	69.0±0.9	79.4±4.0	49.1±2.4	61.3±0.9	81.3±2.9	48.6±3.0
CO (μL/min)	3987±45	6828±268	1772±199	2473±104	3829±219	1324±455

HR, heart rate; ESPVR and EDPVR, end-systolic and end-diastolic pressure volume relation, respectively; dP/dtmax and dP/dtmin, maximum rate of left ventricle (LV) pressure rise and fall, respectively; Pmax, systolic pressure; ESP, end-systolic pressure; EDP, end-diastolic pressure; ESV, end-systolic volume; EDV, end-diastolic volume; SV, stroke volume; SW, stroke work; EF, ejection fraction; CO, cardiac output.

Table S2

	Pkd2; CT-DAu-NPs			*Pkd2;* CT-PLGA-NPs		
	vehicle	**epinephrine**	**diltiazem**	**vehicle**	**epinephrine**	**diltiazem**
HR (beat/min)	136±16	207±19	94±10	143±11	210±18	89±13
ESPVR (mmHg/μL)	4.4±0.10	9.8±1.30	1.8±0.33	4.3±0.14	9.2±2.50	2.5±0.59
EDPVR (mmHg/μL)	0.14±0.01	0.14±0.01	0.13±0.01	0.15±0.02	0.19±0.03	0.17±0.02
dP/dtmax (mmHg/s)	5900±320	16134±594	3356±188	5758±233	15364±757	3776±347
dP/dtmin (mmHg/s)	-1851±99	-3451±226	-1403±132	-2008±199	-4646±283	-1793±427
LV Pmax (mmHg)	54.6±0.3	80.7±3.0	37.3±2.1	53.3±2.1	76.8±3.8	42.0±3.9
LV ESP (mmHg)	41.0±0.2	60.5±2.2	28.0±1.6	40.0±1.5	57.6±2.8	31.5±2.9
LV EDP (mmHg)	5.7±0.1	5.8±0.4	5.2±0.1	6.2±0.6	7.7±1.0	6.6±0.8
LV ESV (μL)	12.4±0.3	8.5±1.0	21.8±2.7	12.4±0.4	8.5±0.9	18.8±2.8
LV EDV (μL)	40.0±0.1	39.9±0.2	40.2±0.5	40.1±0.1	40.0±0.3	40.0±0.1
SV (μL)	27.7±0.3	31.4±1.1	18.4±2.2	27.7±0.3	31.5±0.6	21.2±2.9
SW (mmHg•μL)	1353±52	2354±307	590±19	1305±25	2177±118	749±53
EF (%)	69.1±0.8	78.7±2.6	45.9±6.2	69.1±0.9	78.8±2.0	53.0±7.1
CO (μL/min)	3767±55	6510±448	1654±221	3975±34	6615±110	1910±37

HR, heart rate; ESPVR and EDPVR, end-systolic and end-diastolic pressure volume relation, respectively; dP/dtmax and dP/dtmin, maximum rate of left ventricle (LV) pressure rise and fall, respectively; Pmax, systolic pressure; ESP, end-systolic pressure; EDP, end-diastolic pressure; ESV, end-systolic volume; EDV, end-diastolic volume; SV, stroke volume; SW, stroke work; EF, ejection fraction; CO, cardiac output.

Table S3

	Pkd2; Fenoldopam		
	vehicle	**epinephrine**	**diltiazem**
HR (beat/min)	140±24	219±44	98±9
ESPVR (mmHg/μL)	4.4±0.1	9.7±0.9	2.3±0.1
EDPVR (mmHg/μL)	0.13±0.01	0.16±0.01	0.14±0.01
dP/dtmax (mmHg/s)	7157±211	16864±85	4020±643
dP/dtmin (mmHg/s)	-1624±24	-3843±277	-1537±97
LV Pmax (mmHg)	66.3±2.0	84.3±0.4	44.7±0.7
LV ESP (mmHg)	49.7±1.5	63.2±0.3	33.5±0.5
LV EDP (mmHg)	5.0±0.1	6.4±0.5	5.7±0.2
LV ESV (μL)	15.0±0.1	8.9±0.8	19.5±0.6
LV EDV (μL)	40.0±0.1	39.9±0.1	40.3±0.8
SV (μL)	24.9±0.1	31.1±0.7	20.8±0.8
SW (mmHg•μL)	1530±20	2417±28	812±29
EF (%)	62.5±0.2	77.7±2.0	51.6±1.4
CO (μL/min)	3486±81	6810±347	1873±70

HR, heart rate; ESPVR and EDPVR, end-systolic and end-diastolic pressure volume relation, respectively; dP/dtmax and dP/dtmin, maximum rate of left ventricle (LV) pressure rise and fall, respectively; Pmax, systolic pressure; ESP, end-systolic pressure; EDP, end-diastolic pressure; ESV, end-systolic volume; EDV, end-diastolic volume; SV, stroke volume; SW, stroke work; EF, ejection fraction; CO, cardiac output.

Table S4

Analytes	Vehicle	CT-DAu-NPs	CT-PLGA-NPs
ALB (g/dL)	3.4±0.9	3.1±0.7	3.3±0.6
ALP (U/L)	56±32	38±34	59±28
ALT (U/L)	32±1.6	36±1.8	45±1.4
AMY (U/L)	789±43	730±41	843±51
TBIL (mg/dL)	0.3±0.1	0.3±0.3	0.3±0.2
CA (mg/dL)	9.3±0.8	10.2±0.7	10.6±0.5
PHOS (mg/dL)	8.1±2.1	9.8±3.3	9.0±2.7
CRE (mg/dL)	0.2±0.06	0.3±0.2	0.2±0.07
GLU (mg/dL)	291±54	189±65	327±57
Na^+ (mmol/L)	149±2.1	158±1.9	150±2.0
K^+ (mmol/L)	4.9±0.9	6.5±0.9	5.8±0.6
TP (g/dL)	4.6±0.6	4.4±0.7	5.2±0.5
GLOB (g/dL)	1.4±0.4	1.8±0.4	1.3±0.2

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMY, amylase; TBIL, total bilirubin; CA, calcium; PHOS, phosphorus; CRE, creatinine; GLU, glucose; Na^+, sodium; K^+, potassium; TP, total protein; GLOB, globulin.