Supporting Information

A Physiologically Based Pharmacokinetic Model for Long-circulating Inorganic Nanoparticles

Xiaowen Liang,[†] Haolu Wang,[†] Jeffrey E. Grice,[†] Li Li,[‡] Xin Liu,[†] Zhi Ping Xu,[‡*] and Michael S. Roberts,[#*]*

[†]Therapeutics Research Centre, School of Medicine, The University of Queensland, Translational Research Institute, Woolloongabba, QLD 4102, Australia

[‡]Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, St Lucia, QLD 4067, Australia

[#]School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA 5001, Australia

*Corresponding authors: Dr Xin Liu Email: xin.liu@uq.edu.au
A/P Zhi Ping Xu Email: gordonxu@uq.edu.au
Prof Michael Roberts Email: m.roberts@uq.edu.au

Xiaowen Liang and Haolu Wang contributed equally to this work.

Experimental Methods

Chemicals

Cadmium chloride hydrate ($CdCl_2 \cdot 2.5H_2O$), tri-sodium citrate dihydrate (99.3%), sodium tellurite (Na_2TeO_3, 99%), sodium borohydride ($NaBH_4$, 99%) were purchased from Sigma–Aldrich. Mercaptosuccinic acid (MSA, 99.0%) was ordered from Fluka.

Synthesis and characterization of QDs

The CdTe/CdS QDs were synthesized in aqueous solution using a previously reported method.[1] Briefly, CdTe precursor solution was made by adding sodium tellurite (10 mM, 4 mL), tri-sodium citrate dihydrate (400 mg), MSA (100 mg) and sodium borohydride (50 mg) to 50 mL of cadmium chloride solution (3.2 mM). This solution was heated at 180 °C for 70 min in an autoclave and cooled down to room temperature with ice. QDs were precipitated by adding equal volume ethanol to the aqueous solution and purified by repeated washing. The UV-Vis absorption fluorescence emission spectra were scanned using spectrophotometer (SpectraMax M5 Multi-mode microplate reader) and photoluminescence quantum yield were determined using a spectrophotometer (SpectraMax M5 Multi-mode microplate reader). The morphology of QDs was evaluated by transmission electron microscopy (TEM) (JEOL 1010 and JEOL 2100 electron microscope). The size distribution and zeta potential of QDs were determined by Zeta-sizer (Zetasizer Nano ZS, Malvern Instruments).

Before each injection, the QDs were purified to remove the influence of residual reagents such as Cd^{2+} and Te^{2-} in solution by adding an equal volume of ethanol. The solution was centrifuged at 5000 rpm for 5 min to precipitate QDs. The QDs were then redispersed in

phosphate buffered saline. These procedures were repeated three times. The final QD solution was filtered through a 0.22 μm membrane filter before the injection.

Animals and experimental procedures

Male BALB/c mice (6-8 weeks, ~ 20 g) were purchased from Animal Resource Centre (WA, Australia) and were housed in local animal facility for at least one week before the experiment. The temperature was maintained at 20 ± 1 °C with a 12 h light/dark cycle. The mice were allowed free access to food and water. All animal experiments were approved by health sciences ethics committee in The University of Queensland.

Mice were administered a single dose of QDs (61.5 pmol/g based on QD particles or 3.6 μg/g based on cadmium) by intravenous injection via tail vein or by subcutaneous injection. Control mice were injected the same volume of phosphate buffered saline. At designated time points up to 30 days, animals (n=5 per time point) were sacrificed by CO_2 asphyxiation. Blood was collected by cardiac puncture and plasma was separated by centrifugation. Tissue samples including brain, lung, heart, liver, kidney, spleen, intestine, skin, bone, and muscle were collected at 5 min, 30 min, 2 h, 8 h, 24 h, and 168 h post-injection (and 720 h for liver, kidney, spleen, and blood). Urine and faeces were also collected after QDs injection. The collected tissues were imaged by a Xenogen IVIS® spectrum imaging system (Caliper Life Sciences, Hopkinton, MA). The injection site after subcutaneous injection was also imaged by the same instrument. Filter set (λ_{Ex} = 430 nm, λ_{Em} = 660 nm) was used to acquire the QDs fluorescence. The fluorescence intensity of the region of interest was determined by the Living Image software (version 3.4.1).

Multiphoton microscopy imaging

A DermaInspect system (JenLab GmbH, Jena, Germany) equipped with an ultrashort (pulse width, 85 femtosecond, repetition rate 80-MHz) pulsed mode-locked tunable Titanium: Sapphire laser (Mai Tai, Spectra Physics, 25 Mountain View, USA) was used for MPM imaging of liver and kidney. A bandpass filter (BG39) was employed to detect fluorescence emission in the spectral range of 350 to 650 nm. Both low (10×, NA 1.3, Zeiss) and high (40×, NA 1.3, Zeiss) magnification objectives were used with the laser power set at 20 mW and 15 mW, respectively.

TEM imaging of tissues.

The tissues were perfusion-fixed with 3% glutaraldehyde and kidney tissues were then processed and embedded in Spurrs Resin prior to ultrathin sectioning and examination using a Philips CM10 electron microscope.

Sample analysis

QD analyses were based on the determination of cadmium concentration in plasma and tissue samples using inductively coupled plasma-mass spectrometry (ICP-MS, Agilent 7700). Briefly, tissues were collected, dried, weighted, and digested with 70% nitric acid on a hot plate at 100 °C. The calibration curve ranged from 0 to 500 ng/ml for Cd^{2+}. Standards and samples are prepared in 5% HNO_3 (high purity grade) plus 100 µg/L gold. QC samples are prepared in house and the concentration of QC samples was 0.1 µg/L, 1 µg/L, and 4 µg/L.

Implementation and parameterization of the model

The PBPK model was implemented in Berkeley Madonna version 8.3.18 (Berkeley, CA, USA). Mass balance equations used in the model are presented in the supplementary. All physiological parameter values (body weight, organ volume, interstitial volume, blood

volume, and blood flow) were from the literature and are given in Table S1. QD-specific parameters (maximum uptake rate constant, Hill coefficient, release rate constant and time reaching half maximum uptake rate) were optimized by using both curve fitter in Berkeley Madonna automatically and a manual approach to obtain a visually reasonable fit to the experimental biodistribution data of QDs intravenously injected into mice.

Sensitivity analyses

To identify highly influential parameters on the model solution, sensitivity analysis was performed for each parameter in the target organs. The values of QD-specific parameters were increased by 0.1%, and the model simulations were repeated for QD concentrations in key organs.[2] The relative sensitivity coefficients (RSC) for significant parameters were calculated using the following equation:

$$\text{Relative sensitivity coefficient} = \frac{dC/C}{dP/P} \quad (1)$$

Where C is the concentration of QDs, and P is the parameter value. A positive RSC indicates a direct association between the model output and the corresponding parameter, while a negative RSC suggests the model output is inversely correlated with the specific parameter. The RSC values with absolute values higher than 0.5 are considered as highly sensitive.

Model evaluation with independent data

The predictive capability of our PBPK model was evaluated with inter-router and external datasets from different species.[3-5] The physiological parameter values of rats and mice were obtained from the literature and are given in Table S1. QD-specific parameters were assumed to be the same for mice and rats. The overall goodness-of-fit between predicted

and measured values was further analyzed with linear regression. The statistical analysis was done using GraphPad Prism v 6.04 (GraphPad Software Inc., La Jolla, California).

Supplementary Equations

Mass balance equations

For venous blood:

$$V_{Vb}\frac{dCV_{Vb}}{dt} = (Q_L CV_L + Q_S CV_L + Q_K CV_K + Q_{Bo} CV_{Bo}) - Q_{Lu} CV_{Vb}$$

For arterial blood:

$$V_A\frac{d\,C_A}{dt} = Q_{Lu}(CV_{Lu} - C_A)$$

For lung:

For vascular space

$$V_{V\_Lu}\frac{dCV_{Lu}}{dt} = Q_{Lu}(CV_{Vb} - CV_{Lu}) - PA_{Lu}CV_{Lu} + \frac{PA_{Lu}C_{T\_Lu}}{P_{Lu}}$$

For tissue (interstitial space)

$$V_{T\_Lu}\frac{dC_{T\_Lu}}{dt} = PA_{Lu}CV_{Lu} - \frac{PA_{Lu}C_{T\_Lu}}{P_{Lu}} - k_{up\_Lu}CV_{Lu}V_{V\_Lu} + K_{release\_Lu}A_{PC\_Lu}$$

For phagocytic cells in lung

$$\frac{dA_{PC\_Lu}}{dt} = k_{up\_Lu}CV_{Lu}V_{V\_Lu} - K_{release\_Lu}A_{PC\_Lu}$$

QDs concentration in the lung is given by:

$$C_{Total\_Lu} = \frac{CV_{Lu}V_{V\_Lu} + C_{T\_Lu}V_{T\_Lu} + A_{PC\_Lu}}{V_{Lu}}$$

For liver:

For vascular space

$$V_{V\_L}\frac{dCV_L}{dt} = Q_L C_A + Q_S CV_S - (Q_L + Q_S)CV_L - PA_L CV_L + \frac{PA_L C_{T\_L}}{P_L} - k_{up\_L} CV_L V_{V\_L} + K_{release\_L} A_{PC\_L} - K_{bile} CV_L$$

For tissue (interstitial space)

$$V_{T\_L}\frac{dC_{T\_L}}{dt} = PA_L CV_L - \frac{PA_L C_{T\_L}}{P_L}$$

For phagocytic cells in liver

$$\frac{dA_{PC\_L}}{dt} = k_{up\_L} CV_L V_{V\_L} - K_{release\_L} A_{PC\_L}$$

QDs concentration in the liver is given by:

$$C_{Total\_L} = \frac{CV_L V_{V\_L} + C_{T\_L} V_{T\_L} + A_{PC\_L}}{V_L}$$

For spleen:

For vascular space

$$V_{V\_S}\frac{dCV_S}{dt} = Q_S(C_A - CV_S) - PA_S CV_S + \frac{PA_S C_{T\_S}}{P_S}$$

For tissue (interstitial space)

$$V_{T\_S}\frac{dC_{T\_S}}{dt} = PA_S CV_S - \frac{PA_S C_{T\_S}}{P_S} - k_{up\_S} CV_S V_{V\_S} + K_{release\_S} A_{PC\_S}$$

For phagocytic cells in spleen

$$\frac{dA_{PC\_S}}{dt} = k_{up\_S} CV_S V_{V\_S} - K_{release\_S} A_{PC\_S}$$

QDs concentration in the spleen is given by:

$$C_{Total\_S} = \frac{CV_S V_{V\_S} + C_{T\_S} V_{T\_S} + A_{PC\_S}}{V_S}$$

For kidney:

For vascular space

$$V_{V\_K}\frac{dCV_K}{dt} = Q_K(C_A - CV_K) - PA_K CV_K + \frac{PA_K C_{T\_K}}{P_K} - k_{up\_K} CV_K V_{V\_K} + K_{release\_K} A_{PC\_K} - K_{urine} C_{V\_K}$$

For tissue (interstitial space)

$$V_{T\_K}\frac{dC_{T\_K}}{dt} = PA_K CV_K - \frac{PA_K C_{T\_K}}{P_K} - k_{up\_K} CV_K V_{V\_K} + K_{release\_K} A_{PC\_K}$$

For phagocytic cells in kidney

$$\frac{dA_{PC\_K}}{dt} = k_{up\_K} CV_K V_{V\_K} - K_{release\_K} A_{PC\_K}$$

QDs concentration in the kidney is given by:

$$C_{Total\_K} = \frac{CV_K V_{V\_K} + C_{T\_K} V_{T\_K} + A_{PC\_K}}{V_K}$$

For the rest of body:

For vascular space

$$V_{V\_Bo}\frac{dCV_{Bo}}{dt} = Q_{Bo}(C_A - CV_{Bo}) - PA_{Bo} CV_{Bo} + \frac{PA_{Bo} C_{T\_Bo}}{P_{Bo}}$$

For tissue (interstitial space)

$$V_{T\_Bo}\frac{dC_{T\_Bo}}{dt} = PA_{Bo} CV_{Bo} - \frac{PA_{Bo} C_{T\_Bo}}{P_{Bo}} - k_{up\_Bo} CV_{Bo} V_{V\_Bo} + K_{release\_Bo} A_{PC\_Bo}$$

For phagocytic cells in the rest of body

$$\frac{dA_{PC\_Bo}}{dt} = k_{up\_Bo} CV_{Bo} V_{V\_Bo} - K_{release\_Bo} A_{PC\_Bo}$$

QDs concentration in the rest of body is given by:

$$C_{Total\_Bo} = \frac{CV_{Bo} V_{V\_Bo} + C_{T\_Bo} V_{T\_Bo} + A_{PC\_Bo}}{V_{Bo}}$$

Nomenclature (units)

P: Tissue: plasma distribution coefficient

PA: Permeability area cross product between the blood and the tissue of the organ (L/h)

A_{PC}: Amount of QDs uptake by phagocytic cells (μg)

$C_{A:}$ QDs concentration in the arterial blood (μg/g)

C_T: QDs concentration in the tissue (μg/g)

C_{Total}: Average QDs concentration of each compartment (μg/g)

CV: QDs concentration in the venous blood of each compartment (μg/g)

k_{up}: Uptake rate constant of QDs (h^{-1})

$K_{release}$: Release rate constant of QDs (h^{-1})

Q: Blood flow to each organ (L/h)

V: Total volume of each compartment (L)

V_V: Volume of vascular space of each compartment (L)

V_T: Tissue volume (interstitial space for QDs, L)

$K_{excretion}$: excretion rate constant of QDs (h^{-1})

Subscripts

Vb: Venous blood

A: Arterial blood

Lu: Lung

T: Tissue

L: Liver

S: Spleen

K: Kidney

Bo: The rest of bod

Table S1 Physiological parameters used in the PBPK model

Parameter (unit)	Mouse	Rat
Body weight (kg)	0.02	0.25
Cardiac output (L/hour/kg$^{0.75}$)[a]	16.5	15
Blood flow to organ (fraction of cardiac output, unitless)[a]		
Lung	1.00	1.00
Liver	0.161	0.25
Spleen	0.011	0.01125
Kidney	0.091	0.141
Organ volumes (fraction of body weight, unitless)[a, b]		
Lung	0.007	0.005
Liver	0.055	0.034
Spleen	0.005	0.0025
Kidney	0.0017	0.007
Blood	0.0085	0.074
Volume fraction of interstitial tissue in organs (unitless)[c, d]		
Lung	0.3	0.3
Liver	0.26	0.26
Spleen	0.2	0.2
Kidney	0.34	0.34
Rest of body	0.21	0.21
Volume fraction of blood in organs (unitless)[a, d]		
Lung	0.50	0.36
Liver	0.31	0.21
Spleen	0.17	0.22
Kidney	0.24	0.16
Rest of body	0.04	0.04

[a] From Brown et al.[6]

[b] From Davies and Morris.[7]

[c] Calculated from Davda et al.[2] and Zhu et al.[8]

[d] From Lin et al.[9]

Table S2 Relative sensitivities (unit-less) for the parameters

Parameters	Liver		Kidney		Spleen	
	24 h	720 h	24 h	720 h	24 h	720 h
P_l	0.02	0.01	-0.01	0.00	-0.01	0.00
PAC_l	0.00	0.00	0.00	0.00	0.00	0.00
K_{max_l}	**0.65**	**0.72**	-0.19	-0.21	-0.15	-0.21
n_l	0.01	0.00	0.00	0.00	0.00	0.00
$K_{release\_l}$	-0.09	**-0.72**	0.02	0.21	0.02	0.21
K_{50_l}	-0.10	0.00	0.03	0.00	0.03	0.00
P_k	0.00	0.00	0.00	0.00	0.00	0.00
PAC_k	0.00	0.00	0.01	0.00	0.00	0.00
K_{max_k}	-0.01	-0.11	**0.60**	**0.87**	-0.01	-0.10
n_k	0.00	0.00	0.06	0.00	0.00	0.00
$K_{release\_k}$	0.00	0.06	-0.01	**-0.53**	0.00	0.06
K_{50_k}	0.01	0.00	-0.35	-0.02	0.01	0.00
P_s	0.00	-0.00	0.00	0.00	0.03	0.01
PAC_s	0.00	0.00	0.00	0.00	0.00	0.00
K_{max_s}	-0.01	-0.02	-0.01	-0.01	**1.29**	**1.79**
n_s	0.00	0.00	0.00	0.00	0.00	0.00
$K_{release\_s}$	0.00	0.01	0.00	0.01	-0.06	**-0.90**
K_{50_s}	0.00	0.00	0.00	0.00	0.00	0.00

P_l, P_k, P_s: tissue: plasma distribution coefficient in the liver, kidney, and spleen; PAC_l, PAC_k, PAC_s: permeability coefficient in the liver, kidney, and spleen; K_{max_l}, K_{max_k}, K_{max_s}: maximum uptake rate constant in the liver, kidney, and spleen; n_l, n_k, n_s: Hill coefficient in the liver, kidney, and spleen; $K_{release\_l}$, $K_{release\_k}$, $K_{release\_s}$: release rate constant in liver, kidney, and spleen; K_{50_l}, K_{50_k}, K_{50_s}: time reaching half maximum uptake rate in the liver, kidney, and spleen. The relative sensitivity coefficient (RSC) values with absolute values higher than 0.5 are considered as highly sensitive (labelled as bold).

Figure S1

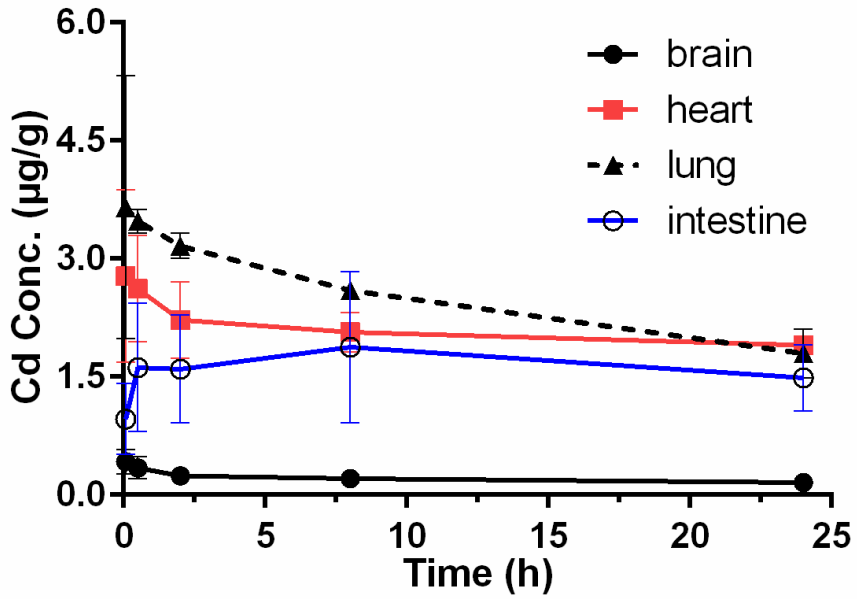

Figure S1. Time-course profile of QDs (3.5 nm) concentration after intravenous injection at the dose of 3.6 µg/g in brain, heart, lung, and intestine measured by ICP-MS.

Figure S2

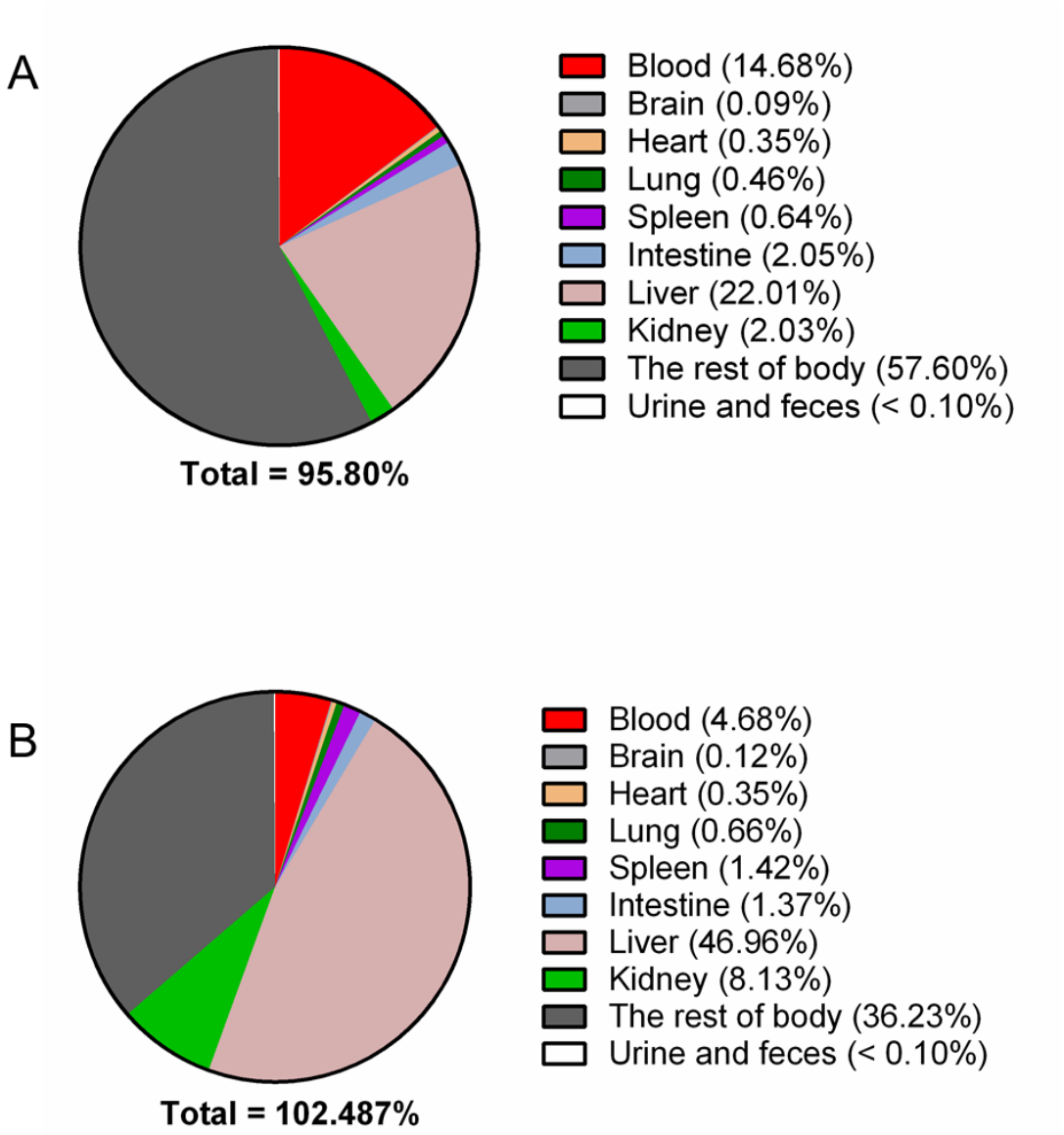

Figure S2. Mass balance studies of an intravenous dose of QDs in mice. Mass balance studies were carried out at 1 day (A) and 7 days (B) after dosing. Overall recoveries for 1 day and 7 days were 95.8% and 102.48%, respectively.

Figure S3

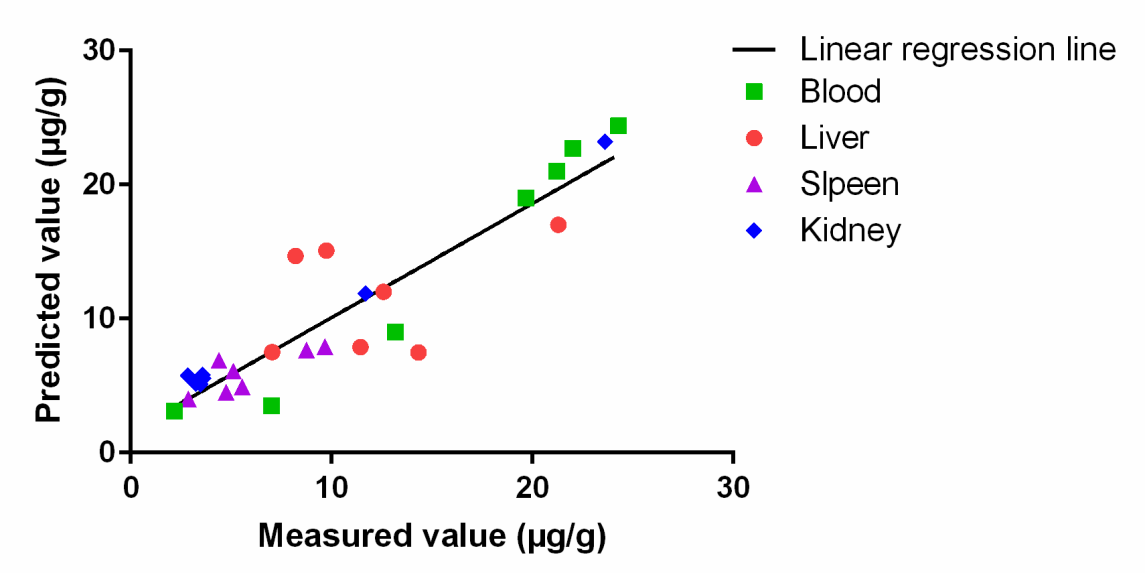

Figure S3. Goodness-of-fit plot of the linear regression analysis of model predictions and experimental data after intravenous injection for model calibration. Experimental data are from our own experiments and the linear regression coefficient (R^2) is 0.84 (n=28).

Figure S4

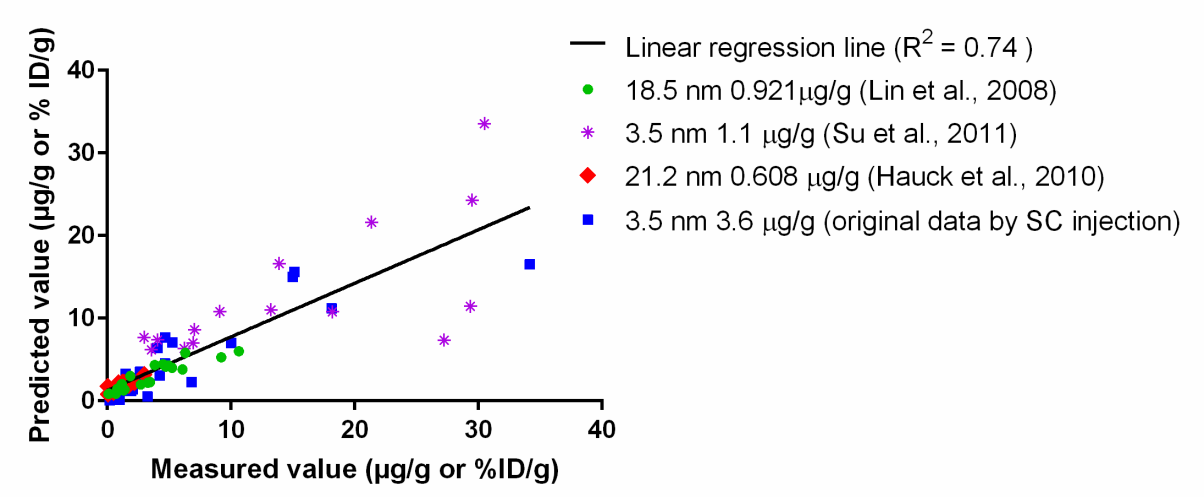

Figure S4. Goodness-of-fit plot of the linear regression analysis of model predictions and measured data for model evaluation. Experimental data are from Lin et al. (2008)[5], Su et al. (2011)[3], Hauck et al. (2010)[4], and our experimental data by subcutaneous (SC) injection. The overall linear regression coefficient (R^2) is 0.74 (n = 81). The linear regression coefficient (R^2) for each independent dataset is 0.84 for Lin et al., 0.5 for Su et al., 0.62 for Hauck et al., and 0.77 for our data by SC injection, respectively. "%ID/g" represents the percentage of injected dose per gram tissue.

Figure S5

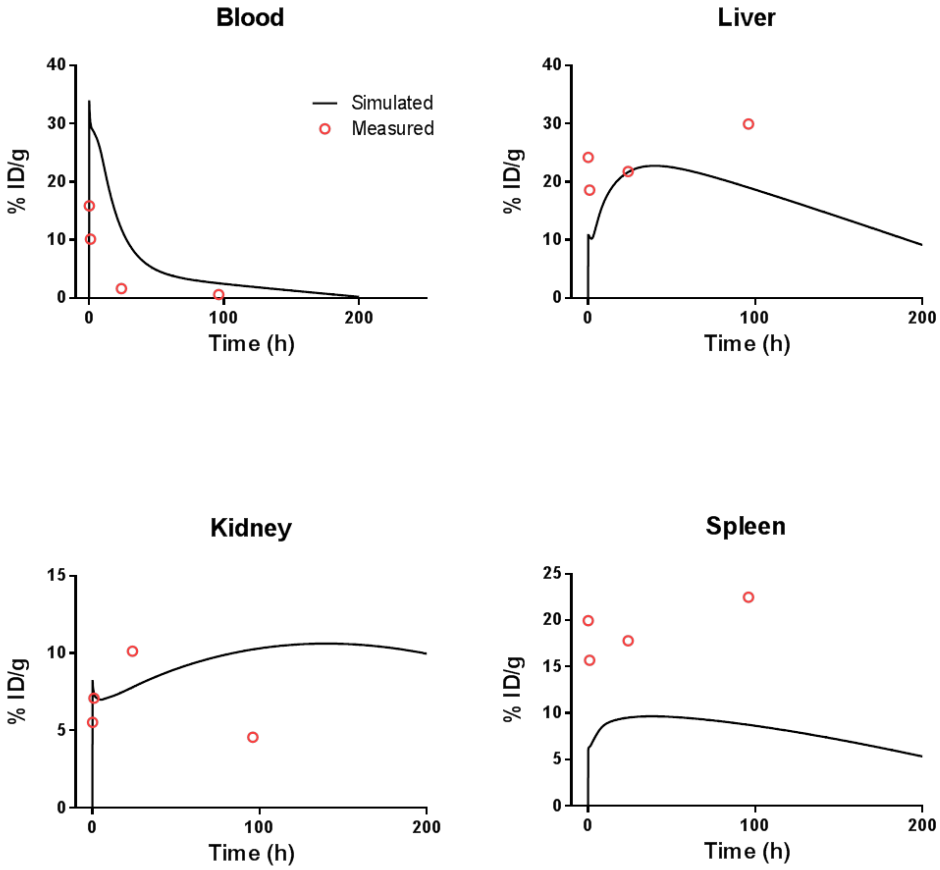

Figure S5. Model evaluation results with independent data from Balogh et al., who studied biodistribution of 5 nm gold nanoparticles after intravenous injection in mice.[10] Solid lines represent simulation results and red circles represent mean value of measured data.

References

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The model code for IV injection of QDs

```
STARTTIME= 0
STOPTIME=720
DTMAX = 0.0005
DTOUT =0.1

; Physiological constants (kg)
BW   = 0.02                ; body weight

; Dose (mg)
IV = 0.072

; Organ volumes (fraction of body weight)
VLuC=0.007                  ; Lung; Brown et al, 1997
VLC=0.0549                  ; Liver; Brown et al, 1997
VSC=0.005                   ; Spleen; Davies and Morris 1993
VKC=0.0167                  ; Kidneys; Brown et al. 1997
VBloodC=0.085               ; Blood; Davies and Morris 1993
VBoC=1-(VLC+VKC+VSC+VBloodC)    ; Rest of body

; Organ volumes (L)
VBlood=VBloodC*BW
VLu=VLuC*BW                 ; Lung
VL=VLC*BW                   ; Liver
VS=VSC*BW                   ; Spleen
VK=VKC*BW                   ; Kidneys
VA = 0.2*VBloodC*BW         ; Arterial blood
VV = 0.8*VBloodC*BW         ; Venous blood
VBo=VBoC*BW                 ; Rest of body

; Organ blood volumes (L)
VLuVES = 0.5*Vlu            ; Lung; Brown et al, 1997
VLVES = 0.31*VL             ; Liver; Brown et al, 1997
VSVES = 0.17*VS             ; Spleen; Brown et al, 1997
VKVES = 0.24*VK             ; Kidneys; Brown et al, 1997
VBoVES = 0.04*VBo           ; Rest of body; Lin et al, 2015; Brown et al, 1997

; Organ tissue (interstitial) volumes (L)
VLuT = 0.3*Vlu              ; Lung; Calculated from Davda et al, 2008
VLT = 0.26*VL               ; Liver; Calculated from Davda et al, 2008
VST = 0.2*VS                ; Spleen; Calculated from Davda et al, 2008
VKT = 0.34*VK               ; Kidneys; Calculated from Davda et al, 2008
VBoT = 0.21*VBo             ; Rest of body; Calculated from Davda et al, 2008
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```
; Blood flow rate (fraction of cardiac output)
QCC=16.5                    ; Cardiac output constant; Brown et al, 1997
QLC=0.161                   ; Liver; Brown et al, 1997.
QKC=0.091                   ; Kidney; Brown et al, 1997
QSC=0.01125                 ; Spleen; Lin et al, 2015; Davies and Morris, 1993
QBoC=1-(QLC+QSC+QKC)        ; Rest of body

; Cardiac output and regional blood flow (L/h)
QC=QCC*BW^0.75
QLu=QC                      ; Lung
QL=QLC*QC                   ; Liver
QS=QSC*QC                   ; Spleen
QK=QKC*QC                   ; Kidneys
QBo=QBoC*QC                 ; Rest of body

; Distribution coefficients (PC), unitless
PLu =0.015                  ; Lung
PL = 0.15                   ; Liver
PS = 0.15                   ; Spleen
PK = 0.015                  ; Kidneys
PBo = 0.15                  ; Rest of body

; Diffusion limitation coefficient constants, unitless
PALuC = 0.0001              ; Lung
PALC = 0.001                ; Liver
PASC = 0.001                ; Spleen
PAKC = 0.0001               ; Kidneys
PABoC = 0.001               ; Rest of body

; Permeability coefficient-surface area cross-product
PALu = PALuC*QLu            ; Lung
PAL = PALC*QL               ; Liver
PAS = PASC*QS               ; Spleen
PAK = PAKC*QK               ; Kidneys
PABo = PABoC*QBo            ; Rest of body

; Endocytosis-related parameters; Lu, L, K, S, and Bo represent the lung, liver, kidneys, and rest of body, respectively
KupLumax=0.0026
KupLu50=7.5
KupLun=5
KoutLu=0.0061
```

```
KupLu=((KupLumax*time^KupLun)/(KupLu50^KupLun+time^KupLun))

KupLmax=0.15
KupL50=2.78
KupLn=7
KoutL=0.011
KupL=((KupLmax*time^KupLn)/(KupL50^KupLn+time^KupLn))

KupSmax=0.09
KupS50=1.5
KupSn=2
KoutS=0.0072
KupS=((KupSmax*time^KupSn)/(KupS50^KupSn+time^KupSn))


KupKmax=0.07
KupK50=6.82
KupKn=3
KoutK=0.002
KupK=((KupKmax*time^KupKn)/(KupK50^KupKn+time^KupKn))

KupBomax=0.2
KupBo50=7.5
KupBon=5
KoutBo=0.0121
KupBo=((KupBomax*time^KupBon)/(KupBo50^KupBon+time^KupBon))

; Urine and biliary excretion
Kurine=0.000000001
Kbile=0.000000001

; Blood compartment
; Venous blood concentration
d/dt (AV)  = (QL*CVL+ QS*CVL + QK*CVK + QBo*CVBo)-(QC*CV)
init AV = IV
CV = AV/VV

; Arterial blood concentration
d/dt (AA)  = QC*(CVLu-CA)
init AA = 0
CA = AA/VA

; Lung compartment; VES, T and RES represent blood vessels, tissue, and phagocytic cells
d/dt (ALuVES) = QLu*(CV-CVLu) - PALu*CVLu + (PALu*CLuT)/PLu
```

```
init ALuVES = 0
CVLu = ALuVES/VLuVES

d/dt (ALuT) = PALu*CVLu - (PALu*CLuT)/PLu + KoutLu *ALuRES - KupLu *ALuVES
init ALuT = 0
CLuT = ALuT/VLuT

d/dt (ALuRES) = KupLu *ALuVES - KoutLu *ALuRES
init ALuRES = 0
CLung = (ALuVES+ALuT+ALuRES)/VLu

; Liver compartment
d/dt (ALVES) = QL*CA+QS*CVS-(QL+QS)*CVL - PAL*CVL + (PAL*CLT)/PL + KoutL *ALRES - KupL
*ALVES - Kbile*CVL
init ALVES = 0
CVL = ALVES/VLVES

d/dt (Abile) = Kbile*CVL
init Abile = 0

d/dt (ALT) = PAL*CVL - (PAL*CLT)/PL
init ALT = 0
CLT = ALT/VLT

d/dt (ALRES) = KupL *ALVES - KoutL *ALRES
init ALRES = 0
CLiver = (ALVES+ALT+ALRES)/VL

; Spleen compartment
d/dt (ASVES) = QS*(CA-CVS) - PAS*CVS + (PAS*CST)/PS
init ASVES = 0
CVS = ASVES/VSVES

d/dt (AST) = PAS*CVS - (PAS*CST)/PS + KoutS *ASRES - KupS *ASVES
init AST = 0
CST = AST/VST

d/dt (ASRES) = KupS *ASVES - KoutS *ASRES
init ASRES = 0
CSpleen = (ASVES+AST+ASRES)/VS

; Kidney compartment
d/dt (AKVES) = QK*(CA-CVK) - PAK*CVK + (PAK*CKT)/PK - Kurine*CVK
init AKVES = 0
```

```
CVK = AKVES/VKVES

d/dt (Aurine) = Kurine*CVK
init Aurine = 0

d/dt (AKT) = PAK*CVK - (PAK*CKT)/PK + KoutK *AKRES - KupK *AKVES
init AKT = 0
CKT = AKT/VKT

d/dt (AKRES) = KupK *AKVES - KoutK *AKRES
init AKRES = 0
CKidney = (AKVES+AKT+AKRES)/VK

; Rest of body compartment
d/dt (ABoVES) = QBo*(CA-CVBo) - PABo*CVBo + (PABo*CBoT)/PBo
init ABoVES = 0
CVBo = ABoVES/VBoVES

d/dt (ABoT) = PABo*CVBo - (PABo*CBoT)/PBo + KoutBo *ABoRES - KupBo *ABoVES
init ABoT = 0
CBoT = ABoT/VBoT

d/dt (ABoRES) = KupBo *ABoVES - KoutBo *ABoRES
init ABoRES = 0
CBody = (ABoVES+ABoT+ABoRES)/VBo
```