

Supplementary information

## **Renal clearable nanocarriers: Overcoming the physiological barriers for precision drug delivery and clearance**

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**Table S1: Representative renal clearable NPs for passive targeting.**

NPs	Material	Size <sup>a</sup>	$T_{1/2}$ <sup>b</sup>	Targeting	Renal Clearance <sup>c</sup>	Tumor	Date [Ref]
		(nm)	(h)	(%ID/g)	(ID)	Model	
PEG-C-dots	PEG-SiO <sub>2</sub>	7	5.6	~1 (4 h)	~72% (96 h)	M21	06/2011 [1, 2]
GS-AuNPs	Au	3.3	0.09 ( $\alpha$ ), 8.5 ( $\beta$ )	3.0 $\pm$ 0.2 (1 h) 2.3 $\pm$ 0.2 (24 h)	>60% (48 h)	MCF-7	03/2013 [3]
PEG-AuNPs	Au	5.5	0.94 ( $\alpha$ ), 9.2 ( $\beta$ )	8.0 $\pm$ 1.5 (1 h) 8.3 $\pm$ 0.9 (12 h)	>50% (24 h)	MCF-7	10/2013 [4]
SPNS-GSH	Pd	7.5	1.25	~5 (24 h)	>20% (96 h)	4T1	04/2014 [5]
<sup>64</sup> CuAuNCs-PEG350	Au	4.3	0.87	~2.5 (24 h)	40.8% (48 h)	PC3	09/2014 [6]
<sup>64</sup> CuAuNCs-PEG1000		6.9	2.62	~2.5 (24 h)	7.9% (48 h)		
CuS NDs	PVP-CuS	5.6	0.43 ( $\alpha$ ), 11.69 ( $\beta$ )	3.6 $\pm$ 0.5 (2 h) 0.22 (24 h)	95% (24 h)	4T1	06/2015 [7]
<sup>111</sup> In-DTPA-PEG5	PEG	4.4	0.57	0.4 $\pm$ 0.0 (24 h)	40% (24 h)	Colon26	03/2016 [8, 9]
<sup>111</sup> In-DTPA-PEG10		6.3	1.24	1.1 $\pm$ 0.3 (24 h)	44.1% (24 h)		
<sup>111</sup> In-DTPA-PEG20		9.3	9.5	6.2 $\pm$ 0.7 (24 h)	42.4% (24 h)		
<sup>111</sup> In-DTPA-PEG40		13.6	22.5	12.9 $\pm$ 1.6 (24 h)	14.7% (24 h)		
AGuIX	Au	4.4	n.a.	2.0 (24 h)	>95% (168 h)	U87MG	06/2016 [10, 11]
ZW800-CDPL <sup>±</sup>	$\beta$ -CD- $\epsilon$ PL	4.6	0.03 ( $\alpha$ ), 0.33 ( $\beta$ )	n.a.	>80% (4 h)	GIST	07/2016 [12]
GS-AgNPs	Ag	3.1	0.03 ( $\alpha$ ), 0.37 ( $\beta$ )	0.75 (24 h)	51% (48 h)	TUBO	11/2016 [13]
TCPP-PEG <sub>2K</sub>	PEG	4.6	0.07 ( $\alpha$ ), 0.18 ( $\beta$ )	2.2 $\pm$ 0.5 (24 h)	n.a.	4T1	07/2017 [14]
TCPP-PEG <sub>5K</sub>		7.5	0.18 ( $\alpha$ ), 0.47 ( $\beta$ )	2.8 $\pm$ 0.5 (24 h)			
TCPP-PEG <sub>10K</sub>		10.1	0.29 ( $\alpha$ ), 0.67 ( $\beta$ )	4.7 $\pm$ 0.4 (24 h)			
CPNs	W-GA-PEG	5.6	0.29 ( $\alpha$ ), 3.62 ( $\beta$ )	4.6 $\pm$ 0.6 (4 h)	86% (168 h)	4T1	08/2017 [15]
BNTs	(BiO) <sub>2</sub> CO <sub>3</sub>	95 $\times$ 8	0.46 ( $\alpha$ ), 26.99 ( $\beta$ )	8.1 (1 h) 18.5 (9 h)	~40% (168 h)	Huh-7	01/2018 [16]
CZTS NCs	Cu <sub>2</sub> ZnSnS <sub>4</sub>	12.6	n.a.	7.0 (24 h)	>40% (168 h)	H22	03/2018 [17]
ICG <sub>4</sub> -GS-Au <sub>25</sub>	Au	3.4	n.a.	4.1 (24 h)	~60% (24 h)	MCF-7	07/2019 [18]

<sup>a</sup> NP sizes are based on hydrodynamic diameter (HD) measurements;

<sup>b</sup> Half-lives ( $T_{1/2}$ ) of different NPs in the pharmacokinetics are either reported with one-compartment (circulation half-life) or two-compartment (distribution and elimination half-lives,  $T_{1/2\alpha}$  and  $T_{1/2\beta}$ , respectively) simulations;

<sup>c</sup> While some of the engineered NPs (highlighted in gray) showed lower renal clearance efficiency (less than 50% ID) within certain time (48 h), herein, we also include these NPs for the more comprehensive comparison and analysis.

**Table S2: Representative renal clearable NPs for active targeting.**

NPs	Material	Size (nm) <sup>a</sup>	Targeting (%ID/g) <sup>b</sup>	Clearance (ID)	Cancer Type <sup>b</sup>	Targeting Moiety	Date [Ref]
QDs-GPI	CdSe(ZnCdS)	~5.5	n.a.	90% (total at 24 h)	LNCap (+) PC-3 (-)	GPI	11/2009 [19]
QDs-cRGD	CdSe(ZnCdS)	~5.5	n.a.	90% (total at 24 h)	M21 (+) M21-L (-)	cRGD	11/2009 [19]
cRGDY-PEG-C-dot	PEG-SiO <sub>2</sub>	6.8	1.8 (cRGDY, 4 h) 1.0 (cRADY, 4 h)	72% (renal at 96 h)	M21	cRGDY	06/2011 [1]
cRGDY-PEG-Cy5-C'-dot	PEG-SiO <sub>2</sub>	6.4	3.8 (+, 4 h) ~1.4 (-, 4 h)	>98% (total at 96 h)	M21 (+) M21-L (-)	cRGDY	09/2017 [20]
DFO-cRGDY-PEG-Cy5-C'-dot	PEG-SiO <sub>2</sub>	6-7	12.0 (+, 24 h) ~4.0 (-, 24 h)	>70% (total at 72 h)	M21 (+) M21-L (-)	cRGDY	09/2017 [21]
DFO- $\alpha$ MSH-PEG-Cy5-C'-dot	PEG-SiO <sub>2</sub>	6-7	5.5 (targeted, 24 h) 3.6 (blocked, 24 h)	>70% (total at 72 h)	B16F10 (+)	$\alpha$ MSH	10/2017 [22]
DFO-PSMAi-PEG-Cy5-C'-dot	PEG-SiO <sub>2</sub>	6.2	9.0 (+, 72 h) 3.5 (-, 72 h)	n.a.	LNCap (+) PC-3 (-)	PSMAi	05/2018 [23, 24]
Ba <sub>2</sub> GdF <sub>7</sub> NPs	Ba <sub>2</sub> GdF <sub>7</sub>	6.5 (EM)	n.a.	80% (renal at 48 h)	A549	pPeptides	07/2018 [25]
DFO-scFv-PEG-Cy5-C'-dot	PEG-SiO <sub>2</sub>	7.3	13.2 $\pm$ 2.9 (+, 24 h) 4.8 $\pm$ 0.9 (-, 24 h)	70% (total at 72 h)	BT-474 (+) MDA-MB-231 (-)	Anti-HER2 scFV	10/2018 [26]
MnIO-MCP	MnIO	10.9	9.8 (MCP, 1h) 4.1 (PEG, 1h)	75% (renal at 24 h)	MCF-7	MCP	07/2019 [27]
<sup>89</sup> Zr-cRGD-C'-dot	PEG-SiO <sub>2</sub>	6-7	~7 (+, 24 h)	>70% (total at 72 h)	mGBM	cRGDY	09.2019 [28]

<sup>a</sup> NP sizes are based on HD measurements;

<sup>b</sup> (+) indicates cancer cell lines with overexpressed receptors for active targeting; (-) indicates control cancer cell lines without overexpressed receptors for active targeting.

**Table S3: Pharmacokinetic parameters of the ultrasmall AuNPs with different size.**

	<b>GS-AuNPs - 3.7 nm<sup>a</sup></b>	<b>PEG-AuNPs - 5.5 nm<sup>b</sup></b>	<b>PEG-AuNPs - 7.5 nm</b>	<b>PEG-AuNPs - 9.5 nm</b>
<b>C<sub>0</sub> / %ID·g<sup>-1</sup></b>	34.04	53.23	31.66	35.93
<b>Vd / mL</b>	2.94	1.88	3.16	2.78
<b>24-h AUC / %ID·hg<sup>-1</sup></b>	47.2	142.8	271.5	445.5
<b>CL / mg·h<sup>-1</sup></b>	2.16	0.70	0.37	0.22
<b>T<sub>1/2α</sub> / h</b>	0.09	0.94	0.20	1.55
<b>T<sub>1/2β</sub> / h</b>	8.5	9.2	11.68	19.08

<sup>a</sup> The parameters of 3.7 nm GS-AuNPs were originated from ref [3];

<sup>b</sup> The parameters of 5.5 nm PEG-AuNPs were originated from ref [4].

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