Supplementary Materials for the Manuscript Entitled

"Improving Tumor-Targeting Capability and Pharmacokinetics of ^{99m}Tc-Labeled Cyclic RGD Dimers with PEG_4 Linkers"

by

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Running Title: PEGylated cyclic RGD Dimers for Improved Tumor Targeting

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Contents of Supporting Information

Table SI. Biodistribution data and T/B radios of ^{99m}Tc-2PEG$_4$-dimer in the athymic nude mice bearing MDA-MB-435 human breast cancer xenografts. The organ uptake is expressed as %ID/g. Each data point represents an average of biodistribution data from four animals.

%ID/gram	30 min	60 min	120 min	Blocking (60min)
Blood	1.06 ± 0.12	0.85 ± 0.42	0.47 ± 0.22	0.85 ± 0.19
Brain	0.2 ± 0.07	0.24 ± 0.10	0.18 ± 0.08	0.08 ± 0.04
Eyes	1.46 ± 0.40	1.96 ± 0.78	1.89 ± 0.68	0.36 ± 0.12
Heart	2.09 ± 0.34	3.07 ± 0.94	1.99 ± 0.53	0.53 ± 0.11
Intestine	10.58 ± 4.17	13.36 ± 10.69	9.84 ± 4.64	1.44 ± 0.67
Kidney	14.37 ± 4.09	17.71 ± 8.83	13.78 ± 5.36	18.34 ± 5.64
Liver	2.97 ± 0.63	3.58 ± 1.72	3.27 ± 1.09	1.49 ± 0.29
Lungs	4.12 ± 0.82	5.01 ± 2.86	4.05 ± 1.20	1.93 ± 0.31
Muscle	1.76 ± 0.56	1.59 ± 1.01	1.51 ± 0.35	0.76 ± 0.47
Spleen	2.27 ± 0.86	3.74 ± 2.26	2.90 ± 1.13	0.52 ± 0.12
MDA-MB-435	5.20 ± 1.84	8.30 ± 3.57	9.77 ± 2.66	2.43 ± 0.07
Tumor/Blood Ratio	4.33 ± 1.82	9.97 ± 2.10	22.82 ± 9.09	2.98 ± 0.68
Tumor/Liver Ratio	1.56 ± 0.37	2.37 ± 0.20	3.09 ± 0.76	1.67 ± 0.28
Tumor/Lung Ratio	1.20 ± 0.19	1.80 ± 0.44	2.45 ± 0.34	1.28 ± 0.20
Tumor/Muscle Ratio	2.53 ± 0.84	6.80 ± 4.43	6.52 ± 1.72	5.09 ± 4.50

Table SII. Biodistribution data and T/B radios of ^{99m}Tc-PEG$_4$-dimer in the athymic nude mice bearing MDA-MB-435 human breast cancer xenografts. The organ uptake is expressed as %ID/g. Each data point represents an average of biodistribution data from four animals.

%ID/gram	30 min	60 min	120 min
Blood	0.63 ± 0.25	0.38 ± 0.13	0.32 ± 0.06
Brain	0.10 ± 0.01	0.10 ± 0.02	0.18 ± 0.03
Eyes	0.75 ± 0.15	1.34 ± 0.49	1.69 ± 0.62
Heart	1.36 ± 0.29	1.84 ± 0.41	1.88 ± 0.44
Intestine	4.64 ± 1.69	6.17 ± 1.07	4.93 ± 0.20
Kidney	13.25 ± 3.20	11.27 ± 2.01	9.26 ± 0.60
Liver	1.49 ± 0.19	1.59 ± 0.31	1.21 ± 0.38
Lungs	2.46 ± 0.29	3.38 ± 0.39	2.63 ± 0.38
Muscle	1.66 ± 0.41	1.72 ± 0.16	1.37 ± 0.17
Spleen	1.08 ± 0.22	1.94 ± 0.68	2.39 ± 0.45
MDA-MB-435	3.12 ± 0.32	3.80 ± 0.88	3.82±0.29
Tumor/Blood Ratio	6.39 ± 1.59	7.06 ± 4.08	10.72 ± 1.73
Tumor/Liver Ratio	2.26 ± 0.21	2.31 ± 0.73	2.46 ± 0.70
Tumor/Lung Ratio	1.30 ± 0.05	1.03 ± 0.16	1.76 ± 0.74
Tumor/Muscle Ratio	2.06 ± 0.29	1.90 ± 0.51	2.91 ± 0.60

Table SIII. Biodistribution data and T/B radios of ^{99m}Tc-2PEG$_4$-dimer in the athymic nude mice bearing U87MG human glioma xenografts. The organ uptake is expressed as %ID/g. Each data point represents an average of biodistribution data from four animals.

%ID/gram	30 min	60 min	120 min
Blood	1.16 ± 0.15	0.57 ± 0.04	0.29 ± 0.05
Brain	0.25 ± 0.03	0.20 ± 0.03	0.18 ± 0.02
Eyes	2.54 ± 1.07	1.88 ± 0.15	1.60 ± 0.11
Heart	3.25 ± 0.27	2.16 ± 0.21	1.65 ± 0.43
Intestine	16.06 ± 6.63	12.50 ± 5.46	9.81 ± 1.98
Kidneys	20.81 ± 2.32	14.33 ± 1.23	10.21 ± 1.37
Liver	4.25 ± 0.51	2.98 ± 0.18	2.46 ± 0.32
Lungs	6.84 ± 0.85	5.38 ± 0.44	3.63 ± 0.69
Muscle	2.18 ± 0.37	1.45 ± 0.30	1.27 ± 0.20
Spleen	4.33 ± 0.72	3.62 ± 0.46	3.42 ± 0.83
U87MG	11.17 ± 1.96	8.62 ± 2.35	8.31 ± 2.31
Tumor/Blood Ratio	9.63 ± 1.32	15.30 ± 4.24	29.12 ± 8.54
Tumor/Liver Ratio	2.59 ± 0.45	2.89 ± 0.95	3.33 ± 0.64
Tumor/Lung Ratio	1.60 ± 0.19	1.59 ± 0.47	2.33 ± 0.73
Tumor/Muscle Ratio	5.07 ± 0.37	6.16 ± 2.77	6.46 ± 1.21

Table SIV. Biodistribution data and T/B radios of ^{99m}Tc-3PEG$_4$-dimer in the athymic nude mice bearing U87MG human glioma xenografts. The organ uptake is expressed as %ID/g. Each data point represents an average of biodistribution data from four animals.

%ID/gram	30 min	60 min	120 min
Blood	1.02 ± 0.22	0.47 ± 0.06	0.17 ± 0.02
Brain	0.21 ± 0.07	0.17 ± 0.03	0.13 ± 0.01
Eyes	1.58 ± 0.17	1.40 ± 0.13	1.50 ± 0.12
Heart	2.24 ± 0.20	1.67 ± 0.15	1.29 ± 0.08
Intestine	10.05 ± 2.47	9.45 ± 1.31	10.11 ± 2.49
Kidney	17.60 ± 0.73	12.28 ± 1.09	9.89 ± 1.20
Liver	3.14 ± 0.18	2.92 ± 0.77	2.50 ± 0.19
Lungs	5.15 ± 0.36	4.25 ± 0.63	3.56 ± 0.41
Muscle	1.45 ± 0.20	1.12 ± 0.15	0.89 ± 0.10
Spleen	3.52 ± 0.16	3.11 ± 0.18	3.05 ± 0.71
U87MG	8.17 ± 0.68	7.24 ± 0.95	9.74 ± 3.22
Tumor/Blood Ratio	6.72 ± 2.88	15.36 ± 1.01	48.84 ± 18.74
Tumor/Liver Ratio	2.13 ± 0.87	2.55 ± 0.36	3.49 ± 1.64
Tumor/Lung Ratio	1.31 ± 0.56	1.71 ± 0.05	2.51 ± 1.32
Tumor/Muscle Ratio	3.39 ± 1.85	6.58 ± 1.58	11.18 ± 4.34

Table SV. Biodistribution data and T/B radios of ^{99m}Tc-PEG$_4$-monomer in the athymic nude mice bearing U87MG human glioma xenografts. The organ uptake is expressed as %ID/g. Each data point represents an average of biodistribution data from four animals.

%ID/gram	30 min	60 min	120 min
Blood	1.31 ± 0.22	0.45 ± 0.04	0.22 ± 0.07
Brain	0.17 ± 0.06	0.10 ± 0.01	0.08 ± 0.01
Eyes	1.52 ± 0.47	0.78 ± 0.07	0.63 ± 0.04
Heart	1.48 ± 0.19	0.80 ± 0.04	0.62 ± 0.10
Intestine	8.06 ± 2.70	3.51 ± 0.78	3.04 ± 0.69
Kidneys	10.78 ± 1.82	5.95 ± 0.34	4.04 ± 0.69
Liver	3.43 ± 1.00	2.17 ± 0.08	1.99 ± 0.44
Lungs	5.14 ± 1.40	2.75 ± 0.11	1.79 ± 0.17
Muscle	1.65 ± 0.25	0.87 ± 0.10	0.62 ± 0.15
Spleen	3.37 ± 0.70	2.83 ± 0.44	2.47 ± 0.54
U87MG	4.74 ± 2.71	4.26 ± 0.93	3.08 ± 0.83
Tumor/Blood Ratio	3.85 ± 2.47	9.47 ± 2.69	15.50 ± 5.47
Tumor/Liver Ratio	1.47 ± 0.91	1.97 ± 0.42	1.55 ± 0.38
Tumor/Lung Ratio	0.95 ± 0.54	1.55 ± 0.31	1.73 ± 0.37
Tumor/Muscle Ratio	2.90 ± 1.67	4.93 ± 1.06	5.12 ± 1.88

^{99m}Tc-PEG$_4$-monomer

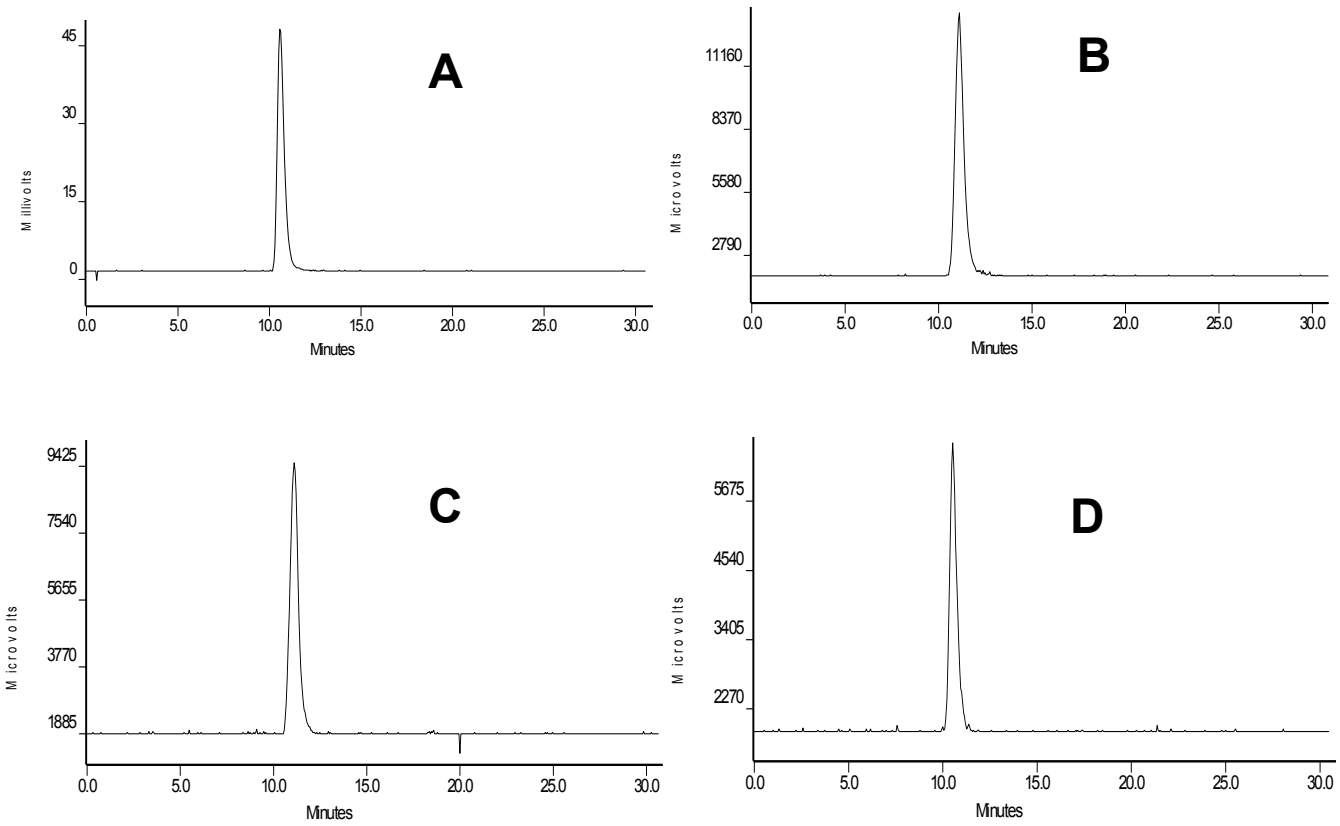

Figure SI. Radio-HPLC chromatograms of ^{99m}Tc-PEG$_4$-monomer in saline before injection (A), in the urine at 30 min p.i. (B), in the urine at 120 min p.i. (C), and in the feces at 120 min p.i. (D). Each mouse was administered with ~ 100 μCi of ^{99m}Tc-PEG$_4$-monomer.

^{99m}Tc-3PEG$_4$-dimer

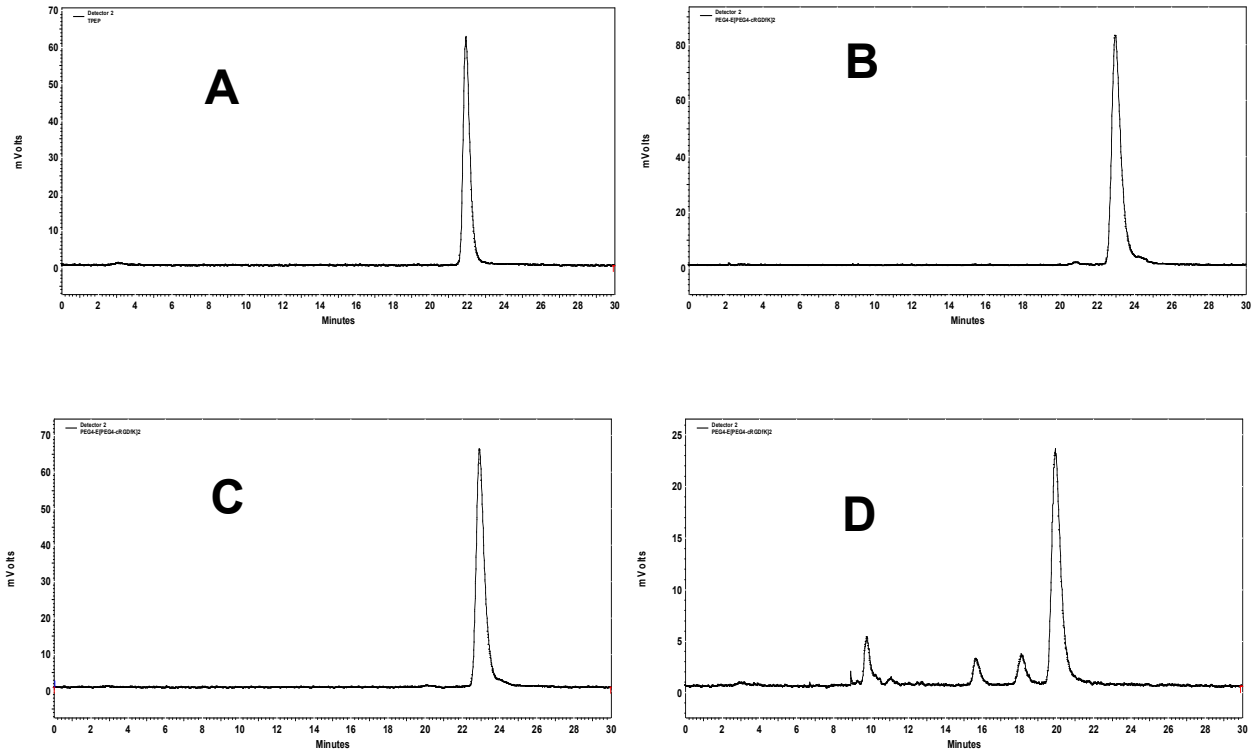

Figure SII. Radio-HPLC chromatograms of ^{99m}Tc-3PEG$_4$-dimer in saline before injection (A), in the urine at 30 min p.i. (B), in the urine at 120 min p.i. (C), and in the feces at 120 min p.i. (D). Each mouse was administered with ~ 100 μCi of ^{99m}Tc-3PEG$_4$-dimer. Variation of HPLC retention times was caused by the presence of acetonitrile in both urine and feces samples.