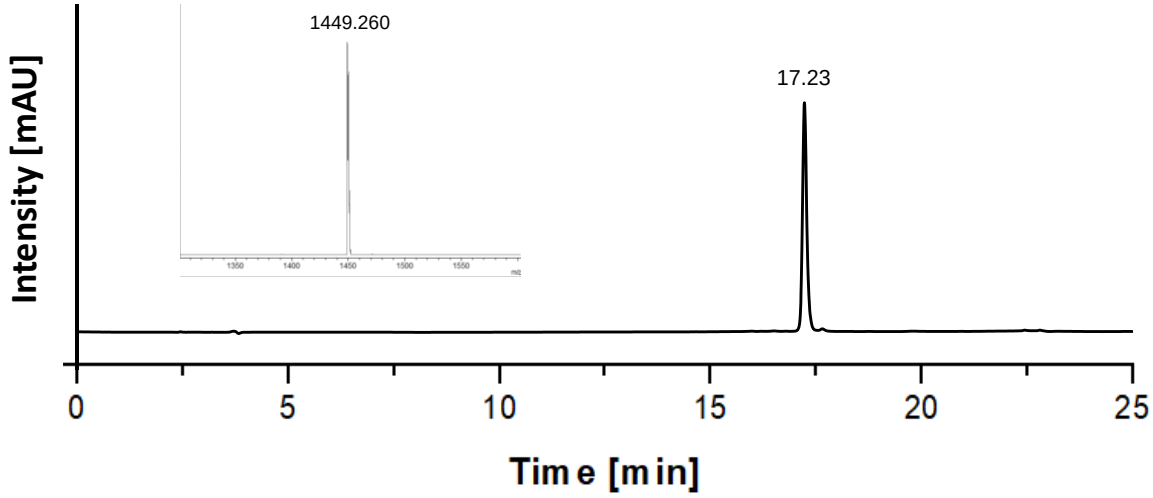
Table of content

(a)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10
15
20
25
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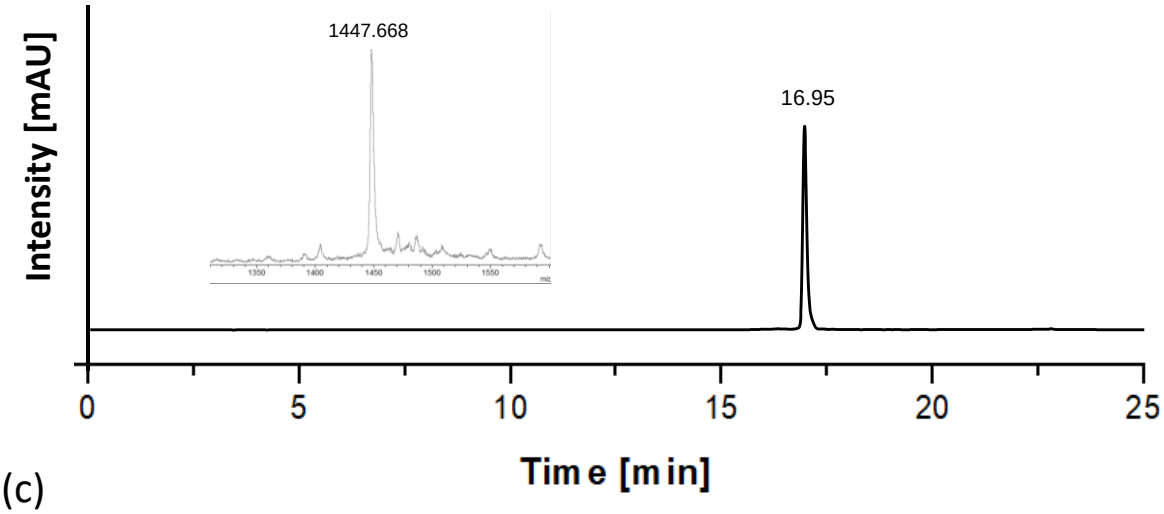
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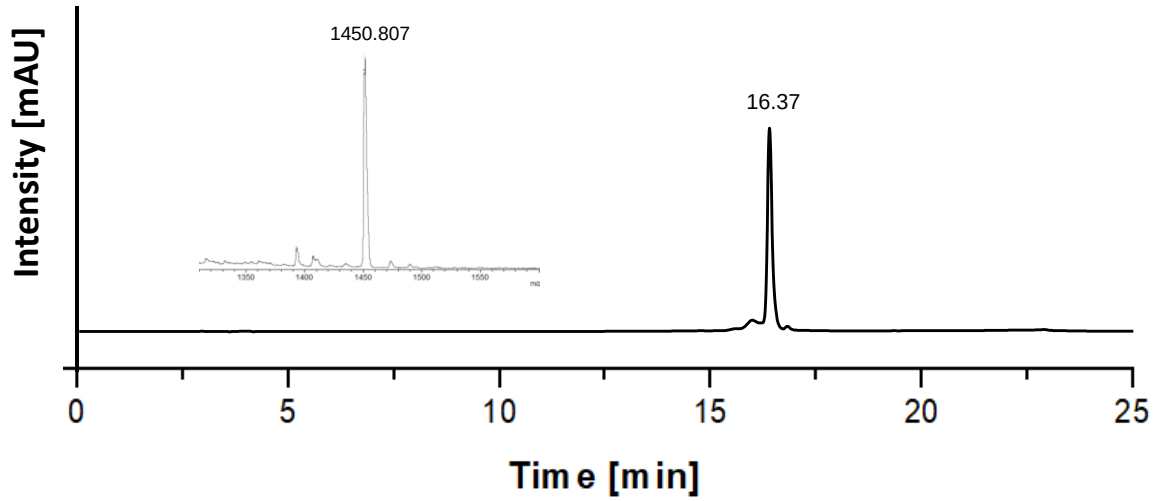
(c)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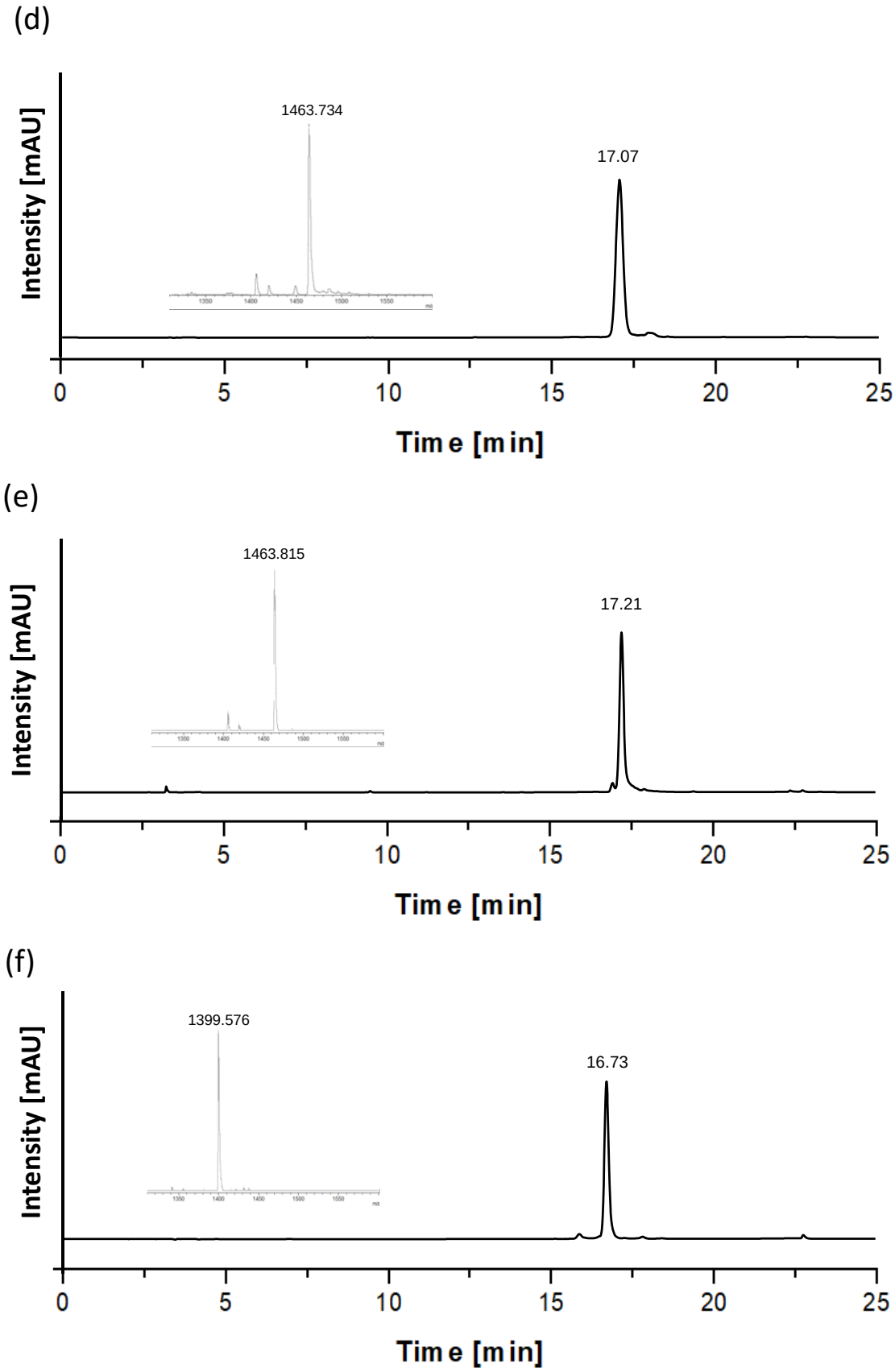

Figure S1. UV-trace and respective MALDI-TOF spectrum of (**a**) DOTA-MGS5 (**b**) DOTA-[2Nal^{8}]MGS5, (**c**) DOTA-[DLys^{1}]MGS5, (**d**) DOTA-[(*N*-Me)1Nal^{8}]MGS5, (**e**) DOTA-MGS5[NHCH$_3$] and (**f**) DOTA-[Phe^{8}]MGS5.

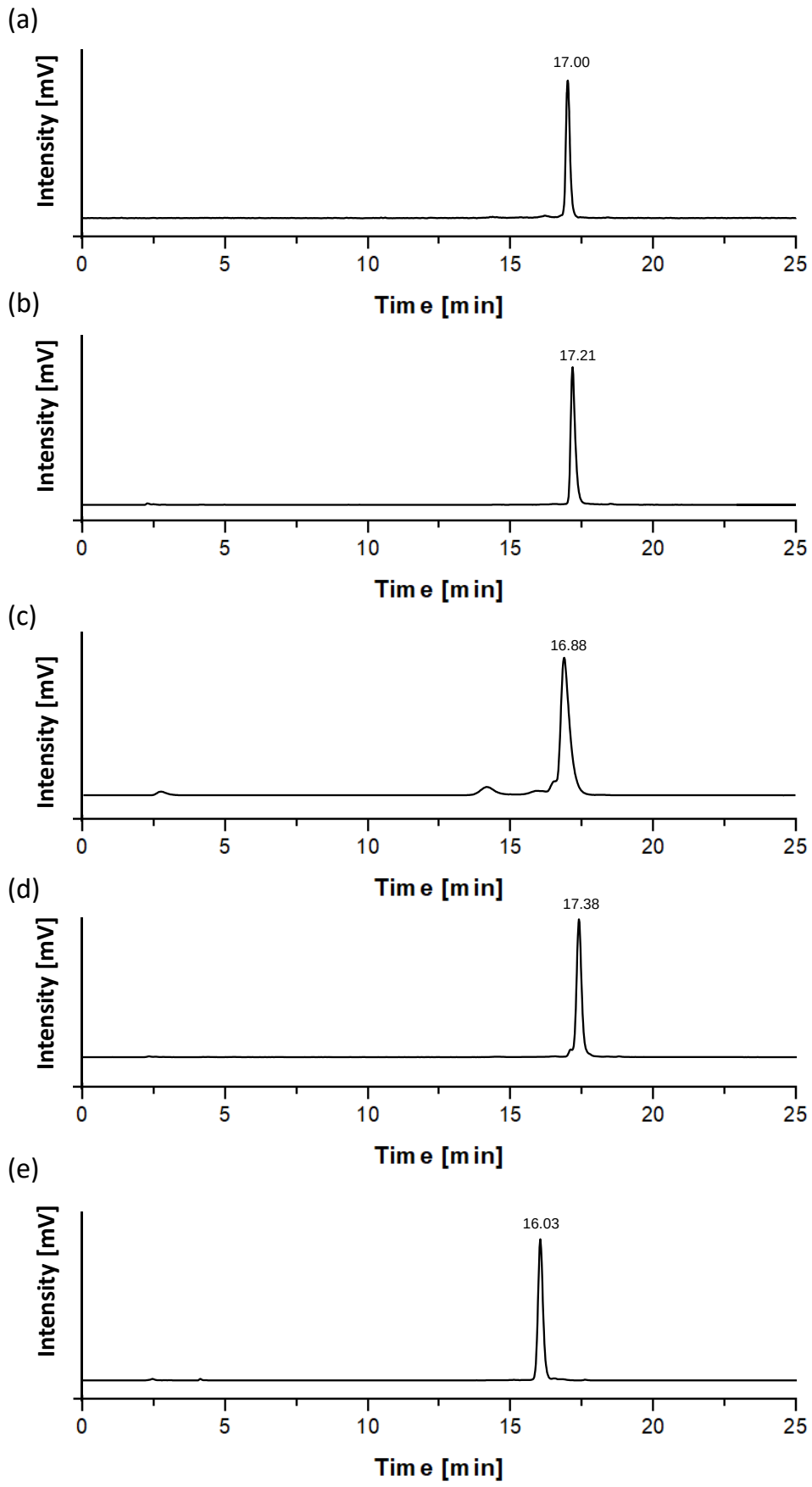

Figure S2. Radiochromatogram of (**a**) [^{111}In]In-DOTA-MGS5 (**b**) [^{111}In]In-DOTA-[2Nal^{8}]MGS5, (**c**) [^{111}In]In-DOTA-[DLys^{1}]MGS5, (**d**) [^{111}In]In-DOTA-MGS5[NHCH$_3$] and (**e**) [^{111}In]In-DOTA-[Phe^{8}]MGS5.

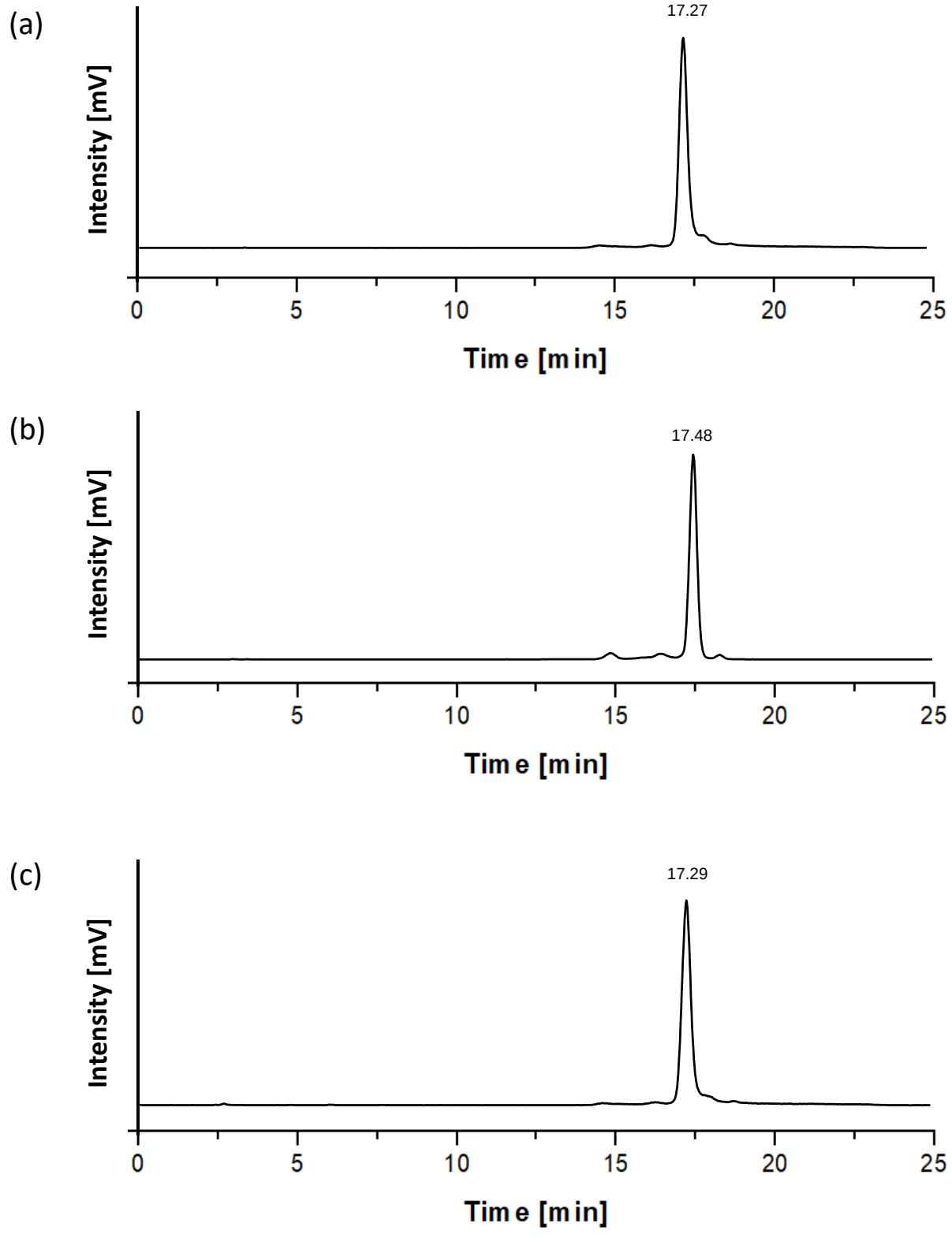

Figure S3. Radiochromatogram of (**a**) [^{111}In]In-DOTA-[(*N*-Me)1Nal^{8}]MGS5 (**b**) [^{68}Ga]Ga-DOTA-[(*N*-Me)1Nal^{8}]MGS5 and (**c**) [^{177}Lu]Lu-DOTA-[(*N*-Me)1Nal^{8}]MGS5.

In vitro Characterization of DOTA-[(N-Me)1Nal[8]]MGS5 Labeled with Different Radiometals

Labeling with different radiometals of DOTA-[(*N*-Me)1Nal[8]]MGS5 resulted in a similar hydrophilicity of DOTA-[(*N-Me*)1Nal[8]]MGS5 labeled with different radiometals with values of −2.4 ± 0.3 for indium−111, −2.0 ± 0.1 for lutetium−177 and −2.2 ± 0.1 for gallium−68. Only minor differences in binding to serum proteins were observed depending on the radiometal used for labeling. For the time point of 4 h after incubation, the highest protein binding was found for [^{111}In]In-DOTA-[Phe[8]]MGS5 (31.9 ± 0.3%), followed by [^{68}Ga]Ga-DOTA-[(*N*-Me)1Nal[8]]MGS5 (25.5 ± 1.5%) and [^{177}Lu]Lu-DOTA-[(*N*-Me)1Nal[8]]MGS5 (25.4 ± 2.3%). Similar values were found also for ^{177}Lu-labeled (28.7 ± 7.3%) and ^{111}In-labeled peptide (39.8 ± 4.2%) DOTA-[(*N*-Me)1Nal[8]]MGS5 for the time point of 24 h after incubation. Incubation in fresh human serum further confirmed a very high stability in vitro of DOTA-[(*N*-Me)1Nal[8]]MGS5 labeled with different radiometals. No free radiometal and only minor amounts of peptide related radiometabolites could be monitored in the radiochromatograms at 4 h after incubation. Also at the later time point of 24 h after incubation, ≥ 98% intact radiopeptide was observed for [^{111}In]In-DOTA-[2Nal[8]]MGS5 and [^{177}Lu]Lu-DOTA-[2Nal[8]]MGS5. The different results of the in vitro characterization of DOTA-[(*N*-Me)1Nal[8]]MGS5 labeled with different radiometals are summarized in Table 1. As a control, the stability in PBS (n = 1) was also tested, confirming a high stability for the DOTA-complex with indium−111 (96.2%), gallium−68 (99.2%) and lutetium−177 (99%) for 4 h after incubation.

Table S1. Summary of the analytical data of DOTA-[(*N*-Me)1Nal[8]]MGS5 labeled with different radiometals

Compound	Binding to Serum Proteins [%] n = 2		LogD n = 8	Intact Radiopeptide in Human Serum [%] n = 2	
	4 h	24 h		4 h	24 h
[^{111}In]In-DOTA-[(*N*-Me)1Nal[8]]MGS5	31.9 ± 0.3	39.8 ± 4.2	−2.4 ± 0.3	99.3 ± 0.9	99.6 ± 0.1
[^{177}Lu]Lu-DOTA-[(*N*-Me)1Nal[8]]MGS5	25.4 ± 2.3	28.7 ± 7.3	−2.0 ± 0.1	98.3 ± 0.5	98.5 ± 1.2
[^{68}Ga]Ga-DOTA-[(*N*-Me)1Nal[8]]MGS5	25.5 ± 1.5	n.d.	−2.2 ± 0.1	99.9 ± 0.0	n.d.

Cell Internalization of DOTA-[(N-Me)1Nal[8]]MGS5 Labeled with Different Radiometals

The receptor-specific internalization of DOTA-[(*N*-Me)1Nal[8]]MGS5 labeled with different radiometals was studied for the time point of 2 h after incubation. In analogy to the varying tumor uptake observed in vivo, [^{111}In]In-DOTA-[(*N*-Me)1Nal[8]]MGS5 demonstrated the highest receptor-mediated cell internalization with the value of 31.5 ± 6.7%. [^{177}Lu]Lu-DOTA-[(*N*-Me)1Nal[8]]MGS5 showed a similar receptor-specific cell uptake of 30.8 ± 5.5%. For [^{68}Ga]Ga-DOTA-[(*N*-Me)1Nal[8]]MGS5 a much lower cell uptake of 20.4 ± 2.3% was found for the same time point.

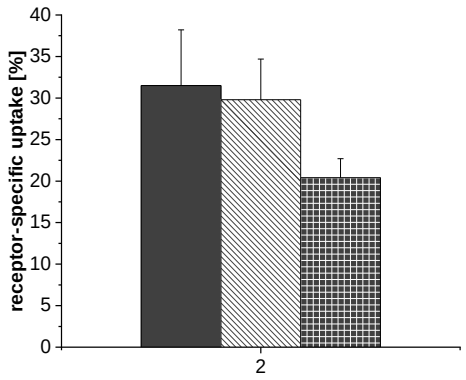

Figure S4. Cell internalization of DOTA-[(*N*-Me)1Nal[8]]MGS5 labeled with different radiometals 2 h after incubation. Gray: indium−111, striped: lutetium−177 and checked: gallium−68.

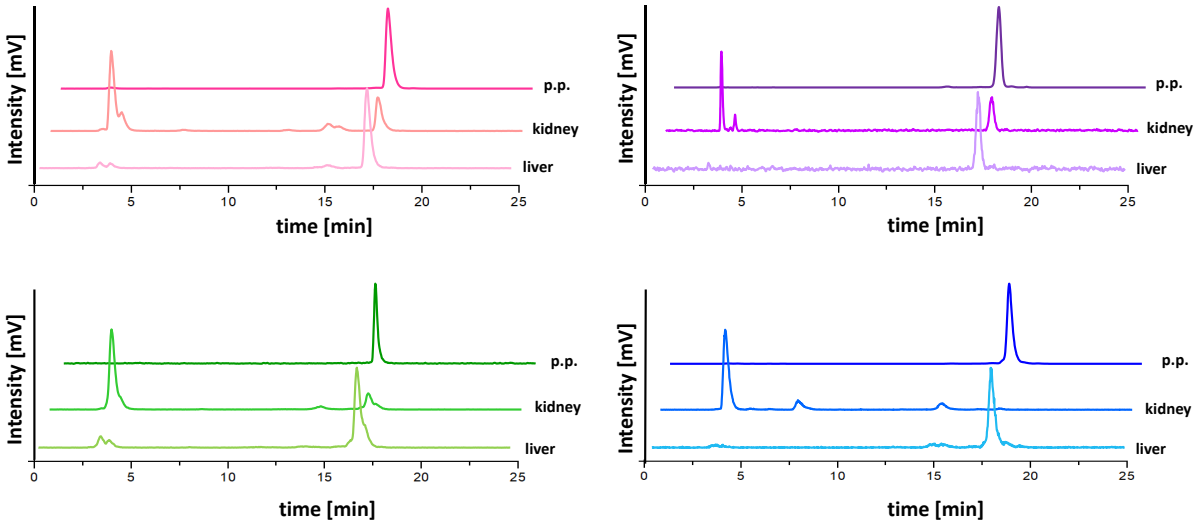

Figure S5. Representative radiochromatograms of the ^{111}In-labeled peptides post preparation (p.p.), as well as kidney and liver samples obtained from BALB/c mice 10 min p.i. Pink: DOTA-[2Nal^{8}]MGS5, green: DOTA-[DLys^{1}]MGS5, purple: DOTA-[(*N*-Me)1Nal^{8}]MGS5, blue: DOTA-MGS5[NHCH$_3$].