Radioisotopes in diagnostics and therapy

(pre-)clinical view

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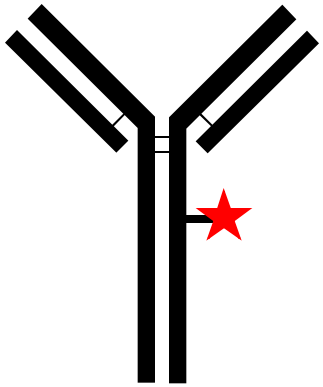
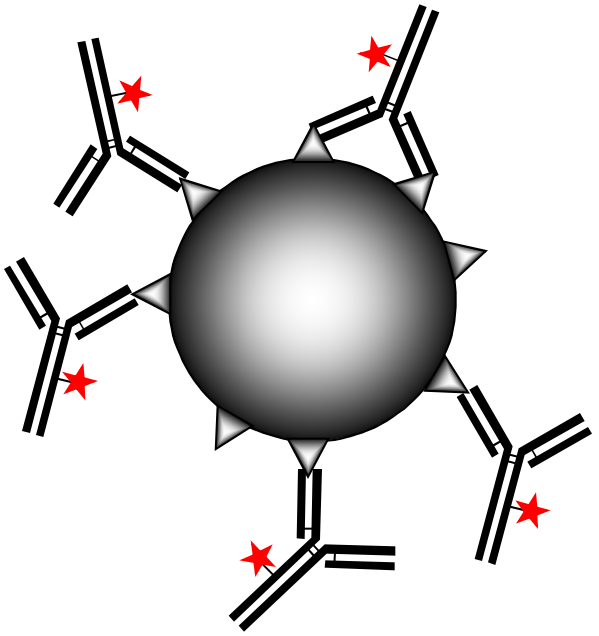
Radioisotopes in diagnostics and therapy

- Radioimmunotherapy of cancer
- Radioimmunoscintigraphy
- Pretargeted imaging of cancer
- Peptide receptor radionuclide imaging
- Peptide receptor radionuclide therapy

Antibody targeting of tumors



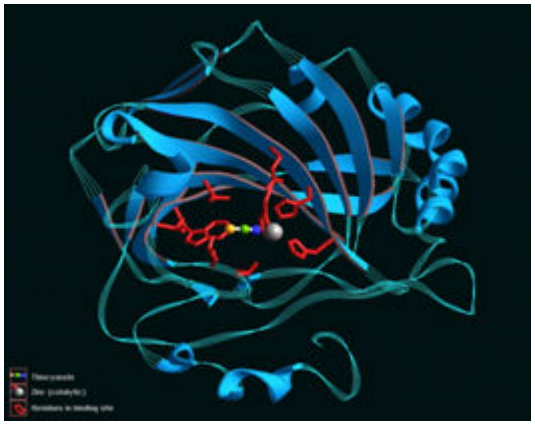
Radiolabeled antibody



Radioimmunotargeting of renal cell carcinoma

G250 Antigen

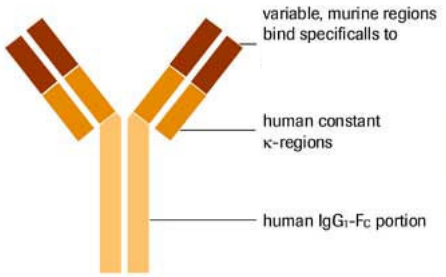
- Identified as Carbonic Anhydrase IX
- Expressed on > 95% of clear cell RCC
- No expression in normal kidney
- Expression in normal tissues restricted to:
  - larger bile ducts
  - Mucosa of the upper gastrointestinal tract
- not detected in serum



Carbonic anhydrase IX

cG250 Antibody

- Chimeric IgG1
- Ka = 4 x 10^{-9} l/mol

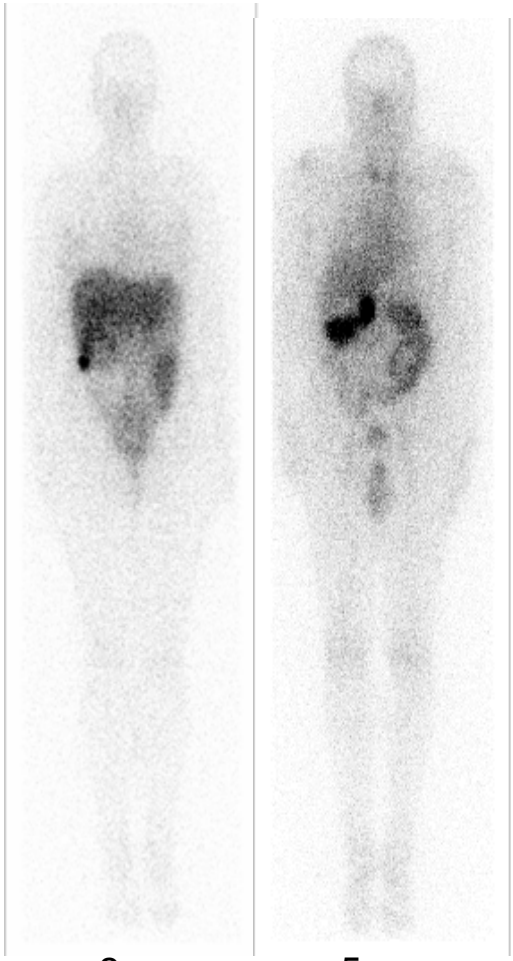


Chimeric G250 IgG1

Radioimmunotargeting of renal cell carcinoma

- Protein dose escalation in RCC patients
- 5 dose levels: 2 - 5 - 10 - 25 - 50 mg
- 3 patients per dose level
- 6 mCi ^{131}I-cG250 i.v.
- Surgery 7 days p.i.

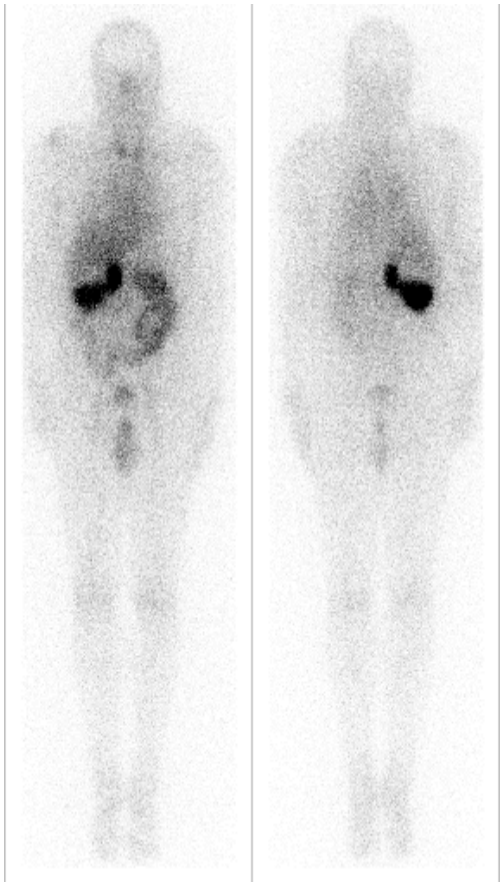
	2 mg	**≥ 5 mg**
Liver uptake (%ID/kg)	3.4 ± 0.2	0.9 ± 0.3
t½ (h)	40 ± 10	69 ± 13



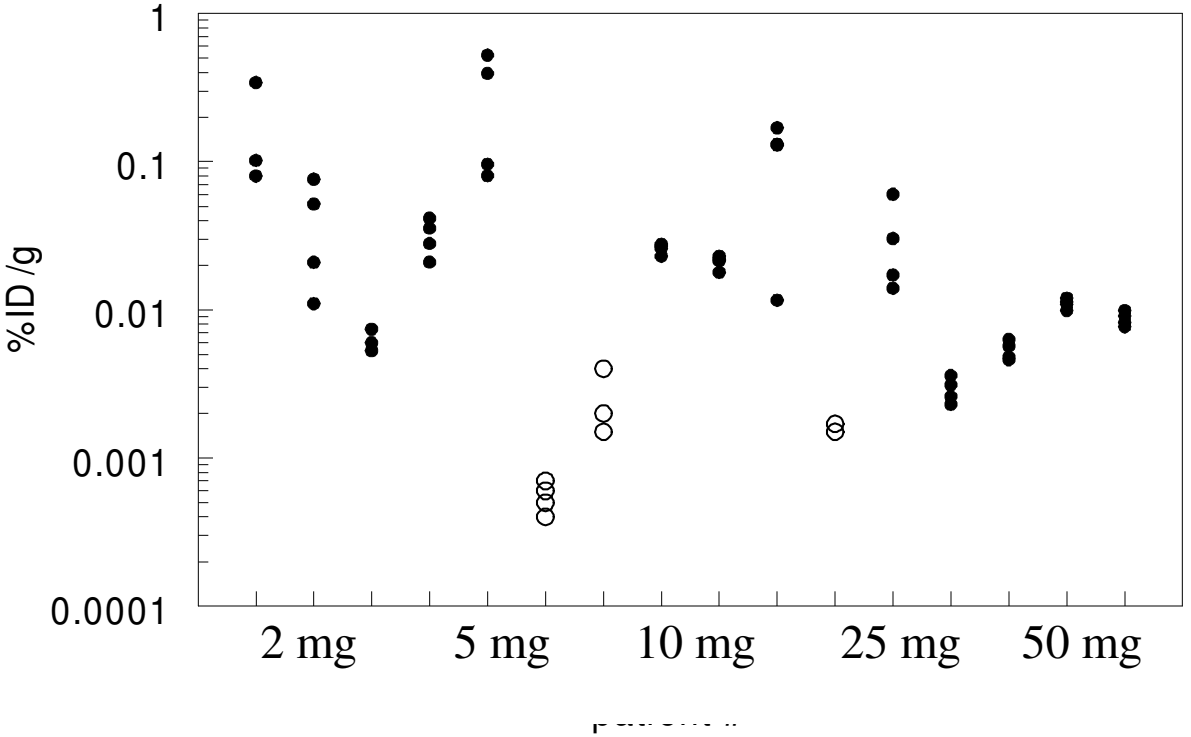
2 mg 5 mg

J Clin Oncol 15: 1529-1537, 1997

Protein Dose Escalation Study

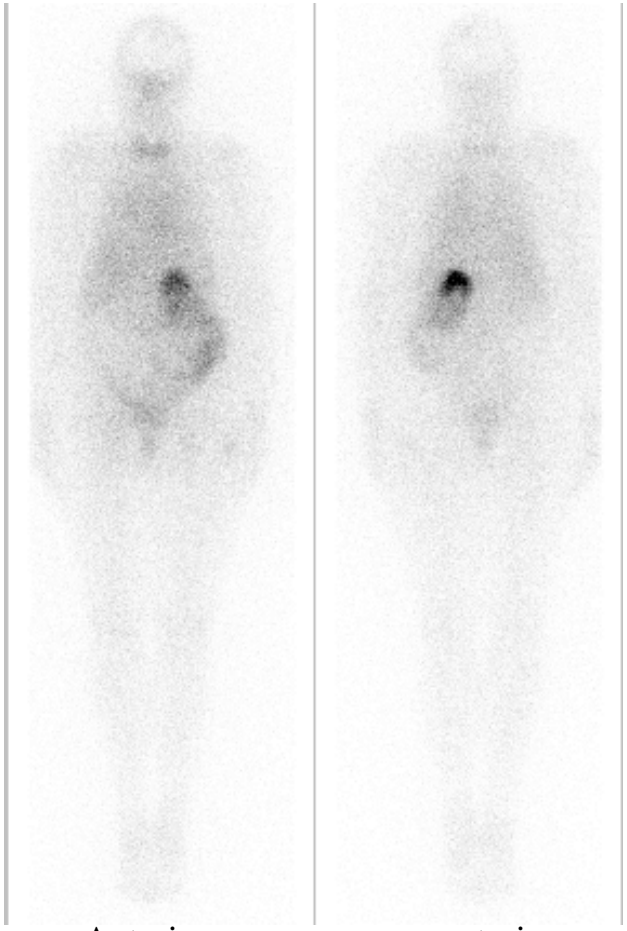


Anterior posterior

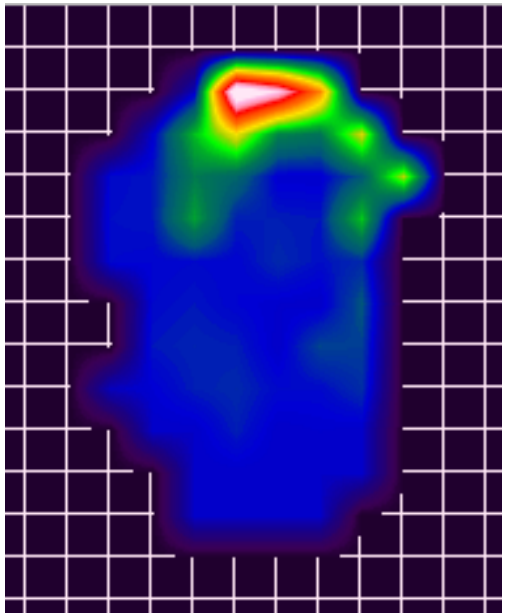


J Clin Oncol 15: 1529-1537, 1997

Heterogeneity of MAb uptake in Renal Cell Carcinoma



Anterior posterior



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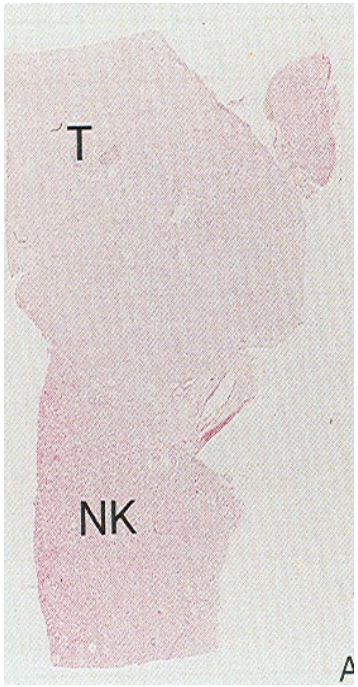
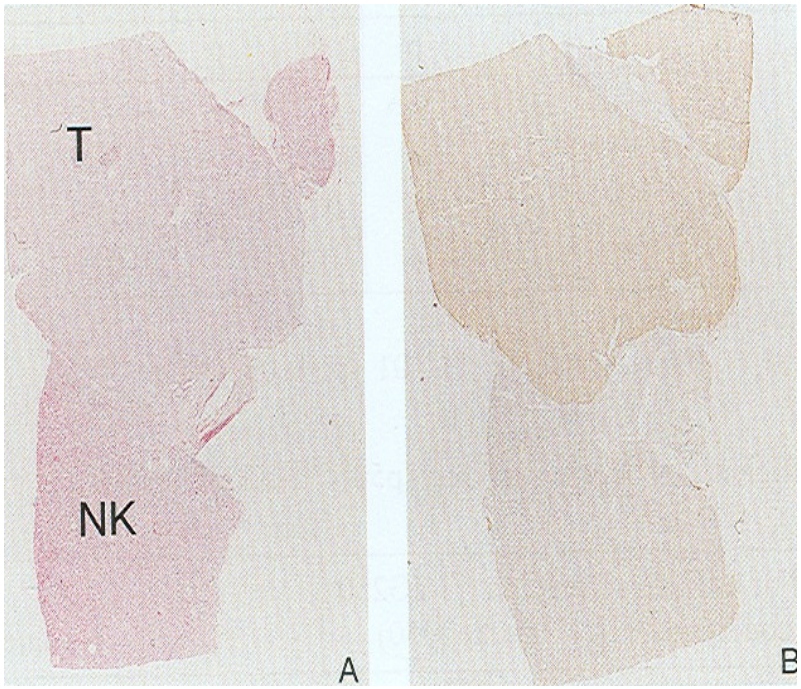
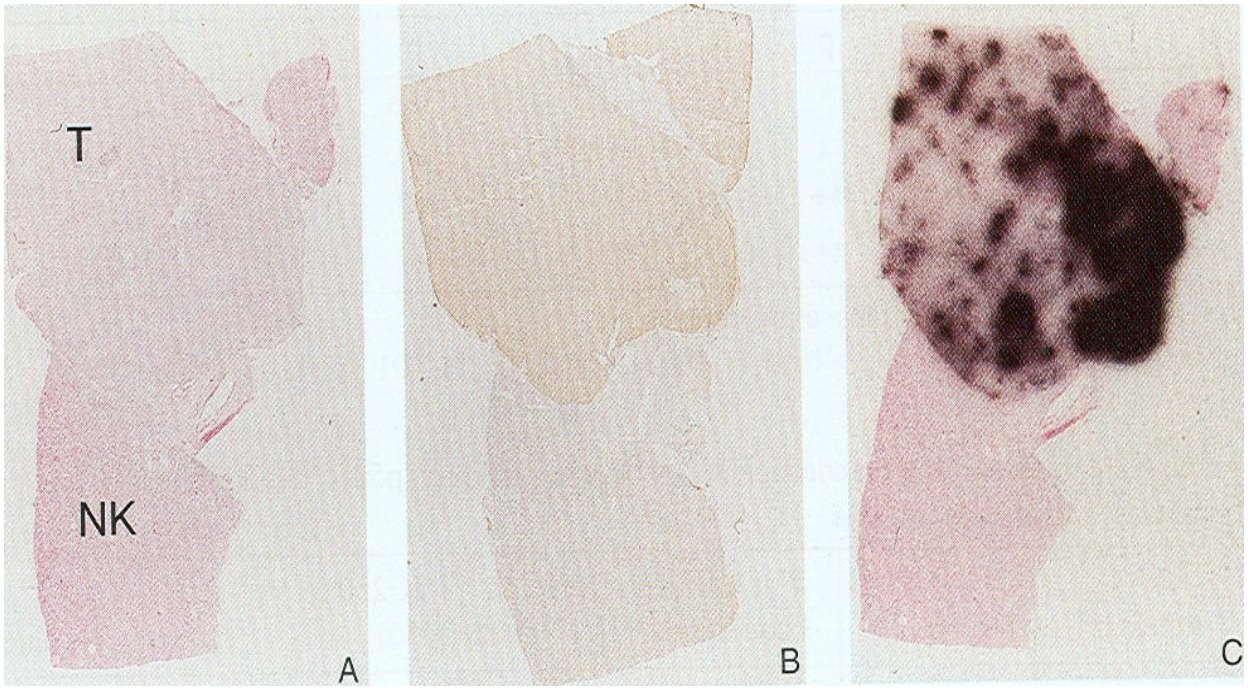


Heterogeneity of MAb uptake in Renal Cell Carcinoma

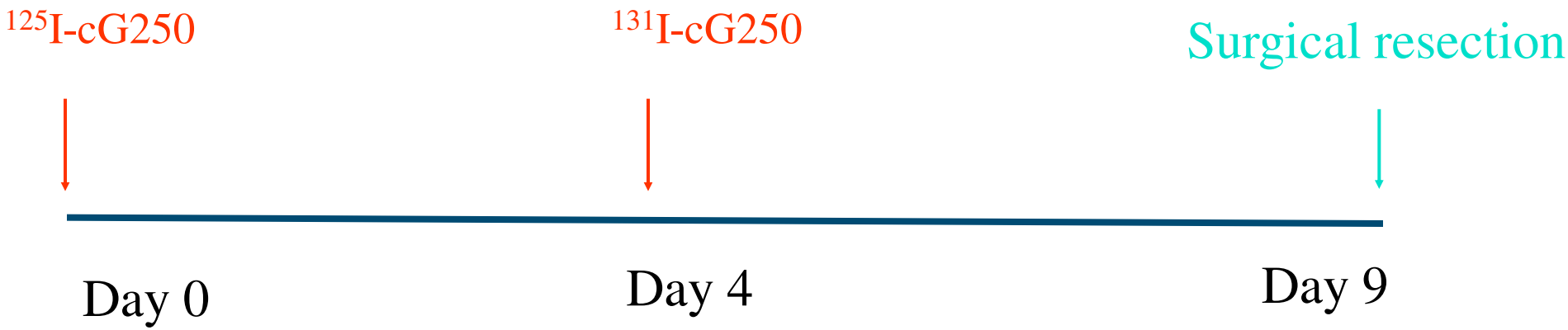


Heterogeneity of MAb uptake in Renal Cell Carcinoma

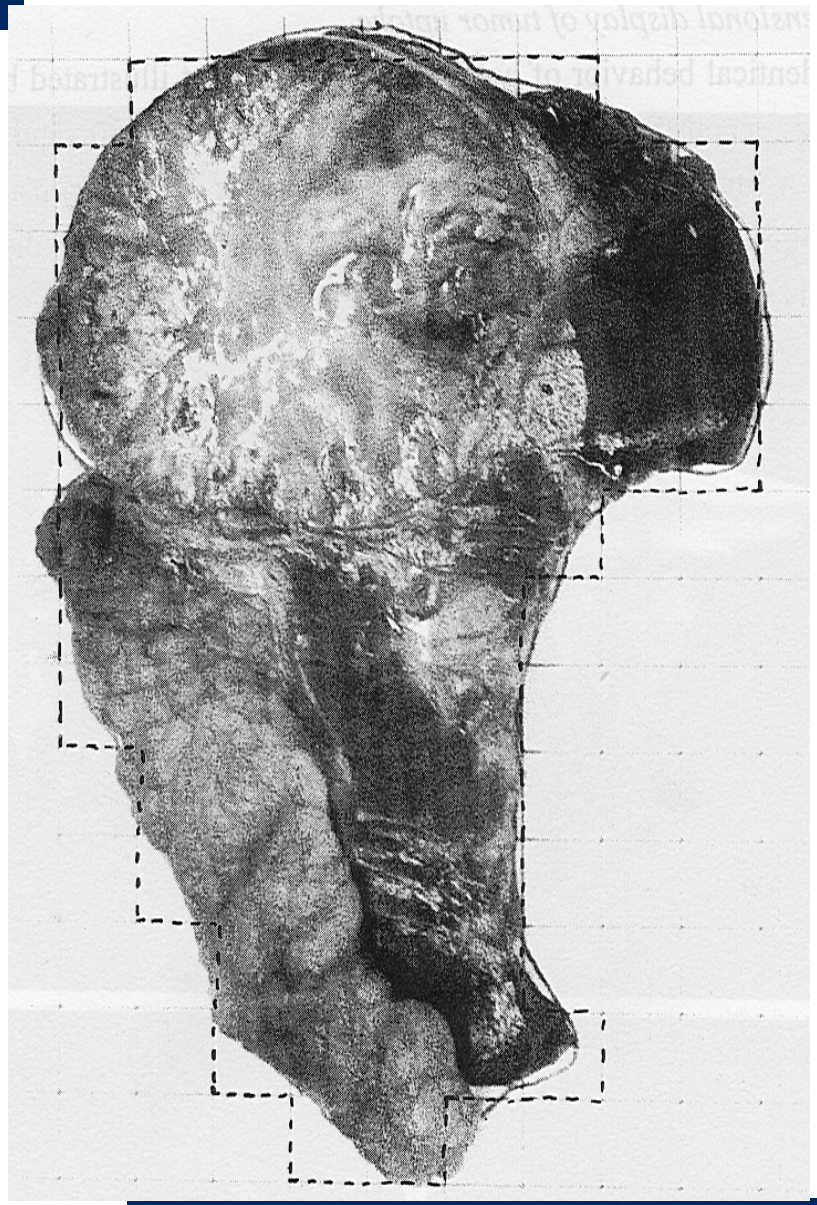


Heterogeneity of MAb uptake in Renal Cell Carcinoma

Analysis of the intratumoral distribution of cG250 of 2 successive injections



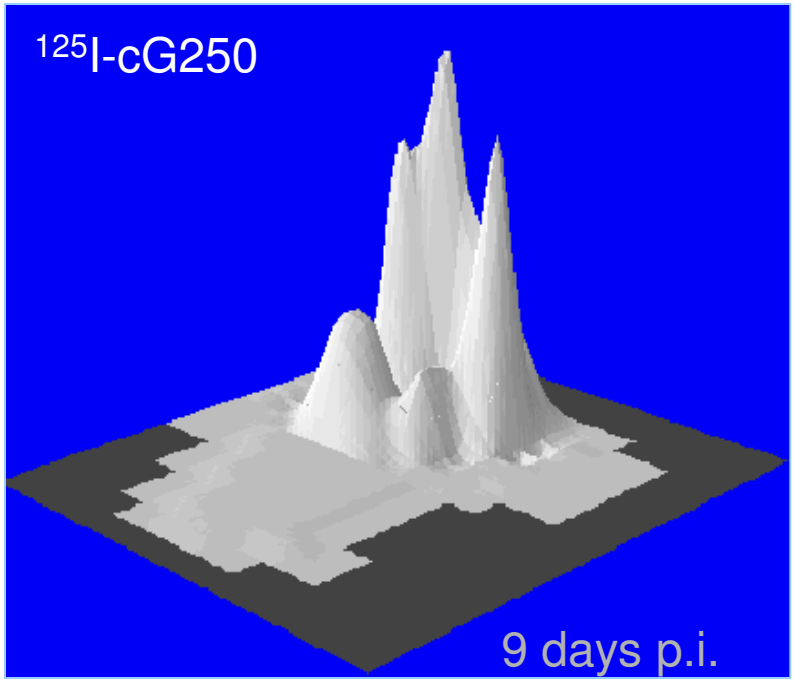
Heterogeneity of MAb uptake in Renal Cell Carcinoma

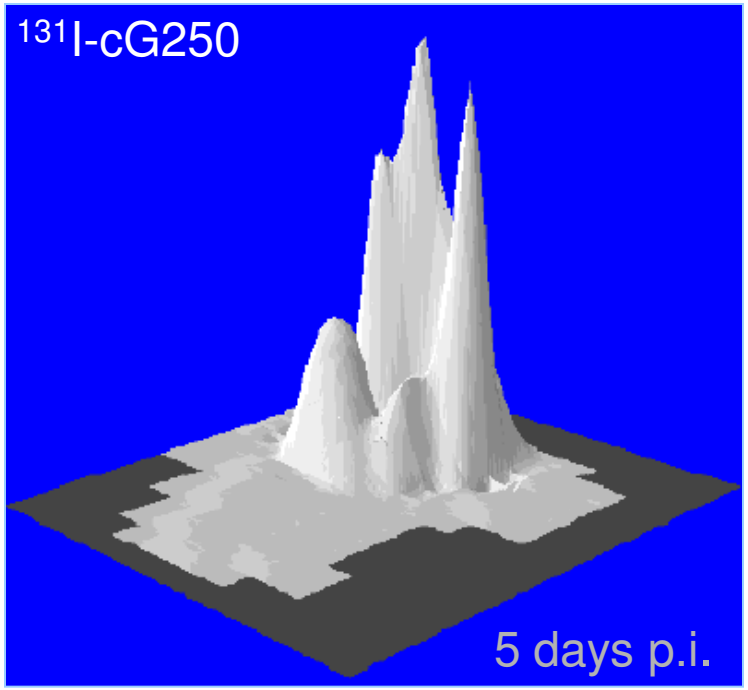


		1 *0.1* *500* 0.1 869	2 *0.0* *968* 0.1 253	3 *0.0* *702* 0.0 897	4 *0.0* *449* 0.0 550	5 *0.0* *203* 0.0 245	6 *0.0* *016* 0.0 010			
	7 *0.1* *109* 0.1 340	8 *0.0* *745* 0.0 914	9 *0.0* *098* 0.0 123	10 *0.0* *061* 0.0 077	11 *0.0* *101* 0.0 117	12 *0.0* *403* 0.0 534	13 *0.0* *008* 0.0 019	14 *0.0* *006* 0.0 016	15 *0.0* *009* 0.0 017	
	16 *0.0* *134* 0.0 204	17 *0.0* *047* 0.0 086	18 *0.0* *028* 0.0 047	19 *0.0* *042* 0.0 051	20 *0.0* *289* 0.0 390	21 *0.1* *290* 0.1 795	22 *0.0* *007* 0.0 017	23 *0.0* *007* 0.0 019	24 *0.0* *008* 0.0 018	
	25 *0.0* *172* 0.0 254	26 *0.0* *104* *0.0* *148*	27 *0.0* *083* *0.0* *112*	28 *0.0* *054* 0.0 071	29 *0.0* *317* 0.0 454	30 *0.0* *175* 0.0 254	31 *0.0* *006* 0.0 015	32 *0.0* *006* 0.0 016	33 *0.0* *008* 0.0 018	
	34 *0.0* *308* 0.0 419	35 *0.0* *460* 0.0 612	36 *0.0* *466* 0.0 625	37 *0.0* *192* 0.0 259	38 *0.0* *328* 0.0 421	39 *0.0* *019* 0.0 030	40 *0.0* *006* 0.0 013	41 *0.0* *006* 0.0 017	42 *0.0* *008* 0.0 017	
	43 *0.0* *057* 0.0 090	44 *0.0* *391* 0.0 533	45 *0.0* *387* 0.0 526	46 *0.0* *178* 0.0 234	47 *0.0* *045* 0.0 064	48 *0.0* *005* 0.0 013	49 *0.0* *006* 0.0 013			
	50 *0.0* *006* 0.0 010	51 *0.0* *006* 0.0 010	52 *0.0* *006* 0.0 015	53 *0.0* *006* 0.0 015	54 *0.0* *006* 0.0 011	55 *0.0* *006* 0.0 011				
1 cm										

remaining normal tissue
(kidney and fat)
average uptake:
^{125}I-cG250: 0.0007
^{131}I-cG250: 0.0012

Heterogeneity of MAb uptake in Renal Cell Carcinoma





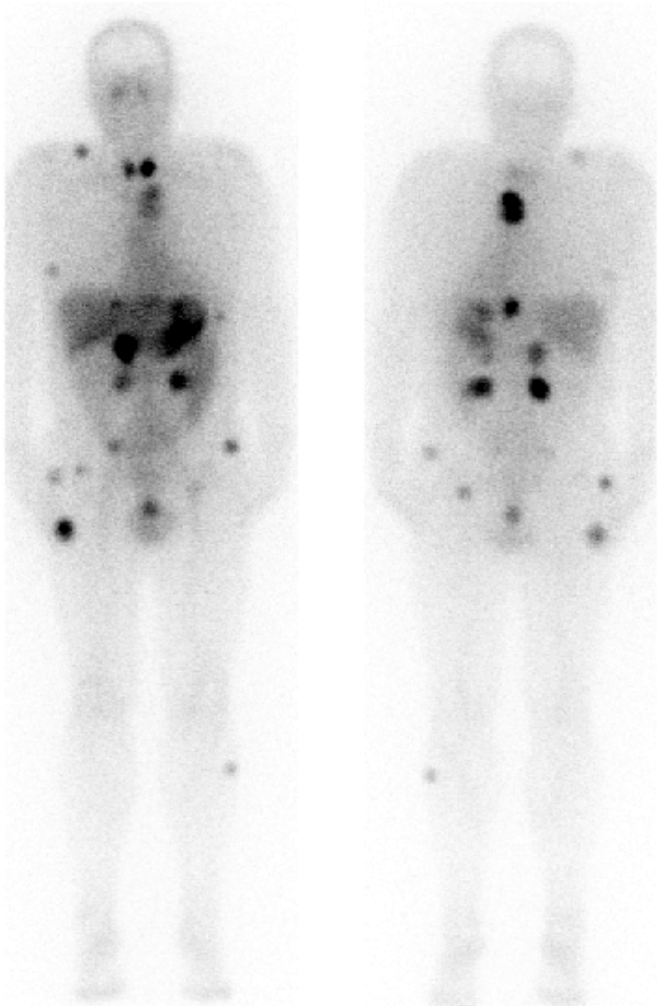
Two successive cG250 injections

- High intratumoral MAb uptake variations
- Minimal variations between ^{125}I and ^{131}I uptake
- Mean ^{131}I/^{125}I uptake ratio: 1.72 ± 0.45
- Intratumoral distribution of ^{131}I and ^{125}I was highly similar

Cancer Res 59:1615-1619, 1999

^{131}I-cG250 activity dose escalation

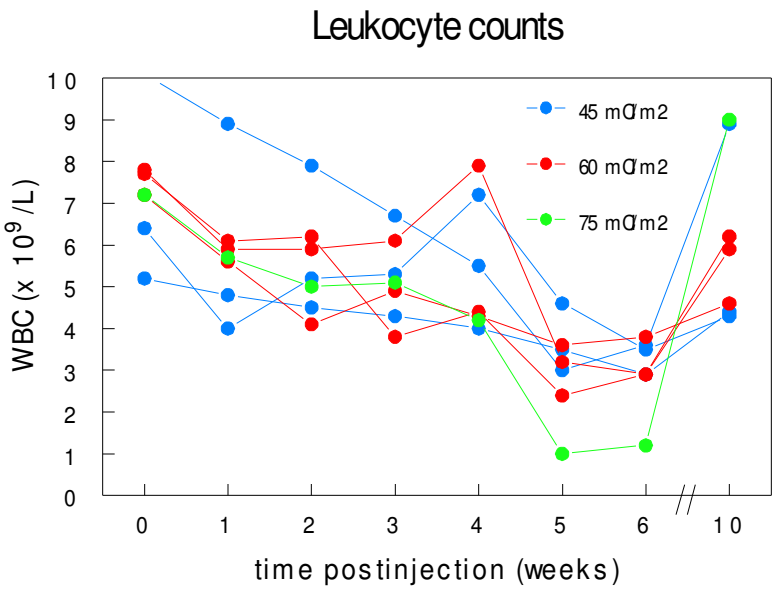
- Patients with progressive metastatic RCC
- Diagnostic dose: 6 mCi ^{131}I-cG250 (5 mg)
- Therapeutic dose: 45 mCi/m^2 (5 mg)
- Dose escalation with 15 mCi/m^2
- 3 patients per dose level

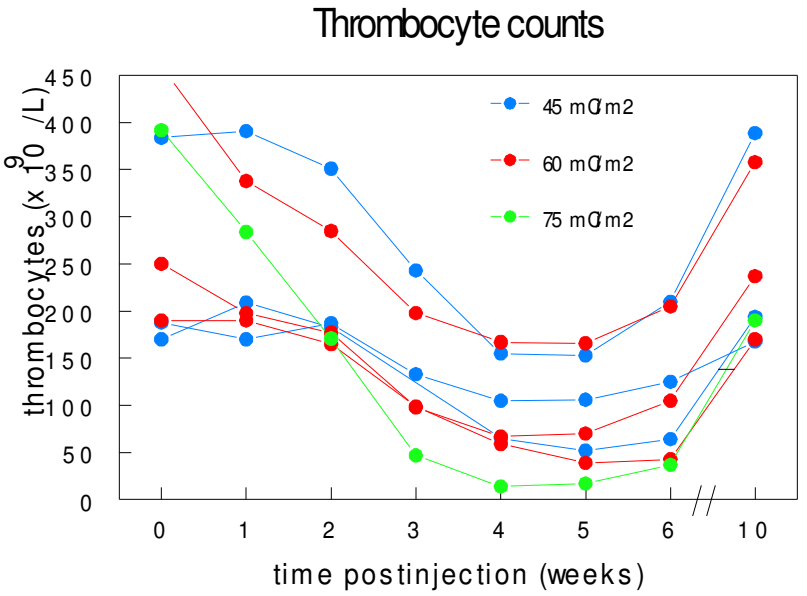


Ant. Post.

Clin Cancer Res 5; 3268-3274, 1999

^{131}I-cG250 Activity dose escalation



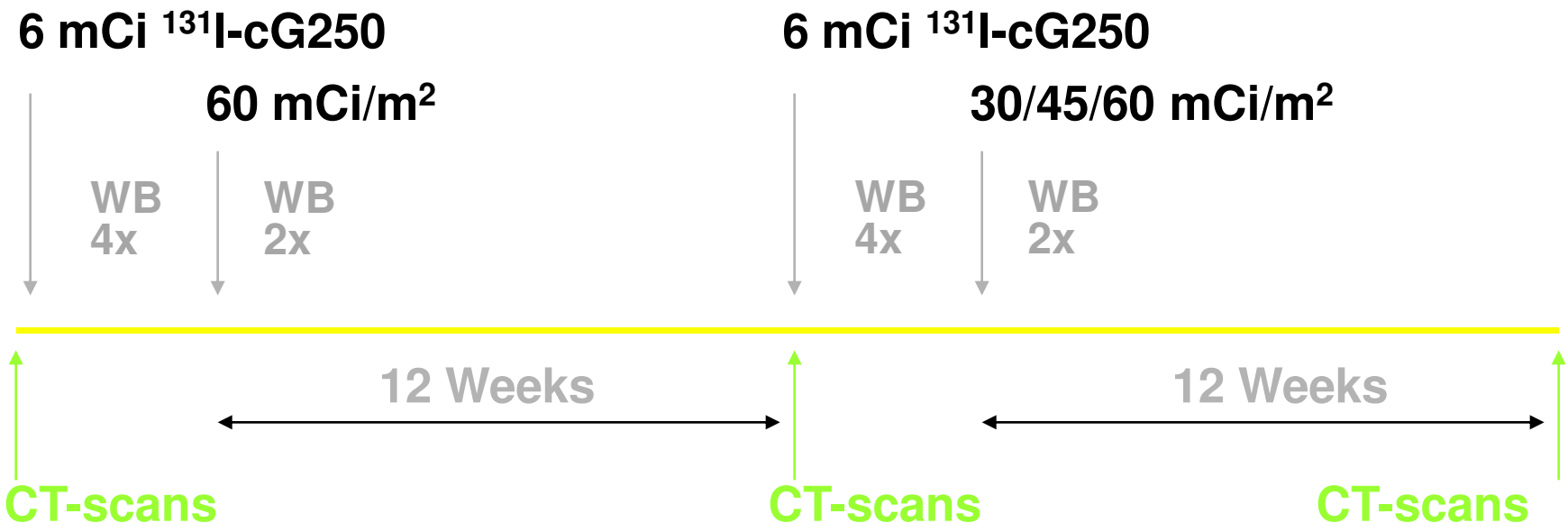


Results of activity dose escalation study:

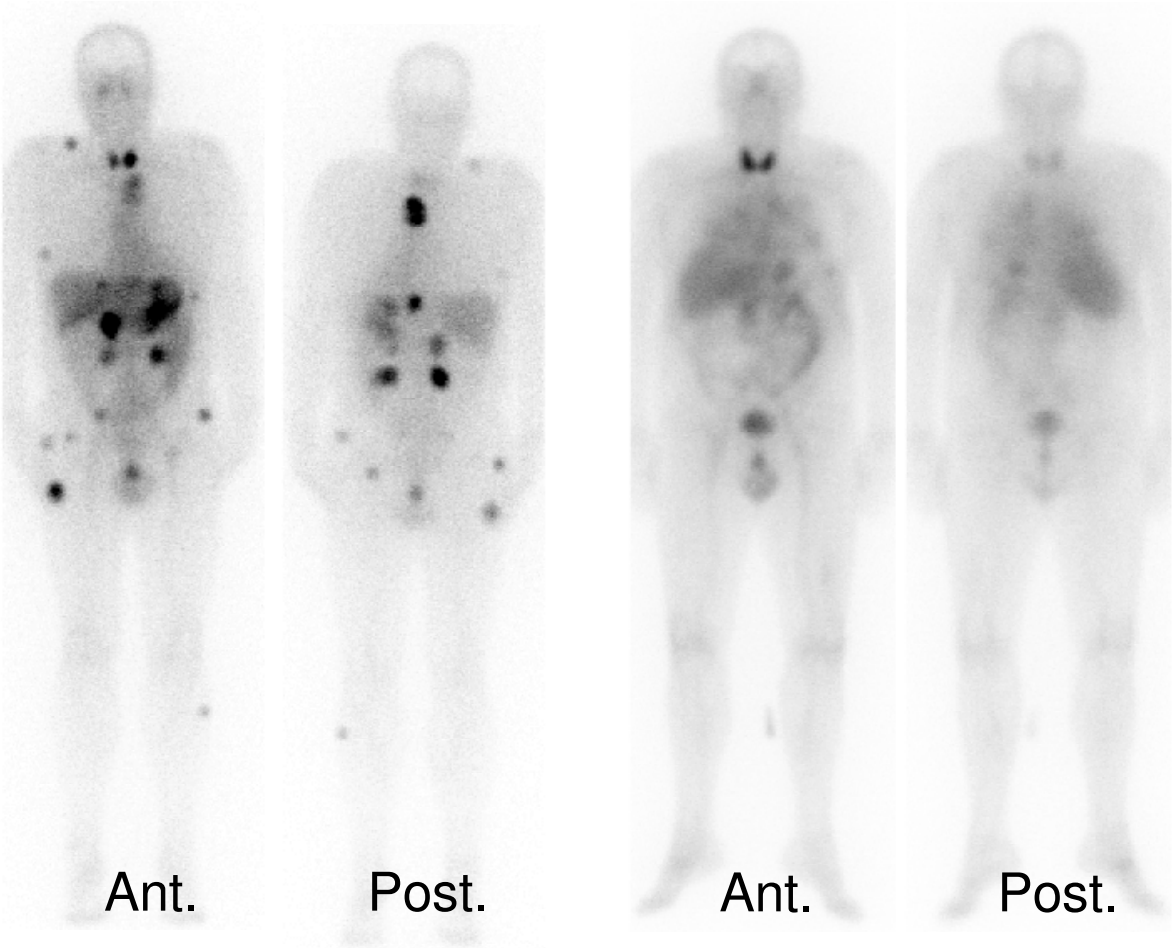
- Dose limiting toxicity: myelotoxicity
- MTD ^{131}I-cG250: 60 mCi/m^2
- 1 PR, 1 SD, 6 PD

Clin Cancer Res 5; 3268-3274, 1999

Phase II Study:
Radioimmunotherapy with two doses ^{131}I-cG250



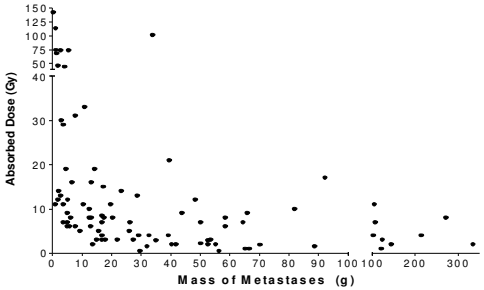
Phase II Study: Radioimmunotherapy with ^{131}I-cG250



2 weeks p.i. 112 mCi

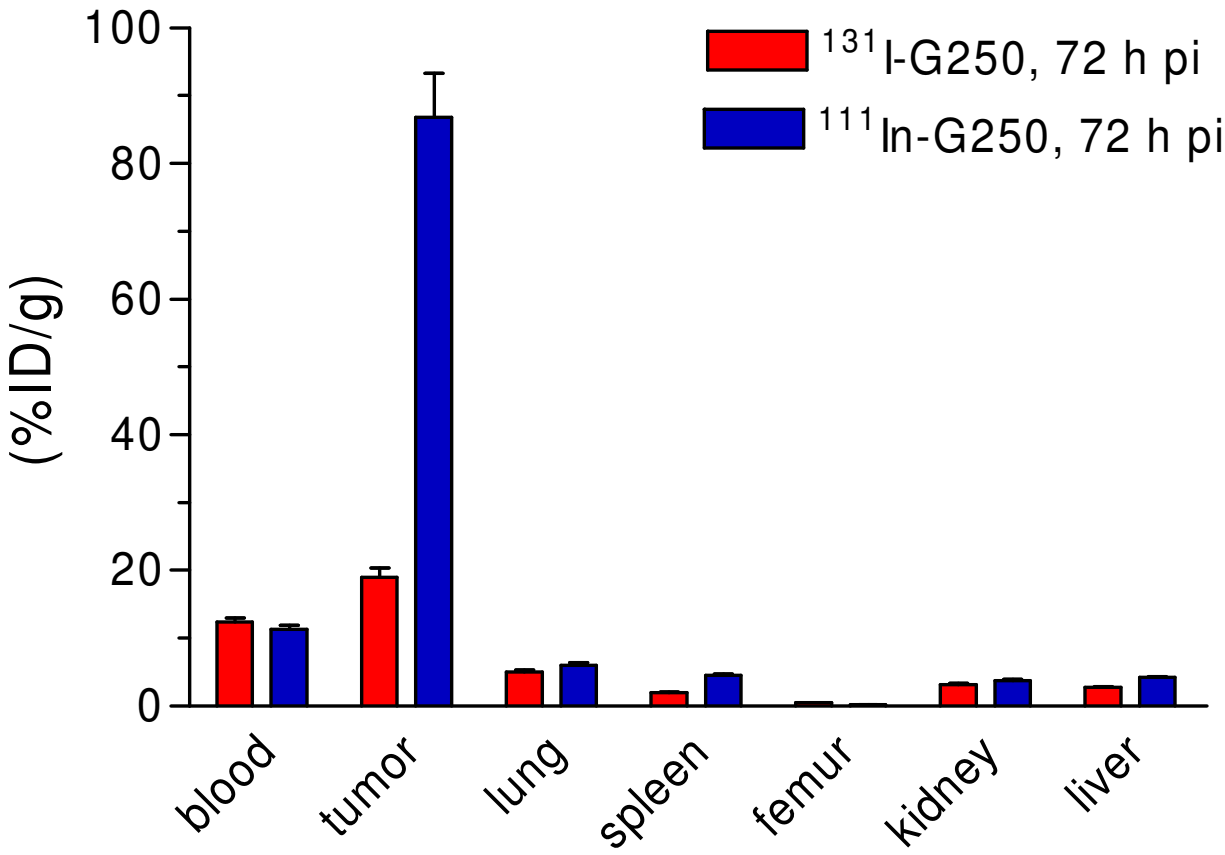
1 week p.i. 109 mCi

- MTD 2nd treatment was 75% of MTD of 1st treatment
- 16 Patients completed two courses of ^{131}I-cG250 RITs at 60 and 45 mCi/m^2.
- 4/16 SD, 12/16 PD
- Highest radiation doses to smaller lesions



J Clin Oncol 23; 6540-8: 2005

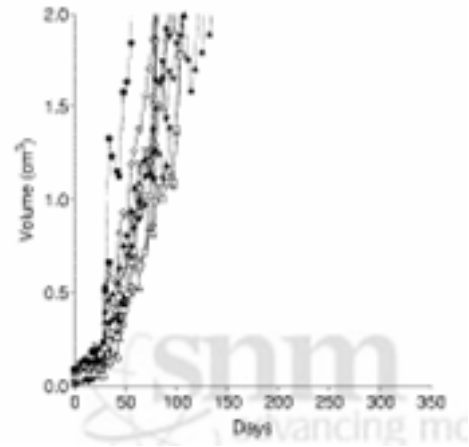
The Quest for the optimal radionuclide for RIT



Radionuclides for radioimmunotherapy

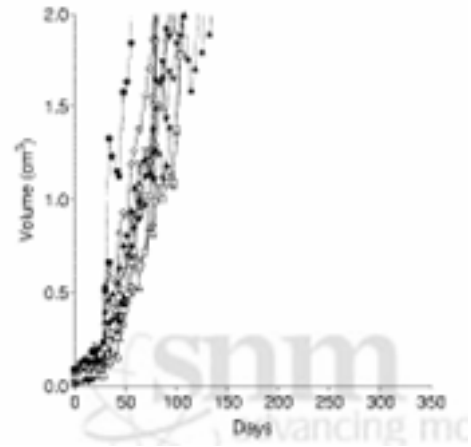
Radionuclide	Half-life	beta	gamma	range
I-131	8 days	192 keV	362 keV	3 mm
Y-90	64 h	935 keV	-	12 mm
Re-186	90 h	362 keV	137 keV	6 mm
Lu-177	7 days	149 keV	208 keV	3 mm
Cu-67	62 h	141 keV	185 keV	2 mm

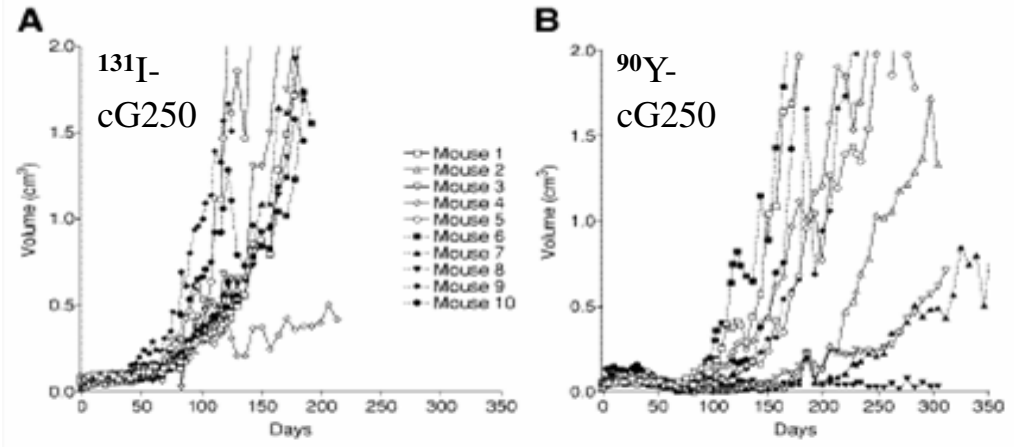
The Quest for the optimal radionuclide for RIT



J Nucl Med. 2004;45:327-337

The Quest for the optimal radionuclide for RIT





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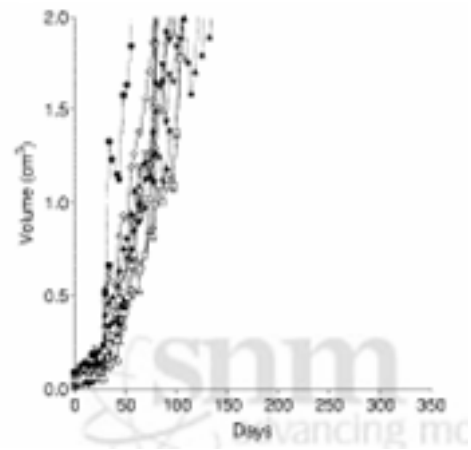
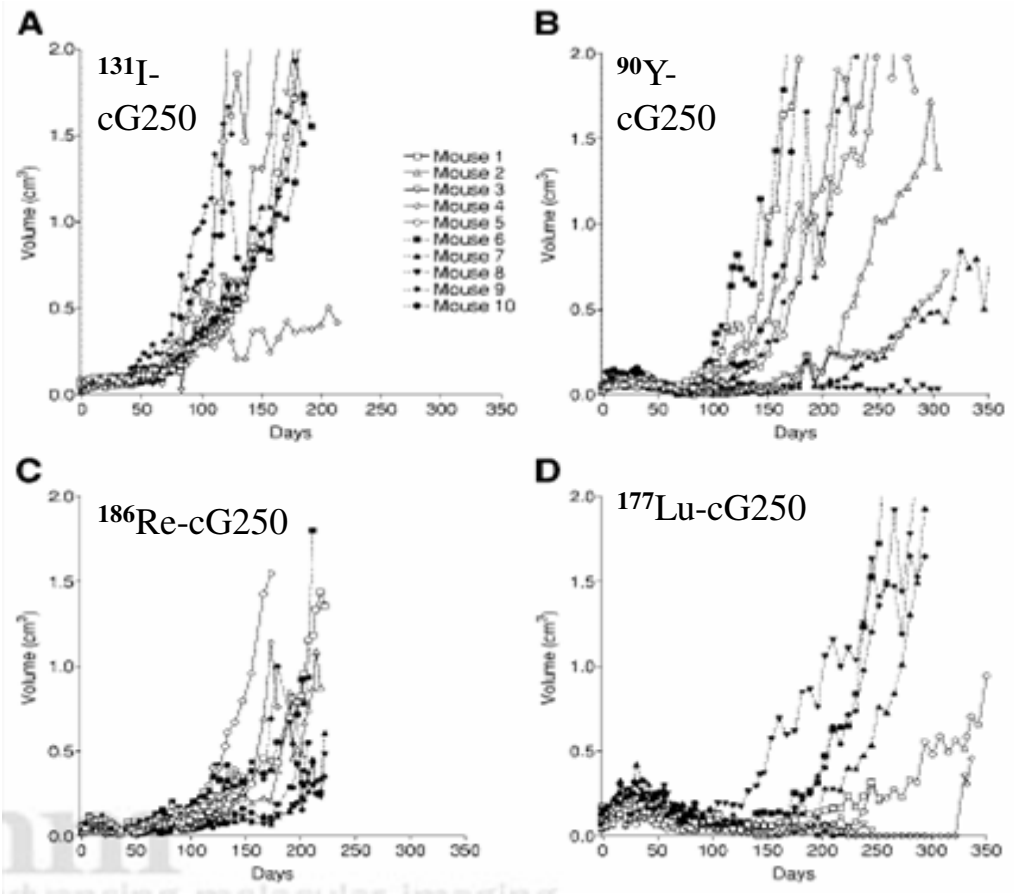
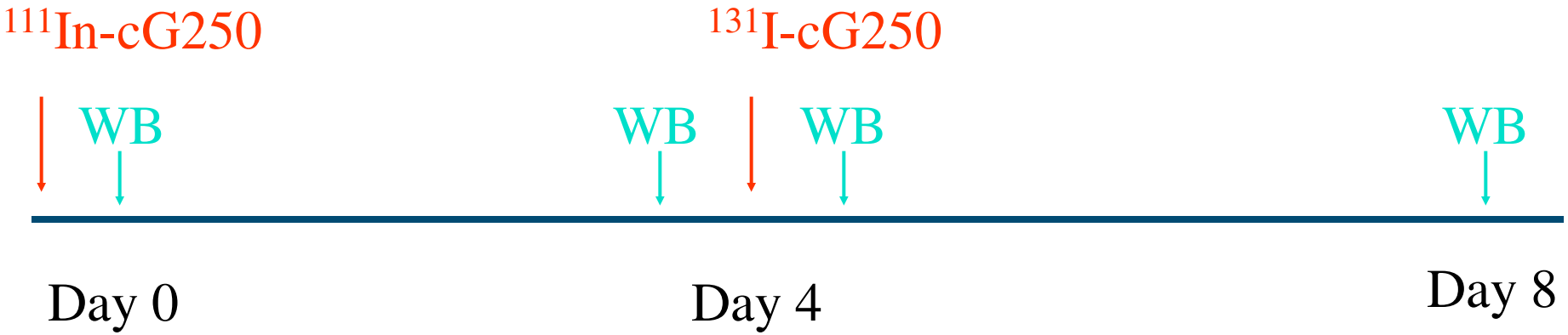




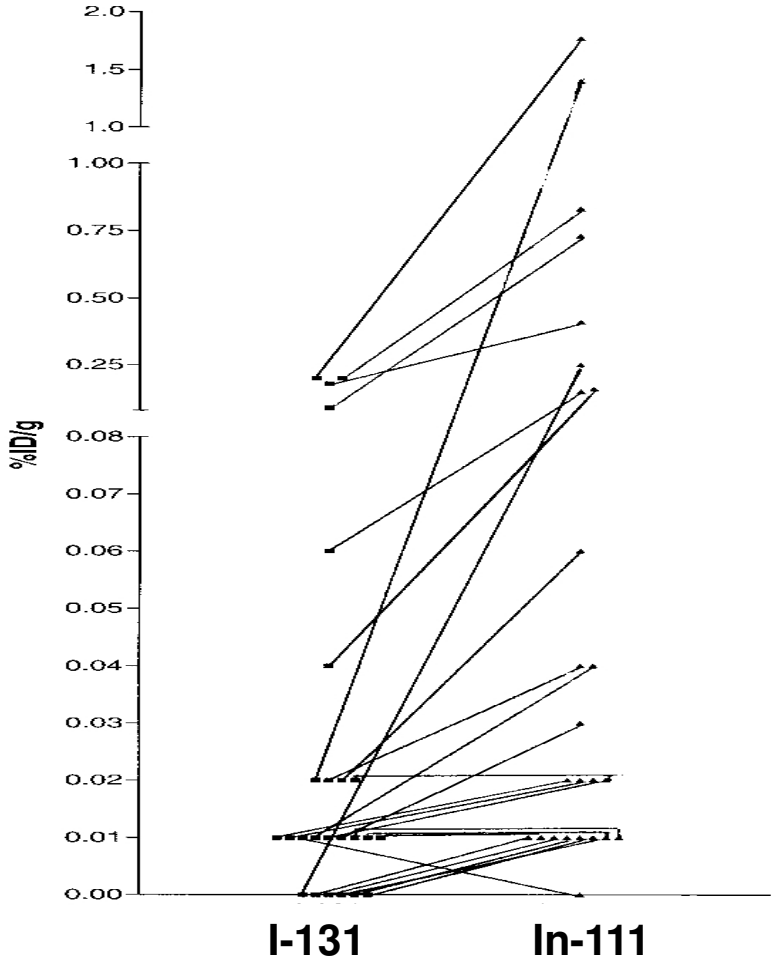
J Nucl Med. 2004;45:327-337

The Quest for the optimal radionuclide for RIT

^{131}I-cG250 vs. ^{111}In-cG250: an intra-patient comparison

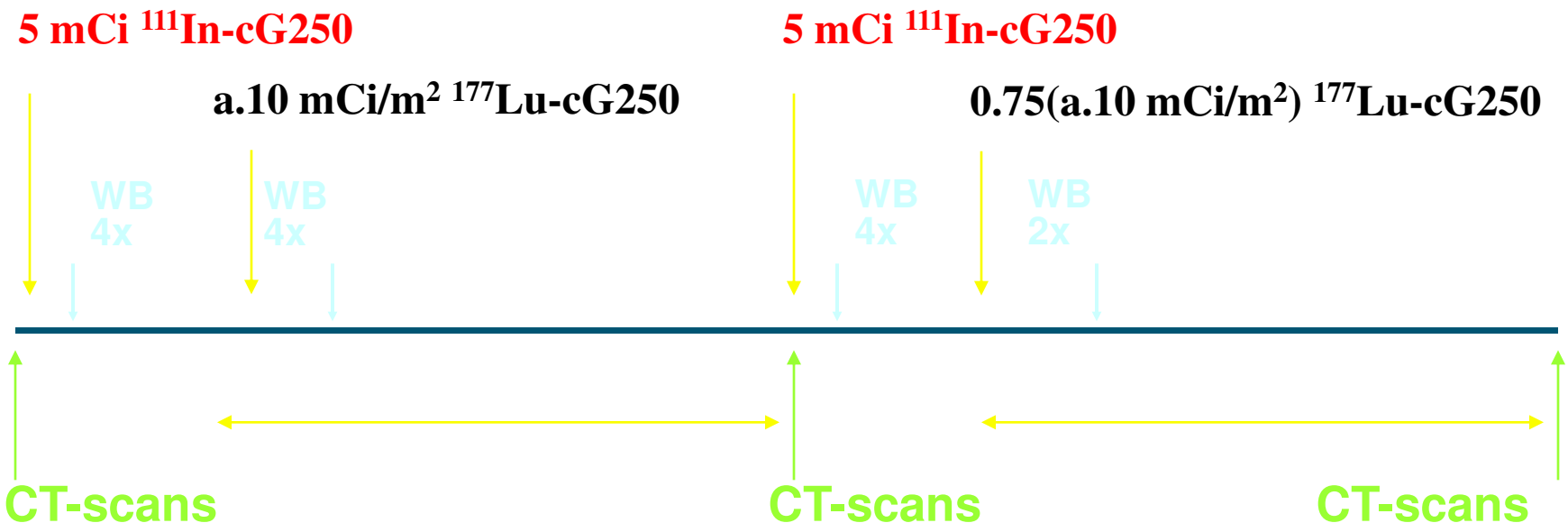


The Quest for the optimal radionuclide for RIT

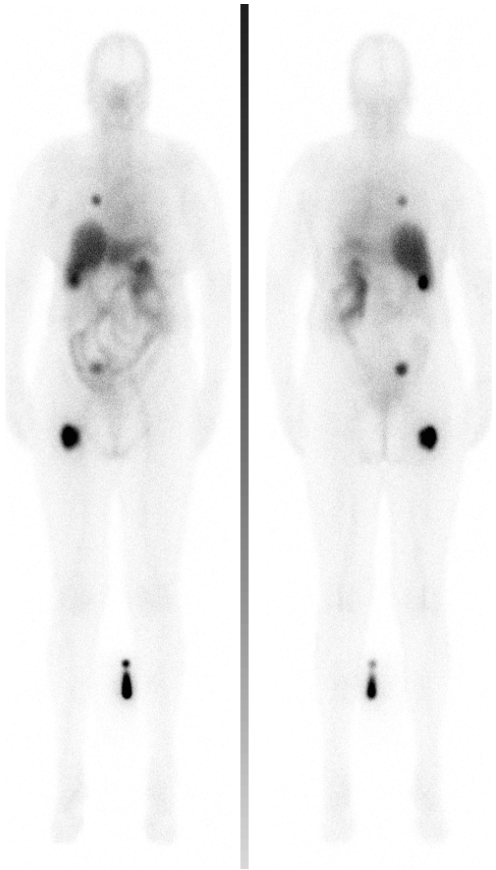


Clin Cancer Res 9: 3953-3960, 2003

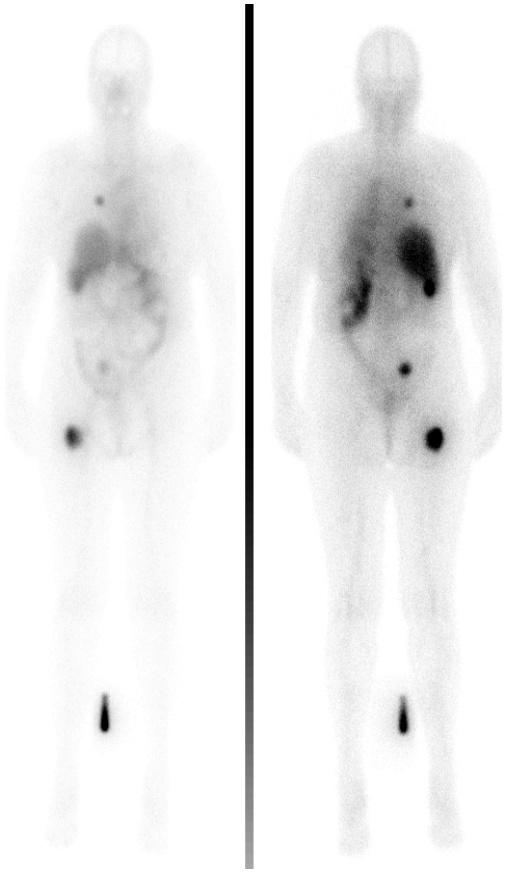
Radioimmunotherapy of RCC with ^{177}Lu-cG250



Radioimmunotherapy of RCC with ^{177}Lu-cG250

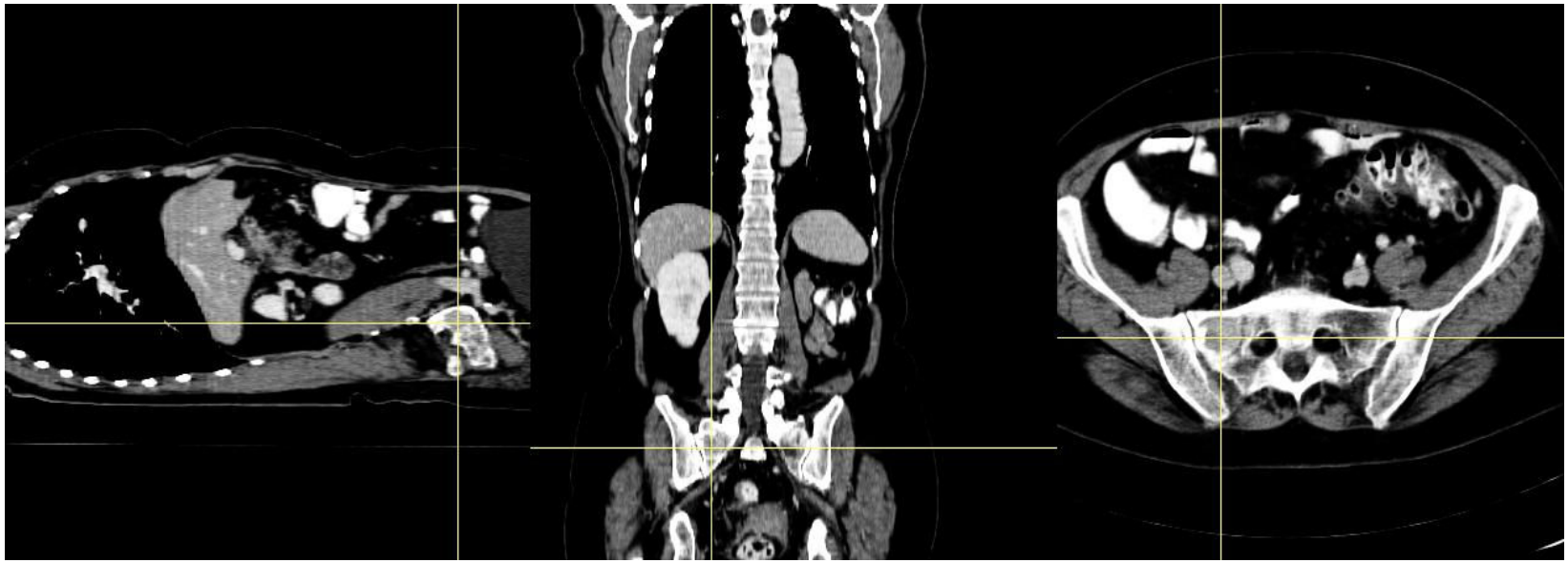


^{111}In-cG250, 6 days p.i.

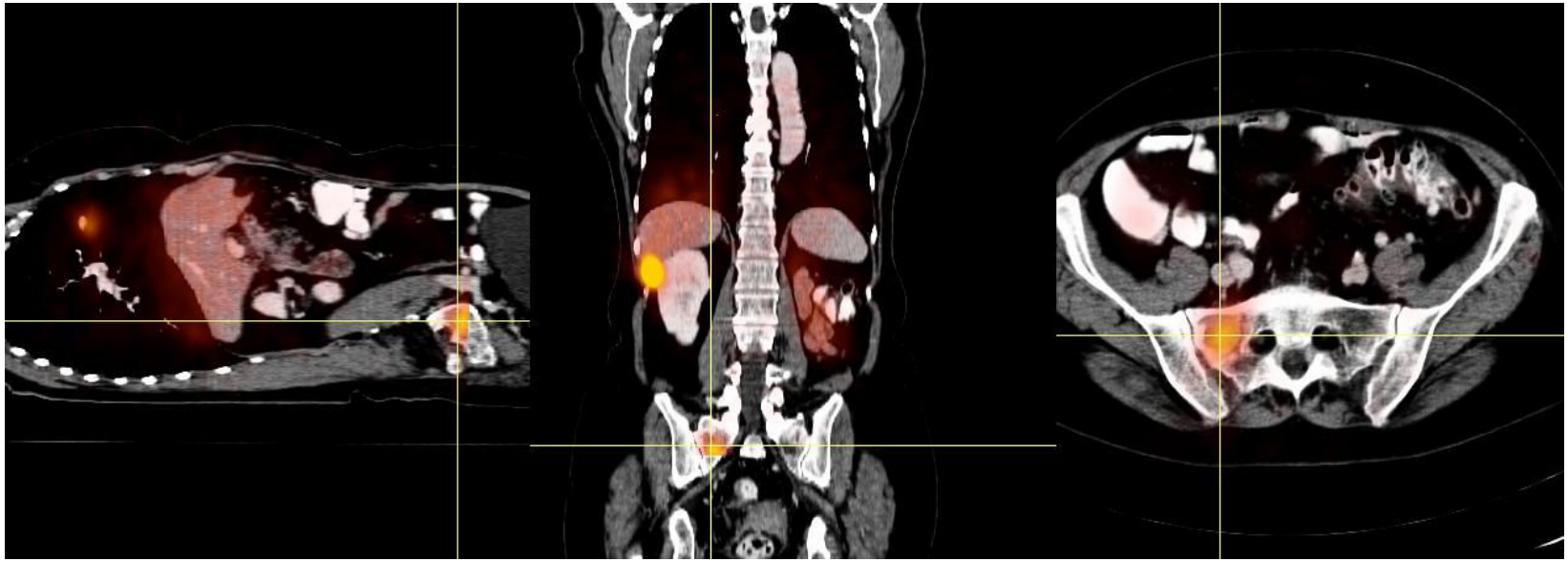


^{177}Lu-cG250, 6 days p.i.

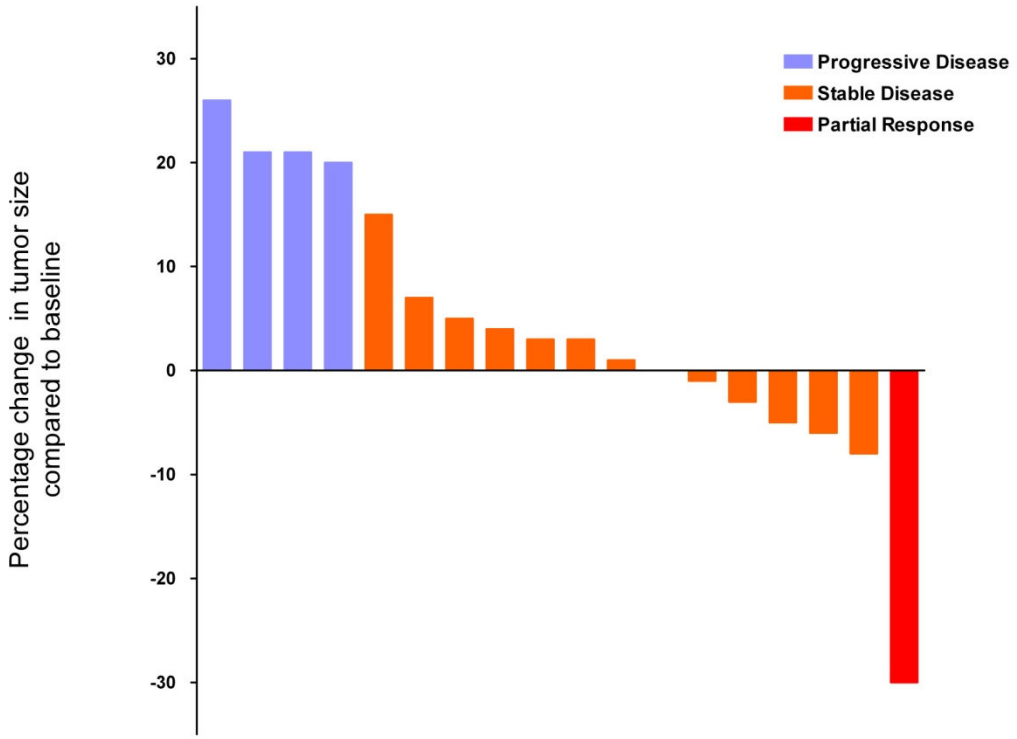
Radioimmunotherapy of RCC with ^{177}Lu-cG250

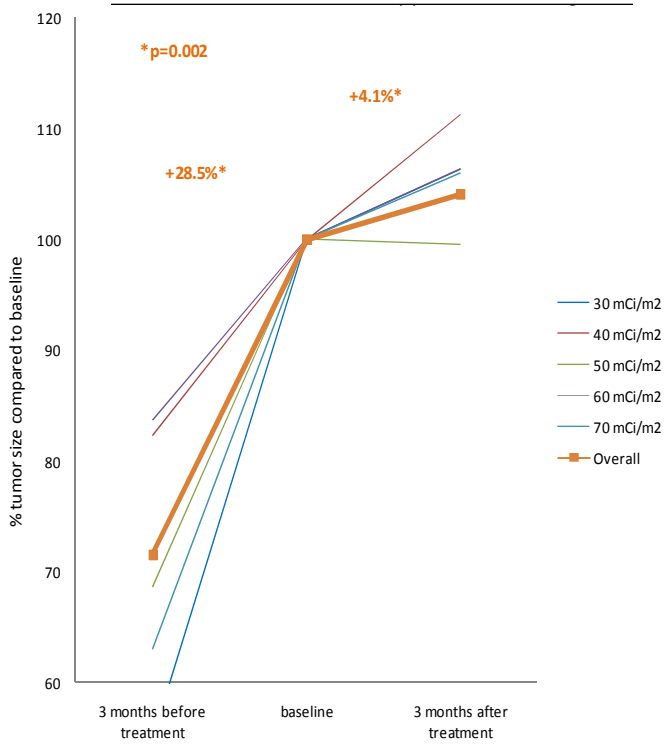


Radioimmunotherapy of RCC with ^{177}Lu-cG250



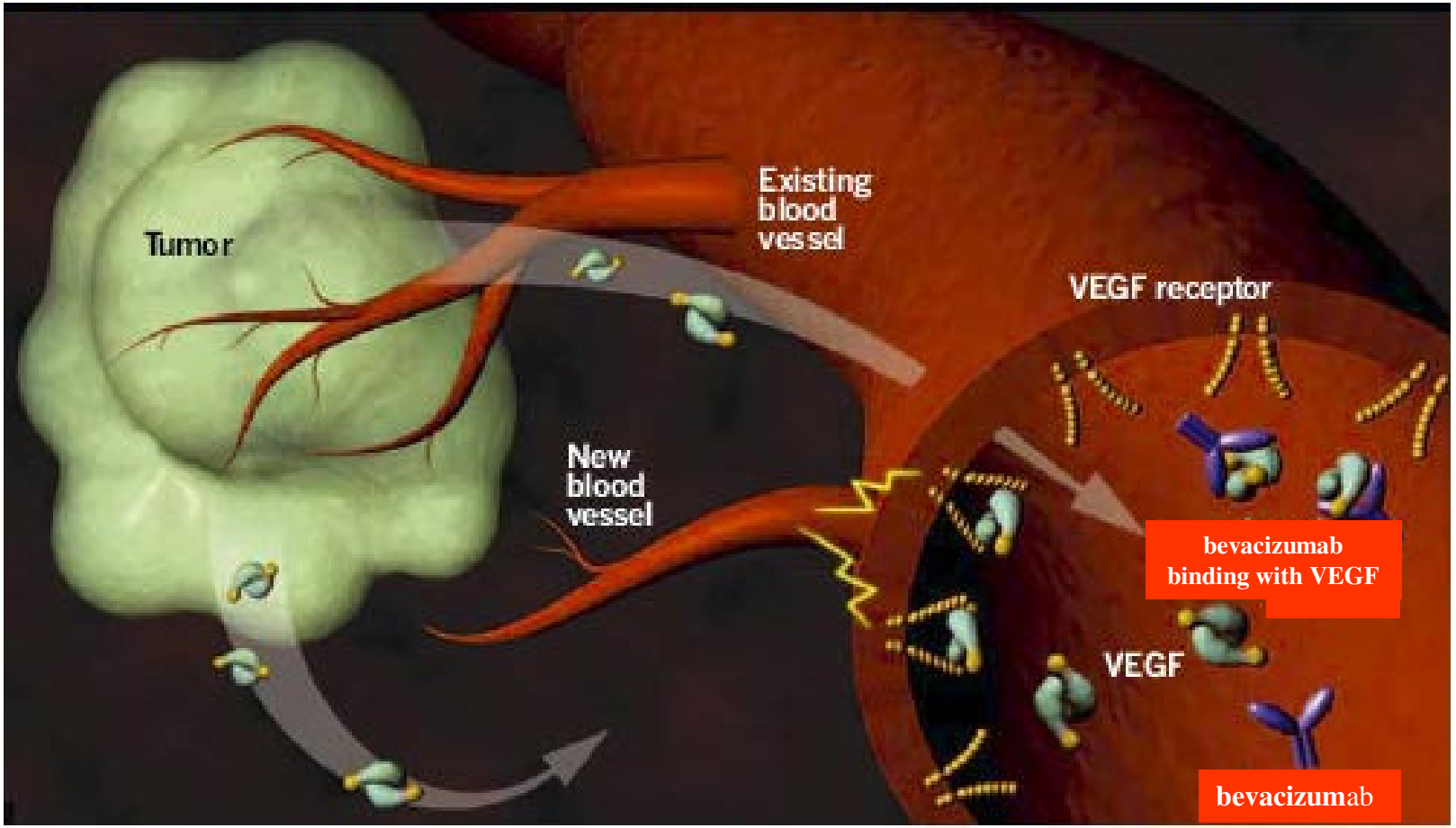
Radioimmunotherapy with ^{177}Lu-cG250 stabilized growth of RCC



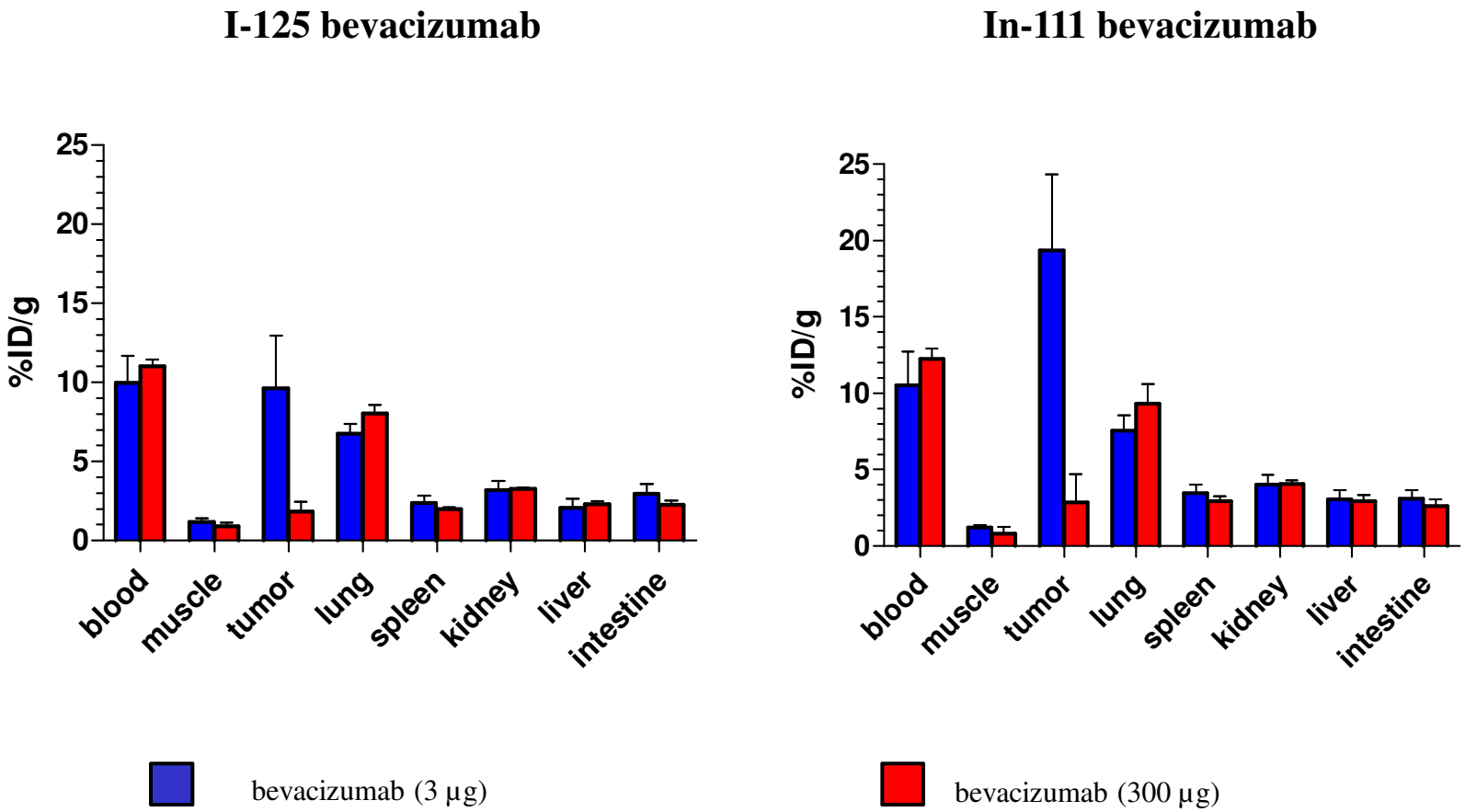


Imaging with radiolabeled antibodies

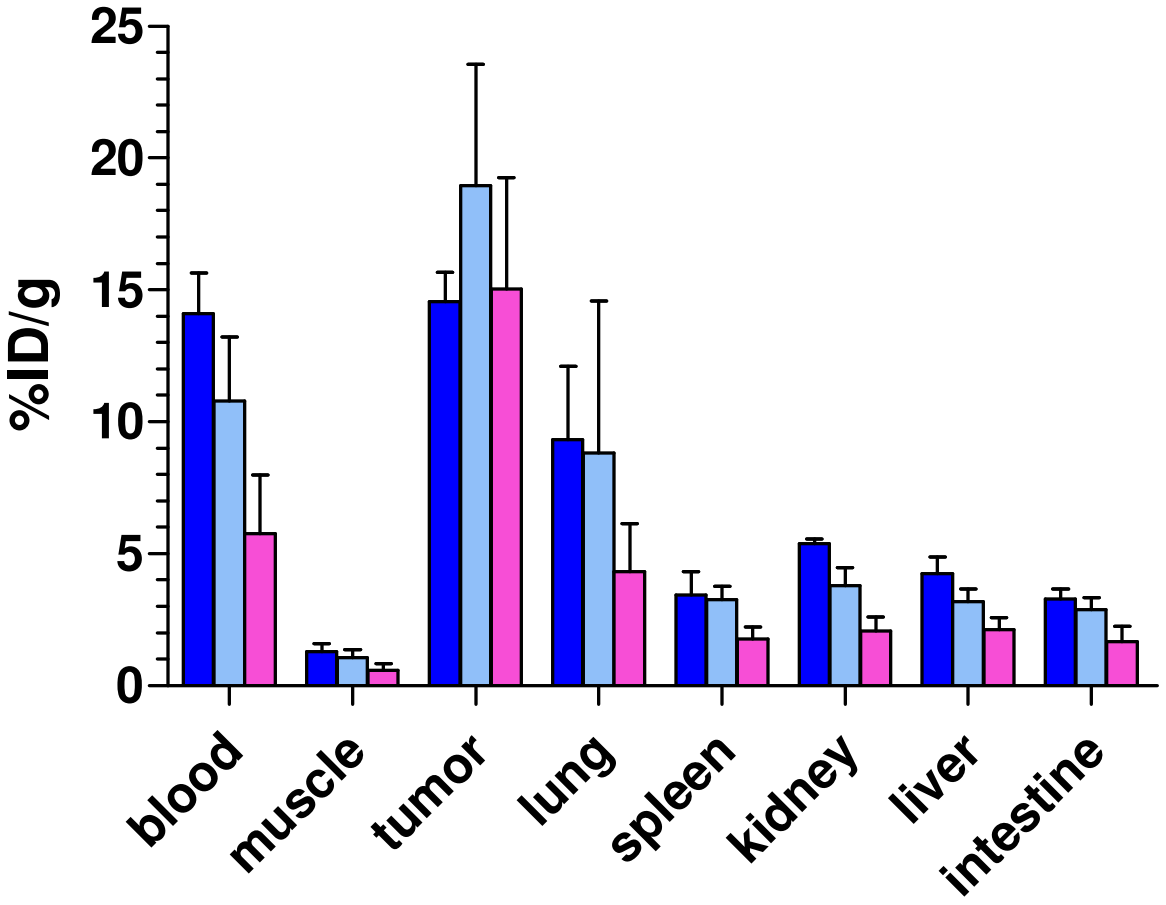
Imaging Angiogenesis in tumors



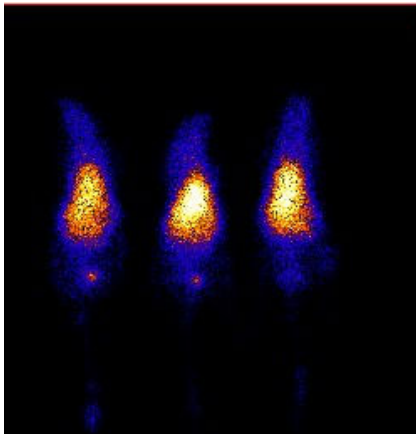
Radiolabeled anti-VEGF antibody in nude mice with LS174T tumors



In-111-bevacizumab at 1, 3 and 7 days p.i.

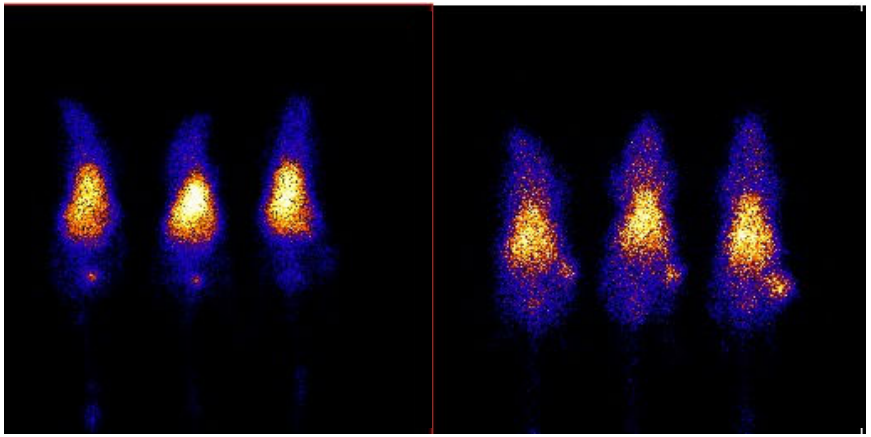


Scintigraphic imaging of VEGF-A expression



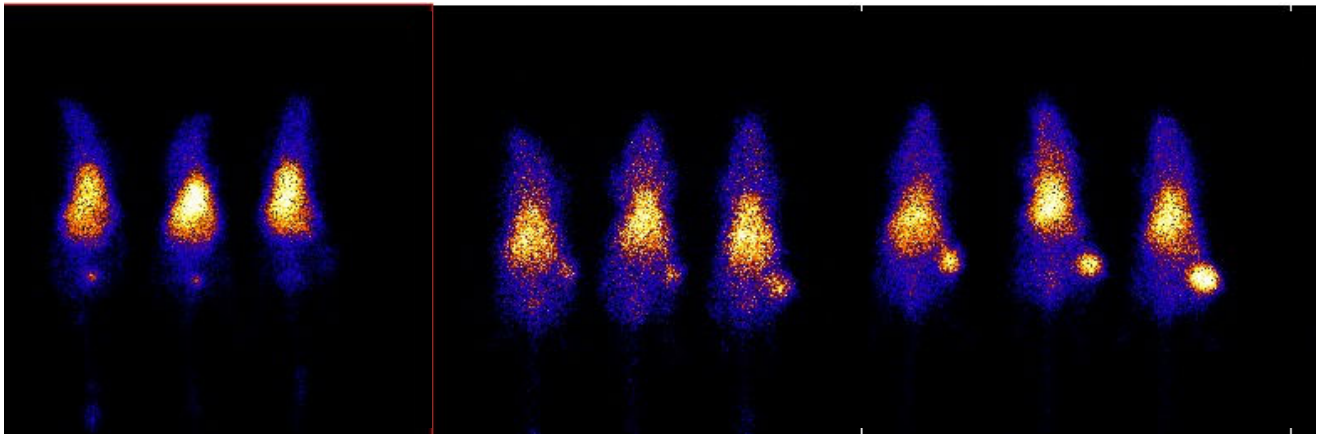
day 0

Scintigraphic imaging of VEGF-A expression



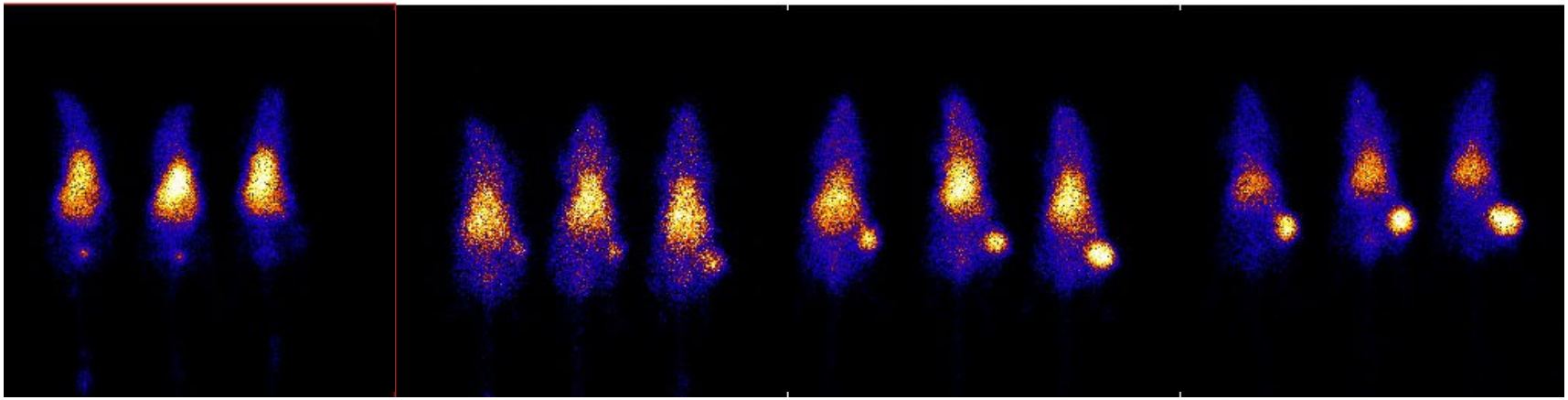
day 0 day 1

Scintigraphic imaging of VEGF-A expression



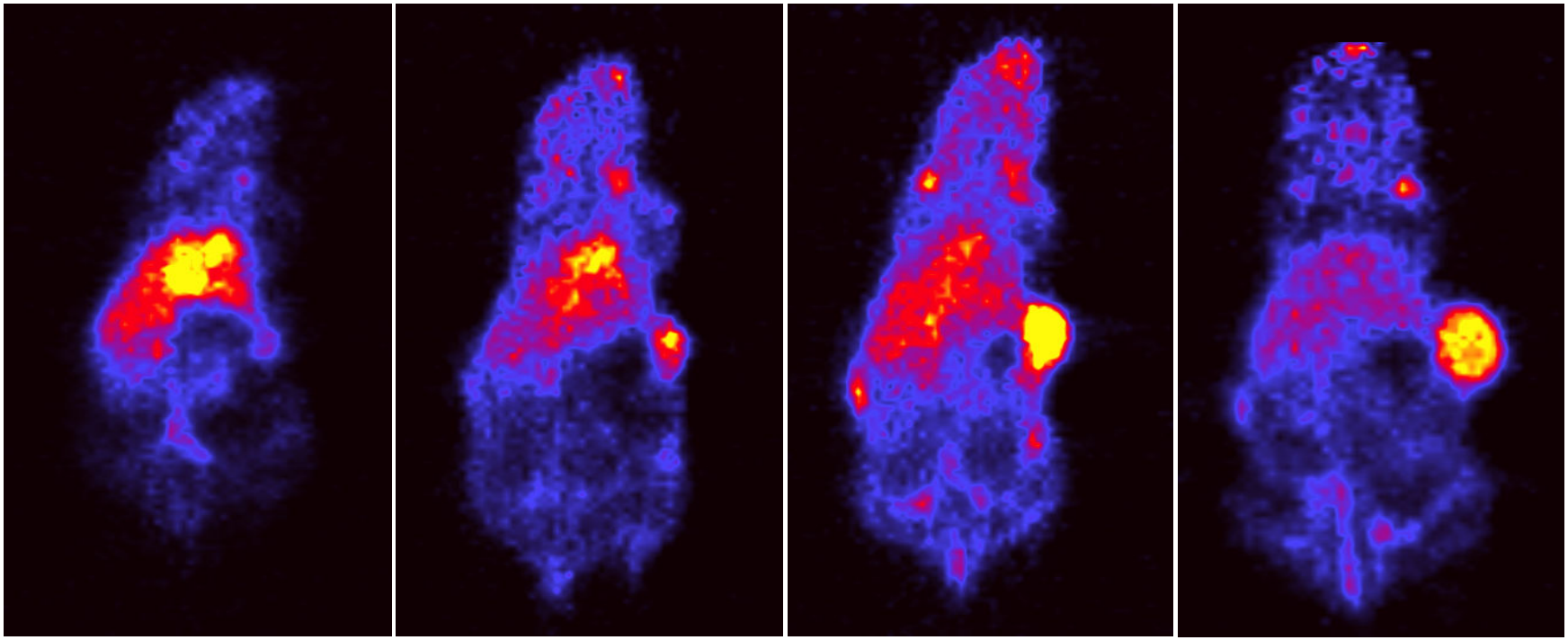
day 0 day 1 day 3

Scintigraphic imaging of VEGF-A expression



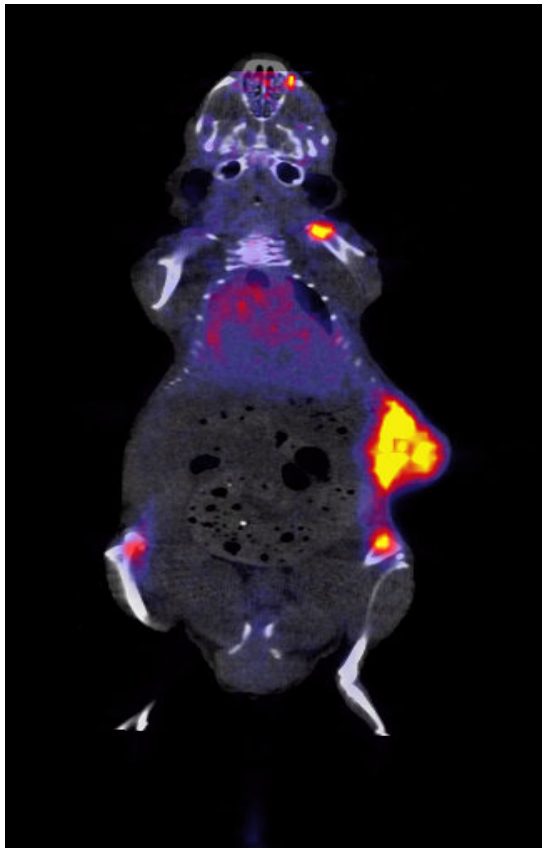
day 0 day 1 day 3 day 7

microPET imaging of VEGF-A expression with ^{89}Zr-bevacizumab

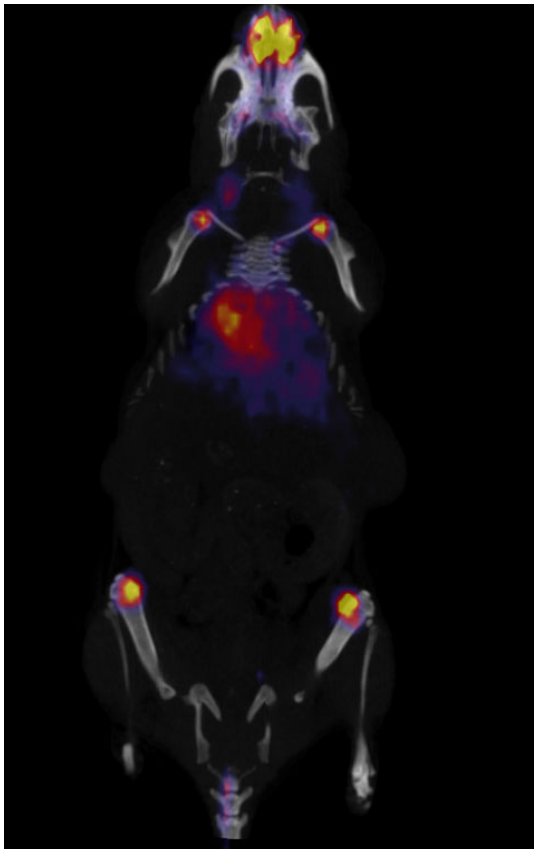


day 0 | day 1 | day 4 | day 7

microPET/CT imaging of VEGF-A expression with ^{89}Zr-bevacizumab

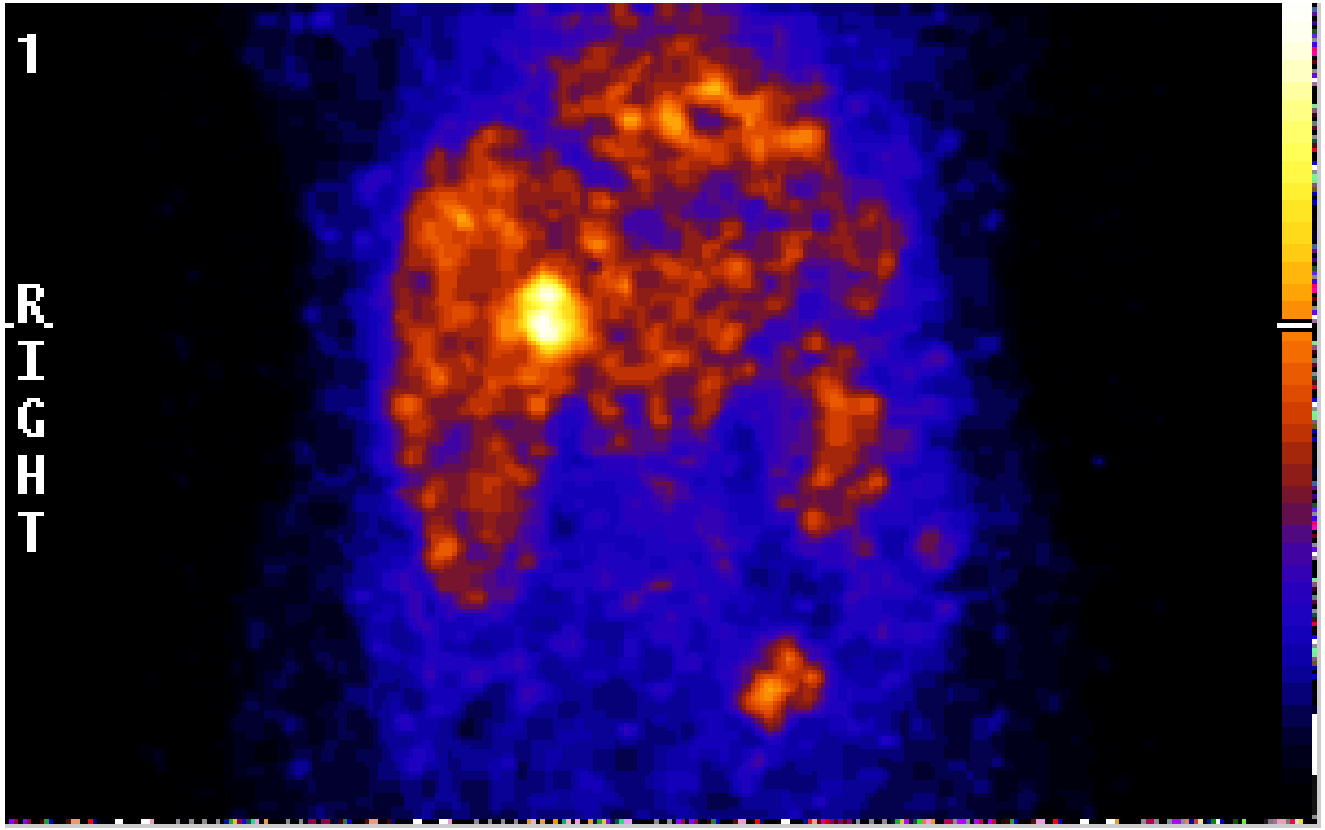


^{89}Zr-bevacizumab, 7 days p.i.

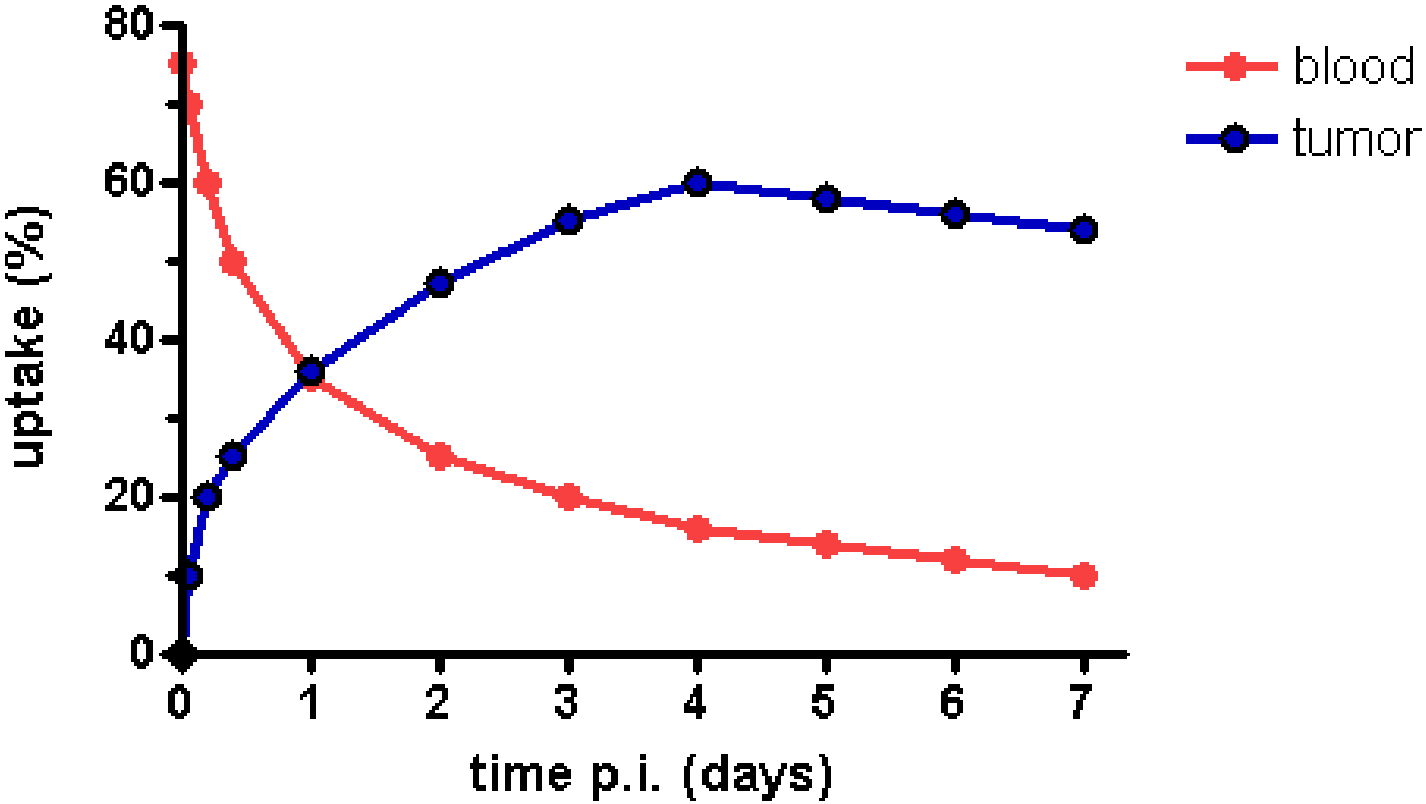


^{89}Zr-bevacizumab + 300 µg cold

Scintigraphic imaging of VEGF expression



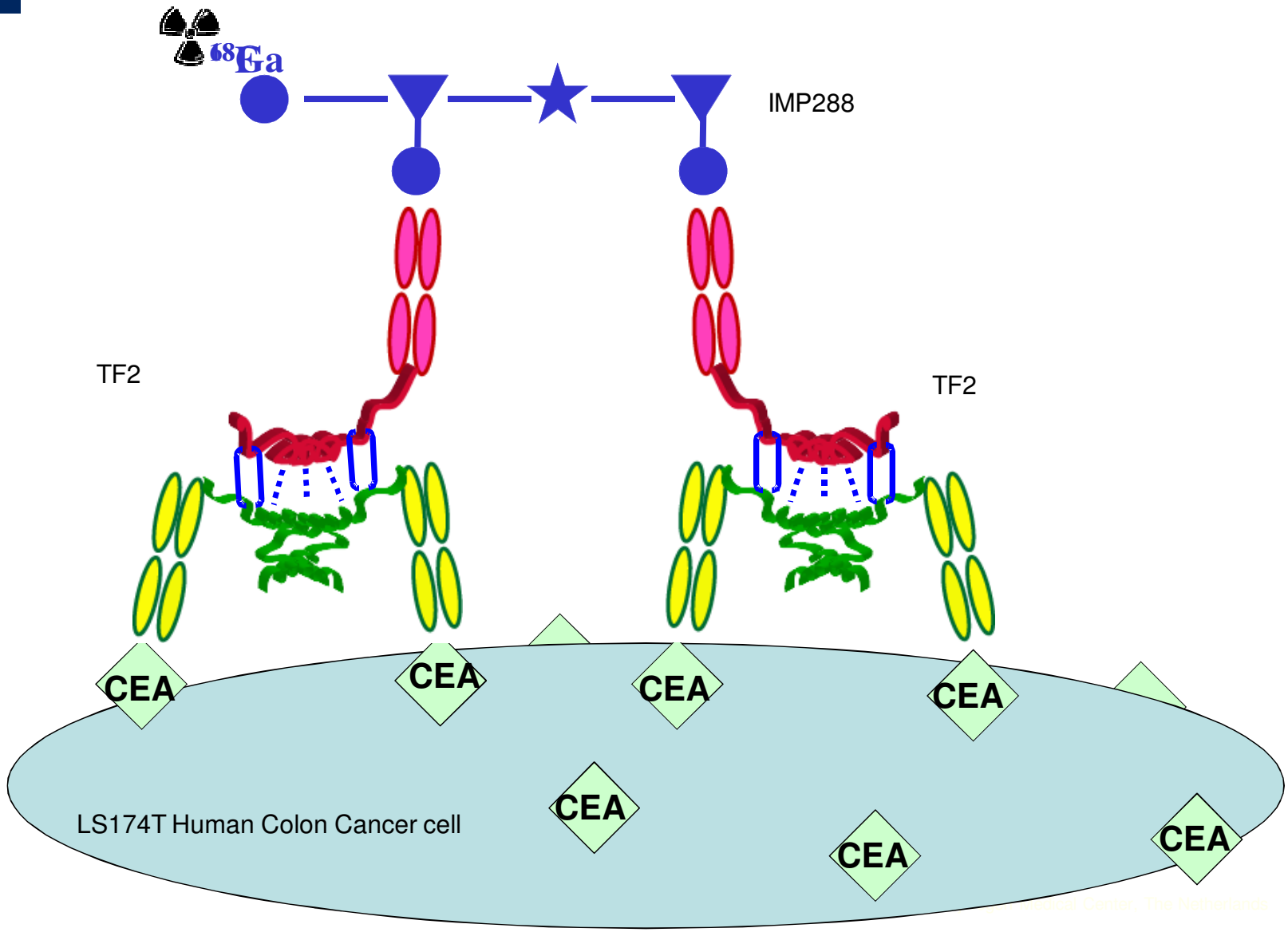
The antibody targeting dilemma



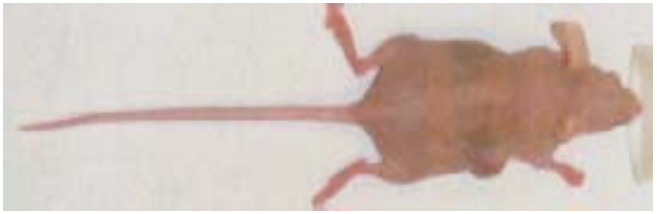
Radionuclides for PET imaging

Radionuclide	Half-life	remarks
I-124	4.2 days	Emits additional gamma photons
Zr-89	78 h	Limited availability
F-18	2 h	
Ga-68	68 min	Generator produced
Cu-64	12.7 h	Limited availability

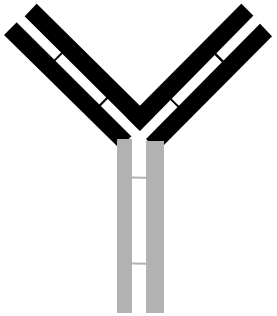
Pretargeted immunoPET imaging



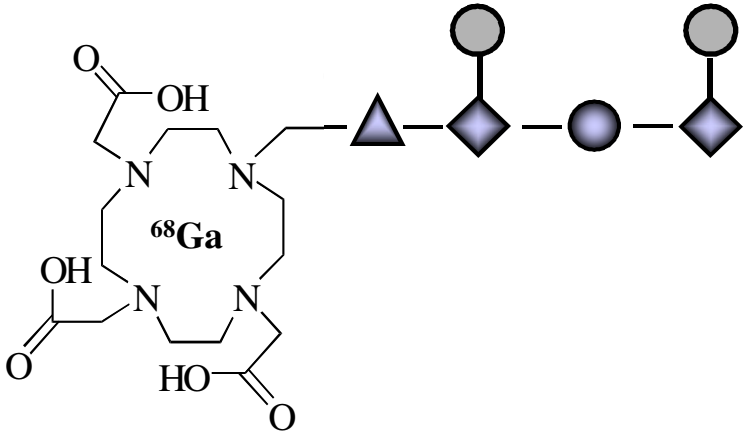
Pretargeted immunoPET using a Ga-68-labeled peptide



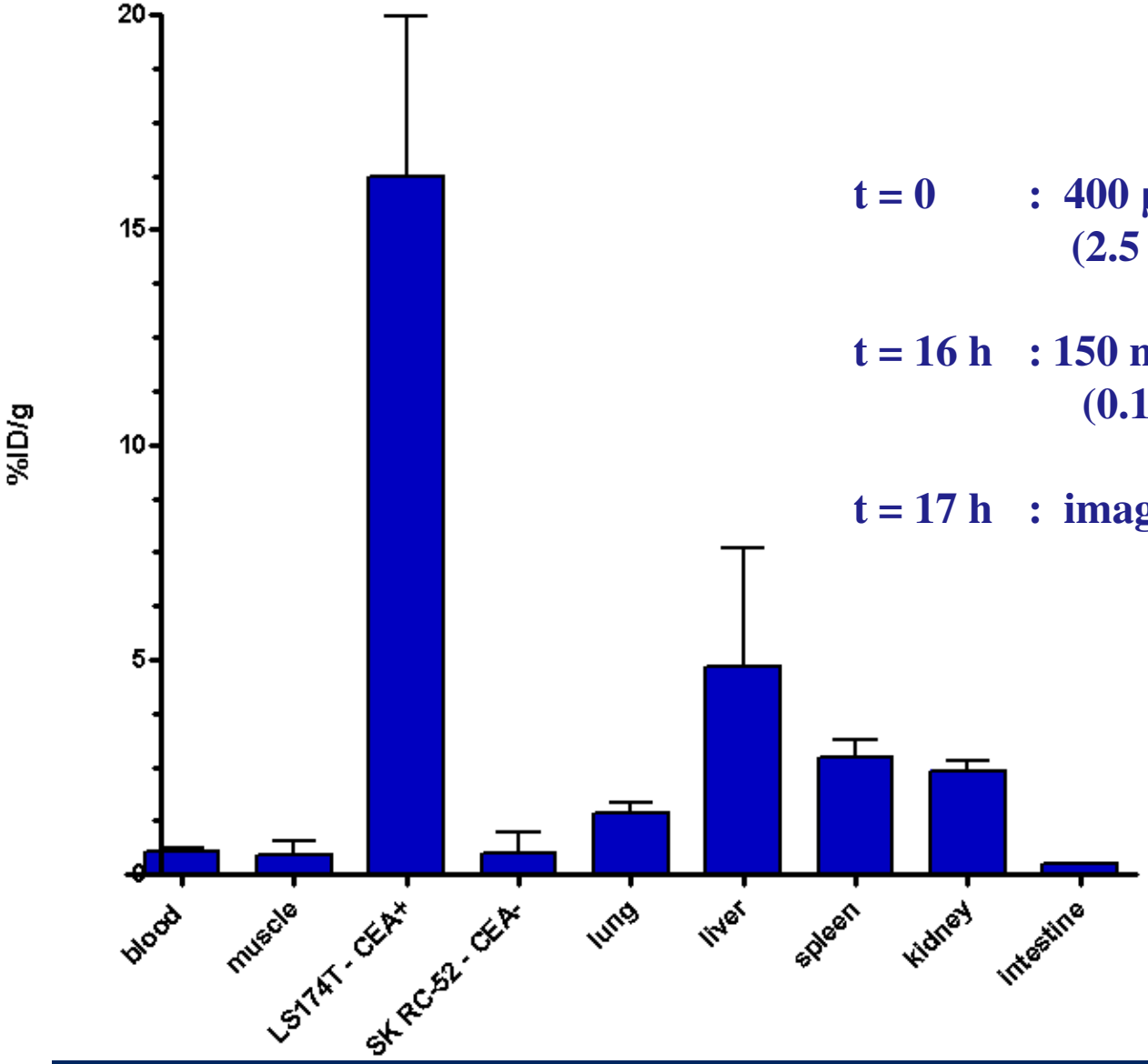
t = 0, trivalent bsAb
anti-CEA x anti-HSG bsAb



t = 16 h, Ga-68-IMP-288
Ga-68-di-HSG-peptide



Biodistribution Ga-68-diHSG peptide



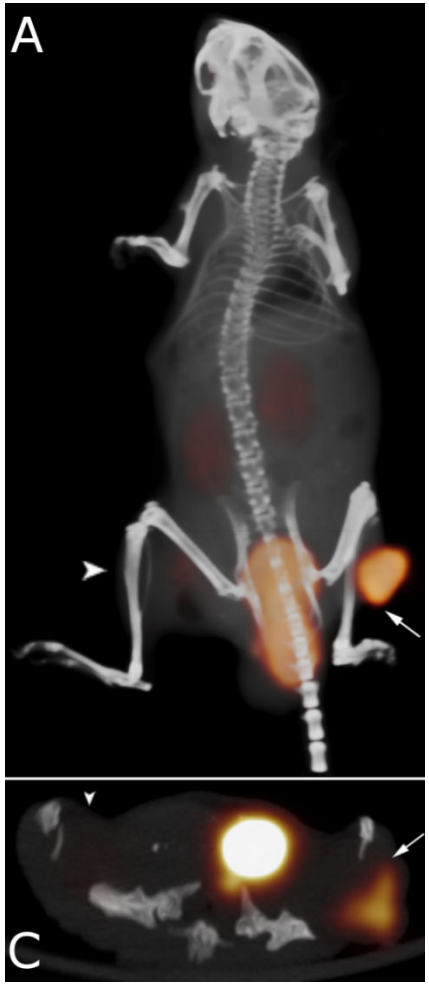
t = 0 : 400 µg TF2 (2.5 nmol)

t = 16 h : 150 ng Ga-68-IMP-288 (0.1 nmol)

t = 17 h : imaging and dissection

Pretargeted immunoPET imaging
Nude mouse with LS174T tumor

Inflammation



Tumor

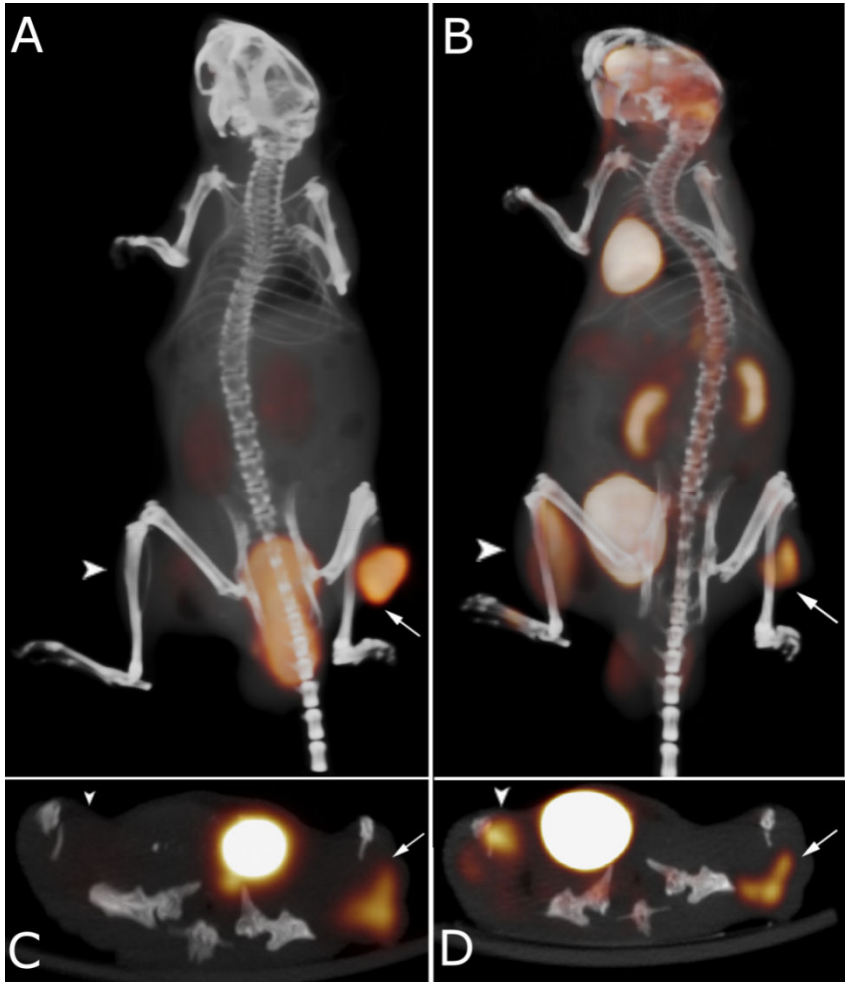
t= 0 : anti-CEA x anti-HSG bsAb
t= 16 h : ^{68}Ga-IMP288
t=17 : microPET imaging

Schoffelen *et al.* Mol Cancer Ther 2009; in press

Pretargeted immunoPET imaging of cancer

^{68}Ga-immunoPET [^{18}F]FDG

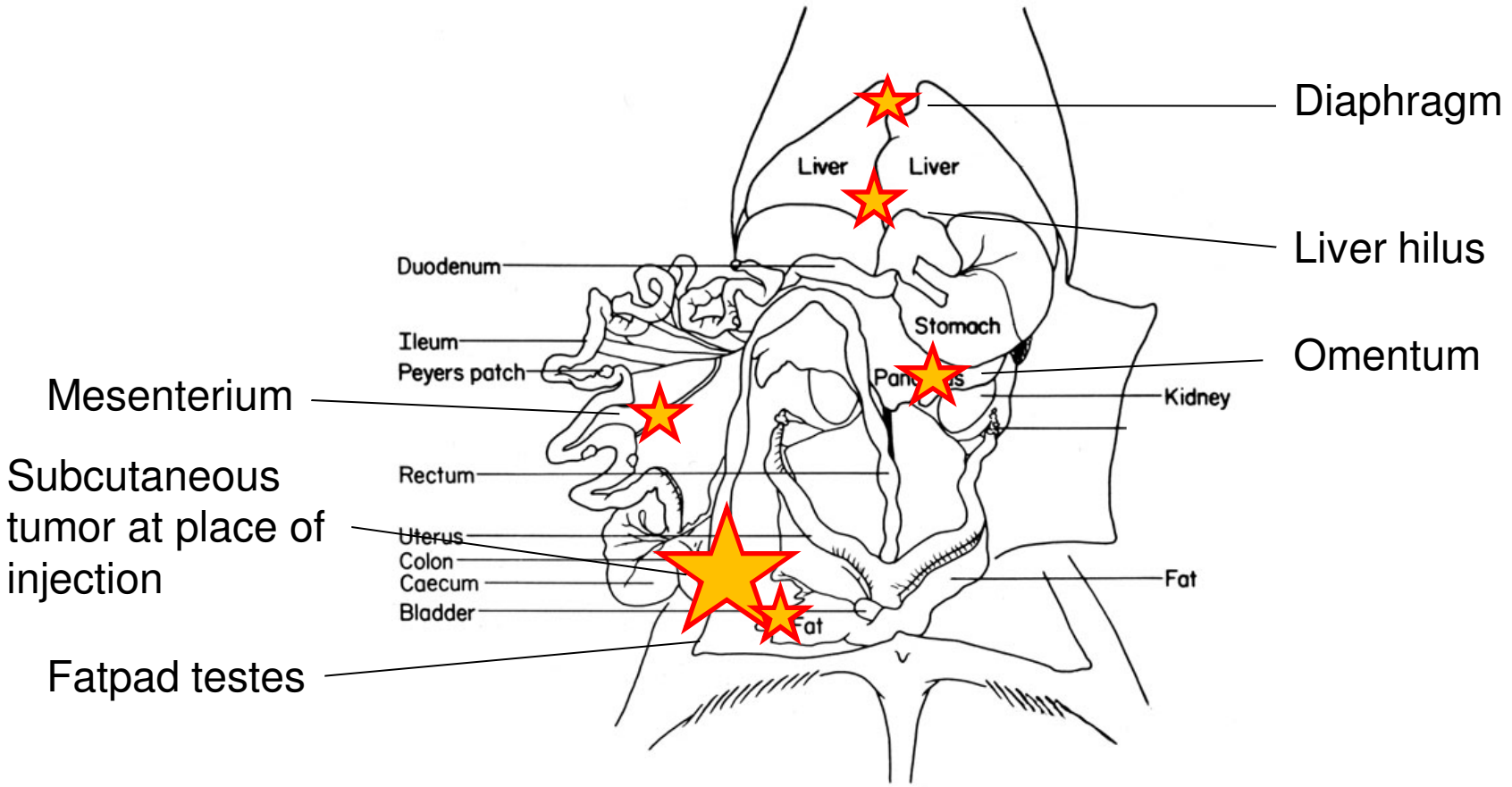
Inflammation



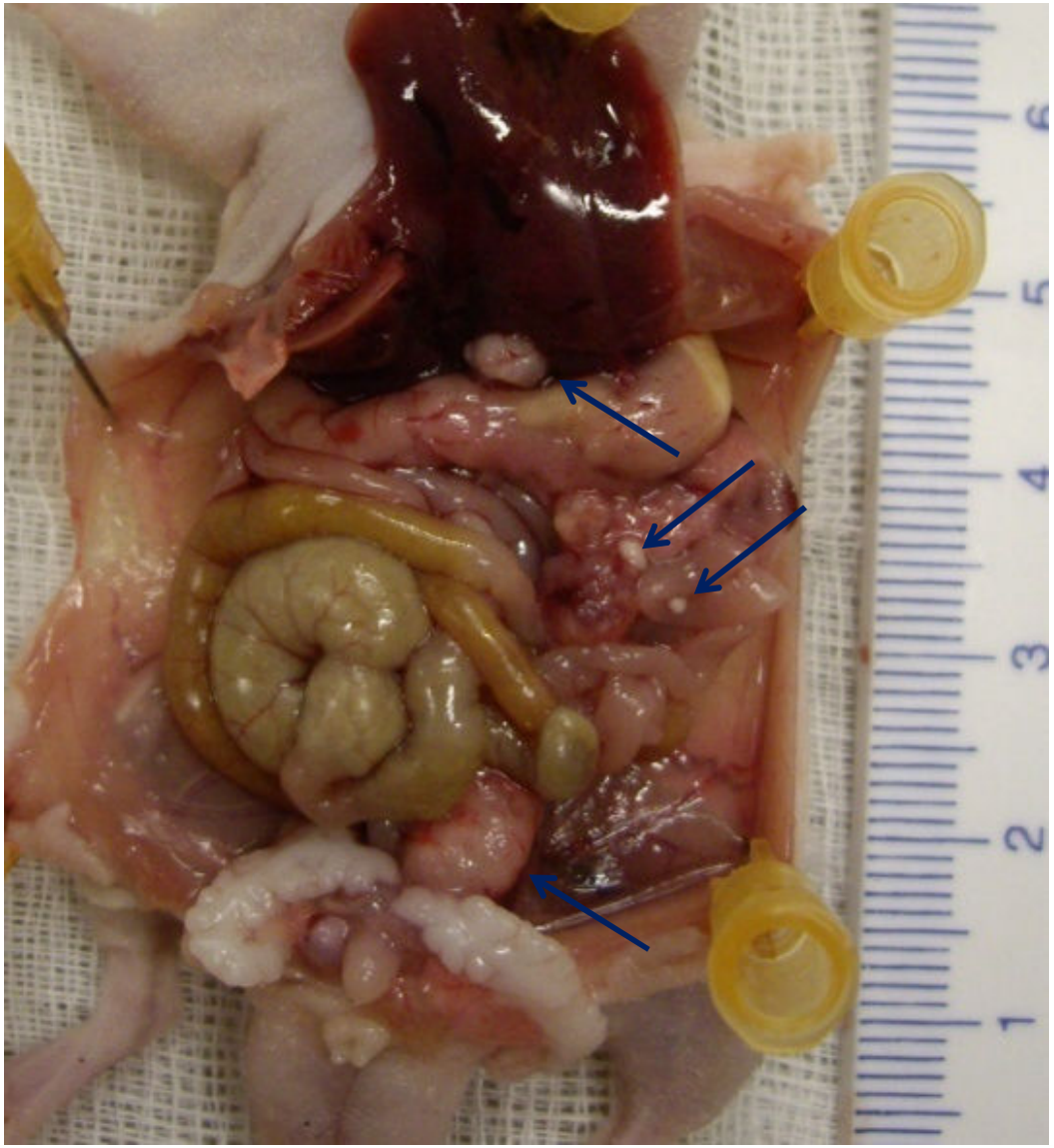
Tumor

Schoffelen *et al.* Mol Cancer Ther 2009; in press

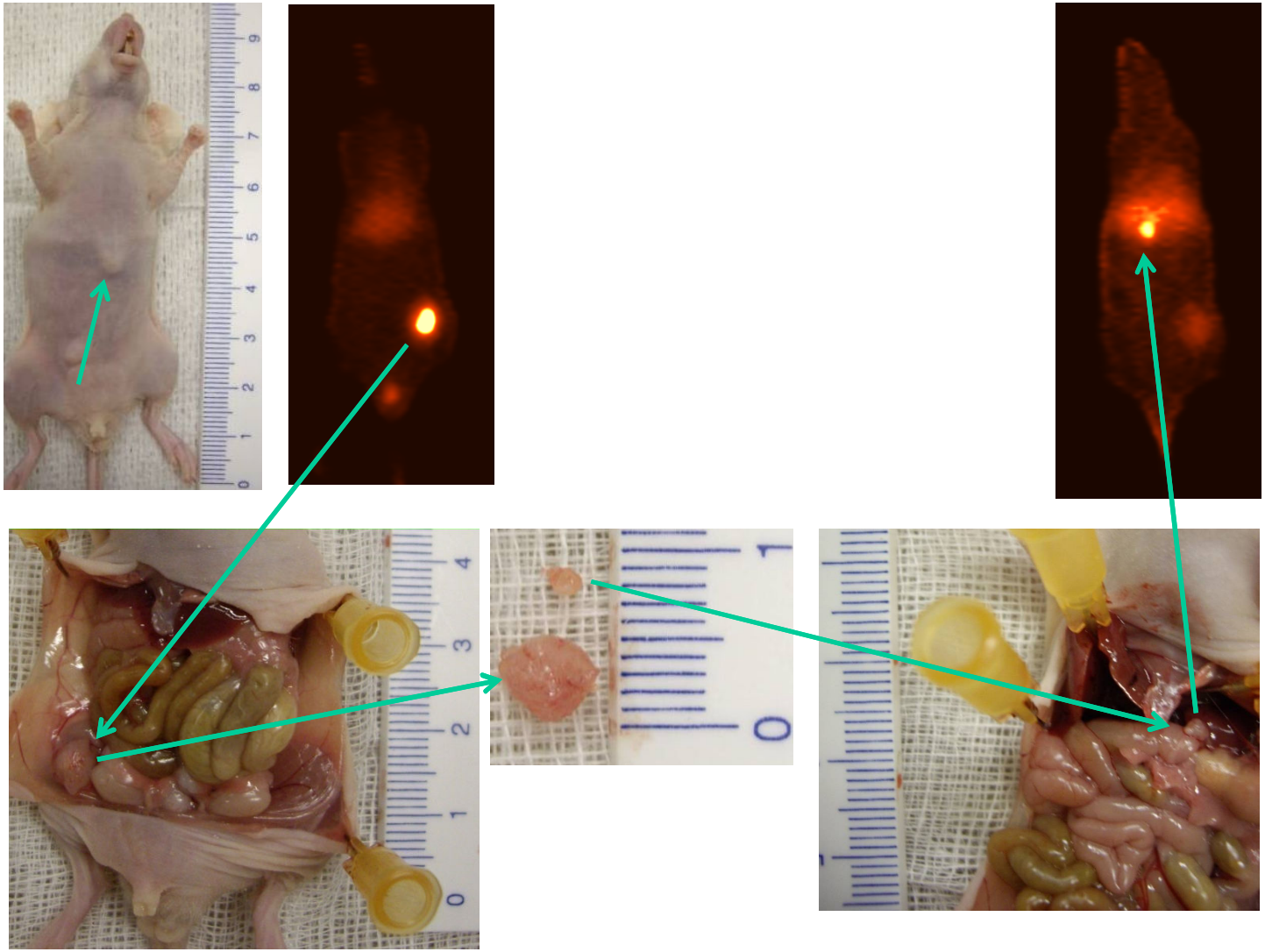
Pretargeted immunoPET imaging of i.p. tumors



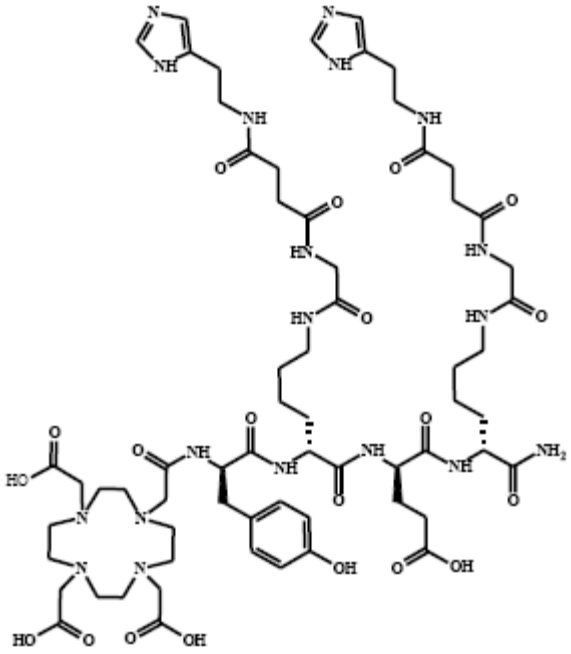
Pretargeted ImmunoPET imaging of i.p. LS174T tumors with ^{68}Ga-diHSG



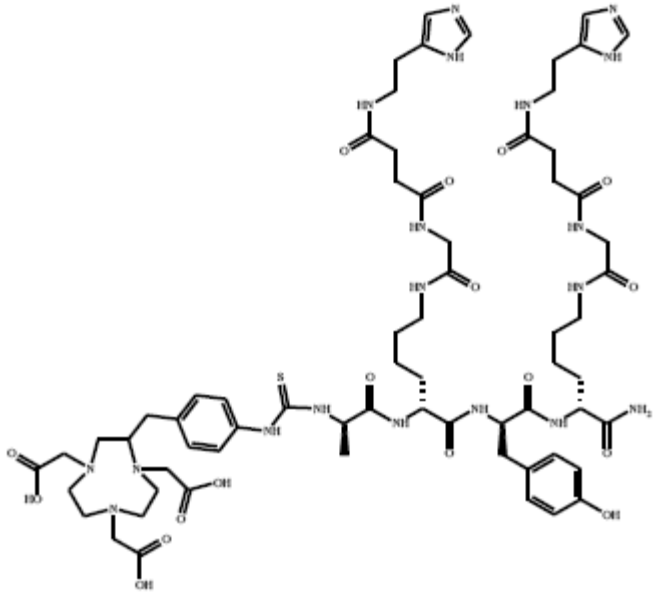
Pretargeted ImmunoPET imaging of i.p. LS174T tumors with ^{68}Ga-diHSG



Pretargeted immunoPET imaging



In-111, Ga-68, Y-90, Lu-177

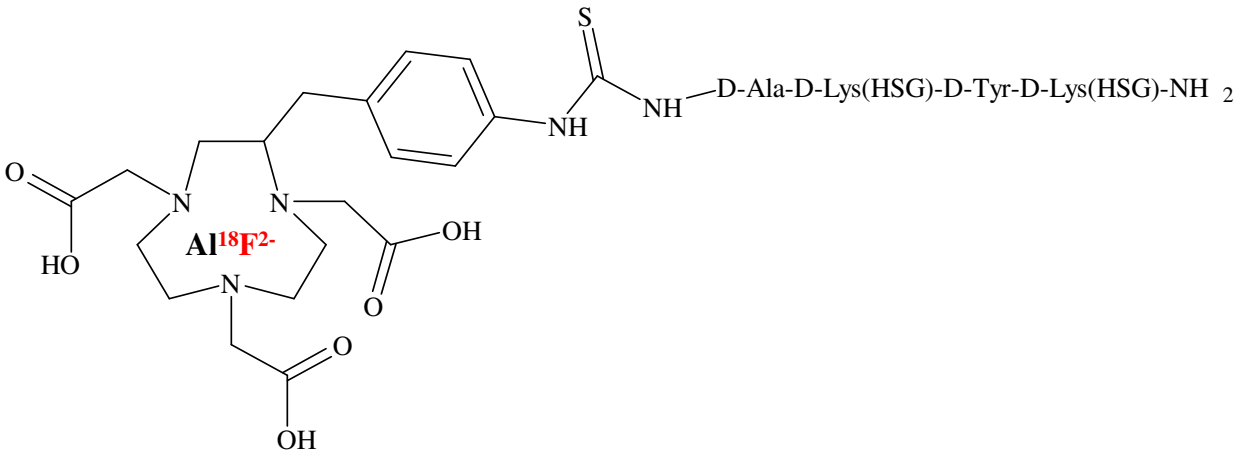


F-18

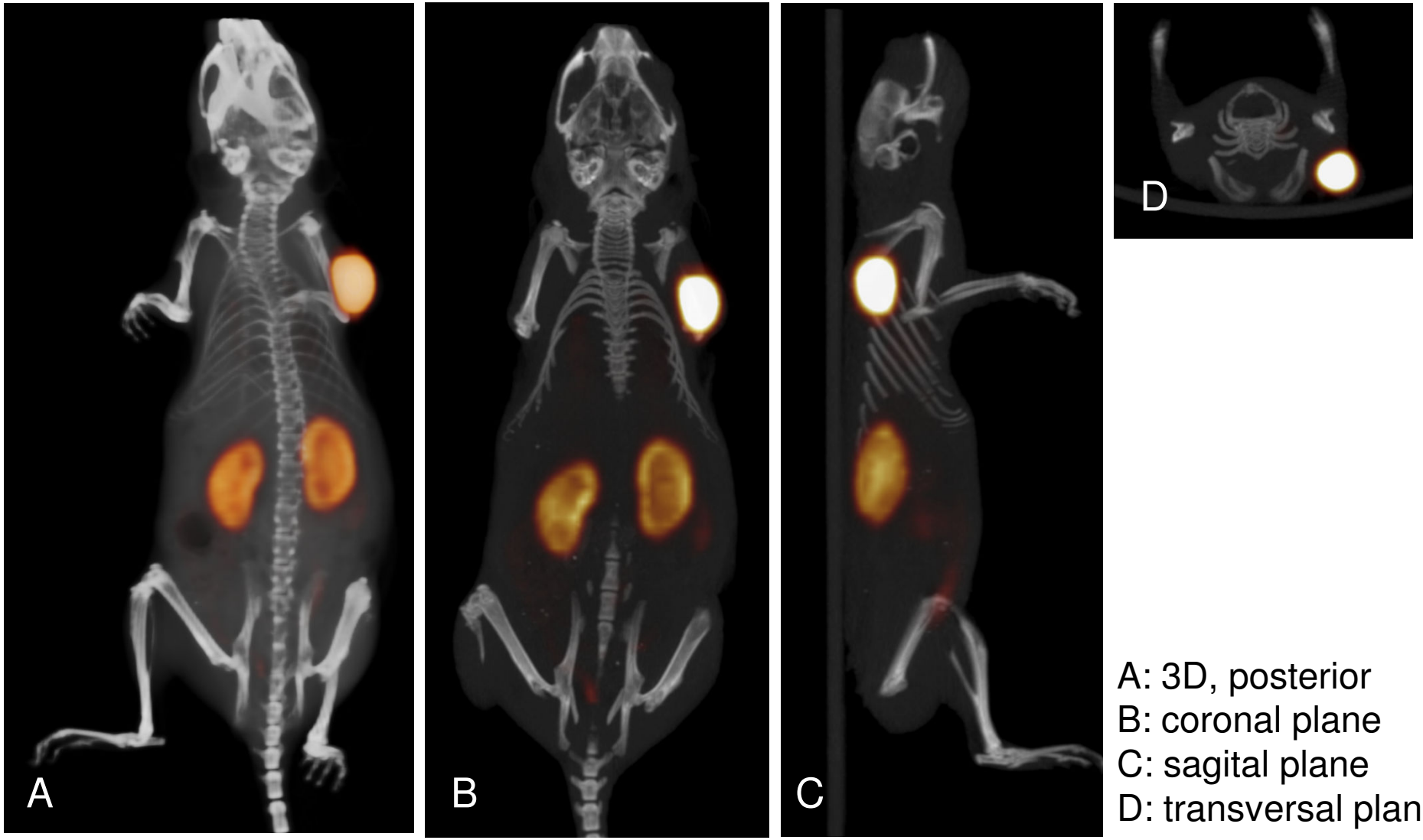
NOTA-conjugated diHSG-peptide

Labeling NOTA-Gly-Lys(HSG)-Tyr-Lys(HSG) with F-18:

- Elute F-18 from QMA with 0.4 M $KHCO_3$ (15 mCi)
- Neutralize with 10 µL HAc
- Add 3 µL 2 mM $AlCl_3$ in 0.1 M NaAc, pH 4
- Add 200 µg IMP449 in 0.5 M NaAc, pH 4
- Incubate 15 min at 100 °C
- Purify by HPLC

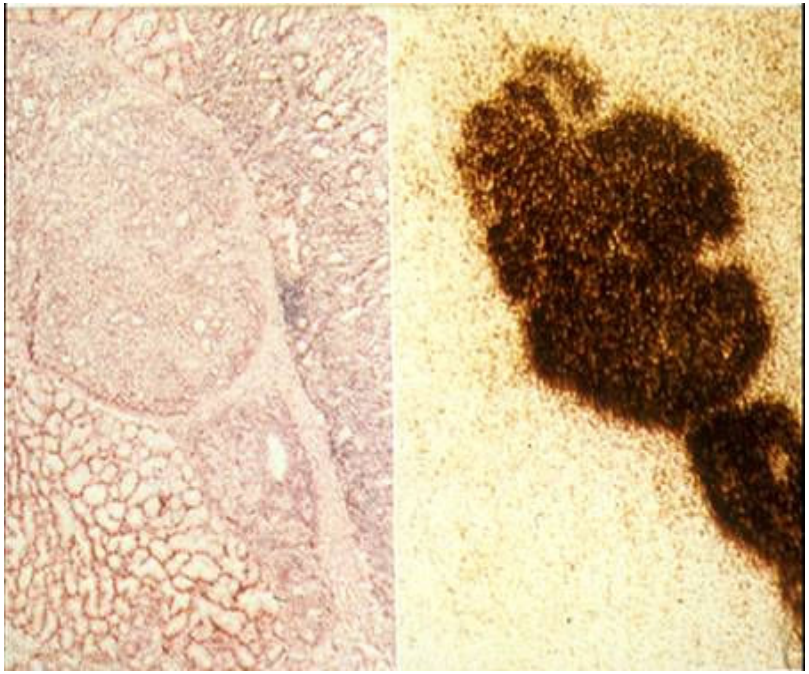


Pretargeted immunoPET imaging with ^{18}F-diHSG



A: 3D, posterior
B: coronal plane
C: sagital plane
D: transversal plane

Peptide receptor radionuclide targeting



Somatostatin receptor expression on neuroendocrine tumors

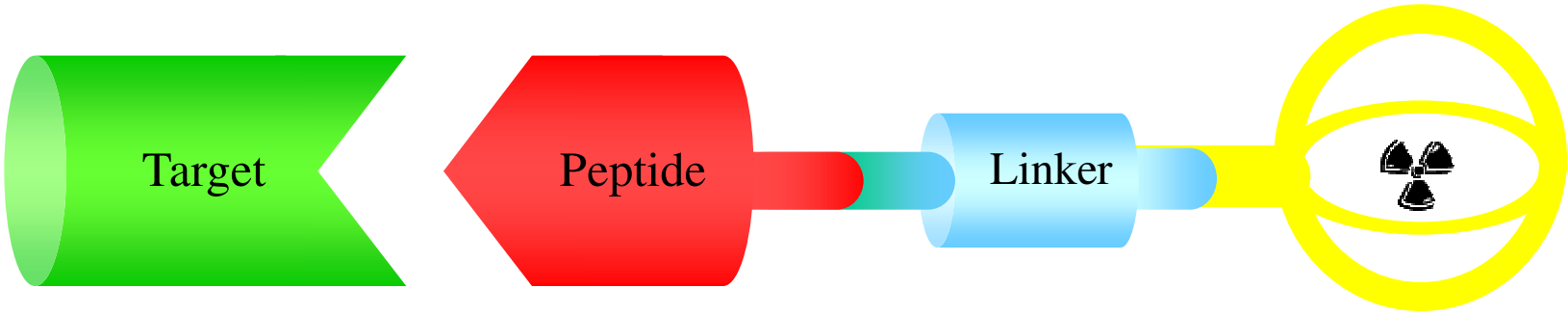
Octreotide

D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr

Peptide receptor radionuclide targeting

• Somatostatin analogs	NET, a.o.	SSTR1-5
• Bombesin analogs	Prostate cancer, a.o.	GRPR, NMBR
• Cholecystokinine	SCLC, MTC, a.o.	CCKR1-2
• Neuropeptide Y	breast , adrenal, a.o.	Y1-Y5
• Neurotensin	pancreas, meningioma	NTR1-3
• Vasointestinal Peptide	adenocarcinoma	VIPAC1-2
• GLP-1	insulinoma	GLP-1R
• RGD peptides	ovarian, melanoma, a.o.	$\alpha_v\beta_3$

Peptide Receptor Radionuclide Targeting



^{111}In-octreotide

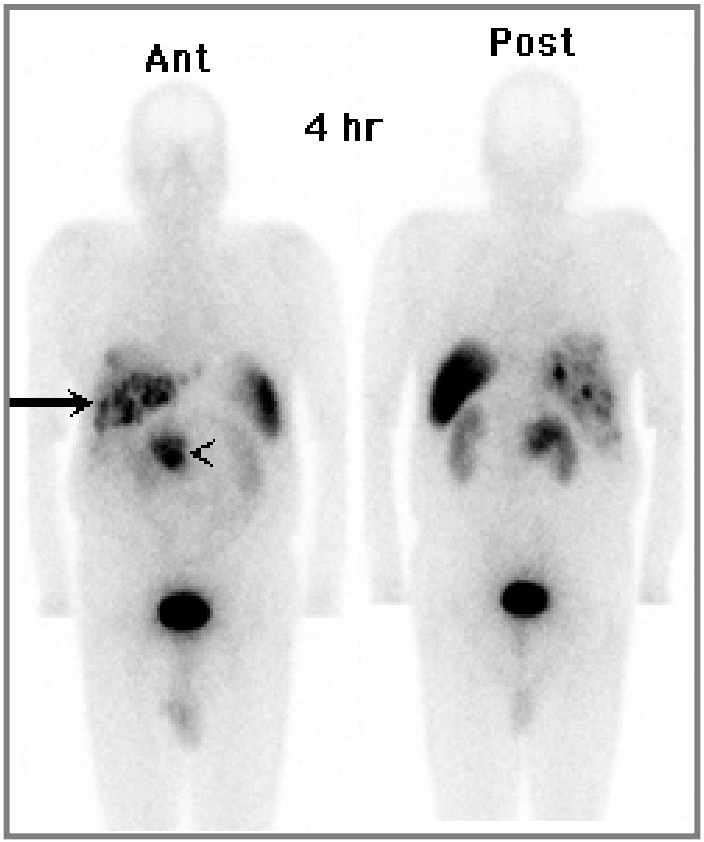
Imaging dose: 5 mCi ^{111}In-octreotide

Peptide dose: 10 µg

Imaging: 4 and 24 h

Sensitivity: 80-90%

Therapy monitoring in patients with neuroendocrine tumors

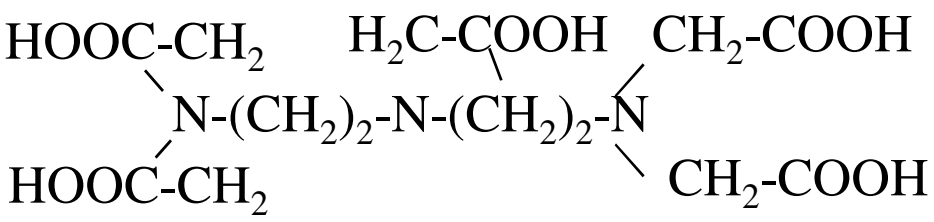


Somatostatin analogs

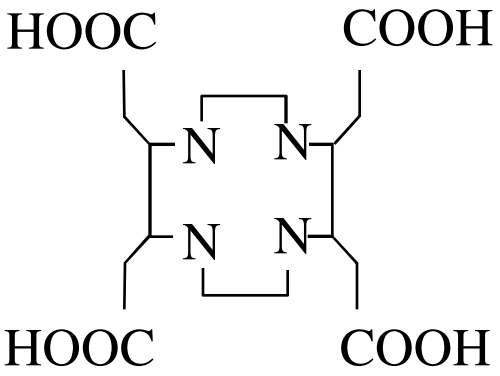
octreotide D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr

[Tyr^3]-octreotide D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr

chelators:

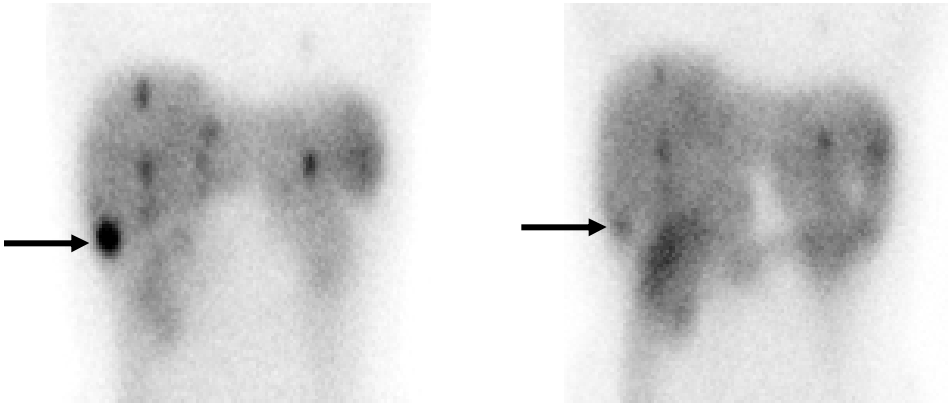


DTPA

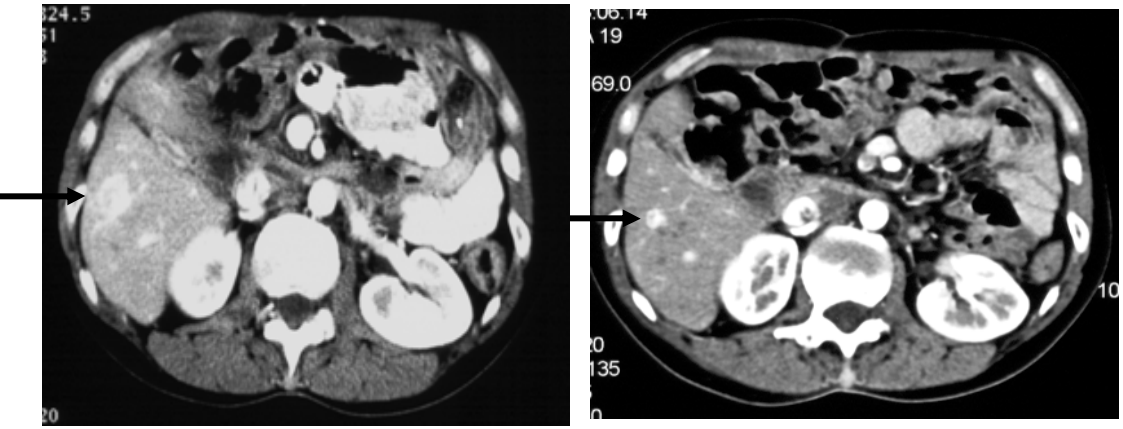


DOTA

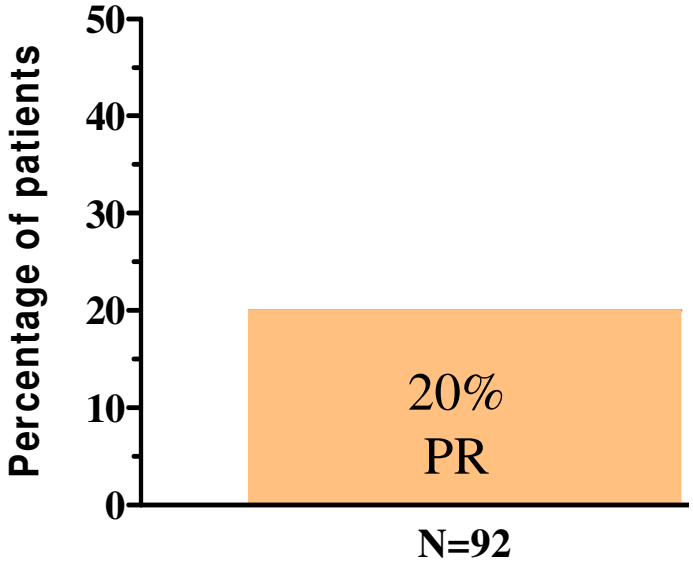
^{90}Y-DOTA-Tyr3-octreotide



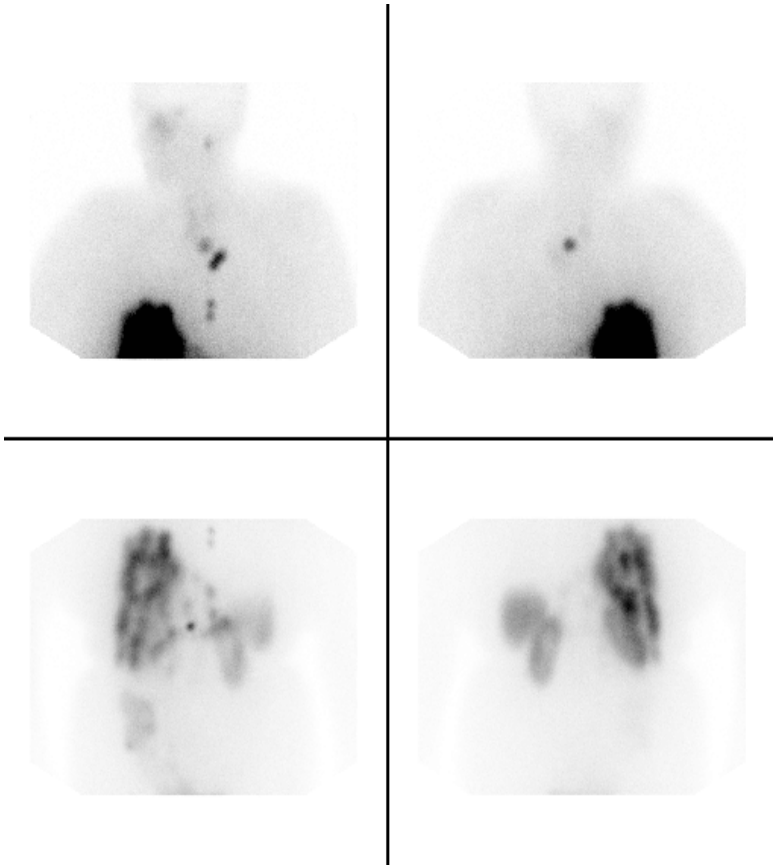
^{90}Y-DOTA-Tyr$_3$-octreotide
± 120 mCi/cycle
3 cycles (6-9 weeks)



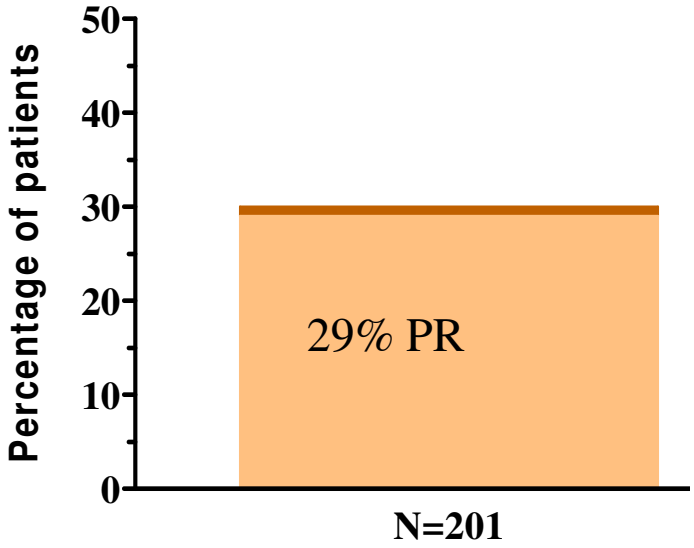
Baseline Post Tx



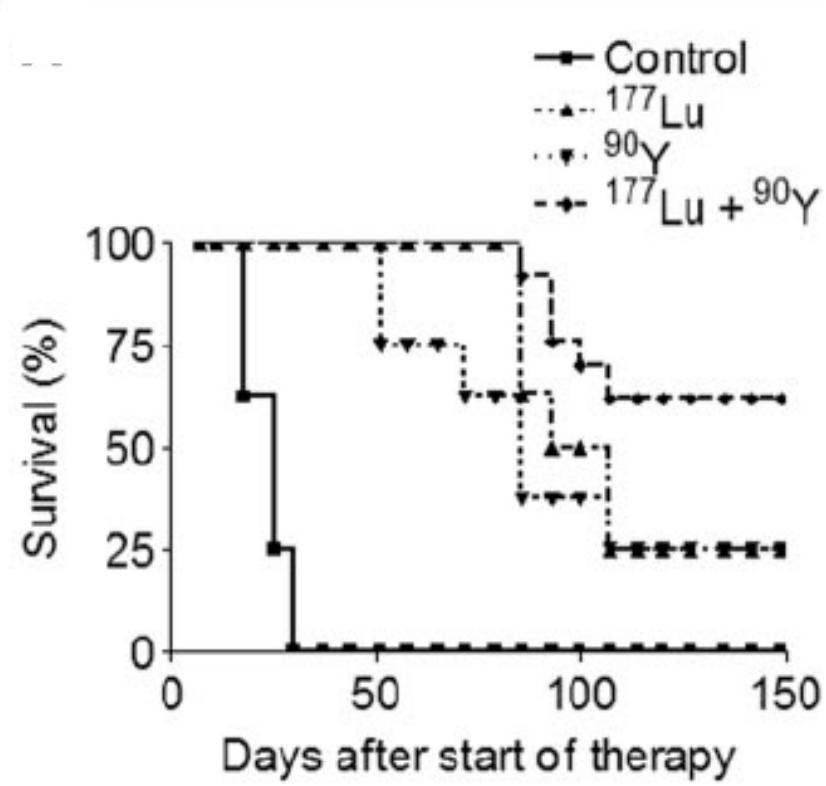
^{177}Lu-DOTA-Tyr$_3$-octreotate



^{177}Lu-DOTA-Tyr3-octreotate
200 mCi/per cycle
Total dose: 600-800 mCi
Lys/Arg coinfusion

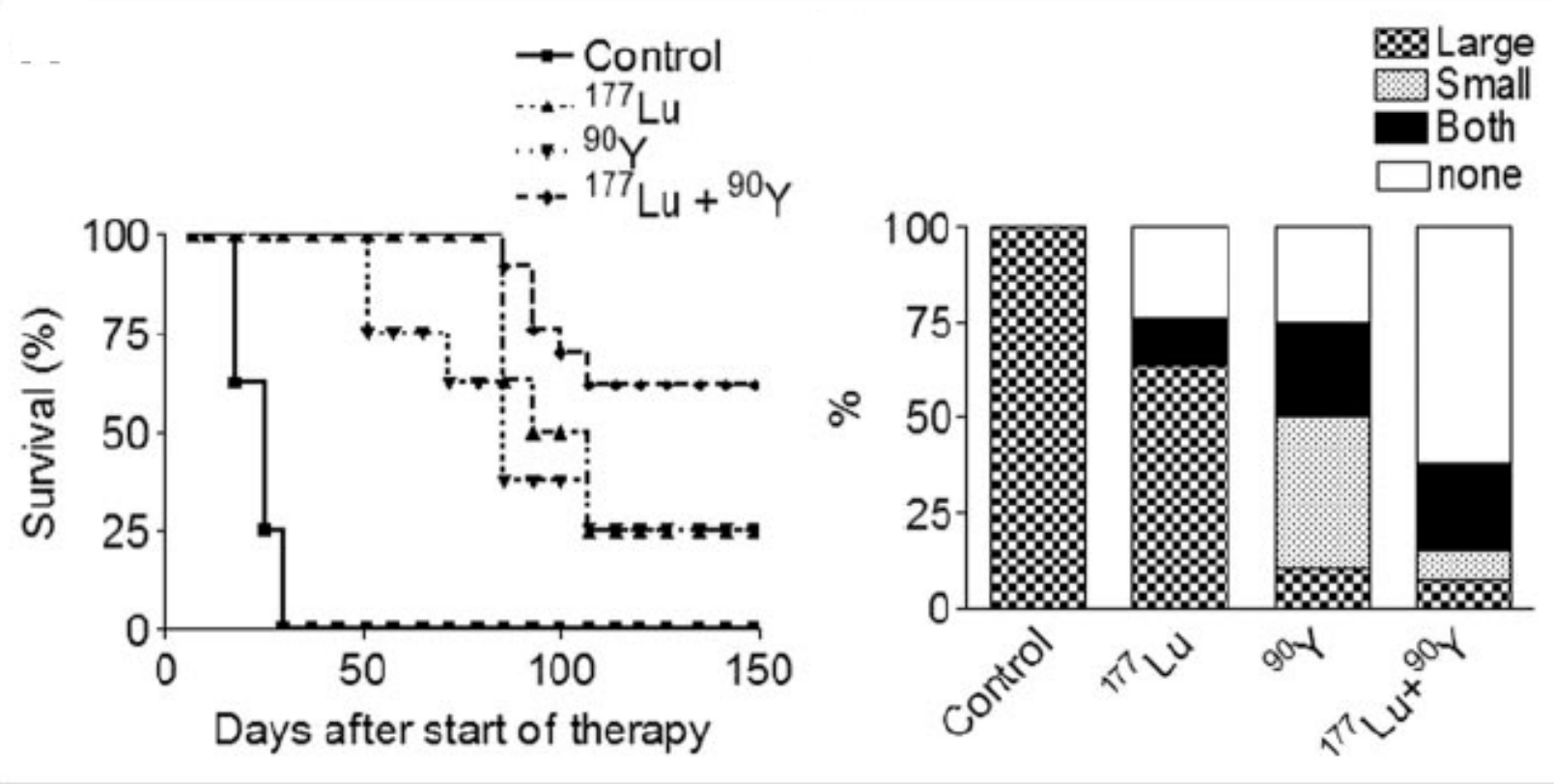


Y-90-DOTA-TOc versus Lu-177-DOTA-TATE



de Jong et al. JNM 2005; 46: 13S-17S

Y-90-DOTA-TOc versus Lu-177-DOTA-TATE

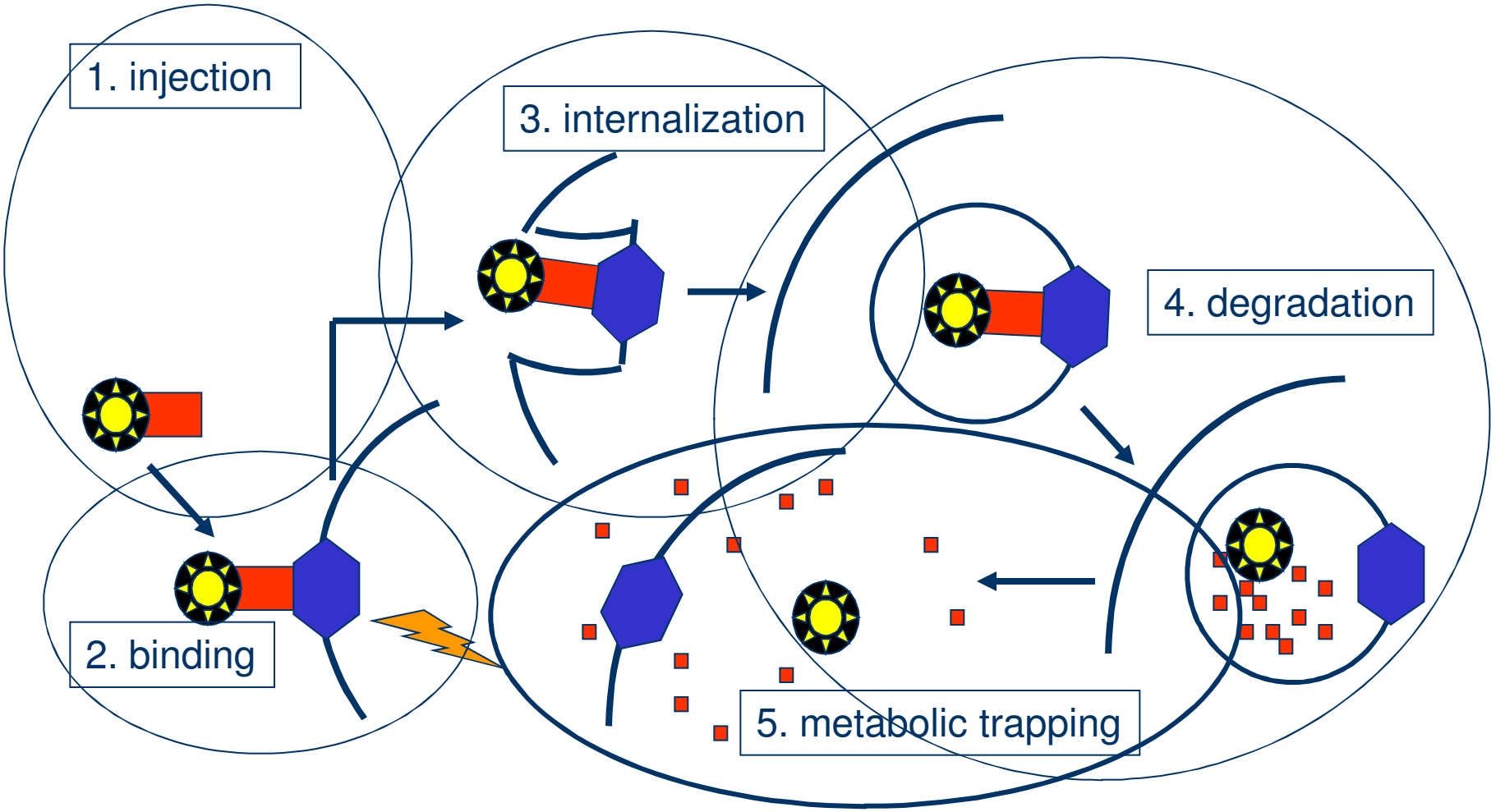


de Jong et al. JNM 2005; 46: 13S-17S

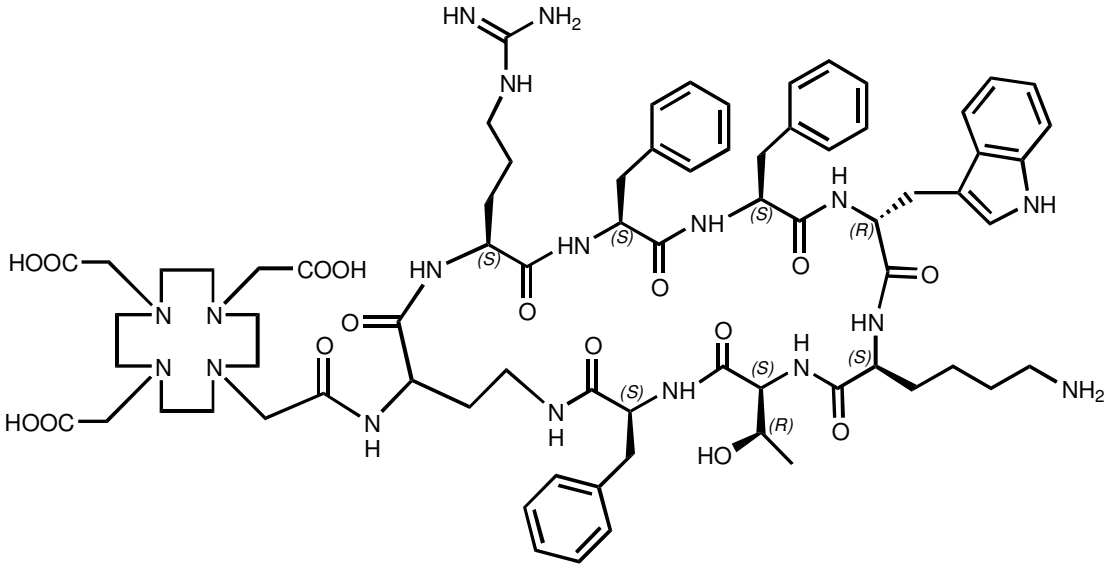
Y-90-DOTA-TOc versus Lu-177-DOTA-TATE

de Jong et al. JNM 2005; 46: 13S-17S

Peptide receptor radionuclide targeting



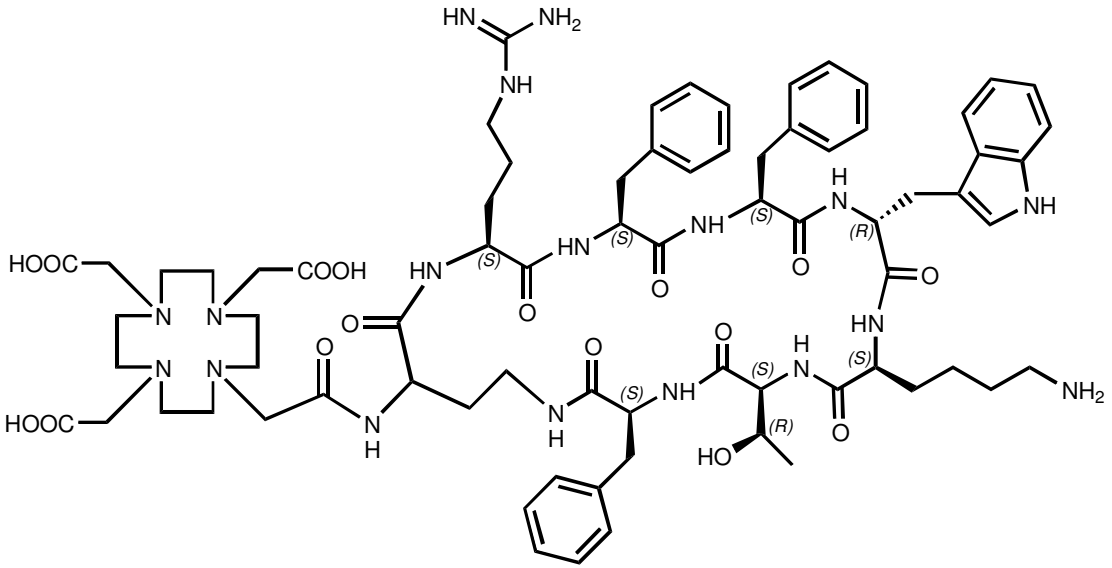
The importance of internalization



KE88, a pan-somatostatin ligand

Compound	IC_{50} (nM)				
	sst1	sst2	sst3	sst4	sst5
SST-28	2.7 ± 0.3 (12)	2.3 ± 0.2 (12)	3.4 ± 0.3 (12)	2.7 ± 0.3 (12)	2.5 ± 0.3 (12)
In-Oct	> 10,000 (5)	22 ± 3.6 (5)	182 ± 13 (5)	>10,000 (5)	237 ± 52 (5)
Y-KE88	4.6 ± 0.4 (4)	2.1 ± 0.4 (4)	2.5 ± 0.2 (4)	2.4 ± 0.3 (4)	3.1 ± 0.5 (4)

The importance of internalization



KE88, a pan-somatostatin ligand

Compound	IC_{50} (nM)				
	sst1	sst2	sst3	sst4	sst5
Somatostatin	2.7 ± 0.3 (12)	2.3 ± 0.2 (12)	3.4 ± 0.3 (12)	2.7 ± 0.3 (12)	2.5 ± 0.3 (12)
In-Oct	> 10,000 (5)	22 ± 3.6 (5)	182 ± 13 (5)	>10,000 (5)	237 ± 52 (5)
Y-KE88	4.6 ± 0.4 (4)	2.1 ± 0.4 (4)	2.5 ± 0.2 (4)	2.4 ± 0.3 (4)	3.1 ± 0.5 (4)

Lack of Internalization of KE88

Radiopeptide	% internalized into AR4-2J	% internalized into HEK-sst2	% internalized into HEK-sst3	% internalized into HEK-sst5
[^{111}In]-KE88	<0.4	<0.5	32.2±2.6	<0.1

Specific internalization after 4 h at 37 °C

Lack of Internalization of KE88

Radiopeptide	% internalized into AR4-2J	% internalized into HEK-sst2	% internalized into HEK-sst3	% internalized into HEK-sst5
[^{111}In]-KE88	<0.4	<0.5	32.2±2.6	<0.1

Specific internalization after 4 h at 37 °C

Ginj et al. Clin Cancer Res. 2008;14:2019-2027

Biodistribution ^{111}In-KE88 in mice with s.c. tumors

Organ	^{111}In-KE88			
	15 min	**1 h**	**4 h**	**24 h**
Blood	5.2±0.7	0.7±0.2	0.1±0.01	0.02±0.002
HEK-sst2	18.5±0.65	13.6±0.95	3.7±0.35	1.14±0.05
HEK-sst3	15.2±1.6	22.9±3.9	23.2±4.2	14.9±2.5

Ginj et al. Clin Cancer Res. 2008;14:2019-2027

Biodistribution ^{111}In-KE88 in mice with s.c. tumors

Organ	^{111}In-KE88			
	15 min	**1 h**	**4 h**	**24 h**
Blood	5.2±0.7	0.7±0.2	0.1±0.01	0.02±0.002
HEK-sst2	18.5±0.65	13.6±0.95	3.7±0.35	1.14±0.05
HEK-sst3	15.2±1.6	22.9±3.9	23.2±4.2	14.9±2.5

Ginj et al. Clin Cancer Res. 2008;14:2019-2027

Therapeutic Radionuclides considered for peptide radionuclide therapy

- Beta-Emitters

  ^{90}Y, $^{186/188}Re$, ^{177}Lu, ^{131}I, ^{165}Dy, ^{166}Ho, ^{105}Rh, ^{111}Ag
- Alpha-Emitters

  ^{212}Bi, ^{213}Bi, ^{211}At, ^{225}Ac
- Auger-Emitters

  ^{125}I, ^{111}In, ^{67}Ga, ^{201}Tl, ^{51}Cr, ^{140}Nd, ^{195m}Pt