Examples for Translational Research Projects
Somatostatin Receptor Ligands

Damian Wild

Professor of Nuclear Medicine

Division Head of Nuclear Medicine

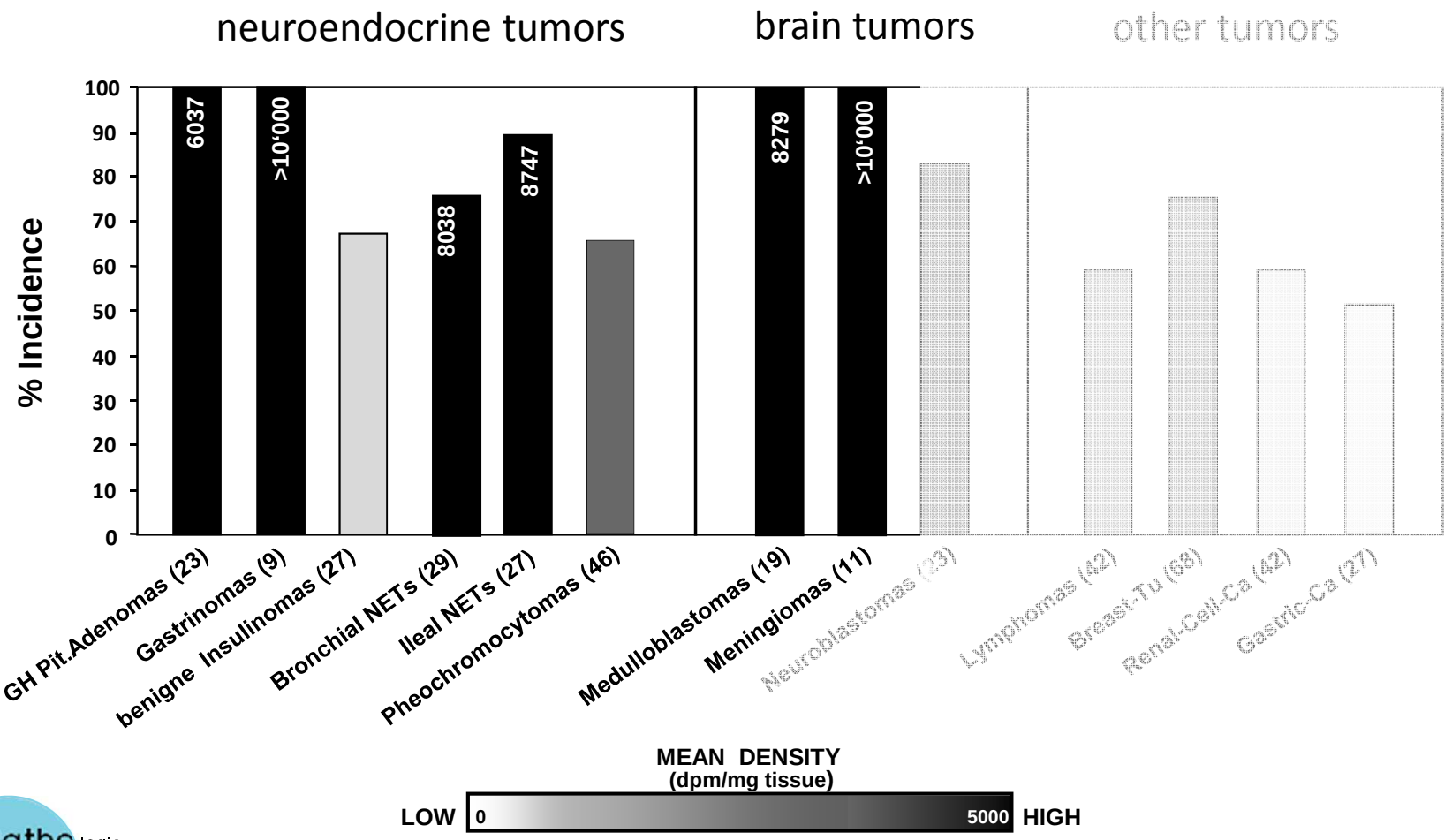
Department of Radiology

Division of Nuclear Medicine

University of Basel Hospital

Universitätsspital Basel

Sst_2 receptors in cancer: incidence and density

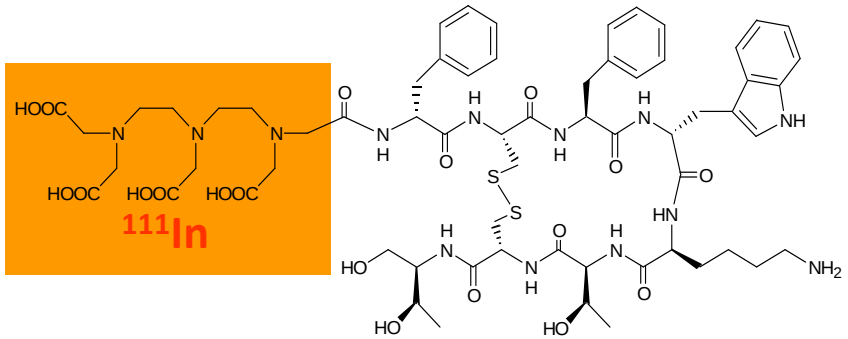


Reubi et al. Pathology University of Bern, Switzerland

Targeting of somatostatin receptors with radiolabelled peptides

[^{111}In – DTPA^{0} - DPhe^{1}] - Octreotide (OctreoScan®)

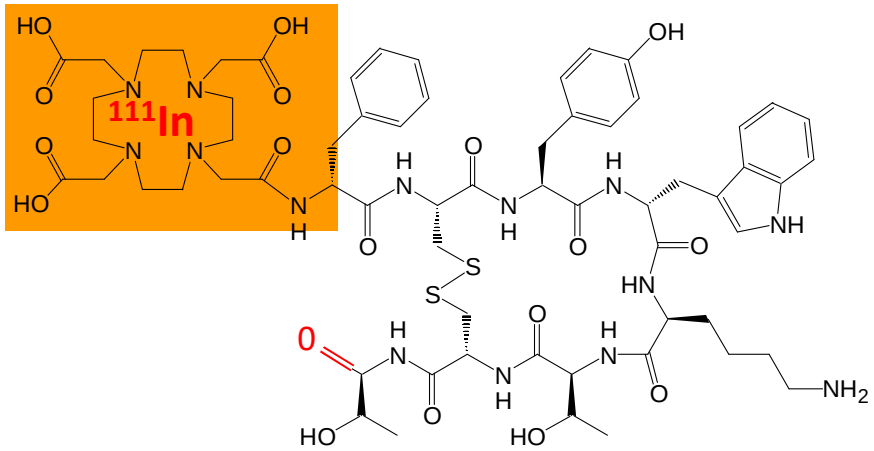
radionuclide chelator peptide



Imaging:

^{111}In for SPECT and SPECT/CT

[^{111}In – DOTA^{0} - DPhe^{1}, Tyr^{3}] - Octreotate (DOTATATE)



Imaging:

1. **^{111}In for SPECT and SPECT/CT**
2. **^{68}Ga for PET and PET/CT**

Therapy:

1. **high energy β-emitter ^{90}Y**
2. **low energy β-emitter ^{177}Lu**
3. **high energy α-emitter ^{213}Bi**

Somatostatin receptor imaging in NETs

FDA etc.
approved

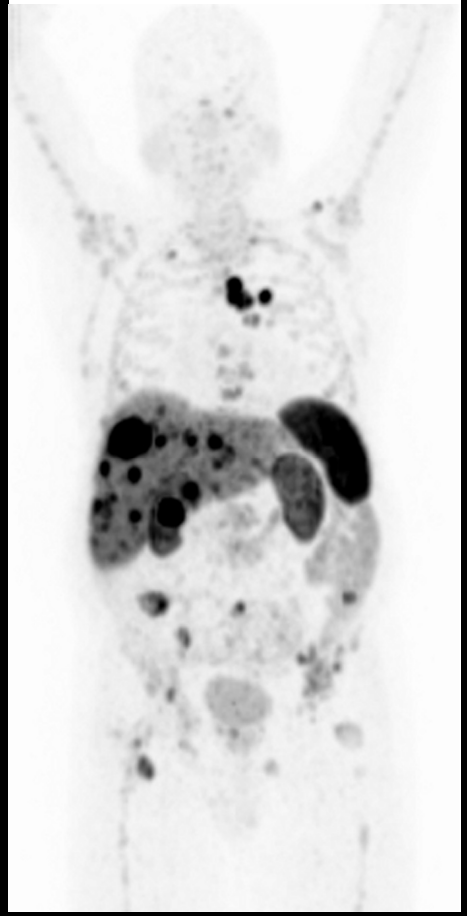
investigation
time: 24 h

radiation-
exposure: 9 mSv

sensitivity: ~ 70%

Octreoscan®
scintigraphy 4 h p.i.

^{68}Ga-DOTA-TOC
PET 1 h p.i.



limited availability
not approved

Investigation
time: 90 min

radiation-
exposure: 3 mSv

sensitivity: > 90%

changes treatment in
~ 70 % of patients with
negative Octreoscan®

M. Gabriel et al. J Nucl Med, 2007;48:508-18
I. Buchmann et al. Eur J Nucl Med Mol Imaging, 2007;34:1617-26
R. Srirajaskanthan et al. J Nucl Med, 2010;51:875-82

Lung- and GEP NETs: sst receptor SPECT vs. PET

Comparison of ^{68}Ga-DOTA-TOC PET and Octreoscan® SPECT in 84 patients with lung- and GEP NETs (patient based analysis)

	^{68}Ga-DOTA-TOC PET	Octreoscan SPECT
Sensitivity	97%	52%
Specificity	92%	92%
Accuracy	96%	58%

Gabriel et al. J Nucl Med, 2007, 48:508-518

Diagnostic performance of Gallium-68 sst receptor PET, meta-analysis in 567 patients (patient based analysis)

	sstR PET
Sensitivity (95% CI)	93% (91 – 95%)
Specificity (95% CI)	91% (82 – 97%)

Treglia et al. Endocrine, 2012, 42:80-87

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"Somatostatin receptor PET is superior to somatostatin receptor SPECT in the detection of NET"

Gabriel et al. J Nucl Med, 2007; 48:508-18

"PET has a much higher spatial resolution and sensitivity than SPECT"

Martin et al. Radiology, 1996; 198:225-31

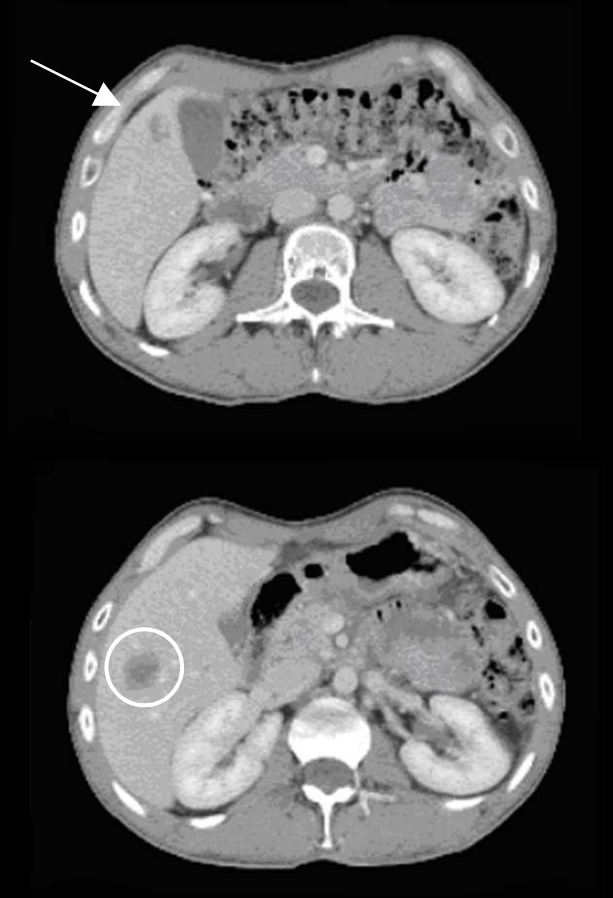
Affinity profile given as IC_{50} (mean ± SEM in nM)

Peptide	sst_1	sst_2	sst_3	sst_4	sst_5
SS-28	5.2 ± 0.3	2.7 ± 0.3	7.7 ± 0.9	5.6 ± 0.4	4.0 ± 0.3
^{111}In-Octreoscan	>10'000	**22 ± 3.6**	182 ± 13	>1'000	237 ± 52
^{68}Ga-DOTATOC	>10'000	**2.5 ± 0.5**	613 ± 140	>1'000	73 ± 21
^{68}Ga-DOTATATE	>10'000	**0.2 ± 0.04**	>1'000	300 ± 140	377 ± 18

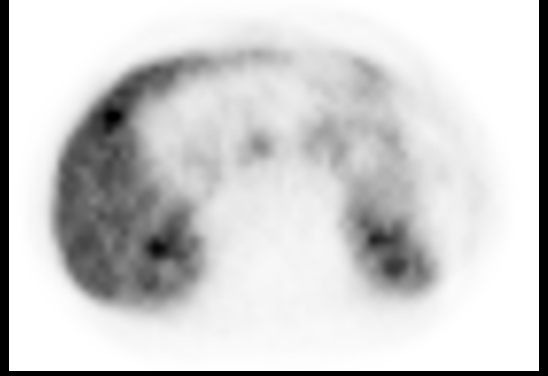
Reubi et al., Eur J Nucl Med, 2000; 27:273-82

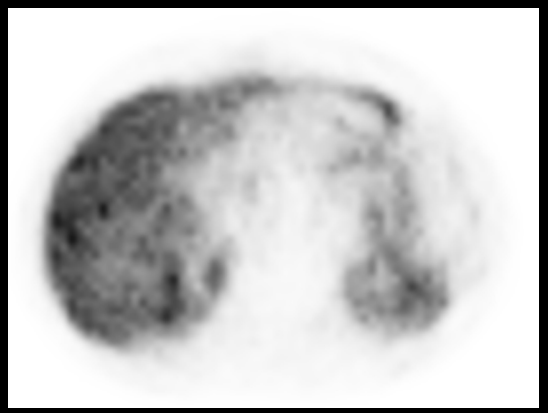
Example of a 37-year old man with a pancreatic NET (G2) who had the primary tumor removed, known liver metastases ? Restaging before surgery

CT scan
portal venous phase



^{68}Ga-DOTATATE PET 1h p.i.
sst_2 receptor PET





^{68}Ga-DOTATATE PET 1h p.i.
sst_2 receptor PET

Lung- and GEP NETs: ^{68}Ga-DOTA-TOC PET vs. triple-phase CT

Comparison of ^{68}Ga-DOTA-TOC PET and triple-phase CT in 51 patients with lung- and GEP NETs, evaluation of 510 lesions (lesion based analysis)

	^{68}Ga-DOTA-TOC PET	Triple-phase CT
Sensitivity	**73%**	**77%**
Specificity	97%	85%
Accuracy	80%	80%
Specific detection rate	16% only PET	20% only tiple-phase CT
Body organs	pancreas, lymph node, liver	lung, bone, liver

Ruf et al. J Nucl Med, 2011, 52:697-704

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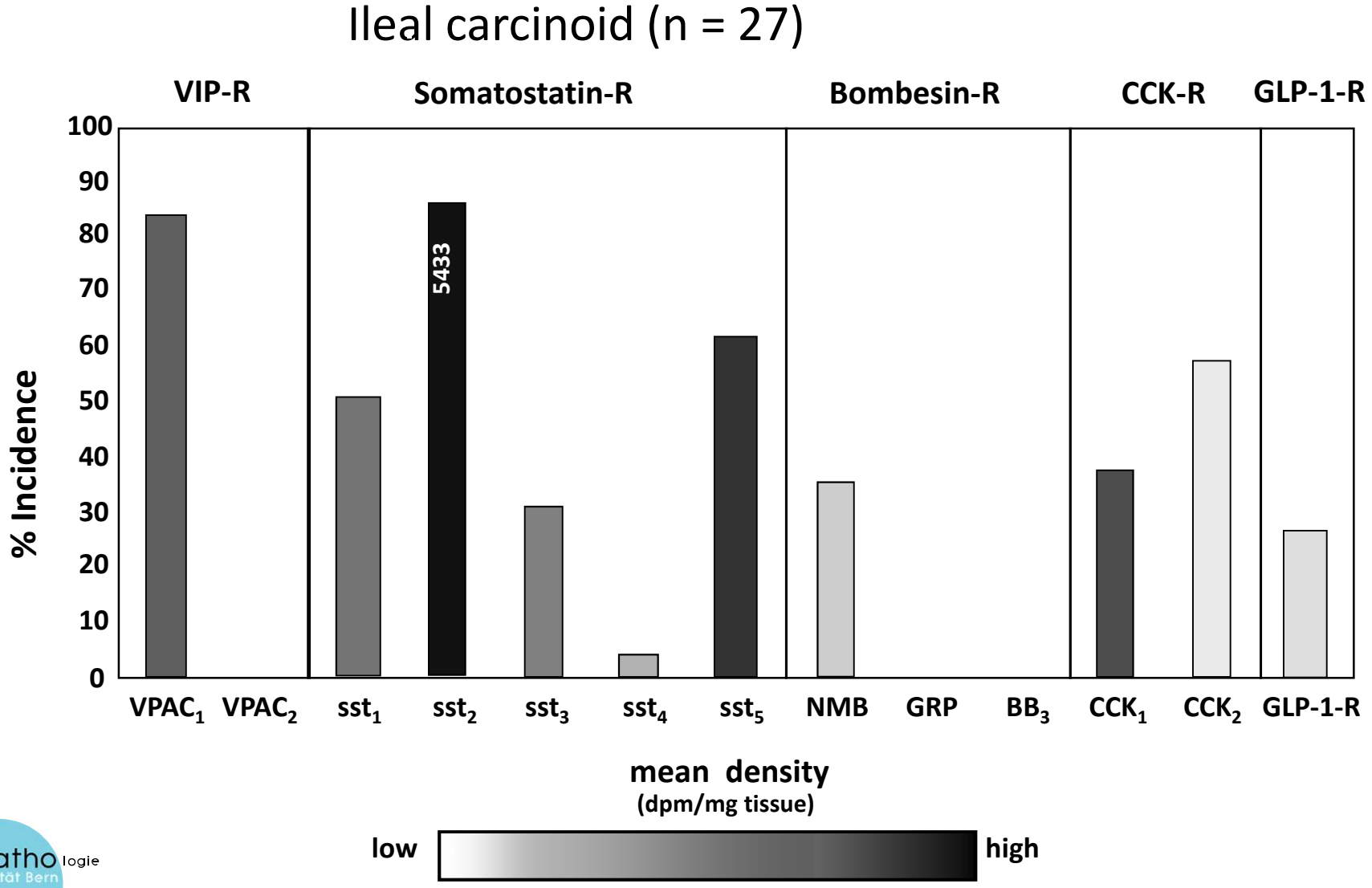
GPCR expression in GEP NETs

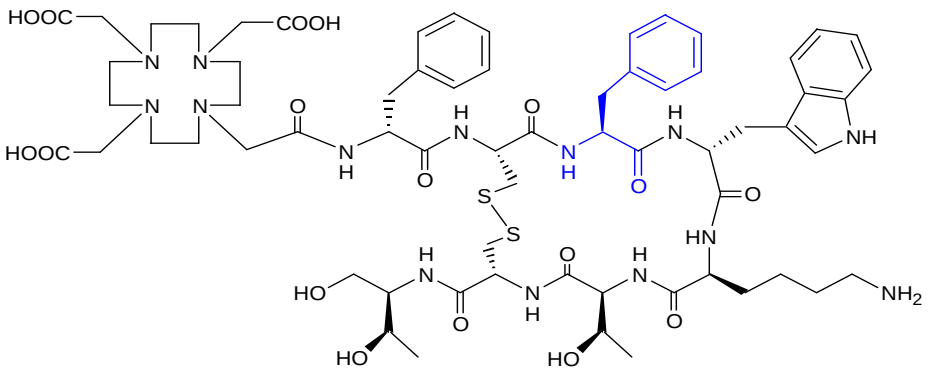


Reubi et al. Pathology University of Bern, Switzerland

[DOTA - Tyr^3] - Octreotide (DOTATOC)

sst_2 receptor specific

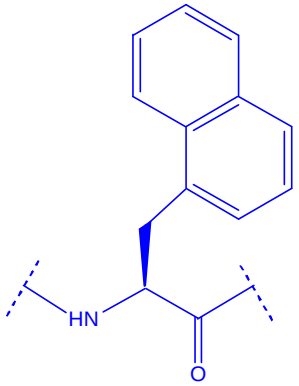
tyrosine (Tyr^3)



[DOTA - Nal^3] - Octreotide (DOTANOC)

sst_2 receptor specific

naphthylalanine (Nal^3)



D. Wild, J. Schmitt, H.R. Mäcke et al., Eur J Nucl Med Mol Imaging, 2003; 30:1338-47

Affinity profile given as IC_{50} (mean ± SEM in nM)					
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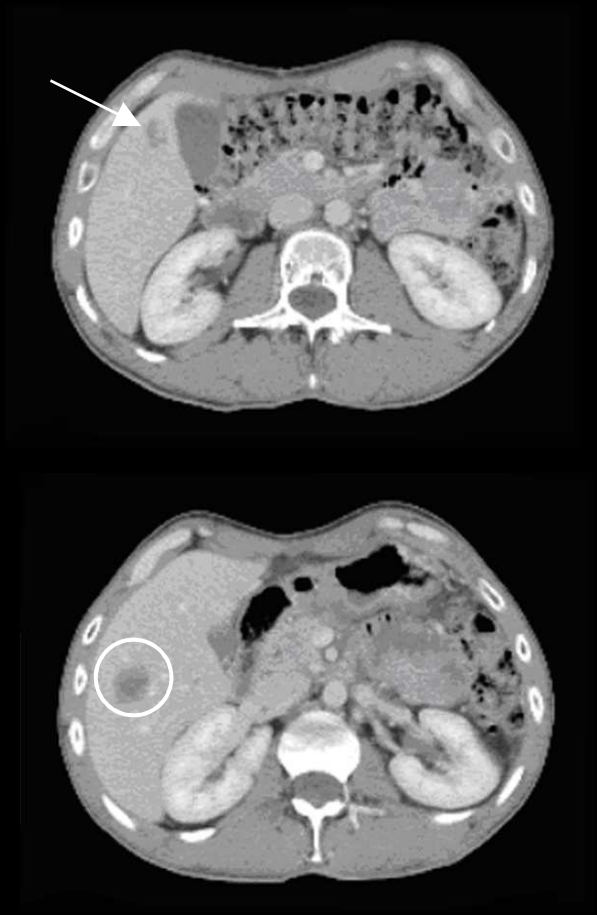

^{68}Ga-DOTATATE PET 1h p.i.
sst_2 receptor PET

^{68}Ga-DOTANOC PET 1h p.i.
$sst_{2,3,5}$ receptor PET

Comparison of ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC PET

Comparison of ^{68}Ga-DOTA-TATE PET and ^{68}Ga-DOTA-NOC PET in 18 patients with GEP NETs using a randomized cross-over design.

		^{68}Ga-DOTATATE PET sst_2 -selective tracer	^{68}Ga-DOTANOC PET $sst_{2,3,5}$ -selective tracer
patient by patient based analysis	sensitivity	**94%** (17/18)	**94%** (17/18)
lesion by lesion based analysis			
all lesions	sensitivity	**86%** (212/250)	**94%** (232/248)
Liver metastases	sensitivity	**73%** (68/93)	**95%** (88/93)
Bone metastases	sensitivity	**100%** (89/89)	**92%** (82/92)

D. Wild et al. J Nucl Med, 2013, 54:364-372

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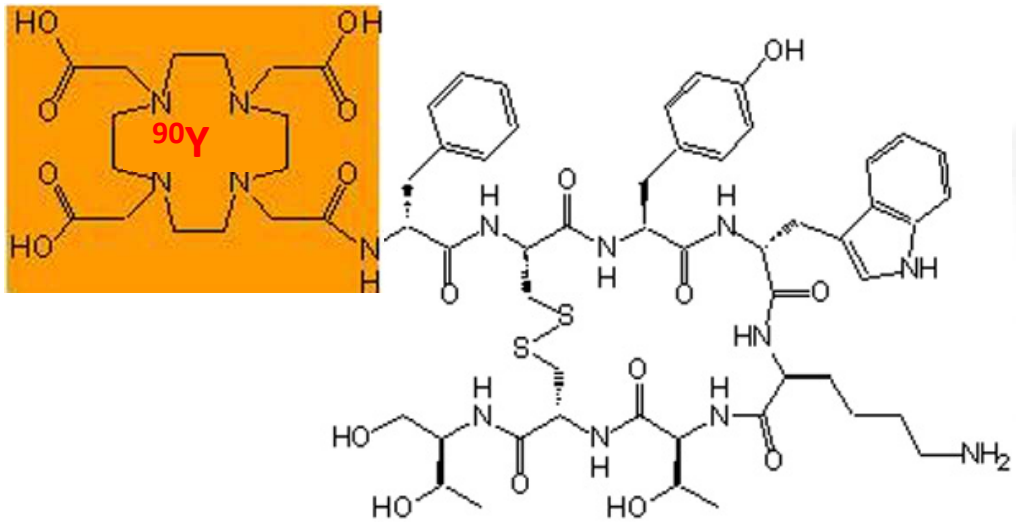
Targeting of somatostatin receptors with radiolabelled peptides

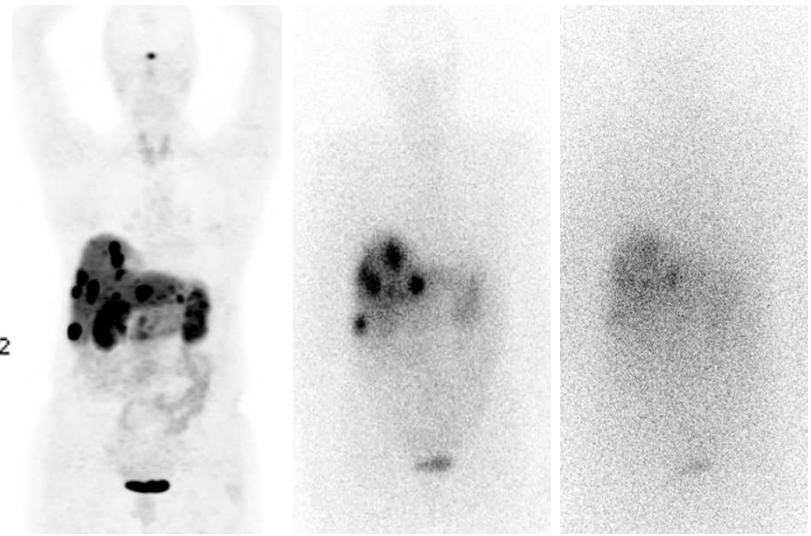
Peptide receptor radionuclide imaging and therapy = theranostic approach

[^{68}Ga – DOTA^{0} - DPhe^{1}, Tyr^{3}] - Octreotide (^{68}Ga-DOTATOC)

radionuclide chelator peptide = carrier



P Powell and HR Mäcke, Basel, 1994



^{68}Ga-DOTATOC PET	^{177}Lu-DOTATOC scintigraphy	^{90}Y-DOTATOC scintigraphy
Positron-Emitter	Gamma-Emitter + Beta-Emitter	Beta-Emitter

Imaging → Therapy

Theranostic approach

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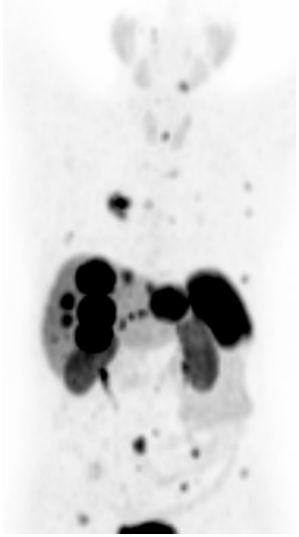
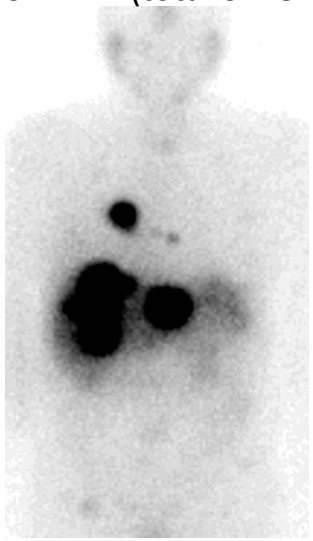
Personalized medicine & PRRT – theranostic approach

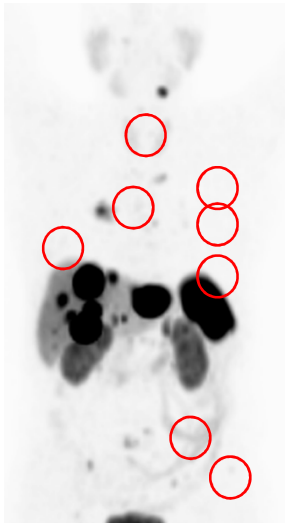
^{68}Ga-DOTATOC PET



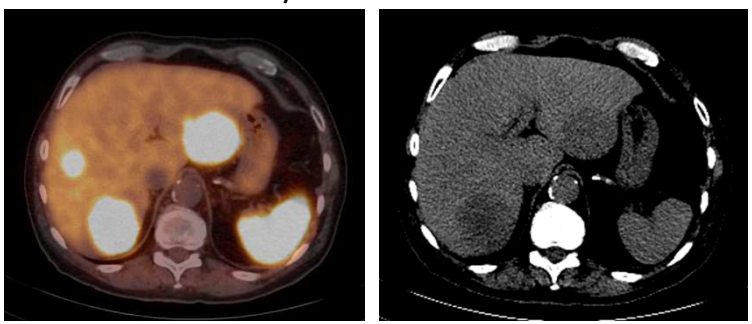
3 cycles of PRRT (total of 15 GBq)



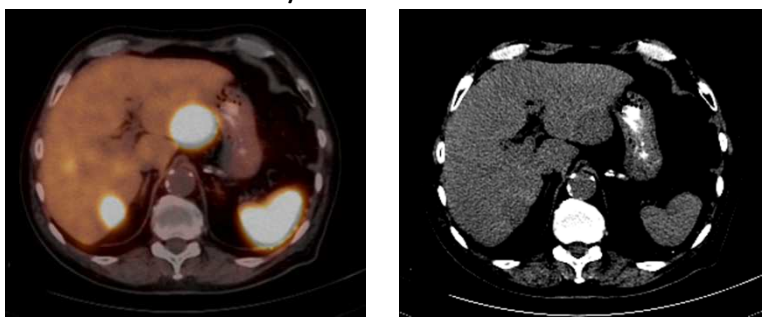
^{68}Ga-DOTATOC PET follow-up



^{68}Ga-DOTATOC PET/CT



^{68}Ga-DOTATOC PET/CT



Summary PRRT-Results

Trial	Protocol	PD at entry	N	CR/PR (%)	Median PFS (months)	Median OS (months)
Open label Phase II Trials Radiotracer (PRRT)	4 x ^{177}Lu-DOTATATE[1]	Not required	310	30	33	46
	2 x ^{90}Y-DOTATOC[2]	Required	1109	34	12.7	44
	3 x ^{90}Y-DOTATOC[3] 1 x ^{90}Y-DOTATOC + 2 x ^{177}Lu-DOTATOC	Required	237 249	28 26	10.4 10.4	47.1 66.1

Trial	Protocol	Histology	CR/PR (%)	Biochemical Response (%)	Clinical Response (%)
Open label Phase II Trial	2 x ^{90}Y-DOTATOC[2]	NET of the pancreas	49	14	38
		NET of the Ileum	27	18	28
		NET of the lung	29	13	28

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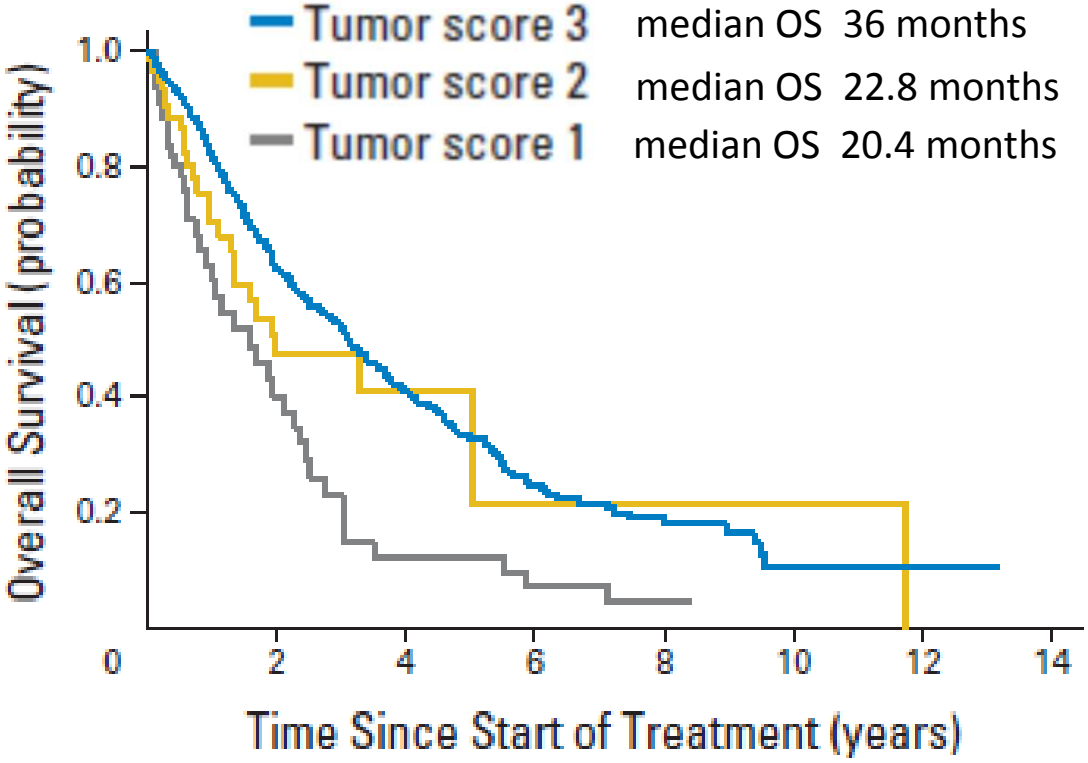
Rotterdam data: 1: Kwekkeboom, JCO, 2008;
Basel data: 2: Imhof, JCO, 2011; 3: Villard, JCO, 2012

2 x ^{90}Y-DOTATOC in NETs (Theranostic approach)

Large open label phase II study, N = 1109

Overall Survival



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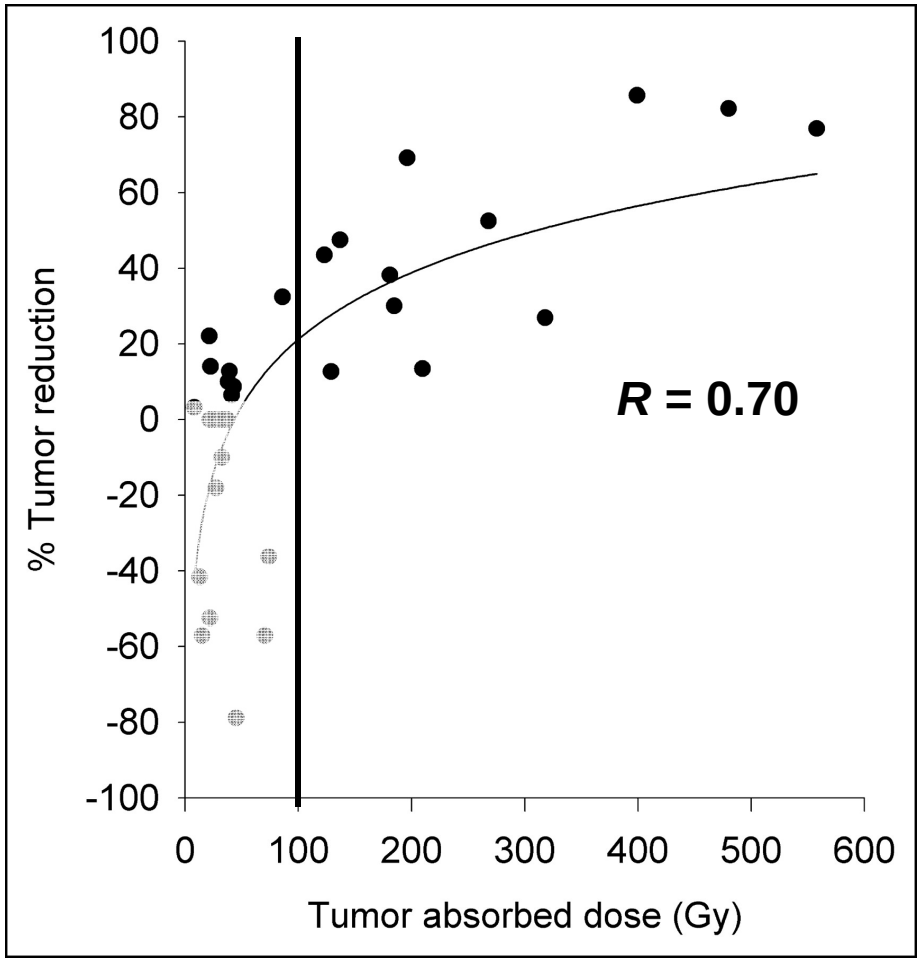
Imhof A et al. J Clin Oncol. 2011;29:2416-2423.

Tumor dose-response relationship in patients with neuroendocrine tumors
Correlation between ^{86}Y-DOTA-TOC dosimetry and treatment outcome

Pauwels et al. J Nucl Med, 2005;46 (Suppl):S92-S98



Tumor dose-response relationship in 13 patients treated with ^{90}Y-DOTA-TOC.

Dosimetric calculations are based on ^{86}Y-DOTA-TOC PET and CT imaging.

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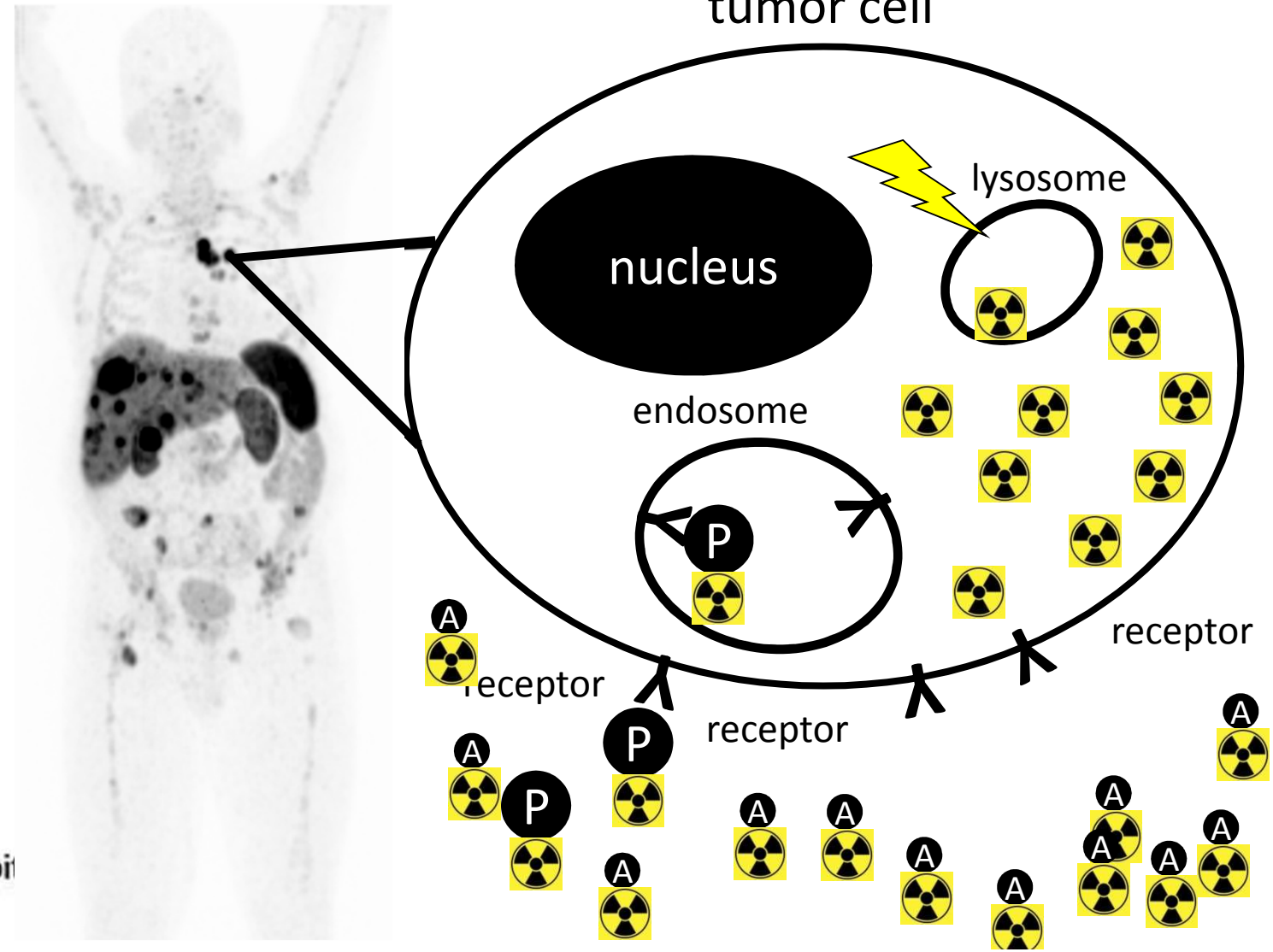
Specific targeting using radiolabeled antagonists

So far only radiolabeled agonists have been used for PRRT



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Sst_2 receptor targeting: agonist vs. antagonist

Scatchard-analysis in HEK-sst_2 cells (B_{max}-values: Mean ± SEM in pM)		
Substance	sst_2- binding sites (B_{max}-values)	Internalization
^{111}In labelled sst_2-agonist	**23 ± 1.0**	sst_2-specific internalization
^{111}In labelled sst_2 antagonist	**354 ± 14**	no internalization

M. Ginj et al. PNAS, 2006; 103:16436-41

Affinity profile given as IC_{50} (mean ± SEM in nM)					
Peptide	sst_1	sst_2	sst_3	sst_4	sst_5
^{68}Ga-DOTA-TATE	>1'000	**0.2 ± 0.04**	>1'000	300 ± 140	377 ± 18
^{68}Ga-NODAGA-JR11	>1'000	**1.2 ± 0.2**	>1'000	>1'000	>1'000
^{177}Lu-DOTA-JR11	>1'000	**0.73 ± 0.15**	>1'000	>1'000	>1'000

M. Fani et al. J Nucl Med, 2013, 54:364-372

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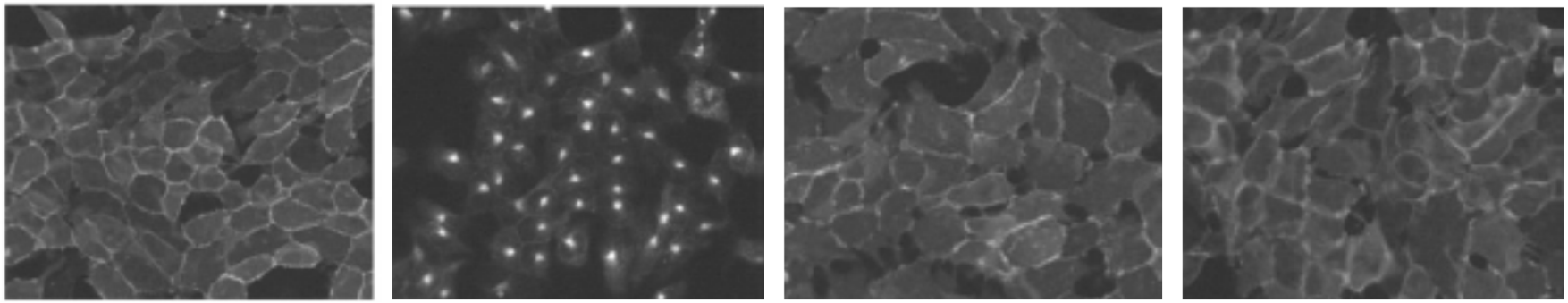
Sst_2 receptor targeting: agonist vs. antagonist

Immunofluorescence microscopy using the sst_2-specific antibody R2-88 in HEK-sst_2 cells

No peptide	DOTA-TOC sst_2-agonist	Ga-NODAGA-JR11 sst_2-antagonist	Ga-NODAGA-JR11 + DOTA-TOC sst_2-antagonist + agonist



M. Fani et al. J Nucl Med, 2013, 54:364-372

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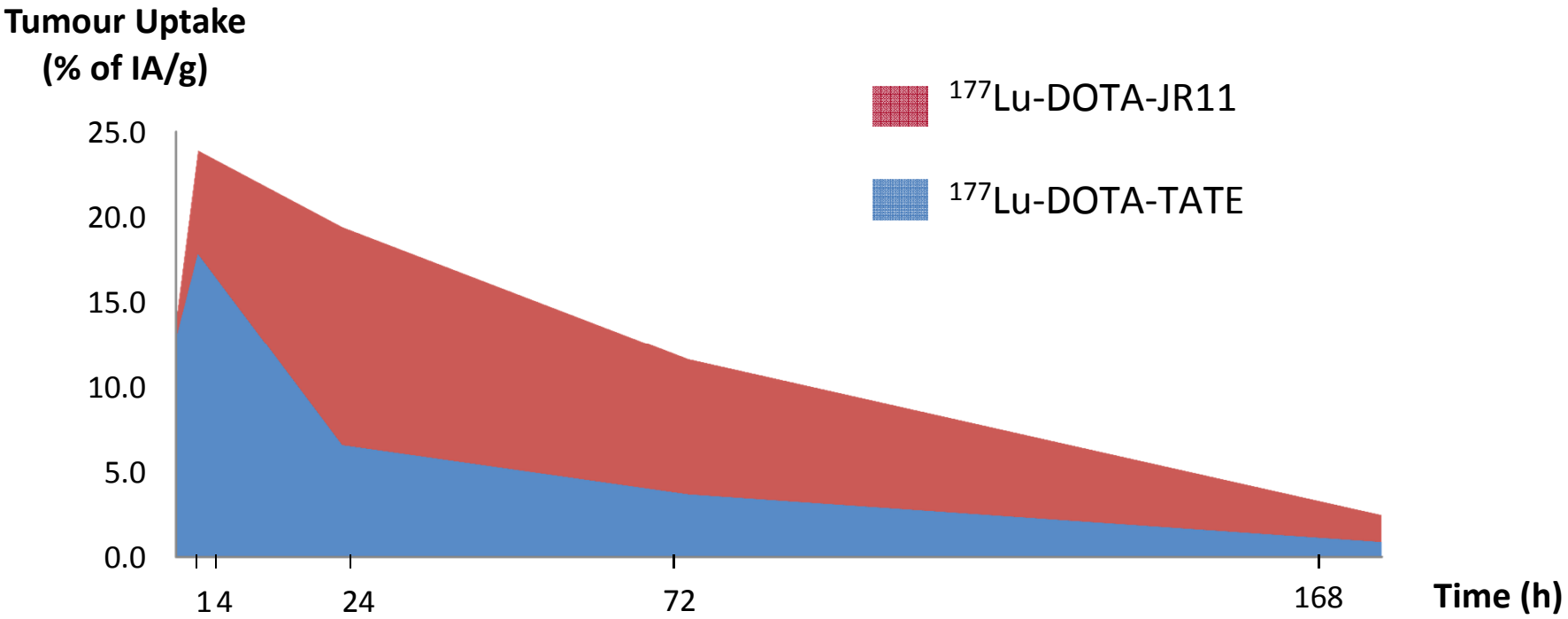
Comparison of ^{177}Lu-DOTA-TATE and ^{177}Lu-DOTA-JR11

Biodistribution results of ^{177}Lu-DOTA-JR11 and ^{177}Lu-DOTA-TATE in nude mice bearing HEK-sst$_2$ cell xenografts



Area under the time activity curve is 2.5 times higher for ^{177}Lu-DOTA-JR11 than for ^{177}Lu-DOTA-TATE

G. Nicolas, D. Wild, M. Fani et al. not published data

Comparison of ^{177}Lu-DOTA-TATE and ^{177}Lu-DOTA-JR11

Pre-treatment Evaluation → **Treatment** → **Post-treatment Evaluation**

Baseline ^{68}Ga-DOTA-TATE PET/CT

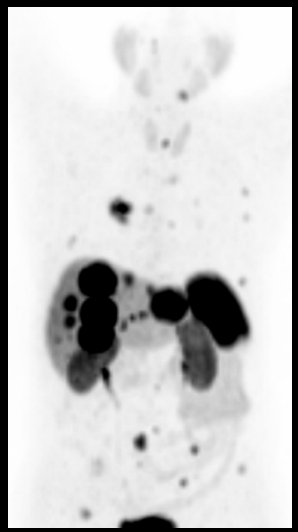
Isodose curves based on 3D voxel dosimetry analysis

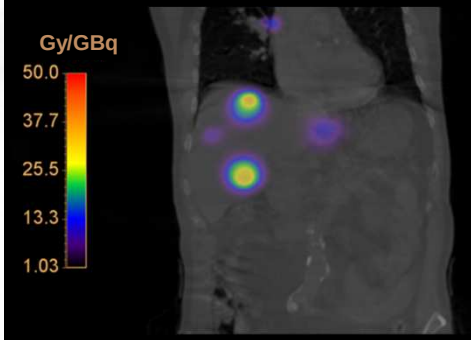
^{177}Lu-DOTA-TATE (agonist)

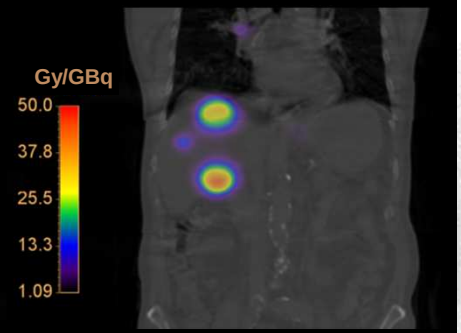
^{177}Lu-DOTA-JR11 (antagonist)

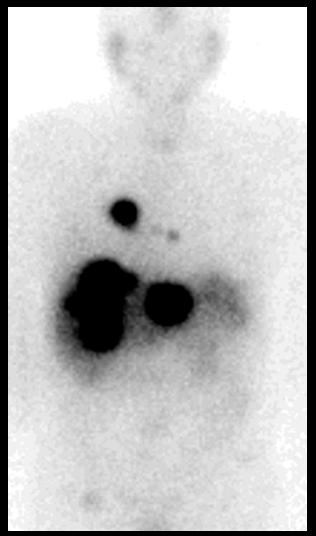
^{177}Lu-DOTA-JR11 therapy

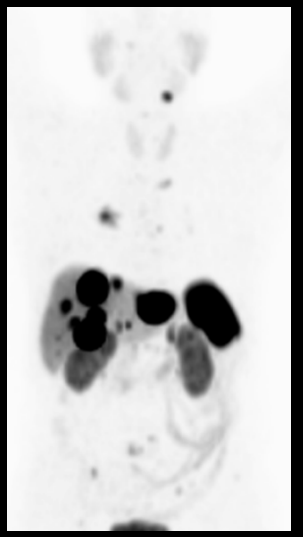
Follow-up ^{68}Ga-DOTA-TATE PET/CT







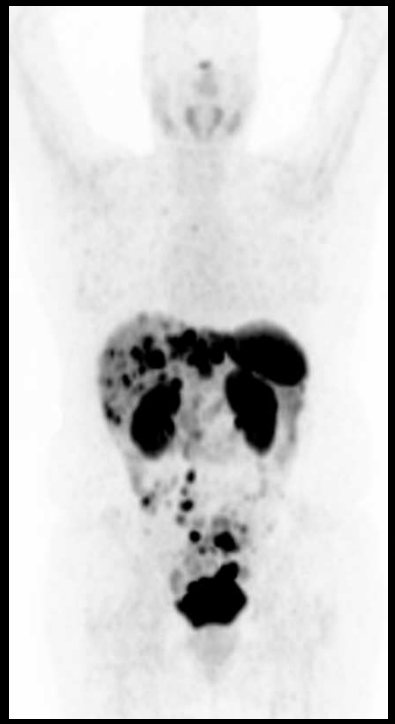




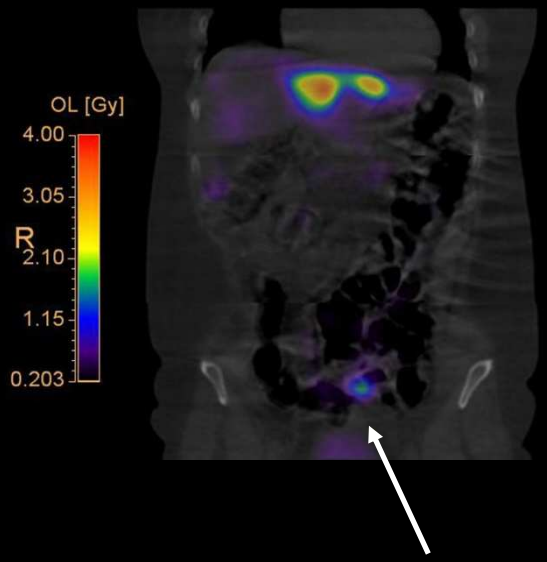
Comparison of ^{177}Lu-DOTA-TATE and ^{177}Lu-DOTA-JR11

Patient with metastatic ileal NET (G2), renal insufficiency grade III

^{68}Ga-DOTA-TATE PET
"baseline"



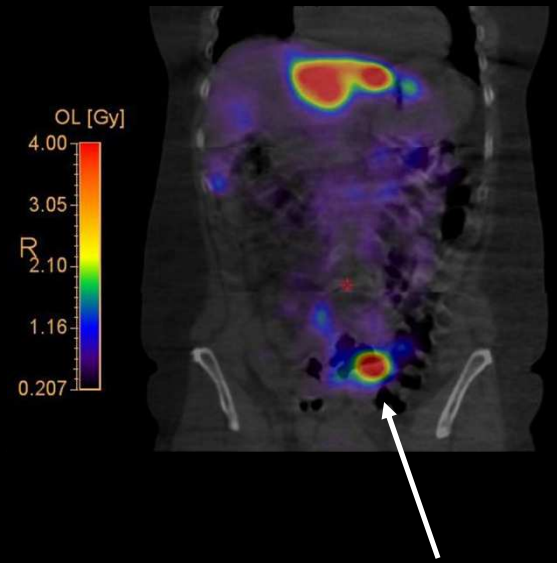
^{177}Lu-DOTA-TATE
(Agonist) Isodose curves



mean dose: 0.5 Gy/GBq

31 Gy/62 GBq

^{177}Lu-DOTA-JR11
(Antagonist) Isodose curves



mean dose: 5.3 Gy/GBq

31 Gy/5.9 GBq

^{68}Ga-DOTA-TATE PET
"follow-up"

Comparison of ^{177}Lu-DOTA-TATE and ^{177}Lu-DOTA-JR11

n = 4 patients with progressive neuroendocrine tumors (NETs), dosimetry results are based on 3D voxel-dosimetry analysis

	Patient 1	Patient 2	Patient 3	Patient 4	**Median (inter quartile range)**
Pre-treatment dosimetry: Comparison of the mean radiation dose to tumors (Gy/GBq)					
^{177}Lu-DOTA-TATE	1,1- 2,0	5,6 - 13	0,5 - 2,7	1,5 - 4,6	**2,0 (1,2-4,6)**
^{177}Lu-DOTA-JR11	5,7 - 7,4	16 - 29	4,8 - 5,9	4,2 - 20	**7,0 (5,7-16)**
Treatment dosimetry: Mean total radiation dose to tumors (Gy)					
^{177}Lu-DOTA-JR11	23 - 59	283 - 487	33 - 130	39 - 302	**47 (37-283)**
Treatment outcome: Response according to RESIST version 1.1					
^{177}Lu-DOTA-JR11	Mixed response	PR	SD	PR	
Treatment toxicity: Toxicity according to WHO Common Toxicity Criteria version 2.0					
Hematologic toxcitiy	Grade 2	Grade 3	Grade 2	Grade 2	**Grade 2**

Wild et al. J Nucl Med, 2014, 55:1248-1252

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Summary and conclusion

- Somatostatin receptor PET is superior to Octreoscan. It is indicated for surgery planning/staging of patients with NETs (G1/G2).
- Targeting of multiple somatostatin receptors might be superior to targeting of sst_2 receptors only. Further evaluation is needed.
- PRRT is a palliative systemic therapy for patients with somatostatin receptor positive advanced NETs who show progression.
- The theranostik approach can select patients who benefit most of PRRT. The treatment benefit is tumor dose dependent.
- Further improvement of somatostatin receptor imaging and PRRT seems possible, e.g. with the use of somatostatin receptor antagonists instead of agonists. Further evaluation is needed.

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Coworkers

MDs: **G. Nicolas**, Ch. Rottenburger, F. Kaul, O. Maas, M. Braun, T. Baumann, A. Sauter, M.

Radiochemistry: Prof. Th. Mindt, **M. Fani,** A. Baumann and coworkers

Med. Physics/Dosimetry: L. McDougall

Technicians: M. Nagy and coworkers

Nurses: M. Speiser and coworkers

Assistant / Logistics: B. Avis, A. Guggiana, Ch. Evard

Collaboration

J.C. Reubi, University of Bern, Switzerland
P.J. Ell, M.A. Caplin, University College London, London, GB
H.R. Mäcke, University Hospital Freiburg, Germany
H. Bouterfa, Octeopharm GmbH, Berlin, Germany

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Thank you for your attention