Targeting the GRPR with Radiolabeled NeoB for Theranostic Purposes

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RADIOTRACER INTERACTIONS GROUP

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University Medical Center Rotterdam

Gastrin Releasing Peptide Receptor (GRPR)

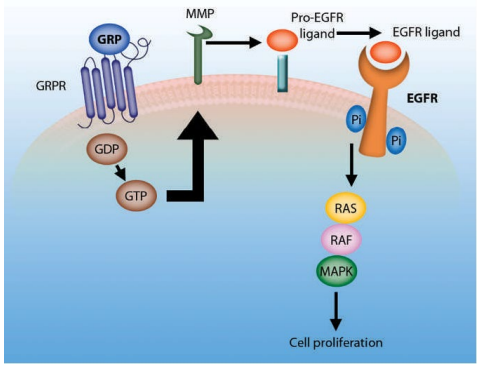
- Family of Bombesin receptors (BBR)
- BB2R
- Glycosylated 7-transmembrane G-protein coupled receptor
- Phospholipase C signaling pathway

Physiological expression

- Pancreas, gastric, respiratory, and nervous systems, endocrine glands and muscle

Physiological function

- Smooth muscle contraction, secretion of gastric acid, regulation of body temperature, glucose intake, secretion of neuropeptides and hormones and regulation of synaptic transmission



Overexpression in various cancers including prostate cancer, breast cancer, lung cancer, gastrointestinal stromal tumors (GIST), pancreatic cancer and neuroblastomas/glioblastomas

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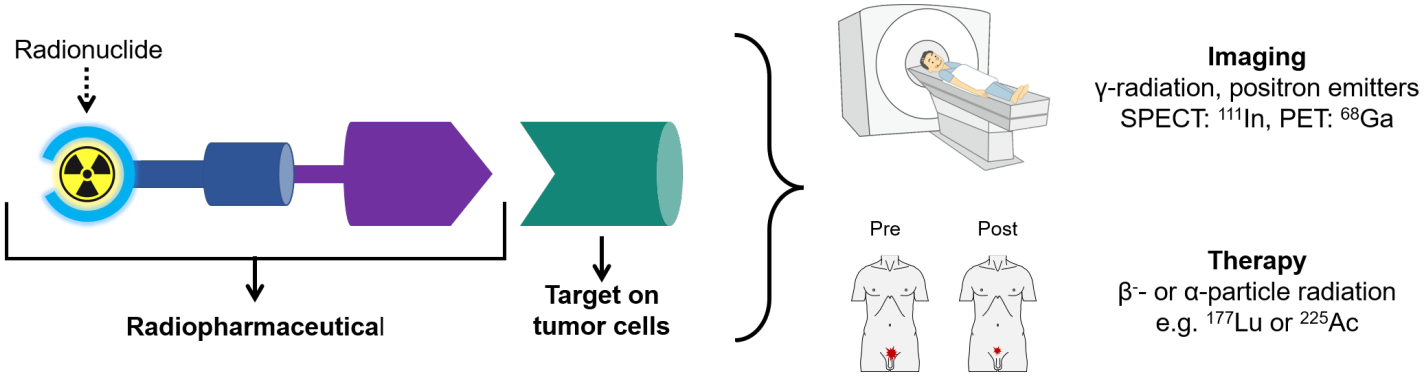
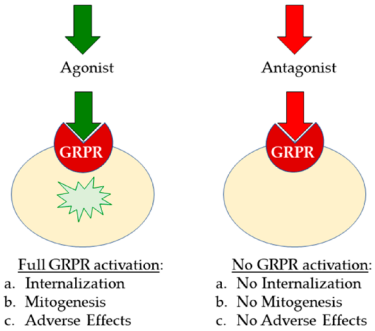
GRPR-mediated Radionuclide Theranostics



GRPR radiopharmaceuticals tested in the clinic	
Agonists	**Antagonists**
[^{99m}Tc]Tc-RP527 [^{99m}Tc]Tc-DB4 [^{68}Ga]Ga-AMBA/ [^{177}Lu]Lu-AMBA	[^{99m}Tc]Tc-DB15 [^{68}Ga]Ga-SB3 [^{68}Ga]Ga-RM2/[^{177}Lu]Lu-RM2 [^{68}Ga]Ga-RM26 [^{68}Ga]Ga-NeoBOMB1/[^{177}Lu]Lu-NeoBOMB1 [^{64}Cu]Cu-CB-TE2A



Mansi et al. Cancers 2021

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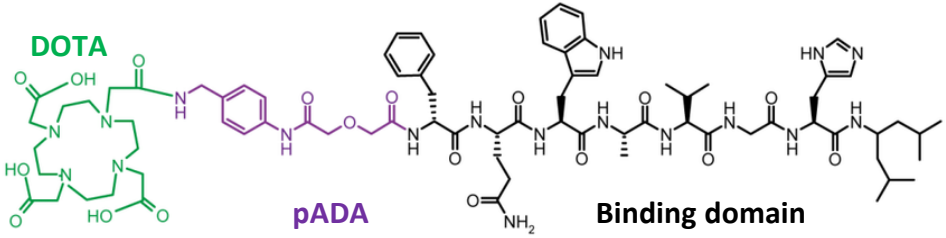
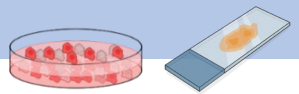
NeoBOMB1, NeoB

- Antagonist
- DOTA-coupled
- ^{68}Ga, ^{111}In and ^{177}Lu-labeled NeoB
- Mostly studied in Prostate Cancer, Breast Cancer and GIST (models)
- Preclinical *In vitro* and *In vivo* evaluations
- Clinical studies ongoing



Molecule development

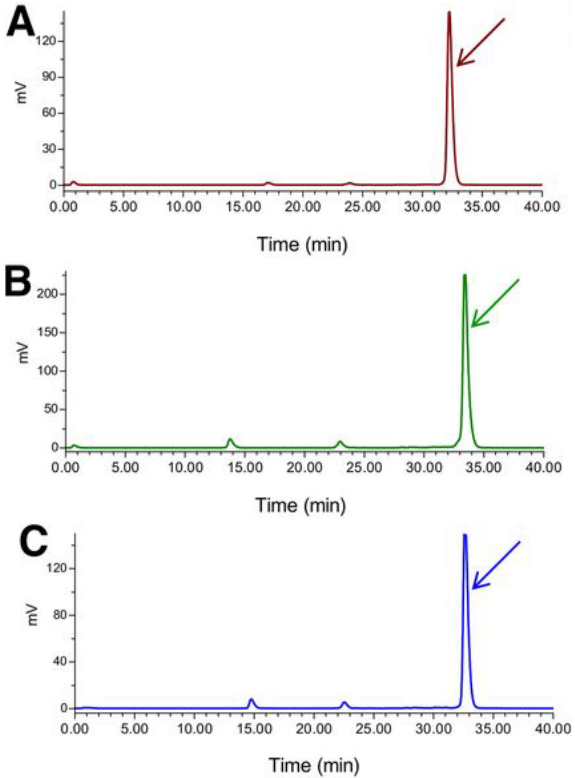
In vitro
- **Radiolabeling**
- **Stability**
- **Affinity**
- **Binding capability**



In vivo
- **Imaging**
- **Biodistribution**
- **Pharmacokinetics**
- **Efficacy**
- **Safety**

Clinical translation

Stability, Affinity and Binding Capability



Red = Gallium (^{Nat}Ga, ^{67}Ga)

Green = Indium (^{Nat}In, ^{111}In)

Blue = Lutetium (^{Nat}Lu, ^{177}Lu)

Human prostate cancer cells: PC-3

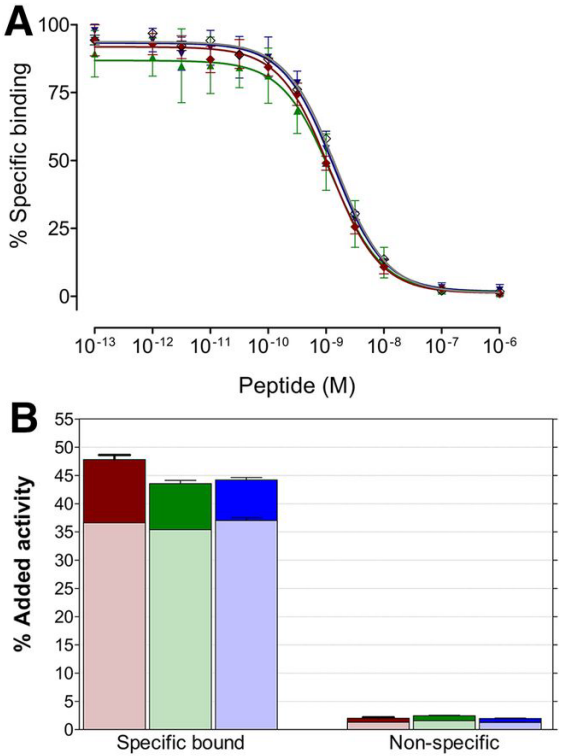
Competition binding assay: [^{125}I]I-Try^{4}-BBN

Internalization assay:

Block: Tyr^{4}-BBN

: Membrane

: Internalized



Nock et al. J Nucl Med 2017

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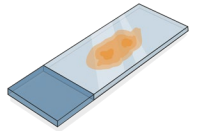
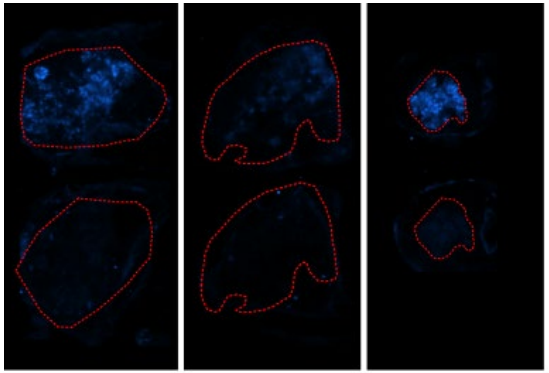
Binding Capability



H&E staining

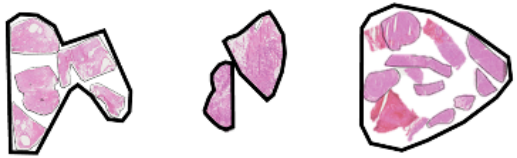
Prostate Cancer

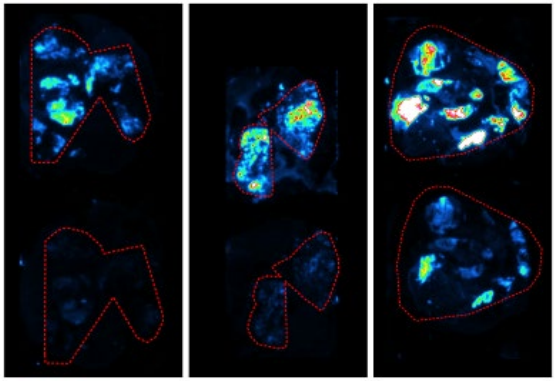


- block

+ block (Tyr^4-BBN)

GIST





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Unpublished data

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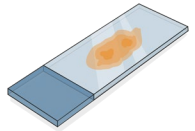
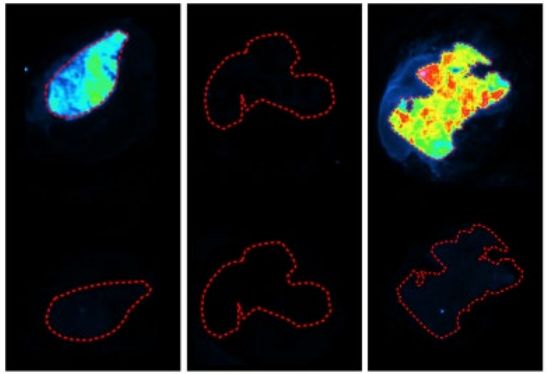
Binding Capability



H&E staining

Breast cancer



- block

+ block (Tyr^4-BBN)

Unpublished data

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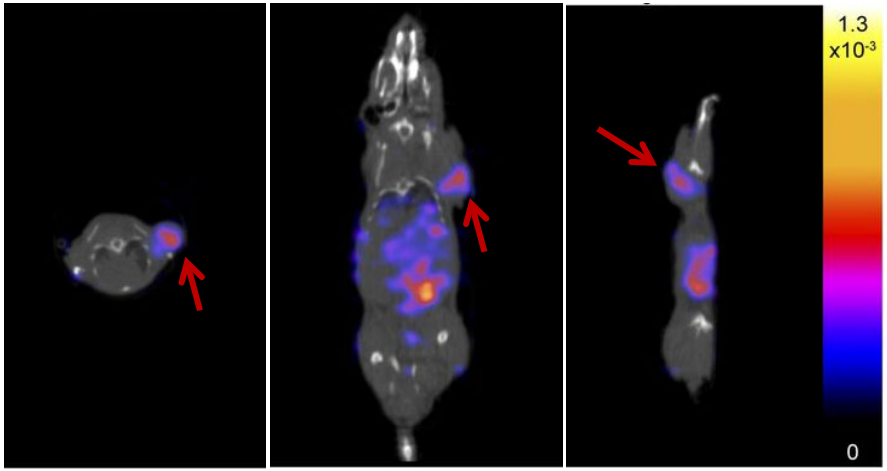
In Vivo Imaging

PC-3 xenografted mice

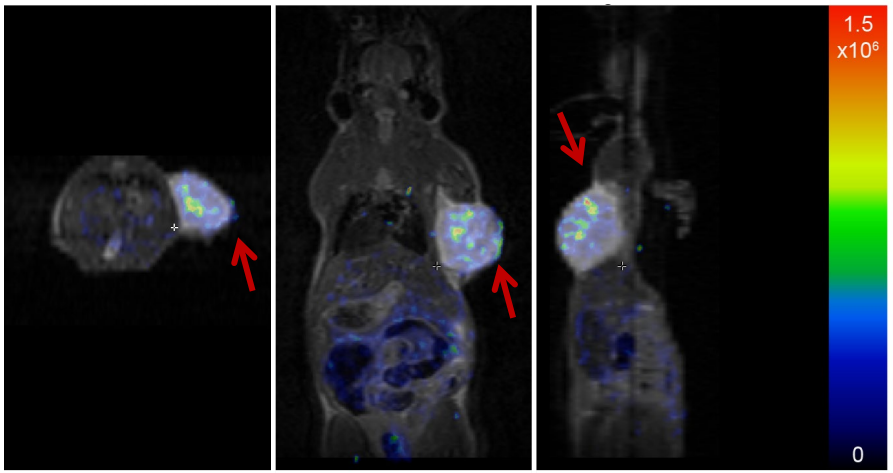
PET/CT
13 MBq/230 pmol [^{68}Ga]Ga-NeoB

Transveral view | Coronal view | Sagital view



SPECT/MRI
20 MBq/200 pmol [^{177}Lu]Lu-NeoB

Transveral view | Coronal view | Sagital view



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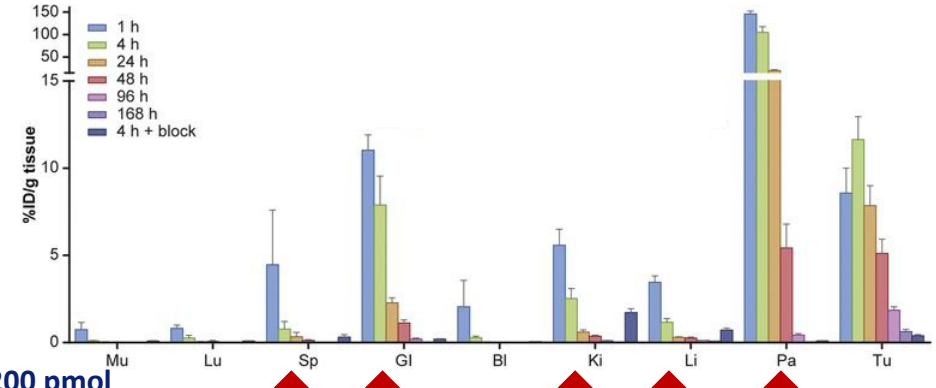
Dalm SU et al. J Nucl Med 2017

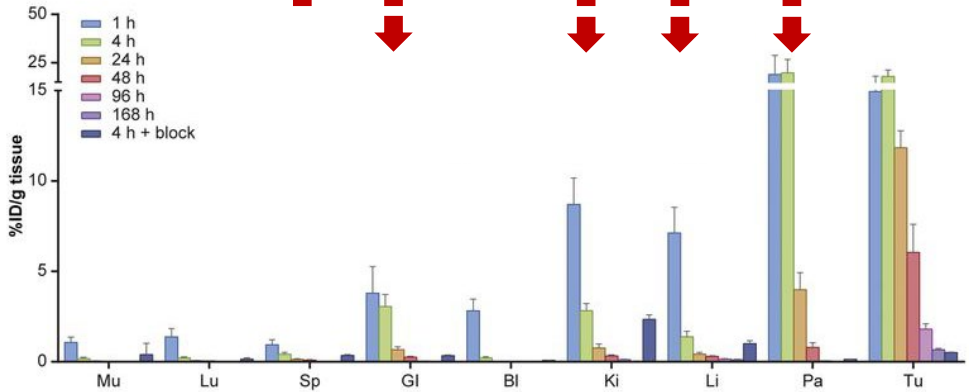
Biodistribution [^{177}Lu]Lu-NeoB

PC-3 xenografted mice

10 pmol



200 pmol



			D(tumor)/D(organ)	
Organ	10 pmol	200 pmol	10 pmol	200 pmol
Tumor	435	570	-	-
Kidneys	58	57	7,5	10
Pancreas	1393	265	0,31	2.15

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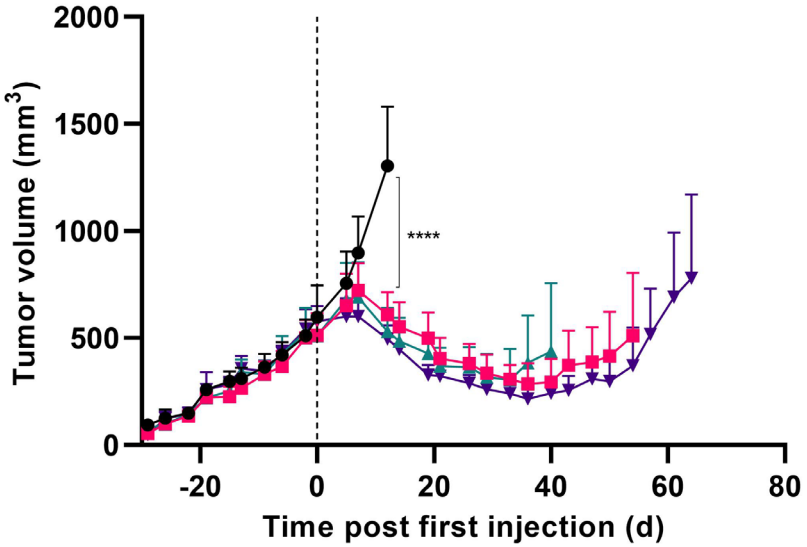
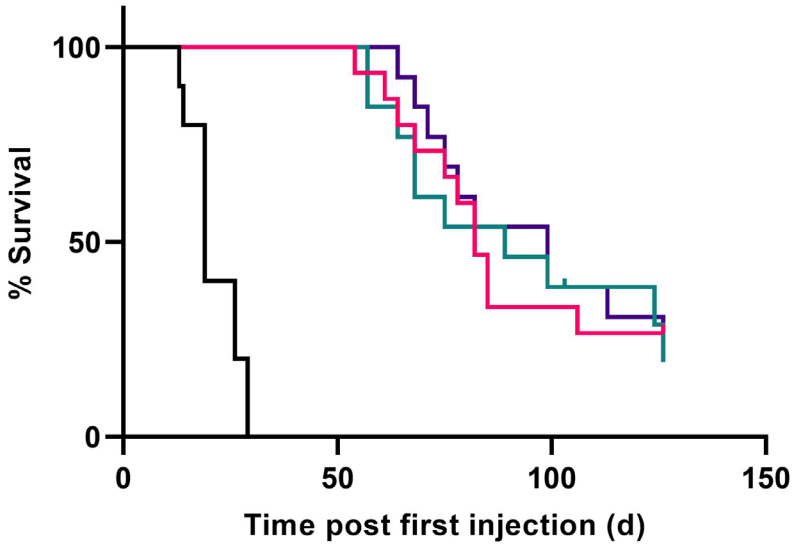
Dalm SU et al. J Nucl Med 2017

Therapeutic Efficacy [^{177}Lu]Lu-NeoB

PC-3 xenografted mice





Control
Group 1 30 MBq/300 pmol
Group 2 40 MBq/400 pmol
Group 3 60 MBq/600 pmol

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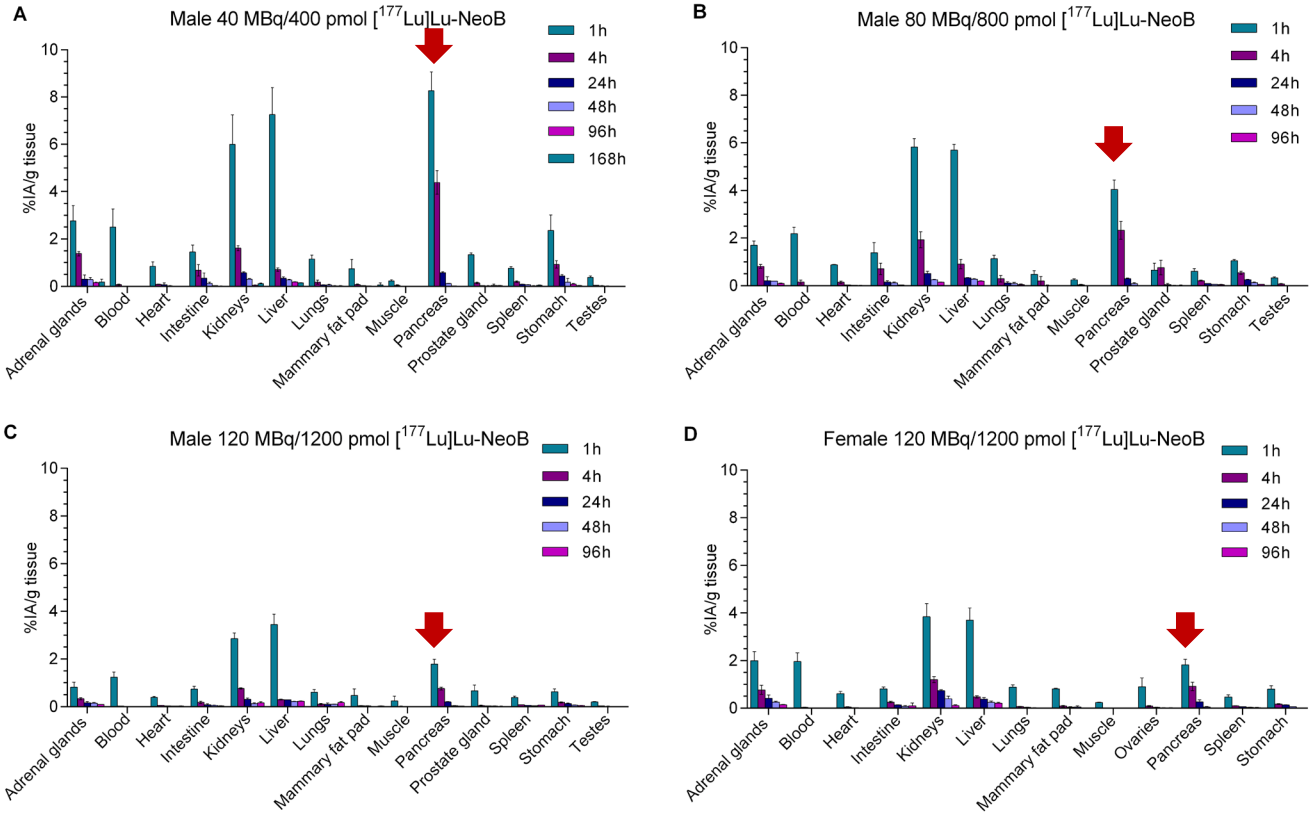
Verhoeven M et al. Mol Imaging Biol 2023

Extensive Dosimetry and Safety



Non-tumor bearing mice

Male vs Female

Dose and schedule:
40 MBq/400 pmol
80 MBq/800 pmol
120 MBq/1200 pmol

3 injections, 1 x per week

Direct, early and late organ toxicity

Ruigrok et al. Eur J Nucl Med Mol Imaging 2022

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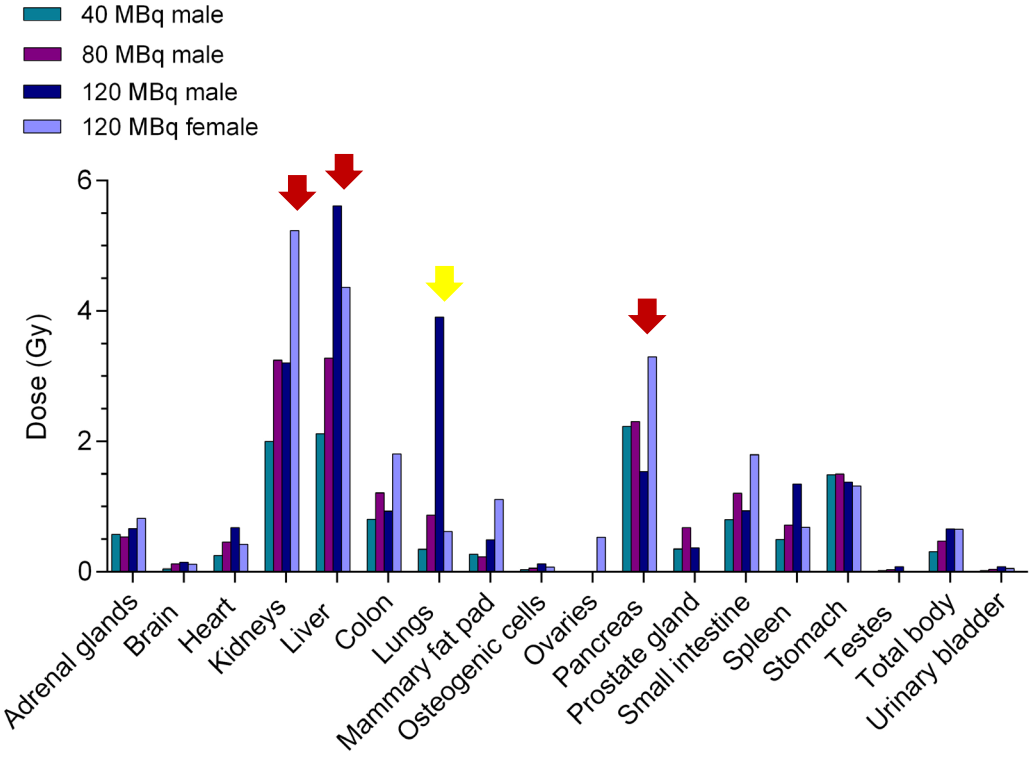
Extensive Dosimetry and Safety

Non-tumor bearing mice



No relevant changes in weight

Histopathology:

Week 5:

- Cytoplasmic vacuolation of urothelial cells in bladder (with inflammatory cell infiltrates in the submucosa)

Week 19:

- Hydronephroses (with ureteral dilatation), mild nephropathy

Week 43:

- Marked or severe hydronephrosis (with associated occasional mild nephropathy and ureteral dilation)
- Marked ovarian atrophy, uterine and vaginal atrophy

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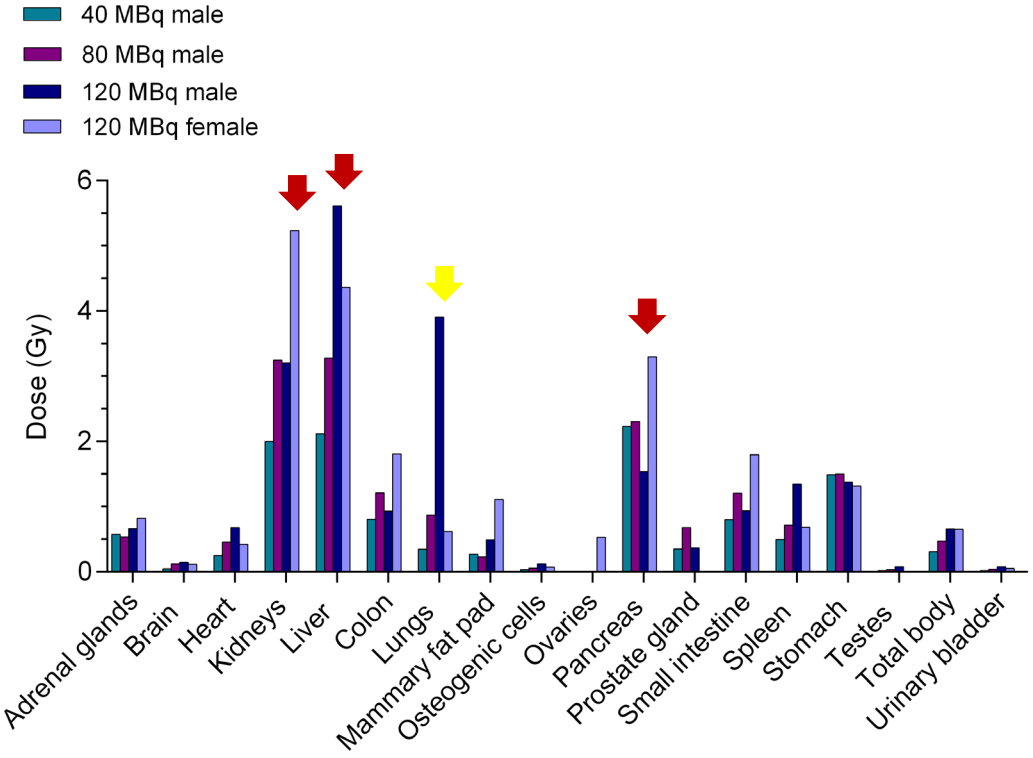
Ruigrok et al. Eur J Nucl Med Mol Imaging 2022

Extensive Dosimetry and Safety

Non-tumor bearing mice



Blood analysis:

- Transient drop in WBC (week 5)
- Abnormalities in urea nitrogen level

Ruigrok et al. Eur J Nucl Med Mol Imaging 2022

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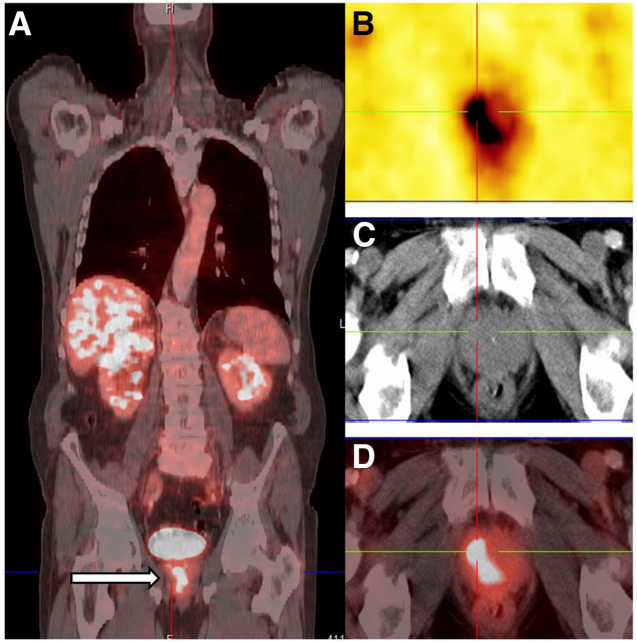
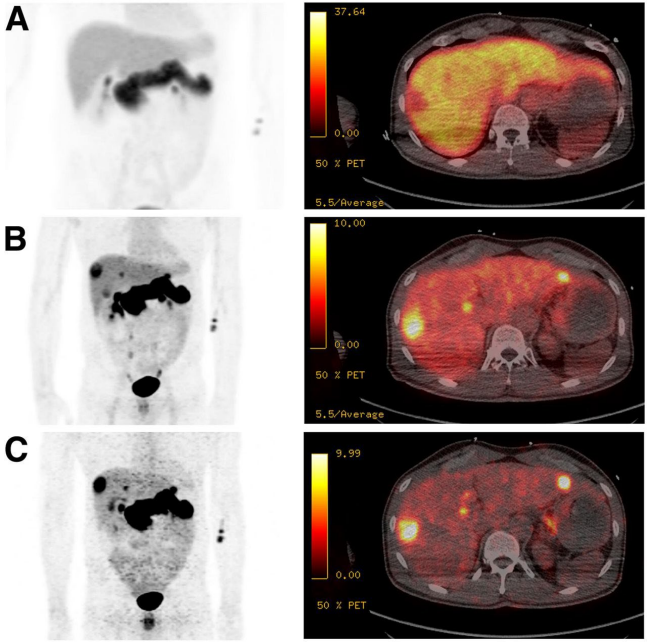
First Clinical Studies with [^{68}Ga]Ga-NeoB

Prostate Cancer



69 y-old male patient
Gleason score: 8 [4+4], PSA: 6.33 ng/mL

GIST



55 y-old male patient, GIST of ileum and histologically verified liver metastases

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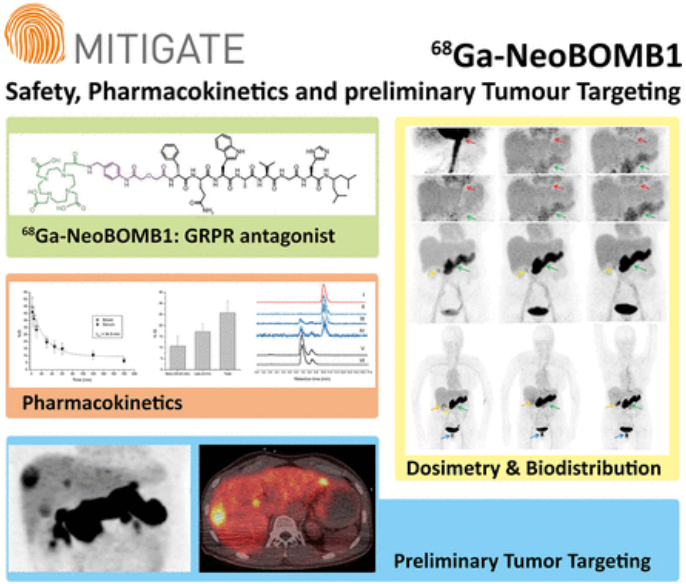
Nock et al. J Nucl Med 2017, Gruber et al. J Nucl Med 2020

Clinical Translation

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Completed	MITIGATE-NeoBOM: A Study to Evaluate 68Ga-**NeoBOMB1** in Patients With Advanced TKI-treated GIST Using PET/CT	• Gastrointestinal Stromal Tumors	• Drug: 68Ga-**NeoBOMB1**, 2-vial kit	• Medical University Innsbruck Innsbruck, Tirol, Austria
2	☐	Active, not recruiting	Gallium Ga 68 DOTA-**NeoBOMB1** and Gallium Ga 68 PSMA-R2 PET/MRI in Diagnosing Participants With Recurrent Prostate Cancer	• Prostate Adenocarcinoma • PSA Progression • Recurrent Prostate Carcinoma	• Drug: Gallium Ga 68 DOTA-**NeoBOMB1** • Device: Gallium Ga 68 PSMA-R2	• Stanford Cancer Institute Palo Alto Palo Alto, California, United States
3	☐	Terminated Has Results	[68Ga]-**NeoBOMB1** Imaging in Patients With Malignancies Known to Overexpress Gastrin Releasing Peptide Receptor (GRPR)	• Breast Cancer • Prostate Cancer • Colorectal Cancer • (and 2 more...)	• Drug: [68Ga]-**NeoBOMB1**	• Medical University Innsbruck Department of Nuclear Medicine Innsbruck, Austria • University of Grenoble - Hopital Michallon, Service de Medicine Nucleaire La Tronche, France • University of Bordeaux, Unite TEP RECHERCHE - Hopital Xavier Arnozan Pessac, France



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KEY POINTS

QUESTION: Is the application of ^{68}Ga-NeoBOMB1 safe for PET imaging applications, and what are the pharmacokinetics, radiation dose, and imaging properties of this novel radiopharmaceutical?

PERTINENT FINDINGS: This study was designed as a phase I/IIa clinical trial, and the outcome of the first 6 patients is reported. ^{68}Ga-NeoBOMB1 showed an excellent safety profile, suitable pharmacokinetics, low radiation dose, and promising targeting properties in GIST tumors.

IMPLICATIONS FOR PATIENT CARE: ^{68}Ga-NeoBOMB1 is a promising radiotracer suitable for PET imaging of GRPR expression in oncologic patients and opens a pathway for translation into a therapeutic approach

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Clinical Translation

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2	☐	Active, not recruiting	Gallium Ga 68 DOTA-**NeoBOMB1** and Gallium Ga 68 PSMA-R2 PET/MRI in Diagnosing Participants With Recurrent Prostate Cancer			
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Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Pilot Trial to Assess 68Ga Bombesin PET/CT (**NeoB**) Imaging for Staging of Breast Cancer	• Breast Cancer	• Drug: [68Ga]GA-**NeoB**	• St Vincent's Hospital Sydney, New South Wales, Australia
2	☐	Not yet recruiting	Dose Finding Study of [177Lu]Lu-**NeoB** in Combination With RT and TMZ in Newly Diagnosed GBM.	• Newly Diagnosed Glioblastoma	• Drug: [177Lu]Lu-**NeoB** • Drug: [68Ga]Ga-**NeoB** • Other: Temozolomide	
3	☐	Not yet recruiting	[177Lu]Lu-**NeoB** in Combination With Ribociclib and Fulvestrant in Participants With ER+, HER2-, GRPR+ Breast Cancer	• Breast Cancer	• Drug: [68Ga]Ga-**NeoB** • Drug: [177Lu]Lu-**NeoB** • Drug: Ribociclib • (and 2 more...)	
4	☐	Recruiting	[177Lu]-**NeoB** in Patients With Advanced Solid Tumors and With [68Ga]-**NeoB** Lesion Uptake	• Neoplasms	• Drug: [177Lu]-**NeoB** • Drug: [68Ga]-**NeoB**	• City of Hope Duarte, California, United States • Stanford University Stanford, California, United States • John Hopkins University Baltimore, Maryland, United States • (and 10 more...)

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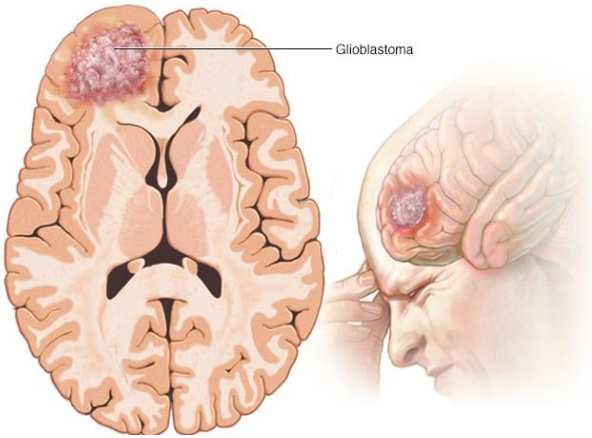
GRPR in Glioblastoma

Glioblastoma

- 77%-81% of all primary malignant CNS tumors (grade IV astrocytomas)
- Incidence rate: 0.59-5 per 100,000
- Median survival: ~14.6 months
- 5-year survival rate: <10 months



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Grech et al. Cureus 2020, Flores et al. Brain Res Bull 2010, Cao et al. Cancer Manag Res 2021

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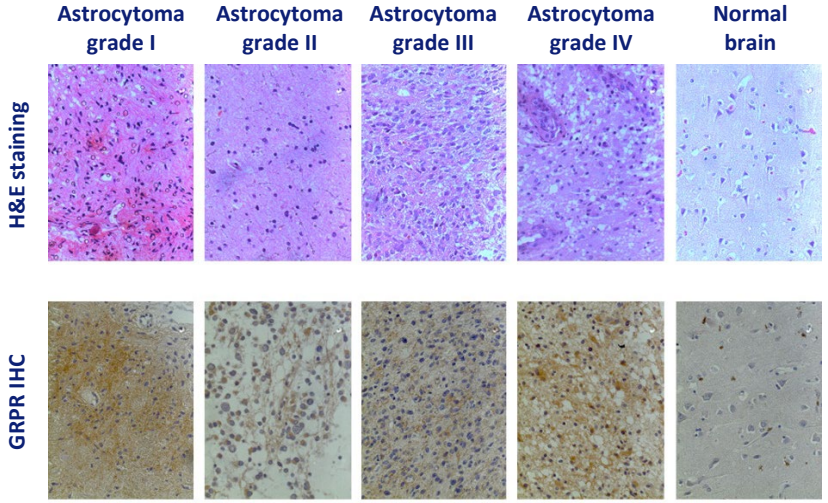
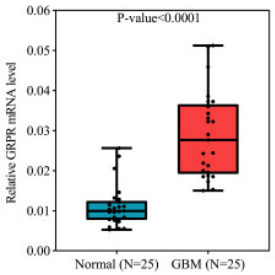
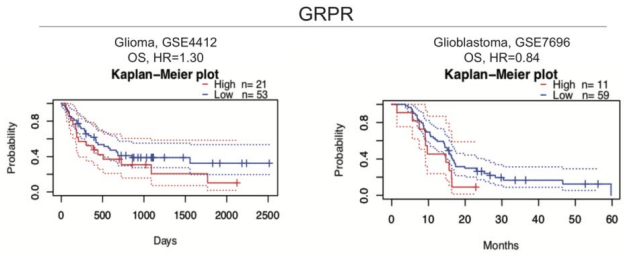
GRPR

- Stimulates growth and proliferation (autocrine manner)
- GRPR antagonists (e.g. RC-3095 +/- chemotherapies)
- GRPR drug conjugates (e.g. AN-215, dox based)
- **GRPR-mediated nuclear imaging of gliomas**







Grech et al. Cureus 2020, Flores et al. Brain Res Bull 2010, Cao et al. Cancer Manag Res 2021

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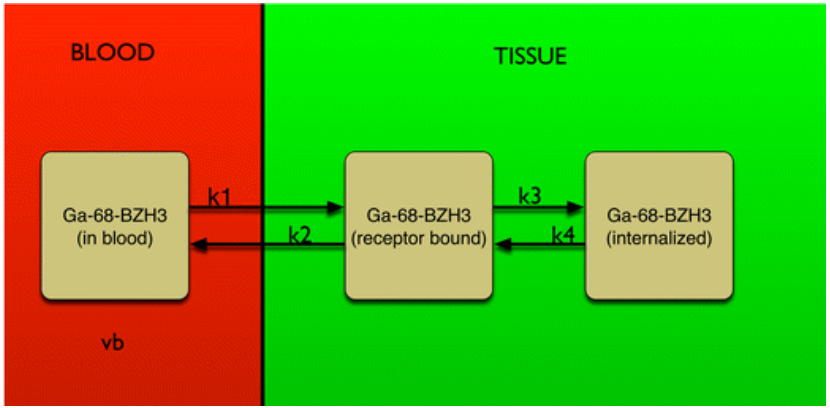
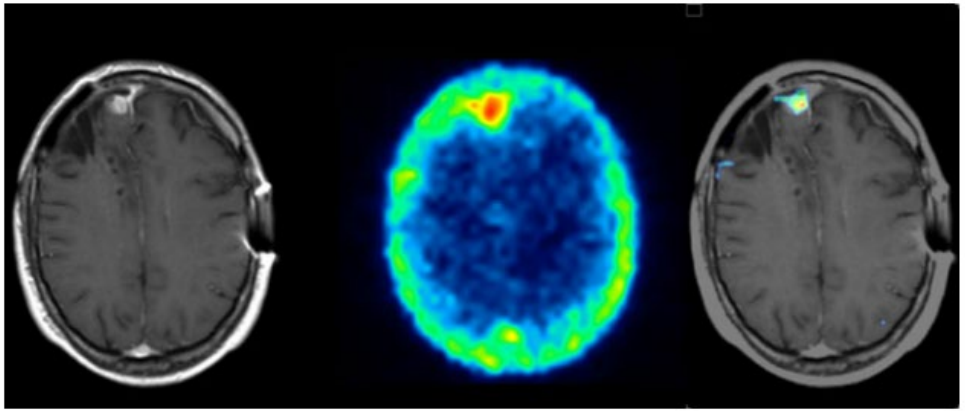
GRPR in Glioma Patients

- 7 patients
- [^{68}Ga]Ga-BZH$_3$ → **agonist (binds to all 3 BBR)**
- Focus on dynamics and kinetics
- Compared to gene array data



MRI **[^{68}Ga]Ga-BZH3 PET** **Fusion MRI/ Paramateric image k1**



The compartment parameter k1 was correlated with the expression of BB2 (r = 0.89), while k3, reflecting the internalization, revealed no significant correlation.

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Straus et al. Mol Imaging Biol 2012

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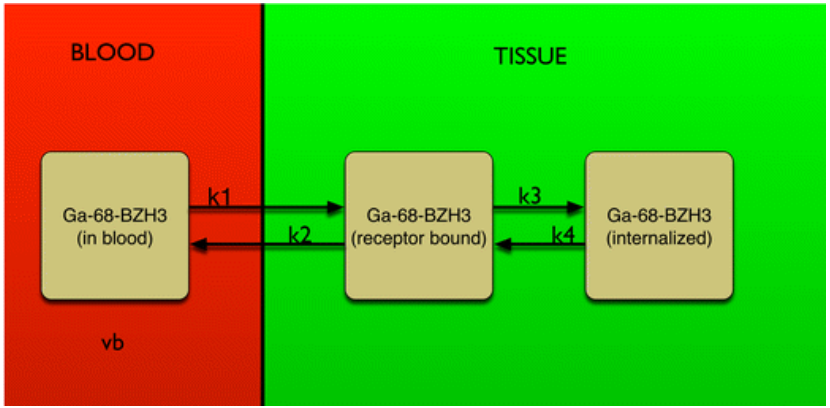

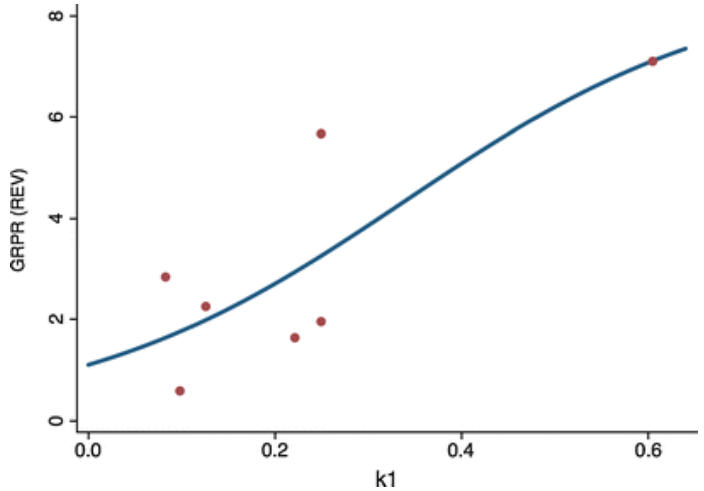

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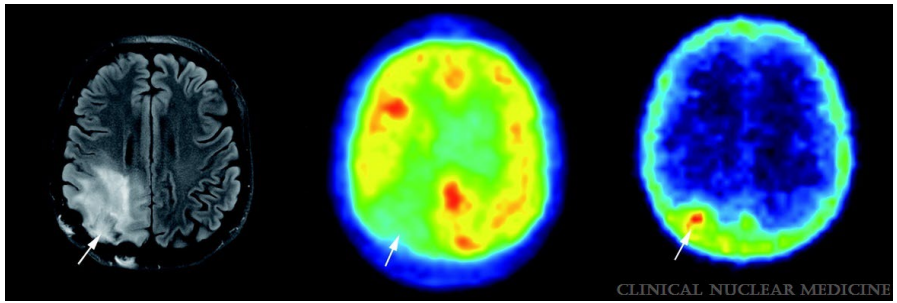
GRPR in Glioma Patients

- [^{18}F]FDG vs [^{68}Ga]Ga-BZH$_3$ in 15 patients (confirmed oligodendrogliomas and astrocytomas)
- Imaging vs Tumor grading

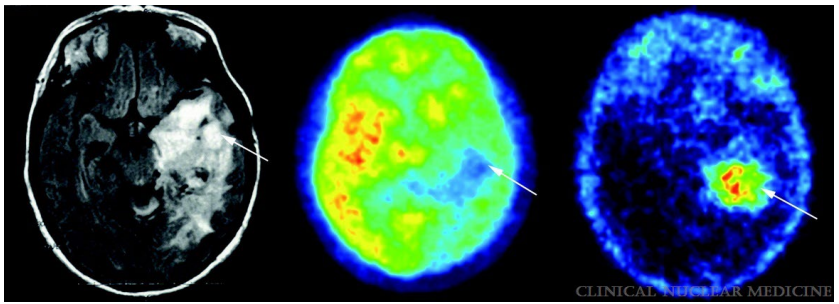
	[^{68}Ga]Ga-BZH$_3$-positive scans	Enhanced FDG metabolism
WHO II	3/6	3/6
WHO III	4/6	3/6
WHO IV	3/3	

3 patients with BBN positive scans also showed enhanced [^{18}F]FDG uptake

MRI [^{18}F]FDG [^{68}Ga]Ga-BZH$_3$



MRI [^{18}F]FDG [^{68}Ga]Ga-BZH$_3$



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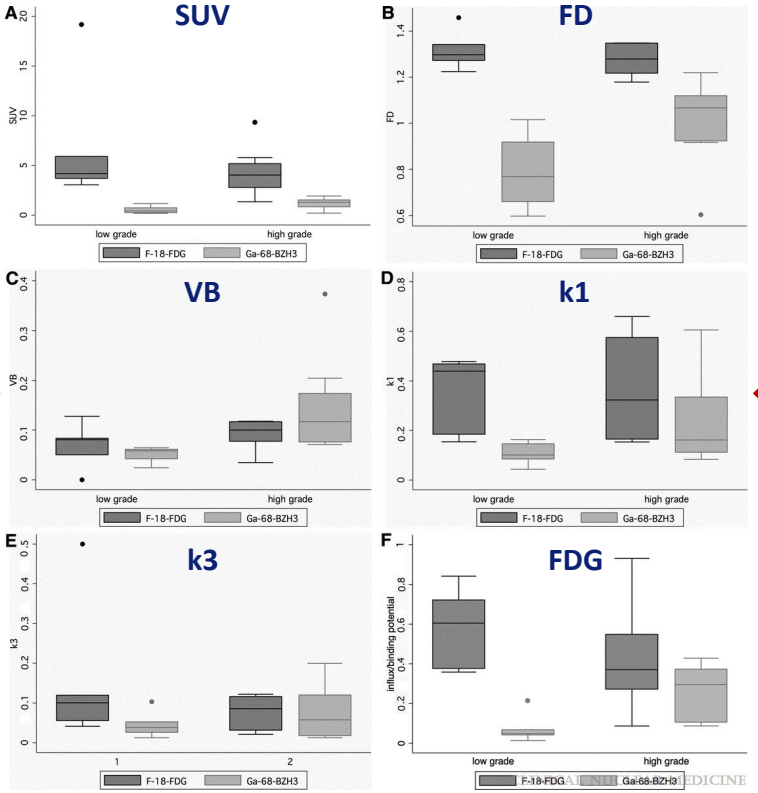
Dimitrakopoulou-Strauss et al. Clin Nucl Med 2011

GRPR in Glioma Patients



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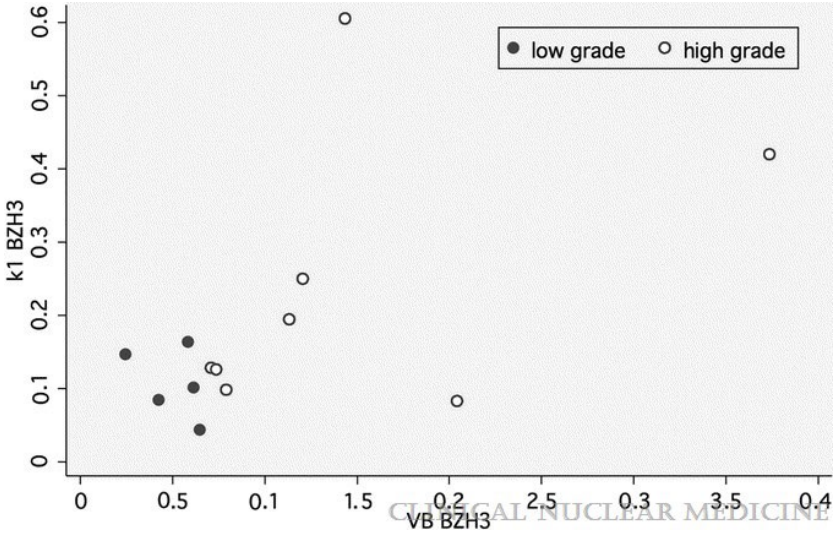

- Quantitative [^{68}Ga]Ga-BZH$_3$ studies are helpful for differentiation between high- and low-grade tumors
- [^{68}Ga]Ga-BZH$_3$ was more helpful than [^{18}F]FDG

Dimitrakopoulou-Strauss et al. Clin Nucl Med 2011

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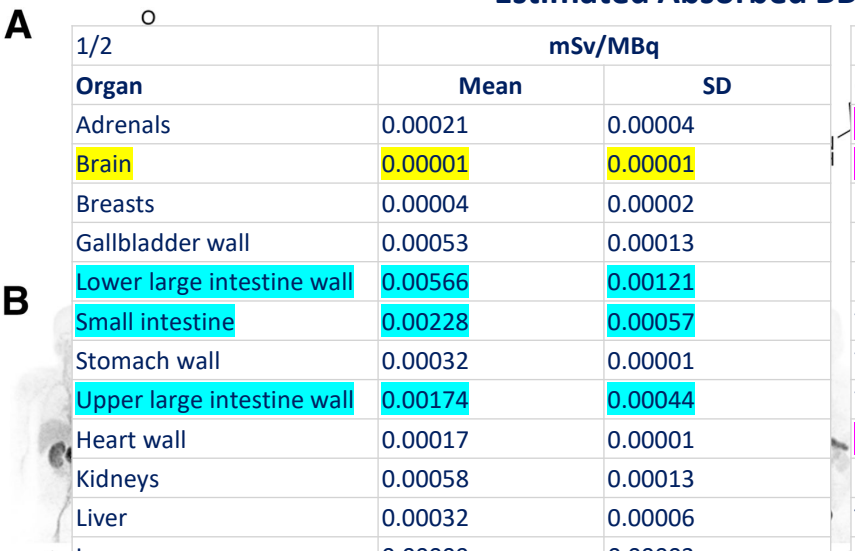
GRPR in Glioma Patients

- 4 healthy volunteers, 12 patients (14 lesions)
- [^{68}Ga]Ga-NOTA-Aca-BBN(7–14) → **agonist**

Estimated Absorbed BBN Dose in Healthy Volunteers

A

B



1/2	mSv/MBq	
Organ	**Mean**	**SD**
Adrenals	0.00021	0.00004
Brain	0.00001	0.00001
Breasts	0.00004	0.00002
Gallbladder wall	0.00053	0.00013
Lower large intestine wall	0.00566	0.00121
Small intestine	0.00228	0.00057
Stomach wall	0.00032	0.00001
Upper large intestine wall	0.00174	0.00044
Heart wall	0.00017	0.00001
Kidneys	0.00058	0.00013
Liver	0.00032	0.00006
Lungs	0.00009	0.00003
Muscle	0.00139	0.00025
Ovaries	0.00530	0.00124

2/2	mSv/MBq	
Organ	**Mean**	**SD**
Pancreas	0.00105	0.00015
Red marrow	0.00098	0.00022
Osteogenic cells	0.00058	0.00011
Skin	0.00050	0.00001
Spleen	0.00032	0.00007
Testes	0.01000	—
Thymus	0.00159	0.00177
Thyroid	0.00004	0.00001
Urinary bladder wall	0.30700	0.35559
Uterus	0.01310	—
Total body	0.00150	0.00029
Effective dose equivalent	0.03350	0.00790
Effective dose	0.02760	0.00660

Zhang et al. J Nucl Med 2016

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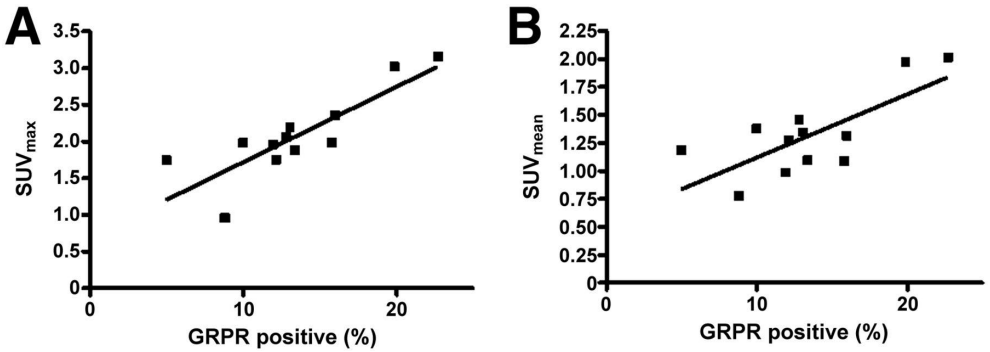
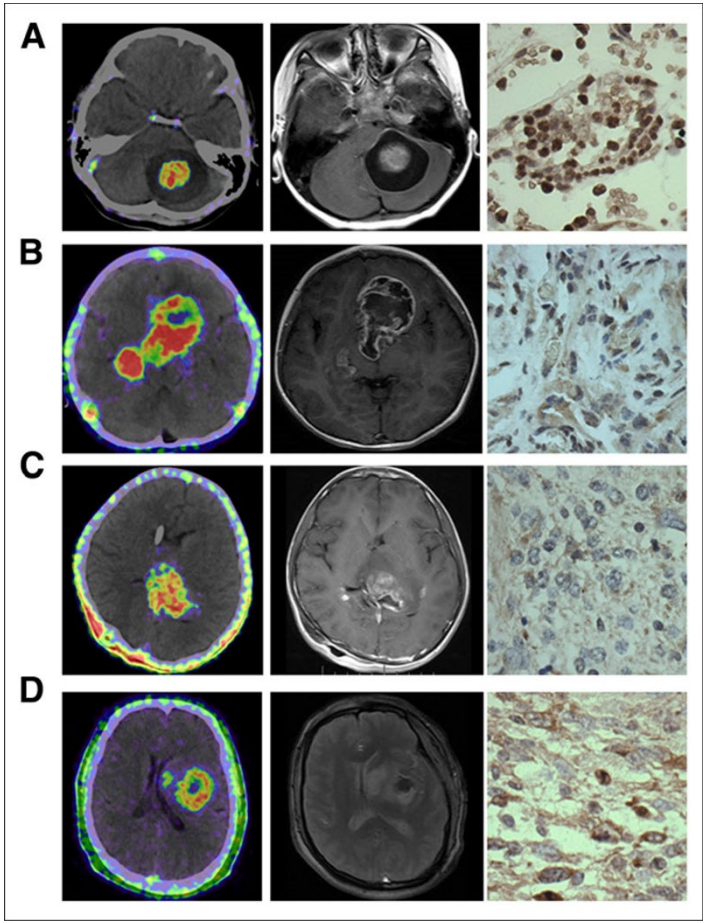
GRPR in Glioma Patients

- 4 healthy volunteers, 12 patients (14 lesions)
- [^{68}Ga]Ga-NOTA-Aca-BBN(7–14) → **agonist**
- **All lesions visualized**
- **Correlation with GRPR expression**





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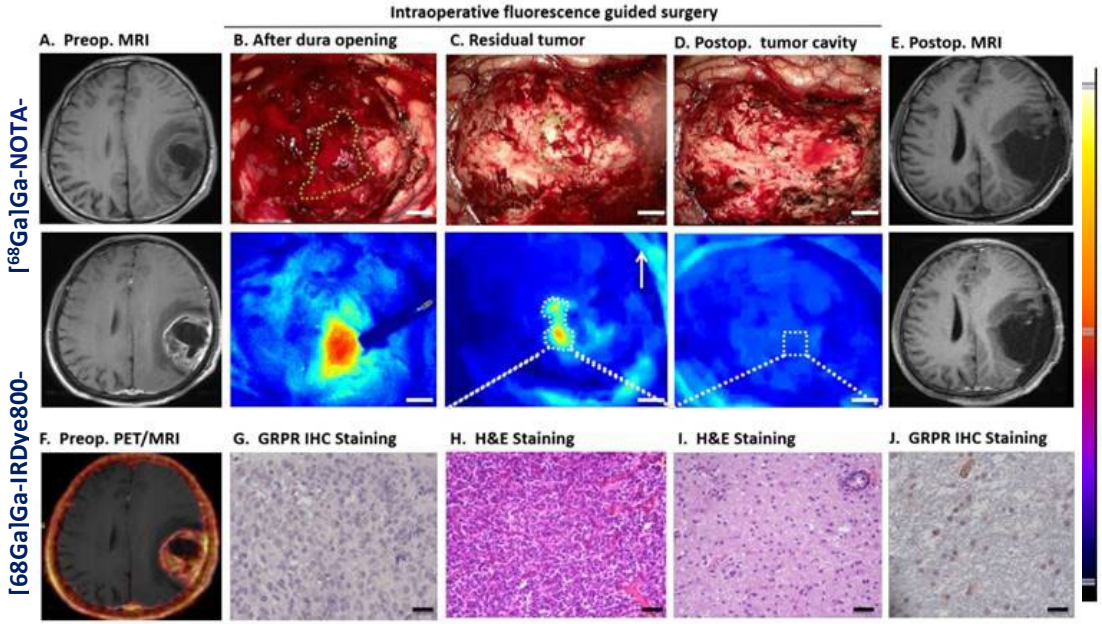
Zhang et al. J Nucl Med 2016

GRPR in Glioma Patients

- 14 Glioblastoma patients
- Image guided surgery
- [^{68}Ga]Ga-NOTA-BBN (7-14) and [^{68}Ga]Ga-IRDye800-NOTA-BBN (7-14)



- **Sensitivity: 93.9% (95% CI 79.8%-99.3%)**
  Specificity: 100% (95% CI 66.4%-100%)
- **The tracer was safe and resection was satisfactory**
- **No newly developed neurologic deficits**
- **PFS at 6 months: 80% (2 newly diagnosed patients achieved long PFS)**

Li et al. Theranostics 2018

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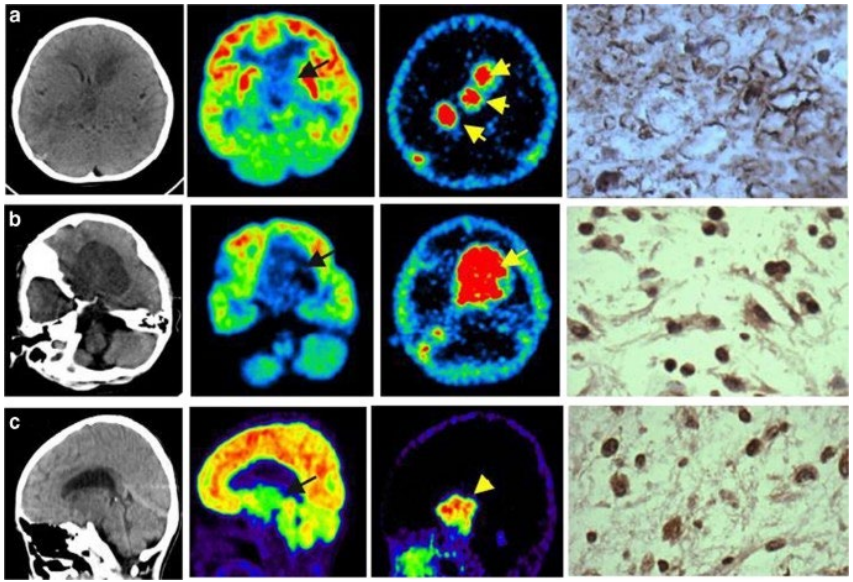
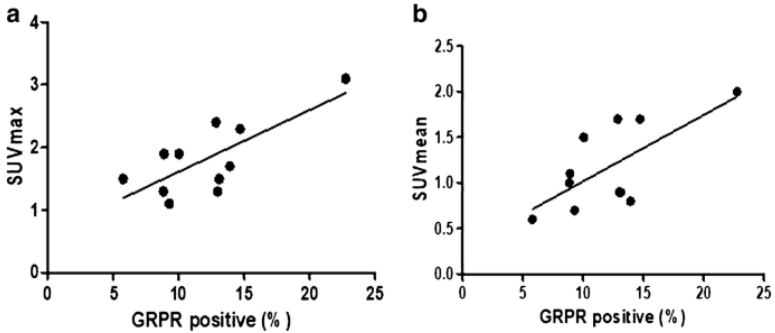
GRPR in Glioma Patients

- GRPR-mediated PET/CT and PET/MRI
- 8 Children (11 lesions)
- Optic pathway glioma
- [^{68}Ga]Ga-NOTA-Aca-BBN(7-14) scan (4 patients also underwent ^{18}F-FDG brain PET/CT)





Zhang et al. Eur J Nucl Med Mol Imaging 2019

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GRPR in Glioma Patients

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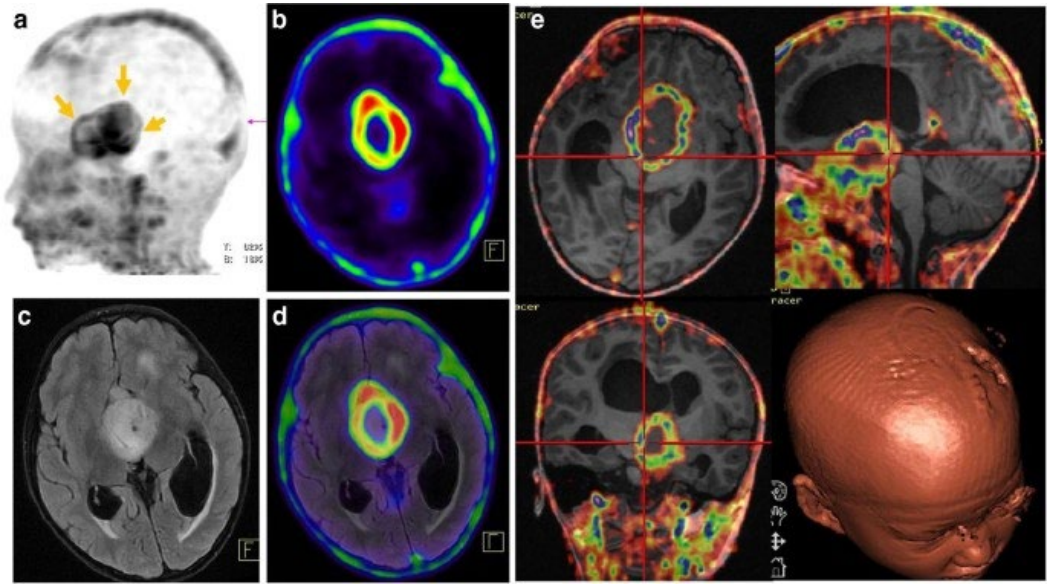

- **All lesions detected with [^{68}Ga]Ga-NOTA-Aca-BBN(7-14)**
- **PET/MRI may be helpful for assisting surgery planning in OPG patients**

Zhang et al. Eur J Nucl Med Mol Imaging 2019

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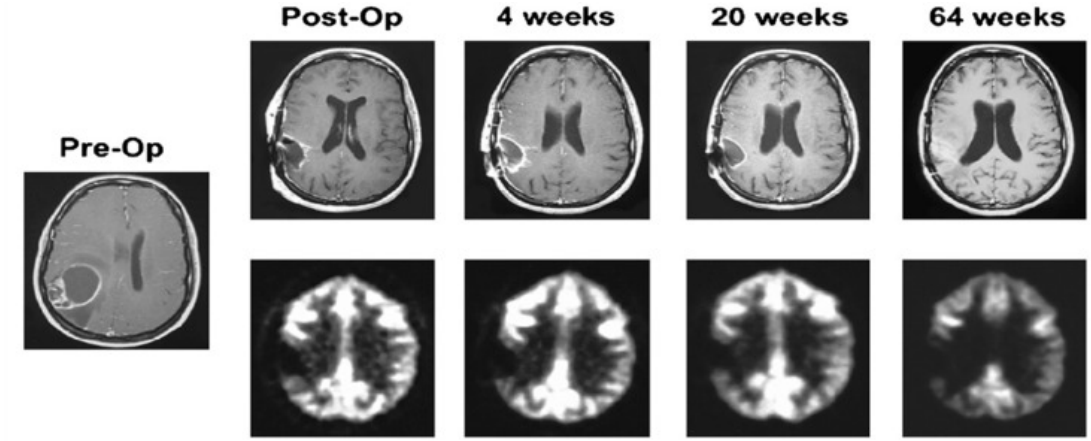
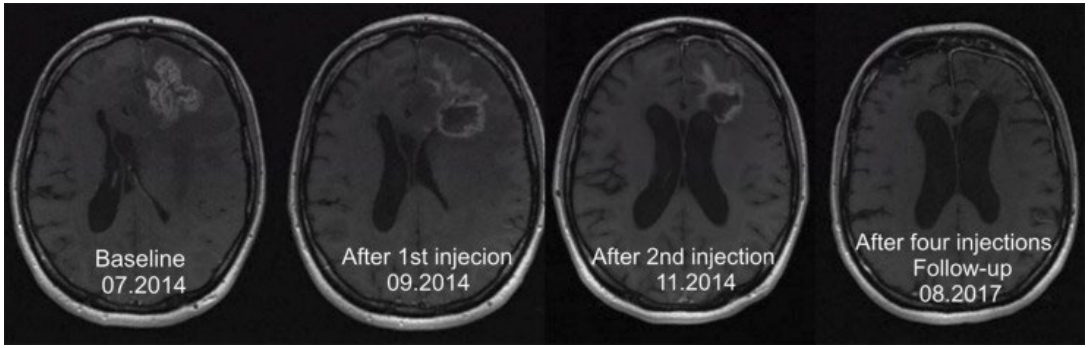
Targeted Radionuclide Therapy in Glioma Patients



- [^{131}I]I-ch81C6 (Tenascin)-targeted therapy
- Median survival increased by 20.6 months for newly diagnosed glioblastomas and 14.5 months for recurrent disease



- 32-y-old woman
- Astrocytoma WHO grade II, conversion into a secondary Glioblastoma
- 4 cycles of [^{213}Bi]Bi-DOTA-substance P
- Tumor shrinkage: 32%

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Reardon et al, J Nucl Med 2006, Królicki et al, Eur J Nucl Med Mol Imaging 2019

Ongoing studies

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Pilot Trial to Assess 68Ga Bombesin PET/CT (**NeoB**) Imaging for Staging of Breast Cancer	• Breast Cancer	• Drug: [68Ga]GA-**NeoB**	• St Vincent's Hospital Sydney, New South Wales, Australia
2	☐	Not yet recruiting	Dose Finding Study of [177Lu]Lu-**NeoB** in Combination With RT and TMZ in Newly Diagnosed GBM	• Newly Diagnosed Glioblastoma	• Drug: [177Lu]Lu-**NeoB** • Drug: [68Ga]Ga-**NeoB** • Other: Temozolomide	

Patients enrolled into this trial will be treated for **up to 32 weeks with the standard regimen TMZ and RT, combined with [177Lu]Lu-NeoB every 4 weeks**. In exceptional cases, where patients **tolerate and benefit from [177Lu]Lu-NeoB, they can receive up to 10 dose administrations, resulting in a treatment duration of up to 37 weeks**. During this period, regular safety and efficacy assessments are planned on a weekly basis. The **primary objective of this trial is to estimate the recommended dose of [177Lu]Lu-NeoB in combination with TMZ and RT in participants with newly diagnosed GBM and to characterize the safety and tolerability of this treatment**. For this reason, patients will be enrolled and treated in cohorts with **increasing dose levels and the totality of available data will be used to define the recommended dose**. In an **expansion cohort**, additional patients will be treated **to further characterize the safety and tolerability, as well as to collect preliminary efficacy data from this cohort**. Contrast enhanced MRI assessments are recommended to be repeated every 8 weeks and patient reported outcomes (PRO) questionnaires will be used to assess the effect of the study treatment on patient reported symptoms and tolerability. Following treatment, all patients will be followed for up to 5 additional years for safety, progression of disease and survival.

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Radiochemistry group

DEMOKRITOS

Advanced Accelerator Applications
A Novartis Company

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