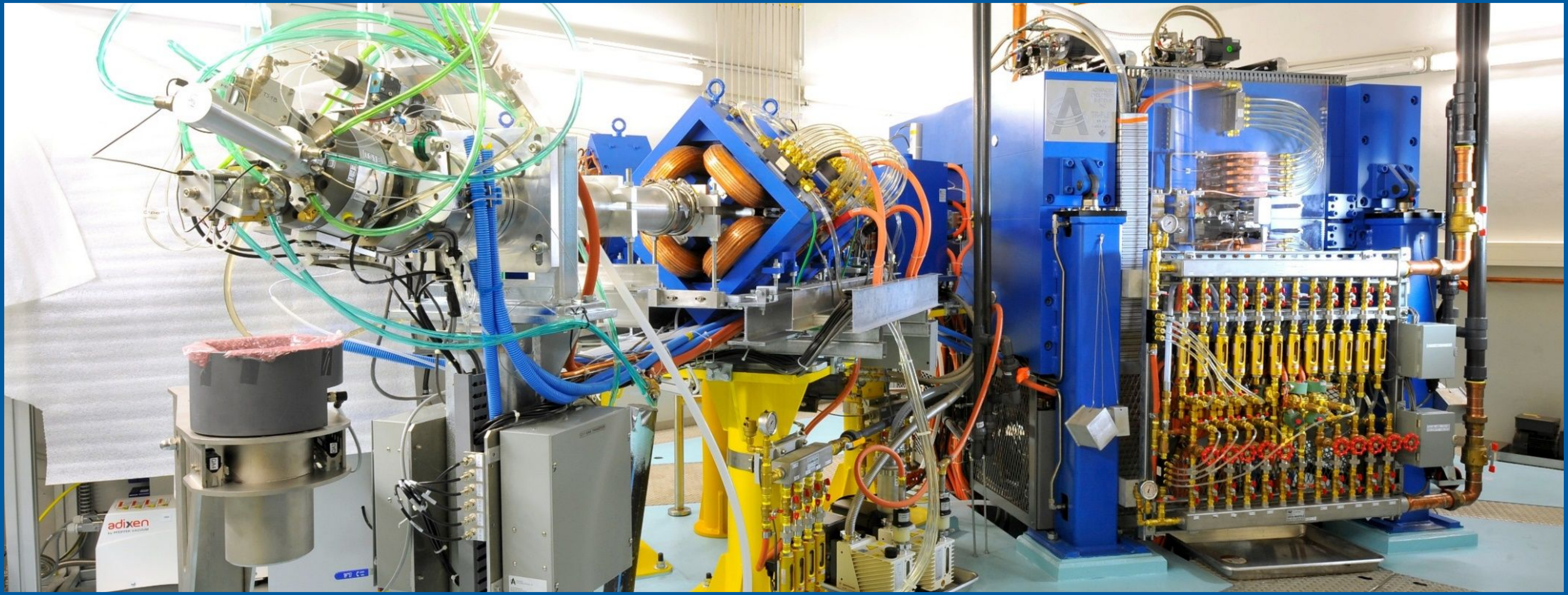
Radionuclide Theranostics through Radiopharmaceutical Sciences

Prof. Dr. rer. nat. Klaus Kopka · Institute of Radiopharmaceutical Cancer Research · k.kopka@hzdr.de · www.hzdr.de



9. Innnovationskongress Chemie, TUD/VCI Landesverband Nordost, Dresden, 31. Mai 2023

1923 Distribution of radioactive lead (ThB = ^{212}Pb) in horse-bean,

Hevesy G. Biochem J. 1923, 17, 439-445.

LIII. THE ABSORPTION AND TRANSLOCATION OF LEAD BY PLANTS.

A CONTRIBUTION TO THE APPLICATION OF THE METHOD OF RADIOACTIVE INDICATORS IN THE INVESTIGATION OF THE CHANGE OF SUBSTANCE IN PLANTS.

BY GEORGE HEVESY.

From the Institute of Plant Physiology of the Agricultural High School, and Institute of Theoretical Physics of the University, Copenhagen.

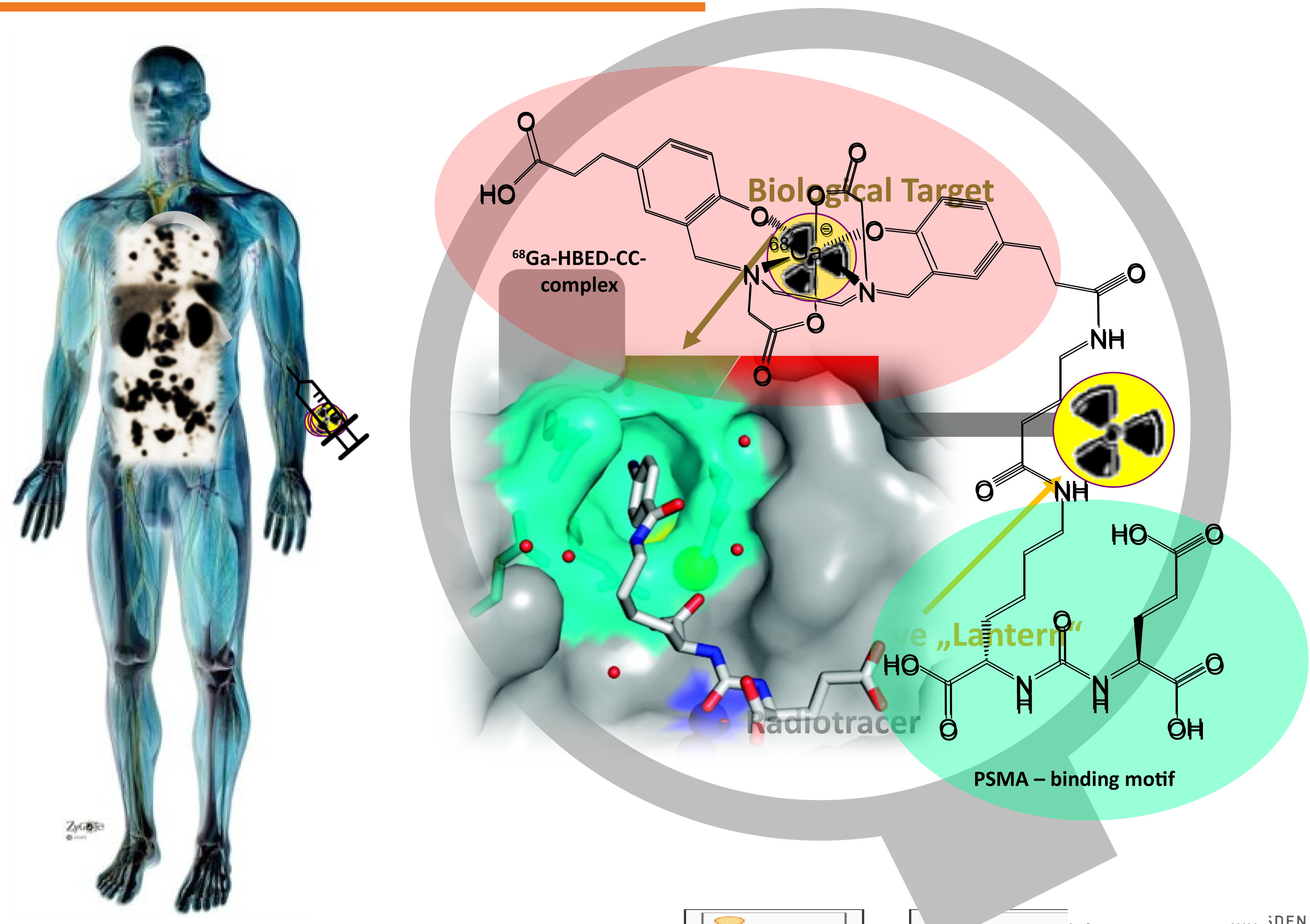
(*Received May 4th, 1923.*)

Georg Karl von Hevesy
(György Hevesy)
August 1st 1885 – July 5th 1966

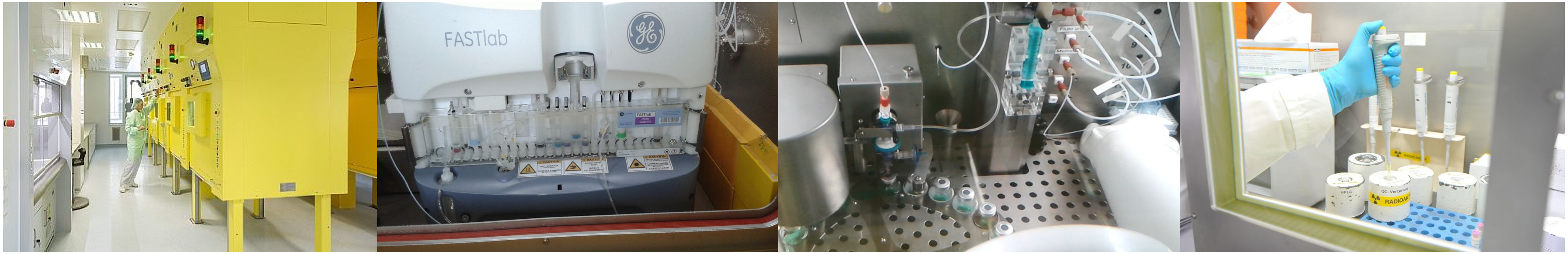
„By making use of radioactive indicators we can label atoms (ions), molecules and even larger units…; subsequently, their path and fate in the living organism can be followed."

Nobel Prize Chemistry 1943

Modern (Radio)Tracer Principle / Radioindicator Principle



GMP-compliant Production of Radiopharmaceuticals@HZDR 2022



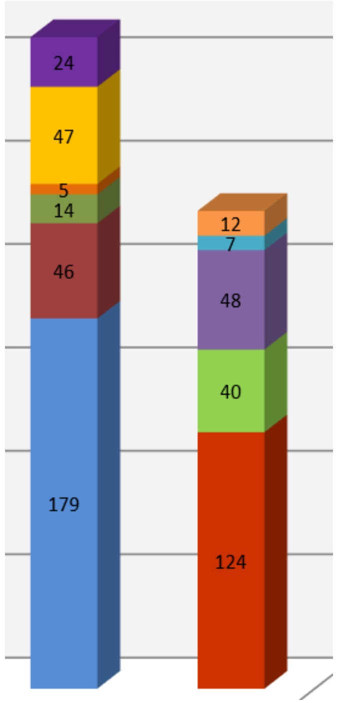
GMP
- 200 m^2 clean room area
- 12 hot cells (class C)
- 2 dispensing cells (class A)
- 8 automated synthesizers
- GMP certificate 2019

Projects with industry
- **GEHC**: approved manufacturing of ^{18}F-Flutemetamol (Vizamyl®)
- **ROTOP-Radiopharmacy**: cyclotron based production of ^{123}I-iodine as radionuclide

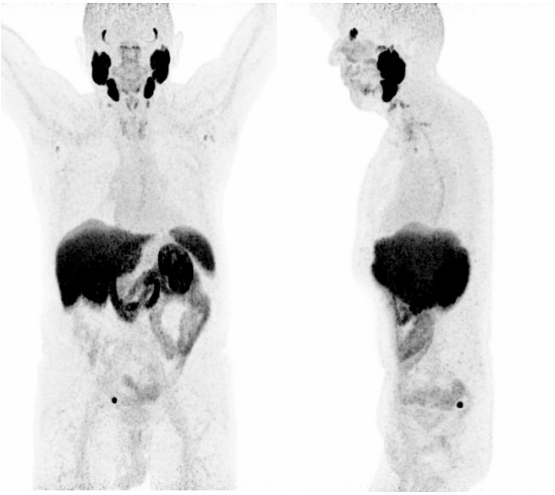
Radiopharmaceuticals produced in 2022 (315 batches)
- [^{18}F]FDG (GlucoRos)*) (179)
- [^{18}F]FDOPA (DOPARos)*) (46)
- Na[^{18}F]F (NaFRos)*) (5)
- [^{11}C]methionine (47)
- [^{18}F]PSMA-1007 (24)
- [^{18}F]Flutemetamol (14)

*) with marketing authorization

Cyclotron TRFlex (+231 batches)
- ^{123}I (124)
- ^{67}Cu (40)
- ^{64}Cu (48)
- ^{133}La (7)
- ^{131}Ba (12)



Recent developments
- transfer of [^{18}F]PSMA-1007 to University Hospital Dresden since 2020 (628 patients)



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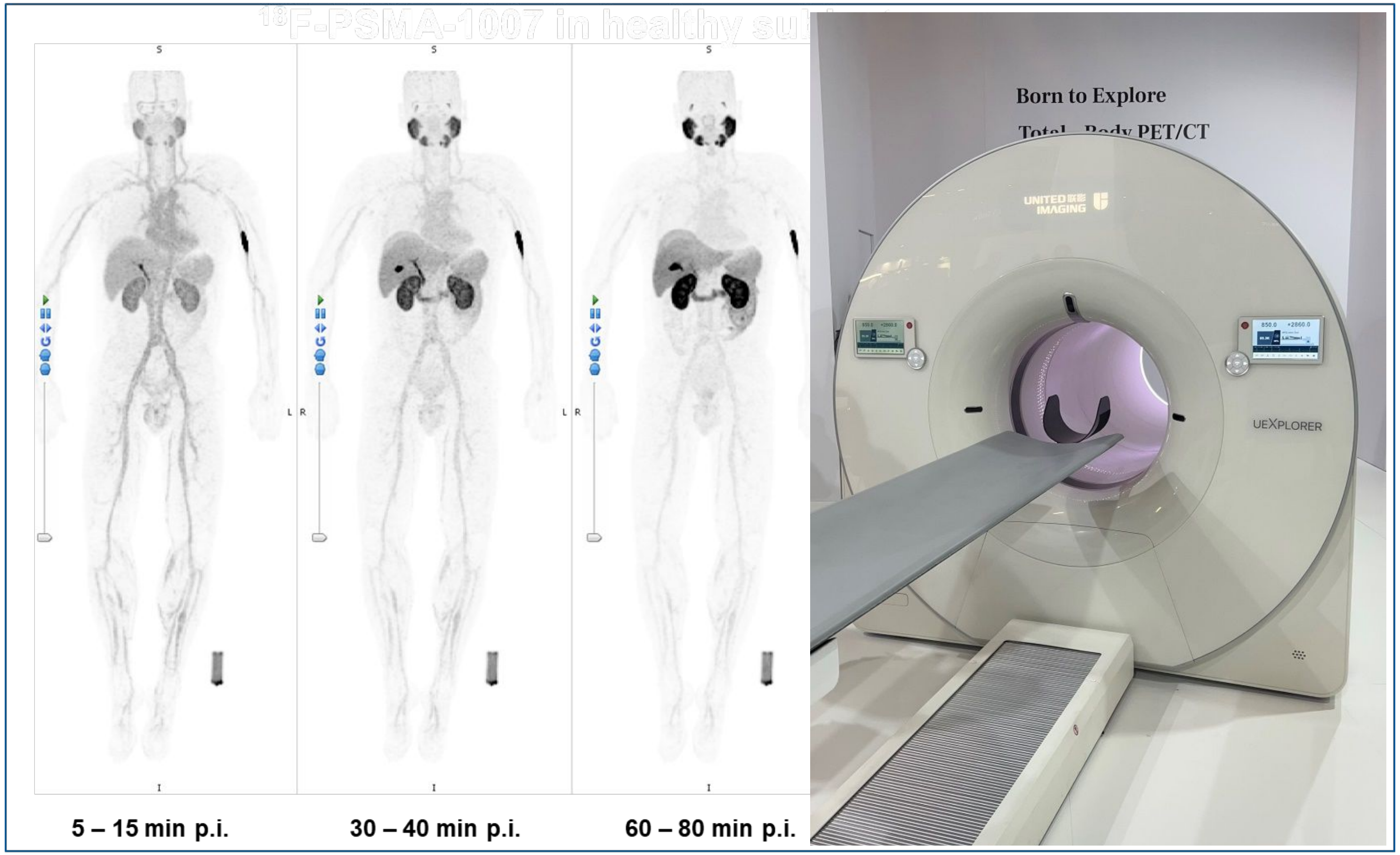
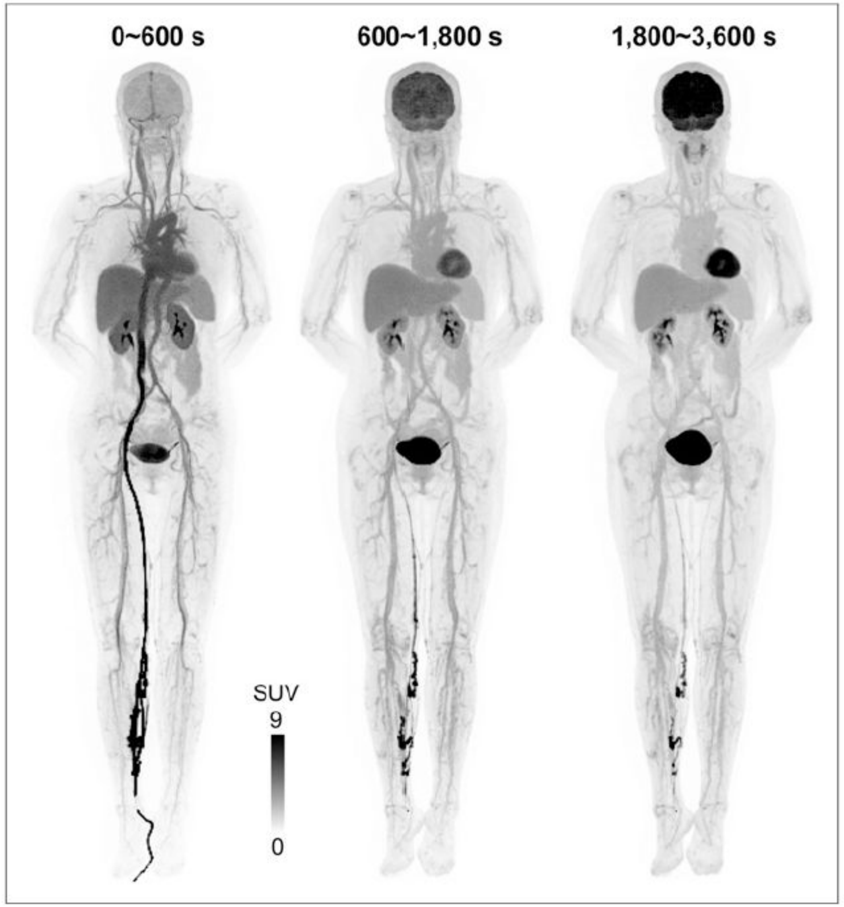
Translation into Total-Body PET/CT

Visionary future Technology: e.g. uEXPLORER

PET Tracer X

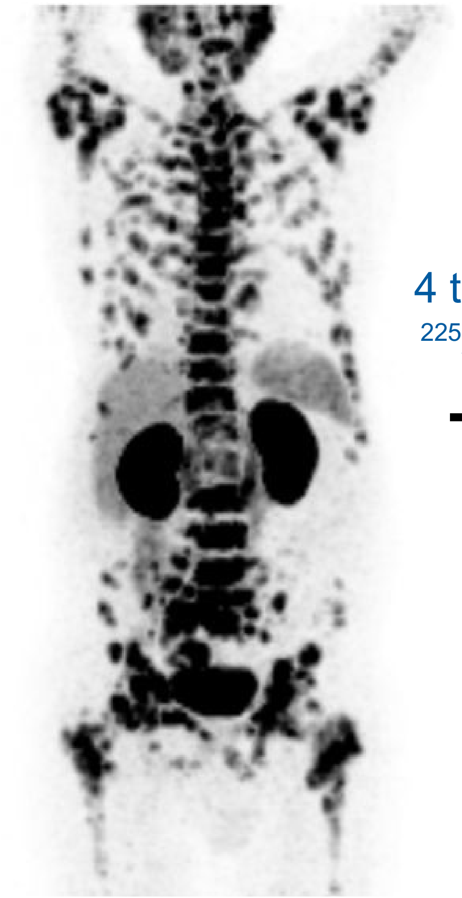


PET Tracer Y



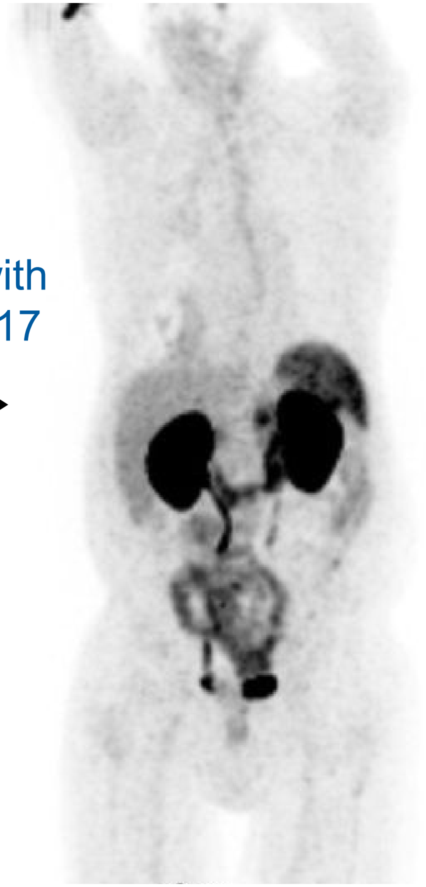
Zhang X et al. J Nucl Med 2020; 61:285–291; Badawi RD et al. J Nucl Med 2019; 60:299–303; https://usa.united-imaging.com; Giesel FL et al. Eur J Nucl Med Mol Imaging 2017 Apr;44(4):678-688.

Imaging & Therapy (TAT) [^{68}Ga]Ga-PSMA-11 & [^{225}Ac]Ac-PSMA-617



12/2014
PSA = 2923 ng/ml

4 treatments with
^{225}Ac-PSMA-617



9/2015
PSA < 0.1 ng/ml

Kratochwil C et al. J Nucl Med 2016;57:1941-1944.

THERANOSTICS

an emerging tool in drug discovery and commercialisation

The term theranostics was probably first used by PharmaNetics president and CEO John Funkhouser in describing his company's business model in developing diagnostic tests directly linked to the application of a specific therapies. In the case of PharmaNetics this takes the form of new generations of point of care coagulation tests supporting coagulation therapies:

Diagnostics – the ability to define a disease state.

Theranostics – the ability to affect therapy or treatment of a disease state.

Some examples of theranostics

CASE STUDY 1: Herceptin® and HercepTest® – the birth of Theranostics?

September 25, 1998 was a key day for theranostics.

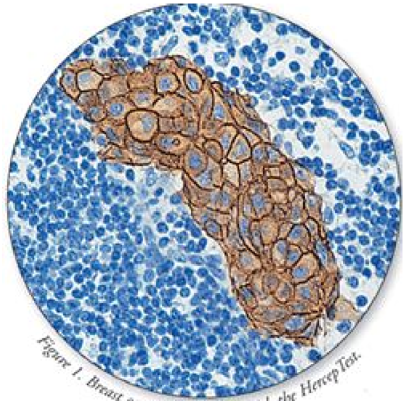


Figure 1. Breast carcinoma stained with the HercepTest.

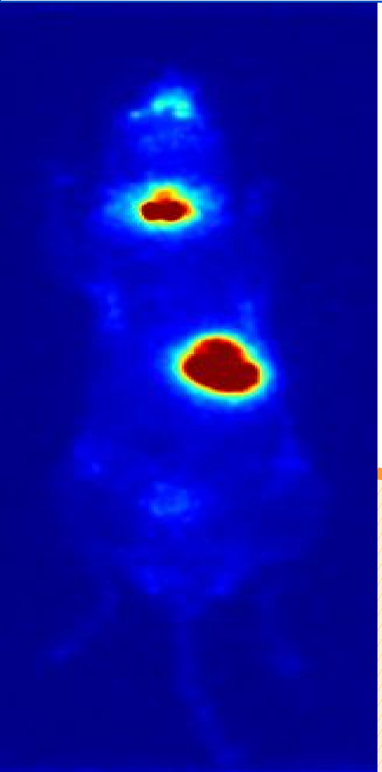
…On that day the FDA granted simultaneous approval for both **Genentech's Herceptin®** for the treatment of stage IV breast cancer and **Dako's HercepTest®** for diagnosis of Her2 overexpression…"

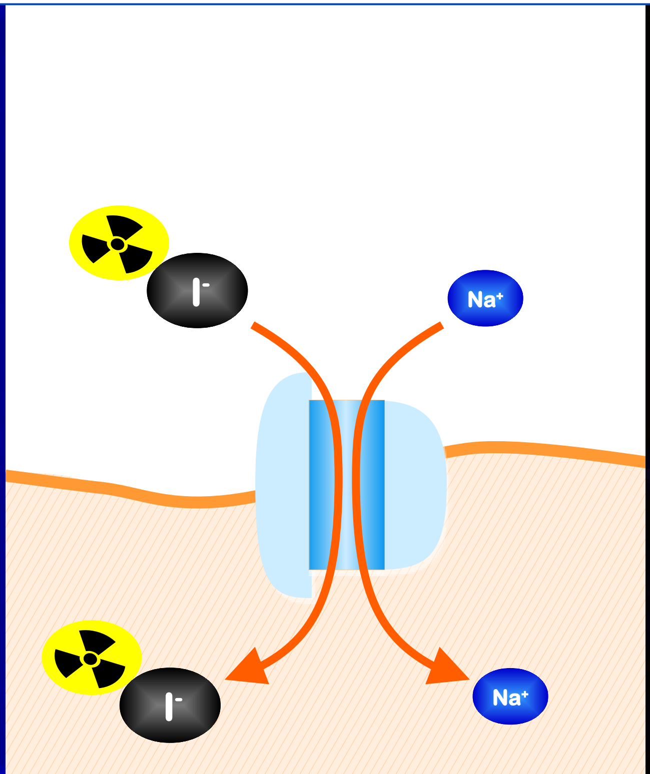
"HercepTest is indicated as an aid in the determination of whether trastuzumab treatment may be considered."

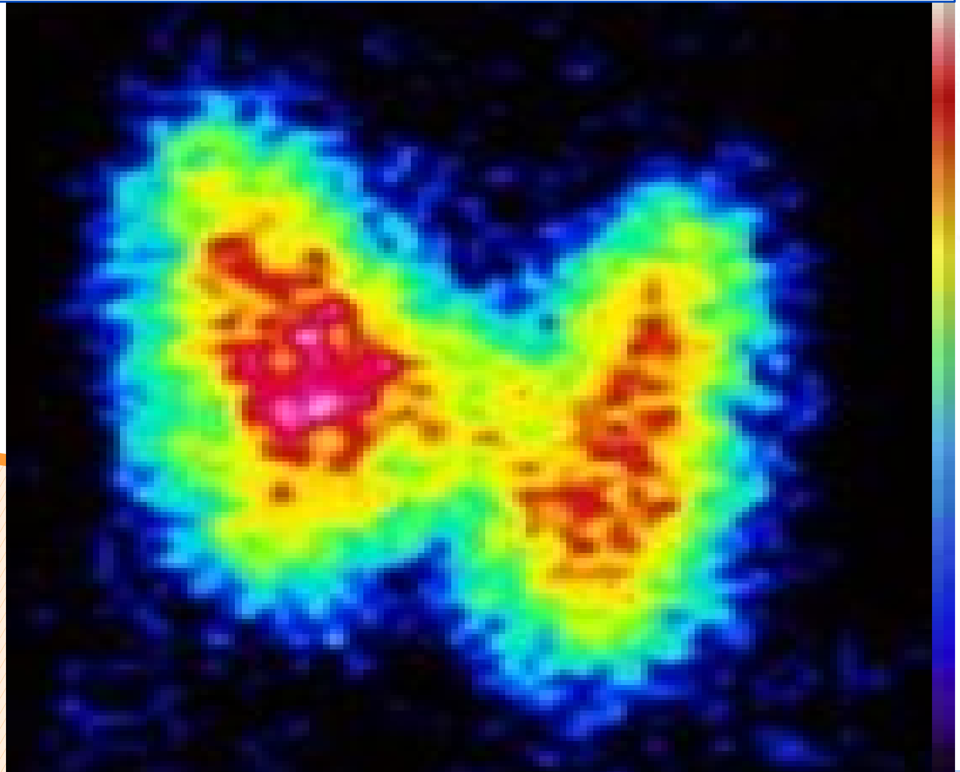
Gilham I. Drug Discovery World Fall 2002; Martinez L et al. US Pharm 2011;36(9):HS25-HS28.

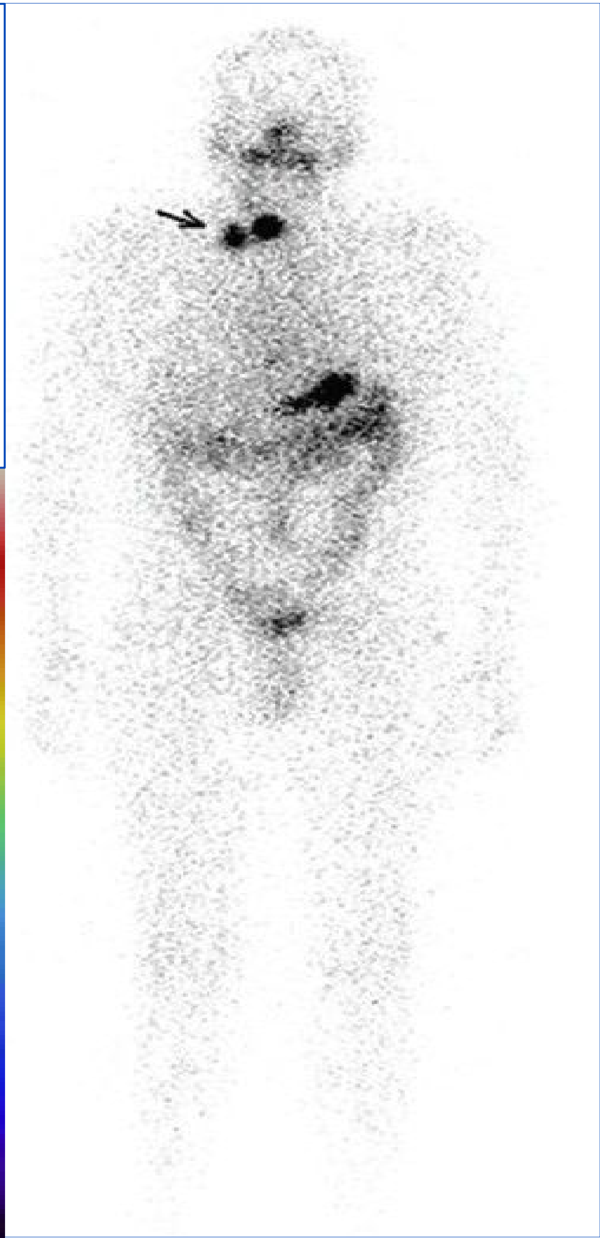
Concept of Radioisotopes
(in principle already theranostic approach)

$^{123}_{53}I$	$^{124}_{53}I$		$^{127}_{53}I$		$^{131}_{53}I$
$T_{1/2}$ = 13.2 h	$T_{1/2}$ = 4.15 d	…	stable	…	$T_{1/2}$ = 8 d
γ	β^+ (+ γ)				β^- (+ γ)





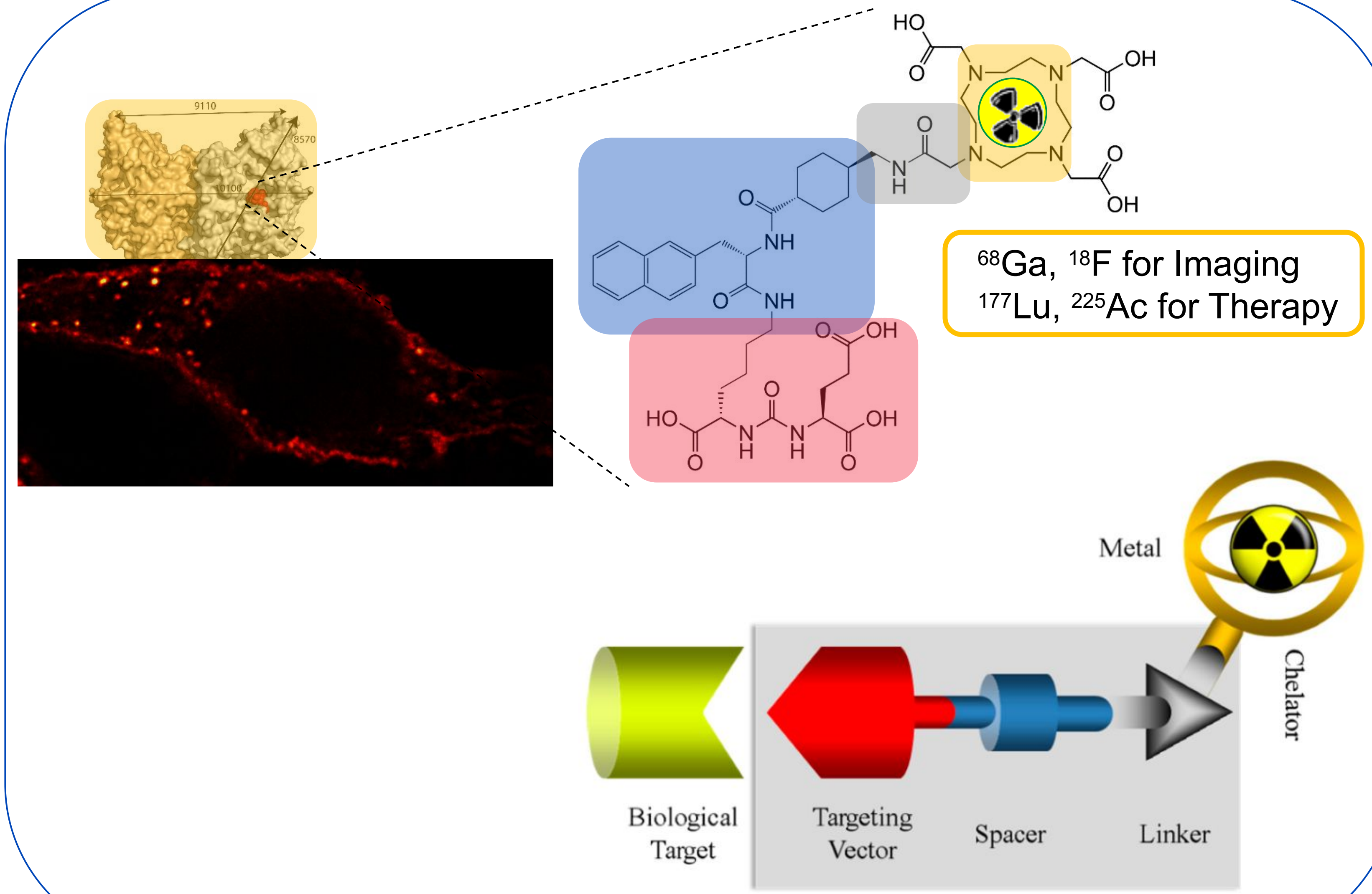




The Concept of Radionuclide Theranostics: Tandem Nuclear Medicine / Radiopharmaceutical Sciences

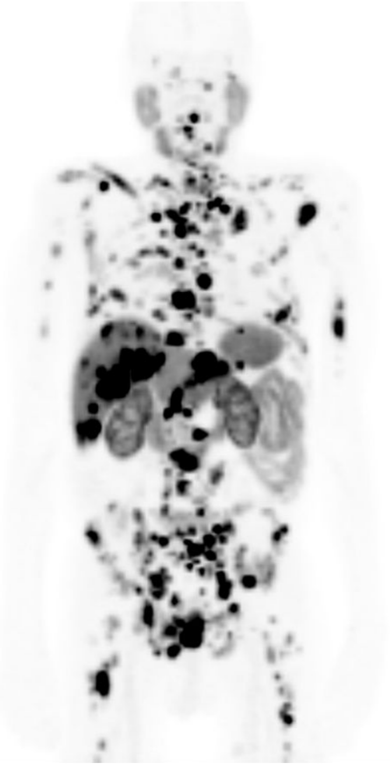
Early Stage

[^{18}F]PSMA-1007
3 h p.i.
Primary



^{68}Ga, ^{18}F for Imaging
^{177}Lu, ^{225}Ac for Therapy

Late Stage



[^{18}F]PSMA-1007
60 min p.i.
mCRPC

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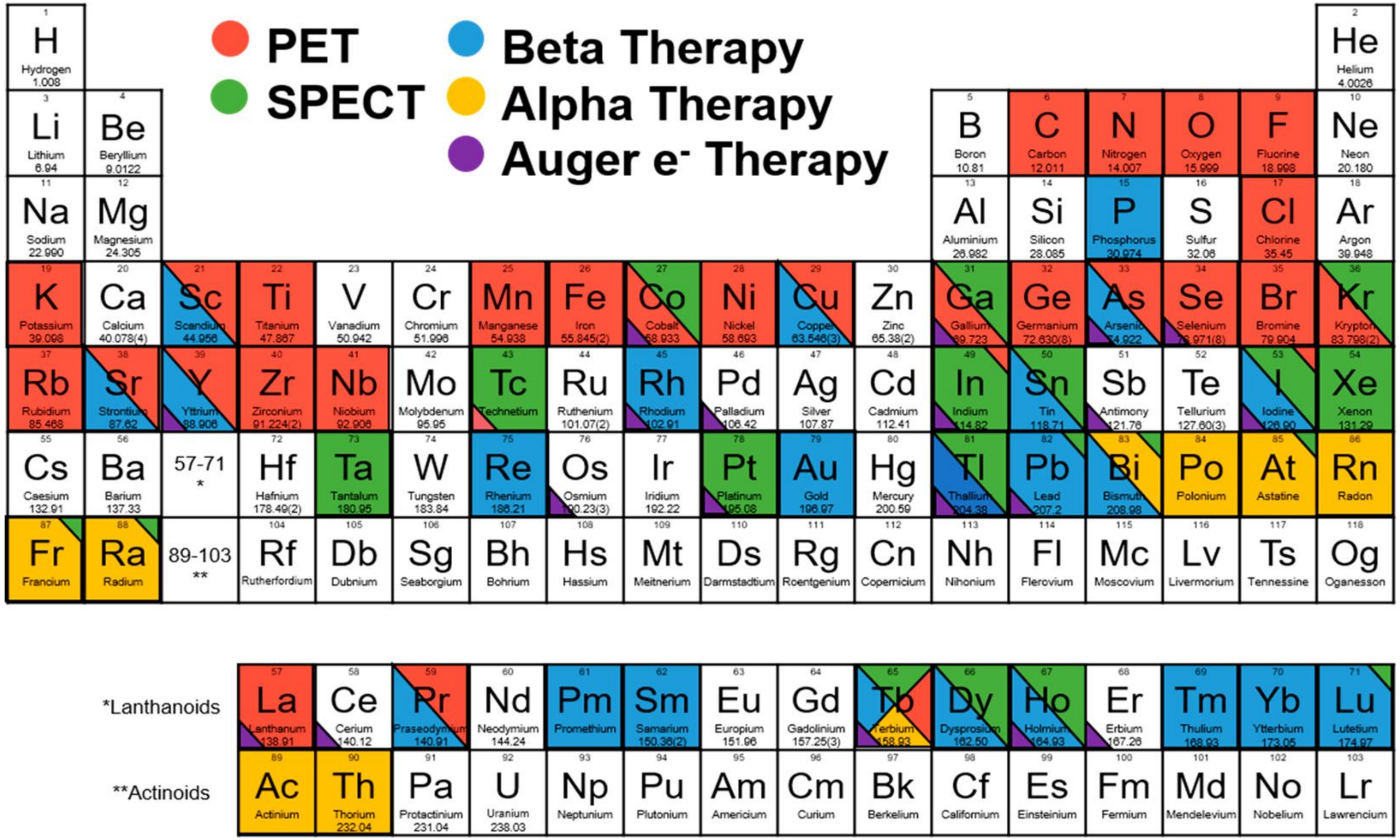
Giesel FL et al. EJNMMI 2017 & 2016 ***IMAGE OF THE MONTH JUNE****; Rösch F et al. Pharmaceuticals (Basel) 2017; Collaboration Cyril Bařinka, Charles University, Prague; Baranski AC et al. Doctoral Thesis 2018.*

Color-coded periodic table with current or potential radionuclide applications

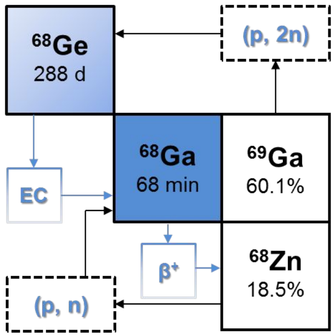


Kostelnik TI, Orvig C. Chem. Rev. 2019;119:902-956.

Availability of theranostic Radionuclides

Challenge Radionuclide Availability [for *in vivo* theranostic approach]

*Positron Emitter Gallium-68 (^{68}Ga)



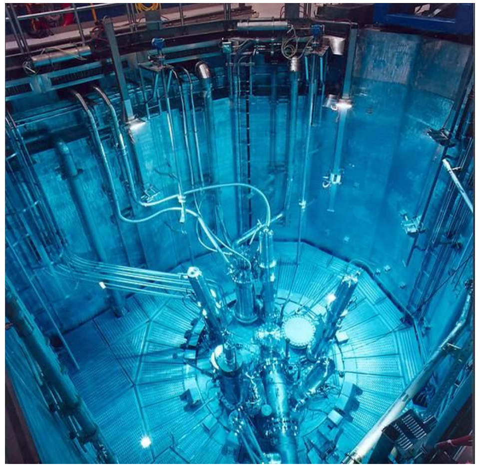
Gallium-68 (^{68}Ga)

$T_{1/2}$ = 68 m

$E_{mean,\beta+}$ = 0.830 MeV (89%)

E_{γ} = 511 keV (Annihilation)

^{68}Ge/^{68}Ga-Generator



^{176}Yb(n,γ)^{177}Yb→^{177}Lu

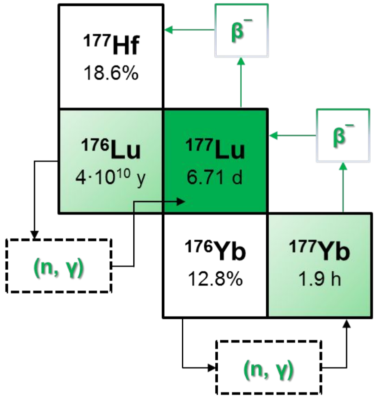
Lutetium-177 (^{177}Lu)

$T_{1/2}$ = 6.71 d

$E_{mean,\beta-}$ = 0.134 MeV (100 %)

E_{γ} = 208 keV (10.4 %)

R_{max} = 2.0 mm

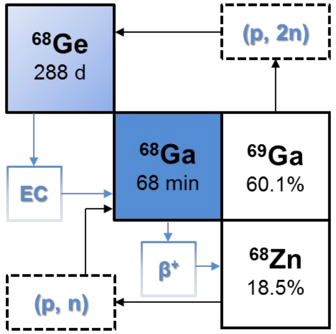


*Beta-Minus Particle Emitter Lutetium-177 (^{177}Lu)

Derived from the Karlsruhe Nuclide Chart.

Challenge Radionuclide Availability [Feasibility of *in vivo* theranostic approach]

*Positron Emitter Gallium-68 (^{68}Ga)



Gallium-68 (^{68}Ga)

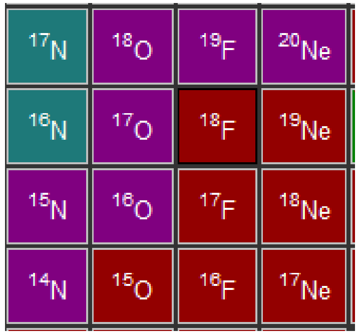
$T_{1/2}$ = 68 m

$E_{mean,\beta+}$ = 0.830 MeV (89%)

E_{γ} = 511 keV (Annihilation)

$^{68}Ge/^{68}Ga$-Generator

*Positron Emitter Fluorine-18 (^{18}F)



Fluorine-18 (^{18}F)

$T_{1/2}$ = 109.8 m

$E_{mean,\beta+}$ = 0.249 MeV (97%)

E_{γ} = 511 keV (Annihilation)

$^{18}O(p,n)^{18}F$

Derived from the Karlsruhe Nuclide Chart.

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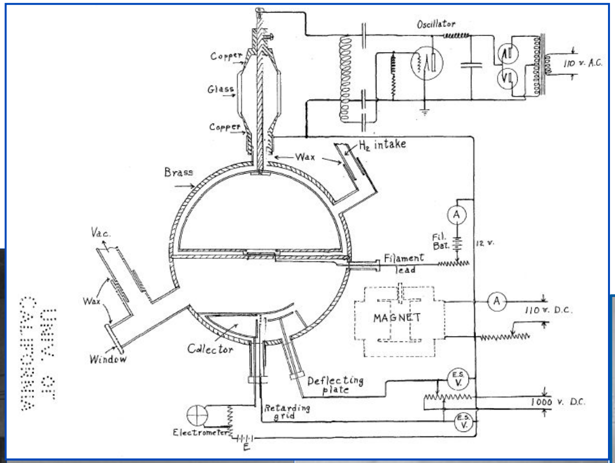
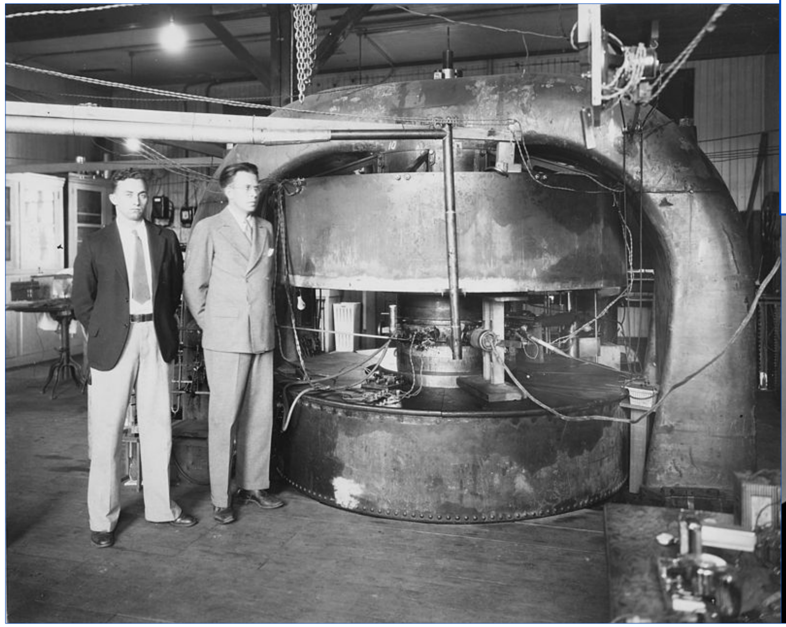
1930 Ernest Orlando Lawrence realises a cyclotron (together with Milton Stanley Livingston)

Nobel Prize Physics 1939
„…especially with regard to artificial radioactive elements"





27 inch cyclotron 1935

4.5 inch cyclotron 1930

IBA film

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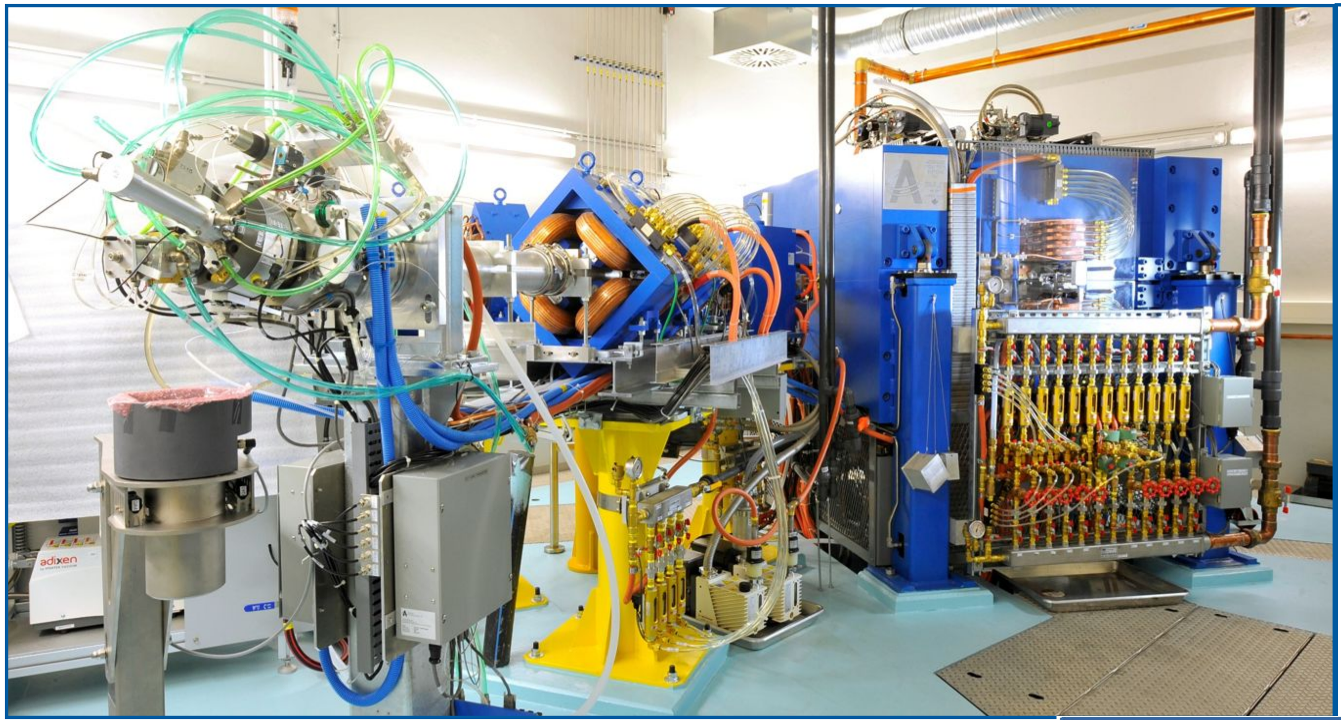
Medical Cyclotron Infrastructure in the D-A-CH Region

…not enough!

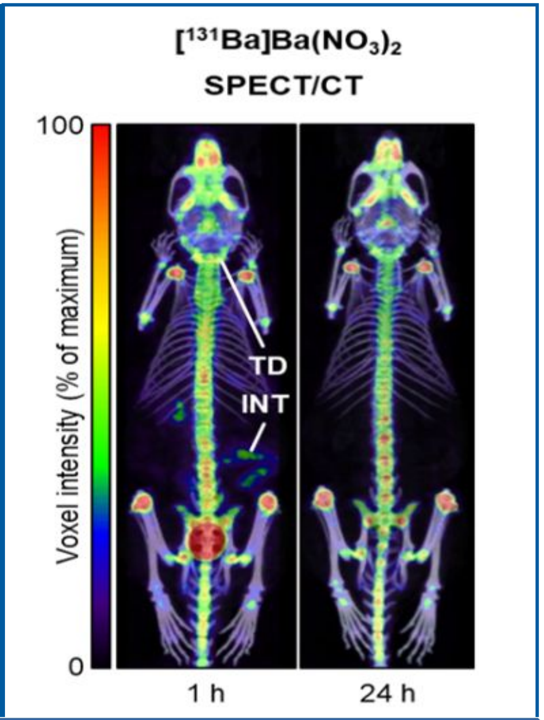
HZDR + Local Partners
Top Nucleus for
for *NextGen* Radionuclide Availability

Her-steller / MeV	GE HEALTHCARE		IBA		Weitere (ACSI, TCC, Siemens usw.)		Gesamt	
	absolut (n)	relativ	absolut (n)	relativ	absolut (n)	relativ	absolut (n)	relativ
≤ 10 MeV	5	12%					**5**	12%
11-20 MeV	19	45%	7	17%	6	14%	**32**	76%
20-30 MeV			1	2%	2	5%	**3**	7%
≥ 30 MeV					2	5%	**2**	5%
Gesamt	**24**	57%	**8**	19%	**10**	24%	**42**	100%

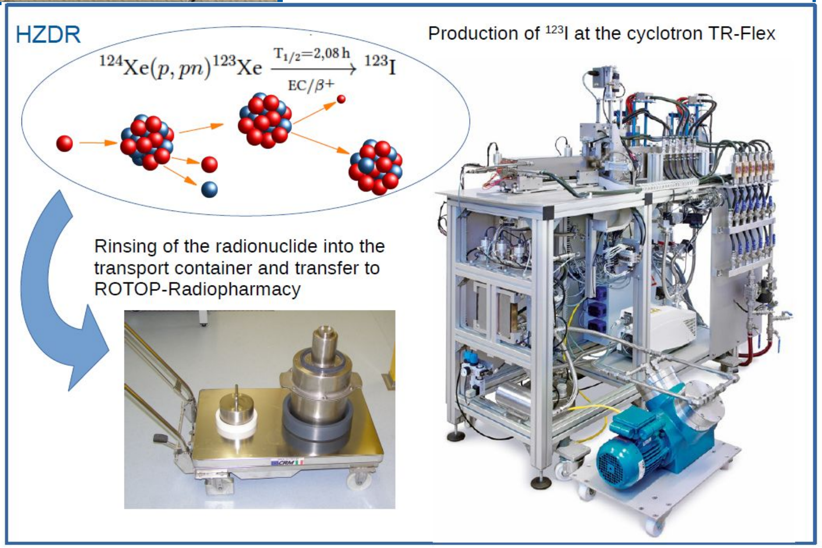
Zippel C et al. Frontiers Nucl Med 2022; 2: 850414.



TR-FLEX-Cyclotron: ^{131}Ba via ^{131}Cs(p,3n)^{131}Ba



nanoScan SPECT/CT free barium-131



KIPROS-200 adapted to TR-FLEX-Cyclotron: ^{123}I via ^{124}Cs(p,pn)^{123}Xe

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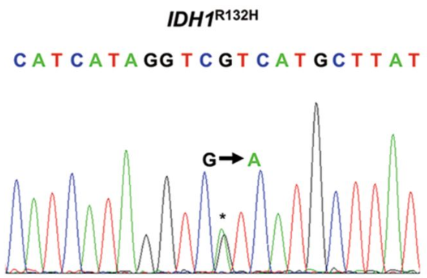
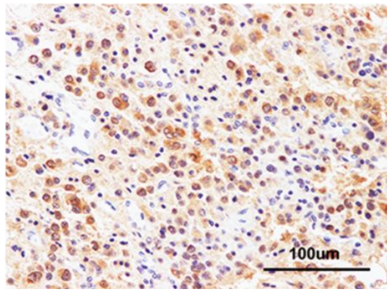
Reissig F et al. Pharmaceuticals 2020; 13: 272.

Genomics



Proteomics



In vivo Molecular (multimodal) Imaging

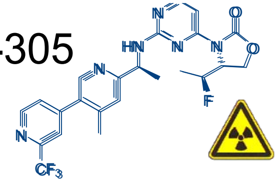
Cryogen-free 7.0T MR/PET scanner

Simultaneous and sequential small animal imaging

Translational research: Tumor-specific imaging biomarkers

PET Radiotracer

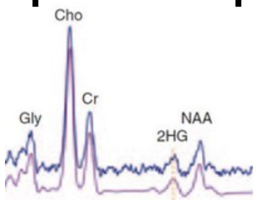
IDH-305

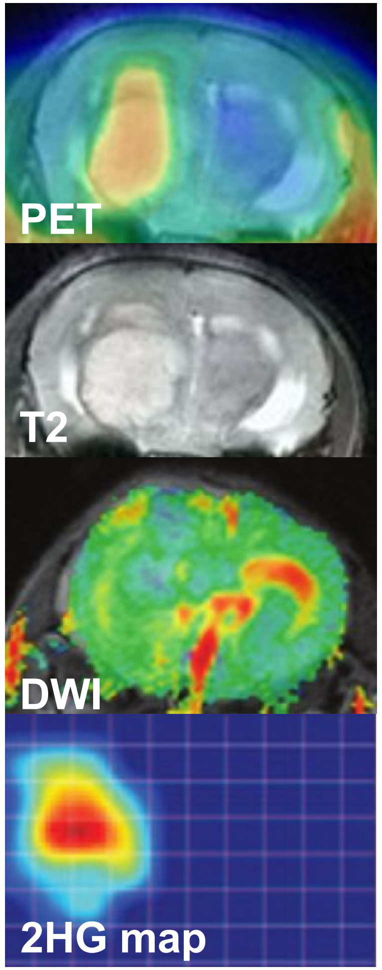


Structural MRI

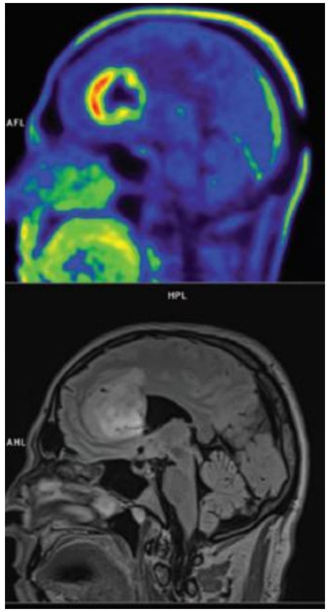
Functional MRI

MR-Spectroscopy





Biology-guided radiotherapy (BgRT)



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**Non-invasive imaging of Glioma-associated Receptors using small animal PET/MRI*

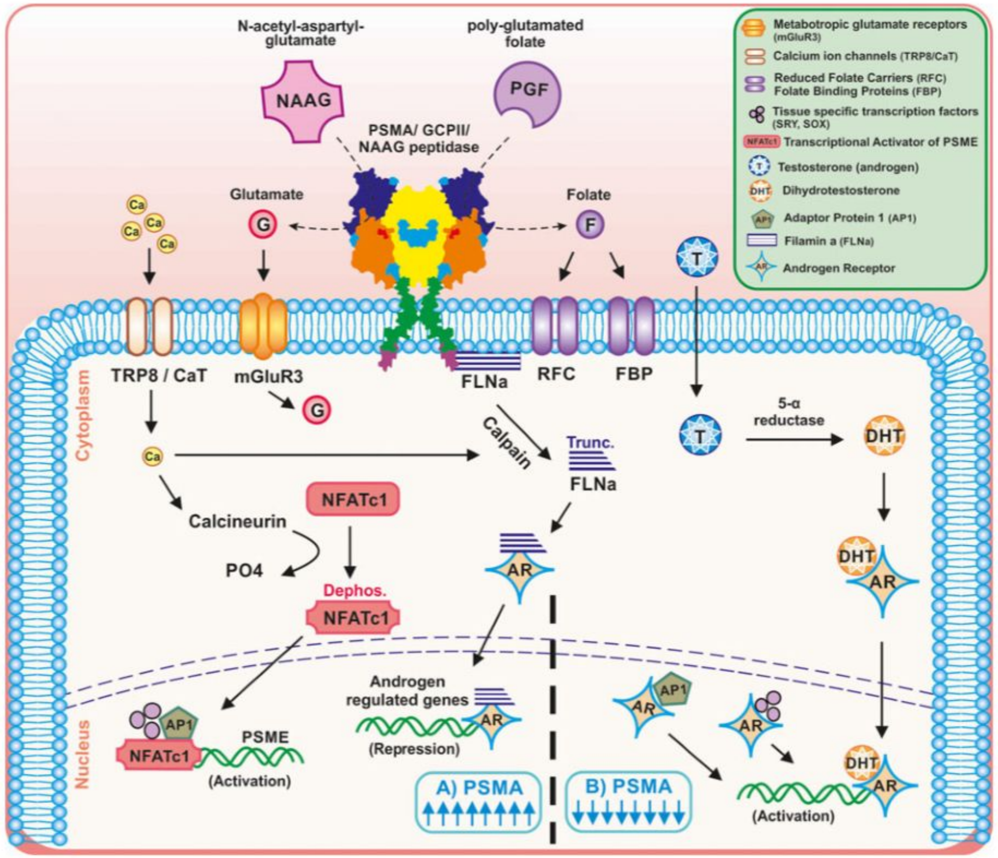
The therapeutic and diagnostic potential of PSMA in cancer

PSMA / GCP II / FOLH1

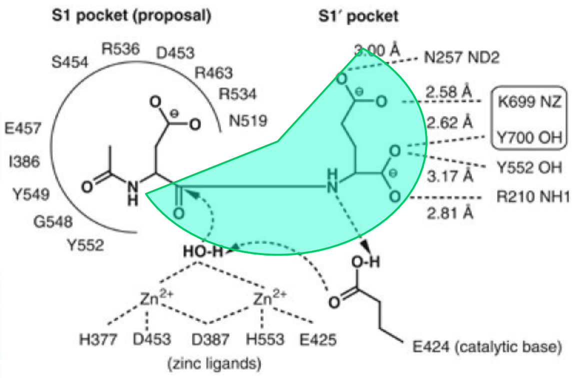
750-amino acid cell surface glycoprotein (100 kDa)

Membrane-bound zinc metallopeptidase

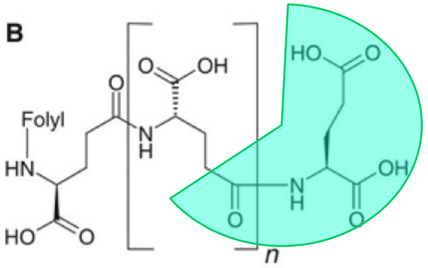
brain, kidney, spleen, intestine, salivary glands, prostate

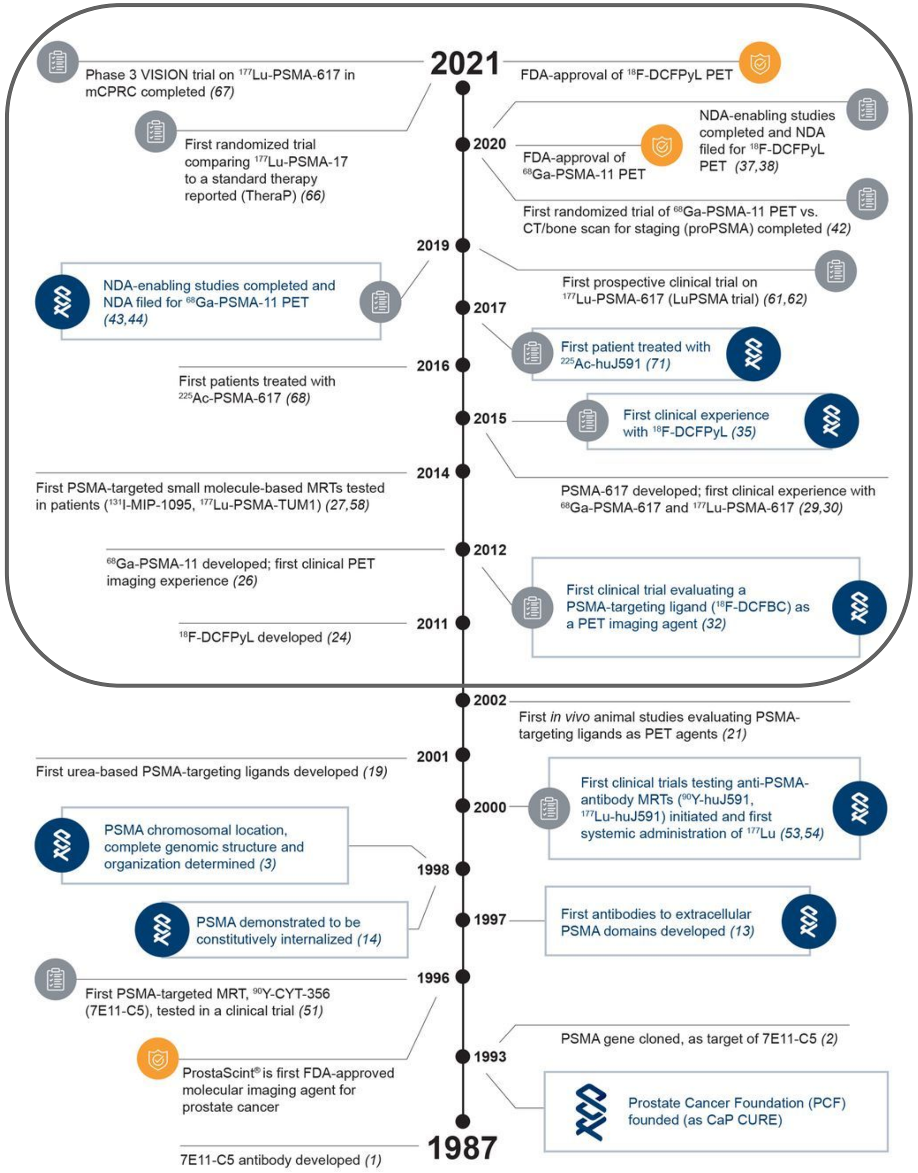


NAAG



folyl-poly-γ-glutamate



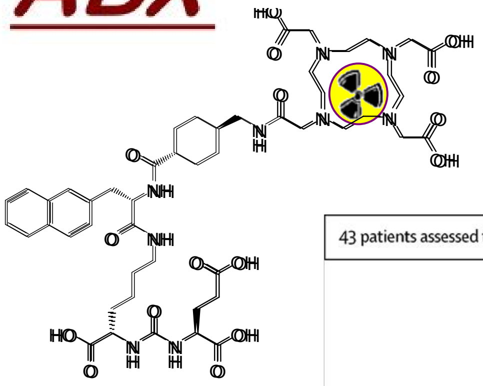


Miyahira AK, Soule HR. J Nucl Med 2022;63:331-338; Evans JC et al. BJ Pharmacol 2016;173:3041-3079; Mesters JR et al. EMBO J 2006; 25: 1375-1384; Bařinka C et al. Curr Med Chem 2012; 19: 856–870.

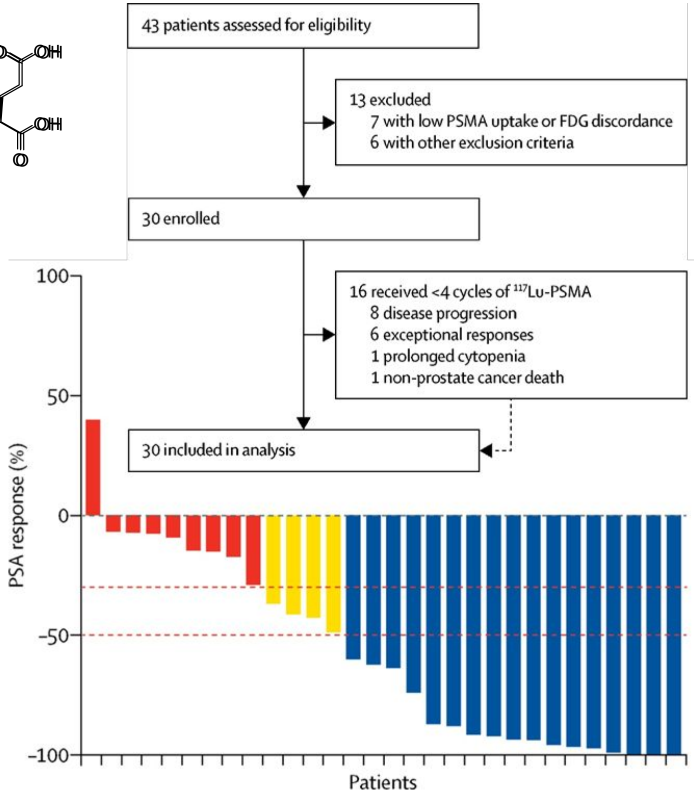
Image of the Year Award 2018 [SNMMI, Philadelphia, USA]

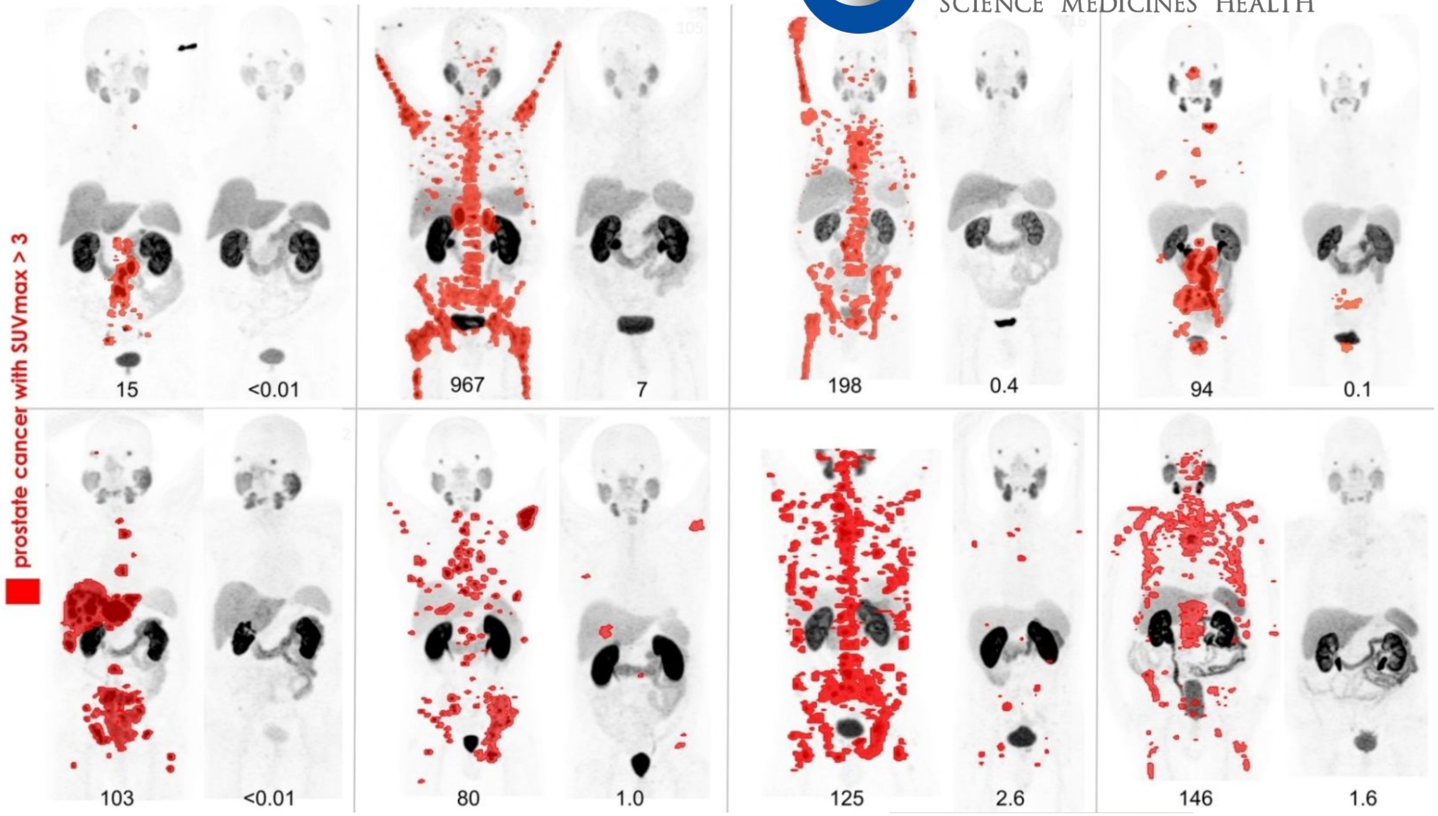
PLUVICTO™
lutetium Lu 177 vipivotide tetraxetan
FDA APPROVED
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ABX



[^{177}Lu]Lu-PSMA-617 (vipivotide tetraxetan)





Michael S. Hofman *et al.*, **2018 Henry N. Wagner, Jr, MD, Image of the Year Award of the Society of Nuclear Medicine and Molecular Imaging.**

ENDOCYTE
NOVARTIS

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Hofman MS et al. Lancet Oncol 2018 Jun;19(6):825-833 [LuPSMA trial: a single-centre, single-arm, phase-II study with [^{177}Lu]Lu-PSMA-617];Sartor O et al. N Engl J Med 2021 Sep 16;385(12):1091-1103. [VISION].

The NEW ENGLAND JOURNAL of MEDICINE

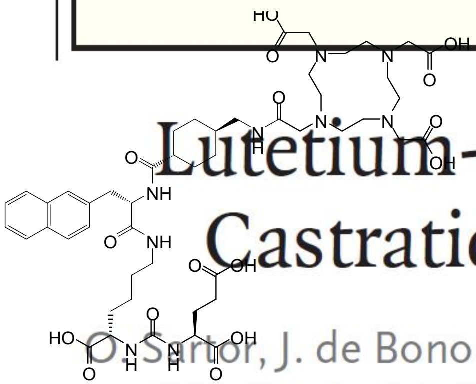
PLUVICTO™
lutetium Lu 177 vipivotide tetraxetan

FDA APPROVED

Year(s)
2013/2022

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

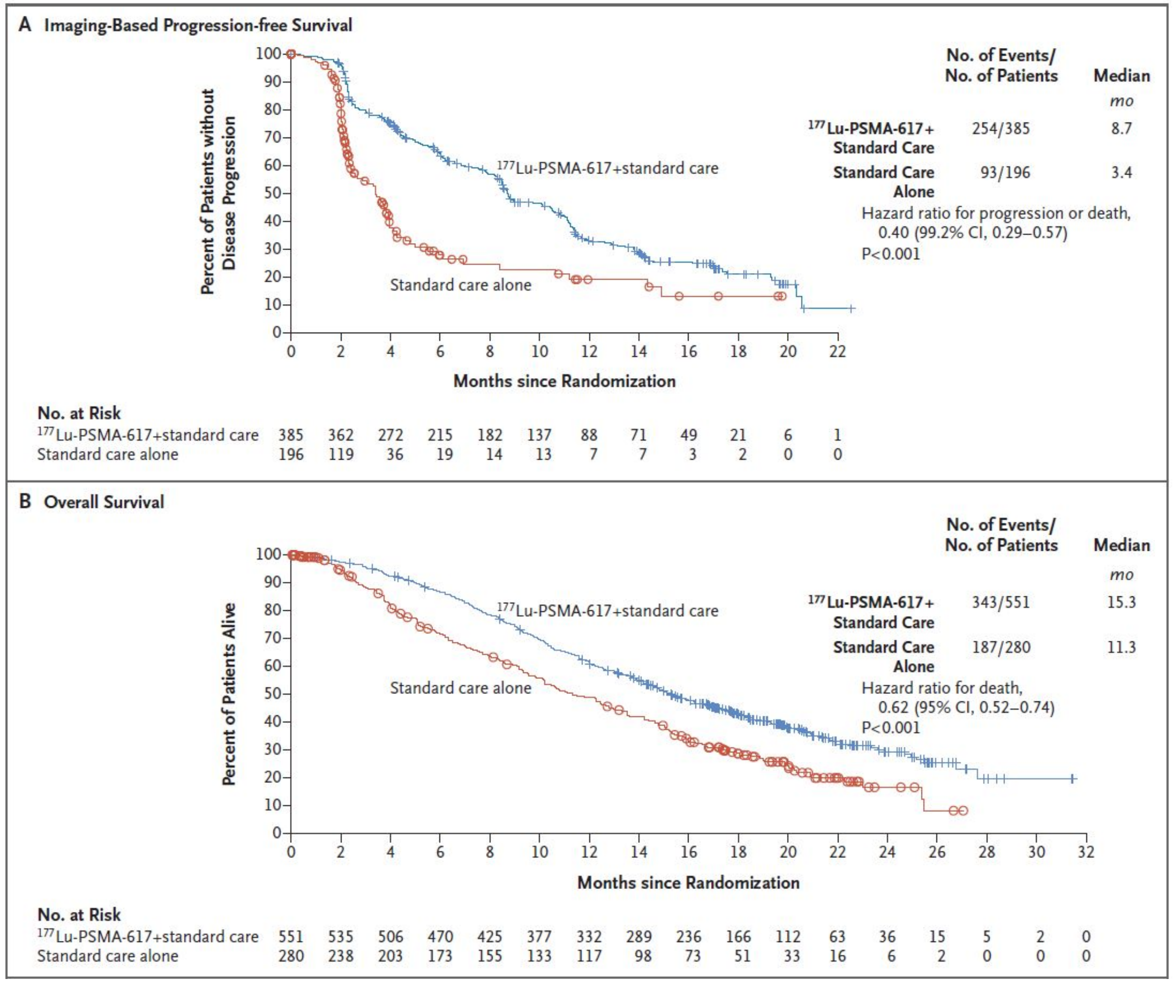
ORIGINAL ARTICLE



Lutetium-177–PSMA-617 for Met Castration-Resistant Prostate Ca

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahba
L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park,
A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan,
R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION I

ABSTRACT



Novartis Pluvicto™ approved by FDA as first targeted radioligand therapy for treatment of progressive, PSMA positive metastatic castration-resistant prostate cancer

Mar 23, 2022

Novartis receives European Commission approval for Pluvicto® as the first targeted radioligand therapy for treatment of progressive PSMA–positive metastatic castration-resistant prostate cancer

Dec 13, 2022

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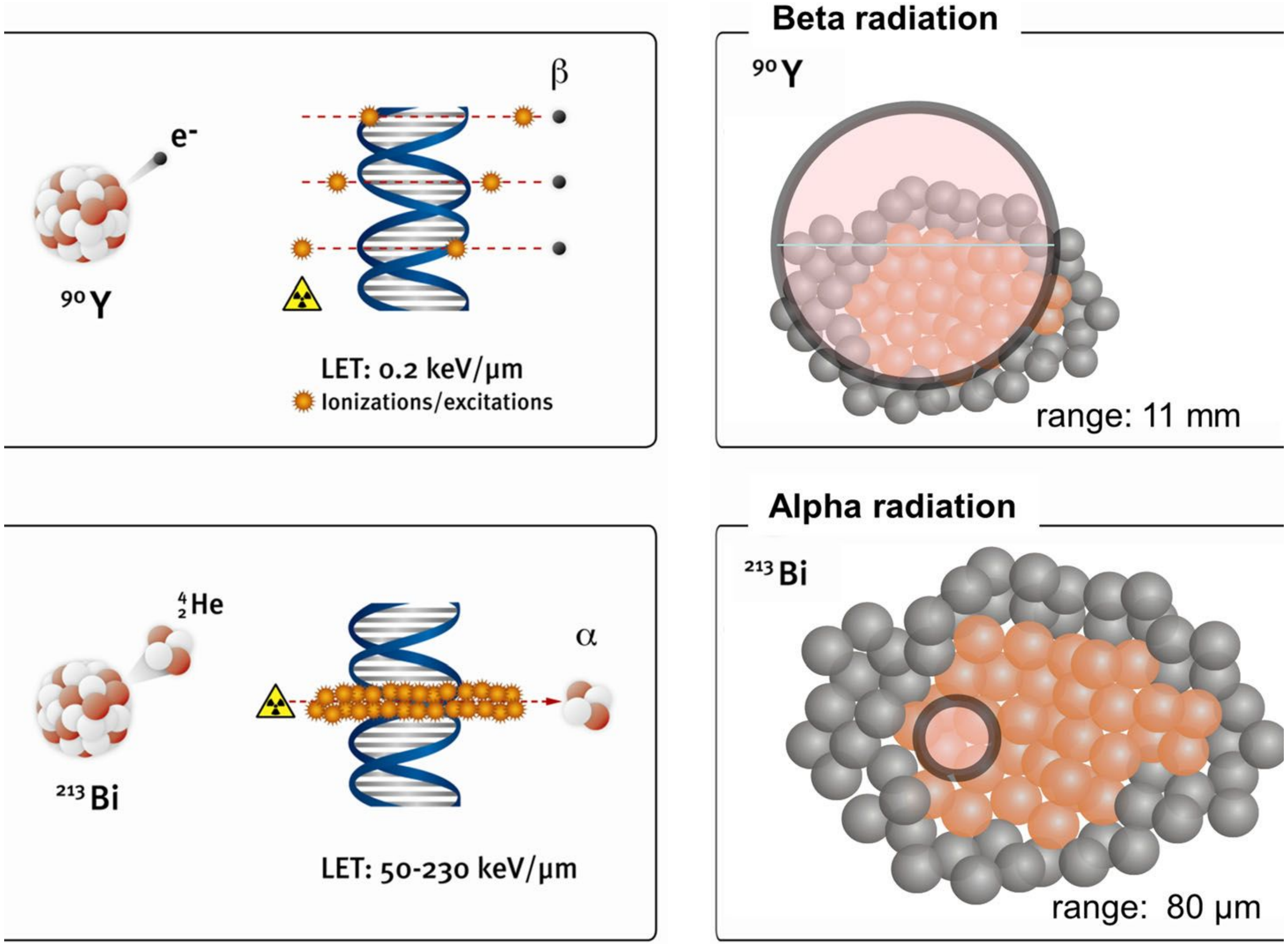
Hofman MS et al. Lancet Oncol 2018 Jun;19(6):825-833 [LuPSMA trial: a single-centre, single-arm, phase-II study with [^{177}Lu]Lu-PSMA-617];Sartor O et al. N Engl J Med 2021 Sep 16;385(12):1091-1103. [VISION].

Late Stage
Radionuclide Theranostics
[beyond Targeted beta-Therapy]

Discussion of alpha emitters for targeted alpha therapy (TAT) *vs.* beta emitters



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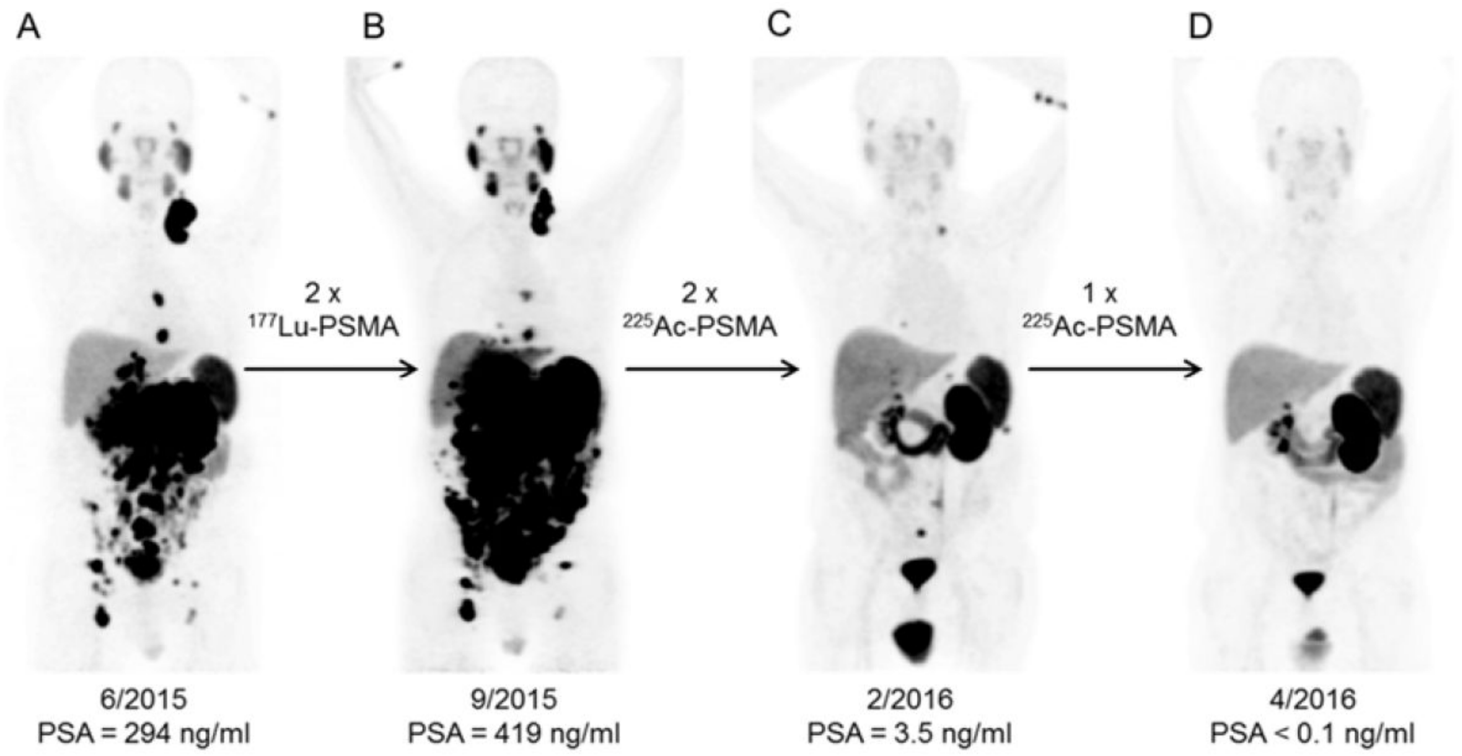
Giesel F et al. Exp. Oncology 2012; Kratochwil C et al. EJNM 2014.

Imaging & Therapy (with TAT) [^{68}Ga]Ga-PSMA-11 & [^{225}Ac]Ac-PSMA-617

… overcoming resistance?



Radical prostatectomy
Radiotherapy of lymph node metastasis
Leuprorelin
Leuprorelin plus bicalutamide, 150 mg/d
Docetaxel (11 cycles)
Cabazitaxel (10 cycles)
Abiraterone
Enzalutamide (not tolerated)

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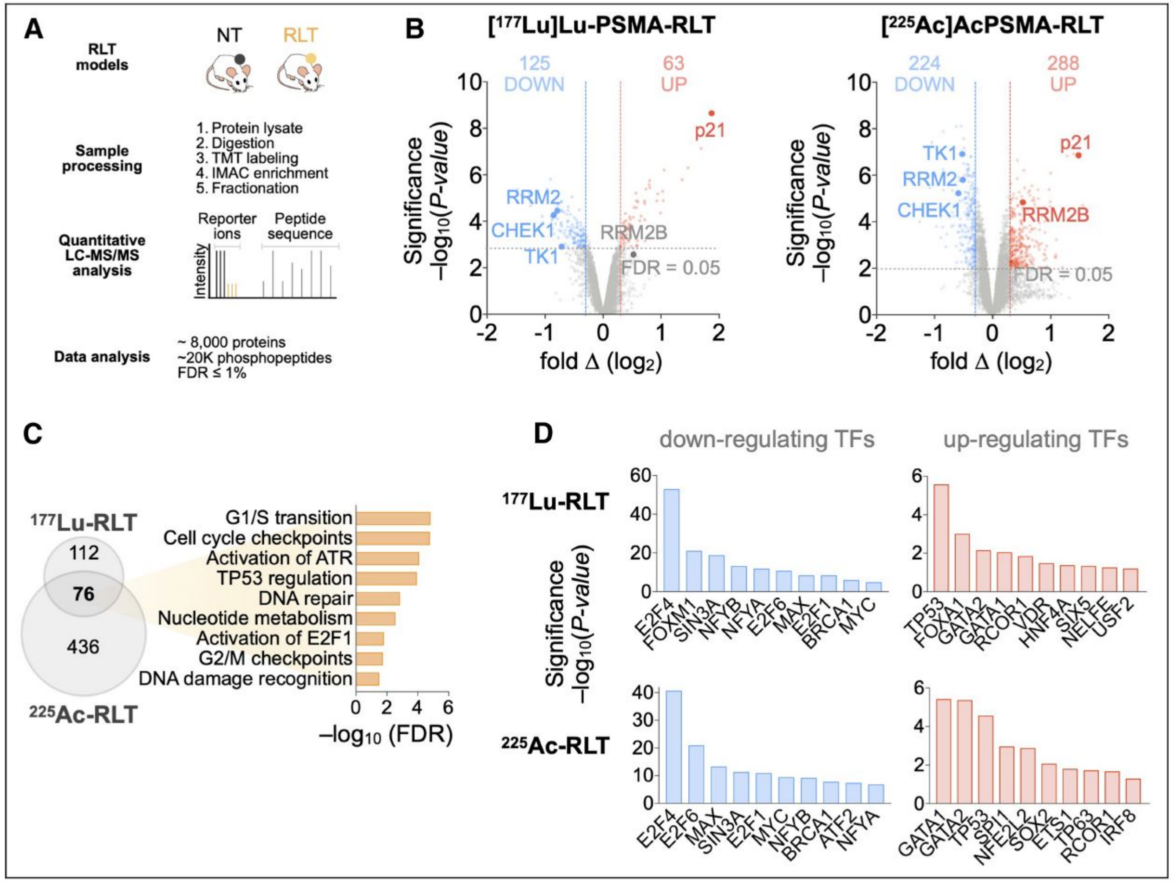
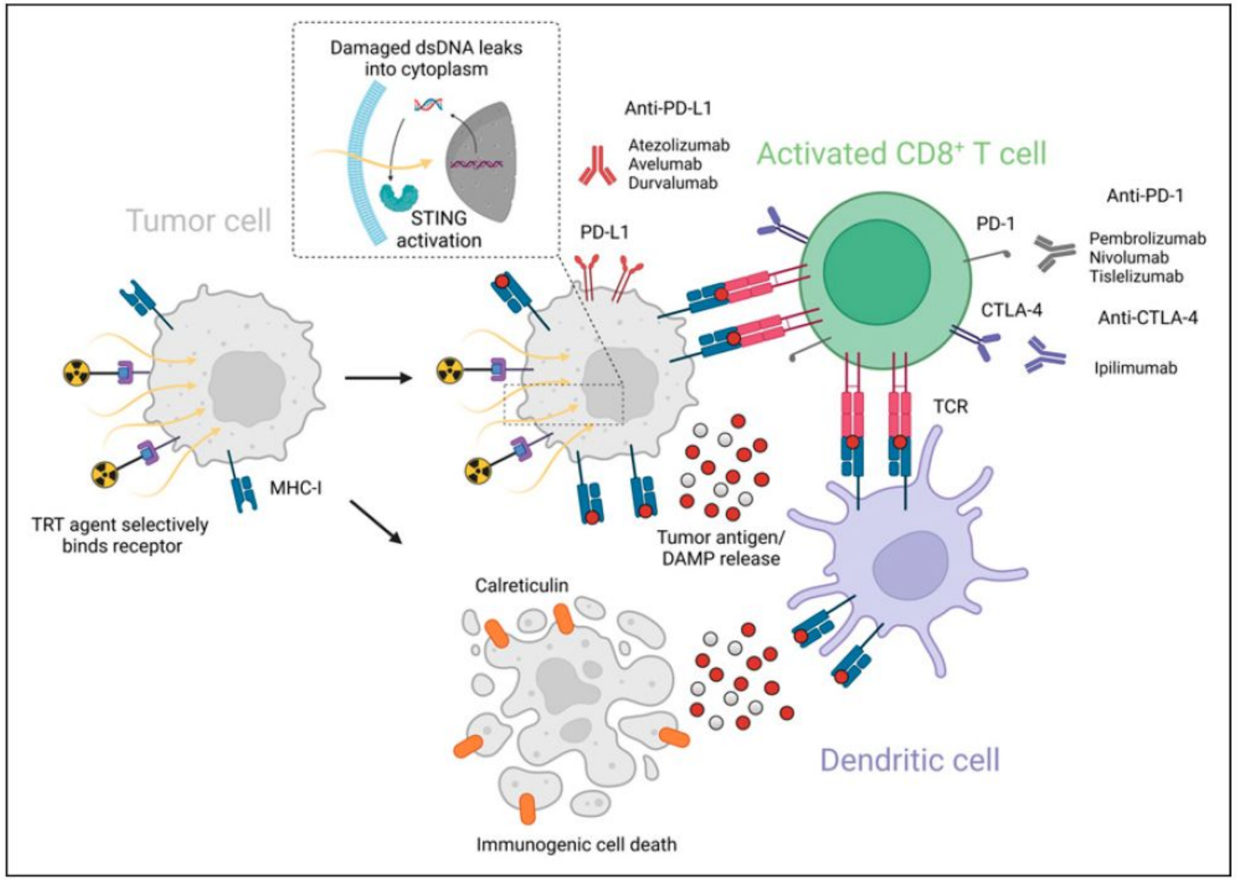
Kratochwil C et al. J Nucl Med 2016;57:1941-1944.

Paradigm: Targeted Radioligand Therapy (RLT) and Immune Checkpoint Blockade in Combination?

Understanding mechanisms…

… to overcome resistance?





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Stuparu AD et al. J Nucl Med. 2021 Jul 1;62(7):989-995; Bellavia MC et al. J Nucl Med 2022 Nov;63(11):1636-1641.

Early Stage
Combining Imaging with Surgery

Surgery: Translational Research Pipeline, Dual-labelled Tracers

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-020-05184-0

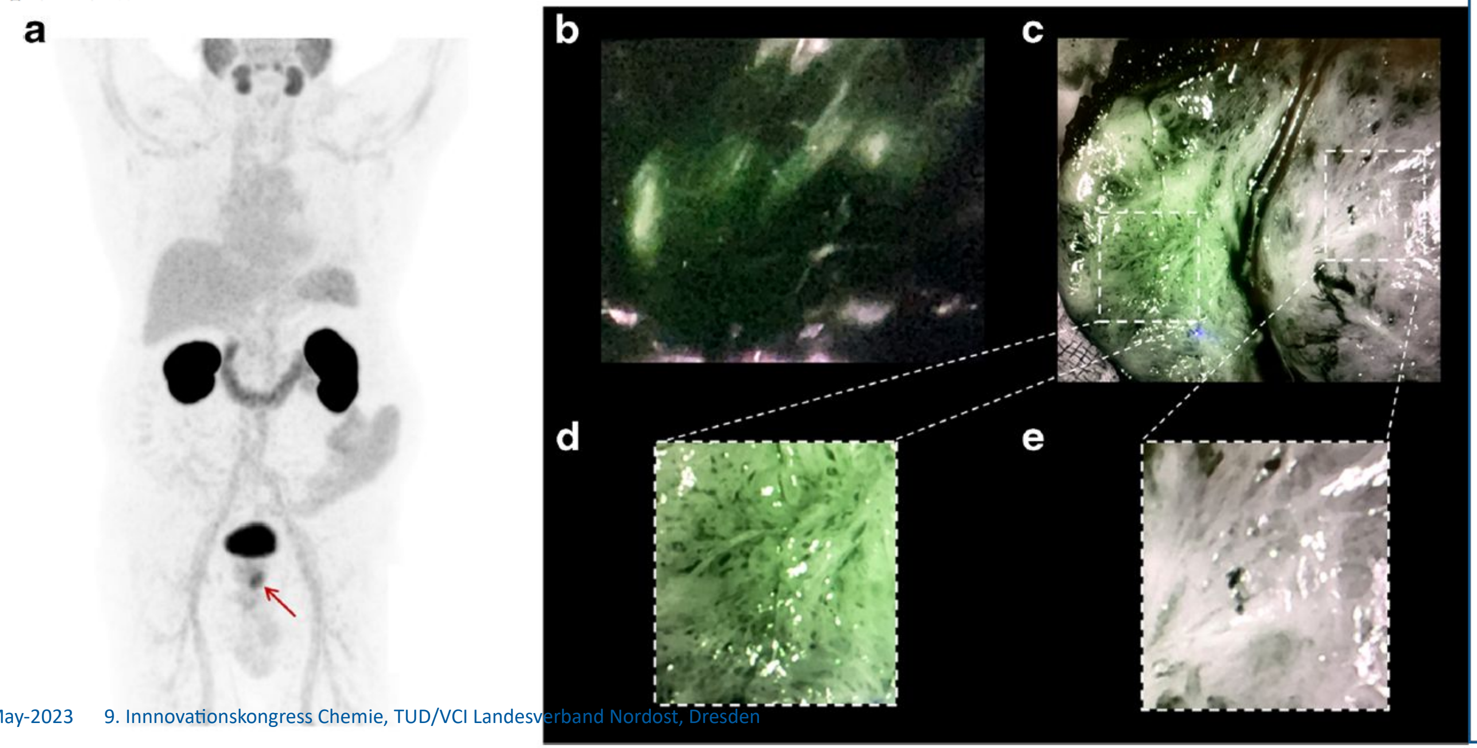
IMAGE OF THE MONTH

Check for updates

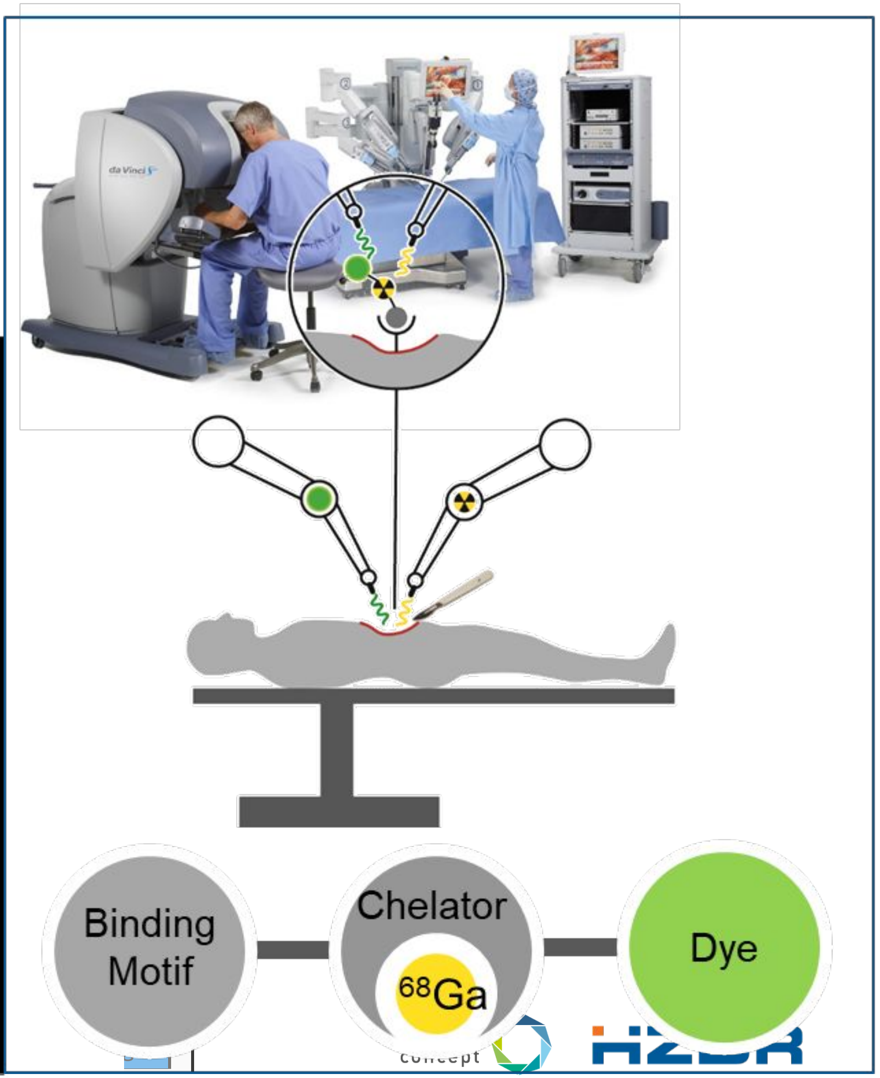
The PSMA-11-derived hybrid molecule PSMA-914 specifically identifies prostate cancer by preoperative PET/CT and intraoperative fluorescence imaging

Ann-Christin Eder[1,2] · Mohamed A. Omrane[1,2] · Sven Stadlbauer[3,4] · Mareike Roscher[3,5] · Wael Y. Khoder[6] · Christian Gratzke[6] · Klaus Kopka[3,4,7,8] · Matthias Eder[1,2] · Philipp T. Meyer[1,9] · Cordula A. Jilg[6] · Juri Ruf[1,9]

Received: 6 November 2020 / Accepted: 27 December 2020



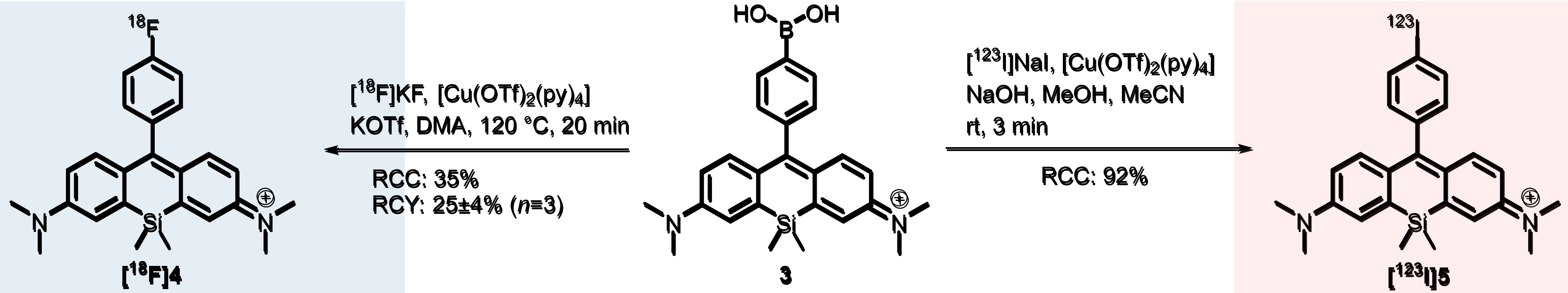
Fluorescence-guided Surgery

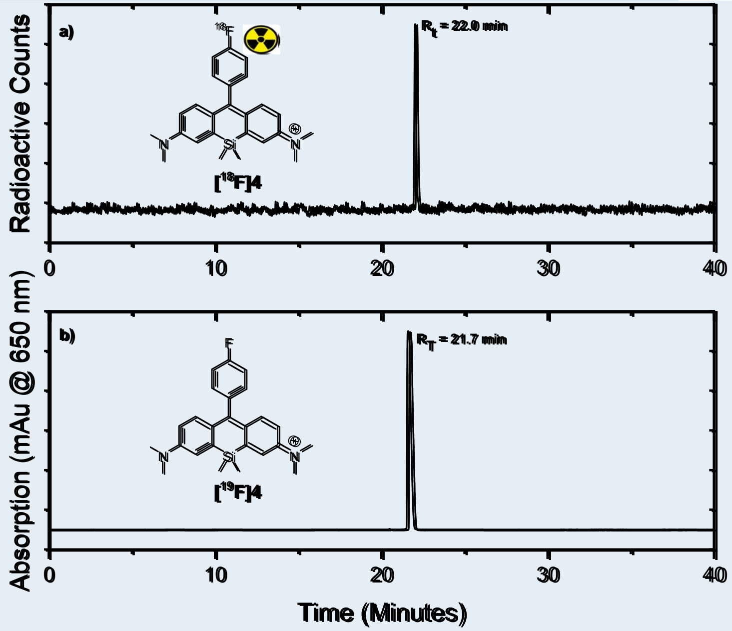


Results – Radiohalogenation of Si-rhodamine

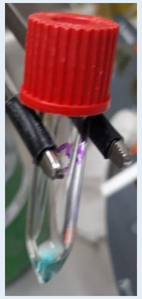
PET

SPECT

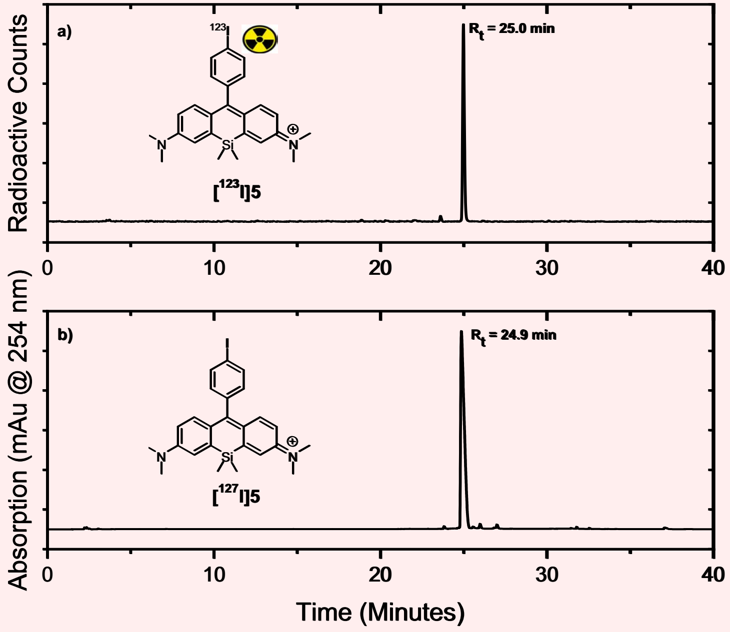




- stable in saline (>99%) and human serum (>80%) after two hours
- $\log D_{pH=7.4}$ = 2.92±0.32 (n=3)
- A_m = 70.1±3.2 GBq/µmol (n=6)



[^{18}F]4

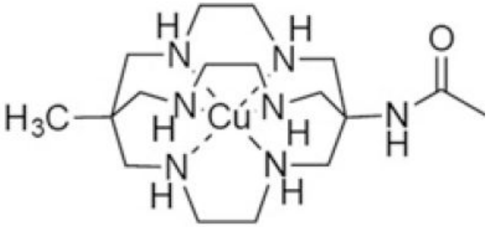


Successful radiofluorination and radioiodination of a boronic-acid functionalized Si-rhodamine

T. Kanagasundaram, M. Laube, J. Wodtke, C. S. Kramer, S. Stadlbauer, J. Pietzsch, K. Kopka, *Pharmaceuticals (Basel). 2021 Nov 12;14(11):1155.*

When producing a radiometal be sure you have a complexing agent in the pocket!

Sarcophargine-based Chelators for Radiocopper



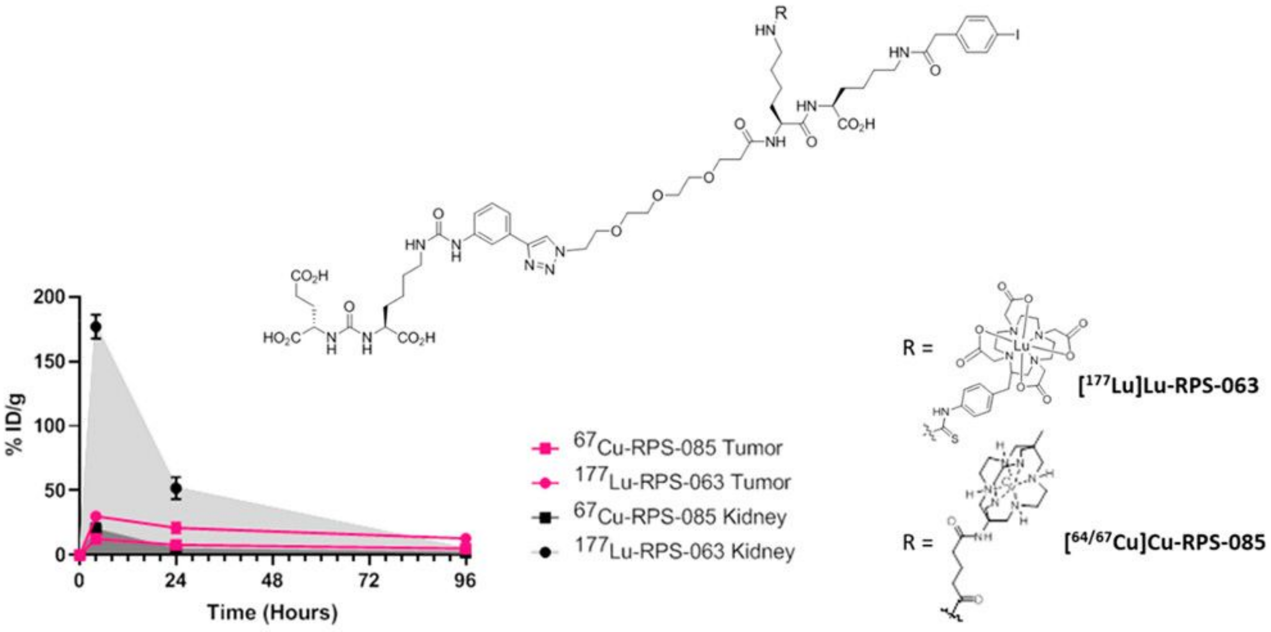
molecular pharmaceutics

pubs.acs.org/molecularpharmaceutics

Article

Preclinical Evaluation of a High-Affinity Sarcophagine-Containing PSMA Ligand for ^{64}Cu/^{67}Cu-Based Theranostics in Prostate Cancer

James M. Kelly, Shashikanth Ponnala, Alejandro Amor-Coarasa, Nicholas A. Zia, Anastasia Nikolopoulou, Clarence Williams, Jr., David J. Schlyer, Stephen G. DiMagno, Paul S. Donnelly, and John W. Babich*

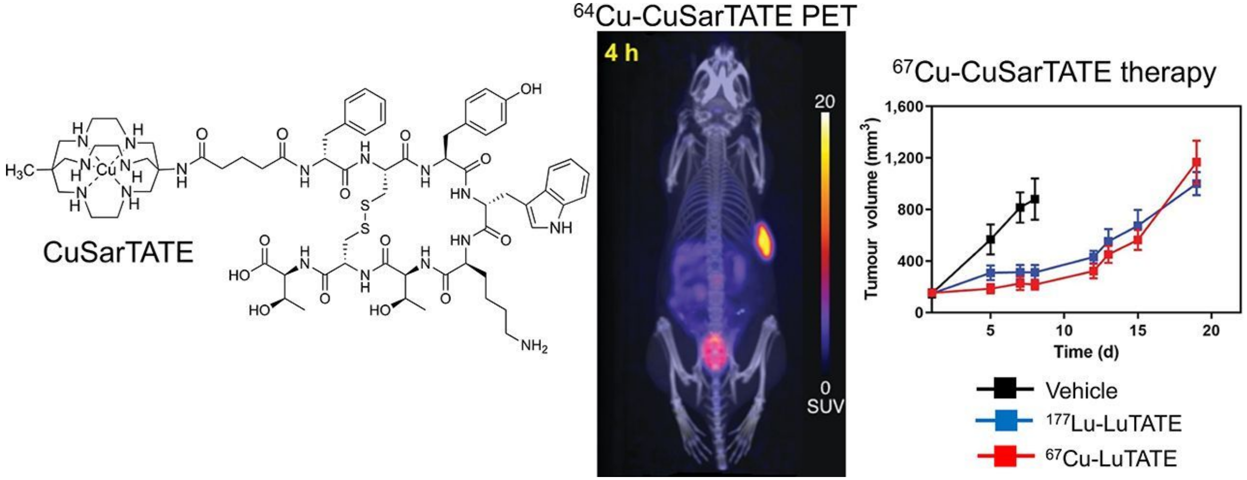


FEATURED BASIC SCIENCE ARTICLE

Peptide Receptor Radionuclide Therapy with ^{67}Cu-CuSarTATE Is Highly Efficacious Against a Somatostatin-Positive Neuroendocrine Tumor Model

Carleen Cullinane[1,2], Charmaine M. Jeffery[3], Peter D. Roselt[4], Ellen M. van Dam[3], Susan Jackson[2], Kevin Kuan[5], Price Jackson[4], David Binns[4], Jessica van Zuylekom[2], Matthew J. Harris[3], Rodney J. Hicks[1,4], and Paul S. Donnelly[6]

[1]Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia; [2]Research Division, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [3]Clarity Pharmaceuticals Ltd., Eveleigh, New South Wales, Australia; [4]Centre for Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [5]Molecular Imaging and Therapy Research Unit, SAHMRI, Adelaide, South Australia, Australia; and [6]School of Chemistry and Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Melbourne, Victoria, Australia



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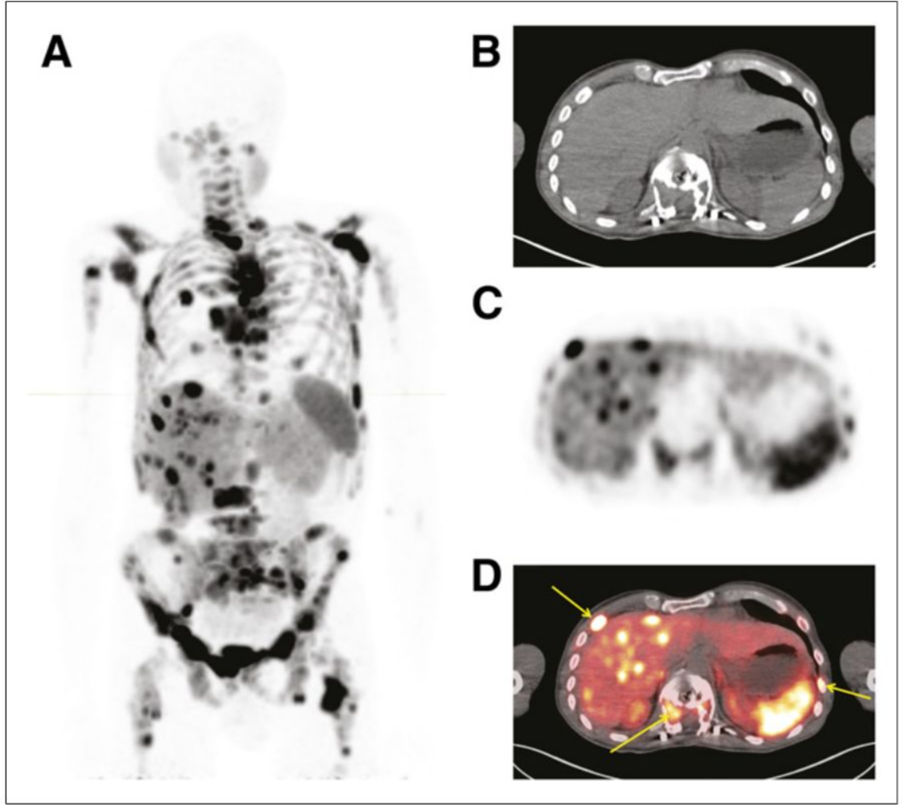
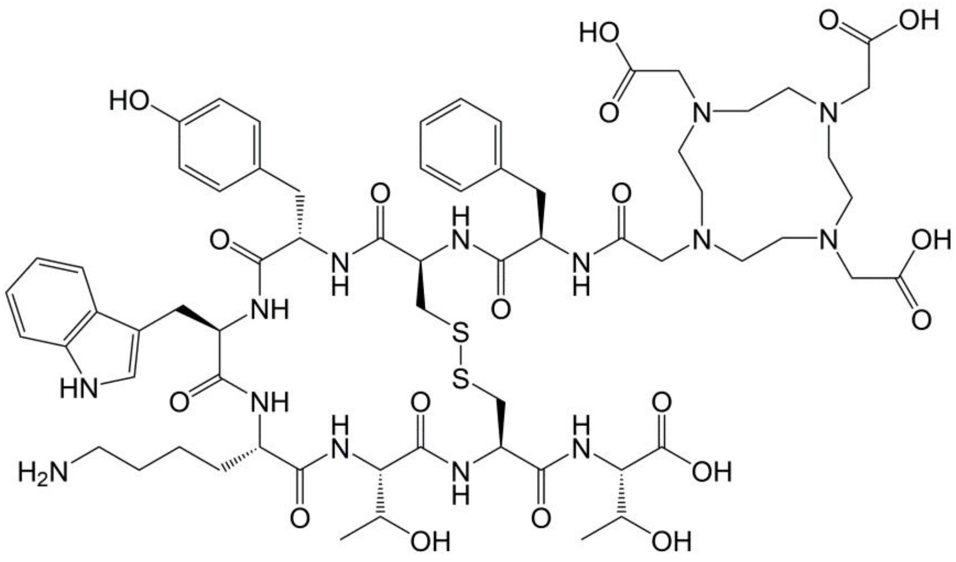
Kelly JM et al. Mol Pharmaceutics 2020; Cullinane C et al. J Nucl Med 2020; Paterson BM et al. Dalton Trans. 2014 Jan 21;43(3):1386-96.

Detectnet (copper Cu 64 dotatate injection) in the U.S.

Year(s)
2020

^{64}Cu-DOTATATE PET/CT for Imaging Patients with Known or Suspected Somatostatin Receptor–Positive Neuroendocrine Tumors: Results of the First U.S. Prospective, Reader-Masked Clinical Trial





DOTA-(Tyr^3,Thr^8)-octreotate

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DRESDEN concept

Delpassand ES et al. J Nucl Med 2020 Jun;61(6):890-896.

One chelator for imaging and therapy with ^{177}Lu and ^{225}Ac, not that easy…

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Article

Toward Personalized Medicine: One Chelator for Imaging and Therapy with Lutetium-177 and Actinium-225

Patrick Cieslik, Manja Kubeil,* Kristof Zarschler, Martin Ullrich, Florian Brandt, Karl Anger, Hubert Wadepohl, Klaus Kopka, Michael Bachmann, Jens Pietzsch, Holger Stephan, and Peter Comba*

Cite This: https://doi.org/10.1021/jacs.2c08438 Read Online

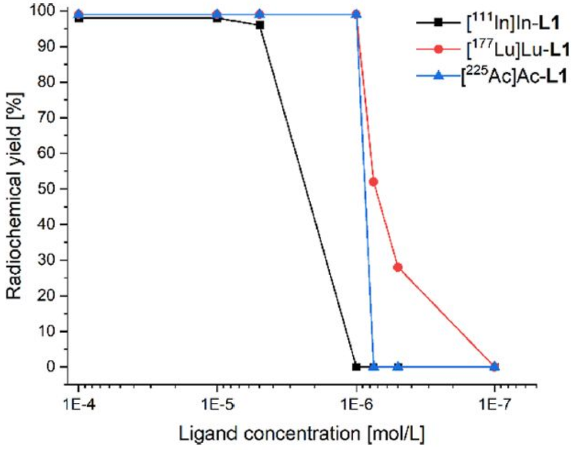
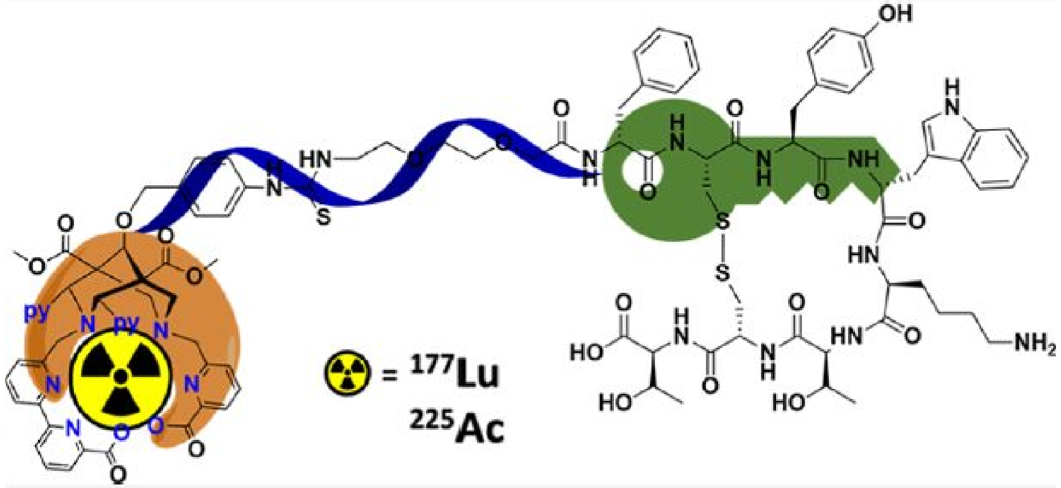
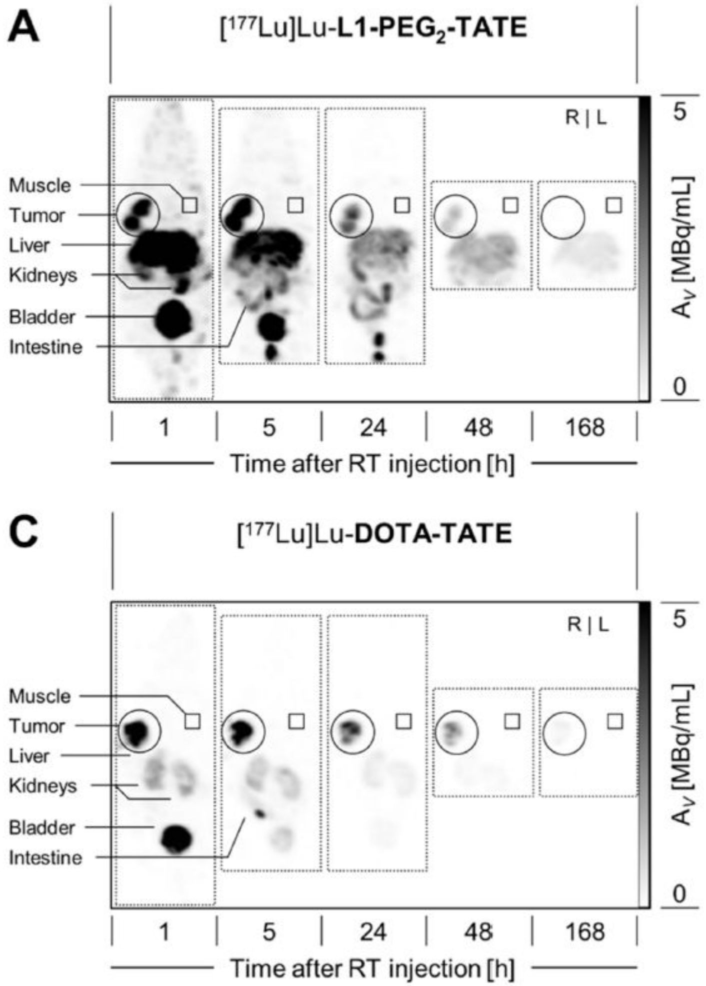


Figure 3. Radiochemical yields at different ligand concentrations (40 °C, 0.15 mM NH_4OAc, pH 6, 5 min, initial A ([^{111}In]In^{3+} and [^{177}Lu]Lu^{3+} = 5 MBq), initial A ([^{225}Ac]Ac^{3+} = 50 kBq), n = 2).





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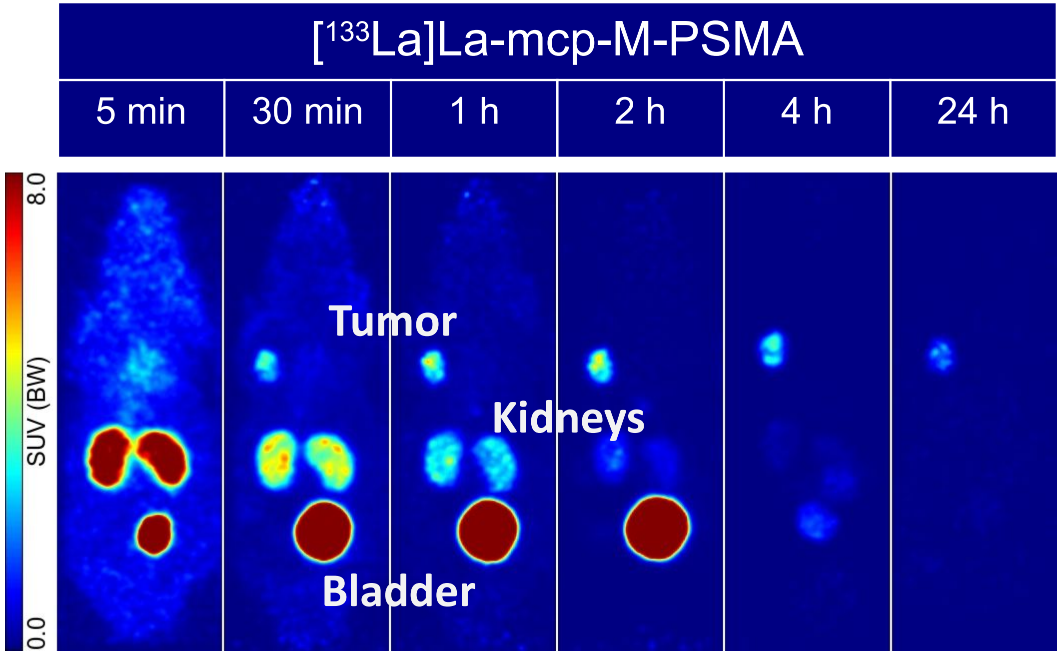
Cieslik P, Kubeil M* et al. J Am Chem Soc 2022 Nov 30;144(47):21555-21567.*

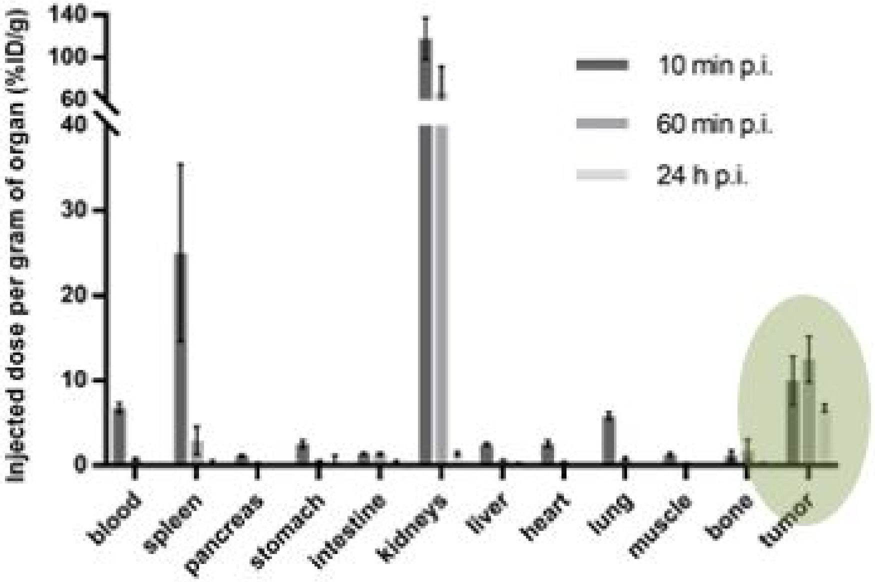
Theranostic Concept: the $^{225}Ac/^{133}La$ matched pair for Radioconjugates

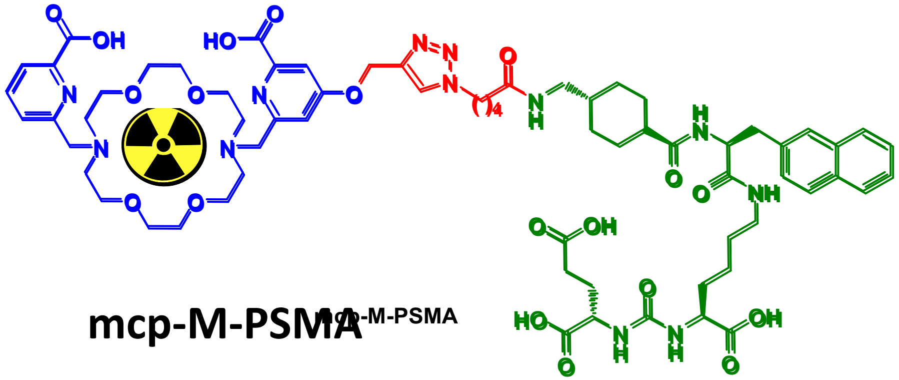
- **easy and mild labeling:** macropa as excellent chelator and target molecule with **high affinity** to PSMA
- **Stability:** no dissociation **over 10 days**
- **Cell binding: high binding affinity**
- **High Tumor uptake:** comparable to PSMA-617



LNCaP-tumor-bearing mouse

(A) [^{225}Ac]Ac-mcp-M-PSMA





mcp-M-PSMA

 = [^{225}Ac]Ac^{3+} or [^{133}La]La^{3+}

Reissig F et al. Cancers 2021;13:1974; Bruehlmann S et al. Pharmaceuticals 2022;15(10):1167

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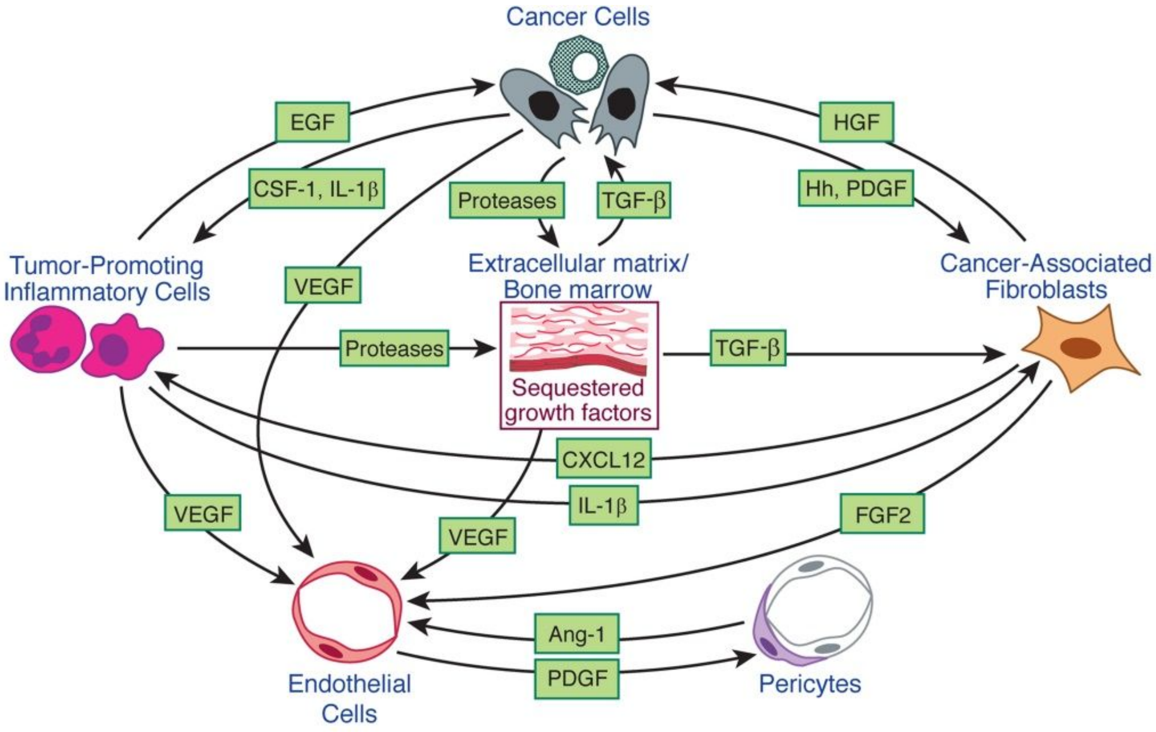
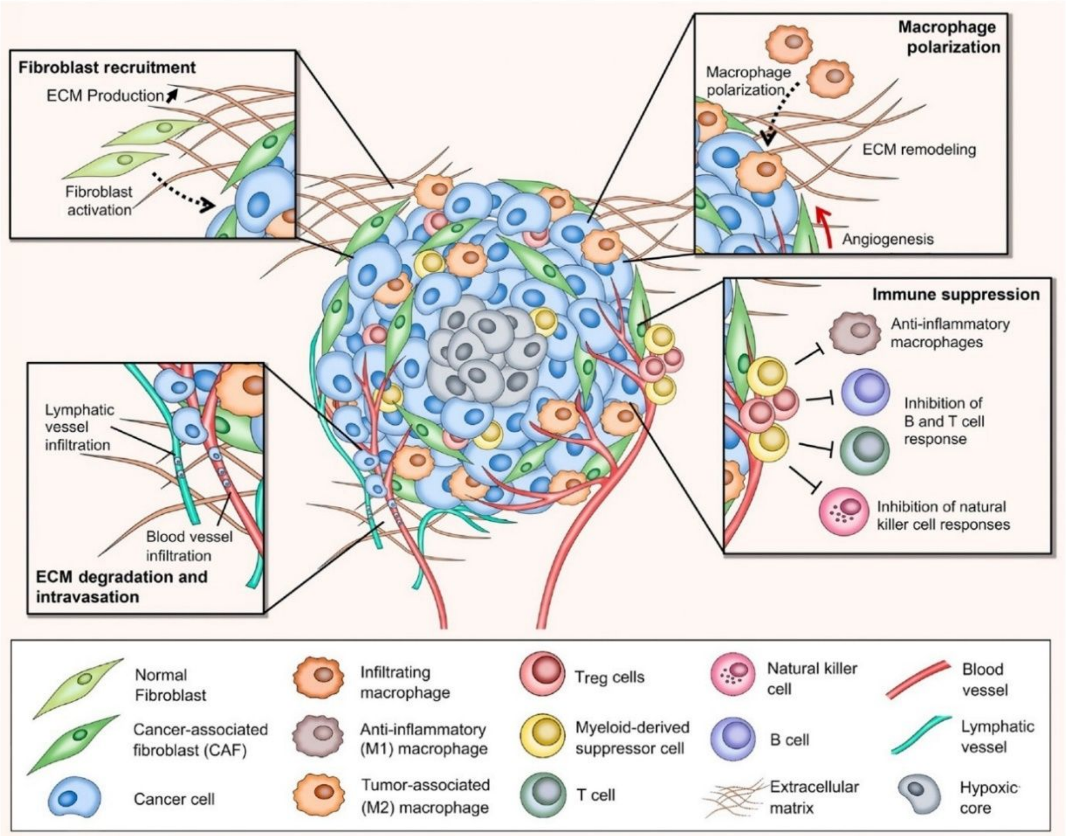
Targeting the tumor microenvironment (TME)

Suddenly you are confronted with cancer research, finding the right unmet clinical need:
Understanding of the tumor microenvironment needed [„The collective contributions of assorted cell types“]





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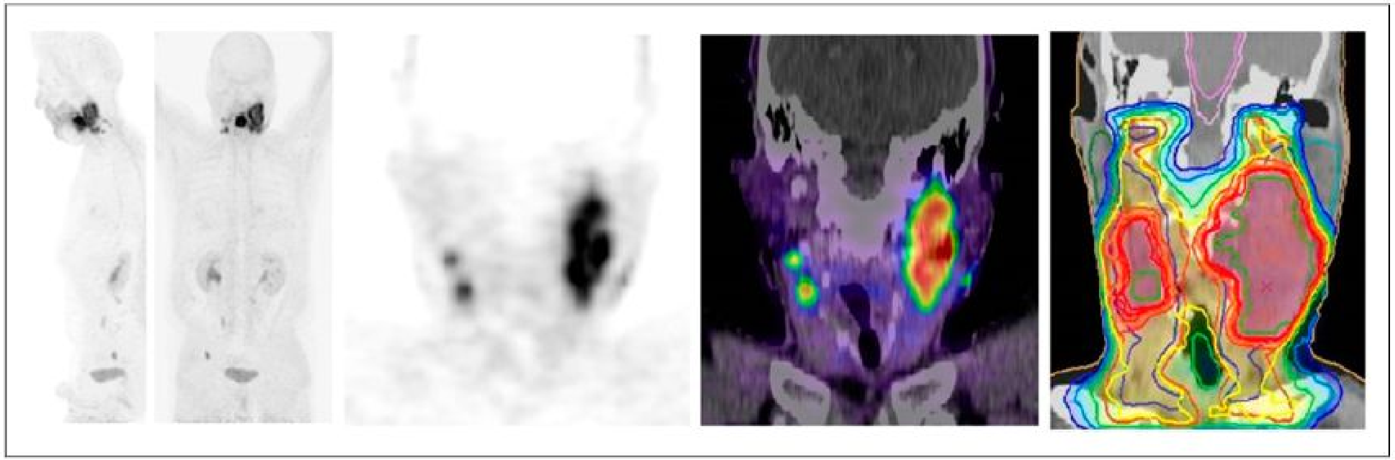
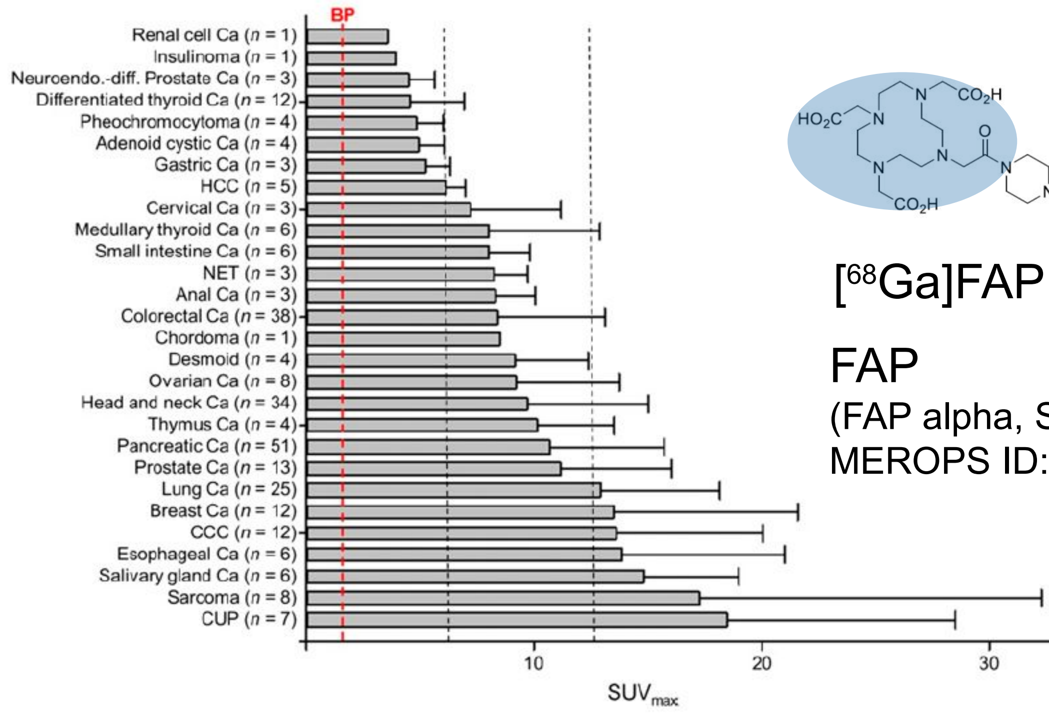
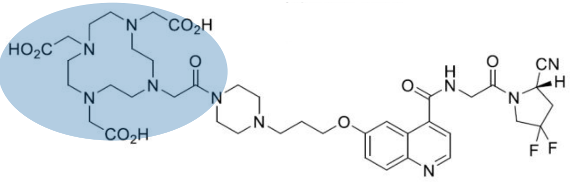
Imlimthan S et al. Pharmaceuticals (Basel) 2022;14(10):1023; Allavena P, Mantovani A Clin Exp Immunol 2012;167:195-2015; Chen X, Song E. Nat Rev Drug Discov 2019 Feb;18(2):99-115.

FAPI PET/CT: Tracer uptake in 28 different kinds of cancer *vs.* prognostic marker after MI

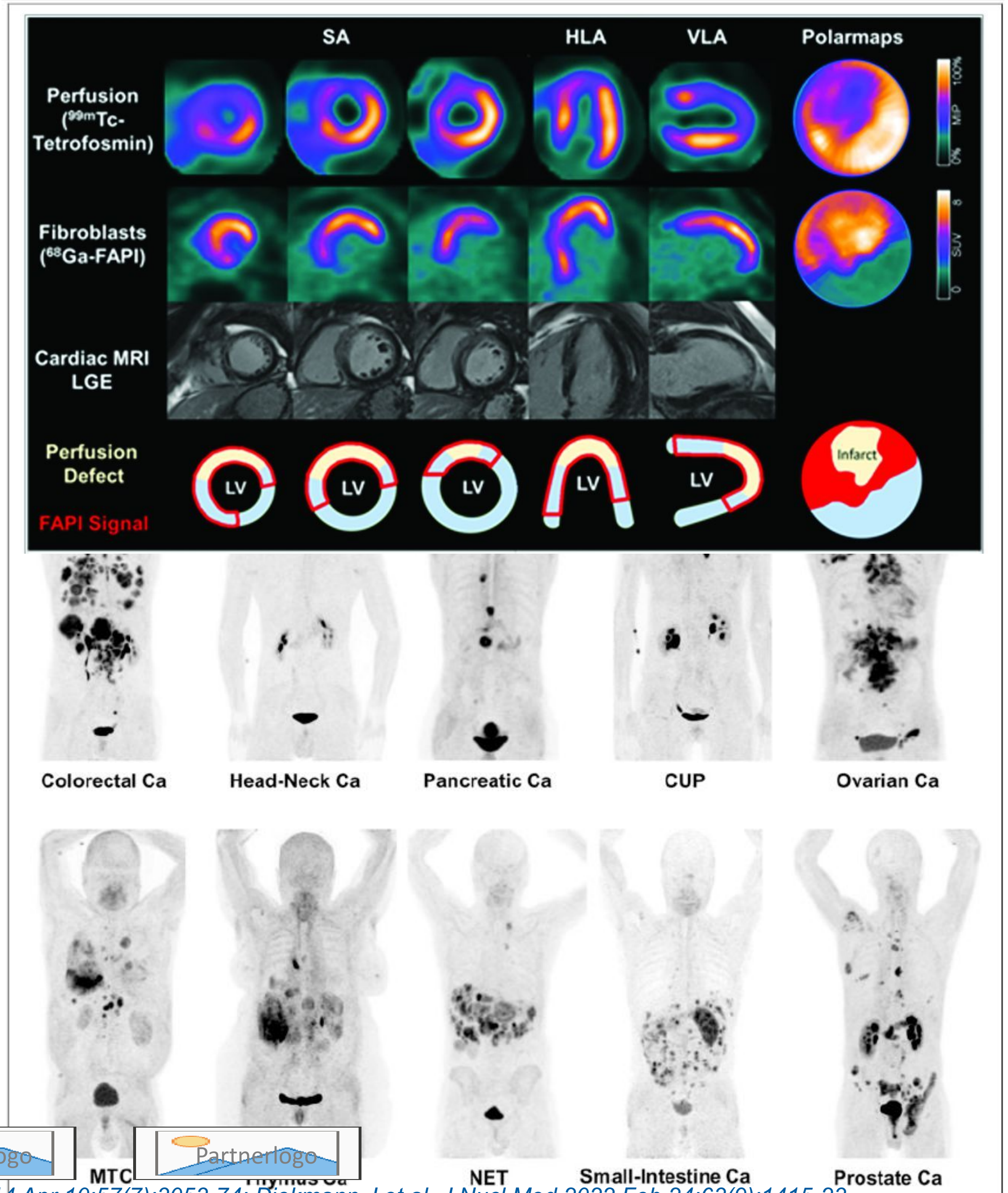






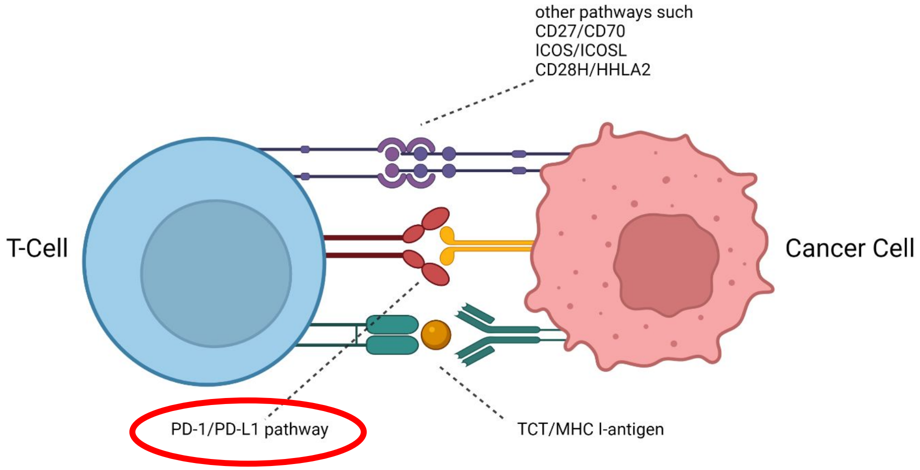
[^{68}Ga]FAPI-04

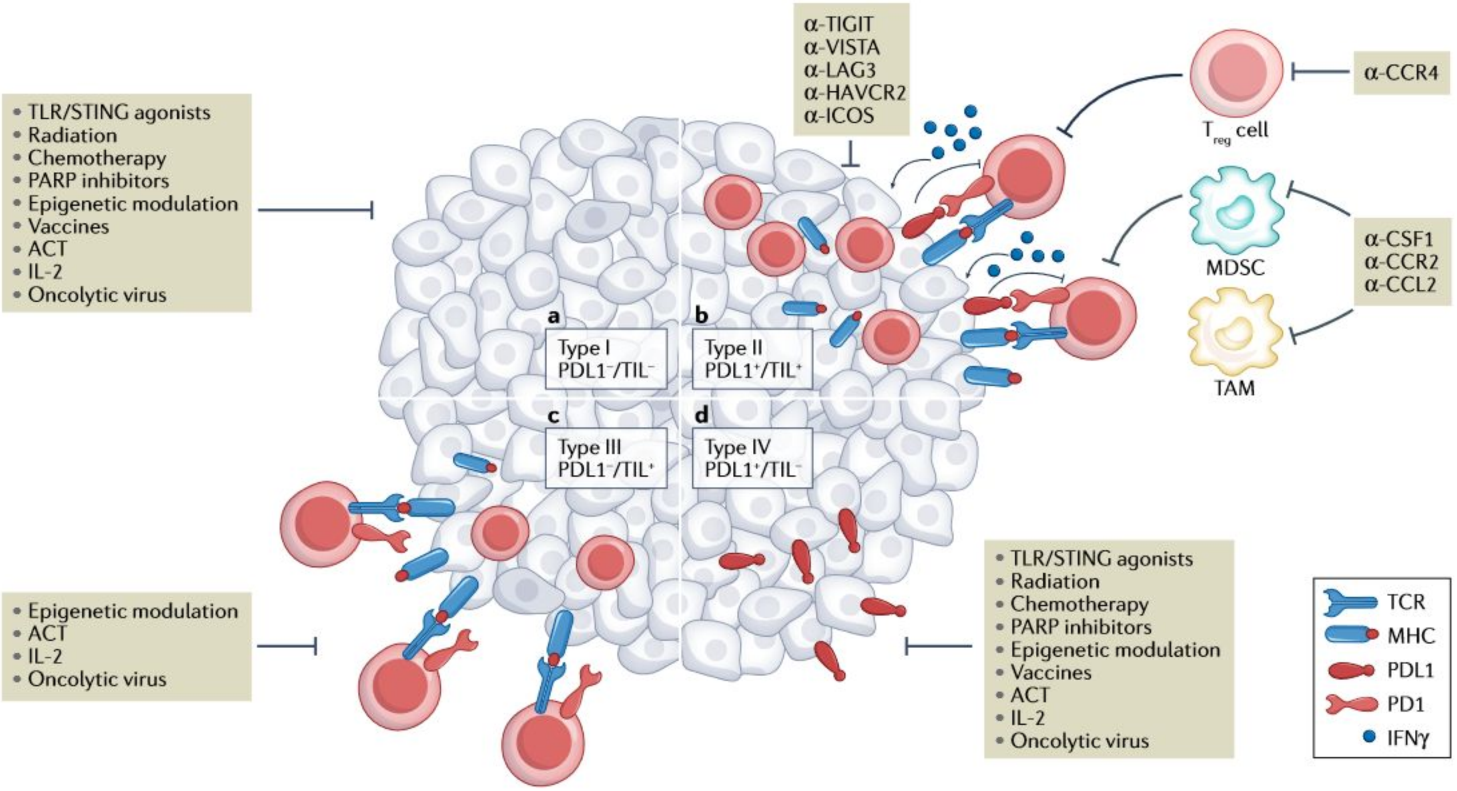
FAP
(FAP alpha, Seprase)
MEROPS ID: S09.007



Kratochwil C et al. J Nucl Med 2019;60:801-805; Lindner T et al. J Nucl Med 2018 Sep;59(9):1415-1422; Jansen K et al. J Med Chem 2014 Apr 10;57(7):3053-74; Diekmann J et al. J Nucl Med 2022 Feb 24;63(9):1415-23.

Clinical need for molecular imaging of PD-1/PD-L1 axis within the TME





- Overexpressed in several cancer types, e.g. lung, colorectal, breast and ovarian cancer, melanoma
- Immune checkpoint inhibitor (ICI) **monotherapy**: only ca. 30% response rate, understanding of **adaptive immune resistance** needed
- Clinicians need a tool for **therapy decision** and **monitoring** of target expression and dynamics over the course of the disease

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Krutzek F, Kopka K, Stadlbauer S. Pharmaceuticals (Basel) 2022;15(6):747; Kim TK et al. Nat Rev Drug Discov 2022 Jul;21(7):529-540.

Clinical need for molecular imaging of PD-1/PD-L1 axis within the TME

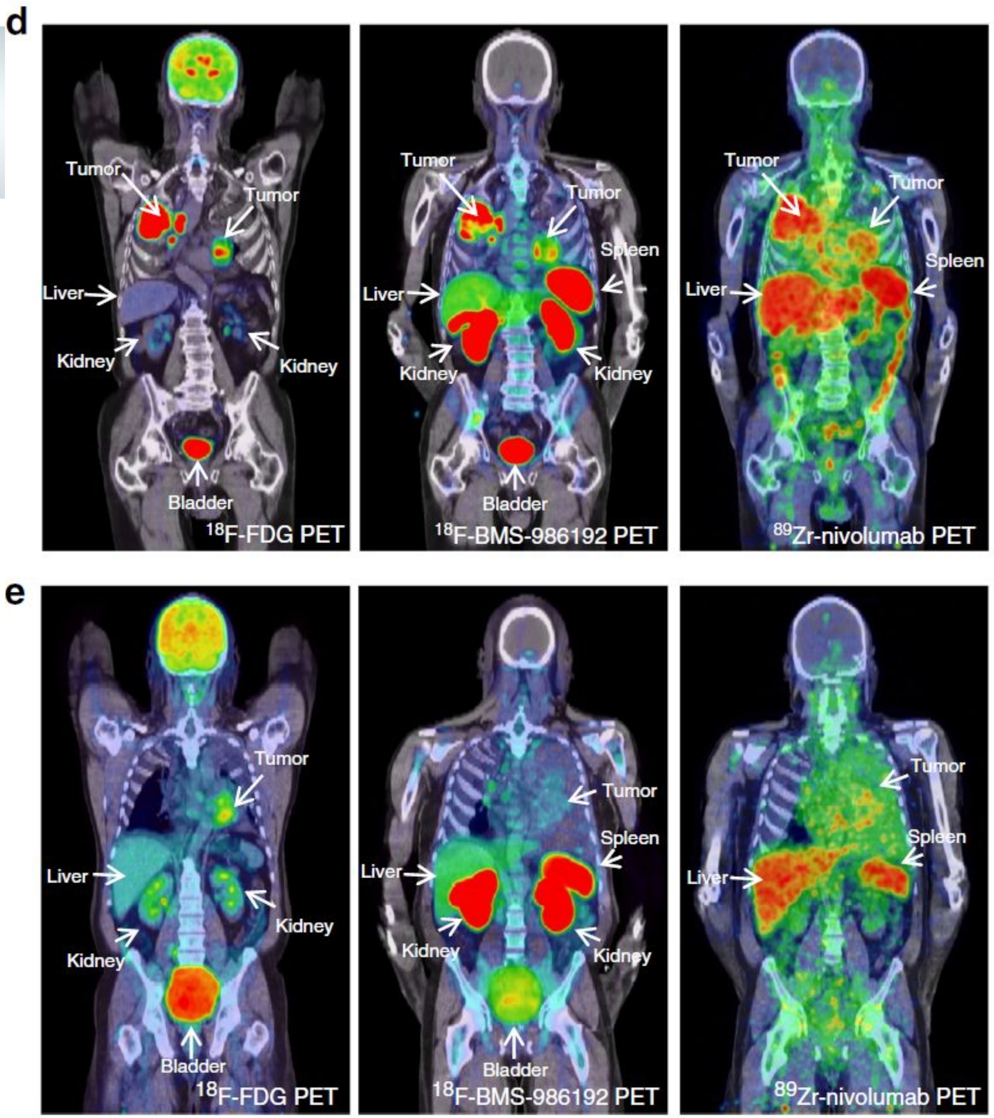
nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-07131-y OPEN

Whole body PD-1 and PD-L1 positron emission tomography in patients with non-small-cell lung cancer

A.N. Niemeijer[1], D. Leung[2], M.C. Huisman[3], I. Bahce[1], O.S. Hoekstra[3], G.A.M.S. van Dongen[3], R. Boellaard[3], S. Du[2], W. Hayes[2], R. Smith[2], A.D. Windhorst[3], N.H. Hendrikse[3], A. Poot[3], D.J. Vugts[3], E. Thunnissen[4], P. Morin[2], D. Lipovsek[2], D.J. Donnelly[2], S.J. Bonacorsi[2], L.M. Velasquez[2], T.D. de Gruijl[5], E.F. Smit[6] & A.J. de Langen[1,6]

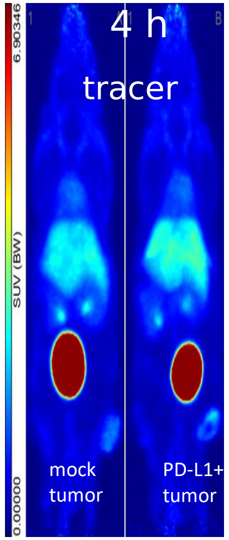


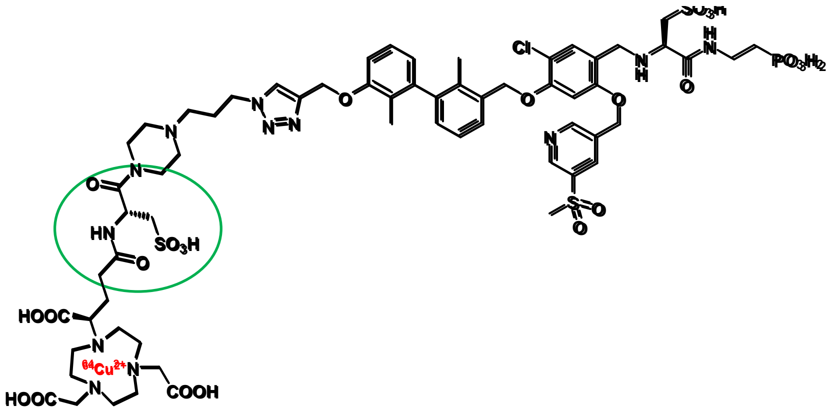
Niemeijer AN et al. Nat Commun 2018, 9, 4664.

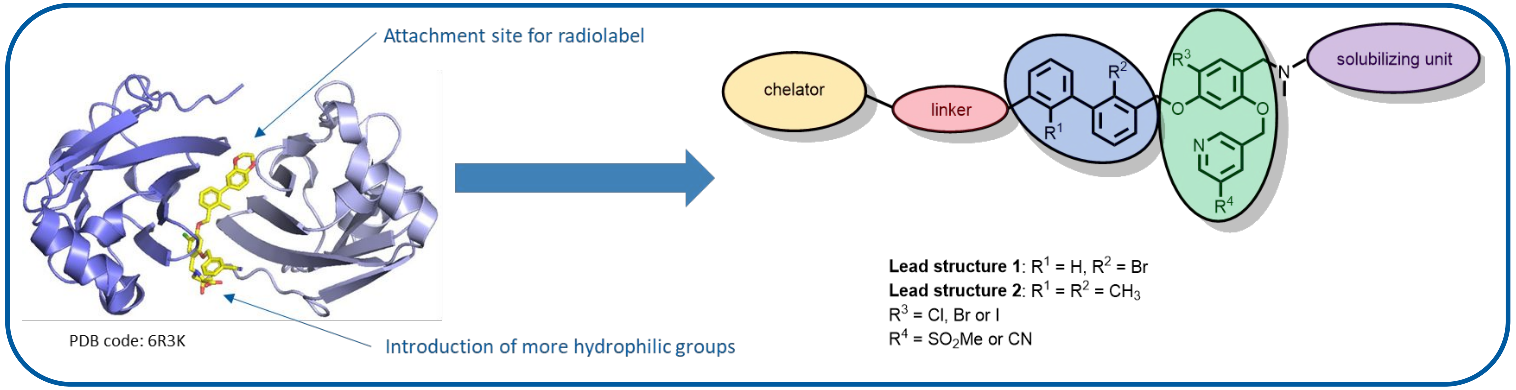
In vivo evaluation of PD-L1 Tracer pipeline

→ renal clearance

→ low tumor uptake

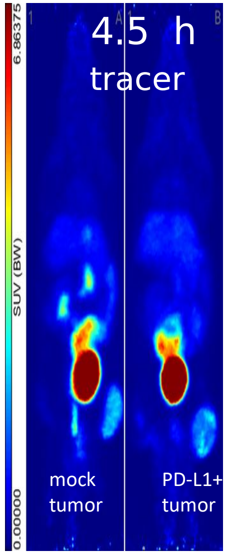


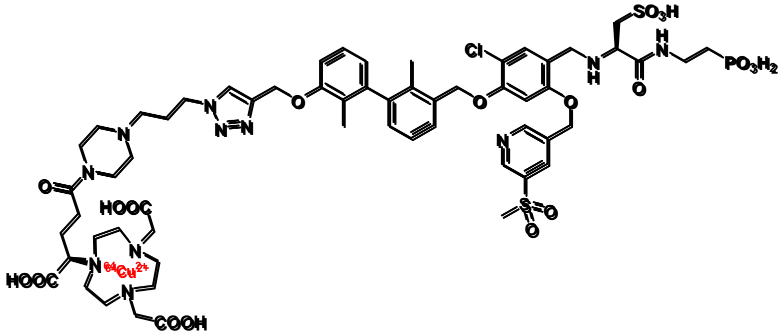




→ renal clearance

→ increased tumor uptake





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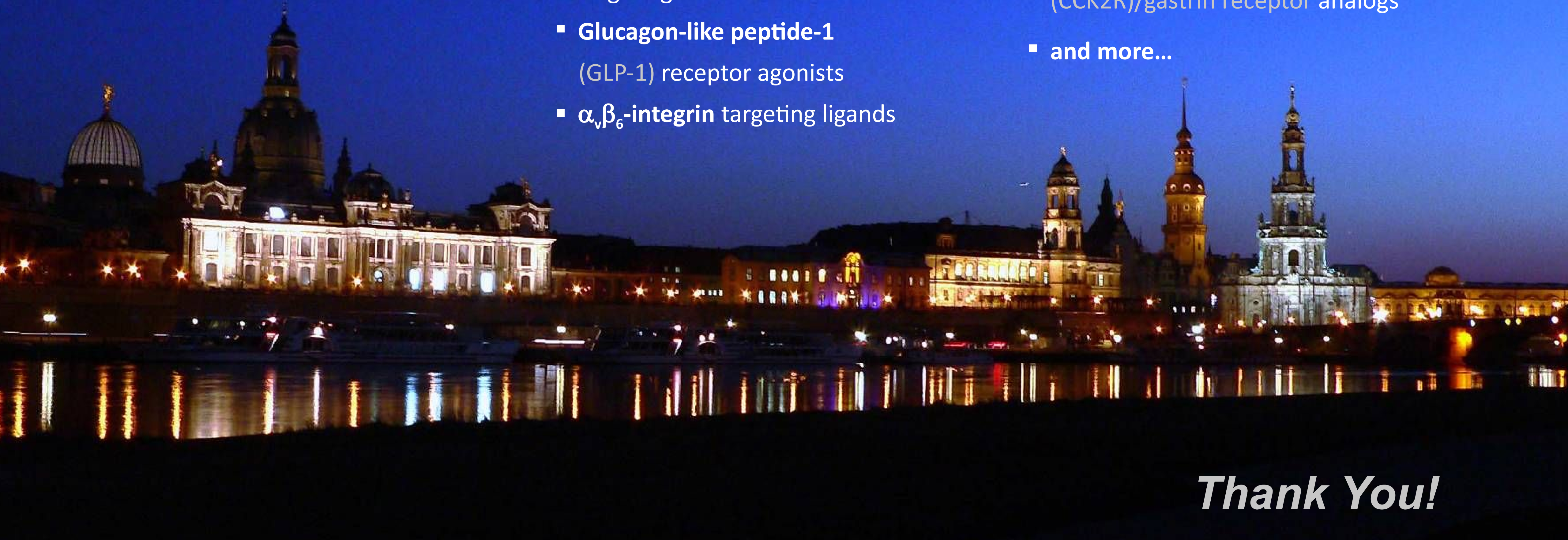
Krutzek F et al. Cancers (Basel) 2023 May 6;15(9):2638; Krutzek F, Kopka K, Stadlbauer S. Pharmaceuticals (Basel) 2022;15(6):747; S. Stadlbauer, F. Krutzek, K. Kopka, patent application EP21212444.0, **2021**.

We should not forget the other Classes of Theranostic Tracers…

- **Somatostatin Receptor** (SSTR)-targeting antagonists
- **Norepinephrine (NE)** analogs
- **C-X-C chemokine receptor 4** (CXCR4)-targeting ligands
- **Carbonic anhydrase IX (CA-IX)**-targeting inhibitors
- **Glucagon-like peptide-1** (GLP-1) receptor agonists
- **$\alpha_v\beta_6$-integrin** targeting ligands
- **Gastrin-Releasing Peptide Receptor** (GRPr)-targeting peptides
- **Cholecystokinin 2 receptor** (CCK2R)/gastrin receptor analogs
- **and more…**



Thank You!

Foto: Dr. Martin Walther