HEIDELBERG UNIVERSITY HOSPITAL

NuclearMedicine
UniversityHospital Heidelberg

„high-specific-activity“

^{153}Sm-FAPI-46

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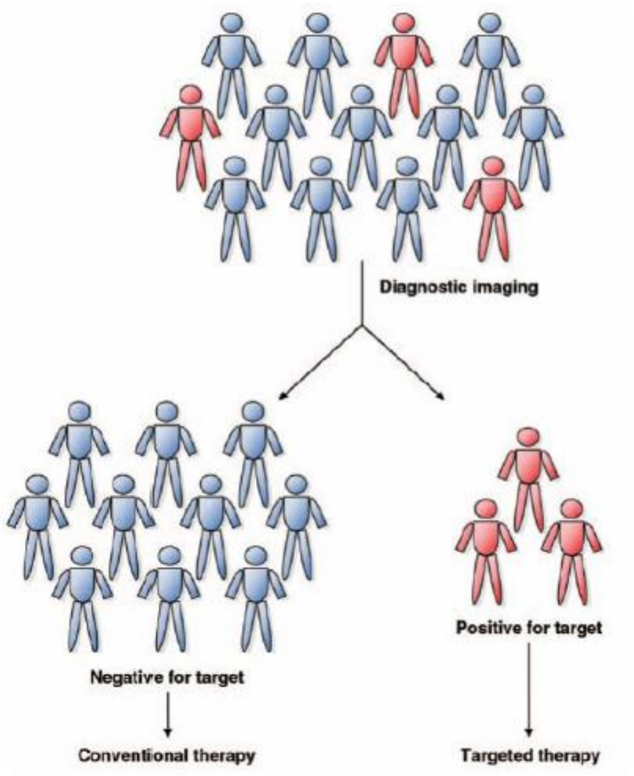
UK HD

Program

- Background on “thera(g)nostics” and “targeted radio-ligand therapy”
  - Dosimetry
  - Pharmacokinetics of shuttle-molecule and physical characteristics of radio-label

- Where do we stand? Own work with radio-labeled FAPI-46
  - Why high-specific activity ^{153}**Sm**-FAPI-46?
  - Challenges of Sm-153

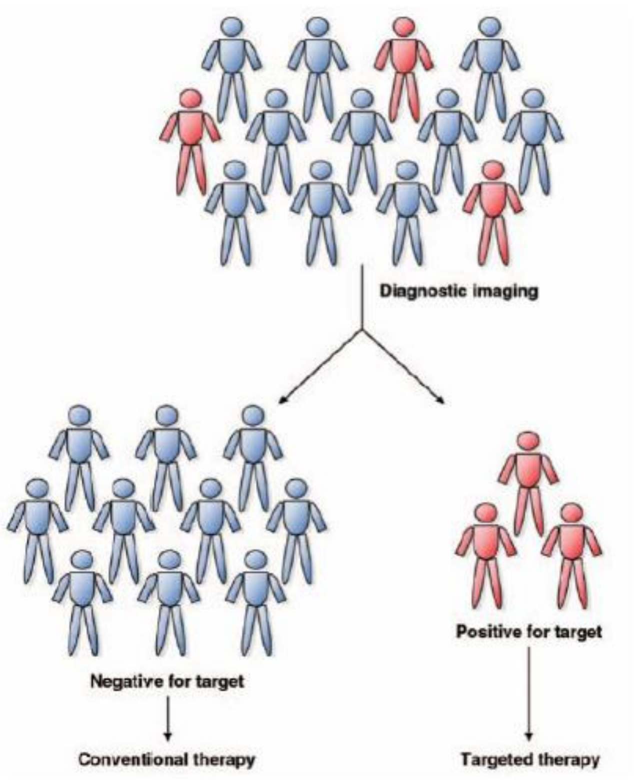
Thera(g)nostics: similar ligand for targeted therapy and diagnostics imaging



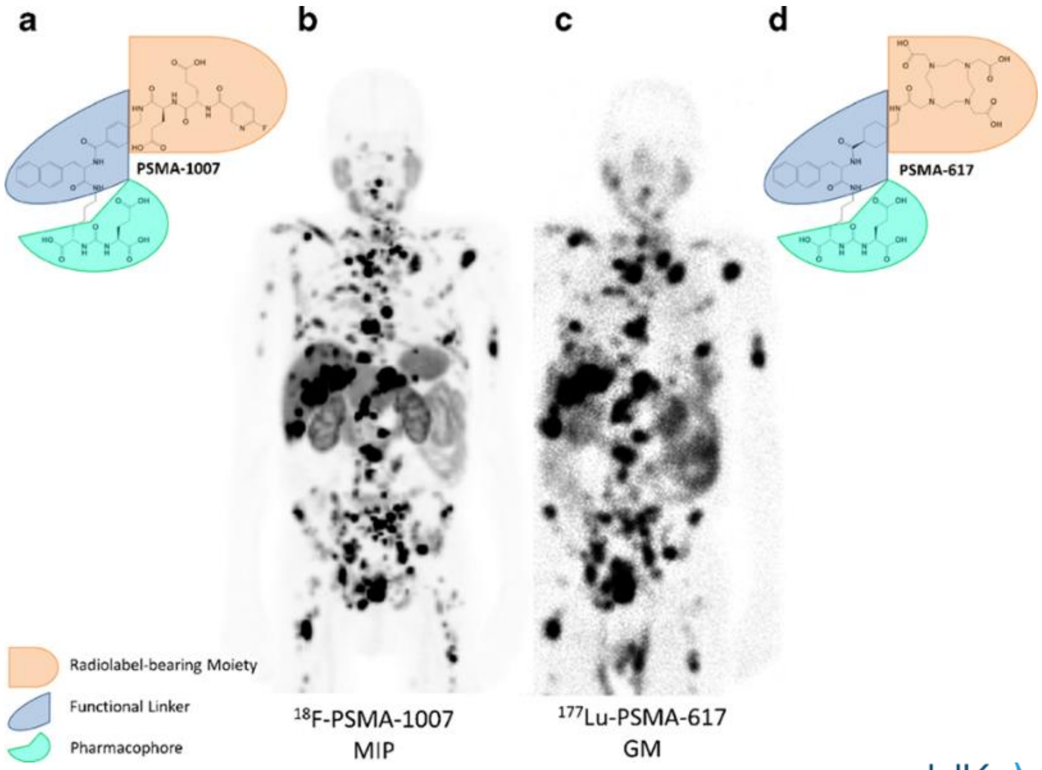
D.Y. Lee, AJR 1997

- Tracer dose of a therapeutic radionuclide with co-emission of gamma photons (e.g. radioiodine-test)
- Identical molecule but different isotope (I-123, I-131)
- Shuttle-molecule tagged with a chelator that can be labeled with various diagnostic and therapeutic radio-metals (e.g. Ga-68, Lu-177, Tb-161, Ac-225)
- Surrogate imaging using an (often faster) ligand binding to the identical target molecule

Thera(g)nostics: similar ligand for targeted therapy and diagnostics imaging

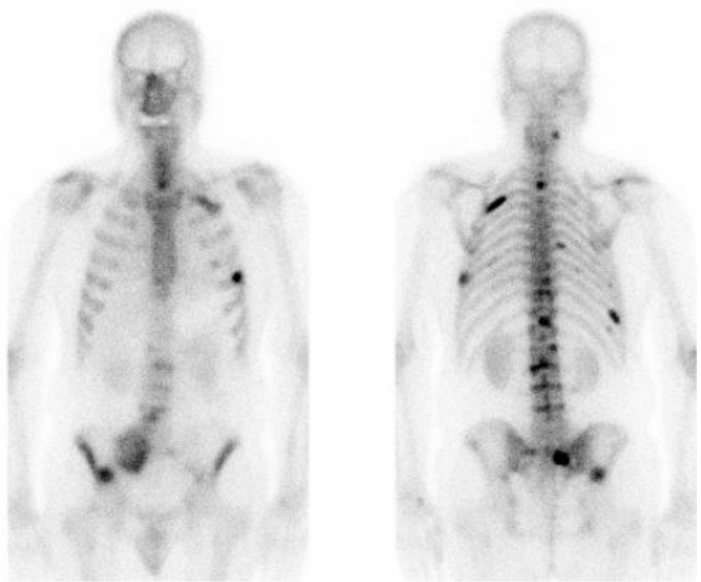


D.Y. Lee, AJR 1997



Giesel FL, Kratochwil C, et al. EJMMI 2016

Thera(g)nostics: Diagnostic imaging as surrogate for treatment dosimetry?

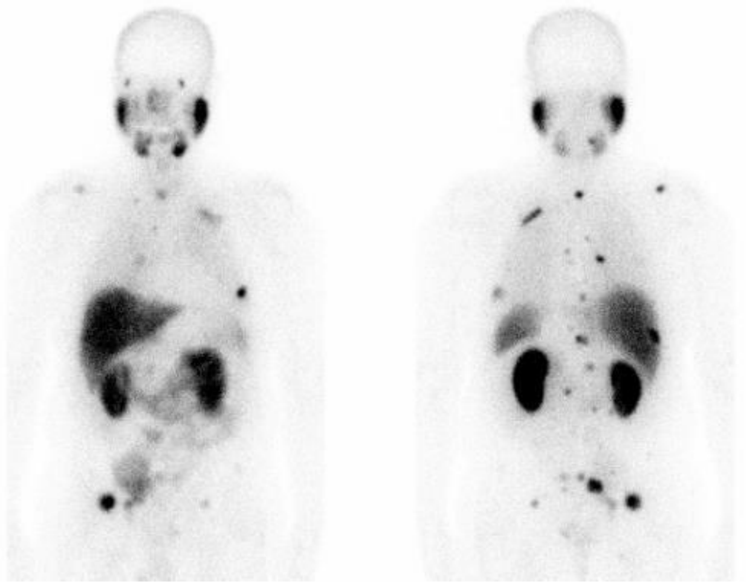


No.	Reference	Tumor Gy / GBq		Osteogenic cells Gy / MBq	Red marrow Gy / GBq
1	Andreou M et al. JoPhysics 2011	22		6,8	1,5

No.	Refer…				…marrow …/ MBq
1	Pacili…				…,14
2	Murra…				…,14

Bone-Seekers:
Tumor to Red Marrow 15 : 1

^{153}Sm-EDTMP, ^{223}RaCl$_2$



No.	Reference	Tumor Gy/GBq	Red marrow Gy/GBq	Kidney Gy/GBq	Salivary Gl. Gy/GBq
1	Kabasakal L, et al. EJNMMI. 2015;42:1976-83		0,03	0,88	1,17
2	Delker A, et al. EJNMMI. 2016;43:42-51	13,1	0,01	0,6	1,4
	Mittelwert	6,00	0,03	0,74	1,26

PSMA-RLT:
Tumor to Red Marrow 150 : 1

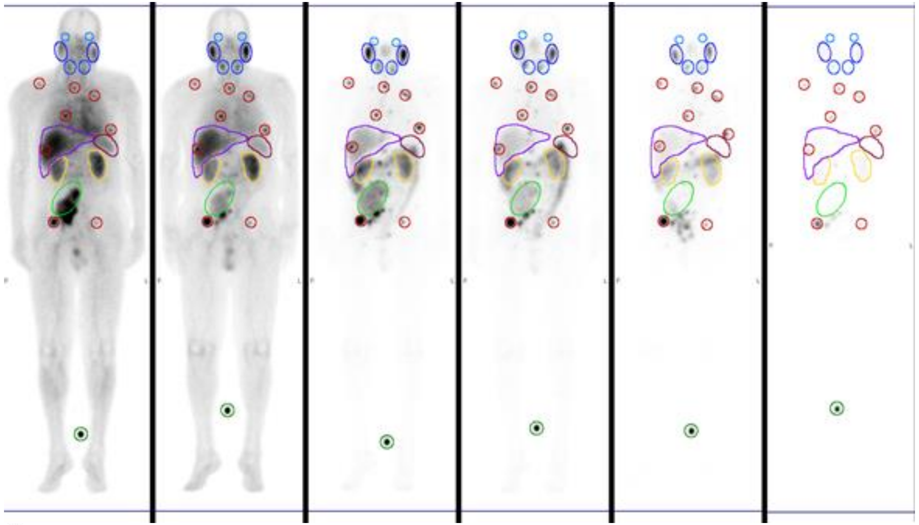
^{177}Lu-PSMA-617

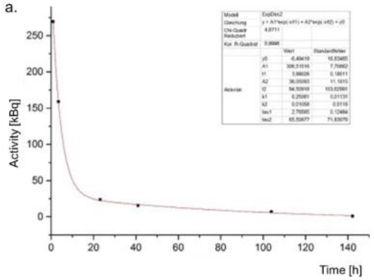
UKHD

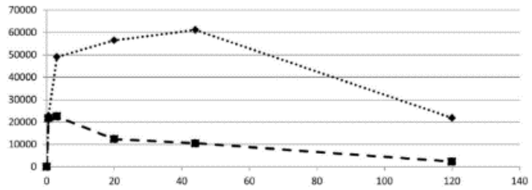
A magic bullet would have perfect tumor vs. normal-organ dosimetry

- Serial imaging and blood sampling
- Segmentation of organs and tumors.
  TAC fitting. Integration of number of decays in target volume.
- Segmentation of target mass per CT
- OLINDA calculates organ und tumor (Sphere model) absorbed dose [Gy]
- Dose-limiting organs:
  Red-marrow: 1-3 Gy
  Kidneys: 23-30 Gy

  Tumor: > 80 Gy needed

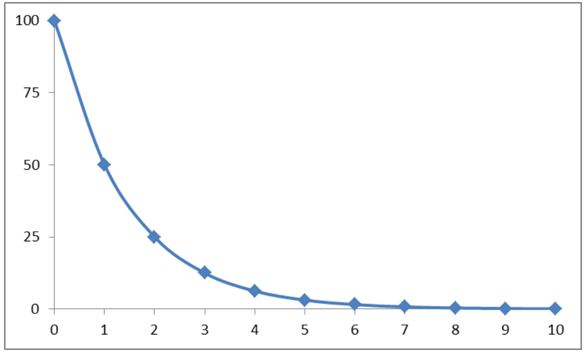




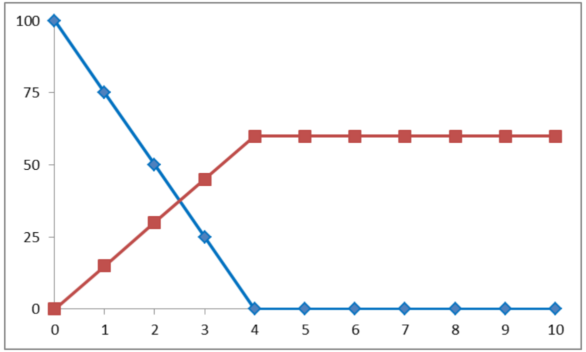


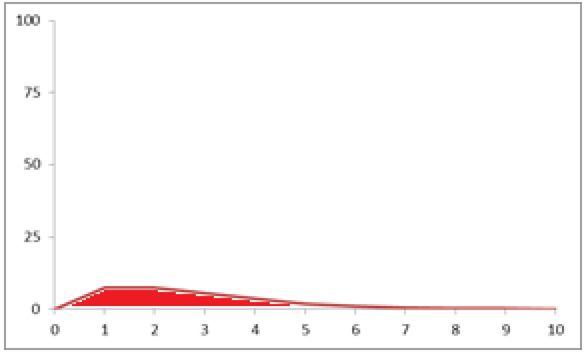
Radiopharmacology: Understanding the basics

Physical half-life

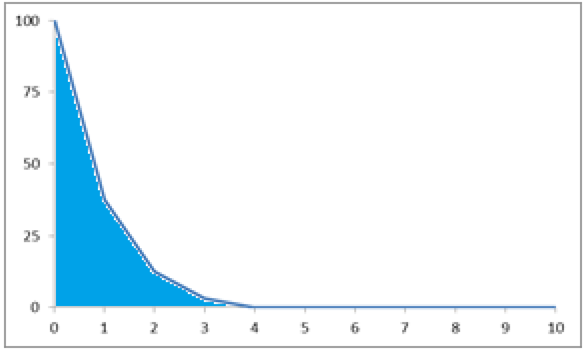


Pharmacokinetics





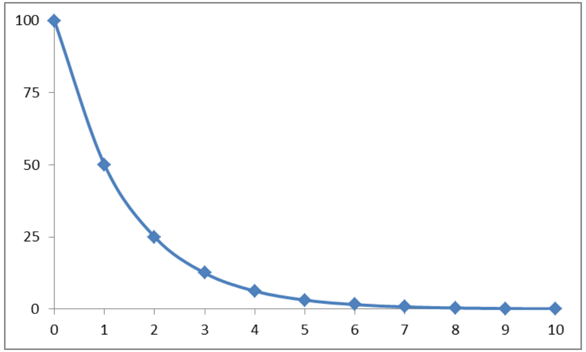
Tumor absorbed dose



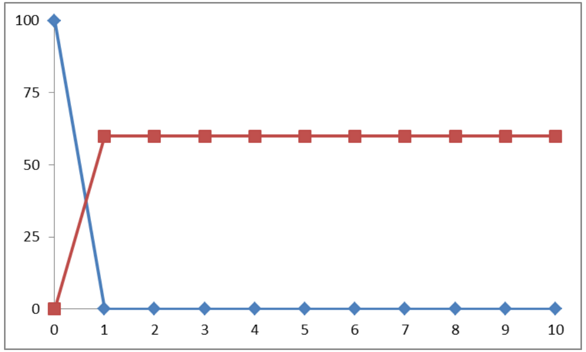
Blood / marrow dose

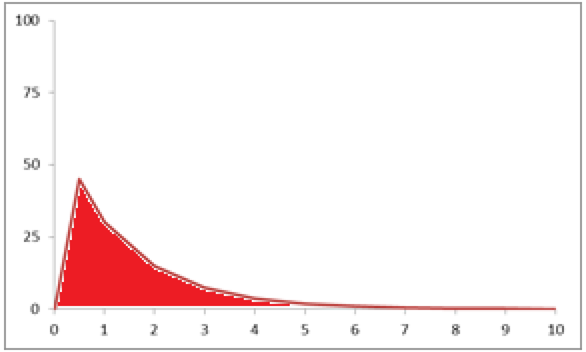
Radiopharmacology: Understanding the basics

Physical half-life

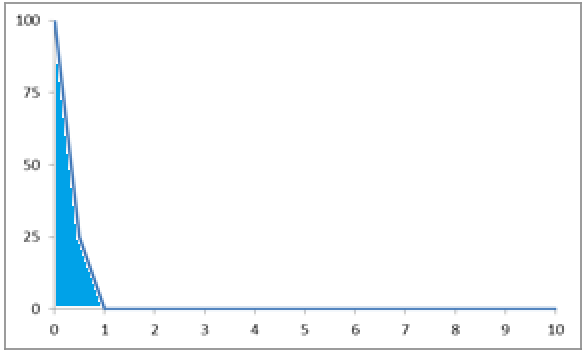


Pharmacokinetics



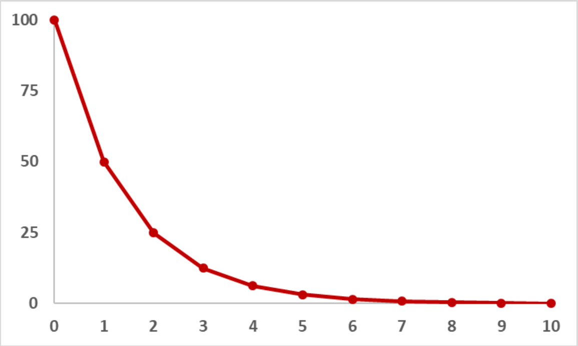


Tumor absorbed dose

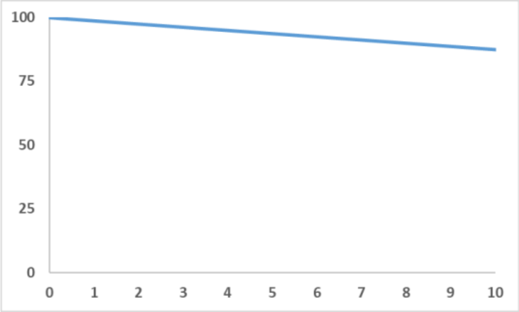


Blood / marrow dose

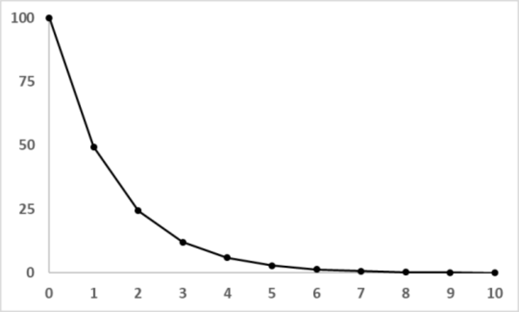
Radiopharmacology: Understanding the basics



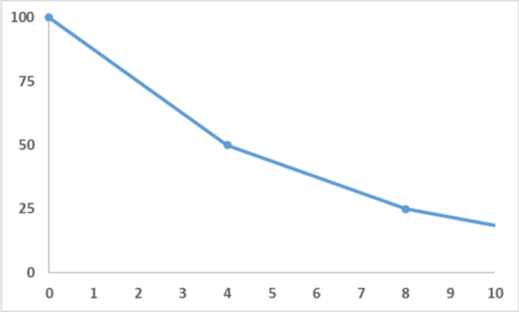
Biological half-life (tumor)



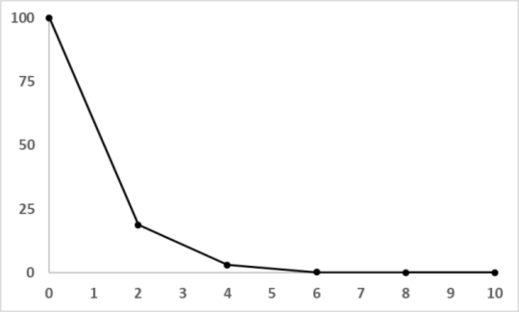
HWZ_{phys} = 40x HWZ_{biol}



Tumor absorbed dose

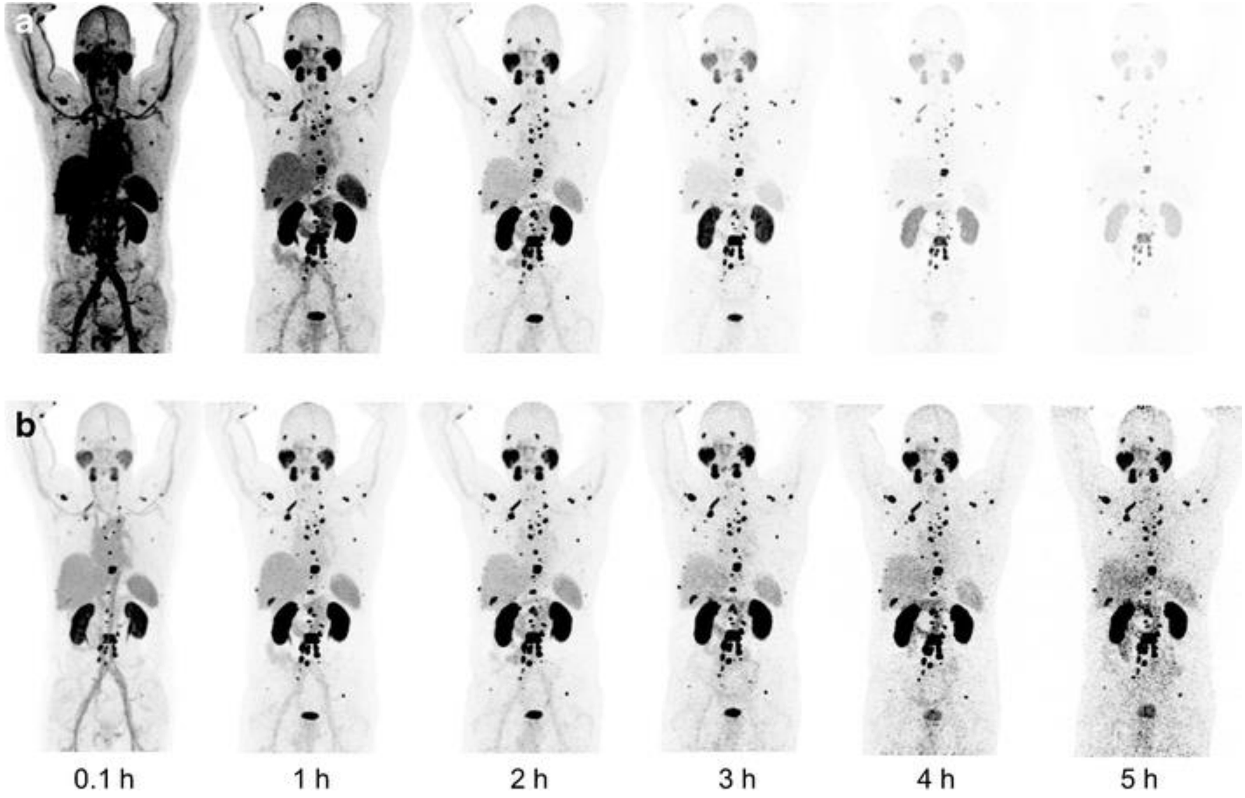


HWZ_{phys} = 4x HWZ_{biol}



Tumor absorbed dose

Radiopharmacology: Understanding the basics



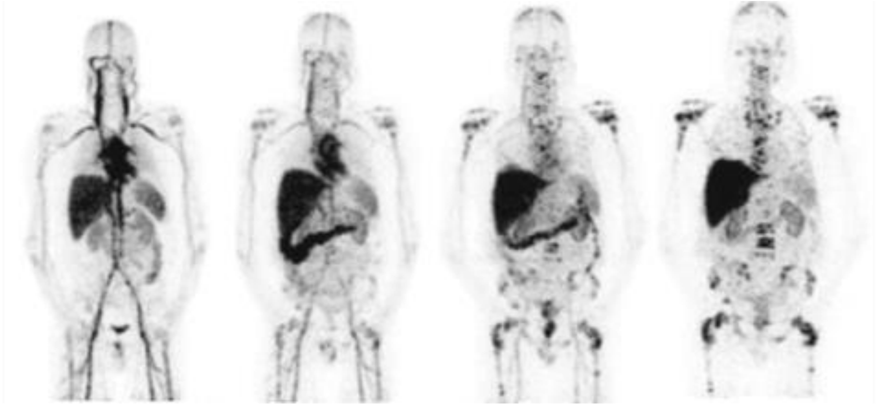
a) ^{213}Bi-PSMA617 (HL 47 min) vs. b) ^{225}Ac-PSMA617 (HL 9.9 d)

(quantitatively correct reconstructed images normalized to 2h p.i.)

Kratochwil, EJNM 2018

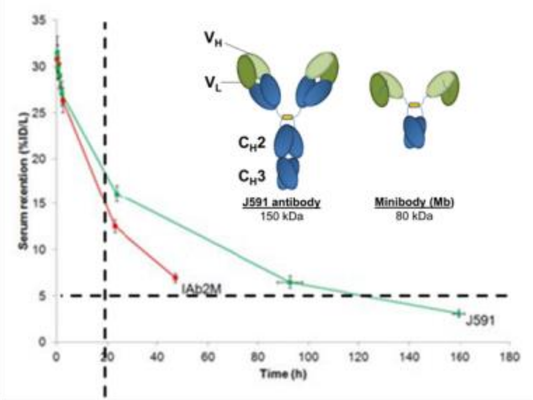
Radio-Ligand-Therapy ≠ Radio-Immuno-Therapy 2.0

hu591

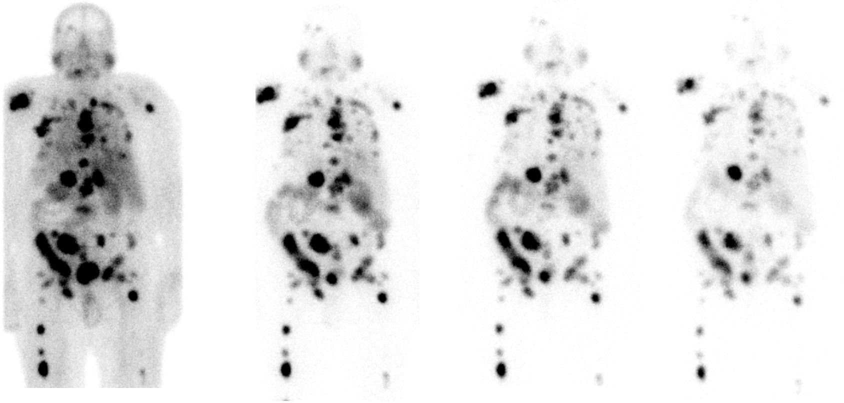


Day 1 Day 2 Day 4 Day 8

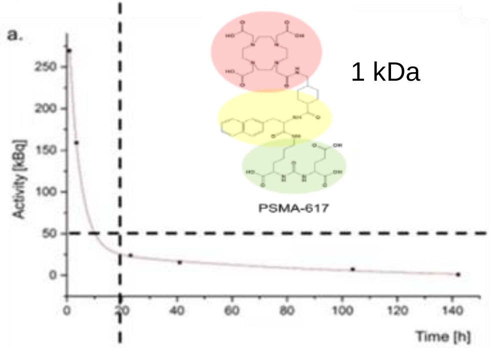
Pandit-Taskar, et al. JNM, 2016



PSMA-617

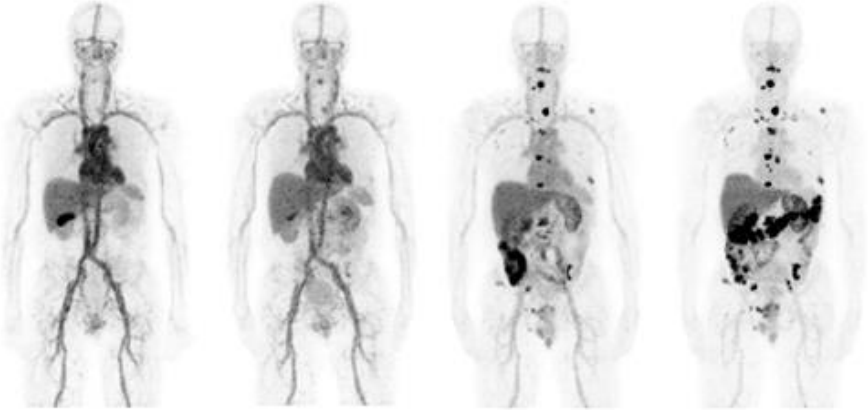


1-4h p.i. 24h p.i. 48h p.i. 96h p.i.



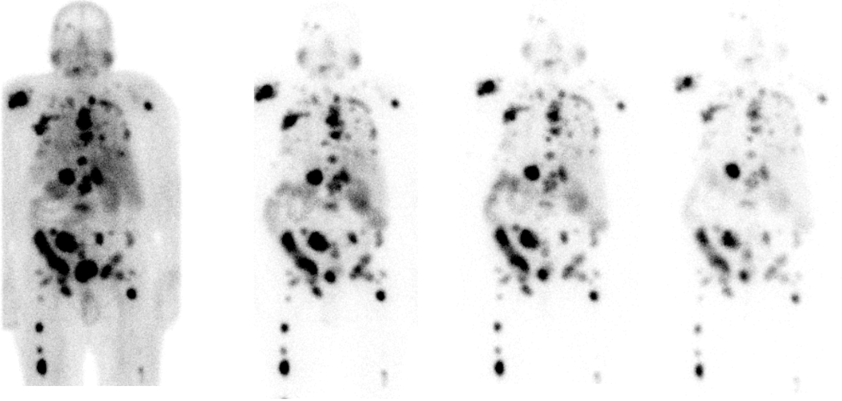
Radio-Ligand-Therapy ≠ Radio-Immuno-Therapy 2.0

IAB2M



1-4h p.i. 24h p.i. 48-72h p.i. 96-120h p.i.

PSMA-617



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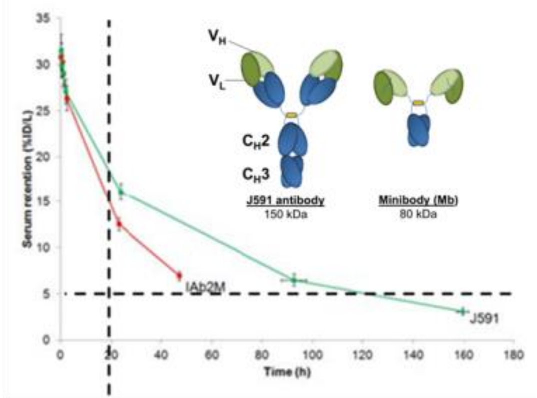
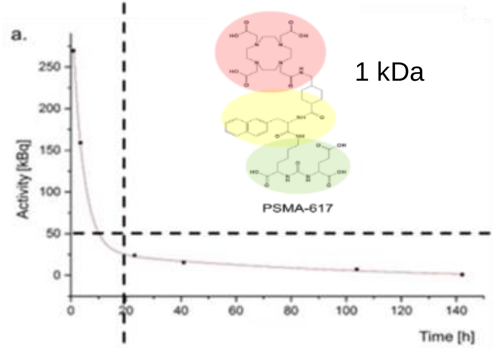
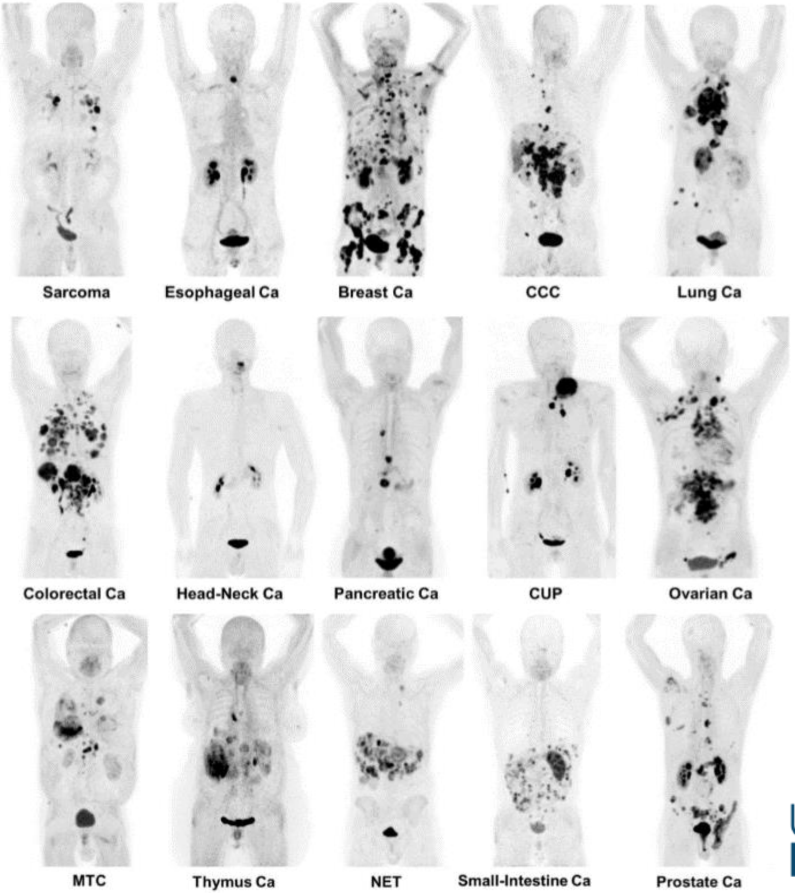
Pandit-Taskar, et al. JNM, 2016





How to construct a magic bullet – FAPI-46

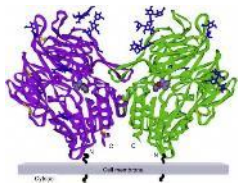
- **Multi tumor targeting molecule**
- **Tumor specific, high uptake (SUV >10)**
- Large extra-cellular domain
- Ligand-induced internalization
- Post-Proline-Cleaving-Protease Inhibitor
- Rapid kinetics of low-molecular-weight ligand
- Universal DOTA-Chelator



^{68}Ga-FAPI-04 PET/CT 1 h p.i.

Image of the year SNMMI / JNM 2019

How to construct a magic bullet – FAPI-46



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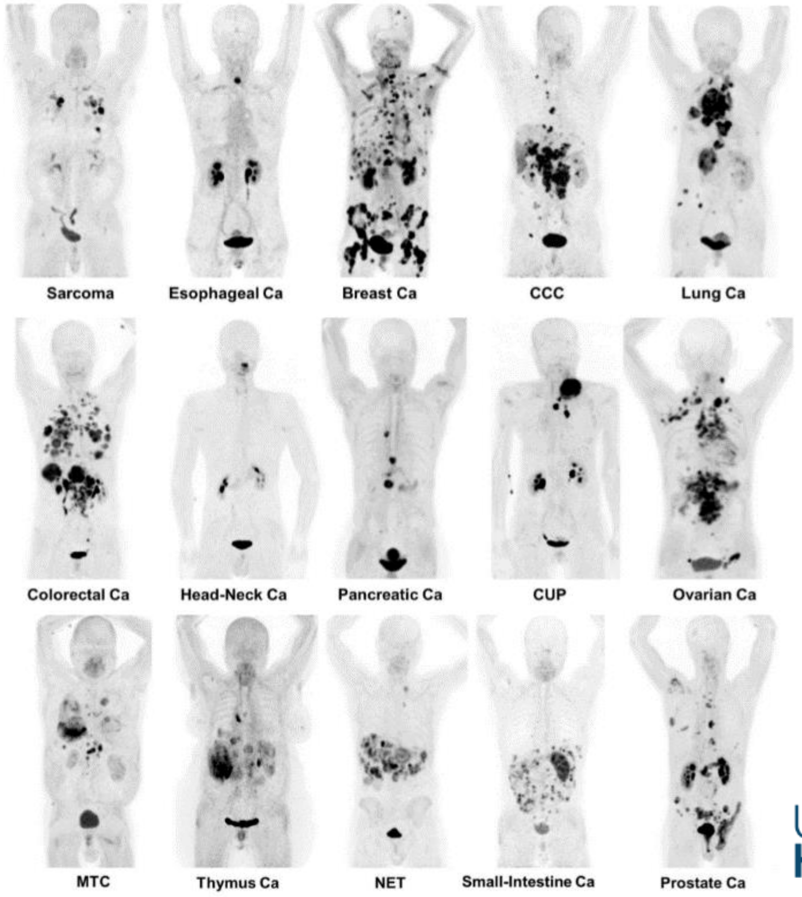
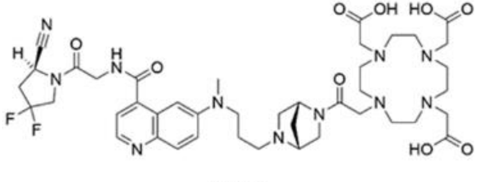


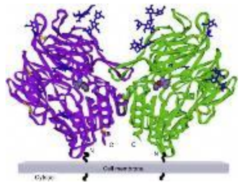
^{68}Ga-FAPI-04 PET/CT 1 h p.i.

Image of the year SNMMI / JNM 2019

How to construct a magic bullet – FAPI-46



FAPI-46



- Multi tumor targeting molecule
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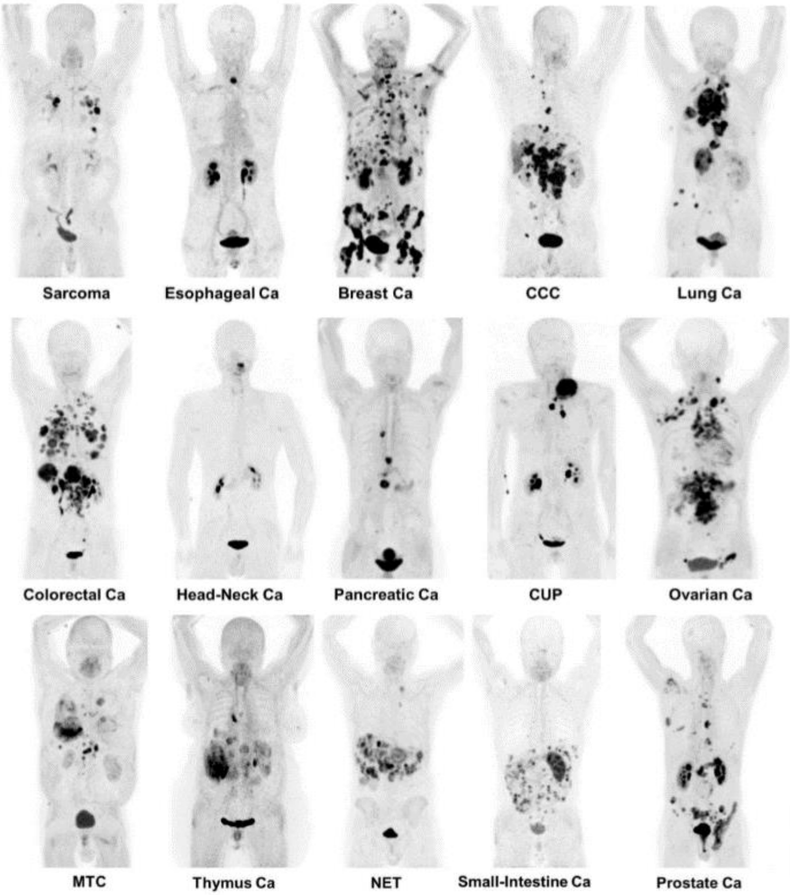


^{68}Ga-FAPI-04 PET/CT 1 h p.i.

Image of the year SNMMI / JNM 2019

FAPI-46 – Optimization of PK

FEATURED BASIC SCIENCE ARTICLE

Development of Fibroblast Activation Protein–Targeted Radiotracers with Improved Tumor Retention

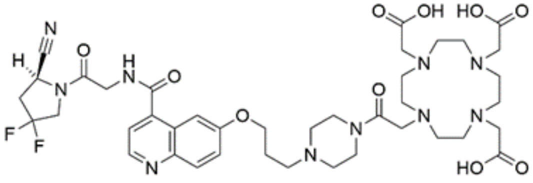
Anastasia Loktev[1,2], Thomas Lindner[1], Eva-Maria Burger[1], Annette Altmann[1,2], Frederik Giesel[1], Clemens Kratochwil[1], Jürgen Debus[3,4], Frederik Marmé[5], Dirk Jäger[6], Walter Mier[1], and Uwe Haberkorn[1,2,7]

[1]Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, Germany; [2]Clinical Cooperation Unit Nuclear Medicine, German Cancer Research Center, Heidelberg, Germany; [3]Department of Radiation Oncology, University Hospital Heidelberg, Heidelberg, Germany; [4]Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center, Heidelberg, Germany; [5]Department of Gynecologic Oncology, National Center for Tumor Diseases and Department of Obstetrics and Gynecology, University Women's Clinic, University Hospital Heidelberg, Heidelberg, Germany; [6]Department of Medical Oncology, National Center for Tumor Diseases, Heidelberg, Germany; and [7]Translational Lung Research Center Heidelberg, German Center for Lung Research, Heidelberg, Germany

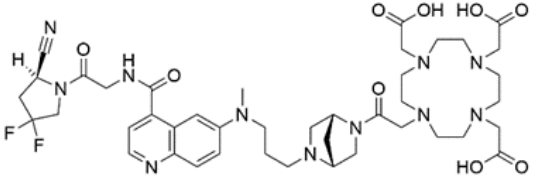
Cancer-associated fibroblasts constitute a vital subpopulation of the tumor stroma and are present in more than 90% of epithelial carcinomas. The overexpression of the serine protease fibroblast activation protein (FAP) allows a selective targeting of a variety of

Key Words: fibroblast activation protein; PET/CT; theranostics; FAP inhibitor; tracer development

J Nucl Med 2019; 60:1421–1429
DOI: 10.2967/jnumed.118.224469



FAPI-04
(Lindner et al. **2018**, [11])



FAPI-46
(Loktev et al. **2019**, [13])

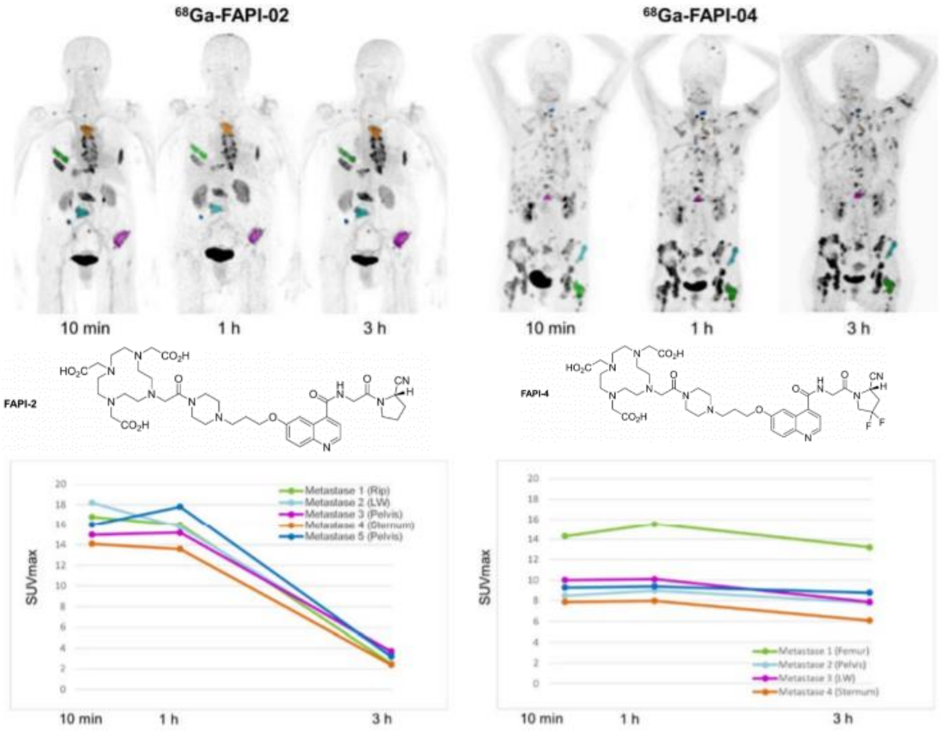
FAPI-46 – Optimization of PK

- **Very short tumor retention time**

  (FAPI-02: ~ 2h,

  FAPI-04: ~8h,

  FAPI-46: ~16h)



FAPI-46 – Optimization of PK

Radiation Dosimetry and Biodistribution of ^{68}Ga-FAPI-46 PET Imaging in Cancer Patients

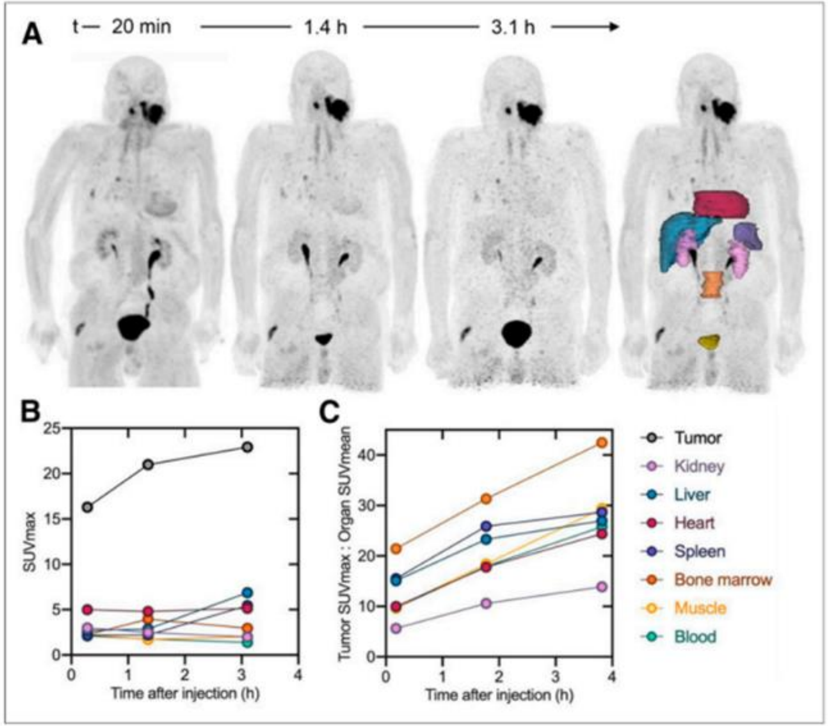
Catherine Meyer[1,2], Magnus Dahlbom[1,2], Thomas Lindner[3], Sebastien Vauclin[4], Christine Mona[2], Roger Slavik[1,2,5], Johannes Czernin[2,6,7], Uwe Haberkorn[3,7,8], and Jeremie Calais[1,2,5,6]

[1]Physics and Biology in Medicine Interdepartmental Graduate Program, David Geffen School of Medicine, UCLA, Los Angeles, California; [2]Ahmanson Translational Theranostics Division, Department of Molecular and Medical Pharmacology, UCLA, Los Angeles, California; [3]Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, Germany; [4]DOSIsoft SA, Cachan, France; [5]Jonsson Comprehensive Cancer Center, UCLA, Los Angeles, California; [6]Institute of Urologic Oncology, UCLA, Los Angeles, California; [7]Clinical Cooperation Unit Nuclear Medicine, DKFZ Heidelberg, Heidelberg, Germany; and [8]Translational Lung Research Center Heidelberg, German Center for Lung Research, Heidelberg, Germany

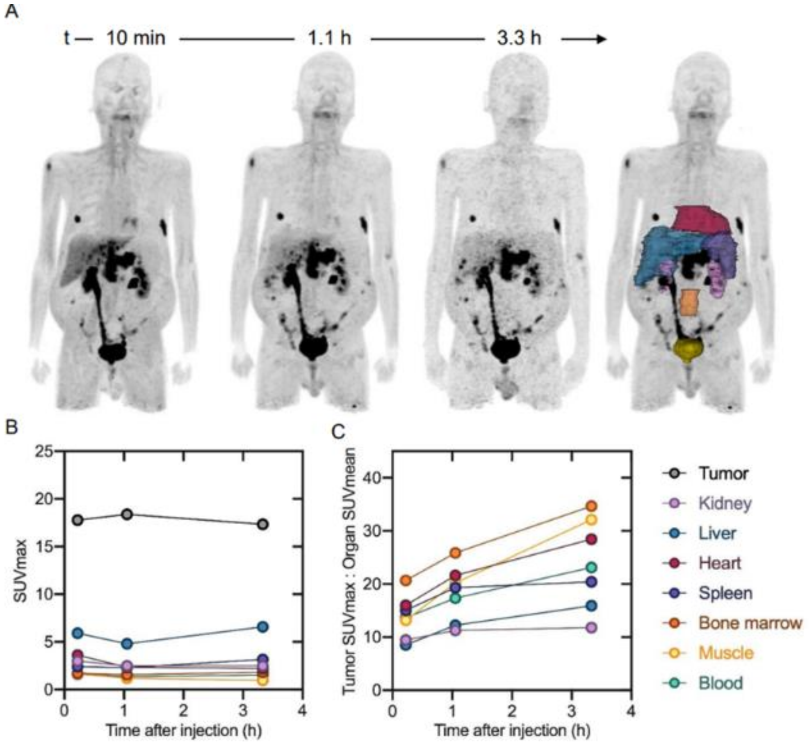
Targeting cancer-associated fibroblasts (CAFs) has become an attractive goal for diagnostic imaging and therapy because they can constitute as much as 90% of a tumor mass. The serine protease fibroblast activation protein (FAP) is overexpressed selectively in

Key Words: FAPI; PET/CT; ^{68}Ga; dosimetry; biodistribution

J Nucl Med 2020; 61:1171–1177
DOI: 10.2967/jnumed.119.236786



FAPI-46 – Optimization of PK



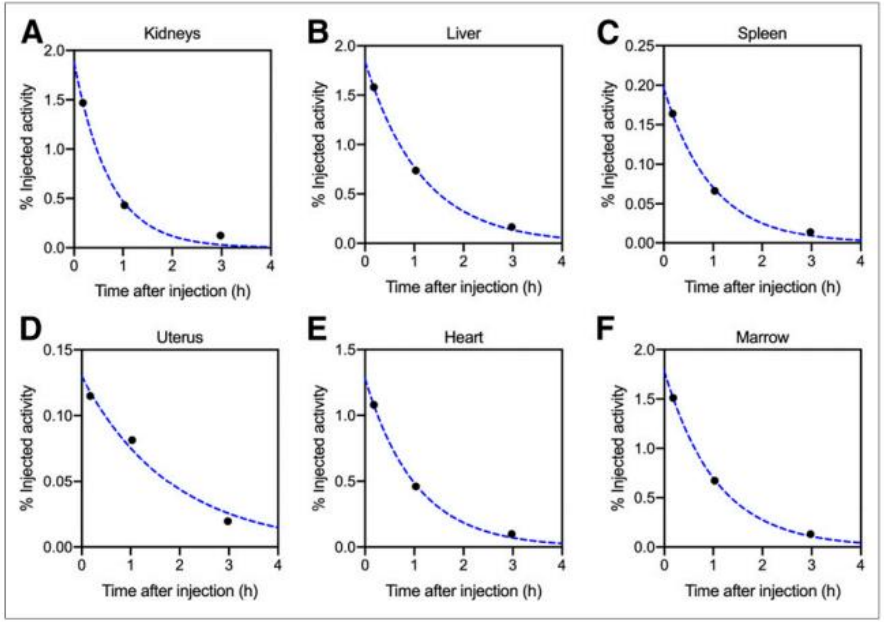


FIGURE 2. Percentage injected activity curves for patient 3 are shown for various source organs. Solid circles are measured values, and dotted lines are monoexponential functions fit to data.

FAPI-46 – Optimization of PK

FAPI-46 HL_{biol}(Tu): 16 h

FAPI-46 HL_{biol}(KM,Nieren): 2 h

Nuclide	HL_{phys}	HL_{eff} (Tu)	HL_{eff} (KM, Ni)
Re-188	16 h	8,0 h	1,8 h
Sm-153	**46 h**	**12,4 h**	**1,9 h**
Y-90	**64 h**	**12,8 h**	**1,9 h**
Lu-177	161 h	14,5 h	2,0 h

Dosimetry of $^{90}Y/^{177}Lu$-FAPI-46

ORIGINAL ARTICLE

Feasibility and Therapeutic Potential of ^{177}Lu–Fibroblast Activation Protein Inhibitor–46 for Patients With Relapsed or Refractory Cancers

A Preliminary Study

Majid Assadi, MD, Seyed Javad Rekabpour, MD,† Esmail Jafari, MSc,* GhasemAli Divband, MD,‡§ Babak Nikkholgh, MD,§ Hamidreza Amini, MD,§ Hassan Kamali, MSc,|| Sakineh Ebrahimi, MD,¶ Nader Shakibazad, MD,** Narges Jokar, MSc,* Iraj Nabipour, MD,†† and Hojjat Ahmadzadehfar, MD, MSc‡‡*

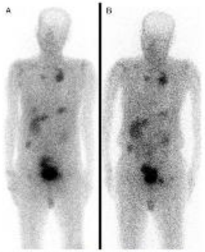


FIGURE 3. A 60-year-old man with metastatic colon cancer with a prior history of surgery and chemotherapy underwent scintigraphy with a diagnostic dose of ^{177}Lu-FAPI-46 that revealed multiple FAPI-avid lesions in the liver, lymph node, bone, and lung (A). The patient underwent 2 cycles of PTRT with ^{177}Lu-FAPI-46 (3.7 GBq per cycle) resulting in stable disease. The patient was still alive after follow-up 5.5 (B).

presented in Table 1. Figures 2 and 3 indicate the PTRT process

0.03 Gy/GBq red-marrow
0.89 Gy/GBq kidneys

Journal of Nuclear Medicine, published on August 12, 2021 as doi:10.2967/jnumed.121.262468

Initial clinical experience with ^{90}Y-FAPI-46 radioligand therapy for advanced stage solid tumors: a case series of nine patients

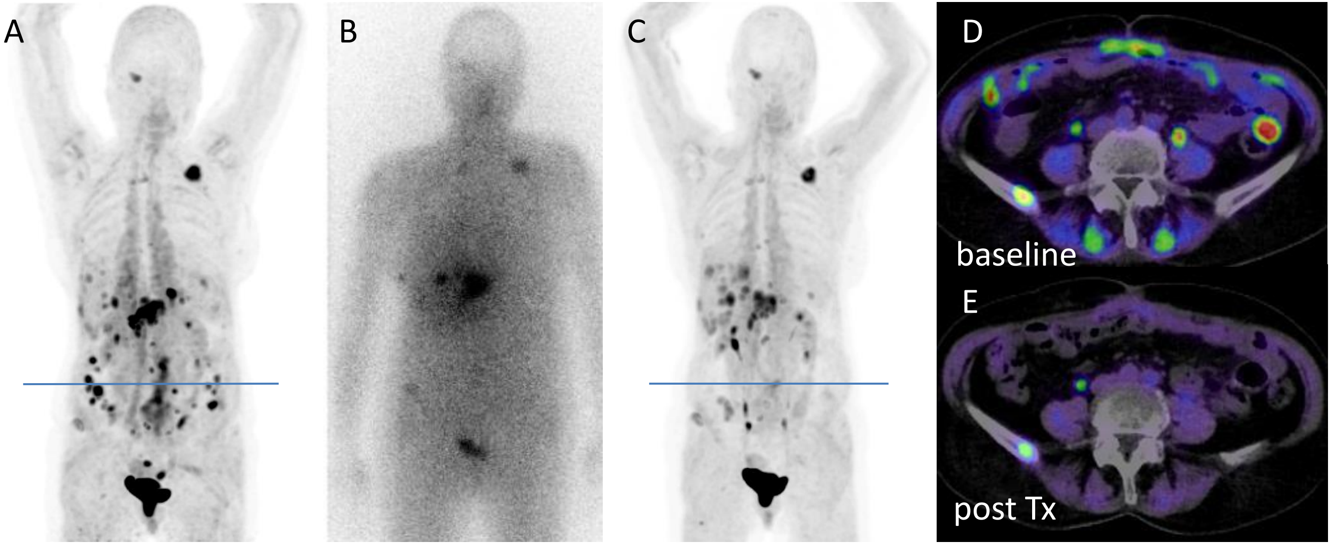
Running title: ^{90}Y-FAPI therapy for advanced cancer

Justin Ferdinandus[1,2], Pedro Fragoso Costa[1,2], Lukas Kessler[1,2], Manuel Weber[1,2], Nader Hirmas[1,2], Karina Kostbade[2,3], Sebastian Bauer[2,3], Martin Schuler[2,3], Marit Ahrens[4], Hans-Ulrich Schildhaus[2,5], Christoph Rischpler[1,2], Hong Grafe[1,2], Jens T. Siveke[3,6,7], Ken Herrmann[1,2], Wolfgang P. Fendler[1,2*], Rainer Hamacher[2,3*]

[1] Department of Nuclear Medicine, West German Cancer Center, University of Duisburg-Essen and German Cancer Consortium (DKTK)-University Hospital Essen, Essen, Germany
[2] German Cancer Consortium (DKTK), Partner Site University Hospital Essen, and German Cancer Research Center (DKFZ), Essen, Germany.

0.04 Gy/GBq red-marrow
0.52 Gy/GBq kidneys
1.28 Gy/GBq tumor/metastasen

^{90}Y-FAPI-46 – Case from Heidelberg



Baseline PET/CT ^{68}Ga-FAPI-04	7,4 GBq ^{90}Y-FAPI-46	Week-6 PET/CT ^{68}Ga-FAPI-04

Theoretical advantage of ^{153}Sm-FAPI-46

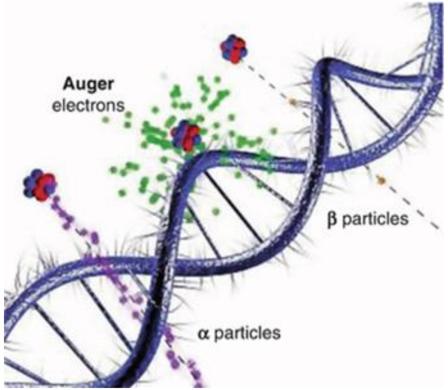
Table 1. Comparison of decay properties of ^{177}Lu and ^{153}Sm.

	^{177}Lu	^{153}Sm
Half-life (days)	6.7	1.9
β-yield (particle/nt)	1	1
β-energy	498 (79%) 385 (9%) 176 (12%)	808 (18%) 705 (50%) 635 (32%)
β-energy (keV/nt)	133	224
β-av. energy (keV/particle)	133	224
IC electrons yield (particle/nt)	0.15	0.81
IC electrons energy (keV/nt)	14	40
IC electrons av. energy (keV/particle)	87	50
AM electrons yield (particle/nt)	1.12	6.58
AM electrons energy (keV/nt)	1	6
AM electrons av. energy (keV/particle)	1	0.9
AM and IC electrons yield (particle/nt)	1.27	7.38

Table adapted with permission from Uusijärvi et al. [1] and IRCP Publication 107—Nuclear Decay Data for Dosimetry Calculations [8]. Nt = nuclear transformation, IC = internal conversion, AM = Auger–Meitner.

Vermeulen K, Van de Voorde M, et al Pharmaceutics 2022

In addition to its more favorable half-life (dose-rate benefit over Lu-177), Sm-153 benefits from higher co-emission of IC- and Auger electrons.



^{153}Sm-FAPI-46 – Case from Heidelberg

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-021-05273-8

IMAGE OF THE MONTH

[^{153}Sm]Samarium-labeled FAPI-46 radioligand therapy in a patient with lung metastases of a sarcoma

Clemens Kratochwil[1] · Frederik L. Giesel[1] · Hendrik Rathke[1] · Rebecca Fink[1] · Katharina Dendl[1] · Jürgen Debus[2] · Walter Mier[1] · Dirk Jäger[3] · Thomas Lindner[1] · Uwe Haberkorn[1,4,5]

Received: 10 February 2021 / Accepted: 18 February 2021
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Image of the month

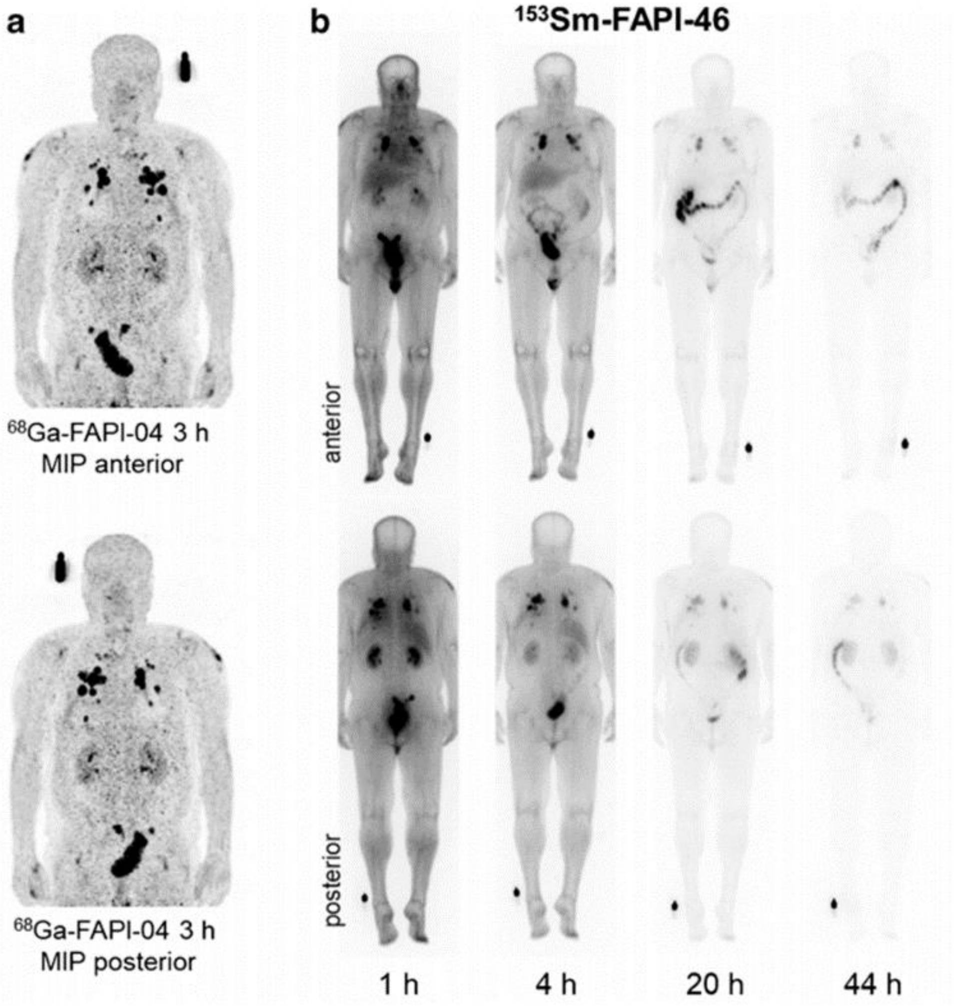
Fibroblast activation protein is overexpressed by cancer-associated fibroblasts (CAFs) in the stroma of several tumor entities and provides anti-immunogenic effects [1]. It can be targeted with radiolabeled small-molecule inhibitors (FAPIs) [2].

This image demonstrates a patient with progression of lung metastatic, fibrous spindle cell soft tissue sarcoma. Primary tumor located between bladder and rectum as well as early generations of oligo-focal metastases had previously been treated by resection and external-beam radiotherapy. In systemic stage, mutanom-based vaccination [3], cyclophosphamide, and pazopanib had already been used but the patient was considered inappropriate for standard chemotherapy with anthracyclines. An interdisciplinary tumor conference considered experimental FAPI-RLT a promising option for this therapy-refractory patient to serve as a "can opener" for succeeding immunotherapy.

FAPI-PET/CT demonstrated target positive tumor phenotype (a). Due to the relatively short biological tumor half-life of quinoline-based FAPI-46 [1], it was labeled with short physical half-life (46.3 h) ^{153}Sm. Emission scans during therapy demonstrate tumor targeting up to 44 h p.i. and rapid clearance from normal organs (b). Three cycles with cumulative 20 GBq ^{153}Sm- and 8GBq Y-90-FAPI-46 (^{153}Sm was not available with sufficiently high specific activity) were well tolerated and achieved stable disease for 8 months (c). Next treatment lines were pembrolizumab, experimentally enhanced with oncolytic parvovirus [4], and nab-paclitaxel. Under both therapies, the patient progressed

This article is part of the Topical Collection on Image of the month

✉ Clemens Kratochwil
Clemens.Kratochwil@med.uni-heidelberg.de



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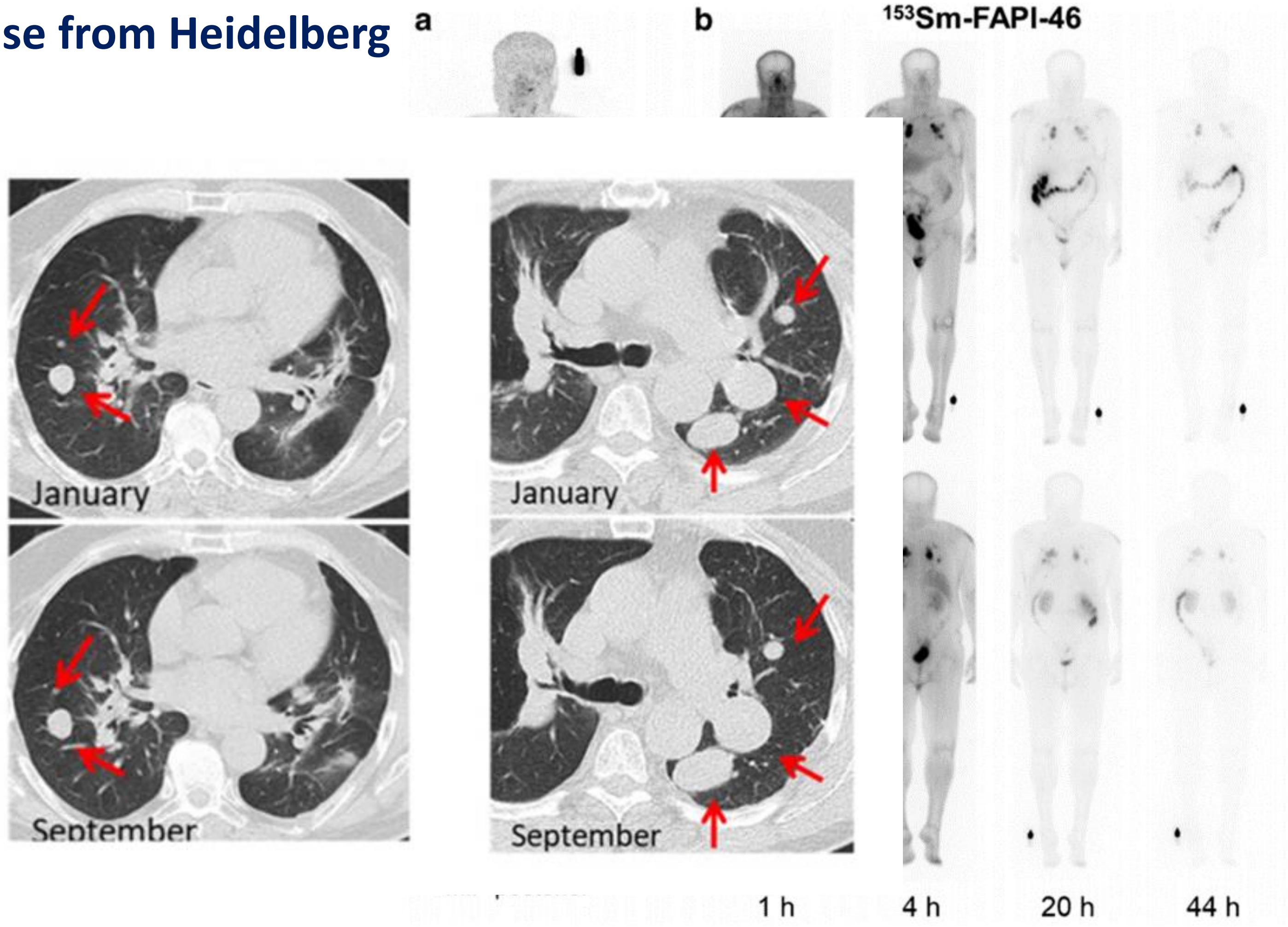


^{153}Sm-FAPI-46 – the issue of "specific activity"

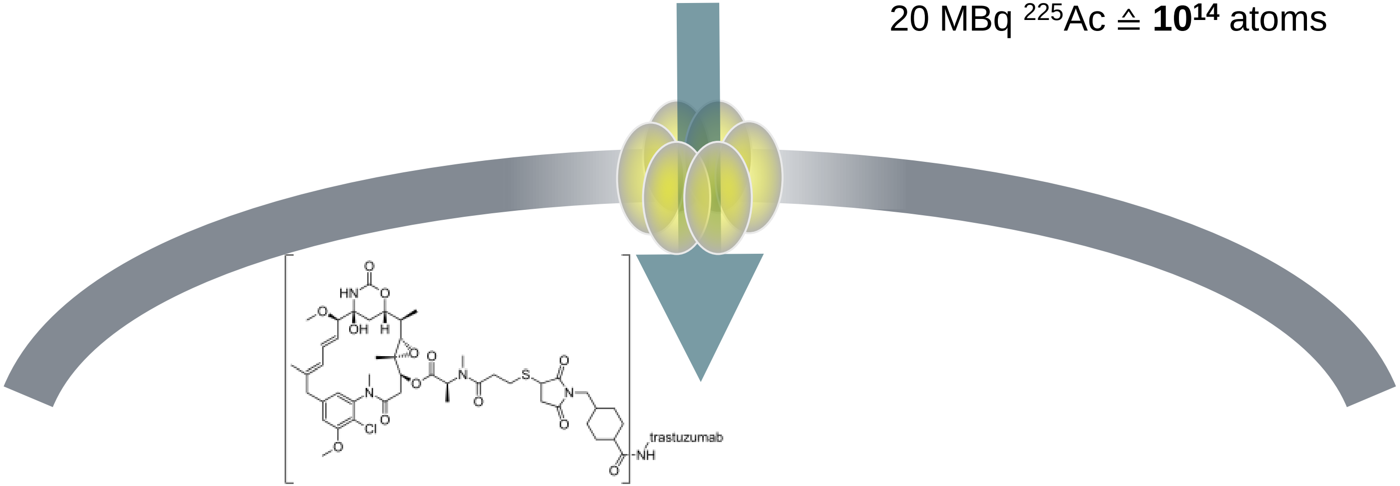
TUMOR SECIFIC UPTAKE: TARGET NUMBERS

RECEPTOR NUMBER

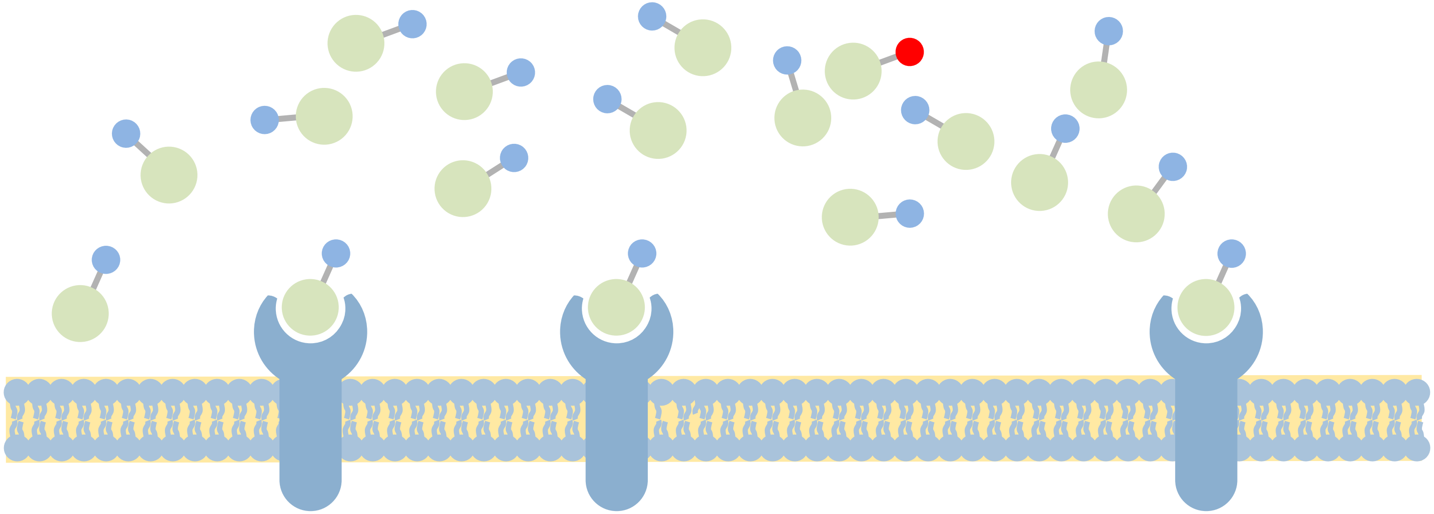
typical example:
10 g tumor ≙ 10^{10} cells
10^5 receptors per cell
patient: **10^{15}** binding sites

TRACER NUMBER

86 mg Doxorubicin ≙ 10^{20} molecules
3.5 mg Vinchristin ≙ 10^{18} molecules
270 mg Kadcyla ≙ 3 x 10^{17} molecules
6 GBq ^{177}Lu ≙ 5 $\times 10^{15}$ atoms
20 MBq ^{225}Ac ≙ **10^{14}** atoms



^{153}Sm-FAPI-46 – the issue of “specific activity”



Sm-152 (stable)	> 99 %
Sm-153 (active)	< 1 %

^{153}Sm-FAPI-46 – the issue of “specific activity”

Limitations of reactor produced ^{153}Sm:

- Eu-152 and Eu-154 impurities (half-life > 8 y)

Applied Radiation and Isotopes 188 (2022) 110386

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

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ELSEVIER

Europium radionuclides in samarium-153-Ethylene Diamine Tetramethylene phosphonic acid (^{153}Sm-EDTMP) radiopharmaceutical waste

S.G. Mishra[a,*], D.K. Sawant[a], A.S. Chindarkar[a], A.N. Thamke[b], B. Sanjeev Kumar[c], A.C. Dey[d], M.S. Kulkani[a]

Table 1
Europium radionuclide and its method of formation in a nuclear reactor.

Radionuclide	$T_{1/2}$	Nuclear reaction
^{152}Eu	13.537 y	^{151}Eu (n,γ) ^{152}Eu
^{154}Eu	8.593 y	^{153}Sm (β, $T_{1/2}$ 46.3 h) → ^{153}Eu (n,γ) ^{154}Eu
^{155}Eu	4.76 y	^{153}Sm (n,γ) ^{154}Sm (n,γ) ^{155}Sm(β, $T_{1/2}$ 22.1 m) → ^{155}Eu
^{156}Eu	15.19 d	^{155}Eu (n,γ) ^{156}Eu

^{153}Sm-FAPI-46 – the issue of "specific activity"

Limitations of reactor produced ^{153}Sm:

- Eu-152 and Eu-154 impurities (half-life > 8 y)
- Sm-152 : Sm-153 is 120 : 1

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frontiers in Medicine

ORIGINAL RESEARCH
published: 19 July 2021
doi: 10.3389/fmed.2021.675221

Production of Sm-153 With Very High Specific Activity for Targeted Radionuclide Therapy

Michiel Van de Voorde[1*], Charlotte Duchemin[2,3], Reinhard Heinke[2,3], Laura Lambert[3], Eric Chevallay[3], Thomas Schneider[4], Miranda Van Stenis[4], Thomas Elias Cocolios[2], Thomas Cardinaels[1,5], Bernard Ponsard[1], Maarten Ooms[1], Thierry Stora[3] and Andrew R. Burgoyne[1*]

UK HD

^{153}Sm-FAPI-46 – the issue of "specific activity"

Limitations of reactor produced ^{153}Sm:

- Eu-152 and Eu-154 impurities (half-life > 8 y)
- Sm-152 : Sm-1

These issues have already been eliminated by mass separation (CERN-MEDICIS):

(135 GBq/ml -> 1.87 TBq/ml (max. 16.4 TBq/ml)

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ELSEVIER

ylene Diamine

MP)

mke[b], B. Sanjeev Kumar[c], A.C. Dey[d],

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frontiers in Medicine

ORIGINAL RESEARCH

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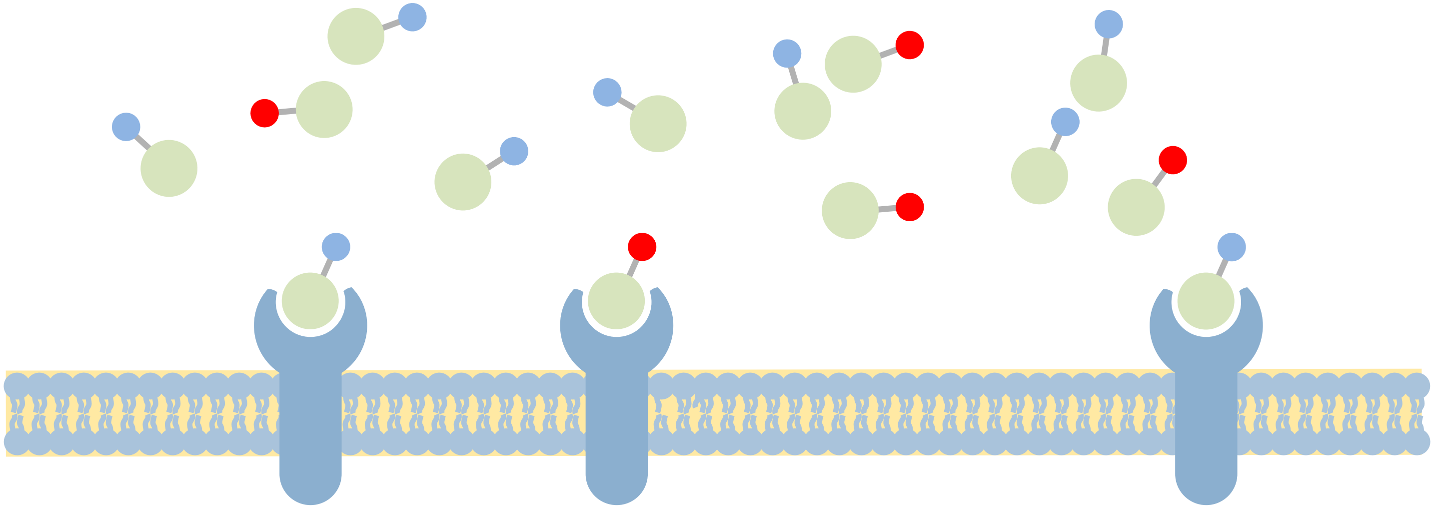
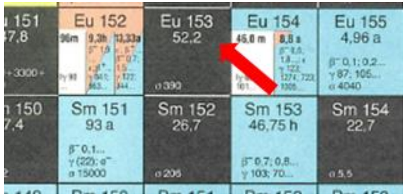
UKHD

^{153}Sm-FAPI-46 – the issue of “specific activity”



Eu-153 (stable)

Sm-153 (active)



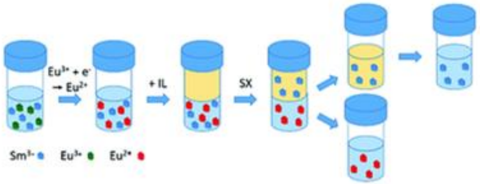
Time dependent (logistic challenge)

Current development: Chemical separation of Sm-153 / Eu-153

Separation of samarium and europium by solvent extraction with an undiluted quaternary ammonium ionic liquid: towards high-purity medical samarium-153†

Check for updates

Michiel Van de Voorde, [ab] Karen Van Hecke, [a] Koen Binnemans [b] and Thomas Cardinaels



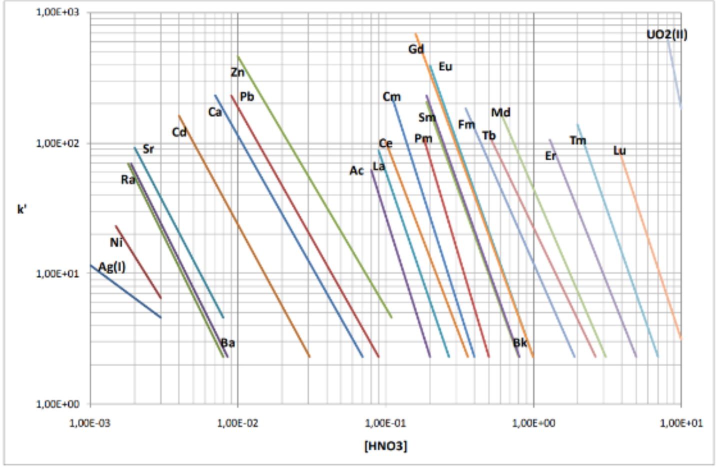


Abb 2. : Affinität verschiedener Elemente für das LN Resin in Funktion der HNO_3 Konzentration (Horwitz 1975)[1]

Summary

- FAP is a very promising target for radioligand therapy of multiple tumor entities.
- Physical half-life of Sm-153 (1.9d = 46h) presents a perfect match for the pharmacokinetics of the FAPI-46 shuttle molecule.
- Issues of (c.a.) low specific activity Sm-152 / Sm-153 and long half-life Eu-152 an Eu-154 impurities after reactor production have been solved by MEDICIS.
- "In-growth" of Eu-153 by beta-decay of Sm-153 is still an issue that cannot be solved with mass separation. Chemical separation is challenging but improving.
- Saturation of tumor binding sites allows for approx. 250 µg of FAPI-46 precursor (estimated from n=1 Heidelberg patient). Yet, 1000 µg precursor was needed for labeling of test-activity HSA Sm-153.
- Future factor-4 improvement in labeling-efficacy appears very reasonable.

(HSA) ^{153}Sm-FAPI-46

Thanks to all my collaborators…

… and for your excellent questions…

… and the fruitful discussion!