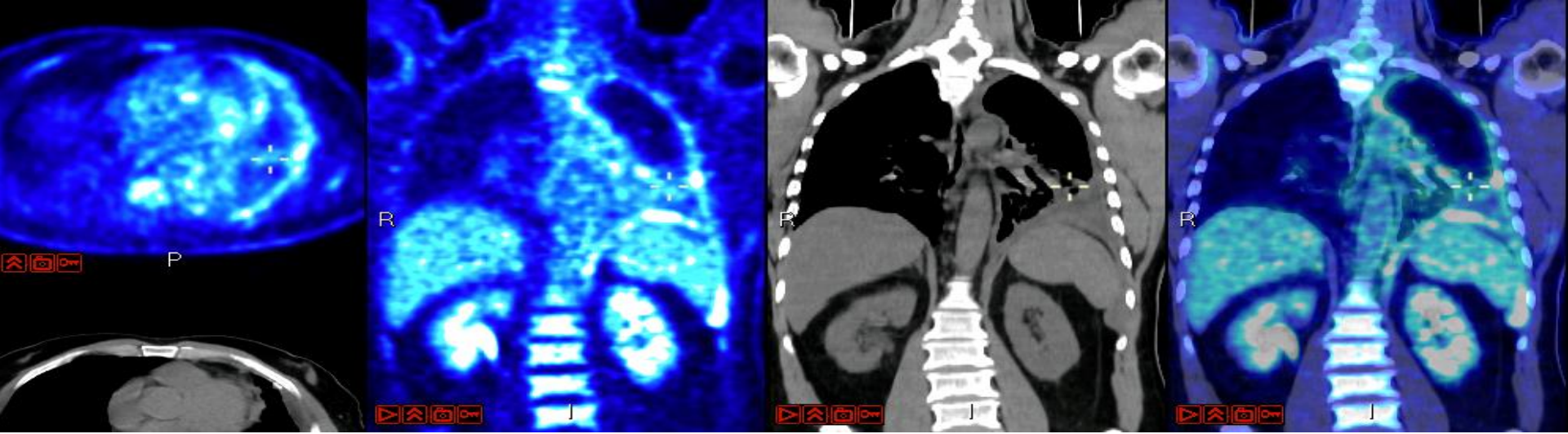


CERN-MEDICIS ANNIVERSARY – DECEMBER 11, 2024

Relevance of MEDICIS for nuclear medicine

Prof. John Prior, PhD MD

Nuclear Medicine and Molecular Imaging, Lausanne University Hospital

canton de vaud

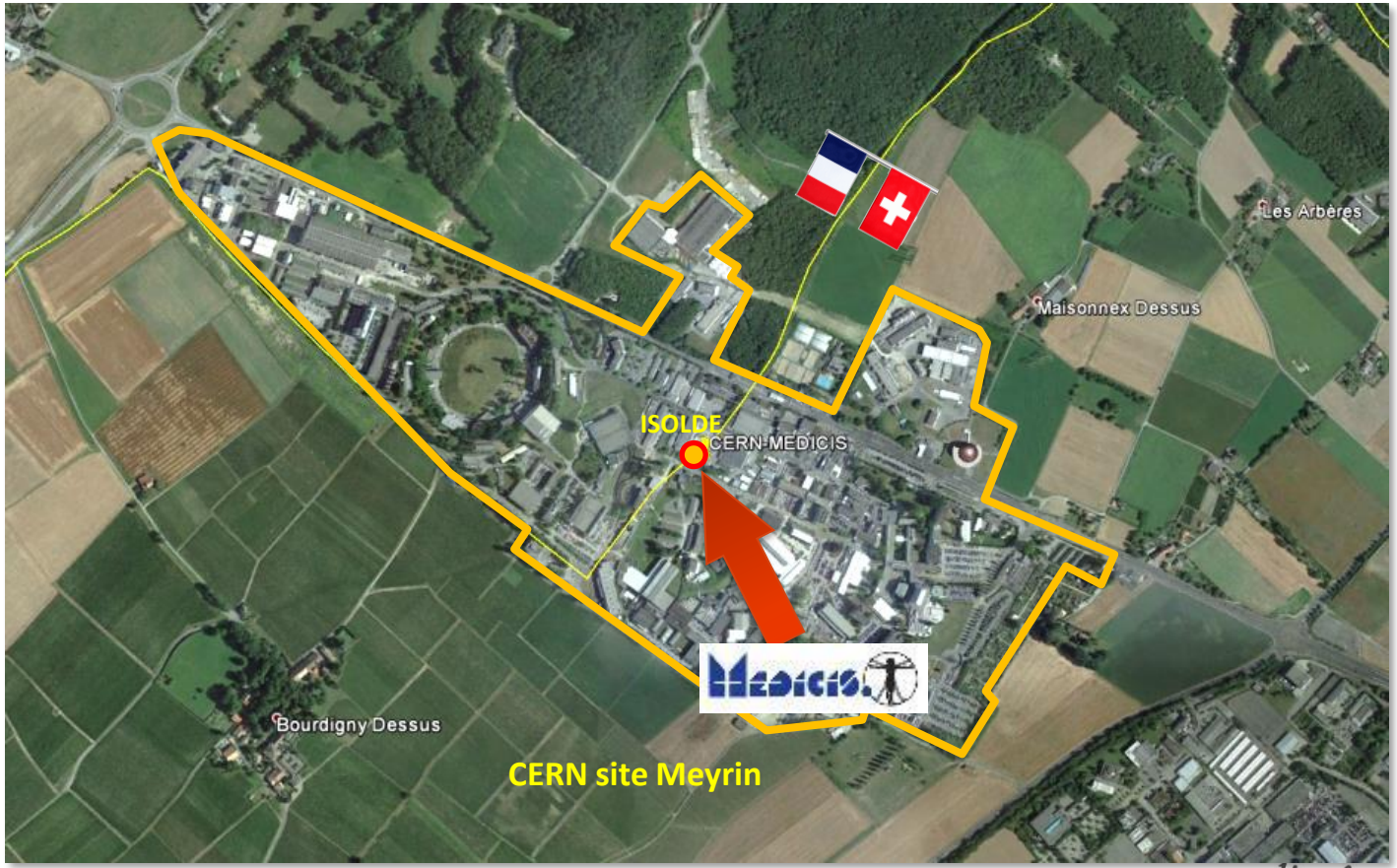
UNIL | Université de Lausanne

CHUV

MARIE SKŁODOWSKA-CURIE ACTIONS
Innovative Training Networks : H2020

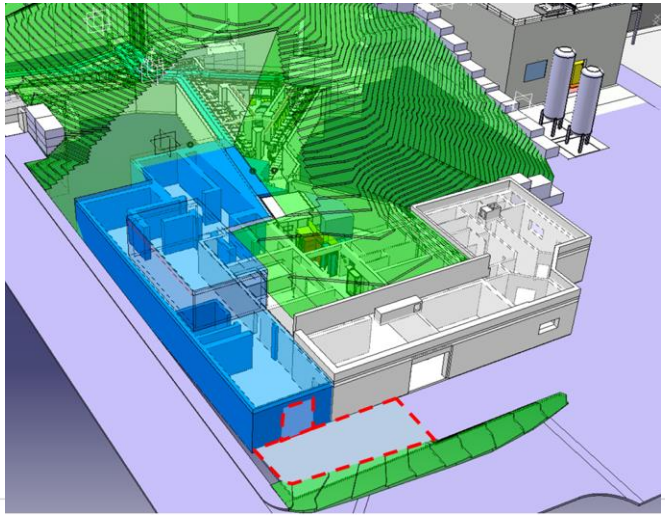
“MEDICIS-produced radioisotope beams for medicine”

MEDICIS : linked to ISOLDE



CERN-MEDICIS

First worldwide facility dedicated to mass-separated radioisotope beams for **medical applications**



CERN-MEDICIS
World-unique facility for novel radioisotopes: CERN-MEDICIS

Centre hospitalier universitaire vaudois

Ground breaking ceremony 4.9.2013

로그인 · 회원가입 · RSS서비스 The Science Times 한국과학창의재단

힉스입자 예측으로 노벨 물리학상 수상자가 결정되는 순간 CERN은 축제분위기에 빠졌다. 그러나 CERN은 제2의 연구소로 재탄생하고 있다. 9월 4일 CERN의 중요 관계자들은 선 메디시스(CERN MEDICIS) 설립을 위한 기공식에 참여해 첫 삽을 떴다.

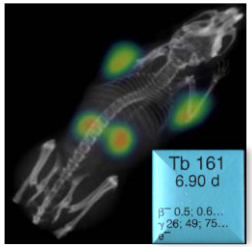
▲ 지난 9월4일 CERN 주요 관계자들이 의료용 방사성동위원소를 생산할 CERN MEDICIS 설립을 위한 기공식에서 첫 삽을 뜨고 있다. 가운데가 롤프 호이어 CERN 사무총장 ©CERN

9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7
2013				2014												2015												2016								

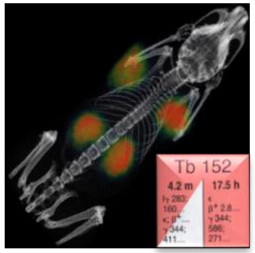
Terbium: Swiss Army Knife of Nuclear Medicine

^{149}Tb-therapy

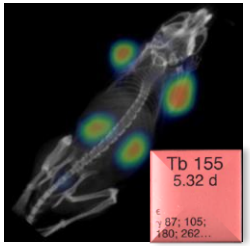
^{161}Tb-therapy & SPECT



^{152}Tb-PET



^{155}Tb-SPECT



Müller et al., JNM 2012

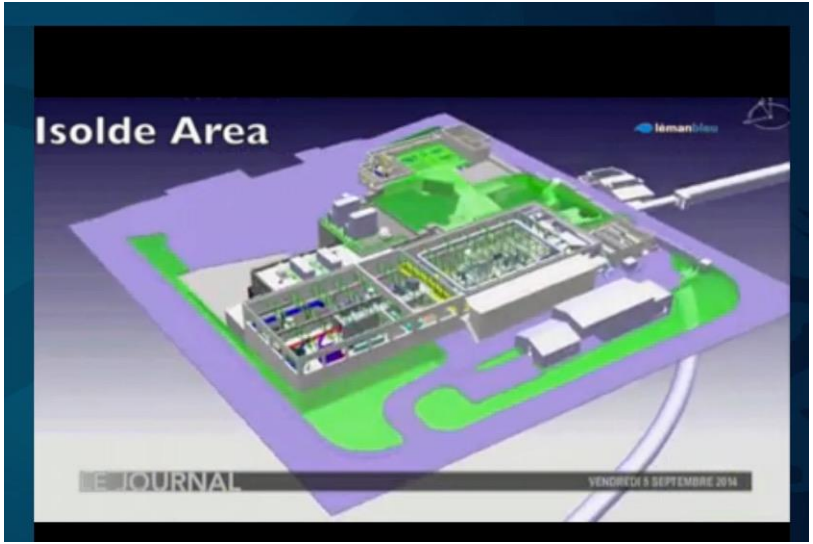
In 2015 CERN-MEDICIS became the first **worldwide facility dedicated to mass-separated radioisotope beams for medical applications**.

Its network, consisting of university hospitals, hadron therapy centers and isotope distribution entrepreneurial companies across France, Italy and Switzerland, is leading the field of oncological research, imaging and personalized treatments.

It will act as the seed for the extended MEDICIS-PROMED network and train a new generation of entrepreneurial scientists to develop systems for new personalized treatments throughout Europe.

(T. Stora, 2014)

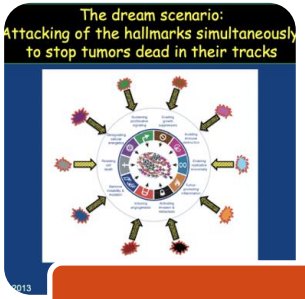
H2020: Marie Curie ITN – € 3.9 mio.
For training 15 PhD within CERN–MEDICIS



CERN-CHUV-HUG-EPFL

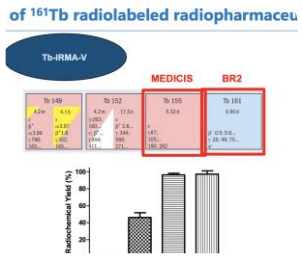
MEDICIS Journey

Medicis Day



2014

2nd Collaboration Board

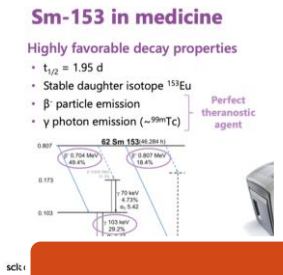


2018

4th Collaboration Board

2019

5th Collaboration Board



2020

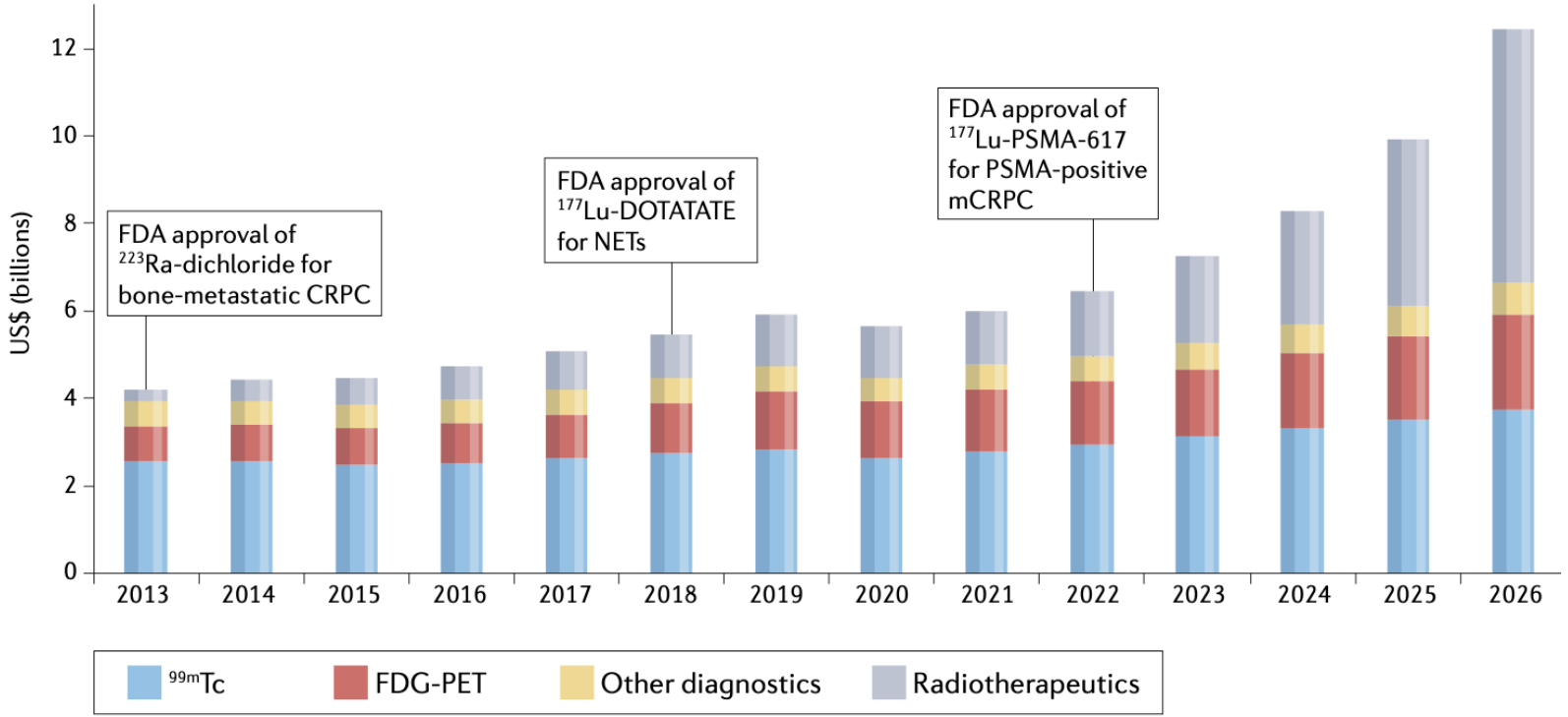
https://indico.cern.ch/event/342013/

https://indico.cern.ch/event/882074/

2024 6th Collaboration Board (TODAY!)

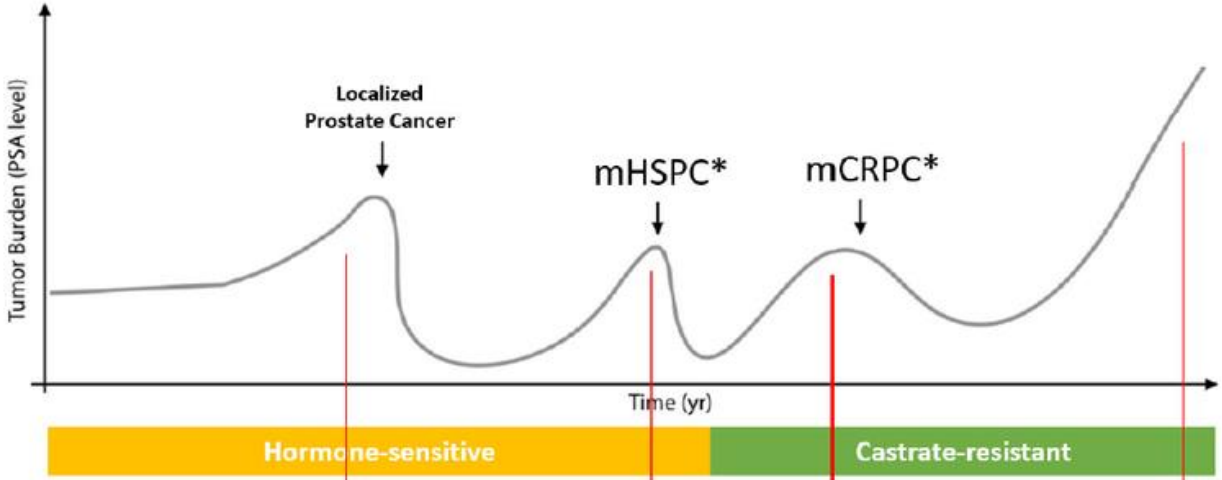
Potentials of Theranostics

Predicted Nuclear Medicine Market 2013–26



Bodei et al. Nat Rev Clin Oncol 19, 534–550 (2022).

PSMA Theranostics Clinical Trials



Poor prognosis of metastatic prostate cancer

17 theranostics clinical trials (as of 2021)

Neoadjuvant therapy for localized disease

1. ^{177}Lu-PSMA-617 (LuTectomy)

First-line therapy for mCRPC

1. ^{177}Lu-PSMA-I&T (Bullseye)
2. ^{177}Lu-PSMA-617 + enzalutamide (ENZA-P)
3. PSMAfore

First-line therapy for mHSPC

1. ^{177}Lu-PSMA-617 (UpFrontPSMA, PSMAddition)

Second-line or later therapy for mCRPC

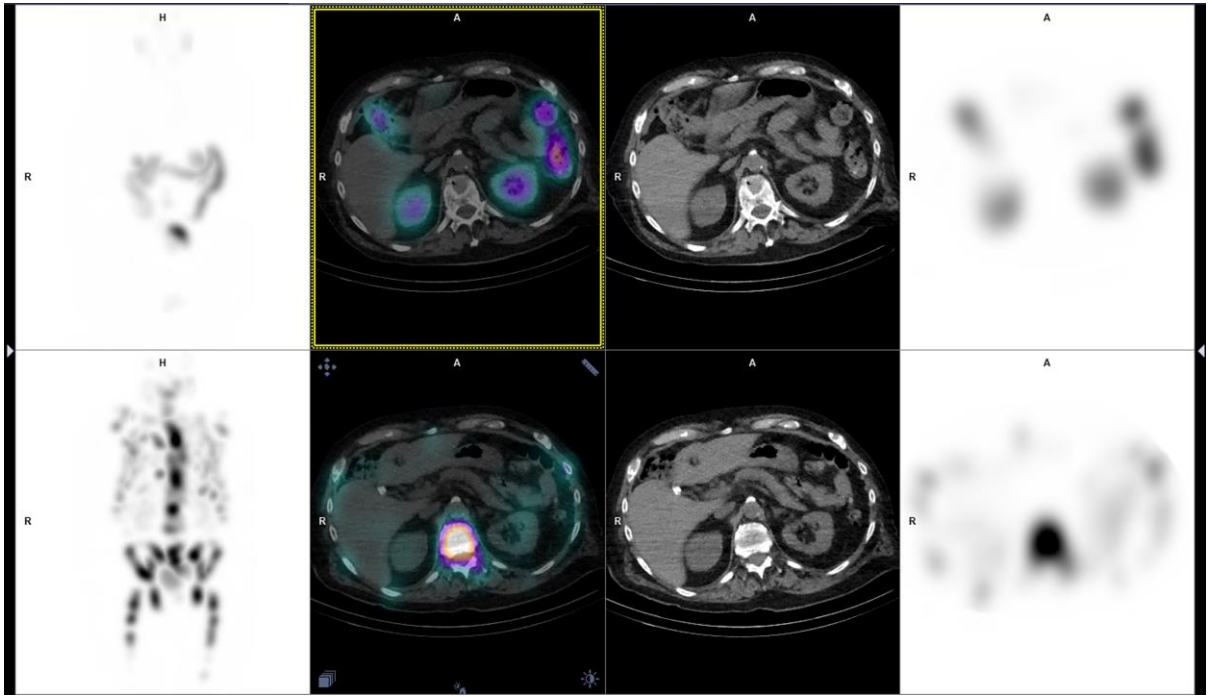
1. ^{177}Lu-PSMA-617 (LuPSMA,TheraP, VISION)
2. ^{177}Lu-PSMA-617 + olaparib (LuPARP)
3. ^{177}Lu-PSMA-617 + pembrolizumab (PRINCE)
4. ^{177}Lu-PSMA-I&T (SPLASH)
5. ^{225}Ac-PSMA-617 (AcTION)
6. ^{177}Lu-J591 (NCT00538668)
7. ^{225}Ac-J591 (NCT04506567)
8. ^{227}Th-PSMA-TTC (NCT03724747)
9. ^{131}I-MIP-1095 + enzalutamide (ARROW)
10. ^{177}Lu-PSMA-R2 (NCT03490838)

*mHSPC (metastatic hormone-sensitive prostate cancer)
*mCRPC (metastatic castrate-resistant prostate cancer)
*Different colours represent various PSMA-targeted radiopharmaceuticals (^{177}Lu-PSMA-617, ^{177}Lu-PSMA-I&T, ^{177}Lu-J591, ^{225}Ac-J591, ^{227}Th-PSMA-TTC, ^{131}I-MIP-1095, ^{177}Lu-PSMA-R2)

Zhang,et al. Cancers 2021, 13, 4023.

Theranostics (Lu-177-based)

Therapy 2



PSA 6 µg/L

Therapy 1

PSA 212 µg/L

82-y-old man with hormonoresistant prostate cancer

KU LEUVEN

NUCLEAR AND RADIATION PHYSICS

Mass separation of ^{225}Ac from ^{227}Ac and from irradiated Th targets to support Targeted Alpha Therapy

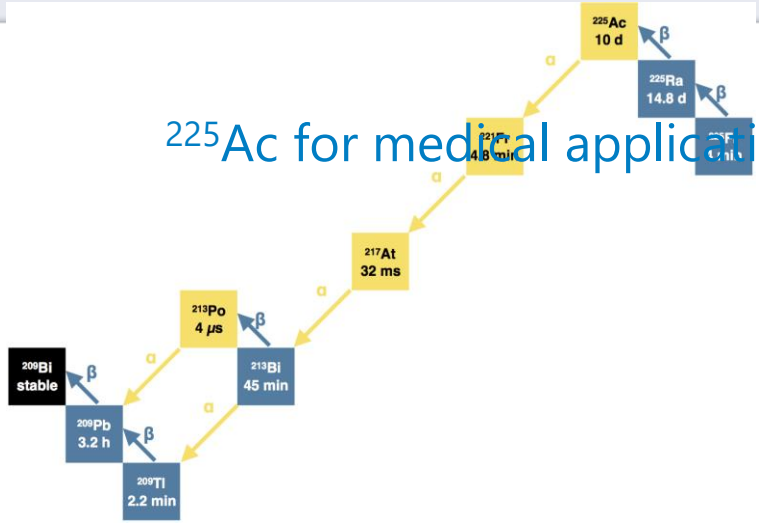
Proposal MED024

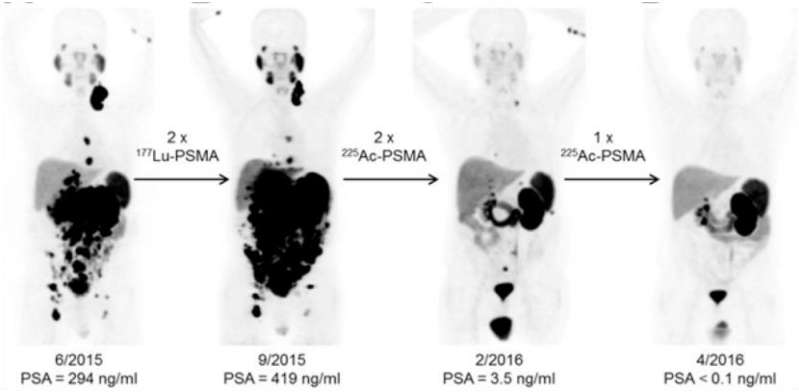
CERN MEDICIS Collaboration Board IV

18 September 2019

^{225}Ac for medical application

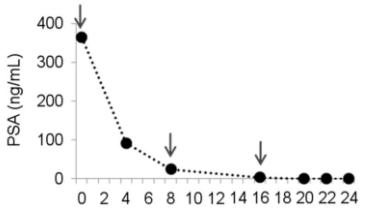
- Direct use as an α emitter
  - 4 α particles in close succession
  - $T_{1/2}$ ~ 10 days
- As a generator for ^{213}Bi
  - 100% α emission
  - $T_{1/2}$ ~ 45 min
- Can be combined with ^{68}Ga for theranostics applications

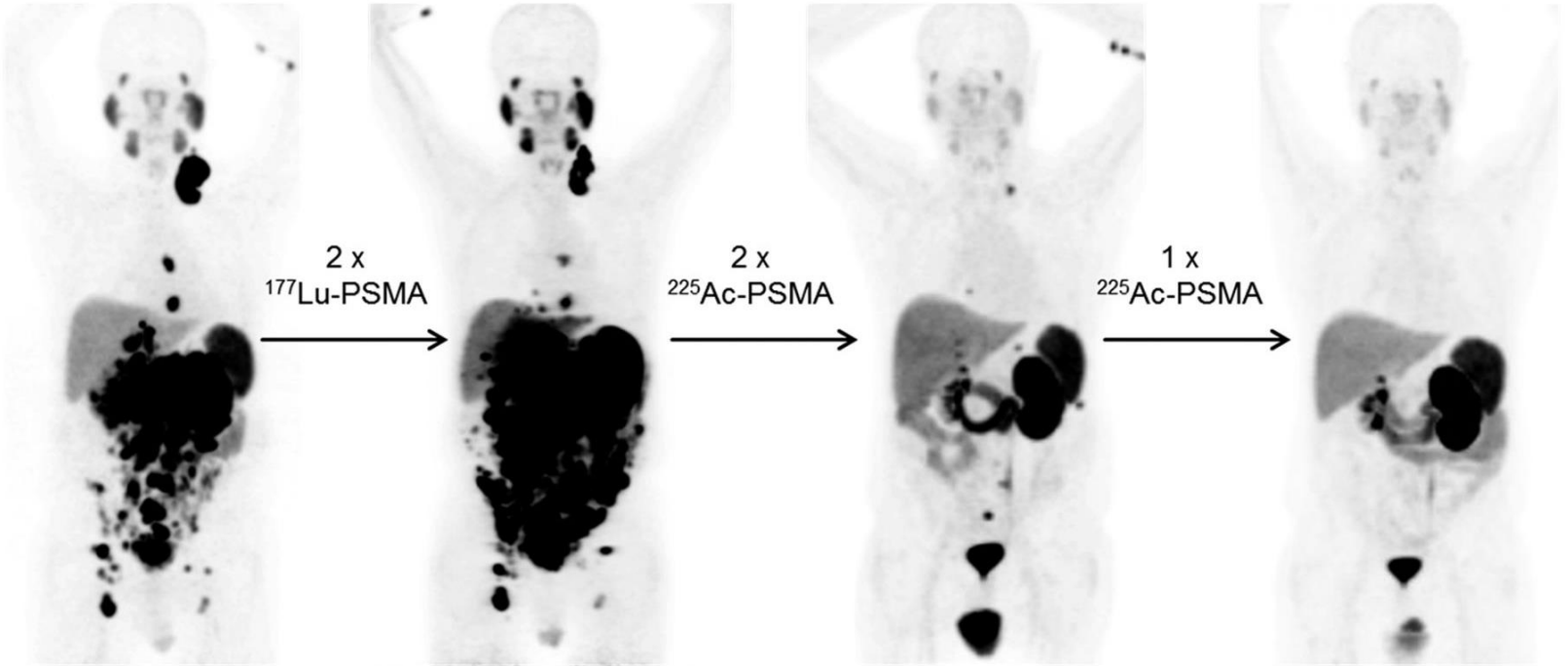




C. Kratochwil et al, The Journal of Nuclear Medicine **57** (2016) 1941-1944

^{225}Ac-PSMA

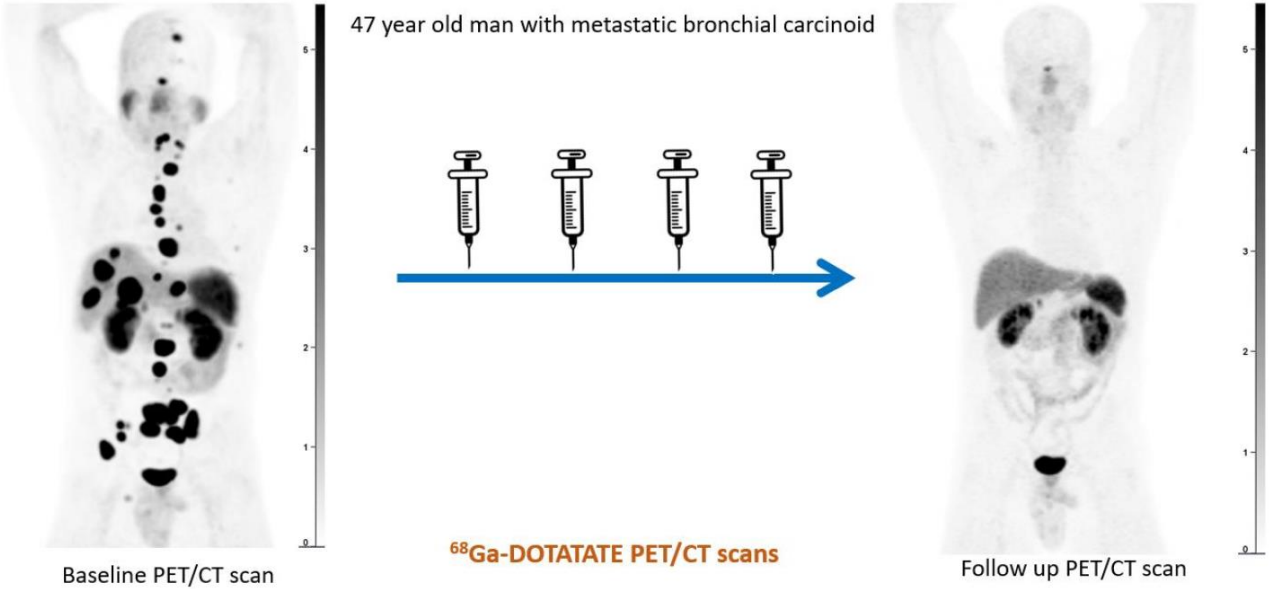




Kratochwil et al, JNM 2016

^{212}Pb-DOTAMTATE

Phase 1 clinical trial of Alpha particle PRRT with ^{212}Pb-DOTAMTATE



Delpassand et al JNM 2022

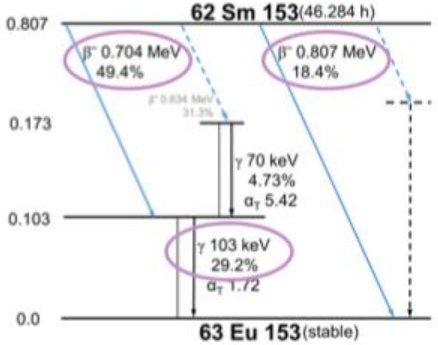
Cocolios et van de Voorde et Oms

Sm-153 in medicine

Highly favorable decay properties

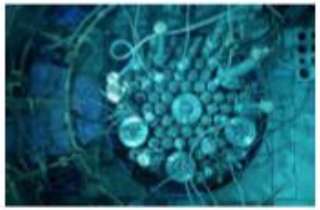
- $t_{1/2}$ = 1.95 d
- Stable daughter isotope ^{153}Eu
- β^- particle emission
- γ photon emission (~^{99m}Tc)

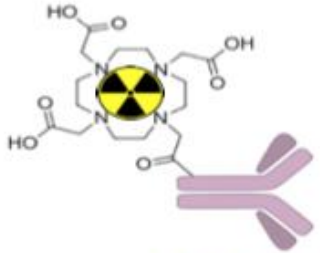
Perfect theranostic agent



Current applications

- Irradiation cancer cells → β^- particles
  ⇒ Bone pain management (palliation)
- Bone (tumor) imaging → γ photons
  ⇒ Visualize infected areas human skeleton





Sm-153 production at BR2

Irradiation of enriched ^{152}Sm targets with high thermal neutron flux

Mass separation at CERN-MEDICIS

Isolation of ^{153}Sm from ^{152}Sm matrix and ^{153}Eu and ^{154}Eu impurities

Radiolabeling studies

Radiolabeling with commercial chelators + comparison ^{161}Tb and ^{177}Lu

sck cen sck cen sck cen sck cen

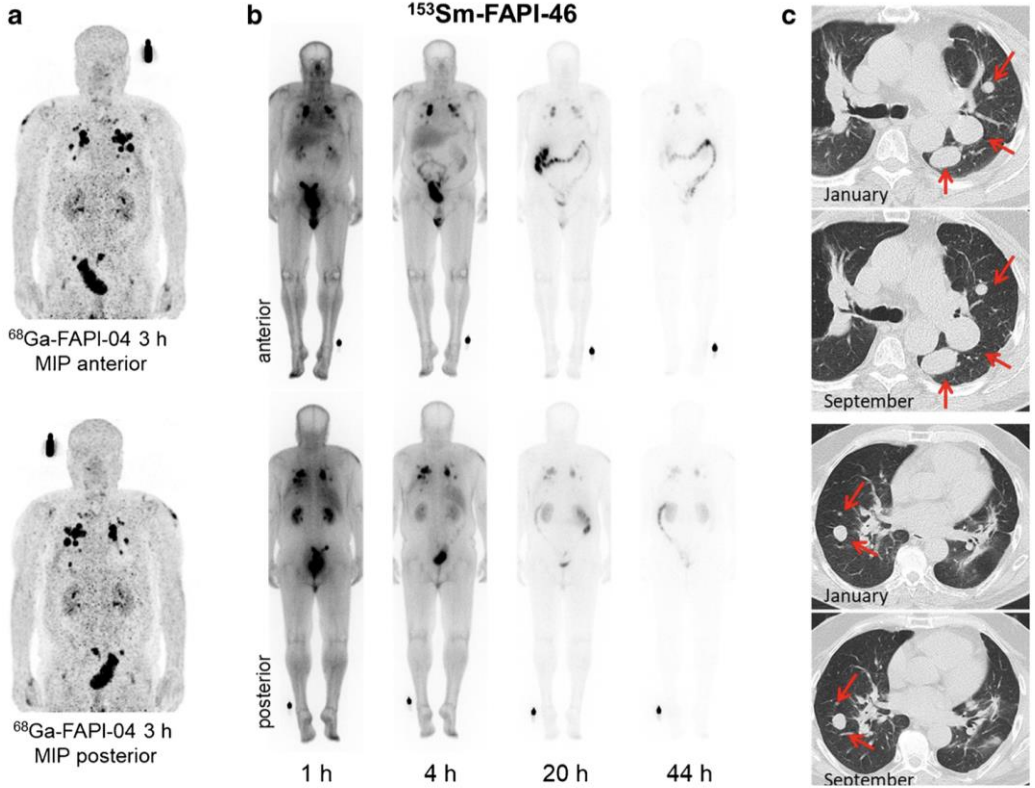
Radiochemical treatment target

Opening of ampoules + dissolution of target material + evaporation onto Re boat

Separation and quality control

Recovery of ^{153}Sm from MS target foil + separation ^{153}Sm/^{153}Eu + QC (gamma spectrometry, ICP-MS, ...)

^{153}SM-FAPI-46 RADIOLIGAND THERAPY WITH HIGH-MOLAR ACTIVITY ^{153}SM



European Journal of Nuclear Medicine and Molecular Imaging (2021) 48:3011–3013
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 / Published online: 17 March 2021

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 after only 3 months.

progression of lung metastatic, fibrous spindle cell soft tissue sarcoma

canton de vaud

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CHUV

^{153}SM-FAPI-46 RADIOLIGAND THERAPY WITH HIGH-MOLAR ACTIVITY ^{153}SM

Project proposal to the MEDICIS Collaboration board

^{153}SM-FAPI-46 RADIOLIGAND THERAPY WITH HIGH-MOLAR ACTIVITY ^{153}SM

J. Prior (CHUV), U. Haberkorn, C. Kratochwill (Heidelberg University Hospital), M. Ooms, M. Van de Voorde, D. Elema (SCK CEN), T. Cocolios (KULeuven), C. Decristoforo (INMUL), C. Bernerd, K. Chrysalidis, C. Duchemin, R. Heinke, L. Lambert, B. Marsh, R. Rossel (CERN)

Prof. J. Prior, CHUV (john.prior@chuv.ch) ; Prof. C. Kratochwill, University Hospital Heidelberg (Clemens.Kratochwil@med.uni-heidelberg.de)

Max 2 pages from Introduction to References and Funding

Introduction & background: (state of the art and goal/motivation for the project)
New radiobioconjugates targeting fibroblast overexpressed in certain forms of cancers have recently been developed by the dept of nuclear medicine in Heidelberg and have shown important results in a range of different preclinical and clinical investigations. It demonstrates the potential of a new generation of radiopharmaceuticals targeting the Fibroblast Activation Protein (FAP), quinolone-based FAP inhibitors (FAPI) with a DOTA-chelator moiety and have shown potential benefits in both diagnosis and treatment, including patients presenting disseminated metastasis in lungs. As already investigated with FAPI-04, rapid tumor-targeting and kidney clearance but also a relatively short residency time in tumor is observed and therefore needs to find better suited radionuclides than 90Y or 177Lu, with shorter physical half-life, beta and photon emitting properties for theranostic investigations. A first pilot study was performed in Heidelberg with Low Molar Activity (LMA) Samarium-153 FAPI-46. Samarium-153 has a half-life of 46.8h, beta particles (Eave 225keV, Emax 806keV), and has a photon (103keV) making it an ideal radionuclide for theranostics investigations with FAPI . Further investigations to identify its potential in imaging contrast, biokinetics and ultimately therapeutics benefits with a High Molar Activity (HMA) grade 153Sm-FAPI46 are required, because according to preliminary data presented at the "Nuklearmedizin-2022" (nuclear-medicine convention of the D-A-CH states), receptor-saturation due to poor specific activity of the radiopharmaceutical likely presents a relevant limitation for this kind of treatment. Indeed, the low molar activity form of Samarium-153 has long been known for pain palliation, marketed as Quadramet ® in the form of 153Sm-EDTMP for patients suffering of an advanced staged cancers with bone metastasis. Until recently it was not possible to target other tumors because of the mode of production by target activation in a nuclear reactor and its production in LMA form. Recently the synthesis of high molar activity (HMA) 153Sm-DOTATATE obtained from an activated target in a nuclear reactor and subsequent mass separation produced HMA 153Sm within MED-025 project has shown its suitability for imaging and therapeutic benefits in animal models to target NET tumors.

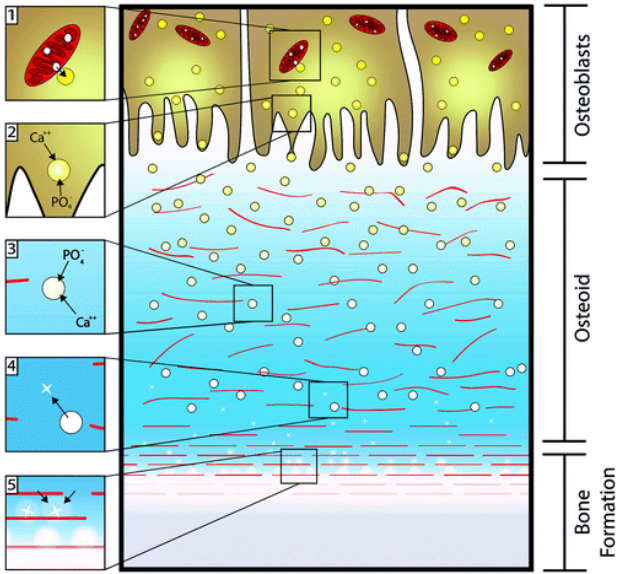
Project description:
This is the development of a short pilot study about the potential of (HMA) 153Sm-FAPI-46 radio-ligand therapy in cancer treatment. Up to 5 patients pre-selected per 68Ga-FAPI-PET scans to have metastatic FAP-positive tumor diseases (e.g. metastatic breast cancer, metastatic sarcoma), that have already exhausted all approved treatment lines are offered to receive experimental therapy according to German Law ("Heilversuch" = compassionate care). Based on previous experience (with (LMA) 153Sm-FAPI-46 and 90Y-FAPI-46), the treatment

POTENTIAL STUDY

- Investigate the potential of (HMA) ^{153}Sm-FAPI-46 radioligand therapy in cancer treatment
- Up to 5 patients pre-selected per ^{68}Ga-FAPI-PET scans to have metastatic FAP-positive tumor diseases (e.g., metastatic breast cancer, metastatic sarcoma)
  - With already exhausted all approved treatment lines
  - Will be offered to receive experimental therapy according to German Law ("Heilversuch" = compassionate care)

Rational:

- $^{128}Ba/^{128}Cs$ enters the bone matrix as a surrogate of Ca^{2+} like ^{223}Ra and ^{89}Sr
- It is metabolized, concentrated secreted through the matrix vesicles by the osteoblast



Kyungsup Shin, Timothy Acri, Sean Geary, and Aliasger K. Salem.Tissue Engineering Part A.Oct 2017.1169-1180

Clinical Trials: Targeted Therapy

Clinical Cancer Research

Alpha Particle Radium 223 Dichloride in High-risk Osteosarcoma: A Phase I Dose Escalation Trial

Vivek Subbiah[1,2], Pete M. Anderson[3], Kalevi Kairemo[4,5], Kenneth Hess[6], Winston W. Huh[7], Vinod Ravi[8], Najat C. Daw[2], Neeta Somaiah[8], Joseph A. Ludwig[8], Robert S. Benjamin[8], Sant Chawla[9], David S. Hong[1], Funda Meric-Bernstam[1], Gregory Ravizzini[4], Eugenie Kleinerman[2], Homer Macapinlac[4], and Eric Rohren[4,10]

Abstract

Purpose: The prognosis of metastatic osteosarcoma continues to be poor. We hypothesized that alpha-emitting, bone-targeting radium 223 dichloride ($^{223}RaCl_2$) can be safely administered to patients with osteosarcoma and that early signals of response or resistance can be assessed by quantitative and qualitative correlative imaging studies and biomarkers.

Patients and Methods: A 3+3 phase I, dose-escalation trial of $^{223}RaCl_2$ (50, 75, and 100 kBq/kg) was designed in patients with recurrent/metastatic osteosarcoma aged ≥15 years. Objective measurements included changes in standardized uptake values of positron emission tomography (PET; 18FDG and/or NaF-18) and single-photon emission CT/CT (99mTc-MDP) as well as alkaline phosphatase and bone turnover markers at baseline, midstudy, and the end of the study.

Results: Among 18 patients enrolled (including 15 males) aged 15–71 years, tumor locations included spine ($n = 12$, 67%), pelvis ($n = 10$, 56%), ribs ($n = 9$, 50%), extremity ($n = 7$, 39%), and skull ($n = 2$, 11%). Patients received 1–6 cycles of $^{223}RaCl_2$; cumulative doses were 6.84-57.81 MBq. NaF PET revealed more sites of metastases than did FDG PET. One patient showed a metabolic response on FDG PET and NaF PET. Four patients had mixed responses, and one patient had a response in a brain metastasis. Bronchopulmonary hemorrhage from Grade 3 thrombocytopenia ($N = 1$) was a DLT. The median overall survival time was 25 weeks.

Conclusions: The first evaluation of the safety and efficacy of an alpha particle in high-risk osteosarcoma shows that the recommended phase II dose for $^{223}RaCl_2$ in osteosarcoma is 100 kBq/kg monthly (twice the dose approved for prostate cancer), with minimal hematologic toxicity, setting the stage for combination therapies.

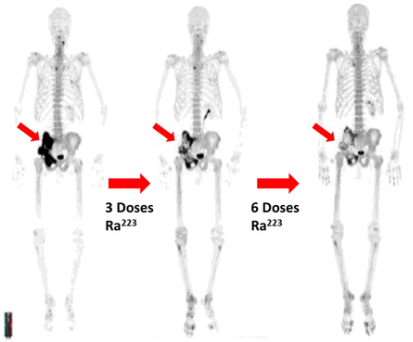


Figure 3. NaF PET–CT in a patient with pelvic osteosarcoma showing decrease in NaF with subsequent doses of $^{223}RaCl_2$.

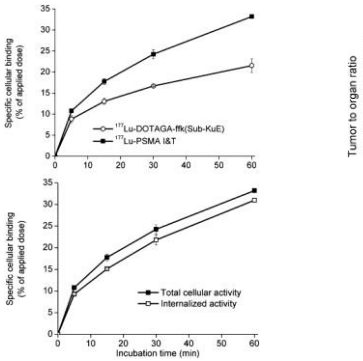
Rational:

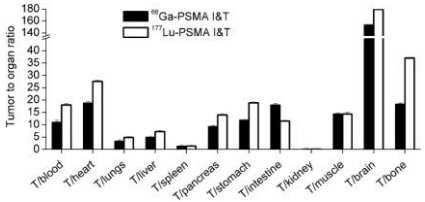
- The PSMA-I&T theranostic tracer is currently used to diagnose (^{68}Ga-PSMA-I&T) and treat (^{177}Lu-PSMA-I&T) patients with prostate cancer
- As Lutetium, Cerium belongs to the lanthanides, and chelation by DOTAGA-PSMA-I&T can be achieved following already established protocols
- The ^{134}Ce/^{134}La in vivo generator will be used to be conjugated to DOTAGA-PSMA-I&T (PSMA-I&T) to target cancer cells expressing PSMA

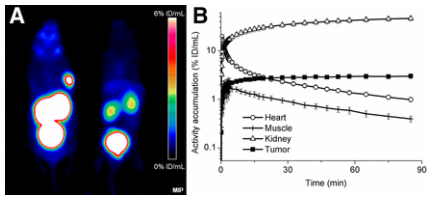
^{68}Ga- and ^{177}Lu-Labeled PSMA I&T: Optimization of a PSMA-Targeted Theranostic Concept and First Proof-of-Concept Human Studies

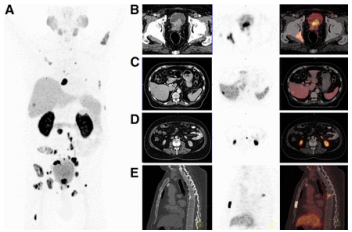
Martina Weineisen[1], Margret Schottelius[1], Jakub Simecek[1,2], Richard P. Baum[3], Akin Yildiz[4], Seval Beykan[5], Harshad R. Kulkarni[3], Michael Lassmann[5], Ingo Klette[3], Matthias Eiber[6], Markus Schwaiger[6], and Hans-Jürgen Wester[1]

[1]Pharmaceutical Radiochemistry, Technische Universität München, Garching, Germany; [2]Scintomics GmbH, Fürstenfeldbruck, Germany; [3]Theranostics Center for Molecular Radiotherapy and Molecular Imaging (PET/CT), Zentralklinik Bad Berka, Bad Berka, Germany; [4]Department of Nuclear Medicine, Medstar Hospital Cancer Center, Antalya, Turkey; [5]Department of Nuclear Medicine, University of Würzburg, Würzburg, Germany; and [6]Department of Nuclear Medicine, Klinikum Rechts der Isar, Technische Universität München, Munich, Germany









Stora et al.

New treatments in nuclear medicine : a large and “recent” interest in Europe

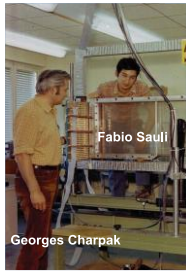
Physics & Chemistry Nobel Prizes

The New York Times.

MME. CURIE PLANS TO END ALL CANCERS

Says Radium Is Sure Cure, Even in Deep-Rooted Cases, if Properly Treated.

Published: May 12th 1921
© The New York Times



Helene Langevin-Joliot at MEDICIS, professor in nuclear physics, grand-daughter of Marie Curie (2017)

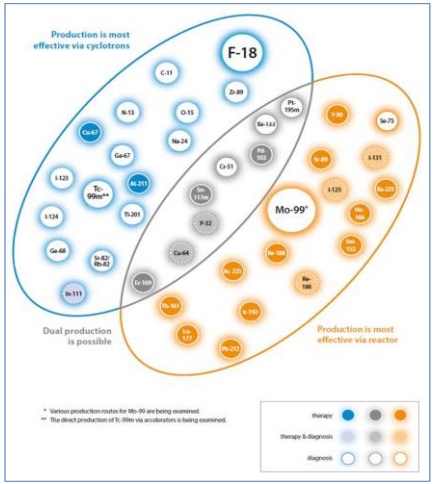


Figure 31 : Main medical radioisotopes production process

European Commission ENER/17/NUCL/SI2.755660 (2018)

Accelerator Labs Worldwide (eg PSI, TRIUMF)

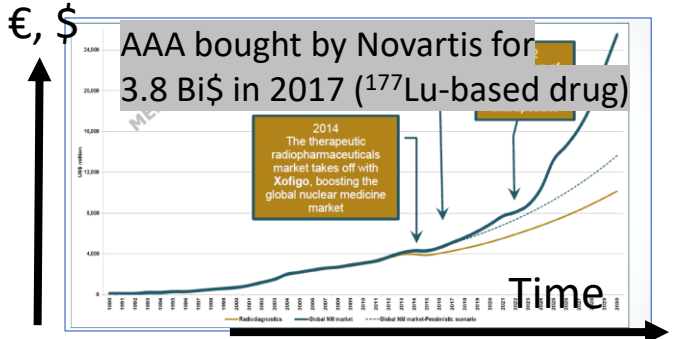


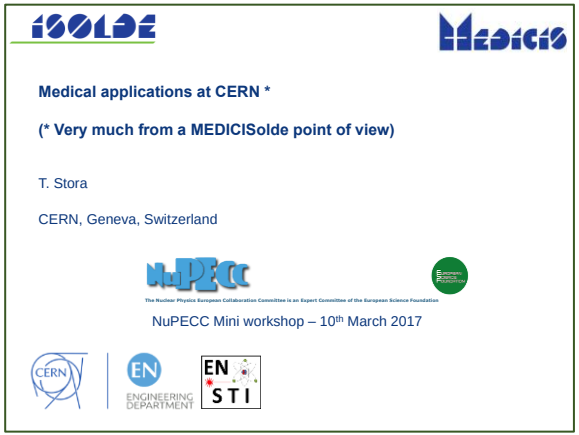
Figure 8: Possible market evolution for radiotherapeutics – source MedRaysIntell (2016)

Economics, Innovators

Finally Monsieur et Madame tout le monde
CERN open days 2019 – MEDICIS press release 2017

Towards an integration at the European level: Some Historical background

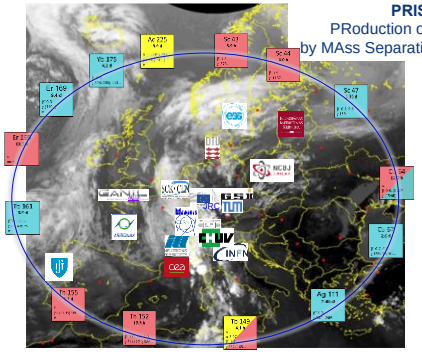
NuPECC miniworkshop
at CERN in 2017



MEDICIS Promed 2015-2019

Marie Curie ITN MEDICIS-Promed Contract number : 642889

PRISM(AS-M)AP
joint ECFA-NuPECC-ApPEC meeting,
France 2019



PRISMAS-MAP :
PRoduction of hIgh purity iSotopes
by MAss Separation for Medical Application

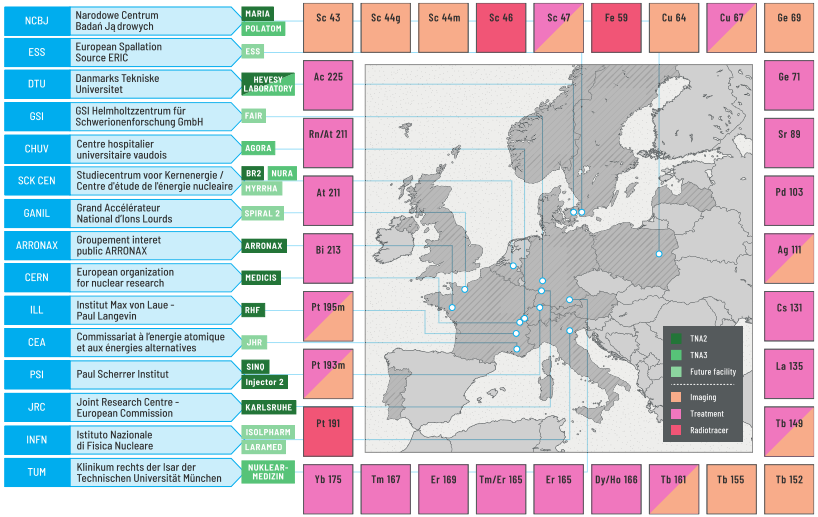
Next H2020-INFRA call

Inspired from the NIDC

Thierry.stora@cern.ch

Idea of INFRA 1st mentioned at the EURISOL-DF Town meeting in INFN-Pisa – Apr 2018
2 “dedicated meetings”, many many phone calls, Emails, meetings, even some lunches

PRISMAP – The European medical isotope programme



Submitted to the INFRA-2-2020 Call
In full of the COVID outbreak …

Kirsten Leufgen 2 November 2020 at 13:10
Re: PRISMAP - any news? Details
To: Nicole Wyss, Cc: Peter Ulrich, Thierry Stora, regina.schneider@euresearch.ch & 1 more

Dear Nicole,

I hope this finds you well, after an enjoyable weekend!

We still **do not have any official news regarding PRISMAP**, even if the evaluation results were **announced for 14 Oct already.**

Last week the officer confirmed that the results would for sure come before the end of October and we heard from a consortium member that PRISMAP would be on the list of funded projects.

- Open key national and regional research infrastructures to all European researchers

https://medicis.cern/prismap-european-medical-isotope-programme

"Writing team" : K. Leufgen (Sciprom), T. Cocolios, F. Haddad, U. Koester, M. Lassman, J. Prior, CERN Colleagues, T.S, …

A BIG THANKS TO ALL THE PEOPLE, GROUPS, SERVICES, INSTITUTES, COLLABORATION … INVOLVED IN MEDICIS!

CERN | SY Accelerator Systems | STI | MEDICIS

canton de vaud

UNIL | Université de Lausanne

CHUV