Delivery of CERN-MEDICIS radionuclides for projects translating to pilot clinical testing

Thierry STORA, with input from previous meetings/materials and colleagues

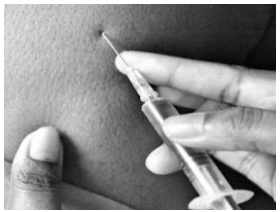
15-May-2024

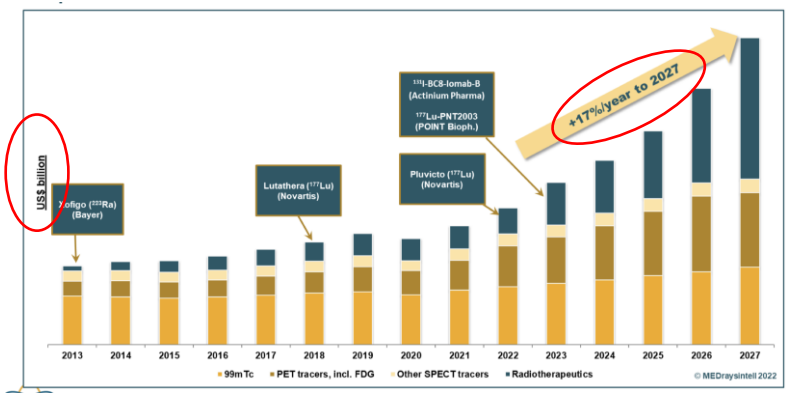
Nuclear medicine : new trends

The New York Times.

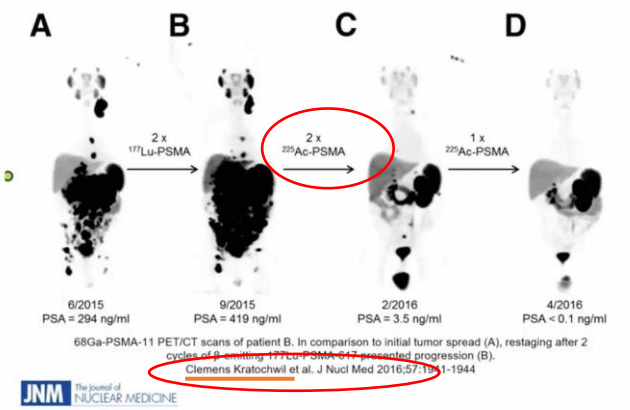
MME. CURIE PLANS TO END ALL CANCERS

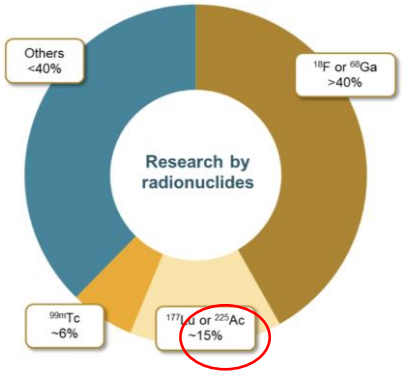
Says Radium Is Sure Cure, Even in Deep-Rooted Cases, if Properly Treated.





Diagnostics + THERAPY



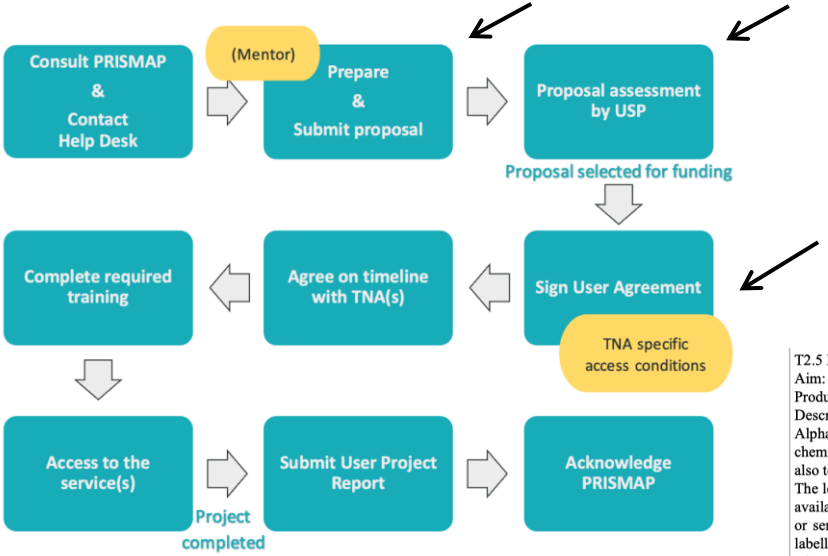


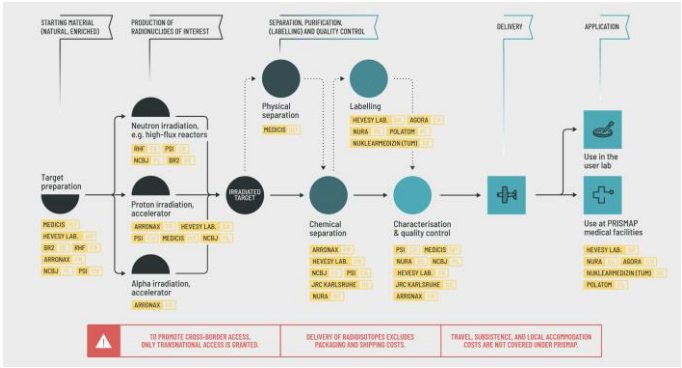
2016

1st report ever of efficacy of 225Ac

PRISMAP (clinical) project Workflow (we will see similarities with MEDICIS)

- PRISMAP is a H2020 EU project. Projects are managed with a User agreement
- (and the project managed by a Grant Agreement with the EU and a consortium agreement (23 institutes)





T2.5 Production of alpha emitters. JRC, CERN, ARRONAX, NCBJ M01-M48
Aim:
Production of alpha emitters for therapeutic applications
Description:
Alpha emitters are particularly promising for therapeutic applications, but only few alpha emitters with nuclear and chemical properties suitable for clinical applications exist. Most of these are severely supply-limited and this applies also to 225Ac, the clinically most advanced alpha emitter.
The leading European actinide lab at JRC-Karlsruhe regularly extracts 225Ac from a 229Th generator and makes this available for preclinical and clinical trials. 225Ac (T1/2=10 d) is either used directly, labelled to a suitable biomolecule, or serves itself as generator for extracting of 213Bi, a short-lived (T1/2=46 min) alpha emitter that is mainly used labelled to small molecules and/or for loco-regional applications.
Given the limited supply of 225Ac from 229Th, additional 225Ac will be provided from MEDICIS by spallation reactions on thorium targets (cf. T2.2). Similarly, MEDICIS can also produce 211Rn (T1/2=14 h) which serves as

PRISMAP User Agreement : project

License to receive and handle radionuclides from local authorities

LANDESAMT FÜR UMWELT, LANDWIRTSCHAFT UND GEOLOGIE | Freistaat SACHSEN

SACHSISCHES LANDESAMT FÜR UMWELT, LANDWIRTSCHAFT UND GEOLOGIE
POSTFACH 54 01 37 | 01311 DRESDEN

Universitätsklinikum Carl Gustav Carus Dresden
- Anstalt öffentlichen Rechts -
Herrn H. Neuhäuser
Strahlenschutzbevollmächtigter
Fetscherstraße 74
01307 Dresden

Ihr Ansprechpartner
Hadi Alborzi

Durchwahl
Telefon +49 351 2612-5302
Telefax +49 351 2612-5399

Hadi.Alborzi@
smekul.sachsen.de

Ihr Zeichen

Ihre Nachricht vom

Aktenzeichen
(bitte bei Antwort angeben)
53-8473/134/3-2023/16492

Dresden,13.02.2023

Vollzug des Strahlenschutzgesetzes (StrlSchG) und der Strahlenschutzverordnung (StrlSchV);

Erteilung der Änderungsgenehmigung VT/1028/97/14 gemäß § 12 Abs. 2 StrlSchG

Antrag vom 01.12.2022

15 Jahre Täglich für ein gutes Leben.

Genehmigungsbescheid VT/1028/97/14

zum Umgang mit offenen radioaktiven Stoffen in der nuklearmedizinischen Therapie

Unique @ MEDICIS (mass separation) + SCK →

In EU: Unique @MEDICIS& JRC-Karlsruhe →

In EU: Unique @ MEDICIS →

3.2. Nuklearmedizinische Therapie

3.2.1. Es wird der Umgang mit sonstigen radioaktiven Stoffen in offener Form für folgende Nuklide und Aktivitäten genehmigt:

Lfd. Nr.	Nuklid	Umgangsaktivität in Bq	Arbeitsaktivität pro Tag in Bq	Bezugsaktivität pro Jahr in Bq
1	P-32	2,00 E+09	1,85 E+08	1,20 E+10
2	Y-90	3,50 E+10	1,85 E+10	3,60 E+11
3	Sr-89	4,00 E+10	1,50 E+09	2,00 E+11
4	I-131	4,50 E+10	3,70 E+09	2,25 E+12
5	Sm-153	1,00 E+10	3,70 E+09	2,00 E+11
6	Er-169	3,00 E+09	7,40 E+07	1,50 E+11
7	Re-186	4,00 E+09	1,50 E+09	2,00 E+11
8	W-188/Re-188	2,00 E+11	6,00 E+10	3,00 E+11
9	Lu-177	3,00 E+10	1,50 E+10	5,00 E+11
10	Ra-223+*	1,00 E+08	1,00 E+07	1,00 E+09
11	Ho-166	3,00 E+10	1,50 E+10	6,00 E+11
12	Ac-225+/Bi-213	1,00 E+07 pro Therapie	1,00 E+07 pro Therapie	geregelt über die Genehmigung V/0948/99
13	Pb-212**	3,00 E+09	3,00 E+08	1,00 E+11

* Ra-223+ darf ausschließlich für die Therapie mit dem als Arzneimittel zugelassenen Präparat Xofigo (Radiom-223-dichlorid) oder im Rahmen der medizinischen Forschung in Verbindung mit einer gültigen Genehmigung gemäß § 31 Abs.1 StrlSchG oder Anzeige gemäß § 32 Abs.1 StrlSchG verwendet werden.

** Pb-212 darf ausschließlich für Heilversuche verwendet werden.

Compassionate care

PRISMAP User Agreement : project

User Agreement

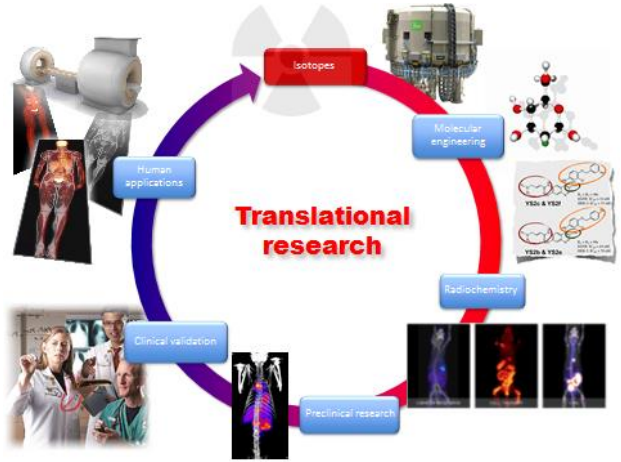
User project identifier: 1695806893 5CNFb
User project title: 203/212Pb-mcp-D-PSMA for an improved tumor therapy: Preclinical evaluation, automatization and translation to clinical application
Main contact of the user group: Dr M. Pretze
PRISMAP facility in charge: CERN-MEDICIS

- *PRISMAP* shall not be liable for, nor made party to, any claim that may arise from the use of any radionuclide it has supplied or medical facility that it has made available. The use of radionuclides and presence of individual users at a PRISMAP facility are at such users' own risk. Neither *PRISMAP* nor any *PRISMAP* personnel accept liability for the damage or loss of any instruments, apparatus and test equipment of the User or their personnel, whether or not such damage or loss was caused directly or indirectly by *PRISMAP* or its personnel's negligence. Individual users will ensure they have appropriate insurance, including personal health, accident cover and personal liability, for their activities.

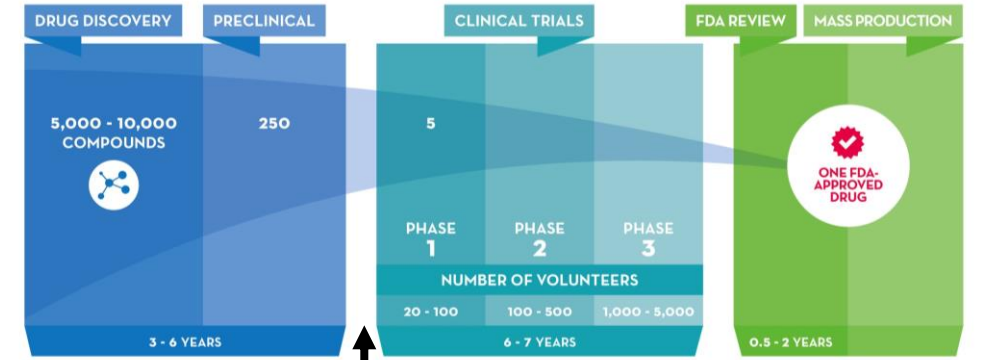
For projects involving medical applications, **ethical issues may apply**. In particular, animal studies or **first-in-human studies** may be included. Before the onset of such activities, the User must fulfil all related ethical requirements and sign a statement that their research complies with these requirements. The two organisations which offer access to first-in-human studies in the frame of the PRISMAP project (TUM and CHUV), both have ethics departments in place to accompany the User in this endeavour. As part of the access procedures, the related ethical requirements will be reviewed, compliance confirmed and documentation collected by the PRISMAP project's Ethics Manager, **David Viertl (CHUV)**, where necessary with the help of external ethics advisors.

Signed by main contact of user groups and facility in charge

Position of CERN-MEDICIS in the context of radiopharma R&D



Courtesy Prof. MD Osman Ratib
in the context of CERN-MEDICIS



We are discussing
crossing from preclinical to (pilot) clinical
For isotope dispatch

Time is require to develop production scheme and preclinical data,
This is the reason why this topics is coming this year (+ the review and CMASC)

MEDICIS: translation to clinical projects – project workflow

1st MEDICIS Collaboration Board Meeting

Wednesday 21 Feb 2018, 09:00 → 17:00 Europe/Zurich

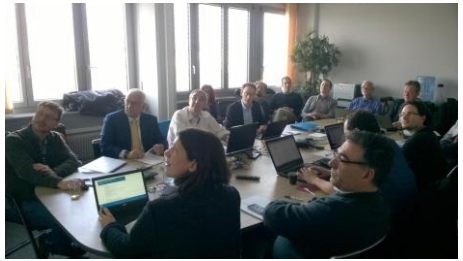
4-3-001 (CERN)

Description **Liste de participants**:

- Thierry Stora (CERN)
- Frédérick Bordry (CERN's Director for Accelerators and Technology)
- Simone Gilardoni (CERN)
- Thomas Elia Cocolios (KULeuven)
- Prof. Oyen Wim (ICR – Institute of Cancer Research, UK)
- Nick van Dermeulen (PSI)
- Antonio Paulo (Instituto Superior Técnico, Portugal)
- Dr. Michel Forni (Hôpital de La Tour, Geneva)
- Prof. Ismael Martel Bravo (FABRIS - Fundación Andaluza Beturia para la Investigación en Salud, Spain).
- Prof. Ferid Haddad (Arronax, France)
- Prof. Klaus Wendt (University of Mainz, Germany)
- Prof. Martin Walter (Head of Nuclear Medicine and Molecular Imaging, Geneva Hospital)
- Gerda Neyens (CERN)
- David Viertl (Lausanne University Hospital Center)
- Dante Gregorio (CERN)
- Tor Bjørnstad (IFE – Institute for Energy Technology, Norway)
- Frank Bruchertseifer (European Commission)

Via remote-connection:

- *Prof. Susanta Lahiri (SINP - The Saha Institute of Nuclear Physics, India)*
- *Dr Martyn Sené (Deputy CEO for the National Physical Laboratory - NPL)*
- *Prof. John Prior Head of Nuclear Medicine and Molecular Imaging, Lausanne University Hospital Center)*



MEDICIS

Project proposal to the MEDICIS Collaboration board

Strengthening theranostics or radionuclide therapy in Pakistan

Irfan Ullah Khan[1], Muhammad Numair[1], Abubaker Shahid[1], Shabana Saeed[2], Moazam Mehmood[3], Umair Khalid[3]

1. Institute of Nuclear Medicine and Oncology (INMOL), New Campus Road, Lahore
2. Pakistan Institute of Engineering and Applied Sciences (PIEAS), Nilore, Islamabad
3. Pakistan Institute of Science & Technology (PINSTECH), Nilore, Islamabad

Project submitted, discussed, and recommandation from the board to CERN

MEDICIS MoU

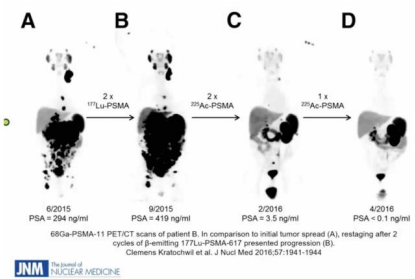
4.6 It is understood and agreed between the Participants that pre-clinical testing, clinical trials or other experimental activities undertaken by a Participant using radioisotopes made available under this MoU are not part of the Project and that CERN shall in no event take part in such activities. It is further understood and agreed that the provision of radioisotopes by CERN is on an 'as-is' basis, without any express or implied warranty, including with respect to quality or fitness for purpose.

Already addressed, but of course clinical testing is real step (see before).

- **Delivery of radionuclides to institutes co-applicants (MED-035 and others to follow)**

- We indeed have a number of cases where there is a single signatory for a consortium, either already (CHUV/Heidelberg Hospital), KULeuven/SCK CEN/U Gent, PAEC/PIEAS/INMOL hospital, Latvia Univ./RTUniv. / HUG/PRISMAP users

- Important project



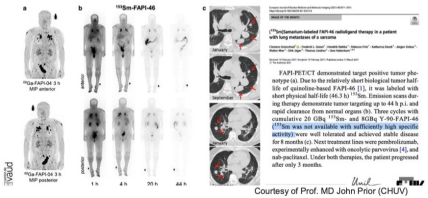
MEDICIS → Project proposal to the MEDICIS Collaboration board → CERN

153SM-FAPI-46 RADIOLIGAND THERAPY WITH HIGH-MOLAR ACTIVITY 153SM

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)

153SM-FAPI-46 RADIOLIGAND THERAPY WITH HIGH-MOLAR ACTIVITY 153SM



Courtesy of Prof. MD John Prior (CHUV)

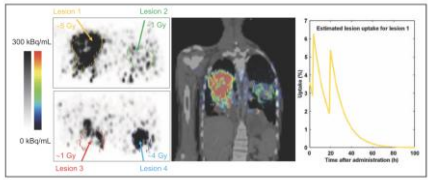


FIGURE 2. Posttreatment ^{90}Y-FAPI-46 PET images 4 h after injection with corresponding absorbed dose estimates for 4 lesions in patient 2.

Extract of the Q&A in preparation of the meeting

What makes this proposed collaboration unique and what is CERN's interest in the project / pilot at Heidelberg University Hospital ?
Univ Heidelberg – prof Kratochwill / prof Haberkorn are renown centers for clinical translation of new radiopharmaceuticals.
This group made the 1st medical publication reporting on the impact of 225Ac based radiopharmaceuticals in this field 10 years ago. This isotope is the one that everyone wants in the field, with forecast to get a share of few % of a multibillion Euros/US $/CHF annual market share.
They have developed a new ligand - FAPI46 - targettting a wide range of tumors ; the biokinetics of this ligands require an imaging and treatment isotope that is compatible with the short biokinetics – Sm-153 was already tested , supplied from reactor in a low activity grade ;
high activity grade Sm-153 is only possible at MEDICIS by mass separation there is the potential to launch a MEDICIS isotope into the clinical treatment area for the 1st time (and follow the same success story as Ac-225)

Can you provide detail on the proposed roles of CHUV and SCK in this project ?
CHUV is member of MEDICIS and in addition has strong expertise in translational medical research + ethical constraints CHUV (is ethical PRISMAP representative, see attached presentation). SCK has also been involved in previous MEDICIS projects that enabled this one, and see below.
The isotopes would be CERN (MEDICIS) made and are transported from CERN (HSE) directly to Heidelberg University Hospital, correct?
Isotopes are 1st produced in external partners at reactors (SCK, now part of MEDICIS collaboration in a belgium consortium), then imported to CERN – enriched by mass separation at MEDICIS – and then sent to Heidelberg (following the ALARA principle, it would make no rationale to deliver them in CHUV)

Any other logistic / transport step?
Yes see above

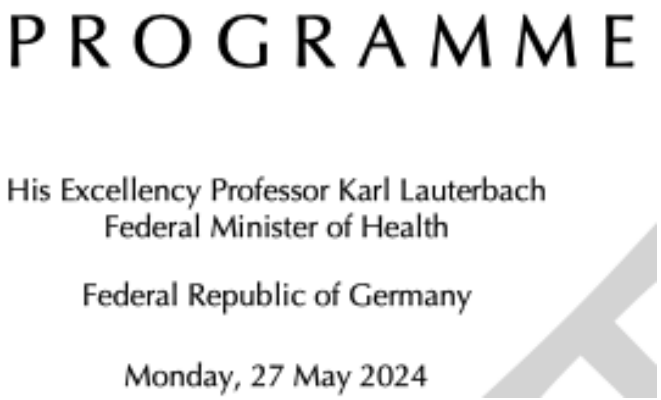
In what way is CERN's involvement in this medical-applications-related project purely a form of research and development ?
CERN is involved through hosting the MEDICIS collaboration, and this is thanks to previous MEDICIS projects that this one has become possible/enabled
CERN mass separation step : mass separation is only possible at MEDICIS

Why does Heidelberg University Hospital specifically need CERN (MEDICIS) isotopes ? Are they available elsewhere in the market ?
This is explained before, there no other places where this could take place for isotope mass separation

I understand that Heidelberg University Hospital is not part of MEDICIS. Is this intended to be a one-off provision of isotopes?
Heidelberg hospital is not part of MEDICIS. It could be in the future, but this is premature at this stage. Upon the successful outcome of this project, this scheme could become a major activity of MEDICIS in the future

- **Visit of german minister for Health and interest from industry**

- Nuclear medical doctor as background (As well as health economics)


PROGRAMME

His Excellency Professor Karl Lauterbach
Federal Minister of Health

Federal Republic of Germany

Monday, 27 May 2024

- Interaction with industry (has expressed interest)


CERN

- **MEDICIS Sm-153 (produced at SCK/ mass purified at MEDICIS) perfect match to FAPI-46 (radio)pharmaceutical**

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

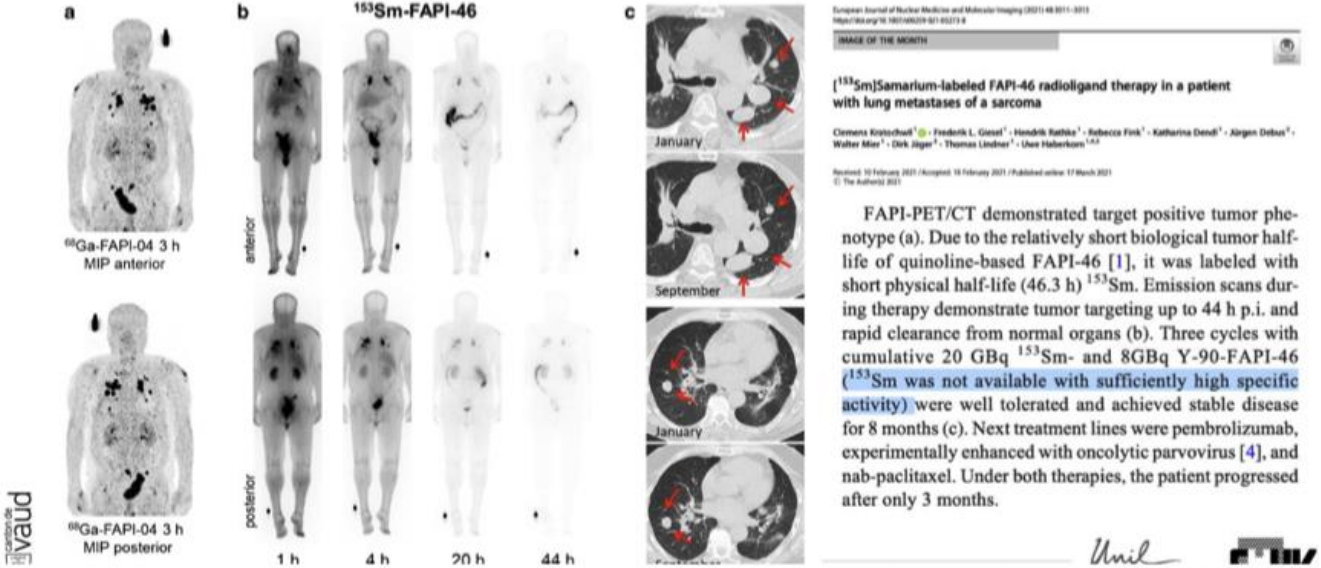


IMAGE OF THE MONTH

[^{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.

Courtesy of Prof. MD John Prior (CHUV)

- **MEDICIS Sm-153 (produced at SCK/ mass purified at MEDICIS) perfect match to FAPI-46 (radio)pharmaceutical**

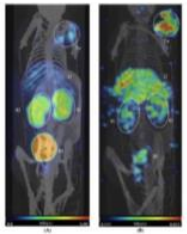
CERN-MEDICIS: radionuclides and research projects

Sm-153

Use of Sm-153 for Targeted Radionuclide Therapy only possible if Sm-153 is produced with higher specific-activity (higher ratio Sm-153/Sm-152)

Need to pass by mass-separation → CERN-MEDICIS !

- Up to 13% separation efficiency, with MELISSA laser ionization
  - **Final product suitable for radiolabelling** at SCK CEN (BE)



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 [1], Eric Chevallay [1], Thomas Schneider [1], Miranda Van Stenis [1], Thomas Elias Cocolios [1], Thomas Cardinaels [1,4], Bernard Ponsard [1], Maarten Ooms [1], Thierry Stora [1] and Andrew R. Burgoyne [1]

pharmaceutics — MDPI

Exploring the Potential of High-Molar-Activity Samarium-153 for Targeted Radionuclide Therapy with $^{[153}Sm]Sm$-DOTA-TATE

Koen Vermeulen [1,2], Michiel Van de Voorde [1], Charlotte Segers [1,2], Amelie Coolkens [1], Ivney Rodriguez Pérez [1], Noami Ducene [1], Charlotte Duchemin [2,3], Melissa Crabbé [1,2], Tomas Opsomer [1,2], Claritz Saldarriaga Vargas [1,2], Reinhard Heinke [2,3], Laura Lambert [1,2], Cyril Bernard [1,3], Andrew R. Burgoyne [1], Thomas Elias Cocolios [1,2], Thierry Stora [1] and Maarten Ooms [1,4,5]

"The Belgian Nuclear Research Centre and the MEDICIS research branch of CERN joined forces to produce high-A_m ^{153}Sm"

This proof-of-concept is now opening doors **towards therapy using Sm-153 mass separated at MEDICIS** → clinical translation from 2024 at the Medical Hospital of Heidelberg in Germany

Melissa Medicis sckcen

MED-035

CHUV KU LEUVEN

153SM-FAPI-46 RADIOLIGAND THERAPY WITH HIGH-MOLAR ACTIVITY 153SM

UNIVERSITÄT HEIDELBERG ZUKUNFT SEIT 1386

"5 patients pre-selected to have metastatic FAP-positive tumor diseases who already exhausted all approved treatment will be offered to receive experimental therapy according to German Law ("Heilversuch" = compassionate care)"

CERN | SY Accelerator Systems | STI | Medicis — 22