



European Organization for Nuclear Research
Organisation européenne pour la recherche nucléaire

**Integrating European Infrastructures for Starting Communities:
Physical mass separation to foster a new research era with emerging medical isotopes**

INFRAIA SEPA-MEDISO



**TOWARDS INTEGRATING EUROPEAN INFRASTRUCTURES FOR STARTING COMMUNITIES:
PHYSICAL MASS SEPARATION TO FOSTER A NEW RESEARCH ERA WITH EMERGING MEDICAL ISOTOPES**

The integration of facilities at the European scale has the potential to foster the collaboration and creation of a new research community in the field of non-conventional medical isotope production and research in radiopharmaceuticals and nuclear medicine. Through this integration, an improved access to new radioisotopes and new grades can open up research opportunities at the European scale that were barely possible because of the fragmented European landscape. In this context, we propose to kick-off the submission of a project for Integrating European Infrastructures for Starting Communities in the Horizon 2020 program of the European Commission during the final conference of MEDICIS-Promed in Erice [1].

The meeting will start with an introduction from the European Association of Nuclear Medicine (**EANM**), the International Federation of Pharmaceutical Manufacturers & Associations (**IFPMA**), and the International Atomic Energy Agency (**IAEA**). It will be followed by an introduction providing information on the path from the preparation to the submission of an INFRAIA project for starting communities in the Horizon 2020 program of the European Commission and the rationale behind the proposed **Physical mass separation to foster a new research era with emerging medical isotopes** by CERN/Sciprom.

The INFRAIA projects are structured along 3 types of Activities:

- ▶ **Trans-national access or virtual access activities**, to support scientific communities in their access to the identified key research infrastructures
- ▶ **Networking activities**, to foster a culture of co-operation amongst research infrastructures, scientific communities, industries and other stakeholders as appropriate, and to help develop a more efficient and attractive European Research Area
- ▶ **Joint research activities**, to improve, in quality and/or quantity, the integrated services provided at European level by the infrastructures

To help in the preparation of the project kick-off consortium on Tuesday 30th in Erice, we invite you to submit a short abstract of ½ page and upload a presentation of up to 5 slides on <https://indico.cern.ch/event/812606/>, should you be willing to propose a:

- ▶ **Facility as key research infrastructure**, providing medical isotope with accelerators, neutrons or mass separation
- ▶ **Network activity** for co-operation between research infrastructures, scientific communities, industries and other stakeholders, that could address, to name but a few, the elaboration of a virtual platform, the liaison with licensing and clinical communities, the production of PET-emitting isotopes for hadron-therapy
- ▶ **Joint research activity**, that will focus on the development of the services provided, and could cover medical isotope production and acceleration techniques, dosimetry reduction through new medical imaging techniques

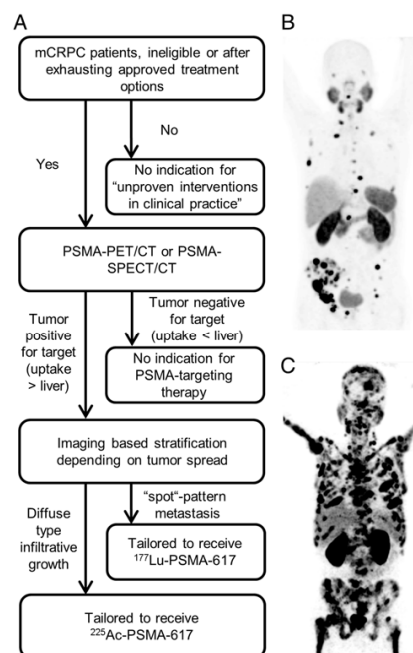
For Network activity and Joint research activity, submissions that already foresee the participation of other institutes are particularly welcome. If you are willing to join the consortium and do not yet know how exactly your activity would fit in, please do submit a proposal.

We are looking forward to meeting you soon in Erice,
Best regards,

Thierry for the starting consortium.

BACKGROUND

The field of precision medicine, notably that of targeted radiotherapy and theranostics combining radiopharmaceuticals for therapy and diagnostics, has shown rapid developments for the past few years. New radiopharmaceuticals have recently been approved for the treatment of cancers, demonstrating efficacies in clinical trials. Xofigo[®] marketed by Bayer is a targeted alpha therapy drug and the theranostic pair ⁶⁸Ga-DOTATATE / ¹⁷⁷Lu-DOTATATE (Netspot[®]/Luthatera[®] marketed by Advanced Accelerator Applications/ Novartis), combines a PET imaging agent and a beta emitting treatment isotope. The successful development of these drugs was made possible by the prior development of radioisotopes in a single or few centers before the European research community, active for the development of new radiopharmaceuticals, and of their tests in preclinical and subsequent clinical phases could actually select a proper isotope-bioconjugate combination able to show efficacy up to the last clinical trial phases [2]. This cycle going from drug development to market requires research activities and access to non-conventional radioisotopes. For instance, the development of Targeted Alpha Therapy (TAT), exploiting treatment radiopharmaceuticals with alpha-emitting isotopes is presently limited at large by the access to these rare isotopes such as ²²⁵Ac or ²¹¹At [3]. The emerging alpha-emitting ²²⁵Ac-PSMA-617 drug can be indicated for cases where the ¹⁷⁷Lu-PSMA-617 treatment was not efficient. This result was made possible with ²²⁵Ac provided by the European Joint Research Center, Karlsruhe.



Reprinted from Ref. 2.: Patient selection criteria: Work-flow how patients were selected to receive PSMA-RLT as an unproven intervention in clinical practice (A). Patients with oligo-metastatic, “hot-spot”- pattern tumor spread (B) were preferably stratified to receive ¹⁷⁷Lu-PSMA-617, patients with “diffuse”-pattern bone marrow infiltration (C) were stratified for ²²⁵Ac-PSMA-617.

These results and various others triggered a recent topical meeting in Vienna dedicated to the supply of ²²⁵Ac in targeted alpha-therapy [4]. There, production with accelerators and nuclear reactors, isotope physical mass separation, and their impact on the obtained purity grade, licensing and waste treatment, recent clinical tests, was reviewed. While a few isotopes and their production routes are well established in nuclear medicine, both for diagnostics and therapy, emerging isotopes and new methods of production are being elaborated and still need to meet the foreseeable market growth for new therapeutic radiopharmaceuticals. In our Marie-Curie training network MEDICIS-Promed, 15 young researchers have been trained in the different scientific fields relevant in isotope production and research in radiopharmaceuticals, across an intersectorial network of academic research institutes, international organizations, private companies and hospitals. We can notably highlight the construction of a new facility MEDICIS at CERN for the improved access to ^{149/152/155}Tb as part of a unique medical isotope quadruplet (with ¹⁶¹Tb) or the production of high-specific activity ¹⁶⁹Er produced in the high neutron flux reactor ILL and separated at MEDICIS.

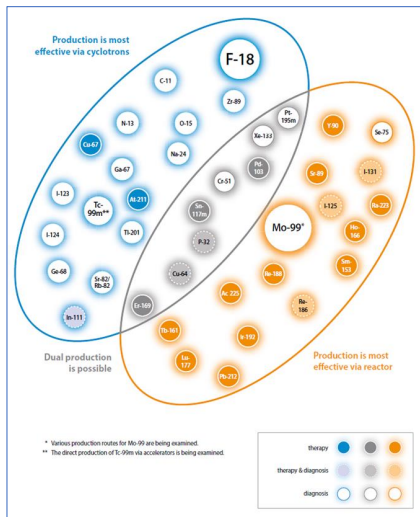


Figure 31 : Main medical radioisotopes production process

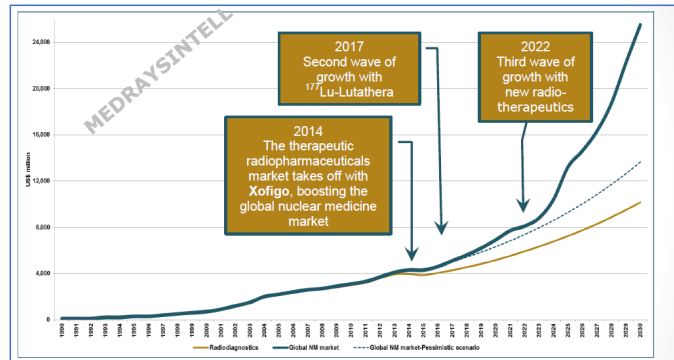
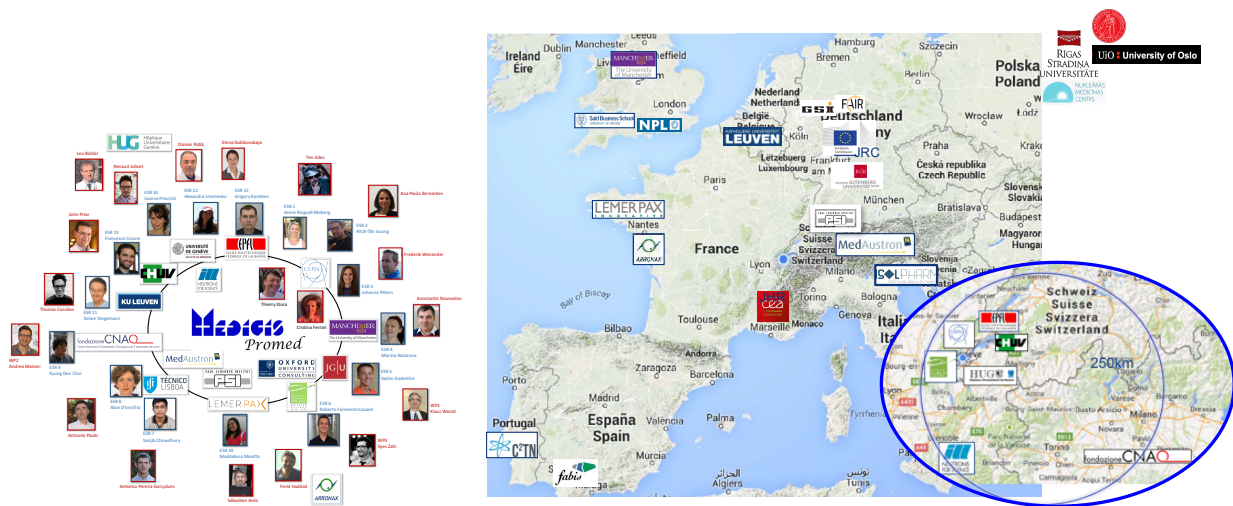


Figure 8: Possible market evolution for radiotherapeutics – source MedRaysIntell (2016)

Reprinted from Ref 5 : Overview of medical radioisotopes production and possible market evolution for treatment radiopharmaceuticals.



Network in Europe across the supply chain from new isotope production to radiopharmaceutical developments
 Left MEDICIS-Promed H2020 ITN [1]. Right, existing network including new institutes foreseen at the kick-off meeting.

References :

- [1] www.cern.ch/medicis-promed (H2020 contract # 642889 **Medicis-Promed**); <https://indico.cern.ch/event/782482/>
- [2] Strosberg J, et al. N Engl J Med. 2017;376:125-35, **Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors**
- [3] Kratochwil C. et al, doi:10.2967/jnumed.117.203539, **Targeted Alpha Therapy of mCRPC with ²²⁵Actinium-PSMA-617: Swimmer-Plot analysis suggests efficacy regarding duration of tumor-control.**
- [4] Joint IAEA-JRC meeting “**Supply of actinium-225**”, Vienna, 9-10 October 2018, under the umbrella of practical arrangement between the IAEA and the European Commission on cooperation of nuclear science applications.
- [5] **European Study on Medical, Industrial and Research Applications of Nuclear and Radiation Technology**, Contract ENER/17/NUCL/SI2.755660, Final Report – EC-01-08-D-30/07/2018.