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D2.5 Report on aspects of the SAMIRA and MEDICIS projects relevant for the EURAMED rocc-n-roll SRA

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The opinions stated in this report reflect the opinions of the authors and not the opinion of the European Commission.

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1. Introduction and Methodology

The aim of this deliverable is to provide an overview of the aspects of the aspects of the SAMIRA and SMER reports and the MEDICIS/PRISMAP projects relevant for the EURAMED rocc-n-roll Scientific Research Agenda (SRA).

Composition of Scientific Panel for Task 2.5

To carry out the task, scientific panel of experts was established. The following experts make up the Task 2.5 panel:

- John Damilakis (WP2 leader; UoC, Greece)
- Kristoff Muylle (Task 2.5 leader for SAMIRA/SMER; VUB, Belgium)
- Thierry Stora (Task 2.5 leader for MEDICIS; CERN, Switzerland)
- Frank Deconinck (VUB, Belgium)
- Francesco Giammarile (IAEA, Austria)
- Oliver Neels (Helmholtz-Zentrum Dresden-Rossendorf (HZDR), Germany)
- Ulli Koester (Institut Laue-Langevin (ILL), France)
- António Paulo (Centro de Ciências e Tecnologias Nucleares (C2TN), Portugal)
- Martin Walter (Switzerland)
- Jing Ma (OVGU, Germany)

Online Meetings

An online kick-off meeting was held on February 24, 2021. This deliverable has been established by online meetings only, mainly because of travel restrictions related to COVID and secondly because of the larger availability of the panel members for online-meetings.

Deliverable Compilation

The deliverable has been developed in 2 parts:

1. SAMIRA-report (2018) & SMER-report (2021):

Selection by the panel members of the most relevant topics after evaluation of recent position papers, editorials, reviews, and research papers from the nuclear medicine community related to both reports (with focus on the most recent one: “Co-ordinated Approach to the Development and Supply of Radionuclides in the EU”) with a potential high impact on research, clinical practice and patient care.

4 research related topics are selected and highlighted:

- Dosimetry
- Radiobiology
- Artificial intelligence
- Research and clinical infrastructures

2. MEDICIS/PRISMAP:

Report by the panel members on the activities of MEDICIS/PRISMAP and update on the submitted research projects on non-conventional radionuclides related to the MEDICIS Collaboration.

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2. SAMIRA- & SMER-report

The recommendations with respect to research needs / topics are related to 2 reports from the European Commission:

Contract ENER/17/NUCL/SI2.755660 Final Report – EC-01-08-D-30/07/2018 ("SAMIRA-report")

Abstract

Since their discovery over a century ago, ionizing radiation (IR) technologies have become key tools to explore matter and biological building blocks. One of the most important discoveries of the 20th century — the structure of DNA — was the result of analysing its X-ray diffraction pattern. Over the years, health has become one of the most important non-energy applications to use IR, including imaging and therapy. IR is also used in many industrial domains, ranging from sterilization and disinfection to security-control systems, and from non-destructive testing to environmental applications. Nanotechnologies, nanoelectronics, photonics, advanced materials, biotechnologies and advanced manufacturing also use IR tools. Not only do these technologies generate high revenues by themselves, they also generate highly skilled innovation-oriented jobs, confer added value to products and services in which they are embedded and prompt other technological developments. Europe hosts a substantial infrastructure of facilities dedicated to fundamental or applied IR research, a broad network of advanced universities and research centres, as well as world-class industrial corporations and innovative SMEs competing at the global level. Such assets should be sustained and developed, alongside its most promising applications, while ensuring the highest level of safety and radiation protection. This report provides up-to-date information on the non-power applications of nuclear and radiation technology in the EU with the view of identifying their key societal benefits and development perspectives. The report proposes a series of actions in this area aimed at contributing to the European citizens' health and to the European economy, competitiveness, jobs and growth.

Co-ordinated Approach to the Development and Supply of Radionuclides in the EU N°ENER/D3/2019-231, reference EC-05-10-E-03/08/2021 ("SMER-report")

Abstract

According to the new European SAMIRA Action Plan2, there is a need to secure the supply of medical radioisotopes in the medium to long term, in order to maintain EU patients' access to vital medical procedures.

The selection of the most representative of current and future-use radionuclides allows to highlight the long-term paradigmatic change towards an increased use of therapeutic radionuclides. Radionuclides supply chains are then extensively analysed. Complementarity between accelerators/cyclotrons and fission/neutron activation installations for producing industrially all necessary isotopes is emphasized, as well as the interest of coordinating the large European Research installations for producing the isotopes necessary for R&D.

If investments are not timely made in Europe for replacement of the ageing production infrastructures and the development of new source materials capabilities (HALEU and enriched stable isotopes), the result will be an increasing dependence of EU on foreign supply.

Diverse options for fostering a sustainable supply of radionuclides in Europe are then presented and screened through a multi-criteria analysis. Possible scenarios for EU rank from

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relatively low to high investments, inversely proportional to levels of reliance upon foreign supply.

4 research related topics with a potential high impact on research, clinical practice and patient care have been selected and highlighted:

- Dosimetry
- Radiobiology
- Artificial intelligence
- Research and clinical infrastructures

Dosimetry

Official guidelines and recommendations for radionuclide therapy (RNT) currently do not include advanced dosimetric calculations. As in chemotherapy, fixed radioactivity doses (with or without visual assessment of pretherapy scans) or activity doses based on body weight or body surface area are considered sufficient in clinical practice for the main clinical RNT protocols. Nevertheless, the European Council Directive 2013/59 [1] (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri= CELEX:32013L0059&from=EN), stipulates that in medical exposures for radiotherapeutic purposes, including RNT, exposures of target volumes shall be individually planned and their delivery appropriately verified.

Dosimetry is an undisputed aspect of radiopharmaceutical pre-clinical development, its clinical use to tailor the administered activity to an individual patient's needs is less evident. Data in the literature clearly and unequivocally establishing the potential of dosimetry to avoid underdosing and overdosing, and to standardize RNT methods are emerging but remain still scarce. Furthermore, dosimetry is a difficult and time consuming procedure that is not available everywhere as specialized knowledge and experience are required. Before transferring complex dosimetry to routine clinical practice, robust scientific justification remains to be established. First and foremost, the nuclear medicine community at large has the obligation to **prove in prospective and randomized trials with adequate methodology, that dosimetry-based RNT has clinically relevant additional benefits for our patients over the currently used, established and safe empirical dosing methods**, whether using fixed-activity concepts or simple characteristics such as body weight and body surface area.[2]

Although in current clinical practice, prescriptions in radionuclide therapy are most commonly based on a fixed amount of activity for all patients, often tailored to patient weight or body surface area, and in some cases considering other clinical and biological parameters, including pre-therapy imaging. While this enables therapy to be performed with minimal resourcing or planning, the development of personalized prescription alternatives based on dosimetry has the potential to improve the outcome and cost-benefit of radionuclide therapies. Obviously, there are a number of challenges to be addressed. These include research, resourcing and training, and possibly new ideas on how to organize the treatment. Such challenges should be considered within the perspective of the introduction and evaluation of new techniques, building on fruitful collaborations between different medical specialties in nuclear medicine, oncology, and medical physics. [3, 4]

The last few years have seen important changes in the development and composition of radiopharmaceuticals introduced in clinical practice. These technical changes have led to new delivery requirements: nowadays, posologies need to be more patient centric. However, EU requirements for the use of radiopharmaceuticals in patients, based on their respective posologies, which are issued as part of their marketing authorization by the European Medicine

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Agency (EMA), are currently not fitting the needs and are partially in contradiction to the Council Directive 2013/59/Euratom, which leads to complex situations in clinical practice. In order to comply with this Council directive, the European Association of Nuclear medicine (EANM) has published a proposal to distinguish 3 levels in compliance to the optimization principle in the directive, inspired by the indication of levels in prescribing, recording and reporting of absorbed doses after radiotherapy defined by the International Commission on Radiation Units and Measurements (ICRU).[5] However, these **contradictory applications between EMA and EURATOM are making the delivery of radiopharmaceuticals to patients very complex**. In this respect, a reconciliation between these differing requirements would be most welcome to improve harmonizing requirements and regulations for therapeutically used radiopharmaceuticals.[6] The following suggestions have been made:

1. DG Energy and the EURATOM treaty article 31 group of experts should acknowledge the fact that treatment with radiopharmaceutical is different as compared to external beam therapy for the following reasons:

- For some radionuclides pre-therapeutic treatment planning or post-therapeutic absorbed dose verification is not possible due to technical limitations in quantitative imaging procedures for dosimetry (e.g. 223Ra or 90Y)
- For some radiopharmaceuticals absorbed dose limits for organs-at-risk derived from data on external beam therapy are not well established
- For some treatments the variability in the pharmacokinetics, and consequently, in the absorbed doses is low; thus reducing the necessity for treatment planning
- The relative biological effectiveness (RBE) for therapeutically administered radiopharmaceuticals labelled with alpha emitters are not established. The determination of absorbed doses only, in particular for treatment planning, might not reflect the dose-effect relationship correctly
- These considerations could be embedded a future revision of the BSS.

2. EMA marketing authorizations schemes for radiopharmaceuticals should be adapted, to follow patient-centric dosimetry, instead of traditional posology schemes. In this respect:

- Early stage clinical trials (phase I/II) for new radiopharmaceuticals should be requested to collect and monitor patient-specific dosimetry data and absorbed doses in order to improve the safety and efficacy of new therapies. These trials should follow the requirement to develop patient-specific prescription of radiopharmaceuticals for an improved assessment of patient dosing in later phases for obtaining marketing authorisations.
- Such requirement for collection of patient-specific dosimetry data in phase III would also support the precise establishment of absorbed dose, which is crucial to limit side-effects.
- Such requirement to gather sufficient dosimetry data from early clinical trials will limit uncertainties in patient treatments in case dosimetry cannot be performed because of technical reasons.
- With such requirement, posologies will contain more detailed and verified information on dosimetry data including the expected uncertainties and range of absorbed dose to organs-at-risk

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- For all marketing authorization applications concerning therapeutic radiopharmaceuticals, an external advisor who is knowledgeable in this kind of treatment should be closely involved.

The contradictory applications between EMA and EURATOM are also addressed by SIMPLERAD [7], a joined initiative by European Institute for Biomedical Imaging Research (EIBIR), EANM Forschungs GmbH (EANM), and European Federation of Organisations for Medical Physics (EFOMP) conducting a SAMIRA study on the implementation of the Euratom and the EU legal bases with respect to the therapeutic uses of radiopharmaceuticals with 4 work packages:

- WP1: Analysis of the interrelations between EU pharmaceutical legislation and Council Directive 2013/59/Euratom
- WP2: Survey and analysis of the implementation of relevant European legal requirements for therapeutic nuclear medicine
- WP3: Advancing coherent implementation of European legal requirements for therapeutic nuclear medicine
- WP4: Organisation of a European workshop

Radiobiology

The **role of radiobiology** to examine the impact of radioresistance, low and continuous absorbed dose rates, and heterogeneity of uptake at either a cellular, microscopic or macroscopic scale is under investigation, and will expand if dosimetry data are made available to compare with outcomes. Furthermore, genetic mechanism affecting individual responses to ionizing radiation should also be considered in the frame of personalized medicine [8, 9]. These research fields should be encouraged to fully develop the theranostic advantage that radionuclide therapy can offer. With an increasing variety of radiopharmaceuticals for diagnostic or therapeutic nuclear medicine as valuable diagnostic or treatment option, radiobiology plays an important role in supporting optimizations. This comprises particularly safety and efficacy of radionuclide therapies, specifically tailored to each patient. As absorbed dose rates and absorbed dose distributions in space and time are very different between external irradiation and systemic radionuclide exposure, distinct radiation-induced biological responses are expected in nuclear medicine, which need to be explored. This calls for a dedicated nuclear medicine radiobiology. To sustain the comprehensive understanding of nuclear medicine radiobiology, the use of relevant cellular and animal models for pre-clinical evaluation is of crucial importance. For instance, there is an increased awareness in the scientific community of the need to transition from 2D to **3D culture models** (e.g. spheroids) better recapitulating the complexity and heterogeneity of tumors, to obtain results with improved translational potential. Furthermore, **organoid models** would be extremely valuable for understanding normal tissue responses. It is also important to develop radiobiology studies in personalized tumor models, based namely on **patient-derived tumor organoids** (PDTO) and **patient-derived xenografts** (PDX). Radiobiology findings and absorbed dose measurements will enable an improved estimation and prediction of efficacy and adverse effects. Moreover, a better understanding on the fundamental biological mechanisms underlying tumor and normal tissue responses will help to identify predictive and prognostic biomarkers as well as biomarkers for treatment follow-up. In addition, radiobiology can form

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the basis for the development of radiosensitizing strategies and radioprotectant agents. Thus, beyond in vitro and preclinical evaluations, radiobiology has the potential to add important value to clinical studies and to clinical teams. Therefore, collaboration between radiochemists, radiopharmacists, radiobiologists, medical physicists, and physicians is essential to foster research toward theranostic and precision nuclear medicine.[10, 11]

Artificial intelligence

The applications of artificial intelligence (AI) in healthcare are potentially numerous, clearly going beyond the field of medical imaging alone. Growing numbers of patients, higher demands for quality like early detection and personalized therapies and an increasing workload for medical and nursing staff creates a demand for automation and the need for extracting more information from acquired data. Potential advantages of AI are already visible in screening routines in which a high number of patients (and associated data) are investigated for the presence or absence of disease, with results that are not worse than human performance. The introduction of AI into the operation of radiology departments has led to optimizing resources. Such operational AI should prove even more relevant in nuclear medicine, which deals with radioactive isotopes, whose shelf-life is limited. Patient scheduling, management of preparation of radiopharmaceuticals, report generation and recovering and organizing previous NM and imaging studies are examples of tasks where AI could contribute to streamlining the operation of a department.

Two major components in which AI can play a part can be discerned. The “physics” component concerns image formation and image processing tasks. The “clinical” component is largely application driven. It concerns routine workflow and final clinical endpoints, e.g. diagnosis, prognosis and prediction of response to therapy. Both components are ultimately connected, the convolutional neural network concepts being similar and very often associated within a single imaging paradigm. In addition, the available data from multimodality devices such as PET/CT or PET/MR and from the emerging total body PET technology is expected to largely increase with the development of (multi)parametric imaging. Within this context deep learning-based reconstruction and analysis, algorithms are potentially more efficient to deal with the increasing volumes of acquired data [12,13,14]. Regarding theranostic, AI can also play an important role in radiation dose estimation [15].

The time to implement AI in medicine is now. Nuclear medicine (NM) and molecular imaging are no exception to that development. AI shows great promise to improve image quality, to personalise dosages (both in diagnosis and theranostics) and to help in image interpretation. It opens ways to fully exploit the potential of NM (which by nature is a numerical specialty), an aspect that has gathered momentum over the past decade with the advent of radiomics. As such, AI has the potential to improve clinical workflows that will increase overall efficiency but also facilitate personalised medicine for the benefit of a patient. Here, we should not forget the introduction of total body scanners which cause an enormous increase of data to be handled. It seems obvious that

AI and total body scanners are natural partners to tackle this problem. **Validation of outcomes/results of individual trials/studies is needed**, and this is where multicentre and multigroup cooperation is of the utmost importance. **Comparing the performance of algorithms through challenges is needed** considering both methodological and clinical outcomes. Demonstrating the potential interest of AI in NM through these challenges represents also an essential element for its adoption within our field. As with any new technology (and even more true for software related) developments, **the field requires also industrial partners to be proactive in facilitating its clinical implementation**. Last but not least is education. The transmission of knowledge for the implementation of AI in NM and

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molecular imaging is dearly needed. These **educational programs** should target both the scientific and clinical aspects.[16]

The application of AI in medical imaging is bringing new possibilities in early detection and diagnosis of diseases, better clinical decisions, outcome prediction, or prognosis evaluation. The finding of the appropriate balance between fully autonomous AI and physician supervision is a new and major challenge. If AI algorithms are at least as accurate and reproducible as assessment by physicians in a dedicated task, it may help in the daily practice by improving patient management.[17]

Last but not least, **ethical standards for the implementation of AI need to be set out**.[18] Currie et al. [19] have recently proposed a set of ethical standards to be followed when evaluating and developing AI in NM, which are applicable to any medical specialty that will employ AI as part of its clinical practice in the future:

1. Beneficence, i.e. common good
2. Non-maleficence, i.e. do no harm
3. Fairness and justice, i.e. equal opportunity and access
4. Safety, i.e. for the patient
5. Reliability, i.e. accuracy and reproducibility in clinical practice
6. Security, i.e. for the data
7. Privacy and confidentiality of data
8. Mitigation of bias, i.e. fair and evidence-based clinical validation
9. Transparency and visibility, i.e. to the patients and community
10. Explainability and comprehensibility
11. Human values: human-in-the-loop process incorporated
12. Autonomy, judgement, and decision-making: human-in-the-loop process
13. Collegiality, i.e. multidisciplinary involvement and commitment
14. Accountability, i.e. among stakeholders
15. Governance, i.e. framework to ensure compliance
16. Inclusiveness, i.e. empowerment of all stakeholders

Research and clinical infrastructures

A tremendous increase in the demand for theranostics procedures can be expected in anticipation of FDA and EMA approval of 177Lu-PSMA-617, and this projected surge in demand for both theranostics infrastructure and appropriately skilled professional staff will pose a challenge and opportunity for healthcare systems. Even in countries with a strong track record in radionuclide theranostics**, the existing infrastructure may be insufficient to meet the growing demand** [20]. Thus, theranostics and radionuclide therapy need to get ready for the demand from cancer patients, referring physicians and society. Recently EANM, SNMMI and IAEA published an enabling guide for stakeholders interested in setting up a dedicated theranostics center [21]. Special attention is given to regulatory considerations and requirements, logistical and technical challenges, medical considerations including training, collaboration with clinical partners and treatment indications and important lessons learnt from early adopters of theranostics.

Despite the major promise that radionuclide therapies hold, the regulatory framework in many European countries is far from optimal for the adoption of radionuclide therapies across the country. As to radionuclide therapy, needs in terms of adequate healthcare professional training, integration in oncology practices, adapted reimbursement and infrastructure are therefore not adequately represented in the national cancer policy of many EU-countries.

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The European Commission's Beating Cancer Plan (BCP) attributes much importance to delivering higher-quality care by improving access and the capacity of Member States to offer innovative treatments. Therefore, the BCP's Strategic Agenda for Medical Ionising Radiation Applications (SAMIRA Action plan) provides an opportunity for national stakeholders to align their regional or national cancer plan with the objectives of the BCP and SAMIRA, including radionuclide therapy as a new pillar of cancer care. Particularly, **strategic planning of hospital investments** taking into consideration the needs of infrastructure (in particular radioprotection rooms and radioactive waste storage solution), appropriate resources, skilled healthcare professionals (e.g. medical physicist and radiopharmacist) and equipment for radionuclide therapy should be ensured to cope with the expected exponential increase in the demand for theranostics procedures.

In-house preparation of radiopharmaceuticals is an essential practice for nuclear medicine in many EU countries. The need for in-house preparations will even increase in the future taking into account the rapid development of the field, both in terms of technical advances (e.g., new radionuclides, new technologies for automated production) and also in utilizing new clinical relevant targets in many fields and further developing personalized medicine approaches, particularly in the context of theranostics.

The development of innovative radiopharmaceuticals usually takes place in radiopharmacies, research centers or nuclear medicine laboratories**. Practically all recent major clinical breakthroughs in Nuclear Medicine over the last decade**, exemplified by the success of theranostics with Somatostatin analogs and prostate cancer applications, **were based on the use of in-house preparations of these innovative products.** In case a new radiopharmaceutical has both the technical (half-life) and clinical potential to be produced and distributed commercially, these new radiopharmaceuticals more frequently make their way to pharmaceutical companies that take over from academia and provide funding for further clinical trials besides phase 0/phase I.

The **current regulatory framework for in-house preparation, unfortunately, is not harmonized throughout Europe and has resulted in unbalanced access to innovative radiopharmaceuticals, based on national particularities**. Future changes in the European legislation should consider the importance of in-house preparation of radiopharmaceuticals, ensuring quality and safety with harmonized standards and dedicated rules taking into account the particular needs for this practice, simply for the benefit of patients otherwise having delayed or even no access to often life-saving treatments.[22]] Beyond that, definitions of terms should be reviewed in European legislation to reflect today's nuclear medicine and radiopharmacy practices and differentiations should be made in regulations between kit-based radiopharmaceutical preparations and complex radiopharmaceuticals preparations.[23]

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3. MEDICIS/PRISMAP.

3.1 Update on the submitted research projects on non-conventional radionuclides

MEDICIS at CERN produces non-conventional radionuclides by isotope mass separation for preclinical research, with the objective to qualify some of the investigated radionuclides for clinical research. It operates as a collaboration with external institutes across the European Union, the JRC from the EC, Switzerland, UK, Pakistan and India. The MEDICIS Collaboration is composed of 13 external institutes, and 19 experts from different disciplines ranging from nuclear physics and chemistry to radiopharmacy up to nuclear medicine. In addition, the scientific liaison officer from EANM participates in the board and provides feedback on the proposed projects from the collaboration [1].

Research projects are developed along different directions exploiting or requesting radionuclides in diagnostics and therapy. They can be classified in the following main categories: Imaging techniques, theranostics, molecular targeted therapy, drug delivery, radiopharmaceutical developments, preclinical research, clinical translation, dosimetry and medical isotope production techniques. The projects are listed and the public abstracts are available on the MEDICIS website [2].

From the 32 projects, 23 different radionuclides have been requested. Most of the radionuclides are radiometals and radiolanthanides, with half-lives from 20 min to 45 days. Others may have radionuclidic contaminants, or daughter products with long half-lives of years. Some projects are addressing one or a few radionuclides to develop nuclear medicine applications and research with non-conventional radionuclides, for example in Flanders in Belgium, in Latvia and in Pakistan. A notable axis of research is supported through the collaboration of metrology institutes NPL in UK and IRA-CHUV in Switzerland. Their contribution has allowed to precisely determine some important properties such as their half-life and primary standards to support the calibration of instruments and, e.g. cameras [3]. The range of radioactive decay schemes, as stated previously, is very wide with, non-exhaustively, pure beta emitters (169Er), alpha emitters (149Tb, 225Ac), SPECT and PET imaging radionuclides (44Sc, 152Tb, 155Tb), radionuclides that combine both gamma and beta emissions (67Cu, 153Sm, 175Yb,), in vivo generators (128Ba/Cs, 134Ce/La), Auger and conversion electron emitters (167Tm, 191Pt, 193mPt, 195mPt), and radionuclides with photon emission that can be polarized for magnetic resonance imaging with γ-ray detection (131mXe, 133mXe).

Research topics that may be proposed on this rich radionuclide portfolio can therefore take different directions.

Radionuclides of interest at MEDICIS:

11C, 44Sc, 47Sc, 52Fe, 59Fe, 64Cu, 67Cu, 82Rb, 128Ba/Cs, 131mXe, 133mXe, 134Ce/La, 149Tb, 152Tb, 155Tb, (161Tb), 153Sm, 167Tm, 169Er, 175Yb, 191Pt, 193mPt, 195mPt, 225Ac.

MED	Radionuclide	Institute	Irradiation point, particle	modality	Comments
7	11C	KUL (BE)	CERN (EU)	Production technique	
1	149Tb	CHUV (CH)	CERN (EU)	antibody	

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2	149Tb, 152Tb	PSI (CH)	CERN (EU)	Preclinical, clinical translation	
3	155Tb	HUG (CH)	CERN (EU)	Drug delivery	
4	149Tb,155Tb, *161Tb*	C2TN (PT)	CERN (EU) + *neutrons ILL*	Radiopharmaceutical research, preclinical	161Tb from reactor
5	155Tb,*161Tb*	C2TN (PT)	CERN (EU) + *ILL*	Radiopharmaceutical research, preclinical	161Tb from reactor
6	155Tb	KUL (BE)	CERN (EU)	Supply chain	
8	67Cu	NPL (UK)	CERN (EU)	Radiopharmaceutical research, preclinical	
9	149Tb, 155Tb, *161Tb*	FABIS (ES)	CERN (EU) + *ILL*	Preclinical, translation	161Tb from reactor
10	47Sc, 169Er, 149Tb	Arronax (FR)	CERN (EU), ILL (FR)	Production technique	169Er from reactor
11	169Er	Arronax (FR)	ILL (FR)	Production technique	
12	47Sc, 149Tb	Arronax (FR)	Intermediate energy p Arronax (FR)	Production technique	
13	131mXe, 133mXe, 82Rb,	CERN (EU)	CERN (EU)	New imaging technique	131mXe, 133mXe from reactor
14	155Tb	KUL (BE)	CERN (EU)	Radiopharmaceutical research, preclinical	
15	44Sc	Latvia	CERN (EU) low energy p Latvia	Production technique	National project (Academy of science)
16	149Tb, 155Tb	FABIS (ES)	CERN (EU)	Radiopharmaceutical research, preclinical	
17	167Tm	PSI (CH)	Intermediate energy p PSI (CH)	Production technique, dosimetry, radiopharmaceutical research, preclinical	
18	169Er	PSI (CH)	Neutrons ILL (FR)	Production technique, dosimetry, radiopharmaceutical research, preclinical	169Er from reactor
19	175Yb	PSI (CH)	Neutrons ILL (FR)	Production technique, dosimetry, radiopharmaceutical research, preclinical	175Yb from reactor
20	155Tb	KUL (BE)	CERN (EU),	Production technique, radiopharmaceutical research, preclinical	National project (FWO)

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21	155Tb/ *161Tb*	C2TN (PT)	CERN (EU)	Radiopharmaceutical research, theranostics, preclinical	161Tb from reactor
22	191, 193m, 195mPt	HUG (CH)	High energy p CERN (EU), neutrons ILL (FR), neutrons PAEC (PK)	Theranostics, preclinical	From reactor
23	52, 59Fe	HUG (CH)	CERN (EU)	new technique	
24	225Ac	KUL (BE)	CERN (EU)	Production	
25	153Sm	KUL (BE)	Neutrons SCK (BE)	Production, dosimetry, radiopharmaceutical research	153Sm from reactor
26					n.a.
27	225Ac, 64Cu	INMOL (PK)	CERN (EU)	Radiopharmaceutical research, preclinical	National project
28	128Ba/Cs	CHUV (CH)	CERN (EU)	Theranostics, preclinical	
29	134Ce/La	CHUV (CH)	CERN (EU)	Theranostics, radiopharmaceutical research, preclinical	
30	225Ac	KUL (BE)	CERN (EU)	Production technique, dosimetry	National project
31	149Tb, 152Tb	KUL (BE)	CERN (EU)	Radiopharmaceutical research, preclinical	

Table 1: List of MEDICIS projects

Figure 1: List of PRISMAP radionuclides.

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3.2 PRISMAP, The European medical radionuclide programme.

PRISMAP, the European medical radionuclide programme, started in May 2021. It is a consortium of 23 institutes, regrouping neutron irradiation facilities, high energy proton facilities, intermediate energy proton and deuteron and alpha beam cyclotrons and associated radiochemical labs as well as the JRC that can supply radionuclides milked from their stock of radionuclide generators. PRISMAP also federates biomedical facilities that act as user facilities and can host users to perform experiments with these radionuclides, providing a considerable added value when short transport distances to the production facilities reduce decay losses or dedicated infrastructures, equipments and expertise are required by the users [4]. An offer of 24 radionuclides are presently available, from research grades to GLP and GMP grades suitable for clinical research. As MEDICIS is part of the consortium, no carrier added grades are also available for radionuclides that are else only available in low specific activity forms (169Er, 153Sm). While some clear overlap exists with the MEDICIS portfolio, the extension of the consortium allows to gain in clinical orientation and explore other radionuclides, for instance 165Er and its generator 165Tm. 15 projects have been approved by a selection board which is composed of some consortium members and of external experts [5]. The scope of the projects deal with radiochemical developments, radiobiology and dosimetry, preclinical research and clinical translation. The logistics chain required to implement the programme is described on Figure 2. This requires steps in the target, irradiation and separation technologies, as well as logistics and licensing on the experimental site together with appropriate training and expertise of the personnel. This programme part of the H2020 INFRA EU portfolio promotes only transnational access and favors cross-border access. This can be in the form of users accessing a biomedical research facility in the consortium, or radionuclides dispatched to other countries. So far accepted projects have been proposed by Belgian, French, Spanish, Italian, German and British groups, sometimes in collaboration with co-investigators from Czech Republic and Portugal [6].

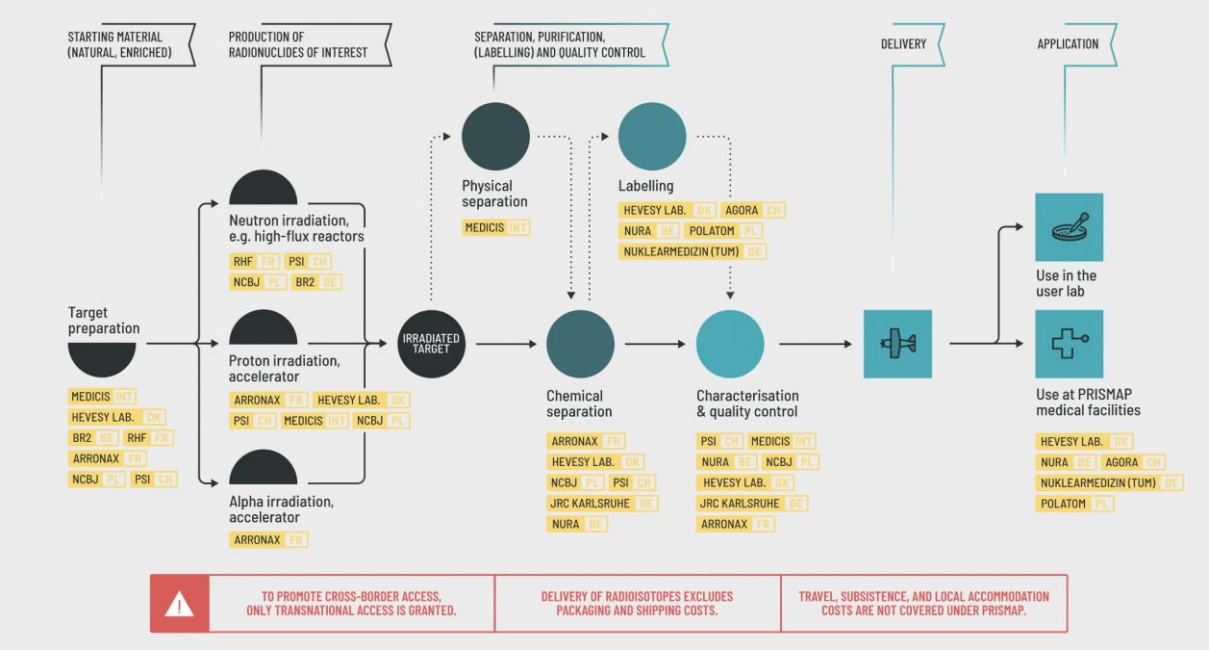

Figure 2: PRISMAP logistics chain

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3.3 Strategic Research Agenda

PRISMAP has already proposed improvements, e.g. in the standardization of the supply of the radionuclides, and also considers efforts into the qualification of radionuclides for research with non-conventional radionuclides. For this purpose, two public reports have been made on the logistics regulations in place, and on the standards for clinical translation respectively [7].

SRA 1: Logistics and transportation of non-conventional radionuclides

Transport regulations and current practice sometimes show bottlenecks for the dispatch of unconventional radionuclides. While efforts are ongoing to understand alternatives, we propose to advance this important topics by:

Identifying radionuclides (and where relevant co-produced radionuclides) that have not been listed with explicit A1/A2 values in the current ADR and IATA transport regulations [8]

SRA 2: Harmonization for qualification of the investigational radiopharmaceuticals for clinical research

There are still large discrepancies among different recommendations for the quality of radionuclides used in clinical settings. The required QA and radionuclidic purities for different applications, should be considered and discussed with both national and European authorities. In particular, alternative approaches to develop and evaluate radiopharmaceuticals should be envisaged [9], particularly for new generation of radionuclides such as Auger electron emitters, in-vivo generators, and radionuclides with complex decay schemes. For this purpose, it is necessary to take into consideration that the radiolabeling chemistry of more exotic and less explored radiometals remains underdeveloped, being necessary in some cases to introduce/evaluate new chelators suitable to obtain stable radiocomplexes and offering the possibility of functionalization with the proper targeting vectors. The different radiolabeled compounds should be evaluated in detail using (cancer) cells and tumor animal models to define the most optimal radionuclide for a disease-specific biological target, as a deep understanding of the biological behavior and radiobiological effects is needed to select the most optimal compounds for further clinical investigation.

SRA 3: Training of personnel for handling and managing unconventional radionuclides and related aspects such as waste, etc.

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