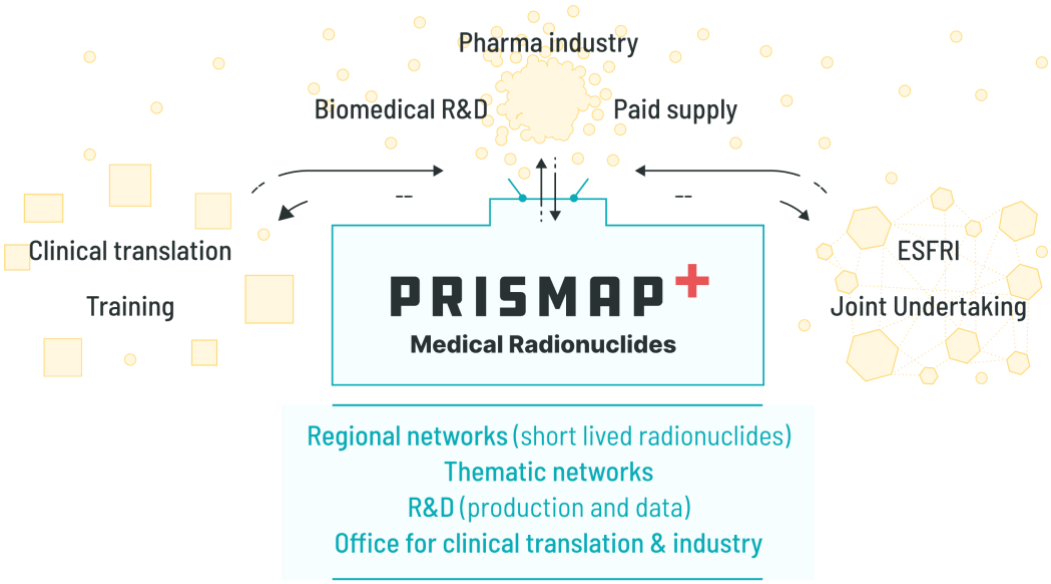
PRISMAP sustainability white paper

Towards PRISMAP+ and a sustainable European medical radionuclide programme

Extract for publication

Thomas E. Cocolios, Seán Collins, Clemens Decristoforo, Charlotte Duchemin, Gilles de France, Mikael Jensen, Ferid Haddad, Ulli Köster, Kirsten Leufgen, Mattia Manzolaro, Nicholas P. van der Meulen, Renata Mikolajczak, Bernard Ponsard, Lucia Popescu, John O. Prior, Maija Radzina, Thierry Stora, Zeynep Talip, David Viertl, Wolfgang A. Weber

on behalf of PRISMAP



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008571 (PRISMAP). This document reflects only the view of the author(s). The Agency is not responsible for any use that may be made of the information it contains.

Contents

Abbreviations

A-CINCH	Augmented Cooperation in Education and Training in Nuclear and Radiochemistry
ARTnet	Australasian Radiopharmaceutical Trials Network
BNL	Brookhaven National Laboratory
BSSD	Basic Safety Standards Directive
CA	Consortium Agreement
COST	European Cooperation in Science and Technology
DG ENER	Directorate General for Energy
DG SANTE	Directorate-General for Health and Food Safety
DoA	Description of Action
EANM	European Association of Nuclear Medicine
EATRIS	ERIC for European Infrastructure for Translational Medicine
EDQM	European Directorate on Quality of Medicines
EMA	European Medicine Agency
ENEN	European Nuclear Education Network
EOSC	European open science cloud
EOSC	European Open Science Cloud
ERIC	European Research Infrastructures Consortium
ERVI	European Radioisotope Valley Initiative
ESFRI	European Strategy Forum on Research Infrastructures
ESFRI	European strategy forum on research infrastructures
FDG	Fluorodeoxyglucose
GA	Grant Agreement
GIP	Groupements d'Intérêt Publiques
GMP	Good Manufacturing Practices
IAEA	International Atomic Energy Agency
IMDP	Investigational Medicinal Product Dossier
INFRA	Research infrastructures project of the Horizon 2020 Work Programme
JRIA	Japan Radioisotope Association
LANL	Los Alamos National Laboratory
LET	Linear Energy Transfer
MOOC	Massive Open Online Course
MRI	Magnetic Resonance Imaging
MRIP	Medical Radionuclide Innovation Programme
NFRF-T	Rare Isotope to Transform Cancer Therapy
NIDC	National Isotope Development Centre
NOAR	Network for Optimized Astatine labelled Radiopharmaceuticals
ORNL	Oak Ridge National Laboratory
PET	Positron Emission Tomography
PRISMAP	The European medical radionuclides programme
R&D	Research and Development
RI	Research Infrastructure
SAMIRA	Strategic Agenda for Medical Ionising Radiation Applications
SPECT	Single Photon Emission Computer Tomography
TRL	Technology Readiness Level

Participant short names

CERN	European organization for nuclear research
NPL	National Physical Laboratory
PSI	Paul Scherrer Institut
CEA	Commissariat à l'énergie atomique et aux énergies alternatives
IST-ID	Associação do Instituto Superior Técnico para a IST-ID Investigação e Desenvolvimento
DTU	Danmarks Tekniske Universitet
CHUV	Centre hospitalier universitaire vaudois
GANIL	Grand Accélérateur National d'Ions Lourds
SCK CEN	Studiecentrum voor Kernenergie / Centre d'étude de l'énergie nucléaire
ARRONAX	Groupement d'intérêt public ARRONAX
ESS	European spallation source ERIC
TUM	Klinikum rechts der Isar der technischen Universität München
KULeuven	Katholieke Universiteit Leuven
MedAustron	Entwicklungs- und Betriebsgesellschaft MedAustron GmbH
SCIPROM	SCIPROM Sàrl
MUI	Medizinische Universität Innsbruck
ILL	Institut Max von Laue - Paul Langevin
JRC	JRC -Joint Research Centre- European Commission
NCBJ	Narodowe Centrum Badań Jądrowych
GSI	GSI Helmholtzzentrum für Schwerionenforschung GmbH
LU	Latvijas Universitāte
INFN	Istituto Nazionale di Fisica Nucleare
UiO	Universitetet i Oslo

Abstract

PRISMAP, the European medical radionuclides programme, is a European Commission funded[1] project delivering research radionuclides produced by eight major European infrastructures. PRISMAP supports researchers in their home institutes or biomedical institute hubs to accelerate medical research based on radiopharmaceuticals. PRISMAP has progressed the implementation and harmonisation of the delivery of these research radionuclides across Europe. PRISMAP radionuclides are made available for submitted research projects that are selected by a panel of experts on the basis of eligibility criteria,[2] which primarily relate to the criteria of scientific quality, transnationality and remote access.

Granted for a duration of four years**, PRISMAP is following five main objectives**:

- Provide access to new radionuclides and new purity grades for the medical research.
- Create a common entry port and web interface to the starting research community.
- Enhance clarity and regulatory procedures to foster research with radiopharmaceuticals.
- Improve the delivered radionuclide data and regulation, along with biomedical research capacity.
- Ensure long-term sustainability of PRISMAP.

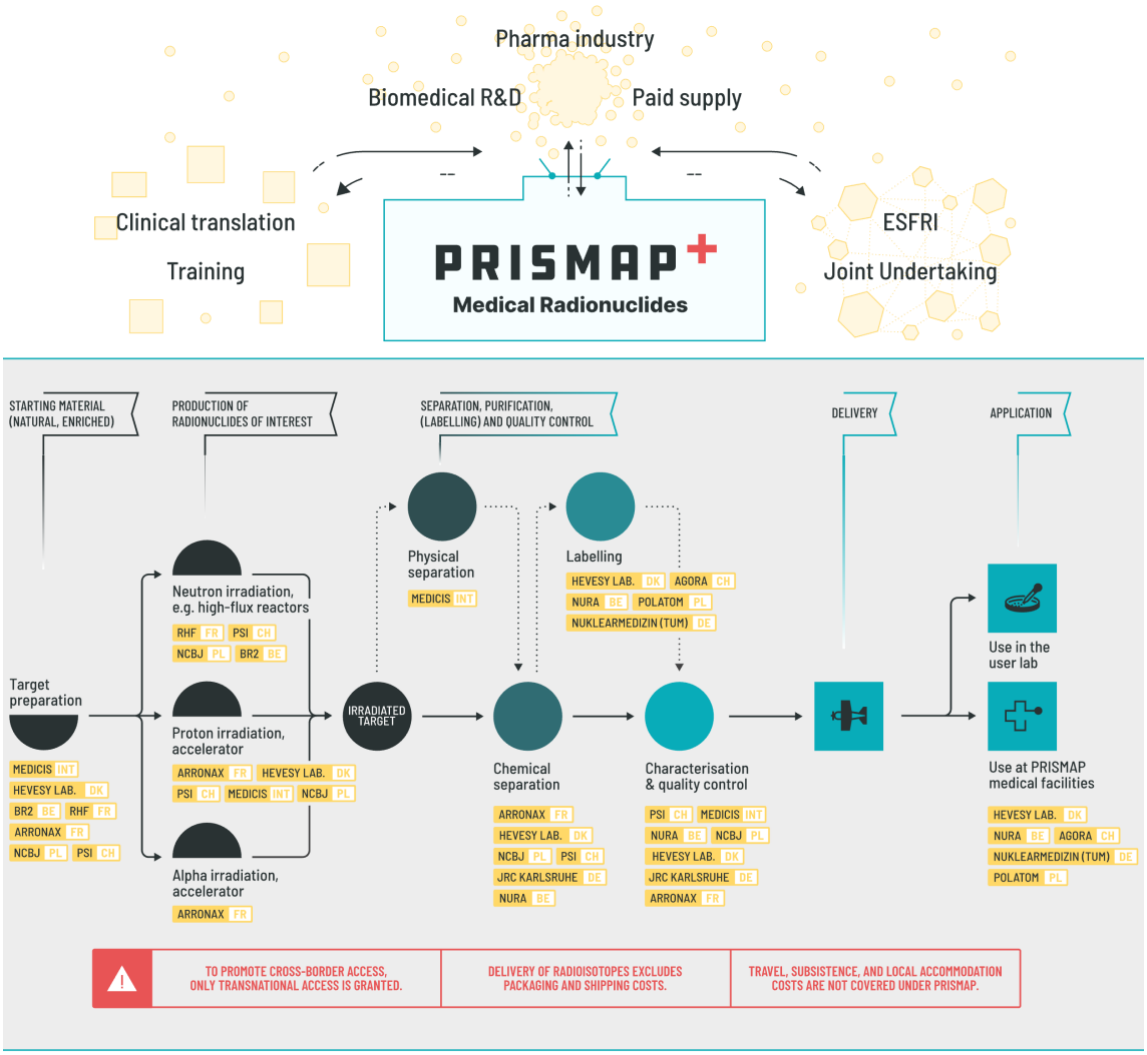


Figure 1. Research medical radionuclides with existing supply chain in PRISMAP (bottom), which needs to expand to fulfil the mission of PRISMAP⁺ (top) towards the European medical radionuclide programme.

[1] INFRA-2-2020 call, H2020 Framework Programme of the European Commission (grant agreement No 101008571)

[2] https://www.prismap.eu/access/

Within three years of implementation, PRISMAP has been able to propose sixteen research radionuclides amongst a portfolio of twenty-eight. The latter has been expanded to address new demands with so-called matched radionuclide pairs in theranostics, an expanding field in personalised medicine combining diagnostics and treatment radiopharmaceuticals, serving thirty-one research groups from twelve countries. PRISMAP radionuclides and access to biomedical research facilities provides new horizons in combined diagnostics and therapeutic strategies, notably in targeted alpha therapy, as shown with the thirty-two selected projects covering the different aspects of translational medical research. Through our PRISMAP web access platform and supply chain across Europe, benefiting from our latest developments and innovative production methods, **cross-national and cross-thematic projects are enabled in the multidisciplinary fields of theranostics**:

- Development and evaluation of a new generation of treatment radiopharmaceuticals, notably with radiolanthanides, with different therapeutic and diagnostic potentials.
- Generators for dispatch of short-lived Auger electron emitters to radiopharmacies across Europe.
- Theranostics developments, notably in targeted alpha therapy, for more appropriate staging and exploitation of the respective radiopharmaceuticals.

As PRISMAP aims for long-term sustainability, this White Paper identifies different directions to further develop access services and prepare for a mature European medical radionuclide programme **PRISMAP^{+}**, as shown in Figure 1, which is currently lacking in Europe.

Figure 2. Visit by Prof. Helene Langevin-Joliot, nuclear physicist and granddaughter of Marie Slodowska-Curie, to CERN-MEDICIS, one of the institutions providing PRISMAP services for biomedical research.

1. Key points

- **Inclusion criteria**

The time to establish radiopharmaceuticals exploiting research radionuclides in medical research is of the order of fifteen years, as recently observed with therapeutic radiopharmaceuticals based on Lu-177 and Ac-225, in which pharmaceutical companies were involved for the last clinical validation phases[3]. While PRISMAP is already federating major infrastructures in Europe, new infrastructures may join to enlarge the capacity offered. From its onset, selected emerging facilities were part of the consortium, and PRISMAP hopes to count on an additional facility before the completion of the project, such as SPES at INFN, Legnaro, Italy or SPIRAL2 at GANIL, Caen, France. Major and future production facilities along the radionuclide supply chain should be approached, extending into new irradiation and purification capacities across a geographically distributed network including biomedical services. The selection of inclusion criteria should be defined considering these objectives, creating geographical and thematic networks.

- **Which radionuclides?**

PRISMAP cannot offer all radionuclides enabling biomedical research in Europe. It has thus to restrict its services to a 'reduced - selected – evolving' set of radionuclides. Emerging mechanisms are in place to receive new requests and offer a limited range of radionuclides. For example, while not available as day-1 radionuclides portfolio in PRISMAP, requests for Pb-212 was put forward at the PRISMAP second call for user projects through the helpdesk interface. The developments at two accelerator and mass-separation facilities allowed PRISMAP to offer the matched theranostics pair of Pb-203 and Pb-212 at our fourth call, a year later, in the field of targeted alpha therapy. Our portfolio covers medical high purity radionuclides enabling research in the field of targeted alpha-particle and Auger-electron therapy, and novel imaging and dosimetric modalities. With 15 years required to register new radiopharmaceuticals using research radionuclides, the improved mechanism in **PRISMAP$^+$** should aim at reducing the timescale for the provision of new research radionuclide offerings. The definition and terminology associated to "research" refers to accessibility, maturity level of the technology required for its production, and where the demand is not yet established beyond the pre-clinical and early clinical phases[4]. Such supply of research radionuclides requires from the producing entities strategic commitment, persistence and flexibility matched with appropriate resources to react to research demands, as symbolised by Figure 2, and make Europe an attractive and dynamic biomedical research landscape.

- **User access**

Transnational access can be provided based on scientific merit evaluated by an independent board (excellence-driven access), as "open source" (wide access), or as an on-pay service (market driven access)[5]. Transnational criteria and excellence-based selection criteria have been implemented in PRISMAP for deliveries of radionuclides to European researchers' groups. Figure 3 shows nuclear scientists receiving PRISMAP radionuclides to develop their biomedical projects.

Extended modes of access should now be explored. The definition of the transnationality criteria, an essential ingredient in PRISMAP, needs to be reformulated allowing groups from the same country as the **PRISMAP$^+$** provider to benefit from the remote access to radionuclides under certain conditions. A dedicated office will be required to efficiently manage this wider access, coordinate requests for industrial projects and plan involvement in more advanced clinical phases with research radionuclides.

[3] An improved method for the production of Ac-225/Bi-213 from Th-229 for Targeted Alpha Therapy, https://doi.org/10.1080/07366290701285108; Actinium-225-PSMA radioligand therapy of metastatic castration-resistant prostate cancer (WARMTH Act): a multicentre, retrospective study, https://doi.org/10.1016/S1470-2045(23)00638-1

[4] Co-ordinated Approach to the Development and Supply of Radionuclides in the EU N°ENER/D3/2019-231 DOI: 10.2833/120792 (2021)

[5] European Charter for Access to Research Infrastructures – EC Research and Innovation

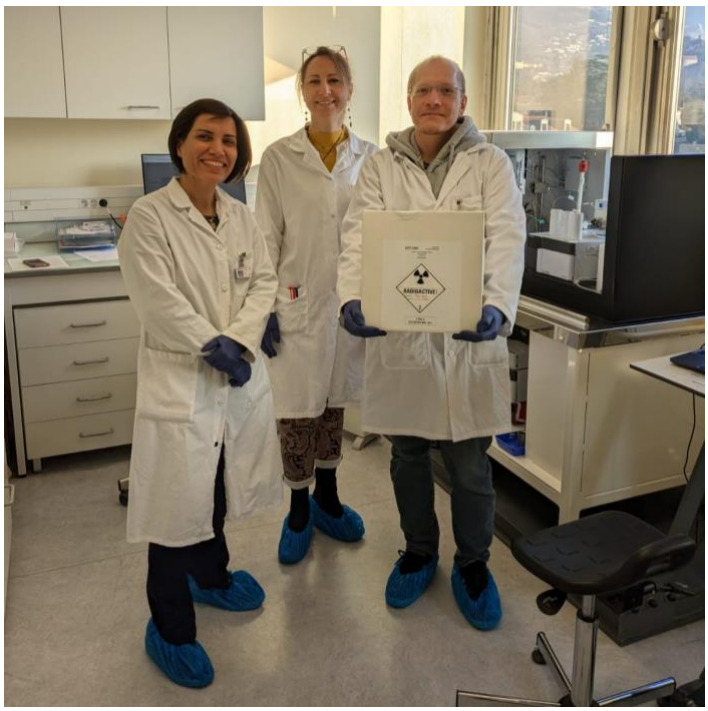


Figure 3. Nuclear scientists receiving PRISMAP radionuclides to develop their biomedical projects.

- **Training and R&D**

The community around PRISMAP and in the future around **PRISMAP**$^{+}$ is based on innovative ideas anchored in the creativity of an interdisciplinary consortium of dynamic actors. These aspects need to be nurtured and fostered in **PRISMAP**$^{+}$ to ensure the growth of its impact. This should be done through dedicated training programmes on the one side, such as those offered in Marie Skłodowska-Curie Action training networks, and on the other side through selected R&D programmes along the supply chain. The development of the techniques and data to provide a robust and efficient supply chain is an integral component for the success of **PRISMAP**$^{+}$, as already implemented and witnessed within PRISMAP. This needs to be expanded in the direction of the new target and irradiation techniques and data, new ion sources and chemical separation approaches, as well as methodologies and infrastructures for an appropriate handling and disposal of the relative radioconjugates and dismantling of infrastructures at their end of use. A particular emphasis needs to be developed for the translation of preclinical to clinical research involving the pharmaceutical industry, be it with small and medium size enterprises (SMEs), such as small and medium scale biotechnology companies, or large international groups.

- **Towards a more appropriate legal framework**

PRISMAP is a four-year project managed through a grant and agreement signed with the European Commission and a consortium agreement signed between the 23 consortium members. PRISMAP therefore develops its programme according to established management guidelines[6]. A novel legal framework needs to be elaborated to sustain its mission and organise the access to research radionuclides in the biomedical field in the long term. Different frameworks exist which can be utilised to propose a sustained **PRISMAP**$^{+}$ programme in the years to come. Whilst the European Commission does not streamline the integration of research infrastructures through a staged starting-consolidating-advanced scheme over a 15-year timescale in Horizon Europe, other routes can be envisaged. It could take the form of constituting a *European Research Infrastructures Consortium* (ERIC), integrating the ESFRI roadmap or establishing a Joint Undertaking action with European dimension[7]. Also, a targeted call for funding through the European commission in line with the ERVI strategy would be conceivable.

[6] https://www.prismap.eu/about/project/

[7] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32013D0640; https://www.esfri.eu/;

- **International context**

The use of research radionuclides for medical research, as provided by PRISMAP, and in the future by **PRISMAP**[+], is embedded in a highly regulated environment, not only in relation to radiation safety but also the pharmaceutical regulatory framework. The European, as well as most other pharmaceutical regulations worldwide, define radioactive substances to be used for a medicinal purpose, including both diagnostic and therapeutic applications, as medicinal products, or drugs. Therefore, this brings PRISMAP's radionuclides for production of novel radiopharmaceuticals under the umbrella of the respective pharmaceutical legislation. Pharmaceutical regulations fall within the responsibility of the DG SANTE with an interface to radiation safety standards, covered by the BSSD (Council Directive 2013/59/Euratom) in the responsibility of the DG ENER. The medical use of radiopharmaceuticals in Europe, and therefore also the use of research radionuclides for medicinal purposes, is well represented by the EANM with 2900 members from 80 countries. Most other regions are streamlining access to research radionuclides for biomedical research and **PRISMAP**[+] will strive to establish links to these different associations (NIDC in the USA, JRIA and *Supply Platform of Short-lived Radioisotopes for Fundamental Research* in Japan, NFRF-T in Canada, *Projects within the MRIP* in UK).

https://eur-lex.europa.eu/EN/legal-content/summary/european-research-infrastructure-consortium-eric.html;
https://www.consilium.europa.eu/en/press/press-releases/2021/11/19/council-commits-to-nine-institutionalised-european-partnerships/

2. Long-term perspective

The establishment of **PRISMAP**[+] as an important stakeholder in the field, based on the existing PRISMAP and with the capacity to supply research radionuclides, will serve as a representative body in the context of radiopharmaceutical manufacturing and (clinical) R&D in Europe within the pharmaceutical regulatory environment, and will need to be developed further in a long-term perspective. Effective communication between the stakeholders involved in the clinical translation of novel radiopharmaceuticals such as researchers, clinicians and regulatory bodies is essential to avoid unnecessary regulatory burden and hurdles, to ensure understanding of the specific requirements in the clinical use of novel radionuclides. The development of a novel radiopharmaceutical, involving a therapeutic component, is a long-lasting process and path towards marketing authorisation and subsequent routine clinical use. This involves radiation safety considerations such as patient release criteria for novel radionuclides, waste management, the design and development of dosimetric tools to select patients and optimise treatment regimen. Again, a strong and sustainable cooperation between professional organisations such as EANM, regulatory bodies and radionuclide producers and researchers from **PRISMAP**[+] is essential to ensure Europe`s future role in radionuclide and radiopharmaceutical development. Those developments will be accompanied by structured training opportunities to ensure the broad reach of the ambition set out in **PRISMAP**[+].

The development and the regular provision of radionuclides for biomedical research will benefit from an integrated R&D radionuclide programme such as that offered in a **PRISMAP**[+] platform. The organisation of geographical centres of excellence and thematic nodes will allow a better access of research radionuclides across Europe. In addition, evolving needs and demands will be more easily streamlined and addressed. The strengths of the European nuclear medicine and radiopharmaceutical landscape that has been able to bring new radiotherapeutics into clinical practice will be furthered. The structured **PRISMAP**[+] European medical radionuclide programme could furthermore establish long-lasting links with the other worldwide programmes present or in development in North America or in Japan. This way the required specialised and competent young workforce will be able to promote rapid innovation and take the field into a new stage, as depicted in Figure 5.

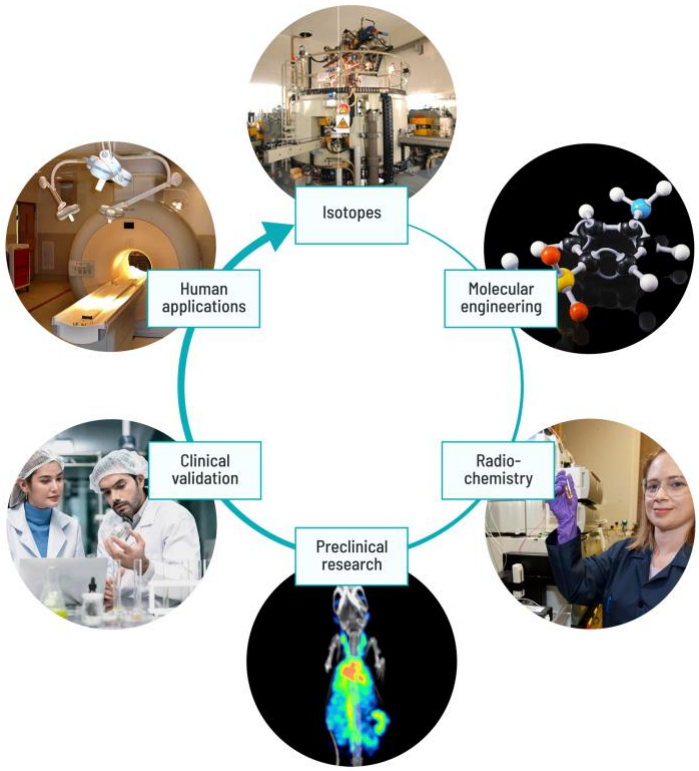


Figure 5. Translational biomedical research using research radionuclides and the benefits of long-term coordination of the European medical radionuclides programme.