European Partnership on Metrology
Call 2022 – Digital Transformation, Health, Integrated European Metrology, Normative and Research Potential

Selected Research Topic number: **SRT-h10**
Version: 1.0

Title: Metrology for emerging targeted alpha therapies

Abstract

The regulatory approval of the first, and so far, only alpha-emitting radiopharmaceutical ($^{223}RaCl_2$), resulted in unprecedented levels of interest and investment in other alpha-emitters to treat a variety of cancers. Targeted alpha therapy is currently showing promising efficacy and increased survival in early phase clinical trials, even in patients not responding to beta-emitting analogues. However, several unmet and unique measurement challenges remain a barrier to the safe and optimised implementation of upcoming targeted alpha therapies into routine clinical practice. The proposed research topic will provide the metrology needed to support end-to-end traceability before wide routine adoption.

Keywords

Cancer, alpha-emitting therapies, radiopharmaceuticals, radionuclide therapy, molecular radiotherapy, targeted alpha therapy, quantitative imaging, dosimetry, radioactivity, traceability.

Background to the Metrological Challenges

Targeted radionuclide therapy (TAT) uses radiopharmaceuticals to target radiation to cancerous cells whilst minimising damage to healthy tissue. According to the Strategic Agenda for Medical Ionising Radiation Applications (SAMIRA), an estimated 6 million annual therapies are delivered across more than 1,500 nuclear medicine centres in the EU. The number of patients diagnosed with cancer is projected to increase 47 % worldwide by 2040, with approximately 25 % of all cases occurring in Europe. However, Alpha-emitting therapies are not individually planned, are still based on fixed activities and verified according to the absorbed doses delivered to targets, as routinely performed in external beam radiotherapy and mandated by the European Commission's directive 2013/59/Euratom. This leads to an undertreatment for many patients and various degrees of efficacy as a result of the wide range of absorbed doses delivered due to the biological variations between patients, which are not considered in therapies. Current measurement challenges in this area include a lack of: (i) validated primary (and secondary) standards for alpha-emitters, (ii) knowledge of the accuracies of the activities administered to patients, and (iii) standardisation and harmonisation of imaging and dosimetry protocols. Due to the potential for the decay products of alpha-emitters to detach from the parent and their high cytotoxicity, accurate and precise measurements of the activity and absorbed doses delivered to the targets and organs at risk are needed. Currently $^{223}RaCl_2$ for the treatment of prostate cancer is the only alpha-emitter with marketing authorisation, whilst new TAT using other alpha-emitters (^{211}At, ^{212}Pb/^{212}Bi, ^{224}Ra, ^{225}Ac and ^{227}Th) are currently undergoing early phase trials for a variety of cancers. The establishment of traceable and harmonised measurements that guide the use of alpha-emitting therapies in a clinical setting is required to support 2001/83/EC for medicinal products and 2001/20/EC for clinical trials. In addition, non-legally binding guidance from the professional organisations EANM, EFOMP, EURADOS and the IAEA will also benefit from measurement accuracy improvements.

The development of harmonised imaging protocols for dual energy CT and MR will provide personalised information of the skeletal and marrow composition, and are therefore needed to improved marrow dosimetry, which is essential for treatment planning and estimating the risk of secondary cancers. This research will provide the tools to enable future personalisation of dosimetry-based cancer treatments and information to support national health services in taking informed decisions on the cost-effectiveness of new treatments. The generated reference data will provide a benchmarking tool for software quantitative imaging and dosimetry applications, contributing towards compliance with accreditation programmes and regulations.

Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the protocol.

The JRP shall focus on the traceable measurement and characterisation of alpha-emitting nuclides for targeted radiotherapy.

The specific objectives are

1. To develop and validate primary and secondary radioactivity standards with traceability to national standards and low uncertainties that consider decay chain progeny in-growth and the separation of decay products for alpha-emitting radionuclides such as ^{211}At, ^{212}Pb/^{212}Bi, ^{224}Ra, ^{225}Ac, and ^{227}Th. In addition, clinical therapy requirements and achievable clinical measurement accuracies are to be assessed by an inter-comparison exercise.
2. To provide guidance for clinical stakeholders on organ activity quantification methods using external monitoring systems and nuclear medicine imaging. This is to be achieved by: (i) the development of methods to quantify the separation of the decay products during imaging at the required levels of therapy activity; and (ii) the performance of a comparison exercise to assess the accuracy, reproducibility, and the quantification of uncertainties of the developed methods in a clinical setting.
3. To establish accurate alpha-emitter dosimetry calculations that enable compliance with 2013/59/Euratom and the assessment of the true dose response relationships. This is to be achieved by: (i) the validation of dosimetry pharmacokinetics models for TAT; (ii) the determination of the uncertainties from measured activity to absorbed dose, including the identification of major factors affecting accuracy and precision for alpha emitting therapies; and (iii) the determination at the tissue level of the significance of mean dosimetry for highly heterogeneous distributions of alpha emitters.
4. To determine a multi-modality imaging protocol that considers differences in bone density and marrow cellularity between individual patients based on: (i) a test object manufactured by 3D printing technology that incorporates relevant tissue-equivalent materials and geometric complexity for the assessment of treatment toxicity and (ii) bone marrow dosimetry.
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain and end-users (e.g., pharmaceutical as well as medical and healthcare products manufacturers, clinical QA laboratories and clinical stakeholders) and the relevant organisations in the context of the regulation (e. g. EANM, EFOMP, IAEA, EURADOS)

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes, and it is expected that multidisciplinary teams will be required. To enhance the impact of the research, the involvement of the appropriate user community such as medical practitioners, medical (academic) hospitals and industry is strongly recommended, both prior to and during methodology development.

Proposers should establish the current state of the art and explain how their proposed project goes beyond this.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 1.9 M€ and has defined an upper limit of 2.6 M€ for this project.

EURAMET also expects the EU Contribution to the external funded beneficiaries to not exceed 35 % of the total EU Contribution across all selected projects in this TP.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the ‘end user’ community, describing how the project partners will engage with relevant communities during the project to facilitate knowledge transfer and accelerate the uptake of project outputs. Evidence of support from the ‘end user’ community (e.g. letters of support) is also encouraged.

You should detail how your JRP results are going to:

- Address the SRT objectives and deliver solutions to the documented needs,
- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Transfer knowledge to the healthcare sector.

You should detail other impacts of your proposed JRP as specified in the document “Guide 4: Writing Joint Research Projects (JRPs)”

You should also detail how your approach to realising the objectives will further the aim of the Partnership to develop a coherent approach at the European level in the field of metrology and include the best available contributions from across the metrology community. Specifically, the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards
- the metrology capacity of EURAMET Member States whose metrology programmes are at an early stage of development to be increased
- organisations other than NMIs and DIs to be involved in the work.

Time-scale

The project should be of up to 3 years duration.