EMPIR Call 2018 – Health, SI Broader Scope, Normative and Research Potential

Selected Research Topic number: **SRT-h20**
Version: 1.0

Title: Metrology for emerging radiopharmaceuticals delivering high linear energy transfer radiation

Abstract

Following the approval of the first alpha emitting radiopharmaceutical by the European Medicines Agency (EMA) in 2013, there has been a significant increase in the development of alpha and Auger radiolabelled drugs. These are promising cancer treatments due to the shorter range in tissue and higher cytotoxicity than first-generation radiopharmaceuticals based on beta emitters. However, a number of unmet unique metrological challenges remain a barrier for their clinical implementation, such as a lack of (i) appropriate nuclear data, (ii) adequate uncertainities for traceable radioactivity measurements and (iii) standardised protocols for quantitative pre-clinical and clinical imaging. Improved metrology is required to address the measurement challenges of emerging radiopharmaceuticals and accelerate their translation from pre-clinical into clinical practice, resulting in cost-effective personalised treatments with potential to improve patient quality of life.

Keywords

Radiopharmaceutical, alpha radionuclides, Auger radionuclides, high linear energy transfer (LET) radiation

Background to the Metrological Challenges

Emerging radiopharmaceuticals are promising cancer treatments due to their shorter range in biological tissue and higher cytotoxicity than first-generation radiopharmaceuticals based on beta emitters. However, so far only a few of these emerging radiopharmaceuticals have reached the clinical trials stage and no Auger therapies are presently approved. Recent market research analysis has indicated that the global radiopharmaceuticals market in nuclear medicine is expected to reach 7.27 billion US Dollars by 2021. In the UK, since the first alpha radiopharmaceutical (^{223}Ra-dichloride) was approved by the EMA for clinical use, the number of ^{223}Ra- dichloride therapies has increased by a factor of 100. A large number of emerging radiopharmaceuticals based on other alpha emitting radionuclides are also under development, e.g. ^{227}Th, ^{225}Ac, ^{213}Bi, ^{212}Pb/^{212}Bi and ^{211}At. In addition, radionuclides emitting low-energy electrons through the Auger effect e.g. ^{111}In or ^{125}I have been identified as promising candidates for cancer treatment.

Traceability to primary (and secondary) standards is vital for ensuring accurate knowledge of the radioactivity administered to patients. However, some secondary standards for ^{223}Ra have been shown to vary in radioactivity measurements and lead to differences of approximately 9 % in the radioactivity administered to patients. Even without this discrepance, radioactivity measurements of alpha emitters are challenging due to the in-growth of their decay products and the lack of robust nuclear decay data for alpha and Auger radionuclides.

Due to the small number of studies on alpha and Auger emitters that include dosimetry, the relationships between administered radioactivity, absorbed dose and biological effects such as relative effectiveness for killing tumour cells, are not well understood. Measuring the distribution of the radiopharmaceuticals in-vivo is also challenging due to the low radioactivity levels administered to patients and the low emission probabilities of the photon energies used for imaging. So far a small number of research studies with low patient numbers treated with ^{223}Ra have shown that imaging and dosimetry is feasible, however the lack of large patient studies and standardised protocols for emerging radiopharmaceuticals remains a barrier for their clinical. Standardised protocols are needed for both pre-clinical and clinical testing, for dosimetry calculation methods, and quantitative imaging (e.g. Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET)).

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The EMPIR initiative is co-funded by the European Union's Horizon 2020 research and innovation programme and the EMPIR Participating States

The European Association of Nuclear Medicine (EANM) Internal Dosimetry Task Force group recently reported a significant expansion in use of radiopharmaceuticals to treat cancer and hence a need to support this use with a public database, that can be used as a universal tool for the benchmarking and standardisation of radionuclide image quantification and dosimetry software. Such a public database would also help tackle the lack of reproducibility of results in multi-centre studies using emerging radiopharmaceuticals. Thereby providing greater statistical power to study correlations between the absorbed dose delivered and patient outcomes, which will in turn accelerate the clinical translation of emerging radiopharmaceuticals.

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 addressing the unique metrological challenges associated with emerging radiopharmaceuticals based on high linear energy transfer (LET) radiation emitted by alpha and Auger radionuclides, to support pre-clinical and clinical development and accelerate clinical translation.

The specific objectives are

1. To develop traceable radioactivity measurements with reduced uncertainties and to improve the nuclear data for a range of medical alpha and Auger emitting radionuclides, essential for accurate image quantification and dosimetry calculations.
2. To optimise and harmonise quantitative multimodality pre-clinical and clinical SPECT/CT/PET (single photon emission computed tomography, positron emission tomography) imaging and quantify associated uncertainties for selected radiopharmaceuticals by: (1) Development of methods to quantify the separation of decay products from alpha emitters at the required low levels of activity; (2) Investigation of correlations between macroscopic SPECT/CT/PET imaging and microscopic imaging techniques such as autoradiography and (3) Development of 3D printed test objects with relevant tissue-equivalent materials and geometric complexity to provide a tool for validation of developed imaging protocols for multi-centre studies.
3. To enable accurate dosimetry calculations for emerging alpha and Auger radiopharmaceuticals: (1) To investigate the validity of available pharmacokinetics models for dosimetry of emerging treatments; (2) to implement suitable dosimetry methods and determination of uncertainties in the measurement chain from activity to absorbed dose; and (3) to study the challenges and uncertainties associated with radiobiology studies to inform the implementation of future traceable measurement capabilities.
4. To develop a public database, that provides a universal tool for the benchmarking and harmonisation of radionuclide image quantification and dosimetry software to address the lack of reproducibility of results in multi-centre studies. The FAIR(findable, accessible, interoperable, reusable) data principles will be applied to these resources to ensure that the data has easy discovery, access, interoperability, and reusability, with appropriate citations and traceability.
5. To facilitate the take up of the project outputs by the measurement supply chain, such as by nuclear medicine associations (e.g. under EANM), IAEA, pharmaceutical companies, scanner manufacturers, clinical partners, and standards developing organisations where appropriate.

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, 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. In particular, proposers should outline the achievements of the EMPIR project JRP 15HLT06 MRTDosimetry and how their proposal will build on those.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 1.8 M€, and has defined an upper limit of 2.1 M€ for this project.

EURAMET also expects the EU Contribution to the external funded partners 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 health 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 EMPIR 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.