Project proposal to the MEDICIS Collaboration board

AlphaMET (Metrology for Emerging Targeted Alpha Therapies)

Ana Denis-Bacelar, National Physical Laboratory, United Kingdom

Introduction & background:

Targeted alpha therapy (TAT) is a rapidly growing cancer treatment modality, whereby alpha-emitting radiopharmaceuticals are combined with a targeting molecule to selectively seek tumours whilst minimising the damage to healthy cells. TAT is showing promising efficacy and increased survival in clinical trials for a variety of cancers; however, several unmet and unique measurement challenges remain a barrier to enable the safe and optimised implementation of emerging TATs. The goal of AlphaMET is to provide the underpinning metrology to support development of TAT through improved methods to quantify activity and absorbed doses for alpha-emitting radiopharmaceuticals. The provision of validated radioactivity standards with recommendations for improving measurements will benefit end-users that rely on such calibration services, including manufacturers of ionising radiation measurement instruments (radionuclide calibrators, gamma counters, imaging scanners), radionuclide production facilities, pharmaceutical companies and hospitals delivering TAT. More specifically, healthcare professionals will be able to administer treatments with traceable activities, and with accuracies within the limits recommended by the IAEA while providing them with methods to standardise and harmonise imaging and dosimetry methods with robust uncertainty budgets will improve reproducibility in multi-centre studies and enable comparison of results, providing greater statistical power to study correlations between absorbed dose and response/outcome measures which are still lacking for TAT. This will provide the basis for evidence-based treatments, facilitating regulatory compliance and marketing authorisation of upcoming alpha radiopharmaceuticals for the pharmaceutical industry, and potentially reducing the development costs by introducing metrology early before routine implementation of TAT.

Project description:

The primary scientific objectives of the project are:

1. To develop and validate **primary and secondary standards for ^{225}Ac, ^{212}Pb and ^{211}At and precision nuclear decay data** traceable to national standards with uncertainties suitable for dissemination to pre-clinical and clinical applications. These standards will be disseminated through calibration factors for radionuclide calibrators used in clinics, with consideration of the effects of the ingrowth of the decay chain progeny. These In addition, clinical therapy requirements and achievable clinical measurement accuracies are to be assessed through an interlaboratory comparison exercise between National Metrology Institutes and Nuclear Medicine clinics across Europe.
2. To provide guidance for clinical stakeholders on organ **activity quantification methods for ^{225}Ac and ^{212}Pb** 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, the assessment of the true dose response relationships and the possibility to incorporate dosimetry to optimise the treatment instead of using a ‘one size fits all’ approach with fixed administered activities. 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. This will allow more accurate red marrow dosimetry which is essential for safety as red marrow is considered a dose-limiting organ at risk that can limit the administered activity.

Materials and Methods:

Objective 1:

- Samples of ^{225}Ac and ^{212}Pb will be disseminated to eight NMIs across Europe and submitted to the International Reference System at BIPM. The NMIs will develop new primary and secondary standards for the activity (Bq) of the referred radionuclides and submit results BIPM to show international equivalence. This will require high purity samples of each radionuclide of at least 10-20 MBq (TBC) per institute. From these samples, using a range of primary counting techniques an absolute activity will be determined which will be transferred to secondary standard ionisation chambers for future dissemination of these standards to clinics. These samples will be used to determine high precision nuclear decay data using the respective NMIs counting capabilities, including half-lives and absolute emission intensities for alpha and gamma ray emissions. High purity samples are required to minimise errors and maintain high precision of the standards. Supply of these radionuclides would be required through 2024.
- Further samples of ^{225}Ac will be needed for performing the calibration of radionuclide calibrators and gamma counters in pre-clinical centres and nuclear medicine clinics traceable to the NMIs. This will require samples of 10-20 MBq's (TBC) to be standardised and shipped to each centre from an NMI after separation from ^{225}Ra. This will require multiple supplies of ^{225}Ra over 2024 and 2025 to achieve a full coverage of clinics.

Objective 2:

- Standardised samples of ^{225}Ac and ^{212}Pb will be distributed to NPL, KULeuven and other pre-clinical and clinical partners in the AlphaMET consortium. These will be used to prepare phantoms with activities mimicking patient does for measurement by single positron emission computer tomography (SPECT) imaging. These will be used to validate models of clinical SPECT cameras to define the ground truth. These will be used to optimise methodology for imaging and quantification of activity from the images. These measurements will take place throughout 2024 to 2025 and will require multiple supplies of ^{225}Ra and ^{224}Ra generators.

References and Funding:

AlphaMET is funded by EURAMET (2.3M€, Sep 2023 – Aug 2026). Deliverables of this project will support EU directive 2013/59/EURATOM mandating dosimetry-guided radiopharmaceutical therapies (including TAT), but also 2001/83/EC for medicinal products, and 2001/20/EC for clinical trials. In addition, AlphaMET will complement and expand ongoing initiatives such as the RATIONALE and NOAR COST Action project by addressing the measurement challenges of establishing traceable and harmonised measurements to guide the use of upcoming TAT in a clinical setting. NPL and IRA are funded by the Horizon 2020 PRISMAP project (grant No 101008571) to develop traceability and nuclear decay data for emerging radionuclides, where ^{225}Ac, ^{212}Pb (via ^{224}Ra) and ^{211}At are part of the radionuclide portfolio.

Isotope requests:

Two productions of 100-150 MBq per year until 2025 of ^{225}Ra which can be used as a generator of ^{225}Ac. The mass separated removal of ^{227}Ac will be required to provide the necessary purity level, this should ideally provide an activity ration better than 10^{-5}. The collections will be shipped to National Physical Laboratory (UK) who will undertake the radiochemistry separation of Ac-225 and ship to partner institutes.

Two productions of 250-400 MBq per year until 2025 of ^{224}Ra which can be used as a generator of ^{212}Pb. The generator can be used to produce multiple samples for distribution from the chosen partner with radiochemical separation experience. The ^{224}Ra should be of a high purity with any contaminants less than 10^{-5}.