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

Selected Research Topic number: **SRT-h14**
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Title: Measurement underpinning theranostic approaches in cancer radiotherapy based on high-Z nanoparticles

Abstract

Novel theranostic irradiation modalities involving high-Z nanoparticles have been shown to enhance the biological effectiveness of cancer radiotherapy through radio-sensitization. However, innovative, traceable measurements and reference standards need to be developed to quantify these radiobiological effects. Therefore, an interdisciplinary metrological framework combining physical, chemical and biological expertise is needed to identify reliable and traceable parameters that describe the radio-biophysically relevant effects of high-Z nanoparticles in radiotherapy. This will result in a framework suitable for regulatory approval and this could lead to personalised radiotherapy based on accurately predicted responses.

Keywords

Advanced radiotherapy, radio-sensitizers, biomarkers, cancer, dose-response-relationship, high-Z nanoparticles, standardisation and traceability of cell techniques, multi-parametric measurements, non-communicable disease, theranostics

Background to the Metrological Challenges

The intravenous injection of high-Z nanoparticles, which are formed from elements with high atomic numbers e.g. non-functionalised gold nanoparticles, has been shown to enhance the biological effectiveness of cancer radiotherapy through radio-sensitization. This was first demonstrated in a mouse experiment in 2004 which resulted in a four-fold increase in tumour control compared to radiation treatment alone. In addition to strongly localised tumour damage, high-Z nanoparticles also act theranostically as molecular contrast agents to enhance tumour imaging. Radio-sensitization mechanisms are complex and are not well understood, but fall into three areas: physical (dose enhancement and changes in the radiation quality), chemical (changes in the spectrum and yield of reactive radical species) and biological (changes to cellular metabolic processes). Metrological research is required to elucidate these mechanisms before regulatory approval and to improve the effectiveness of this treatment.

Recent research has led to the production of a range of biocompatible, functionalised nanoparticles, some of which have even been clinically trialled. However, the evaluation of their radiobiological effectiveness has often produced inconclusive results, which can differ by several orders of magnitude. To address this, an interdisciplinary procedure including the use of standardised protocols and a quality assurance plan need to be developed.

The degree of uptake of nanoparticles into cells, usually through endocytosis, critically depends on many factors related to the nanoparticle as well as to the cell status and its environment. This is important as the degree of uptake can have profound implications for the induction of damage to DNA and other critical sub-cellular structures. Therefore, the effects of high-Z nanoparticles on cellular processes need to be investigated. Techniques like atomic absorption spectroscopy, which are currently used to quantify nanoparticles within cells have significant limitations when applied to live cells not least because there is a lack of cross validation information. Furthermore, the spatial distribution of nanoparticles within cells has not been systematically addressed. Microscopy can also be used, but current investigations either use fixed cells, where the morphology and nanoparticle distribution may be affected, or nanoparticles tagged with fluorescent probes. Such functionalisation can dramatically influence cellular uptake. Live cell and dynamic investigations are needed to elucidate the uptake and turnover of nanoparticles and this needs to be related to the effectiveness of the radiation. Small differences in these parameters could lead to a significant spread in the observed biological effectiveness. Therefore, the uptake, concentration and localisation of high-Z nanoparticles in biological cells needs to be quantitatively determined using a combination of advanced imaging techniques.

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Suitable and robust biomarkers, detected with quantified accuracy, would offer additional insight into the biological mechanisms of radiation effects. However, it may be challenging to evaluate the steep dose gradient that will occur near irradiated nanoparticles. Therefore, the predictability and robustness of radiation effects on cellular biomarkers needs to be investigated in the presence of nanoparticles. The accuracy of the measurement techniques used to detect the cellular biomarkers and to quantify the nanoparticle content of the cells also needs to be determined.

Innovative dosimeters which can measure the radiation-induced impedance change in DNA are currently being developed. These may be suitable to traceably measure radio-sensitization. However, precise measurements of changes in the yield of the reactive species caused by the presence of nanoparticles are only possible in macroscopically homogeneous volumes. These methods need to be extended to cellular studies. Therefore, novel dosimeters with nanoscale resolution need to be developed so that the impact of nanoparticles on water radiolysis in solution and in cellular environments can be quantitatively determined.

Cell experiments are often complemented with Monte Carlo simulations. Particle track structures need to be simulated in order to assess the radiation damage from low-energy electrons at the nanometric scale. However, most codes are currently unable to do this. Similarly, only a few codes are available to simulate the chemical stages of radiation damage. Several Monte Carlo simulations are currently being applied, however they cannot be validated due to the lack of appropriate traceable measurements of the underlying physical, chemical and biological processes. Therefore, new Monte Carlo codes, which simulate the physical and chemical effects of high-Z nanoparticles, need to be developed and validated using traceable measurement data. The relationship between biological endpoints (e.g. cell survival) and individually-measured physico-chemical changes also needs to be modelled.

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 metrology underpinning theranostic approaches in cancer radiotherapy based on high-Z nanoparticles. The relative impact of physical, chemical and biological factors influencing the radiation response of biological cells (early and late effects) in the presence of high-Z nanoparticles should be quantified and key mechanisms should be identified.

The specific objectives are

1. To develop and document an interdisciplinary procedure for investigating the mechanisms regulating the enhancement of radiobiological effects in the presence of nanoparticles. This should include the use of standardised protocols and the development of a quality assurance plan.
2. To investigate the predictability and robustness of radiation effects on cellular biomarkers in the presence of nanoparticles. In addition, to quantitatively determine the uptake, concentration and localisation of high-Z nanoparticles in biological cells using a combination of advanced imaging techniques. The accuracy of the measurement techniques used to detect the cellular biomarkers and to quantify the nanoparticle content of the cells should also be determined.
3. To validate Monte Carlo codes, which simulate the physical and chemical effects of high-Z nanoparticles, using traceable measurement data. In addition, novel dosimeters with nanoscale resolution should be developed and the impact of nanoparticles on water radiolysis in solution, and in cellular environments, should be quantitatively determined.
4. To model the relationship between biological endpoints (e.g. cell survival) and individually-measured physicochemical changes. These models should then be applied to the experimental results and comparisons drawn with existing literature data on the radiobiological effects of high-Z nanoparticles.
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (accredited laboratories, instrumentation manufacturers), standards developing organisations (CEN, ISO) and end users (e.g. hospitals and health centres). This should include the establishment of a European stakeholder network, including NMIs, DIs, relevant medical research communities, and regulatory authorities, to

support the development of a strategy for establishing reference standards and procedures to be used in clinical practice.

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.

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 radiotherapy 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.