EMPIR Call 2015 – Health, SI, Normative and Research Potential

Selected Research Topic number: **SRT-h07**
Version: 1.0

Title: A metrological platform for bio-imaging to support targeted therapies and diagnostics

Abstract

Biomolecules (e.g. metal species) are crucial to the diagnosis and treatment of human diseases through the use of metallodrugs and targeted delivery systems (e.g. nanoparticles). Traceable measurement methodology to determine drug uptake and transformation within individual cells and tissues is essential in establishing the presence or absence of key biomarkers for the successful development of improved targeted therapies and diagnostics. Proposals in response to this SRT should aim to develop a novel metrological platform to determine the spatial distribution of bio-species in micro-volumes of biological samples to aid disease diagnosis and treatment of cancer and neurodegenerative diseases.

Keywords

SI traceable measurements, bio-imaging, quantitative diagnostic, targeted therapies, metal species, nanoparticles, cancer, neurodegenerative disease

Background to the Metrological Challenges

Although cancer remains a major cause of death in the EU, cases of dementia are rising; with Alzheimer's disease (AD) accounting for 2/3 cases of dementia in Western Europe and set to double by 2050. Much clinical interest is in trace elements of iron (Fe) and selenium (Se) present in proteins, which are being associated with the risk/progression of AD disease, and the distribution/metabolism of Se and platinum (Pt) drugs in tumours. Techniques to monitor drug penetration, distribution and metabolism within target tissues are essential for different disease states, including cancer therapy and the progression of AD.

Currently there are no traceable methods to achieve relative limits of quantitation at the low ppb level for bio-species in complex biological tissues such as tumour and brain. Spectrometry methods can determine the distribution of metals and metalloids in biological tissues, but inherent matrix effects can affect quantification. Spatial resolution at the μm scale is sufficient to image metals, metalloids and some non-metals at ppb, but current techniques lack established calibration strategies, standards for traceable quantitative elemental imaging and the ability to provide information on the structural composition of the biomolecule in which the metal or heteroatom is contained. Hence there is a need for enhanced selectivity and signal-to-noise ratio for transient signals of related elements using new technologies and novel approaches in terms of resolution and speed.

Mass spectrometry techniques are useful for structural elucidation of metal-containing species in-tissue, but in-tissue species quantification requires the development of strategies to accurately determine the ablated sample mass for these calibration strategies to be used to minimise uncertainty, improve accuracy and validate routine calibration approaches. One alternative to in-tissue speciation is the use of wet speciation techniques applied after removal of a tissue micro-section and subsequent species extraction. Although invaluable to obtain complementary speciation data and validate imaging data, metrological challenges still remain, such as insufficient detection of target metallospecies in sample micro-volumes, to enable a measurement uncertainty of <20 % to be achieved.

Combining spectrometry methods with microscopy allows 2D and 3D maps of chemical composition to be generated with less than 1 μm resolution, but the ability to further combine with spectroscopic techniques will provide complementary qualitative and quantitative imaging data offering a multi-method approach to the characterisation of complex bio-clinical systems.

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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 bio-imaging to provide a measurement uncertainty of <20 % in the detection of target metallospecies and determine spatial distribution of species in micro-volumes biological samples.

The specific objectives are

1. To develop and validate a mass spectrometry methodology to determine the distribution of elements and elemental ratios (including metals and metalloids) in biological tissue/cell samples at the low ppb level.
2. To develop and validate mass spectrometry methodologies to accurately determine and structurally characterise bio-species within biological tissue/cell samples. This should include a wet speciation and on-tissue speciation technique and provide a measurement uncertainty of <20 % in the detection of target metallospecies in micro-volumes of a biological sample.
3. To develop and validate a spectroscopy methodology to confirm and/or validate the developed spectrometry methodologies for in-tissue bio-speciation. This should allow 2D and 3D maps of the chemical composition to be generated with less than 1 µm resolution.
4. To develop a strategy for correlating in-tissue bio-speciation imaging data with high resolution magnetic resonance imaging (MRI) data from the same sample. This should include the development and validation of new software tools for data reduction, statistical analysis, data presentation, element and biomolecule multivariate analysis and correlation of the imaging data types and should be applied to relevant clinical samples.
5. To facilitate the take up of traceable measurement methods for bio-imaging developed by the project by clinicians and industry to support the development of new therapeutic and diagnostics products.

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. In particular, proposers should outline the achievements of iMERA-Plus JRP T2.J10 ‘Tracebioactivity’ and EMRP JRP HLT05 (Metallomics) ‘Metrology for Metalloproteins’ 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 to the project. Any deviation from this must be justified.

Any industrial partners that will receive significant benefit from the results of the proposed project are expected to be unfunded partners.

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 bio-imaging 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.