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

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

Title: Metrology for reproducible chemical imaging with sub-cellular resolution

Abstract

High resolution chemical imaging of drugs, proteins and metabolites is required to aid drug discovery. The number of new drugs approved per billion US dollars spent on R&D has halved approximately every 9 years since 1950, predominantly due to drug failure, which is a major contributor to the >1.4 billion € cost of developing a new medicine. In order to support new and affordable medicines along the discovery pipeline, earlier identification of potential drug failure is required. However, this necessitates the measurement of sub-cellular drug concentrations and drug target engagement, and requires accurate measurements covering length scales from the organelle (<100 nm resolution) to multi-cellular structures (~ 1 μm resolution). Reliable and validated sample preparation methods and quantification strategies for high-resolution imaging are also needed.

Keywords

Biomedical imaging, sub-cellular, drug failure, high-resolution molecular imaging, medical imaging

Background to the Metrological Challenges

A decade ago, the drug discovery strategy was based on a concept that by increasing the number of compounds entering the pipeline there would be a concomitant increase at the output. That strategy failed and in 2012, Pfizer introduced the concept of the “Three pillars of survival”, which identify the key needs for a candidate molecule to be successful: (i) does the molecule reach the right tissue and cell at sufficient concentration?, (ii) does the molecule bind with its target and (iii) does the pharmacological activity change as expected from the mechanism of action (i.e. is the biology correctly understood?). Furthermore, is the molecule lodging within sub-cellular compartments (organelles) that could cause toxicity?

Each of these ‘Three pillars’ requires demanding measurements in terms of molecular specificity, sensitivity and spatial resolution. However, currently, no single technique, industry or organisation can meet the metrology demanded by them.

Vital for the ‘Second Pillar’ is improved understanding of biological mechanisms and this requires high-resolution imaging of target proteins. The current state-of-the-art uses metal labelled antibody probes combined with imaging using Laser Ablation Inductively Coupled Plasma Mass Spectrometry (LA-ICP-MS) with sub-cellular resolution. LA-ICP-MS allows multiplexed imaging of up to 40 proteins, however reliable and validated sample preparation methods and quantification strategies are needed.

The ‘Third Pillar’ requires the ability to measure changes in metabolites, in particular using MS imaging. Matrix Assisted Laser Desorption Ionisation MS (MALDI MS) and Desorption Electrospray Ionisation MS (DESI MS) currently provide the best molecular information but reproducibility is an issue due to such factors as sample preparation and sensitivity to operating parameters. For sub-cellular resolution, metabolic imaging, 3D OrbiSIMS currently has the highest simultaneous spatial and mass resolutions. However, as it is a vacuum based technique, the dehydration and translocation of molecules is a concern. The 2017 Nobel prize for chemistry highlighted the pivotal role of sample preparation, as the immobilisation of water in biological samples reduces ultrastructural reorganisation and prevents translocation of molecules. So, cryo- protectants that are compatible with advanced MS imaging are required.

A further issue is the lack of reproducibility and reliability of biomedical research. Currently, there is a lack of translational reference materials that are both biological and metrological. A well-controlled model system is needed which will allow cross-platform measurement of intracellular drug concentration in single cells, cellular aggregates and 3D culture models.

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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 development of reproducible chemical imaging measurements with sub-cellular resolution.

The specific objectives are

1. To develop reproducible methods for high-resolution 2D and 3D chemical imaging of pharmaceuticals, proteins, metabolites and medical imaging contrast agents covering length scales from the organelle (<100 nm resolution) to multi-cellular structures (~ 1 μm resolution). This should include multi-modal imaging approaches e.g., mass spectrometries, optical spectroscopies and synchrotron radiation spectroscopies.
2. To establish reliable model systems for cross-platform traceable measurements with sub-cellular (~ 1 μm) resolution of (i) intracellular drug concentration using calibration samples, (ii) 3D cell culture models from phenotypically defined cell lines and (iii) patient derived organoids.
3. To develop traceable and validated methods for multiplexed (> 10) protein imaging with sub-cellular (~ 1 μm) resolution using metal labelled antibodies and mass spectrometry imaging. This should include the development of sample preparation methods, reliable and validated quantification strategies and translation to clinical research.
4. To develop robust and validated sample preparation techniques for high-resolution imaging using both ambient techniques and advanced cryo-preparation methods.
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain, standards and regulations developing organisations and end users (e.g. pharmaceutical and medical imaging scientists and manufacturers).

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 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.