EMRP Call 2011 - Health, SI Broader Scope & New Technologies

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

Title: Traceability for health-related biomarkers

Abstract

Biomedical diagnostic tools are used to help combat diseases such as cancer, cardiovascular disease Alzheimer's disease, and inflammatory diseases. The tools utilise biomarkers to enable the selective and quantitative detection of disease-related pathological changes as well as the assessment of therapeutic strategies and treatment efficiency. Most biomedical diagnostic tools used quantitative, fluorescence-based techniques such as microtitre-based fluorometry, flow cytometry and fluorescence microscopy. However, for any of these methods to be effective they require accurate measurement of and reliable characterisation of fluorescent reporters and biomarker-specific probes. Currently, the metrology supporting theses measurements is lacking and therefore, traceable measurement procedures, standards and reference materials for biomarker detection need to be developed.

Conformity with the Work Programme

This Call for JRPs conforms to the EMRP Outline 2008, section on "Grand Challenges" related to Health on pages 7 and 8 and in the sections on pages 13, 21, 22 and 33.

Keywords

Health, biomarker, fluorescence, *in vitro* diagnostic, imaging techniques, quantification, mass spectrometry, immunoassays, cardiovascular disease, cancer, inflammation

Background to the Metrological Challenges

Although biomarker measurements are increasingly used as diagnostic tools, the value of the measurements is limited by the frequently reported lack of comparability and the unresolved challenges of quantification. These limitations are due to a lack of standard measurement procedures for biomarkers characterisation and the existence of very few certified reference materials.

Current standards and legislation (European *in vitro* device Directive 98/79/EC [1], ISO 17511:2003 [2], ISO 18153:2003 [3]) require the traceability of values assigned to calibrators and control materials for *in vitro* diagnostic devices and that these values must be assured through available reference measurement procedures and/or reference materials. However, without the development of traceable measurement procedures, current biomarker diagnostic tools cannot meet these requirements.

Predominantly, *in vitro* diagnostics use optical detection techniques for biomarkers, these techniques range from microtitre plate -based microfluorometry, to immunochromatography, flow cytometry and fluorescence based microscopy techniques. Furthermore, biomarker imaging of cells and tissues uses optical detection techniques in conjunction with molecular probes and contrast agents, directed at different biomarkers (i.e. targets) such as cell surface-proteins or enzymes.

The majority of complex disease-related targets and biochemical processes require multiparametric detection schemes. This has led to the development of increasingly sophisticated probes for multiplexed biomarker analysis and imposes enhanced challenges on biomarker quantification. In addition, there is a need to combine different detection techniques e.g. fluorescence imaging with magnetic resonance imaging (MRI), which requires multimodality probes that can be quantitified with different detection techniques.

Quantitative and traceable biomarker analysis also relies on the correct design of suitable probes/reporters. To ensure repeatable and comparable measurements these probes/reporters must be carefully chosen with respect to:

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- photoluminescence or fluorescence quantum yield (Ff),
- molar absorption coefficient
- thermal/colloidal and photochemical stability
- reporter-to-ligand (R/L) ratios
- target binding affinity and specificity in *in vitro* to *in vivo* solutions (e.g. bioanalytical buffers, serum, blood and cells)
- for nanocrystalline labels and fluorescent nanoparticles, specifically, characterisation of size, charge, surface chemistry and the number of reporters per particle

Scientific and Technological 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 JRP-Protocol.

This SRT aims to improve strategies for the detection of cancer, Alzheimer's disease, and inflammations through the quantification and characterisation of related biomarkers. Metrological strategies shall be developed for *in vitro* and *in vivo* diagnostics of known and new biomarkers together with imaging of biomarkers in cells and tissue using improved quantification concepts.

The specific objectives shall include:

1. To develop traceable methods for the identification and quantification of biomarkers. Methods should include mass spectrometry and optical imaging and the development of fluorescent probes, optical reporters and dye-biomolecules. Multi-parametric detection schemes for the parallel detection of different biomarkers should also be considered.
2. To develop validated protocols and stable reference materials for these methods.
3. To quantitatively and comparatively evaluate in-vivo and in-vitro biomarker diagnostics, and develop methods for comparable biomarker detection in biological samples.
4. To develop techniques for the reliable and quantitative imaging of biomarkers in both cells and tissues. Labelling techniques should consider the signal relevant properties of probes. Reference materials and standards should also be developed for specific optical detection techniques.

The biomarkers under consideration should be carefully prioritised in consultation with relevant stakeholders such as the International Federation of Clinical Chemistry and laboratory medicine (IFCC) or the International Joint Committee for Traceability in Laboratory Medicine (JCTLM).

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 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.

The total eligible cost of any proposal received for this SRT is expected to be significantly above the 2.7 M€ guideline for proposals in this call.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the "end user" community. This may be through the inclusion of unfunded JRP partners or collaborators, or by including links to industrial/policy advisory committees, standards committees or other bodies. Evidence of support from the "end user" community (eg letters of support) is encouraged.

You should detail other impacts of your proposed JRP as detailed in the document "Guide 4: Writing a Joint Research Project"

You should detail how your JRP results are going to:

- feed into the development of urgent documentary standards through appropriate standards bodies
- transfer knowledge to the medical community.

You should also detail how your approach to realising the objectives will further the aim of the EMRP to develop a coherent approach at the European level in the field of metrology. 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 Member States and countries associated with the Seventh Framework Programme whose metrology programmes are at an early stage of development to be increased
- outside researchers & research organisations other than NMIs and DIs to be involved in the work

Time-scale

The project should be of up to 3 years duration.

Additional information

The references were provided by PRT submitters; proposers should therefore establish the relevance of any references.

[1] European *in vitro* device (IVD) Directive 98/79**/**EC

[2] ISO 17511:2003 In vitro diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of values assigned to calibrators and control materials.

[3] ISO 18153:2003 In vitro diagnostic medical devices -- Measurement of quantities in biological samples -- Metrological traceability of values for catalytic concentration of enzymes assigned calibrators and control materials