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

Selected Research Topic number: **SRT-h02**
Version: 1.0

Title: Advanced cell imaging for neurodegenerative disease

Abstract

Neurodegenerative diseases such as Alzheimer's and Parkinson's disease represent a major challenge for the health and social care systems. The pathogenesis of these diseases occurs at the sub-cellular level, and therefore a better understanding at this level is required to support the development of new treatments and diagnostic tools. However, the limitations of conventional microscopy (it is not quantitative and has significant limitations in resolution or labelling requirements) create a significant barrier, which impedes progress at the sub-cellular level. To overcome this, emerging and advanced imaging techniques need to be refined, characterised and validated such that their results can support research, drug discovery and diagnostic development for neurodegenerative diseases.

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 page 22 and 41.

Keywords

neurodegenerative disease; Alzheimer's disease; Parkinson's disease; label-free microscopy; fluorescence microscopy; imaging mass spectrometry;

Background to the Metrological Challenges

Neurodegenerative diseases such as Alzheimer's and Parkinson's disease are an increasing burden on health and social care systems, and this challenge will only increase over the coming decades with the increasing age of society. Currently there is estimated to be 9.95 million people with dementia in Europe (most of them diagnosed with Alzheimer's disease), however this is expected to grow to 13.95 million by 2030 and 18.65 million by 2050. Therefore, improvements in the treatment and diagnosis of neurodegenerative diseases are vital.

Unfortunately, the mechanisms of pathogenesis have proved difficult to unravel for neurodegenerative diseases. They appear to be rooted in the dysfunction of molecular processes at the sub-cellular level, for example, the pathogenesis of Alzheimer's disease involves the formation of small aggregates (oligomers) of beta amyloid (Aβ) within neurons. In Parkinson's disease, a similar aggregation process involving the oligomerisation of α-synuclein occurs. The ability to understand and quantitatively monitor these sub-cellular processes will be key in the development of new drugs, treatments and diagnostic tools for Alzheimer's and Parkinson's disease. Additionally, it is becoming more and more evident that without a biomolecular understanding of the interaction between the oligomers/proteins and cells, achieving this progress will be impossible.

Microscopy is a central tool in the investigation of biological processes; in both healthy and diseased states. It enables the imaging of cellular structures and the localisation of molecules within cells, as well as being used to follow processes over time. The most widely used form of microscopy in biomedical research is laser-scanning confocal fluorescence microscopy. This technique enables cells and tissues to be imaged in three dimensions, whilst the addition of multiple fluorescent probes can be used to localise specific molecules of interest. However, this technique, as powerful as it is, has a number of significant limitations (e.g. resolution, speed, sensitivity and contrast mechanism) all of which cause significant barriers, in the understanding of neurodegenerative diseases.

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New super-resolution (e.g. stochastic, single-molecule methods; STORM and PALM, stimulated emission depletion; STED and structured illumination microscopy; SIM), imaging mass spectrometry (e.g. TOF-SIMS and the Raman based approaches; CARS and SRS) and label-free methods (e.g. Coherent Anti-Stokes Raman Spectroscopy; CARS, Second Harmonic Generation; SHG, Stimulated Raman Spectroscopy; SRS and Terahertz Scanning Near Field Optical Microscopy; SNOM) are emerging to address these limitations. However, these advanced imaging methods need further development and validation before they can support research, drug discovery and diagnostic development for neurodegenerative diseases.

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.

The JRP shall focus on the traceable measurement and characterisation associated with advanced cell imaging techniques for neurodegenerative diseases such as Alzheimer's and Parkinson's disease.

The specific objectives are:

1. To develop and validate methodologies for studying pathological processes in neurodegenerative diseases. Methods should include:
   - super-resolution, time-resolved, multi-photon and quantitative microscopic imaging techniques and
   - label-free methods such as CARS, SRS, SHG and Terahertz SNOM.
2. To develop and validate advanced cell imaging methodologies for quantifying and characterising protein aggregation and mitochondrial dysfunction in neurodegenerative diseases. Major sources of uncertainty and critical performance criteria should be identified.
3. To quantitatively and comparatively evaluate imaging mass spectrometry (e.g. Time of Flight Secondary Ion Mass Spectrometry) against other advanced cell imaging techniques, in order to quantify any differences and validate its use.
4. To develop methodologies for image formation in super-resolution microscopy techniques. This should include the development of algorithms and software for image reconstruction in stochastic and structured illumination methods.

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.

The total eligible cost of any proposal received for this SRT is expected to be around 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 medical/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.