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

Selected Research Topic number: **SRT-h15**
Version: 1.0

Title: Metrology for the biomolecular origin of disease

Abstract

Current biomolecular structure and function data lacks a sound metrological foundation and is consequently unable to keep up with the demands of molecular medicine. In order to enable major advances in the most pressing health challenges, such as anti-microbial resistance and recurring epidemics, validated measurements and standardisation techniques are required. More specifically, a comprehensive, qualitative and quantitative understanding of biomolecules, such as polypeptides, and their structure-function relationships at the molecular level should provide valuable information for rational drug design, reliable targeting and effective treatment.

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.

Keywords

polypeptide therapeutics; anti-microbial resistance; viral epidemics; MR molecular imaging; structural medicine; biomolecular structure

Background to the Metrological Challenges

The structural determination of biomolecules under native conditions and in complex physiological environments such as cellular membranes and intra- and extra cellular milieu represents an unsolved measurement challenge. For proteins (formed of polypeptides), it is now known that conformational disordering leads to degenerative diseases and that, dynamic transitions in molecular shape are critical for viral infectivity and antimicrobial mechanisms. The poor efficiency of modern medicine can be attributed to the poor understanding of molecular structure-function relationships and these dynamic transitions. Therefore, an understanding of such relationships is vital for addressing the most pressing health challenges such as anti-microbial resistance and recurring epidemics.

As antibiotic resistance increases worldwide, the most pressing challenge is to develop novel classes of antimicrobial agents. Antimicrobial peptides are universal host defence agents found in all multicellular organisms. They function by compromising the integrity of the cell membrane and are being recognised as the main candidates for antimicrobial intervention. Thus far, only selected peptides have been licensed. However, research using new approaches to validate novel antimicrobial peptide therapeutics, and new approaches to delivery and improved stability, could result in an increased range of peptide therapeutics available for broader clinical applications.

To address recurring epidemics such as viral epidemics, fusogenic peptides could be key. Fusogenic peptides are critical structural components of viral proteins, which insert into lipid bilayers and act as anchors bringing two lipid bilayers into proximity, thus promoting infection. The fusion of the bilayers is promoted by gp41, one of two glycoproteins which form the envelope protein complex on the exterior of the virus. gp41 undergoes a series of structural transitions, each of which could be measured and characterised with the aim of disrupting fusion and reducing viral infectivity.

Despite differences in function, many polypeptides display striking sequence similarities, with their structural conformations limited to common secondary structure elements (e.g. helices, beta-strands or turns). Therefore, any development of the underlying measurement science required to identify the links between

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biomolecular structure and function, should provide unambiguous biomolecular structure-function determination. Without clear determination, in a variety of critical application areas, input in to the rational design of new therapeutics cannot be achieved.

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 most pressing health challenges such as anti-microbial resistance and recurring epidemics require an understanding of structure-function relationships at the molecular level, in order to accelerate prevention, early diagnosis, and effective treatment for disease. This SRT aims to develop the underpinning measurement technology required for specific classes of biomolecules such as polypeptides.

The specific objectives are:

1. To develop traceable and comprehensive strategies for biomolecular structure measurement. Expected uncertainty should be <5 %.
2. To develop methods for accurate biomolecular structure-function determination. A combination of methods should be included, such as circular and linear dichroism, Raman/FTIR spectroscopy, and spectroscopy and imaging using MR and synchrotron radiation
3. To characterise the relationships between pathology activity and molecular recognition, folding, energy transduction and biochemistry
4. To produce state-of-the-art computational simulations. Simulations should address these relationships and current predictions of empirical potentials.

The biomolecules under consideration should be carefully prioritised in accordance with the recommendations of relevant stakeholders.

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 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 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.