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

Selected Research Topic number: **SRT-h11**
Version: 1.0

Title: Role of metals and metal containing biomolecules in neurodegenerative diseases such as Alzheimer's disease

Abstract

Neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), are one of the major challenges for health care systems in the Western World. The most common form of neurodegenerative disease is AD (about 70 % of all cases) but approximately only half of the patients suffering from AD are currently diagnosed and therefore, more reliable methods for the detection of biomolecules associated with AD are needed. β-amyloid peptides and tau proteins are known biomarkers in the cerebrospinal fluid (CSF) of AD patients and could be used as biomarkers however they are present at very low levels and therefore require the development of very sensitive methods of detection. Metal ions, such as aluminium and zinc, could also be used as biomarkers for AD however there are no traceable quantification methods currently available for them.

Keywords

Neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, dementia, metal, aluminium, metal containing biomolecules, β-amyloid, tau proteins

Background to the Metrological Challenges

The term dementia is used to describe the symptoms associated with neurodegenerative diseases. There are currently over 6 million people with dementia in the European Union and it is predicted that this number will double over the next 20 years.

As dementia is not currently curable, prevention is the only way of reducing the number of affected patients. Therefore, reliable methods to identify and quantify protein biomarkers and metal adducts involved in the development of dementia will help to understand the origin and progress of the disease and support the development of possible prevention and/or treatment. Information on the profile of essential (e.g. zinc, iron, copper, magnesium and calcium) and non-essential metals (e.g. aluminium, mercury and lead) in AD patients could also support this and complement current information on β-amyloid and tau proteins biomarkers. Metal ions, such as aluminium and zinc, have been shown to be involved in the development of AD and can be found in plaques in the brains of AD patients. Aluminium and zinc are found in many everyday products such as cosmetics, food and drugs and can be incorporated into ferritin, a protein that stores and releases iron. Ferritin is a ubiquitous intracellular protein that is able to easily cross the blood-brain barrier and can therefore act as a carrier for these metals into the brain.

Currently, a definitive diagnosis of AD is only confirmed by post-mortem verification of brain atrophy combined with β-amyloid plaques and tau-based neurofibrillary tangles. Therefore, in living patients, diagnosis of AD has to be achieved via cognitive tests and brain imaging. β-amyloid and tau proteins could be used as biomarkers in living patients, as the biomarkers can be found in the CSF of patients at concentrations of approximately 200 µg/L for tau proteins and 500 µg/L for β-amyloid peptides. However, these very low levels require very sensitive and selective methods for the quantification, as well as the use of small samples volumes. Further to this, β-amyloid plaques and tau proteins are currently quantified using immunoassay or optical methods. However, the results of these methods are often incomparable and the influence of the matrix on the results is not well understood. Therefore, reference materials and measurement procedures for neurodegenerative disease biomarkers are needed.

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The EMPIR initiative is co-funded by the European Union's Horizon 2020 research and innovation programme and the EMPIR Participating States

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 metals and metal containing biomolecules of neurodegenerative diseases.

The specific objectives are

1. To develop methods for the traceable quantification of metals and metal containing biomolecules of neurodegenerative diseases, at µg/L levels or below and in small µL sample volumes. In addition, to use these methods to study the transport of metals into the brain.
2. To produce and characterise isotopically labelled spike materials for metals and metal containing biomolecules of neurodegenerative diseases.
3. To develop new and accurate methods for measuring peptide and protein biomarkers for the onset and progression of neurodegenerative diseases, at µg/L levels and below in small µL sample volumes. In addition, to develop accurate methods for the quantification of metals and the co-localisation of metals with biomarkers relevant for neurodegenerative diseases; in human tissue and liquids.
4. To characterise the uptake and metabolism of metals and metal containing biomolecules of neurodegenerative diseases using the developed methods and spike materials.
5. To facilitate the uptake of the technology and measurement infrastructure developed by the project by the measurement supply chain (accredited laboratories, instrumentation manufacturers), standards developing organisations (ISO, CEN) and end users (medical practitioners, medical (academic) hospitals and industry).

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 and EMRP JRP HLT05 Metallomics.

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 medical 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.