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

Selected Research Topic number: **SRT-h03**
Version: 1.0

Title: Next generation metrology for targeted gene delivery

Abstract

Gene therapy could provide much needed therapeutic solutions to many global diseases, such as cardiovascular and infectious diseases and metastatic cancers. However, the lack of measurement standards for targeted gene delivery, limit its systemic use. Targeted gene delivery also has two major remaining barriers; inefficient gene transfer and uptake. What is needed to address these issues, is the traceable and quantitative assessment of gene transfer into living cells (transfection measurands), the structural reproducibility of delivery vectors (reference materials) and reliable gene expression measurements (reference protocols).

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

Molecular therapy, targeted gene delivery, non-viral vectors, transfection, gene expression

Background to the Metrological Challenges

The global molecular therapy market including cancer gene therapy is estimated to be worth over $100 billion by 2015. The European Commission together with the European Medicines Agency (Committees for Medicinal Products for Human Use, Advanced Therapies and Gene Therapy and Biologics Working Parties) has put a particular stress on the development of a new and standard means for macromolecular transport across biological barriers. Indeed, the future of the commercial drug and gene delivery sector could be dependent on addressing this urgent need for standard gene transfer systems.

Synthetic genes, such as oligonucleotides, are used as drugs to genetically suppress disorders by causing either degradation of targeted genes or inhibiting their expression. These methods have different purposes and applications, but their therapeutic use is subject to the same issues. The current generation of synthetic genes appear to have overcome the issues of stability, excretion and uptake by phagocytes, release from endosomes and entry into the nucleus. However, the major remaining barriers are inefficient gene transfer and uptake by the target cells as a function of structural inconsistency between different transfection vectors and formulations (transfection vectors).

Industry is currently focused on the use of nanoparticles based on gold, polymers, peptides or lipids as vectors. However, their size may restrict their movement through cell membranes, and many formulations lead to levels of heterogeneity in size or composition that would compromise their acceptability as human drug carriers. Here, the solution could be to focus on vectors that can encapsulate therapeutic cargo and allow for surface modifications and tagging (EU Directives 2001/83/EC and 2003/63/EC) [1].

Although new and emerging technologies (e.g. self-assembling capsules and viral mimetics, multi-modal magnetic nanoparticulate sensors, morphologically tunable lipidic and peptide encapsulators and molecular meshes and microbubbles) may help to sustain the use of targeted gene delivery in the medium to long term, the lack of accurate measurement and standard materials limits the uptake and use of such technologies. Therefore, validated measurement standards for targeted gene delivery need to be provided.

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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 of targeted gene delivery, in particular the systemic use of targeted delivery vectors. Currently, targeted gene delivery has two major remaining barriers; inefficient gene transfer and uptake by the target cells as a function of structural inconsistency between different transfection vectors and formulations.

The specific objectives are:

1. To develop methodologies for traceable and quantitative measurement of targeted biological transfection (e.g. biomolecular targeting). These methodologies should be correlated against force-induced targeted transfections (e.g. applied magnetic field, ultrasound). Sources of uncertainty should be reduced to < 10 % and critical performance criteria should be identified.
2. To develop methodologies for temporal monitoring and quantification of vector and cargo uptake, intracellular localisation, gene expression and therapeutic response (e.g. genetic reaction). Uncertainties of < 10 % should be targeted.
3. To produce transfection vector reference materials that are stable and enable repeatable measurements. Methodologies for producing the reference materials should establish:
    - morphological and chemical profiles of monodisperse vectors with a resolution down of 2 nm.
    - functional surface profiles of immobilisation, adsorption, molecular orientation, loading capacities and vector-cargo ratios, with a spatial resolution of <10 nm.
    - interfacial profiles of vector-cell interactions relative to cell-targeting, with a single-cell resolution.

This topic will require a close cooperation with experts from the relevant medical/pharmaceutical area.

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.

Additional information

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

[1] Directive 2001/83/EC and 2003/63/EC on the Community code relating to medicinal products for human use