

# Traceability of Complex Biomolecules and Biomarkers in Diagnostics – Effecting Measurement Comparability in Clinical Medicine (CLINBIOTRACE)

TP2

## JRP Objectives:

Measurements of complex bio-molecules are being used more and more in modern healthcare as diagnostic markers for disease. They critically influence diagnostic and therapeutic decisions. However, the absence of a robust measurement system, where results are traceable to standards which are constant over time, has been highlighted as a key issue in achieving consistent measurement comparability in this vital area. Poor quality measurements can create risks for the patient and lead to inappropriate treatment.

In order to address this problem, the project aims to put the measurements on a sounder metrological basis and improve the comparability of measurement of bio-molecules of clinical significance. This will be done by effecting a secure link between the bio-assay approach, reporting in arbitrary International Units (IU), to a metrologically robust physico-chemical approach reporting in SI units through:

1. Refining the current methods for the traceable value assignment of peptides, which are to be used to quantify proteins
2. Devising methods for the reproducible and quantitative digestion of target proteins to enable the accurate quantification of the protein using the peptide standards
3. Investigating emerging and novel methods for the quantification of different protein structures

## Contribution towards the aim of the TP:

To improve clinical diagnostics by expanding the range of reference measurement procedures and reference materials of a higher order for bio-molecules of clinical significance.

## Workpackages & Key Deliverables:

### WP1 Management & Co-ordination (7.5 man months)

### WP2 Selection & Characterisation of Proteins (13 man months)

2.4 Assessed profiling techniques for relative quantitation of protein isoforms ( $T_0 + 30$ )

### WP3 Labelled amino acid and peptide standards (38 man months)

3.4 Single peptide labelled standards and a research paper on the high accuracy quantification of single peptides ( $T_0 + 24$ )

### WP4 Quantified protein standards (35 man months)

4.3 Stable protein standards with traceable mass fraction and measurement uncertainty ( $T_0 + 24$ )

### WP5 Traceable quantification of a protein in a biological matrix (85.5 man months)

5.6 A matrix material with an assigned value for the concentration of the target protein ( $T_0 + 27$ )

### WP6 Approaches to the quantification of tertiary structure (34 man months)

6.1 An assessment of the peptide H/D exchange technique for the quantification of protein structure ( $T_0 + 24$ )

6.2 An assessment of the peptide H/D exchange rate technique with the addition of ligands/antibodies ( $T_0 + 30$ )

### WP7 Linking immunoassay measurements with SI-traceable approaches (26 man months)

7.2 Link between the biological activity of the model system and protein quantification and isoform distribution ( $T_0 + 33$ )

### WP8 IMPACT: Dissemination, exploitation and knowledge transfer (10 man months)

## Scientific and Technological Excellence

The ambitious challenge addressed by this JRP is to harmonise the IU/SI systems through the application of advanced physico-chemical techniques to clinically relevant biomolecules. This is not a trivial undertaking and will not be achieved for some time, but the project takes the first steps and focuses on some key elements including:

- SI-traceable quantitative measurements of the primary structure of proteins using high accuracy Isotope Dilution Mass Spectrometry (IDMS)
- Investigating and evaluating new physico-chemical approaches for the SI-traceable measurements of tertiary protein structure

The project also sets the scene for the development of key reference standards for clinically relevant materials, which are commutable and whose values are traceable to the SI, thus giving a fundamental underpinning to the clinical analysis of biomolecules.

## Quality and Efficiency of the JRP Consortium and Project Implementation

The project consortium comprises the four most experienced biometrology groups within the EU, who bring a complementary set of expertise to undertake the challenge:

- PTB – Amino acid and peptide quantification by IDMS
- LGC – Protein and glycoprotein quantitation and structural analysis using a comprehensive range of mass spectrometers
- IRMM – Expertise in the development of reference measurement systems for clinical analysis
- NPL – Techniques for the structure-function analysis of proteins

The collaboration is facilitated by the fact that most of the senior scientists from each organisation have worked together before and share a high level of enthusiasm and commitment for addressing the key challenge. This enables us to adopt a flexible approach to the management of the workpackages in order to facilitate the required scientific interaction. The LGC project co-ordinator has technical and impact oversight of the project and is responsible for maintaining project direction and healthcare relevance.

## Project Impact

The comparability of clinical measurements is critical for the health of the European citizen by ensuring that the appropriate treatment is administered. The need for robust measurement systems based on reference measurement methods and traceable reference materials has been highlighted as being key by the International Federation of Clinical Chemists (IFCC). The project addresses the ultimate, but difficult challenge of making the measurements of clinically relevant biomolecules traceable to the SI, rather than the bioassay based reference, the IU.

In order to have impact it is essential that progress towards this goal is communicated effectively to the practitioners and other stakeholders, including the clinical medicine community, diagnostic device manufacturers and standards & regulatory bodies.

This is being achieved through:

- Presentations of the work at key symposia
- Articles in relevant trade journals and newsletters
- An interactive workshop for representatives of the European clinical medicine community
- Frequent contacts with the relevant European and International standards bodies

## Participants

### Co-ordinator

Helen Parkes, LGC

### Partners & Key Staff

Bernd Guttler & Andre Henrion, PTB

Gavin O'Connor & Neil Harris, LGC

Heinz Schimmel & Marc Wellens, IRMM

Anna Hills & Philip Nugent, NPL



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## Improved Diagnostics:- Project Workflow for CLINBIOTRACE

