Research Project

Mass spectrometry in the clinical laboratory: towards SI-standardization of a proteomics based multiplex apolipoprotein test

Traditionally, risk for the development of cardiovascular diseases (CVD) is monitored using classical lipid tests such as serum/plasma total cholesterol, HDLc, LDLc and triglycerides. However, it has become clear now that these tests insufficiently address CVD risk,[1] indicating that a more holistic approach is needed. Lipids are transported in lipoproteins, therefore we consider measuring their functional protein counterpart, the so-called apolipoproteins. New clinical guidelines for dyslipidemia recently included serum apolipoprotein B and / or Lp(a) as secondary line tests beyond traditional lipids. Genetic studies also indicate that apolipoproteins are likely better predictors of CVD risk[2-4] and therefore we recently developed an in-house mass spectrometry (MS) based method for the quantitation of serum apolipoproteins.[5]

A medical test should provide the same results independent of whether you test in Amsterdam or Leiden, or even the US or China. This can only be achieved through global standardization, by making test results traceable to higher order standards, i.e. preferentially to SI. Global and sustainable standardization is an essential prerequisite for the successful implementation of new tests into clinical care pathways for dyslipidemia and CVD risk assessment, and an important aspect of its development. MS allows for in-depth quantification of molecular proteoforms and therefore we believe MS holds strong potential for facilitating standardization efforts.

Within this project we will focus on the development and evaluation of **reference materials** for absolute, multiplex apolipoprotein quantitation according to the standardization objectives of the International Federation of Clinical Chemistry. [http://www.ifcc.org/ifcc-scientific-division/sd-working-groups/wg-apo-ms/]. To his end, different calibration options (matrix-based calibration, peptide based calibration, and if needed, protein based calibration) will be assessed using LC-MS techniques as well as different analytical platforms. Moreover, the behaviour and commutability of transgenic mini-pig apolipoprotein (a) in the multiplex LC-MS test and in immunoassay-based apo(a) tests will be evaluated. The project will be performed within the research and development group of the department of clinical chemistry and laboratory medicine at the LUMC in Leiden, in the context of the research line on quantitative clinical chemistry proteomics for enabling precision diagnostics. The student is expected to actively participate in the group activities,[6,7] as well as the weekly work discussion.

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3. Baig F, Mayr M. What are the prospects of apolipoprotein profiling for cardiovascular disease? Expert Rev Mol Diagn. 2017;17(9):805-7.
4. Pechlaner R, Tsimikas S, Yin X, Willeit P, Baig F, Santer P, et al. Very-Low-Density Lipoprotein-Associated Apolipoproteins Predict Cardiovascular Events and Are Lowered by Inhibition of APOC-III. J Am Coll Cardiol. 2017;69(7):789-800.
5. van den Broek I, Romijn FP, Nouta J, van der Laarse A, Drijfhout JW, Smit NP, et al. Automated Multiplex LC-MS/MS Assay for Quantifying Serum Apolipoproteins A-I, B, C-I, C-II, C-III, and E with Qualitative Apolipoprotein E Phenotyping. Clin Chem. 2016;62(1):188-97.
6. van der Burgt YEM, Cobbaert CM. Proteoform Analysis to Fulfill Unmet Clinical Needs and Reach Global Standardization of Protein Measurands in Clinical Chemistry Proteomics. Clin Lab Med. 2018;38(3):487-97.
7. Ruhaak L, van der Laarse A, Cobbaert CM. Apolipoprotein profiling as a personalized approach to the diagnosis and treatment of dyslipidaemia. Ann Clin Biochem. 2019;56(3):338-56.

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Time period

At least 4 months, preferably longer
Start date is flexible

Supervision

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