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Preface

LC–MS/MS in clinical chemistry

Clinical chemistry, as a medical discipline, plays an essential role in clinical decision making. It is estimated that up to two-third of physicians' decisions take laboratory test results into consideration. Currently available technologies in clinical chemistry can provide a most valuable description of the function and integrity of main organ systems within a very short time frame at very moderate costs. Laboratory tests help to characterize the general health condition of diseased persons, contribute to making diagnoses, can provide prognostic information, trigger therapeutic interventions, and are useful to monitor therapeutic regimens with regard to efficiency or side effects. In addition to routinely providing established and clinically proven laboratory tests, the scope of clinical chemistry also includes the search for and validation of potential innovative laboratory tests and biomarkers, which includes technology transfers from research to routine. Technologies of today's clinical chemistry (most importantly photometry, ligand binding techniques, and electrochemical methods) are powerful and efficient; however, a wide range of unmet needs is well recognised. These needs are addressed by the application of innovative analytical technologies with tandem mass spectrometry readout of liquid chromatography-based separations (LC–MS/MS) being one of the most promising candidates for transfer to routine laboratory settings. Application of mass spectrometry in clinical medicine has a considerable history; GC–MS has found an important role in various fields of medicine such as investigations in suspected metabolic diseases in paediatrics or general unknown screening in clinical toxicology. LC–MS/MS is available now for more than 10 years; due to the extremely wide range of potential target analytes and a rather high degree of robustness and automation it clearly has the potential of a far more widespread application in medicine compared to GC–MS.

Characteristic strengths of LC–MS/MS for clinical chemistry include: straightforward method development, extremely wide range of potential target analytes, high analytical sensitivity, specificity, precision, and accuracy, and the potential of highly multiplexed profiling analyses. Typical problems of the common immunoassay technology – such as high cost per analysis for antibody based reagents, lot-to-lot differences of reagents leading to calibration bias, interference by heterophilic antibodies, cross-reactions, and high-dose-hook effects – are obviated when using mass spectrometric methods.

The technology today finds applications in three areas: clinical research (including biomarker discovery and validation); as a reference technology for quality assurance (reference method and reference material generation, establishment of a traceability chain, proficiency testing, standardisation, support for routine method development) but also increasingly for routine analyses in the context of patients' care. However, at present in the latter field the use of LC–MS/MS is restricted to rather few and specialized laboratories, where – nevertheless – the technology is used for very important analyses in individual applications. The still rather limited use of LC–MS/MS in the clinical laboratory is mainly due to the fact that the handling characteristics of LC–MS/MS applications are still very far from the standards realised in routine clinical chemistry analyzers which are characterised by almost complete automation of all analytical processes.

At this point, it must be noted that the environment of a clinical laboratory fundamentally differs from most of the application areas of chromatography predominantly addressed by articles in the *Journal of Chromatography B*. It is characterised by limited specialisation of the staff, high daily sample workloads, need for short turnaround time, and a strong diversity of different analytical systems. Furthermore, there is an increasing economical challenge for medical systems worldwide consequent to an increasing burden of chronic non-commutable diseases and shifts in the age distribution of population of industrialised and developing countries.

However, diagnostic applications of LC–MS/MS have the potential to substantially improve patients' care, due to analyses on a superior level of analytical reliability (in particular relevant for clinical endocrinology), by flexible implementation of new tests (in particular relevant for therapeutic drug monitoring and clinical toxicology) and by addressing unsolved diagnostic problems with multi-analyte approaches (e.g., addressing early identification of infectious complications preceding fatal courses of septicaemia).

Given a widespread use of LC–MS/MS in the future, physician might envision in particular optimised, individualised drug dosage regimens; method independent reference ranges in the context of diagnostic pathways relying on defined cut-off concentrations; and answers in fields where at present laboratory medicine is of limited help (e.g., early detection of preeclampsia a potentially fatal complication of pregnancy by multi biomarker analyses).

To realise such visions, still tremendous individual efforts are necessary aiming to make LC–MS/MS applicable also in routine clinical laboratories, since industry support is still in its infancies. Evidently it is a huge challenge to make this complex technology compatible with the characteristic workflow of today's standard clinical laboratories which are optimised to high throughput, minimised manual workload, optimised safety, and maximum cost reduction. However, this also was realised within less than two decades in the case of immunometric technologies which are not at all less complex in their mechanisms. So LC–MS/MS will hopefully be established in routine laboratories as complementary

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technology adding to today's standard technologies. Clinical and analytical researchers have the obligation to highlight the way for such development; however, its final realisation will certainly be a task for the medical in-vitro diagnostic (IVD) industry. Although desirable, it is still uncertain if the IVD industry will in fact recognise the potentials of LC–MS/MS and make the investment and cooperation efforts needed to bring forward MS-based routine analyzers for the clinical laboratory. Also in this context it is useful and necessary to summarise the current status (and limitations) of clinical LC–MS/MS applications.

This special issue might contribute to those further processes of technological and analytical developments. Following the more general special issue on the quantitative analysis of biomarkers by LC–MS/MS it is most deserving that the *Journal of Chromatography B* now also more specifically focuses on the field of clinical applications of LC–MS/MS.

We would like to thank all the authors for their excellent and up-to-date contributions, spanning over a very wide range of applications and aspects of LC–MS/MS in clinical chemistry and laboratory medicine. We are most grateful to all reviewers for their very careful examination of the manuscripts and their extremely valuable input. Finally, we thank the Editors of *Journal of Chromatography B* and in particular Dimitrios Tsikas for the invitation to realise this Special Issue and for all the excellent support throughout the process of production.

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