Clinical Mass Spectrometry
and the Laboratory of the Future

Prof. Dr. med. Michael Vogeser

13. Juni 2011
Role of Laboratory Medicine today

*Majority* of individual clinical decisions incorporate laboratory investigations.

- Predisposition to diseases
- Pre-symptomatic diagnosis
- Establishing diagnoses in symptomatic patients
- Assessment of prognosis
- Monitoring of therapy
Role of Laboratory Medicine today

Information about integrity of organs (e.g. heart muscle) function of organs (e.g. kidney) infection / inflammation atypical pharmacokinetic conditions autonomous secretion of hormones autoimmunity response of malignancies to therapy ...

“Type 1 diagnostic situations”: essential role of a marker for a decision e.g., troponin ↑ → angiography of coronaries

“Type 2 diagnostic situations”: concomitant role of a marker e.g., evaluation of renal function before administration of nephrotoxic X-ray contrast agent

→ personalized healthcare
Role of Laboratory Medicine today

Approx. 3% of health care expenses in Germany

Sales volume of diagnostic tests approx. 2.2 billion € per year in Germany

Laboratory results typically crucial for the workflow of clinical units (e.g., haematology results in outpatients’ chemo-therapy)

Key requirements: analytical reliability
short turnaround times
economically priced
Basic technologies in laboratory medicine

Automated cell counting
Photometry (1960-70ies →)
Electrochemical sensors
Immunoassay (1970-80ies →)

Quantification of defined marker compounds

About 700 clinically established routine analytes
endogenous compounds and xenobiotics
small molecules and large molecules

Clinical utility of quantifying a compound related to
defined therapeutic interventions

„Background noise“: age, gender, nutrition, general health status, renal function ....
Working characteristics in today’s clinical laboratories

• Fully automated analyzer systems
• Random-access, walk-away capacity
• Up to 70 test channels per instrument
• Sample volume typically 5-10 µL / test
• Up to 2,000 test per hour
• Test run time few minutes
• Stable calibration
• Clinical chemistry analyzers / immuno analyzers / hybrid instruments
• Laboratory management systems (LAS): full automation from scanning, centrifugation, de-capping ..... to a sample stockyard
Weaknesses and limitations of current standard technologies

• Limited specificity, cross reactions (e.g., cortisol / prednisolone)

• Assay interferences, e.g. due to heterophilic antibodies
  or unidentified „matrix-effects“ in many methods

• Method specific reference ranges, limited commutability of results

• Lot-to-lot variations of reagents; limited long-term reproducibility

• Single-analyte based diagnostics (no profiling)

• Limited availability of innovative markers
Mass spectrometry in Laboratory Medicine

1970ies → **GC-MS** for peak identification in toxicology (small molecules)
   Reference methods for routine assays
   Very poor practicability and robustness
   Limited to few analytes, minimal sample throughput

2000ies → **LC-MS/MS** for target analyte quantification of small molecules
   Far better practicability, high robustness, high throughput
   No limitation regarding target analytes
Strengths of LC-MS/MS in Laboratory Medicine

- High degree of specificity (molecular mass + fragmentation pattern)
- Reliability: compensation of matrix effects by stable-isotope dilution technology
  → Reference method level of accuracy in a routine setting
- Simple reagents: no lot-to-lot variation
- Method independent and commutable reference ranges
  → Consistency of results over time and space
- Straightforward development of new assays
- Extremely wide range of target analytes
- Profiling capacity / multi-analyte patterns
Current application of LC-MS/MS in Laboratory Medicine

• Neonatal screening for inborn errors of metabolism
• Therapeutic drug monitoring (immunosuppressants, psychotropic drugs)
• Toxicology
• Endocrinology (steroids, 25-OH-vitamin D)

• University hospital laboratories
• Core facilities of private laboratory trusts
• About 50 clinical laboratories in Germany
LC-MS/MS in clinical labs: current limitations and problems

- Laboratory specific instrument configurations ("home brew")
- Very limited support by the industry
- High instrument costs (>200 k€)
- Extensive allocation of highly skilled personnel and lab space
- Limited sample throughput
- Very limited degree of automation

→ use restricted to highly specialized laboratories
Our vision

… to overcome these limitation and to make the analytical improvements available for all patients

→ development of MS-based analyzer systems which are compatible with the workflow of today’s clinical laboratories

„workshop“ setting in specialized labs

industry standard for all clinical labs
Complementary MS-module

- for challenging analytes (e.g., steroids)
- for emerging analytes (e.g., new drugs)
- for profiling-type diagnostic tests
.... from an “esoteric” technology to industry standard

The players:

MS-instrument manufacturers (ABSciex, Agilent, Shimadzu, Thermo, Waters)
highly demanding clinical service, regulatory hurdles …..

Dedicated small companies, kit solutions (Chromsystems, Recipe, Biocrates, PE)
no instrumentation, no plug-and-play solutions

Potentially: big diagnostic companies (Abbott, Beckman Coulter, Roche, Siemens)
+ differentiation in the “oligopol” market
- substantial investments required; cannibalism ?

Academy – M.D.s > Pacemaker !
## Potentials and added value of LC-MS/MS in laboratory medicine

<table>
<thead>
<tr>
<th><strong>Today</strong></th>
<th><strong>Tomorrow</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes of reference ranges with test-antibody lots</td>
<td>Assay independent reference ranges</td>
</tr>
<tr>
<td>Spurious results e.g. due to heterophilic antibodies or cross-reactions</td>
<td>Further optimized reliability</td>
</tr>
<tr>
<td>Decades between drug introduction and implementation of TDM-tests</td>
<td>Early companion diagnostics</td>
</tr>
<tr>
<td>PK-monitoring of very few drugs in very specific situations</td>
<td>Comprehensive TDM and routine personalisation of drug therapy</td>
</tr>
<tr>
<td>Very limited set of photometrically detected small-molecule markers</td>
<td>Innovative small molecule markers</td>
</tr>
<tr>
<td>Single-analyte based diagnostics</td>
<td>Metabolic-based pattern recognition</td>
</tr>
</tbody>
</table>

→ 1. improved analytical *quality* + *availability* of innovative tests
Potentials and added value of LC-MS/MS in laboratory medicine

→ 2. entirely new diagnostic concepts

“Metabolomic-type” assays: quantitative patterns of many analytes of different chemical classes derived from different metabolic pathways, with bioinformatics based read-out

Addressing *unmet needs* in diagnostic medicine
e.g., early detection of infectious complications in surgery,
early detection of complications in pregnancy,
small-molecule signatures of predisposition to cancers,
non-invasive detection of early atherosclerosis;
early detection of adverse reaction to drugs and environmental xenobiotics
... our contribution

Development of a variety of assays (TDM, endocrinology, metabolites), in part in industry cooperation

Extensive experience with routine application of LC-MS/MS (12-years of immunosuppressant monitoring)

Systematic evaluation of sources of errors and inaccuracy

Method development in automation and workflow concepts (e.g., two-dimensional chromatography; magnetic particle-based sample pre-fractionation; standardisation)

→ Structured communication with industry partners
  clinical perspective → diagnostic needs
  clinical lab perspective → workflow and practicability requirements
  evaluation of products in a clinical laboratory setting
Conclusions

LC-MS/MS - most relevant future technology of laboratory medicine

- has the potential to become the third main technology in Laboratory Medicine

- very substantial potentials to address unmet needs of diagnostic medicine

- very fruitful field for cooperation between academy and industry