

Swiss group for mass spectrometry
Schweizerische Gruppe für Massenspektrometrie



Groupe suisse de spectrométrie de masse
Gruppo svizzero di spettrometria di massa

Newsletter

2011 SGMS Meeting

and General Assembly

October 27 and 28

Dorint Blüemlisalp Beatenberg

!11:25!

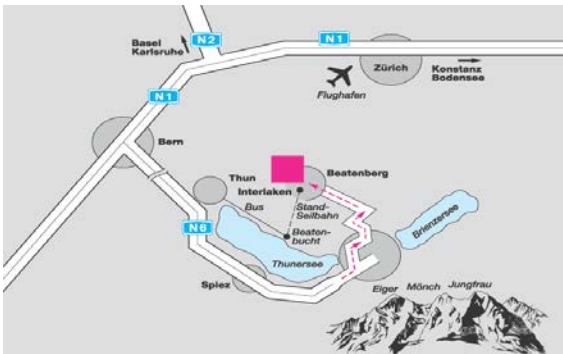
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Travel information

by CAR

Basel	(A3/E60)→Zürich	→A2,1/Bern	→A6/Interlaken	↑ Beatenberg
Zürich	(A1)→Basel/Bern	→A1/Bern	→A6/Interlaken	↑ Beatenberg
Genève	(A9/A12)→Lausanne	→A1/Bern	→A6/Interlaken	↑ Beatenberg



by TRAIN

train leaves (as of September 1, 2011)

Geneva:

IC 717 at 07:45, track 4
Lausanne at 08:20
Fribourg at 09:04
arrives Bern at 09:26, track 7; then see *Bern* below

Basel:

IC 1063 at 08:28, track 8
 stay in the train until Thun

Zürich:

IC 712 at 08:32, track 17
arrives Bern at 09:28, track 4; then see *Bern* below

Bern:

IC 1063 at 09:35, track 3
arrives Thun at 09:52, track 1

Beatenbucht:

take Bus 21064 at 10:02
 the bus will arrive in **Beatenbucht** at 10:33
 take cable car to **Beatenberg** at 10:44

Beatenberg:

arrives at 10:54; then short walk to Dorint Blüemlisalp Beatenberg

Of course there are trains via Interlaken West to Beatenberg but with slightly longer travel times. More info can be found at www.sbb.ch !

Message from the President

With signs of fall all around us after an unusually sunny early September, our annual SGMS meeting approaches rapidly. We have been able to put together an appealing program, which I hope will meet your expectations. We will start with an issue that has been in the media for roughly 10 years now and is very closely connected to the location of our meeting. The rest of the program has been structured around three main topics, instrumentation and methods development (session 2), environmental systems and (eco)toxicology (session 3), and finally human health issues (sessions 4/5). The best student presenter will receive the SGMS Student Award.

Then the Kyoto IMSC 2012 meeting is waiting for us next year and as usual, the IMSF Board has asked us to submit nominations for the Thomson Medal (http://www.imsc2012.jp/pdf/thomson_medal_award.pdf). I would like to ask you to propose candidates to the SGMS board. The candidates do not necessarily have to be from Switzerland.

In 2010 we also had mentioned an MS Alumni page to be started on our site. If you have suggestions please contact Yury Tsybin.

Finally we have started to work on the IMSC2014 site, which currently looks as follows:



The screenshot shows the website for the 20th International Mass Spectrometry Conference (IMSC) in Geneva, Switzerland, August 24-29, 2014. The page features a navigation menu with links for Invitation, Program, Abstracts, Sponsors, Application, Scientific Committee, News, Contact, and Sitemap. A large banner image shows a view of Geneva. Below the banner, there are several content blocks: a sidebar with 'Subnav Eintrag' and 'Place for Sponsor Logos and the like'; a main content area with the headline 'Successful bid for the 20th IMSC to be held in Geneva, in 2014!' and a detailed announcement text; and a right sidebar with 'Place for news, features, and/or image'.

Looking forward to seeing you on Beatenberg!

Marc J-F Suter, President SGMS

Thursday 2011-10-27

Session 1	Chair: Marc J-F Suter, Eawag, Dübendorf
11:25 - 11:30	Welcome
11:30 - 12:15	<u>Helmut Segner</u> , Centre for Fish and Wildlife Health Vetsuisse Faculty, University of Bern <i>The Lake Thun "mystery": high prevalence of coregonids with malformed gonads in Lake Thun.</i>
12:30 - 14:00	Lunch
Session 2	Chair: Andreas Stämpfli, Hoffmann-La-Roche, Basel
14:00 - 14:45	<u>Paola Picotti</u> , Institute of Molecular Systems Biology ETHZ, Zürich <i>Selected reaction monitoring in targeted proteomics: from cellular networks to complete proteome maps</i>
14:45 - 15:05	<u>Yury O Tsybin</u> , Biomolecular Mass Spectrometry Laboratory, EPFL, Lausanne <i>High resolution mass spectrometry at high speed: advances in methods, techniques and applications</i>
15:05 - 15:25	Stephan Graf, Katrin Fuhrer, Marc Gonin, <u>Richard Knochenmuss</u> , TOFWERK AG, Thun <i>Design and performance of a high pressure, multiplexed, high resolution electrospray-ion mobility-TOF mass spectrometer</i>
15:25 - 15:55	Coffee Break

Thursday 2011-10-27

Session 3	Chair: Michael Affolter, Nestlé Research Centre, Vers-chez-les-Blancs, Lausanne
15:55 - 16:40	<p><u>Philippe Schmitt-Kopplin</u>, Institute for Ecological Chemistry, HelmholtzZentrum Munich, Neuherberg, Germany</p> <p><i>Ultrahigh resolution mass spectrometry approaches and new data evaluation strategies for complex environmental mixtures</i></p>
16:40 - 17:00	<p>Lei Chen (1), Diana Hofmann (2), <u>Stephan Küppers</u> (2)</p> <p>1) College of Environmental & Resource Sciences of Zhejiang University, Hangzhou, PRC</p> <p>2) Forschungszentrum Jülich GmbH, Jülich, Germany</p> <p><i>Electrochemistry-mass-spectrometry - a tool for enhanced understanding of mechanisms in environmental systems</i></p>
17:00 - 17:20	<p><u>Ksenia J Groh</u>, Flavio Piccapietra, Renata Behra, Marc J-F Suter, Eawag, Dübendorf</p> <p><i>The effects of silver ions and silver nanoparticles on zebrafish embryos: MudPIT-based assessment of underlying toxicity mechanisms</i></p>
17:20 - 17:40	<p><u>Jean-Christophe Prost</u> (1), Alexander Semmler (2), Michael Linnebank (2), Stefan Bienz (1), Laurent Bigler (1)</p> <p>1) Institute of Organic Chemistry, University of Zürich</p> <p>2) Department of Neurology, University Hospital Zürich</p> <p><i>Determination of the degree of methylation in DNA</i></p>
PhD student lecture	
17:45	General Assembly
19:00	Apéro <i>sponsored by</i>  MS Wil GmbH
20:00	Dinner Buffet ... and later MuhBar

Friday 2011-10-28

Session 4	Chair: Laurent Bigler, University of Zürich
09:00 - 09:45	<p data-bbox="419 472 1326 607"><u>Ian Wilson</u>, Drug Metabolism and Pharmacokinetics, Mereside, Alderley Park, Macclesfield, Cheshire, United Kingdom</p> <p data-bbox="419 622 1246 757"><i>LC-MS-based profiling for metabonomics/metabolomics – the current challenges</i></p>
09:45 - 10:05	<p data-bbox="419 815 1390 949"><u>Julien Boccard</u> (1,2), Flavia Badoud (1-3), Elia Grata (2,3), Jean-Luc Veuthey (1,2), Martial Saugy (2,3), Serge Rudaz (1,2)</p> <ol data-bbox="419 949 1430 1218" style="list-style-type: none">1) School of Pharmaceutical Sciences, University of Geneva and Lausanne2) Swiss Centre for Applied Human Toxicology, University of Geneva3) Swiss Laboratory for Doping Analyses, University Center of Legal Medicine Epalinges <p data-bbox="419 1234 1433 1323"><i>A metabolomic approach to extend the steroid profile monitoring for doping control analysis</i></p>
10:05 - 10:25	<p data-bbox="419 1382 1401 1516"><u>Cédric Bovet</u>, Melanie Erzinger, Paul van Midwoud, Shana J Sturla, Laboratory of Food & Nutrition Toxicology, ETHZ, Zürich</p> <p data-bbox="419 1532 1385 1621"><i>Targeted quantitative strategies for understanding food-drug interactions</i></p>
10:25 - 10:45	<p data-bbox="419 1680 983 1718"><u>Anton Kaufmann</u> (1), Jürg Ruf (2)</p> <p data-bbox="419 1718 1433 1762">1) Kantonales Labor ZH, 2) Kantonales Labor TG, Frauenfeld</p> <p data-bbox="419 1778 1401 1868"><i>Structure elucidation of an unauthorized textile dye discovered in a food product</i></p>
10:45 - 11:15	Coffee Break

Friday 2011-10-28

Session 5	Chair: Jean-Luc Wolfender, University of Geneva
11:15 - 11:35	<u>Guido Vogel</u> , Mabritec AG, Riehen <i>MALDI-TOF MS based identification, differentiation and characterization of biological systems: a cost effective alternative to genetic approaches</i>
11:35 - 11:55 PhD student lecture	<u>Michel Wagner</u> , Eliane Kuehn, Emmanuel Varesio, Gérard Hopfgartner, School of Pharmaceutical Sciences, University of Geneva and Lausanne, Geneva <i>A novel tube-based format for dried blood spots allowing micro cellulose-supported liquid-liquid extraction</i>
11:55 - 12:15	<u>Axel Besa</u> , Pharma, Metabolomics and Lipidomics Applications, ABSCIEX, Darmstadt, Germany <i>Latest hardware developments: where to benefit from differential mobility spectrometry</i>
12:15 - 12:35	<u>Andreas Wiesner</u> , Advion BioSciences Ltd, Edinburgh Way, Harlow, United Kingdom <i>Fully automated surface analysis with the TriVersa NanoMate®</i>
12:35	2011 SGMS Student Award and Closing Remarks

The Lake Thun “Mystery”: high prevalence of coregonids with malformed gonads in Lake Thun



[Helmut Segner](#)

Centre for Fish and Wildlife Health
Vetsuisse Faculty
University of Bern
Bern
Switzerland

Most morphological traits show some degree of quantitative and/or qualitative variation. The question of how to differentiate between ‘normal’ and ‘abnormal’ states of a given trait, and whether an abnormal phenotype is induced genetically, environmentally or by gene-environment interaction, is not trivial to answer. This is particularly true for wildlife species, with an often rather limited knowledge on their biological traits. Whitefish, *Coregonus lavaretus*, from the pre-alpine, oligotrophic Lake Thun, Switzerland, show a remarkable variation of gonad morphology. The variations occur at high prevalence and can be classified into distinguishable morphological categories. As Lake Thun serves as drinking water reservoir for nearly half a million people, and as fish serve as sentinels of environmental quality, the observation of malformed gonads gives rise to the questions if these alterations represent normal or abnormal morphological variations, and what the cause(s) of the alterations are. To answer the first question, an extensive monitoring program was initiated, covering not only Lake Thun, but also two neighboring lakes, i.e. Lake Biel and Lake Brienz. The results were analyzed at three hierarchical levels, i.e. (i) among lakes, (ii) among the ecoforms of whitefish within the lakes, and (iii) among spawning sites within ecoforms. The results revealed that gonad alterations are not restricted to Lake Thun,

but that Lake Thun is unique with respect to frequency and type of malformations. Among the four whitefish forms present in Lake Thun, the so-called “Brienzig” showed the highest frequency of gonad alterations, and males were generally more affected than females. In searching for possible malformation-inducing factors in the Lake Thun ecosystem, we tested a variety of factors that are known to be able to influence gonad morphology of fish, including genetic factors, parasite infections and environmental chemicals. Particular emphasis has been given to endocrine-disrupting compounds, i.e. substances that interfere with the endogenous hormone system. In a series of long-term rearing and exposure experiments, we could provide evidence that (i) the gonad deformations are environmentally, not genetically induced (what does not yet exclude a gene-environment interaction), and (ii) among environmental factors, neither parasites nor endocrine disrupting compounds are responsible for the induction of the gonad malformations, but that the inducing factor is contained in Lake Thun plankton which is the natural food of whitefish. Current research aims to identify the plankton-borne factor(s) being responsible for the induction of the gonad malformations.

Selected reaction monitoring in targeted proteomics: from cellular networks to complete proteome maps



[Paola Picotti](#)

Institute of Molecular Systems Biology, ETHZ
Zürich
Switzerland

To study and model the properties of cellular networks –e.g. metabolic or signaling networks– it is crucial to measure all the elements that constitute them, which are often associated to a wide range of molecular properties and cellular abundances. However, comprehensive measurements are still technically difficult, even in a simple organism such as yeast and especially at the proteome level. To overcome the limitations of classical approaches we applied a targeted proteomic workflow based on selected reaction monitoring (SRM) to the analysis of yeast cellular networks. First, we tested the depth and sensitivity of the SRM-based approach. We demonstrated that proteins spanning the whole range of abundance, between $1.3E6$ copies/cell and <50 copies/cell could be detected by SRM in yeast proteome digests. Then we applied the approach to the analysis of a yeast metabolic network. Proteins in the network were quantified by SRM in yeast grown under a series of conditions inducing radically different metabolic setups and in a growth time-course of yeast cells transiting through a series of metabolic phases. The quantitative dataset generated highlighted how yeast metabolism adapts to changing conditions of supply and demand of nutrients. It indicated that *S cerevisiae* expresses superfluous proteins, not necessarily used in a particular metabolic condition and allowed to suggest differential functionality

for several metabolic isoenzymes. All the SRM assays developed were deposited to the web-accessible SRMAtlas database, which supports the collection and dissemination of the assays. Finally, to overcome the bottlenecks of SRM assay development, we introduced a method based on unpurified synthetic peptide libraries, that allows for the high-throughput and low-cost optimization and validation of SRM assays for any set of proteins or proteome of interest. The approach was used to develop a complete set of SRM assays for the ~6,000 proteins that constitute the proteome of *S cerevisiae*. Similarly, the approach was expanded to the generation of SRM assays for >90% of the human proteome, using a set of 170,000 peptides and the corresponding public human SRM assay library is currently under construction. The power and the bottlenecks of this approach will be discussed.

High resolution mass spectrometry at high speed: advances in methods, techniques and applications

Yury O Tsybin

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High magnetic field Fourier transform ion cyclotron resonance mass spectrometry (FT-ICR MS) provides the unbeatable analytical performance in terms of high resolution measurements. However, the high resolution measurements require a long experimental time, e.g., 1-20 seconds per single mass spectrum acquisition, and thus are incompatible with the current and near-future requirements for the high throughput and fast data acquisition, enforced by the short peptide and protein elution time from the chromatographic column. Here, we will discuss some of the possible solutions to this problem from both, hardware and signal processing development. The FT-ICR MS hardware development follows the implementation of ultra-high, e.g., 21 T, magnetic field environments together with higher acquisition speed and harmonized ICR ion traps. The recent progress in Orbitrap FTMS development has significantly reduced the gap between Orbitrap and ICR FTMS in terms of obtained resolving power required for the mainstream MS applications, 60-200k. Finally, the state-of-the-art time-of-flight (TOF) mass analyzers have demonstrated a substantial progress in the recent years and now offer 30-60k resolving powers achieved at comparable times to the high field ICR and Orbitrap FTMS and faster. On the other hand, incredible progress in the computational power and high frequency electronics opens the doors to the advanced signal processing development, which received a particular attention in the recent years. A number of groups, including ours,

are in the process of tailoring the super-resolution signal processing methods, e.g., filter diagonalization method (FDM), to the needs of the ICR and Orbitrap MS. The goal is to replace the FT-based signal processing with the methods that would require 10-100 times shorter transient time-domain signals to yield a similar level of the resolving power.

Design and performance of a high pressure, multiplexed, high resolution electrospray-ion mobility-TOF mass spectrometer

Stephan Graf, Katrin Fuhrer, Marc Gonin, Richard Knochenmuss
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knochenmuss@tofwerk.com

Ion mobility is an attractive separation technique when coupled to mass spectrometry. It offers speed, stability, reproducibility, transferability and chemical selectivity. However, it often suffers from low separation power and sensitivity, as well as poor coupling to atmospheric pressure ionization techniques.

By interfacing a short atmospheric pressure drift tube with a high repetition rate time-of-flight mass spectrometer, we have eliminated or reduced source coupling problems, while achieving mobility resolving powers suitable for chemical separations. Implementation of an optimized multiplexing scheme regains most of the sensitivity lost in the conventional pulsed mode, while retaining full mobility resolution. Novel post-processing methods in the encoded domain allow further enhancement in mobility resolution.

Applications include protein conformation studies, lipidomics, metabolomics, polymer chemistry, analysis of pharmaceuticals, atmospheric and environmental sampling. Selected examples will be presented to demonstrate the characteristics and performance of the design.

Notes:

Ultrahigh resolution mass spectrometry approaches and new data evaluation strategies for complex environmental mixtures



[Philippe Schmitt-Kopplin](#)

Institute for Ecological Chemistry
HelmholtzZentrum Munich
Neuherberg
Germany

Natural organic matters (NOM) are ubiquitous in terrestrial and aquatic ecosystems and play a fundamental role in the environment. NOM are complex biogeochemical mixtures of non repetitive materials existing in such a vast amount, that their quantity easily exceeds the amount of functional biomolecules. During diagenesis, they continuously undergo degradation and chemical reformation, governed by the fundamental restrains of thermodynamics and kinetics, resulting the extreme intricacy. The natural diversity of these complex organic materials denotes high variability and density of binding sites, which enable them to behave as natural buffer against environmental and chemical extremes. Furthermore natural organic matter defines the bioavailability and cycling of organic and inorganic nutrients and pollutants. Therefore an improved understanding of its composition and the characterization and structural analysis of geopolymers, which feature a substantial extent of both polydispersity and molecular heterogeneity, is most demanding with respect to methodology and concepts. Ultrahigh resolution mass spectrometry is one possible approach among others based on separation and spectroscopy and is shown here in the analysis of such complex mixtures. Besides classical tools developed in

house for the analysis of these materials based on exact mass differences, new approaches in visualizing the vast amount of data and structure information will be presented. The non-targeted way in investigating NOM was the basis of development of non-targeted metabolomics, approaches and data evaluation tools to unravel the metabolite diversity and interconnectivity using network and graph theory approaches.

Electrochemistry-mass-spectrometry - a tool for enhanced understanding of mechanisms in environmental systems

Lei Chen (1), Diana Hofmann (2), Stephan Küppers (2)

1) College of Environmental & Resource Sciences of Zhejiang University
Hangzhou, People's Republic of China

2) Forschungszentrum Jülich GmbH, ZCH, Central Division of Analytical
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Numerous xenobiotics and their derivatives, directly interact with the ecosystem. Some of these compounds undergo chemical and/or microbial transformations after exposure to aquatic and/or terrestrial systems.

In addition it is known that a number of these compounds undergo physical or chemical reactions to form so-called "bond residues". The investigation of these bond residues is extremely difficult because the matrix, i.e. soil, soil organic matter/dissolved organic matter, is extremely complex and the concentration of the compounds of interest is very low [1].

Recently we have shown that electrochemistry coupled to mass-spectrometry (EC-MS) might be a tool to perform a chemical reaction of an antibiotic (sulfadiazine) with catechol, a model substance for soil organic matter (SOM). Changing the reaction conditions in the EC-cell, we found that either a product of sulfadiazine itself or a product of a metabolite generated under oxidative conditions can be received [2].

Starting from this basis we took a look at a model for soil organic matter [3] and choose a number of model substances for the organic part of SOM to find out where typical reaction-sites for bond residues might be. With these chemicals we generated oxidative and reductive degradation products and

performed reactions with the SOM model substances. The structures of reaction products have been elucidated by FT-ICR-MS.

The results of the approach will be presented. It opens a new way for the identification of reaction sites for the formation of bond residues under both oxidative and reductive conditions.

1. Berns A, Conte P, Philipp H, Witte EG, Lewandowski H; *Vadose Zone Journal* 8 (3), 670-676 (2009)
2. Hoffmann Th, Hofmann D, Klumpp E, Küppers S; *Electrochemistry-mass spectrometry for mechanistic studies and simulation of oxidation processes in the environment; Anal Bioanal Chem* 399, 1859 – 186 (2011).
3. Stevenson FJ; *Humus chemistry: genesis, composition, reactions*. 2nd Edition, John Wiley & Sons, New York, 1994, 443.

The effects of silver ions and silver nanoparticles on zebrafish embryos: MudPIT-based assessment of underlying toxicity mechanisms

Ksenia J Groh, Flavio Piccapietra, Renata Behra, Marc J-F Suter
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Widely used silver nanoparticles (AgNPs) may leak into the aquatic environment, raising the need to characterize their potential effects on the biota. Several studies have demonstrated the toxicity of AgNPs to zebrafish embryos. However, the question on whether the effects of AgNPs are due to the physical properties of particles or to the silver ions (Ag^+) present in the solution, has not been addressed properly so far.

By exposing zebrafish embryos to AgNO_3 or AgNP, comparing the effects caused by solutions with presumably equal concentrations of Ag^+ , and employing coexposures with cysteine, a strong Ag^+ ligand, we could show that the toxicity of AgNPs may be largely due to Ag^+ dissolving from particle surfaces. Furthermore, we observed that the severity of toxic silver effects depends on the start of exposure, with the earliest developmental stages being the most sensitive.

To gain further insights into the toxicity mechanisms, we analyzed the proteomes of embryos exposed to AgNO_3 or AgNPs, with or without cysteine. Exposed embryos were euthanized at 5 days post fertilization, depleted of yolk and processed for protein isolation followed by trypsin digestion. The resulting peptides were analyzed by Multidimensional Protein Identification Technology (MudPIT), coupling 2D chromatographic separation with MS analysis on an Orbitrap. Spectral data were searched against the in-house

curated *D. rerio* NCBI protein reference sequence database using OMSSA, and validated by the target-decoy database strategy. This allowed discrete identification (FDR 1%) of roughly 2500 proteins in each sample, representing major cellular processes. Gene enrichment analysis and label-free quantification followed by G-test allowed identification of gene groups or individual proteins whose expression was altered in response to different treatments.

This study adds to the current efforts on evaluating the risks associated with nanoparticle release into the aquatic environment. We demonstrate the power of the global proteome analysis for the initial characterization of the effects caused by novel compounds and generation of hypotheses explaining possible mechanisms of toxicity and resistance.

Determination of the Degree of Methylation in DNA

Jean-Christophe Prost (1), Alexander Semmler (2), Michael Linnebank (2),
Stefan Bienz (1), Laurent Bigler (1)

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2) Department of Neurology, University Hospital Zürich
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PhD student lecture

DNA methylation is an important epigenetic mechanism of transcriptional control that predominantly involves addition of a methyl group to the 5' position of a cytosine that precedes a guanosine in the DNA sequence (CpG dinucleotide). DNA methylation plays an essential role in maintaining cellular function, and changes in methylation patterns are associated with various diseases such as cancer. DNA methylation is dependent on the essential methyl donor S-adenosylmethionine (SAM) and its product S-adenosylhomocysteine (SAH). The ratio SAM/SAH is used as an indicator of the cellular methylation potential. Sepsis, a disease with high mortality, is associated with a significant change in the SAM/SAH ratio in the rodent model and in patients. In this study we performed repeated measurements of DNA-methylation in 11 sepsis patients and 16 controls to analyze potential changes of DNA-methylation in the course of the disease.

Several analytical methods have been used for the determination of the percentage of methylated cytosine in leukocyte DNA, including fluoro-immunoassay, GC-MS, and HPLC combined with UV-diode array detector, ESI-MS or ESI-MS/MS. We developed high throughput analytical methods based on UHPLC-MS to quantify cytosine and 5-methylcytosine. Different mass analyzers and acquisition modes using ion trap, Q-tof and triple

quadrupole instruments have been evaluated. The determinations of cytosine/5-methylcytosine ratios from inter- and intra-assay experiments will be presented. Some incomprehensible divergence of the coefficient of variations obtained will also be discussed.

2011 General Assembly of the SGMS

Thursday October 27, 2011

17:45

Dorint Blüemlisalp, Beatenberg

Agenda

1. Nomination of the scrutineers
2. Approval of the minutes of the 2010 general assembly
3. President's report
4. Treasurer's report
5. Auditor's report
6. Decision on the 2011 membership fee
7. Changes of the statutes
8. Election of one new member of the board
9. Election of the auditors
10. Admission of new members
11. IMSC2014
12. News from the IMSF, EMS and SCS
13. The SGMS homepage
14. Individual proposals
15. Miscellaneous

Individual proposals must be sent to marc.suter@eawag.ch before **October 21, 2011**.

The President, Marc Suter

Changes of statutes: 2011 GA (proposal)

During the past years the committee of the SGMS has been composed of up to 7 members. At the moment only 2 of the current committee members represent the French part of Switzerland. By far too low a number, considering the high number of mass spectrometers in companies and institutes located in the Romandie. Of course more people in the committee would help keeping pace with the fast spread and use of mass spectrometry in nutritional and pharmacological sciences.

The committee of the SGMS proposes therefore the following changes of the statutes (changes in *bold/italic*):

5.1 Composition of the committee

5.1.1 The committee consists of five to *nine* members:

- the president
- the vice president
- the treasurer
- the secretary
- *one to five members-at-large*

Complete section of the current statutes to be replaced:

5.1 Composition of the committee

5.1.1 The committee consists of five to seven members:

- *the president*
- *the vice president*
- *the treasurer*
- *the secretary*
- *one to three assessors*

LC-MS-based profiling for metabonomics/metabolomics – the current challenges



[Ian Wilson](#)

Drug Metabolism and Pharmacokinetics IM
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The discovery of valid biomarkers, present in biofluids and tissues as a means of studying the metabolic response of organisms to normal physiological changes, toxins or disease progression is a major analytical challenge for metabonomics/metabolomics. Whilst the application of powerful analytical methods in an untargeted fashion provides a hypothesis free approach to biomarker discovery there are many pitfalls awaiting the unwary. However, when performed properly these global metabolite profiling methods for the detection of new biomarkers should also be hypothesis generating. Here the use of LC-MS will be described for metabolic profiling investigations that illustrate the great potential of this type of study, as well as some of the more obvious sources of error. These applications will describe studies covering metabolic profiling in animal models, including those dealing with ethanol toxicity and obesity, humans and novel humanised mouse liver models. The many practical challenges faced in the application of LC-MS for the detection of biomarkers in this role will be considered together with some pragmatic solutions. The current challenges, ways of tackling them and the future evolution of metabolic profiling techniques will be considered by references to these applications.

Notes:

A metabolomic approach to extend the steroid profile monitoring for doping control analysis

Julien Boccard (1,2), Flavia Badoud (1-3), Elia Grata (2,3), Jean-Luc Veuthey (1,2), Martial Saugy (2,3), Serge Rudaz (1,2)

1) School of Pharmaceutical Sciences, University of Geneva and Lausanne
Geneva, Switzerland

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3) Swiss Laboratory for Doping Analyses, University Center of Legal
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Analytical procedures regularly applied for steroids misuse control in doping analysis rely on the detection of unexpected variations of the steroid profile. The latter includes a restricted number of endogenous compounds, such as testosterone, epitestosterone, androsterone, etiocholanolone, dehydro-epiandrosterone, 5 α - or 5 β -androstane-3 α ,17 β -diol and dihydrotestosterone. This monitoring is related to the quantification of levels and concentrations ratios of these analytes in urine. An original method based on UHPLC-QTOF-MS was developed as a promising alternative to assess the steroid metabolism by simultaneously measuring compounds in glucuronidated and sulphated forms. A targeted analysis was initially performed with 10 reference compounds of the steroid profile. Time kinetics was assessed and a detection window was confirmed. The results were in accordance with established anti-doping screening protocols mainly based on GC-MS. Thanks to TOF full mass range acquisition, an untargeted steroidomic analysis was further envisaged to provide a broader coverage of urinary steroid metabolites. Automatic peak detection was applied and a filtering procedure ensured the selection of a variable subset of 234 steroid-related peaks among

the 5'750 detected analytes, by using reference m/z values. Chemometric tools, including N-PLS, O-PLS, SUS-plot and ROC curves were used for data mining to provide a deeper insight into the urinary excretion pattern after testosterone oral intake. The filtered temporal monitoring of urine samples provided useful information about kinetics of steroid excretion. Both known metabolites and new biomarkers could be highlighted by these means and allowed the extension of the urinary detection window after testosterone intake. Further investigations of promising candidates by targeted analysis will be performed to ensure proper identification.

Targeted quantitative strategies for understanding food-drug interactions

Cédric Bovet, Melanie Erzinger, Paul van Midwoud, Shana J Sturla
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In Switzerland, colorectal cancer is one of the major causes of death from cancer. DNA-alkylating agents such acylfulvene can potentially cure colorectal cancer through their covalent binding to genomic DNA after bioactivation involving reductase enzymes (1-3). Major drawbacks of DNA-alkylating agents, however, are narrow therapeutic range and poor selectivity for malignant cells. Natural dietary compounds may enhance their tumor-specific cytotoxicity by modulating the expression of redox-regulating enzymes. However, a current gap in knowledge concerns how dietary compounds induce changes in protein profiles that may impact drug cytotoxicity outcomes. Thus, we quantified expression levels of a targeted panel of reductase enzymes and genomic DNA adducts in human colorectal carcinoma cells (HT29) by selected reaction monitoring (SRM). Since the recent development of open-source MS/MS spectra libraries and software, high-quality SRM-based proteomics assays can be developed rapidly for quantifying proteins in complex biological background without fractionation steps. The abundances of the targeted reductases were here quantified relative to two stable isotope-labeled proteotypic peptides per protein. After preconditioning cells with a pure dietary compound, up regulation of the targeted reductases measured by SRM in trypsinized protein extracts was statistically significant ($p < 0.05$) and correlated well with the corresponding enzyme activities measured by UV spectroscopy. The excellent sensitivity and

precision of the SRM method allow detecting differential enzyme expression down to 1.4-fold changes. The human cells were then treated with the DNA-alkylating drug acylfulvene and the level of genomic DNA adducts was quantified by SRM allowing the quantification of one adduct per 10^7 nucleotides. The implication of these sensitive and selective SRM approaches for studying the impact of dietary compounds on the toxicity of cancer drugs will be discussed.

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Structure elucidation of an unauthorized textile dye discovered in a food product

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A spice (Sumach) obtained from the local Swiss market was noted to show a very intense red colour. The responsible compound could be detected but not identified since it neither corresponded to any known natural food dye nor to any authorized or banned food colouring agent. Hence, a structural elucidation based on high resolution mass spectroscopy (Orbitrap) was initiated. The relatively high mass of the unknown compound (m/z : 321) prevented an unequivocal identification by exact mass only. However, observed fragments, isotopic ratios and most importantly the relative abundance of mass spectrometrically resolved ^{15}N isotopes led to an unambiguous elemental composition. Significantly more challenging was the identification of the underlying chemical structure. The presentation focuses on this crucial step. An initial search failed, because of the assumption that the unknown compound would be ionized as $[\text{M}+\text{H}]^+$ in the electrospray. Instead, the compound turned out to be a permanently charged quaternary amine. Furthermore, its elemental composition and consequently the resulting mass was listed in some databanks as the ion pair consisting of the cationic dye and various counter ions like acetate or bromide. The problem was further complicated by the fact that public databanks (ChemSpider, Molport and PubChem etc.) even listed a wrong chemical structure. A double bond present in a heterocyclic moiety was omitted, resulting in an incorrectly

listed elemental composition. It was a Chinese bulk chemical sourcing web site which showed the correct structure.

The presentation focuses on alternative search strategies to be used when classical straightforward searches fail. It gives examples of unique ways to use "www.google.com" as a chemical substructure search tool. Finally, the problem did not end with the proposition of the expected structure. The identified azo dye was neither commercially available as reference substance nor an easy candidate for an in-house synthesis. It was finally obtained by purchasing a consumer product (hair dye). This permitted the unequivocal confirmation of the attempted identification. The compound was found to be present at some 1 g/kg in the investigated spice. It is not permitted to use it as food colorant and it even has been banned as additive to hair dye products. To our best knowledge, this is the first reported finding of such a food adulteration.

MALDI-TOF MS based identification, differentiation and characterization of biological systems: a cost effective alternative to genetic approaches

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MALDI-TOF mass spectrometry is an emerging tool for routine identification of microorganisms in medical diagnostic laboratories. Reliable identification depends upon a validated and comprehensive database of peptide mass fingerprints. Commercial databases for such applications are currently only available for selected human pathogenic bacteria and fungi. Mabritec, the first Swiss service provider in the area of MALDI-TOF MS based identification of biological systems, was founded in 2008 with the clear intention of expanding the applicability of this rapid and cost effective method to other areas such as environmental and industrial microbiology, phytopathology, parasitology, cell line quality insurance as well as plant variety testing. Our presentation will give a representative introduction into this technology and illustrate its potential applications in many fields of research and development.

Notes:

A novel tube-based format for dried blood spots allowing micro cellulose-supported liquid-liquid extraction

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PhD student lecture

Dried blood spots (DBS) have shown their usefulness for a large number of applications as sample collection and storage device, from their early days with newborn screening to their recent use for pharmaco- and toxicokinetics studies. In bioanalytical applications, a portion of the DBS spot is usually punched out of the card, and analytes are then submitted to a generic solid-liquid extraction (SLE) using an organic solvent (or its mixture with water).

We present herein a novel, tube-based format, which allows sample collection on paper, storage and analyte extraction in a single device. This eliminates the need of an often tedious, punching step and prevents any related cross contamination. Moreover, the tube-based format allows, in addition to SLE, the use of micro cellulose-supported liquid-liquid extraction (μ csLLE) on filter paper in a simple and efficient way.

The novel format was investigated for both SLE and μ csLLE, evaluating first the extraction efficiencies obtained for a mixture of 18 analytes, representative of 5 distinct chemical classes (amphetamines, cocaine and metabolites, tricyclic antidepressants, benzodiazepines, antiretroviral drugs). Second, the selectivity of the extraction procedure was studied for SLE and μ csLLE by assessing 1) the removal of interferences, 2) the removal of phospholipids (a possible cause of matrix effects in LC-MS), and 3) the inherent clean-up potential of each sample preparation approach using flow

injection analysis, i.e. without any prior chromatography. For those three aspects, μ csLLE was found of better clean-up value than SLE.

On another hand, the quantitative potential of the tube-based format is demonstrated for the therapeutic drug monitoring of seven antiretroviral (protease inhibitors) drugs in dried blood or plasma spots, using a sample volume of 15 μ l. Fast separation was achieved using a thermostated (50°C) core-shell particle (2.7 μ m) column and a 3 minutes gradient elution with a flow rate of 0.6 ml/min. MS analysis was achieved in the selected reaction monitoring (SRM) mode with a LCMS-8030 (Shimadzu). The total MS duty cycle was of 184ms including eight 20ms SRM transitions, which allowed sufficient (>12) data points for peak description. With one internal standard (i.e. pentadeuterated saquinavir) for quantitation, LOQ of 1 to 2.5 ng/ml, as well as acceptable precisions and accuracies could be achieved for all seven analytes with a dynamic range of about three orders of magnitude.

Latest hardware developments: where to benefit from differential mobility spectrometry

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The common instrumentation for quantitative experiments is still provided by triple quadrupole instruments. Here the multiple reaction monitoring, MRM, mode typically combines adequate sensitivity with sufficient selectivity, which result in good signal-to-noise ratios for a majority of analytes in various matrices and/or applications.

The ongoing process of developing instruments with higher sensitivity often suffers from increased background interferences, coming from solvents and/or matrices. Additionally more and more analytical candidates with either poor or unspecific fragmentation pattern need to be implemented into multi methods. As a result of limited fragmentation patterns of the individual compounds and already developed chromatographic conditions the LC-MS/MS method sometimes do not provide enough selectivity to separate isobaric interferences, to isolate challenging co-eluting contaminants and/or to eliminate high background noise in complex samples.

The Differential Mobility Spectrometry, DMS, is a front end ion mobility separation technology based on a geometrical planar separation area with a high and a low electrical field. Hence, separation process is not done by time and the separation efficiency is additionally supported by gas phase interactions. As a result separation times of 20 ms can be achieved, which enables this technology add-on to be coupled to any fast LC device.

The resulting physical improvement is an additional level of selectivity, which is mainly based on the shape of the precursor molecules. Thus, coupling DMS device, SelexION™, to AB SCIEX 5500 series will enhance selectivity, which could not previously be achieved for analyzing complex samples.

Beside the technical and hardware set-up various data will be shown, which demonstrate the performance and selectivity enhancement of DMS.

Fully automated surface analysis with the TriVersa NanoMate®

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Since many years, the TriVersa NanoMate® is well established as a robotic platform for delivering samples to mass spectrometers via a chip-based nano-electrospray emitter. It enables the online-coupling to HPLC systems as well as parallel fraction collection and direct infusion from titre plates at low flow rates.

More recently, the TriVersa NanoMate was further developed for the automated analysis of surfaces by direct solvent application and immediate infusion of resulting extracts. Originated from collaboration with Oak Ridge National Laboratory, the Liquid Extraction Surface Analysis (LESATM) capability is now readily integrated as an optional component of the Triversa NanoMate.

Since the first publication on this subject (1), where proof-of-principle studies confirmed the usefulness of this technology for dried blood spots, tissue sections as well as MALDI-targets, the LESA-approach was successfully used for a wide range of application areas, including:

- Analysis of lipids (2) and proteins or peptides (3) from TLC-plates.
- Direct analysis of tissue sections for drug distribution studies (4 -7) and lipid profiling (8).
- Pesticide (9) and toxic compounds (10) analysis from food surfaces.
- Direct analysis of hemoglobin variants from dried blood spots (11).

- Comparative lipid profiling directly from atherosclerotic plaques (12).
- The technological background of LESA and recently published results achieved with this approach will become reviewed.

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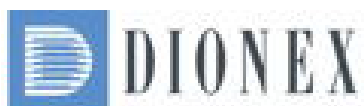
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