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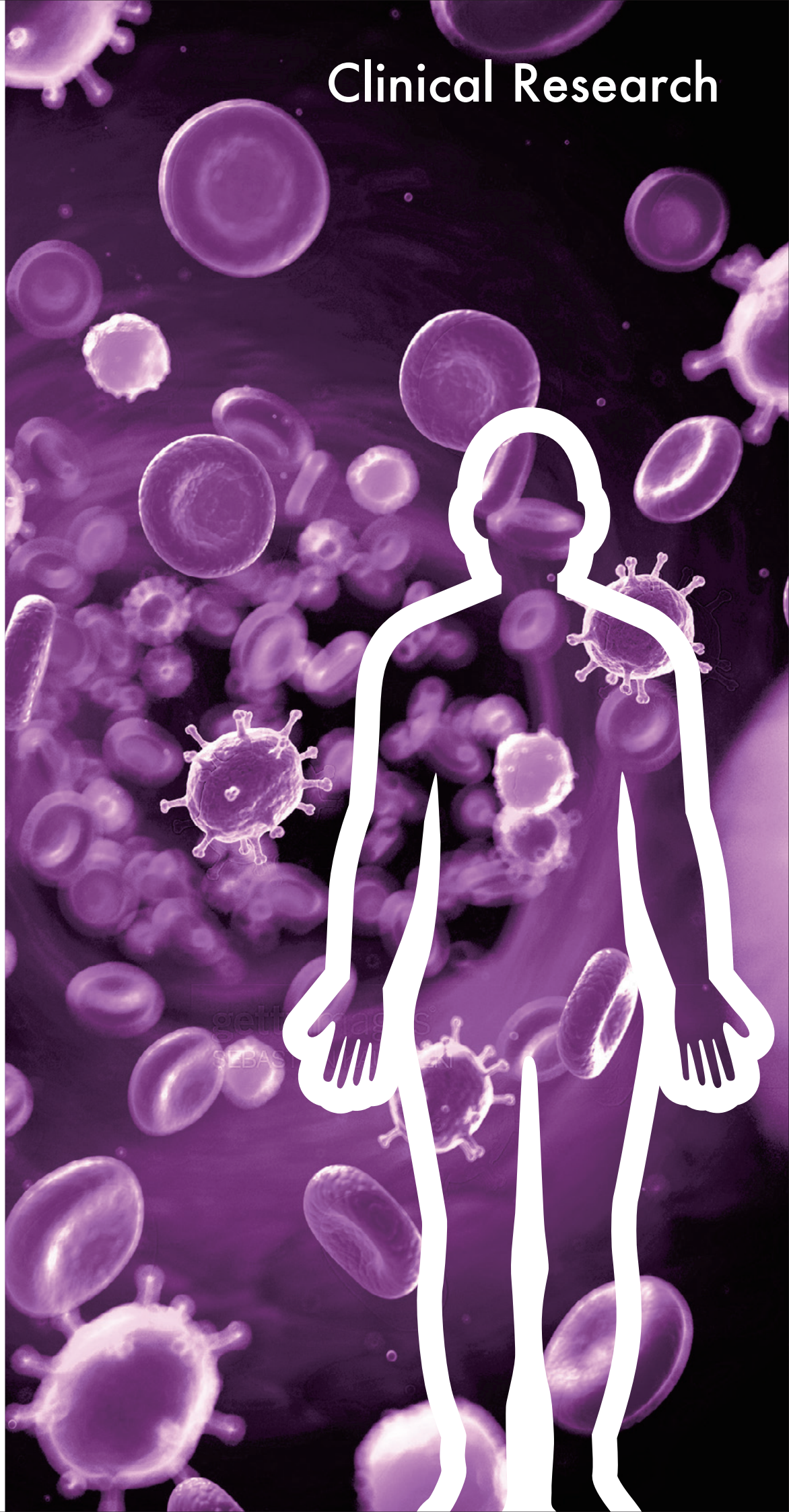
Shimadzu Journal

Clinical Research



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Dear Readers,

Yoshiaki Mase

General Manager,
Analytical & Measurement Instruments Division

I am Yoshiaki Mase, the new General Manager of the Analytical & Measuring Instruments Division. I have replaced Shuzo Maruyama, who was appointed Managing Director of Shimadzu (Hong Kong) Ltd. in China this April.

Prior to this appointment, I worked as Managing Director of Shimadzu (Hong Kong) Ltd. as the general representative for Shimadzu's business activities in China. At the same time, I pursued business activities in the Chinese market as the Director/General Manager of Shimadzu (China) Co., Ltd. While stationed in China, I helped transform the Shimadzu China Mass Spectrometry Center in Beijing, a base for cooperative research in mass spectrometry technologies, into the China Innovation Center, and adjusted the organization to enable cooperative research with customers utilizing technologies from a wider range of fields.

At the China Innovation Center, we pursued specific measures for contributing to society through science and technology. These measures included research and development of revolutionary analytical methods in the ecology field and the clinical domain, and more recently, research and development of multiplex examination methods for multiple human coronaviruses.

This area of R&D has become all too timely with the rapid spread of the COVID-19 coronavirus across the globe. It has continued to develop mutations intermittently for more than a year now and is still having a significant impact on the global economy. In order to mitigate the spread of this virus, it is important to have a diagnosis as quickly and easily as possible in order to take suitable countermeasures at the earliest stage. As a quick and convenient virus detection solution, Shimadzu released the 2019-nCoV detection kit using our Ampdirect technology. In addition, we aim to contribute to suppressing COVID-19 by releasing the AutoAmp fully automatic genetic analyzer.

The spread of this virus gives us a fresh awareness of just how much impact a new infectious disease can have on the world. Shimadzu's current medium-term management plan includes a project to counter infectious diseases by utilizing a wide range of technologies, including both our analytical/measuring technology and medical diagnostic imaging technology. Moving forward, we will continue to advance research and development to enable us to provide solutions as appropriate countermeasures.

This edition of the Shimadzu Journal is a special edition on clinical research. It introduces case studies and applications of the use of Shimadzu analytical instruments in the field of clinical research for the early detection of cancer and the analysis of anticancer agents and therapeutic drugs for COVID-19.

Firstly, we interviewed Professor Uwe Karst of the University of Münster about his participation in the development of a multimodal imaging system. Next, we talked with Dr. Paul Eason at the University of North Florida (UNF) about MedNexus, a facility established by UNF and associated with comprehensive medical treatment and health care, and also about the relationship with Shimadzu.

In addition to these interviews, this issue contains applications related to the screening of anticancer agents using probe electrospray ionization (PESI) and analysis of COVID-19 therapeutic drugs using HPLC and LC-MS/MS. Finally, we introduce the latest initiatives at Shimadzu in the clinical research field.

I believe the importance of a healthy lifespan is increasing in accordance with the anticipated increase in the elderly population in every country and region of the globe. In order to extend this healthy lifespan, I believe it is very important to detect cancer, cognitive illnesses, and other diseases at very early stages and to take appropriate treatments and countermeasures. In order to contribute to these fields, Shimadzu will take proactive measures in the area of cooperative research, deepening our relationships with researchers involved in cutting-edge, revolutionary research and development in these clinical research fields, based on Shimadzu's advanced analytical and measuring technologies.

The corporate philosophy of Shimadzu is "Contributing to Society through Science and Technology." To realize this corporate philosophy, we will continue to maintain a proactive exchange of information and, at the same time, provide useful information to you. We hope that this journal will be a great help for all of you. Your generous feedback is always appreciated.

Yours Sincerely,

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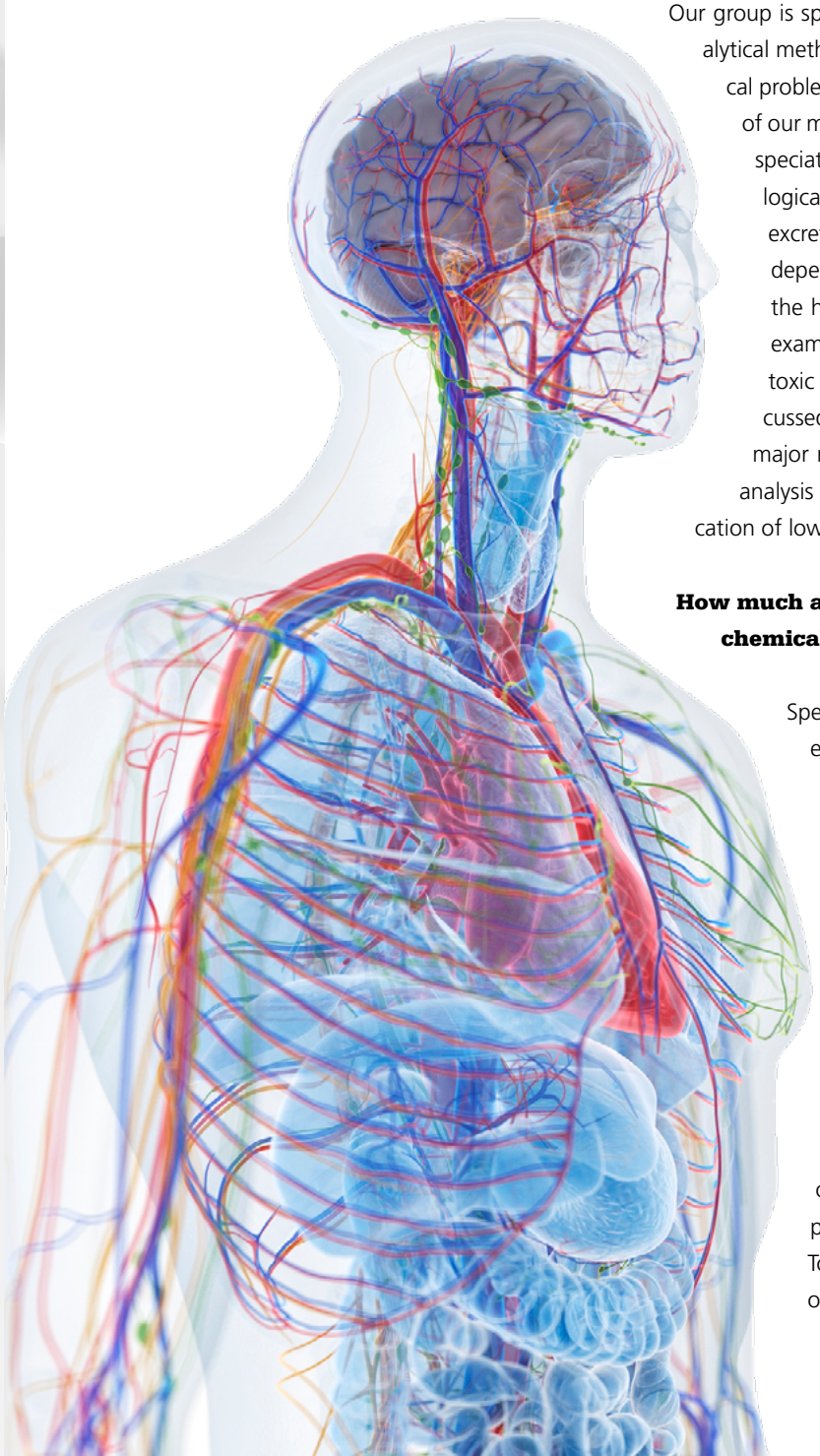
Interview 1 Interview with Prof. Uwe Karst

"Cooperations always are based on trust and on personal relations"

Professor Karst, thank you very much for spending some time for this interview. At first, could you introduce the outline of the research you conduct in general?



Our group is specialized on the development and application of analytical methods and instrumentation to address complex analytical problems, mainly originating from the biomedical area. One of our major research areas is speciation analysis. The need for speciation analysis is caused by the fact that the physiological properties (uptake, distribution, metabolism and excretion), of metal-containing compounds are strongly dependent on the individual metal species rather than on the heteroatom in general. This is easily proven using the example that hexavalent chromium is considered to be toxic and carcinogenic, while trivalent chromium is discussed as possible essential trace metal species. A second major research area of our group is chemical imaging - the analysis of the distribution and the spatially resolved quantification of low molecular weight analytes in biological matrices.

How much are speciation analysis and (multimodal) chemical imaging linked to each other?

Speciation analysis and chemical imaging complement each other perfectly regarding the analysis of metal species in the organism of humans, animals or plants. Speciation analysis mostly uses liquid phase separations to separate the metal or metalloid species prior to identification by electrospray mass spectrometry (ESI-MS) and quantification by inductively coupled plasma-mass spectrometry (ICP-MS). Chemical imaging, on the other hand, is carried out by matrix-assisted laser desorption/ionization-mass spectrometry (MALDI-MS) and related techniques to obtain distribution information about intact molecules, while distribution and quantification of the elements is accessible by laser ablation (LA) coupled to ICP-MS and micro-X-ray fluorescence (μXRF). To provide an example, the investigation of side effects of Cisplatin-based tumor therapy requires speciation

analysis to detect and quantify the individual platinum species formed in body fluids and tissues, while imaging by LA-ICP-MS provides quantitative distribution information on platinum in human or animal tissues.

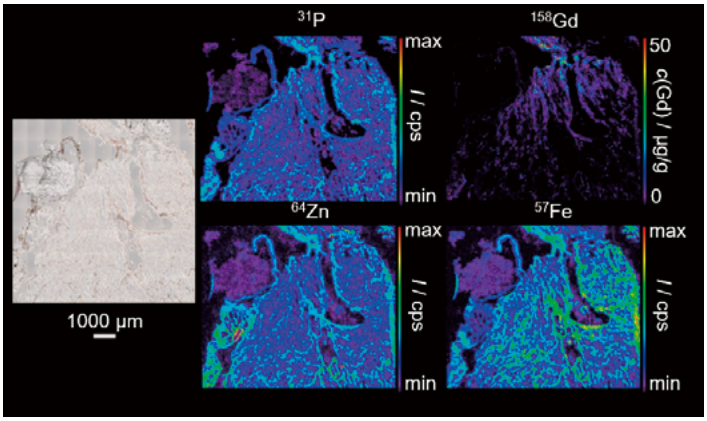


Figure 1. Elemental distribution of P, Zn, Gd and Fe obtained via LA-ICP-MS analysis as well as microscopic image (left) of a sheep kidney sample after treatment of the animal with gadodiamide.

Could you describe the research you have done at the European Innovation Center with Shimadzu?

We are collaborating with the EuIC on Imaging since more than three years, and one major topic at this moment is the further improvement of the combination between liquid chromatography and ICP-MS for speciation analysis as well as laser ablation and ICP-MS for chemical imaging purposes. As in other previous and current cooperations with various instrument manufacturers, we see our role not only in developing applications, but also in contributing to the further development of the actual and future instrument generations, including suggestions for improved hardware, software for instrument control, data evaluation and integration of the instrument´s data with data of other imaging methods. Within our current project, the focus is directed on LC-ICP-MS as well as LA-ICP-MS and its combination with MALDI-MS and MALDI-MS/MS, as many of our current analytical challenges require the combined use of complementary imaging techniques.

Could you share Shimadzu's strengths?

As stated above, combined imaging techniques are particularly intriguing. Therefore, cooperations with manufacturers who are active in several fields of chemical imaging are particular attractive to us (and hopefully for the manufacturers as well). While we have been using chromatography (LC, GC) and spectroscopy (UV/vis, fluorescence, AAS) instrumentation from Shimadzu since more than 20 years for research and education, our cooperation in the imaging field was established five years ago, and is currently

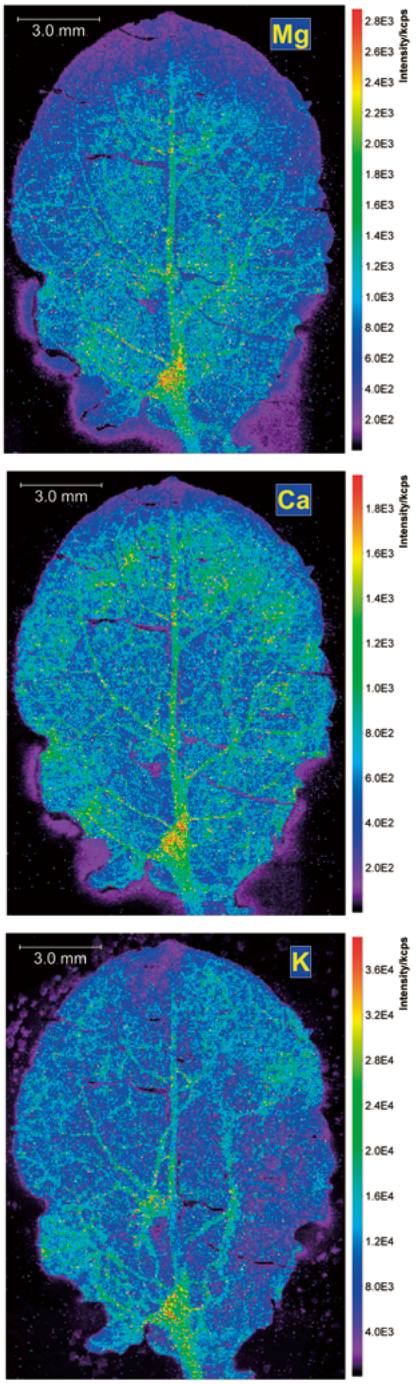


Figure 2. Heatmap of the spatial distribution of 24Mg, 39K and 44Ca in a whole leaf of an Arabidopsis halleri plant recorded by LA-ICP-MS.

Prof. Uwe Karst

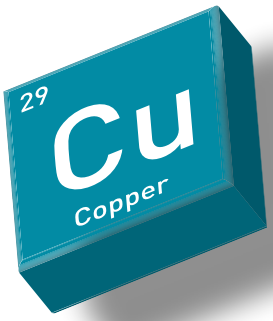
centered around LC-ICP-MS as well as LA-ICP-MS and complementary MALDI-MS work.

Cooperations always are based on trust and on personal relations, and a major reason for us to work with Shimadzu equipment at a larger scale during my Habilitation phase, in which I had very limited equipment, was an excellent relation with the local sales agent, who always was helpful to a much larger extent than we could expect, and who just was an outstanding ambassador for the company. Of course, producing well-performing and robust instrumentation helps as well, but the more complex the analytical challenges get, the stronger dependency will there be on excellent communication and cooperation between individuals on both sides. Additionally, in our current situation, a broad spectrum of imaging instrumentation from any manufacturer is particularly attractive to us due to the complexity of our analytical problems and the increased chances to tackle the most difficult challenges.

Could you share any requests that you have with respect to analytical and measuring instrument vendors?

Let me start with a very general statement that is not addressed to any particular vendor at all: While the world of analytical challenges is converging more and more, including even a vanishing "wall" between "organic" and "inorganic" analysis, there often are business decisions of instrument vendors that lead to fragmentation of product lines and separation of business units that are hard to understand in the light of the increasing complexity of analytical challenges. Sometimes, I wish scientists would be more involved in the business decisions at instrument vendors, as this is not a matter of rapid sales only, but of long-term business relations and business development in a complex market situation. It may be naïve to think that sometimes, wise long-term decisions should overrule rapidly profitable decisions, but it would accelerate technical progress so much …

Back down to earth again, my wish would be that manufacturers decide to improve integration of their major product lines to a larger extent, which would be excellent especially in our research areas of speciation analysis and chemical imaging. This is one of the major factors we are trying to contribute to in our cooperation with the Shimadzu European Innovation Center on Imaging.



Take a look into the future: What will happen in your research field and how will the change influence the instruments/procedures in ten years?

To my opinion, this goes very much in line with my reply to your earlier question: I am aware of the fact that your major markets of today are not the research areas we are currently working on and that your sales will mostly go to the mass markets in the routine labs. However, we are facing an increasing degree of complexity, and being prepared to address this situation will become even more important in the future. While the medical imaging area will continue to expand due to its immediate and obvious benefit for the patient/customer, the chemical imaging area is harder to predict, as the immediate necessity for the paying customer is not as clear, thus hampering massive investments in this field. Regarding the scientific contents, there will be massive progress in chemical imaging as well, leading to strong optimism regarding the future development. However, reaching the mass markets in routine labs (medical, environmental, food) will require a significant reduction of the costs per analysis and of the need for highly qualified personnel. This can only be achieved by strong improvements regarding the speed of the analysis (more spots per second in imaging mode), improved hard- and software integration and possibly even strategic alliances between vendors of complementary instrumentation or between different divisions of one vendor. Let me conclude with the statement that there is an increasing amount of light on the horizon, but that the full sunrise has to be earned by hard work and smart decisions in academia and industry. We will do our best to contribute!

Prof. Uwe Karst

Selected recent publications with Shimadzu instruments:

(1) Von der Au, M; Karbach, H; Bell, AM; Bauer, OB; Karst, U; Meermann, B
Determination of metal uptake in single organisms, Corophium volutator, via complementary electrothermal vaporization/inductively coupled plasma mass spectrometry and laser ablation/inductively coupled plasma mass spectrometry
Rapid Commun. Mass Spectrom. 35 e8953 (2021)

(2) Andersen, MK; Krossa, S; Hoiem, TS; Buchholz, R; Claes, BSR; Balluff, B; Ellis, SR; Richardsen, E; Bertilsson, H; Heeren, RMA; Bathen, TF; Karst, U; Giskeodegard, GF; Tessem, MB
Simultaneous Detection of Zinc and Its Pathway Metabolites Using MALDI MS Imaging of Prostate Tissue
Anal. Chem. 92 3171 (2020)

(3) Richter, H; Bücker, P; Dunker, C; Karst, U; Kircher, PR
Gadolinium deposition in the brain of dogs after multiple intravenous administrations of linear gadolinium based contrast agents
Plos One 15 e0227649 (2020)

(4) Lützen, E; Holtkamp, M; Stamme, I; Schmid, R; Sperling, M; Pütz, M; Karst, U
Multimodal imaging of hallucinogens 25C-and 25I-NBOMe on blotter papers
Drug Testing Anal. 12 465 (2020)

(5) Lohöfer, F; Buchholz, R; Glinzer, A; Huber, K; Haas, H; Kaissis, G; Feuchtinger, A; Aichler, M; Sporns, PB; Höltke, C; Stölting, M; Schilling, F; Botnar, RM; Kimm, MA; Faber, C; Walch, AK; Zernecke, A; Karst, U; Wildgruber, M
Mass Spectrometry Imaging of atherosclerosis-affine Gadofluorine following Magnetic Resonance Imaging
Sci. Rep. 10 79 (2020)

▶ Uwe Karst holds the Chair of Analytical Chemistry at the University of Münster in Germany. After diploma and Ph.D. studies in Münster, which he finished in 1993, he joined the University of Colorado in Boulder as postdoctoral associate. He returned to Münster to obtain his Habilitation and was appointed as Full Professor of Chemical Analysis at the University of Twente in The Netherlands from 2001 to 2005, when he assumed his current position.

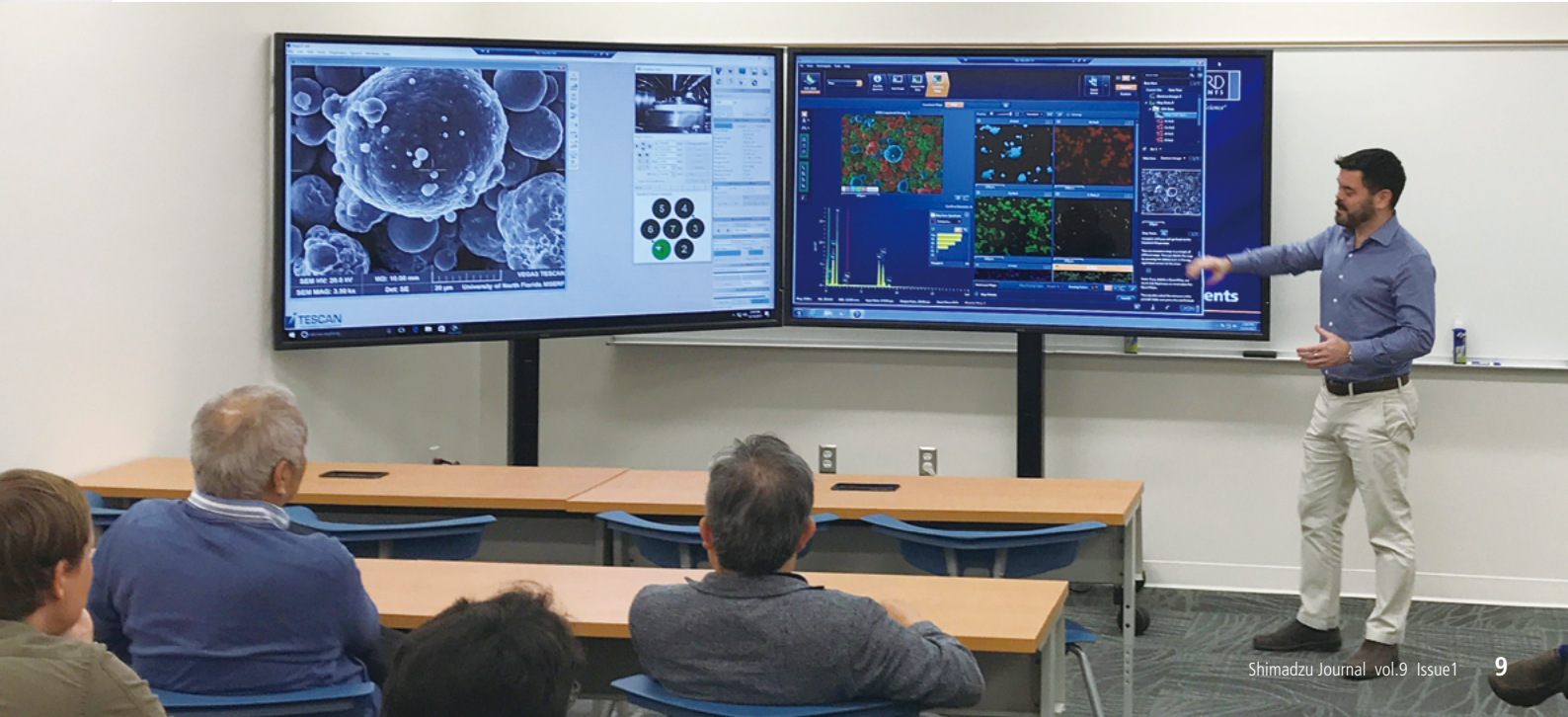
He is author of more than 350 publications in peer-review journals and 18 patents. Together with his research group, Prof. Karst has organized several international and national conferences, including the International Symposium on Chromatography in 2008, the Metallomics conference in 2011, the European Winter Conference on Plasma Spectrochemistry in 2015 and, most recently, ANAKON 2019 and DGMS 2020.

Interview 2 Interview with Dr. Paul Eason

"I truly felt like we aren't just a customer, we are working together to advance science"

Hello Dr. Paul Eason, thank you for taking the time to discuss the new UNF MedNexus project with us today. Can you please tell our readers a little more about yourself and your past and current research efforts?

I appreciate the opportunity to share more about all the great things going on in my research and here at UNF. I accepted a tenure track position at UNF 14 years ago as the only metallurgist and materials science PhD in the college. Over the course of my career here the development of materials characterization capabilities has remained a parallel effort with the pursuit of my own research in the structure processing property relationships of structural metals. As a trained electron microscopist, the creation of a characterization facility on campus was vital to the growth of my research. In my time here we have grown our research capabilities, hired new materials focused faculty and forged partnerships across departments and colleges, and we now have a group of 20 materials research focused faculty rom Engineering, Chemistry, Physics and Biology. I'm excited to tell the readers that out master's degree program in materials science and engineering is launching in the fall of 2021.

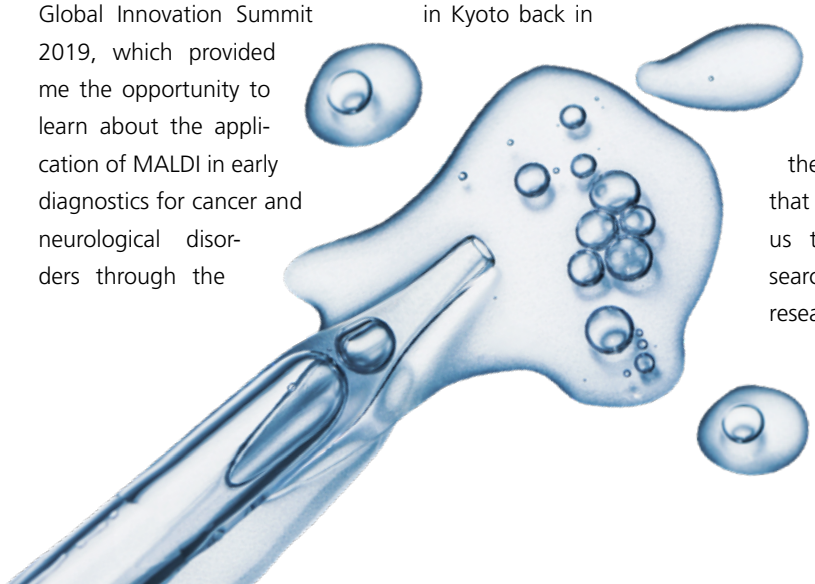


Dr. Paul Eason

How did the UNF & Shimadzu partnership come to fruition? What exactly is the new UNF MedNexus center and how was the MedNexus project conceived/developed?

UNF is a relatively young university with an emerging research enterprise. This provides us the opportunity to create our research capabilities and strengths on a relatively blank canvas. Approximately 10 years ago I saw the opportunity to create a shared mutli-user research laboratory that could serve the characterization needs of faculty across almost every STEM discipline on campus. My background and research are in structural metals for defense applications, but my broad materials science training gives me a deep appreciation for a breadth of imaging and spectroscopic technologies. As such, we created MSERF (the Materials Science and Engineering Research Facility) with key partners in the instrumentation community to provide the broadest set of research capabilities to UNF faculty and the region. Shimadzu was one of our first, and remains our largest partner in supplying the equipment in MSERF. Our primary Shimadzu contact, Paul Rementer, has done an amazing job facilitating our knowledge of new, cutting edge instrumentation, and working with us to strategically equip the center. As we acquired more Shimadzu instrumentation, our ability to support biomaterials research grew, as did my awareness of techniques like MALDI MS.

With Paul Rementer as my guide, I attended a Shimadzu Global Innovation Summit in Kyoto back in 2019, which provided me the opportunity to learn about the application of MALDI in early diagnostics for cancer and neurological disorders through the detection of specific proteins and molecules associated with the early onset of these diseases. As a metallurgist, my knowledge of proteomics is admittedly limited. However, the elegance of the MALDI technique as a pure materials characterization tool became instantly apparent to me. At the summit I was fortunate to meet David Graham, Ph.D., Director of the Johns Hopkins Molecular Determinants & Core, with whom I explored the idea of what this technology could bring to UNF and our facilities. This was a networking opportunity in its purist form. Jacksonville is fortunate to be the home of major research hospitals, including a MAYO clinic and MD Anderson Cancer Center and UNF is uniquely poised to provide medical workforce training and research support to these regional partners. Dr. Graham's center is located in St Petersburg Florida, creating more regional opportunity for partnership. Coincidentally, several weeks after I returned from the summit, I was approached by our administration about how MSERF could participate in a broad university medical research and training initiative, which became the UNF MedNexus. I immediately knew that creating a MALDI MS facility would allow us to support biomedical/biomaterials research while greatly enhancing our own research capabilities.



Dr. Paul Eason

How will the UNF MedNexus become a leader and catalyst in preparing high quality healthcare professionals?

Healthcare and research hospitals provide a significant contribution to the economy of Jacksonville and the surrounding Northeast Florida region. As a state funded institution, UNF's mission is to train the workforce of the region and to improve the lives of our citizens by advancing science and understanding. There exists a natural opportunity for UNF to take the lead on aggregated resources and talent from our own faculty and students to partner with our local hospitals and biomedical companies. The main goal of UNF MedNexus is to position us as the hub for medical training and research support to the surrounding hospitals, clinics and biomedical communities. By serving the research hospitals with state of the art equipment, UNF strengthens its partnerships with these renowned institutions, creating a pipeline for our students to work with some of the brightest minds in medical research. Ultimately UNF MedNexus will create a pathway for UNF students to work in the most advanced areas of medical research, and provide a source of research funding back to our faculty. Connecting technology like the MALDI MS system to frontline medical researchers provides our students the opportunity to train on the most cutting edge methods while working with the best minds in the industry.

What other benefits will this project bring to UNF and the rest of the world?

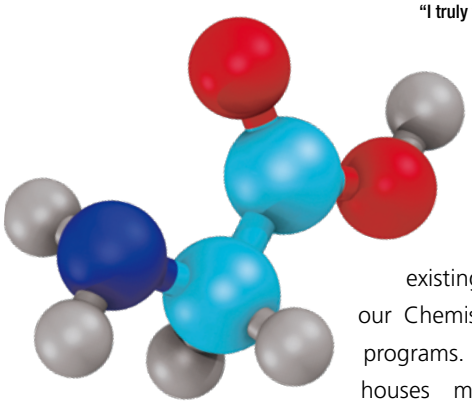
As UNF expands its research capabilities and continues to support STEM education, workforce development and research in the region, our reputation in the scientific community grows. Creating word class facilities like the MedNexus MALDI MS Suite elevates our capacity to attract the best students and faculty to keep this momentum going. This past year has shown us how vital a rapid response from the research community can be in the fight against global health crises. As proteomics and materials science merge to unlock the molecular mechanisms of disease and therapies the possible benefits to the world are simply too vast to speculate on. Nano scale characterization of materials is the future of both medicine and manufacturing, and our goal at UNF is to remain on the cutting edge of it, so we are prepared when the need for novel characterization pushes research into new directions.

What technologies will be integrated into this center and which Shimadzu platforms are/will be utilized? What applications and/or emerging clinical research fields will these platforms be applied to?

The suite of instruments that we are acquiring as part of MedNexus are being housed in our Materials Science and Engineering Research Facility (MSERF). MSERF was created in partnership with Shimadzu and other equipment providers to be a state of the art materials characterization facility to serve many STEM research programs on campus. The MedNexus MS Suite will house the MALDI 7090, MALDI mini and LCMS 9030. These instruments provide fairly comprehensive molecular identification methods, especially as they augment

MALDI mini-1

Dr. Paul Eason



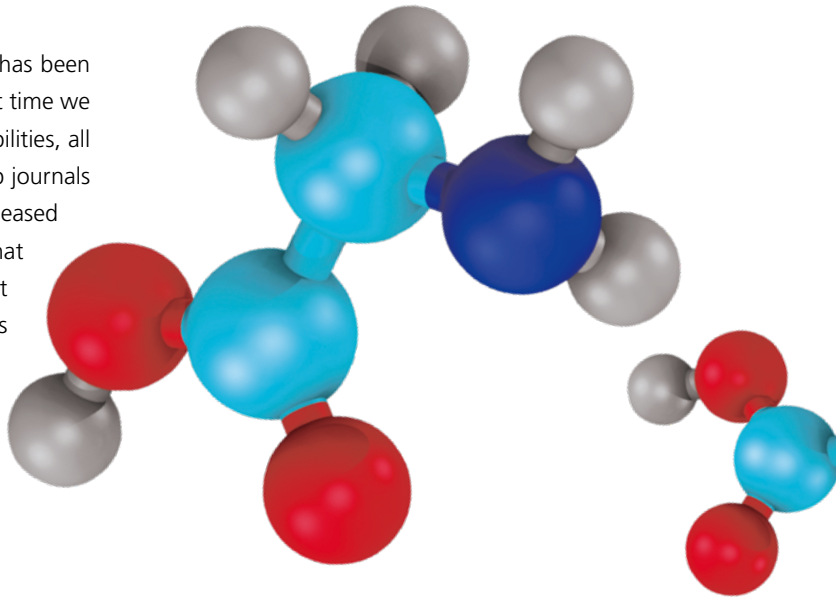
existing equipment in our Chemistry and Biology programs. MSERF currently houses multiple electron microscopes, and high resolution laser optical microscopes covering a breadth of imaging and chemical characterization capabilities. In addition to our Shimadzu UV3600 and AIM900 FTIR Microscope, we recently acquired the SPM9700 scanning probe microscope to create the ability to characterize materials at every length scale from atoms to centimeters. The MS suite fits like a puzzle piece into our existing techniques. Two members of the staff in MSERF obtained their PhD's in biomedical/biomaterials engineering, each of whom brings an unparalleled level of expertise to the application of nano-scale characterization. As the fields of medicine and materials engineering continually converge, I have no doubt we will continue to find new ways to support medical research in ways we can't yet imagine.

Why was Shimadzu selected as a preferred partner for this project? What are some of Shimadzu's strengths other than innovative, powerful and reliable instrumentation?

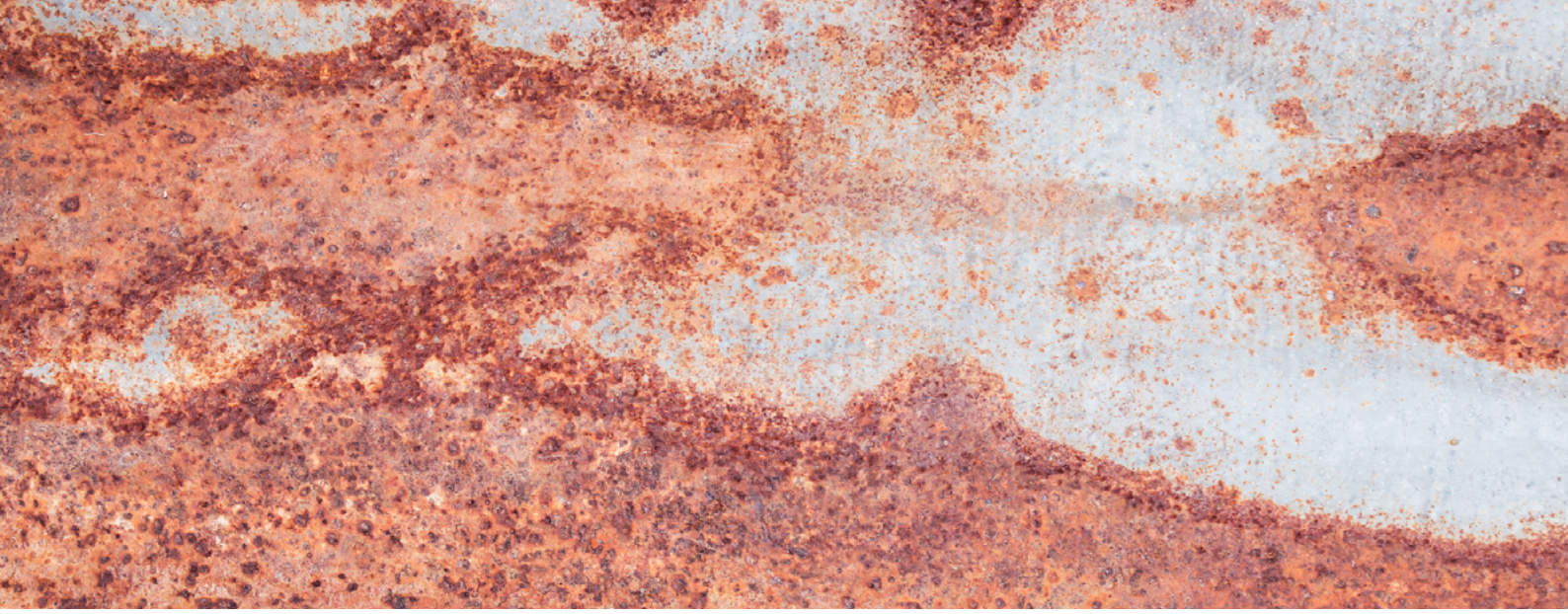
The partnership between UNF and Shimadzu has been strong and fruitful for almost five years. In that time we have grown the breadth of our research capabilities, all the while gathering data and publishing in top journals across many disciplines. We have been very pleased with the quality reliability and value that Shimadzu provides. There are few instrument suppliers that offer the variety of instruments the Shimadzu provides, which makes one the unique benefits the management of our service contracts. Preventative maintenance, calibration and responsive service overall has been a huge benefit of our partnership. We certainly feel like a valued partner in the endeavor and look forward to many more years and new instruments!!

Thank you again for your time today, are there any final thoughts that you would like to add in closing?

I would just like to take this opportunity to thank all of the engineers, scientists and sales people in Shimadzu for making our vision of a materials characterization facility a reality. Starting from a blank slate, we have been able to develop a broad array of equipment and methods that brings the most capability to our faculty. Our successful partnership paved the way for the UNF MedNexus MS suite, which is a huge evolutionary leap for the lab. I have had nothing but fantastic interaction and support from Shimadzu over the last 5 years. With my participation in the Global Summit in 2019, and the idea for the MS Suite coming to fruition so quickly, I truly felt like we aren't just a customer, we are working together to advance science.



▶ Dr. Paul Eason is the Associate Dean of the College of Computing Engineering and Construction and the Director of the Materials Science and Engineering Research Facility (MSERF). While his area of research is focused on structure-processing-property relationships in aerospace alloys, his administration of MSERF affords him the privilege of performing materials characterization in support of numerous disciplines at UNF and beyond. Dr. Paul Eason founded MSERF at UNF with legislative support, and forged the partnership with Tescan and Shimadzu to grow UNF's research capabilities across all stem disciplines.



Clinical Research

Characterization of the Rapid Corrosion of Silver Nanorods in Water and Implications on Sensing Applications

Stephen Stagon / Mechanical Engineering, University of North Florida, Jacksonville, FL USA
Lev Gasparov / Physics Department, University of North Florida, Jacksonville, FL USA
Christopher Mealer / Mechanical Engineering, University of North Florida, Jacksonville, FL USA / Shimadzu Scientific Instruments

Abstract Metallic nanostructures, such as silver (Ag) nanorods, are widely used in biological and chemical sensing applications that rely on the measurement of subtle changes of the optical response of the nanostructures in the presence of a target agent. The optical response of Ag nanorods, like other metallic nanostructures, is highly sensitive to morphology and surface chemical termination. In pristine condition, the optical properties of Ag nanorods and other metallic nanostructures are well documented in the literature. However, almost nothing is known of the structural and optical properties after exposure to solvents, buffered solutions, or similar environments in real applications. This Letter reports on the investigation into the effects of dissolved gasses, which are known to corrode bulk and thin film silver, in deionized water on Ag nanorods. Through SEM, UV-Vis, SPM, and Raman characterization rapid corrosion and morphological changes are observed within minutes when Ag nanorods are exposed to water with dissolved gases present. Conversely, almost no measurable changes are observed when the dissolved gases are removed from the water via boiling.

Keyword *Biological Sensing, Nanomaterials, UV-Vis Spectroscopy, Raman Spectroscopy, Electron Microscopy, Scanning Probe Microscopy*

Introduction

After nearly 30 years of laboratory scale research, metallic nanostructures are finally poised to propel existing and new technologies to meet critical needs in society[1-4]. One such current need is the sensitive, rapid, and low-cost detection of the SARS-CoV-2 virus, which is responsible for the devastating Covid-19 illness[5-6]. Classical detection techniques rely on the replication of the viral RNA and are expensive and slow[7]. In the literature, sensors that rely on the unique optical properties of metallic nanostructures have been widely demonstrated to be rapid and potentially inexpensive at scale[8-11]. These optical sensors typically function based on the plasmonic properties of noble metal nanostructures, like silver (Ag) nanorods or nanoparticles. The plasmonic properties of these nanostructures derive from a combination of length-scales less than 100 nm and appropriate electronic work functions[12]. The functionality of these nanostructures as sensors relies heavily on the surfaces of the metallic nanostructures and binding or proximity of the targeted material to the surfaces[13]. Commonly, the changes that happen within minutes to the surfaces in the presence of the targeted material are measured using optical ultra-violet visible spectroscopy (UV-Vis) or Raman spectroscopy[14].

Unlike ideal laboratory conditions, the conditions experienced by these nanostructures in sensing applications are diverse and not well studied. In biological sensing applications, many different materials, like phosphate buffered saline, are required to maintain

appropriate biological conditions[15]. The effects of these new materials on the morphological and chemical structures of metallic nanostructures has not been the topic of sufficient investigation in the literature. As such, observed differences and claims of detection of biological materials, like SARS-CoV-2, may be observations of changes to the metallic nanostructures caused by buffers and additives rather than the target molecule itself. For example, an extensive review of the literature shows that there has been no investigation into the effects of something as simple as the presence of dissolved gases in the water used in sensing experiments with metallic nanostructures, like Ag nanorods. However, it is well known in the literature and industry that dissolved oxygen in water can rapidly corrode silver[16].

In this technical Letter, a representative study, the authors demonstrate that significant differences exist in the optical reflection and Raman signals of rhodamine-6G (R6G), a classical organic target molecule, absorbed onto the surfaces of Ag nanorods when the samples were exposed to deionized water versus the same water that had been degassed via boiling. Through investigation using scanning electron microscopy (SEM), post operation and *in-situ* UV-Vis spectroscopy, scanning probe microscopy (SPM), and Raman spectroscopy the authors determine that significant chemical and morphological changes occur when Ag nanorods are exposed to water that has not been degassed, compared to negligible measured changes when they have been exposed to appropriately degassed water.

Experimental

Prior to presenting the results we will briefly describe the experiments performed in this investigation. The experiments involve the fabrication of Ag nanorods using glancing angle physical vapor deposition (GLAD PVD), preparation of components and materials used in the study, and then the characterizations carried out using SEM, SPM, UV-Vis spectroscopy, and Raman spectroscopy.

Nanorod fabrication

Ag nanorods are fabricated using GLAD PVD in a custom-built high vacuum chamber and thermal evaporation[13,18,19]. First, Corning glass slides are cleaned sequentially through sonication in acetone, ethanol, and deionized water for five minutes at each stage. The cleaned slides are then dried under a gentle flow of high purity nitrogen. After drying, the slides are placed onto a substrate holder at the top of the vacuum chamber. The vacuum chamber is a stainless-steel cylinder approximately 30 cm in height and 20 cm in diameter. The thermal evaporation source is located at the bottom of the chamber, approximately 25 cm from the slides. The slides are oriented at an incident angle of 87° relative to the source normal to achieve a glancing angle condition. The chamber is evacuated using a mechanical roughing pump and turbomolecular pump until a vacuum level of 5×10^{-5} Torr is reached and maintained for an hour to remove excess adsorbed water from the chamber. Evaporation is performed from a tungsten boat using 99.99% Ag pellets (Kurt J. Lesker Co.). The deposition rate is monitored via quartz crystal microbalance and controlled to 10 A°/s +/- 2 A°/s to a total film thickness of 500 nm. The samples are then held under low to medium vacuum and only removed prior to subsequent experiments.

Degassing of Water

High purity deionized water is obtained and half is degassed through boiling. To degas, the water is placed into a glass jar with a vacuum tight lid, removed during boiling, and heated to rapid boiling on a laboratory hot plate. The water is vigorously boiled for 15 minutes and then immediately sealed with the vacuum tight lid. The sealed container is then allowed to return naturally to room temperature. The boiling method has been shown to produce water with as little as 1 ppm of dissolved oxygen[17].

Electron Microscopy

SEM is performed on a Tescan Mira scanning electron microscope equipped with an Oxford energy dispersive spectroscopy (EDS). Samples are imaged using secondary electrons at magnifications up to 100k X under beam voltages of 10kV and working distances of 10 mm. Samples are imaged immediately after removal from vacuum and immediately after removal from exposure to degassed and non-degassed water with subsequent drying under a gentle flow of dry nitrogen.

SPM

SPM is performed on a Shimadzu SPM-9700 HT equipped with the 10-micron scanner attachment, fiber optic light source, and the high magnification CCD optical microscope unit. The SPM was performed on samples grown onto 12.7 x 12.7 mm corning glass substrates with the evaporated silver nanorod films. The rate of raster scanning was set to 1.00 Hz and the pixel setting was ran with

256 x 256. In the first test, the samples were taken directly out of vacuum and immediately imaged. In the second test, the samples were exposed to non-degassed water for two hours, dried under a gentle flow of dry nitrogen, and then imaged. Contact mode was first used to generate topographical maps of the sample surfaces. Next, the SPM was run the Kelvin Probe Force Microscopy (KFM) mode to analyze the surface potentials and give evidence of surface chemical changes. KFM is a noncontact variation of the SPM where the probe is held at a constant height above the sample and a voltage bias is applied to the probe and the surface is locally mapped.

UV-Vis

UV-Vis spectroscopy is performed on a Shimadzu UV-3600 equipped with the integrating sphere attachment. Spectroscopy is performed in reflection mode with the baseline being a freshly evaporated silver film 500 nm thick on the same type of cleaned Corning glass. The scans are run on the slow speed from 350 nm to 800 nm with a step size of 1.0 nm and slit width of 2.0 nm. First, samples that had been exposed to degassed and non-degassed water for set periods of time were measured after drying the samples in a gentle flow of dry nitrogen. *in-situ* experiments are performed on Ag nanorods that had been deposited onto the interior of polycarbonate cuvettes. As the baseline, a 500 nm silver film is deposited onto the interior back side of a polycarbonate cuvette and the cuvette is filled with degassed water to prevent rapid corrosion of the fresh film. To prevent deposition onto the other interior or exterior sides of the cuvette they are masked with Kapton tape, which is removed after deposition. Next, cuvettes that have Ag nanorods deposited onto the interior back side are measured immediately after filling the cuvette with degassed or non-degassed water, respectively. Measurements are taken at set time intervals to observe time dependent changes in reflective spectra.

Raman Spectroscopy

Raman spectroscopy is performed on a Horiba using Ag nanorod samples that had been sensitized in an aqueous solution of 10^{-5} M R6G. R6G solution was prepared in degassed and non-degassed water by mixing in an appropriate amount of R6G powder and stirring vigorously for one hour. The degassed solution was prepared by stirring the mixing solution while under light vacuum to prevent dissolution of air into the mixture. The samples were placed into the respective solutions for 12 hours, then rinsed five times with degassed deionized water and dried under a gentle flow of dry nitrogen. The instrument used is a Horiba T64000 Raman Spectrometer equipped with the microscope utility and liquid nitrogen cooled CCD detector. A 10 X Olympus objective was used to focus the 532 nm laser to a ~10 µm spot on the surface of the sample. The laser power does not exceed 10 µW. The entrance slit of the spectrometer is set at 200 µm. The accumulation time is set at 1 second with 25 accumulations per spectrum. The spectral range extends from 250 to 2250 wavenumbers and 10 scans are taken for each measurement.

Results

First, we present the morphological and chemical changes of the Ag nanorods after exposure for 168 hours to air, degassed water, and non-degassed water, Figure 1. The time of 168 hours is chosen to get visible changes in morphology. No appreciable difference is observable between the samples stored in air or degassed water. However, the sample stored in non-degassed water exhibits significant coarsening and loss of nanorod morphology. Additional microscopy was performed on sets after one hour and 12 hours and visible morphology changes, not shown here, which shows similar but less significant morphological differences. In passing, we note that EDS was also performed on the samples of Figure 1. Although the results cannot be directly interpreted due to beam penetration differences with varying density and chemical composition, qualitative results indicate an insignificant difference in oxygen between samples in air and degassed water and a significant increase in the non-degassed sample.

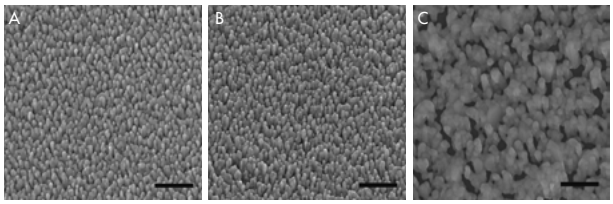


Figure 1. SEM image of Ag nanorods after exposure to (A) air, (B) degassed deionized water, and (C) non-degassed deionized water for 168 hours. The scale bars are 500 nm.

We next present the changes in optical response caused by the exposure to the varied conditions, Figure 2. Samples exposed to air for 12 hours are observed to have multiple absorption peaks and a strong absorption, owing to surface plasmon resonance excitation, centered around ~400 nm. Likewise, after exposure to degassed deionized water, labeled DG H2O in Figure 2, the intensity of absorption decreases but peak locations are unchanged. Alternatively, after exposure to non-degassed water for 12 hours,

labeled H2O in Figure 2, the Ag nanorods do not exhibit any of the secondary peaks and there is a significant decrease in the intensity of and blue shift of the main resonance peak. Surface plasmon resonance is considered to be the dominating factor in most sensing applications using Ag nanorods, and the decrease in resonance peak is expected to result in a decrease in sensing activity[17].

Next, we present the results of a time resolved *in-situ* experiment measuring the optical reflectance of Ag nanorods deposited inside a cuvette exposed to non-degassed water, Figure 3. Scans are taken every 10 minutes over the course of one hour, progressing in the direction of the arrow on Figure 3. It is noted that even within only one hour there is an observable change in reflective spectrum. This is significant as the area of decrease overlaps with the commonly used Raman laser lines of 473 nm and 524 nm, which may lead to changes in measured Raman signals.

Raman spectroscopy is also performed and presented in Figure 4 to correlate changes in the morphology, optical response, and performance as a sensor. 10 spectra each were measured on a sample exposed to non-degassed R6G solution for 12 hours, labeled H2O in Figure 4, and a second sample in degassed R6G solution for 12 hours, labeled DG H2O in Figure 4. While the overall Raman signal is stronger for the same in non-degassed solution, the measured peak to background ratios of both groups of measurements do not have statistically significant variation. We hypothesize that the corrosion of the Ag nanorods is primarily in the form of oxidation, which has been demonstrated to produce significant increases in metal-enhanced fluorescence in the literature. Further, the spread of spectral intensities from the non-degassed sample is approximately double that of the degassed sample. Spectral scatter and

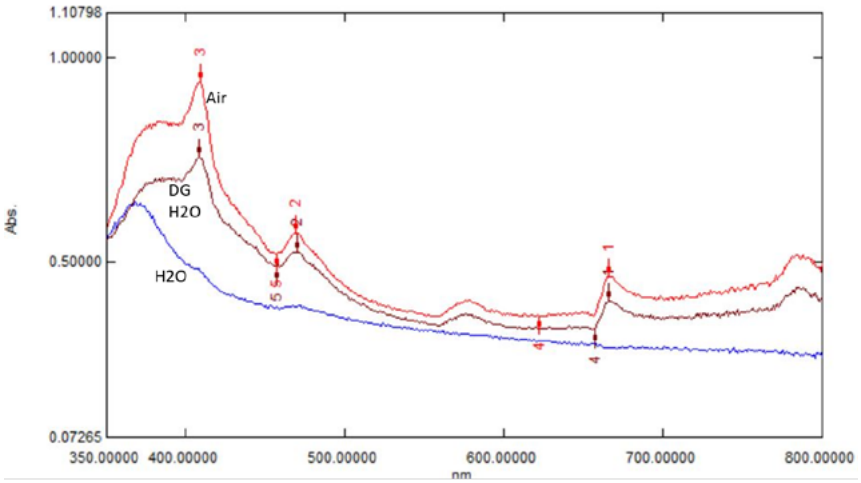


Figure 2. UV-Vis reflection spectra for Ag nanorod samples exposed to varied conditions for 12 hours.

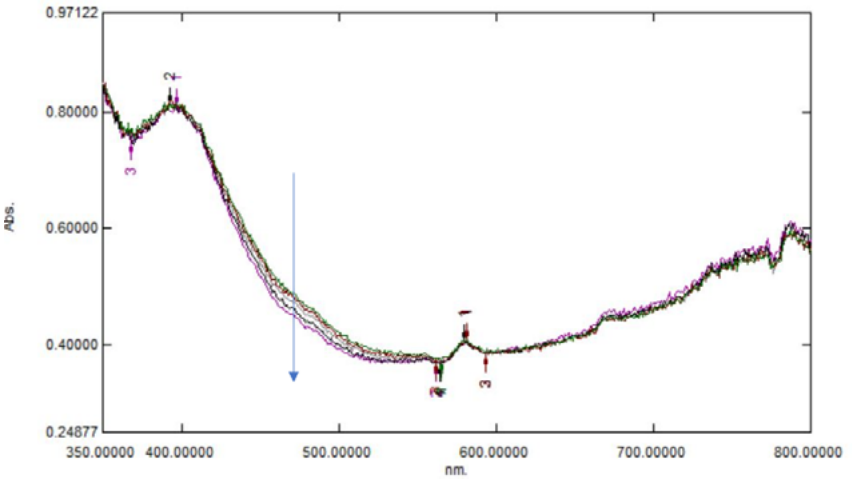


Figure 3. Time resolved UV-Vis reflection spectra for a Ag nanorod sample exposed to non-degassed deionized water. Spectra are taken every 10 minutes over one hour and progress in the direction of the arrow.

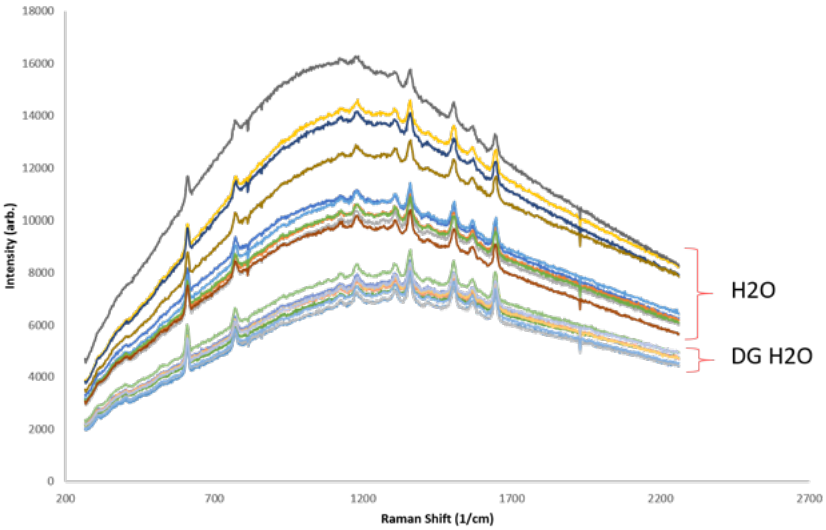


Figure 4. Raman spectra of Ag nanorods sensitized with R6G solution in non-degassed de-ionized water, labeled H2O in the Figure, and degassed water, labeled DG H2O in the Figure.

non-repeatability have been observed and discussed in detail for Raman spectroscopy using nanostructured substrates in the literature[14]. Hypothesized to be intrinsic to the non-periodic structure of the Ag nanorods grown from PVD, a significant contribution from rapid corrosion has likely been overlooked.

Finally, we present SPM measurements of the samples. Five locations were measured using the SPM in contact mode. The first set were measured on a sample immediately after removal from vacuum and represent a clean baseline. Next, the measurements were repeated with a sample that was submerged in non-degassed water for two hours. A representative comparison of the topographies is shown in Figure 5, where the baseline sample is on the left and the submerged sample is on the right. It is evident from the topographical images that even brief exposure to water with dissolved gases results in rapid and dramatic morphological changes to the surfaces.

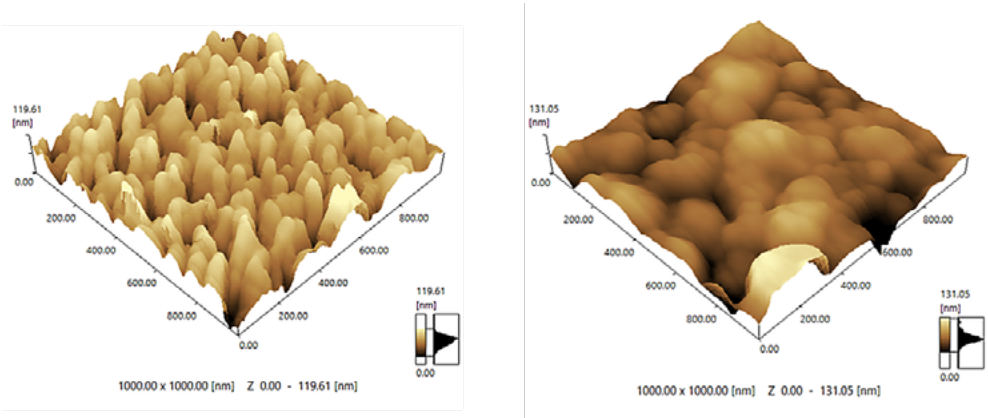


Figure 5: Left: Baseline Ag nanorods topography correlative to the SEM imaging A in Figure 1.
Right: Local mapping of topography for Ag Oxidized Nanorods after sitting in water for 2 hours.

The same samples were analyzed on the SPM using KFM to determine if the surfaces have chemically changed from the baseline state. The baseline, Figure 6 left, shows the potential measured on clean Ag surfaces without significant oxidation or corrosion. The tips of the nanorods are clearly evident in the potential plot. After soaking in the non-degassed water for two hours the average surface potential increases to greater than 3.0 V and there is no evidence for the presence of fine nanorod tips. Based on the measured change in surface potential, the authors hypothesize that the surfaces of the nanorods have undergone oxidation in the non-degassed water. This hypothesis will be tested with future transmission electron microscopy (TEM) analyses.

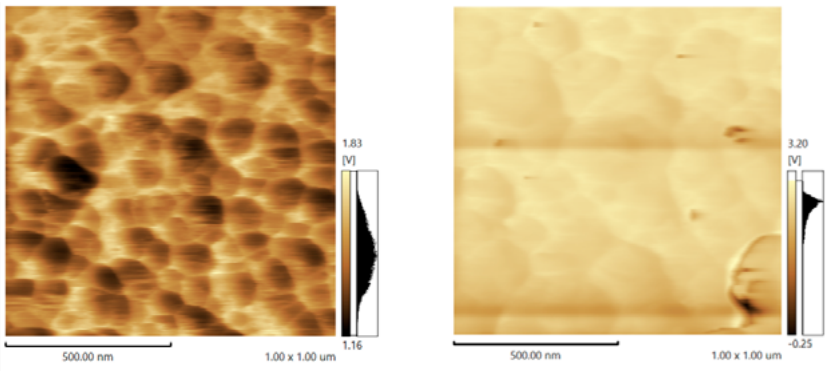


Figure 6: Left: Ag nanorods surface potential contour map taken immediately after removal from vacuum.
Right: Ag nanorod surface potential contour map taken after submersion in non-degassed water for two hours.

Conclusions

This Letter reports on the corrosion of Ag nanorods by dissolved gasses present in de-ionized water, which is commonly used in many nanomaterial sensing experiments without any consideration. Through SEM, UV-Vis reflection, Raman, and SPM characterization it is evident that dissolved gasses in water cause significant corrosion in Ag nanorods, leading to significant morphological and optical response changes on the timescale of hours. These results motivate further investigation into the underlying mechanisms dominating observed spectral changes in nanostructured metals when they are used as biological sensors. Decoupling of spectral changes caused by experimental artifact and unanticipated mechanisms is essential to improving these sensing technologies.

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https://www.ssi.shimadzu.com/about/shimadzu-academic-program.html

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Clinical Research

Towards fast, routine blood sample quality evaluation by Probe Electrospray Ionization (PESI) metabolomics

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Abstract The unique advantages of PESI-MS to deliver full MS spectra within minutes at ambient conditions enables routine, high-throughput applications. A still unresolved obstacle is that pre-analytical sample handling strongly impacts the samples composition. In health care and research, pre-analytical errors often remain undetected and disrupt diagnosis, treatment, clinical studies and biomarker validations incurring high costs. This proof-of-principle study investigates the suitability of PESI-MS for robust, routine sample quality evaluation.

Here, human blood (n=50) was processed immediately or with a time delay of 3 h to simulate the most common pre-analytical issue of transportation time from beside to laboratory. The sample preparation method was developed to deliver ready-to-measure extracts in <8 min. PESI-MS spectra were measured in both ionization modes in 2 min from as little as 2 µl plasma allowing 3 replicate measurements. The mass spectra delivered 1200 stable features covering a broad chemical space with major metabolic classes (e.g. fatty acids, lysolipids, lipids). The time delay of 3 h was well predictable from 18 features with AUC > 0.95 with various machine learning and was robust against loss of single features.

Our results serve as first proof for the unique advantages of PESI-MS in sample quality assessments. The results pave the way towards a fully automated, cost-efficient, user-friendly, robust and fast quality assessment of human blood samples from minimal sample amounts.

Keyword *PESI, Probe electro spray ionization, minimal sample amount, sample quality control, method development, metabolomics*

Introduction

Mass-spectrometry (MS) is a sensitive, valuable analytical tool in many different fields and substantially advanced metabolomics. Metabolomics is defined by measuring small molecules (<2000 Da) which reflect the biological phenotype and allow mechanistic insights, identification of new therapeutic targets or development of diagnostic biomarkers. Typically, MS-based metabolomics relies on liquid or gas chromatography coupled to high resolution mass spectrometers to increase specificity, sensitivity and chemical coverage[1]. Such high-quality metabolomics set ups need extensive expert knowledge, have long measurement times, produce large amounts of data, require complicated analyses for successful research and can struggle with large sample numbers[2].

In contrast, PESI-MS omits chromatography by directly capturing tiny sample amounts with a needle tip from which electrospray is generated in ambient conditions by applying a high voltage[3]. This simplifies handling immensely, shortens measurement times to minutes and allows previously impossible application scenarios[4–6], especially where robust, routine and high-throughput measurements are needed. Sample quality control is one such setting where metabolomics has shown great scientific promise but has not yet entered routine application.

High-quality biospecimens are crucial for reproducible results in *omics or biomedical research, for correct clinical routine diagnostics and for successful biobanking. Currently specific types of preanalytical issues are tested with specific methods[7]. These specific methods are not comprehensive enough to cover the most frequently occurring pre-analytical error sources in one swift measurement. NMR and MS-based metabolomics has shown great capability to detect various pre-analytical errors in one measurement[8–14]. However, costs and complexity precede a wide-spread routine application, despite the numerous benefits of metabolomics for sample quality control.

PESI-MS could overcome this barrier through its unique advantages and capability to deliver full mass spectra within minutes. In our set-up PESI was coupled to a single-quad mass spectrometer, purposely omitting and more sophisticated detectors in order to (1) decrease instrument acquisition and maintenance costs, (2) increase the instruments robustness and operating usability for personnel without extensive MS expertise, and (3) decrease measurement time per sample.

In this proof-of-principle study we concentrated on the single, most common preanalytical issue, the time delay of blood to plasma processing. Our aim was to investigate if PESI-MS is able to robustly classify time delays of 3 h from immediately processed sample.

Materials & Methods

Plasma preparation and PESI-MS measurement

The study was conducted in adherence to the Declaration of Helsinki and was reviewed by the ethical committee of the Medical University of Graz, Austria (31–116 ex 18/19, 16.01.2019). Study details are available at **https://www.drks.de** DRKS-ID: DRKS00024807. Blood samples were donated by 50 volunteers (24 female, 26 male, age 18–90, BMI≥ 18.5 kg/m^2) and were collected within 3 weeks (for details refer to Bordag et al 2021[15]). From each volunteer one sample was immediately centrifugated, while the second was delayed for 3 h.

Plasma aliquots were thawed in a water ice bath (0°C) for 15 min. 10 µl of each plasma sample aliquot was pooled for quality control (QC) and split into 20 µl aliquots. From each sample, QC aliquot and blank a volume of 20 µl were precipitated with 380 µL extraction solution to a final concentration of 10 mM NH_4Ac, 70% MeOH and 5% DMSO. Precipitates were frozen at -80°C until measurement within 3 h after thawing of samples. The measurement was split into 3 batches. Blanks and QC were measured repeatedly throughout the sequence. Precipitated extracts were thawed in 1–2 h sub-batches in water ice baths and precipitates were removed by centrifugation for 5 min at 4°C with 12.000 rpm.

Supernatants were kept in a water ice bath until measured with the DPiMS-2020 (Shimadzu Corporation, Kyoto, Japan). Per measurement 10 µl were deposited on a sample plate and all measurements were replicated until at least two valid TIC patterns for each ionization mode were recorded. TIC patterns were defined as invalid when TIC spiking stopped before at least 30 s of the mode were measured (refer to Fig. 1 for invalid TIC pattern example). For instrument settings refer to Table 1. For each replicate a fresh needle (silicon coated, 18529A1, Shimadzu Corporation, Kyoto, Japan) and sample plate (11A9722418115OMS, Shimadzu Corporation, Kyoto, Japan) was used.

Table 1. Instrument settings for the PESI measurement.

IONIZATION		
Needle position	-37 mm	
Outage time	200 ms	
SAMPLE TAKE		
Needle position	-46 mm	
Outage time	50 ms	
Speed	250 mm/s	
MEASUREMENTS		
voltage segment	Electric potential	Time
1 – Corona	+4.00 kV	3.6 s
2 – neg mode	-4.25 kV	30.0 s
3 – Corona	-4.50 kV	3.6 s
4 – pos mode	+2.75 kV	30.0 s
m/z range	10-2000 m/z	
Scan speed	5000 u/s	

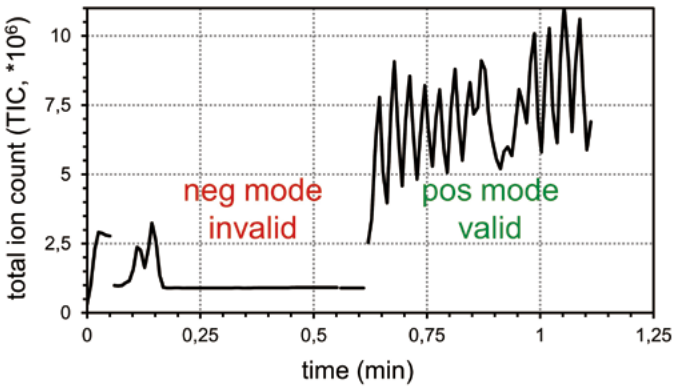

Figure 1. Example graph of a PESI measurement diagram. The negative mode (neg mode) TIC pattern is invalid, the positive mode (pos mode) is valid.

Data extraction and analysis

Mass spectra of all measurements were exported in JCAMP-DX format[16] for each voltage segment. Features were extracted with eMSTAT 1.0 (Shimadzu Corporation, Kyoto, Japan) separate per ionization mode but for all measurements at once by binning with a m/z tolerance of 0.75Da. The intensity threshold was 0.1% for neg mode (voltage segment 2) and 0.01% for pos mode (voltage segment 4). Resulting intensities for each sample (in rows) and each m/z binned feature (in columns) were copied to Microsoft Excel (2013), combining both ionization modes for each measurement resulting in 4702 features.

Further data extraction and pre-processing was performed with Tibco Spotfire. All invalid single modes were excluded from any further calculations. All valid replicate measurements of a sample were averaged and the average was $\log_{10}$-transformation. Low quality features were filtered according to signal intensity (neg $>1*10^3$, pos $>9*10^3$), technical variability (relative standard deviation in QC <50%), missing data (<30%) and blank load (<50%).

Data visualization and statistical analysis was performed with R[17] (v3.5.3, packages *stringr, dplyr, readxl, openxlsx, nlme, emmeans, ggplot2, ggpmisc, pheatmap, RColorBrewer, colorspace, dendsort, missMDA, mixOmics, MetaboAnalystR*), Tibco Spotfire (v7.11.1) and the Orange data mining toolbox[18].

Principal component analysis (PCA) was performed centered and scaled. Orthogonal projections to latent structures discriminant analysis (OPLS-DA) was performed centered and scaled to unit variance with a standard 7-fold cross validation for the classification factor *time_delay*. Model stability was additionally verified with 1000 random label permutations and models with $Q^2>50\%$ were considered significant.

Five common machine learning classifiers with standard configuration as offered by the Orange data mining toolbox were used. Feature importance was calculated for all 1200 features based on five criteria (ANOVA, Gain ratio, Gini, Info.gain, χ^2) and the top 18 features were used for the five machine learning classifiers.

Results & Discussion

In this study we obtained blood plasma samples from 50 volunteers, developed a measurement method covering both ionization modes and used advanced machine learning analysis to conclusively show the potential of PESI-MS for routine sample-quality determination.

One-step precipitation delivers both ionization modes in one run

Blood samples were obtained from 50 volunteers, subdivided into a biologically homogeneous and heterogeneous group (refer to Fig. 2A). The subgrouping was used to create samples with lower biological variability to increase statistical power for detection of sample quality biomarkers. However, this approach failed to improve biomarker detection. Consequently, future studies could omit the cumbersome step of subdividing cohorts when searching for plasma quality biomarkers. From each volunteer one blood sample was processed into plasma immediately (*time_delay = 0 h*), while a second sample was delayed for 3 h (*time_delay = 3 h*).

Metabolites were extracted by a simple one-step 70% MeOH precipitation with 10 mM NH_4Ac and 5% DMSO and the diluted supernatants were measured with the PESI-MS (see Fig. 2A). The whole sample preparation can be performed manually with standard laboratory equipment in less than 8 min total time, including the 5 min centrifugation step. This time can be reduced to >1 min by switching to filtration. For the 2 min PESI-MS measurement 10 µl extract sufficed, so that 2 µl plasma enabled three replicates with the applied 1:20 dilution during precipitation.

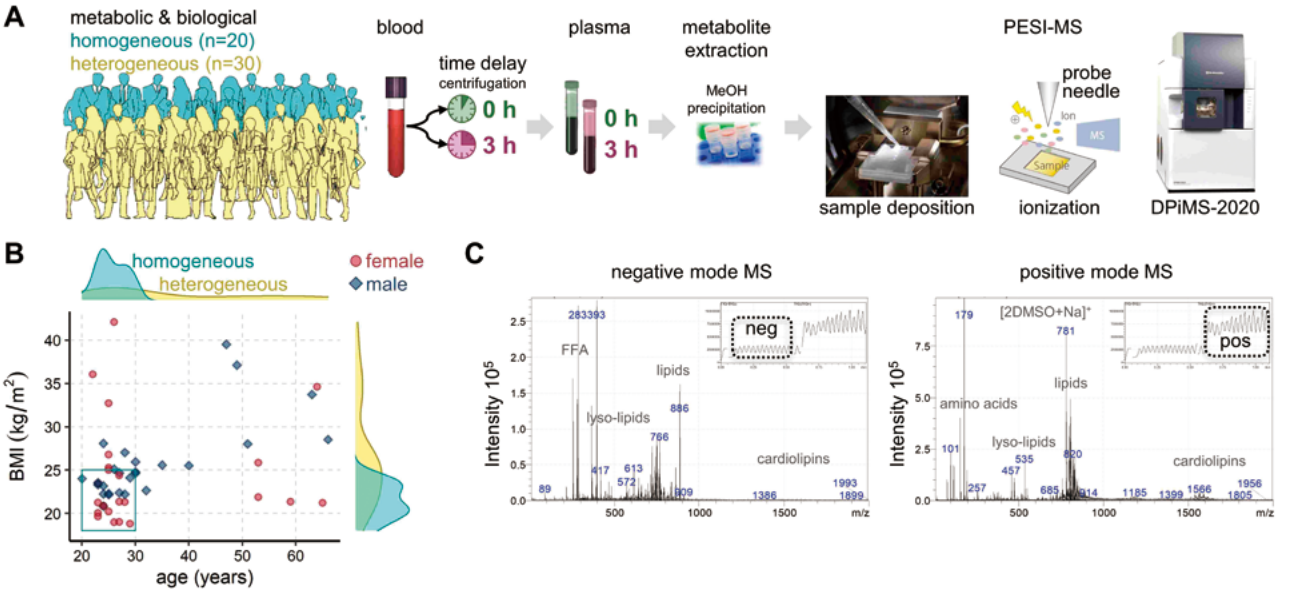

Figure 2. Overview of cohort and measurement workflow.
A: In total 50 volunteers donated blood which was either processed to plasma immediately 0 h or after 3 h (factor termed *time_delay*) simulating a typical transportation time from bed-side to laboratory. Metabolites were extracted by MeOH precipitation and 10 µl supernatant were measured with a DPiMS-2020. Figures of the sample chamber, probe electrospray ionization and DPiMS-2020 table-top instrument are a courtesy of Shimadzu Corporation. B: Age and BMI distribution within the cohort. The age and BMI inclusion cut-off for the homogenous group is marked by a cyan box. C: Example full mass spectra for each ionization mode with the TIC pattern provided as inset. Possible metabolite classes based on mass ranges were added for a tentative orientation.

Instrument settings were optimized to deliver stable results from both ionization in one run covering each the mass range from 50–2000 Da (refer to Fig. 2C). For easier orientation, mass ranges were tentatively marked with one possible metabolite class, which would be expected to exist in sufficient concentration in plasma extracts.

A total of 4702 features were available after combination of both modes. Both ionization modes contributed roughly half of all features and feature mass ranges partially overlapped between both modes (refer to Fig. 2C). Additionally, in each mode features were found in mass ranges not detected in the other mode, e.g. amino acid masses in pos mode, FFA masses in neg mode.

Low quality signals were filtered and excluded, than all valid replicates were averaged and data was $\log_{10}$-transformed. The technical variability (median relative standard deviation RSD) was 34.6% for the filtered 1200 features and thus higher compared to 5–15% in sophisticated metabolomics methods. A reduction of technical variability will be beneficial for future robust high-throughput application. Accordingly the use of internal standard should be investigated, for which others reported an RSD below 20% with PESI-MS[6]. Additionally, automatization and optimization of sample preparation will further decrease technical variability.

Time delay in plasma preparation is predictable with selected features

The main aim is future routine application, therefor analysis was first focused on selecting features of high importance in determining time delays of plasma preparation. The selection was based on five diverse criteria (ANOVA, Gain ratio, Gini, Info.gain, χ^2) to avoid overlooking possibly well performing features when concentrating on one selection criteria. This approach selected 18 features which showed clear group separation between *time_delay* 0 h and 3 h along the first principal component in the unsupervised, multivariate PCA (refer to Fig. 3A, B). The difference in *time_delay* was confirmed to be highly significant with OPLS-DA (Q^2>70%, refer to Fig. 3A). Five other common machine learning approaches were used to classify time_delay of plasma preparation. All five performed consistently excellent with an AUC>0.95 (refer to Fig. 3E).

The selected 18 features were investigated in more detail with a heatmap and single scatter plots (refer to Fig. 4). Most features (16) increased with *time_delay* and only two features showed a decrease (neg 812.1, neg 787.84). Only one feature stemmed from the pos mode (pos 974.8), all other features were negative ions. The neg features consistently showed larger differences with *time_delay*.

Obviously, the concentration on one ionization mode would halve measurement time, doubling throughput and will thus be

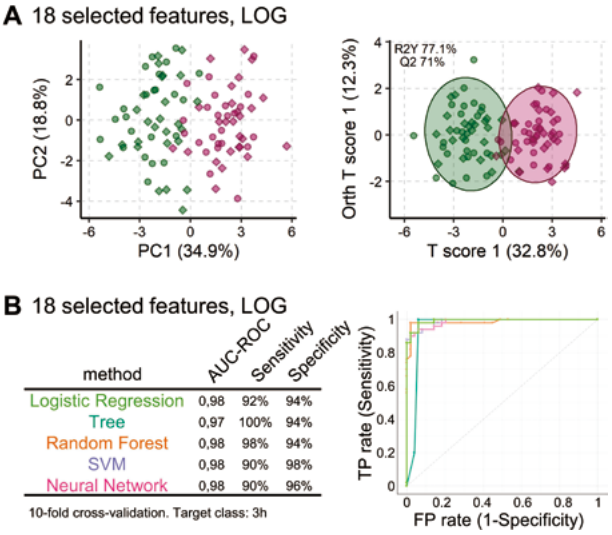

Figure 3. Plasma preparation delay is detectable from selected PESI features with high specificity.
A: Both PCA and OPLS-DA scores plot show a clear and highly significant difference for *time_delay* 0 h vs. 3 h, when based the 18 most important features (LOG). B: All five applied machine learning algorithms delivered excellent predictions of *time_delay* (AUV>0.95) with no false negatives and very similar ROC curves.

very beneficial for future routine applications. Nevertheless, we would not yet recommend to abandon the pos mode. The combination of both modes notably expands the covered chemical space. This could prove crucial when expanding search of sample quality biomarkers into other pre-analytical factors such as freeze thaw cycles, hemolysis, micro-clotting, long-term storage or into other sample types such as serum or urine.

Only one feature stemmed from the pos mode (pos 974.8), all other features were negative ions. The neg features consistently showed larger differences with *time_delay*. The neg mode alone would suffice to predict the *time_delay*. Nevertheless, we would not yet recommend to abandon the pos mode in future studies. The risk is too high that highly predictive features for other sample quality factors (e.g. freeze thaw cycles, hemolysis) could be overlooked because the combination of both modes notably expands the covered chemical space. However, in routine application obviously the reduction to one mode would be very beneficial because measurement time would be halved, doubling throughput.

The best performing feature neg 88.99 stems probably from lactate. Lactate is also well known to increase with time as an end product of erythrocyte driven glycolysis[8,10]. The neg 88.99 performance alone would suffice for very good prediction of a 3 h time delay. Prediction were as good without the neg 88.99, showing that the suggested features form a pattern robust against single feature failures. Robustness against single feature failures is important for routine high-throughput applications reducing the need for repeated measurements. Additionally, medical conditions possibly

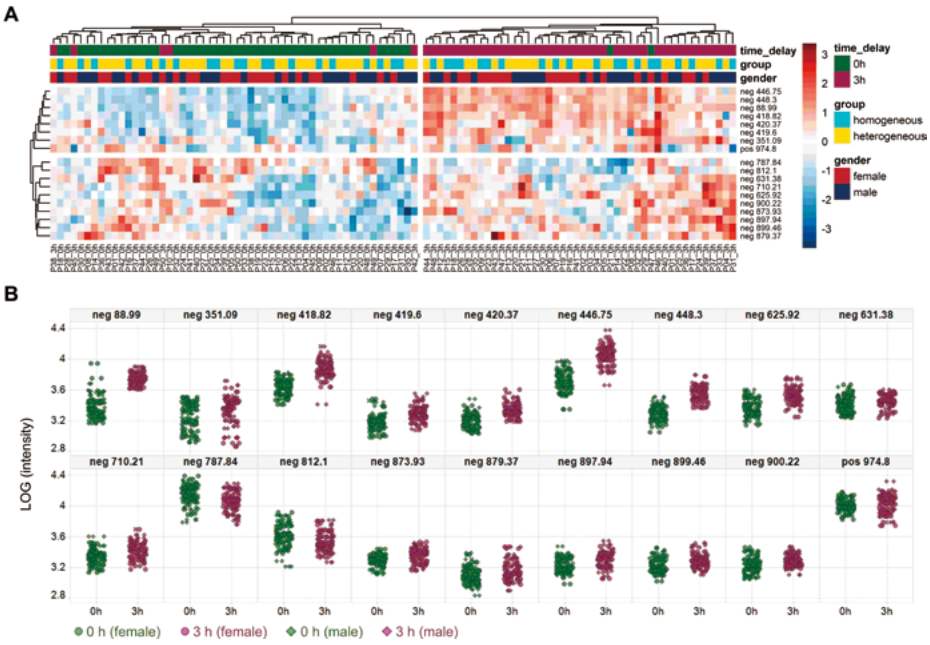

Figure 4. Heatmaps and plots of the 18 selected features in LOG data.
A: Heatmaps with hierarchical clustering underline the clear difference induced by *time_delay* in the 18 most important features. There are no systematic differences between study subgroups or genders. B: Scatter plots showing that from the 18 features, most (16) increased after the 3 h *time_delay* while only two feature levels decreased.

invalidating single features would not impede a sample quality determination based on a multi-feature read-out.

Our aim was to determine whether PESI-MS has the potential to determine sample quality, for which one pre-analytical issue was used as proof-of-principle. Our results demonstrate that PESI-MS spectra contain multiple robust biomarkers. Additionally, many other stable features were detected which renders detection of robust biomarker for other pre-analytical highly likely.

Conclusions

Our results provide a proof-of-concept that PESI-MS is a promising technology for fast and comprehensive quality control of blood samples.

The single-step MeOH precipitation delivered ready-to-measure extracts in <8 min when manually performed and could be considerably speed-up with filtration and automatization. As little as 2 µl plasma sufficed for PESI-MS spectra in both ionization modes in 2 min with 1200 stable features covering a broad chemical space. The time delay of 3 h was well predictable with five common machine learning approaches based on 18 selected features with an excellent AUC > 0.95 and was robust against failure of single features. Although for a future high-throughput application more optimization, reduction of noise and automatization are needed, our results demonstrate the unique advantages of PESI-MS. The results pave the way towards a fully automated, cost-efficient, user-friendly, robust and fast quality assessment of human blood samples from minimal sample amounts.

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Clinical Research

Introduction of HPLC and LC-MS/MS methods for the quantitative analysis of therapeutic drugs for COVID-19

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The number of people infected with SARS-CoV-2 continues to rise rapidly throughout the world. The SARS-CoV-2 virus infects everybody regardless of age and sex, and causes COVID-19, a disease that affects many organs of the body. Unfortunately, new medications that treat COVID-19 have yet to emerge.

At the same time, existing drugs are being tested for their efficacy to treat COVID-19, and Ministry of Health, Labour and Welfare (Japan) has already approved several drugs now relied on doctors in clinical settings. The relationships between monitoring blood concentration levels of these drugs and progress of treatment, or interactions between drugs taken for underlying conditions and drugs intended to treat COVID-19, have yet to be elucidated.

For antibiotics and other drugs, immunological methods of analysis are normally used to measure blood concentration levels. However, given the rapidly rising numbers of people infected with SARS-CoV-2 and that many patients are administered multiple drugs, high performance liquid chromatography (HPLC) or triple quadrupole liquid chromatography / mass spectrometry (LC/MS/MS) would appear superior to immunological methods of analysis , because these techniques can measure blood concentration levels of multiple drugs simultaneously. For this reason, expectations and demand for HPLC and LC-MS/MS are on the rise.

This article introduces applications for two therapeutic drugs requested from customer in clinical. The first application relates to remdesivir. This drug developed by Gilead Sciences, Inc. treats to Ebola hemorrhagic fever. Remdesivir was the first drug approved for treatment of COVID-19 in Japan and is now used clinically for this purpose. Remdesivir is a prodrug with antiviral activity against single-stranded RNA viruses. Since remdesivir is partially metabolized in the body into its active form GS-441524, the analytical method was developed for measurement both remdesivir and GS-441524 simultaneously.

Simultaneous Analysis of Remdesivir and Metabolites in Human Plasma

Simultaneous Analysis of Remdesivir and Metabolites in Human Plasma Using Fully Automated Sample Preparation LC/MS/MS System

The second application highlights favipiravir, an anti-influenza drug developed by FUJIFILM Toyama Chemical Co., Ltd.. Favipiravir is sometimes administered in combination with other

drugs, such as nafamostat (an anticoagulant). While the development of products containing multiple drugs in a single dosage form is also expected, in this second application, analytical conditions were explored for quantitative analysis of just favipiravir.

Analysis of Favipiravir in Human Plasma

Analysis of Favipiravir in Human Plasma Using Fully Automated Sample Preparation LC/MS/MS System

Envisioning that hospitals will use a single analytical system (LC-MS/MS) for multiple investigations, the applications utilized the same type of column and other analytical conditions whenever possible.
In addition, when creating a quantitative analysis method that includes LC-MS/MS, a deproteinization pretreatment step is essential for measuring drug concentration levels in blood. To meet customers' needs, for each application in this article, both manual and automated sample pretreatment methods were used.

This article also describes an HPLC-based quantitative analysis method for favipiravir that uses manual sample pretreatment and a fluorescence detector to detect concentrations in the μg/mL range.

Quantitative Analysis of Favipiravir Spiked in Plasma Using by HPLC

Learn more about the latest application.
Fully automated quantification of Meropenem, Tazobactam, Piperacillin and Dexamethasone in plasma

Learn more about Shimadzu's response to the COVID-19 pandemic
https://www.shimadzu.com/covid-19/

Shimadzu Selection

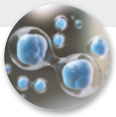
These article were selected by Shimadzu. Relating Clinical analysis and development, they are from posters presented at ASMS 2020. They feature a variety of instruments we produce and include cutting-edge technologies. Please obtain the articles of your interest through the links on the titles.

Evaluation of automated quantitative analysis of the doubly charged glycatedβ-hemoglobin by MALDI-TOF MS

This approach opens a new world to time and cost-effective analysis of HbA1c within the clinical chemistry. Long-term control of the glycemic state of haemoglobin is the most important and reference tool for the management of diabetes. The Dutch diabetic association recommends monitoring the level of glycated haemoglobin (HbA1c) two to four times a year, depending on the type of diabetes. Several procedures and numerous commercial instruments, based mainly on chromatographic separation methods, are currently available for the determination of HbA1c in blood samples. In this study we have developed a method for automated quantification of HbA1c with MALDI-TOF.

Fully automated LC-MS/MS method to assess DPD deficiency in Cancer treatment with 5-FU

Fluoropyrimidines (5-fluorouracil or capecitabine) are anticancer drugs used in nearly 60% of chemotherapy treatment. It is known that they can lead to severe or lethal toxicities in case of dihydropyrimidine dehydrogenase (DPD) deficiency, therefore it is highly recommended to check for that DPD efficiency status. In France, health authorities recommend the determination of uracil concentration to guide dosing of fluoropyrimidines. Numerous LC-MS/MS methods have been proposed but they include complex liquid-liquid or solid-phase extraction procedures. To answer to the need of high throughput and robust analysis, our objective was to develop a method where the extraction was carried out by a programable liquid handler robot directly coupled to a LCMS/MS system.

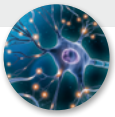


Monitoring of embryonic stem cell differentiation trajectories by intact cell mass spectrometry

Human embryonic stem cells (hESCs) are promising tools for diseasemodeling, cell therapy, bio-industry or drug development. However, longterm cultured hESCs finally develop hidden phenotypic changes, cumulatively acquire various alterations on both the genetic and non-genetic levels and despite advanced culture techniques, the culture-adapted clones with unwanted properties clones are inevitably selected. However, these changes could remain unnoticed until they alter the genome, karyotype or cell phenotype, even in case of the high expression of stemness-associated transcription factors, or their differentiation capacity, or a typical morphology. Furthermore, molecular, genetic, and/or light-microscopy analyses can fail in the case of the genetically or karyotypically silent changes that are evoked in cultured cells. Thus, recent quality control approaches often suffer of low sensitivity or may produce biased output. Therefore, there is an ongoing need for sensitive, robust, feasible and affordable methods revealing abnormalities in cell phenotype.

Cost effective and rapid method for simultaneous determination of vitamin B12, 25-Hydroxyvitamin D2 and D3 from plasma using LC-MS/MS

Lifestyle disorders are manifesting as deficiency of vitamin B12 and vitamin D. Clinicians have always corelated vitamin B12 and D deficiencies to heart diseases and many other health problems. This has led to the demand of simultaneous determination of vitamin B12, 25-hydroxyvitamin D2 and D3 in plasma. To make the analysis cost effective and rapid, in this method the molecules of different polarity are been extracted and processed simultaneously.

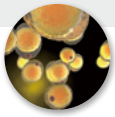


A multiplex targeted Mass spectrometry approach for the quantification of synuclein proteoforms in human biological fluids

Innovative multiplex and targeted mass spectrometry method development for the quantification of the alpha, beta and gamma synuclein in biological samples as CSF and plasma in the context of neurodegenerative diseases. In the synucleopathy field, one of the main goals remains to discover biomarkers allowing to discriminate between Parkinson's disease, Lewy Body dementia or Multi System Atrophy. For this purpose, alpha synuclein has been intensively studied due to its major presence in aggregates such as Lewy bodies, hallmark of these neurodegenerative diseases [Vinnakota et al, 2018; McLean et al, 2012]. Alpha synuclein and its proteoforms are present at different levels in brain and CSF indicating that they might be relevant biomarkers. [Schmid et al, 2013; Otto et al, 2019; Zetterberg et al, 2019]. In this context, our objective is to develop a mass spectrometry multiplex method to quantify proteoforms of the synucleins family (alpha, beta and gamma) in human biological fluid (CSF, plasma).

Evaluation of a rapid LC-MS/MS method to measure simultaneously IDUA and IDS enzymes activities in dried blood spots

A novel and rapid LC-MS/MS method was developed to simultaneously measure the activities of lysosomal enzymes for newborn screening. Mucopolysaccharidoses (MPSs) is a group in lysosomal storage disorders (LSDs) caused by a deficiency of lysosomal hydrolases responsible for the catabolism of glycosaminoglycans (GAGs). Some techniques such as fluorometric and mass spectrometric assays have been developed to measure these enzyme activities for the purpose of newborn screening.The use of mass spectrometric techniques has exhibited advantages over the other techniques in the ability to multiplex several enzymes in one assay. In this study, we report a novel method using tandem mass spectrometry that is capable of simultaneous measurement of the activities of the MPS enzymes including IDUA (MPS I) and IDS (MPS II) in a short time scale. In this presentation, the developed method is detailed.



Untargeted LC-MS/MS-based metabolic phenotyping applied to the CD248 knock out mouse model

Untargeted LC-MS/MS is a powerful tool by which to identify metabolic phenotypes. Here we applied metabolic phenotyping analysis to the CD248 knockout mouse model. CD248 is a transmembrane glycoprotein, expression of which is markedly upregulated in a considerable number of disease models including tumor growth, inflammation and injury-induced fibrosis. In human clinical studies, CD248 expression is upregulated in the fat cells of patients with diabetes, conversely, CD248 expression reverted to a normal range when obesityassociated diabetes was reversed through weight loss. In this work, an untargeted LC-MS/MS metabolic phenotyping analysis, using a reverse-phase LC separation and high resolution accurate mass (HRAM), was applied to a CD248-/-mouse model following high fat diet (HFD) feeding to study the effects of diet on serum metabolite profiles.

Expanding capabilities in routine clinical toxicology screening using HRAM QTOF

Low resolution mass spectrometry with triple quadrupole MS/MS systems deliver highly sensitive, robust, reproducible and proven technology platforms for targeted clinical toxicology screening and identifying unknown compounds in patient samples. However, high resolution accurate mass-spectrometers (HRAM) provide support for targeted and untargeted workflows in which no spectral data are lost and retrospective data analysis can be supported. To reduce false positive reporting a HRAM data-independent-acquisition MS and MS/MS method was used together with a HRAM MS/MS clinical toxicology library for routine screening assays.

High Sensitivity Analysis of Steroid Hormones with modified ESI to improve desolvation efficiency

Development of a high-sensitivity method to assay a steroid panel in serum samples. Thanks to LC-MS/MS with the newly developed ion source IonFocus Unit, the sensitivity of steroid hormone was improved. Steroid hormones play a major role in the control of metabolism, neurotransmission, intracellular signaling, gene expression, reproduction and cardiovascular. Therefore, steroid hormones are very important in elucidating the mechanisms of various diseases. Furthermore, not only do steroids play roles in sedation and seizure prevention, they are known to be effective in cancer treatment and regenerative medicine. Therefore, highly sensitive analytical technologies to steroid hormones quantitation in biological samples are required in clinical research. Here we investigated higher sensitive analytical methods to steroid hormones by improving desolvation efficiency in LC-MS/MS ion source.

MALDI-nanochip based Screening of Exosomal Biomarkers

We previously demonstrated we could rapidly distinguish fluorouracil resistant cancer sample groups based on protein profiling of extracellular vesicles using a linear benchtop MALDI TOF instrument [1]. The aim of this follow up work is to identify the proteins that are differentially expressed in the different sample groups in order to better understand the disease processes and to support the rapid screening approach developed previously. Here we present the results from this study using a high performance reflectron MS/MS MALDI-TOF platform for the comparative proteomic profiling of circulating extracellular vesicles extracted from colorectal cancer plasma samples.

LC-MS/MS method development of aflibercept using Fab-selective proteolysis nSMOL technology

Aflibercept is a biopharmaceutical drug inhibiting of vascular endothelial growth factor (VEGF) signaling and composed of the extracellular domains of human VEGF receptors 1 and 2 that are fused to the Fc portion of the human IgG1 immunoglobulin. It is important to determine an appropriate dose for medical optimization, but little amount of intraocular fluid is able to collect as a specimen in the treatment of retina. To offer the quantitative assessment method of aflibercept in biological matrix, the primary structure was confirmed using a quadrupole time-of-flight (Q-TOF) mass spectrometer LCMS-9030, and quantitative analysis was performed with a triple quadrupole mass spectrometer LCMS-8060 by using nSMOL (nano-surface and molecular orientation limited proteolysis) technology.

Multi-target screening of toxicological compounds in blood on a fully-automated platform consisting of sample preparation module CLAM and LC-MS/MS

Multi-target screening by LC/MS/MS has been widely adopted in detection and quantitation of drugs of abuse (DoA) in forensic investigation and toxicological research. Usually, a wide range of targets are screened in such analysis, including illicit drugs, narcotics, psychotropics, antipsychotics, pharmaceuticals and other toxic compounds in urine, serum/plasma and whole blood samples. Sample preparation is often a bottleneck due to the tedious steps. It is also a factor responsible for inaccurate or false negative results. We describe a solution by using an automated sample preparation module CLAM-2000 TM connected with LC/MS/MS system (LCMS-8060) for multi-target screening of 61 drugs in whole blood. A ready-to-use method package Rapid Toxicology Screening (Shimadzu) was used to set up the screening method with human whole blood (frozen) spiked sample without efforts in LC and MRM method development.

Latest topics 1

Guaranteed Data Quality with No Experience Needed

As HPLC becomes more commonplace, there is growing demand for instruments that cater to both novices and experts. The LC-2030C NT provides a simple touch-screen user interface and a workflow that requires no specialized training. The Shim-pack™ NT-ODS is a slide-in column that can be inserted in one motion, with no need for a wrench or other tools. The column is automatically connected into the flow path with no risk of human error. As a result, the LC-2030C NT enables all users to collect accurate data no matter their level of expertise.

Analytical work using conventional LC systems involves commuting to work each day, starting up the system, and equilibrating the column, and then acquiring and analyzing the data. While hardware and software advances in HPLC over recent years have led to a fully-automated analysis cycle, column installation has remained a manual step requiring user know-how. With the LC-2030C NT, we introduce a dedicated slide-in column, the Shim-pack NT-ODS. The user can simply insert this column into the front slot and it will be automatically incorporated into the flow path. Analysis can then be started from the LCD touch panel. The whole procedure can be carried out by staff without specific training. Equipment status and chromatograms can be monitored from outside the lab during analysis, and data results can be processed remotely through a networked PC, opening up more possibilities for flexible workplaces.

Insert columns easily with one hand

After insertion, the new slide-in column is automatically moved into place and connected to the flow line. No tools or experience are required for installation. Since the Shim-pack NT-ODS is connected automatically by the instrument, there is no need to worry about improper column connections affecting the shape of chromatograms.

User-friendly touch controls

System preparations from startup to column equilibration are all automated. The color LCD touch panel provides user-friendly sample registration and instrument controls.

Stable column performance over a large number of samples

The dedicated Shim-pack NT-ODS is a monolithic-type column. The packing state of its separation medium is maintained over a long continuous analysis, whereas a particle-type column may deteriorate. Therefore, the Shim-pack NT-ODS provides long-term stability even over a large number of continuous injections.

Learn more about the LC-2030C NT
https://www.shimadzu.com/an/products/liquid-chromatography/hplcuhplc/lc-2030c-nt/index.html

Latest topics 2

Shimadzu (Asia Pacific) & Changi General Hospital (CGH) jointly launch centre to conduct mass spectrometry-based clinical testing and research for personalised treatment

The Shimadzu-CGH Clinomics Centre (SC³) aims to improve turn-around time and clinical diagnostic accuracy of diseases such as hypertension and other endocrine conditions in adults

On 27 January 2021, Singapore–The Shimadzu–CGH Clinomics Centre (SC³), a public-private partnership by Changi General Hospital (CGH) and Shimadzu (Asia Pacific), was officially opened by the Guest of Honour, Deputy Prime Minister of Singapore Heng Swee Keat. A satellite laboratory of CGH, the initial SC³ operations will focus on developing and validating various clinical applications and research to improve clinical diagnostics, which lead to better clinical care for patients with hypertension and other chronic diseases.

Professor Ng Wai Hoe, Chief Executive Officer, CGH, very well stated the need and relevance of such collaborations, "The coming together of the clinical and research expertise of CGH and SingHealth with Shimadzu's diagnostic and analytical capabilities will contribute to medical care and treatment in Singapore. At SC³, we will co-create clinical applications through mass spectrometry technologies and instruments that will enhance the standard of care for our patients."

As Shimadzu we are committed to using our years of experience in Analytical and Medical technologies towards Advanced Healthcare initiatives. Mr. Tetsuya Tanigaki, Managing Director, Shimadzu (Asia Pacific) Pte Ltd, highlighted, "Excellence in Science is not only a motto but a way of life in the Shimadzu Family. And it is with this philosophy that we, along with CGH, are powering the SC³ lab with futuristic technologies such as mass spectrometry and Analytical Intelligence among several others, to ensure that we deliver more accurate and faster outcomes to patients. This Centre is an example of how we can collaborate to establish a pioneering partnership for Advanced Healthcare. This is the first time that Shimadzu is working with a public hospital to establish a Clinomics Laboratory in Singapore. Our efforts will certainly transform the healthcare landscape of not only Singapore and the Asia Pacific region but also of the world."

Top image: DPM Heng witnessed the signing of the Research Collaboration Agreement between CGH and Shimadzu (Asia Pacific)

Shimadzu–CGH Clinomics Centre (SC³)–powered by UFMS and Analytical Intelligence (AI)


DPM Heng views the mass spectrometer at the Centre

Changi General Hospital
https://www.cgh.com.sg/pages/home.aspx

Providing precision and personalised medicine for Singaporeans

One in four adult Singaporeans suffers from hypertension, which is a leading cause of heart disease and strokes. It is now understood that hypertension is due to either excessive vasoconstriction (tightening of blood vessels) or excess salt and blood volume. Precise measurements of hormones can identify which spectrum of hypertension a patient has, and which medications are best suited for that patient.

In recent years, hormone measurements also identify many patients with a treatable and curable form of hypertension (Primary Aldosteronism).

Achieving faster turnaround time for test results

With the SC³, it is envisioned that clinical tests based on the LC-MS/MS technology for adult diseases will no longer need to be routinely sent to overseas centres for processing. By developing the capability to conduct such tests in Singapore, local and even regional patients can receive their test results with a significant reduction in waiting time from approximately two weeks to one or two days.

Serving as a regional reference centre

In the long term, the SC³ aims to offer validated tests to patients in Singapore as a clinical laboratory and to serve as a regional reference centre in Asia Pacific for developing mass spectrometry solutions for wider clinical applications for chronic conditions and other areas of clinical diagnostics, such as drug monitoring. Measuring the efficacy of medication for patients with other common conditions, such as diabetes, can allow for more personalised treatment options, which can lead to better patient outcomes.

Finally, Mr Prem Anand, Executive Officer and Senior General Manager, Shimadzu (Asia Pacific) very eloquently summarised the initiative and road ahead “Today, precision and personalised medicines are being fuelled by the merger between analytical and medical technologies. These technologies are more relevant today than ever before, as more and more researchers are now using them concurrently. The fact that Shimadzu is the only company in the world to be a leader in both analytical and medical technologies, gives us the unique opportunity to develop truly synergistic solutions for Advanced Healthcare”

The launch of this Shimadzu–CGH Clinomics Centre is yet another reiteration of how we all can collaborate towards Contributing to Society Through Science and Technology.

Latest topics 3

Sales of Novel Coronavirus PCR Testing Reagent Kits outside Japan Exports Began

Shimadzu Corporation will begin fully rolling out sales of the novel coronavirus (SARS-CoV-2) detection reagent kits outside Japan. On January 19th, Shimadzu obtained provisional authorization from the Singapore Health Sciences Authority (HSA) to sell the kits and will start exporting the kits to Southeast Asian markets through Shimadzu (Asia Pacific) Pte. Ltd., the Asia/Oceania regional headquarter, beginning in early February.

In the United States, sales started in September of last year for use in laboratory developed tests (LDT) based on a U.S. Food and Drug Administration (FDA) emergency use authorization (EUA). In Austria, sales for use as research reagents started in October and preparations are currently underway for exporting the reagents to France, Croatia, and other EU countries.

Shimadzu has been manufacturing the reagent kits for research use in Japan since April of last year and then in September obtained authorization from Japan's Ministry of Health, Labour and Welfare to manufacture and sell the kits as a drug for in vitro diagnostic use. Shimadzu remains committed to increasing its contribution to preventing the spread of infections in Japan and throughout the world by offering testing reagents and instruments in the future as well. Shimadzu expects to produce up to 3,000 kits (for 300,000 tests) per month for export markets.

Learn more about Shimadzu's response to the COVID-19 pandemic:
https://www.shimadzu.com/covid-19/

Latest topics 4

Shimadzu Announces the Start of Its Blood-Based Amyloid Mass Spectrometry Service

Shimadzu Scientific Instruments introduces the Amyloid Mass Spectrometry (MS) Service for early screening of amyloid-positive subjects. This simple blood analysis method enables early and accurate prediction of amyloid pathology in the brain with an easy-to-acquire blood sample.

Although the screening analysis is Research Use Only and cannot diagnose Alzheimer's disease, it is ideal for opening the door to new advancements in research, identifying suitable candidates for clinical trials and helping pharmaceutical companies in their testing of candidate drugs.

Unlike conventional positron emission tomography (PET) imaging and cerebrospinal fluid (CSF) testing methods, Shimadzu's blood amyloid-beta analysis method is minimally invasive and suitable for large-scale deployment. This new approach to blood analysis is capable of being used for predicting abnormal amyloid-beta concentration, which can be a marker for amyloid pathology in the brain. New blood-based biomarkers were discovered in 2014 by Shimadzu Corporation and the Japanese National Center for Geriatrics and Gerontology (NCGG).

The blood analysis works using a combination of immunoprecipitation and MALDI-TOF mass spectrometry (IP-MS). This technique was first established by a team of scientists including Shimadzu's Koichi Tanaka, who was awarded the Nobel Prize in Chemistry in 2002 for developing a method for mass spectrometric analysis of biological macromolecules.

Learn more about Shimadzu's Amyloid MSTM Service:
www.AmyloidMS.com

For more scientific background about Shimadzu's blood amyloid-beta analysis:

A. Nakamura, N. Kaneko et. al., "High performance plasma amyloid-β biomarkers for Alzheimer's disease" doi: 10.1038/nature 25456

RELEASED

New Products

SPM-Nanoa

Scanning Probe Microscope / Atomic Force Microscope

The SPM-Nanoa scanning probe microscope provides high-resolution observations, features a low-noise detection optical mechanism, and automates optical adjustments and the work of setting the observation conditions. Even users unfamiliar with the operating procedures can easily acquire high-resolution observation data.
It will contribute to the evaluation of, and research into, cutting-edge nano materials as a mid-range scanning probe microscope (SPM).

Features
- Automatic Observation
- Extensive Functionality
- Saves Time

Learn more

AOC-30 Series

Autoinjector / Autosampler

ANALYTICAL INTELLIGENCE

Based on Shimadzu's extensive wealth of unique technologies and functionality, AOC-30 series automatic sample injection systems offer the automation, productivity, and remote operability needed for next-generation laboratories. The space-saving design makes it easier to mount on GC or GC-MS systems with limited space availability and facilitates system expansion based on analytical objectives.

Features
- Reliable Automatic Operation
- Space-saving Efficiency
- Sampler Navigator, Built-in Injection Expertise

Learn more

Amyloid MS

Amyloid Mass Spectrometry (MS) Service is a new simple, low-cost* blood analysis for early screening of amyloid-positive subjects. This method enables early and accurate prediction of amyloid deposition in the brain with an easy-to-acquire blood sample.
Unlike conventional methods, Shimadzu's new analysis is minimally invasive, cost-effective* and suitable for large-scale deployment.
It's the only blood analysis capable of predicting abnormal amyloid-beta deposition in the brain with high accuracy.

*Compared to PET test.

Features
- Reduced costs per test
- A less invasive blood-based sampling technique
- Low sample volume requirements (Plasma 250 µL)

For Research Use Only. Not for use indiagnostic procedures.

Learn more

Multimodal Imaging System

Multimodal imaging system consist of a laser ablation inductively coupled plasma mass spectrometer (LA-ICP-MS), an imaging mass microscope, and the IMAGEREVEAL MS mass spectrometry imaging data analysis software. The system is capable of separately acquiring information on the distribution of trace elements and the distribution of various compounds, and performing an integrated analysis of both sets of information. With this system, Shimadzu aims to advance the elucidation of mechanisms of disease onset and the development of therapeutic drugs in the life sciences.

Features
- Integration of complementary imaging technologies
- Analysis of analytical samples at atmospheric pressure and better spatial resolution performance
- Integrated data analysis software

Learn more

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www.shimadzu.com/an/

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