isas Leibniz-Institut für Analytische Wissenschaften

ANNUAL REPORT 2019

advancing analytics

Leibniz Association

PREFACE

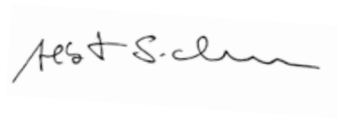
Dear Readers

ISAS is continuously developing its research focus, and the strategic expansion of its scientific and technical competences is also advancing: I am pleased that in the middle of the year 2019, we were able to appoint Professor Dr. Matthias Gunzer, a proven expert in experimental immunology and imaging, as the head of our new department of Biospectroscopy. With his profile, Matthias Gunzer will give a new impetus to our research. The establishment and expansion of the new department in cooperation with the University of Duisburg-Essen (Universität Duisburg-Essen) are well underway, including a joint appointment process for a W2 professor of Experimental Biomedical Imaging and the management of a corresponding working group at ISAS.

In this annual report, we would like to take a closer look at our working groups' innovative technical developments and findings during the past year. This year's feature on the Bioresponsive Materials working group gives you insights into how our (international) teams conduct their interdisciplinary research, the challenges they have to master and the opportunities in their everyday work.

Have a pleasant read!

Prof. Dr. Albert Sickmann



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HIGHLIGHTS 2019

2019
IN REVIEW

January

A team of researchers from ISAS, the University of Jaén (Spain) and the University of Cyprus come together at ISAS City to push forward their joint work in the fields of manufacturing, simulation and modelling of atmospheric pressure plasmas and mass spectrometry. They also agree on trainings and summer schools for doctoral students in the coming years. The cooperation is supported by the EU funding line *Twinning*.

February

ISAS' new intranet site goes live in February. It serves as a virtual reference book for technical and organisational topics.

How can the sick benefit quickly from findings in research? The 6th symposium of the Institute for Education in Pharmaceutical Medicine deals with this question. The symposium at the University of Duisburg-Essen (Universität Duisburg-Essen) is organised by the head of the Biomedical Research department at ISAS, Professor Dr. Kristina Lorenz.

March

The award for one of the best research papers is given to the authors of *Hybrid molecular imprinted polymer for amoxicillin detection* from the Tallinn University of Technology. Among the winners is Dr. Andreas Furchner from the working group In-Situ Spectroscopy at ISAS.

At Girls' Day, girls and young women between the ages of 12 and 15 visit ISAS. Putting on the lab coats for one day, they get to know ISAS' scientific topics through their own guided experiments.

April

In April, Professor Dr. Helmut E. Meyer, an expert in the field of mass spectrometry-based protein research, retires. In the summer of 2014, he took over as the acting head of the new Biomedical research department at ISAS. He helped to establish the cooperation with the University of Duisburg-Essen (Universität Duisburg-Essen), and accompanied the joint recruitment process for the department head. ISAS thanks Helmut Meyer for his outstanding achievements for the institute!

May

The Leibniz Association's Europe working group meets at ISAS Dortmund. The conference's topics include research policy developments as well as application and project management.

Dr. Fiorella Solari from the Protein Dynamics working group receives the German Society for Proteome Research's doctoral award for her outstanding doctoral thesis.

June

Professor Dr. Matthias Gunzer starts working at ISAS. He is the head of the new Biospectroscopy research department. The goal of the department is to further develop imaging methods to improve the early detection of cardiovascular diseases and tumors.

As one of the first events on new approaches in the research of gene and protein signatures (GPS) of patients with neuromuscular diseases (NME), ISAS invites participants to the *NME-GPS-Meeting*. The project is funded by the federal state of North Rhine-Westphalia.

June

At ISAS Berlin, guests get an insight into the work of a scientific institute as part of the so-called training alliance Adlershof (Ausbildungs-Allianz Adlershof). Pupils from grades 9 to 13 get an overview of the development of new sensor and measurement concepts. There is also information on teaching in the fields of biology, physics and chemistry.

July

As part of the programme *A Novel Antimicrobial Polymeric Nanocomposite for Antifouling Water Filtration Membrane* funded by the DAAD, Jordanian students at ISAS explore how water treatment can be improved. ISAS has been offering students from the fields of natural sciences and engineering from universities in Jordan an eight-week summer school on changing topics with high social relevance in the target country for five years.

August

Mental health in the workplace is the topic of the survey on occupational safety, in which ISAS employees actively participated. In August, the project group analyses the results and initiates workshops.

September

At the ISAS doctoral students' summer school, speakers from research-related companies provide information on trends in diagnostic and therapeutic systems and on the founding of start-ups; an excursion to a pharmaceutical company includes tours and other opportunities for scientific debate. The summer school's interdisciplinary format allows for an exchange and interdisciplinary discourse among young researchers.

October

The tour through the ISAS laboratories at the 16th Dortmund Science Day is about insights into processes that are hidden from the eye. The motto is »Nature as a top designer« and visitors learn why dolphin skin is smart and how toxic substances are transported through the liver.

A Leibniz delegation with President Professor Dr.-Ing. Matthias Kleiner and representatives of various Leibniz institutes discuss cooperations between science, politics and business at the *Science And Technology Forum (STS)* in Kyoto (Japan). ISAS is represented by Professor Dr. Albert Sickmann and Dorit Günther.

Professor Dr. Norbert Esser invites visitors from Kenia, India, Chile and Ghana, among others, to the *Falling Walls Conference* in Berlin with a tour of ISAS facilities. The deputy chairman's topic is Raman microscopy.

November

Nationally and internationally recognised top researchers meet at the Lipidomics Forum 2019 at the Research Centre Borstel in November. Dr. Robert Ahrends and Dr. Dominik Kopczynski from the ISAS working group Lipidomics are part of the organising committee.

Big Data: A Quantum Leap in Biology and Medicine is the title of the annual conference of VBIO (German Life Sciences Association), which is organised by ISAS. Professor Dr. Susanne Bickel's greeting as the VBIO NRW (North Rhine-Westphalia) chairwoman is followed by lectures delivered by Professor Dr. Barbara Stecher (Max von Pettenkofer-Institute of the LMU Munich), Professor Dr. Rudi Amman (Max Planck Institute for Marine Microbiology in Bremen) and Professor Dr. Albert Sickmann (ISAS).

November

Dr. Roland Hergenröder speaks about alternative methods to replace animal experiments at *Leibniz at the State Parliament (Leibniz im Landtag)* in Düsseldorf.

December

In terms of sustainability and environmentally conscious behaviour, ISAS offers its employees subsidised tickets for public transportation in cooperation with the TU Dortmund University (Technische Universität Dortmund). Thus, ISAS wants to motivate staff members to use public transport more than cars.

OUR YEAR IN FIGURES

170

Staff members

were employed at ISAS on 31 December 2019, working at the institute's locations in Dortmund and Berlin.

90

Non-scientific and scientific technical employees

work at ISAS. 45 of them are women.

80

Scientists

currently work at ISAS, of which 30 are female scientists.

32

Doctoral candidates

Among the 80 employed scientists are 32 early stage researchers aiming for a PhD.

13

Scientific degrees

In 2019, a total of 13 young scientists graduated at ISAS.

8

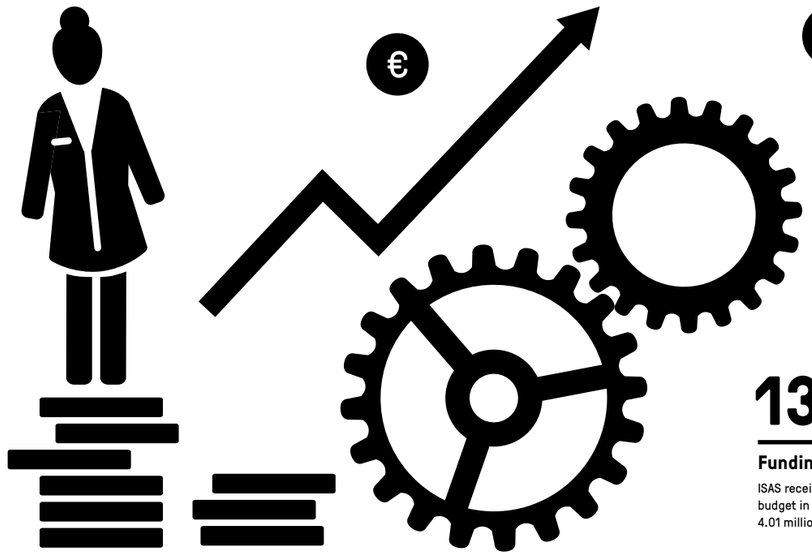
Doctoral theses

Among those were eight doctoral theses ...

5

B Sc. und M Sc.

... and five Bachelor and Master theses.



13.065 Mio.

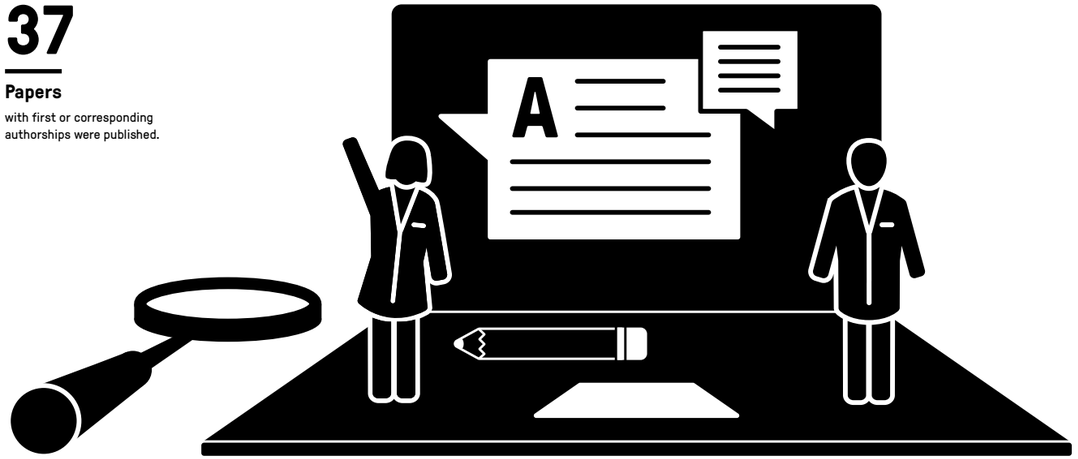
Funding for ISAS

ISAS received 13.065 million Euro funding for its core budget in 2019. In addition, the institute procured another 4.01 million Euro in third-party funding.

37

Papers

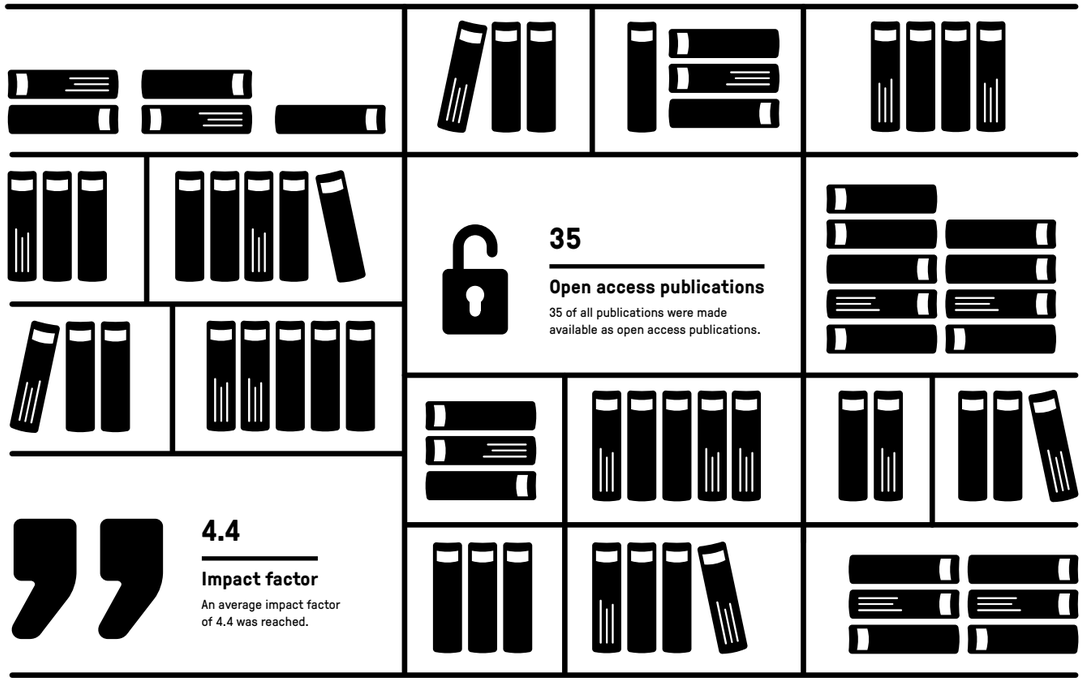
with first or corresponding authorships were published.



70

Publications

In 2019, a total of 70 articles were published in peer-reviewed journals.



35

Open access publications

35 of all publications were made available as open access publications.

4.4

Impact factor

An average impact factor of 4.4 was reached.

17

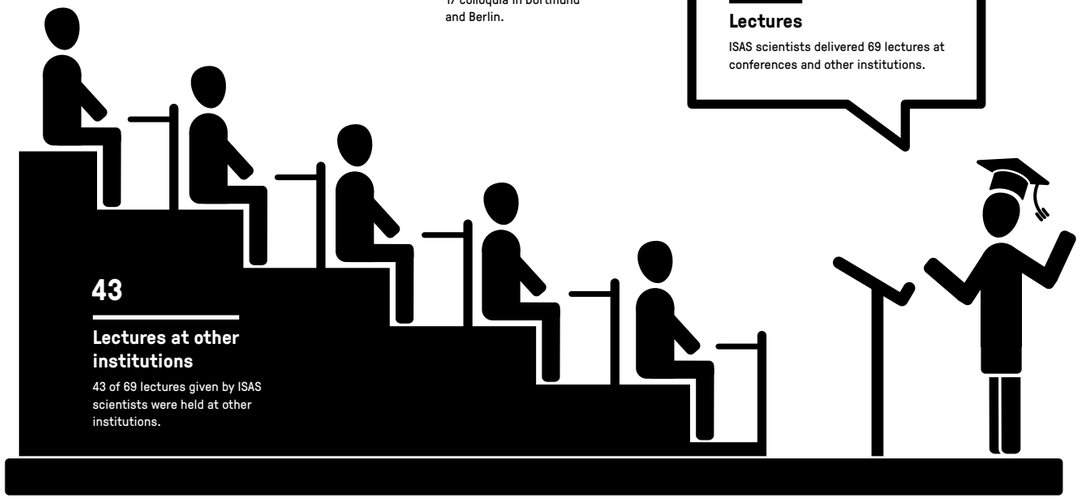
Colloquia at ISAS

In 2019, ISAS organised 17 colloquia in Dortmund and Berlin.

69

Lectures

ISAS scientists delivered 69 lectures at conferences and other institutions.



43

Lectures at other institutions

43 of 69 lectures given by ISAS scientists were held at other institutions.

40

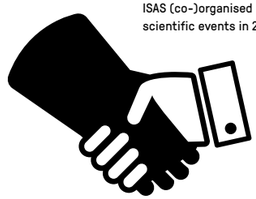
Conferences

In 2019, ISAS scientists attended 40 national and international conferences.

11

Co-Organisations

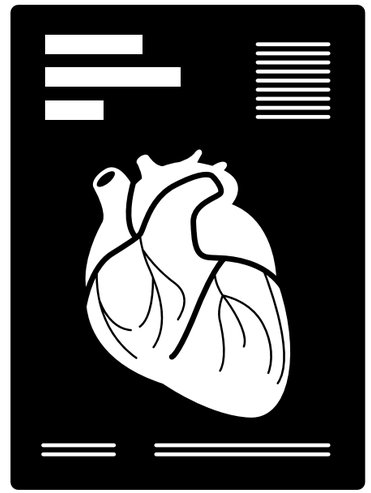
ISAS (co-)organised eleven scientific events in 2019.



30

Poster presentations

were held by ISAS scientists in 2019.



102,000

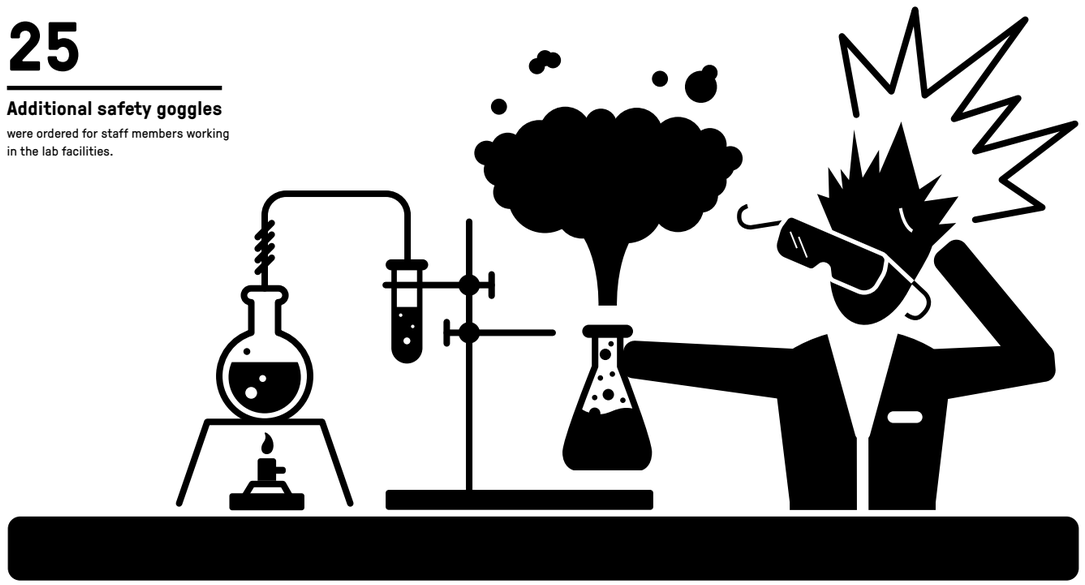
Working gloves

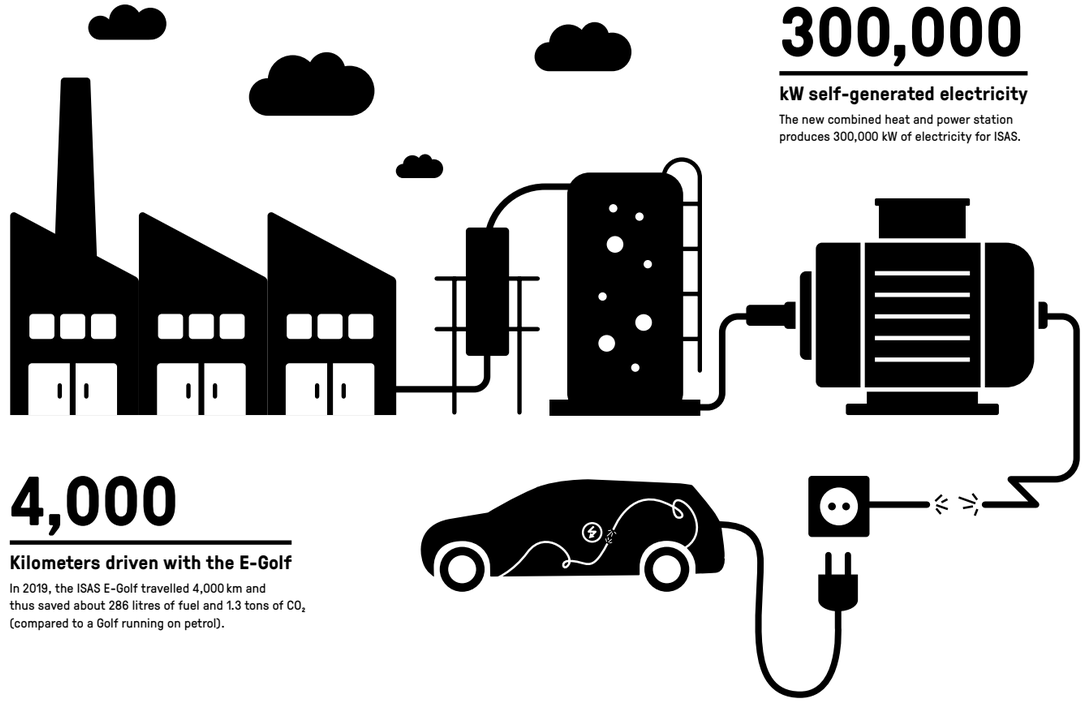
were bought in 2019.

25

Additional safety goggles

were ordered for staff members working in the lab facilities.





300,000

kW self-generated electricity

The new combined heat and power station produces 300,000 kW of electricity for ISAS.

4,000

Kilometers driven with the E-Golf

In 2019, the ISAS E-Golf travelled 4,000 km and thus saved about 286 litres of fuel and 1.3 tons of CO_2 (compared to a Golf running on petrol).

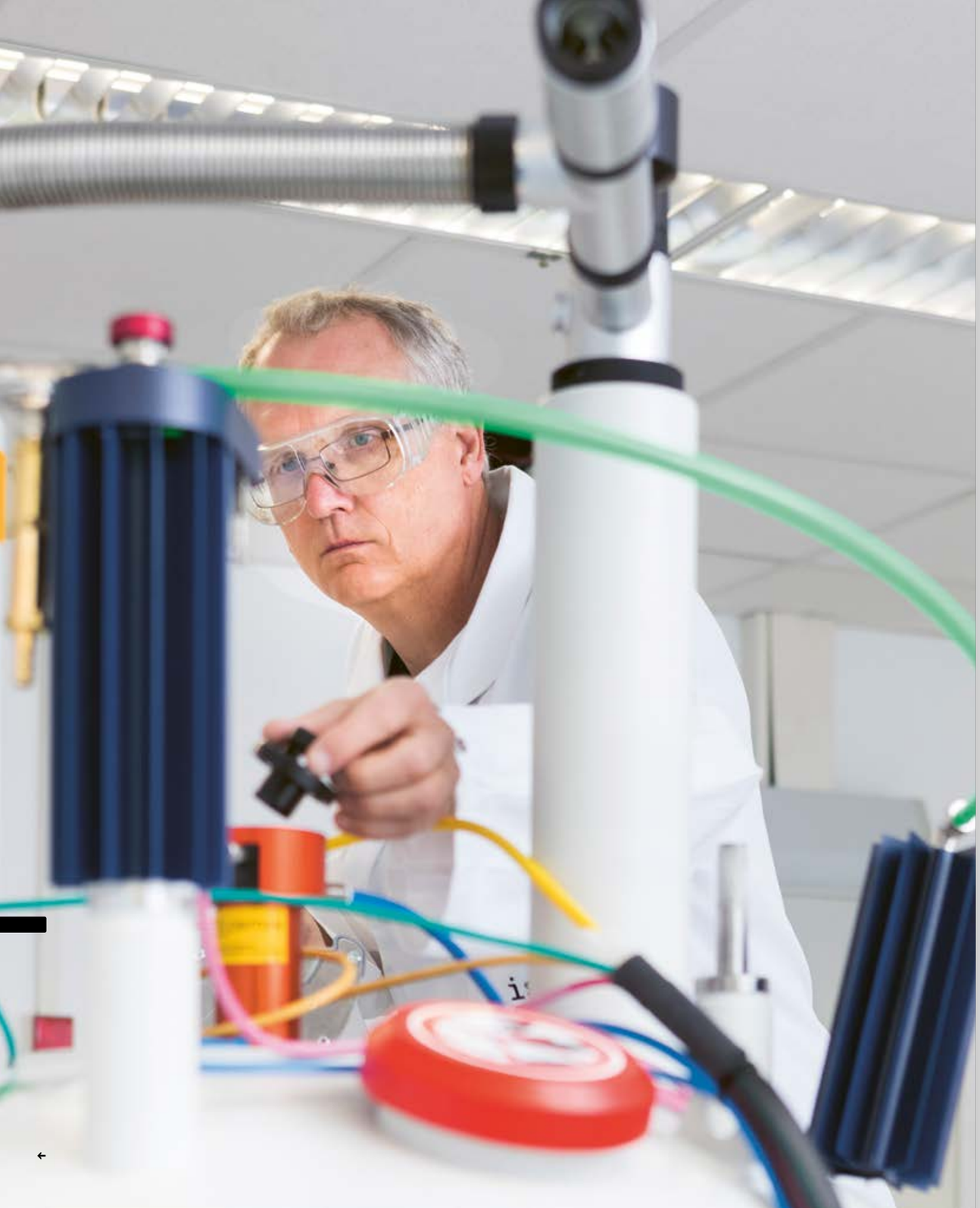
4,600

Green plants

were potted in the vertical garden in the new lobby.

METABOLOMICS AND THE UNDERSTANDING OF COMPLEX SYSTEMS

What do complex metabolic processes in the human body reveal about the origin and development of diseases? The Bioresponsive Materials working group uses highly informative analytical methods to identify the interactions that occur in and between living systems and chemical substances. Among other things, the results of the group's metabolome studies facilitate a better understanding of diseases and the development of new therapeutic approaches. Dr. Roland Hergenröder heads the group. In this interview, he tells us more about the collaborative effort, as well as interdisciplinarity, innovation and — a key instrument.



DR. Hergenröder, in the photos we see you and your team with an instrument known as a NMR spectrometer. What does this mean, and exactly what is it that occurs in the device?

The NMR is a nuclear magnetic resonance spectrometer. It is like a huge refrigerator in which we take measurements within a magnetic field. The NMR spectrometer contains a coil that is cooled with liquid helium and nitrogen, making it superconductive. We introduce the samples from above, and the measuring head enters from below. The measurements are primarily concerned with the characterisation of biological samples, for example to test the effect of chemicals on biological systems: How do living systems, biological systems, humans react to chemical components? This is the focus of our work.

This has nothing to do with medications that combat symptoms. We need to understand complex biological systems at the molecular level.

What do you analyse, and for what purpose?

Ninety percent of our work is on biological samples including fluids and tissues in which we measure the metabolite concentration as well as frozen samples taken directly from a patient. The third variant are self-bred organoid or 3D cell culture models, that are still alive, on which we can test the metabolism. Breast cancer, for example, is a major issue in the area of tissue. There are several gradings of breast cancer which play an important role in treatment. However, the existing analytical methods are not yet accurate enough to determine the grading more precisely. Cardiovascular diseases are also included. Measuring the potential effect of new medications on the heart, for example, is one part of our work. Another part is to further the development of the method. In vitro measurements, i. e. measurements on living tissue, are difficult; there are only a few suitable methods, and only a few are able to accomplish this. However, in vitro measurements constitute a move in the direction of non-animal testing methods, both for ethical reasons with respect to animals and, even more significantly, because animal models, as necessary as they are and will remain, are in many respects inadequate for the evaluation of active substances.

What does your work look like, and what is your role on the team?

Our work is truly teamwork. I set the direction in terms of content, but if I did not have a broad-based team that was prepared to communicate with each other, we would not be able to work on such a complex subject area.

Do you work specifically on methods for certain diseases or on methods that can then be used in different areas?

As a team, we work in both directions. We are attempting to develop methods, for example new probe heads, to further the development of tissue measurement. And we are also working in collaborative partnerships on a disease-specific basis. For example, we are conducting a study on heart diseases with the Julius-Maximilians-Universität Würzburg, and with Heidelberg

University (Ruprecht-Karls-Universität), we are working on a specific cancer, thymoma, which has not yet been sufficiently characterised and for which, in many cases, there is still no treatment option. Samples of this cancer are rare; therefore, it is very important to use a method that does not destroy the samples — like NMR spectroscopy. On medical issues, we cooperate with external partners, such as clinics and university hospitals, to establish methods that we have developed.

Can you give examples of such applications?

These days, medicine and research work a lot with stem cell therapy, but there is still no control over how the stem cells actually arrive in the body. And stem cells cannot be multiplied at will. Eventually, the stem cells begin to differentiate and will become a heart or a muscle. We try to answer important questions with our method of working directly on the living 3D model: How do the cells change? What happens during differentiation? How can we achieve a more precise differentiation? This is what we are currently attempting to do in a project with the Julius-Maximilians-Universität Würzburg.

If I did not have a broad-based team that was prepared to communicate with each other, we would not be able to work on such a complex subject area.

You are also developing your own NMR spectrometer for clinical application.

We are developing a NMR spectrometer »in miniature« for point-of-care applications. Large NMR spectrometers are simply too expensive and their operation is too complex to be used near patients. Therefore, we are trying to break down the concept for specific tasks. If you need a complete spectrum of an unknown sample, the large NMR spectrometers provide a fingerprint of everything that can be measured. But if you know what you are looking for, you can use other strategies.

Some samples are rare, and it is very important to have a method that does not destroy the samples — like NMR spectroscopy.

What role does the Halbach magnet play in this?

Halbach magnets have previously been used in other areas, in high-energy physics for particle detectors and even for magnetic levitation. We use them in combination with the pulse frequency calculation that we developed, a refinement of quantum computing. The hardware is fixed; it is always the same magnet, but the programming is then very easy to configure for dosing a cancer medication or an antibiotic adapted to a person, for example.

It seems that the focus is increasingly on systemic diseases which still require much research before they can be understood.

Yes, that is exactly the idea. This has nothing to do with medications that combat symptoms. With cancer, cardiovascular diseases or even new clinical pictures, there is more to it than that. We need to understand complex biological systems at the molecular level. New approaches to staying and becoming healthy can only emerge when we better understand what balance is. We know that cardiovascular diseases,

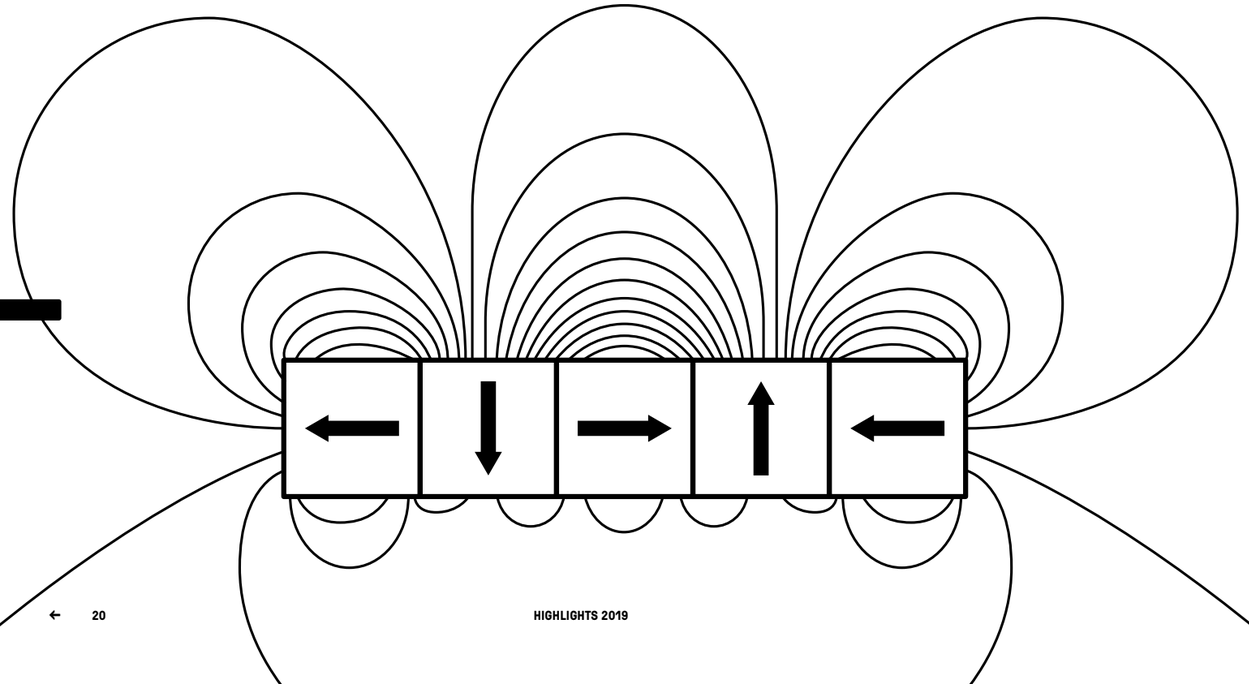
blood diseases, diabetes etc. also have something to do with lifestyle. We must consider the interaction of predisposition, acute illness, lifestyle and medical intervention. If, for example, we are investigating the effect of a medication on the heart, we must also investigate what it does to the liver. That is where the medication is broken down and something new created. The degradation product can also be toxic.

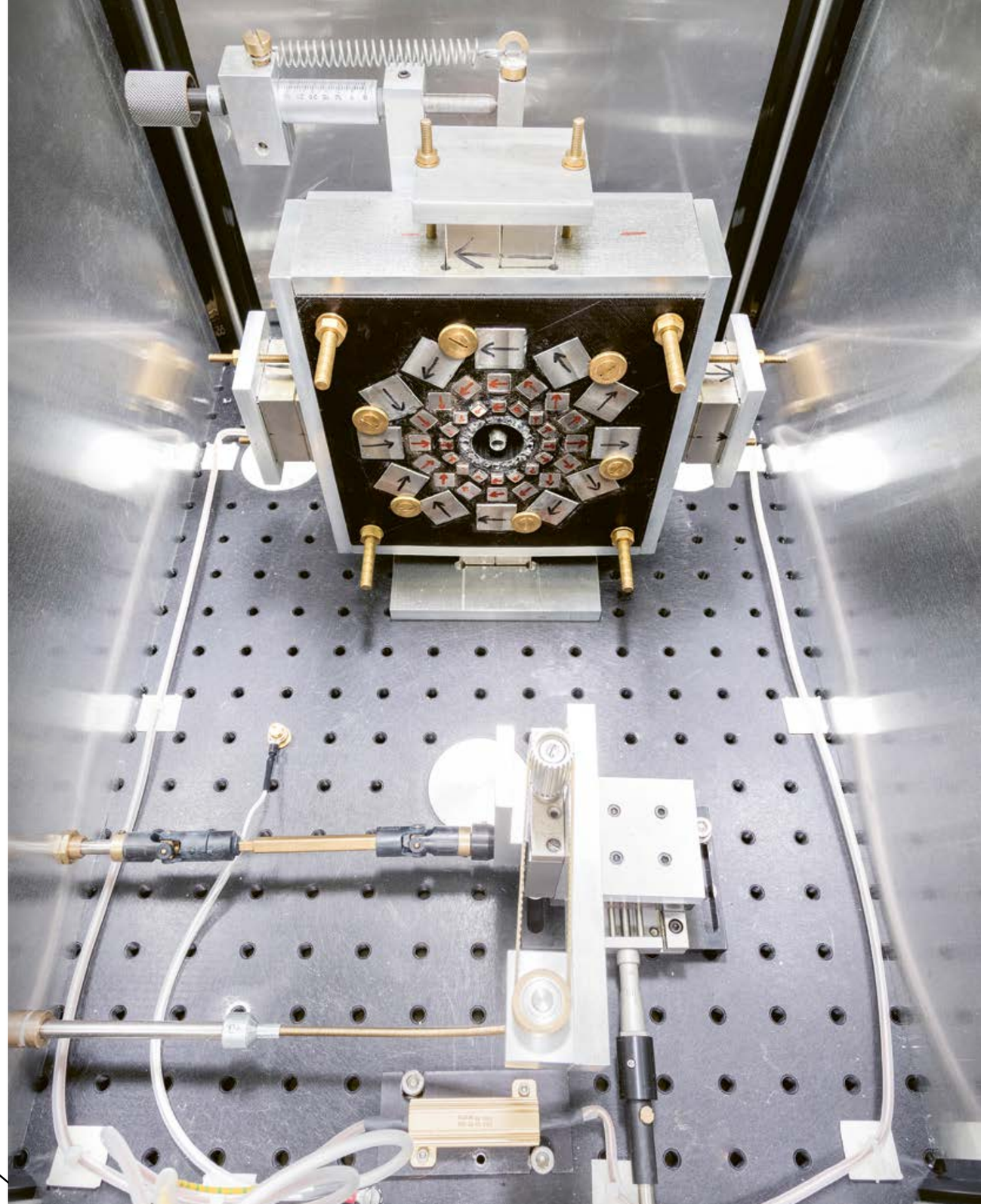
We use the Halbach magnet in combination with the pulse frequency calculation that we developed, a refinement of quantum computing.

What are your greatest challenges?

Technically speaking, it is sensitivity. From an instrumental point of view, we need to increase the measurement sensitivity even more. The control of in vitro systems for our applications on living systems must be improved in order to facilitate more realistic models of biological processes. Of course, measuring complex processes in greater detail also means bringing more data into a common picture. This will require the development of better models on the computer. Models into which we can feed our data to obtain statements regarding possible biological mechanisms of action. I think that managing the growing complexity will be the greatest technical and methodological challenge for us. And of course, finding an even better way of transferring our methods into practice, so that they benefit patients.

001 The Halbach magnet can be programmed differently — for example for an individually adjusted dosage of a cancer drug. Even in earlier times, Halbach magnets were used in other fields: ISAS uses them in combination with pulse rate calculation.





What were the developments that surprised you most in your work?

That we have managed to bring living systems into the NMR spectrometer and measure them there. We are still in the development stage, but we are seeing that it works. When we started, we conducted our measurements with one million cells. Now, we only need 10,000 cells, and I am quite sure that in principle we could measure a single cell, even if the informational value would then be very low. The fact that we can bring in such small systems, keep them alive for days on end and see how they react—that is a development that I never thought would be possible.

What drives you? Is it being able to do something useful by helping to treat diseases, or is it the drive to develop something new?

The two go hand in hand. You always want to do something useful. If I can help provide a therapeutic approach or a better understanding of a disease, and people get healthy as a result, it is of course very satisfying. Moreover, there is always this curiosity to discover and develop something new, to have an idea and see that it works. If, in the end, it can be used somewhere in the hospital, that is of course what you want.

Handling the growing complexity will be the biggest technical and methodological challenge for us.

How do you develop something new? Can innovation be planned? Or does chance also play a role?

Again, there are two possibilities. One way is to look at what the problems are. For example in biology: I want to measure a living cell. Then I begin to calculate and see what works, what is possible, what is conceivable, and what the ultimate limit is. You learn a lot that way. The other way is more random. You have to observe, not take anything for granted, constantly questioning your ideas. Then, you suddenly notice something that does not work as expected and think, »Aha, I do not understand; I always thought otherwise.« Along the way, you have to look in both directions and ask over and over again, what are we stumbling upon? Where did we do something that we had not expected? It is not the innovation you plan that brings something radically new, but it is the surprises along the way.

If I can help provide a therapeutic approach or a better understanding of a disease, and people get healthy as a result, it is of course very satisfying.

Your topics are focused on medical applications. Does this reflect the strategic development of research at ISAS?

Practically all of our topics are related to medicine. This, of course, also shows how ISAS has changed. When I started, we investigated steel, primarily for the automotive industry. Methodically, there is not a great difference between steel and stents; both are made of metallic materials. But working with cells was a huge leap. In 2007, I worked on my last project with Thyssen-Krupp. Now, my focus is elsewhere. The Ruhr area has developed, and we are also continuing to develop.

Does your interdisciplinary group reflect the complexity and interconnectedness of your topics?

You could say that. I am a physicist, but the team includes pharmacologists, biologists, computer scientists, chemists—almost everything from biology to artificial intelligence. It would not be possible without interdisciplinary team members all moving toward each other, each bringing in ideas from their own field and listening in turn to what others say from a perspective of their own fields—both »unfortunately, it does not work that way« and »this is a good idea, we should try it.« At the same time, we benefit from the fact that we have a technical structure for our in-house developments here at the institute. The workshop builds things for us that we can discuss directly. Our small NMR spectrometer can be built, because we have a workshop and electronic engineering at ISAS to support us.

The fact that we can bring in such small systems, keep them alive for days on end and see how they react — that is a development that I never thought would be possible.

Where is the most exciting development for you right now?

The understanding of complex systems. There is a huge upheaval in medicine and biology. 15 years ago, genes, RNA, proteins and metabolites were being researched; now, we know that these are also interconnected. Every detail is important. Analysing these correlations and bringing the huge amounts of data together is exciting, but not easy. We produce measurements with a few thousand molecules, and then we end up with a bar chart that says of which there are more and of which there are fewer. But that does not reflect what is happening in the cell. We are only at the beginning; this is still new territory.

What do you wish for the future?

I would like to continue in this direction and put our work into practice. To that end, I would like to have the peace and quiet to look more deeply into our topics, a bottom current that remains constant and gives us the freedom to take risks and develop something special that really has an impact.

Practically all of our topics are related to medicine. This shows how ISAS has changed.

→ Page 72 ff.

Continue reading: »ISAS International« Portraits of two researchers working in the Bioresponsive Materials group.

SCIENCE AND RESEARCH

ISAS PROFILE

ISAS (Leibniz-Institut für Analytische Wissenschaften – ISAS – e. V.) develops fast, accurate, and cost-effective analytical procedures for health research in order to improve capabilities for the prevention, early diagnosis and treatment of diseases. By combining expertise in chemistry, biology, physics and computer science, we make measurable what cannot be measured yet. Our overriding priority is the question: How much of which substance is where at what time?

4D-Analytics

Our objective is to determine the quantity and nature of the investigated substance, as well as its localisation, as concurrently as possible and at any given moment. Therefore, we have taken on the task of developing and refining »four-dimensional« analytical methods. These form the technological basis for the comprehensive elucidation of pathological processes. In order to determine when and how the »biological decision« between health and disease is made, we need analytical procedures which simultaneously collect information from various classes of molecules (such as proteins, lipids and metabolites). Such simultaneous processes will produce entirely new data types which will in turn require new evaluation strategies.

The main areas of our activity are the elucidation of disease mechanisms, the identification of potential drug targets and biomarkers, and the development of novel imaging and detection methods for biomolecules.

Key Objectives

The key objectives of ISAS are excellent interdisciplinary research, training young scientists and the transfer of our results to science, business and the public.

Research Performance

Indicators of the institute's research performance include its publications, particularly in peer-reviewed journals, as well as its presence through scientific lectures and the procurement of new third-party-funded projects in national and international competitions. In selecting the competitions and funding lines to which we apply for external funds, we strive for the best possible synergies with our long-pursued research programmes and place complementary issues at the forefront.

→ Page 84 ff.
Activities 2019
(see German part)

Young Academics

In order to support our junior researchers, we have established programmes that encompass all stages of their scientific careers, from promoting students at the Bachelor and Master levels, to the structured training of doctoral candidates, to continuing education programmes for postdoctoral researchers and young professionals in science. Junior research groups have also been established at the institute in order to promote career opportunities for outstanding young scientists. In addition, ISAS offers young scientists further development opportunities by delegating the management of research projects to them. This early profiling in management is particularly intended to help young people aiming to pursue a career in science.

Transfer and Service

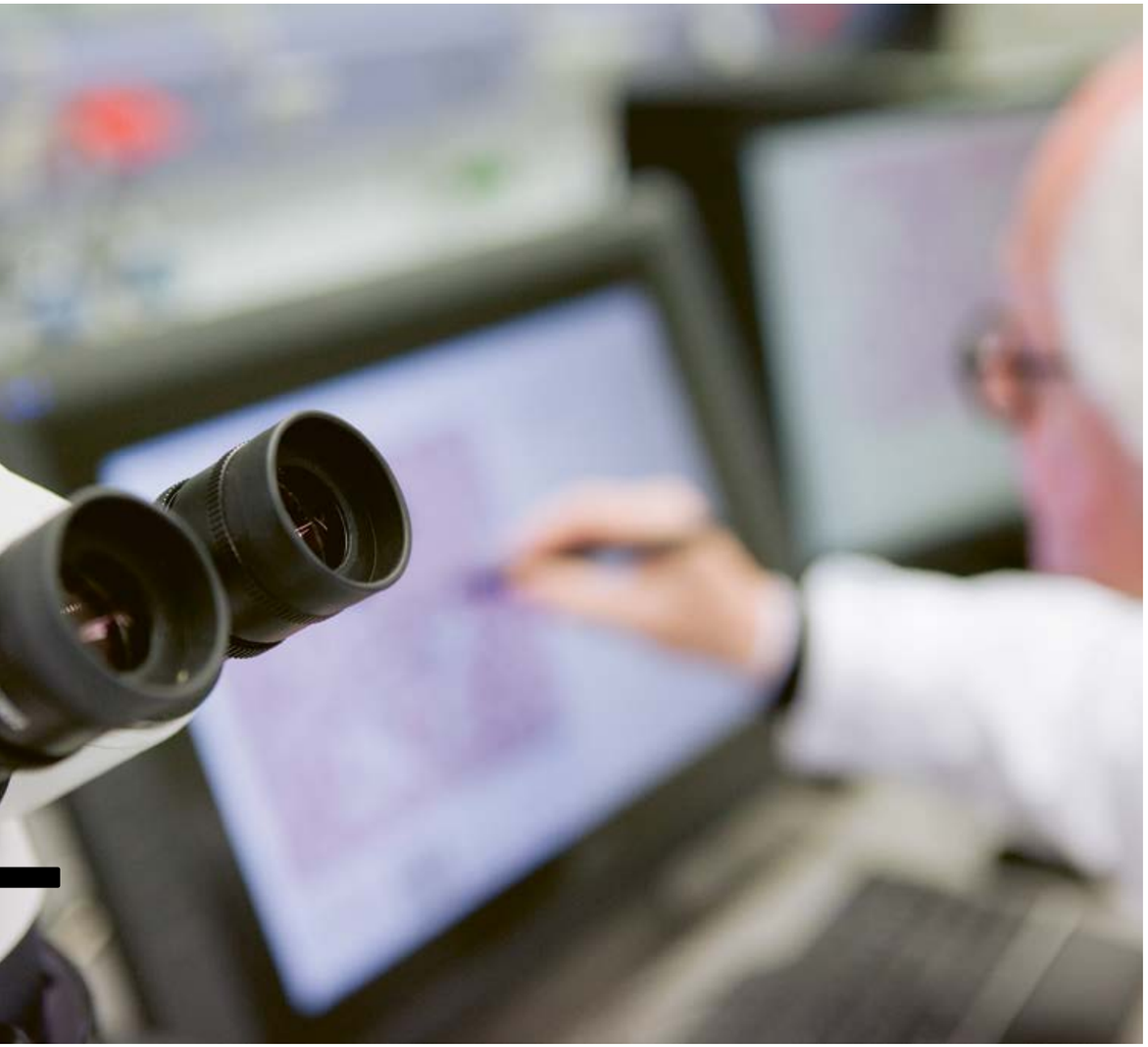
Our transfer and service offerings range from consulting activities for scientists and companies as well as for media and politics, to contract research and customised measurements, to the provision of analytical standards. The institute offers licenses to use its patent-protected innovations and markets its range with the help of external partners. ISAS also promotes spin-off projects of its employees and makes its work accessible to a wider public by regularly presenting its research at trade shows and career fairs, participating in high-profile events such as science nights and the nationwide Girls' Day, actively communicating research results to the media and organising a lively exchange between science and regional politics at the annual event *Leibniz at the State Parliament (Leibniz im Landtag).*

Cooperation

Another important factor for the realisation of our objectives is our interaction with scientists from various disciplines throughout the world. Therefore, ISAS continues to expand not only its own interdisciplinary competences, but also its network in the national and international scientific environment. Of particular significance is our collaboration with with regionally based universities such as the TU Dortmund University (Technische Universität Dortmund), the Ruhr-Universität Bochum, the University of Duisburg-Essen (Universität Duisburg-Essen) and the TU Berlin (Technische Universität Berlin) and with the Julius-Maximilians-Universität Würzburg. Nationwide networking is enhanced by the inclusion of ISAS in Leibniz Research Alliances, such as the *Health Technologies, Healthy Ageing* and *Bioactive Compounds and Biotechnology* networks, and by collaborative projects sponsored by the Federal Ministry of Education and Research. International partners support us in long-term research projects, such as the International Cardio vascular Disease Network, and in EU- funded research consortia.


Thermo
Steri-Cycle
CO2 Incubator
HEPA
Dräger
HERAsafe
Vorsicht Pontochnitte schwerge

DISEASE MECHANISMS AND TARGETS



The Disease Mechanisms and Targets research programme focuses on a key aspect of medical research: the investigation of molecular mechanisms involved in the development and progression of diseases. These studies can make important contributions to the prevention and successful treatment of diseases, as they provide starting points for new concepts in diagnosis and therapy.

In order to obtain a detailed picture of such molecular disease mechanisms, this application-oriented research programme uses multi-method approaches that combine complex data on proteins (proteomics), fats (lipidomics) and the resulting degradation products (metabolomics) to assemble a comprehensive overview of a pathologically relevant process. ISAS has developed these »multiomics technologies« in a manner that bridges the gap between departments and groups and combines physical, spectroscopic, spectrometric and imaging methods. An important focal point of this programme is on cardiovascular diseases, from heart failure and myocardial infarction to thrombocyte dysfunction.

Molecular Tools for the Investigation of Proteases

Working group Protein Dynamics

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Junior research group
CARS Microscopy
Working group Protein Dynamics

The Chemical Proteomics project group uses a synthetic chemistry approach to design and synthesise molecules that covalently modify proteins in order to facilitate or improve their analysis. Notably, the project group is developing fast routes to activity-based and affinity-based probes for proteases as well as linker strategies to identify the binding sites of these molecules. In general, these probes are equipped with identification markers such as fluorophores for use in the high-resolution imaging of active proteases in cells and tissues using fluorescence microscopy. Another identifier concerns an alkyne mini-tag. This label, which consists of only two atoms, minimises problems with cell permeability and prevents any steric collision with the target enzyme that other, more bulky, labels may have. The alkyne mini-tag is used for functionalisation with biotin, which is mediated with click chemistry for enrichment and target identification by means of tandem mass spectrometry. In addition, the alkyne enables CARS imaging of the targets without functionalisation.

During the reporting period, the Chemical Proteomics project group succeeded in developing and incorporating novel photoaffinity building blocks that can be cleaved using mass spectrometry. In particular, these tools contain a sulfoxide MS-cleavable linker and a photoreactive diazirine group. When installed in a chemical probe, photoaffinity labeling and cleavage leads to only a minimal modification at the labeling site, which makes it easier to identify this binding site. In order to verify the concept of this approach and to illustrate the usefulness of these reagents, these building blocks were incorporated into the general aspartyl protease inhibitor pepstatin A at various points. Although aspartyl proteases account for only a small portion of the total amount of proteases in humans, they play an important role in pathophysiological processes such as cathepsin D in cancer and gamma-secretase in Alzheimer's disease. After successful synthesis, the researchers biochemically validated these probes in vitro, which confirmed the covalent binding mechanism and general applicability in the study of aspartic proteases.

Molecular Mechanisms of Heart Failure

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Working group
Bioresponsive Materials
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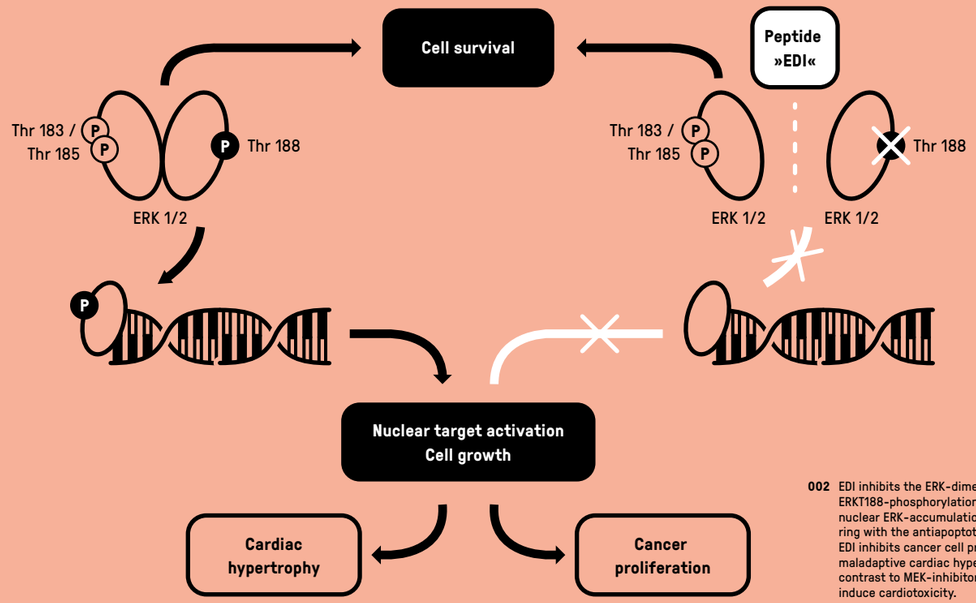
The molecular mechanisms that cause the initiation and progression of a disease and the parameters influencing its course are still largely unknown for many diseases, including the very widespread lifestyle disease, hypertension. In order to improve diagnostics and therapy and establish new therapeutic approaches, it is necessary to precisely define disease mechanisms and identify new target molecules. This project focuses on cardiovascular diseases.

Kinases have many key functions in the body, both physiological and pathophysiological. Consequently, the undirected or non-selective inhibition of kinases can lead to a number of undesirable side effects. The identification of pathogenic modifications or interactions of the kinases could facilitate a targeted therapy. For example, blocking certain protein-protein interactions (PPI) to control the localisation of kinases, instead of inhibiting the catalytic activity, could make it possible to selectively block certain kinase functions. The definition of these signaling pathways is expected to lead to an improvement in the treatment of cardiovascular diseases in the long term. It will also provide information on new approaches to other diseases, such as tumor diseases, for which kinase inhibitors are often used as therapeutic agents.

The group is investigating several strategies for selectively influencing kinase functions in the heart. For this purpose, it conducted an analysis of several inhibition strategies for the ERK1/2 and GRK signaling cascade which assumes important functions in the heart. In this context, the group worked on strategies to activate beta-adrenoceptors via PPI inhibitors and had several collaborations with colleagues in which ERK1/2 regulatory mechanisms in volume-overload and heterotopic heart transplantation as well as the ERK1/2 signaling network were analysed.

The group further collaborated with clinical partners for the retrospective characterisation of several patient entities with aortic valve stenosis to identify prognostic parameters using patient data before and after aortic valve replacement. In addition, the group collaborated with the Standardisation and Protein Dynamics groups to set up quantitative and qualitative mass spectrometric assays for the further definition of key signaling pathways in hypertrophy and heart failure as well as neuromuscular diseases and to advance the analysis of cardiovascular diseases, which could prospectively represent an important translational focus.



002 EDI inhibits the ERK-dimerisation and ERKT188-phosphorylation and thus the nuclear ERK-accumulation without interfering with the antiapoptotic ERK-functions. EDI inhibits cancer cell proliferation and maladaptive cardiac hypertrophy, but in contrast to MEK-inhibitors, it does not induce cardiotoxicity.

Proteomewide Detection of Protein-Protein Interactions

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In this project, the researchers are developing an experimental and informatics approach to identify protein-protein interactions by chemical cross-linking and mass spectrometry (CLMS). This approach uses the specific properties of cyanurbiotindipropionyl-succinimide (CBDPS), an affinity-labeled and isotope-coded cleavable reagent for mass spectrometry.

The use of an in-house software pipeline which uses the specific properties of the reagent for improved data analysis led to a significant improvement in the application of the CLMS technique with regard to the detection, acquisition and identification of the cross-linked peptides. This approach was evaluated on intact yeast mitochondria. The results show that hundreds of unique protein-protein interactions have been identified at the scale of the organelle proteome. Both known and previously unknown protein-protein interactions were identified and the methodology thereby validated. In addition, the project group found that the identified limits of the cross-linking distance were in good agreement with existing structural models of protein complexes involved in the mitochondrial electron transport chain.

Proteogenomics for New Cancer Detection Strategies

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Proteogenomics is an area of life sciences that combines proteomics, genomics and transcriptomics to improve precision medicine based on molecular phenotyping. It can be used to identify and quantify new sequences that have been created by means of point mutations. In 2016, ISAS joined forces with some of North America's leading research institutes to develop new strategies for the detection and treatment of cancer. Our partners include the US National Cancer Institute of the National Institutes of Health and three Canadian universities: McGill University in Montreal, the University of Victoria and the University of British Columbia in Vancouver.

The test for activating KRAS *(KRAS = Kirsten Rat Sarcoma)* mutations is already being used in precision oncology to select those colorectal cancer patients who are eligible for anti-epidermal growth factor receptor treatment (anti-EGFR treatment). Because even tumors with the KRAS gene have EGFR response rates below 30 percent, patients need to be better stratified. In cooperation with international partners, the project group performed proteogenomic phenotyping of KRAS wild-type and KRAS-G12V-CRC liver metastases *(mCRC — metastatic colorectal cancer).* The researchers detected 9000 proteins. They found significant expression changes in many proteins, including those involved in the progression and resistance of CRC. They identified peptides representing a number of predicted somatic mutations, including KRAS-G12V. A multiplexed parallel reaction monitoring (PRM) assay was developed for eight of these peptides to accurately quantify the mutant and canonical protein variants in the samples. This enabled the phenotyping of eight mCRC tumors and six paired healthy tissues by determining mutation rates at protein level D.

Total KRAS expression varied among the tumors (0.47–1.01 fmol/µg total protein) and healthy tissues (0.13–0.64 fmol/µg). The G12V mutation levels were 42 to 100 percent in KRAS-G12V-mCRC, while one patient presented with only 10 percent KRAS-G12V but 90 percent KRAS wild type. This could represent a missed therapeutic opportunity: Based on the DNA sequencing, the patient was excluded from anti-EGFR treatment; instead, he received chemotherapy. And this, despite the fact that PRM-based tumor phenotyping indicated that the patient might potentially benefit from anti-EGFR therapy.

In a later project phase, the researchers demonstrated that proteogenomics, by combining proteomics, genomics and transcriptomics, can considerably improve the annotation of a genome in poorly studied phylogenetic groups for which homology information is missing. For this reason, and because it can be advantageous to re-examine genomes that are already well-annotated, the project group used a newly developed proteomic genomics approach that combines standard proteogenomics with de novo peptide sequencing. The aim: to refine the annotation of the well-studied model fungus Sordaria macrospora. The project group studied samples at different developmental stages and under different physiological conditions. The experiments led to the detection of 104 previously unknown protein and annotation changes in 575 genes. This included a precise determination of 389 of the splice sites. Our strategy provides peptide-level evidence for 113 variations of individual amino acids and 15 C-terminal protein extensions derived from A-to-I RNA editing. Coexpression and phylostratigraphic analyses of the newly annotated proteome suggest that additional functions in evolutionarily young genes can be correlated with different stages of development. This advanced proteogenomics approach, specifically the combination of proteogenomics and de novo peptide sequencing analysis in combination with Blast2GO and phylostratigraphy, thus supports and promotes functional studies and fungal model systems.

The partly completed and planned assay development is also of key importance to the cardiovascular and neuromuscular projects; it promotes analytically strong imaging and ultimately, simpler analysis of signal transduction in the heart, skeletal muscle and thrombocytes, among others while providing direct access to the data of many central signaling cascades in tumor diseases and thus potentially interesting biomarker candidates for other diseases.

New Injection and Ionisation Sources for Small Molecules

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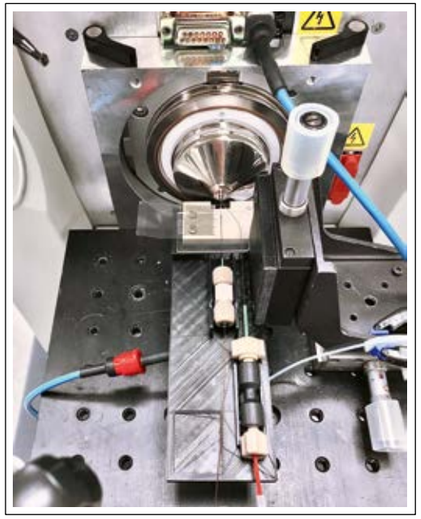
The aim of this project is to develop and investigate a new combined injection and ionisation technique to improve the sensitivity and detection limit of lipids and provide a new fragmentation tool for intact proteins, peptides and synthetically modified peptides.

As the result of the measurements depends on the precise calibration of the ESI and plasma to the MS inlet, the measurements were first repeated on the total lipid extract from bovine liver, and the results were verified. Arsenic-glutathione complexes should be determined using the injection ionisation system which is believed to play an essential role in both the metabolism and transport of inorganic arsenic and its methylated species. Unfortunately, this was not possible with the new injection ionisation system.



003 Synchronisation of Fμtp with ESI as an injection system.

CAP for Tissue Repair and against Myocardial Infarction

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The therapeutic potential of cold atmospheric plasma (CAP) has proven to be a promising new option in clinical studies. In recent years, clinical applications have focused on tissue repair, the treatment of infectious skin diseases, applications in dentistry and cancer treatment. Starting from the basic understanding that the biological effects of CAP are most likely caused by changes in the fluid environment of cells and dominated by reactive oxygen and nitrogen species, the project group has identified the basic mechanisms of biological plasma activity.

In order to obtain a suitable and reliable CAP, more in-depth knowledge is required to control and adjust plasma parameters and plasma geometries. After previously conducted experiments concerning the effect of plasma-treated or plasma-activated Krebs-Henseleit buffers, additional studies were necessary to investigate the influence of the surrounding atmosphere on the interaction between the plasma jet and buffer. To this end, the project team carried out extensive mass spectrometric measurements. These measurements must be carried out on another plasma, the Flexible Microtube Plasma (FμTP). Because other plasma gases can be ignited at relatively low voltages, these studies should also be carried out with several different plasma gases.

The project team also investigated the hypothesis that plasma nitrite levels are reduced in people with endothelial dysfunction, and that the decrease correlates with increasing numbers of cardiovascular risk factors. Therefore, it might be of interest to increase the nitrite concentration with blood plasma treatment in order to reduce the cardiovascular risk factor, for example in ischemia-reperfusion injury. It should be possible to perform this blood plasma treatment by applying a CAP.

In a next step, the idea of a controlled atmosphere will be adapted to the treatment of biologically significant samples. This is done by integrating the newly developed FμTP at ISAS. The combination of FμTP and controlled atmosphere is being studied for its effect in the interaction with cardiomyocytes by varying several parameters and measuring the protection against a simulated myocardial infarction.

BIOMARKERS

As a complement to the Disease Mechanisms and Targets programme, the Biomarkers programme works on finding specific, reliable markers and measuring them with high precision in a biological system. Screenings can identify molecules that are in key positions and whose detection may, for example, facilitate a diagnosis or indicate the success of a therapy. The use of highly precise methods is particularly important here, as there is an enormous number of potential markers in biological systems which are usually influenced by various factors.

The projects in the Biomarkers research programme therefore focus both on the identification and validation of biomarkers and on the detection of these types of molecules in complex biological matrices. Important synergies with the Imaging and Biointerfaces programmes are also being established in this respect; they are developing the necessary technologies to measure validated biomarkers in very small sample volumes and, in the best case scenario, non-invasively, in order to facilitate an early, reliable diagnosis.

Global Characterisation of Proteins and Protein Dynamics

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In recent years, the Protein Dynamics group has developed, among other things, universally applicable standards for mass spectrometric analyses and worked on software solutions for data evaluation. The ISAS researchers have continuously furthered the development of these basic procedures to ensure the quality and reproducibility of the measured data and have consistently integrated them into workflows for the analysis of clinically relevant samples, for example platelets.

This project group's in-house work with human platelets demonstrates that it is possible to obtain a reproducible, time-dependent, quantitative determination of the concentrations of partially modified proteins over four to five orders of magnitude in human cells. Since the beginning of the systematic improvement, the sensitivity of the methods has been increased by a factor of twenty; for example, 50 µg platelets are currently sufficient to perform a quantitative proteome analysis. In parallel, the analysis time has been reduced by a factor of five, the number of quantitatively detectable proteins has been tripled, and the number of detected phosphorylation sites has increased tenfold.

Moreover, the researchers have continued to work on establishing data-independent analyses of complex biological samples. They conducted a worldwide study with eleven partners in Europe, North America, Asia and Australia, which verified that the methodology is very well suited for the application of biological samples of medium and high complexity. The results obtained to date demonstrate that further optimisation of the processes is particularly necessary for post-translationally modified peptides. In cooperation with the Leibniz Institute of Experimental Virology (Heinrich Pette Institute), the researchers were able to identify and quantify new protein targets of E2F-dependent translation. In addition to protein phosphorylations, the studies in the field of O-Glc acylation were also expanded. Modification is found, for example, in serines which can also be modified with phosphorylation. A joint publication with the University Hospital of Heidelberg indicated that this modification has a protective effect on the heart in diabetes.

The project group has also discovered that individual phosphorylation sites can make an important contribution to axonal transport and are therefore of great importance for the development of nerve cells. In collaboration with partners from the University Hospital in Essen and the Catholic University (Katholieke Universiteit) in Leuven, the Cys-BOOST technology was developed to better enrich cysteine residues bearing a nitrosylation. This modification has an important significance in the field of oxidative stress and is generally unstable and therefore difficult to detect.

The continuous development of quality controlled methods for the analysis of biomolecules such as proteins is the basic prerequisite for the high reliability, quality and efficiency of an analysis. Each component — sample collection, sample preparation, chromatographic/electrophoretic separation, high-resolution mass spectrometric analysis and software for intelligent data evaluation — must be refined and validated with regard to its reproducibility, yield and efficiency. This is the only way, for example, to process and display the immense diversity of proteins in a cell in the best possible way with valid identifications.

Quantitative proteome analysis holds enormous potential for basic biological and (bio)medical research as well as clinical research. It helps in deciphering disease mechanisms and enables the detection of potential biomarkers as well as the development of targeted analytical assays for proteins which may be disease-specific.

→ **Page 35 ff.**
Molecular Tools for the Investigation of Intramembrane Proteases

Analytical Methods for Bioactive Lipids Possible Using the Newly Developed mzTab-M Format

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After establishing methods for the analysis of central lipid classes such as phospholipids, sphingolipids, glycerolipids and cholesterol esters, ISAS researchers began to establish methods for the analysis of bioactive lipids. They initially concentrated on the mediators derived from polyunsaturated fatty acids such as eicosanoids, octadecanoids and docosanoids. These mediators pose a particular analytical challenge not only because of their low concentration but also because of their sensitivity to oxidation.

By the end of 2019, the project group had succeeded in establishing methods for 50 different mediators. These are of central importance and indispensable as soon as a comparison of data on signal transduction from lipidomic and proteomic studies is needed.

Mass spectrometry is one of the most important techniques for the analysis of small molecules in metabolomics studies. Thus far, there are only a few approaches to the standardisation of data, which is partly due to the use of numerous software packages for data export. Therefore, the experimental data are presented in different formats. This makes data exchange, database storage and re-analysis very challenging. In cooperation with the Metabolomics Standards Initiative, the Proteomics Standards Initiative and the Metabolomics Society, the project group has developed the mzTab-M format in order to provide a common output format. The format was developed iteratively over several years in cooperation with various stakeholders. mzTab-M is a simple text format separated by tabs, where the structure is realised by a detailed specification document closely linked to the validation software. It also uses a controlled vocabulary. The project group expects broad acceptance due to the flexibility with which the format is implemented.

Metabolomics with the Aid of Scaled-Down NMR Spectroscopy

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NMR spectroscopy is a highly informative method of analysis for which a proton NMR detector based on microslot waveguides was developed at ISAS. The motivation for a development such as this was the obstructive limitation of nuclear magnetic resonance spectroscopy (NMR spectroscopy) in the area of sensitivity, in that the mass and volume of a sample can be used only to a limited extent. One way to get around this limitation is the µscale, i. e. highly sensitive radio frequency detectors based on waveguides. These detectors are typically built with a helical coil geometry, which in turn creates other restrictions for the sample and prevents measurement on microchips. Compared to a standard NMR sample head, this offers approximately 90,000 times higher sensitivity for such volume-limited samples. With a detection volume in the low nanoliter range, the detector is also ideally suited for mass-limited samples. In addition, the planar design of the ISAS probe head allows the geometry-independent use of microfluidic chips independent of the radio frequency coil, thereby drastically reducing the technical effort for the production of the microchip and consequently the overall costs.

In 2019, the group identified technical aspects that are essential for the successful metabolic analysis of breast cancer tissue samples. Their advantage: currently, all nodally negative patients receive postoperative chemotherapy after surgical removal of the primary tumor to reduce the risk of metastasis. Surprisingly, only about 30 percent of nodally negative patients present with metastases or recurrent tumors, which means that approximately 70 percent of all patients do not benefit from postoperative chemotherapy. This underscores the high clinical relevance of diagnostic procedures for the accurate prediction of metastasis formation. The group has also developed a microstrip probe head capable of generating both RF field gradient pulses and homogeneous RF pulses.

004 Top view of the Halbach magnet arrangement.

NMR spectroscopy could also play an important future role in the analysis of a metabolome: in contrast to the genome and transcriptome, inexpensive and efficient diagnostic methods for the analysis of the metabolome are currently still lacking. A large number of metabolites can be determined simultaneously by NMR spectroscopy, as it is a quantitative, non-selective, reproducible, non-destructive method. However, its high degree of complexity and high costs prevent the technology from being used at the point of care. The idea of a freely programmable detector for small molecules suitable for the analysis of a patient's state of health, and with a small footprint of approximately 1000 cubic centimeters, could enable future clinical use. The proposed technique is minimally invasive and quantitative. Up to now, the optimal control pulses used for this purpose within the scope of this project have been used to develop a low-cost method for measuring metabolic profiles using a mini-NMR spectrometer, which can serve as a molecular diagnostic test in intensive care units, clinics and medical practices. For this purpose, spin system-selective radiofrequency pulses, which are used to excite only the NMR signals of one freely selectable metabolite at a time, have been developed. The metabolic status can then be used to determine individual doses, side effects and nutritional interactions for the medications of each individual patient. This could also facilitate clinical trials on small patient groups in the future. Moreover, many diagnostic operations and biopsies could be avoided. One example is endomyocardial biopsy in controlling the success of heart transplants using alternative measurement of the line widths of the NMR-signals of lipoprotein-lipid methyl and methyl groups.

Analytics under Accredited Conditions

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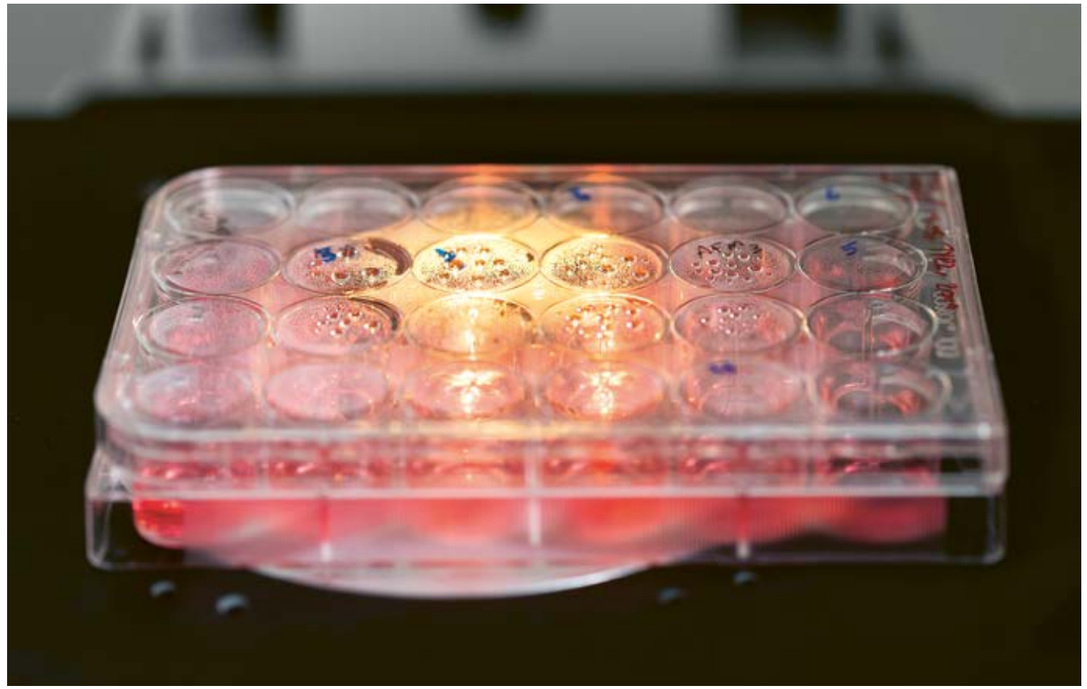
Cardiovascular diseases are the leading cause of death worldwide. According to the Federal Statistical Office, 40 percent of all deaths in Germany alone are attributable to cardiovascular diseases. Consequently, there is an urgent need for new diagnostic procedures that allow improved early diagnosis in order to preventively reduce existing risks and enable the management of treatment. In fact, despite the considerable progress made in medicine, cardiovascular diseases are usually only detectable at an advanced stage. An early, reliable assessment of risks for cardiovascular diseases may lead to a significant increase in the quality of life of those affected.

In the »Cardiovascular Disease (CVD)-Omics« project, mass spectrometric assays are now to be developed based on preliminary work, which will make it possible to detect pathophysiological changes at an early stage of CVD and enable effective prevention and treatment management. The focus here is on the analysis of platelets, which play a key role in hemostasis (blood coagulation) and thrombosis and are therefore integrally involved in the development and progression of CVD. Specific assays that map platelet dysfunction at the molecular level will be developed, certified and transferred to clinics. However, proteins in the blood plasma that are involved in coagulation and/or are risk factors are also taken into account.

Thus far, the project group has developed the respective measurement methods for more than 200 proteins. In addition, it has begun work on the technical validation, which contains information on the limits of detection and determination, specificity, repeatability and reproducibility of the method, and information on the influence of instrumental, human and environmental factors on the uncertainty of the results. The group will continue to perform this validation in accordance with standard ISO 17025.



Quantitative Proteome Analysis in Mice as a Disease Model

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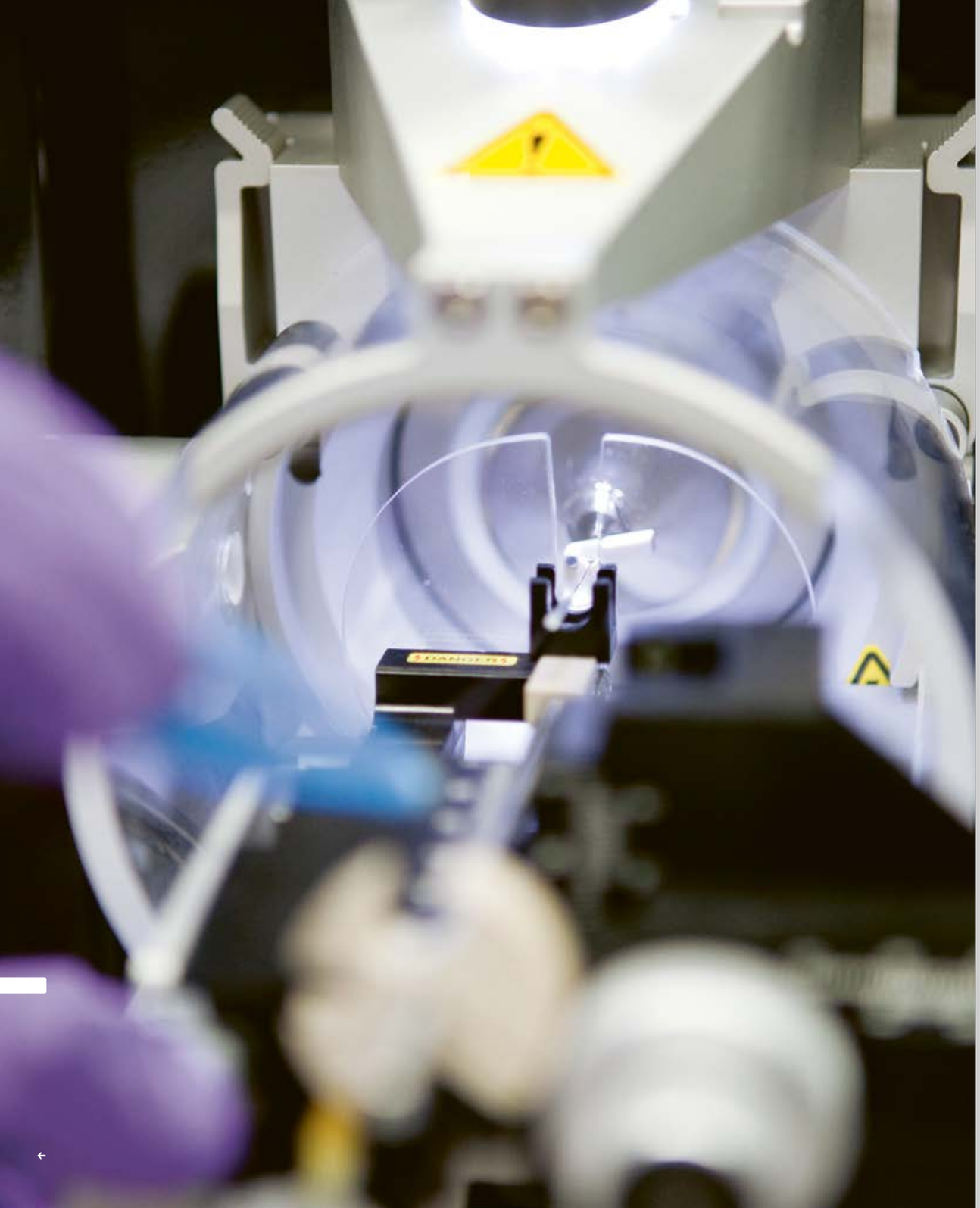
The project to decipher the mouse proteome, which was completed at the end of 2019, resulted in the development and evaluation of more than 1500 Multiple Reaction Monitoring (MRM) and Parallel Reaction Monitoring (PRM) assays for mice. To this end, the researchers synthesised more than 3000 peptides. The basis: mice are the predominant experimental model for the study of human diseases due to their physiological proximity, the ease with which they are bred and the availability of molecular tools for the genetic manipulation of mice.

However, although mice are genetically very similar to humans, it is often difficult to transfer the findings from animal experiments on mouse models to humans. The proteome, which has been studied only to a limited extent up to now due to the sheer number of proteins in a cell and the dynamics of the entire system, is one likely key to this problem. The immunoassay is currently the gold standard in clinical research and diagnostics.

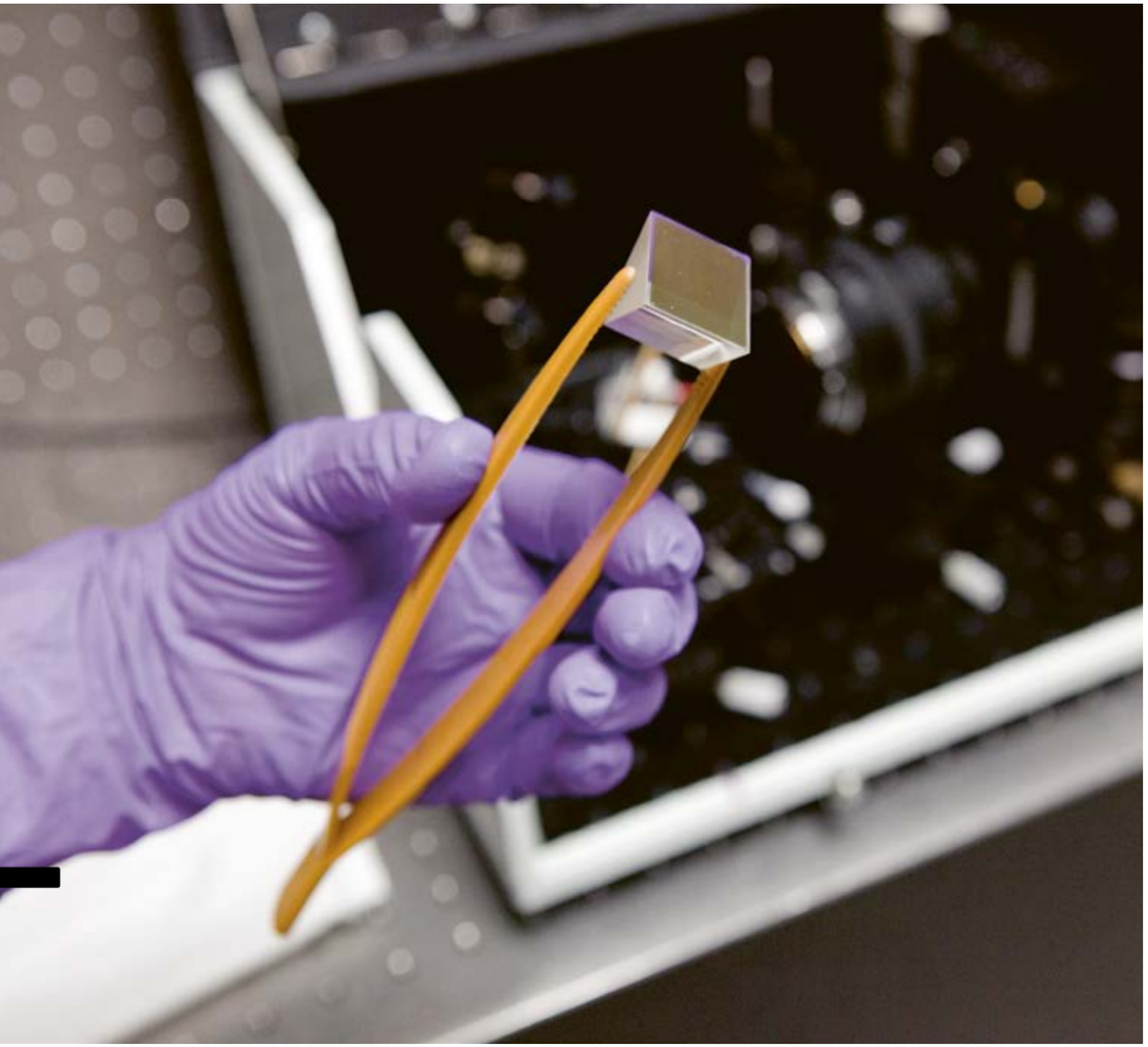


However, it can only provide limited information about individual proteins in a sample and fails to detect many, if not most, of the potentially important proteins. On the other hand, other methods do not provide information regarding protein quantities, which are essential for a true understanding of a dynamic system.

The aim of this project was, therefore, to replace immunoassays in the clinic and in the laboratory with mass spectrometric assays. For this purpose, easy-to-use, quantitative proteomics kits which facilitate the deep molecular phenotyping of mice were developed for 20 different mouse tissues. These comprehensive proteome analyses provide a much deeper insight into cellular systems and processes in diseases than genome data and may therefore also improve the transfer of scientific knowledge from mice to humans.

Advances in genome editing methods, such as CRISPR-Cas9, enable the rapid production of new transgenic mouse strains, which requires complementary high-throughput, systematic protein phenotyping techniques. Unlike conventional protein phenotyping techniques, MRM mass spectrometry can be highly parallelised without sacrificing specificity or quantitative precision. At this point, the project group presents MRM and PRM assays for the quantification of proteins. These assays encompass a wide range of research applications including phenotypic validation of novel transgenic mice and the identification of candidate biomarkers and general research applications requiring parallel, accurate protein quantification. In addition, these results have significantly advanced the work of ISAS in the Disease Mechanisms and Targets and Biomarkers programmes; first, the kits can help to better characterise the mouse models used in some projects and second, they will help in the use of analytical results to improve our understanding of diseases and identify a large number of potential targets.

IMAGING



ISAS has many years of experience in spectroscopy. The project teams in the Imaging research programme are working on improving optical methods for imaging applications in medical research. Their aim is to obtain molecular information with the highest possible spatial resolution using marker-free, marker-based, non-destructive and fluorescence spectroscopy as well as Raman and Coherent Anti-Stokes Raman Spectroscopy (CARS) and multiphotonic-based combination concepts. As both the quantity of a biomarker in a system and its precise spatial location can be essential for a disease mechanism, these optical developments are an important prerequisite for new diagnostic possibilities.

Multimodal and multidimensional identification methods such as these can be used for diagnosis and the selection of treatment in hospitals and clinics, particularly in the case of cardiovascular diseases. Since its inception in 2017, the programme has integrated additional biospectroscopic approaches and biological model systems and advanced methodological cooperation in the projects. Networking with all other research programmes has also been intensified.

Bio / Synthetic Multifunctional Microproduction Units

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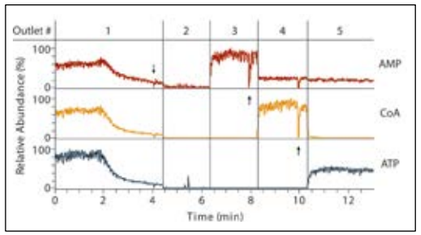
The development of new substances for medicine, food and agriculture poses an enormous challenge for application-oriented research. There is currently a lack of new medications for combatting life-threatening infectious diseases, some of which are no longer treatable with commercially available antibiotics. In agriculture as well, the yields of the few crops used to feed the world are massively threatened by climate change and microorganisms that are increasingly showing resistance to existing plant protection products. Although the pipelines of the big industrial enterprises are largely empty, the extremely successful establishment of new genome-based and metabolome-based methods for drug discovery over the last five years has led to promising new perspectives for the discovery of new natural product-based therapeutics, which are being taken up by many industrial enterprises.

The integration of the new technologies into existing production processes will play an important role in this area in the future. This will entail the mastery of complex biosyntheses and the creation of bio/synthetic multifunctional production units which enable



005 Scheme of µFFE-MS for simultaneous sample separation and analytics (above), measurement result (below) with undivided analytes without voltage (output 1, start) and separation of the analytes with tension to different outputs (3,4,5).

the micro-scale production and de novo design of new active substances. The majority of microorganism species (fungi and bacteria) have not yet been cultivated. Metagenomic studies show that scientists have identified considerably less than one percent of all microorganisms. In order to acquire new products, it is now possible to decipher the genetic information of even previously unknown organisms and decode the information contained in microbial or plant cells or give these organisms new, useful properties.

Such endeavors have previously been associated with considerable problems and are often not technologically feasible. Only in a very few cases has it been possible to optimally adapt these organisms for the production of certain substances or for certain processes. There are usually too many natural barriers, resulting, for example, from genome instability or other restrictions based on the physiology of the organisms. The simple insertion of the decoded genetic information into more industrially acceptable microbial systems is often extremely difficult, and therefore also not an ideal solution. Biotechnology, and cell-free biotechnology in particular, offers solutions that will help to overcome many of these problems, decoupling production from the original organisms or organisms at all.

The institutions of the Leibniz Association have extensive expertise in important core competences of biotechnology (including microbiology, genomics, biotechnological production technologies and biochemistry) and engineering sciences (such as microfluidics, nanotechnology, membrane technology, modelling and simulation and microsystems technology) relevant to this.

After their development and establishment in 2019, the focus for many of these techniques was on optimisation and application as well as preparing the data obtained for publication.

The scientific advisory board of the Leibniz Research Cluster (LRC) attributed promising potential to the Common Demonstrator, which was to summarise the overall results of the LRC as a joint project and was developed and set up at ISAS in communication with the Leibniz Institute for Natural Product Research and Infection Biology —Hans Knöll Institute (HKI) in Jena. The continuing development is now aimed at documenting the potential of the Demonstrator as an analytical and prototype production system, whose possibilities can be used for enzymatic production within the lab or outside in the field.

Laser Desorption Plasma MS for Detection of Small Molecules in Tissue Sections and their Coupling with Raman Spectrometry

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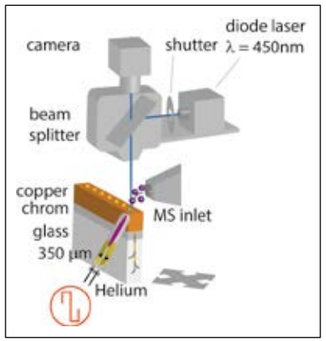
Biological cells and tissues are largely composed of proteins, lipids and nucleic acids. In vibrational spectroscopic methods such as Raman spectroscopy, the contrast of the image is based on molecular properties from which information about chemical compositions and molecular structures in tissues and cells can be obtained directly without the use of markers, as in optical microscopy.

Lasers, with which samples could also be desorbed from the surface at higher coupled power, are used for excitation. In order to be able to determine these using mass spectrometry and ionise them beforehand, the desorbed molecules would have to be removed with the help of a venturi pump.

This allows the spatial resolution of Raman and mass spectra to be determined in two successive steps. In this way, two previously separate methods are coupled, so that information about the structure can be collected and the concentration can be determined at specific locations.

In 2019, it became apparent that both the transport system and the plasma used seemed to be responsible for a poor ion yield. Therefore the laser, the substrate from which the molecules are to be desorbed, and the plasma were positioned as close as possible to the inlet of the mass spectrometer. The plasma jet was replaced by a FμTP to increase ionisation efficiency and minimise space requirements. A camera mounted on the lens tube was used to enable a determination of the desorption site, i. e. the place where the laser beam strikes the substrate. This enabled the installation of the laser beam via a coupling mirror. A camera mounted on the tube from above can determine the location of the laser on the substrate.



006 Experimental setup of the desorption unit in front of the MS inlet.

The next step was to desorb a standard sample of *Avanti Total Liver Extract*. Measurements on free cholesterol and on pure cholesterol ester samples showed that the cholesterol esters did not fragment into cholesterol and ester; rather, larger masses than the cholesterol ester were observed in the measurements. We were able to measure cholesterol calibrations by means of cavities on the surface of the substrate.

With a modified setup and a motorised sliding table, it should be possible to perform measurements on a microtome section of a liver or heart sample. Now, in 2020, the substrate surface should be perpendicular to the axis of the MS inlet, and the laser should be focused on the substrate from behind. The laser and the MS inlet axis form a line. The microtome section is fixed on the side of the substrate facing the MS.

Multimodal Imaging Concepts

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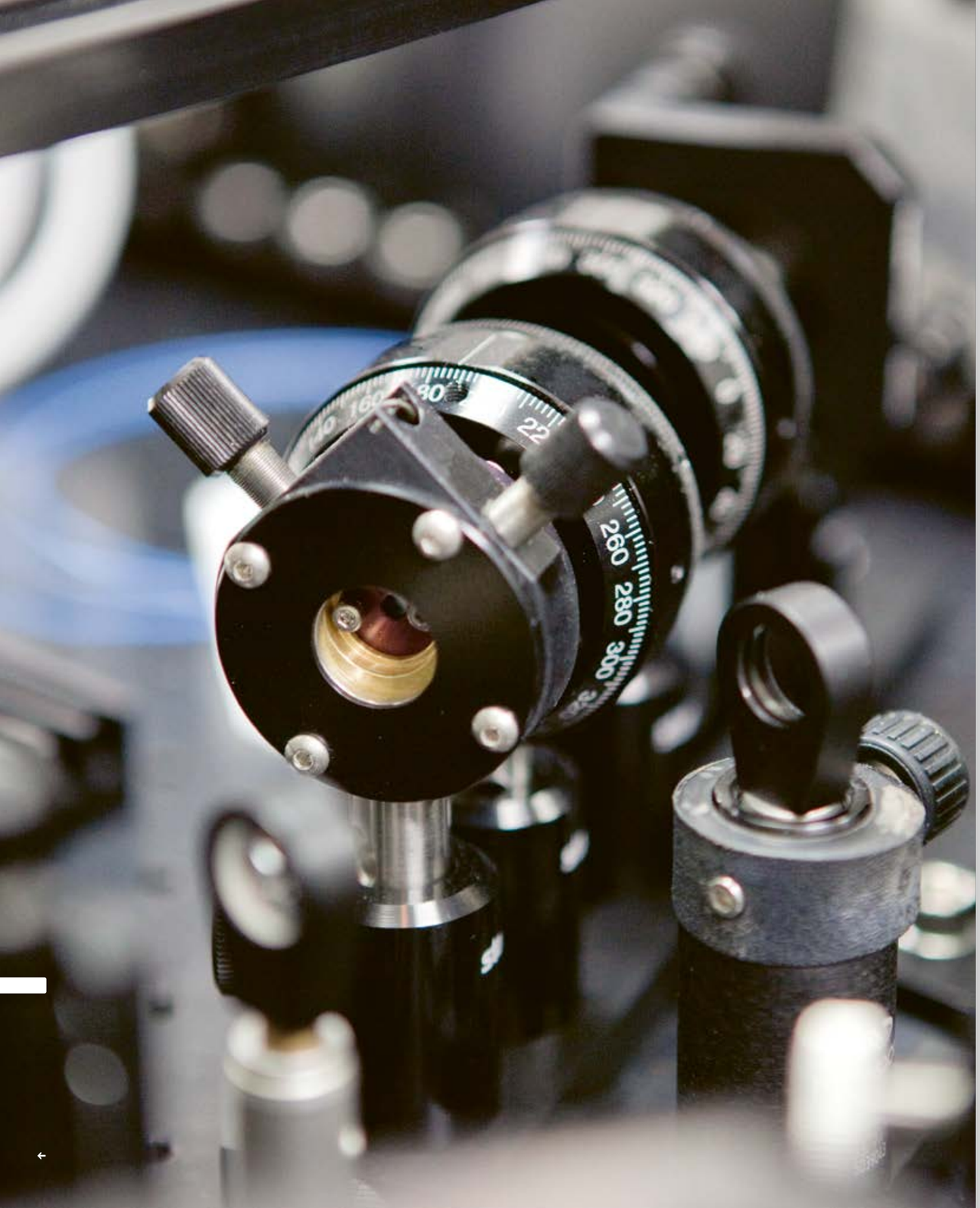
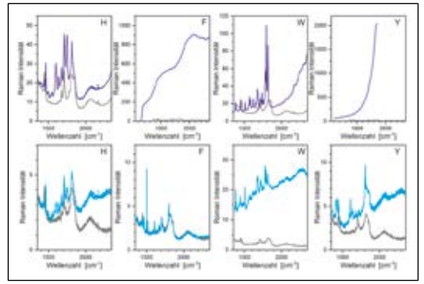
In cooperation with:
Working group
Cardiovascular Pharmacology
Junior research group
CARS Microscopy
Working group Miniaturisation

The aim of this project is the development and application of multimodal and multidimensional methods for the characterisation of heart and muscle tissue. Special emphasis is placed on the acquisition of molecular information with a high spatial resolution, particularly with regard to applications in biomedical research. Therefore, both internal and external partners are involved with corresponding biomedical issues in the project.

The long-term objective is to establish the multimodal approach to issues in biomedical research. Cardiovascular diseases are the most frequent cause of death both in Germany and the world. With this project, the researchers aim to develop a new multimodal, multidimensional approach for the identification of disease mechanisms and to validate this approach using model systems. At the same time, they aim to integrate biospectroscopy into existing structures.





007 Raman measurements of amino acids in acetate buffer solution. Above: Measurements at 266 nm; below: Measurements at 355 nm. The amino acids histidine (H), phenylalanine (F), Tryptophan (W) and Tyrosine (Y) are shown. Reference spectra of the buffer solution are shown in grey.

In 2019, the focus was on the completion of the ultraviolet/deep ultraviolet (UV/DUV) application laboratory and test measurements. Starting with the basic setup, newly developed spectrographs and DUV lasers were installed and tested. Within the scope of the Multimodal Imaging project, the focus was on testing UV/DUV Raman spectroscopy and fluorescence for the examination of biological samples. This is an exploratory approach that has not yet been well established. During the review period, various amino acids were examined particularly with regard to their fluorescence and Raman signal in the UV spectral range with laser excitation at 266 nm and 355 nm (see Figure). This work is motivated by the question to which extent these amino acids are suitable as minimally invasive marker molecules for Raman and fluorescence microscopy on biomedical samples. In this context, it became evident that tryptophan can be used as a minimally invasive marker molecule.

The new setup for laser desorption plasma mass spectrometry (LDPMS) was also completed. We initially used a plasma jet which was later replaced by a flexible micro tube plasma (FμTP) in order to achieve even greater efficiency at a smaller size. A number of different analytes (sphingomeyelin, lecithin, cholesterol, triolein, squalene, palmitoleic, palmitic, oleic, adipic, suberic and azelaic acids) have been successfully tested on various substrates.

Using CARS microscopy, the project team was able to measure much more complex biosamples (human muscle samples) and develop analyses. The aim was to visualise the distribution of lipids and proteins in order to gain information about the effects of the respective diseases.

The Cardiovascular Pharmacology group has extended the cell morphology data obtained thus far, primarily by CARS and Second Harmonic Generation Spectroscopy (SHG), by the spectroscopic characterisation of heart muscle cells and heart tissue sections using CARS and Raman tools. The spectroscopic studies were supported by multivariate data analysis to extract the most important information from complex data sets (in cooperation with the Leibniz Institute of Photonic Technology, Jena).

BIOINTERFACES

The principle aim of the work in the Biointerfaces programme is to provide innovative biosensor concepts for the non-destructive, non-invasive diagnosis of even the smallest patient samples. For this purpose, it is essential to comprehensively characterise the interfaces, as the molecular interaction of a surface with another surface, a liquid or molecules forms the basis for the development of an accurate, clinically applicable biosensor. Another field of application of completely characterised solid-liquid interfaces is the biofunctional coating of implants, such as an artificial joint or a stent for opening blood vessels.

The work of the programme is closely linked with projects from the Biomarkers and Disease Mechanisms and Targets research programmes, because in the process of many projects, measurement systems either have to be newly developed or adapted to specific molecules or environments, and validated.

Biointerface Ellipsometry for Development of Innovative Investigation of Biologically Relevant Samples

Working group
In-Situ Spectroscopy

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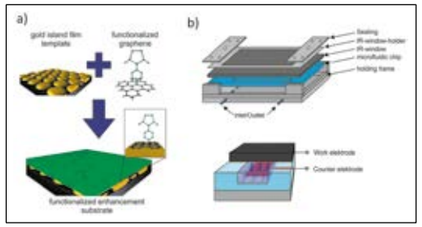

008 Microfluidic sensor for infra-red ellipsometric applications in nano- and microliter analysis:
a) functionalisation with chemically modified graphene,
b) geometry of the cell with and without electrodes.

The In-Situ Spectroscopy group conducts research into biofunctional interfaces and develops infra-red spectroscopic methods to study these surfaces. Several focal points have been defined for the purpose of studying interaction processes on these types of surfaces and make them accessible for innovative analytical methods.

In one of the principle project focal points, the team investigates nanostructured and microstructured functional surfaces and layers by means of polarisation-dependent nanoscopic and microscopic IR spectroscopy. The group is currently also setting up a laser ellipsometry application laboratory. The latter represents the first application of a laser-based »single-shot« concept in the IR range, which will enable infra-red characterisation of biointerfaces with improved temporal and spatial resolution. This is highly relevant, for example, in the characterisation and development of biochips for diagnostics and pharmaceutical research.

Innovative concepts for the investigation of biologically relevant samples, which are often only available in small sample volumes of only a few microliters, will be developed. In this context, the investigation of plasmonic enhancement substrates for surface-enhanced IR spectroscopy plays a key role. For the development of novel sensor surfaces, the project team is studying the use of a transfer of functionalised, large-area graphene. Developments for multiplex analyses with complex fluids, which can serve as models for body fluids, are a long-term objective. Another objective is the sensitive analysis of protein and peptide substrates, the in-situ analysis of biochemical reactions and drug research.

One focus of the project is the characterisation of new biohybrid interfaces, for example polymer hybrids and membranes for nano-biotechnology and medical technology.

New concepts for laser IR microscopy and IR laser ellipsometry have been successfully implemented at ISAS.

Optofluidic Platform for IR and Raman Spectroscopy

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In cooperation with:
Working group Nanostructures

Optofluidics is a field of research and technology that combines the advantages of microfluidics and optics. With the forerunner project from the Integrative Research Strategy Fund, initial steps were taken to develop an optofluidic system for the marker-free and non-destructive detection of bio-relevant molecules and the analysis of interactions in biological model systems. This will form the basis for the continued development of these systems within the scope of this project. Applications of this technology include biosensors, lab-on-chip devices and molecular analysis methods in biochemistry. In particular, optofluidic systems can be used in pharmaceutical and biochemical research for in-situ applications and can also play a role in quality control by means of on-chip detection or in the research and monitoring of molecular interactions or reactions.

The development of such a system for various spectroscopic methods and the elaboration of numerical and analytical optical interpretations will provide the possibility of obtaining complementary information from IR and Raman spectroscopy for the system under investigation and thereby enable improvements in identification and a more detailed analysis. The new platform also enables the marker-free analysis of proteins, for example research into the kinetics of oxidative stress, structural analysis or the analysis and detection of interactions in protein complexes. Synergies will arise between the Biointerface/Ellipsometry project and the Pathology of Neuromuscular Diseases project, as the applicability of the platform can be tested at various stages.

Nitride and Oxide Semiconductors for Biomolecular Sensor Technology

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Many modern applications (for example sensors or optoelectronic switches) are currently based on semiconductor microstructures and nanostructures. In the future, new developments will result from the integration of organic molecules with these types of inorganic structures, i. e. hybrid structures with specific functionalities. The physical and chemical properties of these hybrids are essentially determined by the interfaces. Examples are semiconductor components or molecule-solid-state hybrid structures, which are to be used for various technological applications in sensor technology or optoelectronics. Hybrid structures such as these are thus the basis for the development of novel functional components.

Group III nitrides and their ternary (triple) alloys in particular are very well suited for biosensory applications, as they are non-toxic, have a low solubility in water and are highly stable in biologically relevant fluids (e. g. blood). Their surface stoichiometries can be varied in a controlled manner, and their electronic properties are well known.

Based on studies on single-crystal III nitride surfaces, the properties of semiconducting nanomaterials (e. g. semiconductor nanowires) are being studied within the scope of this project with regard to their use as nanoelectronic components in the field of sensor technology. The aim is a deeper understanding of the interface processes and the electronic coupling between adsorbed molecules and the semiconductor surface under native conditions. This is the prerequisite for a rational design of biosensors in the future.

Spectroscopic Analytics of Hybrid Model Interfaces

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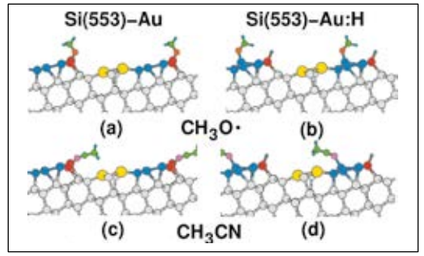
In cooperation with:
Working group
In-Situ Spectroscopy
Working group
Bioresponsive Materials

The focus is on the question of how concrete structural information can be obtained at an atomic or molecular scale at molecule-terminated interfaces from optical fingerprint spectra. For this purpose, an approach combining optical spectroscopy and quantum chemical numerical simulations at atomic or molecularly ordered interfaces is under continued development and will incorporate complementary information from scanning tunneling microscopy and photoelectron spectroscopy.

This approach is used to study hybrid model interfaces, i. e. ordered interfaces between organic molecules and semiconductors. Optical polarisation spectroscopy methods with high sensitivity or selectivity for interface structures are being developed. The molecular or atomic structure of the interfaces or the interaction of molecules and substrate can then be determined using the approach of combining spectroscopic characterisation with quantum chemical modeling. Complementary information on the local structure (scanning tunneling microscopy, STM) and the chemical binding properties (X-ray photoelectron spectroscopy, XPS) are required for validation.



009 a) and c): Adsorption structures of small organic molecules on the Au-modified Si(553) surface. The step edges are the preferential adsorption sites. b) and d): After passivation of the step edges with hydrogen, the molecules on the Si-terraces adsorb, while the Au-chains remain free.

Biohybrid Interfaces and their Application in Diagnostics

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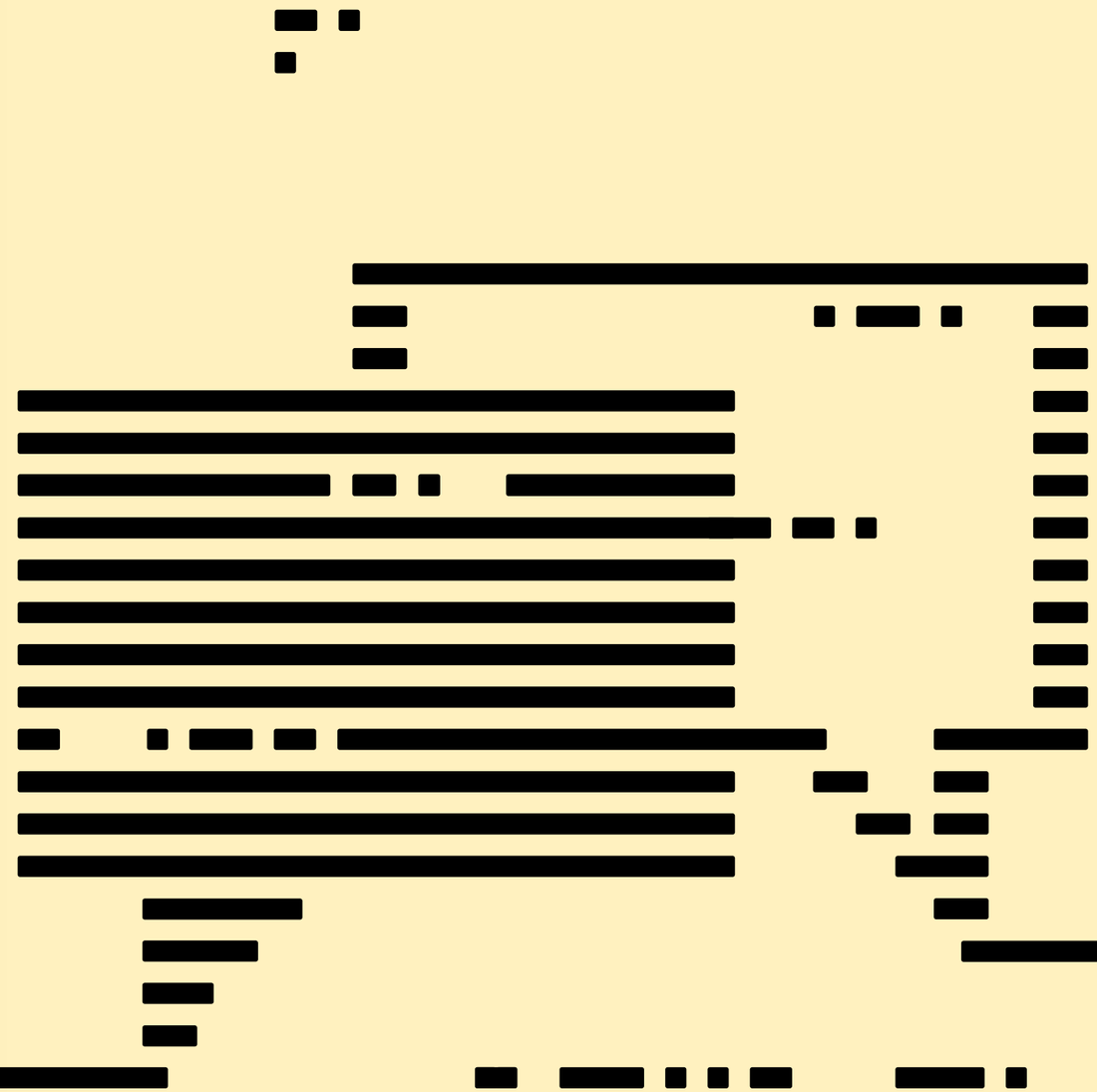
In cooperation with:
Working group Nanostructures

Interfaces constitute an important aspect in the research of new materials with specifically developed functionalities. The investigation of interfaces and interfacial processes is therefore one of the key topics of materials analysis at ISAS. Topics such as the biocompatibility of materials for implants, for example stents, new analytical sensors for the quality control of medical products, for example in the production of vaccines, new diagnostic methods such as those based on extracellular vesicles, or test methods for the biological activity of materials, including thrombogenicity, are concrete applications of the work of this project group. This work is supported by basic research on model systems using photoelectron spectroscopy under near-ambient pressure conditions. It offers an important opportunity to study the desired functionalities of new materials under realistic conditions.

For the year 2019, the successful reconstruction of Au surfaces is particularly noteworthy. This largely completed the work on the adsorption of amino acids on Au under humid conditions. The members of this project group also improved the thrombogenicity tests according to the Hemker method. However, these tests are not yet specific enough, for example to measure the improvement of strongly thrombogenic materials through specific coatings.

ABOUT ISAS



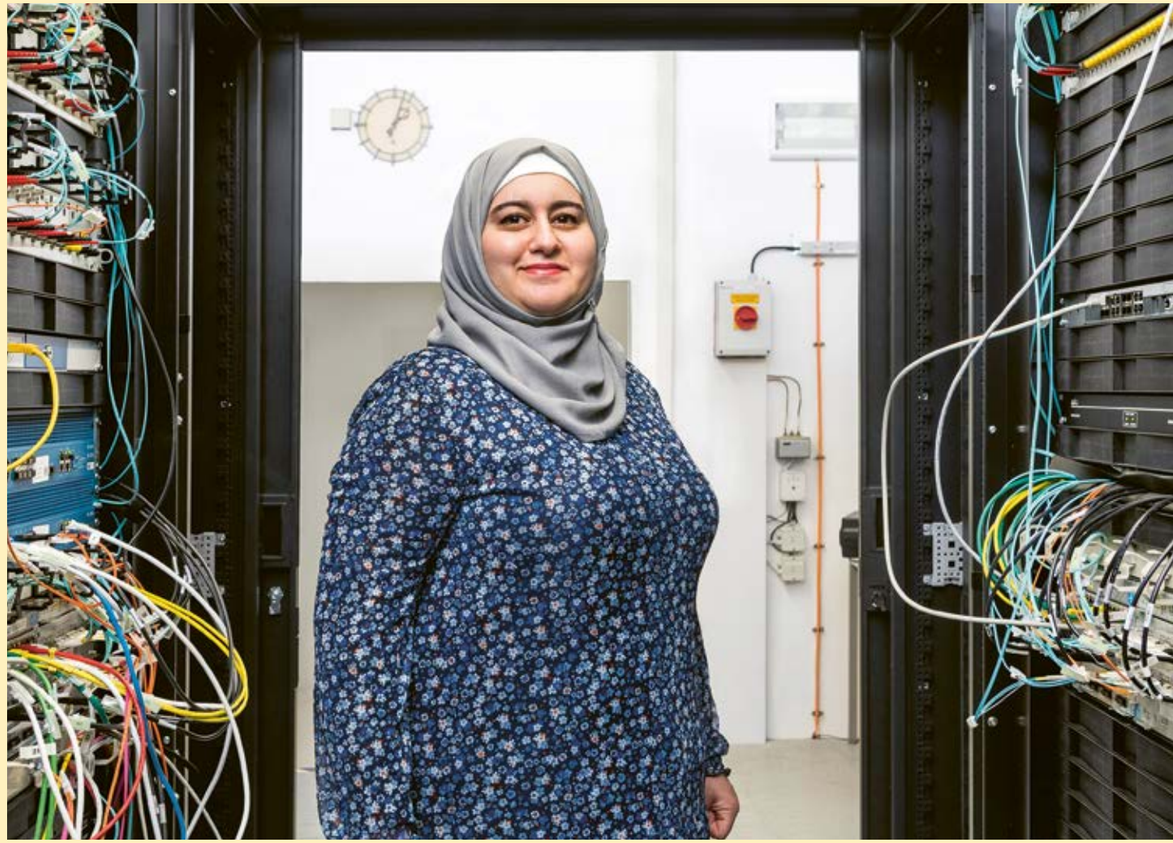
ISAS INTERNATIONAL

The Bioresponsive Matrials working group has 18 members from eight countries of origin. The group is as diverse in its disciplines as it is international. »It does not matter where people come from, it is important that they are motivated and creative«, says Dr. Roland Hergenröder, head of the working group. In his team, different personalities have come together to share their career path, their skills and their know-how at ISAS.

We have met with two of them, PhD-candidates Lubaba Yousef Hazza Migdadi and Mohammad Ibrahim Alwahsh. ISAS maintains a regular exchange programme with Jordan, their home country. There are also close ties with Heidelberg University (Ruprecht-Karls-Universität) and the TU Dortmund University (Technische Universität Dortmund), where Lubaba and Mohammad have registered their doctoral theses. Both of them come from different fields of research and, with their individual backgrounds, ideas and goals, add up to their team's versatility.

→ Page 14 ff.

See feature »Metabolomics and the Understanding of Complex Systems«



Lubaba Yousef Hazza Migdadi

Working group
Bioresponsive Materials

PhD student at TU Dortmund University (Technische Universität Dortmund)

Machine Learning Methods for Analysing 2D NMR TOCSY Spectra of Metabolite Samples

Lubaba Yousef Hazza Migdadi is a computer scientist. Her focus is on machine learning and pattern recognition. She holds a master's degree in software technology (Hochschule für Technik Stuttgart) and a master's degree in automation und robotics (TU Dortmund University). For her PhD at TU Dortmund University (Professor Dr. Christian Wöhler), Lubaba is currently working on the development of automated computer based analysis of 2D-NMR spectrums based on algorithms of machine learning which allow fast, precise and systematic evaluations. This analysis enables measurements with low resolutions and more people who can take them. Until now, this kind of analysis could only be conducted manually, by specialists, and in a slower manner. It therefore represents an important step in the further development of metabolome analyses with the NMR spectrometer.

»My work mostly consists of programming. With machine learning strategies, it is possible to evaluate data quickly and reliably.« For her, success means »finding ways and solutions in a complex data environment that will make work easier in the future.« In addition, Lubaba is also the coordinator for a DAAD joint project between Jordan and ISAS, which she co-organises and accompanies: an annual exchange of students and researchers for the mutual transfer of knowledge.

Lubaba's other big project is her family. She has a husband, who is a scientist as well, and three children between two and twelve years. »It is important to be realistic and organised, not to delay work and to use your time well,« she explains. At ISAS, Lubaba benefits from »flexible working hours and an attentive boss who supports me in reconciling my family and my research.«

Whether with or without a family, as a woman, a career in computer science is nowadays still special. Lubaba hopes that more women will discover such career paths for themselves, and whishes for them to be heard and to be able to give new impetus to industries designed by men. »Women can bring new perspectives to problem solving in every area.« As a specialist in the networking of knowledge, she is against the »waste of talent« due to many obstacles for women. Lubaba does not yet know which direction she and her family will take after she has completed her PhD. But she wants to continue to share her knowledge and help other women carry out their talents. She does not recall how she found her own way: »I have always been interested in science. I just saw myself there rather than in the social area. I do not know how it happened, it was just like that, it is my life.«

Mohammad Ibrahim Alwahsh

Working group
Bioresponsive Materials

PhD student at
Heidelberg University
(Ruprecht-Karls-Universität)

Analytical Toxicology and Desease Modeling

Mohammad Ibrahim Alwahsh loves scientific work: researching, experimenting, developing, taking the next step, for him ideally seven days a week. As a child, he wanted to be a doctor so that he could heal (also his own) football injuries. Now he is writing his doctoral thesis at Heidelberg University (Professor Dr. Alexander Marx and Dr. Djeda Belharazem) and working on new treatment methods for rare types of cancer, thymomas and thymic carcinoma. At ISAS, Mohammad creates 3D tumor models and examines their reactions to certain anti-cancer drugs. For this, a new technique of nuclear magnetic resonance (NMR) spectroscopy is developed and used. Thus, for the first time, online toxicity tests in living cell systems as well as metabolic profiling for human tissue samples of thymoma and thymic carcinoma are possible.

Mohammad came to ISAS as an exchange student and has been part of Roland Hergenröder's team for three years. He is a pharmacologist who mostly undertakes interdisciplinary research. »In my work I combine toxicology, biology and analytical chemistry. I can carry out biological experiments and at the same time work analytically with the NMR spectrometer. This is really special.« Mohammad considers solely working with colleagues of the same field of research nice, but »it is an advantage for our working group that we come from different disciplines and that we can help each other and increase our knowledge.« The opportunities for scientists and the good collaboration at ISAS were the reasons why Mohammad chose to continue his career in Germany.

For Mohammad as an international PhD candidate, cultural differences play a minor role. He was raised in Dubai and has been used to travelling on his own since he was a child. He is open minded—scientifically and personally. »I feel comfortable with every culture. You can learn new things everywhere, that's what I have experienced.« What he appreciates most about Germany is the high quality of research—and the good public transport system. Only his German language skills have to wait, because for him, research is just too exciting.

What is he going to do after he has obtained his PhD? Mohammad is willing to think about different ideas. In his home country, a long-term employment at Al-Zaytoonah-University of Jordan, which supported his studies, awaits him. He has already worked in the industry during his studies and has declined a good job offer because he sees himself more in science. »I love doing research and teaching. I want to share my knowledge. If I cannot make my knowledge accessible to others, I have not understood things myself.«

Therefore, his main goal is on completing his thesis and then deciding on a habilitation. »Right now, I'm concentrating on my PhD. Some people tell me to take it easy and enjoy myself. But that is what I am doing—I am young and I want to make the most of my time, every single day.«

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Jürgen Bethke,
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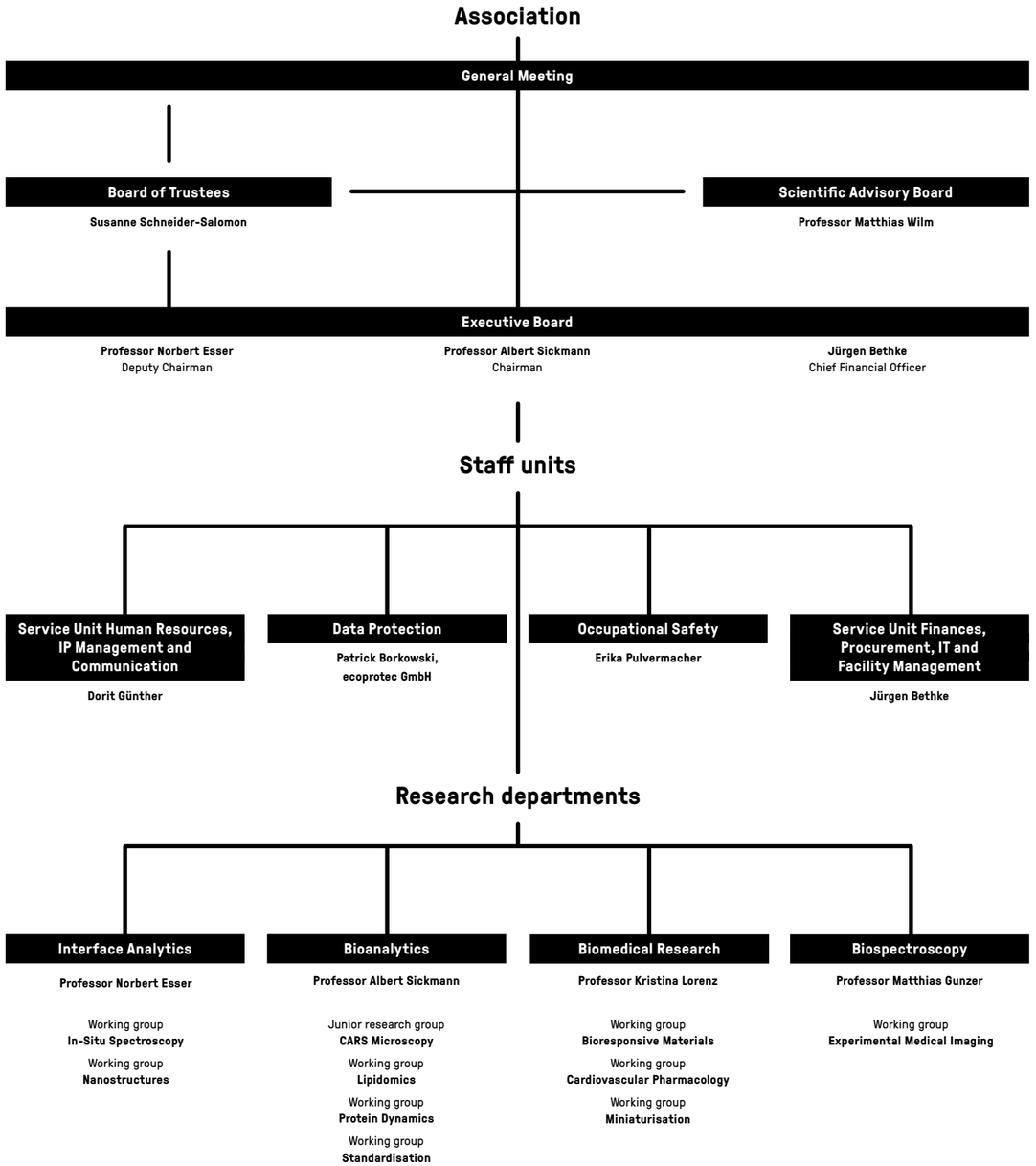

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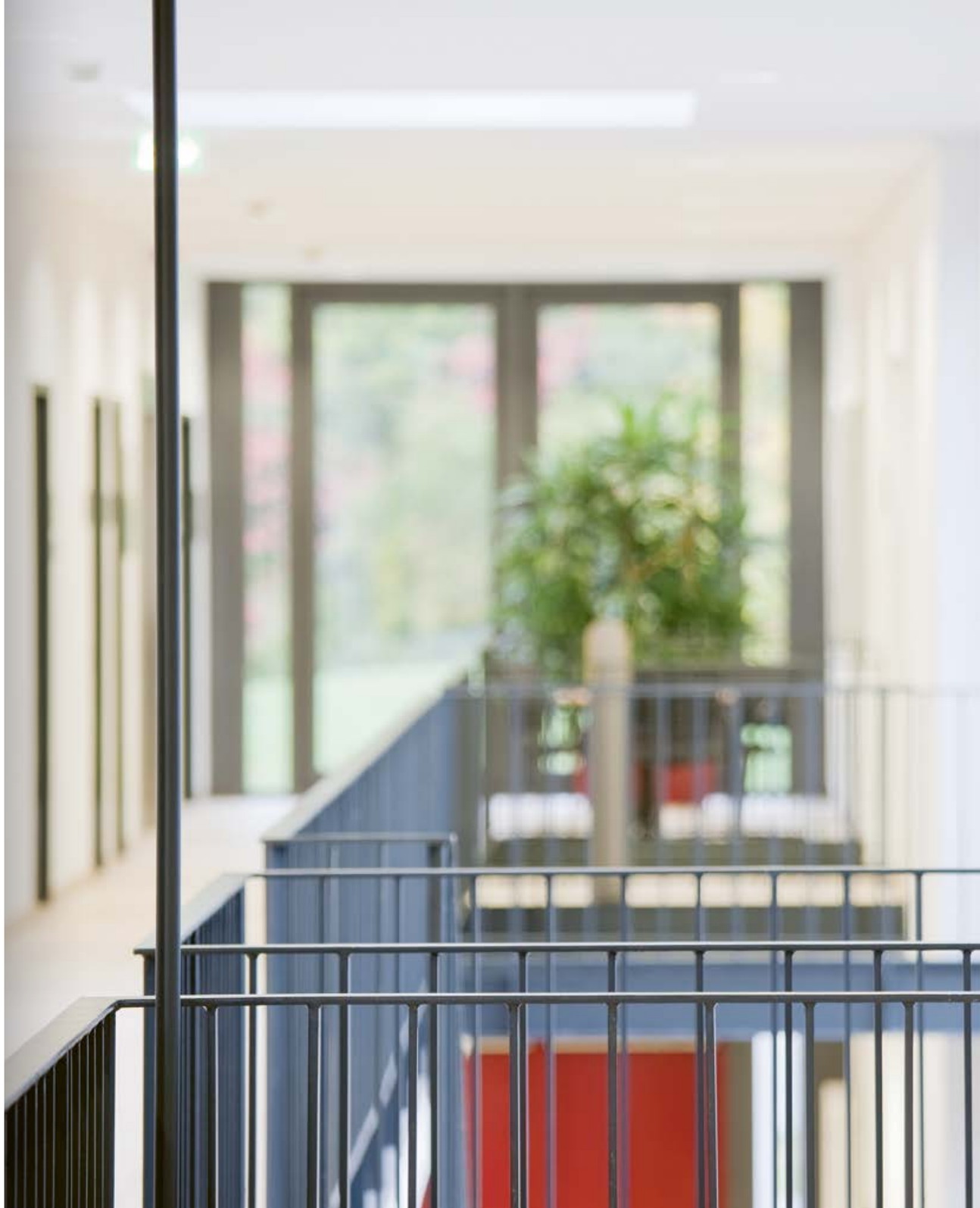

AKTIVITÄTEN 2019

ACTIVITIES 2019

Publikationen
Publications

Publikationen in referierten Zeitschriften
Peer-reviewed Papers

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Ahrends R
From lipid structure to lipid function
Analytica Vietnam 2019
Saigon, Vietnam

From lipid structure to lipid function
3rd Symposium Platelets
Tübingen, Deutschland

SIMPLEX: A Lipid Centered Multiomics Approach for Neurobiology Approach for Neurobiology
3rd International Symposium Healthy Ageing
Berlin, Deutschland

Lipidomics: from Lipid Analysis to Biological Function
3rd International Symposium Healthy Ageing
Berlin, Deutschland

LIFS: A sofware suite for the lipidomics community
Summer school on Integration of Large Scale
Lipidomics Data in Systems Medicine Research
Leipzig, Deutschland

LipidCreator a sofware suite for targeted lipidomics
52. Jahrestagung der Deutschen Gesellschaft
für Massenspektrometrie
Rostock, Deutschland

Integration of large scale lipidomics data in systems medicine research
Summer school on Integration of Large Scale
Lipidomics Data in Systems Medicine Research
Leipzig, Deutschland

LipidomicsBioinformatics
52. Jahrestagung der Deutschen Gesellschaft für
Massenspektrometrie
Rostock, Deutschland

Lipidomics Standard Initiative
5. Lipidomics Forum
Borstel, Deutschland

Borchers C
Multiplexed targeted proteomic assays for clinical studies.
EMBO Practical Course on Targeted Proteomics:
Experimental design and data analysis
Barcelona, Spanien

Modern approaches in structural and quantitative proteomics for clinical research
Douglas Hospital Montreal
Montreal, Kanada

Introduction of the Integrated McGill Proteomics Centre
Seminar at Inaugural Symposium of the Integrated McGill
Proteomics Centre
Montreal, Kanada

Clinical proteomics for improved precision medicine
3rd International Summer School PROTEOMICS – from
Introduction to Clinical Applications
Iasi, Rumänien

Relative and absolute quantitative proteomics for clinical research and diagnostics
Mass Spectrometry Imaging and Natural Products
Symposium at China Pharmaceutical University
Nanjing, China

Proteogenomics of colorectal cancer samples – from discovery to targeted analysis
EUPA 2019
Berlin, Deutschland

Modern mass spectrometry-based quantitative proteomic approaches for clinical research and diagnostics
Seminar at National Institute of Biological Sciences
Beijing, China

Multiplex targeted protein assays for clinical research and diagnostics
Seminar at University of Iceland
Reykjavik, Island

Modern mass spectrometry-based quantitative proteomic approaches for clinical research and diagnostics
Seminar at the Children's Hospital of Fudan University
Shanghai, China

Proteogenomics of Colorectal Cancer liver Metatases: Completing Precision Oncology with Phenotypic Data
14th Annual Meeting of ICG (ICG-14)
Shenzhen, China

Big Data Omics Technologies for Clinical Research and Personalized Medicine in Cancer
Seminar at Skoltech – Skolkovo Institute of Science
and Technology
Moskau, Russland

Introduction in quantitative and clinical proteomics
Seminar at Skoltech – Skolkovo Institute of Science
and Technology
Moskau, Russland

Proteogenomics of colorectal cancer tumors
13th National Cancer Center Korea International
Symposium Cancer Proteogenomics: The Force Awakens
Goyang, Südkorea

Absolute and relative proteomics for clinical research and diagnostics
Seminar at Thermo Fisher Scientific
Bremen, Deutschland

Development of 3000 proteomics assays in mouse
Molecular Phenotyping / OMICS at the KOMP2 /
IMPC Fall Meeting
Rockville, USA

Burhenn S
Detection and quantification of arsenic in a dielectric barrier discharge with spatial and temporal resolution
DPG-Frühjahrstagung 2019 der Sektion
Materie und Kosmos
München, Deutschland

Brand T
RKIP translates ß-adrenergic receptor signaling into mitochondrial protection
4th German Pharm-Tox Summit
Stuttgart, Deutschland

Drees C
Surveillance of bacteria growth using Gc-Ims
28th International Conference on Ion Mobility
Spectrometry
Hannover, Deutschland

Esser N
Surface Atomic Structure Analysis by Raman Spectroscopy
17th International Conference on the Formation
of Semiconductor Interfaces
Shanghai, China

Surface Analysis by Optical Spectroscopy
31. Tag der Chemie
Berlin, Deutschland

Structural phase transitions in nanowires: Analysis of In/Si(111) and Au/Si(553) by Raman Spectroscopy
2. IBS Conference on Surface Atomic Wires
Pohang, Südkorea

Franzke J
Characterisation of Dielectric Barrier Discharges for analytical Applications
DPG-Frühjahrstagung 2019 der Sektion Materie
und Kosmos, München, Deutschland

Freier E
Status and Future of LRC JRG 5
LRC Workshop 2019-2
Berlin, Deutschland

NMD-GPS -IMAGING Techniques
1. NME GPS meeting 2019
Dortmund, Deutschland

Freier E, Münchberg U
Status and Future of LRC JRG 5
LRC Workshop 2019-1
Dresden, Deutschland

Furchner A
Ultra-Sensitive Infrared Mueller-Matrix Ellipsometry For Structure And Thin-Film Analysis
8th International Conference on
Spectroscopic Ellipsometry
Barcelona, Spanien

Hinrichs K
Sensing and structure analysis by in situ IR spectroscopy: From ml flow cells to microfluidic applications
DPG Frühjahrstagung 2019 der Sektion
Kondensierte Materie
Regensburg, Deutschland

Einblicke ins Innere der Materie
Ausbildungs-Allianz-Adlershof
Berlin, Deutschland

Plenary talk: Spectroscopic Ellipsometry and Nanopolarimetry of Organic Thin Films Using Brilliant Light Sources in the Mid Infrared Spectral Range
8th International Conference
on Spectroscopic Ellipsometry
Barcelona, Spanien

Infrared nanopolarimetric analysis of structure and anisotropy of thin films
OSI-13 Optics of Surfaces and Interfaces
Leon, Mexiko

Polarization dependent AFM-IR for analysis of the structure and anisotropy of thin films at the nanoscale
Invited talk 4th Annual European Forum on Nanoscale IR Spectroscopy
Berlin, Deutschland

Spektroskopische Infrarot-Ellipsometrie für die Polymeranalytik: Anisotrope Filme und schaltbare Bürsten
Festkolloquium: 30 Jahre Polymer-Spektroskopie und Ellipsometrie am IPF Dresden e.V.
Dresden, Deutschland

Polarization dependent AFM-IR for analysis of the structure and anisotropy of thin films at the nanoscale
Invited talk 4th Annual European Forum on Nanoscale IR Spectroscopy
Berlin, Deutschland

Hoffmann N
Data Standardization and Exchange for Metabolomics and Lipidomics – the mzTab-M format and its reference implementation
International Symposium on Integrative Bioinformatics 2019
Paris, Frankreich

Towards better data standards and workflow interoperability in metabolomics and lipidomics
3. Munich Metabolomics Meeting
München, Deutschland

Hoffmann N, Peng B
Quantitative Lipidomics – LipidCreator and Skyline for targeted lipidomics
Summer school on Integration of Large Scale Lipidomics Data in Systems Medicine Research
Leipzig, Deutschland

Janasek D
Microfluidics for Life Science Applications and Analytics
17th International Conference on Nanochannels, Microchannels, and Minichannels
St. John's, Kanada

Kratz C
Broadband Laser – for Based Single-Shot Ellipsometer Sensitive Time-Resolved Infrared Ellipsometric Studies
19. Time Resolved Vibrational Spectroscopy Conference
Auckland, Neuseeland

Kopczynski D
Lipid Pathways: The Proteomic Side of the Coin – STAMPS
Summer school on Integration of Large Scale Lipidomics Data in Systems Medicine Research
Leipzig, Deutschland

Simple targeted assays for metabolic pathways and signaling: a powerful tool for targeted proteomics
XIII. Annual Congress of the European Proteomics Association
Potsdam, Deutschland

Lorenz K
b-adrenergic receptor mediated protection of cardiac mitochondria
Spring School 2019 in Birmingham
Birmingham, Großbritannien

Karrierewege in der medizinischen Forschung
Kick-off-Meeting UNION CVD Clinician Scientist-Programm
Würzburg, Deutschland

Selective inhibition of nuclear ERK1/2 functions – two quite distinct implications: cardiac hypertrophy and cancer?
DPhG Jahrestagung 2019
Heidelberg, Deutschland

Moreno-Gonzales D
Miniaturized plasma based ionization sources for mass spectrometry
3rd STARSS conference on Separation Science
Hrardec Kralove, Tschechische Republik

Münchberg U
Analysis in miniaturized enzymatic reaction systems
Jahrestagung 2019 der Vereinigung für Allgemeine und Angewandte Mikrobiologie
Mainz, Deutschland

Peng B
A workbench to probe the lipidomic landscape
60. International Conference on the Bioscience of Lipids
Tokyo, Japan

Plaickner J
The role of step edge fluctuations and hydrogen in the phase transition of Si(553)-Au
17th International Conference on the Formation of Semiconductor Interfaces
Shanghai, China

Sickmann A
Development of ms based assays for dection of a protein biomarker
Symposium »Vom Labor zum Patienten«
Essen, Deutschland

Plenarvortrag / Chair: Protein-MS in clinical applications
XIII. Annual Congress of the European Proteomics Association
Potsdam, Deutschland

Keynote Lecture: Quantification of biomolecules in biological matrices
Role of metals and metal containing biomolecules in neurodegenerative diseases such as Alzheimer's disease
Braunschweig, Deutschland

Development of Quantitative MRM Assays for the Measurement of 3,000 Proteins across 20 Mouse Tissues
ASMS 2019
Atlanta, USA

Platelet activation and risk prediction of thrombovascular events in Chronik Kidney Disease
mit Olga Shevshuk
DKFZ Heidelberg
Heidelberg, Deutschland

Multi omics for biology and medicine
VBIO Biologen Tag
Dortmund, Deutschland

Proteomics and LC-MS
Jahrestagung der Deutschen Gesellschaft für Klinische Chemie und Laboratoriumsmedizin
Magdeburg, Deutschland

OMICS tools to characterize platelet function
Università Cattolica del Sacro Cuore, Policlinico Universitario Agostino Gemelli
Rom, Italien

Post-translation modifications of the synaptic scaffold controlling age-induced memory impairment
mit Laxmikanth Kollipara
Freie Universität Berlin, Fakultät für Biologie
Berlin, Deutschland

Meeting TR 240: Analysing signalling molecules and modifications in platelets by proteomics, lipidomics and bioinformatics
Meeting Sonderforschungsbereich Transregio 240
Neckarsulm, Deutschland

Vogel P
Influence of Atmospheric Compounds on Dielectric Barrier Discharge Ionization for Mass Spectrometry
DPG-Frühjahrstagung 2019 der Sektion Materie und Kosmos
München, Deutschland

Weber G
Importance of oxidation products in coumarin-mediated Fe(hydr)oxide mineral dissolution
The Seventh International Symposium on Metallomics 2019
Warschau, Polen

EC-MS investigation into the coumarin-mediated dissolution mechanism of Fe(hydr)oxide minerals in soil
5. International Workshop on Electrochemistry / Mass Spectrometry
Münster, Deutschland

Veranstaltungen
Events

Mit-Organisation und Organisation wissenschaftlicher Veranstaltungen des ISAS
Co-organisation and Organisation of Scientific Events by ISAS

EuBIC Winter School 2019
Zakopane, Polen, Januar 2019

Forum Junge Wissenschaft auf dem 4. German Pharm-Tox Summit 2019
Stuttgart, Februar 2019

Symposium »Vom Labor zum Patienten«
Essen, Februar 2019

52. Jahrestagung der Deutschen Gesellschaft für Massenspektrometrie
Rostock, März 2019

Summer School on Integration of Large Scale Lipidomics Data in Systems Medicine Research
Leipzig, März 2019

XIII. Annual Congress of the European Proteomics Association
Potsdam, März 2019

Tagung des Arbeitskreises Europa der Leibniz-Gemeinschaft
Dortmund, Mai 2019

1. NME-GPS-Meeting
Dortmund, Juni 2019

Falling Walls Conference
Berlin, Oktober 2019

5. Lipidomics Forum
Borstel, November 2019

Biologentag »Big Data: Ein Quantensprung in Biologie und Medizin«
Dortmund, November 2019

Wissenstransfer und Öffentlichkeitsarbeit
Knowledge Transfer and Public Relations

Twinning-Treffen mit Vertretern der Universitäten Zypern und Jaén
Dortmund, Januar 2019

6. Symposium des Institute for Education in Pharmaceutical Medicine
Essen, Februar 2019

Girls' Day
Dortmund, März 2019

16. Dortmunder Wissenschaftstag
Dortmund, Oktober 2019

Science And Technology Forum (STS)
Kyoto, Japan, Oktober 2019

Leibniz im Landtag
Düsseldorf, November 2019

Auftritte auf Karrieremessen
Appearance at Career Fairs

Stellenwerk Bochum
Bochum, Mai 2019

Ausbildungs-Allianz-Adlershof
Berlin, Juni 2019

Lehrveranstaltungen
Teaching Activities

Sickmann A
Biochemie I
mit Albrecht Wegner
Ruhr-Universität Bochum
Wintersemester 2018 / 2019

Biochemie II
mit Jörg Reinders
Ruhr-Universität Bochum
Sommersemester 2019

Analysis of Proteins and peptides
The University of Aberdeen
November 2019

Proteomik und Metabolomik
mit Jörg Reinders
Hochschule Hamm-Lippstadt
Wintersemester 2019 / 2020

Chemische Analytik
mit Dirk Janasek
Technische Universität Dortmund
Sommersemester 2020

Bioanalytik
mit Dirk Janasek
Technische Universität Dortmund
Wintersemester 2019 / 2020

Kratz C
Spektroskopische Ellipsometrie
Technische Universität Berlin
April 2019

Janasek D
Physiologie & Anatomie
Fachhochschule Dortmund
Wintersemester 2018 / 2019

Analytische Anwendungen von »Lab-on-a-Chip«-Systemen
Technische Universität Dortmund
Wintersemester 2018 / 2019

Biochemie
Fachhochschule Dortmund
Sommersemester 2019

Physiologie & Anatomie
Fachhochschule Dortmund
Wintersemester 2019 / 2020

Analytische Anwendungen von »Lab-on-a-Chip«-Systemen
Technische Universität Dortmund
Wintersemester 2019 / 2020

Kopczynski D
Schulungsseminare
Ruhr-Universität Bochum
Sommersemester 2019

Freier E
Biomedizinische Anwendungen von Multiphotonenspektroskopie und abbildenden Techniken
Università Cattolica del Sacro Cuore
Sommersemester 2019

Franzke J
Dielectric Barrier Devices applied as excitation and ionisation sources for analytical chemistry
Westfälische Wilhelms-Universität Münster
Sommersemester 2019

Furchner A
IR Ellipsometrie, Fortgeschrittenenpraktikum
Technische Universität Berlin
Wintersemester 2018 / 2019

IR Ellipsometrie, Fortgeschrittenenpraktikum
Technische Universität Berlin
Sommersemester 2019

Hinrichs K
IR-Mikroskopie
mit Timur Shykhutdinov
Technische Universität Berlin
Wintersemester 2018 / 2019

Spektroskopische Ellipsometrie
mit C. Kratz
Technische Universität Berlin
Sommersemester 2019

IR-Mikroskopie
mit Timur Shykhutdinov
Technische Universität Berlin
Sommersemester 2019

Ellipsometry
Technische Universität Dresden
Wintersemester 2019

Lorenz K
Sympathikus I
Universität Duisburg-Essen
April 2019

Sympathikus II
Universität Duisburg-Essen
Mai 2019

Kolloquien in Dortmund
Colloquia in Dortmund

Univ.-Prof. Dr. rer. nat. Ulrich Flögel
Institut für Molekulare Kardiologie,
Universitätsklinikum Düsseldorf
Heinrich Heine Universität Düsseldorf
Cardiovascular Magnetic Resonance in Mice: Beyond Vasculature and Cardiac Function
März 2019

Dr. rer. nat. Judith Golda
Experimentelle Plasmaphysik, Institut für Experimentelle und Angewandte Physik,
Sektion Physik, Mathematisch-Naturwissenschaftliche Fakultät, Christian-Albrechts-Universität zu Kiel
Electron kinetics and reaction mechanisms in atmospheric pressure RF plasmas
Mai 2019

Prof. Dr. Lutz Schmitt
Institut für Biochemie, Chemie,
Mathematisch-Naturwissenschaftliche Fakultät,
Heinrich Heine Universität Düsseldorf
Maturation and Secretion of Nisin – a Model System for Lantibiotics
Mai 2019

Dr. Rainer Burhenn
Max-Planck-Institut für Plasmaphysik
First Operation of the Stellarator Wendelstein 7-X
Juni 2019

PhD Miranda Nabben
Department of Genetics and Cell Biology,
Faculty of Health, Medicine and Life Sciences,
Maastricht University, Niederlande
Signaling pathways involved in regulation of cardiac substrate preference
Juli 2019

PD Dr. Thomas Bocklitz
Forschungsabteilung Photonic Data Science,
Leibniz-Institut für Photonische Technologien e.V.
Chemometrics and machine learning based data pipelines for the analysis of Raman related data
Juli 2019

Prof. Dr. Matthias Gunzer
Leibniz-Institut für Analytische Wissenschaften – ISAS – e.V., Institut für Experimentelle Immunologie und Bildgebung
Universitätsklinikum Essen, Universität Duisburg-Essen
The impact of inflammation and especially of neutrophil granulocytes on the physiology of entire organs
September 2019

Prof. Dr. Matthias Vorgerd
Arbeitsgruppe Klinische und experimentelle Myologie,
Neurologische Universitätsklinik und Poliklinik,
Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil, Ruhr-Universität Bochum
Translation bei Gliedergürtelmuskeldystrophien am Beispiel der Calpain3-Defizienz
November 2019

Prof. Dr. André Anders
Leibniz-Institut für Oberflächenmodifizierung e.V.
Diagnostics of process plasmas for thin film deposition
Dezember 2019

Prof. Dr. Klaus Dreisewerd
Biomedizinische Massenspektrometrie,
Institut für Hygiene, Medizinische Fakultät,
Westfälische Wilhelms-Universität Münster
MALDI-2: An innovative tool to boost the analytical sensitivity and spatial resolution for MS imaging of lipids, metabolites, and glycans
Dezember 2019

Kolloquien in Berlin
Colloquia in Berlin

Prof. Dr. Andreas Fery
Institut für Physikalische Chemie und Physik der Polymere,
Leibniz-Institut für Polymerforschung Dresden e.V.
Polymer Surfaces for Guiding Nanoparticle Assembly
Februar 2019

Prof. Dr. Peter Hildebrandt
Technische Universität Berlin, Fakultät II Mathematik und Naturwissenschaften, Institut für Chemie
Proteins at work – towards elucidating cause-effect relationships. A case study on phytochromes
März 2019

Prof. Dr. Michael Gensch
Institut für Optische Sensorsysteme, Deutsches Zentrum für Luft- und Raumfahrt
THz Spektroskopie:
Von Graphen und Röntgenlasern zu den Sternen
April 2019

Dr. Katja Fricke
Leibniz Institute for Plasma Science and Technology
On the application of atmospheric pressure plasma polymerization for the generation of functional coatings aimed at biosensing
April 2019

Dr. Manuela Schiek
Institut für Physik, Fakultät V: Mathematik und Naturwissenschaften,
Carl von Ossietzky Universität Oldenburg
Giant Excitonic Circular Dichroism and its Added Value inOrganic Opto-Electronics
Juli 2019

Dr. Conor Hogan
Institute of Structure of Matter, National Research Council, Italien
Phase transition and electronic structure of the antimonene / Bi2Se3 van der Waals heterostructure
August 2019

Prof. Dr. Christiane Becker
Helmholtz-Zentrum Berlin für Materialien und Energie
Light management in solar energy devices
November 2019

Drittmittelprojekte
Third-Party-Funded Projects

Proteogenomics to solve the unsolved exemplified by gene identification in congenital myasthenic syndromes
AFM-Telethon, April 2018 – Oktober 2019

AntiThromb
Verbundprojekt: Entwicklung von biofunktionellen Gefäßimplantaten mit antithrombogener Beschichtung
BMBF, April 2018 – April 2020
AntiThromb Teilprojekt
Charakterisierung der generierten Oberflächen und oberflächennahen Schichten und Bewertung der Thrombogenität
BMBF, April 2018 – April 2020

Biotechnologie 2020+ Strukturvorhaben
Leibniz Research Cluster (LRC) – Bio-/Synthetische multifunktionale Mikro-Produktionseinheiten – Neuartige Wege zur Wirkstoffentwicklung
BMBF, April 2015 – September 2020

de.NBI Service Center – Structural Bio- and Chemoinformatics
Etablierungsphase Leistungszentrum BioInfra.Prot im Rahmen des de.NBI-Konsortiums
BMBF, März 2015 – Dezember 2021

de.NBI LIFS
Service Unit »Lipidomics Informatics for Life Sciences«
BMBF, November 2016 – Dezember 2021

DZHK-Initiative
Platelet signatures and psoriasis in cardiac dysfunction
BMBF, Januar 2018 – Juni 2020

Enzyme evolution by catalsysis enhanced diffusion (EVO-DIFF)
Seed Money Leibniz-Forschungsverbund Wirkstoffe und Biotechnologie
Leibniz Strategische Vernetzung, Mai 2019 – April 2020

FAST IMS
Früher adäquate Sepsis-Therapie mittels Ionenmobilitätsspektrometrie-basierter Diagnostik
BMBF, September 2017 – August 2020
FAST IMS Teilvorhaben
Referenzanalytik für die Keimidentifikation und sterile Probenahme
BMBF, September 2017 – August 2020

Sektorale Verwertung
Strategische Weiterentwicklung und Professionalisierung des Wissens- und Technologietransfers im Leibniz-Institut für Analytische Wissenschaften – ISAS – e.V.
BMBF, Mai 2016 – April 2019

NephrESA
Modellbasierte Optimierung der Anämiebehandlung für den einzelnen Patienten mit chronischer Nierenerkrankung
BMBF, Juni 2019 – Mai 2022

QS-Listeria
Entwicklung eines Schnellnachweissystems für die Detektion von Listeria monocythoenes in Milch
BMWi, Dezember 2017 – November 2020

TRFA-KAL
Standardisierung der Totalreflexions-Rötgenfluoreszenz-analyse durch neuartige nanoskalige Kalibrierproben
BMWi, Oktober 2018 – September 2020

AntiMicFilter (Forschungspartnerschaft)
A Novel Antimicrobial polymeric Nanocomposite For Antifouling Water Filtration Membrane Using Controlled Doping With Nano Cobalt Cerium Dioxide (Ce02:Co)
DAAD, März 2019 – Dezember 2020

Master switches bei kardialer Ischämie (Sonderforschungsbereich)
Teilprojekt: Funktionelles, Metabolisches und Multi-Omics Phänotypisierung bei akutem Myokardinfarkt
Teilprojekt: Kinasemodulator RKIP: Protektive Mechanismen bei Myokardinfarkt
DFG, Januar 2019 – Dezember 2022

Aufklärung von Dissoziationsmechanismen dielektrisch behinderter Entladungen für flüchtige Elementspezies
DFG, Juli 2016 – Juli 2020

Eindimensionale spektroskopische Magnetresonanz-Bildgebung mit Radiofrequenzfeldgradienten / Radiofrequenzphasengradienten und einem Mikrostreifenleiter als Sender und Empfänger zur Untersuchung von 3D-Zellkulturmodellen
DFG, Januar 2017 – Dezember 2019

Interplay of chelating and reducing root exudates in plant iron acquisition
DFG, Oktober 2016 – Dezember 2019

Rolle und Wirkmechanismus anaboler Stimuli auf die neuromuskuläre Trophik
DFG, Oktober 2017 – Oktober 2020

SFB 876: Verfügbarkeit von Information durch Analyse unter Ressourcenbeschränkung
Teilprojekt: Ressourcen-optimierte Echtzeitanalyse stark Artefakt-behafteter Bildsequenzen zur Detektion von Nanoobjekten
DFG, Januar 2011 – Dezember 2020

Surface optical spectroscopy of phonon and electron excitations in quasi-one-dimensional metalic nanostructures
DFG, Juni 2016 – Dezember 2019

TRR240-Platelets – Molecular, cellular and systemic functions in health and disease (SFB / Transregio)
Teilprojekt: Analyse von Signalmolekülen und Protein-Modifikationen von Thrombozyten mit Hilfe von Proteomik, Lipidomik und Bioinformatik
DFG, Juli 2018 – Juni 2022

Verständnis der Signalweitergabe durch den »striatin interacting phosphatase and kinase« (STRIPAK) Komplex im Verlauf der eukaryotischen Entwicklung
DFG, Juli 2018 – Dezember 2019

Untersuchung von Aminosäurewechselwirkungen auf funktionalisierten Galliumnitrid (GaN)-Oberflächen unter verschiedenen Bedingungen bei Verwendung von oberflächenempfindlichen spektroskopischen Techniken
DFG, Juni 2019 – September 2019

Applikationslabor Hochauflösende Breitbandspektroskopie
EFRE, August 2016 – Dezember 2019

Applikationslabor für die Infrarot-Laser Ellipsometrie
EFRE, Februar 2017 – Oktober 2020

DDHD – Drug Discovery Hub Dortmund
Drug Discovery Hub Dortmund am ZIW – Translation akademischen Know-hows in die Anwendung
EFRE, April 2018 – März 2021
Teilprojekt: Kardiotoxizität
EFRE, April 2018 – März 2021

SEVRIT
Produktion und Qualitätssicherung von stammzell-abgeleiteten extrazellulären Vesikeln für neuartige regenerative und immunmodulierende Therapieansätze
EFRE, Juli 2016 – Juni 2019

Gen und Protein Signaturen als GPS für Patienten mit Neuromuskulären Erkrankungen (NME-GPS)
EFRE, Januar 2019 – Dezember 2021

TAPAS (MSCA-ITN)
Targeting Platelet Adhesion Receptors in Thrombosis
EU, Januar 2018 – Dezember 2021

TImPANI (Widening Action)
Twinning in atmospheric Plasma science and applications
EU, November 2018 – Oktober 2021

TICARDIO (MSCA-ITN)
Thrombo-inflammation in cardiovascular disease
EU, April 2019 – März 2023

BIOplasma (MSCA-IF)
Use flexible Tube Micro Plasma (FμTP) for Lipidomics
EU, Mai 2019 – April 2021

MULTI-GC
Multiplexing GC-MS analysis for a generic high throughput enzyme screen
Leibniz Forschungsverbund, Januar 2018 – Dezember 2019

Strategiediskussion in den Sektionen
Strategieworkshop der Sektion D
Leibniz Strategiefond, Januar 2018 – Dezember 2019

Strategiediskussion in den Sektionen
Strategieworkshop der Sektion D
Leibniz Strategiefond, Januar 2019 – Dezember 2020

Strategiediskussion des Verwaltungsausschusses der Leibniz-Gemeinschaft
Strategieworkshop des Verwaltungsausschusses
Leibniz Strategiefond, Januar 2019 – Dezember 2020

A synaptoneurolipidomics view on neuronal plasticity in insulin resistance and Alzheimer's disease
Leibniz Wettbewerb, Januar 2017 – Dezember 2020

Post-translational modifications of the synaptic scaffold controlling age-induced memory impairment
Leibniz Wettbewerb, Juli 2019 – Juni 2022

Strategien zur personalisierten Frühdiagnose, Prävention und dem Monitoring von Therapien für kardiovaskuläre Erkrankungen (CVD-OMICS)
MKW NRW, April 2015 – September 2020

Detection of after treatments with softeners on table tennis rubbers using GC-ion mobility
ITTF, März 2019 – Juli 2019

Seed Money
Enzyme evolution by catalsysis enhanced diffusion (EVO-DIFF)
Vorhaben Leibniz-Forschungsverbund »Bioactive Compounds and Biotechnology«
Leibniz Strategische Vernetzung, Mai 2019 – April 2020

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Industrial Property Rights

Patente
Patents

Anordnung und Verfahren zur Wellenlängenkalibration bei einem Echelle-Spektrometer
amtl. AZ: 102 05 142.9
EP-Patent: EP1472512 (erteilt und validiert in Großbritannien, Schweden, Schweiz, Frankreich und Deutschland)
US-Patent: US7215422
AU-Patent: AU2003210190
CN-Patent: CN1630811
JP-Patent: JP4534487B2

Anordnung für Polarisations-Anisotropie – Spektroskopie mit parallelem Reflektionsstrahleneingang
DE-Patentanmeldung: DE102014119228
EP-Patent: EP3035034 (erteilt und validiert in Deutschland)

Anordnung zur gleichzeitigen Messung der Raman-Streuung und Fluoreszenz
DE-Patentanmeldung: DE102016110210

Biomolekulare Marker zur in-ovo Geschlechtsbestimmung von Vögeln mit Hilfe der Magnetischen Resonanz-Spektroskopie »Birdsexing«
EP-Patentanmeldung: EP18214008
Current Delay Shift Detektor
DE-Patent: DE102016112629

Doppelresonanz-Mikrostreifenleiter-Probenkopf mit nur einer Aussparung und magnetischer Suszeptibilitätsanpassung »Mehrfachresonanzkopf mit Hilfsinduktivität«
DE-Patent: DE102014115572

Doppelresonanz-Probenkopf auf Mikrostreifenleiterbasis für die kernmagnetische Resonanzspektroskopie an massen- und volumenbegrenzten Proben
DE-Patent: DE102014107296

Duales Ionenmobilitätsspektrometer
DE-Patent: DE102009008266

Echelle-Spektrometer mit verbesserter Detektorenausnutzung »Aryelle«
EP-Patent: EP1754032 (erteilt und validiert in Großbritannien, Frankreich, Östereich und Deutschland)
US-Patent: US7804593
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Ellipsometervorrichtung und Ellipsometrieverfahren zur Untersuchung einer Probe – Einzelschusselllipsometer
DE-Patentanmeldung: DE102016202971

Flexibles Röhren µ-Plasma für die weiche Ionisierung
DE-Patentanmeldung: DE102017112726
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EP-Patent: EP2082221 (erteilt und validiert in Großbritannien, Frankreich, Spanien und Deutschland)
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Marker sequences for Parkinson's disease and use thereof »PARKCHIP«
EP-Patentanmeldung: EP2867678

Microfluidic Gradient Generator including active mixing capabilities »micro2FFE«
DE-Patentanmeldung: DE102018116528

Microfluidic mixing device »Ultra-fast cell µmixer«
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Vorrichtung zur Detektion und Charakterisierung von organischen Molekülen in einem flüssigen Probenvolumen
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DE-Patentanmeldung: DE102017116055

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DE-Patentanmeldung: DE102009003548
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EP-Patent: EP2990787 (erteilt und validiert in Frankreich, Spanien und Deutschland)
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EP-Patentanmeldung: EP3430640

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EP-Patentanmeldung: EP13739621

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US-Patent: US7876435
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EP-Patent: EP2068134 (erteilt und validiert in Großbritannien, Frankreich, Österreich, Schweiz und Deutschland)

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DE-Patent: DE102011015517
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Verfahren zur Identifizierung von Markerproteinen zur Diagnose und Risikostratifizierung von Störungen der Blutgerinnung
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