isas Leibniz-Institut für Analytische Wissenschaften

ANNUAL REPORT 2023

advancing analytics

Leibniz Gemeinschaft

FOREWORD

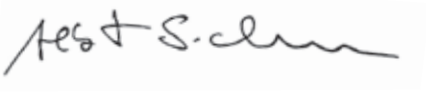
Dear Readers

When this annual report is published in 2024, we'll be preparing for evaluation by the Leibniz Association, our umbrella organisation, in December. As part of these preparations, we are currently working at full speed to 'roll up' our activities over the last three to seven years. I would like to use that as an opportunity to recall the changes that have taken place in recent years.

In 2014, after intense discussions with funding providers, various bodies and employees, we changed the focus of the institute's work to the shared objective of providing analytical techniques for health research. Those who have followed our annual reports on an ongoing basis will have gained an insight into the significant changes ISAS has undergone in light of this decision: we have not only realigned the specialist content of our research but ISAS has had a 'facelift' in its structures. Over recent years, some of the changes involved the setting up of the Biospectroscopy department, reinforcing our expertise in bioinformatics with two junior researcher groups and establishing mass spectrometry-based imaging as a new field of technology at ISAS. At the same time, we have significantly expanded our collaboration with hospitals, most recently by setting up the Preclinical Metabolomics research group headed by Prof Dr Dr Alpaslan Tasdogan (University Hospital Essen). Without the dedication of our employees, the members of our boards and the universities affiliated with us, we would never have been able to implement these changes. I am delighted and grateful that ISAS was able to rely on such support!

Our objective is to make a contribution, with our analysis techniques, to refining precision medicine and improving the quality of life of patients. In order to anchor the expertise gradually established at ISAS in the medium- to long-term planning in the best possible way, we critically examined our research programmes over the course of 2023. This resulted in updated and, in some cases, new programmes with interdisciplinary research projects, on the basis of which we intend to contribute our analytical solutions to meet challenges in health research. On the following pages, we would like to give you an insight into events at the institute and present some of our research achievements, employees and collaboration partners.

Enjoy reading!



Prof Dr Albert Sickmann

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VALUABLE CONNECTIONS STRENGTHEN COOPERATION

The exchange of ideas, data and methods across disciplines and national borders is crucial for scientific progress. At ISAS, employees from all over the world therefore collaborate on interdisciplinary research. Six former and current employees shared with the editorial team how their work at the institute and the experience they gained in Dortmund shaped their future careers or why their path led them to ISAS.

Not only do the diverse perspectives and experiences of the employees enable innovative research approaches, they also form the foundation for all kinds of internal cooperation as well as external, national and global partnerships.

The connection to ISAS remains even after leaving the institute. Former researchers remain an integral part of the ISAS network. Whether they are now working in industry, at universities or in other research institutions - through ongoing exchange and close collaboration with the institute, they contribute to the transfer of scientific findings from ISAS to their own fields. These networks are often the starting signal for new cooperations. The following pages provide an insight into these valuable connections.

(CP)

Adrian Sebuliba

Why did you decide to switch to health research and work in AMBIOM?
For as long as I can remember, I've had a passion for using science and technology to solve real-life problems, especially in healthcare. Biomedical research offers the chance to make a direct, positive impact on healthcare practices. This field's potential to change peoples lives inspired my switch.

Were you already familiar with the scientific system in Germany?
I had some exposure through joint projects, academic conferences and journals, for example. Watching scientific documentaries and attending webinars also gave me some insights. However, working directly within the German research setup has provided me with a much deeper understanding and appreciation of its benefits.

How does working at a non-university research institution like ISAS differ from your previous activities?
At ISAS, I'm experiencing a refreshing change from my previous tech industry roles. Here, I focus on interdisciplinary collaboration and applying technology to facilitate research. This approach significantly enhances problem-solving, making the process more dynamic and innovative. Additionally, ISAS provides strong support for converting research findings into usable tech products.

Prof Dr René Zahedi

Together with my research group, I worked at ISAS to develop and optimise techniques to examine the way in which proteins are dynamically regulated by post-translational modifications (PTMs) such as protein phosphorylation. Our focus was primarily on improving the sensitivity of the techniques for analysing clinical samples, the quantity of which is often severely limited. These techniques were then deployed to examine changes in the phosphorylation of proteins in human thrombocytes as well as cancer cells from patients with chronic lymphocytic leukaemia.

The strongly multidisciplinary work at ISAS was a great help for me in understanding that researchers from different specialist areas often speak 'different languages'. This allowed me to rethink my own way of communicating – and hopefully improve it. Also in the context of the collaborations with clinical partners, it was extremely helpful to understand the differing perspectives, objectives and ways of communicating. One important instance of collaboration that I built up with an oncologist during my time at ISAS continues to this day.

Prof Dr René Zahedi holds a professorship at the University of Manitoba, Canada, and is the director of the Manitoba Centre for Proteomics and Systems Biology. From 2008 to 2017, Zahedi headed a junior research group and a research group at ISAS as well as holding other functions.

ISAS

Where do you experience the biggest differences between your life in Uganda and in Dortmund?
Cultural and environmental contrasts are very noticeable in Dortmund. Life here moves faster. The infrastructure, for example the transport system, is rather diverse – that's both exciting and overwhelming. It definitely took me some time to get used to the cold. However, Dortmund's open-hearted, multicultural society makes it easy to move around socially.

What advice do you have for prospective or experienced researchers or developers who want to pursue an academic career in Germany?
I recommend staying open-minded and proactive in seeking opportunities. Network through conferences, webinars, and tech social media groups. Collaborate on large-scale, challenging projects through work experience, volunteering, or just for fun. Learning some conversational German can enhance both your career and personal life. Lastly, be flexible and resilient to overcome any adversity during your academic journey.

Adrian Sebuliba has been a software engineer in the ISAS junior research group AMBIOM since 2023. Before coming to Dortmund, he worked for a digital commerce platform for the chemical industry.

Andela via Kampala, Uganda

ISAS

Furthermore, the optimum conditions at ISAS allowed me to make important international contacts, for example, by being able to invite leading researchers in my field to come to Dortmund to give talks. In particular, my colleagues at ISAS were fantastic – from the building technology, workshop and administrative teams to the other research groups, there was a great working atmosphere.

> *"The potential provided by proteome research for clinical translation is enormous."*

University of Manitoba, Canada

I now conduct research in Canada and, in addition, I provide training for the researchers of tomorrow at the University of Manitoba. For me, translation is the most exciting of my activities. The Manitoba Centre for Proteomics and Systems Biology is located at the largest hospital in Winnipeg, which treats in excess of 550,000 patients each year. The collaboration taking place each day between the people conducting fundamental research, technologists and clinicians gives rise to exciting projects relating directly to patients. Our work, for example, concerns severe disorders in neonates. We would like to use our techniques to improve the diagnosis of congenital metabolic defects and thus ensure the affected individuals receive the necessary treatment more quickly. The potential provided by proteome research for clinical translation is enormous – and this is precisely one of the central messages of my teaching.

Dr Saskia Venne

Dr Saskia Venne is head of the Scientific Monitoring Bioanalysis team in the Development NCE (New Chemical Entity) division at Boehringer Ingelheim Pharma. From 2012 to 2016, she was a doctoral candidate at ISAS.

ISAS → **Boehringer Ingelheim Pharma, Biberach**

Why did you make the decision in 2012 to pursue your PhD at ISAS?
It was important to me to gain experience outside of university, because I was looking for more international and cross-functional cooperation, for instance with hospitals or other non-university institutions. The Leibniz Network seemed to me to be a good starting point and ISAS offered a very impressive portfolio of state-of-the-art technologies.

What did your research focus on during your time at ISAS?
The title of my PhD was "Characterisation of the Interaction of Post-translational Modification by means of Mass Spectrometry-based Proteome Research". You can envisage this as the cell attempting to use post-translational modifications to react to external influences or disease to maintain homeostasis. By throwing light on these modulations, the hope is to obtain a better understanding of these processes and, ideally, also new approaches for treatment. So I established a method with which it was possible to determine three specific post-translational modifications in proteins. We then deployed these in various cooperation projects.

Did you benefit personally in any way from your time at the institute?
Yes, of course, doing independent scientific work and independently driving forward a project. This means maintaining a high level of self-motivation over a long period of time, not being disheartened by failed attempts and trying again with a different approach. And lastly, I learnt that a well-maintained network is always a benefit and can open up many new opportunities.

Was the experience you gained from ISAS cooperation arrangements with hospitals useful for your ongoing professional career?
It was a great opportunity to learn how to interact with cooperation partners in a professional manner and to develop a sense for the ways in which the interests, approaches and issues may vary between different partners. Understanding other people's position and striving to ultimately achieve a good result for all involved is a valuable characteristic for all later positions, especially for leadership positions.

Would you advise young researchers to become acquainted with scientific work at a non-university research institution before switching to industrial research?
Yes, definitely. Firstly, doctoral or postdoctoral positions are still few and far between in the industrial sector. Secondly, the scientific supervision and the environment at a non-university research institution are significantly more intense. It is worthwhile to gain initial experience here with other doctoral candidates and a PhD supervisor, and in a scientific environment, to work out where you as an individual want to go, what you like and to hone your own scientific expertise. In the industrial sector, you are often hired as an expert for a specific area and afterwards there may be very little help or opportunities for discussion – a solidly based scientific profile and a good network are extremely helpful in this respect.

Dr Jianxu Chen

My background is in computer science, but I developed a passion for working with biological data early on. If I can use my skills to develop a software to classify one image as dog or cat, or classify one image of tissue as benign or malignant, I feel the latter one would be more impactful and therefore more attractive to me. That's why I dedicate my work at ISAS towards developing AI-based biomedical image analysis algorithms, especially for large 3D microscopy image data *(► p. 30).*

"The key is to have an open mind."

Before coming to Dortmund, I conducted research in China and the USA. Living in three very different cultures and navigating various research systems taught me, that the key is to have an open mind. My advice would also be to learn the language, especially if you have kids. It helps to understand the local culture and embrace it. Even though I miss authentic Chinese food, I have to admit that I am really falling in love with those simple foods in Germany – especially high-quality breads. Nonetheless I am still struggling to find some good Pad Thai in town.

Dr Jianxu Chen heads the junior reseach group AMBIOM – Analysis of Microscopic BIOMedical Images at ISAS since 2021. Previously, he worked at the Allen Institute for Cell Science in Seattle.

Allen Institute for Cell Science, USA

ISAS

20 different nationalities

The staff at ISAS is international. The institute currently employs people from 20 nations. These include Bangladesh, Belarus, England, China, France, Germany, Greece, India, Italy, Jordan, Myanmar, the Netherlands, the Palestinian Territories, Russia, Serbia, Spain, Syria, Taiwan, Turkey and Uganda.

Dr Julia Lill

I joined ISAS when I was between the conclusion of my PhD project at University Hospital Essen and the commencement of a postdoctoral position. My research at the institute focused on optimising the procedures for isolating proteins from cells. The aim was to generate meaningful proteome analysis with very limited cell material. This comes into play if you are examining changes in the proteome of neutrophilic granulocytes that were isolated from healthy versus cancerous tissue.

For this project, we collaborated very closely with University Hospital Essen. The Essen team performed the cancer studies and isolated the neutrophils whereas I prepared the cells and conducted the proteome analyses. Over the course of this collaboration, I learnt how important clear communication is to research projects. In collaborative research, people often have very different backgrounds – this is what makes it so interesting. But details might be assumed as given by one collaboration partner whereas they might be perceived as new by the other. Such minor barriers to communication might seem trivial but they can jeopardise entire projects if you don't identify them and work to overcome them.

When joining ISAS, I was rather new to the topic of proteomics, so I learned a lot during my time there.The discussions with colleagues were often a

During his PhD studies, Dr Mohammad Ibrahim Alwahsh worked as a research associate at ISAS. The pharmacologist was already familiar with the research at the institute due to a scholarship that had led him to Dortmund in 2018. The 30-year-old is now an Assistant Professor of Toxicologic Pathology at the Faculty of Pharmacy at Al-Zaytoonah University of Jordan.

Prof Dr Mohammad Ibrahim Alwahsh

I was a PhD student at the Medical Faculty Mannheim of Heidelberg University, when I decided to pursue the work for my dissertation at ISAS. I chose the institute because of its high-quality research, supportive academic environment, and the opportunity to collaborate with excellent colleagues. I found all the techniques and instruments necessary for my research, where I focused on developing methods to improve the treatment of a rare form of cancer in the thymus gland. Using nuclear magnetic resonance (NMR) spectroscopy, me and my colleagues managed to measure the live reaction to chemotherapeutic agents in 3D models for the first time. We were also able to highlight potential biomarkers for diagnosis and treatment of thymoma and thymic carcinoma.

ISAS

Al-Zaytoonah University, Jordan

> *"I gained invaluable research skills."*

During my time as a PhD student and PhD representative at ISAS I gained invaluable research skills, a deeper understanding of my field and lifelong connections with great colleagues. The most important thing is to be patient, knowing that everything

Dr Julia Lill
worked as a trained immunologist at ISAS from 2020 to 2021. After completing her PhD, she went to Massachusetts General Hospital in Boston, USA, the largest teaching hospital of Harvard Medical School, to work as a research associate. Since February 2023, Lill has been working as a researcher in BioNTech's team for cancer immunology in Cambridge, USA.

decisive factor in my learning process, helping me to learn and deepen my understanding. Creating a functioning network in which you surround yourself with knowledgeable, ambitious peers and build up purposeful connections with them may take some time. But I learnt that, over the long term, this is time well invested.

As my PhD focused on questions in immunology, I encountered analytics for cancer research for the first time during my time at ISAS. Since then, I have dedicated my career to cancer research – first as a postdoc at Massachusetts General Hospital and Harvard Medical School, and now as a researcher at BioNTech in Cambridge, Massachusetts. I would encourage people to be courageous and look beyond the limits of your own 'scientific comfort zone'. This shift can ignite a new passion, as it did for me with cancer research, or reinforce your love for your current field, motivating you to deepen your expertise. Venturing into new areas can also be eye-opening, revealing how much there is to learn outside of your area of expertise. Lastly, and for me most strikingly, such experiences foster understanding and patience. By adopting the perspective of a non-expert, you learn how to effectively communicate and interact with those who are unfamiliar with your specialty.

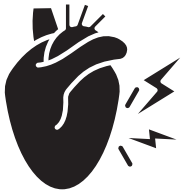
will eventually work out – even if it takes longer than expected. As a significant benefit of my time in Dortmund, I have published numerous papers in high-ranking journals and worked on a patent. This work is ongoing and continues to become increasingly interesting. Even though I have completed my PhD, I still visit ISAS annually for collaborative projects.

Additionally, I thoroughly enjoyed experiencing different cultures, which I consider one of the most important aspects of my time at ISAS. The institute actively promotes not only internal, but national and international collaboration by encouraging students and research associates to participate in workshops and conferences. I can also recommend exchange programmes, for example with the German Academic Exchange Service (Deutscher Akademischer Austauschdienst). In my case, it introduced me to the NMR Metabolomics group at ISAS and was the starting point for the collaboration with Dr Roland Hergenröder.

Currently, I am balancing teaching and research, which is undoubtedly more challenging than focusing solely on research. However, with time, I have been able to adapt and manage both responsibilities efficiently. This is also due to numerous workshops and training programmes that were offered during my PhD at Heidelberg and Dortmund, that enable students to prepare for their next steps in academia or the industry.

New Research Training Group of Essen University Medical Centre & ISAS is Dedicated to Consequential Injury Following a Heart Attack

When the blood supply to the heart muscle is blocked in an acute myocardial infarction (heart attack), every second counts. But even when the obstructed vessels open up again thanks to emergency medical treatment, the long-term consequences for patients are often devastating. The new Research Training Group »RTG 2989 Targeting Cellular Interfaces in Reperfused Acute Myocardial Infarction (TCI repAMI)« is dedicated to one aspect of such consequential damage. This is an instance of cooperation between the University of Duisburg-Essen, including University Hospital Essen, and ISAS. A new tandem supervision strategy is intended to provide doctoral candidates with the best possible training at the interface between the laboratory and clinical practice. In 2023, the cooperation partners received approval from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), which will fund the Research Training Group with eight million euros from April 2024 to March 2029.



What is known as reperfusion injury may occur once the blood flow is restored following an acute myocardial infarction. As the blood suddenly starts to flow again, it floods the affected heart muscle cells with oxygen and nutrients, thereby triggering inflammation processes, for example. The objective of the »TCI repAMI« Research Training Group is to analyse and characterise the interaction underlying this process between specific immune cells, vessel cells and cardiomyocytes (heart muscle cells). By doing so, the researchers intend to identify new targets for treatment approaches.

The bed-to-bench-to-bed principle

The Research Training Group comprises eleven sub-projects, each forming part of the three research areas of immune cells, vessel cells and cardiomyocytes. In each project, two experts from clinical practice and fundamental research form a tandem team to provide the total of 33 doctoral candidates (22 from the natural sciences and eleven from medicine) with the best possible interdisciplinary training. In this context, the consortium follows the bed-to-bench-to-bed principle: starting with problem identification at the patient's bedside, the project groups are intended to cover experimental design, the analysis and evaluation of the research data, and the contextualisation of the findings in a clinical context.

(CP) ■

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Funded by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) Project number 517043330.

AI for Image Analysis: Cooperation with the Allen Institute for Cell Science

Understanding and predicting the behaviour of cells in normal, regenerative and pathological contexts – this is what the Allen Institute for Cell Science, Seattle (U.S.) is all about. To do this, the non-profit research organisation develops multi-scale modellings of cell organisation, dynamics, and activity. Its software programmes are worldwide accessible free of charge (open source). The resources can be found on the Allen Cell Explorer, an online portal for cells, cell biology, data and tools. It provides an insight into the organisational diversity of human stem cells and delivers matching open data, cell lines, plasmids, methods, and models.

ISAS has been collaborating with the Allen Institute for Cell Science since 2022. At ISAS, the AMBIOM research group led by Dr Jianxu Chen, a former scientist at the Allen Institute for Cell Science, is in charge. Together, the researchers have already developed an open source toolkit (Allen Cell & Structure Segmenter) for the 3D segmentation of intracellular structures in fluorescence microscopy images. Building on this, the Dortmund and Seattle teams have continued their collaboration. In 2023, the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) granted Chen and his team funding to improve the quality assurance of this open source software for the bioimaging community (► p. 26). The AI expert and Dr Susanne Rafelski, Deputy Director of the Allen Institute for Cell Science, also designed and prepared a seminar in 2023 (that was to take place the following year) with the aim of initiating an intensive discussion about emerging issues in AI research and publications in the field of bioimaging.

(SR) ■

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PEOPLE

Sven Heiles Awarded for Research on Lipids

Lipids have a variety of functions in the human body. The water-insoluble molecules regulate the growth of cells, for example, or provide chemical building blocks for several hormones. The lipid signature – the amount, type and chemical structure of lipids – in tissue or blood is different in healthy and sick people. Sven Heiles' goal is to use this lipid knowledge to predict and treat diseases. To achieve this, the chemist has developed methods with which lipids can be specifically fragmented for the analysis in the mass spectrometer. The German Society for Mass Spectrometry (Deutsche Gesellschaft für Massenspektrometrie, DGMS) awarded Heiles the Mattauch Herzog Award for his research in Dortmund on May 14, 2023.

Mattauch Herzog Award 2023. The winners of previous years are Prof Dr Charlotte Uetrecht and Dr Jens Soltwisch (right).

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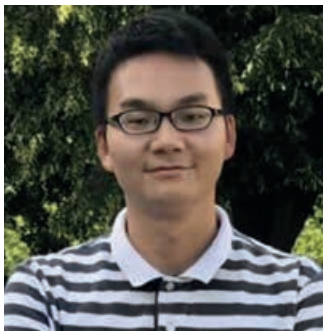
"Sven Heiles's research is an important step towards deciphering changes in the lipid metabolism of different diseases in the future. We congratulate him and look forward to his further work," said Prof Dr Albert Sickmann after the award ceremony. Heiles received the prestigious prize of 12,500 euros for his outstanding achievement in the structural and local differentiation of lipids. His methods are based on photochemical derivatisation (2-benzylpyridine, 2-acetylpyridine) and fragmentation techniques (ultraviolet photodissociation). This allows lipids to be broken down into their individual parts when analysed in the mass spectrometer and thus to be characterised structurally. The information about the structure provides insight into how a disease has influenced the lipids. In the tissue of mice, the researcher was able to use his methods to show which lipids change and how for diabetes (type I and II) and the worm disease schistosomiasis (bilharzia).

(SR) ■

Xiaowei Xu Plans to Join ISAS as a Humboldt Fellow

AI expert Prof Dr Xiaowei Xu from the Chinese Guangdong Cardiovascular Institute plans to conduct his research in ISAS's AMBIOM group as a fellow of the Alexander von Humboldt Foundation over a period of 18 months. His research interests include artificial intelligence for cardiovascular diseases, including deep learning, and the processing of medical images. Xu has already worked as a researcher in the US and Canada several times. The 37-year-old already set the course for his time as a Humboldt Fellow in 2023. In this interview, he explains why he applied for the guest residency in Germany and what he plans to do in Dortmund.



Prof Dr Xiaowei Xu forscht am Guangdong Cardiovascular Institute in China.

Prof Xu, why did you decide to do a research stay at ISAS?

Xu: Gottfried Wilhelm Leibniz is one of the most well-known scholars in history, and I have known about him since my middle school time. So, it is an honour and quite appealing to stay at ISAS, one of the Leibniz institutes, and by that have some connection with Leibniz's legacy.

How do you want to spend your time as a guest researcher at AMBIOM?

Xu: I will work most of the time with Dr Jianxu Chen and his team to conduct research on efficient AI for biomedical image segmentation. I will also spend some time visiting the other research groups at ISAS and partner hospitals. Collaboration and networking are important for scientific activities and research.

In your opinion, how does Germany compare internationally when it comes to AI in health research?

Xu: First, on the industry side, Germany is at the top positions in the medical field with a group of famous companies like Siemens and Bayer. And I believe these top medical companies will soon become the industry pioneers in AI in health research. Second, on the research side, for example nnU-Net is the leading tool for image segmentation. It is currently the most famous AI framework which has been proposed by a group of researchers from the German Cancer Research Center – Deutsches Krebsforschungszentrum, DKFZ. Though there are not as many research papers coming from Germany compared to the number of publications from other countries, the quality is impressive. So, all in all, I think Germany is definitely in the top position in AI in health research.

(The interview was conducted by SR.) ■

HUMBOLDT RESEARCH FELLOWSHIP

The Alexander von Humboldt Foundation's research fellowship is aimed at academics from abroad with above-average qualifications who wish to work at German research institutions. Applicants first apply to the research institution with their own project or topic. If accepted, they can then conduct research there for between six and 24 months with the help of the Humboldt Research Fellowship. Among other benefits, the fellows receive monthly financial support and a language course.

Born in Groß-Gerau, Hesse, Prof Dr Sven Heiles received his doctorate with distinction from the TU Darmstadt in 2012 after studying chemistry there. His dissertation was followed by research stays at the University of Birmingham and the University of California, Berkeley. The chemist then conducted his research at JLU Gießen as a postdoc and, from 2016, as a junior research group leader. Since August 2022, Heiles has been junior professor at the University of Duisburg-Essen's Faculty of Chemistry and head of the Lipidomics Research Group at ISAS.

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ISAS Congratulates Sven Heiles on his Habilitation

With his research on the structure and spatial distribution of lipids, Sven Heiles successfully habilitated in the field of analytical chemistry at Justus Liebig University (JLU) Giessen. A talk on this subject within the field of palaeontology – the scientific study of prehistoric beings, for example on the basis of fossils – concluded the procedure. Habilitation lectures are dedicated to an academic topic that originates from the candidate's area of expertise, but does not belong to the candidate's narrower field of research, in order to prove their ability to teach the subject. Heiles therefore addressed the following question in his lecture: How can analytical methods tell us more about the life of dinosaurs? In front of the Faculty Council as well as about 60 other guests, Heiles answered this question in an entertaining presentation.

Technologies like the isotope ratio mass spectrometer, the scanning electron microscope or the orbitrap mass spectrometer can be used to analyse the body temperature, physiology and biochemistry of dinosaurs as well as draw conclusions about their visual appearance. The 38-year old explained, for example, how analysing stable CO_2 isotopomers (such as carbon dioxide molecules with the same number of protons but a different amount of neutrons and, therefore, a distinguishable mass) in fossils can provide information on dinosaurs' body temperature. In addition, Heiles discussed the work of other researchers and explained how lipid signatures give an insight into the climate conditions of the time. Lastly, the chemist gave an intriguing outlook on controversially discussed aspects such as evidence of proteins and cells in dinosaur fossils.

(BD / SR) ■

Kristina Lorenz Voted on to the DFG's »Medicine« Review Board

Prof Dr Kristina Lorenz, head of the Translational Research department and the Cardiovascular Pharmacology research group at ISAS.

Every four years about 150,000 researchers throughout Germany vote on which of their number will be a member of one of the 49 Review Boards at the German Research Foundation (DFG). These elections are an important part of self-governance in research.

The members of the Review Boards assess funding applications submitted to the DFG. The most recent elections for the 2024 to 2028 term of office were held in autumn 2023. All eligible individuals were called upon to cast their ballot online in November and December. All researchers with a doctoral degree who actively conduct research in Germany and are affiliated to a voting centre are eligible to vote.

Prof Dr Kristina Lorenz was one of the 1631 candidates. She heads the Translational Research department and the Cardiovascular Pharmacology research group at ISAS and the Institute of Pharmacology and Toxicology at the University of Würzburg. Lorenz was proposed for the »Medicine« Review Board, subject Pharmacology. She stood successfully for election, and the trained pharmacologist took up her voluntary work on this Review Board in spring 2024.

(SR) ■

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3D MOLECULAR PATHOLOGY

Modern imaging methods are regarded as a key technology in first-class medical research. At ISAS, the research programme 3D Molecular Pathology focuses on temporally and spatially high resolution visualisations and measurements of physiological and pathological states in whole organs, the tissue structures and cells of which they are composed of, down to the molecular components which are essential for the function of the cells.

Researchers at ISAS are developing and optimising imaging methods to analyse the infiltration of immune cells in knee joints and their interaction in rheumatoid arthritis, for example. Using a confocal microscope, the immunologists analyse cryosections of murine (from mice) knee joints in a healthy and diseased state.

Inflammation as a basis of many pathological processes & positive events

Various research groups at ISAS are working on different projects to elucidate the molecular and cellular processes that underlie immuno-vascular interactions under inflammatory conditions. The researchers investigate these cell-cell interactions, both in acute inflammatory processes and in chronic autoimmune disorders. Inflammation is the basis of many pathological processes in the human body. In addition to injuries or infections as triggers, also internal events like a vascular blockage can lead to an inflammatory reaction. Examples for these so-called sterile or aseptic inflammations (meaning no pathogens are involved in their development) are for example heart attacks, strokes, autoimmune diseases like rheumatoid arthritis, or cancer. Sterile inflammation is characterised by a massive infiltration of activated immune cells ("inflammatory cells") into the inflamed tissue and a systemic flooding (of the whole body) with soluble inflammatory mediators.

However, immune cells that migrate into inflammatory sites can also perform important positive tasks in sterile inflammation, such as the regeneration of tissue damage, the local restriction of inflammatory foci by encapsulation or the fight against tumours. For this reason, it is difficult to clearly classify the role of an immunological infiltrate as "harmful" or "beneficial". Both, the molecular context in which the immune reaction takes place and its timing in relation to the triggering event are essential when evaluating the impact of an immune response to sterile inflammation, and thus also for the question of how to treat patients most efficiently.

Combination of complementary methods for full-scale analyses

Using Light Sheet Fluorescence Microscopy (LSFM), high-resolution Confocal Laser Scanning Microscopy (CLSM) and Raman Microscopy for example, scientists at ISAS identify and validate biomarkers to accelerate the early detection of adverse conditions such as cardiovascular or autoimmune diseases, and their impact on systemic integrity (for example resulting in an immune dysfunction). To translate this basic research into clinical practice, there is a close cooperation, for example, with the Institute for Experimental Immunology & Imaging at the University Hospital Essen.

Moreover, the researchers develop complementary new microscopy techniques which are designed to massively increase the throughput of samples, and therefore the speed of analyses. In addition, the scientists use artificial intelligence (AI) to analyse entire organs down to the level of individual cells in experimental disease models in mice or in tissue and blood samples from patients. Depending on the microscope used, one individual sample can produce hundreds of images. Without AI, an in-depth rapid quantification and understanding of the biological information contained in these images would not be possible, nor would it be possible to administer it efficiently. Therefore,

microscopy is only one of many areas of application in medical imaging where AI is continuously revolutionising the processing of huge quantities of data.

The combination of LSFM and CLSM allows scientist to carry out a three-dimensional analysis of biological samples from the macroscopic to the subcellular level. However, in order to be able to characterise morphological and functional changes in inflammatory tissues with their fundamental mechanisms in molecular detail and over a period of time, scientists at ISAS combine time-resolved CLSM, LSFM and complementary analytical technologies such as mass spectrometry (MS), mass spectrometry imaging (MSI), and high-dimensional flow cytometry.

Striving towards a multimodal analytics workflow with non-destructive, integrative analyses

Since a disease mechanism is not only decisively influenced by the function of a biomolecule in a system but also its precise occurrence in time and space, combining microscopic methods with general and locally-resolved MS paves the way for entirely new diagnosis options in the future. At present, many of the stated imaging methods still inevitably lead to a destruction of the samples. This means that analyses are restricted to using individual techniques, which may also be mutually exclusive. This is problematic, especially regarding rare samples like human tissue biopsies, because comprehensive analyses are only possible to a limited extent. In the 3D Molecular Pathology programme, ISAS researchers therefore work on harmonising and combining complementary imaging and analytical methods with the aim of obtaining new non-destructive integrative measurement strategies. The purpose of this cross-scale multi-method concept – in the form of 4D analyses – is to enable the location- and time-resolved, quantitative in vivo analysis of biologically relevant components at the cellular to molecular level. Key technical innovations are required to enable a truly comprehensive multimodal and multidimensional analysis, and therefore for an overall understanding of biomedically relevant processes. In the long run, these emerging new analytical technologies are supposed to be integrated into clinical diagnostics which in turn should lead to improved prevention and early disease diagnosis as well as personalised therapies.

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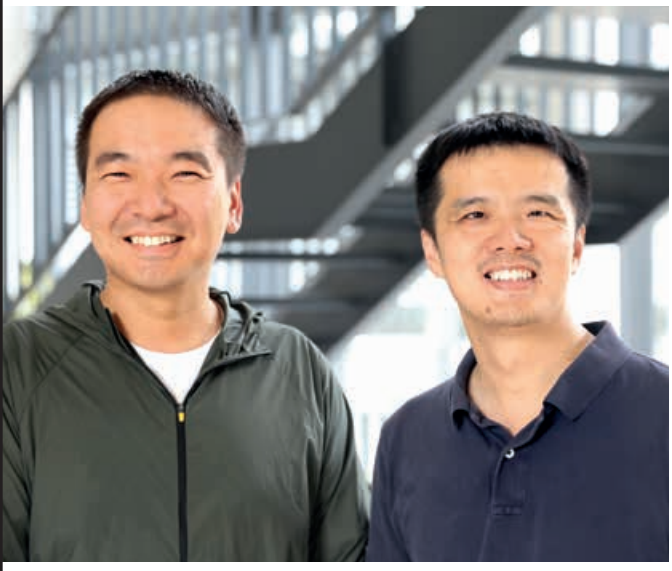
GEFÖRDERT VOM

Bundesministerium für Bildung und Forschung

Between Progress and Footprint: Artificial Intelligence in Healthcare

Sustainability is a key topic of our time and permeates all scientific disciplines. Whether in energy generation or mobility – many researchers are looking for ways to make processes more resource-efficient and yet more efficient. In the healthcare sector, artificial intelligence (AI) is already helping to analyse medical images and continuously monitor health data. The potential areas of application, especially for machine learning (ML; ► p. 62), are constantly increasing. However, with increasing size and complexity, AI models require more resources – including not only energy, computing power and memory, but also expertise, for example. This increased resource consumption will soon pose serious sustainability issues for some hospitals and research institutes, warns a team of researchers from the USA, China and Germany (ISAS). The AI experts presented their reasoning and solutions for sustainable AI in healthcare in the journal *Nature Machine Intelligence* in 2023.



Dr Jianxu Chen (left) from the ISAS research group AMBIOM and Prof Dr Yiyu Shi from the University of Notre Dame (USA) are among the authors of the publication in *Nature Machine Intelligence*. The photo was taken during a guest lecture at ISAS .

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The resource requirements of AI systems vary over the entire life cycle, from development to final use. The authors, including Dr Jianxu Chen from ISAS, therefore want to take a holistic view of sustainability. Their approach starts before an AI/ML model is even used. This is because careful and time-consuming preparation of the training data is crucial for its performance. However, with the growing volume of medical images, the number of medical specialists remains limited, which is already leading to bottlenecks in data preparation. Technical and structural factors also play a role. For example, the often limited budgets in hospitals can hardly be reconciled with the necessary upgrading and maintenance of existing storage infrastructures. The network structures for data transmission, which are generally not designed for the data volumes of AI models, could also lead to delays or data loss. At the same time, access to powerful servers and supercomputers provides researchers with the necessary basic framework, but presents them with the problem of almost unsustainable energy consumption.

Optimising models step by step

In order to meet these challenges as quickly as possible, there are already ways of adapting existing models. Instead of developing systems from scratch, researchers could, for example, apply and adapt pre-trained models from similar medical systems to new domains. Such an approach would not only require comparatively ▸

little training data and expertise, but would also deliver the desired results faster and more easily. According to the authors, another option is to compress existing AI/ML models. This involves using certain algorithms to reduce the number of calculations in the models while maintaining a comparable level of predictive accuracy. In this way, the ecological footprint can be reduced in the long term through reduced energy costs and reduced data storage requirements.

A proactive approach to resource sustainability issues

In the long term, however, the researchers recommend a proactive approach that focuses on various aspects of sustainability. Going forward, it will be important to co-ordinate hardware, algorithms and models from the very beginning in order to determine the best configurations for resource-saving solutions. In the best-case scenario, a cost model should accurately predict the sustainability of a system and estimate the resources required for model updates and adjustments over time. In addition, ML models could relieve experts of the burden of data preparation through a kind of transparent "autonomy". The authors suggest that more use should be made of so-called self-supervised learning, where the model annotates the training data without human assistance before the learning phase. For some processes, such as segmentation, this can not only be significantly faster, but also more objective (► p. 32). The team focuses on transparency and traceability: continuous feedback from medical experts should improve the efficiency and accuracy of the models and strengthen trust in the technology.

(CP) ■

Prof Dr Yiyu Shi knows the interface between science and clinic particularly well. He teaches at the University of Notre Dame (USA) and conducts research at Boston Children's Hospital.

Jia, Z., Chen, J., Xu, X., Kheir, J., Hu, J., Xiao, H., Peng, S., Hu, X. S., Chen, D., Shi, Y.
(2023) The importance of resource awareness in artificial intelligence for healthcare.
Nature Machine Intelligence
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AI in Healthcare: Why Is it Better to Think Small Instead of Big?

Prof Dr Yiyu Shi holds a professorship in computer science and engineering at the University of Notre Dame, U.S., and is Director of their Sustainable Computing Laboratory. His research focuses on deep learning, hardware acceleration, and medical applications. Since he is also a visiting scientist at Boston Children's Hospital, the primary paediatric programme of Harvard Medical School, Shi is very familiar with the interface between science and clinic. The 40-year-old researcher is the corresponding author of the Perspective article in *Nature Machine Intelligence*.

Professor Shi, do you think that when it comes to energy costs, hospitals may need to not only concentrate on how to reduce energy costs for the buildings and medical equipment like MRIs, but also think about how they handle their data?

Shi: Yes, of course. Energy is always a problem, because many hospitals have to store their data locally. And this can become more of a problem in the future as not every hospital has all the facility that would be necessary for a full-scale data centre. In terms of using the data, you want to analyse them or apply state-of-the-art machine learning models or other advanced techniques. But these consume a big amount of energy as well. That is why we are looking at the sustainability of these kind of AI techniques. We want to help reduce the energy footprint for the data storage and analysis at the same time.

When thinking of the technological aspects, why do you and your co-authors make a case for recycling and thinking small by using algorithms designed for tiny networks or reducing the size of your models?

Shi: It takes a lot of resources to train a model from scratch. I understand the idea because every individual hospital has its own specific data. There is a need to work out a personalised model for each individual centre or hospital, but I think it is more or less a waste to train every model from scratch. You can start from a pre-trained model that has certain knowledge of a particular problem and then fine tune it, based on the specific needs. This would save a lot of resources. So yes, to some extent we can recycle. The size of the model also matters because even if you take a model that has already been trained for a particular hospital, every time you have to run inference on that part, this will lead to a big energy consumption. A smaller model would not necessarily maintain the same performance as regular sized model, but the smaller it is, the better it is in terms of resource consumption. To put it in a nutshell: It is best to find a model that is just big enough to meet the need and at the same time not too big to overconsume your resources.

You state that right now, the network infrastructure in hospitals and other healthcare facilities is not designed to handle massive amounts of data that, for example, deep learning requires. Regarding training deep neural networks collaboratively, what would it take to be able to do this?

Shi: For example, to share the data in order to train a model, you need to remove all the personal patient information, which is still quite a lot of work. However, there are public domain datasets available. It would make sense to pre-train a model on whatever public domain data set can be obtained. And then start from that model to adapt it to the individual data from a particular hospital. However, at least in the U.S., it is relatively easy to work together and share data if the hospitals belong to the same management. When it comes to hospitals across different states, it is much more difficult due to privacy and security concerns. My and my co-authors' vision is that there will be ways possible – not just from a scientific perspective, but rather from a public, policymakers' perspective – to have an umbrella agreement that allows easier data sharing or at least some kind of experiments.

You advocate for more medical domain experts in order to be able to keep up with the increasing number of medical images needed for training the AI models, and also to assure a good training. What benefit do AI models have over telemedicine, where you still need a doctor to "see" the patient remotely and make the diagnosis?

Shi: Telemedicine makes healthcare accessible to a broader population, especially in rural areas. Nonetheless, you still have a limited number of physicians with limited time to participate. So there is a restriction of how much the population can really benefit from telemedicine. With the help of AI, there is basically an unlimited availability for at least some screenings for simple healthcare problems. Me and my team at Boston Children's Hospital are working on a diagnosis app for common skin diseases. Our goal is that using AI models, we can – with the help of medical expertise – train the app at least to tell patients with high accuracy whether they should see a doctor immediately or whether they are dealing with symptoms that are not urgent and can wait for a scheduled appointment. Everyone with a mobile phone will have access to the app.

(The interview was conducted by SR.) ■

Bone Research: ISAS Participates in the new »DIONE« Collaborative Research Centre

What is the connection between our immune system and bone fractures? Why can autoimmune diseases such as rheumatoid arthritis, illnesses such as psoriatic arthritis or chronic inflammatory bowel diseases affect the skeleton? For the first time, scientists will be investigating these questions in the new Collaborative Research Centre (CRC) / Transregio 369 »DIONE«. Researchers at Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg, Technische Universität Dresden, ISAS and the University of Ulm will be looking into inflammation-induced bone degeneration. The German Research Foundation is funding »DIONE – Degeneration of bONE induced by inflammation« for an initial period of four years.

It is known that the immune system reacts to inflammation and releases various mediators such as metabolites. The latter have an effect on bone remodelling by influencing the balance between osteoblasts (bone-building cells) and osteoclasts (bone-degrading cells). However, how exactly the intracellular and extracellular regulatory circuits control inflammation and skeletal reactions has not yet been explored. The scientists at »DIONE« want to change this by incorporating the latest developments and findings on inflammatory diseases from immunology and bone biology into their research project.

This is why researchers at ISAS and FAU will use various microscopy techniques to investigate whether different osteoclast subpopulations have different activation profiles and functions in addition to their different origins. Scientists at ISAS want to find out more about the individual regulatory mechanisms of different osteoclast subtypes during different inflammatory processes and their influence on disease-specific bone damage. They would like to use these new findings to identify potential targets for more specific therapies for various skeletal-associated diseases such as rheumatoid arthritis and osteoporosis. The corresponding »DIONE« sub-project is headed by Prof Dr Anika Grüneboom from ISAS's Bioimaging research group, together with Prof Dr Gerhard Krönke (FAU / Charité – Universitätsmedizin Berlin).

(SR) ■

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DFG

Quality Assurance for Biomedical Images Segmentation Software

High-quality microscopy image analysis software is critical for creating customised image analysis solutions for various biomedical studies. Ideally, it comes with a short development time. In an ideal world, open-source microscopy image analysis software would be accessible for users without a lot of coding experience, by design extendable for experienced developers, independent from specific databases and therefore re-usable, and have undergone quality assurances. But in reality, even the most popular software programmes in the field of bioimage analyses do not combine all of the above-mentioned attributes.

SOFTWARE: SEGMENTATION

»Allen Cell and Structure Segmenter«
https://www.allencell.org/segmenter.html

napari-allencell-segmenter
https://www.napari-hub.org/plugins/napari-allencell-segmenter

That is why Dr Jianxu Chen and his AMBIOM team have decided to concentrate on the further development of the »Allen Cell and Structure Segmenter« (Allen Institute for Cell Science, U.S.). It is the state-of-the-art open-source software when it comes to the structural analysis of live cells. With their project »Quality Bioimage SEGmentation – QBSEG« Chen and his colleagues in Dortmund intend to extend the »Allen Cell and Structure Segmenter« software and provide AI templates and testing suites for the quality assurance and reusabil-ity in a broader bioimaging community.

Chen is utmost familiar with the »Allen Cell and Structure Segmenter«, since he was the core designer and developer of its prototype while working at the Allen Institute for Cell Science before he joined ISAS. He also led a team of software engineers and designers to develop the napari plugin for classic segmentation workflows. The AI expert established the collaboration between ISAS and the Allen Institute for Cell Science (► p. 13) in machine learning research and open-source microscopy image analysis software development. His former employer and now ISAS's collaborating partner supports Chen's project and the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) will be funding his project over the next three years.

(SR) ■

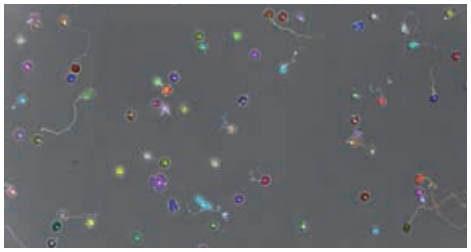
Funded by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) – Project number 528777169.

The diameter of a single ComplexEye lens (photo: centre) is 8 mm. It fits exactly under one 9 mm cavity of a standard 96 well plate. In a 384 well plate, cavities have a diameter of 4.5 mm. One ComplexEye lens is therefore many times more delicate and yet almost as capable as the 28.5 mm objective (right) of a conventional microscope.

ComplexEye & AI Enable Faster Migration Analysis of Immune Cells

Immune cells fight infectious intruders, for example, or search for incipient cancers. To do this, they are constantly migrating through the tissues of our body. However, in the wrong place, immune cells such as neutrophil granulocytes can also cause damage: If these white blood cells infiltrate tumours, this is often associated with a poor prognosis for patients. This is why these patients could benefit from drugs that prevent neutrophils from migrating into tumours. Until now, investigating this migration behaviour has been conducted by using conventional video microscopy. With this technique, a single camera objective observes the movement of cells under the microscope – one sample at a time. Researchers at the University of Duisburg-Essen (UDE) and ISAS have now developed a microscope for the high throughput analysis of compounds. It enables them to analyse 64 and in future 384 samples simultaneously. The researchers presented their microscope, named ComplexEye, in *Nature Communications* in 2023.

"If we knew how to control the migration of neutrophils, many diseases would be easier to treat," says Prof Dr Matthias Gunzer, Director at the Institute of Experimental Immunology and Imaging (UDE) and head of the Biospectroscopy Department at ISAS. But so far, there has been a lack of methods ▸



With the help of AI, neutrophil migration behaviour can be visualised in the form of trajectories (movement paths) using the segmentation software (from the ISAS research group AMBIOM).

The two corresponding authors Dr Reinhard Viga (left) from UDE and Prof Dr Matthias Gunzer (UDE / ISAS) are standing in front of the ComplexEye microscope with one of the two first authors, Dr Zülal Cibir.

to further this kind of research, especially for the small, fast-moving immune cells. Now, Gunzer and his co-authors have been

”In our test runs, we were able to analyse the samples around 60 times faster than it would have been possible with conventional video microscopy.

able to drastically increase the speed of migration analyses using ComplexEye.

Jacqueline Hassel is one of two first authors of the publication in *Nature Communications*.

“In our test runs, we were able to analyse the samples around 60 times faster than it would have been possible with conventional video microscopy,” explain the two lead authors Dr Zülal Cibir and Jacqueline Hassel (UDE). In order to investigate the influence of existing compounds on the migration of neutrophils, the researchers from Essen tested around 1,000 substances from a chemical library at the Lead Discovery Center in Dortmund. For the subsequent analysis, the AI experts at ISAS programmed customised software. Using the AI-supported ComplexEye system, within just four days, the researchers then identified 17 substances that can strongly influence the mobility of human neutrophils.

ComplexEye: further diagnostic procedures possible

Initially, the findings are of basic scientific value, but the researchers hope that they will open up many new therapeutic options. “With a few minor adjustments, ComplexEye can also be used for other cells, for example to monitor the progression of diseases, and detect early warning signs of

a worsening of infections such as imminent blood poisoning," says the immunologist Gunzer.

About ComplexEye

To develop ComplexEye, scientists from the Faculty of Medicine, the Department of Electrical Engineering and Information Technology at UDE and ISAS in Dortmund worked closely together. "The challenge was to build miniaturised microscopes, make them moveable and assemble them so tightly into one system that they can record videos from each of the 384 chambers of a well plate, a common examination tray," says Dr Reinhard Viga from the Electronic Components and Circuits division at UDE. The electrical engineer was in charge of the technical construction of the new microscope. Like the multi-lens compound eye of a fly, ComplexEye moves under the well plate and simultaneously takes images with all its lenses every eight seconds. The researchers then combine these images to create time-lapse sequences. Migrating cells visible in these movies are then tracked individually by AI. In the future, ComplexEye will be expanded to include additional lenses so that even more images can be captured.

(MH / SR) ■

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Cibir, Z., Hassel, J., Sonneck, J., Kowitz, L., Beer, A., Kraus, A., Hallekamp, G., Rosenkranz, M., Raffelberg, P., Olfen, S., Smilowski, K., Burkard, R., Helfrich, I., Tuz, A. A., Singh, V., Ghosh, S., Sickmann, A., Klebl, A.-K., Eickhoff, J. E., Klebl, B., Seidl, K., Chen, J., Grabmaier, A., Viga, R.* & Gunzer, M.*
(2023) ComplexEye: a multi-lens array microscope for high-throughput embedded immune cell migration analysis.
Nature Communications, 14:8103.

https://doi.org/10.1038/s41467-023-43765-3

(* corresponding authors)

The Art of Balancing: Accuracy in Image Analysis

Centuries ago, the invention of the microscope opened a window to a tiny, previously invisible world. Since then, it is not only the quality of images that has changed dramatically, but also the way in which we interpret them. Instead of just optically revealing the depths of the smallest structures, we can now translate biological processes into precise figures using modern image analysis methods. But for this translation to succeed, all researchers must first ask themselves the same questions: What do we want to measure? How precise do these measurements need to be so that we can interpret them in a meaningful way?

Modern microscopes generate enormous amounts of data. A light sheet fluorescence microscope at ISAS, for example, produces an average of well over 500 high-resolution images per sample. Handling this amount of data and then efficiently analysing it requires innovative approaches to data analysis. Specialised software or image analysis methods find use here, with the increasing help of artificial intelligence (AI). However, there is no such thing as a universally applicable approach to image analysis. “Just as there is no ‘one size fits all’ microscope, different research projects require customised image analysis workflows or software tailored to the specific requirements,” explains Dr Jianxu Chen. He leads the AMBIOM – Analysis of Microscopic BIOMedical Images junior research group at ISAS, which is working on these types of AI-based biomedical image analysis algorithms.

Dr Jianxu Chen heads the research group AMBIOM at ISAS since September 2021.

A checklist to validate bioimage analysis results

When analysing images, the challenge is to ensure that the findings obtained are not only quantitatively or statistically accurate, but also biologically meaningful to the research question. “To achieve this, researchers should fine-tune the experimental design, the details of the microscopic imaging and the target metrics of the image analysis from the start,” advises Chen. Together with Dr Susanne Rafelski and Dr Matheus Viana from the Allen Institute for Cell Science in the USA, he recently published some key considerations for researchers in the journal *Nature Methods*. Researchers can

The checklist (► p. 33) is about the balance between analysis and accuracy. This image was created by Dr Jianxu Chen (AMBIOM) on December 13, 2023, using ChatGPT, model "DALL-E". See next page for details including prompt.

utilise them as a type of checklist (► p. 33) when considering how to analyse their image data.

> **It is important that the validation is application-oriented and geared towards the specific objectives of the research.**

Just how good is good enough?

A key step on the way to a biologically valid image analysis is the question of validation, meaning how accurate and precise the measurements should be. "It is important that the validation is application-oriented and geared towards the specific objectives of the research," emphasises Chen. In practice, this means that researchers need to consider beforehand how accurate their measurements should be and how many errors they can tolerate. For example, if they want to measure cell parts like the nucleus or mitochondria, they could ask themselves the question: Do the exact volumes of the organelles matter, or is it more about comparing different volumes? In the latter case, the exact volume may not play a major role, but for the comparison, however, the computer programmes used must perform all the more consistently in different situations.

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Constant adaptation – with the help of AI

However, not even the best image recognition algorithms always work equally well if, for example, the shape of the organelles changes just slightly. Researchers therefore have to regularly check and validate their measurements, adjust individual parameters or, at worst, even use a completely different programme. “If such adjustments are not taken into account, this can lead to fundamental misinterpretations of the biological results,” warns Chen. To him, one solution is deep learning, a form of machine learning that can automatically extract patterns and features from large amounts of data. His research group has already developed a plug-in based on deep learning for the segmentation (see infobox) of immune cells. In the future, deep learning could help researchers to automatically recognise drops in performance in their image analysis algorithms during validation.

The future of image analysis is interdisciplinary

But Chen and his colleagues are not just interested in finding better ways to analyse images. They are keen to ensure that their methods can be understood and applied in both biology and computer technology. “We need more interdisciplinary collaboration between researchers in the lab and AI experts, preferably early on in each of their training,” Chen urges. For those who cannot wait to get started, but do not have a computer vision specialist nearby, Chen recommends online learning materials such as The Bioimaging Guide or Resources via the German Network for Bioinformatics Infrastructure – de.NBI. For specific questions there is also an online forum called image.sc. “Collaboration is the only way that quantitative microscopy image analysis can really evolve,” Chen concludes.

(CP) ■

Chen, J., Viana, M. P., Rafelski, S. M.
(2023) When seeing is not believing: application-appropriate validation matters for quantitative bioimage analysis.
Nature Methods, 20(7), 968–970.

https://doi.org/10.1038/s41592-023-01881-4

SEGMENTATION

In biomedical research, it can be helpful to recognise and differentiate between different structures such as cells in an image. This process is called segmentation. For a long time, it was common practice to go through the images individually and annotate (assign) them by hand. However, as data volumes and image sizes increase, researchers are increasingly turning to deep learning-based programmes. These are not only significantly faster, but also much more objective and accurate. Nevertheless, manual annotations often still serve as a training basis for these deep learning algorithms. Compared to models trained with biological ground truth, models trained with manual annotations have an error rate of over 30 per cent (see Sonneck 2023). By biological ground truth, AI experts mean the optimal approach to objective reality, which is difficult to determine with a single analysis. Instead of using manual annotations, experts determine the biological ground truth using experimental computer-aided analyses.

CHECKLIST

Basics

- ☐ Should the measurements be relative or absolute?
- ☐ Which measurements or variables are required?
- ☐ Do you want to do Segmentation, deep learning prediction or do you have a specific quantification goal?

Boundaries

- ☐ What experimental factors need to be considered?
- ☐ Which microscope types and settings are suitable?
- ☐ What are the limits of resolution?

Validation

- ☐ Relative or absolute validation?
- ☐ Is the goal a one-off or a robust, scalable result?
- ☐ Should the accuracy apply to the entire image or specific features?
- ☐ Qualitative or quantitative error bars?

Time and Effort

- ☐ What is the best approach for the analysis?
- ☐ How much time and effort should the analysis cost?

About the illustration: Prompt = "I am creating a picture illustration for my article with name 'The Art of Balancing: Accuracy in Image Analysis'. It is a press article about how to do bioimage analysis validation. Could you help make an illustration, as normal as possible, and as simple as possible?" ChatGPT only provides the following information about the image: "Here is the illustration representing the concept of 'The Art of Balancing: Accuracy in Image Analysis' for your article. It features a balance scale with a magnifying glass on one side and a checkmark on the other, symbolizing the equilibrium between analysis and accuracy in bioimage validation."

GEFÖRDERT VOM

Bundesministerium
für Bildung
und Forschung

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Using the Russian Doll Principle to Analyse Biological Structures

Inflammatory or rejection responses following a heart attack or an organ transplant, for example, are highly complex immunological processes. To understand these in their entirety, it is necessary to analyse the biological structures from the whole organ through individual cells down to the molecular level – just like with a Russian doll (► p. 37). To this end, several ISAS research groups are working on how to combine various microscopy and mass spectrometry techniques within the scope of the project »AI-assisted Imaging of Large Tissues«. Within this project, the interdisciplinary team employs murine samples (from mice) and human samples. These samples are obtained from clinical cooperation partners such as Charité – Universitätsmedizin Berlin and University Hospital Essen. The project's objective is to perform cross-scale analyses to obtain from the same sample detailed information on the cellular composition and interactions within a tissue.

This makes it possible to perform analyses that are not only more precise but also require fewer resources. Combining various microscopy techniques (including a special clearing method that renders organs transparent ► info box) as well as artificial intelligence (AI) to analyse the images contributes to a significant reduction in the number of samples. In addition, AI experts are working to minimise the amount of energy consumed in data storage and nevertheless increase the analysis quality of the ultra-high resolution microscopic images (► p. 21).

CLEARING

Tissue and bone can influence light in different ways: by absorbing, reflecting or scattering it. Consequently, researchers must chemically treat a sample before they can examine it in its entirety beyond the surface using a lightsheet fluorescence microscope. For this purpose, Prof Dr Anika Grüneboom has developed a technique that makes the samples transparent using ethyl cinnamate, a naturally occurring aromatic substance. Optical clearing leaves the samples intact and is reversible. This means researchers can subsequently examine the same bone or the same tissue under a confocal microscope, for example.

Before going deep into the molecular structures using mass spectrometry, the researchers initially analyse various tissue samples as a whole. Using a lightsheet fluorescence microscope, doctoral candidate Flora Weber examines intact organs such as kidneys or bones from mice, for example. Inside the microscope, a thin sheet of light illuminates the individual layers of a sample rendered transparent by clearing and records an image of each one. The researchers obtain an average of around 500 images per sample, which are then combined into a 3D model on a computer. Afterwards, they reverse the clearing, which means that the same sample can be analysed on a confocal microscope. For this, the researchers do have to slice the organ or tissues, but this is the only way to render the cellular details visible by means of the higher optical resolution of confocal microscopes.

Microscopy delivers different data than mass spectrometry, for example. By combining different techniques, the researchers intend, over the long term, to generate what is known as multimodal data. This information consisting of different data types is integrated and analysed at ISAS in cooperation with the junior researcher groups AMBIOM – Analysis of Microscopic BIOMedical Images and Multidimensional Omics Data Analysis.

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Dr Martin Stenzel uses the flow cytometer to analyse individual cells at a high throughput. With the help of imaging, he introduces a liquid sample, in this case blood cells from a tumour patient, into the device. Inside the device, a narrow flow of fluid takes it past various laser sources. When the cells pass though the light beam, they scatter the light in characteristic ways. Sensors record the scattered light, including radiation in the visible wavelength range and fluorescence radiation. The signals reveal exactly which cell types and cell components are present in a sample and in what quantities. To integrate flow cytometry into the workflow, the Bioimaging research group is currently developing an alternative way of preparing samples for lightsheet fluorescence microscopy. For this type of microscopy, they have to first fix the samples, i.e. chemically stabilise the cells or tissue structures so that they maintain their shape and position during analysis. The new approach by the researchers aims to achieve a reversible fixing technique so that parts of the same sample can subsequently be analysed using flow cytometry.

The researchers test their workflow using various samples including murine hearts as well as murine and human kidney samples in the context of reperfusion injury. This kind of injury occurs when the blood flow is restored to a tissue following an interruption – for example, following a heart attack or a kidney transplant when closed-off vessels are opened again.

The figure shows murine jawbones from a model of medication-related osteonecrosis of the jaw (MRONJ). In this condition, parts of the jawbone die off, due to medication against osteoporosis, for example. Using a clearing technique developed by Prof Dr Anika Grüneboom, the researchers first render the bones transparent for analysis with a lightsheet fluorescence microscope (picture on right). Bone tissue is very heterogeneous: while the cortical bone, the outer layer, is hard, the bone marrow inside is comparatively soft. There are, in addition, cartilage tissue, tendons and muscles on the outer bone interfaces. The various tissue types each require appropriate methods of chemical preparation to make them accessible for the different analytical methods. For this reason, the researchers are investigating an approach that unites the contrasting requirements for sample preparation within the workflow.

Russian doll principle

The principle applied by the researchers is similar to a Russian doll. Rather than uncovering ever smaller wooden dolls nested inside each other, each step taken by the ISAS team allows them to gain a deeper insight into the biological structures of a sample. Starting with whole organs and going down to the molecular details, this approach facilitates a precise understanding of biological processes.

(CP) ■

PATHO-MECHANISMS

In addition to regular fluorescence images, researchers are able to use the confocal microscope with a temperature-controlled, transparent incubator unit to examine, for example, cardiomyocytes (heart muscle cells) from mice using live cell imaging.

The research programme Pathomechanisms concentrates on the analysis of disease mechanisms with focus on cardiovascular diseases (CVDs), in particular heart failure due to myocardial infarction (heart attack), pathological cardiac hypertrophy (heart growth) or cardiotoxic cancer therapies. The overall goal of the programme is to identify molecular changes that are causative for the development of these diseases and are suitable as targets – and possibly as biomarkers.

Within the multiple pathomechanisms that can underlie for example heart failure, the scientists address the ones that

- are of translational potential like cardio-safe targeting of certain kinase (specific enzymes) cascades,
- represent common pathomechanisms or events in the heart and in cancer, for example cellular growth mechanisms and coagulation (clotting of blood),
- involve toxic side effects of drugs like cardiotoxicity of cancer drugs, and
- those that are relevant for the further optimisation of analytical methodologies.

Until today, the molecular causes and the course of many diseases of the cardiovascular system are still largely not understood. Many CVDs have multi-factorial causes – genetic constellations play a part in addition to environmental as well as nutritional factors, platelet disorders or cardiotoxic cancer therapies. To obtain a multidimensional picture of the pathomechanisms underlying cardiovascular diseases, to enable doctors to diagnose these illnesses earlier in future, and to carry out individual therapies more effectively and with fewer side effects, researchers at ISAS apply methods that

comprise genomic, proteomic and metabolomic parameters. They develop, combine, or optimise various analytical technologies to identify disease mechanisms and potential target molecules for the treatment of different cardiovascular diseases.

Development of analytical tools and combination of new methods

The scientists involved in this research programme combine traditional molecular genetic and biochemical methods with high throughput mass spectrometry methods and spectroscopic approaches. This enables them to cover the entire bandwidth of the analysis – from detailed investigation of individual components through to analysis of entire cellular systems.

They aim, for example, to work out spectroscopic and metabolic characteristics of certain diseases with protein or lipid deposition like amyloidosis or Fabry disease in close collaboration with clinician scientists at the Julius-Maximilians-Universität of Würzburg and University of Duisburg-Essen (University Hospital Essen). The scientists at ISAS continue to press ahead intensively with the applications of biospectroscopic analyses, in particular Coherent Anti-Stokes Raman Scattering (CARS) and Raman spectroscopy combined with vibrational microscopy and MALDI (matrix-assisted laser desorption/ionisation) imaging. Moreover, they develop AI methods to optimise the analyses of the obtained data in order to identify early metabolic or structural changes within the myocardium (cardiac muscle).

Gained insights into metabolic events are supplemented by research that aims to optimise nuclear magnetic resonance (NMR) for a longitudinal monitoring of metabolic fluxes with high sensitivity and spatial as well as temporal resolution. It is an analytical method that is of great relevance for a better understanding of cytotoxicity (quality of being toxic to cells) mechanisms of certain drugs.

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Application of different model systems

The researchers use cell- and mouse-based model systems that are able to recapitulate central features of CVDs. For example: They work with platelets that can agglomerate and thereby simulate thrombi or cardiomyocytes that beat and thereby serve for the readout of contraction and relaxation. The scientists also work with genetic mouse models that represent a phenotype of pathological heart growth in children or due to lipid depositions in the heart.

Precision medicine: potential of insights into platelet activation

In heart attacks, which are among the top two causes of death worldwide[1], platelet aggregation plays a central role. ISAS has many years of analytical expertise regarding research into thrombocytes (blood platelets). This includes the comprehensive investigations into the population based proteome of thrombocytes and in-depth research of thrombocyte malfunctions. More insights into platelet activation/inhibition have the potential to further precision medicine for CVDs. Therefore, the researchers at ISAS have been creating a standard platelet data base. It allows the application of machine learning models to predict platelet aggregation and ultimately haemostasis (blood clotting) in patients with heart failure or stroke – a strategy that is being further advanced as a blueprint for other blood cells.

(SR) ■

1 http://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

Two-step Analysis is a Thing of the Past Thanks to Innovative Mass Spectrometry

Cholesterol is vital for the body. It serves as a building block for many hormones and is an essential component of cell membranes. However, if you have too much cholesterol in your blood, you carry a higher long-term risk of cardiovascular disease. Unfortunately, so far this hugely important health parameter has been difficult to measure. As a largely non-polar substance, cholesterol is not detected well in mass spectrometric analyses targeting the polar, i.e. water-soluble, substances in the blood. This means a separate round of analysis using a different ionisation source must be carried out to detect cholesterol. However, researchers at ISAS and the University of Vienna have now jointly developed a system allowing non-polar substances such as cholesterol together with polar substances to be detected quickly and accurately in a single step using mass spectrometry. They report on their development in *Analytical Chemistry*.

Dr Daniel Foest is a research associate in the ISAS Miniaturisation research group.

In mass spectrometric analysis, the constituents of blood samples are ionised, then accelerated by an electric field and separated based on their mass-to-charge ratio. Separated in this way, it is easy to determine how much of which substance is present in the blood. Polar blood components such as electrolytes are best ionised using an electrospray (► p. 44).

Combination method unites ionisation sources for different analytes

For non-polar substances, however, ionisation in liquids does not work sufficiently well. To detect such substances, the sample is instead usually vaporised in a thermospray at several hundred degrees Celsius and then ionised by a plasma. “In the same measurement, mass spectrometers can only use one ionisation source, either electrospray or plasma-based techniques,” says Dr Daniel Foest, research associate in the ISAS Miniaturisation research group and lead author of the publication. “This means you are always blind in one eye.”

If researchers wish to detect non-polar substances, particularly in the lowest concentrations, this in practice means that they either

need two separate devices equipped with different ionisation sources or they have to convert the mass spectrometer before the second round of analysis. “We first have to disassemble one ionisation source, set up the other ion source and then recalibrate the mass spectrometer, which usually takes around an hour,” says Foest. Researchers have long been looking for a way to efficiently analyse both polar and non-polar substances in a single analysis step.

Success with two operating modes

Many researchers start with the sample and manipulate it at molecular level. However, this so-called derivatisation (► info box) is time-consuming and, in the case of cholesterol, can even falsify the analysis. In their search, the Dortmund scientists led by Foest therefore concentrated on the ionisation source. “As an approach, this may seem unusual,” says Dr Sebastian Brandt, corresponding author and former member of the ISAS Miniaturisation research group. He adds: “The ionisation source is supplied by the mass spectrometer manufacturers and is therefore a black box for many users. Our aim was to simplify the ionisation process by combining two sources in one setup.”

> ***With the FµTP as a hardware add-on, there are two operating modes and we can switch back and forth between them.***

Specifically, they attached a flexible microtube plasma (FµTP) developed at ISAS (patent pending) to a mass spectrometer already equipped with an electrospray ionisation source as standard. “With the FµTP as a hardware add-on, there are two operating modes and we can switch back and forth between them. For example, we can first ionise the polar and then the non-polar substances without having to disassemble and reassemble the mass spectrometer in between,” says Brandt in summary. When the FµTP was connected and activated, the cholesterol yield in a liver sample improved by a factor of 49 compared to conventional electrospray ionisation.

DERIVATISATION

When researchers wish to analyse complex molecules, they often encounter challenges due to the natural diversity of the molecular structures they contain. One approach to overcoming these obstacles and improving the analysis is derivatisation. This process involves the targeted modification of a molecule’s functional groups in order to alter or improve certain properties, such as polarity. Although this is possible in the case of cholesterol, it results in the formation of cholesterol esters, which are often present in the samples and ultimately produce false results, making additional measurements necessary.

Dr Sebastian Brandt is a physicist and until recently was a research associate in the ISAS Miniaturisation group.

Automatic temperature control optimises new hybrid variant

According to Foest, both electrospray and plasma ionisation are extremely temperature-dependent and work best in different temperature ranges. After months of tinkering, during his dissertation Foest thus developed a model in which a cooling gas on the one hand and a heating element on the other support the different ionisation steps. While in the first version the analytical chemist still had to manually switch back and forth between the two ionisation sources, an electronic system now regulates this automatically. “The switching between the two ionisation sources is so fast it is almost simultaneous,” says Foest. “Both ionisation sources now work at optimum efficiency and the mass spectrometer is completely unaware of the switch,” adds Brandt.

For Foest and Brandt this combination method represents a real improvement in mass spectrometry. Not only does it save time and effort, it also allows samples in small quantities to be analysed in a single step – and therefore more efficiently. This approach is particularly useful for analysing tissue samples that are only available in extremely small quantities.

(UE)

Foest, F., Knodel, A., Ahrends, R., Coman, C., Franzke, J., Brandt, S.
(2023) Flexible Microtube Plasma for the Consecutive-Ionization of Cholesterol in Nano-Electrospray Mass Spectrometry. *Analytical Chemistry*, 95, 8423–8432.

https://doi.org/10.1021/acs.analchem.2c04052

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ELECTROSPRAY IONISATION

Electrospray ionisation (ESI) is a soft ionisation technique used in mass spectrometry. Here, a sample to be analysed is mixed with a solvent and sprayed through a fine metal capillary tube into an electrostatic field. The droplets of discharged solution repel each other electrostatically and disintegrate more and more until only floating, single, ionised molecules remain. While the solvent evaporates, the charged analyte molecules are directed into the mass spectrometer and analysed. In their study, the researchers used a so-called nano-electrospray variant (nano-ESI), which produces extremely fine droplets.

What's going on here, Stefanie Dörr?

The photo shows me working as part of the Collaborative Research Centre (CRC) »Local Control of Thyroid Hormone Action – LOCOTACT« (► p. 46) in a laboratory at University Hospital Essen. The videographer you can see on the right of the photo is André Zelck, who followed a few of the CRC's doctoral candidates in October 2023. The video was designed to give experts from the German Research Foundation (DFG) a clear picture of our research. When this photo was taken, I was using the ultrasound scanner to examine a mouse heart. In this CRC, which is funded by the DFG and led by University Hospital Essen, our ISAS research group is part of a research alliance with the University of Lübeck, Leipzig University, Charité – Universitätsmedizin Berlin and the Helmholtz Munich centre, which is investigating the local control of thyroid hormone action. In our case, we are looking specifically at the effect of thyroid hormones on chronic ischaemic heart disease.

Stefanie Dörr is a doctoral candidate in the Cardiovascular Pharmacology research group at ISAS.

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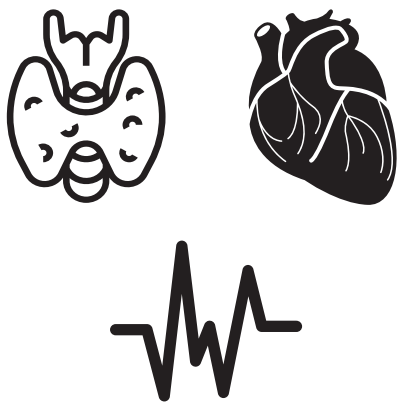
Thyroid Hormones: Timers for the Heart?

The butterfly-shaped thyroid gland is located below the larynx and produces hormones that affect tissues and organs throughout the body – especially the heart. Having a thyroid that is even slightly overactive or underactive can increase the risk of vascular disease and mortality by 20 to 80 percent.[1] ISAS researchers investigated how thyroid hormones affect heart tissue and which control mechanisms they are subject to in the heart. As part of the Collaborative Research Centre (CRC) »Local Control of Thyroid Hormone Action – LOCOTACT«, they want to work together with other scientists to answer the question: how does the body control the transport, metabolism and mode of action of thyroid hormones in the heart? Their aim is to find new treatment approaches to cardiovascular diseases, for example.



Funded by Deutsche Forschungsgemeinschaft (DFG) – project number 424957847-TRR 296.

A focus on local control mechanisms

Even a slight excess or deficiency of the thyroid hormones triiodothyronine (T3) and thyroxine (tetraiodothyronine, T4) can change a person's heart rate and blood pressure, for instance. This could lead to cardiovascular conditions including arrhythmia, atherosclerosis (hardening of the arteries) and heart failure. Only in recent years has the world of medicine realised that it is not enough to simply test how much T3 and T4 is released into the blood throughout the body when diagnosing thyroid conditions. That's because this systemic value has little to do with the specific level of thyroid hormones in organs such as the liver, brain and heart. Receptors and transport molecules in these organs affect the quantity of thyroid hormones transported into and out of single cells – and how they act on the functions of the relevant organ cells. Understanding how this process occurs or how it is disrupted can help to prevent stroke, cardiac insufficiency (heart failure) or hepatopathy (liver disease), for example, or to treat these conditions in a more targeted way than before.

1 https://www.intechopen.com/chapters/85639

CRC LOCOTACT is interested in this local control of thyroid hormones. Led by University Hospital Essen (UK Essen) and funded by 13.7 million euros from the German Research Foundation the researchers form an interdisciplinary team hailing from the University of Lübeck, Charité – Universitätsmedizin Berlin, the Helmholtz Zentrum Munich, Leipzig University and ISAS.

Which receptor makes the heart "beat faster"?

In 2023 a team of LOCOTACT researchers, including Prof Dr med. Lars C. Möller (UK Essen) and Prof Dr Kristina Lorenz (head of the Cardiovascular Pharmacology research group at ISAS), investigated which of the two thyroid hormone receptors TRα and TRβ controls the heart rate and can potentially cause the heart muscle to thicken. They were primarily interested in understanding the fundamental processes involved. On the one hand, thyroid hormones can act directly on the genome of the heart muscle cells by means of receptor binding, i.e. they can alter the gene expression. And on the other, they can also act non-genomically: in the ion channels of the cell membrane, for example.

The researchers studied the effect of treating genetically modified mice, which were missing one of these two receptors (TRα or TRβ), with T3. There was a control group made up of mice that were not genetically modified and that had both receptors. The researchers were able to determine from the animals' different responses to the T3 treatment that the receptor TRα mainly regulates the heart rate in mice – and it does so by acting on the genome. Indirectly, or non-genomically, TRα can also cause the cardiac chambers to enlarge. TRβ plays only a supporting role in this, although it does also have an effect on heart rate. The researchers have published their results on bioRxiv as a preprint (pre-release of a scientific paper that has not yet been peer reviewed) in 2023. The following year, their results were also published in the journal *Thyroid*.

Geist, D., Hönes, G.S., Grund, S. C., Pape, J., Siemes, D., Spangenberg, P., Tolstik, E., Dörr, S., Spielmann, N., Fuchs, H., Gailus-Durner, V., Hrabe de Angelis, M., Mittag, J., Engel, D. R., Führer, D., Lorenz, K., Moeller, L. C.
(2024) Canonical and noncanonical contribution of thyroid hormone receptor isoforms alpha and beta to cardiac hypertrophy and heart rate in male mice. *Thyroid*.

https://doi.org/10.1089/thy.2023.0683

Rare genetic defect provides an insight into how heart rate is controlled

One series of investigations had a surprising result for the researchers working with Prof Dr Jens Mittag (University of Lübeck). The starting point for this study were three patients in whom the TRα receptor was not completely absent, but a genetic defect meant the receptor responded to thyroid hormones less sensitively than in healthy individuals. The inherited defect RTHα – which affects one in 40,000 newborns worldwide[2] – causes hypothyroidism in some tissues even when blood levels are normal.

This can lead to growth retardation and other developmental disorders. In theory, the defect can be balanced out by giving the patient extra thyroid hormones (T3). However, since the receptor concerned, TRα, regulates the heart rate, there is some concern that this could give rise to tachycardia (palpitations). Contrary to expectations, this effect was not observed in the three patients. This led the researchers to conduct further studies on mice, which indicate that RTHα affects not only the receptor itself: the genetic defect also causes specific genes in the heart tissue to be less active than in healthy individuals.

It is particularly interesting to note that this not only affects genes that were already known to control heart rate (specifically, genes that play a part in potassium and calcium flow in heart tissue), but also genes that previously had no known link to this process. The study, published in the journal *Nature Communications*, therefore suggests that thyroid hormones affect the heart in a way that is more complex than previously thought. But it also means that RTHα patients can be given hormone treatment without the risk of tachycardia.

Dore, R., Watson, L., Hollidge, S., Krause, C., Sentis, S. C., Oelkrug, R., Geißler, C., Johann, K., Pedaran, M., Lyons, G., Lopez-Alcantara, N., Resch, J., Sayk, F., Iwen, K. A., Franke, A., Boysen, T. J., Dalley, J. W., Lorenz, K., Moran, C., Rennie, K. L., Arner, A., Kirchner, H., Chatterjee, K., Mittag, J. (2023). Resistance to thyroid hormone induced tachycardia in RTHα syndrome. *Nature Communications,* 14:3312.

https://doi.org/10.1038/s41467-023-38960-1

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2 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4790576/

The response to thyroid hormones: A question of age?

Lorenz's team in Dortmund, together with other researchers working with Prof Dr Führer-Sakel (UK Essen), demonstrated the variety of ways in which thyroid hormones act on the heart in a publication in the journal *Frontiers in Endocrinology* (The article was previously published on bioRxiv as a pre-print in 2023). Their investigation focused on identifying the possible consequences of giving thyroid hormones to patients with heart conditions.

The researchers added T4 to the drinking water of 12-month-old mice in the initial stages of heart failure. They observed that administering the hormone to the animals had no effect whatsoever on cardiac function. This was surprising, as a previous study[3] published by the team looking at eight-week-old mice had shown low doses of T4 improved cardiac function (whereas high doses led to further deterioration). The results indicate that local control of thyroid hormones in the heart tissue changes over a lifetime. If this is also confirmed in humans, it could mean that elderly hearts – which are at elevated risk of cardiac diseases – respond to thyroid hormones less directly.

(UE) ■

Kerp, H., Gassen, J., Grund, S. C., Hönes, G. S., Dörr, S., Mittag, J., Härting, N., Kaiser, F., Moeller, L. C., Lorenz, K.*, Führer, D.*

(2024) Cardiac recovery from pressure overload is not altered by thyroid hormone status in old mice. *Frontiers in Endocrinology,* 15:1339741.

https://doi.org/10.3389/fendo.2024.1339741

(* Corresponding authors)

3 https://www.frontiersin.org/articles/10.3389/fcvm.2021.683522/full

One of the technologies that plays a central role in the Multi-Omics research programme is mass spectrometry.

MULTI-OMICS

The aim of the Multi-Omics research programme is to develop bioanalytical and computational technologies for prognostic, diagnostic, and predictive biomarkers. The scientists research methods which can be used to more effectively to detect markers in complex biological matrices. These biological markers are intended for cardiovascular diseases (CVDs), cancer, and metabolic disorders.

Most diseases are caused by the deregulation of metabolic and signalling pathways at different molecular levels, from genes to lipids to proteins and metabolites. The regulation of metabolic pathways and their interaction with environmental factors requires the use of multiple analytical methods for the detection of proteins, lipids, metabolites, and their dynamics. A single analytical technology is neither sufficient for a comprehensive understanding of select biological model systems, nor for identifying biomarkers. In view of the huge number of potential analytes in biological systems, all measurements need to be carried out to a high degree of precision. That is why a multi-omics approach, a combination of different omics – meaning

addressing the entire characterisation of all genes (genomics), metabolites (metabolomics) or proteins (proteomics) – approach is needed.

Multi-omics strategies: indispensable for precision medicine

Omics technologies (► p. 55) are an important starting point in personalised therapies (precision medicine). On the one hand, they produce multi-dimensional data sets (in unprecedented quality), which bring insights into disease processes and potential treatment approaches. On the other hand, multi-omics data sets for non-directional analyses can be used to demonstrate new correlations (generating new hypotheses) between various molecule classes. However, these large and complex data sets also need to be managed adequately.

One of the main focus areas: omics approaches for CVDs

Regarding CVDs, many factors including genetic predisposition, gut microbiome, lifestyle, and environmental factors, can have an impact. In addition, current therapeutic approaches to tumour diseases and inflammations can have side effects on the cardiovascular system. ISAS' Multi-Omics programme therefore particularly focuses on developing multi-omics technologies and assays with regard to heart attacks (myocardial infarction), heart failure, cardiotoxicity, and cardio-oncology. With omics-integrative models and the combination of lipidomic, proteomics, and metabolomic data, and by using graph databases and AI, researchers at ISAS aim to gain comprehensive insights into CVDs' complex molecular aspects. The analytical challenges that the scientists are tackling include molecular coverage, analytical sensitivity, data integration, and interpretation, as well as issues related to data quality, reproducibility, and standardisation.

Besides developing technologies to shed light on molecular mechanisms and identify biomarkers, the programme addresses the identification of new therapeutic targets. Therefore, unravelling the molecular mechanisms underlying CVDs is crucial. Systems biology approaches using multi-omics data play a critical role in identifying cellular changes and signalling events associated with disease genesis and progression.

High-throughput / High-resolution technologies with new bioinformatic strategies

In general, multi-omics technologies comprise analytical methods which can be used to investigate biomolecules from tissue samples or other biological samples like blood at a global level. Scientists at ISAS devote their time to developing such tools for integrating multi-omics data sets. They combine various analysis techniques such as electrospray ionisation mass spectrometry (ESI-MS), MALDI (matrix-assisted laser desorption/ionisation), light and fluorescence microscopy, and they develop new bioinformatic strategies for data analyses.

(SR) ■

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Thrombocyte Proteome: Tracking down Life-threatening Events in the Bloodstream

In most humans, every millilitre of blood contains more than 200 million thrombocytes (platelets).[1] These smallest of blood cells can play an enormous role in the most common causes of death worldwide: ischaemic (coronary) heart disease and stroke.[2] Thrombocytes can bind together in a flash, forming a thrombus (blood clot), which can plug a vessel and stop the flow of blood – this is how they can cause heart attacks and strokes. Proteins on the surface of the platelet cells are amongst others responsible for thrombogenesis. These proteins control activation of the thrombocytes – but the details of exactly how the proteins do this are still unclear. That is why ISAS researchers are working to decode the subtle changes that take place in the protein structure of these platelets. They want to identify the molecular markers that indicate thrombocyte activation so that, in future, medical experts will be able to detect and respond to a thrombosis before it even occurs.

Thrombocytes, from the Ancient Greek *θρόμβος* or "clot", are flat and round, like a discus, for most of their existence. The body produces them in the bone marrow. The important role thrombocytes have to play in blood clotting has been known since the late 19th century: if a blood vessel is injured anywhere in the body, thrombocyte receptors detect this and cause platelets to stick together in that location. This produces a plug, or thrombus, which seals the blood vessel. However, if a clot like this forms away from a "leak", this creates thrombosis. Many people take medication every day in an effort to prevent this. One such drug is Aspirin® (acetylsalicylic acid), which reduces thrombocytes' ability to stick together. This medication therefore inhibits blood clotting and helps to prevent heart attacks and strokes, amongst other things.

Prof Dr Albert Sickmann's team carries out multi-omics analyses at ISAS.

Exhausted and sticky

Thrombocytes are able to alter their form dramatically and ad hoc, as when clotting the blood, but they can also change slowly

1 https://www.ahajournals.org/doi/full/10.1161/01.CIR.0000086897.15588.4B
2 https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

Prof Dr Tienush Rassaf is Director of the Department of Cardiology and Angiology at Essen University Hospital.

> ***We do not yet have any reliable biomarkers that can act as an early warning system for the various processes involving thrombocytes.***

and subtly – meaning they feature in many other processes in the body too. Platelets are involved in inflammatory processes, play a part in spreading metastases and respond to bacterial or viral pathogens (causative organisms) by forming thrombi, for example.

"We do not yet have any reliable biomarkers that can act as an early warning system for the various processes involving thrombocytes," says Prof Dr Albert Sickmann, Chair of ISAS's Board of Directors and an expert in clinical proteome research. Until now, researchers worldwide have made do with cataloguing sub-populations of thrombocytes and giving them names like procoagulant, coated, exhausted or sticky.

To establish which proteins are responsible for which particular behaviour of the platelets, researchers at ISAS conducted mass spectrometry analyses and identified 5500 proteins that are found, in varying constellations, in thrombocytes (thrombocyte proteome). They created a database containing information about every single one of these proteins. Together with their cooperation partners from University Hospital Essen, the ISAS researchers now want to perform extensive analyses to figure out how thrombocyte protein profiles differ between people with varying physical conditions and increasing age. "We really hope that this work will help us to better understand the mechanisms that cause diseases," says Prof Dr Tienush Rassaf, Director of the Department of Cardiology and Angiology at University Hospital Essen.

A database that's free to access all over the world

ISAS has many years of experience in analysing thrombocytes to fall back on. The researchers are currently investigating thrombocytes from a group of over a thousand people, some with heart conditions and some healthy controls. It is the world's biggest study into the thrombocyte proteome. A similar-sized analysis of the blood of stroke patients is set to follow. "In most patients we are able to quantitatively record 4000 to 4200 proteins, which is

over 80 percent of the total proteins in a thrombocyte – in other words, the thrombocyte proteome," explains Sickmann. The biochemist expects that comparing these protein profiles will shed light on the details of how thrombocytes are activated. "We are also excited to see whether we will find any clues as to why one person suffers a stroke, while another has a heart attack," says Sickmann. Once they have completed their analyses, the ISAS researchers want to open up their thrombocyte proteome database so as many scientists as possible all over the world can access it for help in answering their medical questions.

Finding a handful of proteins amongst thousands

In their multi-omics analyses (► p. 55), the researchers at ISAS manage with tiny sample volumes. To be more precise, ten samples of 10 millilitres of blood are enough to elucidate complex molecular mechanisms and identify patterns of biomolecular changes that are associated with activating or inhibiting platelets. In 2023 the team of researchers working with Sickmann summarised the possible methods for analysing thrombocytes in a review article in the journal *Current Opinion in Chemical Biology*. Alongside proteomics, these methods are transcriptomics, phosphoproteomics, N-terminomics, glycoproteomics and lipidomics (► p. 55). They conclude that integrating multi-omics technologies further will open up new perspectives for explaining molecular and biochemical processes, including with regard to thrombocyte activation.

Reliable parameters for clinical diagnostics

The process of creating molecular profiles for inclusion in the thrombocyte proteome database is laborious. "We suspect that, out of thousands of proteins in a thrombocyte, only a handful need to change to affect a person's health. And because the differences between the proteins could be incredibly small, we must compare the blood of an enormous number of patients and healthy individuals in order to find them," explains Sickmann.

In the medium term the researchers hope to identify reliable parameters for conditions such as heart attacks or strokes with the help of protein profiles. Where possible, the findings from the analyses could also help patients whose blood clotting ability is impaired due to a genetic condition. This is the case with Glanzmann's thrombasthenia, for example, which affects one person in every million worldwide.[3] In this disorder, patients' thrombocytes are missing a receptor, which means that platelets do not clump together as well as in a healthy person. If the condition remains undiagnosed it can be life-threatening, as patients can easily lose dangerous amounts of blood when undergoing only minor surgery.

(UE) ■

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3 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6742499/#

Dr Fiorella Solari is a research associate in the Proteomics research group.

Multi-omics: From proteomics to N-terminomics and transcriptomics

Omics technologies are molecular biological methods such as genomics, lipidomics, metabolomics or proteomics, which we researchers use to study biomolecules from tissue samples or blood, for example, at a global level. Since they cover multiple molecular levels, multi-omics technologies can provide results that give a full picture of a sample. Omics technologies are an important starting point in personalised medicine as they produce huge amounts of data, which shed light on disease processes and potential treatment approaches.

Proteomics is the analysis of the proteome, which is the entire set of all proteins in an organism; phosphoproteomics focuses on adding and removing phosphates as molecular switches for proteins; N-terminomics is a branch of proteomics that studies how proteins degrade; glycoproteomics concentrates on proteins that contain carbohydrates as a result of post-translational modifications; transcriptomics is the study of the relative frequency of RNA transcripts; lipidomics refers to the large-scale analysis of the entire set of lipids.

Protein Interaction Paralyses a Young Patient

When doctors and scientists at University Hospital Essen (UK Essen) were examining a six-year-old child with the neuromuscular disorder NEDHFBA, they could not imagine the results that one single patient sample would provide. Researchers from ISAS and the Department of Neuropaediatrics at UK Essen worked out how proteins affect the development of this rare condition for the first time. Their extensive analysis could also shed light on other neuromuscular disorders.

The six-year-old boy could smile, but he could not speak. His muscles were so poorly developed that he was not able to sit up unaided. Walking was impossible. When he drifted off to sleep, his eyes stayed half open. The paediatric neurologists in Essen suspected a neurological developmental disorder. An analysis of the boy's genome showed that he had two mutations in a gene called *PPP1R21*. The protein produced by this gene affects many important processes within cells, including how a number of different proteins interact. Both of the patient's parents were healthy. However, despite being completely unaware of it, both the mother and father had a modified variant of PPP1R21 in their genome as well as a "normal" version. Purely by chance, both had passed down the modified variant to their son. Now present in duplicate, this homozygous mutation exerted its harmful effect on the boy.

Medics group the impairments caused by the *PPP1R21* variant together under the abbreviation NEDHFBA, which stands for neurodevelopmental disorder with hypotonia, facial dysmorphism and brain abnormalities. The young patient's dysfunctions were still mild; for example, none of the brain abnormalities typical of NEDHFBA could be observed. Many patients affected by this disorder have a decreased volume of white matter in the brain, an underdeveloped cerebellum and enlarged ventricles (cavities).

PD Dr Andreas Roos is Adjunct Professor at the University of Ottawa and Head of Preclinical Research at the Department of Neuropaediatrics at the University Medicine Essen.

Combination of biochemical, microscopic and cytological analyses

"Until now, we knew little about the pathomechanism of NEDHFBA or, in other words,

Dr Andreas Hentschel is a research associate in the ISAS Proteomics research group.

the origin of the disorder," says PD Dr Andreas Roos from the Department of Neuropaediatrics at University Hospital Essen (UK Essen) and the Department of Neurology at the Children's Hospital of Eastern Ontario (Ottawa, Canada). Roos is an Adjunct Professor at the University of Ottawa. He and ISAS researchers working in collaboration with scientists from UK Essen had already proven back in 2021 that an easily accessible cell type, the fibroblast skin cell, offered a good way of studying neuromuscular disorders. The researchers at ISAS now examined the boy's tissue sample to figure out which molecular processes are relevant for NEDHFBA.

The team used a DNA sequencing method in which specifically the protein-coding regions of the genome – the exons of all the genes – are sequenced, then examined them for mutations. In addition, the researchers created cell cultures of the fibroblasts to track which processes in the cells were not working normally. Using highly sensitive mass spectrometers, the team working with Dr Andreas Hentschel was also able to analyse the boy's proteome, i.e. the complete set of proteins in his cells, qualitatively and quantitatively. "Every analyte in a sample has a particular mass, which can be uniquely assigned. We can then use that to identify the protein in question via mass spectrometry," says Hentschel, summing up the principle of comprehensive proteomic analysis.

The various biochemical, microscopic and cytological investigations showed that mutations in the *PPP1R21* gene mean specific proteins are still produced in the patient's cells, but they are present in varying concentrations or are unstable. In total this affects around 18 percent of the proteins that were examined via mass spectrometry, according to the researchers' joint report published in the journal *Molecular Neurobiology*.

Dysregulation of various proteins

The information obtained about which proteins were affected was revealing as well. On the one hand, it appears the proteasome is overactivated in the young patient's cells. The proteasome is a cellular apparatus that gets rid of unwanted or overaged proteins. According to Roos, this will likely result in an excessive degradation. At the same time, and presumably linked to the overactivated proteasome, the cytoskeleton of the cells – the architecture built from protein fibres – is dysregulated. This in turn affects the organisation of certain structures, also known as cell polarity. "Polarity is tremendously important for nerve cells, or neurons, in particular. It is how the cells know which direction they must grow out to," says Roos.

There are only around a dozen known cases of NEDHFBA worldwide. But the disease falls under the wider umbrella of neuromuscular disorders, which is estimated to affect between seven and 80 children in every 100,000[1]. This equates to a couple of

1 https://www.mdpi.com/journal/children/special_issues/Neuromuscular_Disorders_Children_Adolescents

hundred newborns every year in Germany. "When we researchers study disorders like these, we are basically trying to identify any similarities or recurring patterns," explains Hentschel. He goes on: "Perhaps in various neuromuscular disorders the stability and/or activity of proteins and, consequently, of certain metabolic pathways is repeatedly wrong. If this is the case, we can ask ourselves what needs to happen for these protein functions to work correctly again?"

One basket for multiple disorders

Further studies are vital for these young patients and their families. Usually, the number of patients affected by each individual disorder is too small for the pharmaceutical industry to invest money in developing a treatment for a specific condition. "If we can understand the pathomechanism and it turns out that similar processes have a role to play in several disorders, this could make the market for new drugs large enough to warrant investment," says Roos. In the industry this approach is known as a basket trial, since different disorders are placed into the same basket with a uniform treatment strategy.

In the best-case scenario, however, there will be no need for any new medication if drugs that are already approved for other conditions could also be effective for NEDHFBA. Further research is required in this area.

"A game-changer for our understanding of neuromuscular disorders"

The findings of the fibroblast analysis conducted on the six-year-old NEDHFBA patient garnered a great deal of attention. "The findings are incredibly powerful," says Roos, who as one of the paper's corresponding authors has received enquiries from medics all over the world since it was published. The method employed by Hentschel and his colleagues also enables scientists to predict whether the children of carriers of other diagnosed mutations in the *PPP1R21* gene could also be prone to neurological dysfunctions.

"We have laid the foundations and shown at a cellular level how fibroblasts can be used to reveal the pathogenic action of gene mutations in neuromuscular disorders like NEDHFBA," says Roos. "That is not only pathbreaking when it comes to our understanding of these disorders, it could also enable us to give specific genetic advice to couples who have known mutations in the *PPP1R21* gene and who want to have children."

(UE) ■

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Hentschel, A., Meyer, N., Kohlschmidt, N., Groß, C., Sickmann, A., Schara-Schmidt, U., Förster, F., Töpf, A., Christiansen, J., Horvath, R., Vorgerd, M., Thompson, R., Polavarapu, K., Lochmüller, H., Preusse, C., Hannappel, L., Schänzer, A., Grüneboom, A., Gangfuß, A., Roos, A. (2023). A Homozygous PPP1R21 Splice Variant Associated with Severe Developmental Delay, Absence of Speech, and Muscle Weakness Leads to Activated Proteasome Function. *Molecular Neurobiology,* 60:2602–2618.

https://doi.org/10.1007/s12035-023-03219-9

Leibniz Competition Provides Funding for Collaborative Project on Metabolism Research

How cells react to a change in nutrient supply is of fundamental importance to the health of the entire body. Dysfunctional nutrient processing has been associated with disorders such as obesity and type 2 diabetes. But exactly what effects are caused by differing nutrient quantities and why the reactions to them differ in various parts of the body are questions that have so far been poorly understood. Researchers from the Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), the German Institute of Human Nutrition Potsdam-Rehbrücke (DIfE) and ISAS intend to get to the bottom of these questions. The consortium qualified for funding in the 2024 Leibniz Competition with the project »PIPMet – Phosphoinositides in Metabolic Disease«.

The functioning of cells and tissues depends on their absorbing and processing of nutrients such as glucose, amino acids and fatty acids. These processes are controlled by complex networks that comprise various signalling pathways and cell components. Previous work from the FMP shows that certain membrane lipids, the phosphatidylinositol phosphates (PIPs), play a central role in this respect. With this project, the researchers intend to investigate PIPs and their degrading enzymes in nutrient signal transmission, at both the molecular and functional levels. The findings obtained in this way are intended, going forward, to form the basis for developing approaches to the prevention and treatment of obesity and the associated metabolic disorders.

Interdisciplinary collaboration for analysing PIPs

PIPMet stands out with a collaborative and interdisciplinary team from specialist areas such as analytical chemistry, cell and molecular biology, and diabetology. The researchers plan to combine techniques from genetics, pharmacology, proteomics, lipidomics, metabolomics and cell biology as well as in vivo experiments. At ISAS, Prof Dr Sven Heiles and his Lipidomics research group will first develop mass spectrometry techniques to analyse the frequency and the identity of PIPs in cells, tissues and purified organelles. To date, researchers have lacked the necessary analytical techniques, which made it difficult to obtain a better understanding of the PIP signalling pathways. The consortium intends to use this as a basis to investigate the physiological role of changes in the cellular PIP content due to changes in the nutrient supply in selected cell systems. The team will then use these findings to examine the PIP metabolism in vivo (in a mouse model) with normal and elevated levels of nutrient supply.

(CP) ■

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The Leibniz Association is funding this project in the scope of the Leibniz Competition 2024.

Leibniz Gemeinschaft

Machine Learning for Early Warning Systems in a Clinical Setting?

Artificial intelligence (AI) has evolved into an indispensable health research tool in recent years, with researchers increasingly relying on machine learning (ML) to analyse the huge data sets involved. This sub-field of AI enables computers to learn from data and recognise patterns within it, allowing researchers to better understand complex relationships, such as those that exist between courses of disease and symptoms. However, clinical data is often multi-layered. Variable and interconnected data points, such as results from a series of blood tests, quickly push standard ML algorithms to their limits. That is why researchers from ISAS, the Otto von Guericke University of Magdeburg, Bielefeld University and the German Centre for Higher Education Research and Science Studies in Hanover, together with cooperation partners from the University of Leipzig Medical Centre and Greifswald University Hospital, are turning to an alternative ML method. Taking a model for predicting sepsis (blood poisoning) as an example, the team was able to show that not only the data itself, but also the connections between the data points provide important information to facilitate early diagnosis.

Clinical practice is often a race against time. So, to be able to treat illnesses appropriately, it is essential to diagnose them early. This is exactly the case with sepsis (► p. 61). This life-threatening infection often progresses so rapidly that the risk of the patient dying increases by around eight percent with every hour that it goes untreated.[1] But in its early stages, imminent sepsis is frequently hard to detect. If sepsis is suspected, doctors can treat it initially with a broad-spectrum antibiotic, but to diagnose it specifically using a bacterial culture or by evaluating symptoms takes time. By the time the medical experts are certain which bacteria they need to treat and how, they are often battling what is already an advanced and difficult-to-treat inflammation.

Machine learning to facilitate early diagnosis

In future, machine learning (► p. 62) could help doctors to diagnose time-critical diseases at an early stage: “Using AI, we are able to look at blood counts and predict which patients may be at risk of developing sepsis, for example,” says Prof. Dr Robert Heyer, head of the Multidimensional Omics Data Analysis junior research group at ISAS. He goes on to say that corresponding models do already exist: “But they reach their limits when asked to take complex time series

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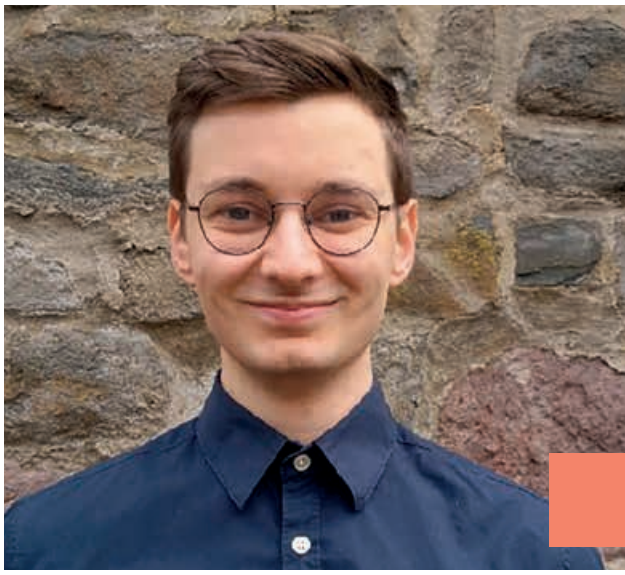
1 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8210984/

into account." Time series are made up of sequences of data points, which are collected at regular intervals. In a hospital setting they may contain information about changes to patients' vital signs such as blood levels, heart rate or blood glucose level, for example.

The team of interdisciplinary researchers put a specific type of algorithm, called a graph neural network (GNN), to the test. These networks are particularly well suited to analysing data organised in the form of graphs – such as time series. In a graph, the data points (nodes) are connected to one another by "edges", which represent the relationships between the nodes. This gives rise to complex network structures, in which the nodes take their own information into account as well as information about their neighbouring nodes. By following the links within the data network, GNNs decode how various factors affect one another and reveal hidden connections. "Our objective was to find out how suitable GNNs are for analysing complex clinical data and whether integrating time series improves the predictive accuracy of the models," says Daniel Walke, doctoral candidate at the Otto von Guericke University of Magdeburg and lead author of the joint preprint (pre-release of a scientific paper that has not yet been peer reviewed).

Time series improve predictive power

The researchers based their work on a data set containing information about over 528,000 people, who were treated on the wards (with the exception of intensive care) at the University of Leipzig Medical Centre and Greifswald University Hospital between the years 2014 and 2021. Some of them suffered from sepsis during their time in hospital, while others did not. The researchers used the extensive data from Leipzig to first train their GNNs to retrospectively predict the probability of sepsis. Applying the GNNs to the data set from Leipzig, and another from Greifswald, showed similar results to those achieved using conventional ML algorithms and other types of neural network. However, applying GNNs to time series data, which incorporate test results for the same patients, gave significantly better results. Unlike previously, when similar test results from various patients were linked to one another, the nodes now represent full blood counts from just one person at different points in time. The researchers used the AUROC (Area Under the Receiver Operating Characteristic) curve to measure the reliability of the predictions. The closer the value is to 1, the better the model is performing. Heyer and his team were able to improve the AUROC values from under 0.88 to over 0.95 by integrating time



Daniel Walke is a PhD student in the Database and Software Engineering group at Otto von Guericke University Magdeburg.

SEPSIS

Sepsis, also known as blood poisoning, is a deadly disease that costs more lives every year than breast, prostate and bowel cancer combined.[2]
The disease is caused by the immune system failing to contain a localised infection and allowing messengers and toxins to spread through the bloodstream. The body responds by sending out leukocytes (white blood cells) to fight the pathogens (causative organisms). This can cause the blood vessels to expand. Since the patient's blood pressure then falls, vital organs such as the lungs, kidneys or heart are no longer being supplied with enough oxygen via the blood and, in serious cases, may fail. The patient enters septic shock, which means their life is in acute danger.

2 https://www.england.nhs.uk/blog/beating-sepsis-with-early-detection-and-prompt-treatment/

series. “The fact that time series have such a big impact on the reliability of the predictions underlines how important data collected regularly from patients is in providing basic information for predictive models in the field of health research,” sums up Heyer.

Not a black box: medicine needs transparency

At the moment, how well GNNs can really be integrated into everyday medicine is still largely untested. Another challenge is this: “GNNs and other complex machine learning algorithms (e.g. XGBoost) are often treated as black boxes limiting their interpretability and transparency which is essential for medical applications,” write Heyer and his fellow researchers in their paper. It was therefore important for the authors to understand exactly what the algorithms were basing their predictions on. “That’s why we didn’t just leave it as a black box. We tried to find out what the algorithms had learnt from the patient data. We wanted to know what factors were behind their predictions,” says Heyer. When it comes to sepsis, the analysis shows that, besides the varying number of white blood cells, the key factor is their interactions with other types of blood cell.

Advanced ML tools could potentially save countless lives – not only from sepsis, but from other diseases too. In future, GNN analyses of blood count data could help to diagnose thrombosis or leukaemia, for example.

(CP/UE) ■

MACHINE LEARNING

Machine learning (ML) is a discipline of artificial intelligence. With the help of ML, computers are trained to process data and previous experiences independently and adapt to them accordingly. An example of ML are artificial neural networks (ANNs), which are modelled on the human brain. They consist of artificial neurons, which are arranged in layers and connected to one another. These neurons process inputs, perform calculations and provide outputs. Training the network on sample data allows it to detect patterns and relationships so it can perform tasks such as making predictions or recognising patterns, for example. Graph neural networks (GNNs) are a particular kind of ANN. They can also take account of additional information from linked measurements, often referred to as “message passing”. To make their predictions and classifications, GNNs use the structure and relationships (edges) within a graph to understand how the data points (nodes) interact with and influence one another.

Walke, D., Steinbach, D., Gibb, S., Kaiser, T., Saake, G., Ahrens, P., Broneske, D., Heyer, R. (2023) Edges are all you need: Potential of Medical Time Series Analysis with Graph Neural Networks. Preprint available at Research Square:

https://doi.org/10.21203/rs.3.rs-3573549/v1

JUNIOR SCIENTISTS

From Internships to Postdoctoral Positions – Supporting Junior Researchers

To support young researchers, ISAS has set up programmes covering all stages of a research career. These programmes are aimed at bachelor's and master's students, including interns, enabling them to spend time in the research groups, or in the communications team, for example. They include a structured graduate programme for doctoral candidates and further study options for postdocs.

Over the first three years of the PhD phase, the curriculum of the structured training at ISAS for doctoral candidates includes ten workshops, an information event on career planning, an internal lab rotation and an optional PhD-related stay at a research institution in another country (► p. 68). In the final stage, the focus shifts to completing the work and the PhD thesis. How long a PhD takes at ISAS depends on the specialist field and averages between three and a half and four and a half years.

Science communication for doctoral candidates and postdocs

ISAS regularly holds training sessions on science communication (► p. 64) for doctoral candidates and postdocs to help them share their knowledge and research effectively with a wider audience. The Postdoc Pitch Day, for example, is a career development tool designed to provide a relaxed and friendly platform to present initial research ideas and to receive feedback from experienced researchers. The event is intended firstly to motivate participants to expand their skills in communicating research topics in an easily comprehensible manner. Secondly, the Postdoc Pitch Day serves to refine participants' own research ideas in such a way that, going forward, they ideally lead to funding measures, applications for external funding or further activities relating to career development (such as interdisciplinary cooperation arrangements with internal and external partners, or patent registration).

Close contact with cooperating universities

ISAS promotes the career opportunities of outstanding young researchers by deploying junior researcher groups to enable them to lead research projects. Being given responsibility in a leadership role as early as possible is intended to support those young researchers who aspire to an ongoing professional career in research.

With regard to the training of junior researchers, the institute takes part in a regular exchange of ideas and information with the universities with which it cooperates in research and teaching: ISAS works closely together with TU Dortmund University, Ruhr University Bochum, the University of Duisburg-Essen and Bielefeld University.

(SR) ■

Science Slam: Humorous Science Communication Is Fun for Everyone

Psychologist Leon Windscheid sells 100,000 tickets for his stage performance "Gute Gefühle" (Good Feelings), science programmes presented by physician Eckart von Hirschhausen have been on prime time television for years, and videos by chemist Mai Thi Nguyen-Kim were at times the most clicked on YouTube. All of the people mentioned prove that science does not have to be complicated and therefore dry. When done well, science communication is pure entertainment. Four ISAS employees wanted to demonstrate this and took to the stage for the institute's own science slam in December 2023.

"Science slam means science communication!" – Cheyenne Peters opened the event at ISAS Campus with these words. The science editor had already organised the kick-off meeting for the science slam in October 2023, and had begun training the researchers shortly afterwards. "How do I communicate science? How do I develop a story? I want to show young scientists in particular ways in which they can present their research in an unconventional, relaxed and for laypeople understandable way," says Peters.

Good science succeeds through teamwork

The participants presented themselves to the audience with creative contributions about their research or self-chosen topics. Each participant had ten minutes. Darleen Hüser was the first to take to the stage. In candlelight and with a thick book, the PhD student reminded the audience of a Christmas storyteller: one night in

> ***I want to show young scientists ways in which they can present their research in an approachable way.***

Cheyenne Peters is a science editor in the team Communications and conducted the individual training sessions for the science slam.

The four participants shared the proud moment after their slams for a photo with Luisa Becher, author of this article and intern in the Communications team at ISAS.

Luisa Becher (30), a microbiologist from the Rhineland, realised after completing her Master's degree that she preferred to report on many different areas of research. This is why she is now studying science journalism at TU Dortmund University. She took her first steps in journalism at Radio Bonn/Rhein Sieg and WDR. As an intern in the Communications team, she spent three months starting from December 2023 getting to know the press and public relations at ISAS.

the lab, all the microscopes and tools such as a pipette come to life. Hüser researches molecular and cellular processes that are triggered by inflammation. To clarify her immunological questions, the biologist uses various analytical methods, such as the light sheet fluorescence microscope or the confocal microscope. With a great deal of humour and in English, the scientist rhymed about fluorophores, the Stokes shift, and the advantages of the individual microscopy techniques. Her poem, accompanied by colourful animations (► p. 66) quickly made it clear that the strength of each technique does not lie in their uniqueness, but in being used together. That is why in the poem the little pipette squeals with delight "with your strengths combined as a team, together you are a microscopic dream." In addition to her scientific message, that was exactly what Hüser wanted to convey: "Teamwork is always the key to success. We have a great deal of different expertise at ISAS, and we can utilise it in an interdisciplinary way. That is our methodological and human strength!"

SCIENCE COMMUNICATION TRAINING

At science slams, young researchers have the opportunity to gain their first experience in science communication in an entertaining way. They can practise strengthening their ability to communicate complex content in a clear and convincing manner – a key skill for their future scientific career. Before the participants took to the stage at the ISAS Science Slam, an in-depth training by the Communications team was on their agenda. A joint kick-off event initially focused on some fundamental questions. For example: Why should I communicate my research to laypeople at all? How do I find a topic including a common thread in the context of my scientific work? What are my goals, including key messages? All slammers then took part in two individual training sessions. These sessions provided an opportunity to train the structure of their slam, including the dramaturgy, to receive feedback and to refine their own presentation technique.

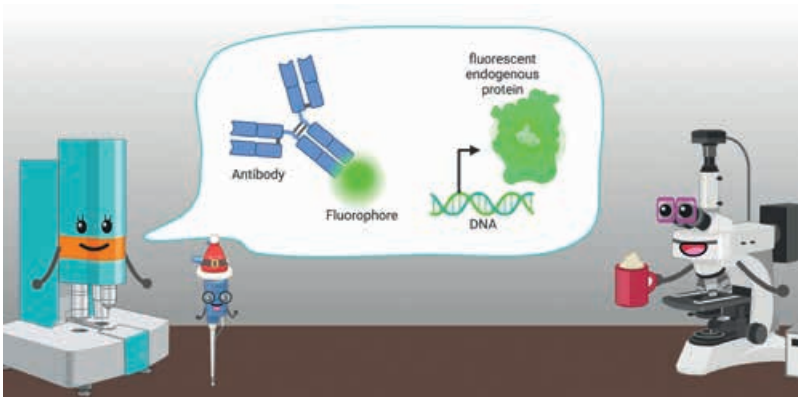
Virtual research you can touch

Interdisciplinarity and interest in various research topics were also evident in Johann Dierks' presentation. The science slam offered participants the opportunity to engage scientifically with a topic outside their own field of research. Dierks is passionate about artificial intelligence (AI). The physicist has already built a self-flying drone with his father. A drone crash gave him the idea for his contribution to the science slam. Among other things, Dierks addressed the question of who in the future will have to take responsibility for mistakes and accidents caused by AI.

Kathrin Krieger also confronted the audience with a computer science question: Why is virtual reality (VR) needed in a research institution like ISAS? Not to play computer games, as the gaming-enthusiastic researcher emphasised, but to make science tangible in the truest sense of the word. Krieger is working on haptic gloves. These VR gloves allow its wearers to touch virtual objects – and thus grasp them. "I think science communication is extremely important. On the one hand, to familiarise people with a scientific topic and allow them to participate in the culture of debate. One the other hand, to educate each other in interdisciplinary teams like the ones we have here at ISAS," says Krieger. The scientist then used numerous interactions and props to encour-age the audience to test their own visual perception. At the same time, she showed the audience the advantages of haptic gloves. For example, researchers could one day touch 3D-computer models of their microscopic images using haptic gloves. In the future, doctors could prepare for operations by examining tissue or organs in the virtual world, for example.

"Science is in the everyday"

Luisa Röbisch's presentation was also a plea for more networking and more communication. The technical assistant was inspired by her hobby of theatre acting and was motivated to give a comic presentation. ISAS became Northpole University, the employees turned into busy elves and Röbisch herself became Dr Dr rer. chris. Eugenia F. Stardust. With bouncing pink curls and glistening cheeks, Stardust explained the chemical composition of mulled wine. "Science is in the everyday. All you have to do is observe the world around you with curiosity," commented Röbisch on her choice of topic. A positive side effect of the presented hot drink, which is full of plant-based secondary metabolites, is that drinking it makes communication easier. With a wink and an appeal to savour a mulled wine or two, the biotechnologist dismissed the audience for the vote.



The debate between light sheet fluorescence microscope (left), pipette and confocal microscope in Darleen Hüser's science slam won over the audience.

99.4 decibels for the win

At the end of the science slam, it was up to the audience to choose a winner. A decibel meter was used to determine the loudest applause per slam. Only a few decibels, barely perceptible to the ear, made the difference. Darleen Hüser won the ISAS Science Slam 2023 with her elaborate poem and lovingly crafted presentation. The smiling winner immediately had a plan for another science slam: "Next time, it's our principal investigators' turn."

(LB) ■

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What are you doing at ISAS, Joy?

Joy Amrei Brummel (24) is studying Chemical Biology at TU Dortmund. Since her initiative application at ISAS in May 2022, she has been working as a student assistant in the Proteomics research group alongside her university studies. She also wrote her bachelor's thesis at ISAS. To learn more about her work in the laboratory, the editorial team asked her to complete the following sentences.

Joy Amrei Brummel purifies the thrombocytes at the centrifuge and isolates the cells for analysis in the mass spectrometer.

As a student assistant in the Proteomics research group ...

I help prepare samples for mass spectrometric analysis. I also assist my colleagues in the lab. For example, I take inventory of the samples in storage or prepare buffers, chemical solutions that maintain the stable pH value in a sample. It's great to apply the methods you learned about in theory during your studies in an intensive and practical manner here.

My bachelor thesis deals with ...

the topic of thrombosis. More precisely, it's about the mass spectrometric analysis of proteins during the activation of blood platelets (thrombocytes). This causes the platelets to clump together and a blood clot (thrombus) to appear.

I am investigating ...

how the proteins' activation in the thrombocytes changes under reduced oxygen levels. It is still unclear whether a reduced oxygen concentration activates the thrombocytes and thus leads to thrombosis, or whether it's the activated thrombocytes that trigger an oxygen deficiency in the blood. The setting in which I conduct my experiments is important. To date, experiments with thrombocytes have mostly been conducted at an oxygen level of 21 % – that of the air. In the blood vessels, however, the oxygen content is lower and can drop further during activation. My work will help to better understand the effect of oxygen deficiency on thrombocytes under real-life conditions.

For my bachelor's thesis, I conducted research at ISAS because ...

I am interested in analytical chemistry in the context of health research. I was immediately fascinated by the idea of being able to do research on thrombocytes from human samples. I hope that my work can support the scientists at ISAS in identifying markers for an early thrombocyte reaction in patients – and thus ultimately helps to reduce the risk of thrombosis.

From ISAS to Harvard: a Special Research Stay During the PhD Programme

To do good research it's vital to keep looking beyond your own horizons and learning about different perspectives. That is why I decided to swap my workstation at ISAS for a little while in favour of a research visit to the USA. The country is often a pioneer when it comes to scientific innovation – and it is particularly strong and a key cooperation partner in the field of biomedical research.

Prof Dr Anika Grüneboom, who leads my research group, put me in touch with Prof Dr Phil Iannis Adamopoulos, professor at Harvard Medical School. His group conducts its research in the Department for Rheumatology and Clinical Immunology at the Beth Israel Deaconess Medical Center, one of the teaching hospitals at Harvard Medical School. After I told him I was interested in a research stay abroad, he invited me to spend a couple of months at his laboratory in Boston. I then consulted my research group leader to devise a concrete project plan and applied for a PhD student grant from the German-American Fulbright Commission (Fulbright Germany) in May 2023. I found out my grant had been approved in September. Fulbright Germany is supporting my four-month stay, which started in February 2024, not only financially, but also by helping with my visa application, for example.

Harvard University is renowned above all for its excellent teaching and research. But like a lot of US universities, it has incredible sports programmes too. So I'm looking forward to forging some lasting friendships in the USA during my stay through my hobby of climbing.

In Dortmund I'm researching medication-related osteonecrosis of the jaw (MRONJ). In this condition, medication prescribed for osteoporosis, for example, causes parts of the jawbone to die. In an attempt to understand the mechanism behind MRONJ, I use various microscopes to look at how the cells of the bone tissue in the jaw differ from those in the rest of the skeleton. I'm mainly interested in osteoclasts, which are the cells that degrade the bone. Dr Adamopoulos is doing in-depth research into osteoclasts as well. My time in Boston will be a great opportunity to gain an insight into the methods he and his team use to cultivate and treat those cells in the lab. The team also makes use of special gene-transfer mouse models. Administering sRANKL MC-DNA, for example, could allow me to analyse male animals with non-inflammatory bone loss in my project. Until now I have only been able to examine female animals, since the model I use is based on an ovariectomy (surgical removal of the ovaries). In return I'm happy to share our research group's experience with light sheet and confocal microscopy with his team.

(protocol: CP) ■

Flora Weber is a doctoral candidate in the Bioimaging research group.

Our research group at ISAS works closely with institutions all over the world. We collaborate with Prof Dr Phil Iannis Adamopoulos at Harvard Medical School, who is also head of the Department for Rheumatology and Clinical Immunology at the Beth Israel Deaconess Medical Center in Boston. Like him, I also conduct research on immune cells, especially on neutrophil granulocytes primarily found in rheumatic illnesses. Our collaboration involves analysing mouse samples at ISAS using various fluorescence microscopy methods. In bone samples, for example, we are able to physically show changes in the vascular system, the vessels that

Flora Weber (left) and Darleen Hüser not only share an office at ISAS, but also spend their time abroad in the USA in the same research group.

3 Questions for … Prof Dr Anika Grüneboom

Prof Dr Anika Grüneboom coordinates the research programme 3D-Molecular Pathology at ISAS and heads the Bioimaging research group.

Prof Dr Anika Grüneboom, immunologist and head of the Bioimaging research group, spends several months without her two doctoral candidates Darleen Hüser and Flora Weber. Since the two up-and-coming researchers headed for the USA, they are missed by the ISAS research group – but Grüneboom is certain that ultimately all those involved will benefit from this research sojourn. She wants to inspire as many young scientists as possible to get involved in research outside Germany at some point.

1 You supported your doctoral candidates in gaining this experience abroad. Why is this important to you?

Grüneboom: I generally want my team members to see how other research groups approach their work. When you live and work abroad, you learn about self-

supply blood to the tissue. Furthermore, we can investigate the extent to which immune cells infiltrate joints during inflammatory processes, for instance. We discuss our results regularly in meetings with Prof Dr Adamopoulos's research group. This is where we came up with the idea of expanding our collaboration by allowing me to spend some time researching at their facilities in Boston.

An overseas research stay is an optional part of the structured training programme for doctoral candidates at ISAS. The institute actively supports us doctoral candidates through the Grant Management Team and I continue to receive my PhD salary for the duration. Furthermore, the German Academic Exchange Service (Deutscher Akademischer Austauschdienst, DAAD) has awarded me a research grant to support my project. Quite a few steps are involved and there are many details to consider, from project planning through to preparing the documents for the grant application and applying for a visa. This requires time, attention to detail and an effective strategy. Working through this process has enabled me to develop my planning and organisational abilities. The effort was worth it and I have been researching in the USA for four and a half months since mid-March 2024.

As a doctoral candidate at ISAS, I am part of the special research division TRR 332 »Neutrophil Granulocytes: Development, Behaviour & Function«, which is subsidised by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG). I am investigating the role of possibly different subtypes of neutrophils in the development of rheumatoid arthritis and how they affect the inflammatory responses of other immune cells. The research group led by Dr Adamopoulos is using an exciting technology for my project: in vivo gene transfer by hydrodynamic injection of minicircle DNA vectors (MC-DNA). This involves injecting small, circular DNA molecules into living organisms, such as mice, to simulate different di-

organisation and how to adapt to new processes in an unfamiliar environment. It is also important to start networking early on, both nationally and internationally. When they go abroad, doctoral candidates get to know cooperation partners on a personal level. This time they spend together can undoubtedly lay the foundations for lifelong professional ties.

I'm speaking from experience: when I started my PhD, I spent two weeks at the University of Bern. I was actually going to study the technology of optical projection tomography but I randomly stumbled upon a light sheet fluorescence microscope during my time there.

This instrument intrigued me, so I made some additional light sheet images of murine bones, meaning mouse bones, which I took back with me. I then continued working with light sheet microscopy in Essen when preparing my dissertation. If everything had gone exactly according to plan in Bern, who knows whether I would ever have discovered my passion for the "light sheet". So I am curious to see what surprises Darleen and Flora will bring back with them.

2 Why do you think this research stay with your colleague Prof Dr Phil Iannis Adamopoulos in particular will be so enriching?

Grüneboom: I have been working with Prof Dr Phil Adamopoulos of Harvard Medical School for quite a long time now. He is conducting research into different methods and disease models that are extremely compatible with the investigations my research group is currently undertaking. He is an expert in arthritis models that I have not come across in Germany so far. Darleen and Flora will also learn new methods from this colleague. Ideally, they will then be able to use these insights for their PhD theses during subsequent ISAS

sease profiles. I am particularly interested in the interleukin-23 MC-DNA model, which causes the animals to develop arthritis. As it is relatively straightforward and resource-friendly to create MC-DNA in bacteria, it could be an interesting addition to the arthritis models we already use at ISAS.

I am happy to consolidate our partnership in the USA and to provide the team around Prof Dr Adamopoulos with an insight into the imaging techniques we use in our research group. Apart from my research project, I am also very excited to familiarise myself with day-to-day scientific activities at an internationally renowned university hospital, to share ideas and experiences with colleagues and expand my professional horizon. This valuable experience could also be crucial in helping me to decide whether to go abroad again as a post-doc in future.

(protocol: CP) ■

Darleen Hüser, PhD student in the Bioimaging research group.

research projects. Ultimately, it is not just them who will benefit, but our research work too.

3 Can you imagine a guest researcher being part of your team?

Grüneboom: Yes, of course. Doctoral candidates from our national cooperation partners already visit ISAS regularly. They spend a few days and sometimes up to three weeks here, working alongside our permanent staff in the laboratory. Up until now, the purpose of these stays was always training, in other words learning specifically how to use the instruments. The guest researchers normally have no or very little imaging expertise and need our support. Although none of the guest researchers we have hosted from abroad so far have been so deeply involved in our work as Darleen and Flora are in the USA, I think it could actually work out very well because an experience like that would be beneficial for all involved. Training the next generation of scientists should ideally be about give and take – and that includes national and international exchanges for our doctoral candidates.

(The interview was conducted by CM.) ■

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FULBRIGHT

DAAD Deutscher Akademischer Austauschdienst
German Academic Exchange Service

Latest Spatial Multi-Omics Techniques: PhD Student Takes Over 𝕏

The added value that spatially resolved analysis methods and single-cell techniques and their combination offer for the biochemical investigation of a system is undisputed. However, in order to apply these multi-omics methods, it is necessary to keep pace with the rapid development of technologies. Textbooks are no longer able to keep up. To give young researchers an up-to-date overview, the Bioanalytics Study Group of the German Society for Biochemistry and Molecular Biology (Gesellschaft für Biochemie und Molekularbiologie, GBM) and ISAS organised the »Spatial Multi-Omics« workshop in Dortmund in October 2023.

The two-day workshop targeted young researchers who wanted to learn more about multimodal imaging of tissue, imaging mass spectrometry and data analysis in pathology, spatial proteomics, single cell proteomics, spatial transcriptomics and bioinformatics of spatial multi-omics. Felix-Levin Hormann was also among the young scientists. The PhD student from the Lipidomics research group supported the event with a lab tour as well as with communication: for the duration of the workshop, he took over the institute channel on X (formerly Twitter) and provided an insight into the events at ISAS Campus.

(SR) ■

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isas **Leibniz-Institut für Analytische Wissenschaften** 26. Okt. 2023
Today is the start of our @GBM_eV Bioanalytics Workshop for young scientists at #ISAS. 🏫 Therefore, we are handling over our channel for the next hours to Felix. 😀 He's a chemist, PhD student @unidue & he works in our @SvenHeiles #Lipodomics research group. #multiomics #massspec

isas **Leibniz-Institut für Analytische Wissenschaften** 26. Okt. 2023
Hi, it's Felix. 👋 More and more participants are arriving and fueling up for the start of our workshop on Spatial Multiomics!

isas **Leibniz-Institut für Analytische Wissenschaften** 26. Okt. 2023
Impressive talk on the capabilities and recent development of high resolution transmission-model #MALDI-2 with in source bright field and fluorescence #microscopy by Alexander Potthoff (@UK_Munster).

isas **Leibniz-Institut für Analytische Wissenschaften** 26. Okt. 2023
We are taking a break from the sessions. I was happy to show everyone around our labs. You can see me in front of our AP-SMALDI source explaining for what #imaging analyses we use it and how. #omics @SvenHeiles

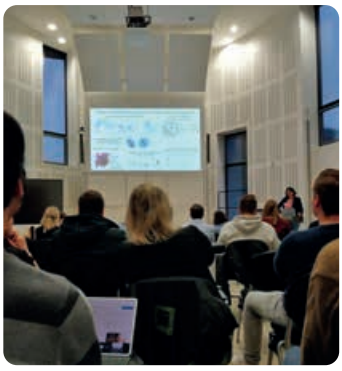
Leibniz-Institut für Analytische Wissenschaften 26. Okt. 2023
Came from the ScilLifeLab in Sweden: @thrane_kim. She is demonstrating Spatial #Transcriptions of VDJ sequences for T and B cells – a powerful technique I haven't encountered so far!

Leibniz-Institut für Analytische Wissenschaften 26. Okt. 2023
We are having a short 🍪☕ break before our last lecture for today at our @GBM_eV workshop! Next is Nicole Strittmatter on drug delivery using multimodal #imaging. Very excited to learn more!

Leibniz-Institut für Analytische Wissenschaften 26. Okt. 2023
It's a wrap for today's @GBM_eV #ISAS workshop. I have learned a lot. And I enjoyed listening to each expert! I also had so much fun talking about my day here. We are headed off to dinner now. 🥱😋🍝 Bye, Felix!

Leibniz-Institut für Analytische Wissenschaften 27. Okt. 2023
Good morning! It's Felix again. I am already in the lecture hall and excited for the second day of our @GBM_eV #ISAS workshop – starting with a talk by @HannahSpitzer1 on spatial single #cell analysis. #biomedical research

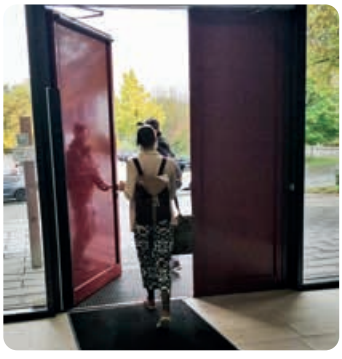
Leibniz-Institut für Analytische Wissenschaften 27. Okt. 2023
Now @HannahSpitzer1 is demonstrating the extensive capabilities of their #Python framework #Squidpy for single cell analysis. #omics



Leibniz-Institut für Analytische Wissenschaften 27. Okt. 2023
Last but not least, @MCFoell is giving insights into how #pathology can benefit from mass spectrometry #imaging techniques! #massspec

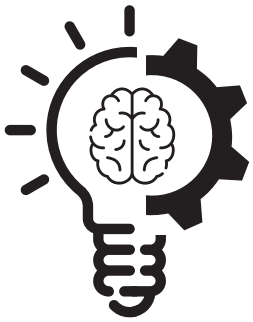
Leibniz-Institut für Analytische Wissenschaften 27. Okt. 2023
This is an impressive tour through the developments in a single cell #proteomics and the way to characterize 6000 proteins by Karl Mechtler (@tu_wien)! 😍 #omics

Leibniz-Institut für Analytische Wissenschaften 27. Okt. 2023
After 2 days of talks from a broad variety of topics revolving around Spatial #Multiomics, #lab tours and engaging discussions during coffee breaks and dinner, we at #ISAS @SvenHeiles and @GBM_eV wish all our participants a safe travel home. Bye-bye! Over and out, Felix! ✌



PROGRAMME DEVELOPMENT: A COMPASS

Research that is both socially relevant and future-oriented must undergo constant transformation. For ISAS, this means: in order to be able to pursue its mission – developing analytical methods that can be combined to create new integrative measurement strategies for health research – it firstly requires continuous fine-tuning of its own direction. And secondly, budding ideas need sufficient time, resources and space to take shape. This is what the institute's own programme development is designed for.



In this way, ISAS promotes promising new scientific ideas that do not (yet) fit into the canon of one of the research programmes. These ideas have the opportunity to grow beyond the established programmes and thus, prospectively, with their potential inclusion, provide approaches for the further development of ISAS research.

(SR) ■

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“I see us as a bridge between fundamental research and clinical practice”

At the Department of Dermatology at University Hospital Essen, Prof Dr Dr Alpaslan Tasdogan heads the Institute of Tumour Metabolism. Together with his research group, he conducts research into metastases and the metabolism of skin cancer cells, among other things. The specialist dermatooncologist and immunologist has held the professorship for dermatology and tumour metabolism at the medical faculty of the University of Duisburg-Essen since winter 2021. In recognition of his outstanding scientific work, he has already received a number of awards and grants, most recently the ERC Starting Grant from the European Commission. The findings from his research are not only highly relevant to scientific research but also to clinical practice for cancer patients. ISAS succeeded in recruiting the research clinician to head a second research group in Dortmund from 2024 onwards.

Prof Dr Dr Alpaslan Tasdogan heads the Institute of Tumour Metabolism at Essen University Hospital. Together with his research group, he conducts research into metastases and the metabolism of malignant melanomas. Both a clinical practitioner and a researcher, he is also to head a second research group at ISAS. Tasdogan has already received several awards for his research work; these include an ERC Starting Grant, an Emmy Noether Independent Junior Research Group and an endowed Peter Hans Hofschneider Professorship of Molecular Medicine.

Professor Tasdogan, with your Preclinical Metabolomics group at ISAS, your approach will centre on application-specific fundamental research. What is the objective pursued by this new research group?

Tasdogan: The objective is to use the technologies developed at ISAS to increase our understanding of metabolic vulnerability and the metabolic changes in cancer cells in a way that wasn’t previously possible. Building on clinical research questions, our work will use murine models, in vitro models such as cell cultures and samples from patients. We intend to perform in-depth examinations of all these using the most recent analytical approaches to explain certain processes in metastasisation. Translating these results into clinical practice, i.e. the “from bench to bedside” principle, is fundamental to my research group at ISAS. We intend to use the findings for new and targeted treatments in clinical practice that take as their starting point the changes in the metabolism of cancer cells during treatment or metastasisation.

"To date, however, we haven't had the technologies required to conduct further research into such heterogeneity."

To what extent will the analytical methods developed at ISAS contribute to providing a better understanding of clinical and molecular research questions in malignant melanomas?

Tasdogan: We are aware, for example, that every patient is unique and that every tumour has different cancer cells. And in my previous work in the US, I was able to demonstrate, together with my team there, that there is always a metabolic heterogeneity. To date, however, we haven't had the technologies required to conduct further research into such heterogeneity. With the analytical methods developed or combined at ISAS, for example using mass spectrometry and MALDI Imaging mass spectrometry, we intend to find out where the metabolic heterogeneity takes place in the tumours. Will we find it in the primary tumour, in the metastases or in the organs? We want to understand not only how the metabolites are spatially distributed within the tumour but ideally also how they are spatially distributed in individual cells in the entire organism. And we want to find out how what is known as metabolomic communication between tumour cells, stroma cells and immune cells works. Great importance is attached to interdisciplinary collaboration at ISAS.

Where do you see potential for cooperation arrangements, including with respect to the successful translation of research findings into the preclinical phase?

Tasdogan: I have already been collaborating for some time with the Lipidomics, Proteomics and Spatial Metabolomics research groups at ISAS. I also see great potential for collaboration with the Biofluorescence, Bioimaging and AMBIOM research groups. For example, when it's a matter of optimizing analytical methods in such a way that, in future, we will require only a very small number of tumour samples to obtain meaningful findings. This is an area where analytical methods and artificial intelligence go hand in hand.

In every cooperation arrangement, the clinical relevance of the question underlying a research project is decisive. It is of no use, for example, to identify markers or inhibitors that work well in murine models but are out of the question for use in patients because there are better alternatives. As a scientist and physician, I am very familiar with both sides. Consequently, I see my research group at ISAS as a bridge between fundamental research and clinical practice. When it comes to cooperation, I find it important to better familiarise all those involved with clinical aspects and critical research questions arising from clinical practice to ensure that the analytical methods we are investigating together are of high relevance for translation.

(The interview was conducted by SR.) ■

Hydrogen Sulfide: The Surprising Molecule That Regulates Life's Vital Functions & Fights Ageing

Long before life began, there was hydrogen sulfide (H_2S). Belched out by the countless volcanoes that dotted Earth's primordial surface, the foul-smelling gas saturated the atmosphere and dissolved into the oceans. There, it formed one of the building blocks for the biomolecules that later became living organisms. And although considered highly toxic when inhaled, recent research shows that H_2S still plays many vital roles in our cells. A team of ISAS scientists that is pioneering some of the research into how H_2S helps our bodies function recently discovered that H_2S plays a vital role in ensuring a level supply of oxygen in the blood.

Dr habil Miloš Filipovićs leads the ISAS research group ERC-Sulfaging and has been conducting research with his team at ISAS since 2020.

On a mundane level, we know hydrogen sulfide as the stench that rises from sewage and rotting marshes. But in our body, H_2S serves an important purpose. It is part of a group of gaseous molecules, called gasotransmitters, that can transmit signals within and between cells. "What we are seeing is that all the small molecules that existed in the primordial soup at the beginning of life remain embedded into our cells," says Dr habil Miloš Filipović, leader of the ISAS research group ERC-Sulfaging (an amalgamation of the words, *sulfur* and *ageing*, which designate the focal points of the group's work that has been funded by a European Research Council grant). Even more notable: H_2S seems so vital in the functioning of the body that "every cell produces its own sulfide."

Could H_2S help regulate hypoxia?

Yet even Filipović was surprised when he discovered how uniquely some important cellular mechanisms rely on H_2S. Specifically, Filipović and collaborators at the University of Chicago, Illinois, recently studied the role of H_2S in the activation of the carotid body, a small cluster of cells that sits near where the carotid arteries branch off in the neck.

The carotid body's primary function is to monitor how much oxygen and carbon dioxide is dissolved in the blood at any given moment. Our bodies need oxygen to function but certain factors can make its supply dip, ranging from lung and heart diseases to common disorders such as sleep apnoea, in which a sleeper intermittently stops breathing.

When the carotid body senses such a decrease in blood oxygen, called hypoxia, it sends signals to the brainstem, which, in turn, activates a process that makes our heart pump stronger and our lungs work harder to breathe. "This is why people who go through episodes of sleep apnoea start to breathe again," says Filipović. "It's a sort of survival mechanism."

Persulfidation as a natural oxygen sensor

Previous studies suggested, that H_2S plays an important role as a mediator of this process. However, the underlying signalling mechanisms had been unclear. Until now: In their study, Filipović and his collaborators used a powerful analytical technique called MS/MS analysis or tandem mass spectrometry to study the protein Olfr78 which belongs to the olfactory receptor family, but plays a crucial role in the carotid body in detecting oxygen.

For his work, Filipović conducts research using the model organism *Caenorhabditis elegans*, among others. This is a nematode worm. During its life span of around two to three weeks, the entire ageing process can be tracked. *C. elegans* is about 1 mm long. The image shows it under a fluorescence microscope.

In MS/MS analysis, a mass spectrometer selects an ion of interest, then fragments it into smaller pieces that are analyzed to provide information about the molecular structure of the original particle. When the researchers applied the technique to Olfr78, they saw that the relative lack of oxygen in the blood allows a higher-than-normal number of hydrogen sulfide molecules in the cell to bind themselves to Olfr78, a process called persulfidation. In this case, persulfidation becomes possible because the sulfide occupies the "slots" that would normally be taken up by oxygen molecules. As the number of persulfidated Olfr78 molecules in the cells rise, it triggers a cascade of biochemical processes that ultimately up-regulate our heartbeat and breathing. In other words: H_2S provides the crucial signal that spurs the carotid body into action. The study breaking down this process in detail, was published in the journal *Science Advances* in July 2023.

ANOTHER SURPRISING WAY IN WHICH H_2S PROTECTS CELLS

Recently Filipović discovered yet another way in which H_2S seems to protect cell proteins: by subtly changing their biophysical properties. As proteins crowd together in the highly confined environment of the cell, they often "melt" into a different state in which they are essentially liquid, says the biochemist. "You'll see something that looks like a lipid droplet except that it's a protein droplet." This "melting" allows proteins to nestle together more closely but also makes them vulnerable to becoming misfolded and forming aggregates, which can lead to "all sorts of problems," says Filipović. In the brain, for example, amyloid aggregates have been associated with Alzheimer's Disease and other neurodegenerative diseases.
Hydrogen sulfide seems to guard against this by preventing proteins in the droplet state from collapsing completely and aggregating, says Filipović. "This was unexpected."

A versatile protection mechanism for cell proteins

Other research by Filipović already suggests that a similar process involving hydrogen sulfide and oxygen might also help the body fight off **a**geing. Because as essential as oxygen is for the body – dealing with this chemical also exposes cells to highly reactive versions of oxygen molecules called oxygen radicals. This oxidative stress can damage proteins and other vital cell components.

Persulfidation makes proteins more resistant to such damage. Filipović and his group have discovered that hydrogen sulfide binds itself to reactive oxygen molecules that have attached themselves to proteins. This results in a sulfide-oxygen compound which can then get biochemically cleaved off, restoring the protein to its undamaged form.

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Peng, Y.-J., Nanduri, J., Wang, N., Kumar, G. K., Bindokas, V., Paul, B. D., Chen, X., Fox, A. P., Vignane, T., Filipović, M. R., Prabhakar, N. R. (2023) Hypoxia sensing requires H_2S-dependent persulfidation of olfactory receptor 78. *Science Advances,* 95, eadf3026.

https://doi.org/10.1126/sciadv.adf3026

This “protective loop” is particularly important for proteins that contain the amino acid cysteine, “since cysteine is the most sensitive” to oxygen-induced damage, says Filipović. “We think that this is linked to anti-ageing effects that could result in a longer, healthier life.”

How could H_2S help intervene with ageing?

Unfortunately, as we grow older, our bodies become less adept at producing hydrogen sulfide, making our cells more vulnerable to damage. Diminished persulfidation has been associated with age-related diseases ranging from cardiovascular problems to cancer to neurodegenerative decline. “We are trying to understand how this is happening. And is there a way that we can intervene?,” says Filipović.

Recently, his group started looking into a specific compound produced by a plant or fungus. The so-called phytochemical releases H_2S as it becomes metabolized in the body. Together with cooperating partners at the University of Belgrade, Cambridge University and Heidelberg University, the scientists started to feed the substance to worms and rodents, expecting that this might lead to “some mild effects.” However, initial results seem to be promising. The worms – Filipović works with the model organism *Caenorhabditis elegans* which usually dies after 20 days – started living longer. First attempts with rodents, appeared very promising as ageing mice and rats that had consumed the compound experienced a noticeable boost in energy.

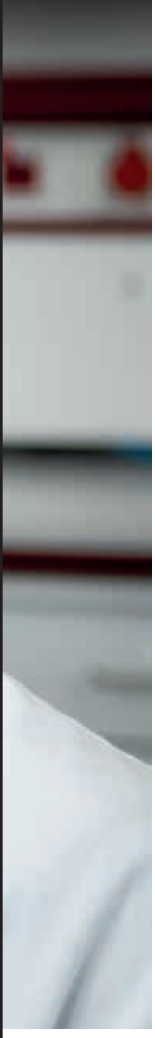
More work needs to be done before Filipović and collaborators are ready to release further details. But already, some of his team members have started adding the compound to their own diets. “It’s a compound that is already commercially available and used in human applications,” he says. Filipović expects interest in H_2S to stay strong. “Our biannual international meeting for hydrogen sulfide now attracts 150 to 200 scientists. That’s just for this very specialized molecule.”

(UE) ■

Sulfaging has received funding from the European Research Council (ERC) under the European Union’s Horizon 2020 research and innovation programme (grant agreement No. 864921).

MS-BASED IMAGING

Most illnesses or medical conditions, including cardiovascular diseases or tumours, are associated with localised and heterogeneous changes of biochemical cascades within some cells. The reason is that cells often respond differently when triggered with external stimuli such as low oxygen levels, viruses, bacteria, or when genetic alteration occurs. This leads to a complex spatial assembly of diseased or infected cells surrounded by healthy tissue, which is responsible for the medically relevant phenotype (referring to the appearance, development, and behaviour of an organism). To fully understand these phenotypes on a molecular level, analytical methods need to be capable of mapping spatially confined molecular changes.



Mass spectrometry imaging enables the examination of tissue slices and the precise localisation of thousands of molecules in one experiment.

Mass spectrometry imaging (MSI) enables the label-free localisation of hundreds of biochemical substances such as metabolites, lipids, peptides, drugs etc. from single cells to tissue sections. This technical capability has provided new molecular insights into diseases such as cancer, diabetes, neurodegenerative, and metabolic disorders. Although MSI methods have been developed and refined in recent years, multiple key aspects of the analysis pipeline need to be improved to fully benefit biomedical and clinical research.

The aim of the Mass Spectrometry- (MS) Based Imaging research programme is to develop and combine matrix-assisted laser desorption ionisation (MALDI) MSI with microscopy techniques. The overall goal is to enable a spatial tracking of downstream products of proteins that indicate the actions of enzymes within cells, for instance lipids and metabolites. The method development of MS-based imaging methods goes hand in hand with applications in the field of heart in rare genetic disease, mechanistic understanding of metabolite and lipid regulation in cardiovascular disfunctions, tumourous changes, and the influence of small molecules during parasite or virus infection.

Improving the performance of MALDI-MSI sources

One requirement for the visualisation of small molecules in tissue sections is sufficient ion signal throughout the measurement, ideally without influences from matrix background or other analytes. Therefore, the scientists involved in this programme are dedicating a huge part of their work to improving the performance of MALDI-MSI sources with regard to the overall ion signal, reduced ion suppression effects, increased coverage of lipids and metabolites in one MSI run. For this, the researchers are combining different ionisation sources with MALDI-MSI, for instance ISAS's flexible microtube plasma (FμTP). The scientists will then test the optimised ion sources for the analysis of lipids and metabolites in cells and cardiovascular disease-associated tissues (inflamed heart tissue after an infarction and Fabry Disease) obtained from mouse models and human samples.

Developing and optimising different sample preparation strategies

Another aspect that can significantly influence the quality of MSI results is sample preparation. Tissue washing steps may lower the total salt content, additives may improve ionisation efficiency, or chemical derivatisation can enhance the signal of select **c**ompound classes and help elucidate the molecular structure of analytes. For this reason, the

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development and improvement of sample preparation strategies is part of the work in the MS-based imaging research programme. Specifically, these include:

- optimising protocols for MSI metabolites of the citric acid cycle,
- minimising ion suppression effects by removing salts or suppression analytes,
- on-tissue derivatisation methods to target low abundant or hard to ionise compounds focusing on steroids, oxidised lipids, sphingolipids,
- chemical derivatisation methods to structurally characterise analytes or validate compound annotations, and
- increasing the compatibility of MSI sample preparation with modalities such as fluorescence and Raman microscopy.

Library of quantified lipid and metabolite values

Quantification is difficult with MSI, because ion suppression effects could depend on the tissue type or the histological structures of the tissue. That is why the researchers at ISAS intend to combine their improved ion sources and optimised sample preparation strategies with absolute quantification results from established shotgun and liquid chromatography (LC) MS/MS experiments. One of their goals is to create a library of quantified lipid and metabolite data for a range of tissue samples using MALDI-MSI and to compare the results with established shotgun and LC-MS/MS values. Another aim is to develop a software tool that allows to use these libraries to quantify compounds in preclinical samples (genetically altered mouse models) and clinical samples.

(SR) ■

3D-PRINTED FUNNEL AND ION MOBILITY SPECTROMETER

Combination is also key when it comes to MSI set-ups. In the MS-Based Imaging research programme, the scientists aim to develop a miniaturised ion funnel and a 3D printed stand-alone drift tube ion mobility spectrometer that is compatible with MSI technologies to improve the ion transfer, its sensitivity, and enable separation of ion populations, respectively. It is expected that these devices can significantly improve the performance of MSI set-ups for molecularly resolved spatial profiling, are customisable in size thanks to 3D printing, and are therefore compatible with multiple MSI set-ups.

Mass Spectrometry Imaging Provides Insight into Tumour Metabolism

Lipids (fats) are not only essential building blocks for cell membranes but also important signalling molecules in the body. This group includes glycerophospholipids (GPLs). Their lipid signature (quantity, nature and chemical structure) may vary in healthy and diseased tissue, such as tumours. However, the biochemical origin of these variations so far remains unclear. Even state-of-the-art methods of mass spectrometry imaging (MSI) are not yet able to identify GPL structures in detail. This makes it more difficult for researchers to analyse structural GPL changes and to interpret the findings in the context of metabolic processes, for example in tumour genesis.

This challenge is being addressed by researchers in the project "Development of Methods of Differentiation and in situ Visualisation of Glycerophospholipid Isomers in Tissue Section using Mass Spectrometry Imaging," which has already entered the second period of funding from the German Research Foundation. Under the leadership of Prof Dr Sven Heiles, the team is developing MSI techniques using matrix-assisted laser desorption/ionisation (MALDI). To this end, they specifically analyse GPLs that synthesise tumour cells as a consequence of their metabolic activity. They intend to investigate structural changes to the GPLs in the primary tumour, in metastases and in the control tissue in order to better understand the modified metabolic pathways. In this context, ISAS is cooperating closely with University Hospital Essen (Prof Dr Dr Alpaslan Tasdogan, ► p. 76, and Prof Dr Matthias Gunzer). At ISAS, the Proteomics and Biofluorescence research groups are involved.

(CP) ■

Funded by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) – Project number 426062756.

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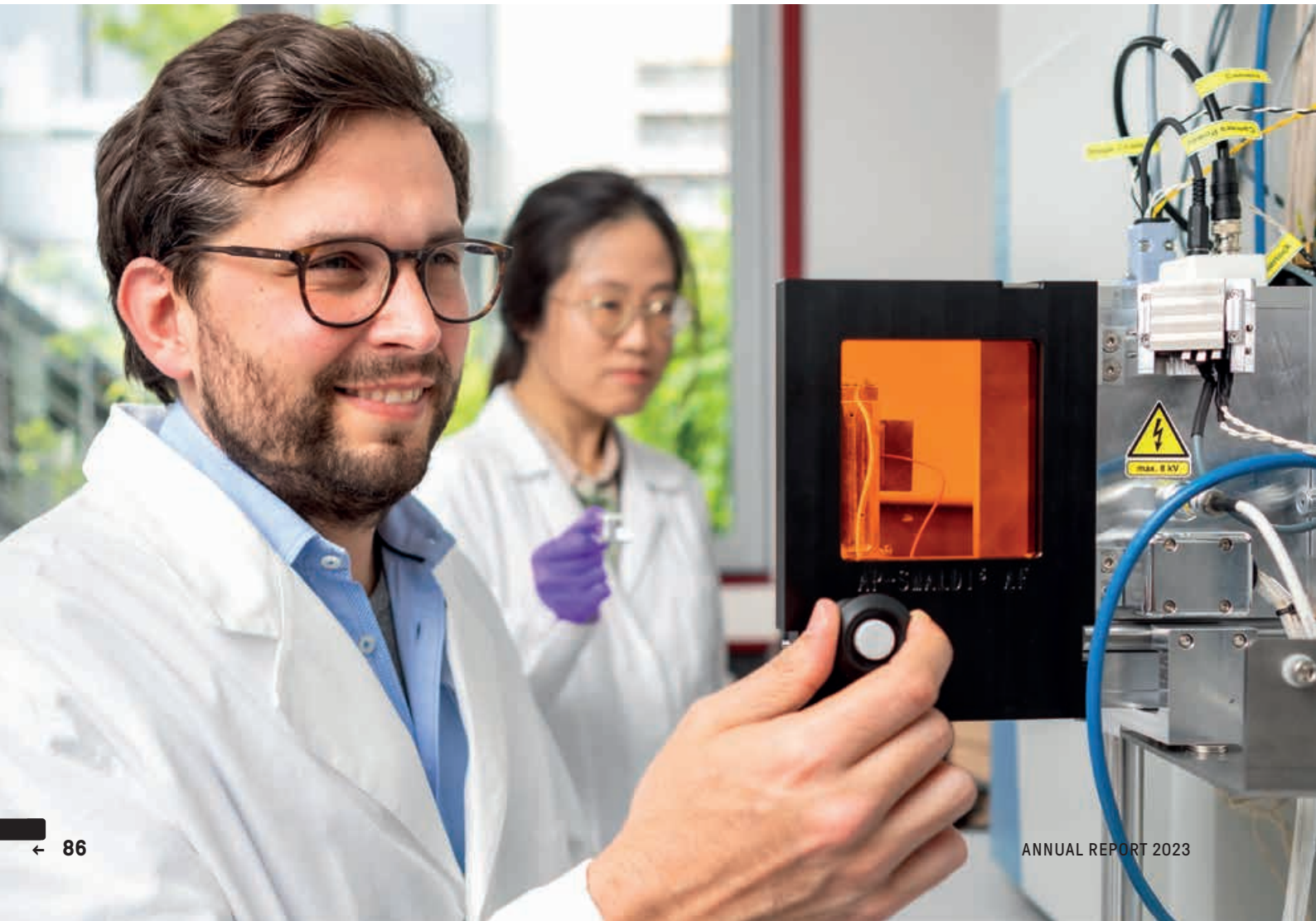
“Fatty” Signatures: How Lipid Patterns Can Be Used as a Diagnostic Tool

When pathogens attack our brain or spine, they’re on the scene right away: microglial cells are a type of immune cell found in the central nervous system. They can play a key role in the development of neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease or multiple sclerosis. Microglial cells are known for their ability to exhibit different phenotypes (observable characteristics) despite having an identical genetic blueprint. This heterogeneity at RNA and protein level has been known for a long time. But now researchers from the Justus Liebig University Giessen, Imperial College London and ISAS have been able to show for the first time that this heterogeneity also exists at lipid and, therefore, metabolic level for single cells. To do this, the scientists recorded the lipid signatures of single microglial cells: their unique, “fatty” signature. Until now, it had only been possible to observe heterogeneity in cell cultures. The authors presented their research findings in the journal *Analytical Chemistry*.



Lipids are a molecular all-rounder: they form part of cell membranes, play an important role in a person's hormonal balance and provide cells with energy. Researchers describe the quantity, type and chemical structure of all the lipids in a particular area, such as a tissue or blood sample, using the lipid signature. They can use this unique signature to identify single cells and deduce how a particular cell metabolises the nutrients that are made available to it. So, the lipid signature helps to clarify which metabolic pathways may be affected by conditions such as Parkinson's disease, tumours or heart attacks. These diseases are highly heterogeneous, not all cells are affected equally and they have very different lipid signatures as a result.

The researchers used atmospheric pressure matrix-assisted laser desorption/ionisation mass spectrometry (AP MALDI-MSI, ► info box) to decipher the signature of the microglial cells. Firstly, the scientists used laser beams to break the samples down into their molecular components so they could determine their type and frequency. Then they transformed this information into an image by means of software, which they could then use to determine the lipid signature and spatial distribution.

Better lasers allow for a higher resolution

To be able to detect the lipid signature of the minuscule cells involved, the authors first had to improve the local resolution of the chemical analysis. They used a specially made ionisation source, adjusted the laser energy and optimised the distance between the MS inlet capillary and the laser focal point. One single microglial cell has a diameter of 45 µm. Thanks to these optimisations, the researchers were ultimately able to maintain the signal intensity and record more than 100 different species of lipid per pixel.

AP MALDI-MSI

Atmospheric pressure matrix-assisted laser desorption/ionisation mass spectrometry is a mass spectrometry imaging procedure. **AP MALDI-MSI** is especially suitable for analysing small biomolecules such as metabolites and lipids. A sample, such as a microglial cell in the case of the specified publication (► p. 89), is exposed to a laser beam. This causes a fraction of the ablated sample material to desorb and ionise. A mass spectrometer can be used to detect the escaping molecular ions. The masses of the molecular ions are determined during this process, like on a scale. The measurements are usually accurate enough that conclusions can be drawn about the elemental composition and, thus, the type of biomolecule. The laser irradiation of the sample is repeated in the lab point by point. The researchers then obtain specialised software distribution images of the individual molecular ions.

The team around Professor Dr-Ing. Sven Heiles, head of the Lipidomics junior research group, combines complementary techniques such as imaging mass spectrometry (MALDI: matrix-assisted laser desorption/ionisation) and light or fluorescence microscopy for their analyses. The photo shows Heiles (left) and doctoral student Chiahsin Chi at the MALDI mass spectrometer.

Tell-tale fats point to inflammation

The researchers studied microglial cells in order to test their method on single cells. The authors simulated a bacterial inflammation and compared untreated cells against those stimulated with lipopolysaccharides (LPS). LPS is a molecule that is present in bacterial membranes. Treating cells with LPS therefore suggests an infection to them. The cells react to the supposed bacterial attack with an immune response designed to fight off the fictitious attackers. During this process, however, single cells "wear out" and can no longer handle the energy that is generated. These subgroups of cells store this excess energy in the form of triglycerides in lipid droplets. Triglycerides are lipids used by an organism to store energy. They can be found in lipid droplets or fat tissue, for example. The scientists were able to use the AP MALDI-MSI method that has been developed to distinguish the still active cells from the population of "worn-out" cells. This allowed the researchers to show the heterogeneity of single microglial cells within a cell population at lipid level for the first time.

Optimised treatment plans: The lipid signature could help

The Lipidomics junior research group at ISAS is collaborating with scientists from University Hospital Essen who are conducting research into skin cancer. Together, they want to use the lipid signature to determine whether heterogeneous behaviour – in this case, the aggressiveness of melanoma cells – depends on the lipid metabolism. In the long term, the ISAS researchers want to shed more light on how different cell types interact in living organisms. In future, the lipid signature could help to detect diseases such as skin cancer in diagnostic tissue – and, together with partners from clinical practice, to optimise treatments.

(LB) ■

Sven Heiles holds a professorship at the University of Duisburg-Essen and heads the Lipidomics junior research group at ISAS.

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“We want to improve the fundamental understanding of disease models”

Decoding the unique signature of lipids (fats) is Prof Dr-Ing. Sven Heiles’s area of expertise. As head of the Lipidomics junior research group at ISAS, he is doing all he can to perform in-depth analyses on these biomolecules in tissue or blood, for example. He uses a special mass spectrometry imaging procedure to do this work. Together with his team and researchers from the Justus Liebig University Giessen, Heiles has succeeded in decoding the lipid signature of single cells for the first time. In this interview, the analytical chemist explains the benefits of single-cell analysis and why the researchers chose microglial cells, of all things, as their model.

Müller, M. A., Zweig, N., Spengler, B., Weinert, M., Heiles, S.
(2023) Lipid Signatures and Inter-Cellular Heterogeneity of Naïve and Lipopolysaccharide-Stimulated Human Microglia-like Cells. *Analytical Chemistry,* 95, 11672–11679.

https://doi.org/10.1021/acs.analchem.3c01533

What information can be gleaned from the lipid signatures of single cells?

Heiles: The specific pattern created by the quantity, type and spatial distribution of lipids is what we call the lipid signature. It gives us valuable information about the lipid metabolism, which can vary between people who are healthy and those who are ill. Until now we have only been able to decode lipid signatures for larger areas, such as tissue or blood samples. But recently we managed to decode single cells for the first time too. Through the example of microglial cells, we were able to show in a cell culture that genetically identical cells sometimes respond to stimulation completely differently at the lipid level. We saw, for instance, that microglial cells which are no longer functioning correctly accumulate more so-called lipid droplets than normal microglial cells. We were able to make these droplet-shaped fat deposits and their molecular composition visible using mass spectrometry imaging, AP MALDI-MSI (► p. 87).

Why did you study microglial cells, of all things?

Heiles: Although microglial cells are incredibly fascinating, for us it was less about the cells themselves and more about their heterogeneous properties. We already know that genetically identical microglial cells are often very different at the transcription and protein level – meaning they have different phenotypes, or observable characteristics. Based on previous research, we expected that these different subtypes would also exhibit differences in terms of lipid metabolism. But until now the technology to prove this just did not exist. We wanted to study the microglial cells to ascertain whether it is possible in principle to make these differences visible using AP MALDI-MSI. Of course, we were also interested in finding out whether our method is sensitive enough and able to image metabolic products that are sufficiently relevant. The hard work was all worthwhile. We delivered the proof of concept and were therefore able to prove that our approach is suitable for investigating subtype heterogeneity amongst cells in a cell culture.

What is the benefit of using AP MALDI-MSI over other imaging procedures?

Heiles: There are a few different procedures for imaging cells in detail. In fluorescence microscopy, for example, specific dyes and the corresponding microscopes are used to make selected structures visible. This is a targeted approach, which allows certain parts of a cell to be visualised selectively. But what happens if we don't even know what we want to see or if no suitable fluorescent dyes exist? That's where AP MALDI-MSI comes in. We don't need any dyes and in principle anything that we are able to ionise, we can make visible. Plus, unlike in fluorescence microscopy, we are not making the dye visible, but the biomolecules themselves.

"But what happens if we don't even know what we want to see or if no suitable fluorescent dyes exist?"

You've shown that your method works. What's next?

Heiles: Information about the metabolism of single cells could be really exciting, as it could give us a greater understanding of highly heterogeneous conditions such as heart attacks or tumours. Not every cell inside a tumour is identical. Factors such as the local environment and, consequently, the supply of nutrients may vary. Now that we know our method works in principle, we are already working on studying cardiac and tumour cells too. In the long term, however, we want to move away from cell cultures and optimise our method such that we can perform single-cell analyses on complex samples like tissue sections. If we can better understand how nutrients are supplied to single cells under real conditions, that could help to elucidate disease mechanisms related to the metabolism of cells. Ultimately, our technology aims to improve our fundamental understanding of disease models and so to further the development of new treatments, for example, together with partners from clinical practice.

(The interview was conducted by CP and LB.) ■

OUR YEAR IN FIGURES

163

employees

As at December 31, 2023, ISAS had 74 female and 89 male members of staff at its locations.

66

researchers (m/f/n-b)

were employed at the institute in 2023, of whom 28 were women and 38 men.

38

doctoral candidates (m/f/n-b)

Among the 66 researchers, there were 18 female and 20 male PhD students.

27

scientific technical staff members (m/f/n-b)

currently work at ISAS, of whom 16 are women and 11 men.

7.03

impact factor

The average impact factor of the publications in peer-reviewed journals.

120

publications

were published in peer-reviewed journals.

54

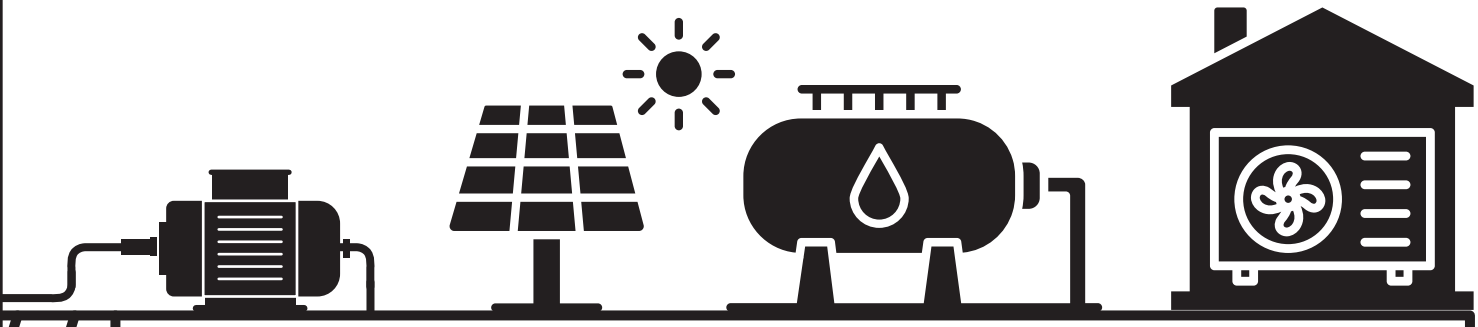
papers

with a lead or corresponding author from ISAS were published in 2023.

10

software & tools (open source)

were published by the AI experts and bioinformaticians in 2023.



The ISAS City location generates 550,000 kilowatts of electricity each year by means of the photovoltaic system and the generation plant. Of this total, 150,000 kilowatt hours of electricity are produced by 338 photovoltaic modules that were mounted on 624 m^2 (85%) of the roof area. Four liquid gas tanks of 2,700 litres each ensure that the institute at the City site is independent of natural gas. In addition to the gas heating, ISAS City also uses an air source heat pump for heating.

37

academic qualifications

Of the 37 final theses, 15 were internal papers.*

20

BSc, MSc

These included two bachelor's and three master's students who wrote their final theses at ISAS.*

16

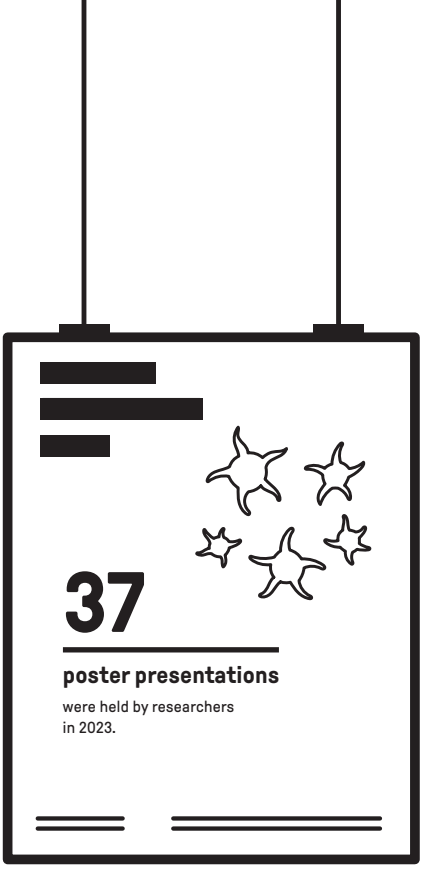
PhD theses

These included 16 PhD dissertations, of which four were written at ISAS.*

* The other projects were external expert assessments.

1

postdoctoral qualification



37

poster presentations

were held by researchers in 2023.

53

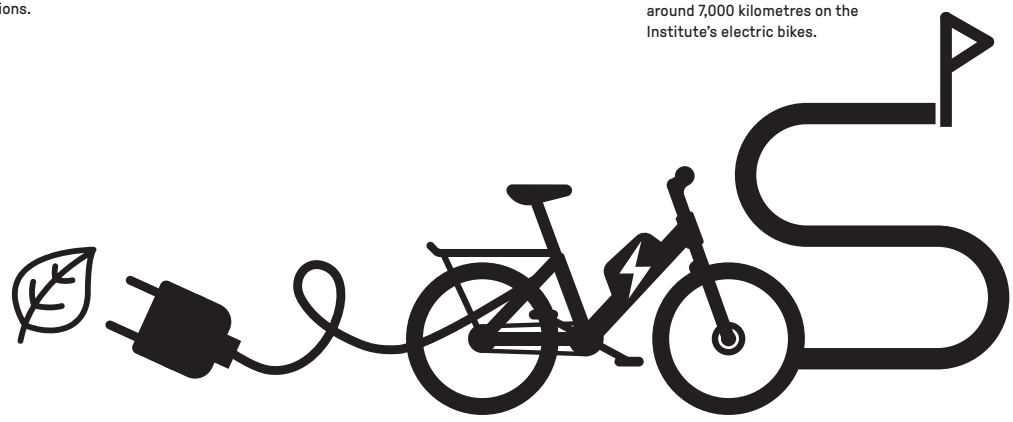
lectures

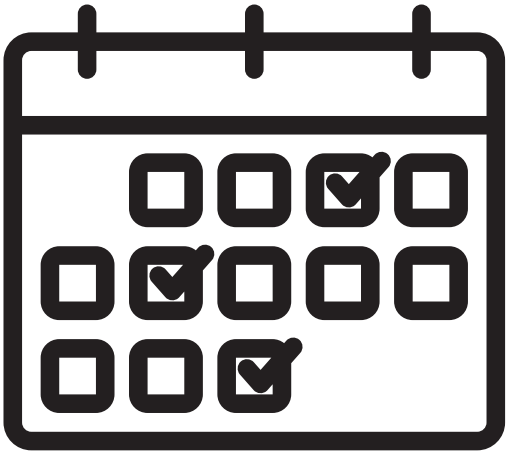
were given by ISAS researchers at conferences and other institutions.

approx. 7,000

kilometres travelled with e-bikes

When commuting between the ISAS City and ISAS Campus sites, the employees of the Facility Management & Workshop team alone covered around 7,000 kilometres on the Institute's electric bikes.





11

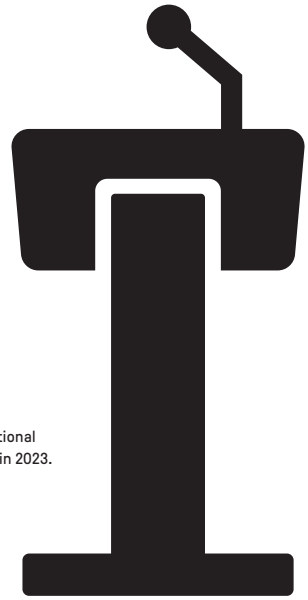
scientific events

were (co-)organised by ISAS in 2023.

39

conferences

In 2023, ISAS researchers contributed at 39 specialist conferences.



14

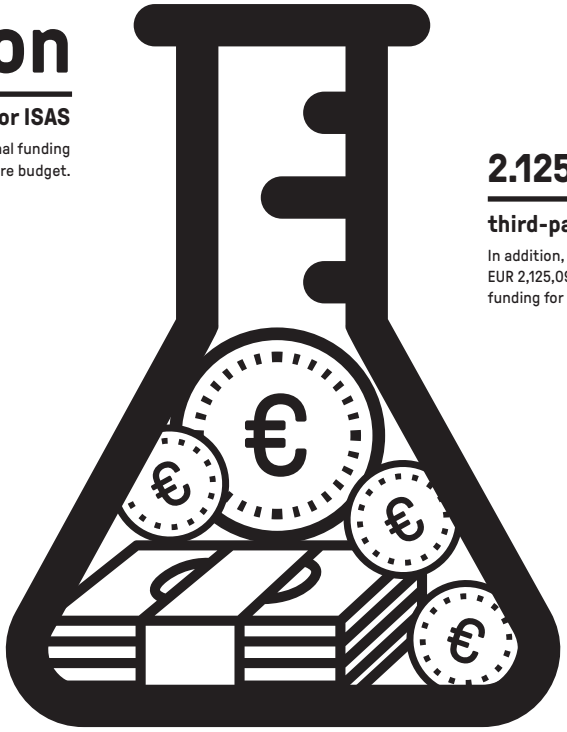
colloquia at ISAS

with international and national guests were taking place in 2023.

14.256 million

total funding for ISAS

ISAS received EUR 14,255,780 in institutional funding from the federal and state governments for its core budget.



2.125 million

third-party funding

In addition, the institute received EUR 2,125,093 in third-party funding for 2023.

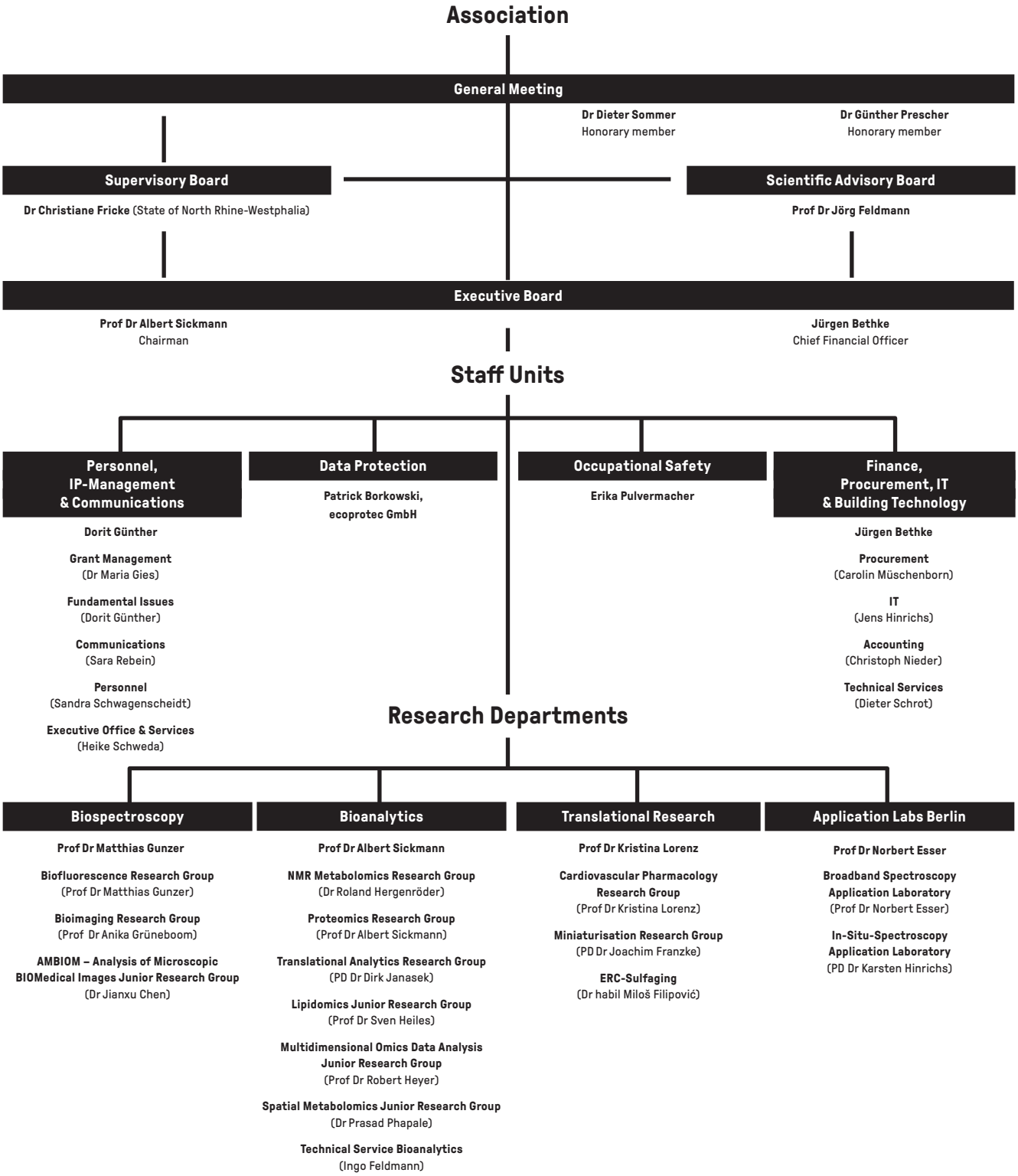
ORGANISATION

ISAS Executive Board

Prof Dr Albert Sickmann, Chairman (left)
Jürgen Bethke, Chief Financial Officer

As at December 31, 2023

Organisation Chart



BOARDS

As at December 31, 2023

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Università Cattolica del Sacro Cuore
Italy

Prof Dr Heike Walles
Core Facility Tissue Engineering,
Otto von Guericke University
Magdeburg

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State of North Rhine-Westphalia

TechnologieZentrumDortmund GmbH

Thermo Fisher Scientific GmbH (Bremen)

Thermo Fisher Scientific GmbH (Dreieich)

TU Dortmund University

AKTIVITÄTEN 2023

ACTIVITIES 2023

Publikationen
Publications

Publikationen in referierten Zeitschriften*
Peer-reviewed Papers

Bioanalytik

Ababneh, R., Smadi, M., Bensiradj, N. E. H., Al-Akhras, M. A., Al-Hiari, Y., Jum'h, I., Abu-Dahab, R., Al Bataineh, Q. M. & Telfah, A.
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Vorträge
Lectures

Konferenzvorträge
Conference Talks

Bioanalytik

Sven Heiles
MS-based Multiparametric Coagulation Diagnostics
Deutscher Kongress für Labormedizin 2023
Mannheim

Revealing local lipid C=C isomerism in tissues with mass spectrometry imaging
4th EpilipidNet Meeting
Toulouse, Frankreich

Single Cell Mass Spectrometry Imaging for Clinical Applications
DPhG 2023: Translational Pharmacy – Practice & Perspective
Tübingen

Robert Heyer
Bioinformatics for Metaproteomics
Proteome Alliance Rhine Ruhr (PAR2) Meeting
Dortmund

Bioinformatic methods for analyzing multidimensional omics data from clinical applications
15th Winter seminar of Medical Faculty of University Duisburg-Essen, Pichl
Pichl, Österreich

Introduction to Metaproteomics
BSPR /EuPA 2023 Conference: Annual Scientific Meeting
Newcastle upon Tyne, UK

Overview of informatics platforms available for functional microbiome analysis
Fifth Metaproteomics Symposium
Avignon, Frankreich

Siva Swapna Kasarla
Quantitative analytical and computational workflow for large-scale targeted metabolomics
51st International Symposium on High Performance Liquid Phase Separations and Related Techniques (HPLC 2023)
Düsseldorf

Emanuel Lange
Leveraging the monorepo pattern to build scientific web-applications
BIBI/ZB MED Workshop
Köln/Bonn

Prasad Phapale
Large-Scale Metabolite Imaging Gallery of Mouse Organ Tissues to Study Spatial Metabolism
International Spatial Biology Congress 2023
Rotterdam, Niederlande

Molecular deciphering of disease processes in SLC12A6-associated sensorimotor neuropathy
26. Kongress des Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) e.V.
Essen

Gina Piontek
Developing a protein assay for the investigation of the coagulation cascade in human blood plasma by LC-MS/MS
Proteome Alliance Rhein-Ruhr (PAR2) Meeting
Bonn

Julia Sophie Rauch
The challenge of preparation and measurement of red blood cell samples for proteomics
33. Doktorandenseminar des Arbeitskreises Separation Science der Gesellschaft Deutscher Chemiker (GDCh)
Hohenroda

Kay Schallert
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Frankfurt

Fiorella Solari
Clinical Proteomics towards a fast Elucidation of Stroke Risks
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Protaras, Zypern

Biospektroskopie

Jianxu Chen
EfficientBioAI: Making Bioimaging AI Models Efficient in Energy, Latency and Representation
Bio-image Analysis Symposium
Dresden

Susmita Ghosh
Comprehensive proteome analysis of circulatory neutrophils co-cultured with tumor cells
Proteome Alliance Rhine Ruhr (PAR2) Meeting
Dortmund

Profiling of few neutrophils isolated freshly from healthy and diseased species using highly sensitive LC-MS based proteomics
ESCP 2023
Wien, Österreich

Matthias Gunzer
About neutrophil migration
The Granulocyte Meeting
Singapur, Singapur

Blood flow, innate and adaptive immunity in long bones
ASBMR Annual Meeting 2023
Vancouver, Kanada

Imaging innate immunity in infectious and sterile inflammation
RTG Materials Microbes Microenvironments
Dornburg

Mechanisms of immune suppression after sterile tissue injury
3rd Inflammation and Imaging Symposium
Münster

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15th annual Virology Conference
online

The role of neutrophils in infectious and sterile inflammation
The ZMBE Symposium
Münster

Justin Sonneck
On the risk of manual annotations in 3D confocal microscopy image segmentation
International Conference on Computer Vision – ICCV23
Paris, Frankreich

Translationale Forschung

Stefanie Dörr
Thyroid hormone (TH) action in acute and chronic ischemic heart disease
EYES/YARE 2023
Würzburg

Annika Fechner
Development of a seamless non-radioactive liquid phase IMS device
32nd International Conference on Ion Mobility Spectrometry
Maastricht, Niederlande

Miloš Filipović
Disrupted thiol redox homeostasis controls protein phase separation and aggregation in aging
Groningen-Jena Aging Meeting
Groningen, Niederlande

Disrupted thiol redox homeostasis controls protein phase separation and aggregation in aging
The 10th Aging Research and Drug Discovery Meeting
Kopenhagen, Dänemark

Molecular mechanisms of hydrogen sulfide signaling: from origin of life to cell death
15th Winter seminar of Medical Faculty of University Duisburg-Essen, Pichl
Pichl, Österreich

Molecular mechanisms of hydrogen sulfide signaling: from origin of life to cell death
15th Winter seminar of Medical Faculty of University Duisburg-Essen, Pichl
Pichl, Österreich

Protein persulfidation in aging and aging-related diseases
Workshop on Bioenergetic, Redox, Ferroptosis & Cancer
Monaco, Monaco

Joachim Franzke
Diagnosis and applications of atmospheric plasmas applied in Analytical Chemistry for soft ionisation
International Symposium on Plasma and Energy Conversion (iSPEC)
Nanjing, China

Elucidation of Soft Ionisation Mechanism in a He-, Ne, Ar, Kr, Xe- Flexible µ Tube Plasmas by Temporally and Spatially Resolved Plasma Optical Emission Phoresis Spectroscopy
32nd International Conference on Ion Mobility Spectrometry
Maastricht, Niederlande

Simon Höving
Functionalization of a Next-Generation Material for 3D-Printed IMS and Analytical Detectors
32nd International Conference on Ion Mobility Spectrometry
Maastricht, Niederlande

Kristina Lorenz
Experimentelle Kardiologie
89. Jahrestagung der Deutschen Gesellschaft für Kardiologie (DGK)
Mannheim

Herzinsuffizienz mit erhaltener Pumpfunktion (HFpEF)
89. Jahrestagung der Deutschen Gesellschaft für Kardiologie (DGK)
Mannheim

Intracellular thyroid hormone sensitivity and their possible role for heart diseases
89. Jahrestagung der Deutschen Gesellschaft für Kardiologie (DGK)
Mannheim

RKIP – a Regulator of Beta-Adrenergic Signaling in the Heart
1st Joint International Symposium on "Prognostic and Therapeutic Implications of RKIP and YY1 in Cancer, Diabetes and Cardiovascular Diseases"
Catania, Italien

Target-Kandidaten für eine Translation in die Klinik
89. Jahrestagung der Deutschen Gesellschaft für Kardiologie (DGK)
Mannheim

Arthur Schiller
Flexible Drift Tube Manufacturing with Different 3D Printing Technologies Using Conductive and Non-Conductive Cyclic Olefin Copolymer
32nd International Conference on Ion Mobility Spectrometry
Maastricht, Niederlande

Hao Song
Excitation and Ionisation of a Diagnosis Gas in Front of the Flexible µ Tube Plasma and in a Diagnosis Capillary
International Symposium on Plasma and Energy Conversion (iSPEC)
Nanjing, China

Luisa Speicher
New Ionisation Source: The Closed µ-Tube Plasma
32nd International Conference on Ion Mobility Spectrometry
Maastricht, Niederlande

Caiyan Tian
Elucidation of Discharge Mechanism in He-, Ne, Ar, Kr, Xe-Flexible μ Tube and Their Transition to Ambient Air
International Symposium on Plasma and Energy Conversion (iSPEC)
Nanjing, China

Elen Tolstik
Application of Raman spectroscopy for the monitoring of drug delivery and sustained release via porous silicon nanoparticles
89. Jahrestagung der Deutschen Gesellschaft für Experimentelle und Klinische Pharmakologie und Toxikologie (DGPT)
Ulm

Raman spectroscopy of the heart
NOTICE (Novel Optical Technology in Cardiac Electrophysiology)
Glasgow, Schottland

Applikationslabore Berlin

Karsten Hinrichs
Analytical interpretation of polarimetric IR spectra of thin films and interfaces
12th Workshop on Spectroscopic Ellipsometry (WSE)
Prag, Tschechische Republik

Infrared Ellipsometry: Recent Progress in Mueller-Matrix and Laser-Based Instrumentation
12th Workshop on Spectroscopic Ellipsometry (WSE)
Prag, Tschechische Republik

IR dual-comb polarimetry of anisotropic nanofibers
86. Jahrestagung der DPG und DPG-Frühjahrstagung der Sektion Materie und Kosmos (SMuK)
Dresden

Laser based IR spectroscopic methods for analysis of nanofiber scaffolds
ACS Spring 2023
Indianapolis, USA

Multiscale IR polarimetry of anisotropic nanofibers
SPIE – Photonics West
San Francisco, USA

Optical Monitoring During the Electrochemical Deposition of Organic Layers (AM1A.1)
Optica Sensing Congress
München

Veranstaltungen
Events

Mitorganisation & Organisation wissenschaftlicher Veranstaltungen
Co-organisation & Organisation of Scientific Events

Bioanalytik

ISAS Skyline Course
20.03.2023 – 24.03.2023
Dortmund

54. Jahrestagung der Deutschen Gesellschaft für Massenspektrometrie (DGMS)
14.05.2023 – 17.05.2023
Dortmund

Proteome Alliance Rhine Ruhr (PAR2) Meeting
25.01.2023
Dortmund

Metaproteomics Symposium
24.04.2023
Avignon, Frankreich

Workshop Spatial Multiomics
26.10.2023 – 27.10.2023
Dortmund

Bioanalytik + Translationale Forschung

20th Dutch-German Joint Meeting 2023
16.03.2023 – 18.03.2023
Würzburg

Biospektroskopie

Trends in Microscopy 2023
20.03.2023 – 24.03.2023
Münsingen

Translationale Forschung

1st Joint International Symposium on Prognostic and Therapeutic implications of RKIP and YY1 in Cancer, Diabetes and Cardiovascular Diseases
08.03.2023 – 11.03.2023
Catania, Italien

89. Jahrestagung der Deutschen Gesellschaft für Kardiologie
12.04.2023 – 15.04.2023
Mannheim

Wissenstransfer & Öffentlichkeitsarbeit
Knowledge Transfer & Public Relations

Personal, IP-Management & Kommunikation

„Eine anhaltende Frage der Nachhaltigkeit: Wie viel Energie benötigt das ISAS heute sowie in Zukunft – und wofür?“
22.02.2023
Dortmund

Postdoc Pitch Day
28.03.2023

„Eine anhaltende Frage der Nachhaltigkeit: Wie viel Energie benötigt das ISAS heute sowie in Zukunft – und wofür?“
27.04.2023
Dortmund

Leibniz im Bundestag
13.06.2023
online

Book a Scientist
12.09.2023
online

Postdoc Pitch Day
08.12.2023

Science Slam
08.12.2023
Dortmund

Lehrveranstaltungen
Teaching Activities

Bioanalytik

Sven Heiles
Lipidomics – Biochemical Importance and Analytical Methods
Universität Duisburg-Essen,
Sommersemester 23

Modern Analytic Method for systems medicine
Universität Duisburg-Essen,
Wintersemester 23/24

Robert Heyer
Graphdatenbanken und Wissensgraphen in den Lebenswissenschaften
Universität Bielefeld,
Wintersemester 23/24

Omics Data Analysis
Universität Bielefeld,
Sommersemester 23

Reaktionstechnik
Universität Bielefeld,
Wintersemester 22/23

Reaktionstechnik
Universität Bielefeld,
Wintersemester 23/24

Dirk Janasek
Analytische Anwendungen von „Lab-on-a-Chip"-Systemen
Technische Universität Dortmund,
Wintersemester 22/23

Analytische Anwendungen von „Lab-on-a-Chip"-Systemen
Technische Universität Dortmund,
Wintersemester 23/24

Biochemie
Fachhochschule Dortmund,
Sommersemester 23

Physiologie & Anatomie
Fachhochschule Dortmund,
Wintersemester 22/23

Physiologie & Anatomie
Fachhochschule Dortmund,
Wintersemester 23/24

Prasad Phapale
Measuring Metabolisms across Scales: Molecular, Spatial, Temporal Resolution
Universität Duisburg-Essen,
24.04.2023

Spatial Metabolomics: Visualizing Metabolisms at Scale
Universität Duisburg-Essen,
28.06.2023

Yvonne Reinders
Hands-on: Absolute quantification of peptides and small molecules
ISAS: Skyline Course 2023,
21.03.2023

Albert Sickmann
Biochemie I
Ruhr-Universität Bochum,
Wintersemester 22/23

Biochemie I
Ruhr-Universität Bochum,
Wintersemester 23/24

Biochemie II
Ruhr-Universität Bochum,
Sommersemester 23

Proteomik und Metabolomik
Hochschule Hamm-Lippstadt,
Wintersemester 22/23

Proteomik und Metabolomik
Hochschule Hamm-Lippstadt,
Wintersemester 23/24

Albert Sickmann, Dirk Janasek
Bioanalytik
Technische Universität Dortmund,
Wintersemester 22/23

Bioanalytik
Technische Universität Dortmund,
Wintersemester 23/24

Chemische Analytik
Technische Universität Dortmund,
Sommersemester 23

Steven Verhelst
Chemical probes for proteases: application in imaging and target identification
Technische Universität Berlin,
Wintersemester 22/23

Biospektroskopie

Anika Grüneboom
Immunologie – Allergische Reaktionen
Universität Duisburg-Essen,
Wintersemester 22/23

Moderne Mikroskopie – Lichtblattmikroskopie
Universität Duisburg-Essen,
Sommersemester 23

Translationale Forschung

Sebastian Brandt
Angewandte Spektroskopie
Technische Universität Dortmund,
Wintersemester 22/23

Miloš Filipović
Sulfaging: Redox-signaling of Thiol Modifications in Aging and Stress Resistence
Universität zu Köln,
12.10.2023

Joachim Franzke
Angewandte Laserspektroskopie
Technische Universität Dortmund,
Wintersemester 23/24

Angewandte Plasmaphysik
Technische Universität Dortmund,
Sommersemester 23

Angewandte Spektroskopie
Technische Universität Dortmund,
Wintersemester 22/23

Grundlagen Analytischer Methodik
Fachhochschule Südwestfalen,
Sommersemester 23

Kristina Lorenz
Grundlagen der Organtoxikologie und -pathologie Teil 1: Experimentelle Kardiotoxizitätsprüfung
Gesellschaft für Toxikologie – Deutsche Gesellschaft für experimentelle und klinische Pharmakologie und Toxikologie e. V. ,
15.02.2023

Grundlagen der Organtoxikologie und -pathologie Teil 1: Pathophysiologie
Gesellschaft für Toxikologie – Deutsche Gesellschaft für experimentelle und klinische Pharmakologie und Toxikologie e. V. ,
15.02.2023

Grundlagen der Organtoxikologie und -pathologie Teil 1: Physiologie
Gesellschaft für Toxikologie – Deutsche Gesellschaft für experimentelle und klinische Pharmakologie und Toxikologie e. V. ,
15.02.2023

Grundlagen der Organtoxikologie und -pathologie Teil 1: Toxikologie
Gesellschaft für Toxikologie – Deutsche Gesellschaft für experimentelle und klinische Pharmakologie und Toxikologie e. V. ,
15.02.2023

Organtoxikologie: Kardiotoxizität
Universität Leipzig,
17.01.2023

Elen Tolstik
Raman-Spektroskopie in der Biomedizin – Spektroskopische Analyse mit Fokus auf Krebs- und Herz-Kreislauf-Erkrankungen
Technische Universität Dortmund,
09.05.2023

Applikationslabore Berlin

Norbert Esser
Festkörperspektroskopie: Grundlagen und Methoden
Technische Universität Berlin,
Wintersemester 22/23

Festkörperspektroskopie: Grundlagen und Methoden
Technische Universität Berlin,
Sommersemester 23

Festkörperspektroskopie: Grundlagen und Methoden
Technische Universität Berlin,
Wintersemester 23/24

Oberflächenphysik
Technische Universität Berlin,
Sommersemester 23

Raman Spectroscopy at Surfaces: Fundamentals and Applications
Johannes Kepler Universität Linz,
Wintersemester 22/23

Karsten Hinrichs
Ellipsometry
Technische Universität Dresden,
Wintersemester 22/23

Festkörperübungen zu Ellipsometrie
Technische Universität Berlin,
Sommersemester 23

IR Molekülspektroskopie
Technische Universität Berlin,
Wintersemester 22/23

Optische Spektroskopie an Oberflächen und Grenzflächen
Technische Universität Berlin,
Wintersemester 22/23

Interpretation von IR-mikroskopischen Molekülspektren
Technische Universität Berlin,
Sommersemester 23

Interpretation von IR-mikroskopischen Molekülspektren
Technische Universität Berlin,
Wintersemester 23/24

Kolloquien
Colloquia

Dortmund

Prof. Dr. Thorsten Kaiser
Future Laboratory Diagnostics – Combining Multiparametric Spectroscopy with Clinical Decision Support Addressing Precision Medicine
Universitätsinstitut für Laboratoriumsmedizin, Mikrobiologie und klinische Pathobiochemie, Campus Klinikum Lippe, Universitätsklinikum OWL der Universität Bielefeld, Deutschland
12.01.2023

Dr. Susanne Rafelski
Integrated Intracellular Organization and its Variations in Human iPS Cells
Eberhard Karls Universität Tübingen, Allen Institute for Cell Science, USA
07.02.2023

Prof. Dr. Markus Ludwigs
Gute wissenschaftliche Praxis und wissenschaftliches Fehlverhalten – der DFG-Kodex und seine Umsetzung
Julius-Maximilians-Universität Würzburg, Lehrstuhl für Öffentliches Recht und Europarecht, Deutschland
10.02.2023

Prof. Dr. Katja Kotsch
Kidney-resident Immunity – Who's Good and Who's Bad for Allograft Survival for the Detection and Prognosis of COVID-19
Charité – Universitätsmedizin Berlin, Klinik für Allgemein-, Viszeral- und Gefäßchirurgie, Deutschland
23.03.2023

Prof. Dr. Burkhart Schraven
Biochemical, Microscopic and Systems Biology Approaches to Understand Principal Molecular Mechanism of Immune Cell Activation
Otto-von-Guericke-Universität, Institut für Molekulare und Klinische Immunologie, Universitätsklinikum Magdeburg, Deutschland
27.04.2023

Dr. Yvonne Reinders
MicroRNAs: From Basic Research into Translation
Leibniz-Institut für Analytische Wissenschaften – ISAS – e. V.
01.06.2023

Dr. Manjeet Kumar
Short Linear Motifs (SLiMs) in Health and Disease
European Molecular Biology Laboratory (EMBL), Heidelberg, Deutschland
15.06.2023

PD Dr. Thilo Muth
Tales from Developing Software for Omics-driven Microbiome Research & Virus Diagnostics, also Featuring Novel Insights: How to Make Science More Sustainable Using Research Data Management
Bundesanstalt für Materialforschung und -prüfung (BAM), Deutschland
22.07.2023

Dr. Steffen Mayerl
Impact of thyroid hormone on brain development and function
Universitätsklinikum Essen, Klinik für Endokrinologie, Diabetologie und Stoffwechsel, Deutschland
15.08.2023

Dr. Anne Kathrin Bendt
Plasma Lipidomics – from Cohorts to Clinical Applications
National University of Singapore, Centre for Life Sciences, Singapore Lipidomics Incubator – Life Sciences Institute, Singapur
07.09.2023

Fabian Guth
Sustainability Reporting in Research Institutions – A Case Study in Cooperation with Leibniz-Institut für Analytische Wissenschaften – ISAS – e. V.
Ruhr-Universität Bochum, Fakultät für Wirtschaftswissenschaft, Deutschland
20.09.2023

Prof. Dr. Yiyu Shi
AI Fairness for Dermatological Disease Diagnosis
University of Notre Dame, Department of Computer Science and Engineering, USA
21.09.2023

Jun.-Prof. Dr. Silvio Waschina
Gut Microbial Metabolism in Inflammatory Bowel Disease: Leveraging Metabolic Modeling to Predict Patient Response to Immunomodulatory Therapy
Christian-Albrechts-Universität zu Kiel, Institut für Humanernährung und Lebensmittelkunde, Deutschland
02.11.2023

M.Sc. Patrick Hellwig
The Use of BONCAT and Click Chemistry for the Analysis of Newly Synthesized Proteins in Microbial Communities
Otto-von-Guericke-Universität Magdeburg, Institut für Verfahrenstechnik, Deutschland
12.12.2023

Drittmittelprojekte
Third-Party-Funded Projects

Bioanalytik

Analyse differenzieller Gen- und Proteinexpression zum In-Vitro-Nachweis einer Arzneimittelallergie
INA
Januar 2020 – März 2023
EFRE

Biochemical annotations of mass spectrometry imaging data
November 2022 – Oktober 2023
Chan Zuckerberg Initiative

Nachwuchsgruppe Spatial Metabolomics
Oktober 2020 – März 2026
BMBF

NephrESA – Modellbasierte Optimierung der Anämiebehandlung für den einzelnen Patienten mit chronischer Nierenerkrankung
NephrESA
Juni 2019 – November 2025
BMBF

Post-translational modifications of the synaptic scaffold controlling age-induced memory impairment
SyMetAge
Juli 2019 – Dezember 2023
Leibniz-Wettbewerb

Sonderforschungsbereich / Transregio 240: Platelets – Molecular, cellular and systemic functions in health and disease
Teilprojekt Z02: Analysing signalling molecules and modifications in platelets by proteomics, lipidomics and bioinformatics
TRR 240
Juli 2018 – Juni 2023
DFG

Thrombo-inflammation in cardiovascular disease
TICARDIO
April 2019 – November 2023
EU

Functional profiling and routine diagnosis of humane microbiomes by metaproteomics
MetaProt
NFDI4Microbiota Use Case
Januar 2023 – Dezember 2023
DFG

Creating 'Leibniz Mass Spectral Imaging library' for identification of primary and secondary metabolites
Januar 2023 – Dezember 2023
Leibniz-Forschungsnetzwerk »Wirkstoffe«

Investigation of anticancer MOAs of plant products by AI-enhanced CARS microscopy
MOA-CARS
Januar 2023 – Dezember 2023
Leibniz-Forschungsnetzwerk »Wirkstoffe«

Biospektroskopie

Human-in-the-loop Cell Tracking in napari
November 2022 – Oktober 2023
Chan Zuckerberg Initiative

Nachwuchsgruppe AMBIOM – Analysis of Microscopic BIOMedical Images
Oktober 2020 – März 2026
BMBF

Sonderforschungsbereich / Transregio 332: Neutrophils – origin, fate, and function
Teilprojekt C05: Phagocytic crosstalk between neutrophils and macrophages
TRR 332
Juli 20222 – Juni 2026
DFG

Synthese, Struktur und biologische Effekte von ultrakleinen (1-2 nm) bimetallischen Silber-Platin-Nanopartikeln
SE2449/2-1
Dezember 2021 – April 2025
DFG

National Research Data Infrastructure for Microscopy and Bioimage Analysis
NFDI4BIOIMAGE
März 2023 – Februar 2028
DFG

Translationale Forschung

Decoding protein persulfidation signaling
SULFAGING
Oktober 2020 – September 2026
EU ERC Consolidator Grant

Entwicklung eines schnellen und kostengünstigen Detektionssystems zum Nachweis der zoonotischen Erreger Campylobacter und Salmonella in der Schlachtindustrie (FastMeatControl)
FMC
Juli 2022 – Juni 2025
BMBF

Entwicklung und Optimierung von GRK5-Inhibitoren für die Therapie von Herzinsuffizienz und Herzhypertrophie
ChInValue
Januar 2020 – Juni 2023
BMBF

Herzschützendes Targeting von ERK
ERK-CASTing
August 2020 – Februar 2023
BMBF

Nicht-Radioaktive Ionisierung für Spektrometrie und Spektroskopie
NORISC
Juli 2020 – September 2023
BMBF

The Role of Zinc Fingers in H_2S Signaling
September 2020 – Juli 2024
University of Maryland

Sonferforschungsbereich / Transregio 296: Lokale Kontrolle der Schilddrüsenhormonwirkung
Teilprojekt P10: Local TH action in acute and chronic ischaemic heart disease
LOCOTACT
Juli 2020 – Juni 2025
DFG

Schutzrechte
Industrial Property Rights

Patente
Patents

Anordnung zur Erfassung von Reflexions-Anisotropie
EP-Patent: EP3035034
(erteilt und validiert in Deutschland)

Detektor für die kernmagnetische Resonanzspektroskopie »Mehrfachresonanzkopf mit Hilfsinduktivität«
DE-Patent: DE102014115572

Echelle-Spektrometer mit verbesserter Detektorausnutzung »Aryelle«
EP-Patent: EP1754032
(erteilt und validiert in Großbritannien, Frankreich, Österreich und Deutschland)
US-Patent: US7804593
AU-Patent: AU2005252809
CN-Patent: CN101014841

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

Probenkopf für die kernmagnetische Resonanzspektroskopie »Mikrostreifenleiter Probenkopf mit dreiecksförmiger Einschnürung«
EP-Patent: EP3350610
(validiert in Deutschland)

Probenkopf für die kernmagnetische Resonanzspektroskopie »Mikrostreifenleiter-Probenkopf zur Erzeugung von Gradienten des äußeren Magnetfeldes in kernresonanzspektroskopischen Messungen«
DE-Patent: DE102015115996

Spektrometer
DE-Patentanmeldung: DE102016110210

Spektrometeranordnung »SuZee«
EP-Patent: EP2516975
(validiert in Großbritannien, Frankreich und Deutschland)
US-Patent: US8873048
CN-Patent: CN102656431

Verfahren zur Analyse des Metaboloms dreidimensionaler lebender Zellkulturen mittels NMR-Spektroskopie »SLRO-NMR«
DE-Patentanmeldung: DE102021103574

Verfahren zur Detektion und Quantifizierung von einzelnen Analyten in flüssigen Analytgemischen »Pocket-NMR«
EP-Patent: EP355603 (validiert in Deutschland, Italien, Spanien und Frankreich)
DE-Patentanmeldung: DE102016124177
US-Patent: US10782256

Verfahren zur dielektrisch behinderten Elektrosprayionisierung von flüssigen Proben und zur nachfolgenden massenspektrometrischen Analyse der erzeugten Probenionen »Getaktetes DB-Elektrospray«
DE-Patent: DE102011015517
EP-Patent: EP2691974
(validiert in Deutschland, Spanien, Frankreich und Großbritanien)
JP-Patent: JP5814458

Verfahren zur Herstellung eines dreidimensionalen, einen elektrischen Widerstand bildenden Körpers »Filament«
DE-Patentanmeldung: DE102020109649.6

Verfahren zur hochaufgelösten Erfassung von Nanopartikeln auf zweidimensionalen Messflächen
DE-Patentanmeldung: DE102009003548
US-Patent: US8587786

Verfahren zur Identifizierung von Markerproteinen zur Diagnose und Risikostratifizierung von Störungen der Blutgerinnung
EP-Patent: EP3295177
(validiert in Großbritannien, Frankreich, Schweiz, Österreich, Spanien, Italien und Deutschland)
US-Patentanmeldung: US15/572391
CN-Patent: CN202010371718.7
JP-Patentanmeldung: JP2018521306

Verfahren zur Ionisierung von gasförmigen Proben mittels dielektrisch behinderter Entladung und zur nachfolgenden Analyse der erzeugten Probenionen in einem Analysegerät »FµTP«
DE-Patentanmeldung: DE102017112726
EP-Patentanmeldung: EP187306501
US-Patent: US 16/615172

Verfahren zur Ionisierung von gasförmigen Proben mittels Gasentladung
DE-Patentanmeldung: DE102022121736

Verfahren zur Messung der Thrombozytenfunktion »Blutplättchenmesssytem«
EP-Patent: EP2990787
(validiert in Frankreich, Spanien, Österreich, Großbritanien, Italien und Deutschland)
US-Patent: US9778248
JP-Patent: JP2016048236
CN-Patent: CN105388202

Vorrichtung zur Detektion und Charakterisierung von organischen Molekülen in einem flüssigen Probenvolumen
DE-Patent: DE102016101001

Absolvent:innen
Graduates

Dissertationen
Dissertations

Bioanalytik

Suyuan Chen
Photoaffinity probes for aspartic proteases with target identification and binding site mapping by tandem MS.
Technische Universität Dortmund

Yam Fung Hilaire Cheung
PIntegrating Phosphoinositide Metabolism, Platelet Functional Data and Computational Modelling to Decipher GPVI-Signalling in Platelet Activation.
Universität Maastricht

Lubaba Yousef Hazza Migdadi
Metabolic profiling on 2D NMR TOCSY spectra using machine learning.
Technische Universität Dortmund

Translationale Forschung

Daniel Foest
Development and characterisation of quasi-simultaneous electrospray and plasma ionisation for the analysis of polar and less polar compounds in mass spectrometry.
Universität Wuppertal

Habilitationen
Habilitations

Bioanalytik

Sven Heiles
Lipid structures and lipid distributions elucidated by high-performance mass spectrometry.
Justus-Liebig-Universität Gießen

Abschlussarbeiten
Degree Theses

Bioanalytik

Katharina Brandner, B. Sc.
Entwicklung eines zielgerichteten LC-MS basierten Assays für die Quantifizierung von Antikörpern zur Analyse von Krebserkrankungen.
Westfälische Hochschule, Gelsenkirchen

Joy Amrei Brummel, B. Sc.
Etablierung einer gezielten LC-MS/MS Analysemethode zur Untersuchung von Thrombozytenaktivierungskaskaden unter hypoxischen Bedingungen.
Technische Universität Dortmund

Rob Dahlmann, M. Sc.
Quantitativer Vergleich der Effizienz und Spezifität von Proteasen.
Hochschule Hamm-Lippstadt

Antonia Fecke, M. Sc.
Construction of relative response factor-based mass spectral library for large-scale quantitative metabolomics.
Hochschule Hamm-Lippstadt

Lennart Frederic Laube, B. Sc.
Entwicklung einer zielgerichteten proteomischen Analyse zur Untersuchung von Proteinen des zentralen Kohlenstoffstoffwechsels in einem Tumormausmodell unter Verwendung der Flüssigchromatographie-Tandem-Massenspektrometrie.
Hochschule Hamm-Lippstadt

Gina Piontek, M. Sc.
Entwicklung eines Protein-Assays zur Untersuchung der Gerinnungskaskade in humanem Blutplasma mittels LC-MS/MS.
Technische Hochschule Nürnberg

Leon Welter, B. Sc.
Entwicklung eines zielgerichteten LC-MS basierten Assays für die Quantifizierung von Antikörpern zur Analyse von Autoimmunerkrankungen.
Westfälische Hochschule, Gelsenkirchen

Biospektroskopie

Jan Sollmann, M. Sc.
Image Compression for Microscopy Images in the Era of AI: Theories, Models and Applications.
Ruhr-Universität Bochum

Translationale Forschung

Janik Ahlmann, B. Sc.
Design und additive Herstellung eines Widerstandsheizers auf Polymerbasis zur Verbesserung der analytischen Leistung in der Ionenmobilitätsspektrometrie.
Technische Universität Dortmund

Carolin Zimmer, B. Sc.
Entwicklung und Charakterisierung der Kopplung einer Papersprayionisationsquelle mit einem Ionenmobilitätsspektrometer zur schnellen Detektion von Propofol.
Hochschule Hamm-Lippstadt

Finanzen, Beschaffung, IT & Gebäudetechnik

Fabian Guth, M. Sc.
Sustainability Reporting in Research Institutions A case study in cooperation with "Leibniz-Institut für Analytische Wissenschaften – ISAS – e. V.".
Ruhr-Universität Bochum

Stipendat:innen
Scholarship Holders

Qais Al Bateineh
Jordan University of Science and Technology,
Jordanien
September 2021 – Juli 2024

Ahmed Bahti
An Najah National University,
Palästinensische Gebiete
Januar 2023 – Juni 2024

Auszeichnungen
Awards

Bioanalytik

Sven Heiles
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