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Customer Insights

MALDI Mass Spectrometry Advances Medical Research

Scientists at the University Medical Center Utrecht chart new territory in pathology research with the Bruker timsTOF fleX.

Working with Bruker

Amongst a long list of scientific collaborations, Dr. Sonnen and his team are working on a joint project with Bruker on spatial proteomics and glycomics, which integrates cell biology and medical research as a discovery tool to unravel disease mechanisms and potentially enable the development of novel treatments. Dr. Sonnen describes the possibilities of this joint project:

"We're using laser microdissection in combination with the Bruker timsTOF fleX instrument's MALDI Imaging capability, and these are the methods that could become increasingly important in the future for this field. There's a lot of potential for this technology."

University Medical Center Utrecht

The University Medical Center Utrecht (UMCU) is the main hospital of the city of Utrecht in the Netherlands. With over 11,000 employees, the hospital is one of the largest public healthcare institutions in the Netherlands, as well as the biggest employer in the region. Affiliated with Utrecht University, UMC Utrecht comprises the academic hospital, the medical school, and the Wilhelmina Children's Hospital. The UMC Utrecht and its Pathology Department also work closely with the Princess Maxima Center for child oncology in Utrecht, one of the largest centers for child oncology in Europe.

In addition to training tomorrow's healthcare workers via its medical degree program, UMCU and Utrecht University have invested heavily in research to improve healthcare for patients and to find new treatment possibilities for diseases. The hospital's Pathology Department is a forerunner in digital pathology and the implementation of artificial intelligence in its diagnostics routines. To complement its already strong research into the molecular nature of diseases, an infrastructure grant from Utrecht University and the UMCU has recently enabled the installation of a Bruker timsTOF fleX. This grant was awarded to a joint initiative between the Medical Imaging Division of the hospital and the Pathology Department. Now housed in the institute's research environment, members of the Imaging Division and the Pathology Department make heavy use of the timsTOF fleX as a molecular imager with the goal to integrate clinico-pathological data, genomics data and medical imaging data with mass spectrometry imaging data.

Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) has shown potential for improving diagnostic speed and accuracy in medical research. In particular, the technique has emerged as an important, rapid, and accurate tool for the field. Dr. Andreas Sonnen, Assistant Professor in the Department of Pathology at UMC Utrecht, describes the impact of the Bruker timsTOF fleX instrument on his team's research:

"One of our key research questions is how we can use MALDI Imaging and MS for better clinical diagnostics directly inside a pathology department, which has complex needs, standard operating procedures, and specific regulations to follow.

Our goal is to not only use the Bruker timsTOF fleX as a research tool to study various types of cancers and other diseases, but also to establish it as a reliable diagnostic imaging modality within the foreseeable future."

Investments in Medical Research

For decades, UMC Utrecht has been investigating the causes and treatments of disease with a strong emphasis on improving patient care. While much progress has been made, the hospital continues to push boundaries by unraveling the molecular mechanisms that underpin diseases and by finding new approaches for treatments that will improve patient outcomes. The long-term goal is to take these medical discoveries from the laboratory and eventually move them into clinical practice, which drew the interest of Dr. Sonnen, as he explains:

"Having trained as a biochemist/biophysicist I realized that I wanted to conduct medical research where I had access to patient samples and complex patient histories, while also working with colleagues to develop new and interesting research questions that actually mean something for the patient."

The hospital's emphasis on research has led to significant investments in new scientific technology to expand the understanding of disease. The recent acquisition of the Bruker timsTOF fleX instrument to evaluate the potential of MALDI-TOF MS in improving diagnostic speed and accuracy in medical research suits this strategy well. The initial research grant to install the instrument and to set up a MALDI mass spectrometry imaging facility was awarded to Clemens Bos and Roel Deckers, both Associate Professors from the Imaging Division and Professor Paul van Diest from the Pathology Department. Prof. Goldschmeding, pathologist, and head of the pathology research facility in which the Bruker timsTOF fleX is embedded, describes how this instrument fits into the pathology laboratory:

"We have a very modern and fully digital pathology pipeline for our diagnostics, which also includes artificial intelligence algorithms for image analysis that are now routinely used by pathologists in the department. The Bruker timsTOF fleX is part of the research facility of the department, which is open to scientists from outside and inside the UMCU. Besides large tissue banks, it includes a range of advanced technologies, such as tissue preparation devices, an intricate digital pathology platform, a laser microdissection microscope, high-end digital scanners, automated tissue stainers also for immunohistochemistry and access to molecular pathology techniques.

> *We utilize the Bruker timsTOF fleX with different applications, from small molecules and lipids up to peptides, and with different samples, fresh-frozen to fixed tissue and purified samples."*

MALDI-TOF MS with TIMS capability

Built on Bruker's pioneering timsTOF Pro platform, the timsTOF fleX is a high-speed, high-sensitivity electrospray ionization (ESI) instrument that is designed with a high spatial resolution MALDI source and stage for resolving molecular distributions and bringing a spatial dimension to Omics analyses. For medical researchers, that capability can transform proteomics analysis into spatial proteomics, glycomics into spatial glycomics, lipidomics into spatial lipidomics, and metabolomics into spatial metabolomics by providing tissue context to data.

Having shifted from the field of structural biology and cryo-electron microscopy, Dr. Sonnen considers himself relatively new to mass spectrometry. His team of students and technicians in the Pathology Department have all learned to use the instrument quickly. He explains:

"After initial training, everybody can handle the Bruker timsTOF fleX without supervision, and they are able to do measurements by themselves. Training was straightforward for them. Bruker provides fully automated workflows which makes application of the technique even easier."

Since ions produced by MALDI and ESI travel the same path to the detector from the source, MALDI workflows can take advantage of the most advanced features found in the timsTOF fleX, including trapped ion mobility separation (TIMS) based on the collisional cross section (CCS) of detected molecules. Tuning and calibration can be performed in ESI mode and used for the MALDI experiment for additional ease of optimization.

TIMS allows for the separation of molecules dependent on the shape of the ions. Ions enter the dual TIMS device together with a gas stream and are accumulated in the first section by an electrical field. The actual separation takes place in the second part of the TIMS cartridge, where ions are eluted in a temporal and spatial fashion by lowering the electrical potential. Variable ramp speed and mobility range adaptation give rise to optimization of different classes of molecules allowing high flexibility for the user.

Using CCS as an outcome of TIMS to validate the identity of an analyte offers researchers an additional quality criterion. CCS-enabled software intelligently matches spatial MALDI-TIMS imaging data with Omics results and enables vital morphological context to identification lists. Dr. Sonnen describes the impact in the UMC Utrecht's laboratory:

"We are currently testing the Bruker timsTOF fleX instrument's TIMS capabilities in the analysis of spatially resolved lipid oxidations maps. Here, the ability to sort molecules according to shape is very important."

Research Interests

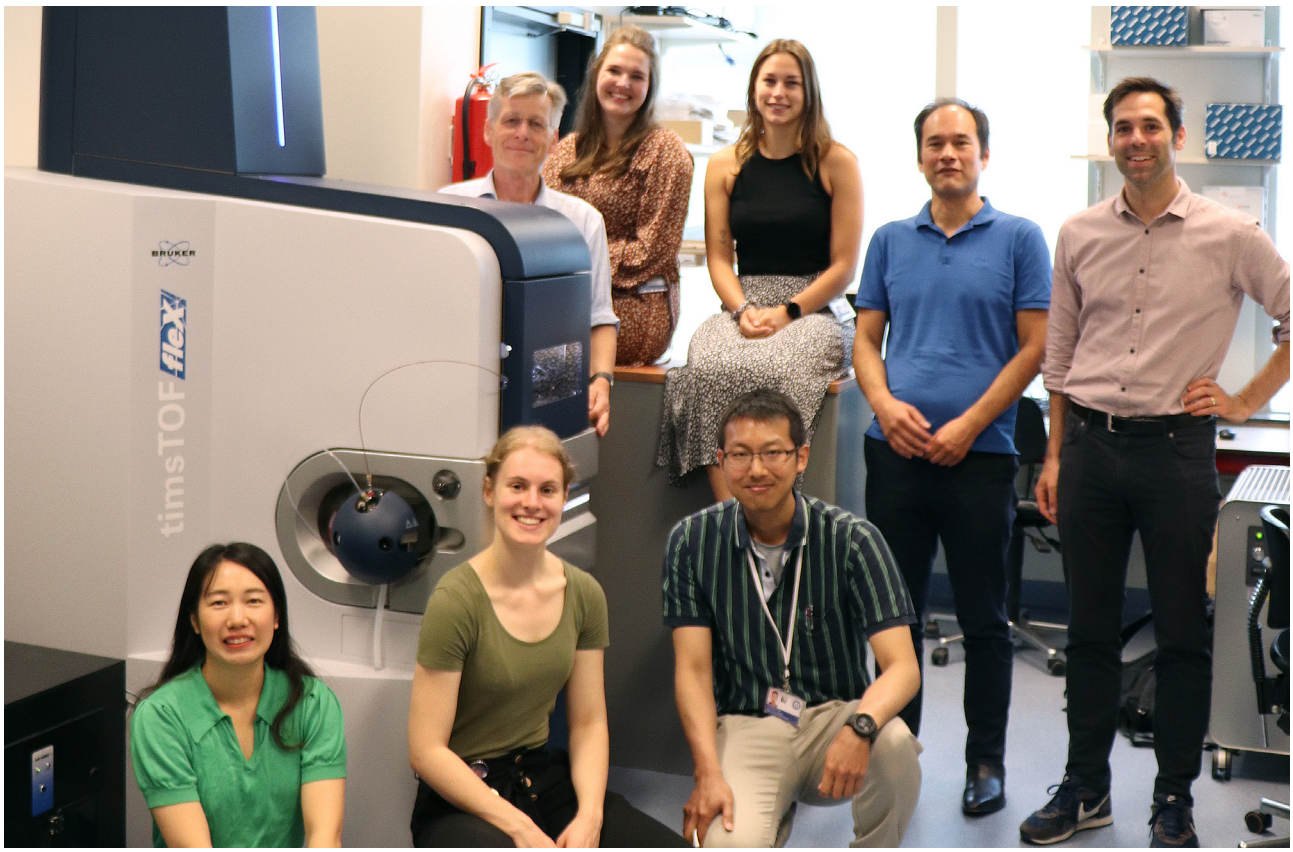
This recent implementation of the Bruker timsTOF fleX instrument at UMC Utrecht has already demonstrated new capabilities for medical research. The analyses of complex samples such as tissue sections benefit from TIMS because it can separate isobaric or isomeric metabolites, lipids, peptides or glycans to get the true spatial localization of an analyte. The timsTOF fleX offers a chance to differentiate isomeric distributions where high mass resolution fails.

Among the many research interests of UMC Utrecht's Pathology Division, the treatment of cancer is high on the list. Cancer cells have significant genetic and epigenetic modifications that influence protein expression and their metabolic state. When looking at the proteome, lipidome or metabolome, the spatial distribution of compounds contains valuable information. Understanding complex samples requires the analytical depth provided by the ion mobility option of the timsTOF fleX in addition to mass and charge.

In a collaborative effort between the Eindhoven University of Technology, Utrecht University, UMC Utrecht and recently also Wageningen University, Dr. Sonnen and collaborators look at how cold atmospheric plasma can be used in the treatment of different cancers. He describes the role of the Bruker timsTOF fleX instrument in this study:

"Plasma medicine is a new field of research. We are trying to visualize lipid and protein modifications generated by plasma treatment, mostly oxidation. We study the effects of plasma on a molecular scale using MALDI Imaging.

The Bruker timsTOF fleX gave us a large push in the project. We are excited because now we can spatially resolve the oxidation products, which was not possible before."



The microenvironment of tumors contains a combination of healthy cells, tumor cells, connective tissue, blood vessels, and inflammatory cells in different ratios. Each of these components will have their own unique molecular signature. Researchers like Dr. Sonnen's team, who study disease states often rely heavily on interpreting tissue pathology and creating molecular maps, can bridge the gap between traditional Omics and traditional histology. Dr. Sonnen explains:

"We have a research project in which we study pancreatic cancer. We aim to find different molecular biomarkers for different subtypes of pancreatic neuroendocrine tumors for which we know that there are different prognostic subclasses. To do so, we investigate these different subclasses to see whether we can use MALDI Imaging to further subclassify them, as well as to find biomarkers for them. Surprisingly, these cancers are quite heterogeneous."

A different research collaboration uses a combination of cutting-edge technologies to study pediatric and adult brain tumors. This joint effort between the Princess Máxima Center, KiTZ, the Hopp Children's Cancer Centre in Heidelberg, the Neuropathology Department in Heidelberg and the UMC Utrecht, works towards combining spatial proteomics and glycomics, with spatial transcriptomics and artificial intelligence-guided histology interpretation. Dr. Sonnen explains:

"We hope the spatial proteomics and glycomics will give us an additional layer of information that can be used for the classification of these diseases. We have an AI group inside the Pathology Division that has so far applied AI to histological stains, since our department is completely digital. We already use some of these algorithms for diagnostics.

We intend to implement the same or similar algorithms in the analysis of the MALDI images we generate in the future."

"Another important area where we are exploring the potential diagnostic value of Omics imaging is discrimination between early (T1-) colorectal carcinomas that do or don't require invasive surgery for lymph node resection. With this approach we hope to identify determinants of metastatic spread within the tumor and in its microenvironment. Currently, the vast majority of lymph node resections turn out not to contain any metastasis, so identification of such determinants will lead to an enormous reduction in surgical procedures and associated morbidity and costs."

Future Developments

While the research interests and collaborative efforts of Dr. Sonnen and his team at UMC Utrecht reflect a range of health conditions and diseases, they all hold potential in the advancement of personalized medicine, which experts believe could result in new therapies that can improve a patient's response and ensure better care.

For example, a patient's gene variations may guide the selection of drugs or treatment protocols that minimize harmful side effects or ensure more successful outcomes. Additionally, such personalized medicine approaches could also indicate an individual's susceptibility to certain diseases, allowing physicians to monitor and possibly prevent the manifestation of a future health condition. Preventive medicine works best with a network of electronic health records that link clinical and molecular information to make it easier to help patients and their physicians make appropriate treatment decisions. Dr. Sonnen explains:

"The ultimate goal is to use the Bruker timsTOF fleX to get spectral information, and maybe together with LC-MS, create a molecular map of the tumor and the tumor heterogeneity.

Based on that molecular map, physicians can decide which treatments are suited for the patient. This field is developing rapidly and finding new targets or new molecular markers for these tumors can help researchers develop other treatment possibilities in the future."

The result will be a new way to provide healthcare, where physicians can classify and treat diseases by their molecular profiles, instead of simple physical indications and symptoms. Combining this knowledge with a patient's genomic information can help medical professionals make more effective decisions for the individual patient. By enabling each patient to receive earlier diagnoses, risk assessments and optimal treatments, personalized medicine holds the promise for improving healthcare while also lowering costs. Prof. Goldschmeding and Dr. Sonnen describe their perspective on how their team's research can contribute to the field:

"We clearly see MALDI mass spectrometry imaging as a tool for personalized medicine, and not simply as a potential substitute for immunohistochemistry or other techniques. Additionally, as the treatments become more specialized, you need more information about the patient to begin with.

We will study how the Bruker timsTOF fleX can contribute to this emerging field."

For more information about UMC Utrecht, please visit https://www.umcutrecht.nl/en/.

For more information about the Bruker timsTOF fleX, please visit https://www.bruker.com/en/products-and-solutions/mass-spectrometry/timstof/timstof-flex.

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About University Medical Center Utrecht

The University Medical Center Utrecht (Dutch: Universitair Medisch Centrum Utrecht) or UMC Utrecht is the main hospital of the city of Utrecht. It is affiliated with the Utrecht University. Since the foundation of the university in 1636 an academic hospital has existed in various forms. Nowadays the UMC Utrecht comprises the academic hospital, the Faculty of Medicine as well as the Wilhelmina Children's Hospital. In total approximately 11,000 people work at the UMCU including medical staff, nursing staff, residents, support personnel and researchers, making it one of the largest hospitals in the Netherlands.

About Bruker Corporation

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