Professor Thomas Moritz

Customer Insights

Understanding metabolic diseases through small molecule analysis using the timsTOF Pro

Scientists in the Moritz Group at the Novo Nordisk Foundation Center for Basic Metabolic Research (University of Copenhagen), are using the Bruker timsTOF Pro to enhance their understanding of the metabolome.

Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen

The Moritz Group uses metabolomics approaches to study the role of metabolites and lipids in metabolism.

Working with Bruker

Thomas Moritz and his team bought their first Bruker instrument, the timsTOF Pro, in 2019, to help with large scale studies that require high-throughput analysis of metabolites and lipids.

Moritz explains, "*It was the first time that I had worked directly with Bruker. We use the timsTOF Pro across many diverse methods in a range of larger studies, and with its good detection levels for many metabolites, it helps to support our understanding of various metabolic diseases*."

Researchers in the Moritz Group at the Novo Nordisk Foundation Center for Basic Metabolic Research (CBMR)* are using metabolomics approaches to better understand the development of metabolic diseases and how effective diagnostics and treatments might be developed. Defined as the comprehensive analysis of metabolites in a biological specimen, metabolomics is an emerging technology that holds promise to inform the practice of precision medicine [1]. Using mass spectrometry (MS) as a cornerstone technology in their program, they can screen thousands of compounds or target specific compounds in diverse sample types from different biological systems. Thomas Moritz and his team in the Moritz Group are looking to uncover the basic function of metabolites in metabolism and their role in developing diseases:

"I came to CBMR in March 2019, having studied metabolomics for around 15 years. We currently focus on a broad range of metabolic diseases, from type 2 diabetes to liver diseases, and we are always trying to find new ways to understand the role of metabolites in these diseases to develop better and more personalized treatments."

Thomas Moritz is also Platform Leader of the Metabolomics Platform, one of five shared Enabling Biology and Technology Platforms at CBMR. The platform's goal is to develop analytical strategies for metabolomics-driven systems biology in personalized health strategies. The center also houses a Single-Cell Omics Platform, a Computational Chemistry Unit, a Phenomics Platform, and a Rodent Metabolic Phenotyping Platform. The platforms all work together to strengthen interdisciplinary research that transforms the basic understanding of the mechanisms involved in metabolic health and disease.

Metabolomics and its application in clinical research

Researchers in the Moritz Group look into the metabolome and fluxome in different cell types as well as perform large scale analysis on human plasma cohorts. An important part of the research is developing methodologies for analyzing the metabolome. This method development covers strategies for sample preparation, MS analysis, and data processing.

The Moritz Group works on a variety of medical research challenges including inflammatory bowel disease, inborn errors of metabolism, and the dynamic modelling of the metabolome in pancreatic β-cells during glucose-stimulated insulin secretion.
Thomas Moritz explains:

"Metabolites in our bodies are not only produced by our cells, they come also from what we eat, from food, and the microbiota that we have in our bodies. By analyzing the make-up and composition of these metabolites, we get a better idea about the molecular processes taking place in our cells.

We currently focus on a range of diseases, and my personal aim is to bring metabolomic understanding and analysis to the group leaders across the center, and in a longer perspective, to improve overall human health with more personalized and targeted treatment options."

The Metabolomics Platform is currently supported by seven staff who work across mass spectrometry, data analysis, and sample preparation. The platform offers experimental and computational services, assisting with metabolomics-based projects on a case-by-case basis. They support researchers with sample extractions, metabolomics and lipidomic analysis, analysis of labelling in stable isotope labelling experiments (fluxes), and support with biostatistics.

Thomas Moritz talks through the reason for setting up the platform to serve the whole Center:

"My research has evolved over the years, and so has the data we now have available to us. Because of this, we needed to have better metabolic analysis methods to support research capabilities across the center. We have developed new methods, started to incorporate labelling studies, and created a bioinformatic workflow to help both the platform and others requiring our research services.

Our shared goal is to support the notion of precision medicine, and the Metabolomics Platform strengthens the rest of the center in this mission."

Using trapped ion mobility spectrometry (TIMS) to achieve greater depths in metabolomic profiling

Trapped ion mobility spectrometry (TIMS) is a gas-phase separation technique that can resolve otherwise unresolvable analytes in complex samples. This in turn provides confidence in the measurement specificity and molecular characterization of metabolites and lipids. The Bruker timsTOF achieves this while simultaneously accumulating and concentrating ions of a given mass and mobility to increase both sensitivity and speed.

Since 2019, the Metabolomics Platform has relied on the Bruker timsTOF Pro for their metabolomics and lipidomics profiling experiments. Thomas Moritz explains this choice:

"Another scientist had recommended the timsTOF Pro for my research, so I was interested by the thought that this instrument could support our investigations with quicker sample times. The robust hardware of the timsTOF Pro has enabled us to undertake high throughput analysis for larger studies, as data becomes vaster and more complex.

It also has very good detection levels for many metabolites that we are trying to analyse and its stability and sensitivity are key in the work we are doing."

He continues, *"We see the Metabolomics Platform as a collaborative research facility rather than an individual research entity or traditional service facility. As such, people come to us requiring various forms of support for different research projects, and we're always working on a large number of projects.*

The timsTOF Pro has allowed for quick and easy high-resolution analysis across the unique experiments that we do."

An example of what the timsTOF Pro is currently being used for in a collaboration between the Metabolomics Platform and Group Leaders at CBMR, is measuring nicotinamide adenine dinucleotide (NAD) metabolites. NAD is a key coenzyme that joins in different energy metabolism pathways, including glycolysis, β-oxidation, and oxidative phosphorylation. It is also a required cofactor for post-translational modifications [2]. Modified levels of the NAD metabolome may embody a likely indicator of poor metabolic function. Accurate measurement of the NAD metabolome is crucial for biochemical research and developing interventions for ageing and neurodegenerative diseases [3]. The instrument allows the Moritz Group to work with large cohorts and thousands of samples, enabling a more automated approach to sample preparation and decreasing labor-intensive preparation, reducing overall experiment times.

Sensitivity is key

Another area of focus for the Moritz Group, in collaboration with a group at Rigshospitalet in Copenhagen, is in diseases arising from inborn errors of metabolism. Inborn errors are rare genetic disorders whereby defects in the enzymes and transporters responsible for supporting normal healthy physiological functions cause altered metabolism and disease, often presenting as complicated medical conditions involving several organs [5]. Thomas Moritz continues:

"We need to find out how to quickly identify genetic diseases based on their metabolic profiles, thereby find the diseases and treatments at the earliest age possible. We must constantly ask ourselves the questions, 'Can you find new biomarkers? Can you understand the disease better?'

Ultimately, we're trying to help researchers find answers to these questions through metabolomic approaches."

In 2020, the Metabolomics Platform expanded its platform with the purchase of a Bruker Impact II to support an increasing pace of sample analysis.

Moritz in the lab

A recent paper involving Moritz has looked at how mixed-mode chromatography-mass spectrometry enables targeted and untargeted screening of carboxylic acids in biological samples, using the Bruker timsTOF Pro in part of its experimental workflow. Carbohydrates, lipids, and proteins serve as sources of cell energy, with glycolysis being the primary metabolic pathway in central carbon metabolism (CCM). Research dependent on the analysis of metabolites involved in CCM requires fast separation and sensitive detection of carboxylic acids using liquid chromatography-mass spectrometry (LC-MS). Successful separation of this acid remains challenging, so the study used LC-MS to develop a new separation method to identify the metabolome secreted from human brown adipocytes. Using mass spectrometry, including the timsTOF Pro, a large number of organic acids were identified and quantified in a 10-minute sample time [4].

The team also acquired Bruker's new vacuum insulated probe heated electrospray ionization (VIP-HESI) source and routinely uses it as part of the timsTOF Pro system. Heated electrospray helps to increase ion yield and compared to standard electrospray, the offers a solid gain in sensitivity for the compounds of interest in metabolomics and pharmaceutical research. For a wide range of compounds, VIP-HESI enables sensitivities that rival those of industry-leading QQQs while still providing the known benefits of high resolution, accurate mass and true isotopic pattern. Thomas Moritz explained why the VIP-HESI has been useful to the platform:

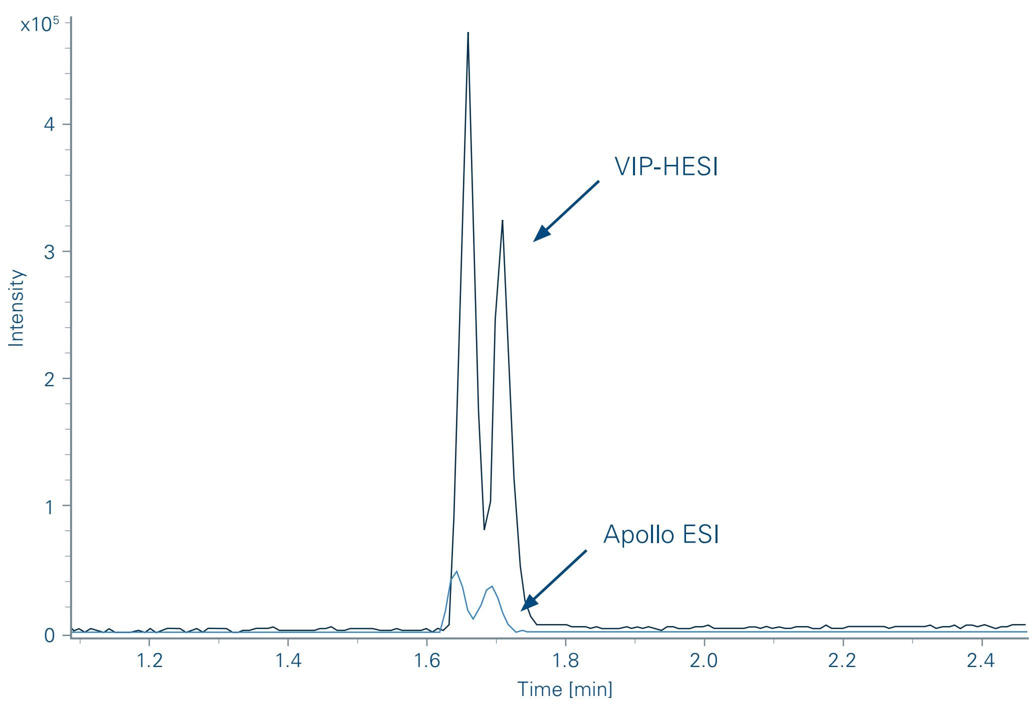
"The VIP-HESI has certainly improved our work, from two to 10 times better sensitivity when analyzing small molecules. This makes a big difference when collaborating with different partners and supporting them with their efforts."

The future of metabolomics

With precision medicine high on the agenda, the future of metabolomics presents huge opportunities for individual treatments and discoveries of new diseases. Thomas and his teams are excited about the future ahead:

"If we can expand the center in the future, we hope to be able to work more with larger cohort studies across the omics. We hope to create strategies and workflows to really understand more about the role and behavior of metabolites, to help us ask questions and support in solving more problems.

A long-term goal for the industry would be to make metabolomics part of the clinic, but in order to do this, we must make metabolic data more quantitative. To ensure we stay on this path, collaboration and sharing ideas with industry experts is key to progressing the field."



Comparison in sensitivity between VIP-HESI and Apollo ESI source.
The figure shows mass chromatogram traces for two butyryl carnitine isomers from a human plasma sample. LC-MS were performed by reversed phase chromatography and mass spectrometer was operated in positive ion mode. The increase in sensitivity varies between 2-10 times dependent on compound. LC-MS analysis by Dr. Adnan Khan, CBMR.

For more information about the timsTOF Pro, please visit https://www.bruker.com/products/mass-spectrometry-and-separations/lc-ms/o-tof/timstof-pro.html.

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About the Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen

Novo Nordisk Foundation Center for Basic Metabolic Research (CBMR) was established in 2010 at the Faculty of Health and Medical Sciences, University of Copenhagen. The vision of the center is to strengthen interdisciplinary research that transforms the basic understanding of the mechanisms involved in metabolic health and disease, and to accelerate this knowledge toward new prevention and treatment strategies. Via dynamic collaborative research projects that integrate different levels of exploration from single cell to whole body physiology, to effectively connect basic biological knowledge to translational and innovation outcomes, the Center will:

- Identify and understand fundamental mechanisms and biological pathways underlying metabolic health and disease
- Foster an environment for top level scientists and innovators of the future
- Enable a richer cultural understanding of the complexity of metabolic health and disease

For more information, please visit: https://cbmr.ku.dk/.

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