Agilent Case Study: Ghent University

How Quantifying Metals in Single Cells and Nanoparticles Is Unlocking New Areas of Research

The determination of trace elements in single cells using the ICP-MS technique is becoming a key research tool for health and biomedical researchers.

Agilent recently spoke with Frank Vanhaecke, Senior Full Professor in analytical chemistry at Ghent University in Belgium, where he is head of the Atomic and Mass Spectrometry (A&MS) research group. We discussed his application of ICP-MS for the research he undertakes.

Q. What do you use ICP-MS for in your lab?

Within our research group, ICP-MS is the star. Our main activity is the development of analytical methodologies to address real-world problems. Once we have developed the methodology, then we work with other scientists to apply the methods in various areas, including, archaeology, geo- and cosmochemistry, material sciences, the environmental sciences, and especially biomedical research.

Over time, the requests we received were becoming more and more complicated. At the same time, we also discovered new capabilities offered by more recently developed ICP-MS instruments, in terms of the elements that can be measured and the detection limits that can be achieved. So nowadays, next to bulk analysis, we are also involved in single-cell analysis—ICP-MS is used for element determination in single cells and in the nanoparticles that are used, for example as transporters of drugs.

This is carried out in cooperation with researchers from the medical faculty and from the pharmaceutical department. We share ideas about the types of measurements that are possible, and they help us understand what information they would like about their samples.

"I'm amazed by the possibility of determining elements in single cells at the femtogram levels."

Professor Frank Vanhaecke
Senior Full Professor in Analytical Chemistry
Ghent University

Q. Who are you collaborating with on your life science projects?

We are a member of the Cancer Research Institute Ghent. This is a multidisciplinary group that includes the medical and pharmaceutical faculties. One of our collaborations is with the Laboratory for Experimental Cancer Research—who are at the cutting edge of cancer research. They are not always aware of what is analytically possible, particularly as ICP-MS has historically been seen as an instrument that's mainly suitable for metals analysis. It's only with the relatively recent development of tandem ICP-MS that the technique can now also be used for trace analysis of other biologically critical elements such as sulfur and phosphorus. As a result, we've been able to unravel their samples to give them deeper insight into the origin and development of cancer.

Q. So you are doing measurements on single cells?

Yes, we analyze single cells. We use a dilute suspension of cells, and this solution is aspirated into the ICP. As each single cell passes through the ICP, its elemental content is converted into ions. We measure these ions and this gives us an indication of the content of the target element in that one cell. Using this approach we can, for example, determine the concentrations of elements that enter the cell from the use of a drug, such as a chemotherapeutic drug. Or we can measure the endogenously present elements to see whether a drug has an effect on their content.

Q. What ICP-MS system are you using?

We have eight ICP-MS systems in the lab with different capabilities, and of course also limitations. One is a quadruple-based Agilent ICP-MS instrument and we have two Agilent tandem ICP-MS units. We have high-resolution ICP-MS units, so based on the use of a sector field mass spectrometer. We have an ICP-MS instrument equipped with a time-of-flight analyzer, and we have two multicollector ICP-MS units as dedicated tools for isotopic analysis.

Q. What has been your experience working with Agilent?

Agilent attracted our attention in 2012 when they introduced the first tandem ICP-mass spectrometer, or ICP-MS/MS. I was invited to Germany for the launch of the instrument, and immediately, we had some ideas on how this instrument could be used for tackling challenging applications. Then, one of my team, Eduardo Bolea Fernandez, started his PhD on this instrument. He developed a number of exciting applications, and that led to a partnership with Agilent very shortly after our acquisition of the first instrument. When we needed to buy another single-quad ICP-MS for more routine applications, we also opted for Agilent. We have recently purchased a second Agilent tandem ICP-mass spectrometer. This second instrument can operate with a shorter dwell time, which enables it to run the faster scanning acquisitions that are required for applications with short transient signals such as single-cell ICP-MS and elemental mapping or imaging using laser ablation ICP-MS.

Q. Are there any specific measurements you are excited about?

One exciting area of our work is the elemental mapping of human tissue. This delivers spatially-resolved information showing which elements are present in different tissues, and at what concentrations, which can be very useful for our colleagues in medical departments. We have been working on hardware improvements for laser ablation ICP-MS and we think we have the fastest mapping system in the world. The system has a pixel acquisition rate for elemental maps of up to 1,000 per second (1,000 Hertz). The fast detector in our newest tandem ICP-MS instrument is a key enabler of this system.

Q. What are your research plans for the future?

I must say that I'm amazed by the possibility of determining elements in single cells at the femtogram levels. In the past it was unthinkable that these limits of detection would be achievable, but now it seems to work. Partly this is due to developments in ICP-MS capability. ICP-MS/MS instruments provide lower backgrounds and much better control of spectral overlaps, which improves detection limits, sometimes by several orders of magnitude compared to single-quadrupole instruments.

Our collaborators from the medical departments are very impressed with what we can do. Our measurements give them not only information on elemental concentrations in cells, but also a view of how different individual cells take up drugs and how they are affected by exposure to drugs. We hope this new information can lead to new insights into diseases and the mechanisms of delivering drugs to specific targets.

As well as elemental determination and speciation, we are also interested in isotopic analysis. We purchased a multicollector ICP-MS unit, which is a dedicated tool for isotopic analysis, used predominantly in areas like geo- and cosmochemistry. We have been exploring its use in the context of biomedical sciences.

We have been able to show that high precision determination of isotope ratios actually allows us to unravel biochemical processes. We have also shown that isotopic analysis is an interesting potential tool for diagnosis and prognosis. Some diseases affect the metabolism of essential mineral elements. This process impacts the elements' isotopic composition, for instance, in fluids like human serum. We've been able to show the difference in isotopic composition of some mineral elements in diseases like liver cirrhosis, different types of cancer, and diabetes.

We've also studied AIDS and HIV infection, which also seem to have an effect on iron isotope ratios.

Q. Why did you become a scientist and focus your work in this area?

I choose to study chemistry due to having a very stimulating teacher in high school. I was a bit disappointed studying chemistry at university until I discovered instrumental analytical chemistry during my MSc thesis.

I did a PhD on the topic of ICP-MS, and I seem to be very loyal as I'm still working on ICP-MS! But of course, we have seen tremendous evolution, not only in the instrumentation, but also in the application areas. That is a big driver for me—to do our best to advance the technique in any direction possible. I'm also stimulated by conversations with people from other areas of science. I come into contact with scientists from many different fields and listening to their stories and what is driving them is also very stimulating.

Q. What are your projects aiming to contribute?

For me, it's important that our work can be applied in real life. Over the years we have had some applications that have made a difference. For example, we were involved in the metabolite profiling of a new drug against tuberculosis. This drug had a long residence time in the lungs, and the traditional approach with radionuclides could not be used with human volunteers. We used ICP-MS to develop an alternative method relying on Bromine monitoring, which did not require a radiotracer. This was the first ever drug for which such ICP-MS data were accepted by the US Food and Drug Administration.

We also work in other application areas such as the environmental sciences, materials sciences, geo- and cosmochemistry, in collaboration with scientists from those fields. But our focus has shifted more and more in the direction of health and biomedical applications. I think that's because the capabilities of the latest ICP-MS instruments are enabling us to perform new types of measurements of elements associated with the biomolecules that are important in these fields.

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RA44789.6248148148

Published in the USA, February 15, 2023
5994-5233EN