

# Scientist uses mass spectrometer to weigh virus particle, von Willebrand factor

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With unprecedented sensitivity, Carnegie Mellon University's Mark Bier has characterized large viral particles and bulky von Willebrand factors using a novel mass spectrometer. These exciting results may lead to new biological discoveries and represent a step closer to rapid disease diagnosis using mass spectrometry.

"This is a new frontier in mass spectrometry research," said Bier, associate research professor and director of the Center for Molecular Analysis in the Department of Chemistry in the Mellon College of Science. "We anticipate that this work will help to advance research in proteomics, virology, molecular biology and nanotechnology." Bier will present his research Thursday, Aug. 23 at the 234th national meeting of the American Chemical Society in Boston.

Mass spectrometers, which separate molecules based on their mass-to-charge ratio, can help researchers identify compounds based on their unique mass and are routinely used to determine the weight, structure and amount of small molecules or fragments of molecules. Conventional instruments, however, are not equipped to sensitively characterize large molecules over 150 kiloDaltons (a measure of mass) at a low-charge state.

Using a Macromizer™ mass spectrometer, Bier's group successfully analyzed the outer shell of the HK97 virus. They collected a mass spectrum of the mature protein shell, which weighs 12.9 megaDaltons (12,900 kiloDaltons) and the uncleaved protein shell (17.7

megaDaltons), which revealed an unprecedented 30+ positive charges. They also collected an improved mass spectrum of a von Willebrand factor (0.2 to 1.1 megaDaltons), a protein complex in blood necessary for proper coagulation. The ability to directly mass-analyze these heavy biological molecules intact and at a low-charge state represents a new level of analysis previously unattainable using conventional detector technology, according to Bier.

Many biological molecules are too big to be analyzed efficiently at low-charge states using current mass spectrometers, so most scientists break proteins down into smaller fragments before analyzing them in the mass spectrometer. Although an effective and powerful technique, this bottom-up approach typically takes days to complete and does not allow scientists to use mass spectrometers to directly study many large, intact proteins and other macromolecular complexes.

Bier conducted his studies using a top-down approach of the intact complex using a cryodetector-based MALDI TOF mass spectrometer (Macromizer) equipped with 16 superconducting tunnel junctions. Carnegie Mellon houses the only two of these instruments in the U.S. Bier's group can use the Macromizer to measure the molecular weight of a large, intact protein or a protein complex in a matter of seconds. Because it can measure intact protein complexes, this approach also avoids the sample loss that typically occurs during the bottom-up approach.

“Our results are a first step toward our ultimate goal — to identify a virus, clotting factor or any type of large biological molecule by just weighing it or its gas-phase-generated fragments,” said Bier. “This would provide a rapid clinical tool to diagnose a viral infection or a blood disease, for example.”

Bier is collaborating with Roger Hendrix, a professor of biological

sciences at the University of Pittsburgh, who studies how the outer shell of the HK97 virus assembles. Because Hendrix characterizes viral proteins, particles and subunits that are too heavy to study using currently available mass spectrometers, Bier hopes that his data will help them discover new biology. Bier is also collaborating with Dominic Chung, a research professor in the Department of Biochemistry at the University of Washington in Seattle, and Tom Howard, a medical doctor at the VA Greater Los Angeles Healthcare System, who together study von Willebrand factors.

“Mark’s analysis by mass spectrometry displays a lot of the details about the composition of normal human plasma von Willebrand factor. This spectrum is truly amazing and very revealing,” Chung said.

Bier’s current work is part of a grant from the National Science Foundation’s (NSF) Biological Infrastructure program, which supports varied activities that provide the infrastructure for contemporary research in biology. With this NSF support, Bier is also building a next-generation heavy ion mass spectrometer.

Source: Carnegie Mellon University

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