

Carnegie Mellon scientist to build unique mass spectrometer

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Carnegie Mellon University's Mark Bier has received a \$546,000 grant from the National Science Foundation's Instrument Development for Biological Research program to build a heavy-ion mass spectrometer. This one-of-a-kind mass spectrometer will characterize with unprecedented sensitivity large biomolecules, such as intact proteins, protein complexes, virus particles and DNA. It may also provide a new tool for analyzing large man-made polymers used in nanotechnology.

"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."

While mass spectrometers are routinely used to determine the weight, structure and amount of small molecules or fragments of molecules, commercial instruments are not equipped to sensitively characterize large molecules over 150 kiloDaltons (a measure of mass). Many biological molecules are too big to be analyzed efficiently using current mass spectrometers, so most scientists have all but abandoned direct studies by mass spectrometry, according to Bier. Instead, they have resorted to a bottom-up approach, which requires scientists to break down proteins into smaller fragments before analyzing them in the mass spectrometer. Although an effective and powerful technique, this approach typically takes days to complete and does not allow scientists to use mass spectrometers to directly study large intact proteins and other

large molecules.

Bier's innovative mass spectrometer design will permit an iterative top-down approach that should measure the molecular weight of an intact protein or protein complex in a matter of seconds. Because it can measure intact protein complexes, this top-down approach will also avoid the sample loss that typically occurs during the bottom-up approach.

"Routinely mass-analyzing large protein complexes in a mass spectrometer, breaking-up the complexes and then analyzing the subunits would provide a powerful research approach," said Bier. "We hope that our new mass spectrometer will help scientists to better understand protein complexes, analyze a mixture of different protein complexes and identify previously uncharacterized particles by mass."

A typical mass spectrometer consists of three components: an ion source to electrically charge the sample; a mass analyzer to separate the newly charged ions by their unique mass-to-charge ratio; and a detector to generate a recordable ion signal. The end result is a mass spectrum of the sample, which can help reveal the sample's composition.

Bier's mass spectrometer is unique because it combines a cryodetector with a linear ion trap, which he co-invented and patented while working at Thermo Electron Corporation. Commercialized in 2002 and now used worldwide, the linear ion trap was a breakthrough over older ion traps because it operates faster and offers significantly improved sensitivity. Cryodetector technology, originally developed for particle physicists, was further developed by engineers at Comet AG in Flamatt, Switzerland, for use with mass spectrometry. To couple the cryodetector to the linear ion trap, Bier will be assisted by Randy Pedder, president of Ardara LLP, a mass spectrometry components company in Pennsylvania.

Bier is also collaborating with John Woolford, professor of biological sciences in the Mellon College of Science, who will provide ribosomal protein particles. Woolford's lab is unraveling the assembly pathway of ribosomes, cellular components that make proteins. Ribosome assembly involves hundreds of proteins and intermediate protein complexes. Bier will also acquire samples from Roger Hendrix, a professor of biological sciences at the University of Pittsburgh who studies virus assembly. Hendrix characterizes viral proteins, particles and subunits that are too heavy to study using currently available mass spectrometers. Bier will work to develop iterative methods to weigh, isolate and fragment both the large viral complexes and the ribosomal particles for further characterization.

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