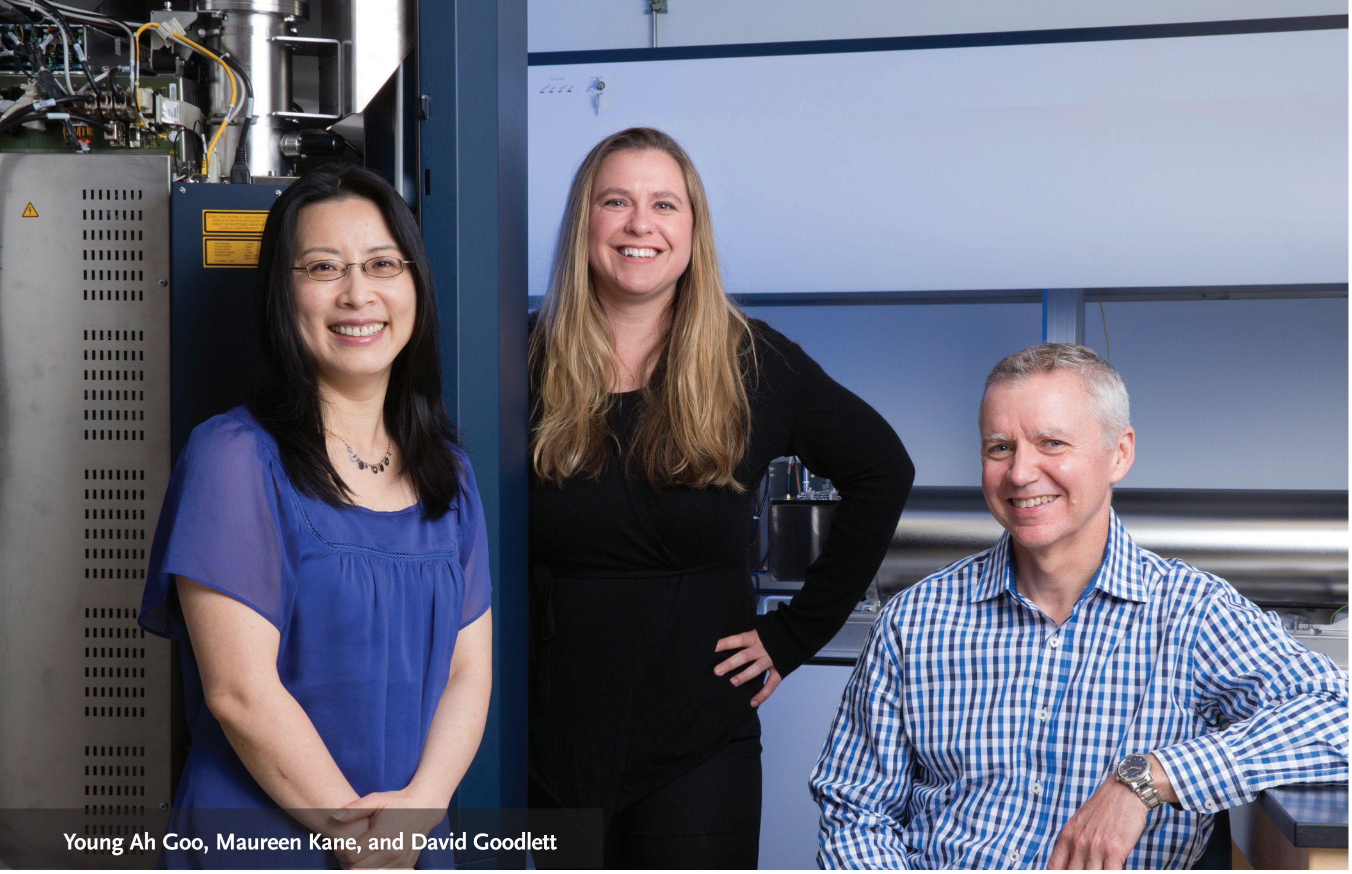


Young Ah Goo, Maureen Kane, and David Goodlett

Amazing Rebirth

Mass Spectrometry Center is now flooded with talent, potential after early 'disaster'

BY RANDOLPH FILLMORE

It may be a bit melodramatic to suggest that the School of Pharmacy's new Mass Spectrometry Center rose phoenix-like from the ashes and puddles of the School's old mass spectrometry facility after it was ravaged by fire and water. But it's true.

"Eight months into my assistant professorship, on June 28, 2010, we had a fire that destroyed all of our mass spectrometry resources, which included six instruments located in Health Sciences Facility II," recalls Maureen Kane, PhD, an assistant professor in the Department of Pharmaceutical Sciences (PSC) and co-director of the School's new Mass Spectrometry Center. "A flood ensued when the sprinklers went off. It was a world-class mess. The fire wiped out the analytical tools I needed to conduct my research program."

Fortunately for Kane, the School's Pharmacy Hall Addition, a seven-story academic, clinical, and research building, was due to open in the fall of 2010. A strategic decision was made to dedicate space on the new building's seventh floor to an expanded and enhanced mass spectrometry facility. So, for the 14 months following the fire, Kane led the instrument replacement effort and helped with space renovations in the new building, now known as Pharmacy Hall North. She also headed the acquisition effort and oversaw the installation of four instruments purchased with funds for equipping the new building and the replacement of those instruments lost in the fire and flood.

Photography by Tracey Brown

"I can't say enough about Dr. Kane's leadership, her efforts in overseeing the renovations, and her vision for a fresh start after the disaster," says Andrew Coop, PhD, professor and chair of PSC. "Mass spectrometry [which is defined in a box on page 16] has seen explosive growth in its applications over the last decade, and we have realized our strategic goal to be an unparalleled, premier center with any and all mass spectrometry capabilities under one roof."

With new instrumentation and added expertise coming on board soon after the rebirth of the facility, the School's mass spectrometry capabilities "more than doubled," says Coop. That new expertise came with the recruitment of David Goodlett, PhD, in 2012, and Young Ah Goo, PhD, in 2013, both from the University of Washington. The added capabilities — instrumental and intellectual — resulted in the world-class facility receiving center status from the University of Maryland, Baltimore (UMB) in December 2013.

Coop confirms that it took 18 months for everything to work out, but eventually Goodlett, a proven leader and visionary in his field, left his nine-year post at the University of Washington in Seattle and came on board as the center's director and the School's Isaac E. Emerson Chair of Pharmaceutical Sciences. Along with Goo, who had worked with him for many years, Goodlett brought five instruments to add to those already acquired by Kane.

A biological mass spectrometry expert, Goodlett's research centers on the structural and functional relationships in molecules such as proteins and lipids. Goo, a research assistant professor in PSC and associate director of the center, focuses on mass spectrometry-based applications to study biological questions aimed at discovering diagnostic and prognostic biomarkers and therapeutic targets for human diseases. She also runs the business aspects of the center as they engage in fee-for-service activities for collaborators and clients at UMB, in University System of Maryland institutions, and beyond.

Adding Proteomics

Prior to the fire, the facility had expertise in small molecules and metabolites/metabolomics, says Kane, but it lacked expertise in large molecules such as proteins. That changed with the arrival of Goodlett and Goo, who both have extensive experience in proteomics, the large-scale study of protein structure and function.

"The new center is now a complete toolbox," says Kane, meaning that its combined analytical expertise in both large and small molecules creates a unique research environment with experts in both kinds of molecules under one roof.

Their collective focus is on the global and systemic analysis of both large and small molecules using information about their structure and function to better understand systems biology, and also to use that knowledge in technology development.

"Proteins are the ultimate working molecules in the body," explains Goo. "We analyze large molecules — proteins or peptides — using mass spectrometry, but we can also look at small molecules — such as metabolites — which are the end product of a metabolic process and Dr. Kane's area of expertise."

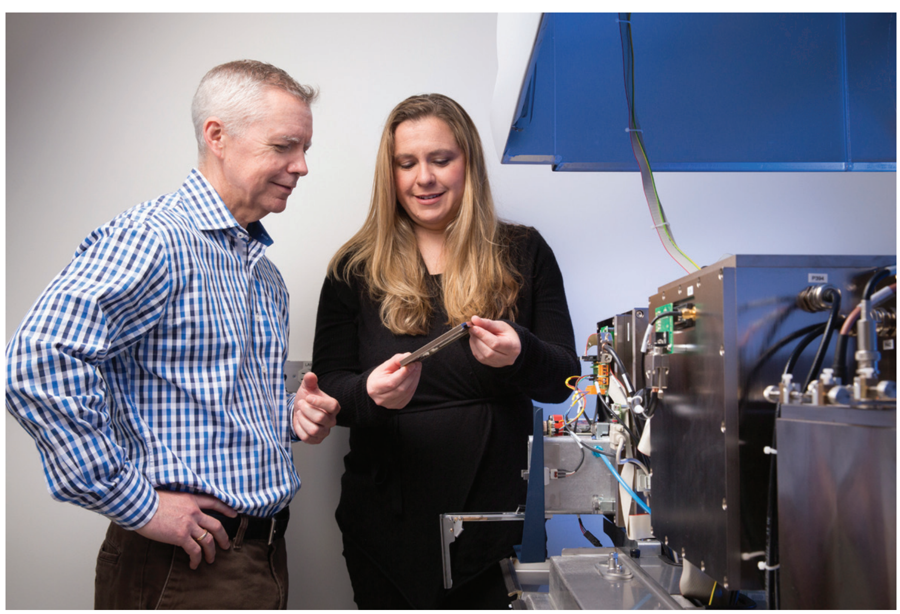
Their analysis also is aimed at understanding how proteins interact, or how they "talk" to one another in a global, systems approach.

In the analysis of small molecules or metabolites, liquid chromatography is similarly employed to separate metabolites before detecting them with mass spectrometry. And, whether used in a large-scale screening or a targeted assay, is focused on quantifying specific molecules; the metabolomic approach provides a unique representation of what is going on in the cell.

"The metabolite signature gives you a readout of what is happening now," says Kane. "It complements the proteomic data and reveals unique information about physiological changes that can result from disease, a toxic insult, or a drug treatment."

Open for Business

The *Field of Dreams* line "build it and they will come" aptly applies to the new Mass Spectrometry Center. Clients from UMB, other universities in the area, and collaborators from



Goodlett brought five instruments to add to those already acquired by Kane.

around the globe are relying on the center to help further their research by furnishing what one researcher calls "incredible data."

Joseph Mougous, PhD, an associate professor of microbiology at the University of Washington, and John Whitney, PhD, a postdoctoral fellow at the university, are using the center's mass spectrometry capabilities to help discover effector proteins, important for the actions of bacteria, but present at vanishingly small levels in bacterial cells.

"We began our collaboration with Drs. Goodlett and Goo before they relocated to the University of Maryland," says Mougous. "I am pleasantly surprised that the thousands of miles between us now have not slowed our rate of progress. We've sent complex samples for quantitative proteomics analysis on a Monday and gotten back incredible data by week's end."

Getting "incredible data" is an interest for Mark Marten, PhD, MS, a professor in the Department of Chemical, Biochemical and Environmental Engineering at the University of Maryland, Baltimore County who will be using the center's services to further his genetic research aimed at understanding what he calls "the underlying genetic network."

"Their tools are much more sensitive than any others around, allowing us to generate better data and come to better understandings," explains Marten.

Besides researchers from other universities, researchers from within the School of Pharmacy and the other schools at UMB are lining up to use the center. For example, Kane is collaborating with James Polli, PhD, the School's Shangraw/Noxell Endowed Chair in Industrial Pharmacy and Pharmaceutics in PSC, to use mass spectrometry to analyze and quantify the pharmacokinetics of a generic epilepsy drug as compared to the patented drug.

"Cutting-edge pharmaceutical research requires cutting-edge bioanalytical methods," says Polli. "The Mass Spectrometry Center is a necessary complement to our drug delivery and clinical research. Without it, we would be at a competitive disadvantage."

What The Future Holds

"There has been a shift in mass spectrometry applications for protein research," explains Goodlett. "In the past, we have been using a 'bottom up' perspective that digests proteins into smaller peptides. With this approach we can lose track of which peptides came from which proteins. With new instrumentation, we can now take a 'top down' approach, which is more accurate. However, the process of sequencing whole proteins is not as simple as for peptides."

WHAT IS MASS SPECTROMETRY?

Mass spectrometry is an analytical technique and accompanying technology that produces a spectrum of the masses of atoms or molecules in a sample. The spectrum is used to determine the "fingerprint," or signature of the sample, whether in terms of mass or chemistry. The analysis works by first ionizing — or charging by electron bombardment, among other methods — molecules or fragments of molecules and measuring their mass-to-charge ratio. The process is similar for solids, liquids, or gases. The atoms or molecules in the sample can be identified by comparing their determined masses to known masses, or through patterns of fragmentation characteristic of known masses.

The mass spectrometer has three major components: the ion source, a mass analyzer, and a detector. The ions are transported to the mass analyzer via magnetic or electric fields. Data gathered are in the form of a mass spectrum. A pharmacokinetic analysis using mass spectrometry seeks information related to dose and metabolism.

Proteomics, the large-scale analysis of proteins using mass spectrometry, seeks information about the identification and quantification of hundreds to thousands of proteins simultaneously, determines translational modifications and protein-protein interactions, and ultimately characterizes proteins. Metabolomics is the analysis of small molecules, or metabolites, which are the products of biological processes and are often key signals that direct cellular events.

To help with the complex issues of interpreting protein spectra, the center hired David Kilgour, PhD, CChem, in early 2014.

"Dr. Kilgour brings significant experience in both the development of instrumentation for mass spectrometry and the application of artificial intelligence in the next generation of data processing software," says Goodlett. "He joins the center from the University of Warwick in the United Kingdom and brings unique perspectives from his previous eight years at the UK's Ministry of Defense."

Goodlett also is working on applications with miniaturized mass spectrometry instrumentation and new ways to profile and identify bacteria more quickly. The current method of identification requires a time-consuming, preliminary pure culture, he explains. The new method skips the culturing step. Besides saving time, the new method can identify components in complex mixtures, such as wounds or urine, and see changes in molecular structure, which indicate antibiotic resistance such as with MRSA (Methicillin-resistant *Staphylococcus aureus*).

Kane also is adding another dimension to her metabolomics work through mass spectrometry imaging. In this type of work, spectra are collected at many points in a grid-like array across the surface of a slice of tissue. The resultant mass spectrometry images create a spatial map of the molecular fingerprint. She is using this technique to characterize biomarkers in regions of tissue damage and also to localize the distribution of drugs and drug metabolites within tissue.

While the mission of the center is driven by research and its fee-for-service activities, Goodlett embraces education as a third component. He aims to eventually begin a formal program of instruction for those seeking expertise in mass spectrometry, either for research or in practical applications.

Coop shares that vision and sees the educational mission as an additional return on the bigger and better Mass Spectrometry Center investment.

"We owe much to Dean Eddington and President Perman for their support," says Coop. "They shared the vision and helped make the Mass Spectrometry Center an unparalleled asset for the School of Pharmacy, UMB, and beyond." ☀

MASS SPECTROMETRY CENTER AT A GLANCE

The expertise and experience of the Mass Spectrometry Center staff span a broad range of biomedical research from basic biology and medicine to technology development and translational research including: chemical biology; pharmaceutical biology; cancer biology; microbial biology; infectious disease; metabolic disease; chronic pain research; quantitative biosciences; translational and regulatory sciences; nanotechnology; instrumentation; bioinformatics and technology development.

The center is home to 15 state-of-the-art mass spectrometers for use in biomedical research and technology development:

- AB Sciex 5500 QTRAP Hybrid Tandem Quadrupole - Linear Ion Trap Mass Spectrometer with a Shimadzu Prominence UFLCXR
- Agilent 7700 ICP-MS Inductively Coupled Plasma Mass Spectrometer
- Bruker AmaZon X Ion Trap Mass Spectrometer
- Bruker Autoflex Speed MALDI-TOF/TOF Mass Spectrometer
- Bruker UltrafleXtreme MALDI TOF/TOF Mass Spectrometer
- Bruker Solarix 12 Tesla Fourier Transform-Ion Cyclotron Resonance Mass Spectrometer
- Thermo Q-Exactive Quadrupole-Obitrap Mass Spectrometer with Waters NanoACQUITY UPLC
- Thermo Exactive Orbitrap Mass Spectrometer
- Thermo TSQ Quantum Ultra Triple Stage Quadrupole Mass Spectrometer with Dual Pump Dionex UltiMate 3000 Rapid Separation UHPLC
- Thermo Orbitrap Elite Hybrid Mass Spectrometer with Waters NanoACQUITY UPLC
- Thermo Orbitrap Fusion Tribrid Mass Spectrometer
- Waters ACQUITY TQD Tandem Quadrupole Mass Spectrometer with Alliance HPLC
- Waters ACQUITY TQD Tandem Quadrupole Mass Spectrometer with AQUITY H-Class UPLC
- Waters SYNAPT G2 HDMS Q-TOF Mass Spectrometer with Ion Mobility Separation coupled with Nano ACQUITY UPLC System with HDX Technology
- Waters SYNAPT G2S HDMS Q-TOF Mass Spectrometer with Ion Mobility Separation