New studies power legacy of UW-Madison research, 60 years later

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Frederick Crane was a researcher under David E. Green in the mid-1950s, during the early days of the University of Wisconsin-Madison Enzyme Institute, when he made his defining discovery.

The lab group was on a mission to determine, bit by bit, how mitochondria—the power plants of cells—generate the energy required to sustain life. What Crane found, a compound called coenzyme Q, was a missing piece of the puzzle and became a major part of the legacy of mitochondrial research at UW-Madison. But it was no accident.

"It was the result of a long train of investigation into a mechanism of, and compounds involved in, biological energy conversion," Crane wrote in a 2007 review article of his discovery.

Almost six decades later, that "long train" has grown even longer. Dave Pagliarini, a UW-Madison assistant professor of biochemistry, has established a new laboratory studying these dynamic organelles, the mitochondria. He recently published two studies shedding more light on coenzyme Q and how it's made, one in the *Proceedings of the National Academy of Science* (*PNAS*) in October and another today in *Molecular Cell*.

"Mitochondria are tiny structures in nearly all of our cells that are essential for producing our cellular energy and that house a wide array of metabolic processes," Pagliarini says. "When mitochondria don't work properly, many different human diseases can arise."

These include cerebellar ataxia, certain kidney diseases and severe childhood-onset multisystemic disease. Coenzyme Q deficiency is a hallmark of these diseases, but scientists aren't sure why.

"Nearly 60 years later, there is still much we don't know about how mitochondria make coenzyme Q and that has complicated our ability to target this pathway therapeutically," Pagliarini says.

The new studies, he says, are about two proteins known to be important in the coenzyme Q production pathway. Mutations in them lead to human disease. But before now, no one knew a thing about their biochemical functions.

One of these proteins is COQ9, and graduate student Danielle Lohman, co-lead author of the *PNAS* study, explains it's somehow involved in making coenzyme Q in mitochondria. The other lead author is Farhad Forouhar at Columbia University.

The study team—which includes researchers from UW-Madison and other universities in the U.S. and Spain—found COQ9 is essential for coenzyme Q production in mice. To study what it looks like, they created crystals of COQ9 in the lab and found it binds to compounds like coenzyme Q.

The team also found that COQ9 cooperates with another protein called COQ7, lending credence to the prevailing notion in the field that coenzyme Q is made through the actions of a collaborative complex of proteins.

Currently, Pagliarini and Lohman believe COQ9 may grab hold of immature coenzyme Q and help it along in its development, but more work is needed to find out. The current study gives them a place to start.

"We went from not knowing why this protein would be needed to make coenzyme Q, to having a model for what it might be doing," Lohman says.

Two other graduate students in Pagliarini's lab, Jonathan Stefely and Andrew Reidenbach, worked together to lead the *Molecular Cell* study of a human mitochondrial protein also involved in building coenzyme Q, called ADCK3.

"Like COQ9, there are patients with mutations in ADCK3 who have really bad cerebellar ataxia, described in the medical literature not too long ago," says Stefely.

Also like COQ9, ADCK3's biochemical function was previously unknown. The research team—from UW-Madison, the University of Georgia and the University of San Diego—similarly created a crystal of the protein and determined the protein family it's related to: the kinase superfamily. Craig Bingman, a research scientist at UW-Madison, performed the challenging crystal work.

While solving the crystal structure revealed the protein's genealogy, it also provided the researchers with information that could have implications for cancer and other cellular processes that may rely on the actions of this protein and its close relatives. It provides a platform for further discovery.

"It has some very specific and unique features that separate it from the rest of this kinase superfamily," says Reidenbach.

"We were also able to show the first enzymatic activity for ADCK3, which was a major milestone in this field," Stefely adds.

With these mitochondrial proteins and many others, much is still

unknown. They represent an untapped resource, Pagliarini says, but the mining for answers is happening right here, where coenzyme Q was first found.

In his lab, Pagliarini is on a quest to describe the hundreds of mitochondrial proteins with functions yet unknown. With colleagues, he has amassed a collection of them in an inventory they've called the MitoCarta.

"I stumbled into mitochondrial biology early in my graduate career and spent my postdoctoral years systematically identifying new mitochondrial proteins" says Pagliarini. "Now, I am very interested in annotating the functions of these 'orphan' proteins."

For Pagliarini and his students—the future of UW-Madison mitochondrial research—the old, yet still-wide-open field of study offers plenty of opportunity for curiosity, and promise.

"It gives you a sense of wonder; for me, like all scientists, I just want to know how things work," says Lohman. "This seemed like fruit ripe for the picking."

Provided by University of Wisconsin-Madison

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