Pioneers in kidney research

WHEN JAMES CALVET, PH.D., CAME TO WORK AT THE UNIVERSITY OF KANSAS MEDICAL CENTER IN 1981, HE DIDN’T KNOW ANYTHING ABOUT THE KIDNEY.

Calvet’s background was genetics and cell biology. He’d just finished postdoctoral studies at the Worcester Foundation for Experimental Biology in Massachusetts, where he had been researching the mechanisms of gene expression and ribonucleic acid (RNA) structures in cultured cells—the HeLa cells made famous in Rebecca Skloot’s bestselling “The Immortal Life of Henrietta Lacks”.

“I was one of the people growing here and liters of those cells,” says Calvet, now a professor in KU’s Department of Biochemistry and Molecular Biology. Watching as newly synthesized RNAs turned into messenger RNAs, he eventually discovered new ways to determine how RNA worked without extracting it from cells. It had nothing specifically to do with the kidney.

Three decades later, however, Calvet would be recognized as an international authority on kidney research. In April 2011, at a ceremony in Vancouver, British Columbia, he was awarded the Lillian Jean Kaplan international authority on kidney research. In April 2011, at a ceremony in Vancouver, British Columbia, he was awarded the Lillian Jean Kaplan International Award for Research in Nephrology’s Homer Smith Award, the association’s highest honor, as well as its John P. Peters Award for substantial research achievements and sustained achievements.

PKD is not the world’s most common kidney disease—approximately 600,000 people in the U.S. have it, out of the 26 million American adults who have chronic kidney disease. But it is one of the most common life-threatening genetic diseases—more widespread than cystic fibrosis, muscular dystrophy, hemophilia and sickle cell anemia combined.

For people who have inherited the mutated PKD gene, cysts probably begin growing in their kidneys before they are born, Calvet says. But patients can be asymptomatic for years. “By ultrasound, you would see a person in their 20s or 30s who has many cysts but the kidney will function normally for years,” he says. “Patients can have these huge kidneys, carrying this weight and this mass. They can be uncomfortable but their kidneys still function.”

When he turned his attention toward kidney research, Calvet wanted to know what it was about mutations in PKD genes that led to PKD growth. Examining the behavior of cells in culture, Calvet and his colleagues determined that the intracellular second messenger molecule known as cyclic AMP was causing fluid secretion at the same rate as it was being absorbed. In 2005, PKD researchers would use this information to develop drugs designed to block cell proliferation and cyst-filling fluid secretion in animal models. By 2005, the first patients were enrolled in studies.

Among the patients now on tolvaptan trials is Nicole Harr, 45, who was diagnosed with PKD about 10 years ago.

“All of the relatively common problems in those with PKD or any of the renal cystic diseases is an inability to concentrate urine,” Gattone explains. “It just has to slow down the process. If we could change the trajectory of this disease, essentially a patient’s kidneys would outlive them.”

“My was diagnosed I was really worried because my dad and my grandfather both had PKD and they both passed away at around 57 years old,” Harr says. “My dad was very, very ill at the end of his life.”

Harr’s father and grandfather came from generations of people who didn’t talk about their medical problems.

“I knew what PKD was, but just basically that you had cysts on your kid- neys and eventually your kidneys don’t work,” she says. Harr educated herself and sought specialists, ultimately finding Frances Winkworth, an associate professor of nephrology in the KU School of Medicine, who suggested that she take part in the tolvaptan trial.

As part of the study, Harr makes regular visits for blood and urine tests and has an MRI scan once a year. She hopes that tolvaptan is slowing the progression of her disease, though she can’t tell for certain whether it is. But she has other reasons for taking part in the study.

“I have two children. I don’t know whether they have PKD or not, but I want to do whatever I can to help with the research.”

KU scientists are trying to solve some of the world’s biggest kidney problems. Their research helped attract the kidney institute’s new director, Alan Yu, M.D., who came to KU last year from Keck School of Medicine at the University of Southern California. Yu is also the new director of the medical center’s Division of Nephrology and Hypertension.

“KU has a fantastic reputation for kidney clinical care and research,” Yu says. “It’s definitely one of the top kidney programs in the country.”

In his own work as a transport physiologist—understanding how compounds such as salt and water pass across the membranes junctions between cells—complements the work historically done at KU, he says.

“Jared Grantham was a transport physiologist when the world wasn’t that much all that was done in kidney research, and he made a seminal discovery in how we make urine,” Yu says.

Now, Yu says, scientists have moved on to solving the 3-D structure of proteins so they can design drugs that work.

“If tolvaptan works,” he adds, “it’s the first clinical treatment of PKD. We are right on the doorstep of finding a treatment. It would be revolutionary to have any drug that could work for this disease.”

Calvet says a drug doesn’t have to eradicate PKD in order for it to work. “I just has to slow down the process. If we could change the trajectory of the disease, essentially a patient’s kidneys would outlive them.”

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BY CJ Janovy

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When he arrived at KU, Calvet found himself among physician scientists who had helped establish the field of nephrology. The chair of Calvet’s department, Kurt Ebner, Ph.D., introduced him to Jared Grantham, M.D., who had been among the first to develop an understanding of polycystic kidney disease (PKD), leading to new treatments and the promise of a cure.

When he turned his attention toward kidney research, Calvet wanted to know what it was about mutations in PKD genes that led to PKD growth. Examining the behavior of cells in culture, Calvet and his colleagues determined that the intracellular second messenger molecule known as cyclic AMP was causing fluid secretion at the same rate as it was being absorbed. In 2005, PKD researchers would use this information to develop drugs designed to block cell proliferation and cyst-filling fluid secretion in animal models. By 2005, the first patients were enrolled in studies.

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SUMMER 2012

KANSAS MEDICINE + SCIENCE