New drug shows promise for kidney disease

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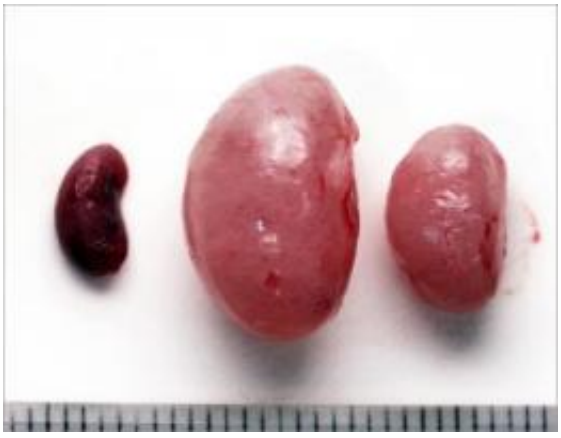

On the left is a kidney of a normal mouse. The middle kidney is from a mouse with polycystic kidney disease, and on the right is a kidney of a mouse with polycystic kidney disease after treatment with FC-rapa. Credit: Weimbs lab, University of California - Santa Barbara

Scientists at UC Santa Barbara have demonstrated in the laboratory that a new drug is effective in treating a very common kidney disease — although it will be a few years before it becomes available for clinical testing. The findings resulted from a collaboration between UCSB and a biotech firm based in Indiana. The study is published in this week's *Journal of the American Society of Nephrology*.

Over 600,000 people in the U.S., and 12 million worldwide, are affected by the inherited kidney disease known as autosomal-dominant polycystic kidney disease (ADPKD or PKD). The disease is characterized by the

proliferation of thousands of cysts that eventually debilitate the kidneys, causing kidney failure in half of all patients by the time they reach age 50. PKD is one of the leading causes of renal failure in the U.S.

The research effort was directed by Thomas Weimbs, associate professor in the Department of Molecular, Cellular, and Developmental Biology. He has been studying the disease for more than a decade. The current findings build on research performed in 2006 in the Weimbs lab, showing that the drug rapamycin, which has been in use for years as an immunosuppressive agent, was highly effective in stopping disease progression in mouse models of polycystic kidney disease.

The previous research by Weimbs came to the attention of Christopher P. Leamon, vice president for research of the biotech firm Endocyte, Inc., which is based in Indiana and focuses on cancer drugs. Leamon was particularly interested in the rapamycin research because Leamon himself has polycystic kidney disease. He immediately contacted Weimbs and flew out to Santa Barbara to develop a research partnership on a new drug for PKD — based on Weimbs' earlier research.

Weimbs said he was very excited to begin brainstorming ideas with Leamon. "He is at the right place at the right time to do something about his own disease," said Weimbs. "He happens to be the chief scientist at a biopharmaceutical company that may have the technology to make a better drug that could work for PKD patients."

In an earlier study by Weimbs and other researchers, a signaling protein called mTOR was found to drive cyst growth in polycystic kidney disease. Weimbs then found that rapamycin inhibited the growth of cysts, which caused great excitement in the field. However, when the drug was used in large clinical trials in Europe, the results were disappointing. The dose at which this drug could safely be used proved too low to affect kidney cysts.

But Leamon and Weimbs found a way around this problem. Endocyte Inc., Leamon's firm, specializes in linking or "conjugating" small molecules to target diseased cells, primarily cancer cells. Leamon explained that many cancers have a high affinity for folate, and that by linking folate to certain cancer drugs, his company has been successful in targeting cancer cells with these drugs. Leamon and Weimbs wondered if the same strategy could be used in treating the kidney cysts found in PKD. They examined both mouse and human PKD cysts and found that they did, in fact, express folate receptors.

Endocyte chemically synthesized a new version of rapamycin called folate-conjugated rapamycin (FC-rapa). Weimbs' laboratory tested this new drug and found that it was still highly effective in preventing kidney cyst growth in mice with PKD, but that it had fewer systemic side effects compared to regular rapamycin. The results suggest that FC-rapa could also be effective in human PKD patients without causing the significant unwanted side effects of regular rapamycin.

"FC-rapa is a fascinating drug because it combines an extremely specific drug with a delivery approach that targets it to a specific organ, the kidney," said Weimbs. "Rapamycin is already one of the most specific drugs on a molecular level, as it only affects the mTOR protein. The problem is that mTOR is needed in many tissues and organs, which causes the side effects of rapamycin. Delivering rapamycin preferentially to the kidneys — in the form of FC-rapa — gets around this problem."

In 2006, based on Weimbs' findings, Leamon began taking regular rapamycin for his diseased kidneys, with the permission of his doctor. The treatment was ineffective, and he eventually had kidney failure. In 2010, he underwent a kidney transplant, thanks to the donation of his sister's kidney, and says he is now in perfect health. However, he remains committed to finding a cure for polycystic kidney disease.

"Hopefully, this story is ongoing, and we can find an effective drug for treating this disease," said Leamon.

Weimbs said they will repeat the FC-rapa tests in his lab, and include testing of some similar drugs. "After that, the research may progress to phase one clinical trials for safety, and phase two clinical trials for efficacy," he said.

Provided by University of California - Santa Barbara