Promising Proteases Have Potential To Reverse Incurable Kidney Disease

Tufts Medical Center
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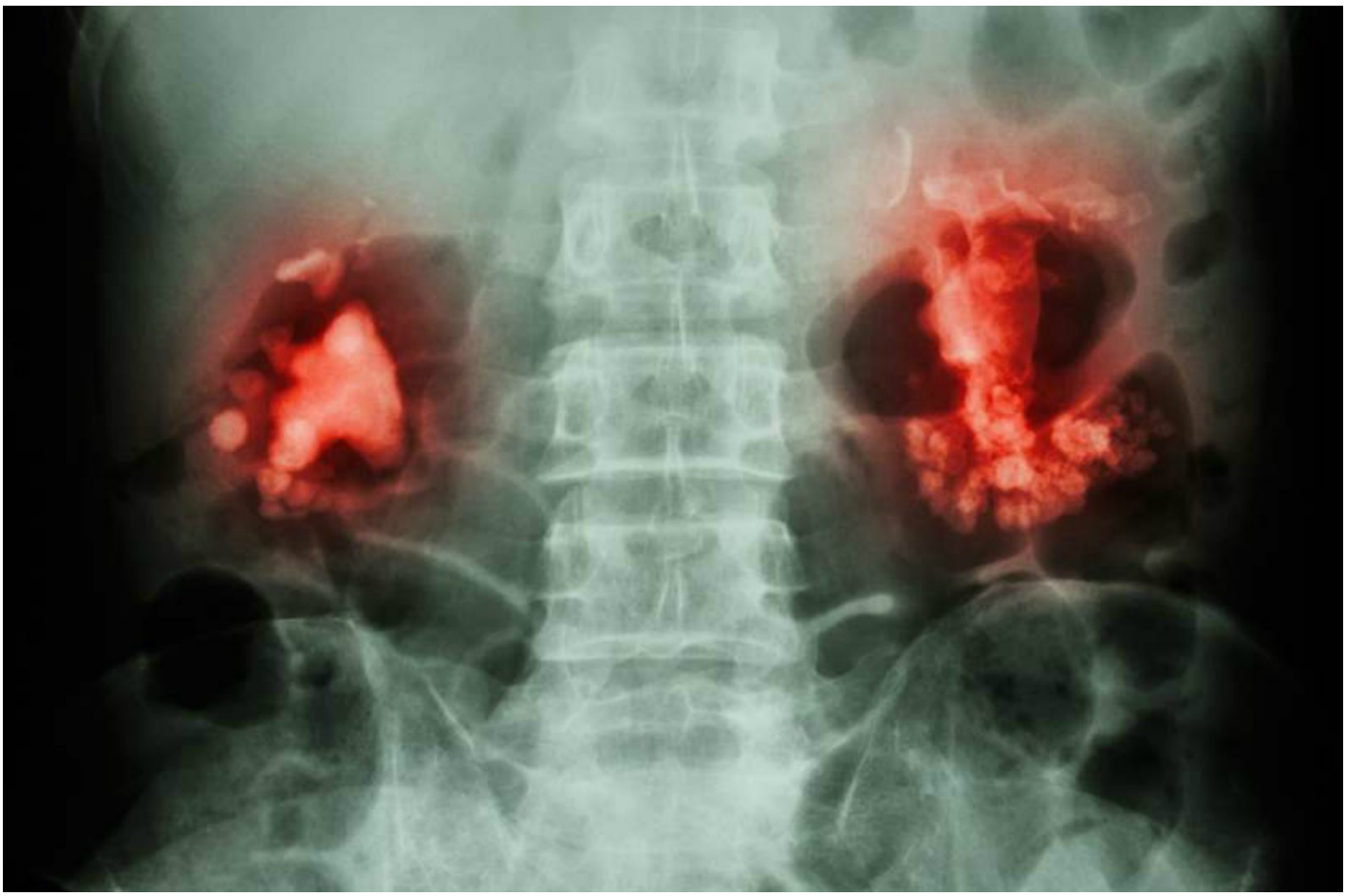

As diseases go, IgA nephropathy (IgAN) has a low profile among Americans. A disorder that can lead to total kidney failure, it is present in the United States, but it is much more prevalent in Asia. Often, it is not recognized until it is far along.

"Several factors make this illness fly under the radar in the Western world," says Andrew G. Plaut, M.D., a professor of medicine at Tufts University School of Medicine in Boston. "It's not common in the West, it has a very slow progression and it requires a kidney biopsy for diagnosis — a procedure many clinicians are reluctant to order because effective treatment is not available.

"The illness is common in Japan, which screens children for IgAN rigorously. It's estimated that more than 1 percent of the population in China is afflicted with it. Singapore and South Korea have similar numbers, and it's probably abundant in India. It's a serious problem but there really are no effective treatments and no cures."

That, hopefully, will change as a result of work done by Plaut and Jiazhou Qiu, M.D., at Tufts Medical Center, where they've pioneered techniques of using proteases — enzymes whose many functions include roles in immunity — to eliminate IgA1 protein from kidneys and clear the disease. Patented by Tufts Medical Center in 2003, development of the technology is in the preclinical stage by IGAN Biosciences Inc., a Boston-based company founded by Plaut and Qiu, and by BioMarin Pharmaceutical Inc. in Novato, Calif.

IgA Nephropathy

IgAN develops when immunoglobulin A(IgA1) proteins in the blood accumulate in an affected kidney's million glomeruli — the tiny capillaries that filter wastes from the bloodstream. As these deposits build up over time, the glomeruli become inflamed and damaged, slowly losing function and eventually closing down altogether. Treatment has generally been focused on drugs that limit inflammation, but, at best, they only slow the loss of kidney function.

> *IgA is one of five major types of antibodies — gamma globulin proteins found in bodily fluids — that play important roles in fighting off pathogens. IgA1, present in the blood of all healthy persons, is the version of IgA that causes IgAN.*

"In patients with IgAN, the protein is already a bit larger than normal as it circulates in the plasma," Plaut notes.

"It also has a tendency to aggregate into small clumps. And it looks like an abnormal protein to the immune system, which binds antibodies to it — making it even bigger. As it passes through the glomeruli, it settles, building up and degrading the kidney's ability to function."

Numbers of patients with IgAN are hard to pin down, since the only definite numbers apply to the 40 percent of IgAN sufferers who have progressed to end stage renal failure. An IGAN Biosciences analysis suggests as many as 125,000 cases of IgAN in the United States and, because of large Asian populations, as many as 2 million worldwide. Regardless, IgAN is considered to be the most common cause of glomerulonephritis worldwide, and one of the leading causes of kidney failure.

It's not even clear what causes the disease. There appears to be a genetic factor that groups it in families, and perhaps among populations, but it isn't understood. The incidence of IgAN is low among Africans and high among members of the Zuni Indian tribe in the American Southwest. Asian countries like Japan and China may report higher levels because they are more likely to screen for it.

"It's most likely underdiagnosed," Plaut says, "because biopsying someone's kidney to prove a diagnosis is pretty invasive — it requires a long needle, some pain and potential risk. And since there aren't any cures, diagnosing it may be a Pyrrhic victory."

The Protease Approach

Working with bacteria in the 1970s, Plaut realized that an IgA protease produced by a bacterium called Haemophilus influenza — already known to help bacteria avoid immune attack by IgA antibodies — could be used to clear IgA1 proteins. Proteases are proteolytic enzymes found in living organisms — they have the ability to cut proteins. Hundreds of types are known, ranging from papain, the agent in meat tenderizer, to the virus protease targeted in HIV therapy.

"We studied the unique IgA proteases for a long time," Plaut notes. "In the 1980s we began to gain insight as to how these enzymes could be used to cut the human IgA1 molecule. It's effective for bacteria because it cuts IgA antibody in

half, making it useless. And the only thing that it cuts is IgA1. This makes it very useful for our treatment plan."

Understanding the concept of cutting a protein is different from having a protease that can clear it from a kidney. One question was whether IgA1 in the kidney is permanently attached to the glomeruli. The answer turned out to be no. While recurrences develop in IgAN patients who receive transplants of non-IgAN kidneys, in cases where non-IgAN patients (mistakenly) receive IgAN kidneys, the IgA proteins disappear from the kidneys within weeks.

The next question was how much enzyme was needed. The answer was a lot. Qiu, who began working with Plaut as a member of the scientific staff in 1987, first focused on growing the bacteria and identifying interactions between the enzyme and human IgA1.

"During the 1990s," he notes, "I worked on purifying the enzyme. It was difficult to get the high levels needed for animal studies."

Working with a Case Western Reserve University team headed by Michael E. Lamm, M.D., and Steven Emancipator, M.D., Plaut and Qiu conducted animal tests in 2004. They demonstrated that the protease efficiently removed some 85 percent of human IgA1 they had deposited into the kidneys of mice. The group published the results in the American Journal of Pathology in January 2008.

Seeking a Partner

While Plaut's and Qiu's initial research was supported by National Institutes of Health grants, it became clear early on that developing the protease concept further would require additional, outside funding.

"Andrew and Jiazhou disclosed their invention to us in 2003," notes Nina Green, director of the Office for Technology Licensing and Industry Collaboration at Tufts Medical Center. "We filed a patent and immediately began seeking a corporate partner to work with us.

"Andrew felt very passionate about this work. Progress was slow. Some companies said it was too early in the development process, and Andrew and Jiazhou decided to start their own company." They secured private funding from a senior portfolio manager at Boston-based Ironwood Investment Management.

IGAN Biosciences was founded in 2005, with Plaut serving as chief medical officer and Qiu as chief scientific officer. Tufts executed an exclusive license with the company in 2007. That same year, IGAN began collaboration with BioMarin in California.

"Preclinical work is something BioMarin is good at," Qiu says. "They're doing the animal testing, developing techniques for producing the protease in large amounts, everything needed to take the product to the Food and Drug Administration to apply for clinical trials." It's a three-party agreement between Tufts Medical Center, IGAN and BioMarin.

While BioMarin is working with the original protease version, Plaut and Qiu have moved on to a second generation, filing a patent in 2009 to modify the protein to make it smaller.

"Todd Holyoak, Ph.D., a colleague at the University of Kansas, worked with us to develop an image — a crystal structure — of the protein so that we can understand how it's shaped," Plaut notes. "If we want to make changes, knowing the structure can tell us where the changes would be tolerated. I'm prepared to see obstacles rise up, but everything we've seen in the animal studies is favorable.

"As many as 40 percent of IgAN patients go on to experience complete kidney failure and the need for renal dialysis or a kidney transplant. This is a disease that severely impacts people's lives. It can kill them. We have a chance to eliminate it."

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