

SUCCESS STORIES

USING ENZYMES TO REVERSE KIDNEY DISEASE

Imagine that a bacterial enzyme that digests protein in your throat and intestines could also be used to treat and possibly reverse one of the most deadly and common kidney diseases. That's exactly what three researchers, bridging Tufts Medical Center's Gastroenterology Division and Tufts Departments of Biochemistry and Molecular Biology and Microbiology, collectively imagined and are trying to find out.

Yet, these three researchers could not be more different in their backgrounds. Andrew Plaut, MD, is a Tufts CTSI Portal Co-Director and Professor of

Medicine at Tufts University School of Medicine, a physician with clinical interests in gastrointestinal and liver disease and research interests in how bacteria cause human infections. William Bachovchin, PhD, a Professor in Tufts Department of Biochemistry and Microbiology, is the Director of Tufts Biological NMR Center—a research facility that uses nuclear magnetic resonance to understand protein and nucleic acid structure and function. And Jiazhou Qiu, is a physician trained in China and a Research Associate in the Division of Gastroenterology at Tufts Medical Center.

Combining their interests and their diverse research experience into a translational triumvirate, this team set out to test if an IgA protease, an enzyme produced and used by bacteria to defend itself against our antibodies, can in fact also be used to treat IgA nephropathy—a kidney disorder caused by deposits of the protein immunoglobulin A (IgA) inside the glomeruli or filters within the kidney. If the glomeruli are blocked, like they are by IgA, they become inflamed and can't filter wastes and excess water from the blood. Consequently, blood and protein appear in the urine and the patient experiences high blood pressure and swelling of the hands and feet. Eventually the deposits can lead to end-stage renal disease, requiring dialysis or a kidney transplant. Affecting some 80,000 proven cases in the US alone, many of whom are in our own Chinatown, Boston neighborhood, the stakes are high to develop a treatment for this disease.

Now in its pre-clinical phase, this truly translational research has taken what was originally learned about enzymes in Dr. Bachovchin's Boston equipment lab and the genetics of bacteria in Dr. Andrew Wright's microbiology research lab to allow Tufts Medical Center's scientists to learn how the enzyme actually works. To do this basic research they worked with Dr. Todd Holyoak at the University of Kansas, who was coming full circle to the project that he first heard about during his training in the Brandeis University Department of Biochemistry. Now, knowing the structure of one such enzyme from the bacterium *Haemophilus influenzae*, Drs. Plaut and Qiu are collaborating with a California pharmaceutical, BioMarin Pharmaceutical, to produce and later modify the *Haemophilus* IgA structure for human injection.

Looking ahead to T2 and T3 (and eventually a T4 worldwide policy change in treating the disease), a patent was sought and issued to Tufts Medical Center for this innovative approach to treatment of IgA nephropathy. Most recently, working with colleagues at Case Western Reserve Medical Center in Ohio, the research team was successful in using intravenous injections of *Haemophilus* IgA protease to remove human IgA1 deposits introduced into mouse kidneys. This successful result decisively indicated the feasibility of using IgA proteases for therapy to remove damaging IgA



Three-dimensional structure of the to-be-developed IgA protease.

proteins from the human kidney. The research continues.

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[Tufts CTSI](#) | 35 Kneeland Street | 7th - 11th Floors | Boston, Massachusetts | T: 617-636-CTSI

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