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"Adding Harrington's deep drug development expertise to our experience in protein structure and function makes for a powerful combination."

THE ANSWER TO A RARE KIDNEY DISEASE

MAY BE IN THE LIVER

FOCUS: Inhibitors of primary hyperoxaluria, a cause of kidney failure.

Primary hyperoxaluria type 1 (PH1) is a rare kidney disease caused by a genetic defect on the liver enzyme AGXT. Kidney stones are the most common symptom of PH1, although it can also affect the eyes, skin, and heart. The usual treatment for PH1, liver and kidney transplantation and lifelong immunosuppression, is associated with high risk of morbidity and mortality.

This buildup of kidney stones is due to the defective metabolism and consequential accumulation of the molecule glyoxylate. Professor Yue and his team have developed a promising strategy to mitigate this accumulation.

"In the human body, a sort of metabolic conveyor belt is responsible for manufacturing a certain chemical substance from raw materials, through a number of enzyme steps. Each enzyme catalyzes a reaction that transforms a precursor substance (known as the substrate) to the next substance," Professor Yue says. "If a certain enzyme becomes defective and less active, slowing down this conveyor belt, the key is to inhibit (slow down) the enzyme that's before the defect—this is known as substrate reduction."

"We were able to pinpoint the enzyme, HAO1, which comes before the defective liver enzyme, AGXT. Inhibiting HAO1 will tune the manufacturing process to be in sync with the less active AGXT enzyme. The hope is that doing so will prevent the accumulation of molecules harmful to kidneys."

Harrington Discovery Institute is helping Professor Yue and his team to design drugs specifically targeting HAO1, and with the ability to efficiently reach liver cells. The substrate reduction approach has interesting potential for the treatment of many other metabolic disorders.

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