

Ambitious Drug Discovery Effort Indicates Safer Options for Patients

Findings point to a safer, more effective means of treating conditions like kidney disease and, eventually, cancer.

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Patients with kidney disease who are undergoing dialysis often need to take a drug called a calcium-sensing receptor (CaSR) agonist to regain normal calcium levels in their blood. Unfortunately, inhibiting CaSR can sometimes reduce calcium levels too much, resulting in a condition known as hypocalcemia that carries serious adverse side effects. A major question in pharmacology, then, is how to modulate CaSR activity such that patients receive the benefits and not the risks. As CaSR has also been implicated in several cancers, including breast, lung, prostate and kidney cancers, this is also a major question in cancer research.

A new study from Damon Runyon Fellow Fangyu Liu, PhD, and her colleagues at the University of California, San Francisco may provide some answers. Structural analysis of CaSR has revealed two possible binding sites for an inhibitor. Both are allosteric sites—the protein’s “side doors”—rather than the active site, where calcium itself binds. Knowing this, the team conducted a mass trial-and-error: through a process called “library docking,” they systematically tested how each molecule in a large library of molecules fit into these allosteric sites and affected CaSR function. Their goal was to discover new CaSR modulators that are shaped differently, and thus act differently, than current CaSR drugs.

Typically, library docking involves testing hundreds-to-thousands of possible drug candidates. Nothing if not thorough, Dr. Liu and her team docked libraries of 1.2 billion molecules against the CaSR structure. Not surprisingly, they got some hits. In ex vivo organ tests, one of the newly discovered modulators proved a hundredfold more potent than current standard-of-care drugs, reducing calcium levels in mice without inducing the hypocalcemia typical of CaSR drugs. These findings point to a safer, more effective means of treating conditions like kidney disease and, eventually, cancer.

This study also highlights the importance of a large library size in the discovery of new drugs for challenging protein targets.

“The Damon Runyon Fellowship’s emphasis on innovation inspired me to pursue bold, high-risk ideas that I might have otherwise hesitated to explore,” said Dr. Liu. “This ambitious approach

exceeded our expectations, yielding invaluable insights that we believe will culminate in a landmark paper for the field.”

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