# Scientists paint new picture of dance between protein and binding partners

January 10 2012

Using a blend of technologies, scientists from the Florida campus of The Scripps Research Institute have painted a new picture of how biochemical information can be transmitted through the modification of a protein. Previously, scientists believed that during the pairing of proteins and their binding partners ("ligands"), proteins modified their shape while ligands remained stable. The new study shows this one-size-fits-all solution is not entirely accurate.

Instead, the situation resembles a kind of complex but carefully organized dance routine, where the ligand samples a variety of binding modes while the protein also modifies its shape, a process that results in their pairing and changes in the protein critical for its function.

These new findings, published in the January 11, 2012 edition of the journal *Structure*, could affect future drug design.

"Using a multidisciplinary approach, we gleaned something from our data that no one else has," said Douglas Kojetin, an assistant professor on the Scripps Florida campus who led the study. "The conventional wisdom is that ligands bind in one orientation but our study shows that they can bind in multiple modes. That means if we can optimize a ligand to bind in mode B rather than mode A, we might be able to select the therapeutic results we want."

The new study—which used a number of complementary technologies including NMR spectroscopy and hydrogen/deuterium exchange (HDX)

coupled to mass spectrometery, combined with previous x-ray crystallography analyses—provides detailed insights into the real-time actions of molecules that could never be determined with a single technology.

Specifically, the researchers revealed insights into ligand and receptor dynamics in the nuclear receptor known as PPARγ (peroxisome-proliferator-activated receptor). PPARγ has been implicated in metabolic diseases including obesity, diabetes, and atherosclerosis.

The study also found that various gradations in these ligands influence the dynamics of this exchange, adding another layer of complexity. "One of the compounds, MRL24, binds to the receptor and has anti-diabetic efficacy, but doesn't activate it very well," Kojetin said. "This is what you want because when the receptor is activated you get side effects such as weight gain and brittle bones."

"This study in particular highlights the importance of multidisciplinary collaborative efforts to truly understand the molecular details of drug-receptor interactions", says Kojetin. "This work is an excellent example of the strong campus collaborations we have with the laboratories of Patrick Griffin, Thomas Burris, and Theodore Kamenecka."

**More information:** The first author of the study, "Ligand and Receptor Dynamics Contribute to the Mechanism of Graded PPAR γ Agonism," is Travis S. Hughes of Scripps Research. Other authors include Michael J. Chalmers, Scott Novick, Dana S. Kuruvilla, Mi Ra Chang, Theodore M. Kamenecka ,Thomas P. Burris, and Patrick R. Griffin of Scripps Research; Mark Rance of the University of Cincinnati; and Bruce A. Johnson of One Moon Scientific Inc.

Provided by The Scripps Research Institute