# Researchers find docking sites for glucocorticoid receptor and Hsp90

*by Bend Weekly News Sources*

University of Oregon researchers have identified protein interactions that regulate the response of cells to steroid hormones. The discovery, they say, could lead to new ways to boost the effectiveness and reduce undesired side effects of steroid-hormone treatments and cancer drugs.

The study, published online this week ahead of regular publication in the Proceedings of the National Academy of Sciences, also uncorks an almost 15-year bottleneck in research caused by difficulties in deciphering the actions of a heat-shock protein known as Hsp90.

Hsp90 belongs to a family of proteins called chaperones that help other proteins achieve and maintain their 3-D structure. Unlike most chaperones, Hsp90 is dedicated to assist a restricted yet diverse group of regulatory proteins, such as the glucocorticoid receptor, which requires help from Hsp90 to interact with hormones. Scientists had been stymied with how Hsp90 recognizes and interacts with client proteins.

Hsp90 activity is becoming a target for drug manufacturers, because cancer cells frequently overproduce this chaperone. Two drugs used commonly to fight cancer, geldanamycin and cisplatin, have been used with success, but researchers only recently learned that the drugs actually act in some as-yet-undetermined way to inhibit Hsp90 interaction with client proteins.

Tapping into that knowledge, scientists may be able to develop synthetic molecules that would control specific Hsp90 activity, such as directing the response of cells to glucocorticoids, said the study's principal investigator Beatrice D. Darimont, a professor of chemistry and researcher in the Institute of Molecular Biology at the University of Oregon.

Glucocorticoids are naturally produced by the adrenal glands and are important for a variety of tissue-related activities. They are immune-suppressive and anti-inflammatory, and are prescribed for such conditions as adrenal insufficiency as in Addison's disease, arthritis, asthma, inflammatory bowel disease and childhood acute lymphoblastic leukemia.

"Glucocorticoids are very commonly used in the treatment of diseases," Darimont said. "They have a bunch of physiological activities and functions, and responses are very different depending on the cells involved. The treatments are extremely effective, and glucocorticoids have been used in huge amounts in the last 40 years. Unfortunately, they are associated with very severe side effects."

Side effects include osteoporosis, cataracts, ulcers, hypertension, impaired wound healing, diabetes and depression. Thus narrowing the point of attack, such as by manipulating Hsp90-glucocorticoid receptor

interaction, is of growing importance, Darimont said.

The PNAS paper and a second publication that is under review cover the identification of the features of the glucocorticoid receptor (GR) recognized by Hsp90 and two sites on Hsp90 that interact with GR. To identify these sites, Darimont's team investigated 49,000 randomly introduced GR mutants and 11 specifically designed Hsp90 mutants for their binding and activation abilities. Finding and confirming the two binding sites were boosted by the recently published crystallized structures of both Hsp90 and GR, Darimont said.

"Our results suggest that Hsp90 binds GR with the help of specific docking sites in the C-terminal domain of Hsp90," she said. "This finding opens the possibility to develop small molecules that block specific Hsp90-client protein interactions. As part of our work, we also have identified GR mutants that are able to bind hormones without Hsp90, which may facilitate the development of novel synthetic glucocorticoids."

Co-authors of the PNAS study were Darimont, graduate students Lin Fang and Derek Ricketson, and research technician Lawrence Getubig, all of the University of Oregon. The entire project also has included contributions from postdoctoral fellow Ute Hostick and undergraduate students Ryan Holly, Ryan Salvador and Margaret Mueller.

The Leukemia and Lymphoma Society, Philip Morris USA Inc. and Philip Morris International funded the project. Ricketson was supported by a training grant from the National Institutes of Health. Holly, a chemistry major, and Salvador, an exchange student from the University of Hawaii who participated as part of the UO Summer Program for Undergraduate Research, received awards from the Endocrine Society for their contributions.

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