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Researchers Unveil Image of Prostate Cancer Drug Target

Howard Hughes Medical Institute researchers have published the first atomic picture of a molecule active in the brain and plentiful on prostate cancer cells. Information emerging from these studies has the potential to lead to new therapies for one of the most commonly diagnosed cancers and for a wide range of neurological disorders from Alzheimer's disease to strokes.

For reasons that scientists do not yet fully understand, cancerous prostate cells can sprout many thousands of the molecules, called prostate-specific membrane antigen (PSMA). Scientists do not know why the molecule appears or what it does, but they are rushing to find ways to use it for detection and therapy.

On the surface of neurons and other brain cells, the same molecule goes by a different name, glutamate carboxypeptidase 2. In the brain, the molecule modulates the activity of the peptide NAAG and the excitatory neurotransmitter glutamate. This process plays a key role in normal brain activity and may malfunction or cause problems in schizophrenia, amyotrophic lateral sclerosis (ALS), stroke, and other neurological conditions.

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- **Mindy I. Davis**

Now, using advanced imaging technology known as x-ray crystallography, Howard Hughes Medical Institute (HHMI) researchers at California Institute of Technology have found the specific components of the molecule that attract other proteins or small molecules and then cut them or carry them into the cell.

The discovery, described in the April 14, 2005, *Proceedings of the National Academy of Sciences Early Edition*, provides scientists with a blueprint for designing drugs that can target this molecule on prostate cancer cells more precisely and with fewer side effects.

"The structure itself is a starting point for understanding how the molecule functions in the brain and for being able to design various drugs and imaging agents for prostate cancer applications," said lead author Mindy I. Davis, a postdoctoral fellow in the Caltech lab of HHMI investigator Pamela Bjorkman.

"I am one of the people who has been waiting for a long time for this crystal structure to be elucidated," said Neil Bander, the Bernard and Josephine Chaus professor of urological oncology at Weill Medical College of Cornell University, who was not involved in the study. "This crystal structure will be a significant aid in designing prostate cancer therapies and may be of even more benefit in the neurosciences."

Bander developed the first antibody that locks onto the extracellular domain of PSMA molecules covering prostate cancer cells. In early stage clinical trials, Bander and his colleagues have shown that the antibody precisely delivers a radioactive agent to metastasized prostate cancer cells in men with advanced cancer. The researchers have also linked the antibody with a chemotherapy drug, creating a package they hope will be deadly only to the prostate cancer cells.

"PSMA is a perfect target for prostate cancer," Bander said. "It's the single most well-established prostate cancer-restricted cell surface molecule that has ever been defined." PSMA resides on all prostate cancers, he said. In contrast, the Her2/Neu receptor, the target of the drug herceptin, is found on only 25 percent of breast cancers.

The antibody is too large to cross the blood-brain barrier. But smaller molecules that bind PSMA could work in neurological disorders, Davis said.

According to the new study, the PSMA molecule that sticks out of a cell has the shape of a butterfly. Using a powerful computer to simulate the chemical interactions, Davis and her colleagues docked PSMA with a neuropeptide and three other molecular partners to discern the crucial components needed for a good fit. The structure also shows the region of PSMA that is recognized by the antibody studied by Bander.

The results suggest a range of approaches that may work for future therapies. For example, new drugs may bind to the PSMA and be carried into the cell. Another approach would be to design a drug that will become active when it is selectively cleaved by the PSMA molecule. Or researchers may identify a small molecule to send in and stop the PSMA machinery, a direction that may be helpful in treating neurological disorders.

"There are a lot of ways to construct something that would work," Davis said.
"A lot of companies are interested in this molecule. People are approaching the design of imaging and therapeutic agents from many different angles."