VANDERBILT UNIVERSITY MEDICAL CENTER

REPORTER

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'Missing link' may spur new brain disorder drugs

by Bill Snyder

Researchers at the Scripps Research Institute in San Diego and Vanderbilt University have discovered a "missing link" in the structure of a transmembrane receptor that could lead to new treatments for autism, schizophrenia, Parkinson's disease and Alzheimer's disease.

In an article posted online last week in *Science* magazine, the researchers, led by senior author Raymond Stevens, Ph.D., professor of Molecular Biology and Chemistry at Scripps, achieved the first high-resolution crystal structure of a metabotropic glutamate receptor, mGlu1.

The receptor, which binds the neurotransmitter glutamate, is a member of the class C subfamily of G protein-coupled receptors (GPCRs) through which hormones, neurotransmitters and more than a third of all therapeutic drugs exert their effects.

"This receptor family is an exciting new target for future medicines for treatment of brain disorders," said P. Jeffrey Conn, Ph.D., director of the Vanderbilt Center for Neuroscience Drug Discovery (VCNDD), who contributed to the study.

"This new understanding of how drug-like molecules engage the receptor at an atomic level promises to have a major impact on new drug discovery efforts," said Conn, the Lee E. Limbird Professor of Pharmacology.

The researchers determined the crystal structure of the receptor's "transmembrane domain" bound to a "negative allosteric modulator" or NAM. The compound "tunes down" the receptor when activated by glutamate like the dimmer switch of an electrical circuit.

The Scripps team included first author Huixian Wu and Chong Wang, both graduate students, staff scientist Gye Won Han, Ph.D., assistant professor Vsevolod Katritch, Ph.D., and associate professor Vadim Cherezov, Ph.D.

The Vanderbilt team included Colleen Niswender, Ph.D., VCNDD director of Molecular Pharmacology and research associate professor of Pharmacology; Jens Meiler, Ph.D., associate professor of Chemistry and Pharmacology; former postdoctoral fellow Karen Gregory, Ph.D.; drug discovery scientist Hyekyung Cho, Ph.D.; and graduate student Yan Xia.

"This work leveraged the unique strengths of the Vanderbilt and Scripps teams in applying structural biology, molecular modeling, allosteric modulator pharmacology and structure activity relationships to validate the receptor structure," Niswender said.

National Institutes of Health grants that supported the research included GM094618, GM073197, NS031373, NS078262 and MH090192; additional support was provided by the International Rett Syndrome Foundation. ❑

Health informatics services reorganizes to meet users' needs

by Paul Govern

Support for Medical Center operations is now named Informatics Officer.

On March 5 in 208 Light Hall, Middleton announced

The team studying beta-cell regeneration includes, from left, Chunhua Dai, M.D., Kristie Aamodt, Marcela