

# First detailed map of human neuroreceptor generated

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For the first time, USC scientists have mapped out a neuroreceptor. This scientific breakthrough promises to revolutionize the engineering of drugs used to treat ailments such as Alzheimer's disease and schizophrenia.

The team produced the world's first high-resolution images of the  $\alpha 7$  (Alpha 7) receptor, a molecule responsible for transmitting signals between neurons – particularly in regions of the brain believed to be associated with learning and memory.

Using the image, scientists will be better equipped to design pharmaceuticals specifically to interact with the receptor, instead of blindly using a trial-and-error approach.

"A lot of interest in this work will come from pharmaceutical companies," said corresponding author Lin Chen, professor of biological sciences and chemistry at the USC Dornsife College of Letters, Arts and Sciences. "They really have no clear picture of this. They don't know how or why [their drugs] work."

The high-resolution image will also help neuroscience researchers study how these receptors receive and transmit neuronal signals, a question that has puzzled researchers for decades.

The article, co-authored with scientists from the Keck School of Medicine of USC and the Mayo Clinic College of Medicine, appears in

*Nature Neuroscience* this month.

The findings follow up on Chen's earlier landmark achievement, deciphering the inner workings of a nicotine receptor in 2007.

Developing an image of the  $\alpha 7$  receptor was no simple task, which is partly why it has taken until now to achieve this despite the wide interest in the understanding the receptor's structure. Attempts to decipher neuroreceptors have been ongoing for 30 years.

"This has been a longstanding challenge," Chen said. The challenge is twofold, he said. It is difficult to obtain enough receptor protein for structural analysis, and the flexible nature of these receptors makes them difficult to crystallize — a necessary step for high-resolution imaging.

The biologist's usual go-to method to study such molecules — growing a large quantity using molecular cloning — failed to produce enough correctly structured  $\alpha 7$  to study.

"You can't study it directly in its natural form, so you have to engineer it," Chen said.

In the case of  $\alpha 7$ , Chen's collaborator, Dr. Steve Sine from Mayo Clinic, engineered a chimera, a Frankenstein molecule sharing about 70 percent of its structure in common with the  $\alpha 7$  that reacted to stimuli in the same way that natural  $\alpha 7$  does.

The next step was to form crystals with these proteins for high-resolution study. This turns out to be particularly difficult for neuronal receptors because they are intrinsically flexible — they need to bind to a neurotransmitter, a small molecule that acts as a messenger in the nervous system, and transmit the signal across the protein body. Moreover, these receptors are decorated with sugar molecules that add

further flexibility to the system.

The crystallization of  $\alpha 7$  was a painstaking process carried out by Shu-xing Li, the first author of the study and a postdoctoral fellow in Chen's lab. For every hundred crystals obtained, only one or two were good enough for structural analysis. Li had to sort through hundreds of crystals to collect enough data for structural analysis.

"In a sense, these crystals are probably among the world's most expensive crystals, certainly more expensive than diamond," Chen said. "But considering the rich information we can get from these crystals about human neuronal receptors, and the potential impact on [drug](#) development that can benefit human health, they are worth the effort."

Provided by University of Southern California

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