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NEW DISCOVERIES ABOUT G PROTEINS OFFER INSIGHT INTO MOLECULAR BASIS OF HUMAN SENSES, DISEASE

DALLAS — February 16, 1996 — New findings by UT Southwestern Medical Center at Dallas researchers that reveal the structure of a G protein molecule may ultimately lead to the development of new drugs that are more effective in treating illness.

"G proteins act as molecular 'mail sorters' by directing sensory and hormonal signals to the appropriate targets within the cell," explained Dr. Stephen Sprang, professor of biochemistry and associate investigator in the Howard Hughes Medical Institute at UT Southwestern. He is the senior author of two recent articles on G protein structure published in the journals *Cell* and *Science*.

"The G protein we studied is coupled to the receptors of certain neuroactive hormones produced in human tissue. When activated by the receptor, this G protein acts on proteins that regulate the rate and strength of heart contractions." Researchers so far have identified approximately 20 different G proteins.

In the articles, Sprang and his colleagues, including Chairman of Pharmacology Dr. Alfred G. Gilman, who shared the 1994 Nobel Prize in physiology or medicine for his role in discovering G proteins, showed for the first time the structure of the three molecular subunits that make up the G protein: alpha, beta and gamma. The G protein is inactive when the three subunits are bound together in a complex. Revealing the structure of the complex will eventually help researchers deduce how receptors might pry them apart. The signaling mechanism is expected to be the same for many hormone receptors, as well as for those responsible for basic senses like vision, taste and smell. For example, G proteins help the

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brain transform the information received by the eyes into images that are seen.

"Individual alpha subunits contain their own internal clocks, which cause them to deactivate after a matter of seconds. In this way they act as a timing mechanism for the receptors," Sprang said.

Earlier research by Gilman, who holds the Raymond Willie and Ellen Willie Distinguished Chair in Molecular Neuropharmacology, in Honor of Harold B. Crasilneck, Ph.D., found that any alteration in the pattern of signal reception or the process of transforming the G protein alpha subunit from its "off" to "on" state, can lead to disease. For example, the cholera toxin alters the G protein, leaving it in the "on" position, which prevents the normal absorption of salt and water by the intestines. The loss of salt and water can lead to dehydration or even death.

To study the structure of the G protein, Sprang and his colleagues grew crystals of the G protein, which were then examined by special X-ray technology, allowing the researchers to map a three-dimensional image of the protein. The scientists described the image of the beta subunit produced through X-ray crystallography as a "seven-bladed propeller." The design of the propeller graphically illustrates how the beta subunit binds to the alpha subunit and deactivates it.

"We have learned how release of the alpha subunit from the complex turns the molecule 'on,' but we still want to learn how alpha binds to signal receptors," Sprang said. That kind of information could one day make the molecule the basis for new drugs. Sprang believes that drugs eventually will be targeted to G proteins because of the important role these molecules play in controlling essential cell activities.

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