Chemists Patent Method for Assembling Receptor-Signaling Complexes for Engineering New Compounds and Drugs

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(PhysOrg.com) -- University of Massachusetts chemistry professor Bob Weis, with former doctoral students Anthony Shrout and David Montefusco, recently received a U.S. patent for their invention, template-directed assembly (TDA) of receptor-signaling complexes, a new method for studying signaling processes found in all cells. Abnormal signaling contributes to many diseases such as cancer and diabetes, so the method can be used in the search to develop new drugs for these diseases.

As Weis explains, the new method reassembles “teams” of signaling proteins normally found on the cytoplasmic side of the cell membrane by simply mixing together individual components with a synthetic scaffold membrane to facilitate the reassembly process. The reassembled team has many of the functions it would have in the cell, which allows drug developers and researchers to conduct rapid, accurate assessments of molecules that target a specific pathway. For example, it is possible to study the teams of proteins found in tyrosine kinase pathways, a type frequently involved in cancer. Using the new tool in such studies, researchers can test for new drugs to target these pathways.

Scientists now understand the cell’s interior to be more like a thick porridge packed with proteins, nucleic acids, interior membranes and other components, and less like a thin soup. In this crowded environment, proteins carry out thousands of cell operations, many of

which involve the transfer or transduction of information signals via these protein interactions. This work is carried out in part by the proteins achieving a “lock and key specificity,” but also by organizing the necessary components near one another in the cell and in appropriate orientation.

Researchers have long tried to mimic these delicate phenomena accurately and efficiently in the laboratory, but without a way to hold several dynamic puzzle parts together in the correct alignment, the key proteins drift away from each other and fail to interact in the way they normally would in a cell. The new invention provides a way to bring the signaling proteins together and in the arrangement needed to function.

Weis, with chemistry degrees from the University of Michigan and Stanford, invented the core technology. Since 1988, he has been at UMass Amherst, where he conducts research in transmembrane signaling. Shrout, with an undergraduate chemistry degree from Indiana State University, and Montefusco, with an undergraduate chemistry degree from Connecticut State University, worked with Weis at UMass Amherst to develop the new technology using the chemotaxis signaling system of E. coli.

According to Weis the invention is “generally applicable to many cellular signal transduction systems of interest to the pharmaceutical industry.” As a result, Weis and colleagues formed Protein Attachment Technologies LLC, or P.A. Tech, in 2006, which licensed the technology from UMass Amherst to develop and sell the new reagents and assay methods that result from the combination of engineered proteins and chemical self-assembly.

The company’s products and reagents are “designed to be particularly well-suited for biochemical tests of function in complex-signal transduction pathways involving membrane-associated receptors and

proteins, a difficult but important set of targets in the pharmaceutical industry," the researchers explain.

Weis says the company has optimized reagents and assays for ease of use, reliability, and broad utility in basic research and high throughput analyses. "The ubiquitous role of transmembrane receptor proteins in cellular signaling pathways, coupled with the significant challenges for their isolation and study has generated this need," the firm's web site explains. Thus it provides researchers and industry with ahead-of-the-curve technologies that enable efficient and effective analysis.

"Because of the broad applicability to many different membrane-associated proteins, P.A. Tech sought out and formed an alliance with a sublicensee, Blue Sky Biotech of Worcester, a firm established in the area of protein engineering and expression technologies. This means "things will happen better and faster for our new technology, because they're expert in this area," Weis explains.

Provided by University of Massachusetts Amherst