Crystal clear: Eureka! moment leads to major breakthroughs in structural biology

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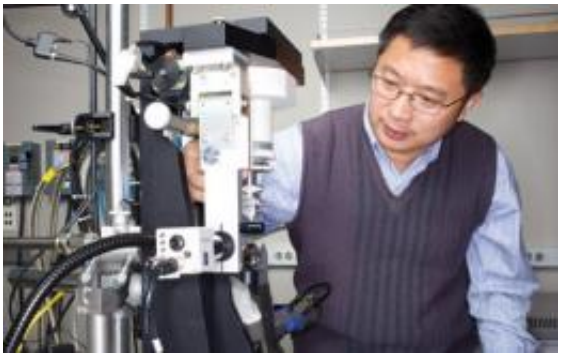

Lin Chen, professor of biological sciences and chemistry, aligns a protein crystal on an X-ray diffractometer. He uses X-ray crystallography to analyze the molecular details of key proteins and their complexes in physiological and disease processes. Photo credit Max S. Gerber.

(PhysOrg.com) -- Tuning out the noise of fellow passengers and the incessant hum of the turbojet engine, Lin Chen pored voraciously over the pages of James Watson's *The Double Helix*. The words and ideas flowed from the book's pages, drowning out other considerations of how he would spend his life. Eureka! It was his moment of self-realization.

It sounds like the beginning of a science-fiction story — it's not. It was the 1980s, but not George Orwell's 1984. Chen knew without any trace of doubt that he would pursue the field of gene regulation and expression like Watson, Francis Crick and others before him.

Chen, professor of biological sciences and chemistry in USC College since 2003, was en route from Beijing to Boston, where he would earn a Ph.D. in chemistry from Harvard University.

Today Chen and his colleague Xiaojiang Chen, professor of biological sciences, have built two of the most successful structural and biomedical research laboratories in the United States. Their labs, supported by USC and competitive national research grants, have gained international prominence in cancer biology, immunology, cardiovascular biology and neurology.

Researchers in their laboratories use X-ray crystallography and biophysical/biochemical methods to analyze the molecular details of key proteins and their complexes in physiological and disease processes.

Lin Chen's research is a hybrid of his education in chemistry and his appreciation and deep understanding of the structural intricacy of biology. "In my early career, I was consumed with examining biology on the atomic level — what bio-molecules look like and how they function," he said. "After six or seven years, I grew to appreciate the different disciplines and combined them together in my research."

After only 3 1/2 years at USC, Chen made a major breakthrough in the atomic structure of a protein involved in neuronal signaling called the nicotinic acetylcholine receptor, or nAChR. For decades scientists have debated how signals pass from the outside to the inside of a cell through this protein. "This molecule is a key component for the central nervous system — for you and me talking, listening and moving," Chen explained.

Chen co-wrote a paper on these findings in *Nature Neuroscience* with Zuo-Zhong Wang, associate professor of cell and neurobiology at the Keck School of Medicine of USC. "I could not sleep all night when I

realized how everything had all come together so nicely," Chen said. "It was like the tale of the six men and the elephant and we had all felt various parts of it such as a leg or the trunk but could not tell the whole story."

Using atomic resolution structure, Chen discovered water molecules buried inside the protein. This is a very unusual phenomenon since most proteins have a dry interior to maintain stability in aqueous solution. Through further evolution and biochemical analyses, Chen postulated that the wet interior of nAChR may have evolved to facilitate protein conformation changes that are needed for signal transmission. This hypothesis, while requiring further experimental testing, may hold true for a variety of other signaling proteins.

Another surprising and exciting result from the high-resolution structural study is the sugar molecule revealed on the surface of nAChR. It turns out that sugar was more than icing on the cake. The studies by Chen and Wang revealed that sugar serves as a flexible door or hinge that opens and closes a gate in the cell membrane, demonstrating how the signals pass from the outside to the inside of a cell.

For example, when nicotine binds to a neuron, it is sugar that lets the cell know to send a signal announcing the thrilling sensation experienced by smokers.

Structural biologist Raymond Stevens (Ph.D., chemistry, '88) of the Scripps Research Institute called the study's suggestion of a simple mechanical role for sugar molecules attached to the surface of the receptor as nothing less than "a landmark accomplishment for the fields of structural biology and neuronal cell signaling."

Chen said that study's findings stand to impact the development of improved therapeutics for epilepsy, schizophrenia, depression and

substance addiction. These new insights were advanced by X-ray crystallography that facilitated an intricate view of the molecular structure.

The bottom line in specific fields of science is that a very important molecule is known to have a critical function. According to Chen, "These fields can benefit from breakthroughs made possible through high-resolution detail." And in this case Chen said integrating structural biology with results accumulated by others in related fields worked splendidly.

Now in 2010, the year that commemorates the 50th anniversary of a transformative event in science, the discovery of the first 3-D structure of a protein, Chen is on the verge of yet another major scientific breakthrough with a family of proteins called Myocyte Enhancer Factor-2, or MEF2.

According to Chen, MEF2 possesses the ability to alter the expression of genes and the structure of chromatin. He examines how these systems of genes function using an interdisciplinary approach by combining high-resolution structures and chemical design.
"MEF2 is emerging as a potential therapeutic target for a number of human diseases, including neurodegenerative diseases such as Alzheimer's and Huntington's diseases, autoimmune disorders and transplant rejection," Chen said.

A major effort is currently under way to design and screen inhibitors to bind MEF2 and block the recruitment of other molecules such as HDACs and p300 that are believed to be dysregulated in the aforementioned diseases. Experimental results suggest that HDAC inhibitors may also help in treating heart failure and cancer.

As a structural biologist, Chen searches for connections between what

appear to be irrelevant pieces of information. “My work is not as intensely focused as my biology colleagues who study one specific biological question. I provide a bridge and through interactions with my colleagues I am able to catalyze interdisciplinary thinking,” he said.

As an example of interdisciplinary collaboration, he cites that together with Nicos Petasis, professor of chemistry, a chemical compound was designed that modulates the MEF2 function. He then conferred with suite-mate Don Arnold, associate professor of biological sciences, regarding the testing of the compound in cell culture. Two days later they found that the chemical compound was indeed active in regulating synaptic structure in neurons, a result consistent with the proposed roles of MEF2 in neuronal plasticity and learning and memory.

“USC College has one of the best chemistry groups in the U.S. and the Keck School of Medicine of USC provides fertile ground to explore numerous areas of strong research with implications to medical and clinical development,” Chen said.

Combined with his unique insight on a molecular detail level, Chen is able to leverage vast amounts of existing biochemical and biomedical data for the direct benefit of society. Eureka! indeed — all this of great import — in a job he considers unbelievably exciting and terrific fun.

Provided by University of Southern California

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