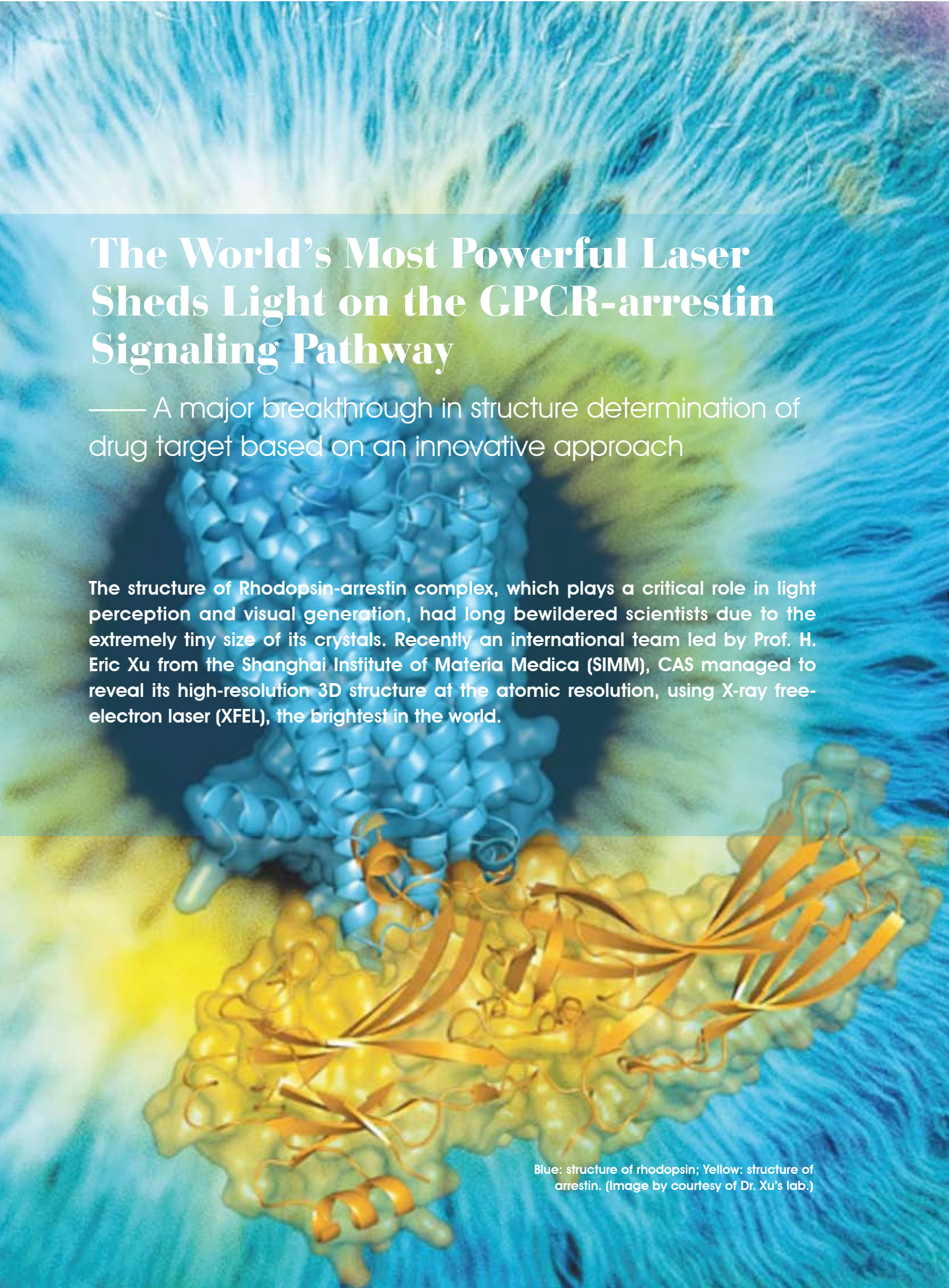
The World's Most Powerful Laser Sheds Light on the GPCR-arrestin Signaling Pathway

—— A major breakthrough in structure determination of drug target based on an innovative approach

The structure of Rhodopsin-arrestin complex, which plays a critical role in light perception and visual generation, had long bewildered scientists due to the extremely tiny size of its crystals. Recently an international team led by Prof. H. Eric Xu from the Shanghai Institute of Materia Medica (SIMM), CAS managed to reveal its high-resolution 3D structure at the atomic resolution, using X-ray free-electron laser (XFEL), the brightest in the world.



Blue: structure of rhodopsin; Yellow: structure of arrestin. (Image by courtesy of Dr. Xu's lab.)

Using one of the brightest X-ray lasers in the world, a joint research team joining forces from 28 laboratories led by Dr. H. Eric Xu, a professor from the Shanghai Institute of Materia Medica (SIMM), CAS, have determined the structure of a molecular complex that is responsible for regulating vital physiological function. The new findings provide scientists with a new model for major pharmacological drug targets. The study, *Crystal structure of rhodopsin bound to arrestin determined by femtosecond X-ray laser*, was published online as an article in the journal of *Nature* on 22nd July, 2015.

The Nobel Prize in chemistry 2012 was shared by Robert J. Lefkowitz and Brian K. Kobilka for their studies on G-protein-coupled receptors (GPCRs). They uncovered the secret of human information communication system, *i.e.* how cells sense their environment, and transduce external signals into the cell through G protein. However, how GPCRs activate arrestin signaling pathway, a vital issue in the field of GPCR signaling transduction, remained unanswered, despite the years of efforts made by scientists.

"Arrestin and G proteins are playing "*Yin*" (negative) and "*Yang*" (positive) roles in regulating GPCR function," Xu introduced. Arrestins, as well as other signaling proteins known as G proteins, link up with GPCRs to convey important instructions for many essential physiological functions. Besides the regulation of arrestins in desensitization and internalization of GPCRs, recent research focused on their function on biased GPCR signaling transduction.

The structure determination of membrane proteins has remained a largely unconquered area. It is even more challenging to remap the structural image of a large membrane protein complex. For the last decade, the team led by Prof. Xu has been working to unravel the structure of a complex made up of arrestins and rhodopsin, which is a prototypical GPCR responsible for light perception and activation of visual function.

The most challenging part of the work is that the tiny size of arrestin-GPCR crystals, which Xu's team had painstakingly produced at the cost of years' efforts, makes it too difficult to study even with the most advanced type of synchrotron, a conventional X-ray source. Thanks for the powerful innovation derived from inter-disciplinary cooperation, the team managed to determine the three-dimensional image of Rhodopsin-arrestin complex at the atomic level – a much higher resolution than possible to gain with older X-ray technologies, utilizing X-ray free-electron laser (XFEL), which is the brightest laser in the world. This newly determined structure reveals the overall architecture of the rhodopsin-arrestin assembly, in which the arrestin uses a distinct mode of interaction with GPCR compared with G protein. This provides a basis for understanding GPCR-mediated arrestin-biased signaling and demonstrates the power of X-ray lasers for advancing the frontiers of structural biology.

The discovery solved a world-class scientific issue in the field of GPCR signaling transduction, providing a roadmap for developing more selective therapy strategies. "GPCRs are major targets in the development of new therapies and account for almost 40 percent of current drug targets", said Xu. "In the realm of drug development, a detailed understanding of the structure, interaction and function of each of these groups of proteins is vital for developing effective therapies. The more specific the targeted interaction, the better the drugs tend to work, and meanwhile the lower the chance for side effects." Therefore, drugs that only activate either the arrestin or G protein signaling pathway, not both instead, can achieve better therapy benefits with fewer undesirable effects, compared with non-selective drugs.

"This project addressed a significant challenge and was accomplished through the work of a multidisciplinary team from many institutions around the globe," commented Xu. "Success in utilizing the X-ray laser also opens the door for solving future challenging problems."

"Xu's group has put together an important story that provides significant insight into our understanding of G-protein-coupled receptor function," said Dr. Jeffrey Benovic, Thomas Eakins Professor at Thomas Jefferson University. "The rhodopsin-arrestin structure helps to explain the process of desensitization and provides a roadmap for obtaining the structure of additional GPCR complexes."

This work was conducted by Xu's laboratory at Van Andel Research Institute (VARI), in collaboration with his VARI colleague, Dr. Karsten Melcher's lab, and collaborators across the globe, including those from the Joint Center for Structural Genomics, Stanford Synchrotron Radiation Light source; LCLS, SLAC National Accelerator Laboratory; VARI-Shanghai Institute of Materia Medica (VARI-SIMM); Arizona State University; University of Southern California; University of California at Los Angeles; DESY's Center for Free Electron Laser Science; University of Singapore; New York Structural Bio-XFEL Biology Center; The Scripps Research Institute; University of Toronto; Vanderbilt University; NSF Science and Technology Center; University of Wisconsin-Milwaukee; Shanghai Institute of Materia Medica, CAS; Paul Scherrer Institute; Trinity College Dublin; University of Chicago; Universität Konstanz; Institute of High Energy Physics, CAS; Centre for Ultrafast Imaging; and University of Toronto.

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For more information please refer to:

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