PI Biographical Sketch

NAME: Stevens, Raymond C.

eRA COMMONS USER NAME (credential, e.g., agency login): RSTEVENS

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Southern Maine, Portland, ME	B.A.	1986	Chemistry
University of Southern California, Los Angeles, CA	Ph.D.	1988	Chemistry
Harvard University, Cambridge, MA	Postdoc	1989-1992	Chemistry

A. Personal Statement

My laboratory has been focused on human G protein-coupled receptor research since the early 1990's. After 17 years of effort including the technology development of protein crystallography robotics for membrane protein structural biology research, in 2007 we solved the crystal structures of the human β_2-adrenergic receptor bound to the partial inverse agonist carazolol at 2.4 Å. Since that time, we have solved a total of 20 distinct GPCR structures and more than 34 complexes including receptors from the rhodopsin (adrenergic, adenosine, dopamine, sphingolipid, opioids, purinergic, histamine, cannabinoid, chemokine, angiotensin), secretin (glucagon), glutamate (mGluR1) and frizzled (smoothened) families. Our highest resolution structures of the delta opioid and A_{2A} adenosine receptor at 1.8 Å have shed new light into the allosteric control of GPCRs by sodium and cholesterol. Our research program is focused on understanding the structural diversity among the GPCR family, as well as technology development to understand mechanisms of signal transduction and coupling of GPCRs with their partners including G proteins, GPCR receptor kinases, and arrestin. In combination to the crystallographic studies, we have collaborated with key leaders in the field to use NMR, HDX, and EM techniques as well as biochemistry, chemistry, and biology studies to understand the structure and function of this important protein family. As part of a larger program, we seek to collectively realize a dynamic atomic level model of man to accelerate the creation and implementation of novel therapies and cures for a host of intractable diseases and conditions. The program described in this proposal contributes to that larger goal by focusing on the receptors involved in diabetes - the glucagon-like peptide 1 receptor (GLP1R) and glucagon receptor (GCGR) – and seeks to establish a dynamic 3-D atomic structure of the receptors as well as the biological structures where they reside -- the pancreatic beta cell.

B. Positions and Honors

Positions

1/89 – 6/92 NIH Postdoctoral Research Fellow, Chemistry Department, Harvard University. Postdoctoral Advisor: Professor William N. Lipscomb.

1/90 – 5/90 Teaching Fellow, Chemistry Department, Harvard University.

7/92 – 6/99	Assistant Professor of Chemistry, University of California, Berkeley.
9/93 – 6/01	Principal Investigator, Lawrence Berkeley National Laboratory, Berkeley.
7/95 – 6/99	Assistant Professor of Neurobiology, University of California, Berkeley.
2/99 – 9/01	Founding Scientist and Director of Science and Technology, Syrrx, San Diego.
6/99 – 1/15	Professor of Integrative Structural and Computational Biology (formerly, Molecular Biology) and Chemistry, The Scripps Research Institute, La Jolla, CA.
12/99 – 11/04	Founding Scientist, Joint Center for Structural Genomics
7/02 – 6/04	Founding Scientist, MemRx Corporation. Merged with Sagres Discovery in March 2003. Acquired by Chiron/Novartis, July, 2004.
7/03 – 12/14	Founding Scientist and Director, Joint Center for Innovative Membrane Protein Technologies
3/03 – 7/04	Chairman, Sagres Discovery Scientific Advisory Board.
11/07 – 7/14	Scientific Advisory Board, Novo Nordisk Foundation Center for Protein Research
12/07 – 7/14	Scientific Advisory Board, BioMarin Pharmaceuticals, Novato, CA
8/08 – 6/12	Founding Scientist and Board of Director, Receptos, San Diego, CA
7/10 – present	Founding Scientist and Director, GPCR Network
8/11 – present	Chinese Academy of Sciences Senior Distinguished Visiting Professor, Shanghai Institute of Materia Medica, Shanghai, China
7/11 – present	Founding Scientist and Chairman Board of Directors, RuiYi, Inc. (Shanghai, China) Acquired by Anaphore, October 2011.
8/12 – present	Founding Director, iHuman Institute, Shanghaitech University (Shanghai, China)
7/14 – present	Provost Professor of Biological Sciences, Chemistry, Neurology, Physiology & Biophysics, and Chemical Engineering and Materials Science, University of Southern California, Dornsife College of Letters, Arts and Sciences, Los Angeles, CA
7/14 – present	Founding Director, The Bridge Institute, University of Southern California
10/14 – present	Chair, Scientific Advisory Board, Biophysics and Drug Discovery Program at the Moscow Institute of Physics and Technology (Moscow, Russia)
6/16 – present	Founding Scientist, ShouTi, Inc.

Honors

Student/Faculty Research Summer Program Support Award, Brookhaven Natl Lab., Summer/Winter 1984 & Summer 1985.
Walter C. Hamilton Memorial Scholarship for research in neutron diffraction, 1987.
International Travel Award from U.S. National Committee for Crystallography and National Science Foundation, 1987.
National Institute of Health Postdoctoral Fellowship, 1989.
Sidhu Award from Pittsburgh Diffraction Society, 1992.
National Science Foundation Young Investigator Award, 1994.
Beckman Foundation Young Investigator Award, 1994.
Lawrence Berkeley Laboratory Outstanding Performance Award, 1995.
Society of Bioinorganic Chemistry Award, “Metals in Biology” Gordon Conference, 1997.
Distinguished Alumni Award, University of Southern California, 2005.
Honorary Doctorate of Science, University of Southern Maine, May 2008
Qian Ren Award, Chinese Academy of Sciences (Shanghai, China). April 2012
Max T. Rogers Distinguished Lectureship in Chemistry, Michigan State University, September 2012.
National PKU Alliance, Outstanding Service Award, September 2013.
Zhao Chenggu SIMM Award for International Drug Discovery, March 2014

Thomson Reuters Highly Cited Researcher, 2014 (Biology & Biochemistry); 2015 (Biology & Biochemistry; Pharmacology & Toxicology).
Shanghai International Cooperation Award, 2016
Elected Member of the Norwegian Academy of Science and Letters, 2016.

C. Contribution to Science

My work has been focused on understanding the structure and function of the critical cell signaling receptor family of G protein coupled receptors (GPCRs) since the early 1990s. My earliest studies were focused on developing the methods, techniques, and technologies that would ultimately be necessary to address this key biomedically-relevant protein family. Methodological and instrumental advancements were required in many areas concurrently – including development of protein expression methods for integral membrane proteins, nanovolume crystallization robotics, crystal imaging robotics, lipidic cubic phase pre-crystallization technologies, sample screening and data collection methodologies at new micro-focus synchrotron beamlines. With funding and support by the NIGMS Protein Structure Initiative, my lab developed numerous technologies to accelerate protein structure determination including nanovolume crystallization and automation/ miniaturization of all steps in the gene to structure process – in the early years this work focused principally on soluble protein samples as proof of principle and enabled a faster development timeline.

a. B.D. Santarsiero, D.T. Yegian, C.C. Lee, G. Spraggon, J. Gu, D. Scheibe, D.C. Uber, E.W. Cornell, R.A. Nordmeyer, W.F. Kolbe, J. Jin, A.L. Jones, J.M. Jaklevic, P. G. Schultz, R.C. Stevens "An approach to rapid protein crystallization using nanodroplets" *J. Appl. Crystallogr.*, 35, 278-281 (2002).
b. S.A. Lesley, P. Kuhn, A. Godzik, A.M. Deacon, I. Mathews, A. Kreusch, G. Spraggon, H.E. Klock, D. McMullan, T. Shin, J. Vincent, A. Robb, L.S. Brinen, M.D. Miller, T.M. McPhillips, M.A. Miller, D. Scheibe, J.M. Canaves, C. Guda, L. Jaroszewski, T.L. Selby, M.A. Elsliger, J. Wooley, S.S. Taylor, K.O. Hodgson, I.A. Wilson, P.G. Schultz, R.C. Stevens "Structural genomics of the *Thermotoga maritima* proteome implemented in a high-throughput structure determination pipeline" *Proc. Natl. Acad. Sci. USA*, 99, 11664-11669 (2002). PMCID: PMC129326.
c. D. Hosfield, J. Palan, M. Hilgers, D. Scheibe, D. McRee, R.C. Stevens "A fully integrated protein crystallization platform for small molecule drug discovery" *J. Struct. Biol.* 142, 207-217, (2003).
d. R. Page, K. Moy, E.C. Sims, J. Velasquez, B. McManus, C. Grittini, T.L. Clayton, R.C. Stevens "Scalable high-throughput micro-expression device for recombinant proteins" *BioTechniques* 37, 364-370 (2004).

While high-throughput methods were developed and advanced enabling an exponential growth in the number of soluble protein structures in the PDB, membrane proteins as a target for these methodologies continued to be largely intractable. The NIH and NIGMS recognized this need and issued a call for centers to develop methods and technologies that would advance integral membrane protein research. With funding from the NIGMS Common Fund – Roadmap Initiative for Membrane Protein Structural Biology, my laboratory was a key leader in these areas in developing protocols for protein expression (including the use of fusion partners), purification, crystallization (via lipidic cubic phase), and sample screening and data collection at micro-focus synchrotron beamlines like those at the Advanced Photon Source GM/CA CAT. These advances in integral membrane protein work were a key stepping stone to the efforts that subsequently lead to the structure determination of the first human GPCR – the β_2-adrenergic receptor (β_2AR) at 2.7 Å in 2007.

a. M.A. Hanson, A. Brooun, K.A. Baker, V.-P. Jaakola, C. Roth, E. Chien, A. Alexandrov, J. Velasquez, L. Davis, M. Griffith, K. Moy, B. Ganser-Pornillos, P. Kuhn, S. Ellis, M. Yeager, and R.C. Stevens "Profiling of membrane protein variants in a baculovirus system by coupling cell-

surface detection with small-scale parallel expression" *Protein Expr. Purific.* 56, 85-92 (2007). PMCID: PMC2274776.

b. V. Cherezov, J. Liu, M.T. Griffith, M.A. Hanson, R.C. Stevens. "LCP-FRAP assay for pre-screening membrane proteins for in meso crystallization." *Crystal Growth & Design*, 8, 4307-4315 (2008). PMCID: PMC2645078.
c. V. Cherezov, M.A. Hanson, M.T. Griffith, M.C. Hilgart, R. Sanishvili, V. Nagarajan, S. Stepanov, R.F. Fischetti, P. Kuhn, and R.C. Stevens "Rastering strategy for screening and centering of microcrystal samples of human membrane proteins with a sub 10 micron size X-ray synchrotron beam" *J. Royal Soc. Interface* 6 Suppl 5, S587-S597 (2009). PMCID: PMC2843980.
d. E. Chun, A.A. Thompson, W. Liu, C.B. Roth, M.T. Griffith, V. Katritch, J. Kunken, F. Xu, V. Cherezov, M.A. Hanson, R.C. Stevens. "Fusion partner toolchest for the stabilization and crystallization of G protein-coupled receptors" *Structure*, 20, 967-976 (2012). PMCID: PMC3375611.

GPCRs make up 80% of the body's cell signaling receptors and are the targets of more than 40% of drugs currently on the market. Involved in a diverse array of medical conditions – from diabetes to heart disease, cancer to embryonic development, neurodegenerative diseases like Alzheimer's and Parkinson's to our very sense of taste and smell. Capitalizing on the methods and technologies we developed, my laboratory has been involved in the structure solution of 18 unique human GPCR structures, the significance of each new receptor evidenced by the high profile journal where the work was ultimately published including *Science*, *Nature* and *Cell* (over two dozen papers in all). Key to maintaining this high profile has been our ability to work closely with collaborators with complementary expertise in the biochemistry or pharmacology or some other aspect of work with the receptor, and capitalize on that momentum to conduct follow-on studies that were also published. Combining our research efforts with these collaborators has led to significant discoveries that are only beginning to be capitalized upon by the scientific and medical research communities at large. The studies include the use of x-ray crystallography, NMR, HDX, EM complemented by chemistry and pharmacology studies, and protein-protein interactions; these studies have proven to be essential in our understanding of molecular recognition, GPCR signaling, and GPCR evolution and have led to drug candidates. We have been a major force in illuminating one of the most sophisticated and complex signal transduction systems found in mammals.

a. V. Cherezov, D.M. Rosenbaum, M.A. Hanson, S.G.F. Rasmussen, F.S. Thian, T.S. Kobilka, H.-J. Choi, P. Kuhn, W.I. Weis, B.K. Kobilka, R.C. Stevens "High resolution crystal structure of human β2-adrenergic G protein coupled receptor" *Science* 318, 1258-1265 (2007). PMCID: PMC2583103.
b. V.P. Jaakola, M.T. Griffith, M.A. Hanson, V. Cherezov, E.Y.T. Chien, J.R. Lane, A.P. IJzerman, R.C. Stevens. "The 2.6Å crystal structure of a human A2A adenosine receptor bound to an antagonist." *Science* 322, 1211-1217 (2008). PMCID: PMC2586971.
c. H. Wu, C. Wang, K. J. Gregory, G. W. Han, H. P. Cho, Y. Xia, C. M. Niswender, V. Katritch, J. Meiler, V. Cherezov, P. J. Conn, R. C. Stevens "Structure of a class C GPCR metabotropic glutamate receptor 1 bound to an allosteric modulator" *Science*, 344, 58-64 (2014). PMCID: PMC3991565.
d. L. Qin, I. Kufareva, L.G. Holden, C. Wang, Y. Zheng, C. Zhao, G. Fenalti, H. Wu, G.W. Han, V. Cherezov, R. Abagyan, R.C. Stevens, T.M. Handel "Crystal structure of the chemokine receptor CXCR4 in complex with a viral chemokine" *Science* 347, 1117-1122 (2015). PMCID: PMC4362693.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/raymond.stevens.1/bibliograpahy/40521653/public/?sort=date&direction=ascending