

## ***Curriculum Vitae***

### **Daniel M. Rosenbaum**

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### **PERSONAL STATEMENT**

My lab studies the structural and dynamic properties of integral membrane signaling proteins. These proteins sense changes in the cellular environment, such as the presence of hormones or alteration of lipid composition, and their disruption is involved in many human diseases. My group focuses on the mechanisms of G protein-coupled receptors (GPCRs), as well as proteins in the SREBP pathway that regulate sterol and lipid homeostasis. I pioneered the use of protein engineering and lipid-mediated crystallization to overcome numerous challenges associated with human membrane protein structure determination. These techniques led to the first atomic structures of GPCRs for soluble hormones and neurotransmitters, and have now been used by labs in academia and industry to obtain atomic structures of over 50 human GPCRs. My lab has applied these technologies to solve structures of CNS GPCRs, including the human orexin receptors and the CB1 cannabinoid receptor, representing major breakthroughs in understanding these therapeutically important GPCRs. We are now using techniques such as NMR and cryo-electron microscopy to understand how lipid membrane composition modulates receptor structure and function. This goal overlaps with our work on the SREBP pathway, where we have made progress toward structure determination of the endoplasmic reticulum membrane protein Scap. This molecule is a critical sensor and modulator of cholesterol concentration in mammalian cells. We operate at a very basic biophysical level to unravel the atomic molecular mechanisms of these proteins, but each of the systems we study has immediate therapeutic importance in human disease, and we aim to translate our biophysical insights into new therapeutic strategies.

### **EDUCATION**

1999-2005                      Ph.D., Chemistry and Chemical Biology, Harvard University,  
Cambridge, Massachusetts.

1995-1999 B.A., Chemistry, Princeton University, Princeton, New Jersey.

## **POSITIONS**

2017-present Associate Professor, Department of Biophysics, University of Texas Southwestern, Dallas, Texas.

2010-2017 Assistant Professor, Department of Biophysics, University of Texas Southwestern, Dallas, Texas.

2005-2010 Postdoctoral Fellow, lab of Dr. Brian Kobilka, Department of Molecular and Cellular Physiology, Stanford University.

1999-2005 Graduate Student, lab of Dr. David Liu, Department of Chemistry and Chemical Biology, Harvard University.

## **AWARDS**

2017 Mallinckrodt Scholar

2016 Amgen Young Investigator Award

2012 Packard Fellowship

2012 Searle Scholar

2010-present UT Southwestern Endowed Scholar

2007-2009 NIH NRSA Postdoctoral Fellowship

2000-2005 Hertz Foundation Graduate Fellowship

1999 *Phi Beta Kappa*, Princeton University

1999 Merck Index Senior Thesis Award, Department of Chemistry, Princeton University

## **TEACHING**

2017-present University of Texas Southwestern Medical Center at Dallas. Director of Proteins Curriculum of the Core Course for first-year graduate students.

- 2011-present University of Texas Southwestern Medical Center at Dallas. Taught lectures in the Core Course for first-year graduate students, and Medical Biochemistry for medical students.
- 2006-2010 Department of Molecular and Cellular Physiology, Stanford University School of Medicine. Mentored graduate students and undergraduates in the lab of Dr. Brian Kobilka.
- 2002 Department of Chemistry and Chemical Biology, Harvard University. Helped to develop graduate course "Macromolecular Structure and Function."

### **CURRENT RESEARCH SUPPORT**

NIH R01 NS097594 9/1/17 – 8/31/21

Title: "Structural elucidation and development of agonists for the human orexin receptors"

NIH R01 GM113050 1/01/15 – 12/31/20

Title: "Molecular mechanism of a master regulator of sterol homeostasis"

Welch Foundation I-1770 6/01/14 – 5/31/17

Title: "Structural studies of active and inactive conformations of G protein-coupled receptors"

Mallinckrodt Scholar 10/01/17 – 10/01/21

Title: "Allosteric mechanism and modulation of CNS GPCRs"

### **PREVIOUS RESEARCH SUPPORT**

Packard Fellowship 10/01/12 – 10/01/17

Title: "Structure determination of eukaryotic membrane proteins using eukaryotic thermophiles"

Searle Scholars

6/01/12 – 6/01/15

Title: “Mechanisms of integral membrane signaling proteins involved in human disease”

NIH NRSA (NIGMS)

5F32GM082028-02

8/01/07 – 1/31/09

Title: “Structural elucidation of GPCRs using engineered protein fusions”

## **INVITED LECTURES**

- 2019 Texas Tech, Lubbock TX
- 2019 University of Pittsburgh, Pharmaceutical Sciences
- 2019 University of Florida, Dept. of Chemistry
- 2018 UNT Health Sciences Center, Fort Worth TX
- 2018 Royal Society Symposium on GPCRs, Verona Italy
- 2018 Washington University, Dept. of Biochemistry and Biophysics
- 2018 Keystone Meeting, GPCRs
- 2017 Oklahoma University Health Science Center
- 2017 Goethe University Frankfurt
- 2017 NIH Membrane Protein Interest Group
- 2017 Harvard Medical School, BCMP
- 2016 Amgen Young Investigators Symposium, Cambridge MA
- 2016 American Chemical Society Meeting, Galveston TX
- 2016 University of California, Santa Cruz, Dept. of Chemistry
- 2016 Mount Sinai School of Medicine, Dept. of Pharmacology
- 2015 Membrane Protein Structures 2015, APS, Argonne IL
- 2015 GPCR-Ligand Interactions, Structures, and Transmembrane Signaling, Allschwil, Switzerland.

- 2015 Philipps-University Marburg, Germany, Dept. of Pharmaceutical Chemistry.
- 2010 Gordon Conference: Biopolymers.
- 2008 Drug Discovery Chemistry: GPCR Drug Discovery, San Diego, CA.

## BIBLIOGRAPHY

28. Shao Z, Yan W, Chapman K, Ramesh K, Ferrell A, Yin J, Wang X, Xu Q, **Rosenbaum DM**. Structure of an allosteric modulator bound to the CB1 cannabinoid receptor., *Nat. Chem. Biol.* 15: 1199-1205 (2019).
27. Ali R, Clark LD, Zahm JA, Lemoff A, Ramesh K, **Rosenbaum DM**, Rosen MK. Improved strategy for isoleucine 1H/13C methyl labeling in *Pichia pastoris*, *under revision*, *J. Biomol. NMR.* 73: 687-697 (2019).
26. Uchanski T, Zogg T, Yin J, Yuan D, Wohlkonig A, Fischer B, **Rosenbaum DM**, Kobilka BK, Pardon E, Steyaert J. An improved yeast surface display platform for the screening of nanobody immune libraries. *Sci. Rep.* 9: 382 (2019).
25. Dikiy I, Clark LD, Gardner KH, **Rosenbaum DM**. Isotopic labeling of eukaryotic membrane proteins for NMR studies of interactions and dynamics. *Methods Enzymol.* 614: 37-65 (2019).
24. Yin J, Chapman K, Clark LD, Shao Z, Borek D, Xu Q, Wang J, **Rosenbaum DM**. Crystal structure of the human NK<sub>1</sub> tachykinin receptor. *Proc. Natl. Acad. Sci. USA.* 115: 13264-13269 (2018).
23. Clark LD, Dikiy I, **Rosenbaum DM**, Gardner KH. On the use of *Pichia pastoris* for isotopic labeling of human GPCRs for NMR studies. *J. Biomolecular NMR.* 71: 203-211 (2018).
22. Suno R, Kimura KT, Nakane T, Yamashita K, Wang J, Fujiwara T, Yamanaka Y, Im D, Horita S, Tsujimoto H, Tawaramoto MS, Hirokawa T, Nango E, Tono K, Kameshima T, Hatsui T, Joti Y, Yabashi M, Shimamoto K, Yamamoto M, **Rosenbaum DM**, Iwata S, Shimamura T, Kobayashi T. Crystal structures of human orexin 2 receptor bound to the subtype-selective antagonist EMPA. *Structure.* 26: 7-19 (2018).
21. Clark LD, Dikiy I, Chapman K, Rodstrom KE, Aramini J, LeVine MV, Khelashvili G, Rasmussen SG, Gardner KH, **Rosenbaum DM**. Ligand modulation of sidechain dynamics in a wild-type human GPCR. *Elife.* Oct 6; 6: e28505 (2017).

20. Lee JY, **Rosenbaum DM**. Transporters revealed. *Cell*. 168: 951-953 (2017).
19. Yin J, **Rosenbaum DM**. The human orexin/hypocretin receptor crystal structures. *Curr. Top. Behav. Neurosci.* Dec 27, 1-15 (2016)
18. Shao Z, Yin J, Chapman K, Grzemska M, Clark L, Wang J, **Rosenbaum DM**. High-resolution crystal structure of the human CB1 cannabinoid receptor. *Nature*. 540: 602-606 (2016).
17. Lee JY, Kinch LN, Borek DM, Wang J, Wang J, Urbatsch IL, Xie XS, Grishin NV, Cohen JC, Otwinowski Z, Hobbs HH, **Rosenbaum DM**. Crystal structure of the human sterol transporter ABCG5/ABCG8. *Nature*. 533: 561-564 (2016).
16. Zhang Y, Lee KM, Kinch LN, Grishin NV, **Rosenbaum DM**, Brown MS, Goldstein JL, Radhakrishnan A. Direct demonstration that Loop1 of Scap binds to Loop7: A crucial event in cholesterol homeostasis. *J. Biol. Chem.* 291: 12888-12896 (2016).
15. Yin J, Babaoglu K, Brautigam CA, Clark L, Shao Z, Scheuermann TH, Harrell CM, Gotter AL, Roecker AJ, Winrow CJ, Renger JJ, Coleman PJ, **Rosenbaum DM**. Structure and ligand-binding mechanism of the human OX1 and OX2 orexin receptors. *Nat. Struct. Mol. Biol.* 23: 293-299 (2016).
14. Clark L, Zahm JA, Ali R, Kukula M, Bian L, Patrie SM, Gardner KH, Rosen MK, **Rosenbaum DM**. Methyl labeling and TROSY NMR spectroscopy of proteins expressed in the eukaryote *Pichia pastoris*. *J. Biomolecular NMR*. 62: 239-245 (2015).
13. Yin J, Mobarec JC, Kolb P, **Rosenbaum DM**. Crystal structure of the human OX<sub>2</sub> orexin receptor bound to the insomnia drug suvorexant. *Nature*. 519: 247-250 (2015).
12. Kruse AC, Hu J, Pan AC, Arlow DH, **Rosenbaum DM**, Rosemond E, Green HF, Liu T, Chae PS, Dror RO, Shaw DE, Weis WI, Wess J, Kobilka BK. Structure and dynamics of the M3 muscarinic acetylcholine receptor. *Nature*. 482: 552-556 (2012).
11. **Rosenbaum DM**, Zhang C, Lyons JA, Holl R, Aragao D, Arlow DH, Rasmussen SGF, Choi HJ, DeVree BT, Sunahara RK, Chae PS, Gellman SH, Dror RO, Shaw DE, Weis WI, Caffrey M, Gmeiner P, Kobilka BK. Structure and function of an irreversible agonist-beta2 adrenoceptor complex. *Nature*. 469: 236-240 (2011).
10. Rasmussen SGF, Choi HJ, Fung JJ, Pardon E, Casarosa P, Chae PS, DeVree BT, **Rosenbaum DM**, Thian FS, Kobilka TS, Schnapp A, Konetzki I,

Sunahara RK, Gellman SH, Pautsch A, Steyaert J, Weis WI, Kobilka BK. Structure of a nanobody-stabilized active state of the beta2 adrenoceptor. *Nature*. 469: 175-180 (2011).

9. Bokoch MP, Zou Y, Rasmussen SG, Liu CW, Nygaard R, **Rosenbaum DM**, Fung JJ, Choi HJ, Thian FS, Kobilka TS, Puglisi JD, Weis WI, Pardo L, Prosser RS, Mueller L, Kobilka BK. Ligand-specific regulation of the extracellular surface of a G-protein-coupled receptor. *Nature*. 463: 108-112 (2010).
8. **Rosenbaum DM**, Rasmussen SGF, Kobilka BK. The Structure and Function of G-Protein-Coupled Receptors. *Nature*. 459: 356-363 (2009).
7. Kolb P\*, **Rosenbaum DM\***, Irwin JJ, Fung JJ, Kobilka BK, Shoichet BK. Structure-based discovery of beta2-adrenergic receptor ligands. *Proc. Natl. Acad. Sci. USA*. 106: 6843-6848 (2009).
6. **Rosenbaum DM\***, Cherezov V\*, Hanson MA, Rasmussen SG, Thian FS, Kobilka TS, Choi HJ, Yao XJ, Weis WI, Stevens RC, Kobilka BK. GPCR engineering yields high-resolution structural insights into beta2-adrenergic receptor function. *Science*. 318: 1266-1273 (2007).
5. Cherezov V\*, **Rosenbaum DM\***, Hanson MA, Rasmussen SG, Thian FS, Kobilka TS, Choi HJ, Kuhn P, Weis WI, Kobilka BK, Stevens RC. High-resolution crystal structure of an engineered human beta2-adrenergic G protein-coupled receptor. *Science*. 318: 1258-1265 (2007).
4. Rasmussen SG\*, Choi HJ\*, **Rosenbaum DM\***, Kobilka TS, Thian FS, Edwards PC, Burghammer M, Ratnala VR, Sanishvili R, Fischetti RF, Schertler GF, Weis WI, Kobilka BK. Crystal structure of the human beta2 adrenergic G-protein-coupled receptor. *Nature*. 450: 383-387 (2007).
3. Phillips KM, **Rosenbaum DM**, Liu DR. Binding and stability determinants of the PPAR gamma nuclear receptor-coactivator interface as revealed by shotgun alanine scanning and in vivo selection. *J. Am. Chem. Soc.* 128: 11298-11306 (2006).
2. **Rosenbaum DM**, Liu DR. Efficient and Sequence-specific DNA-templated Polymerization of PNA aldehydes. *J. Am. Chem. Soc.* 125: 13924-13925 (2003).
1. **Rosenbaum DM**, Roy S, Hecht MH. Screening Combinatorial Libraries of *De Novo* Proteins by Hydrogen-Deuterium Exchange and Electrospray Mass Spectrometry. *J. Am. Chem. Soc.* 121: 9509-9513 (1999).

\* contributed equally

## Book Chapters

1. **Rosenbaum DM**, Rasmussen SGF, Kobilka BK. The  $\beta_2$  Adrenergic Receptor as a Model for G-Protein-Coupled Receptor Structure and Activation by Diffusible Hormones. *In Handbook of Cell Signaling 2<sup>nd</sup> Ed.*, Chapter 25, pp. 163-169 (2009).

## Patents

2. **Rosenbaum DM**, Kobilka BK. "Method and Composition for Crystallizing G Protein-Coupled Receptors." US Patent No. 7,790,850 (2008).
1. Liu DR, Gartner Z, **Rosenbaum DM**, Gruen M, Doyon J. "In Vivo Selection System for Enzyme Activity." US Patent No. 7,476,500 (2002).