BIOGRAPHICAL SKETCH

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NAME: Gibbs, Eric

eRA COMMONS USER NAME (credential, e.g., agency login): EGIBBS2

POSITION TITLE: Postdoctoral Scholar

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
Brigham Young University, Provo UT	B.S.	08/2007	08/2013	Physics
Duke University, Durham NC	PhD.	08/2013	12/2018	Biomedical Engineering
Case Western Reserve University, Cleveland OH	Postdoctoral	01/2019	Present	Biophysics

A. Personal Statement

My career vision is to combine a deep curiosity of fundamental processes with outcomes relevant to human health. This has led me to develop the broad skillset and character necessary to succeed in research. I did my doctoral research under Dr. Chunlei Liu, whose interests include studying molecular structure by MRI and protein engineering. I developed a passion for ion channel research and did my dissertation research on the in vitro properties of purportedly radiofrequency wave (RF)-sensitive ion channels. My doctoral research resulted in a broad skillset in MRI, image processing, RF engineering, molecular biology, cell culture and calcium imaging. Aside from my technical skills, I faced significant challenges when Dr. Liu changed institutions in the middle of my PhD. Through this process I learned to become an independent and intrinsically motivated researcher.

These skills have been useful during my four years of postdoctoral research under Dr. Sudha Chakrapani. My research has focused on the structure and function of the glycine receptor, a pentameric ligand-gated chloride channel. During this time, I have expressed and purified a heteromeric glycine receptor for cryo-EM studies and solved its structure in several different ligand states. This work has resulted in a first author publication that has recently been accepted.

I plan to use the remainder of my postdoctoral mentorship to do further work with glycine receptors and expand my technical expertise in cryo-EM. I also plan to expand to other proteins that are relevant to glycine receptor signaling and incorporate new techniques such as cryo-ET and native mass spectrometry to my research. My long-term goals are to expand my studies beyond glycine receptors to other proteins relevant to the maintenance and function of glycinergic synapses. This will provide a broader paradigm that will be useful for therapeutic intervention of chronic pain.

1. **Gibbs E.**, Klemm E., Seiferth D., Kumar A., Ilca S.L., Biggin P.C, Chakrapani S. “Conformational transitions in a heteromeric glycine receptor associated with antagonism, agonism, and positive allosteric modulation.” Accepted manuscript.
2. Basak, S., Kumar A., Ramsey S., **Gibbs E.**, Kapoor A., Filizola M., and Chakrapani S. "High-resolution Structures of multiple 5-HT3AR-setron complexes reveal a novel mechanism of competitive inhibition." *Elife* 9 (2020): e57870.
3. **Gibbs, E.** and Chakrapani, S. Structure, Function and Physiology of 5-Hydroxytryptamine Receptors Subtype 3 in Subcellular Biochemistry: Macromolecular Protein Complexes III. Editors: Dr. J. Robin Harris and Dr. Jon Marles-Wright

4. Hutson, M. R., Keyte, A. L., Hernández-Morales, M., **Gibbs, E.**, Kupchinsky, Z. A., Argyridis, I., Erwin, K.N., Pegram, K., Kneifel, M. Rosenburg, P.B., Matak, P., Xie, L., Grandl, J., Davis, E.E., Katsanis, N., Liu, C., Benner, E.J. (2017). Temperature-activated ion channels in neural crest cells confer maternal fever–associated birth defects. *Science signaling*, *10* (500).
5. **Gibbs, E.**, & Liu, C. (2015). Feasibility of imaging tissue electrical conductivity by switching field gradients with MRI. *Tomography*, *1*(2), 125.

B. Positions and Honors

Positions and Employment

2017 Summer internship program at Genentech, S. San Francisco, CA

NIH Grants

F32 Cryo-EM Studies of the Structure and Allosteric Mechanisms of Heteromeric Glycine Receptor, Case Western Reserve University, Feb.2022 – Jan. 2023
T32 Medical Imaging Training Program, Duke University. Sept. 2015 – Nov. 2017
T32 Structural Biology and Biophysics, Duke University. Sept. 2013 – Sept. 2015

Other Experience and Professional Membership

2019-present Member, Biophysical Society

Honors

2023 Travel Award for the 2023 Annual Meeting of the Biophysical Society
2022 Discussion Leader at the Gordon Research Seminar: Ion Channels
2013 *magna cum laude,* Department of Physics, Brigham Young University, Provo UT
2013 Chancellor's scholar at Duke University
2013 Appointment to the Structural Biology and Biophysics training program at Duke University
2013 Appointment to the Medical Imaging Training Program at Duke University

C. Contributions to Science

1. **Postdoctoral Research**: My research focus has been on structural studies of heteromeric glycine receptors by cryo-EM. Heteromeric glycine receptors are ligand-gated chloride channels that provide inhibitory input to spinal cord neurons. I led this project by expressing and purifying hetero-GlyR, preparing cryo-EM grids, cryo-EM imaging and data processing. This resulted in high resolution structures in the presence of different ligands that represent multiple functional states. A paper describing this work has recently been accepted. I also contributed to a 5-HT_3R project done by Sandip Basak by creating quantitative visual representations of differences between setron-bound structures and wrote a book chapter on 5-HT_3R structure function and physiology.
   -**Gibbs E.**, Klemm E., Seiferth D., Kumar A., Ilca S.L., Biggin P.C, Chakrapani S. "Conformational transitions in a heteromeric glycine receptor associated with antagonism, agonism, and positive allosteric modulation." Accepted manuscript
   -Basak, S., Kumar A., Ramsey S., **Gibbs E.**, Kapoor A., Filizola M., and Chakrapani S. "High-resolution Structures of multiple 5-HT3AR-setron complexes reveal a novel mechanism of competitive inhibition." *Elife* 9 (2020): e57870.
   -**Gibbs, E.** and Chakrapani, S. Structure, Function and Physiology of 5-Hydroxytryptamine Receptors Subtype 3 in Subcellular Biochemistry: Macromolecular Protein Complexes III. Editors: Dr. J. Robin Harris and Dr. Jon Marles-Wright
2. **PhD. Dissertation Research**: Ferritin-based magnetogenetic ion channels have been proposed as tools for non-invasive manipulation of ion channel activity. Initial positive reports of their use *in vivo* and *in vitro* has sparked significant controversy in the field because predicted interactions are negligible between ferritin and a static or alternating magnetic field. My dissertation research directly addresses this controversy for reported magnetogenetic channels $TRPV1^{FeRIC}$ and $TRPV4^{FeRIC}$ by re-examining original *in vitro* experiments, addressing possible conflicting factors and conducting more definitive Fura-2 calcium imaging experiments. Careful analysis of thousands of cells demonstrated, contrary to

initial reports, that an alternating magnetic field does not differentially affect HEK 293 cells expressing TRPV1^{FeRIC} or TRPV4^{FeRIC}. This does not necessarily conflict with *in vivo* results but suggests that additional factors are required for the reported *in vivo* effects. This work was done at Duke University under the guidance of my PhD. advisor, Chunlei Liu and in close collaboration with Dr. Eric Benner and Dr. Mary Hutson also at Duke.

-Hutson, M. R., Keyte, A. L., Hernández-Morales, M., **Gibbs, E.**, Kupchinsky, Z. A., Argyridis, I., Erwin, K.N., Pegram, K., Kneifel, M. Rosenburg, P.B., Matak, P., Xie, L., Grandl, J., Davis, E.E., Katsanis, N., Liu, C., Benner, E.J. (2017). Temperature-activated ion channels in neural crest cells confer maternal fever–associated birth defects. *Science signaling*, *10*(500)

3. **Additional PhD. Research:** Low-frequency tissue conductivity is a potential biomarker of disease and an important safety consideration in certain medical procedures. However, tissue conductivity is not easily measured in living patients. It was proposed that under certain conditions, there is a portion of the MRI signal that could be used to non-invasively measure low-frequency tissue conductivity. I explored sequences and post-acquisition processing to maximize this signal. I demonstrated by simulation and MRI experiments that the noise inherent to MRI is much greater than the conductivity dependent signal. This work was done at Duke University under the guidance of my PhD. advisor, Chunlei Liu.

   -**Gibbs, E.**, & Liu, C. (2015). Feasibility of imaging tissue electrical conductivity by switching field gradients with MRI. *Tomography*, *1*(2), 125.

4. **Undergraduate Research:** Neutron diffraction data can be used to determine the magnetic properties of novel materials. My research focused on methodology for determining the magnetic properties of complex magnetic materials. Dr. Branton Campbell developed a sparse representation of magnetic crystal properties known as magnetic symmetry mode analysis. To test this method, I prepared a sample of anti-ferromagnetic $LaMnO_3$ and collected neutron diffraction data at Oak Ridge National Laboratory. With this data, I applied magnetic symmetry mode analysis and global search techniques to determine the magnetic structure $LaMnO_3$. This work was done under the guidance of Dr. Branton Campbell at Brigham Young University.

D. Additional Information: Research Support and/or Scholastic Performance

YEAR	COURSE TITLE	GRADE
	DUKE UNIVSERITY	
2013	Structural Biochemistry I	A
2013	Structural Biochemistry II	A
2013	Physical Biochemistry	A
2013	Responsible Conduct in Research	CR
2014	Intro to Physiology	B
2014	Radiation Therapy Physics	A
2014	Nuclear Medicine Physics	A-
2014	Signals and Systems	B
2014	Random Signals and Noise	A-
2014	Scientific Computing	A
2015	Digital Signal Processing	A
2015	Biophysics of Neuroscience Tools	A
2015	MRI: Principles and Sequence Design	A
2015	Radiology in Practice	A-

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Chakrapani, Sudha

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

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 Madras, Chennai, India	B.S.	06/1995	Chemistry
University of Pune, India	M.S.	06/1997	Biochemistry
Indian Institute of Technology, India	M.Tech.	02/1999	Biomedical Engineering
University at Buffalo, Buffalo, NY	Ph.D.	05/2004	Physiology & Biophysics
University of Virginia, Charlottesville, VA	Postdoctoral	01/2006	Physiology & Biophysics
University of Chicago, Chicago, IL	Postdoctoral	07/2008	Physiology & Biophysics

A. Personal Statement

My long-standing scientific interest has been in developing a molecular-level understanding of the ion-transport phenomenon across cellular membranes that occurs under normal and pathophysiological conditions. My research over the last 23 years has focused on ion channels that mediate fast synaptic transmission at the neuronal and neuromuscular junction; namely, ligand- and voltage- gated ion channels. My scientific approach is a combination of cutting-edge multidisciplinary tools that includes Cryo-EM and X-ray crystallography for high-resolution structure determination, EPR spectroscopy for protein dynamic measurements, and electrophysiology for functional characterization of ion channels. We solved the first cryo-EM structure of the full-length 5-HT_{3A}R channel in its resting conformation and the structures of full-length glycine receptors in a lipid environment (*Nature Communications, 2018, 2020*). Our findings have revealed the intricate details of conformational changes underlying channel activation and allosteric modulation by endogenous ligands and drug molecules (Nature, 2018; *Nature Communications, 2019, 2022; eLIFE 2020)*. Using a range of diverse structural, dynamics, and functional approaches, we are continuing to address some of the fundamental questions in the membrane protein field that have remained elusive so far.

Administrative and leadership experience: In 2018, I took on the Directorship of the Cryo-Electron Microscopic Core (Cryo-EM Core) at the CWRU SOM and oversaw the establishment of the high-resolution imaging facility including building renovation, installation of the Titan Krios, recruitment of technical staff, and the development and administration of the Cryo-EM Pilot Grant Program. In 2020, I was appointed as the Director of the Cleveland Center for Membrane and Structural Biology (CCMSB). In this role, I am directly involved in many initiatives at CWRU SOM to strengthen the structural biology area including NIH-funded expansion of Cryo-EM instrumentation, development of a formal multi-institution training program in structural biology and molecular biophysics, and recruitment of tenured and tenure-track faculty in these areas.

Teaching and Mentoring: I have been extremely fortunate to work with and mentor extremely talented individuals who have helped build my research program and are an integral part of what we have achieved as a team. In the last 10 years, *I have trained 7 graduate students (past and current) of which 5 are female.* All my predoctoral trainees and postdoctoral trainees have remained in biomedical science professions. Among past trainees from

the lab, two of the five predoctoral trainees hold leadership positions in pharmaceutical industries and two of the three postdoctoral trainees are independent PIs with faculty positions. In addition, I have participated in 33 graduate student thesis progress committees, of which I am Chair on 7 of them. Among the accolades won by my trainees, the notable ones include postdoctoral Fellowships from the American Heart Association by Dr. Basak, and Dr. Arvind Kumar; F31 NIH postdoctoral Fellowship to Dr. Gibbs, Biophysical Society Student Travel Award and the University of Chicago postdoctoral Fellowship by Dr. Nicholas Schmandt, and the *Recknagel Award* from the DPB by Ms. Yvonne Gicheru and Ms. Kayla Kindig. Over the last ten years, my lab has hosted nine students from the DPB Summer Undergraduate Research Program and the Heart Lung Blood Summer Research Program. Two of these students, Ross Bonner and Lauren Talley (URM), are contributing authors on a paper in *Journal of General Physiology, 2015*. I am on the mentoring Committee of 6 Junior faculty members to provide them guidance on grants, tenure, promotion, and professional growth. Since 2012, I serve on the Graduate Education Committee at the Department of Physiology and Biophysics, and in 2019 was appointed to the MSTP Steering Committee. I am certified as a Trained Facilitator of the *Entering Mentoring* curricula published by CIMER and will be leading mentoring training for the Faculty at the CWRU SOM. Toward contributing to the Cleveland community, I participate in *True2U*, a volunteer mentoring program that helps Cleveland Metropolitan School District 8th graders prepare to make the most of high school and put them on a path to career readiness. The Cryo-EM Core and CWRU SOM are working with the Ohio Academic Resources Network (OARnet) on a proposal to develop statewide research and teaching DMZ and VPN network infrastructure for secure, high-quality access to the shared network-accessible resources. We hope to provide teaching tools and virtual sessions on Cryo-EM applications to nine smaller higher education institutions in the state. These efforts are geared toward improving the exposure of these students to various science and research-related career paths.

Specific to Dr. Gibbs' K99/R00 Proposal. Dr. Gibbs and I have worked for the last four years on a challenging system of pentameric ligand-gated ion channels- the heteromeric GlyR. Together, we have developed several tools and uncovered many exciting properties of these channels that set the stage for the proposed work in the K99 mentored phase and extend to new directions planned for the R00 phase. I am deeply committed to Dr. Gibbs' development as an independent scientist. I will ensure an enriching mentored phase and help lay the groundwork for a productive independent academic career.

Ongoing and recently completed projects that I would like to highlight include:
NIH R35 GM134896
Chakrapani (PI)
01/01/20 – 12/31/24
Structure and Function of Pentameric Ligand-Gated Ion Channels

Completed Research Support
NIH R01 GM131216
Chakrapani (PI)
01/1/19 – 12/31/22
Structure, Function, and Modulation of Serotonin (3A) receptors"
(Rolled into R35 MIRA Award).

NIH R01 GM108921
Chakrapani (PI)
09/1/14 – 08/31/20
Molecular Mechanisms of Desensitization and Drug Modulation in Ligand-Gated Ion Channels.
(Renewal funded as R35 MIRA Award)

Citations:

1. Basak S, Gicheru Y, Rao S, Sansom MSP, **Chakrapani S***. (2018) Cryo-EM reveals two distinct serotonin-bound conformations of full-length 5-HT3A receptor. ***Nature***.;563(7730):270-4. doi: 10.1038/s41586-018-0660-7. PubMed PMID: 30401837; PMCID:PMC6237196 (*Article Recommended by Faculty 1000)*
2. Basak S[a], Gicheru Y[a], Kapoor A., Mayer ML., Filizola M, and **Chakrapani S***. (2019) Molecular mechanism of setron-mediated inhibition of full-length 5-HT3A receptors. ***Nature Communications*** 10, 3225, doi:10.1038/s41467-019-11142-8. PMCID:PMC6642186

3. Basak S, Kumar A, Ramsey S, Gibbs E, Kapoor A, Filizola M, Chakrapani S. High-resolution structures of multiple 5-HT3AR-setron complexes reveal a novel mechanism of competitive inhibition. **eLife**. 2020;9. Epub 2020/10/17. doi: 10.7554/eLife.57870. PubMed PMID: 33063666.
4. Kumar A, Kindig K, Rao S, Zaki AM, Basak S, Sansom MSP, Biggin PC, Chakrapani S. Structural basis for cannabinoid-induced potentiation of alpha1-glycine receptors in lipid nanodiscs. ***Nature Communications***. 2022;13(1):4862. Epub 2022/08/19. doi: 10.1038/s41467-022-32594-5. PubMed PMID: 35982060; PMCID: PMC9388682.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022-present Interim Chair, Department of Pharmacology, Case Western Reserve University, Cleveland, OH
2020-present Director, Cleveland Center for Membrane and Structural Biology, Case Western Reserve University, Cleveland, OH
2020-present Professor, Department of Physiology and Biophysics, Case Western Reserve University, Cleveland, OH
2018-present Director, Cryo-Electron Microscopy Core, Case Western Reserve University, Cleveland, OH
2017-2020 Associate Professor (Tenured), Department of Physiology and Biophysics, Case Western Reserve University, Cleveland, OH
2010-2017 Assistant Professor (Tenure-track), Department of Physiology and Biophysics, Case Western Reserve University, Cleveland, OH
2008-2010 Research Assistant Professor, Department of Biochemistry and Molecular Biology, University of Chicago, Chicago, IL

Other Experience and Professional Memberships

2026 *Co-Chair*, Ion Channels Gordon Research Conference
2025 *Program Co-Chair*, 2025 Annual meeting of the Biophysical Society.
2022 *Mentor*, Junior Faculty Mentoring Cohort, *Journal of General Physiology*.
2019-2023 *Permanent Member*, Biochemistry and Biophysics of Membranes, NIH Study Section.
2022-2025 Associate Editor, Biophysical Journal
2018-2020 Reviewer, United States-Israel Binational Science Foundation
2018-present Editorial Advisory Board, Journal of General Physiology
2018 Reviewer, French National Research Agency (ANR), France
2018 Ad hoc Reviewer, NIH BPNS study Section (Feb cycle).
2017-2018 Reviewer, MCMB grant proposal, Medical Research Council (MRC) UK
2016-2019 Ad hoc Reviewer, NIH BBM study Section
2015-2018 Councilor (elected to office), Society for General Physiologists.
2015-2021 Committee for Professional Opportunities for Women Committee (CPOW), Biophysical Society
2015-2017 Reviewer, American Heart Association (Basic Cell, Proteins & Crystallography1 and Proteins & Crystallography 1 and 3)
2015-present Member, Society for General Physiology
2014 Reviewer, NIGMS Program Projects Grants (P01) special emphasis panel
2012-2013 Panelist, Early Career Development Committee, Biophysical Society
2010-present Member, American Heart Association
2003-present Member, Biophysical Society

Honors

2022 *Keynote Speaker*, Ion Channels GRC at Mt. Holyoke College MA
2019-present Joseph T. Wearn, MD, University Professorship in Medicine
2018 CWRU nominee for the Mallinckrodt Scholar Program.
2012-2016 Scientist Development Grant, American Heart Association.
2007-2008 Postdoctoral Fellowship (Competitive Renewal), American Heart Association

2005-2008	Postdoctoral Fellowship, American Heart Association
2004	University at Buffalo nominee for the CGS/UMI Distinguished Dissertation award.
2004	Dean's Award for Outstanding Dissertation, First Prize. University at Buffalo, SUNY.
2004	Herbert Schuel Award for outstanding research in the field of Cell and Developmental Biology, University at Buffalo, SUNY.
1999	Selected for the Cambridge Commonwealth Trust Scholarship and Overseas Research Scholar Award.
1997-1999	Biomedical Engineering Scholarship, Indian Institute of Technology, Bombay, India
1997	Selected for Junior Research Fellowship, Council for Scientific and Industrial Research, India
1995-1997	National Chemical Laboratory Scholarship, Pune, India

C. Contributions to Science

1. Structure-function relationships in nicotinic Acetylcholine receptors. One of the fundamental challenges in the ion channel field is to understand how spatially-separated structural motifs of the channel communicate in order to fine-tune its function. In my doctoral research, I addressed this question in nicotinic acetylcholine receptor-channels (nAChR) that belong to the neurotransmitter gated Cys-loop receptor family. These channels are responsible for mediating fast synaptic transmission in neuronal and neuronal muscular junctions. Through single-channel current measurements of over 100 mutations and extensive model-based kinetic analysis within the framework of linear free energy relationships, I found that signal transduction occurs as a sequential movement of rigid "blocks" or "micro-domain" originating at the extracellular ligand-binding domain and culminating at the gate within the transmembrane region. Such an organized and linked motion of rigid bodies may underlie fast dynamics of the allosteric conformational change in these channels. This system also proved ideal to probe the speed-limits of global protein motions in the membrane.

a. **Chakrapani, S**., T.D. Bailey, and A. Auerbach. (2003). The role of loop 5 in acetylcholine receptor channel gating. ***J Gen Physiol***. 122:521-539. PMCID:PMC2229574
b. **Chakrapani, S**., T.D. Bailey, and A. Auerbach. (2004). Gating Dynamics of the Acetylcholine Receptor Extracellular Domain. ***J Gen Physiol***. 123: 341-356. (Featured on the Cover). PMCID:PMC2217457
c. **Chakrapani, S**., and A. Auerbach. (2005). A speed limit for conformational change of an allosteric membrane protein. ***Proc Natl Acad Sci U S A***, 2005. 102(1): p. 87-92. PMCID:PMC544059

2. C-type inactivation and modal gating behavior in K^+ channels. Studying prokaryotic channels provides a unique advantage to draw direct information from structural, dynamics, and functional measurements. However, unlike eukaryotic channels most of the bacterial members were not well-characterized at the functional level, this was particularly the case for KcsA, a pH-activated K^+ channel. As a part of my postdoctoral training, I carried out extensive kinetic analysis both at the macroscopic and single-channel level to characterize C-type inactivation and fast gating events that underlie KcsA function. To obtain high resolution structure of KcsA in multiple conformational states, I crystallized the channel in various mutant forms and in the presence of several modulators. Equating functional states to structural snapshots from crystallography, have led to a better understanding of the structural basis for inactivation from pre-open states, interaction of ions with the channel, modal gating behavior, and transitions that lead to fast gating events.

a. **Chakrapani, S**., Cordero-Morales, J. F., and Perozo, E. (2007a). A quantitative description of KcsA gating I: macroscopic currents. ***J Gen Physiol*** *130*, 465-478. PMCID:PMC2151670
b. **Chakrapani, S**., Cordero-Morales, J. F., and Perozo, E. (2007b). A quantitative description of KcsA gating II: single-channel currents. ***J Gen Physiol*** *130*, 479-496. PMCID:PMC2151667
c. **Chakrapani, S[a].**, Cordero-Morales, J. F[a]., Jogini, V., Pan, A. C., Cortes, D. M., Roux, R., and Perozo, E. (2011) On the structural basis for modal gating in K^+ channels ***Nature Structure & Molecular Biology*** *18 (1),* PMCID:PMC3059741. *[a]equal contribution.*
d. Ostmeyer J, **Chakrapani S**, Pan AC, Perozo E, Roux B. (2013) Recovery from slow inactivation in K+ channels is controlled by water molecules. ***Nature***. 501(7465):121-4. PubMed PMID: 23892782; PMCID:PMC3799803

3. Voltage-sensing mechanism and slow-inactivation in ion channels. Voltage-gated channels play a critical role in cellular excitability and thereby form the basis for initiation and propagation of nerve impulses. The structure of the voltage-sensor and the mechanisms underlying gating-charge movement have been areas intensively

studied. Both the structure and the protein motions in the sensor are critically governed by the local membrane environment. Also as a part of my postdoctoral training, I used site-directed spin labeling and electron paramagnetic resonance (EPR) spectroscopy to directly investigate the architecture of the sensor in a reconstituted system. I studied the dynamics of the isolated voltage-sensors of prokaryotic K^+ (KvAP) and Na^+ (NaChBac) channels by EPR spectroscopy. These findings provided an in-depth view of the architecture of this domain on the membrane along with insights into the open-inactivated state of the channel. More recently, my lab characterized the molecular motions underlying slow-inactivation in voltage-gated Na+ channel (NavSp1) by pulsed-EPR spectroscopy.

a. **Chakrapani, S**., Cuello, L.G., Cortes, D.M., and Perozo, E. (2008). Structural dynamics of an isolated-voltage sensor domain in lipid bilayer. ***Structure*** *16, 398-409* PMCID:PMC2703488
b. **Chakrapani, S**., Sompornpisut, P., Intharathep, P., Roux, B. & Perozo, E. (2010). The activated state of a sodium channel voltage sensor in a membrane environment. ***Proc Natl Acad Sci U S A*** 107, 5435-40. PMCID:PMC2851821
c. **Chakrapani, S**. (2015) EPR studies of gating mechanisms in ion channels ***Methods in Enzymology*** 557:279-306 PMCID:PMC4503332
d. Chatterjee S, Vyas R, Chalamalasetti SV, Sahu ID, Clatot J, Wan X, Lorigan GA, Deschenes I, **Chakrapani S***. The voltage-gated sodium channel pore exhibits conformational flexibility during slow inactivation. ***J Gen Physiol***. 2018;150(9):1333-47. doi: 10.1085/jgp.201812118. PubMed PMID: 30082431; PMCID: PMC6122925.
*This article was featured in a commentary "Progress in Understanding Slow Inactivation Speeds up" Payandeh, J ***Journal of General Physiology*** (2018)

4. Gating mechanisms in pentameric ligand-gated ion channels. Since joining the faculty at Case Western Reserve University as an Assistant professor in 2010, a major research focus of my lab has been to understand allosteric mechanisms in pentameric ligand-gated ion channels (pLGIC). Using prokaryotic homologues GLIC and ELIC as model systems, we elucidated the ligand-induced pore opening mechanism by EPR spectroscopy. Patch-clamp measurements from reconstituted channels were used to show the salient features of desensitization in GLIC that bears resemblance to the mechanism observed in the eukaryotic counterpart. These methods have allowed us to directly measure the effect of membrane lipid constituents on channel function and to determine the underlying changes in protein dynamics under these conditions. In addition, we studied long-range allosteric communications by engineering functional chimeric channels that incorporates domains from different members of the family. By using X-ray crystallography and pulse-EPR measurement, we determined the crystal structure of the chimera and measured ligand-induced structural changes which reveal conformational coupling between domains. More recently, my lab is geared towards applying these approaches in combination with cryo-EM to complex eukaryotic pLGIC. We recently determined the structures of the full-length 5-HT_{3A}R in the apo, and serotonin-bound conformations by single-particle cryo-EM. The structure reveals salient features of the resting, state and the conformational changes underlying serotonin-mediated activation. I served as the principal investigator in all these studies.

a. Basak, S. [a], Schmandt, N. [a], Gicheru, Y [a]., and **Chakrapani, S*.** (2017) Crystal structure and dynamics of a lipid-induced potential desensitized state of a pentameric ligand-gated channel (***eLIFE,*** doi: 10.7554/eLife.23886). PMCID:PMC5378477
b. Basak S, Gicheru Y, Rao S, Sansom MSP, **Chakrapani S***. Cryo-EM reveals two distinct serotonin-bound conformations of full-length 5-HT3A receptor. ***Nature***. 2018;563(7730):270-4. doi: 10.1038/s41586-018-0660-7. PubMed PMID: 30401837. PMCID:PMC6237196 (*Article Recommended by Faculty 1000)*
c. Basak S[a], Gicheru Y[a], Kapoor A., Mayer ML., Filizola M, and **Chakrapani S***. (2019) Molecular mechanism of setron-mediated inhibition of full-length 5-HT3A receptors. ***Nature Communications*** 10, 3225, doi:10.1038/s41467-019-11142-8. PMCID:PMC6642186
d. Kumar A, Basak S, Rao S, Gicheru Y, Mayer ML, Sansom MSP, **Chakrapani S*.** (2020) Mechanisms of activation and desensitization of full length glycine receptors in lipid nanodisc. ***Nature Communications*** Jul 27;11(1):3752. doi: 10.1038/s41467-020-17364-5.PMID: 32719334

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/sudha.chakrapani.1/bibliography/50561146/public/?sort=date&direction=ascending