BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Erlandson, Sarah Cecilia

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

POSITION TITLE: PhD Candidate

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 South Carolina, Columbia	B.S.	05/2015	Biological Sciences, Chemistry (minor), French (minor)
Harvard University	Ph.D.	(05/2021)	Biological and Biomedical Sciences

A. Personal Statement

My long-term research interests involve elucidating the structure and function of therapeutically-relevant cell surface receptors, with the goal of providing a mechanistic understanding of potential drug targets. My academic training and research experience to date have provided me with an excellent background in molecular biology, cell biology, and biochemistry. As an undergraduate, I completed extensive coursework in biological sciences with a minor in chemistry. To complement these studies, I gained experience in biological research through working in the lab of Dr. David Reisman at the University of South Carolina (USC). While at USC, I studied the expression of the Wrap53 gene, an antisense gene to the tumor suppressor p53. I discovered that Wrap53 mRNA levels rise after DNA damage through a mechanism of increased post-transcriptional stability, and I presented this work as my Senior Thesis for South Carolina's Honors College.

During this period, I also explored different areas of biological research and gained skills in a variety of experimental techniques through summer research experiences. To this end, I worked at New England Biolabs, Eisai, the Ecole Polytechnique Fédérale de Lausanne (EPFL), and Pfizer before beginning my graduate education at Harvard University. At EPFL, I participated in project to investigate the mechanism of the depalmitoylation enzyme APT1, which led to my decision to pursue protein structure and function in graduate school.

My goal in graduate school is to receive the best possible training in protein biochemistry and structural biology that will lead to a successful postdoctoral fellowship and eventually an academic faculty research position. Upon beginning the Biological and Biomedical Sciences PhD Program at Harvard University, I completed three rotations in membrane protein biochemistry and chose to join the lab of Dr. Andrew Kruse to work with the relaxin receptor, RXFP1. Over the course of my PhD, I developed an expression and purification strategy for obtaining stable, homogenous RXFP1 and its ligand, relaxin-2. I began cryo-electron microscopy (cryo-EM) studies of an active-state complex of RXFP1 bound to relaxin-2 and have been optimizing grid preparation and data collection parameters over the past year. These efforts have resulted in a preliminary 3D cryo-EM map for the complex. Access to the NCCAT for preparing cryo-EM grids with the Spotiton system/Chameleon has the potential to make a significant impact on my PhD project and may be the key to determining a higher resolution structure of RXFP1.

B. Positions and Honors

Positions and Employment

08/2015 – present	Ph.D. Student, Program in Biological and Biomedical Sciences, Harvard University
08/2016 – 12/2016	Graduate Course Teaching Assistant, Harvard Medical School
06/2015 – 08/2015	Summer Intern, Pfizer
07/2014 – 08/2014	Summer Research Student, Ecole Polytechnique Fédérale de Lausanne
08/2013 – 05/2015	Undergraduate Research Student, University of South Carolina
05/2013 – 08/2013	Summer Intern, Eisai
05/2012 – 08/2012	Summer Intern, New England Biolabs

Honors

2011	Cooper Scholars Award, USC Academic Merit Scholarship
2014	Magellan Scholar Grant from USC's Office of Undergraduate Research
2014	A.C. Moore Scholarship, USC Biological Sciences Departmental Award
2014	*Phi Beta Kappa*
2015	USC Discovery Day Poster Session, First Place, Biological Sciences
2015	Graduated *summa cum laude* from USC and with Honors from the South Carolina Honors College
2018	F31 Fellowship from the NIH (5F31GM128233-02)
2019	Van Maanen Fellowship from the Department of Biological Chemistry and Molecular Pharmacology at Harvard Medical School

C. Contribution to Science

1. Undergraduate Research: My research as an undergraduate in the lab of Dr. David Reisman at USC centered on the regulation of expression of the Wrap53 gene in response to DNA damage. The Wrap53 gene is an antisense gene to p53, an important tumor suppressor, and plays a role in the p53-mediated DNA damage response. It had been reported that the level of Wrap53 mRNA transcript increased upon treatment of cells with DNA damaging agents, and the goal of my undergraduate research was to assess the transcriptional and post-transcriptional components of this induction. My experiments showed that the Wrap53 mRNA half-life was ~2X longer after treatment with particular DNA damaging agents, providing one mechanism for increasing Wrap53 mRNA levels. At USC, I presented these results as my Senior Thesis and through a poster at USC's Discovery Day. The Reisman lab is continuing to investigate the Wrap53 gene, and our collective results will be published in a scientific journal. This work will increase our knowledge of mechanisms involved in DNA damage responses, which are important cellular processes that maintain genomic stability and prevent the development of cancers.
    a. Erlandson S and Reisman D. Wrap53, a modulator of the p53 tumor suppressor, is regulated at both the transcriptional and post-transcriptional levels. 2015. Abstract for poster presentation, USC Discovery Day, Columbia, SC.
2. Graduate Research: My ongoing work as a graduate student in the lab of Dr. Andrew Kruse at Harvard Medical School centers on the relaxin receptor, RXFP1, which is a complex, multi-domain GPCR involved in regulating cardiovascular biology. Despite therapeutic interest in targeting RXFP1 and other leucine-rich repeat-containing GPCRs (LGRs), they remain poorly understood due to a lack of structural data. One major obstacle to structural studies of LGRs is expression and purification of homogeneous receptors on a large scale. Within the past year, I have overcome these challenges for RXFP1 by developing a new strategy for GCPR expression and purification using protein engineering and an inducible mammalian expression system. Additionally, I have established a new method for expression of RXFP1's ligand, relaxin-2, which is also difficult to produce recombinantly. These advances will

greatly contribute to our ability to study the structure and function of RXFP1 and represent techniques that may be applicable to other difficult transmembrane proteins.

D. Research Support

5F31GM128233-02 05/01/18-04/30/21
NIH/NIGMS
The molecular mechanism of relaxin receptor signaling
Goals: The proposed research will provide insights into the structure and function of the G protein-coupled receptor RXFP1, a drug target for the treatment of acute heart failure. A better understanding of the mechanisms underlying RXFP1 signaling will ultimately improve our ability to target this receptor as a therapy for multiple cardiovascular diseases.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Kruse, Andrew Curtis

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

POSITION TITLE: Associate 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 Minnesota, Twin Cities	B.S.	06/2009	Biochemistry, Chemistry (minor)
University of Minnesota, Twin Cities	B.S.Math	06/2009	Mathematics
Stanford University	Ph.D.	04/2014	Structural Biology

A. Personal Statement

My scientific interests center on the structure, dynamics, and therapeutic modulation of integral membrane proteins, with a particular focus on G protein-coupled receptors (GPCRs) important in cardiovascular biology. Previously as a member of the Kobilka lab at Stanford University I developed new technologies for GPCR-targeted antibody discovery and used these to investigate muscarinic acetylcholine receptors. My work led to breakthroughs in understanding the mechanistic basis for GPCR activation and allosteric modulation.

I joined the faculty at Harvard in 2014, and as an independent investigator I have continued to focus on the study and manipulation signal transduction proteins. Important achievements include the development of the GPCR-APEX method for tracking GPCR signaling in live cells, as well as the creation of a synthetic camelid antibody fragment library now in use by more than 300 research groups around the world. My laboratory has made important discoveries regarding the biology and pharmacology many important membrane signaling proteins including sigma receptors, tetraspanins, and immune checkpoint receptors. These experiences have qualified me to be an effective mentor for cryo-electron microscopy studies of the relaxin receptor.

1. Zheng S, Abreu N, Levitz J, Kruse AC. Structural basis for KCTD-mediated rapid desensitization of $GABA_B$ signaling. (2019) ***Nature*** 567, 127-131. PMCID: PMC6405316.
2. McMahon C, Baier AS, Pascolutti R, Wegrecki M, Zheng S, Ong JX, Erlandson SC, Hilger D, Rasmussen SGF, Ring AM, Manglik A*, Kruse AC*. Yeast surface display platform for rapid discovery of conformationally selective nanobodies. (2018) ***Nat. Struct. Mol. Biol***. 25(3):289-296. *Corresponding authors. PMCID: PMC5839991
3. Paek J, Kalocsay M, Staus DP, Wingler L, Pascolutti R, Paulo JA, Gygi SP, Kruse AC. Multidimensional tracking of GPCR signaling via peroxidase-catalyzed proximity labeling. (2017) ***Cell*** 169, 338-349. PMCID: PMC5773094.
4. Zimmerman B, Kelly B, McMillan BJ, Seegar TCM, Dror RO, Kruse AC*, Blacklow SC*. Crystal structure of a full-length human tetraspanin reveals a cholesterol binding pocket. (2016) ***Cell*** 167, 1041-1051. *Co-corresponding. PMCID: PMC5127602.

B. Positions and Honors

Positions and Employment

2017 – present	Associate Professor of Biological Chemistry and Molecular Pharmacology, Harvard Medical School
2014 – 2017	Assistant Professor of Biological Chemistry and Molecular Pharmacology, Harvard Medical School

Honors

2009	Graduation *summa cum laude* and with high distinction, University of Minnesota, Twin Cities
2010	National Science Foundation Graduate Research Fellowship
2015	NIH Director's Early Independence Award
2015	Smith Family Award for Excellence in Biomedical Research
2015	Forbes 30 under 30 list
2016	Vallee Scholars Award
2016	Klingenstein-Simons Fellowship in Neuroscience
2017	Alfred P. Sloan Research Fellowship
2019	Amgen Young Investigator Award

C. Contribution to Science

1. My contributions to GPCR research began with my doctoral work and have continued in my own lab. As a member of the Kobilka lab I determined the first structures of muscarinic acetylcholine receptors, which at the time were among the first structures for any GPCR. I determined the structure of the M_3 muscarinic receptor bound to tiotropium, a drug widely used for the treatment of chronic obstructive pulmonary disease. This research revealed the molecular architecture of the muscarinic receptor family and showed in atomic detail the mechanisms of tiotropium/receptor interaction. In related work, I determined the molecular basis for allosteric modulation of GPCRs by drug-like molecules as well as the activation mechanism for the M_2 muscarinic acetylcholine receptor, in each case employing new methods for antibody fragment discovery to stabilize active states of the receptor. More recently, my GPCR research has focused in large part on the angiotensin II receptor type 1. Using a synthetic antibody discovery platform my group developed we were recently able to determine the structure of this receptor in an activated state, uncovering unique features of activation not seen in other GPCRs.
    a. Haga K*, Kruse AC*, Asada H*, Yurugi-Kobayashi T, Shiroishi M, Zhang C, Weis WI, Okada T, Kobilka BK, Haga T, Kobayashi T. Structure of the human M_2 muscarinic acetylcholine receptor bound to an antagonist. (2012) ***Nature*** 482, 547-551. *Equal contributors. PMCID: PMC3345277
    b. 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 M_3 muscarinic acetylcholine receptor. (2012) ***Nature*** 482, 552-556. PMCID: PMC3529910
    c. Kruse AC*, Ring AM*, Manglik A, Hu J, Hu K, Eitel K, Hübner H, Pardon E, Valant C, Sexton PM, Christopoulos A, Felder CC, Gmeiner P, Steyaert J, Weis WI, Garcia KC, Wess J, Kobilka BK. Activation and allosteric modulation of a muscarinic acetylcholine receptor. (2013) ***Nature*** 504, 101-106. *Equal contributors. PMCID: PMC4020789
    d. Wingler LM, McMahon C, Staus DP, Lefkowitz RJ*, Kruse AC*. Structure of active-state angiotensin receptor stabilized by a synthetic nanobody. (2019) ***Cell***, 176, 479-490. *Co-corresponding. PMCID: PMC6367718.

2. In my own lab, my group members and I have extended techniques and approaches from GPCR research to the study of other integral membrane proteins, including the enigmatic sigma receptors. These highly conserved proteins were originally classified as opioid receptors but were later shown to be unrelated. They are potential targets for treatment of neurodegenerative diseases, psychiatric diseases, and cancer. In 2016, we determined the crystal structure of the human sigma-1 receptor, revealing the molecular basis for disease-associated loss of function mutations and the molecular details of ligand recognition. In subsequent work my lab has studied the sigma-2 receptor, which is

pharmacologically similar to sigma-1 but is genetically unrelated. The identity of the gene encoding the sigma-2 receptor has remained unknown since 1990, until being revealed by my group to be TMEM97, a protein regulator of cholesterol homeostasis. Other efforts in this area have helped to define the chemical features that underlie sigma receptor ligand binding and subtype selectivity.

a. Schmidt HR, Betz RM, Dror RO, Kruse AC. Structural basis for sigma-1 receptor ligand recognition. (2018) ***Nat. Struct. Mol. Biol.*** 25, 981-987. PMCID: PMC6261271
b. Alon A, Schmidt HR, Wood MD, Sahn JJ, Martin SF, Kruse AC. Identification of the gene that codes for the sigma-2 receptor. (2017) ***Proc. Natl. Acad. Sci. U.S.A.*** 114, 7160-7165. PMCID: PMC5502638
c. Schmidt HR, Zheng S, Gurpinar E, Koehl A, Manglik A, Kruse AC. Crystal structure of the human sigma-1 receptor. (2016) ***Nature*** 532, 527-530. PMCID: PMC5550834.

3. In addition to work on human receptors, a new area of research for my group is investigating bacterial membrane protein structure and function with the goal of laying a foundation for novel antibiotic development. This work is part of a collaborative effort with several labs in the Harvard department of Microbiology supported by a Center of Excellence in Translational Research grant from NIAID. In this area, we have contributed to the discovery that proteins of the SEDS family are peptidoglycan polymerases, and more recently we have determined the first crystal structure for a member of this family. In addition, we have solved the structure of the lipid II flippase MurJ from *Escherichia coli*, providing a template for computational inhibitor screens that are now underway.

a. Sjodt M, Brock K, Dobihal G, Rohs PDA, Green AG, Hopf TA, Meeske AJ, Srisuknimit V, Kahne D, Walker S, Marks DS, Bernhardt TG, Rudner DZ, Kruse AC. Structure of the peptidoglycan polymerase RodA resolved by evolutionary coupling analysis. (2018) ***Nature***. 556, 118-121. PMCID: PMC6035859
b. Zheng S, Sham LT, Brock K, Marks DS, Bernhardt TG, Kruse AC. Structure and mutagenic analysis of the lipid II flippase MurJ from *Escherichia coli*. (2018) ***Proc. Natl. Acad. Sci. U. S. A.*** 115, 6709-6714. PMCID: PMC6042122.
c. Meeske AJ, Riley EP, Robins WP, Uehara T, Mekalanos JJ, Kahne D, Walker S, Kruse AC, Bernhardt TG, Rudner DZ. SEDS proteins are a widespread family of bacterial cell wall polymerases. (2016) ***Nature*** 537, 634-638. PMCID: PMC5161649
d. Owens TW, Taylor RJ, Pahil KS, Bertani BR, Ruiz N*, Kruse AC*, Kahne D*. Structural basis of unidirectional export of lipopolysaccharide to the cell surface. (2019) ***Nature*** 567, 550-553. PMCID: PMC6629255. *Co-corresponding

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1b9qt-vwts5AQ/collections/47423175/public/

D. Research Support

Ongoing research support

DP5OD021345 09/15/15-08/31/20
NIH/Office of the Director
Molecular mechanisms of adiponectin signaling and PAQR function
Goals: This project aims to investigate the molecular and mechanistic basis for the signaling of the protein hormone adiponectin, which shows insulin-sensitizing and cardioprotective effects.
Role: PI

Dean's Initiative Grant 07/01/18-06/30/20
Dean's Innovation Fund
Nutrient Sensing and Spore Germination
Goals: This exploratory research grant supports pilot research to investigate the structural basis of nutrient sensing by integral membrane receptors, as well as methods development for evolutionary sequence analysis and antibody fragment targeting of membrane proteins in general.

R01GM119185 08/15/17-04/30/21
NIH/NIGMS
Molecular mechanisms of sigma receptor signaling
Goals: This project seeks to understand sigma receptor function at the molecular level using crystallography and biophysical methods, which with the objective of developing a better understanding of this important protein and its therapeutic potential.
Role: PI

No Project Number 07/01/16-08/31/19
The Esther A. and Joseph Klingenstein Fund
Structure and function of the sigma-1 receptor
Goals: This project supports studies of the sigma-1 receptor ligands with a particular focus on applying computational methods and chemical synthesis to develop new modulators for this receptor and for the poorly characterized sigma-2 receptor.
Role: PI

FG-2017-9226 09/15/17-09/14/19
Alfred P. Sloan Foundation
Goals: This project supports research in transmembrane receptors of the nervous system.
Role: PI

No Project Number 09/01/16-08/31/21
Bert L. and N. Kuggie Vallee Foundation
Mechanisms of sigma-1 receptor function
Goals: This award supports general laboratory research including technology development for antibody fragment discovery targeting integral membrane proteins. Because of remaining funds available from U19AI109764 and short-term foundation grants, expenditure of remaining funds on this award has been delayed to 9/01/18 with the consent of the foundation.
Role: PI

Blavatnik Accelerator Award 07/01/18-09/30/19
Blavatnik Biomedical Accelerator Program
Relaxin receptor agonists as next-generation therapies for heart failure
Goals: The goal of this project is to generate and optimize protein agonists of the relaxin receptor RXFP1 as research tools and potential therapeutic leads targeting this receptor.
Role: PI

Completed research support

U19AI109764 03/01/16-02/28/19
NIH/NIAID
Structural and mechanistic basis for bacterial cell wall assembly
Goals: This project is a supplement to a Center of Excellence in Translational Research Grant. It supported research to investigate the structure and mechanisms of integral membrane proteins involved in bacterial cell wall biosynthesis in collaboration with several labs in the Harvard Medical School Department of Microbiology.
Role: Co-investigator

No Project Number 01/01/16-12/31/18
Richard and Susan Smith Family Foundation
A new approach to targeting GPCRs
Goals: This project supports the development of novel antibody fragment discovery platforms for the development of tools, reagents, and therapeutics targeting G protein-coupled receptors.
Role: PI

A33633 10/01/17-09/30/18
Morphic Therapeutic
Single domain antibody fragments to study integrins
Goals: This project involves using a yeast-displayed antibody fragment library to discover stabilizers and modulators of integrin signaling.
Role: PI

No project number (Kruse) 11/03/16-07/31/17
Morphic Therapeutic
Derivation of two-domain integrins
Goals: This project involves application of yeast surface display to the engineering of minimized integrins comprised of only the two ligand binding domains. This work, if successful, will enable both basic science research and also drug discovery.
Role: PI

No Project Number 07/01/16-12/31/17
Winthrop Fund/Harvard Brain Science Initiative
Molecular mechanisms of sigma receptor function
Goals: This project supported discovery and engineering of antibody fragments and small molecule ligands of the human sigma-1 receptor.
Role: PI