BIOGRAPHICAL SKETCH

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NAME: Krumm, Brian Eugene

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

POSITION TITLE: Research Assistant 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 Delaware	BS	05/1996	Biochemistry/Biology (minor)
Oklahoma State University	PHD	07/2012	Biochemistry and Molecular Biology
National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health	Postdoctoral	05/2016	Structural Biology
University of North Carolina at Chapel Hill	Postdoctoral	05/2021	Pharmacology and Structural Biology

A. Personal Statement

My interest in understanding proteins began as an undergraduate at the University of Delaware in which I studied the effects of point mutations on the catalytic activity of lysozyme. After receiving my undergraduate degree in Biochemistry from the University of Delaware I relocated to Seattle, WA, where I joined the laboratory of Professor Wim Hol at the University of Washington as a Research Scientist and furthered my understanding of proteins by learning x-ray crystallography. For my PhD research at Oklahoma State University, I focused on understanding protein-protein interactions by determining the three-dimensional structure of Interleukin-18 in complex with a viral inhibitory protein (IL-18BP). Using structural and biophysical methodologies, I identified a common mechanism explaining how viral proteins help circumvent the host innate immune system. For my Postdoctoral research, I chose to change the direction of my research by understanding integral membrane proteins, specifically GPCRs, with the goal of defining how extracellular stimuli translates into an intracellular response and what are the structural effects of this process on the G Protein Coupled Receptor (GPCR). I joined the laboratory of Reinhard Grisshammer at the National Institutes of Health (NIH) and determined three structures of the Neurotensin Receptor (NTSR1), a Class A GPCR, in different activation states that furthered the understanding of how peptide GPCRs are activated. Due to an unexpected closure of the laboratory at NIH, I continued my postdoctoral research by joining the laboratory of Bryan Roth at the University of North Carolina at Chapel Hill to not only broaden my training in GPCR pharmacology but to also continue my efforts in GPCR structural determination. During this period, I helped successfully facilitate the structural determination of multiple GPCRs including the first crystal structure of the active-state kappa opioid receptor in complex with state-distinct nanobody along with the crystal structure of the serotonin 5-HT2A GPCR and the Cryo-Em structure of this receptor and other GPCRs in complex with its cognate G-protein. My efforts along with these structures ultimately will guide pharmacological insights into their activation mechanism and functional selectivity of these receptors.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021 – Present	Research Assistant Professor, University of North Carolina at Chapel Hill
2015 – 2020	Postdoctoral Fellow, University of North Carolina at Chapel Hill
2012 – 2016	Postdoctoral Fellow, National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health
2008 – 2012	Graduate Research Assistant, Oklahoma State University
2008 – Present	Member, American Crystallographic Association
1996 – Present	Member, National Academic Honor Society

Honors

2011 – 2012	Paul and Ruth Jonas Distinguished Graduate Fellowship, Oklahoma State University
2008	2nd Place, Biochemistry and Molecular Biology Graduate Student Symposium, Oklahoma State University
1995 – 1996	Academic Merit Scholarship, Gregory R. Baker '83 Fund, University of Delaware

C. Contributions to Science

1. Through comprehensive studies involving mutagenesis, kinetics, signaling and chemical biology, my future research will reveal new features upon GPCR activation to understand 1) how the binding of agonists from the extracellular side induces allosteric conformational changes in the intracellular part and 2) the structural features responsible for receptor selectivity and biased signaling and identify unique features which confer difference between receptor subtypes. These findings will allow us to identify which parts of the receptor are important for binding to drug-like compounds and where we could chemically modify to make them selectively bind to produce desired effects.
    a. Xu P*, Huang S*, Mao C*, **Krumm BE***, Zhou XE, Tan Y, Huang XP, Liu Y, Jia C, Shen D, Jiang Y, Yu X, Jiang H, Melcher K, Roth BL, Cheng X, Zhang Y, Xu HE (2021) - Structures of the Human Dopamine D3 Receptor-Gi Complexes. Mol Cell, 81(6):1147-1159. *Denotes Equal Contribution
    b. Zhuang Y*, Xu P*, Mao C*, Wang L, **Krumm BE***, Zhou XE*, Huang S, Liu H, Cheng X, Huang XP, Sheng D, Xu T, Liu Y, Wang Y, Guo J, Jiang Y, Jiang H, Melcher K, Roth BL, Zhang C, Zhang Y, Xu HE (2021) – Structural insights into the human D1 and D2 dopamine receptor signaling complexes. Cell, 184(4):931-942. *Denotes Equal Contribution
    c. Zhuang Y*, **Krumm B***, Zhang H*, Zhou E, Wang Y, Guo J, Huang XP, Liu Y, Wang L, Cheng X, Jiang Y, Jiang H, Melcher K, Zhang C, Yi W, Roth BL, Zhang Y, Xu HE (2021) – Mechanism of dopamine binding and allosteric modulation of the human D1 dopamine receptor. Cell Res, 31(5):593-596. *Denotes Equal Contribution
    d. Cao C, Kang HJ, Singh I, Chen H, Zhang C, Ye W, Hayes BW, Liu J, Gumpper RH, Bender BJ, Slocum ST, **Krumm BE**, Lansu K, McCorvy JD, Kroeze WK, English JG, DiBerto JF, Olsen RHJ, Huang XP, Zhang S, Liu Y, Kim K, Karpiak J, Jan LY, Abraham SN, Jin J, Shoichet BK, Fay JF, Roth BL (2021) - Structure, function and pharmacology of human itch GPCRs. Nature, 600(7887):170-175.
    e. Zhang S, Chen H, Zhang C, Yang Y, Popov P, Liu J, **Krumm BE**, Cao C, Kim K, Xiong Y, Katritch V, Shoichet BK, Jin J, Fay JF, Roth BL. (2022) - Inactive and active state structures template selective tools for the human 5-HT_{5A} receptor. Nat Struct Mol Biol, 29(7):677-687.
    f. Cao C, Barros-Álvarez X, Zhang S, Kim K, Dämgen MA, Panova O, Suomivuori CM, Fay JF, Zhong X, **Krumm BE**, Gumpper RH, Seven AB, Robertson MJ, Krogan NJ, Hüttenhain R, Nichols DE, Dror RO, Skiniotis G, Roth BL (2022) - Signaling snapshots of a serotonin receptor activated by the prototypical psychedelic LSD. Neuron, 110(19):3154-3167.
    g. Liu Y, Cao C, Huang XP, Gumpper RH, Rachman MM, Shih SL, **Krumm BE**, Zhang S, Shoichet BK, Fay JF, Roth BL (2022) - Ligand recognition and allosteric modulation of the human MRGPRX1 receptor. Nat Chem Biol (Accepted).

2. **Postdoctoral Career:** my postdoctoral research contributions include determining the three-dimensional structures and pharmacology of G-Protein Coupled Receptors (GPCRs). For my postdoctoral career, I chose to change the direction of my research by understanding integral membrane proteins, specifically GPCRs with the goal of elucidating how extracellular stimuli translates into an intracellular response and what are the structural effects of this process on the GPCR. For the first part of my postdoctoral career I joined the laboratory of Reinhard Grisshammer at the National Institutes of Health (NIH) and focused on using x-ray crystallography to determine the three-dimensional structures of the Neurotensin Receptor (NTSR1), a Class A GPCR, in different activation states. These structures and studies furthered the understanding of how peptide GPCRs are activated. Additionally, I was the first to determine the structure of a GPCR in which a key toggle switch of the CWxP motif was "flipped" for activation. I continued my postdoctoral research by joining the laboratory of Bryan Roth at the University of North Carolina at Chapel Hill to broaden my training in GPCR pharmacology and to continue my efforts in GPCR structural determination. In Dr. Roth's laboratory, I focused on understanding the pharmacology and structural determination of the serotonin, opioid, and dopamine receptors while also continuing my efforts on NTSR1.
    a. **Krumm BE**, White JF, Shah P, Grisshammer R (2015) - Structural prerequisites for G protein activation by the neurotensin receptor. Nature Commun 6:7895.
    b. **Krumm BE**, Lee S, Bhattacharya S, Botos I, White CF, Du H, Vaidehi N, Grisshammer R (2016) - Structure and dynamics of a constitutively active neurotensin receptor. Sci Rep, 6:38564.
    c. Che T, Majumdar S, Zaidi SA, Ondachi P, McCorvy JD, Wang S, Mosier PD, Uprety R, Vardy E, **Krumm BE**, Han GW, Lee MY, Pardon E, Steyaert J, Huang XP, Strachan RT, Tribo AR, Pasternak GW, Carroll FI, Stevens RC, Cherezov V, Katritch V, Wacker D, Roth BL (2018) - Structure of the Nanobody-Stabilized Active State if the Kappa Opioid Receptor. Cell, 172(1-2):55-67.
    d. **Krumm B**, Roth BL (2018) - Activation mechanism for a universal signaling protein. Nature, 557(7705):318-319.
    e. Che T, English J, **Krumm BE**, Kim K, Pardon E, Olsen RHJ, Wang S, Zhang S, Diberto JF, Sciaky N, Carroll FI, Steyaert J, Wacker D, Roth BL (2020) - Nanobody-enabled monitoring of kappa opioid receptor states. Nat Commun, 11(1):1145.
    f. **Krumm B**, Roth BL (2020) - A self-activating orphan receptor. Nature, 579(7797):35-36.
    g. **Krumm B**, Roth BL (2020) - A Structural Understanding of Class B GPCR Selectivity and Activation Revealed. Structure, 28(3):377-379.
    h. Olsen RHJ, DiBerto JF, English JG, Glaudin AM, **Krumm BE**, Slocum ST, Che T, Gavin AC, McCorvy JD, Roth BL, Strachan RT (2020) - TRUPATH, an open-source biosensor platform for interrogating the GPCR transducerome. Nat Chem Bio, 16(8):841-849.
    i. Kim K, Che T, Panova O, DiBerto JF, Lyu J**, Krumm BE**, Wacker D, Robertson MJ, Seven AB, Nichols DE, Shoichet BK, Skiniotis G, Roth BL (2020) - Structure of a Hallucinogen-Activated Gq-Coupled 5-HT2A Serotonin Receptor. Cell, 182(6):1574-1588.

3. **Graduate Career:** My graduate research contributions focused on understanding how dsDNA viruses such as poxviruses evade host immune systems by attenuating the host's immune response via down modulating interleukin/cytokine signaling responses using x-ray crystallography. I was the first to determine two three-dimensional structures of a cytokine (interleukin-18, IL18) in complex with a viral inhibitory protein (IL-18BP). Using structural and biophysical methodologies, I identified a common mechanism explaining how these viral proteins help circumvent the host innate immune system.
    a. **Krumm B**, Meng X, Li Y, Xiang Y, Deng J (2008) Structural basis for antagonism of human interleukin-18 by poxvirus interleukin-18 binding protein. PNAS, 105(52):20711-20715.
    b. **Krumm B**, Meng X, Wang Z, Xiang Y, Deng J (2012) A Unique Bivalent Binding and Inhibition Mechanism by the Yatapoxvirus Interleukin 18 Binding Protein. PLoS Pathog 8(8):e1002976.
    c. Meng X*, **Krumm B***, Li Y, Deng J, Xiang Y (2015) - Structural basis for antagonizing a host restriction factor by C7 family of poxvirus host-range proteins. PNAS, 112(48):14858-63. *Denotes Equal Contribution
    d. **Krumm B**, Meng X, Xiang Y, Deng J (2017) - Identification of small molecule inhibitors of Interleukin-18. Sci Rep, 7(1):483-490.