BIOGRAPHICAL SKETCH

NAME: Nicholas Gene Brown

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

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
Texas A&M University, College Station, TX	B.S.	12/2005	Biomedical Sciences
Baylor College of Medicine, Houston, TX	Ph.D.	07/2011	Biochemistry
St. Jude Children's Research Hospital, Memphis, TN	Postdoctoral Fellowship	08/2017	Structural Biology

A. Personal Statement

My long-term research interest is to understand the structural and biochemical mechanisms of molecular machines that are manipulated in cancer. As a graduate student, I developed a strong background in molecular biology, biochemistry, biophysics, and X-ray crystallography while studying the well-characterized bacterial enzyme-inhibitor interactions under Dr. Timothy Palzkill. For my postdoc, I wanted to extend my experience in structural biology by using cryo-EM to investigate multi-protein eukaryotic complexes and ubiquitination with Dr. Brenda Schulman. My postdoc project involved dissecting the mechanisms of ubiquitination by the massive 1.2 MDa Ub ligase known as the Anaphase-Promoting Complex or Cyclosome (APC/C), which is regarded as a master regulator of the cell cycle. As an independent investigator, I aim to understand how other molecular machines. These structural and mechanistic studies will provide fundamental contributions to our understandings of cell cycle regulation and therefore cancer.

SELECTED PUBLICATIONS (OUT OF 38)

1. Martinez-Chacin RC, Bodrug T, Bolhuis DL, Kedziora KM, Bonacci T, Ordureau A, Gibbs ME, Weissmann F, Qiao R, Grant GD, Cook JG, Peters JM, Wade Harper J, Emanuele MJ[#], **Brown NG[#].** [#]Corresponding Author. Ubiquitin chain-elongating enzyme UBE2S activates the RING E3 ligase APC/C for substrate priming. Nat Struct Mol Biol. 2020 May 11;. doi: 10.1038/s41594-020-0424-6.

2. Sonn-Segev A, Belacic K, Bodrug T, Young G, VanderLinden RT, Schulman BA, Schimpf J, Friedrich T, Dip PV, Schwartz TU, Bauer B, Peters JM, Struwe WB, Benesch JLP, **Brown NG[#],** Haselbach D[#], Kukura P[#]. [#]Corresponding Author. Quantifying the heterogeneity of macromolecular machines by mass photometry. Nat Commun. 2020 Apr 14;11(1):1772. doi: 10.1038/s41467-020-15642-w. PubMed PMID: 32286308.

3. Kernan JL, Martinez-Chacin RC, Wang X, Tiedemann RL, Bonacci T, Choudhury R, Bolhuis DL, Damrauer JS, Yan F, Harrison JS, Major MB, Hoadley K, Suzuki A, Rothbart S, **Brown NG[#]**, Emanuele MJ[#]. [#]Corresponding Author. *In silico* identification of APC/C substrates reveals temporal cell cycle destruction of key chromatin regulators including UHRF1. In revision at PLOS Biology. 2020. BioRxiv https://doi.org/10.1101/2020.04.09.033621.

4. **Brown NG***, VanderLinden R*, Watson ER*, Weissmann F, Ordureau A, Wu KP, Zhang W, Yu S, Mercredi PY, Harrison JS, Davidson IF, Qiao R, Lu Y, Dube P, Brunner MR, Grace CR, Miller DJ, Haselbach D, Jarvis MA, Yamaguchi M, Yanishevski D, Petzold G, Sidhu SS, Kuhlman B, Kirschner MW, Harper JW, Peters JM, Stark H, Schulman BA. *Equal first author. Dual RING E3 Architectures Regulate Multiubiquitination and Ubiquitin Chain Elongation by APC/C. *Cell*. 2016 Jun 2;165(6):1440-53. PubMed PMID: 27259151.

B. Positions and Honors

Positions and Employment

07/2011 – 08/2017 Postdoctoral Research Associate, Dept. of Structural Biology, St. Jude Children's Research Hospital, Memphis, TN (Dr. Brenda Schulman's Lab)

09/2017 – Present Assistant Professor, Dept. of Pharmacology, University of North Carolina – Chapel Hill, Lineberger Comprehensive Cancer Center

Honors/Awards

2006 Baylor College of Medicine Verna and Marrs McLean Award
2008-2010 Gulf Coast Consortia/Keck Center Pharmacoinformatics Training Program Fellowship
2010-2011 Gulf Coast Consortia/Keck Center Biomedical Discovery from Large Scale Data Sets Training Program Fellowship
2012-2015 Jane Coffin Childs Memorial Fund for Medical Research Fellowship
2015-2017 Leukemia and Lymphoma Society Special Fellowship
2017-2018 National Cancer Institute (NCI) Career Transition Award
2018-2023 National Institute of General Medicine Sciences Maximizing Investigators' Research Award for New and Early Stage Investigators
2019-2020 UNC Lineberger Development Award
2020 IBM Junior Faculty Development Award

C. Contributions to Science

1. Structural and functional studies revealed the amino acid requirements for protein stability and enzymatic function essential to the evolution of the antibiotic resistance family of enzymes known as β-lactamases.

a. Marciano DC, **Brown NG**, Palzkill T. Analysis of the plasticity of location of the Arg244 positive charge within the active site of the TEM-1 beta-lactamase. *Protein Sci.* 2009 Oct;18(10):2080-9. PubMed PMID: 19672877; PubMed Central PMCID: PMC2786972.

b. **Brown NG**, Shanker S, Prasad BV, Palzkill T. Structural and biochemical evidence that a TEM-1 beta-lactamase N170G active site mutant acts via substrate-assisted catalysis. *J Biol Chem.* 2009 Nov 27;284(48):33703-12. PubMed PMID: 19812041; PubMed Central PMCID: PMC2785212.

c. **Brown NG**, Pennington JM, Huang W, Ayvaz T, Palzkill T. Multiple global suppressors of protein stability defects facilitate the evolution of extended-spectrum TEM β-lactamases. *J Mol Biol*. 2010 Dec 17;404(5):832-46. PubMed PMID: 20955714; PubMed Central PMCID: PMC3032993.

d. **Brown NG***, Horton LB*, Huang W*, Vongpunsawad S, Palzkill T. Analysis of the functional contributions of Asn233 in metallo-β-lactamase IMP-1. *Equal first author. *Antimicrob Agents Chemother.* 2011 Dec;55(12):5696-702. PubMed PMID: 21896903; PubMed Central PMCID: PMC3232802.

2. Biophysical and kinetic approaches uncovered the binding forces and the binding residues required for affinity and specificity of the highly potent β-lactamase Inhibitory protein-II (BLIP-II).

a. **Brown NG**, Palzkill T. Identification and characterization of beta-lactamase inhibitor protein-II (BLIP-II) interactions with beta-lactamases using phage display. *Protein Eng Des Sel.* 2010 Jun;23(6):469-78. PubMed PMID: 20308189; PubMed Central PMCID: PMC2865362.

b. **Brown NG**, Chow DC, Sankaran B, Zwart P, Prasad BV, Palzkill T. Analysis of the binding forces driving the tight interactions between beta-lactamase inhibitory protein-II (BLIP-II) and class A beta-lactamases. *J Biol Chem.* 2011 Sep 16;286(37):32723-35. PubMed PMID: 21775426; PubMed Central PMCID: PMC3173220.

c. **Brown NG**, Chow DC, Ruprecht KE, Palzkill T. Identification of the β-lactamase inhibitor protein-II (BLIP-II) interface residues essential for binding affinity and specificity for class A β-lactamases. *J Biol Chem*. 2013 Jun 14;288(24):17156-66. PubMed PMID: 23625930; PubMed Central PMCID: PMC3682521.

d. **Brown NG**, Chow DC, Palzkill T. BLIP-II is a highly potent inhibitor of Klebsiella pneumoniae carbapenemase (KPC-2). *Antimicrob Agents Chemother.* 2013 Jul;57(7):3398-401. PubMed PMID: 23587951; PubMed Central PMCID: PMC3697393.

3. Discovery of the multiple mechanisms of substrate ubiquitination by the Anaphase-Promoting Complex/Cyclosome (APC/C) and its inhibition by EMI1 and the Mitotic Checkpoint Complex (MCC). These studies include the first structures of a RING E3 ubiquitin ligase (the largest family with >600 members) mimicking ubiquitin transfer to a disordered substrate or building a polyubiquitin chain.

a. Frye JJ*, **Brown NG***, Petzold G*, Watson ER, Grace CR, Nourse A, Jarvis MA, Kriwacki RW, Peters JM, Stark H, Schulman BA. Electron microscopy structure of human APC/C(CDH1)-EMI1 reveals multimodal mechanism of E3 ligase shutdown. *Equal first author. *Nat Struct Mol Biol*. 2013 Jul;20(7):827-35. (News and Views, *Nat Struct Mol Biol.* **20:** 773-4; Leading Edge, *Cell* **154**: 475, 2013). PubMed PMID: 23708605; PubMed Central PMCID: PMC3742808.

b. **Brown NG**, Watson ER, Weissmann F, Jarvis MA, VanderLinden R, Grace CR, Frye JJ, Qiao R, Dube P, Petzold G, Cho SE, Alsharif O, Bao J, Davidson IF, Zheng JJ, Nourse A, Kurinov I, Peters JM, Stark H, Schulman BA. Mechanism of polyubiquitination by human anaphase-promoting complex: RING repurposing for ubiquitin chain assembly. *Mol Cell*. 2014 Oct 23;56(2):246-60. (Previews, *Mol Cell*. **56:** 189-1). PubMed PMID: 25306923; PubMed Central PMCID: PMC4272865.

c. **Brown NG**, VanderLinden R, Watson ER, Qiao R, Grace CR, Yamaguchi M, Weissmann F, Frye JJ, Dube P, Ei Cho S, Actis ML, Rodrigues P, Fujii N, Peters JM, Stark H, Schulman BA. RING E3 mechanism for ubiquitin ligation to a disordered substrate visualized for human anaphase-promoting complex. *Proc Natl Acad Sci U S A*. 2015 Apr 28;112(17):5272-9. PubMed PMID: 25825779; PubMed Central PMCID: PMC4418899.

d. **Brown NG***, VanderLinden R*, Watson ER*, Weissmann F, Ordureau A, Wu KP, Zhang W, Yu S, Mercredi PY, Harrison JS, Davidson IF, Qiao R, Lu Y, Dube P, Brunner MR, Grace CR, Miller DJ, Haselbach D, Jarvis MA, Yamaguchi M, Yanishevski D, Petzold G, Sidhu SS, Kuhlman B, Kirschner MW, Harper JW, Peters JM, Stark H, Schulman BA. *Equal first author. Dual RING E3 Architectures Regulate Multiubiquitination and Ubiquitin Chain Elongation by APC/C. *Cell*. 2016 Jun 2;165(6):1440-53. PubMed PMID: 27259151.

4. As a new independent investigator, we have uncovered new mechanisms of APC/C activation in mitosis. These studies include dissecting a paradigm-shifting mechanism by which the E2 UBE2S stimulates the E3 APC/C through positive allosteric feedback, and we determined how an APC/C inhibitor becomes an APC/C activator during the mitotic checkpoint.

a. Martinez-Chacin RC, Bodrug T, Bolhuis DL, Kedziora KM, Bonacci T, Ordureau A, Gibbs ME, Weissmann F, Qiao R, Grant GD, Cook JG, Peters JM, Wade Harper J, Emanuele MJ[#], **Brown NG[#].** [#]Corresponding Author. Ubiquitin chain-elongating enzyme UBE2S activates the RING E3 ligase APC/C for substrate priming. Nat Struct Mol Biol. 2020 May 11;. doi: 10.1038/s41594-020-0424-6.

b. Sonn-Segev A, Belacic K, Bodrug T, Young G, VanderLinden RT, Schulman BA, Schimpf J, Friedrich T, Dip PV, Schwartz TU, Bauer B, Peters JM, Struwe WB, Benesch JLP, **Brown NG[#],** Haselbach D[#], Kukura P[#]. [#]Corresponding Author. Quantifying the heterogeneity of macromolecular machines by mass photometry. Nat Commun. 2020 Apr 14;11(1):1772. doi: 10.1038/s41467-020-15642-w. PubMed PMID: 32286308.

c. Richeson KV, Bodrug T, Sackton KL, Yamaguchi M, Paulo JA, Gygi SP, Schulman BA, **Brown NG,** King RW. Paradoxical mitotic exit induced by a small molecule inhibitor of APC/C^{Cdc20}. Nat Chem Biol. 2020 May;16(5):546-555. PubMed PMID: 32152539.

d. Kernan JL, Martinez-Chacin RC, Wang X, Tiedemann RL, Bonacci T, Choudhury R, Bolhuis DL, Damrauer JS, Yan F, Harrison JS, Major MB, Hoadley K, Suzuki A, Rothbart S, **Brown NG[#]**, Emanuele MJ[#]. [#]Corresponding Author. *In silico* identification of APC/C substrates reveals temporal cell cycle destruction of key chromatin regulators including UHRF1. In revision at PLOS Biology. BioRxiv https://doi.org/10.1101/2020.04.09.033621.

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