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: Richard W. Baker

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

POSITION TITLE: Assistant Professor of Biochemistry and Biophysics

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 North Carolina at Chapel Hill	B.S.	05/2008	Biology
Princeton University	Ph.D.	11/2015	Molecular Biology
University of California, San Diego	Postdoctoral Training	12/2019	Structural Biology

A. Personal Statement

I am an Assistant Professor of Biochemistry and Biophysics at UNC Chapel Hill and my group studies the molecular mechanisms of endocytosis and exocytosis. We use a combination of biochemical, biophysical, and structural techniques to better understand how misregulation of these vital functions results in disease phenotypes, with a focus on cryo-electron microcopy (cryoEM) as our technique of choice.

A hallmark of eukaryotic cell biology is a complex and dynamic organellar architecture. The process of forming and maintaining this architecture requires a regulated cycle of budding and fusion events and is broadly called *membrane trafficking*. Cells constantly modulate the composition of their plasma membrane through a coordinated interplay of endocytosis and exocytosis. As cells communicate with their environment through their plasma membrane, precise control of its structure and composition underpins many processes including signaling, synaptic transmission, and host-pathogen interactions. There is emerging evidence that subversion of membrane traffic at the cell surface is a hallmark of many human diseases. In particular, misregulation of signaling proteins at the cell surface (TGF-beta receptor, etc.) may play a pivotal role in cancer development and progression. My group uses a variety of techniques (high-resolution cryoEM, biochemical reconstitution) to understand these systems in molecular detail. Additionally, we collaborate with several groups that use a variety of model systems (*Saccharomyces, C. elegans*) and experimental approaches (unbiased genetic screens, fitness assays, live cell microscopy).

As PI or co-Investigator on multiple private- and NIH-funded grants, I have developed an extramurally funded research portfolio that seeks to leverage cutting-edge imaging techniques to answer fundamental questions in the field of membrane trafficking. As such, I am responsible for the recruitment, training, and career development of lab members across career stages, including undergrads, graduate students, and post-doctoral researchers. I am dedicated to training and mentoring and I strive to promote an inclusive and supportive scientific research environment. To this end, I have completed multiple University-lead training programs, including the UNC Mentor Training and UNC Safe Zone Training. Additionally, training in my laboratory involves not only hands-on science training, but career development, with an emphasis on completion of graduate training in a timely fashion. Overall, my group seeks to drive important areas of biomedical research while being focused on training and development in a supportive and inclusive environment.

Ongoing projects that I would like to highlight include:

5 R01 GM127548-02 (NIH/NIGMS)
Gunther Hollopeter (PI), Role: co-investigator
1/1/2020 - 3/31/2024
Molecular Regulation of the AP2 Clathrin Adaptor Complex

2 R01 GM054712-23 (NIH/NIGMS)
Patrick Brennwald (PI), Role: co-investigator
12/1/20-11/30/25
Polarized Exocytosis: Rabs, Tethers and SNAREs

Citations:

1. **Baker RW**, Jeffrey PD, Zick M, Phillips BP, Wickner WT, Hughson FM. (2015). A direct role for the Sec1/Munc18-family protein Vps33 as a template for SNARE assembly. *Science.* 4;349(6252):1111-4. PMCID: PMC4727825.
2. **Baker RW**, Hughson FM. (2016). Chaperoning SNARE assembly and disassembly. *Nature Reviews Molecular and Cell Biology*. Aug;17(8):465-79. PMCID: PMC5471617.
3. Partlow EA*, **Baker RW***, Beacham GM, Chappie JS, Leschziner AE, Hollopeter G. (2019). A structural mechanism for phosphorylation-dependent inactivation of the AP2 complex. *Elife.* 2019 Aug 29;8. PMCID: PMC6739873. *equal contribution.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020-Present	Assistant Professor, Dept. of Biochemistry and Biophysics, School of Medicine, University of North Carolina at Chapel Hill
2019-Present	Member, UNC Lineberger Comprehensive Cancer Center, School of Medicine, University of North Carolina at Chapel Hill
2019	Nominated Research Assistant Professor, Dept. of Biochemistry and Biophysics, School of Medicine, University of North Carolina at Chapel Hill
2015-2019	Postdoctoral Fellow, Dept. of Cellular and Molecular Medicine, School of Medicine, UC San Diego

Professional Memberships

2018-current	Member, American Society for Cell Biology

Honors

2016-2019	Postdoctoral Fellowship, Damon Runyon Cancer Research Foundation (awarded, accepted)
2016	Postdoctoral Fellowship, The Helen Hay Whitney Foundation (awarded, declined)
2016	Postdoctoral Fellowship, Alfred and Mabel Beckman Foundation (awarded, declined)
2011-2014	Graduate Research Fellowship, National Science Foundation (NSF)
2011-2013	Member, Science Program for Excellence in Science, American Association for the Advancement of Science (AAAS)
2008	Senior Thesis, Honors Distinction, University of North Carolina at Chapel Hill
2004-2008	University Trademark Scholarship, University of North Carolina at Chapel Hill
2004-2008	Dean’s List, University of North Carolina at Chapel Hill

C. Contributions to Science

My group is interested in how large macromolecular complexes bend and shape membranes throughout the membrane trafficking cycle, with an emphasis on the mechanisms of endocytosis and exocytosis. We use a

combination of biochemical, biophysical, and structural techniques to tackle this question, with a focus on cryo-electron microcopy (cryoEM) as our technique of choice.

We are interested in the mechanisms of membrane trafficking, with a particular emphasis on (1) assembly of coat proteins and cargo selection during endocytosis and (2) assembly and chaperoning of the SNARE complex during exocytosis. More broadly, we seek to understand how the membrane itself serves as a general platform for cell biology.

Mechanisms of endocytosis and receptor recycling

A major mechanism that cells employ to control the composition of their plasma membrane is clathrin-mediated endocytosis (referred to here as endocytosis). This process requires a host of proteins that coordinate to recognize cargo and form a coat of proteins that deform the membrane and bud a vesicle. In this manner, cells can target proteins on the cell surface for internalization. Many proteins with prominent roles in cancer, such as receptor tyrosine kinases and GPCRs, must be recycled from the plasma membrane and misregulation of recycling is likely a key factor in disease progression. We are interested in understanding the precise mechanisms that cell use to decide when and where to undergo endocytosis. In particular we are interested in how cells recognize cargo in the context of the membrane, and how the dozens of proteins involved in endocytosis coordinate to decide when and where a budding event takes place.

Clathrin mediated endocytosis proceeds in three broad steps: (1) Recognition of cargo, (2) formation of the inner and outer coat components, and (3) deformation of the membrane and eventual scission of the vesicle from the membrane. While the molecular mechanisms of clathrin cage formation and membrane scission by the Dynamin-family proteins are relatively well characterized, how the dozens of proteins involved in the earliest steps of endocytosis coordinate to decide when and where to bud a vesicle is still unknown. In conjunction with the Gunther Hollopeter group at Cornell University, we have been studying the role of negative regulatory elements within the endocytosis pathway, i.e. inhibitory mechanisms of endocytosis. While the vast majority of the literature focuses on activating mechanisms for endocytosis, we have shown that a conserved family of proteins called NECAPs can actually inhibit the earliest stages of endocytosis. Using a combination of high-resolution cryo-EM, *in vitro* reconstitution, and *C. elegans* genetics, we showed that NECAP directly binds to an early regulator of endocytosis called AP2. This interaction requires a phosphorylation event on a highly conserved threonine, suggesting that cells seek tunable mechanisms to precisely control endocytosis. Intriguingly, other groups show that under certain circumstances NECAP is an activator of endocytosis, suggesting that this protein might have dual functions as an inhibitor of poorly formed endocytic pits but an activator under favorable circumstances. In this manner, NECAP might act as a quality control mechanism that actually serves to inhibit or promote endocytosis based on cellular context.

1. Partlow EA*, **Baker RW***, Beacham GM, Chappie JS, Leschziner AE, Hollopeter G. (2019). A structural mechanism for phosphorylation-dependent inactivation of the AP2 complex. *Elife.* 2019 Aug 29;8. PMCID: PMC6739873. *equal contribution.

Mechanisms and regulation of membrane fusion

After a vesicle is budded from one cellular compartment, it must be trafficked to its final destination and fused with another membrane. Control of vesicle fusion underpins many important cellular processes, including neurotransmitter release, bulk organelle traffic, and regulated exocytosis. At the heart of the fusion reaction are the SNARE proteins, which are membrane-embedded proteins that pair across membranes to directly catalyze fusion. While SNAREs are the minimal component for vesicle fusion *in vitro*, they require a host of proteins to correctly assemble into fusion-competent SNARE complexes *in vivo*. My group seeks to understand the mechanisms of SNARE-mediated fusion and the regulatory proteins that chaperone formation of fusion-competent SNARE complexes. We employ a combination of reconstituted fusion assays and high-resolution cryoEM to understand in molecular detail how SNARE complexes are assembled. As a model system, we study how fusion is regulated at the cell surface, including the action of the Exocyst complex.

One family of SNARE regulators is the Sec1/Munc18 (SM) proteins, which are required for every SNARE-catalyzed fusion event. As a graduate student I determined many crystal structures of the SM protein Vps33, which regulates fusion in the endosomal and lysosomal systems. Most illuminating was the determination of multiple crystal structures of Vps33 in complex with SNARE proteins. These structures, and accompanying biochemical experiments performed in conjunction with the Wickner Laboratory at Dartmouth College, were

vital in proposing a new model of SNARE regulation. This model posits that SM proteins serve as the initial template for assembly of the SNARE complex, and form a ternary complex containing an SM protein and two SNARE proteins embedded in separate membranes. This model for SM protein function has since been validated by several groups and represents a new paradigm in SNARE-regulation.

1. **Baker RW**, Jeffrey PD, Zick M, Phillips BP, Wickner WT, Hughson FM. (2015). A direct role for the Sec1/Munc18-family protein Vps33 as a template for SNARE assembly. *Science.* 4;349(6252):1111-4. PMCID: PMC4727825.
2. **Baker RW**, Hughson FM. (2016). Chaperoning SNARE assembly and disassembly. *Nature Reviews Molecular and Cell Biology*. Aug;17(8):465-79. PMCID: PMC5471617.
3. **Baker RW**, Jeffrey PD, Hughson FM. (2013). Crystal Structures of the Sec1/Munc18 (SM) Protein Vps33, Alone and Bound to the Homotypic Fusion and Vacuolar Protein Sorting (HOPS) Subunit Vps16*. *PLoS One*. 2013;8(6):e67409. PMCID: PMC3693963.
4. Jiao J, He M, Port SA, **Baker RW**, Xu Y, Qu H, Xiong Y, Wang Y, Jin H, Eisemann TJ, Hughson FM, Zhang Y. (2018). Munc18-1 catalyzes neuronal SNARE assembly by templating SNARE association. *Elife*. Dec 12;7. PMCID: PMC6320071.

Complete list of my published work in MyBibliography
https://www.ncbi.nlm.nih.gov/myncbi/18M9yQao9CkIpm/bibliography/public/