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: Rachel Redler

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

POSITION TITLE: Associate Research Scientist

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
Texas A&M University College Station, TX, USA	B.S.	05/2006	Biochemistry
University of North Carolina at Chapel Hill Chapel Hill, NC USA	Ph.D.	05/2014	Biochemistry and Biophysics
New York University School of Medicine New York, NY USA	postdoc	07/2019	Neurobiology and Structural Biology

A. Personal Statement

I have broad interest in protein structure:function relationships and the use of single-particle cryoEM and cryoET to provide new insights into long-inaccessible targets. My graduate education and training were primarily in the fields of biochemistry, biophysics, and structural biology. Under the direction of Nikolay Dokholyan at UNC Chapel Hill, I pursued the biochemical and biophysical characterization of misfolded conformers of Cu/Zn superoxide dismutase (SOD1), which are potential cytotoxic agents in amyotrophic lateral sclerosis (ALS). Through my doctoral studies related to ALS, I became interested in the cellular mechanisms required to maintain the neuromuscular junction (NMJ). These interests led me to Steven Burden's lab at NYU, where I studied protein-protein interactions that underlie the formation and maintenance of neuromuscular synapse. In particular, I was interested in the structural basis by which Agrin secreted from motor nerve terminals stimulates muscle-specific kinase (MuSK) on the skeletal muscle plasma membrane, a process which requires low-density lipoprotein receptor-related protein-4 (Lrp4) as a co-receptor. My pursuit of structural knowledge of Lrp4, alone and as part of an Agrin/Lrp4/MuSK signaling complex, led me to the cryo-EM field and the labs of Gira Bhabha and Damian Ekiert. I joined the Bhabha / Ekiert labs as a research scientist in 2019 and began collaborating with David Baker at the University of Washington Institute of Protein Design to structurally characterize *de novo* protein designs using cryo-EM and X-ray crystallography.

B. Positions and Honors

Position and Employment

2019 – present Associate Research Scientist, Labs of Gira Bhabha and Damian Ekiert, Skirball Institute of Biomolecular Medicine, New York University Langone Medical Center, New York, NY, USA.

2014 – 2019 Postdoctoral Fellow, Skirball Institute of Biomolecular Medicine, New York University Langone Medical Center, New York, NY, USA. Advisor: Steven J. Burden

2008 – 2013 Graduate Research Assistant, Department of Biochemistry and Biophysics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. Advisor: Nikolay V. Dokholyan

2006 – 2008 Teacher of Chemistry and Integrated Physics & Chemistry, Hearne High School, Hearne Independent School District, Hearne, TX, USA.

Honors

2015 – 2018 Ruth L. Kirschstein National Research Service Award Postdoctoral Fellowship, National Institute of Neurological Disorders and Stroke, National Institutes of Health

2011 – 2013 Ruth L. Kirschstein National Research Service Award Predoctoral Fellowship, National Institute of Neurological Disorders and Stroke, National Institutes of Health

2007 – 2008 Noyce Fellow, Robert Noyce Teacher Scholarship Program, Baylor College of Medicine, National Science Foundation

2002 – 2006 Minnie Stevens Piper Foundation Scholarship

2002 – 2006 IBM Thomas J. Watson Memorial Scholarship

2002 – 2006 Terry Foundation Scholarship

2002 – 2006 National Merit Scholar Finalist, Texas A&M University Scholarship

Other Professional Experience

2011 – present Reviewer, *Neuroscience, Scientific Reports, Stem Cell Reviews and Reports, Biochimica et Biophysica Acta- Molecular and Cell Biology of Lipids* and *BBA-Molecular Basis of Disease*

2012 – 2014 Associate Faculty Member, Faculty of 1000

2012 – 2013 Member, UNC Biochemistry and Biophysics Department Graduate Education Committee

C. Contributions to Science

1. Protein misfolding and aggregation in human disease

Protein destabilization by missense mutations is proposed to play a prominent role in widespread inherited human disorders, not just those known to involve protein misfolding and aggregation. As a graduate student, I used computation and experiment to probe the role of protein misfolding and aggregation in diverse human disorders, with a particular focus on the involvement of non-native Cu/Zn superoxide dismutase (SOD1) in amyotrophic lateral sclerosis (ALS). Soluble misfolded SOD1 is implicated in multiple cell-autonomous and non-cell-autonomous mechanisms of motor neuron death in ALS; however, the relative toxicities of the various non-native species formed by SOD1 as it misfolds and aggregates are unknown. We found that early stages of SOD1 aggregation involve the formation of non-native oligomers, including trimers, that contain an epitope found in ALS-relevant misfolded SOD1. Computational design and experimental validation of point mutations that promote or inhibit trimer formation allowed us to discover a correlation between trimerization propensity and motor neuron cytotoxicity. These findings suggest that soluble non-native SOD1 oligomers, rather than misfolded monomers or large-scale aggregates or fibrils, share structural similarity to pathogenic misfolded species found in ALS patients, and therefore represent potential cytotoxic agents and therapeutic targets in ALS.

Proctor, E.A., Fee, L., Tao, Y., **Redler, R.L**., Fay, J.M., Zhang, Y., Lv, Z., Mercer, I.P., Deshmukh, M., Lyubchenko, Y.L., and Dokholyan, N.V. " Nonnative SOD1 trimer is toxic to motor neurons in a model of amyotrophic lateral sclerosis " (2016) *Proceedings of the National Academy of Sciences USA, 113:614-619*

Redler, R.L., Das, J., Diaz, J.R., Dokholyan, N.V. "Protein destabilization as a common factor in diverse inherited disorders" (2016) *Journal of Molecular Evolution*, 82:11-16

Redler, R. L., Fee, L., Fay, J. M., Caplow, M., and Dokholyan, N. V. "Non-native soluble SOD1 oligomers contain a conformational epitope linked to cytotoxicity in ALS" (2014) *Biochemistry,* 53:2423-2432

Redler, R. L., Shirvanyants, D., Dagliyan, O., Ding., F., Kim, D. N., Kota, P., Proctor, E. A., Ramachandran, S., Tandon, A., and Dokholyan, N. V. "Computational approaches to understanding protein aggregation in neurodegeneration" (2014) *Journal of Molecular Cell Biology,* 6:104-115

Nedd, S., **Redler, R. L.**, Proctor, E. A., Dokholyan, N. V., Alexandrova, A. "Cu,Zn-Superoxide Dismutase without Zn is Folded but Catalytically Inactive" (2014) *Journal of Molecular Biology,* 426:4112-4124

Redler, R. L. and Dokholyan, N.V. "The complex molecular biology of amyotrophic lateral sclerosis (ALS)" (2012) *Progress in Molecular Biology and Translational Science*, 107:215-262

2. Impact of post-translational modifications of SOD1 on protein stability

Mutation of the ubiquitous cytosolic enzyme SOD1 is hypothesized to cause familial amyotrophic lateral sclerosis (FALS) through structural destabilization leading to misfolding and aggregation. Considering the late onset of symptoms as well as the phenotypic variability among patients with identical SOD1 mutations, it is clear that non-genetic factor(s) impact ALS etiology and disease progression. We found that SOD1 isolated from human erythrocytes contains multiple post-translational modifications, including phosphorylation and oxidative modification of free cysteines with the tripeptide glutathione. Using experimental and computational strategies, we found that glutathionylation of Cys-111, located proximal to the native SOD1 homodimer interface, induces structural rearrangements that modulate stability of both wild type and FALS mutant SOD1 dimers. The destabilizing effect of glutathionylation, a modification that acts in part as a mechanism to counteract oxidative stress, suggests a novel mode by which redox regulation and aggregation propensity interact in ALS.

Redler, R. L., Wilcox, K. C., Proctor, E. A., Fee, L., Caplow, M., and Dokholyan, N. V. "Glutathionylation at Cys 111 triggers dissociation of wild type and FALS mutant SOD1 dimers" (2011) *Biochemistry*, 50:7057-7066 **[Recommended by Faculty of 1000]**

Wilcox, K. C., Zhou, L., Jordon, J., Huang, Y., Yu, Y., **Redler, R. L.**, Chen, X., Caplow, M., and Dokholyan, N. V. “Modifications of SOD1 in human erythrocytes: A possible role in ALS” (2009) *Journal of Biological Chemistry*, 284: 13940-13947

3. MuSK auto-antibodies in myasthenia gravis

Muscle-specific kinase (MuSK) is a crucial signaling hub at the neuromuscular junction and is targeted by auto-antibodies in some patients with myasthenia gravis (MG), causing debilitating muscle weakness. We characterized three MuSK auto-antibodies derived from MG patients in both affinity-matured and germline states and found that mutations acquired during affinity maturation enable anti-MuSK Fabs to reach the high affinity threshold required to disrupt MuSK signaling.

Fichtner, M. L., Vieni, C., **Redler. R. L.**, Kolich, L., Jiang, R., Takata, K., Stathopoulos, P., Suarez, P., Nowak, R. J., Burden, S. J., Ekiert, D. C., O’Connor, K. C. “Self-antigen driven affinity maturation is required for pathogenic monovalent IgG4 autoantibody development” (2020) bioRxiv 2020.03.14.988758

D. Research Support

Completed research support Redler (PI) 04/01/2015 - 03/31/2018
F32NS092296
NIH/NINDS
Mechanisms of Agrin-Lrp4-MuSK signaling at the neuromuscular junction
The objective of this project is to probe structural transitions that govern Agrin-Lrp4-MuSK signaling, both *in vitro* and *in vivo*, in order to advance the long-term goal of understanding the crucial molecular interactions in this pathway. Specifically, we aimed to: (1) Characterize Agrin-induced conformational changes in Lrp4 and MuSK that facilitate MuSK activation; (2) Characterize conformational changes in MuSK induced by binding of an agonist antibody; and (3) Determine whether cleavage of Lrp4 is required for presynaptic differentiation.

Completed research support Redler (PI) 02/01/2011 - 01/31/2014
F31NS073435
NIH/NINDS
The impact of post-translational modification on SOD1 aggregation in ALS
The objective of this proposal was to characterize the effect of modifications on the structural changes that occur as SOD1 transitions from its native homodimer into monomeric and non-native oligomeric states. We compared the influence of post-translational modification on the oligomerization of wild type and mutant SOD1 using X-ray crystallography, analytical size-exclusion chromatography, and computational modeling.

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: Gira Bhabha

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

POSITION TITLE: 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
The University of Chicago	A.B.	09/01-06/05	Molecular Genetics
The Scripps Research Institute, La Jolla, CA	Ph.D.	09/06-08/11	Structural Biology
The University of California, San Francisco	postdoc	02/12-12/16	Structural & Cell Biology

A. Personal Statement

I have a long-standing interest in protein structure, dynamics and mechanism, and in studying how structural interactions and coordinated movements within proteins and between proteins facilitate biological function. I began my independent lab in 2017, and currently, my lab focuses on unraveling the structural basis of transport mechanisms in eukaryotic (motor proteins) and prokaryotic (lipid transport) systems.

My training is in structural biology (NMR, X-ray crystallography and cryo EM), protein biochemistry and optical microscopy. As a graduate student with Peter Wright at the Scripps Research Institute, I studied the role of enzyme dynamics in catalysis. Using a combination of X-ray crystallography (to solve structures) NMR (to understand atomic-level protein dynamics at different timescales) and kinetic measurements (to assay enzyme activity), I showed that in the model enzyme, DHFR, coordinated movements on the millisecond timescale are necessary for the catalytic step of enzyme activity. During the first part of my postdoc at UCSF with Ron Vale and Yifan Cheng, I used cryo EM, TIRF microscopy and biochemistry to study the allosteric motility mechanism of the motor protein dynein, which hydrolyzes ATP as an energy source to move directionaly along microtubules. Using this combination of techniques, and obtaining structural snapshots of dynein in different nucleotide states allowed us to propose a model for the nucleotide-dependent conformational changes that occur during dynein's mechano-chemical cycle. During the second part of my postdoc I began working together with my colleague, Damian Ekiert, on the MCE (Mammalian Cell Entry) family of proteins, originally discovered in Mycobacterium tuberculosis (*Mtb*), and at the time, thought to be important for mediating entry of the pathogen into host cells. Subsequent studies in homologs from *E. coli* and plants implicate the proteins in outer membrane integrity and the transport of hydrophobic molecules including lipids that are the building blocks of both inner and outer membranes. Using cryo EM and X-ray crystallography, we recently showed that MCE proteins from *E. coli* can form stunning, large macromolecular machines based upon a variable number of modular hexameric rings, that result in channels primed for transport of hydrophobic molecules. Thus, I have experience working on the structure, dynamics and functional mechanisms of several different biological systems, and cryo EM is one of the main tools my lab uses.

This long-term collaboration with David Baker and Damian Ekiert's labs focuses on optimizing a high throughput X-ray crystallography and cryo EM pipeline for structure determination of *de novo* designed proteins, as well as assessment of the conformational ensemble within each sample.

B. Positions and Honors

Positions

06/2005-05/2006	Research Assistant (full-time). Dept. Of Medicine, Section of Cardiology, The University of Chicago. Supervisor: Elizabeth McNally
06/2006-08/2011	Graduate Student (full-time). Dept. of Molecular Biology, The Scripps Research Institute. Supervisor: Peter Wright
09/2011-01/2012	Postdoc (full-time). Dept. of Molecular Biology, The Scripps Research Institute. Supervisor: Peter Wright
02/2012-12/2016	Postdoctoral Fellow (full-time). Dept. of Cellular and Molecular Pharmacology, University of California, San Francisco. Supervisor: Ron Vale
01/2017-present	Assistant Professor (full-time). Skirball Institute of Biomolecular Medicine, New York University School of Medicine.

Honors

2004	Howard Hughes Medical Institute (HHMI) Undergraduate Fellowship
2011	Travel award, IXth European Symposium of the Protein Society
2012	NIH NRSA postdoctoral fellowship (declined)
2012	Jane Coffin Childs postdoctoral fellowship (declined)
2012	Merck fellow of the Damon Runyon Cancer Research Foundation
2015	K99/R00 Pathway to Independence grant, NIH/NIGMS
2017	Damon Runyon Dale F. Frey award for breakthrough scientists
2018	Searle Scholar
2019	PEW Scholar

C. Contributions to Science

1. Role of protein dynamics in enzyme catalysis

Understanding the role that protein conformational changes play in enzyme catalysis is an area of intense research. Describing the dynamics of a protein in detail on many timescales can be quite feasible using NMR spectroscopy. However, assigning a role to the observed dynamics is challenging. As a graduate student, I worked with Peter Wright at The Scripps Research Insitute to study the role of protein dynamics in the model enzyme, dihydrofolate reductase (DHFR). DHFR is found in almost all cells, and reduces dihydrofolate to tetrahydrofolate (THF), most often being the sole source of THF in a cell. Much work has been done on *E. coli* DHFR using X-ray crystallography (Kraut and others), NMR (Wright and others) and kinetic measurements (Benkovic and others), making it a paradigm for studying catalytic mechanisms. As part of my graduate work I was able to show that conformational fluctuations on the millisecond timescale can have an important influence on the chemical step of an enzymatic reaction. In subsequent collaborative work, we harnessed recently developed methods in room temperature crystallography coupled with novel computational tools to gain further insights into how our mutant impacts *ec*DHFR catalysis. These results led to our current view: the mutation inhibits millisecond timescale conformational fluctuations that are conducive to formation of an optimal transition state configuration.

- **Bhabha G**, Lee J, Ekiert DC, Gam J, Wilson IA, Dyson HJ, Benkovic SJ, Wright PE (2011). A dynamic knockout reveals that conformational fluctuations influence the chemical step of enzyme catalysis. *Science*. 332:234-8

- van den Bedem H, **Bhabha G**, Yang K, Wright PE, Fraser JS (2013). Automated identification of functional dynamic contact networks from X-ray crystallography. *Nature Methods.* 10(9):896-902

2. Evolution of protein dynamics at an atomic level

As a graduate student, I was particularly interested in understanding how not just protein structures, but also protein dynamics have been shaped by evolution. A detailed study of human DHFR (hDHFR) revealed that both the timescale and nature of the dynamic motions (and therefore the dynamic mechanism underlying function) in hDHFR differ from that of its bacterial counterpart, *E. coli* DHFR (ecDHFR). A comparison of DHFRs from a number of different species revealed that although the 3-dimensional structure of DHFR is very similar across all kingdoms of life, the dynamics of the enzyme are indeed divergent. Moreover, while both the hDHFR and *ec*DHFR are highly active *in vitro*, hDHFR cannot complement an *E. coli* DHFR knockout cell. In a comprehensive analysis of available DHFR sequences, we were able to identify several keys features at the primary sequence level that dictate the dynamic mechanisms of the enzymes. Notably, we found that the sequence features that modulate DHFR dynamics are not randomly distributed across species but correlate with the position of an organism in the tree of life. Our results suggest that changes in the intracellular environment in some lineages may have driven the divergent evolution of dynamics, and thereby differences in the kinetics of ligand flux in the DHFR family (perhaps due to changes in the ratio of NADPH to $NADP^+$ between bacteria and higher eukaryotes). We were able to demonstrate that enzyme dynamics, like protein structure, are subject to evolutionary pressure and environmental influences, leading us to a model for how protein dynamics in the DHFR protein family have evolved. This work provides unprecedented and exciting new glimpses into the evolution of protein dynamics, and many novel details remain to be elucidated.

- **Bhabha G**, Ekiert DC, Jennewein M, Zmasek CM, Tuttle LM, Kroon G, Dyson HJ, Godzik A, Wilson IA, Wright PE (2013). Divergent evolution of protein conformational dynamics in dihydrofolate reductase. *Nat Struct Mol Biol.* 20 (11):1243-9

- **Bhabha G,** Tuttle L, Martinez-Yamout MA, and Wright PE (2011). Identification of endogenous ligands bound to bacterially expressed human and *E. coli* dihydrofolate reductase by 2D NMR. FEBS Lett. 585(22):3528-32

3. Mechanism of the motor protein dynein

Dynein is a large microtubule based, minus-end directed AAA motor protein that is critical for the proper functioning of most eukaryotic cells. Cytoplasmic dynein actively transport cargos and plays a role in the cell cycle. Dyneins were first discovered over 50 years ago by Ian Gibbons, and since then much work has been done on understanding dynein function. Understanding the structural basis and mechanism of dynein howver, was more challenging, due to the large size and inherent flexibility of the motor proteins. Initial breakthroughs were made by imaging axonemal dynein using negative stain EM (Burgess), and then obtaining the first crystal structures for cytoplasmic dyneins (Carter, Vale and co-workers, and Sutoh, Kon and coworkers) as recently as 2011. Beginning in 2012, my postdoctoral work focused on using hybrid methods to capture snapshots of yeast cytoplasmic dynein in different in different stages of its ATP cycle, and understand the conformational changes that correlate with its chemical cycle. In an exciting effort led together with my colleague, Hui-Chun Cheng, we were able to use X-ray crystallography, EM, biochemical and functional assays to generate a model for dynein's mechanochemical cycle, and dissect the roles of it's individual AAA domains. Most recently, in my first paper as a corresponding author, we have uncovered the role of dynein's very conserved stalk in motility, and found that the length is a key contributor to directionality and regulation of ATPase activity.

- **Bhabha G**, Zhang N, Moeller A, Liao M, Speir J, Cheng Y, Vale RD, Cheng HC (2014). Allosteric communication in the dynein motor domain. *Cell.* 159(4):857-68

- **Bhabha G**, Johnson GT, Schroeder CM, Vale RD (2016). How dynein moves along microtubules. *Trends Biochem Sci*. 41(1):94-105

- Niekamp S., Coudray N., Zhang N., Vale RD and **Bhabha G*** (2019). Coupling of ATPase activity, microtubule binding and mechanics in the dynein motor domain (BioRxiv preprint)

4. Architectures of the MCE family of bacterial lipid transporters

How phospholipids are trafficked between the bacterial inner and outer membranes through the intervening hydrophilic space of the periplasm is not known. We recently discovered that members of the mammalian cell entry (MCE) protein family form structurally diverse hexameric rings and barrels with a central channel capable of mediating lipid transport. The *E. coli* MCE protein, MlaD, forms a ring as part of a larger ABC transporter complex in the inner membrane, and employs a soluble lipid-binding protein to ferry lipids between MlaD and an outer membrane protein complex. In contrast, our cryo EM structures of two other *E. coli* MCE proteins show that YebT forms an elongated tube consisting of seven stacked MCE rings, and PqiB adopts a syringe-like architecture. Both YebT and PqiB create channels of sufficient length to span the entire periplasmic space. This work has revealed for the first time the diverse architectures of highly conserved protein-based channels implicated in the transport of lipids between the inner and outer membranes of bacteria and some eukaryotic organelles. This work is a long-term collaboration with my colleague, Damian Ekiert.

- Ekiert DC*, **Bhabha G***, Isom GL, Greenan G, Ovchinnikov S, Henderson IR, Cox JS, Vale RD. Architectures of lipid transport systems for the bacterial outer membrane. *Cell.* 169 273-285 (2017). *Preprint posted on BioRxiv. July 18 (2016). doi: 110.1101/064360.*

- Isom GL*, Coudray N*, MacRae MR, McManus CT, Ekiert DC$, Bhabha G$. Structure of LetB reveals a tunnel for lipid transport across the bacterial envelope. *Cell.* In Press (2020). *Preprint on BioRxiv: https://www.biorxiv.org/content/10.1101/748145v1*

5. Mechanism of invasion organelle firing in microsporidian parasites

Microsporidia, a divergent group of single-celled eukaryotic parasites, harness a specialized harpoon-like invasion apparatus called the polar tube (PT) to gain entry into host cells. The PT is tightly coiled within the transmissible extracellular spore, and is about 20 times the length of the spore. Once triggered, the PT is rapidly ejected and is thought to penetrate the host cell, acting as a conduit for the transfer of infectious cargo into the host. The organization of this specialized infection apparatus in the spore, how it is deployed, and how the nucleus and other large cargo are transported through the narrow PT are not well understood. We have used serial block-face scanning electron microscopy to reveal the 3-dimensional architecture of the PT and its relative spatial orientation to other organelles within the spore. Using high-speed optical microscopy, we have also captured and quantified the entire PT germination process *in vitro*. Our results show that the emerging PT experiences very high accelerating forces to reach velocities exceeding 300 $\mu m \cdot s^{-1}$, and that firing kinetics differ markedly between species. Live-cell imaging reveals that the nucleus, which is at least 7 times larger than the diameter of the PT, undergoes extreme deformation to fit through the narrow tube, and moves at speeds comparable to PT extension. Combining imaging techniques, we have shed new light on the 3-dimensional organization, dynamics, and mechanism of PT extrusion, and have provided new insights into how infectious cargo moves through the tube to initiate infection.

- Jaroenlak P, Cammer M, Davydov A, Sall J, Usmani M, Liang F, Ekiert DC$, **Bhabha G$**. 3-Dimensional organization and dynamics of the microsporidian polar tube invasion machinery. *PLoS Pathogens.* In Press (2020). *Preprint posted on BioRxiv. April 4 (2020). doi: https://doi.org/10.1101/2020.04.03.024240.*

Complete list of published works (via My Bibliography):
https://www.ncbi.nlm.nih.gov/sites/myncbi/gira.bhabha.1/bibliography/41601565/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support Bhabha (PI) 08/01/2019 – 06/30/2021

PEW-00033055
Pew Biomedical Scholars
How microsporidia parasites deploy harpoons to infect cells
The objective of this grant is to study the invasional organelle in a subset of microsporidian parasites.

Ongoing Research Support Bhabha (PI) 07/01/2018 – 06/30/2021
SSP-2018-2737
Searle Scholars Program
How ballistic organelles invade host cells
The objective of this grant is to understand the structural and mechanistic basis of how ballistic organelles invade host cells to initiate infection.

Ongoing Research Support Bhabha (PI) 07/01/2017 – 06/30/2020
R00GM112982
NIH/NIGMS
Structure and mechanism of cytoplasmic and axonemal dyneins
The objective of this grant is twofold: first, to characterize the dynamics of cytoplasmic dynein using SAXS, single molecule light microscopy and electron microscopy, and second, to structurally characterize axonemal dyneins using cryo electron microscopy. Thus far, we have completed a comprehensive study on the stalk element of cytoplasmic dynein, which sheds light on allosteric communication in the protein (EMBOJ, 2019) and have used cryo EM to map dynein inhibitors, giving the first insights into how one class of dynein inhibitors modulates allostery in the motor protein.

Ongoing Research Support Bhabha (co-PI) 03/01/2020 – 02/28/2025
R01AI147131-01
NIH/NIAID
Structural basis of the polar tube invasion machinery from microsporidia parasites
The goal of this work is to use structural biology and cell biology to study the mechanism of infection initiation in microsporidian parasites.

Ongoing Research Support Bhabha (co-PI; PI Emily Troemel) 08/01/2019 – 07/31/2023
2R01GB114139
NIH/NIGMS
The intracellular pathogen response triggers defense against co-evolved pathogens
The goal of this work is to use structurally characterize the PALS proteins that are upregulated in *C. elegans* in response to infection with specific pathogens

Ongoing Research Support Bhabha (co-PI) 07/01/2019 – 06/30/2021
N/A
Open Philanthropy (subcontract via University of Washington)
X-ray crystal structure determination of computationally designed proteins
This is award is shared between myself and another PI, Damian Ekiert. The goal is to determine structures of novel computationally designed proteins in collaboration with the lab of David Baker.

Completed Research Support Bhabha (PI) 03/01/2015 – 02/28/2016
K99GM112982
NIH/NIGMS
Structure and mechanism of cytoplasmic and axonemal dyneins
The objective of this grant is twofold: first, to characterize the dynamics of cytoplasmic dynein using SAXS, single molecule light microscopy and electron microscopy, and second, to structurally characterize axonemal dyneins using cryo electron microscopy.

Completed Research Support Bhabha (PI) 07/01/2012 – 02/28/2015
DRG-2136-12
Damon Runyon Cancer Research Foundation
High-resolution studies of dynein structure and mechanism
The goal of this project was to understand the structural mechanism of the dynein, a negative end directed microtubule based motor protein. A hybrid approach, including X-ray crystallography and cryo electron microscopy, was used to elucidate conformational changes in yeast cytoplasmic dynein as it steps along a microtubule. This work resulted in a new model and mechanistic insights into nucleotide-dependent conformational changes in dynein, published in 2014.

Completed Research Support Bhabha (PI) 01/01/2017 – 12/31/2018
DFS-20-16
Damon Runyon Cancer Research Foundation
High-resolution studies of dynein structure and mechanism
The goal of this project is to characterize how dynein mechanisms relate to ciliary function. Both motile and primary cilia are dependent on dynein 2 for retrograde intraflagellar transport. Motile cilia are additionally dependent on several axonemal dyneins that facilitate microtubule sliding in axonemes, which results in ciliary beating. We will use hybrid methods to address how both kinds of dyneins function in the context of cilia.

Completed Research Support Bhabha (co-PI) 05/01/2018 – 04/30/2020
N/A
Colton Center for Autoimmunity (internal)
Defining the antigenic landscape of MuSK autoantibodies to design therapies for Myasthenia Gravis
This is a pilot internal award, shared between myself and two other PIs, Steve Burden and Damian Ekiert. The goal is to biochemically characterize auto-antibodies that are generated against Muscle-specific kinase (MuSK) in the neuromuscular disease myasthenia gravis.

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: Damian C. Ekiert

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

POSITION TITLE: 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 Chicago, Chicago, USA	BA	06/2005	Biology
Scripps Research Institute, La Jolla, USA	Ph.D.	08/2011	Chemical & Biological Sciences
University of California, San Francisco	Postdoctoral	12/2016	Microbiology

A. Personal Statement

I have ~15 years experience using biophysical methods to investigate the structure and function of proteins. My lab has extensive experience in the production and study of soluble and membrane proteins of bacterial, viral, and mammalian origin This work has resulted in numerous high profile publications, 75 X-ray and cryo EM structures in the PDB, and has served as the basis for several therapeutic antibodies and immunogens in clinical development. As a graduate student in Ian Wilson's lab at the Scripps Research Institute and the Joint Center for Structural Genomics, I gained exposure and experience in the operation of a high-throughput structural biology pipeline, which will be an asset for the proposed work here. I have been collaborating with David Baker for ~10 years, and together we have determined the structures of ~20 computationally designed proteins. The strong, long-standing collaborations with Gira Bhabha, an expert in cryo EM, will allow us to make rapid progress on difficult protein structures.

B. Positions and Honors

Positions and Employment:
2017- Assistant Professor, Depts. Cell Biology and Microbiology, NYU School of Medicine, NY, NY

Honors:
2008-2011 ARCS Foundation Pre-doctoral Fellowship
2012 Rosalind Franklin Young Investigator Award, APS, Argonne National Laboratory
2014 Influenza Award for Young Scientists, European Scientific Working Group on Influenza
2012-2016 Damon Runyon Post-doctoral Fellow
2017 Whitehead Fellowship

C. Contributions to Science

1) **Influenza virus neutralization, and the prospect for novel therapies and vaccines**. As a graduate student in Ian Wilson's lab, I focused on how we might develop improved vaccines for influenza. An influenza vaccine has been available for decades, but it suffers from a major problem: the vaccine must be reformulated annually due to the high rate of antigenic drift/shift. This poses a difficult challenge: how can we elicit protective immunity against a variable pathogen such as HIV or influenza if the vaccinee will likely be exposed to a strain that is antigenically distinct from the vaccine?

In a series of papers with a number of collaborators, we identified and characterized several of the first human, broadly neutralizing antibodies against influenza. These antibodies typically neutralize ~50% or more of all influenza A viruses and are protective *in vivo*, even when administered after the onset of symptoms. The crystal structures of several of these antibodies bound to the virus shed light on how these incredible antibodies worked, and suggested how we might design new therapeutics and vaccines that target the same site. In the ensuing years, we and others have described numerous other broadly neutralizing antibodies against influenza, and many of these antibodies are in human clinical trials. Synthetic molecules targeting this site also inhibit virus replication and have the potential for development into novel antivirals. Finally, a number of immunogens inspired by this work have been reported that can re-elicit similar, broadly neutralizing antibodies against flu.

a) Ekiert DC, *et al.*, Antibody recognition of a highly conserved influenza virus epitope. *Science* **324**, 246–251 (2009).
b) Ekiert DC, *et al.*, A highly conserved neutralizing epitope on group 2 influenza A viruses. *Science* **333**, 843–850 (2011).
c) Ekiert DC, *et al.*, Cross-neutralization of influenza A viruses mediated by a single antibody loop. *Nature* **489**, 526–532 (2012).
d) Fleishman SJ*, Whitehead T*, and Ekiert DC*, *et al.*, Computational design of proteins targeting the conserved stem region of influenza hemagglutinin. *Science* **332**, 816–821 (2011).

2) **An unconventional mode of antigen recognition by bovine antibodies.** The antibody CDR H3 loop (Heavy chain Complementarity Determining Region 3) is highly variable and dominates most antibody-antigen interactions. While in mice CDR H3 might be just 5-10 residues long, in cattle this loop can be nearly 70 residues long and rich in cysteines. To understand how these unique antibodies recognize antigens, we determined the crystal structures of two such bovine antibodies. The structures revealed a remarkable, disulfide stabilized "ball-and-chain"-like architecture extending far from the conventional antigen binding site, and we showed that the "ball" mediated antigen binding. Like the discovery of camelid and shark IgNAR antibodies that completely lack conventional light chains, this work revealed a completely new mechanism of antigen recognition.

a) Wang F*, Ekiert DC*, Ahmad I, Yu W, Zhang Y, Bazirgan O, Torkamani A, Raudsepp T, Mwangi W, Criscitiello MF, Wilson IA, Schultz PG, Smider VV. Reshaping antibody diversity. *Cell*. **153**(6):1379-93 (2013).

3) **Secretion of PE-PPE cell surface antigens from *M. tuberculosis*.** The PE and PPE proteins are a highly expanded and diverse family of cell surface antigens in the important human pathogen, *M. tuberculosis*. While it was previously known that PE and PPE proteins are exported through the multiple ESX/type VII secretion systems encoded in the TB genome, it was not well understood how these and other substrates are target for secretion. We determined the crystal structures of EspG3 and EspG5, and showed that EspG3 and EspG5 interact with distinct subsets of the PE and PPE protein familes. By determining the crystal structures of EspG5 in complex with a PE-PPE heterodimer, we were able to map the surfaces of EspG and PPE important for the interaction, defining a “secretion sequence” and allowing us to predict which PPE substrates would be secreted through each ESX system *M. tuberculosis*.

a) Ekiert DC, Cox JS. Structure of a PE-PPE-EspG complex from Mycobacterium tuberculosis reveals molecular specificity of ESX protein secretion. *Proc Natl Acad Sci U S A*. **111**:14758-63 (2014).

4) **Lipid transporters important for outer membrane integrity in bacteria and organelles.** How phospholipids are trafficked between the bacterial inner and outer membranes through the intervening hydrophilic space of the periplasm is not known. We recently discovered that members of the mammalian cell entry (MCE) protein family form structurally diverse hexameric rings and barrels with a central channel capable of mediating lipid transport. The *E. coli* MCE protein, MlaD, forms a ring as part of a larger ABC transporter complex in the inner membrane, and employs a soluble lipid-binding protein to ferry lipids between MlaD and an outer membrane protein complex. In contrast, our cryo EM structures of two other *E.*

coli MCE proteins show that YebT forms an elongated tube consisting of seven stacked MCE rings, and PqiB adopts a syringe-like architecture. Both YebT and PqiB create channels of sufficient length to span the entire periplasmic space. This work has revealed for the first time the diverse architectures of highly conserved protein-based channels implicated in the transport of lipids between the inner and outer membranes of bacteria and some eukaryotic organelles.

a) Ekiert DC, Bhabha G, Isom GL, Greenan G, Ovchinnikov S, Henderson IR, Cox JS, Vale RD. Architectures of lipid transport systems for the bacterial outer membrane. *Cell*. 169:273-85 (2017).
Pre-print posted on BioRxiv. July 18 (2016). doi: 110.1101/064360.
b) Isom GL, Coudray N, MacRae MR, McManus CT, Ekiert DC‡, Bhabha G‡. LetB Structure Reveals a Tunnel for Lipid Transport across the Bacterial Envelope *Cell*. 181:653–664 (2020).
Pre-print posted on BioRxiv. August 28 (2019). doi: 10.1101/748145.
c) Kolich L, Chang Y, Coudray N, Giacometti SI, MacRae MR, Isom GL, Teran EM, Bhabha G, Ekiert DC. Structure of MlaFB uncovers novel mechanisms of ABC transporter regulation.
Pre-print posted on BioRxiv. April 27 (2020). doi: 10.1101/2020.04.27.064196
d) Coudray N, Isom GL, MacRae MR, Saiduddin MN, Bhabha G, Ekiert DC. Structure of MlaFEDB lipid transporter reveals an ABC exporter fold and two bound phospholipids.
Pre-print posted on BioRxiv. June 2 (2020). doi: 10.1101/2020.06.02.129247

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40901430/?sort=date&direction=ascending

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

ONGOING

NIH/GM
1R35GM128777-01 Ekiert (PI) 08/01/2018 - 07/31/2023
Unravelling lipid trafficking for the bacterial outer membrane.
The goal of this project is to characterize the function of the *E. coli* Mla, Pqi, and Let systems, and MCE lipid transport systems more broadly, using structural, biochemical, and genetic approaches.

COMPLETED:

NYU Whitehead Fellowship
N/A Ekiert (PI) 09/01/2017 - 08/31/2018
Building a wall: How bacterial outer membrane is assembled and maintained.
The goal of this project was to extend our previous studies of the *E. coli* Mla and Pqi systems to an additional MCE transporter, for which two proteins have been identified: YebS and YebT. With an ultimate goal of determining the structures of YebT, YebS, and understanding how they interact with lipids, this small grant supported our initial efforts to produce high quality samples for structural studies and to obtain reagents required for mapping the lipid translocation pathway through the YebST complex.

Colton Center for Autoimmunity
n/a Ekiert (PI) 05/01/2018 - 04/30/2021
Defining the antigenic landscape of MuSK autoantibodies to design therapies for Myasthenia Gravis.
The goal of this project was to characterize the pathological autoimmune response in patients with myasthenia gravis, and develop new biologics that may serve as the basis for future therapies.

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: David Baker

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

POSITION TITLE: Professor of Biochemistry, University of Washington; Investigator, Howard Hughes Medical Institute (HHMI); Adjunct Professor of Computer Science, Physics, Genome Sciences, Bioengineering, Chemical Engineering

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
Harvard University	B.A.	06/1984	Biology
University of California, Berkeley	Ph.D.	06/1989	Biochemistry
University of California, San Francisco	Postdoctoral	11/1993	Biophysics

A. Personal Statement

My colleagues and I have developed the Rosetta computational methodology for predicting and designing macromolecular structures, interactions, and functions. We have used this methodology to predict the structures and interactions of naturally occurring biomolecules, and to design new proteins with new structures, interactions and functions. We have made substantial advances in *ab initio* protein structure prediction, and more recently the generation of high-resolution structure models from limited co-evolution experimental data.

B. Positions and Honors

Positions and Employment

1993-2000 Assistant Professor, Department of Biochemistry, University of Washington.
2000-2003 Associate Professor, Department of Biochemistry, University of Washington
2000-2005 Associate Investigator, Howard Hughes Medical Institute
2003- Professor, Department of Biochemistry, University of Washington
2003- Adjunct Professor of Bioengineering, Genome Sciences, Chemical Engineering and Physics
2005- Investigator, Howard Hughes Medical Institute

Other Experience and Professional Memberships

2006 National Academy of Sciences
2009 American Academy of Sciences

Honors

1993 Boyer Foundation Fellowship
1994 Packard Fellowship in Science and Engineering
1994 National Science Foundation Young Investigator Award
1995 Beckman Young Investigator Award
2000 Protein Society Young Investigator Award
2002 International Society for Computational Biology Overton Prize
2004 Foresight Institute Feynman Prize
2004 AAAS Newcomb Cleveland Prize
2007 Editorial Board, Proceedings of the National Academy of Sciences (PNAS)
2008 Sackler Prize in Biophysics

2011 University of Washington Inventor of the Year Award
2012 Biochemical Society Centenary Award
2014 ACS Perlman Memorial Award
2017 Henrietta and Aubrey Davis Endowed Professorship in Biochemistry
2018 Solvay Public Lecture
2018 Protein Society Hans Neurath Award
2020 Fellow, AIMBE - American Institute for Medical and Biological Engineering (Class of 2020)

C. Contributions to Science

1. **How proteins fold.** We investigated the extent to which amino acid sequence determines protein folding rates by using selection methods to identify very different sequences that folded to the same structure. While the stabilities of these proteins were generally less than the native protein, the folding rates were as often faster as slower, suggesting that evolution has not optimized sequences for rapid folding. Since introducing substantial sequence variation did not significantly affect protein folding rates, we sought other factors that determined the rate of folding. A series of experimental and computational analyses established that protein folding rates and mechanism are largely determined by the topology of the native structure. A particularly notable observation was that protein folding rates are strongly correlated with the contact order of the native structure (the sequence separation between contacting residues in the protein structure), with low contact order proteins folding orders of magnitude faster than high contact order proteins.

(1) Plaxco, K.W. et al. (1998) Contact order, transition state placement and the refolding rates of single domain proteins. J. Mol. Biol. 227:985-94. PMCID: PMC20199.
(2) Riddle, D.S. et al. (1999) Experiment and theory highlight role of native state topology in SH3 folding. Nat. Struct. Biol. 6:1016-24.
(3) Alm, E. and Baker, D. (1999) Prediction of protein-folding mechanisms from free-energy landscapes derived from native structures. Proc. Natl. Acad. Sci. U.S.A. 96:11305-10. PMCID: PMC18029.
(4) Rocklin G.J. et al. (2017) Global analysis of protein folding using massively parallel design, synthesis, and testing. Science. 357:168-175. PMCID: PMC5568797.

2. **Protein structure prediction and determination of macromolecular structure from sparse data sets.** Guided by the insights gained in our studies of protein folding mechanism, we developed the Rosetta *ab initio* structure prediction methodology which builds protein structures by fragment assembly. The CASP blind structure prediction experiments showed that the Rosetta protein structure prediction methodology was a significant improvement over previous approaches. We developed methods for efficiently refining protein models in a physically realistic all atom potential, coupled this with lower resolution conformational search methods, and showed that not only monomeric protein structures but also protein-protein complexes (the docking problem), higher order symmetric protein assemblies, membrane proteins, and RNA structures could be modeled accurately by searching for the lowest energy state provided the space to be searched was not too large. We then showed that the Rosetta approach could generate quite accurate models of more complex systems when provided with limited experimental data to guide conformational sampling. Rosetta supplemented with experimental data has become a powerful and widely used approach to solve macromolecular structures using sparse NMR data (CS-Rosetta), low-resolution x-ray diffraction data (MR-Rosetta), cryo-electron microscopy data, and co-evolution sequence information (Gremlin-Rosetta).

(1) Gray, J.J. et al. (2003) Protein-protein docking with simultaneous optimization of rigid-body displacement and side-chain conformations. J. Mol. Biol. 331:281-99.
(2) Raman, S. et al. (2010) NMR structure determination for larger proteins using backbone-only data. Science. 327:1014-18. PMCID: PMC2909653.
(3) DiMaio, F. et al. (2011) Improved molecular replacement by density- and energy-guided protein structure optimization. Nature. 473:540-43. PMCID: PMC3365536.
(4) Ovchinnikov, S. et al. (2017) Protein structure determination using metagenome sequence data. Science. 355:294-298. PMCID: PMC5493203.

3. **Design of protein structure and immunogens.** The Rosetta structure prediction methodology described above searches for the lowest energy structure for a given sequence, and we realized that we could invert the process to search for the lowest energy sequence for a desired structure—the protein design problem. We demonstrated proof-of-concept for *de novo* protein design with the design of TOP7, a novel protein with a fold not found in nature, and later developed general principles for designing hyperstable idealized alpha-beta

proteins and helical bundles. With the capability of designing stable protein structures in hand, we developed methods for stabilizing both linear and complex epitopes from pathogen proteins, and showed that these could elicit neutralizing antibodies in animals, opening up computational design approaches to developing improved vaccines.

(1) Kuhlman, B. et al. (2003) Design of a novel globular protein fold with atomic-level accuracy. Science. 302:1364-68.
(2) Koga, N. et al. (2012) Principles for designing ideal protein structures. Nature. 491:222-27. PMCID: PMC3705962.
(3) Correia, B.E. et al. (2014) Proof of principle for epitope-focused vaccine design. Nature. 507:201-06. PMCID: PMC4260937.
(4) Hosseinzadeh P. et al. (2017) Comprehensive computational design of ordered peptide macrocycles. Science 358:1461-1466. PMID: 29242347. NIHMSID: 931150.

4. **Design of small molecule binding, catalysis, protein interactions, and self-assembly.** A grand challenge in computational protein design is creating new binding proteins *de novo* for use in therapeutics and diagnostics. We have developed general methods for designing proteins which bind with high affinity/specificity to sites of interest of therapeutic importance on protein targets, both human and pathogen (influenza, bacterial toxins, oncogenic proteins). We developed general methods for designing catalysts for arbitrary chemical reactions starting from a description of the reaction transition state geometry, and used the approach to design catalysts for a number of reactions not catalyzed by naturally occurring enzymes. We have developed an approach to computationally designing self-assembling nanomaterials and used it to design new proteins that self assemble into regular tetrahedral, octahedral and icosahedral structures as well as two dimensional layers with near atomic-level accuracy. We are now developing these self-assembling materials for targeted delivery and vaccine applications.

(1) Siegel, J.B. et al. (2010) Computational design of an enzyme catalyst for a stereoselective bimolecular Diels-Alder reaction. Science. 329:309-13. PMCID: PMC3241958.
(2) King NP et al. (2014) Accurate design of co-assembling multi-component protein nanomaterials. Nature. 510:103-8. PMCID: PMC4137318.
(3) Tinberg, C.E. et al. (2013) Computational design of ligand-binding proteins with high affinity and selectivity. Nature. 501:212-6. PMCID: PMC3898436.
(4) Chevalier A. et al. (2017) Massively parallel *de novo* protein design for targeted therapeutics. Nature. 550:74-79. PMID: 28953867.

5. **Involving the general public in Science**. We created a distributed computing project called Rosetta@home in which volunteers donate spare cycles on their computers to carry out protein folding trajectories. We extended Rosetta@home to the interactive multiplayer online game Foldit which allows players to guide the course of the protein structure prediction and design calculations. By relying on human intuition and 3-D problem solving skills, Foldit players have made a number of important contributions: solved the structure a retroviral protease, developed new algorithms for finding low-energy protein conformations, and designed a novel synthetic enzyme by large-scale redesign of the active site.

(1) Cooper, S. et al. (2010) Predicting protein structures with a multiplayer online game. Nature. 466:756-60. PMCID: PMC2956414.
(2) Khatib, F. et al. (2011). Crystal structure of a monomeric retroviral protease solved by protein folding game players. Nat Struc Mol Biol. 18:1175-77. PMCID: PMC3705907.
(3) Khatib, F. et al. (2011) Algorithm discovery by protein folding game players. Proc. Natl. Acad. Sci. U.S.A. 108:18949-53. PMCID: PMC3223433.
(4) Eiben, C.B. et al. (2012) Increased Diels-Alderase activity through backbone remodeling guided by Foldit players. Nat. Biotechnol. 30:190-2. PMCID: PMC3566767.

Complete list of published work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/david.baker.2/bibliography/40635205/public/?sort=date&direction=ascending

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

Ongoing Research Support

1629214 **9/1/16 – 8/31/20**

NSF
Generalization, Functionalization and Distribution of De Novo Designed Protein Nanomaterials
This research integrates theory, computation and experiment to close the design cycle on creation of new protein-based nanomaterials that are not currently accessible using conventional protein engineering approaches.
Role: PI

OPP1156262 **11/1/16 – 10/31/21**
Bill & Melinda Gates Foundation
Structure based immunogen design: IPD
This project will focus on structure based immunogen design for next-generation vaccines.
Role: PI

FA8750-17-C-0219 **8/24/17 – 8/24/21**
DARPA
Data Driven Design of Protein Function
The goal of this grant is to dramatically improve capabilities for designing new proteins with new functions by transforming protein design into a data driven science.
Role: PI

HDTRA1-18-1-0001 **10/3/17 – 11/15/22**
DTRA
Computational Epitope Design for Protective Vaccines
The goal of this project is to develop and validate a new Rosetta vaccine design platform for rapid computational epitope design combined with a novel next-generation protein nanoparticle strategy to display the designed immunogens as nucleotide-based or recombinant protein vaccines, amenable to rapid and cost-effective manufacture.
Role: PI

FA9550-18-1-0297 **6/15/18 – 6/14/21**
US Air Force Office of Sponsored Research
New Sensing Modalities Based on Designed Self-Assembling Protein Nanomaterials
The goal of this project is to harness the power of protein chemistry to program self-assembly of molecular nanosensors in lipid bilayers.
Role: PI

DE-SC0019288 (PI: Baneyx) **8/1/18 – 7/31/22**
Department of Energy
Center for the Science of Synthesis Across Scales (CSSAS)
The goal of this project is to understand the design of self-assembling non-natural protein systems.
Role: Co-PI

HDTRA1-19-1-0003 **11/5/18 – 11/4/21**
Defense Threat Reduction Agency
De Novo Computational Design of Catalytic Peptide and Peptoid Macrocycles
The goal of this project is to discover fundamental computational design methods to iteratively produce and optimize small macrocyclic catalysts capable of neutralizing chemical warfare agents.
Role: PI

DE-SC0018940 **8/15/18 – 8/14/21**
Department of Energy
Principles of De Novo Protein Nanomaterial Assembly in 1, 2 and 3 Dimensions
The goal of this project is to harness the power of protein chemistry to program self-assembly of molecular frameworks that direct formation of inorganic materials with 3D spatial control to derive new functionality.
Role: PI

P41 GM103533 (Maccoss) **4/1/20 – 3/31/21**
NIH
Comprehensive Biology: Exploiting the Yeast Genome
The goal of this grant is to develop and apply technologies for understanding the function of yeast proteins.
Role: Co-PI

2-SRA-2018-605-Q-R **12/1/18 – 11/30/20**
Juvenile Diabetes Research Foundation
Computational design of saccharide responsive macrocycle peptides

The goal of this work is to apply Rosetta algorithms to design short synthetic peptide macrocycles which are capable of binding with high affinity and specificity to saccharides under physiological pH conditions.

N/A **12/13/18 – 12/31/20**

Amgen

Tolerizing Nanoparticle Vaccine

We will generate functional peptide-bound MHC protein nanocages to engage T cells while engaging signaling pathways to induce durable regulatory phenotypes.

Role: PI

N/A **12/13/18 – 12/31/20**

Amgen

Opening the Therapeutic Window in Solid Tumors with a Cagted BiTE

We propose a strategy to increase the therapeutic window for a BiTE by requiring binding of two adjacent tumor cell surface antigens for activation.

Role: PI

1 R01 AG 063845-01 **8/15/19 – 4/30/24**

NIH

Designed Vehicles for Blood Brain Barrier Traversal

The goal of this project is to deliver large therapeutic cargo into the brain using designed BBB-crossing drug-delivery vehicles.

Role: PI

1 R01 CA 240339-01 **9/1/19 – 8/31/24**

NIH

Design of De Novo Interleukin Mimics for Targeted Immunotherapy

The goal of this project is to produce targeted anti-cancer cytokine mimetics with reduced toxitcity. We will apply recent breakthroughs in de novo protein design to yield a new category of targeted, non-toxic, immunostimulatory proteins.

Role: PI

2019PG-T1D026 **12/1/18 – 11/30/20**

The Leona M. and Harry B. Helmsley Charitable Trust

Computational design of glucose responsive cyclic peptides

The goal of this grant is to computationally design glucose responsive peptides that can be conjugated to commercial long acting forms of insulin to confer upon them a glucose responsiveness.

Role: PI

CMS-625209 **12/19/18 – 12/18/20**

Novo Nordisk A/S

Computational design of peptides for carbohydrate recognition

The goal is de novo computational design of novel peptide carriers for blood brain barrier transport.

Role: PI

NIA U19 AG062156 (Maccoss, PI) **9/1/19 -8/31/24**

NIH/NIA

Next Generation Translational Proteomics for Alzheimer’s and Related Dementias

The goal of this project is to unite a unique team with the specific goal of vastly improving the molecular characterization of CSF as predictors of cognitive decline and AD pathophysiology.

Role: Co-PI

1U01AI151698-01(Van Voorhis, Wasserheit, Rabinowitz, Gale, PI) **5/22/20-4/30/25**

NIH/NIAID

Univ. of Wash. Arboviral Research Network (United World Antiviral Research Network, UWARN)

This UWARN center for the Centers Researching Emerging Infectious Diseases will establish research and coordination with arboviral research laboratories in Brazil, Pakistan, Senegal, South Africa, and Taiwan.

Role: co-PI

1U01HL152401-01 (Ho, RY, PI) **9/1/19 – 8/31/22**

NIH/NHLBI

Washington Entrepreneurial Research Evaluation and Commercialization Hub

This hub will accelerate the creation of small businesses using biomedical discoveries to launch products that impact health outcomes.

Role: Co-PI