BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
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NAME	POSITION TITLE
Wu, Hao	Asa and Patricia Springer Professor of Biological Chemistry and Molecular Pharmacology
eRA COMMONS USER NAME (credential, e.g., agency login) haowuwmc	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Peking University, Beijing, China	B. Sc. Equiv.	1982-1985	Biology
Peking Union Medical College, Beijing, China	MD candidate	1985-1988	Medicine
Purdue University, West Lafayette, Indiana	Ph.D.	1988-1992	Biochemistry
Columbia University, New York, New York	Postdoc	1992-1997	Biochemistry

A. Personal Statement

Since starting her laboratory in 1997, the PI has focused on structural immunology, in particular, the structural basis of intracellular signal transduction in the mammalian innate immune system. The PI is experienced in many aspects of structural biology, including protein crystallography, cryo-electron microscopy, biochemistry and biophysics. Her current work also extends structure-based drug design.

I enthusiastically support this application for data collection at NCCAT. The present project extends our work on inflammasomes, supramolecular protein signaling complexes, to a protein with a novel domain architecture and activation mechanism. I strongly believe in the abilities of my student to complete this project, given his preliminary data (featured in the supplemental section of this application) and their work ethic in the lab.

B. Positions and Honors

7/2012- Asa and Patricia Springer Professor of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, and the Program in Cellular and Molecular Medicine, Boston Children's Hospital
2003-7/2012 Professor of Biochemistry, Weill Medical College of Cornell University.
2001-2003 Associate Professor of Biochemistry, Weill Medical College of Cornell University.
1997-2001 Assistant Professor of Biochemistry, Weill Medical College of Cornell University.

2015 Election to the National Academy of Sciences
2015 Pioneer Award from the National Institute of Health
2013 Purdue University Distinguished Science Alumni Award
2013 Elected AAAS Fellow
2012-2022 NIH Merit Award
2012- Editorial Board, F1000 Research
2012- Editorial Board, Cancer Cell
2003 Mayor's Award for Excellence in Science and Technology
2003 Margaret Dayhoff Memorial Award, Biophysical Society
7/2002-6/2004 Rita Allen Scholar Award
7/2000-6/2004 Pew Scholar Award
6/1993-6/1996 Aaron Diamond Foundation Postdoctoral Fellowship
4/1989-10/1992 Howard Hughes Medical Institute Predoctoral Fellowship
4/1989-10/1992 Member of Gamma Sigma Delta
1982-1988 Top in class and outstanding academic achievement, Peking Union Medical College
1982 Highest entering grades to Peking Union Medical College in National College Entrance Examination

C. Contributions to Science (in approximate chronological order)

Elucidation of the specificity and oligomerization mechanism of TNF receptor associated factors (TRAFs, 1/2/3/5 and 6), which are the major signaling proteins for TNF receptor family-, IL-1R family-, and TLR-family-induced NF-κB activation. When the PI started working on TRAFs, no structural information was

available. The PI identified consensus motifs for different TRAFs using structural studies, which became widely used tools for biologists. The PI's work also led to understanding the ubiquitin ligase activity of TRAF6 and its dependence on dimerization and higher-order oligomerization.

Y. C. Park, V. Burkitt, A. R. Villa, L. Tong and H. Wu (1999). Structural basis for self-association and receptor recognition of human TRAF2. ***Nature*** 398: 533-8

Y. C. Park, H. Ye, C. Hsia, D. Segal, R. L. Rich, H. C. Liou, D. G. Myszka and H. Wu (2000). A novel mechanism of TRAF signaling revealed by structural and functional analyses of the TRADD-TRAF2 interaction. ***Cell*** 101: 777-87

H. Ye, J. R. Arron, B. Lamothe, M. Cirilli, T. Kobayashi, N. K. Shevde, D. Segal, O. K. Dzivenu, M. Vologodskaia, M. Yim, K. Du, S. Singh, J. W. Pike, B. G. Darnay, Y. Choi and H. Wu (2002). Distinct molecular mechanism for initiating TRAF6 signaling. ***Nature*** 418: 443-7

Q. Yin, S. C. Lin, B. Lamothe, M. Lu, Y. C. Lo, G. Hura, L. Zheng, R. Rich, A. D. Campos, D. G. Myszka, M. J. Lenardo, B. G. Darnay and H. Wu (2009). E2 interaction and dimerization in the crystal structure of TRAF6. ***Nat Struct Mol Biol*** 16: 658-66 PMC2834951

Elucidation of activation and inhibitory mechanisms of caspases and kinases. These enzymes are critically important for apoptotic and inflammatory signaling and were often difficult to obtain structures of. The understanding on their regulatory mechanisms revealed by work from the PI's lab is now being used for discovery of small molecule inhibitors for potential disease therapy.

Y. Huang, Y. C. Park, R. L. Rich, D. Segal, D. G. Myszka and H. Wu (2001). Structural basis of caspase inhibition by XIAP: differential roles of the linker versus the BIR domain. ***Cell*** 104: 781-90

G. Xu, M. Cirilli, Y. Huang, R. L. Rich, D. G. Myszka and H. Wu (2001). Covalent inhibition revealed by the crystal structure of the caspase-8/p35 complex. ***Nature*** 410: 494-7

G. Xu, Y. C. Lo, Q. Li, G. Napolitano, X. Wu, X. Jiang, M. Dreano, M. Karin and H. Wu (2011). Crystal structure of inhibitor of κB kinase β (IKKβ). ***Nature*** 472: 325-30 PMC3081413

Ferrao R, Zhou H, Shan Y, Liu Q, Li Q, Shaw DE, Li X and Wu H (2014). IRAK4 Dimerization and Trans- autophosphorylation are Induced by Myddosome Assembly. ***Mol Cell*** 55:891-903 PMC4169746

Identification of functional amyloid assembly in TNF-induced programmed necrosis. The PI's lab showed the surprising finding that the RHIM domain-containing proteins assemble into amyloid filaments to activate kinases and to induce cell death. These studies opened up new directions of research.

J. Li, T. McQuade, A. B. Siemer, J. Napetschnig, K. Moriwaki, Y.-S. Hsiao, E. Damko, D. Moquin, T. Walz, A. McDermott, F. K.-M. Chan, and H. Wu (2012). The RIP1/RIP3 necrosome forms a functional amyloid signaling complex required for programmed necrosis. ***Cell*** 150: 339-50 PMC3664196

Discovery of helical signaling complexes including helical filaments formed by the death domain superfamily proteins. These protein domains were known for their tendencies to aggregate. The PI's lab elucidated that they assemble into either relatively defined helical complexes or helical filaments. These structures help to establish a new paradigm of signal transduction in innate immunity.

H. H. Park, E. Logette, S. Rauser, S. Cuenin, T. Walz, J. Tschopp and H. Wu (2007). Death domain assembly mechanism revealed by crystal structure of the oligomeric PIDDosome core complex. ***Cell*** 128: 533–46

S. C. Lin, Y. C. Lo and H. Wu (2010). Helical assembly in the MyD88-IRAK4-IRAK2 complex in TLR/IL- 1R signaling. ***Nature*** 465: 885-90 PMC2888693

Q. Qiao, C. Yang, C. Zheng, L. Fontan, L. David, X. Yu, C. Bracken, M. Rosen, A. Melnick, E. H. Egelman and H. Wu (2013). Structural Architecture of the CARMA1/Bcl10/MALT1 Signalosome: Nucleation-Induced Filamentous Assembly. ***Mol Cell*** 51: 766-79 PMC3929958

A. Lu, V. G. Magupalli, J. Ruan, Q. Yin, M. K. Atianand, M. R. Vos, G. F. Schröder, K. A. Fitzgerald,

H. Wu* and E. H. Egelman (2014). Unified Polymerization Mechanism for the Assembly of ASC-Dependent Inflammasomes. ***Cell*** 156: 1193-206 PMC4000066 *Sole corresponding author

Discovery of the overarching principle of higher order assemblies and their important properties in signaling.

H. Wu (2013). Higher-order assemblies in a new paradigm of signal transduction. ***Cell*** 153: 287-92 PMC3687143

Kagan JC, Magupalli V, Wu H. (2014). Supramolecular Organizing Centres (SMOCs): Site-Specific Higher Order Signalling Complexes that Control Innate Immunity. ***Nature Rev Immunol***. 14:821-6 PMC4373346

Liu X, Zhang Z, Ruan J, Pan Y, Magupalli VG, Wu H*, Lieberman J* (2016). Inflammasome-activated gasdermin D causes pyroptosis by forming membrane pores. ***Nature*** 535: 153-8. PMID: 27383986 PMCID: PMC5539988 *dual correspondence

Ruan J, Xia S, Liu X, Lieberman J, Wu H (2018). Cryo-EM structure of the gasdermin A3 membrane pore. *Nature*. 557(7703):62-67.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40701424/?sort=date&direction=descending

D. Research Support

Ongoing Support

1DP1 HD087988-01 (Wu, H) 09/30/2015-07/31/2020 NIH/NICHD (Role PI)
SMOCs: Novel Signal Transduction Complexes as New Targets for Drug Discovery
The major goal of this project is to investigate signal transduction in order to guide the development of new models for targeted drug discovery.

1R01 AI139914 (Wu, H) 06/12/18-05/31/23 NIH/NIAID (Role PI)
Elucidating the Structural Mechanism of Pore Formation by the Gasdermin (GSDM) family
The major goal of the project is to elucidate the mechanism of GSDM pore formation through biochemical and structural studies on mouse GSDMA3 and human GSDMD.

5R37 AI050872-13 (Wu, H) 01/01/02-03/31/22 NIH/NIAID (Role PI)
Structural & Functional Studies of TLR/IL-1R Signaling
The major goal of this project is to assemble the membrane-proximal signaling complexes and to elucidate the molecular basis of this signal transduction.

1R01AI125535 (Wu, H) 07/01/16-06/30/21
Molecular mechanisms of the RAG recombinase in V(D)J recombination and disease
The major goal of the this project is to elucidate the molecular basis of RAG in V(D)J recombination.

1R01 Al124491-01A1 7/01/16 - 6/30/21 NIH/NIAID (Role: PI)
Mechanistic Elucidation of Inflammasome Assembly and Regulation

The major goal of this project is to elucidate structural and mechanistic information on AIM2, NLRP3 and NAIP inflammasomes.

Completed Support:

1R01 CA182736-01 (Gray, N) 09/26/13-08/31/18 NIH/NCI (Role: Co-Investigator)
MALT1 inhibitors for the treatment of chemo-resistant ABC-DLBCL
The major goal of this project is to optimize MALT1 inhibitors using structure-based chemical approaches.

5R01 AI045937-12 (Wu, H) 07/01/99-06/30/2017 NIH/NIAID (Role: PI)
Structural and functional elucidation of the necrosome in innate immune signaling
The major goal of this project is to elucidate the molecular basis of TNF-induced necrosis.

5R01 AI089882-05 (Wu, Hao) 05/01/2010 – 04/30/2015 NIH/NIAID (Role: PI)
Molecular Elucidation of the CBM complex in NF-kappaB Activation by Antigen Receptors
The major goal of the project is to elucidate the molecular basis of CBM signaling in TCR and BCR activation

5R01 AI079260-06 (Wu, Hao) 06/25/09-06/30/14 NIH/NIAID (Role: PI)
Structural and Functional Studies of the IkappaB Kinase (IKK) Complex
The major goal of the project is to enhance the understanding of kinase activation and inhibition in general.

5R21 AI096554-02 (Menon, AK) 06/01/11 – 05/31/13 NIH/NIAID (Role: Co-Investigator)
Structural Analysis of the GPI Transamidase Complex
The main objective is to analyze the GPI transamidase complex from a structure-function perspective. The complex will be isolated from yeast and studied by electron microscopy; subunits, sub-complex and eventually the entire transmembrane complex will be characterized by X-ray crystallography.

7R01 AI076927-05 (Wu, Hao) 07/01/08-06/30/13 NIH/NIAID (Role:PI)
Structural and Functional Studies of the Caspase Activating Complex Piddosome
The major goal of the project is to elucidate the molecular basis of PIDDosome formation.

BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Hollingsworth, Louis "Bobby"	Graduate Student
eRA COMMONS USER NAME (credential, e.g., agency login) bobbyh11	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Virginia Tech, Blacksburg, VA	B.S.	05/2017	Chemical Engineering
Virginia Tech, Blacksburg, VA	B.S.	05/2017	Biochemistry
Virginia Tech, Blacksburg, VA	B.A.	05/2017	Chemistry
Harvard University, Boston, MA	Ph.D. Candidate	08/2017-Present	Biological and Biomedical Sciences

A. Personal Statement

B. Positions and Honors

08/2017- Ph.D. Candidate, Harvard University

Barry M. Goldwater Scholarship, Sophomore	2015, 2016
Harry S. Truman Scholarship Finalist	2016
PKP Marcus L. Urann Graduate Fellowship	2017
Outstanding Senior, Virginia Tech College of Engineering	2017
Outstanding Undergraduate Researcher, Virginia Tech College of Science	2017
Outstanding Senior, Virginia Tech Departments of Chemistry and Chemical Engine	2017
PEARC17 Conference Travel Award	2017
Howe Award for Outstanding Senior, Blue Ridge ACS Section	2017
Phi Beta Kappa	2017
Department of Chemistry Poster Symposium: 3rd Place	2015, 2017
Biophysical Society Conference Poster Symposium: 2nd Place	2017
Curiosity Aspire! Award, Virginia Tech Division of Student Affairs	2017
Phi Kappa Phi	2016
ACS National Symposium COMP Workshop and Travel Grant	2016
High Performance Computing Day: 1st Place Poster Presentation	2016
University Honors Class of 1954 Odyssey Fellowship	2015
Virginia Tech Illuminator Award	2015
ACC Creativity and Innovation Fellowship	2015
ICAT Student Research Grant	2015
Chem-E-Car National Poster Competition: 1st Place, 2nd Place	2015-2016
Chem-E-Car National Design Competition: 4th Place, 6th Place, 7th Place	2014-2016

C. Contributions to Science (Chronological order)

1. Hun, J. J.*; Liu, X.*; Xia, S.; Zhang, Z.; Zhao, J.; Ruan, J.; Luo, X.; Lou, X.; **Hollingsworth, L. R. IV**; Magupalli, V. G.; Kim, J.; Lieberman, J.; Wu, H. Disulfiram inhibits pyroptosis by selectively and covalently modifying a reactive cysteine in gasdermin D. *Submitted*.

2. Hilu, K. W.; Friend, S.; Vallanadu, V.; Brown, A. M.; **Hollingsworth, L. R. IV**; Bevan, D. R. Molecular Evolution of Two Allergenic Genes Across the Peanuts Genus Arachis Underscores Promising Implications for Allergenicity. *Submitted.*

3. **Hollingsworth, L. R. IV**; Lemkul, J. A.; Bevan, D. R.; Brown, A. M.; The HIV-1 Transmembrane Domain Modulates Membrane Stability and Water Permeation, *Biophys J.* **2018**, *115(1)*, *84-94*.

4. **Hollingsworth, L. R. IV**; Brown, A. M.; Gandour, R. D.; Bevan, D. R. Computational Study of HIV gp120 as a Target for Polyanionic Entry Inhibitors: Exploiting the V3 Loop Regions, *PLoS One* **2018**.

5. **Hollingsworth, L. R. IV;** Veeraraghavan, P.; Wu, K. J; McCoy, D. E.; Van Dervort, A.; Gunther, K. E. Speak out against tuition waiver taxes. *Science* **2017**, *358*, *1395*.

6. **L.R Hollingsworth IV**, A. M. Brown and D. R. Bevan. **2017**. In *Proceedings of Practice & Experience in Advanced Research Computing conference, New Orleans, Louisiana USA, July 2017 (PEARC17)*, 4 pages. http://dx.doi.org/10.1145/3093338.3104154

7. Barrow, J. J.*; Balsa-Martinez, E.*; Verdeguer, F.; Tavares, C. D. J.; Soustek, M. S.; **Hollingsworth, L. R. IV**, Jedrychowski, M.; Vogel, R.; Paulo, J. A.; Smeitink, J.; Gygi, S. P.; Doench, J.; Root D. E.; Puigserver, P. Bromodomain Inhibitors Correct Bioenergetic Deficiency Caused by Mitochondrial Disease Complex I Mutations. *Molecular Cell* **2016**, *64*, 163-175.

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

Scholastic Performance

Harvard University, Cambridge, MA
Ph.D. Candidate, Biological and Biomedical Sciences (BBS)
GPA: 3.8/4.0

Virginia Tech, Blacksburg, VA
B.S., Honors Scholar in Chemical Engineering
B.S., Honors Baccalaureate in Biochemistry
B.A., Honors Baccalaureate in Chemistry
GPA: 3.95/4.00 ***summa cum laude***
Honors Thesis: “Molecular Dynamics Simulations of gp120 Provide Basis for anti-HIV Ligand Strain Specificity”

Ongoing Support

5T32GM007226-43 (Van Vactor, D) 07/01/2018-06/30/2019 NIH (Role: Trainee)
Molecular, Cellular, & Developmental Dynamics PhD Program