BIOGRAPHICAL SKETCH

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NAME: Matthew S. Bogyo

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

POSITION TITLE: Professor of Pathology, Professor of Microbiology and Immunology, Professor by courtesy of Chemical and Systems Biology

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
Bates College	B.Sc.	06/1993	Chemistry
Massachusetts Institute of Technology	Ph.D.	08/1997	Biochemistry
Harvard Medical School	Postdoc	10/1998	Chemical Biology

A. Personal Statement

My background is in synthetic organic chemistry with applications to protease biology. While completing my Ph.D. in chemistry at MIT I developed ways to use small molecule probes to study the role of the multi-catalytic proteasome. After completion of my doctoral and post-doctoral studies in this area, I established an independent research group at UCSF where I continued to develop chemical tools to study the functional roles of proteases, with a focus on the lysosomal cysteine cathepsins and the proteasome. My lab has been studying the roles of various cysteine proteases, including the cathepsins to understand their roles in cancer and inflammation as well as serine and cysteine protease targets that play important roles in pathogen infections. My group at Stanford is made up of a mixture of synthetic chemists, cell biologists, biochemists and biologists. We currently are actively working with both parasite and bacterial pathogens including *P. falciparum*, *T. gondii*, *S. aureus*, *M. tuberculosis* and *C. difficile*. I also had the opportunity to lead a group in industry at Celera Genomics for two years as the Head of Chemical Proteomics prior to moving to Stanford. During that time, I lead projects related to the development and application of small molecule protease inhibitor drugs to various stages of the discovery process. My experience in industry helped me to develop my skills in project team management and meeting goals within deadlines as well as to learn the many steps of pre-clinical IND enabling studies. In summary, I am ideally suited to carry out my proposed role on this project. I have the leadership skills and resources available to rapidly advance the goals of the proposal.

B. Positions and Honors

<u>Positions and Employment</u>

1991-93 Council on Undergraduate Research AIURP Fellow- Bates College, Lewiston, ME
1993-97 Graduate Student- Massachusetts Institute of Technology, Cambridge, MA.
1997-98 Post-Doctoral Fellow- Harvard Medical School, Boston, MA
1998-01 UCSF Faculty Fellow- University of California, San Francisco, San Francisco, CA.
2001-03 Group Leader, Head of Chemical Proteomics- Celera Genomics, South San Francisco, CA.
2002- Adjunct Faculty Member – UCSF Department of Pharmaceutical Chemistry
2003-09 Assistant Professor - Department of Pathology, Stanford University.
2004-09 Assistant Professor - Department of Microbiology and Immunology, Stanford University.
2005-09 Assistant Professor by courtesy – Department of Molecular Pharmacology, Stanford University
2009-13 Associate Professor - Department of Pathology, Stanford University.
2009-13 Associate Professor - Department of Microbiology and Immunology, Stanford University.
2009-13 Associate Professor by courtesy – Department of Molecular Pharmacology, Stanford University
2013- Professor - Department of Pathology Stanford University.

2013-	Professor - Department of Microbiology and Immunology Stanford University.
2013-	Professor by courtesy – Department of Molecular Pharmacology, Stanford University

Other Experience and Professional Memberships

2000-01	Scientific Consultant- ActivX Biosciences, La Jolla, CA.
2000-01	Scientific Consultant- Rigel Pharmaceuticals, South San Francisco, CA.
2000-01	Scientific Consultant- Axys Pharmaceuticals, South San Francisco, CA.
2002-06	Editorial Board Member – *Biochemical Journal.*
2003-06	Scientific Consultant- Celera, South San Francisco, CA.
2002-	Editorial Board Member – *Chemistry and Biology.*
2002-	Editorial Board Member – *Molecular & Cellular Proteomics.*
2011-14	Academic Editor – *PLoS One.*
2014-	Section Editor – *PLoS One*
2003-10	Scientific Consultant- Proteolix, South San Francisco, CA.
2005-09	Council Member – International Proteolysis Society
2005-07	Secretary of International Proteolysis Society
2007-09	President of the International Proteolysis Society
2005-16	Faculty Member, Faculty of 1000
2007-09	Member, DARPA funded Defense Science Study Group
2009	Co-Chair, Seventh International Proteolysis Society General Meeting, San Diego 2011
2008-	Co-Founder and Member, Board of Directors – Akrotome Imaging Inc.
2009	Ad-Hoc Member – SBCB, DDR, EBIT, MSFE Study sections
2009	NIH Peer Review – ARRA Challenge Grants
2000-	Member, American Chemical Society
2003-	Member of the American Society of Microbiologists
2016	Scientific Consultant- Vergent Biosciences
2016	Vice Chair – Gordon Research Conference – “Proteolytic Enzymes and Their Inhibitors”
2017-23	Member – National Institutes of Health SBCA Study section
2018	Chair – Gordon Research Conference – “Proteolytic Enzymes and Their Inhibitors”

Honors

1991	Recipient of pre-doctoral fellowships from Council on Undergraduate Research
1992	American Chemical Society-Div. of Polymer Chemistry award for outstanding organic synthesis
1992	American Institute of Chemists award for outstanding performance in chemistry
1995	Recipient of MIT-Japan Science and Technology Prize
2003	Recipient of Stanford University Terman Fellowship
2004	Searle Scholar Award
2005	Burroughs Wellcome Fund – Investigators in Pathogenesis of Infectious Disease Award
2008	Strategic Program for Asthma Research – Early Excellence Award
2014	Election to American Association of University Pathologists – Pluto Society

C. Contributions to Science

My primary research accomplishments have been centered around the development of a novel platform technology termed activity-based protein profiling (ABPP) that makes use of small molecules that covalently target enzymatic proteins. These probes can be used for diverse applications ranging from basic biochemical studies of enzymes to use as high-resolution contrast agents for imaging applications in models of human disease, and more recently, in human clinical trials. Over the past decade, my lab has successfully implemented this core probe technology into many biological fields including cancer biology, inflammation and immunology and infectious disease. We have used probes to find new activation intermediates in established cell death pathways, assigned function to proteases and identified proteases that are important regulators of processes such as host cell invasion by parasites and have developed lead drug candidates that target essential parasite enzymes such as the proteasome. In addition, we have begun to build next-generation technologies that will allow the use of activity-based probes to perform non-invasive imaging of a number of important human disease conditions. This includes optical probes for use in surgical guidance applications in cancer and more recently optical and ultrasound probes for detection and therapy monitoring of infectious diseases.

Contribution 1 – Generation of probes for *in vivo* imaging of cancer and infectious diseases.
One of my major accomplishments has been to develop fluorescently quenched probes that activate upon binding to an active protease as well as fluorescent substrates that are activated by proteases. The cysteine cathepsins are proteases that have been shown to have roles in various aspects of immune cell function and are also important regulators of multiple disease pathologies. Because their activity is dynamically regulated, it is often difficult to use classical methods to study their biological functions. The probes that we have developed can be used to image the location and activation of these important lysosomal enzymes *in vivo*, thus providing a functional activity readout that can both shed light on aspects of cathepsin biology and also aid in diagnosis and disease monitoring in conditions, such as cancer and inflammation, that depend on cathepsin activity. Specifically, we have shown that cathepsins serve as ideal imaging biomarkers of inflammation because they are highly expressed in activated macrophages. Thus, probes that target cathepsins can be used for non-invasive optical and radiological imaging of disease pathologies that involve inflammation. We have demonstrated the utility of ABPs for imaging tumor margins, tumor response to chemotherapy, atherosclerosis, asthma and most recently pulmonary fibrosis. We have also used fluorescently quenched substrates and activity based probes to target a bacterially derived serine proteases. These probes can be used to specifically detect infection. A sample of my most relevant papers are:

1. Blum, G., von Degenfeld, G., Merchant, M.J., Blau, H.M., and **Bogyo, M**. (2007) Optical Imaging of Cysteine Protease Activity in Living Subjects Using Quenched Near Infrared Fluorescent Activity Based Probes (NIRF-qABPs). *Nature Chemical Biology* 3, 668-677.

2. Ofori LO, Withana NP, Prestwood TR, Verdoes M, Brady JJ, Winslow MM, Sorger J, **Bogyo** M. (2015) Design of Protease Activated Optical Contrast Agents That Exploit a Latent Lysosomotropic Effect for Use in Fluorescence-Guided Surgery. *ACS Chem Biol.* 10(9):1977-88.

3. Lentz CS, Ordonez AA, Kasperkiewicz P, La Greca F, O'Donoghue AJ, Schulze CJ, Powers JC, Craik CS, Drag M, Jain SK, **Bogyo M.** (2016) Design of Selective Substrates and Activity-Based Probes for Hydrolase Important for Pathogenesis 1 (HIP1) from *Mycobacterium tuberculosis*. *ACS Infect Dis*. 2, 807-81.

4. Yim JJ, Tholen M, Klaassen A, Sorger J, **Bogyo M.** (2018) Optimization of a Protease Activated Probe for Optical Surgical Navigation. *Mol Pharm*. 15, 750-758.

Contribution 2 – Validating the proteasome as a target for anti-malarial therapy.
We have been working over the past 5 years to demonstrate that it is possible to selectively target the malaria proteasome as a strategy to effectively treat infection. We have shown that inhibitors of at least two of the three primary active sites of the core 20S complex can effectively kill parasites at all of the asexual blood stages as well as insect stage sporozoites. We also have shown that the human and malaria enzymes are sufficiently different in their active sites that it is possible to make inhibitors that have sufficient selectivity to allow treatment without causing excessive toxicity to the host. Finally, we have shown that proteasome inhibitors synergize with artemisinin and are effective at killing resistant field isolates from Southeast Asia. Together, these findings that have been published serve as the key preliminary results for this proposal.

1. Li H, van der Linden WA, Verdoes M, Florea BI, McAllister FE, Govindaswamy K, Elias JE, Bhanot P, Overkleeft HS, Bogyo M. (2014). Assessing subunit dependency of the Plasmodium proteasome using small molecule inhibitors and active site probes. *ACS Chem Biol.* 9(8):1869-76.

2. Li H, Tsu C, Blackburn C, Li G, Hales P, Dick L, **Bogyo M.** (2014) Identification of Potent and Selective Non-covalent Inhibitors of the Plasmodium falciparum Proteasome. *J Am Chem Soc.* 136(39):13562-5.

3. Li, H., O'Donoghue, A.J., van der Linden, W.A., Xie, S.C., Too, E., Foe, I.T., Tilley, L., Craik, C.S., da Fonseca, P.C.A, Bogyo, M. (2016) Structure and function-based design of Plasmodium-selective proteasome inhibitors. *Nature*. 530, 233-6.

4. Yoo E, Stokes BH, de Jong H, Vanaerschot M, Kumar T, Lawrence N, Njoroge M, Garcia A, Van der Westhuyzen R, Momper JD, Ng CL, Fidock DA, **Bogyo M**. (2018) Defining the Determinants of Specificity of Plasmodium Proteasome Inhibitors. *J Am Chem Soc.* 140, 11424-11437.

Contribution 3 – Using small molecules to identify and target regulators of parasite pathogenesis
Parasite pathogens are major worldwide health threats that kill millions of people each year. Virtually all parasites make use of proteases and other related hydrolase enzymes to infect their hosts. However, it remains difficult to use genetic tools to directly assess the function of these enzymes during parasite pathogenesis. Therefore, my lab has pioneered the use of libraries of small molecule covalent inhibitors to identify important regulators of pathogenesis by the apicomplexian parasites *Toxoplasma gondii* and *Plasmodium falciparum*. We have performed numerous phenotypic screens and have identified key protease and hydrolase enzymes that regulate the process of host cell invasion and egress. Several of these enzymes have now been validated as therapeutic targets for the treatment of malaria and toxoplasmosis. The most relevant papers that outline this work are:

1. Arastu-Kapur S., Ponder E.L., Fonovic U., Yeoh S., Yuan F., Fonovic, M., Grainger M., Phillips C.I., Powers J.C., and **Bogyo M**. (2008) A small molecule screen identifies proteases that regulate erythrocyte rupture by the human malaria parasite *Plasmodium falciparum*. *Nature Chemical Biology*, 4, 203-213.

2. Hall CI, Reese M, Weerapana E, Child MA, Bowyer PW, Albrow VE, Haraldsen JG, Phillips MR, Deu E, Ward GE, Cravatt BF, Boothroyd JC, and **Bogyo M.** (2011) A chemical genetic screen identifies Toxoplasma DJ-1 as a regulator of parasite secretion and invasion. *Proc. Natl. Acad. Sci. USA* 108, 10568-73.

3. Child, MA, Hall, CI, Beck, JR, Ofori, LO, Albrow, VE, Garland, M, Bowyer, PW, Bradley, PJ, Powers, JC, Boothroyd, JC, Weerapana, E, **Bogyo, M.** (2013) Small-molecule inhibition of a depalmitoylase enhances Toxoplasma host cell invasion. *Nature Chemical Bio*logy 9, 651-6.

4. Foe IT, Child MA, Majmudar JD, Krishnamurthy S, van der Linden WA, Ward GE, Martin BR, **Bogyo M**. (2015) Global Analysis of Palmitoylated Proteins in Toxoplasma gondii. *Cell Host Microbe*. 18, 501-11.

Contribution 4 – Developing small molecules to define the function of bacterial virulence factors
Multiple species of pathogenic bacteria use virulence factors to productively colonize their hosts. However, how these factors become activated inside a host cell is complex and often poorly understood. Using our small molecule protease probes, we made the discovery that virulence factors produced by *Vibrio Cholerae* and *Clostridium difficile* contain cysteine protease domains (CPDs) that are activated by an allosteric mechanism upon binding to the host cell factor, inositol hexakisphosphate (IP6). This was the first discovery of a naturally occurring small molecule allosteric activator of a protease. Recently, we have completed an HTS screen to identify novel small molecule inhibitors of the CPD found in *C. diffcile* toxins A and B. We have used one of our lead compounds from the screen to show that inhibiting the CPD blocks disease pathology in a mouse model of *C. difficile* infection. The most relevant papers that outline this work are:

1. Shen A. Lupardus PJ, Albrow VE, Guzzetta A, Powers JC, Garcia KC, **Bogyo M**. (2009) Mechanistic and structural insights into the proteolytic activation of *Vibrio cholerae* MARTX toxin. *Nature Chemical Biology*, 24, 469-478.

2. Shen A., Lupardus, P.J., Puri, A.W., Albrow,V.E., Gersch, M.M., Garcia, K.C., and **Bogyo, M.** (2011) Defining an allosteric circuit in the cysteine protease domain of *Clostridium difficile* glucosylating toxins. *Nature Structure and Molecular Biology*. 6, 415-419.

3. Bender KO, Garland M, Ferreyra JA, Hryckowian AJ, Child MA, Puri AW, Solow-Cordero DE, Higginbottom SK, Segal E, Banaei N, Shen A, Sonnenburg JL, **Bogyo M**. (2015) A small-molecule antivirulence agent for treating *Clostridium difficile* infection. *Science Translational Medicine*. 7(306):306ra148.

4. Lentz CS, Sheldon JR, Crawford LA, Cooper R, Garland M, Amieva MR, Weerapana E, Skaar EP, **Bogyo M**. (2018) Identification of a S. aureus virulence factor by activity-based protein profiling (ABPP). *Nature Chemical Biology* 14, 609–617.

Contribution 5 – Development and application of small molecule probes to study cell death
The process by which cells die is highly dynamic and controlled by a number of carefully regulated proteins. One of the key regulatory protein families in various forms of cell death is the caspases. In order to understand their roles in activation of specific death signals, it is necessary to have tools that enable direct visualization of caspase activity in living cells and whole organisms. One of our significant accomplishments has been the development of fluorescent probes that can be used to biochemically monitor and image caspase activation in complex biological systems. We have demonstrated that our probes can be used to study the activation of both apoptotic and inflammatory caspases on a cellular level as well as in whole organisms. Relevant papers:

1. Berger AB, Witte M, Sadaghiani AM, Sexton KMB, Denault JB, Salvesen GS, and **Bogyo, M.** (2006) Identification of early intermediates of caspase activation during intrinsic apoptosis using selective inhibitors and activity based probes. *Molecular Cell*, 23, 509-521.

2. Edgington LE, Berger AB, Blum G, Albrow VE, Lineberry N, **Bogyo M**. (2009) Imaging apoptosis *in vivo* using caspase-targeted activity based probes, *Nature Medicine*, 15, 967-973.

3. Edgington LE, van Raam BJ, Verdoes M, Wierschem C, Salvesen GS, and **Bogyo M** (2012) An optimized activity-based probe for the study of caspase-6 activation. *Chemistry & Biology*. 19, 340-52.

4. Puri AW, Broz P, Shen, A, Monack DM, **Bogyo M**. (2012) An activity-based probe reveals caspase-1 activity is required to bypass apoptosis upon bacterial infection. *Nature Chemical Biology* 8, 745-7.

A complete list of my 243 publications can be found at:
http://www.ncbi.nlm.nih.gov/sites/myncbi/matt.bogyo.1/bibliography/40494487/public/?sort=date&direction=ascending

D. Research Support

Active Research Support:
R01 CA179253 Bogyo (PI) 03/01/2014 – 02/28/2019
Chemical Probes for Specific Targeting of Matrix Metallo Proteases
This proposal is focused on plans to generate probes and apply them to study the function of MMP-14 and MMP-15 in cell morphogenesis and cancer progression.

R01 EB026332 Bogyo (PI) 05/01/2018 – 01/31/22
Staphylococcus serine hydrolases as targets for therapeutic and imaging contrast agents
Develop chemical probes that target a newly identified family of serine hyrdolases in S. aureus. These probes will be used to validate new therapeutic targets for treatment and for non-invasive imaging of Staph infections.

R01 EB026285 Bogyo (PI) 04/01/2018 – 01/31/22
Generation of highly selective activity-based probes using chemically modified phage
Develop chemical probes that are highly selective for protease targets using phage screening methods. This approach uses phage that display bicyclic peptides that are chemically modified with active site labels to identify highly selective covalent probes for imaging applications.

R21 AI127581 Bogyo, Fidock (PIs) 12/01/2016 – 11/30/2018
Parasite Specific Proteasome Inhibitors to Combat Multi-Drug Resistant Malaria
This proposal is focused on developing new classes of parasite-specific proteasome specific inhibitors and examining mechanisms of how parasites can become resistant to these inhibitors as well as their synergy with other classes of antimalarial agents.