BIOGRAPHICAL SKETCH

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NAME: **Matthew Bogyo**

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

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	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 laboratory is focused on using chemical tools to target diverse families of proteins with a focus on proteases and hydrolases involved in the pathogenesis of cancer and infectious diseases. Our work includes screening of focused libraries of covalently binding molecules and design and synthesis of new classes of optical imaging probes that target inflammation and infection. My training is in synthetic organic chemistry as well as biochemistry, cell biology, immunology and animal models of disease. I completed my Ph.D. in biochemistry at MIT where I worked with world renowned immunologist, Dr. Hidde Ploegh. During my PhD studies, I developed ways to use small molecule covalent probes to study the role of the multi-catalytic proteasome and helped to discover a primary mechanism for regulation of misfolded proteins known as the Endoplasmic-Reticulum-Associated protein Degradation (ERAD) pathway. I also developed several of the first activity-based chemical probes for tracking protease activity in live cells. After completion of my doctoral studies and short 1-year post-doctoral period in the Ploegh Lab, I established an independent research group at UCSF as a Faculty Fellow. During this time, I recruited several postdoctoral fellows, students and technicians to continue to develop chemical tools to study the functional roles of proteases. My laboratory, along with the Cravatt Laboratory at Scripps, has been credited with establishing the field Activity-Based Protein Profiling (ABPP). Because of my interest in therapeutically relevant proteases, while at UCSF, I also served as a consultant to several Bay Area biotechnology companies including Axys Pharmaceuticals. I assisted Axys in lead compound optimization and functional assessment of target engagement for several of their key pipeline drug discovery projects. I was then recruited from UCSF to Celera Genomics as the Head of Chemical Proteomics when they acquired Axys Pharmaceuticals in 2001. During the period from 2001 to 2003, I led a group of scientists at Celera developing applications for covalent protease probes to various stages of the drug discovery process. This included involvement in both the early ‘hit to lead’ and later clinical stages of drug development. I also helped to develop covalent probes for protein kinases as tools to help advance compounds into clinical trials for Celera’s Bruton’s tyrosine kinase (BTK) project. A probe developed in my group at Celera was sold to Pharmacyclics that eventually became the multi-billion-dollar drug Ibrutinib. My experience in industry helped me to understand the drug discovery process and learn how to advance lead molecules through the drug discovery pipeline up to FDA approval. It also helped me develop skills in project team management and meeting goals within deadlines. I made the decision to move back to academia in 2003 when I joined the Department of Pathology at Stanford. For the past 20 years, my lab has been studying the roles of various proteases and hydrolases in infectious diseases, cancer and inflammation. I have published over 300 papers and mentored over 50 postdoctoral fellows and 10 Ph.D. students. Furthermore, one of our fluorescent imaging probes for targeting lysosomal cysteine proteases, VGT-309, is currently in phase I and II clinical trials for use in image guided surgy of colorectal and lung cancer (NCT05400226, NCT06034197, NCT06145048).

In addition to my experience in both academics and industry, I have had significant experience with managing and participating in collaborative research grants funded by the NIH and the DoD. This has included being part

of several large, multi-center center grants including the “Center on Proteolytic Pathways” as part of the “National Technology Centers Network and Pathways Directory” at NIH and a Breast Cancer Center of Excellence (BCCOE) award from the DoD to study the role of proteolysis in breast cancer pathogenesis and recently two NIH program project grants funded through the Antiviral Drug Discovery (AViDD) program. All of these projects involve investigators from multiple universities around the world and contained central projects and support cores. In addition, I have been a primary investigator on 16 NIH grants over the past 19 years. Many of these grants have involved multi-PI leadership plans and have resulted in numerous collaborative publications and the advancement of an imaging agent into human clinical trials. This experience has helped me further develop my skills in team management and collaboration towards a common goal.

B. Positions, Scientific Appointments and Honors

Positions and Employment

1991-93	Council on Undergraduate Research AIURP Fellow- Bates College, Lewiston, ME
1993-97	Graduate Student- Hidde Ploegh Lab Massachusetts Institute of Technology, Cambridge, MA.
1997-98	Post-Doctoral Fellow- Hidde Ploegh Lab 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.
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 – Dept. of Chemical and Systems Biology, 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 – Dept. of Chemical and Systems Biology, Stanford University
2013-	Professor - Department of Pathology Stanford University.
2013-	Professor - Department of Microbiology and Immunology Stanford University.
2013-	Professor by courtesy – Dept. of Chemical and Systems Biology, Stanford University

HONORS AND AWARDS

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

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
2005-12	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 NIH Study sections
2014-22	Standing member – SBCA Study section

2009 NIH Peer Review – ARRA Challenge Grants
2000- Member, American Chemical Society
2003- Member of the American Society of Microbiologists
2016 Vice Chair – Gordon Research Conference – "Proteolytic Enzymes and Their Inhibitors"
2018 Chair – Gordon Research Conference – "Proteolytic Enzymes and Their Inhibitors"

C. Contributions to Science

As of Feb 1, 2024, I have published 301 articles in peer-reviewed journals which have collectively received over 30,000 citations in the literature. My current h-index is 93 and i10-index is 270. 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 two decades, 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, identified enzymes that are important regulators of processes such as host cell invasion by parasites and have developed lead drug candidates and optical imaging contrast agents. In addition, we have begun to build next-generation technologies that will combine the many benefits of the general probe technology with screening strategies that will allow highly specific tracking and inhibition of a single target in complex cellular and animal models.

Contribution 1 – Chemical probes to detect pathogenic bacteria

We are currently using strategies to develop covalently binding small molecule probes to detect various types of pathogenic bacteria for the purpose of diagnosis of an infection as well as monitoring response to therapy. Specifically, we have designed fluorescent and chemiluminescent probes to detect *Mycobacterium tuberculosis* (Mtb) and *Staphylococcus aureus* infections. For both bacteria, we target hydrolases that are specifically expressed by the target bacteria.

1. Chen L, Keller LJ, Cordasco E, **Bogyo M**, Lentz CS. (2019) Fluorescent Triazole Urea Activity-Based Probes for the Single-Cell Phenotypic Characterization of *Staphylococcus aureus*. *Angew Chem Int Ed Engl*. 58:5643-5647. **PMCID: PMC6456404**
2. Yim JJ, Singh SP, Xia A, Kashfi-Sadabad R, Tholen M, Huland DM, Zarabanda D, Cao Z, Solis-Pazmino P, **Bogyo M**, Valdez TA. (2020) Short-Wave Infrared Fluorescence Chemical Sensor for Detection of Otitis Media. *ACS Sens*. 5(11):3411-3419. **PMCID: In process**
3. Babin BM, Fernandez-Cuervo G, Sheng J, Green O, Ordonez AA, Turner ML, Keller LJ, Jain SK, Shabat D, Bogyo M. (2021) A chemiluminescent protease probe for rapid, sensitive, and inexpensive detection of live *Mycobacterium tuberculosis*. *ACS Cent Sci.* 7:803-814. **PMCID: PMC8161474**
4. Jo J, Upadhyay T, Woods EC, Park KW, Pedowitz NJ, Jaworek-Korjakowska J, Wang S, Valdez TA, Fellner M, **Bogyo M.** Development of Oxadiazolone Activity-Based Probes Targeting FphE for Specific Detection of *S. aureus* Infections. bioRxiv 2023 Dec 12:2023.12.11.571116. doi: 10.1101/2023.12.11.571116. [Preprint]. **PMCID: PMC10760020**

Contribution 2– Chemical probes to study bacterial hydrolases

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 covalent 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. We identified novel small molecule inhibitors of the CPD found in *C. diffcile* toxins A and B and used one of our lead compounds to show that inhibiting the CPD blocks disease pathology in a mouse model of *C. difficile* infection. In addition, we have identified homologs of the human DPPIV protease in the commensal bacteria *Bacteroides thetaiotaomicron*. Finally, we have used covalent probes to identify serine hydrolases in *Mycobacterium tuberculosis* (Mtb) involved in lipid metabolism. The most relevant papers that outline this work are:

1. 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. **PMCID: PMC3076311**
2. 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. **PMCID: PMC6025901**
3. Keller LJ, Nguyen TH, Liu LJ, Hurysz BM, Lakemeyer M, Guerra M, Gelsinger DJ, Chanin R, Ngo N, Lum KM, Faucher F, Ipock P, Niphakis MJ, Bhatt AS, O'Donoghue AJ, Huang KC, **Bogyo M.** (2023) Chemoproteomic identification of a DPP4 homolog in Bacteroides thetaiotaomicron. *Nat Chem Biol.* 19(12):1469-1479. **PMCID: In process**
4. Babin BM, Keller LJ, Pinto Y, Li VL, Eneim AS, Vance SE, Terrell SM, Bhatt AS, Long JZ, **Bogyo M.** (2021) Identification of covalent inhibitors that disrupt M. tuberculosis growth by targeting multiple serine hydrolases involved in lipid metabolism. *Cell Chem Biol.* 29(5):897-909. **PMCID: PMC9252067**

Contribution 3 – Generation of probes for *in vivo* imaging of cathepsin activity in cancer and inflammatory diseases

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 during surgery, tumor response to chemotherapy, atherosclerosis, asthma and most recently pulmonary fibrosis. A sample of my most relevant papers are:

1. Verdoes M, Oresic Bender K, Segal E, van der Linden WA, Syed S, Withana NP, Sanman LE, **Bogyo M**. (2013) An improved quenched fluorescent probe for imaging of cysteine cathepsin activity. *J Am Chem Soc*. 135, 14726-30. **PMCID: PMC3826460**
2. Widen JC, Tholen M, Yim JJ, Antaris A, Casey KM, Rogalla S, Klaassen A, Sorger J, **Bogyo M**. (2020) AND-gate contrast agents for enhanced fluorescence-guided surgery. *Nature Biomedical Engineering* Sep 28.doi: 10.1038/s41551-020-00616-6. **PMCID: PMC7969380**
3. Chen S, Lovell S, Lee S, Fellner M, Mace PD, **Bogyo M.** (2021) Identification of highly selective covalent inhibitors by phage display. *Nature Biotechnol* 39: 490-498. **PMCID: PMC8043995**
4. Faucher FF, Liu KJ, Cosco ED, Widen JC, Sorger J, Guerra M, **Bogyo M.** (2023) Protease Activated Probes for Real-Time Ratiometric Imaging of Solid Tumors. *ACS Cent Sci.* 9(5):1059-1069. **PMCID: PMC10214504**

Contribution 4 – 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 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*. *Nat. Chem. Bio.*, 4, 203-213.
2. 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. *Nat. Chem. Bio*. 9, 651-6. **PMCID: PMC3832678**

3. Foe IT, Onguka O, Amberg-Johnson K, Garner RM, Amara N, Beatty W, Yeh E, **Bogyo M**. (2018) The Toxoplasma gondii Active Serine Hydrolase 4 Regulates Parasite Division and Intravacuolar Parasite Architecture. *mSphere*. 3(5). pii: e00393-18. **PMCID: PMC6147133**
4. Yoo E, Schulze CJ, Stokes BH, Onguka O, Yeo T, Mok S, Gnädig NF, Zhou Y, Kurita K, Foe IT, Terrell SM, Boucher MJ, Cieplak P, Kumpornsin K, Lee MCS, Linington RG, Long JZ, Uhlemann AC, Weerapana E, Fidock DA, **Bogyo M**. (2020) The Antimalarial Natural Product Salinipostin A Identifies Essential α/β Serine Hydrolases Involved in Lipid Metabolism in *P. falciparum* Parasites. *Cell Chem Biol.* 27(2):143-157. **PMCID: PMC8027986**

Contribution 5 – Validating the proteasome as a target for anti-malarial therapy.
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 enough 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.

1. 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. **PMCID: PMC4755332**
2. 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. **PMCID: PMC6407133**
3. Stokes BH, Yoo E, Murithi JM, Luth MR, Afanasyev P, da Fonseca PCA, Winzeler EA, Ng CL, **Bogyo M***, Fidock DA*. (2019) Covalent Plasmodium falciparum-selective proteasome inhibitors exhibit a low propensity for generating resistance in vitro and synergize with multiple antimalarial agents. *PLoS Pathog.* 15(6):e1007722. **PMCID: PMC6553790**
4. Bennett JM, Ward KE, Muir RK, Kabeche S, Yoo E, Yeo T, Lam G, Zhang H, Almaliti J, Berger G, Faucher FF, Lin G, Gerwick WH, Yeh E, Fidock DA, **Bogyo M.** (2023) Covalent Macrocyclic Proteasome Inhibitors Mitigate Resistance in Plasmodium falciparum. *ACS Infect Dis*. 9(10):2036-2047. **PMCID: PMC10591878**

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