BIOGRAPHICAL SKETCH

NAME: Samantha Lynn Bell, Ph.D.

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POSITION TITLE: Assistant Professor, Rutgers New Jersey Medical School

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Pittsburgh	B.S.	04/2010	Molecular Biology
University of California, San Francisco	Ph.D.	06/2015	Biomedical Sciences
Texas A&M Health Science Center	postdoc	07/2021	Microbial Pathogenesis

A. Personal Statement

My lab studies the host-pathogen interactions between macrophages and *Mycobacterium tuberculosis* (Mtb), the bacterium that causes tuberculosis (TB). Mtb causes ~10 million new infections each year and kills ~1.5 million people annually, making it a major threat to world public health. Treating TB requires a lengthy course of several antibiotics that can have numerous unpleasant side effects, and antibiotic resistance to first- and second-line drugs is becoming increasingly common, making successful treatment even more difficult. As a result, there is an urgent need to develop new therapies for TB. We probe the interface between the host and the bacterium using bacterial genetics, host genetics, cell biology, biochemistry, molecular biology, immunology, and in vivo infection approaches. We investigate how macrophages—the first line of defense against pathogens like Mtb—detect, respond to, and control infection. We are especially interested in identifying the "danger signals" sensed by macrophages upon Mtb infection, characterizing the downstream pathways that kill Mtb or worsen infection, and defining the regulation and resolution of these potent immune responses. We also investigate how Mtb uses virulence factors to survive in a macrophage and establish infection with a focus on Mtb's many secreted virulence factors to understand what proteins are secreted into a macrophage, when they are secreted, what host pathways they target, how they mechanistically manipulate host cell biology, and how they ultimately impact infection outcomes. Ultimately, we hope to leverage our understanding of the molecular interface between the macrophage and Mtb to develop more effective therapeutics to treat TB. As a mentor, I strive to foster an inclusive, supportive, and productive lab environment. I hope to train scientists that are not only technically skilled with field-specific knowledge, but also creative, collaborative researchers with create communication and leadership skills. I am committed to promoting diversity, inclusion, and equity in science and academia, and I aim to use my position and privilege to advocate for these values.

Ongoing research support:

DP2 AI154429-01 (NIAID) Bell (PI) 08/10/21-07/31/26
Investigating the role of liquid-liquid phase separation in the interaction between *Mycobacterium tuberculosis* and macrophages

Citations:

1. Watson RO*, **Bell SL***, MacDuff DA, Kimmey J, Diner EJ, Vance RE, Stallings CL, Virgin HW, Cox JS. The cytosolic sensor cGAS detects *Mycobacterium tuberculosis* DNA to induce type I interferons and activate autophagy. *Cell Host & Microbe*. 2015 June 1 pii:S1931-3128(15)002208-5. PMID: 26048136.
2. Weindel CG*, **Bell SL***, Vail KJ, West KO, Patrick KL, Watson RO. LRRK2 maintains mitochondrial homeostasis and regulates innate immune responses to *Mycobacterium tuberculosis*. *eLife*. 2020;9:e51071 doi: 10.7554/eLife.51071; PMID: 32057291.

3. Hoffpauir CT, **Bell SL**, West KO, Jing T, Torres-Odio S, Cox JS, West AP, Li P, Patrick KL, Watson RO. TRIM14 is a key regulator of the type I interferon response during *Mycobacterium tuberculosis* infection. *J Immunol*. 2020 May 13, ji1901511; doi: 10.4049/jimmunol.1901511; PMID: 32404352.
4. **Bell SL**, Lopez KL, Cox JS, Patrick KL, Watson RO. Galectin-8 senses phagosomal damage and recruits selective autophagy adaptor TAX1BP1 to control *Mycobacterium tuberculosis* infection in macrophages. *mBio*. 2021 Jul 6;e0187120; doi: 10.1128/mBio.01871-20. PMID: 34225486.

authors contributed equally to this work

B. Positions, Scientific Appointments, and Honors

Positions and Appointments

2021-present	***Assistant Professor, Center for Emerging & Re-Emerging Pathogens, Rutgers New Jersey Medical School***
2015-2021	***Postdoctoral Research Associate, Department of Microbial Pathogenesis and Immunology, Texas A&M Health Science Center***
2021	Reviewer, SACNAS National Diversity in STEM Conference
2020-2021	Judge, Texas Science & Engineering Fair
2019	President, Texas A&M University Postdoctoral Association
2018-2021	Active Listener, Undergraduate Research Symposium, Texas A&M University
2018-2019	Instructor & Creator, Bullet Journal Workshops, Texas A&M University Postdoctoral Association
2018	Vice President, Texas A&M University Postdoctoral Association
2017-2021	Judge, Student Research Week, Texas A&M University
2017-2020	Judge, Texas Sciences & Humanities Symposium
2017-2020	Judge, Texas Junior Academy of Sciences
2016-2019	Committee Chair, Events Committee, Texas A&M University Postdoctoral Association
2016-2018	Postdoc Coordinator, Host-Pathogen Journal Club, Texas A&M Health Science Center
2016-2018	Treasurer (member of founding executive committee), Texas A&M University Postdoctoral Association
2016	Discussion Leader, Responsible Conduct of Research, Texas A&M Health Science Center
2010-2015	***Graduate Student, University of California, San Francisco***
2012-2014	Tutor, Cell Biology, Biomedical Science Program, University of California, San Francisco
2012-2014	Instructor & Mentor, NSF Fellowship Workshop, Biomedical Sciences, University of California, San Francisco
2012-2014	Judge, Regional Intel Science Fair, San Francisco & Alameda Counties
2012-2014	Judge, Junior Sciences & Humanities Symposium, California-Nevada Region
2011	Teaching Assistant, Cell Biology, Biomedical Sciences, University of California, San Francisco
2007-2010	***Undergraduate Researcher, University of Pittsburgh***
2009	Mentor, HHMI Summer Undergraduate Research Program, University of Pittsburgh

Honors

2020-2021	Cain Fellowship, Microbial Pathogenesis & Immunology, Texas A&M University
2019	Postdoctoral Association Travel Award, Texas A&M Health Science Center
2018	People's Choice Distinguished Flash Talk Presentation, Postdoctoral Research Symposium, Texas A&M
2018	Postdoctoral Scholar Travel Award, Texas A&M University
2017	1st Place Distinguished Poster Presentation, Postdoctoral Research Symposium, Texas A&M University
2012-2015	NSF Graduate Research Fellowship
2009-2010	Horowitz Fellowship, University of Pittsburgh
2009	HHMI Summer Undergraduate Research Fellowship, University of Pittsburgh
2008	Chancellor's Undergraduate Research Fellowship, University of Pittsburgh
2008	Summer Undergraduate Research Fellowship, University of California, San Diego
2007-2008	HHMI Undergraduate Research Fellowship, University of Pittsburgh

C. Contribution to Science

1. *Mycobacterium tuberculosis* (Mtb) is a major global health threat, but little is known about how this bacterium interfaces with the host to modulate innate immunity and promote infection. Upon phagocytosis by macrophages, Mtb permeabilizes the phagosomal membrane using its virulence-associated ESX-1 secretion system. I characterized the role of galectins, one class of host "danger sensors", in recognizing damaged Mtb-containing phagosomes and targeting Mtb to selective autophagy for destruction. In these studies, I found that galectin-3, -8, and -9 colocalize to Mtb-containing phagosomes, and the galectin+ bacilli are targeted to selective autophagy for killing. Interestingly, deletion of galectin-8, but not galectin-3 or -9, impaired macrophages' ability to target Mtb to selective autophagy and to control Mtb replication; macrophages lacking all these galectins of interest did not amplify these phenotypes, indicating galectin-8 plays a unique role in recognizing, targeting, and controlling Mtb infection. I further identified a specific interaction between galectin-8 and the selective autophagy adapter TAX1BP1, and discovered this interaction was required for targeting Mtb to selective autophagy. In addition, overexpression of galectin-8 in macrophages increased the efficiency of targeting and killing by selective autophagy, identifying this recognition and targeting pathway as a valuable target for future host-directed therapies. Future work in my lab will explore how galectins' regulation via binding partners, biophysical properties, and post-translational modifications contribute to host defenses against bacterial infection.

a. **Bell SL**, Lopez KL, Cox JS, Patrick KL, Watson RO. Galectin-8 senses phagosomal damage and recruits selective autophagy adaptor TAX1BP1 to control *Mycobacterium tuberculosis* infection in macrophages. *mBio*. 2021 Jul 6;e0187120; doi: 10.1128/mBio.01871-20. PMID: 34225486.
b. Vail KJ, da Silveira BP, **Bell SL**, Cohen ND, Bordin AI, Patrick KL, Watson RO. The opportunistic intracellular bacterial pathogen *Rhodococcus equi* elicits type I interferon by engaging cytosolic DNA sensing in macrophages. *PLoS Pathog*. 2021 Sep;17(9):e1009888. doi: 10.1371/journal.ppat.1009888; PMID: 34473814.

2. Phagosomal permeabilization that occurs during Mtb infection releases bacterial-derived DNA into the host cytosol, which triggers a pro-bacterial type I interferons (IFN) response via the STING/TBK1/IRF3 signaling axis. The notion of cytosolic bacterial DNA as an agonist for this response was provocative, and the evidence supporting this model was circumstantial. We demonstrated that the host cytosolic DNA sensor cyclic AMP-GMP synthase (cGAS) is required for detecting cytosolic DNA and inducing type I IFNs in macrophages infected with Mtb and other intracellular bacterial pathogens. Furthermore, cGAS is crucial for the efficient targeting of Mtb to selective autophagy pathway, which controls bacterial replication in macrophages. Importantly, I developed a ChIP assay to determine precisely what DNA is sensed by cGAS and demonstrated that cGAS binds to Mtb genomic DNA during infection. This study firmly established that cytosolic bacterial DNA is a bona fide ligand recognized by the innate immune system during Mtb infection. We went on to assist our collaborator Pingwei Li in defining the biochemical interactions between members of the STING/TBK1/IRF3 cascade and to identify TRIM14 as a novel regulator of TBK1 that impacts early and late type I IFN levels during Mtb infection. My independent lab will continue to explore the regulation of the cGAS-dependent type I IFN response during Mtb infection and how Mtb actively modulates the initiation, regulation, and resolution of the type I IFN response.

a. Watson RO*, **Bell SL***, MacDuff DA, Kimmey J, Diner EJ, Vance RE, Stallings CL, Virgin HW, Cox JS. The cytosolic sensor cGAS detects *Mycobacterium tuberculosis* DNA to induce type I interferons and activate autophagy. *Cell Host & Microbe*. 2015 June 1;17(6):811-9.
b. Patrick, KL*, **Bell SL***, Watson RO. For better or worse: Cytosolic DNA sensing during intracellular bacterial infection induces potent innate immune responses. Review. *J Mol Bio*. 2016 Apr 29 pii: S0022-2836(16)30111-5.
c. Zhao B, Du F, Xu P, Chang Shu, Sankaran B, **Bell SL**, Liu M, Lei Y, Gao X, Ji J, West AP, Watson RO, and Li P. A conserved PLPLRT/SD motif within the C-terminal tail of STING mediates the recruitment and activation of TBK1. *Nature*. 2019 May;569(7758):718-722. doi: 10.1038/s41586-019-1228-x.
d. Hoffpauir CT, **Bell SL**, West KO, Jing T, Odio-Torres S, Cox JS, West AP, Li P, Patrick KL, Watson RO. TRIM14 is a key regulator of the type I interferon response during *Mycobacterium tuberculosis* infection. *bioRxiv* 828533; doi: https://doi.org/10.1101/828533.

authors contributed equally to this work

3. Bacterial pathogens use secreted effectors to modulate host cells, establish replicative niches, and cause disease. The molecular functions of many of these effectors have remained mysterious due to the genetic intractability of organisms, functional redundancy of effectors, lack of sequence homology, and other technical challenges. To overcome these hurdles, we adopt unbiased and high throughput approaches to discover novel effector functions. First, we performed an affinity tag purification mass spectrometry screen to identify protein-protein interactions between a large collection of Mtb secreted effectors and the host proteome. I helped perform and validate this screen, which not only provided a valuable resource for the TB field, but also identified the E3 ligase Cbl as a novel host restriction factor and interaction partner of the Mtb effector LpqN. Second, we performed a quantitative yeast genetic interaction screen to study a large set of effector proteins from diverse intracellular pathogens: *Salmonella enterica* Typhimurium, *Coxiella burnetii*, and *Brucella melitensis*. This study predicted highly specific and novel biological functions for many of these effectors, including the *Salmonella* effector SseC. I helped perform the follow-up cell biology experiments that revealed SseC interacts with the retromer complex to maintain the integrity of the *Salmonella*-containing vacuole. Work in my lab continues to use proteomics- and genomics-based screens to identify and functionally characterize Mtb effectors proteins.

a. Penn BH, Netter Z, Johnson JR, Von Dollen J, Jang GM, Johnson T, Ohol YM, Maher C, **Bell SL**, Geiger K, Golovkine G, Du X, Choi A, Parry T, Mohapatra BC, Storck MD, Band H, Chen C, Jäger S, Shales M, Portnoy DA, Hernandez R, Coscoy L, Cox JS, Krogan NJ. An Mtb-human protein-protein interaction map identifies a switch between host antiviral and antibacterial responses. *Mol Cell*. 2018 Aug 16;71(4):637-648.e5. doi: 10.1016/j.molcel.2018.07.010.
b. Patrick KL*, Wojcechowskyj JA*, **Bell SL**, Riba MN, Jing T, Talmage S, Xu P, Cabello AL, Xu J, Shales M, Jimenez-Morales D, Ficht TA, de Figueiredo P, Samuel JE, Li P, Krogan NJ, Watson RO. Quantitative yeast genetic interaction profiling of bacterial effector proteins uncovers a role for the human retromer in *Salmonella* infection. *Cell Syst*. 2018 Sep 26;7(3):323-338.e6.

4. LRRK2 is a large, multifunctional kinase that has been linked to both Parkinson's Disease (PD) and leprosy, an infection caused by *Mycobacterium leprae* that has type I IFN-dependent disease pathology. While LRRK2 has been studied in the context of neuronal health and mitochondrial homeostasis, how it participates in the innate immune response was poorly understood. Working with another postdoc, we showed that LRRK2-deficient macrophages are defective at inducing a type I IFN during Mtb infection. This defect arises from chronic upregulation of type I IFNs in resting LRRK2-deficient macrophages caused by mitochondrial damage, increased mitochondrial fission, and leakage of mitochondrial DNA into the cytosol. This inappropriate response to Mtb infection in macrophages translated *in vivo*, where we saw enhanced inflammation, neutrophil infiltration, and neutrophil death in the lungs of Mtb-infected LRRK2 knockout mice. Furthermore, in collaboration with neurobiologist Rahul Srinivasan, we investigated how Mtb infection affected neuroinflammation in wild-type and LRRK2 knockout mice. We discovered that Mtb infection induced inflammation in PD-relevant regions of the brain; infected mice had more activated microglia (brain-resident macrophages) and more damage to dopamine-producing neurons. This inflammation was LRRK2-dependent, suggesting that LRRK2 mutations coupled with chronic infection could impact the development of neurodegenerative diseases like PD.

a. Patrick KL, **Bell SL**, Weindel CG, Watson RO. Exploring the "multiple-hit hypothesis" of neurodegenerative disease: bacterial infection comes up to bat. Review. *Front Cell Infect Microbiol*. 2019;9:138. doi: 10.3389/fcimb.2019.00138.
b. Weindel CG*, **Bell SL***, Huntington TE, Vail KJ, Srinivasan R, Patrick KL, Watson RO. LRRK2 regulates innate immune responses and neuroinflammation during *Mycobacterium tuberculosis* infection. *bioRxiv* 699066; doi: https://doi.org/10.1101/699066.
c. Weindel CG*, **Bell SL***, Vail KJ, West KO, Patrick KL, Watson RO. LRRK2 maintains mitochondrial homeostasis and regulates innate immune responses to *Mycobacterium tuberculosis*. *eLife*. 2020;9:e51071 doi: 10.7554/eLife.51071; PMID: 32057291.

authors contributed equally to this work

5. During my undergraduate research career, I utilized yeast expression systems to study various aspects of important molecular chaperone proteins, including the *Plasmodium falciparum* Hsp70, PfHsp70-1, and the mammalian AAA+ ATPase associated with torsion dystonia, TorsinA. Because *P. falciparum* has an abnormally large number of Hsp70s, we were interested in targeting them with small molecule inhibitors in order to develop potential new antimalarial therapies. In addition to testing the efficacy of these compounds *in vitro*, I also

established an *in vivo* system for studying the cellular functions of PfHsp70-1. Because *P. falciparum* was genetically intractable at the time, I expressed PfHsp70-1 in the well-characterized yeast model, *Saccharomyces cerevisiae*, and I demonstrated that the yeast expression model could be used to assay numerous chaperone functions, including protein folding, protein trafficking, and protein degradation. In a subsequent study, I generated a similar yeast expression system to study the human AAA+ ATPase, TorsinA, which when mutated is associated with a devastating movement disorder called torsion dystonia. Here, we were able to identify several molecular chaperones involved in folding, stabilizing, and degrading TorsinA. By using the genetically tractable yeast model for exogenous protein expression, we could rapidly ascertain proteins' functions and regulators. Furthermore, we established *in vivo* systems that could be utilized in the future to help identify novel small molecules for modulating these processes.

a. Chiang AN, Valderramos JC, Balachandran R, Chovatiya RJ, Mead BP, Schneider C, **Bell SL**, Klein MG, Huryn DM, Chen XS, Day BW, Fidock DA, Wipf P, Brodsky JL. Select pyrimidinones inhibit the propagation of the malarial parasite, *Plasmodium falciparum*. *Bioorg Med Chem*. 2009 Feb 15;17(4):1527-33.

b. **Bell SL**, Chiang AN, Brodsky JL. Expression of a malarial Hsp70 improves defects in chaperone-dependent activities in *ssa1* mutant yeast. *PLoS One*. 2011;6(5):e20047.

c. Zacchi LF, Wu HC, **Bell SL**, Millen L, Paton AW, Paton JC, Thomas PJ, Zolkiewski M, Brodsky JL. The BiP molecular chaperone plays multiple roles during the biogenesis of TorsinA, an AAA+ ATPase associated with the neurological disease early-onset torsion dystonia. *J Biol Chem*. 2014 May 2;289(18):12727-47.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1ly4ql9Wx2LQw/bibliography/41466120/public/?sort=date&direction=ascending