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BIOGRAPHICAL SKETCH

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NAME: Prigge, Sean

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

POSITION TITLE: 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 |
| --- | --- | --- | --- |
| Amherst College  Johns Hopkins School of Medicine | B.A.  Ph.D. | 1991  1997 | Physics  Biophysics |

1. **Personal Statement**

My laboratory investigates biochemical pathways found in human parasites with the goal of uncovering unique aspects of parasite metabolism. We approach these questions with a combination of cell biology, genetic, biophysical and biochemical techniques. We are particularly interested in the interface between host metabolism and that of the parasites during different stages of the parasite life cycle. Recent projects focus on host vitamins and nutrients, particularly those thought to be critical for the function of the mitochondrion and apicoplast organelles in malaria parasites. We are interested in these host factors, how they are acquired, how they are used, and whether they are essential for growth during different stages of parasite development. As part of these inquiries, we analyze the responses to biochemical or genetic perturbations with a combination of transcriptomic and metabolomic profiling. Ultimately, we want to understand how to interfere with vulnerable aspects of parasite metabolism.

1. Positions and Honors

**Positions and Employment**

1998-2002 Captain, Division of Experimental Therapeutics, Walter Reed Army Institute of Research

2002-2009 Assistant Professor,

2010-2016 Associate Professor,

2016- Professor, Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health; Biochemistry and Molecular Biology, Johns Hopkins Bloomberg School of Public Health; Biophysics and Biophysical Chemistry, Johns Hopkins School of Medicine

**Other Experience and Professional Memberships**

1995- Member, Biophysical Society

1996- Member, American Crystallographic Association

1999- Peer reviewer for 40 research journals

2000- Member, American Association for the Advancement of Science

2003- *Ad hoc* grant reviewer for the Wellcome Trust,

2004 Reviewer, NIH-NRSA Study section (ZRG1 F08) 3-5 March 2004 and 3-5, November 2004

2005 *Ad hoc* reviewer, NIH (ZAI1 AR-M), June 23 2005

2005- Reviewer, NIH-NRSA Study section (ZRG1 F13) 9-11 March 2005, 20-22 July 2005, 31 Oct-1Nov 2005, 15-16 March 2006, 20-21 November 2006, 19-20 March 2007, 19 November 2010, 18 July 2011, 22-23 March 2012, 15-16 November 2012, 19 December 2013, 10-11 July 2014, 18-19 March 2015, 9-10 November 2016

2006 *Ad hoc* reviewer, NIH (ZRG1 BCMB-Q), 28 Feb 2006

2006 *Ad hoc* reviewer NIH (PTHE), 7-9 June 2006, 4-6 October 2006, 7-8 June 2007, 24-25 January 2008, February 2018

2008 *Ad hoc* reviewer NIH (MGC), 14-15 Oct 2008

2014- Editorial board, *Eukaryotic Cell (2014-16), Molecular Microbiology (2017-19)*

**Honors**

1991 Magna cum laude

1991-2 Amherst Memorial Fellowship

1993-5 Forris Jewett Moore Fellowship

1997 Biophysical Society Travel Award

1997 Ehrlich Graduate Student, Johns Hopkins Young Investigator Day

1997 American Crystallographic Association Travel Award

2002 Faculty Development Award

2003 Faculty Innovation Award

2005 Marjorie Gilbert Award

1. Petroleum Research Fund, American Chemical Society

2007,12 Session Chair, Molecular Parasitology Meeting

2015 Organizer, Mid-Atlantic Crystallography Meeting

1. **Contribution to Science**
2. Discovery of lipoate as an essential host factor

In the early 1980’s Jensen and coworkers used the newly discovered *in vitro* culture conditions for *Plasmodium falciparum* to define the essential nutrients necessary for the growth of malaria parasites. In retrospect, it is easy to see how they missed lipoate. Lipoate is found in small quantities in red blood cells, but it is not an explicit component of the growth medium. We found that this small quantity of lipoate is essential for parasite survival and that scavenged lipoate is used exclusively in the mitochondrion. We have further investigated the role of scavenged lipoate and a biosynthetic pathway found in the apicoplast organelle, and concluded that scavenging is essential throughout the parasite life cycle, while lipoate synthesis is important only during liver stage development. Recently, we focused our attention on how scavenged lipoate is used in the mitochondrion and discovered a novel mechanism that is gated by redox potential. Under very reducing conditions, components of the citric acid cycle are activated by lipoate, however, subtle increases in redox potential lead to deactivation of these enzymes and activation of an alternate pathway. Understanding this phenomenon at the cellular and atomic levels is an active area of research.

H. Jhun, M. S. Walters, and S. T. Prigge, Using lipoamidase as a novel probe to interrogate the importance of lipoylation in *P. falciparum. mBio*, 9, e01872-18 (2018). PMC6247088

G. A. Afanador, A. J. Guerra, R. P. Swift, R. E. Rodriguez, D. Bartee, K. A. Matthews, A. Schon, E. Freire, C. L. Freel Meyers, and S. T. Prigge, A novel lipoate attachment enzyme is shared by *Plasmodium* and *Chlamydia* species. *Mol Micro,* 106, 439-451 (2017). PMC5653438

G. A. Afanador, K. A. Matthews, D. Bartee, J. E. Gisselberg, M. S. Walters, C. L. Freel Meyers, and S. T. Prigge, Redox dependent lipoylation of mitochondrial proteins in *Plasmodium falciparum*. *Mol Micro,* 94, 156-171 (2014). PMC4177315

M. Allary, J. Z. Lu, L. Zhu, S. T. Prigge, Scavenging of the cofactor lipoate is essential for the survival of the malaria parasite *Plasmodium falciparum. Mol. Micro.* 63, 1331-1344 (2007). PMC2796473

1. Structural enzymology: How oxygen is activated by copper

A class of copper-containing dioxygenases are responsible for generating a wide array of hormones and bioactive compounds (amidated peptide hormones, epinephrine, nicotinamide, oleamide, etc.). We gained mechanistic insight into these enzymes through a combination of biochemical assays, mutagenesis and atomic resolution x-ray crystal structures. These data provided a framework for understanding the substrate specificity of these enzymes, the residues critical for activity and the mechanism for the chemical and electron transfer steps in catalysis. To date, this body of work remains the only atomic level description for this important class of enzymes.

E. E. Chufán, S. T. Prigge, X. Siebert, B. A. Eipper, R. E. Mains, L. M. Amzel. Differential reactivity between two copper sites in peptidylglycine α-hydroxylating monooxygenase. *J. Am. Chem. Soc.* 132, 15565-15572 (2010). PMC3025614

S. T. Prigge, R. E. Mains, B. A. Eipper, L. M. Amzel, Dioxygen binds end-on to mononuclear-copper in a precatalytic enzyme complex, *Science* 304, 864-867 (2004).

S. T. Prigge, A. S. Kolhekar, B. A. Eipper, R. E. Mains, L. M. Amzel, Substrate-mediated electron transfer in peptidylglycine alpha-hydroxylating monooxygenase, *Nature Struct. Biol.* 6, 976-983 (1999).

S. T. Prigge, A. S. Kolhekar, B. A. Eipper, R. E. Mains, L. M. Amzel, Amidation of Bioactive Peptides: The Structure of Peptidylglycine alpha-Hydroxylating Monooxygenase, *Science* 278, 1300-1305 (1997).

1. Essential role of protein posttranslational modifications in the apicoplast organelle

Malaria parasites rely on the host for iron and are negatively impacted by anemia. Despite the clinical importance of host iron status, little is known about iron utilization by the parasites. We investigated the use of iron for the synthesis of enzyme cofactors called iron-sulfur (FeS) clusters. Little is known about the role of FeS proteins in malaria parasites or the machinery required to activate them with FeS clusters. We identified two complete biosynthetic pathways for the synthesis of FeS clusters in malaria parasites and localized these pathways to the mitochondrion and the apicoplast organelles. We used a variety of approaches including a dominant negative probe in conjunction with a chemical bypass system to define the role of the apicoplast FeS cluster machinery. Disruption of the apicoplast system led to loss of the apicoplast genome and fragmentation of the organelle. These experiments demonstrated the independence and the essentiality of FeS cluster synthesis in the apicoplast. In addition, this work exposed the down-stream pathway (the ferredoxin redox pathway) likely responsible for the catastrophic phenotype associated with disruption of FeS cluster synthesis.

A. D. Roberts, S. C. Nair, A. J. Guerra and S. T. Prigge, Development of a conditional localization approach to control secretory protein trafficking in malaria parasites. *Traffic,*20, 571-582 (2019). PMC6663561

T. A. Dellibovi-Ragheb, H. Jhun, C. D. Goodman, M. S. Walters, D. R. T. Ragheb, K. A. Matthews, K. Rajaram, S. Mishra, G. I. McFadden, P. Sinnis and S. T. Prigge, Host biotin is required for liver stage development in malaria parasites. *Proc Natl Acad Sci U S A*, 115, E2604-E2613 (2018). PMC5856565

J. E. Gisselberg, T. A. Dellibovi-Ragheb, K. A. Matthews, G. Bosch and S. T. Prigge, The suf iron-sulfur cluster synthesis pathway is required for apicoplast maintenance in malaria parasites. *PLoS Pathog*, 9, e1003655 (2013). PMC3784473

T. A. Dellibovi-Ragheb, J. E. Gisselberg and S. T. Prigge, Parasites FeS up: iron-sulfur cluster biogenesis in eukaryotic pathogens. *PLoS Pathog*, 9, e1003227 (2013). PMC3617024

1. Characterization and exploitation of Type II fatty acid biosynthesis in apicomplexan parasites

It was thought that malaria parasites were not able to make fatty acids until the first chromosome of *P. falciparum* was sequenced and found to contain two genes (*ACP* and *KASIII*) similar to bacterial Type II fatty acid biosynthesis genes. We produced the proteins that these genes encode, as well as other enzymes from this pathway that were subsequently discovered. Biochemical characterization demonstrated that the parasite proteins comprise a biosynthesis pathway starting with acetyl-CoA and malonyl-CoA building blocks. This work helped to establish the existence of a functional FASII pathway in malaria parasites and paved the way for exploitation of this pathway in other apicomplexan parasites. In all we have published 19 papers on proteins from FASII pathways in *P. falciparum, T. gondii* and *E. tenella*. These publications detail the initial characterization of these pathways, the trafficking of the nuclear-encoded FASII proteins to the apicoplast, and efforts to target FASII enzymes with novel antiparasitic agents.

G. A. Afanador, S. P. Muench, M. McPhillie, A. Fomovska, A. Schon, Y. Zhou, G. Cheng, J. Stec, J. S. Freundlich, H. M. Shieh, J. W. Anderson, D. P. Jacobus, D. A. Fidock, A. P. Kozikowski, C. W. Fishwick, D. W. Rice, E. Freire, R. McLeod and S. T. Prigge, Discrimination of Potent Inhibitors of *Toxoplasma gondii* Enoyl-Acyl Carrier Protein Reductase by a Thermal Shift Assay. *Biochemistry*, 52, 9155-66 (2013). PMC3953223

J. R. Gallagher, K. A. Matthews, S. T. Prigge, *Plasmodium falciparum* apicoplast transit peptides are unstructured *in vitro* and during apicoplast import. *Traffic,* 12, 1124-1138 (2011). PMC3629917

J. R. Gallagher, S. T. Prigge, *Plasmodium* ***falciparum* acyl carrier protein crystal structures in disulfide-linked and reduced states and their prevalence during blood stage growth**. *Proteins* 78, 575-588 (2010). PMC2805782

S. T. Prigge, X. He, L. Gerena, N. C. Waters, K. A. Reynolds, The initiating steps of a Type II fatty acid synthase in *Plasmodium falciparum* are catalyzed by pfACP, pfMCAT and pfKASIII, *Biochemistry* 42, 1160-1169 (2003).

**Complete List of Published Work in MyBibliography (64 publications):**

<https://www.ncbi.nlm.nih.gov/myncbi/sean.prigge.1/bibliography/public/>