BIOGRAPHICAL SKETCH

NAME: Photini Sinnis

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Swarthmore College, Swarthmore PA	B.A.	1981	Biology
Dartmouth Medical School, Hanover NH	M.D.	1988	Medicine
Columbia-Presbyterian Hospital, New York NY	Residency	1991	Internal Medicine
New York University School of Medicine	PostDoc	1998	Parasitology

A. Personal Statement

I have been studying the pre-erythrocytic stages of malaria parasites for 20 years. Our research is focused on elucidating the molecular interactions that guide the infective stage of the malaria parasite through its mosquito and mammalian hosts, with a recent focus on the skin phase of infection, and understanding the transmission dynamics of sporozoites. We have made important contributions on the role of the sporozoite's major surface protein in guiding sporozoites through the mammalian host, the behavior of rodent and human malaria sporozoites at the inoculation site and the importance of antibody at the inoculation site in preventing sporozoite exit. Our transmission studies have shown that this is a severe bottleneck for the parasite, with the majority of mosquitoes inoculating few sporozoites, most of which do not successfully leave the skin and our recent demonstration that the majority of infected mosquito bites do not result in malaria infection. Overall the goal of our studies is to gain a better understanding of sporozoite-host interactions that can be used to validate new drug targets and vaccine strategies and to understand the quantitative aspects of transmission to build better epidemiological models to inform intervention strategies.

B. Positions, Scientific Appointments and Honors

Academic Positions

1993 – 1998 Research Assistant Professor, Dept. Parasitology, NYU School of Medicine
1993 – 2008 Assistant Attending Physician, Dept. Medicine, NYU Medical Center
1998 – 2008 Assistant Professor, Dept. Medical Parasitology, NYU School of Medicine
2008 – 2011 Associate Professor, Dept. Medical Parasitology, NYU School of Medicine
2008 – 2011 Associate Professor, Dept. Medicine, NYU School of Medicine
2011 – 2013 Associate Professor, Dept. Molecular Microbiology & Immunology, Johns Hopkins Bloomberg School of Public Health
2011 – present Associate Professor, Dept. Medicine, Johns Hopkins School of Medicine
2014 – present Professor, Dept. Molecular Microbiology & Immunology, Johns Hopkins Bloomberg School of Public Health

Scientific Appointments

2009 – present Deputy Editor, *PLoS Neglected Tropical Diseases*, 2009 – present
2011 – 2014 Ad-Hoc Member, Pathogenic Eukaryotes Study Section, NIH
2011 – 2014 Module Director, Biology of Parasitism, Marine Biological Laboratory,
2014 – present Deputy Director, Johns Hopkins Malaria Research Institute

2016 – present Member, Pathogenic Eukaryotes Study Section, NIH
2015 – 2019 Co-Director, Biology of Parasitism Course, Marine Biological Laboratory
2019 – present Associate Editor, *Science Advances*

Honors and Awards

B.A. with Distinction, Swarthmore College, 1981
Howard Hughes Medical Institute Research Scholarship, 1986 - 1987
M.D. with Honors, Dartmouth Medical School, 1988
Alpha Omega Alpha, Dartmouth Medical School, 1988
Board Certified, American Board of Internal Medicine, 1992
National Institutes of Health Physician Scientist Award, 1993 - 1998
Irma T. Hirschl Trust Career Scientist Award, 1997 - 2002
Edward Mallinckrodt Foundation Scholar, 2000 - 2003
Honorable Mention, Nikon Small World in Motion Competition 2017
Fellow of the American Academy of Microbiology 2017

C. Contribution to Science

1. Transmission Dynamics of Sporozoites. Little is known about this important bottleneck in the malaria life cycle. Our early studies investigating the kinetics with which sporozoites left the inoculation site found that sporozoite exit resembled a slow trickle occurring from 10 minutes to 3 hrs after inoculation and that most mosquitoes inoculate very few sporozoites, <1% of those found in their salivary glands. More recently we have taken this one step further and determined the likelihood that a single infected mosquito bite would initiate a malaria infection. Importantly, we found that the majority of infected bites do not result in a blood stage infection and that the likelihood of initiating infection was significantly correlated to the mosquito's salivary gland sporozoite load.

   Medica D and **Sinnis P.** Quantitative Dynamics of *Plasmodium yoelii* Sporozoite Transmission by Infected Anopheline Mosquitoes Feeding on Vertebrate Hosts. *Infect Immun* 73:4363-4369, 2005.

   Yamauchi LM, Coppi A, Snounou G and **Sinnis P.** *Plasmodium* Sporozoites Trickle Out of the Injection Site. *Cell Microbiol* 9:1215-1222, 2007.

   Aleshnick M, Ganusov VV, Nasir G, Yenokyan G, **Sinnis P.** Experimental determination of the force of malaria infection reveals a non-linear relationship to mosquito sporozoite loads. PLoS Pathog. 16:e1008181. doi: 10.1371/journal.ppat.1008181, 2020.

   Graumans W, Jacobs E, Bousema T, **Sinnis P.** When Is a Plasmodium-Infected Mosquito an Infectious Mosquito? Trends Parasitol. 36:705-716. doi: 10.1016/j.pt.2020.05.011, 2020.

2. Sporozoite Biology in the Skin of the Mammalian Host. Our work, together with studies from other laboratories, has established that sporozoites are deposited into the dermis as mosquitoes probe for blood. The skin phase of infection represents the first contact between parasite and host, and is the location where the malaria parasite is extracellular for the longest period of time in the mammalian host. We found that this is a time of great vulnerability for the parasite, with antibodies having their greatest impact on sporozoites at this location. Using quantitative imaging approaches, we describe components of sporozoite motility that are critical for dermal exit and compared motility parameters and blood vessel entry success of human and rodent malaria sporozoites in mouse skin. We found that the skin phase is not a species-specific barrier to infection and that imaging of *P. falciparum* sporozoites in the mouse can be used as a platform to test antibodies targeting the migratory sporozoite.

   Yamauchi LM, Coppi A, Snounou G and **Sinnis P.** *Plasmodium* Sporozoites Trickle Out of the Injection Site. *Cell Microbiol* 9:1215-1222, 2007.

Moreira CK, Templeton TJ, Lavazec C, Hayward RE, Hobbs CV, Kroeze H, Janse CJ, Waters AP, **Sinnis P** and Coppi A. The *Plasmodium* TRAP/MIC2 family member, TRAP-Like Protein (TLP), is involved in tissue traversal by sporozoites. Cell Microbiol 10:1505-16, 2008.

Voza T, Miller JL, Kappe SH and **Sinnis P.** Extrahepatic exoerythrocytic forms of rodent malaria parasites at the site of inoculation: Clearance after immunization, susceptibility to primaquine and contribution to blood stage infection. Infect Immun 80:2158-64, 2012.

Sinnis P and Zavala F. The skin: where malaria infection and the host immune response begin. Semin Immunopathol. 2012 34:787-92.

Sack BK, Miller JL, Vaughan AM, Douglass A, Kaushansky A, Mikolajczak S, Coppi A, Zavala F, **Sinnis P**, Kappe SH. A model for in vivo assessment of humoral protection against malaria sporozoite challenge by passive transfer of monoclonal antibodies and immune serum. Infect Immun 82:808-817, 2014.

Hopp CS, Chiou K, Ragheb DRT, Salman A, Khan SM, Liu AJ, **Sinnis P.** Longitudinal analysis of *Plasmodium* sporozoite motility in the dermis reveals component of blood vessel recognition. eLife 4, doi: 10.7554/eLife.07789, 2015.

Flores-Garcia Y, Nasir G, Hopp CS, Munoz C, Balaban AE, Zavala F, **Sinnis P.** Antibody-Mediated Protection against Plasmodium Sporozoites Begins at the Dermal Inoculation Site. MBio. 9(6): e02194-18. doi: 10.1128/mBio.02194-18, 2018.

Hopp CS, Kanatani S, Archer NK, Miller RJ, Liu H, Chiou KK, Miller LS, **Sinnis P**. Comparative intravital imaging of human and rodent malaria sporozoites reveals the skin is not a species-specific barrier. EMBO Mol Med. 13:e11796. doi: 10.15252/emmm.201911796. 2021.

3. Structure-Function Studies of Plasmodium Circumsporozoite Protein (CSP). A central focus of my laboratory, from the beginning of my independent research career, is the structural and functional biology of the sporozoite's major surface protein, CSP. This protein is the basis of the only malaria vaccine candidate that has shown efficacy in Phase III clinical trials, a finding that has fueled our desire to learn more about how it functions. The overall structure of CSP is conserved among all *Plasmodium* species, with a central repeat region flanked by two conserved sequences: region I, a 5 amino acid sequence immediately upstream of the repeats, and a type I thrombospondin domain (TSR) in the carboxy-terminus. We found that CSP has two conformational states: As sporozoites journey from mosquito midgut to mammalian liver, the TSR is masked by the N-terminus, maintaining sporozoites in a migratory state. When sporozoites arrive in the liver, proteolytic cleavage of CSP exposes the TSR and sporozoites arrest and enter hepatocytes to initiate the next lifecycle stage. We have mapped the cleavage site to Region I and are now working to determine how this finding can benefit the pre-erythrocytic stage vaccine effort as well as to identify the protease that cleaves CSP.

   Coppi A, Pinzon-Ortiz C, Hutter C and **Sinnis P.** The *Plasmodium* Circumsporozoite Protein is Proteolytically Processed During Cell Invasion. *J Exp Med* 201:27-33, 2005.

   Coppi A, Tewari R, Bishop JR, Bennett BL, Lawrence R, Esko J, Billker O and **Sinnis P.** Heparan sulfate proteoglycans provide a signal to *Plasmodium* sporozoites to stop migrating and productively invade cells. *Cell Host Microbe*, 2:316-327, 2007.

   Coppi A, Natarajan R, Pradel G, Bennett BL, James ER, Roggero MA, Corradin G, Persson C, Tewari R and **Sinnis P.** The malaria circumsporozoite protein has two functional domains each with distinct roles as sporozoites journey from mosquito to mammalian host. J Exp Med 208:341-36, 2011.

   Ferguson DJ, Balaban AE, Patzewitz EM, Wall RJ, Hopp CS, Poulin B, Mohmmed A, Malhotra P, Coppi A, **Sinnis P***, Tewari R*. The repeat region of the circumsporozoite protein is critical for sporozoite formation and maturation in *Plasmodium*. *PLoS One* 9:e113923, 2014.
   *co-corresponding authors

Espinosa DA, Gutierrez GM, Rojas-López M, Noe AR, Shi L, Tse SW, **Sinnis P,** Zavala F. Proteolytic Cleavage of the *Plasmodium falciparum* Circumsporozoite Protein Is a Target of Protective Antibodies. J Infect Dis 212:1111-9, 2015.

Swearingen KE, Lindner SE, Shi L, Shears MJ, Harupa A, Hopp CS, Vaughan AM, Springer TA, Moritz RL, Kappe SH, **Sinnis P.** Interrogating the *Plasmodium* Sporozoite Surface: Identification of Surface-Exposed Proteins and Demonstration of Glycosylation on CSP and TRAP by Mass Spectrometry-Based Proteomics. PLoS Pathog 12:e1005606, 2016. PMC4851412

Kisalu NK, Idris AH, Weidle C, Flores-Garcia Y, Flynn BJ, Sack BK, Murphy S, Schön A, Freire E, Francica JR, Miller AB, Gregory J, March S, Liao HX, Haynes BF, Wiehe K, Trama AM, Saunders KO, Gladden MA, Monroe A, Bonsignori M, Kanekiyo M, Wheatley AK, McDermott AB, Farney SK, Chuang GY, Zhang B, Kc N, Chakravarty S, Kwong PD, **Sinnis P**, Bhatia SN, Kappe SHI, Sim BKL, Hoffman SL, Zavala F, Pancera M, Seder RA. A human monoclonal antibody prevents malaria infection by targeting a new site of vulnerability on the parasite. Nat Med. 24(4):408-416. doi: 10.1038/nm.4512, 2018.

4. The Role of Proteases in the Sporozoite's Journey to the Liver. We have found that parasite proteases play critical roles in the establishment of malaria infection; they control exposure of adhesion domains in surface proteins during cell invasion and release adhesive interactions to enable movement of parasites through matrix and into cells.

   Coppi A, Pinzon-Ortiz C, Hutter C and **Sinnis P.** The *Plasmodium* Circumsporozoite Protein is Proteolytically Processed During Cell Invasion. *J Exp Med* 201:27-33, 2005. PMC1995445

   Coppi A, Cabinian M, Mirelman D and **Sinnis P.** Antimalarial Activity of Allicin, a Biologically Active Compound From Garlic Cloves. Antimicrob Agents Chemother 50:1731-1737, 2006.

   Hobbs CV, Voza T, Coppi A, Marsh K, Borkowsky W and **Sinnis P.** HIV protease inhibitors affect development of pre-erythrocytict stage *Plasmodium*. J Infect Dis 199: 134-141, 2009.

   Vera IM, Beatty WL **Sinnis P** and Kim K. Plasmodium protease ROM1 is important for proper formation of the parasitophorous vacuole. PLoS Pathogens, 7:e1002197, 2011.

   Ejigiri I, Ragheb DRT, Pino P, Coppi A, Bennett BL, Soldati-Favre D and **Sinnis P.** Shedding of TRAP by a rhomboid protease from the malaria sporozoite surface is essential for gliding motility and sporozoite infectivity. PLoS Pathogens 8:e1002725, 2012. PMC3406075

   Lehmann C, Heitmann A, Mishra S, Burda PC, Singer M, Prado M, Niklaus L, Lacroix C, Ménard R, Frischknecht F, Stanway R, **Sinnis P**, Heussler V. A cysteine protease inhibitor of *Plasmodium berghei* is essential for exo-erythrocytic development. PLoS Pathog 10:e1004336, 2014.

Complete List of Published Works in PubMed:
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