January 19, 2009

CURRICULUM VITAE
DAVID J. SULLIVAN JR. M.D.

PERSONAL DATA

Home Address

117 Hawthorn Rd.
Baltimore, MD 21210
Telephone: (410) 889-1614

Office Address

Department of Molecular Microbiology and Immunology
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe St. Rm E5628
Baltimore, MD 21205
Telephone: (410) 502-2522
Fax: (410) 955-0105
email: dsulliva@jhsph.edu

EDUCATION AND TRAINING

Education

BA/1983 University of Virginia / Biology
MD/1988 University of Alabama at Birmingham/Medicine

Postdoctoral Training

Residency Internal Medicine. Barnes Hospital,
1988-1991 Washington University, St. Louis, MO
Fellowship Infectious Diseases. Washington University
1992-1997 and Barnes-Jewish Hospital

Medical License

Current state of Maryland/DEA

Certification

American Board of Internal Medicine-1991, Recertified 2004
Board Certified Infectious Diseases-1994, Recertified 2004

PROFESSIONAL EXPERIENCE

Position

Associate Professor May 1, 2006- present,
Assistant Professor November 1,1997-April 30, 2006
JHU School of Public Health
Department of Molecular Microbiology and Immunology

Responsibilities

Research on *Plasmodium* metal metabolism, cerebral malaria, diagnostics and participation in Malaria Research Institute

Position

JHU Infectious Diseases Consult Physician

Responsibilities

Consult Service for Johns Hopkins Hospital Infectious Diseases

PROFESSIONAL ACTIVITIES

Society membership

Infectious Diseases Society of America
American Society of Tropical Medicine and Hygiene
International Bioiron Society
East Coast Iron Club

Advisory Panel

Joint Military Medical Infectious Diseases Workshop 2003
Reviewed army malaria chemotherapy program

Consultations and Testimony

1. Yunnan province of China invited me to review their malaria control program. I spent 10 days in China, giving lectures and interacting with their staff. 2000

2. Clinical anthrax committee with BSPH and ID department. 2001
Handled phone calls from press regarding anthrax outbreak and participated in initiative to document clinical biological agent algorithms with JHU SOM ID dept.

3. Help to reinstate (plus-up) military adenovirus vaccine. Lobbied Bill Howell at Army Material Command, Logistical branch, Wyeth representatives, Ben Cardin and Navy representatives and Joel Gaydos Dec. 2000-March 2001

4. Hemozoin Discussion web forum set up at JHSPH website
http://jhmalaria.jhsph.edu/hemozoin/
Download review and original pdfs, and answers questions on topic of hemozoin.

5. Testimony-Interview on mefloquine and Fort Bragg suicide/murders for military magazine, Today show and MSNBC

6. Voice of America (Talk to America) July 15 2005 “Malaria”

7. Paid legal consultant for Kirkland and Ellis LLP-Mutual vs. IVAX and TEVA quinine marketing-2007

8. Paid legal consultant- Sedgewick Claims Management Services-thrombocytopenia-2007

9. Iron and Malaria- Technical Working Group- NICHD/NIH consultation

EDITORIAL ACTIVITIES

Journal ad hoc reviewer for:

Acta Tropica, American Journal Pathology, American Journal Trop Med and Hygiene, Antimicrobial Agents and Chemotherapy, Biochemical Pharmacology, Biochemistry, Bioorganic & Medicinal Chemistry, Biophysical Journal, Drug

Design Reviews, European Journal of Parasitology, Experimental Parasitology, Expert Review of Anti-infective Therapy, FEBS Letters, Future Drugs, Future Microbiology, Infection and Immunity, International Journal Parasitology, Journal Biological Chemistry, Journal of Infectious Diseases, Journal of Inorganic Biochemistry, Lancet, Lancet Infectious Diseases, Medicinal Research Reviews, Molecular & Biochemical Parasitology, Nature, Parasitology International, Plos Pathogens, Proc Natl Acad Sci USA, Trends in Parasitology, Trends in Pharmacological Sciences, Wiley Encyclopedia of Chemical Biology

2008- American Journal Trop Med and Hygiene, Antimicrobial Agents and Chemotherapy, Biochemistry, Biophysical Journal, Chemical Research in Toxicology, Current Genetics, Experimental Parasitology, Inorganic Chemistry, Journal Biological Chemistry, Journal of Immunological Methods, Malaria Journal, Nature, STMS Books Wiley-VCH Verlag GmbH & Co. KGaA

Faculty1000 Biology 2007- Faculty member- Antimicrobial agents Section of the PHARMACOLOGY & DRUG DISCOVERY

Books/Monographs

Coeditors (**D.J. Sullivan** and Sanjeev Krishna) of Current Topics in Microbiology and Immunology vol 295 "Malaria: Drugs, Disease and Post-genomic Biology" 16 chapters, 444 pages.

Grant ad hoc reviewer for

1. Israel Science Foundation-two grants in 1999
2. WHO Special Programme Research and Training in Tropical Diseases Drug Discovery Research category 1999
3. NIH R15 Metallobiochemistry study section 1999
4. Veteran's Administration Tropical Medicine and Parasitology study section-Teleconference of three R01's 2000
5. Reviewed 4 grants for R21 study section on Special Emphasis Panel (ZRG1-MBC1(2001)) to review Exploratory/Developmental Grants in Microbiology.
6. NSF-RO1 one grant 2003
7. Israel Science Foundation 2003
8. JHU CFAR Study Section for HIV grants 2005
9. Ad hoc for JHU Malaria Research Institute pilot grant (2-3 times only)
10. Samsung Biomedical Research Institute Grant, Korea 2004 and 2005
11. Australian Nat. Health Medical Res Council Grant 2005
12. South Dakota Defense 2007 Experimental Program to Stimulate Competitive Research (DEPSCOR) 2006
13. NIH RO1 and R21 Biology of Plasmodium and Trypanosome Vectors Special Review Panel /10 ZRG1 IDM-N (02) 2006
14. Health Research Board, Ireland single grant 2006
15. England-MRC Senior Non-Clinical Fellowships 2007-08
16. NIH NIAID Loan Repayment Applications ZAI1 ESB-M (S2)-2007

17. NIH NIAID Clinical Trial Planning (R34) Grants and Implementation (U01) Cooperative Agreements Special Emphasis Panel ZAI1-BDP-M-M2 PAR-06-384 and PAR-05-113 Feb 2008
18. NSF USA, Symbiosis, Defense and Self-Recognition Advisory Panel

HONORS AND AWARDS

Class Citizenship Award (The Netter Series) for Community Service (1988)
MAP Readers Digest International Fellowship (1988, Mussoorie, India)
Burroughs Wellcome Leadership Award A.M.A. (1994)
Healthcare for the Homeless Coalition, St. Louis, Outstanding Volunteer Service (1997)
National Foundation of Infectious Diseases (NFID) New Investigator Matching Award (1999)
Burroughs Wellcome Career Award in the Biomedical Sciences (1997-2000)
Pew Scholars Award in Biomedical Sciences (2000-2004)
Inventor of Year Award (2003) from APL shared with Drs. Kumar, Scholl, Feldman, Demirev and student Darin Kongkasuriyachai

PUBLICATIONS

1. **Sullivan Jr.,** D, Gluzman, IY, and Goldberg, DE, *Plasmodium* hemozoin formation mediated by histidine-rich proteins. **Science**, 1996. 271(5246): p. 219-22.
2. **Sullivan Jr.,** D, Gluzman, IY, Russell, DG, and Goldberg, DE, On the molecular mechanism of chloroquine's antimalarial action. **Proc Natl Acad Sci U S A**, 1996. 93(21): p. 11865-70.
3. **Sullivan Jr.,** D, Ayala, YM, and Goldberg, DE, An unexpected 5' untranslated intron in the *P. falciparum* genes for histidine-rich proteins II and III. **Mol Biochem Parasitol**, 1996. 83(2): p. 247-51.
4. Francis, SE, **Sullivan Jr.,** D, and Goldberg, DE, Hemoglobin metabolism in the malaria parasite *Plasmodium falciparum*. **Annu Rev Microbiol**, 1997. 51: p. 97-123.
5. Mamoun, CB, **Sullivan Jr.,** D, Banerjee, R, and Goldberg, DE, Identification and characterization of an unusual double serine/threonine protein phosphatase 2C in the malaria parasite *Plasmodium falciparum*. **J Biol Chem**, 1998. 273(18): p. 11241-7.
6. **Sullivan Jr.,** D, The *Plasmodium* Heme Problem: Polymerization and inhibition by the quinolines, in **International Symposium on Biopolymers Muenster Germany**, A. Steinbuchel, Editor. 1998, Wiley-VCH Verlag: Weinheim, Germany.
7. **Sullivan Jr.,** D, Matile, H, Ridley, RG, and Goldberg, DE, A common mechanism for blockade of heme polymerization by antimalarial quinolines. **J Biol Chem**, 1998. 273(47): p. 31103-7.

8. Hayward, RE, **Sullivan Jr.,** D, and Day, KP, *Plasmodium falciparum*: histidine-rich protein II is expressed during gametocyte development. **Exp Parasitol**, 2000. 96(3): p. 139-46.
9. Chen, MM, Shi, L, and **Sullivan Jr.,** D, *Haemoproteus* and *Schistosoma* synthesize heme polymers similar to *Plasmodium* hemozoin and beta-hematin. **Mol Biochem Parasitol**, 2001. 113(1): p. 1-8.
10. Akompong, T, Kadekoppala, M, Harrison, T, Oksman, A, Goldberg, DE, Fujioka, H, Samuel, BU, et al., Trans expression of a *Plasmodium falciparum* histidine-rich protein II (HRPII) reveals sorting of soluble proteins in the periphery of the host erythrocyte and disrupts transport to the malarial food vacuole. **J Biol Chem**, 2002. 277(32): p. 28923-33.
11. Coban, C, Ishii, KJ, **Sullivan Jr.,** D, and Kumar, N, Purified malaria pigment (hemozoin) enhances dendritic cell maturation and modulates the isotype of antibodies induced by a DNA vaccine. **Infect Immun**, 2002. 70(7): p. 3939-43.
12. Demirev, PA, Feldman, AB, Kongkasuriyachai, D, Scholl, P, **Sullivan Jr.,** D, and Kumar, N, Detection of malaria parasites in blood by laser desorption mass spectrometry. **Anal Chem**, 2002. 74(14): p. 3262-6.
13. **Sullivan Jr.,** D, Theories on malarial pigment formation and quinoline action. **Int J Parasitol**, 2002. 32(13): p. 1645-53.
14. Brahmbhatt, H, Kigozi, G, Wabwire-Mangen, F, Serwadda, D, Sewankambo, N, Lutalo, T, Wawer, MJ, et al., The effects of placental malaria on mother-to-child HIV transmission in Rakai, Uganda. **Aids**, 2003. 17(17): p. 2539-41.
15. Chong, CR and **Sullivan Jr.,** D, Inhibition of heme crystal growth by antimalarials and other compounds: implications for drug discovery. **Biochem J**, 2003. 66(11): p. 2201-12.
16. Iyer, JK, Shi, L, Shankar, AH, and **Sullivan Jr.,** D, Zinc protoporphyrin IX binds heme crystals to inhibit the process of crystallization in *Plasmodium falciparum*. **Mol Med**, 2003. 9(5-8): p. 175-82.
17. Noland, GS, Briones, N, and **Sullivan Jr.,** D, The shape and size of hemozoin crystals distinguishes diverse *Plasmodium* species. **Mol Biochem Parasitol**, 2003. 130(2): p. 91-9.
18. Rasoloson, D, Shi, L, Chong, CR, Kafsack, BF, and **Sullivan Jr.,** D, Copper pathways in *Plasmodium falciparum* infected erythrocytes indicate an efflux role for the copper P-ATPase. **Biochem J**, 2004. 381(Pt 3): p. 803-11.
19. Scholl, PF, Kongkasuriyachai, D, Demirev, PA, Feldman, AB, Lin, JS, **Sullivan Jr.,** D, and Kumar, N, Rapid detection of malaria infection in vivo by laser desorption mass spectrometry. **Am J Trop Med Hyg**, 2004. 71(5): p. 546-51.
20. Jain, SK, Persaud, D, Perl, TM, Pass, MA, Murphy, KM, Pisciotta, JM, Scholl, PF, et al., Nosocomial malaria and saline flush. **Emerg Infect Dis**, 2005. 11(7): p. 1097-9.
21. Nyunt, M, Pisciotta, J, Feldman, AB, Thuma, P, Scholl, PF, Demirev, PA, Lin, JS, et al., Detection of *Plasmodium falciparum* in pregnancy by laser desorption mass spectrometry. **Am J Trop Med Hyg**, 2005. 73(3): p. 485-90.
22. Pisciotta, JM, Ponder, EL, Fried, B, and **Sullivan Jr.,** D, Hemozoin formation in *Echinostoma trivolvis* rediae. **Int J Parasitol**, 2005. 35(10): p. 1037-42.

23. Scholl, PF, Tripathi, AK, and **Sullivan Jr.,** D, Bioavailable iron and heme metabolism in *Plasmodium falciparum*. **Curr Top Microbiol Immunol**, 2005. 295: p. 293-324.
24. Chen, X, Chong, CR, Shi, L, Yoshimoto, T, **Sullivan Jr.,** D, and Liu, JO, Inhibitors of *Plasmodium falciparum* methionine aminopeptidase 1b possess antimalarial activity. **Proc Nat Acad Sci U S A**, 2006. 103(39): p. 14548-53.
25. Chong, CR, Chen, X, Shi, L, Liu, JO, and **Sullivan Jr.,** D, A clinical drug library screen identifies astemizole as an antimalarial agent. **Nat Chem Biol**, 2006. 2(8): p. 415-6.
26. Chong, CR, Qian, DZ, Pan, F, Wei, Y, Pili, R, **Sullivan Jr.,** D, and Liu, JO, Identification of type 1 inosine monophosphate dehydrogenase as an antiangiogenic drug target. **J Med Chem**, 2006. 49(9): p. 2677-80.
27. Hiremath, GS, **Sullivan Jr.,** D, Tripathi, AK, Black, RE, and Sazawal, S, Effect of *Plasmodium falciparum* parasitemia on erythrocyte zinc protoporphyrin. **Clin Chem**, 2006. 52(4): p. 778-9.
28. Mharakurwa, S, Simoloka, C, Thuma, PE, Shiff, CJ, and **Sullivan Jr.,** D, PCR detection of *Plasmodium falciparum* in human urine and saliva samples. **Malar J**, 2006. 5: p. 103.
29. Tripathi, AK, **Sullivan Jr.,** D, and Stins, MF, *Plasmodium falciparum*-infected erythrocytes increase intercellular adhesion molecule 1 expression on brain endothelium through NF-kappaB. **Infect Immun**, 2006. 74(6): p. 3262-70.
30. Byrne, ST, Gu, P, Zhou, J, Denkin, SM, Chong, C, **Sullivan Jr.,** D, Liu, JO, et al., Pyrrolidine dithiocarbamate and diethyldithiocarbamate are active against growing and nongrowing persister *Mycobacterium tuberculosis*. **Antimicrob Agents Chemother**, 2007. 51(12): p. 4495-7.
31. Chong, CR and **Sullivan Jr.,** D, New uses for old drugs. **Nature**, 2007. 448(7154): p. 645-6.
32. Chong, CR, Xu, J, Lu, J, Bhat, S, **Sullivan Jr.,** D, and Liu, JO, Inhibition of angiogenesis by the antifungal drug itraconazole. **ACS Chem Biol**, 2007. 2(4): p. 263-70.
33. Howard, CT, McKakpo, US, Quakyi, IA, Bosompem, KM, Addison, EA, Sun, K, **Sullivan Jr.,** D, et al., Relationship of hepcidin with parasitemia and anemia among patients with uncomplicated *Plasmodium falciparum* malaria in Ghana. **Am J Trop Med Hyg**, 2007. 77(4): p. 623-6.
34. Mlambo, G, Sullivan, D, Mutambu, SL, Soko, W, Mbedzi, J, Chivenga, J, Jaenisch, T, et al., Analysis of genetic polymorphism in select vaccine candidate antigens and microsatellite loci in *Plasmodium falciparum* from endemic areas at varying altitudes. **Acta Trop**, 2007. 102(3): p. 201-5.
35. Mlambo, G, **Sullivan Jr.,** D, Mutambu, SL, Soko, W, Mbedzi, J, Chivenga, J, Gemperli, A, et al., High prevalence of molecular markers for resistance to chloroquine and pyrimethamine in *Plasmodium falciparum* from Zimbabwe. **Parasitol Res**, 2007. 101(4): p. 1147-51.
36. Pisciotta, JM, Coppens, I, Tripathi, AK, Scholl, PF, Shuman, J, Bajad, S, Shulaev, V, et al., The role of neutral lipid nanospheres in *Plasmodium falciparum* haem crystallization. **Biochem J**, 2007. 402(1): p. 197-204.

37. Szklarczyk, A, Stins, M, Milward, EA, Ryu, H, Fitzsimmons, C, **Sullivan Jr.,** D, and Conant, K, Glial activation and matrix metalloproteinase release in cerebral malaria. **J Neurovirol**, 2007. 13(1): p. 2-10.
38. Tripathi, AK, **Sullivan Jr.,** D, and Stins, MF, *Plasmodium falciparum*-infected erythrocytes decrease the integrity of human blood-brain barrier endothelial cell monolayers. **J Infect Dis**, 2007. 195(7): p. 942-50.
39. Brahmbhatt, H, **Sullivan Jr.,** D, Kigozi, G, Askin, F, Wabwire-Mangenm, F, Serwadda, D, Sewankambo, N, et al., Association of HIV and malaria with mother-to-child transmission, birth outcomes, and child mortality. **J Acquir Immune Defic Syndr**, 2008. 47(4): p. 472-6.
40. Downey, AS, Chong, CR, Graczyk, TK, and **Sullivan Jr.,** D, Efficacy of pyrvinium pamoate against *Cryptosporidium parvum*infection in vitro and in a neonatal mouse model. **Antimicrob Agents Chemother**, 2008. 52(9): p. 3106-12.
41. Kifude, CM, Rajasekariah, HG, **Sullivan Jr.,** D, Stewart, VA, Angov, E, Martin, SK, Diggs, CL, et al., Enzyme-linked immunosorbent assay for detection of *Plasmodium falciparum* histidine-rich protein 2 in blood, plasma, and serum. **Clin Vaccine Immunol**, 2008. 15(6): p. 1012-8.
42. Mlambo, G, Vasquez, Y, LeBlanc, R, **Sullivan Jr.,** D, and Kumar, N, A filter paper method for the detection of *Plasmodium falciparum* gametocytes by reverse transcription polymerase chain reaction. **Am J Trop Med Hyg**, 2008. 78(1): p. 114-6.
43. Pisciotta, JM and **Sullivan Jr.,** D, Hemozoin: oil versus water. **Parasitol Int**, 2008. 57(2): p. 89-96.
44. Srivastava K, Cockburn IA, Swaim A, Thompson LE, Tripathi A, Fletcher CA, Shirk EM, Sun H, Kowalska MA, Fox-Talbot K, **Sullivan D**, Zavala F, Morrell CN. Platelet factor 4 mediates inflammation in experimental cerebral malaria. **Cell Host Microbe**, 2008. 4(2): p. 179-87.

<u>Publication Of Major Representative Articles In Respected Journals (Selected From Above)</u>

Sullivan Jr. DJ, Gluzman IY, Russell DG and Goldberg DE: On the molecular mechanism of chloroquine's antimalarial action. *Proc. Natl. Acad. Sci. USA* 93:11865-70 (1996).

Chong C and **Sullivan, D** Inhibition of heme crystal growth by antimalarials and other compounds: implications for drug discovery *Biochem. Pharm.* 66:2201-2212 (2003).

Nyunt M, Pisciotta J, Feldman AB, Thuma P, Scholl PF, Demirev PA, Lin JS, Shi L, Kumar N and **Sullivan DJ** Detection Of *Plasmodium Falciparum* In Pregnancy By Laser Desorption Mass Spectrometry *Am J. Trop Med. Hyg*. 73:485-490 (2005).

Mharakurwa S, Simoloka C, Thuma PE, Shiff CJ, **Sullivan DJ**. PCR detection of *Plasmodium falciparum* in human urine and saliva samples. Malar J. Nov 8;5:103 (2006)

Chong CR, Chen X, Shi L, Liu JO, **Sullivan DJ Jr**. A clinical drug library screen identifies astemizole as an antimalarial agent. Nat Chem Biol. 2(8):415-6 (2006)

Chong CR, **Sullivan DJ Jr**. New uses for old drugs. Nature. 2007 Aug 9;448(7154):645-6.

Pisciotta JM, Coppens I, Tripathi AK, Scholl PF, Shuman J, Bajad S, Shulaev V, **Sullivan DJ**. The role of neutral lipid nanospheres in *Plasmodium falciparum* heme crystallization. Biochem J.402(1):197-204 (2007)

Authorship Of Major Text, Chapters And Invited Reports Synthesizing Knowledge In The Field

Francis SF, **Sullivan Jr. DJ** and Goldberg DE: Hemoglobin metabolism in the malaria parasite *Plasmodium falciparum.* Ann. Rev. Micro. 51:97-123 (1997).

Sullivan Jr. DJ: The *Plasmodium* Heme Problem: Polymerization and inhibition by the quinolines. International Symposium on Biopolymers; Muenster, Germany Wiley-VCH Verlag (Weinheim, Germany) (1998).

Sullivan DJ Hemozoin a biocrysal synthesized during degradation of hemozoin p 975-1010 in Biopolymers for Medical and Pharmaceutical Applications, Edited by Alexander Steinbüchel and Robert H. Marchessault volume 9 in series Biopolymers
Wiley-VCH ISBN: 3-527-31154-8

Sullivan D Theories on malarial pigment formation and quinoline action Int. J. Parasit. 32:1645–1653 (2002).

Scholl PF, Tripathi AK and **Sullivan DJ**. Bioavailable Iron And Heme Metabolism In *Plasmodium falciparum* Curent Topics in Microbiology and Immunology vol 295 Malaria: Drugs, Disease and Post-genomic Biology Springer-Verlag Berlin Heidelberg Germany 2005

CoEditor (**D.J. Sullivan** and Sanjeev Krishna) of Current Topics in Microbiology and Immunology vol 295 Malaria: Drugs, Disease and Post-genomic Biology 16 chapters 444 pages

Pisciotta JM, **Sullivan D**, Hemozoin: Oil versus water, Parasitol Int (2007), doi:10.1016/j.parint.2007.09.009

Sullivan D and Gandhi N Malaria, in Post-Infectious Sequelae And Long-Term Consequences Of Infectious Diseases Amercian Society of Microbiology submitted 2008

Reports Of Inventions Submitted For Patent

1) Detection of malaria parasites by laser desorption mass spectrometry
   Inventors Plamen Demeriev, Andrew Feldman Darin Kongkasuriyachai, Nirbhay Kumar, Peter Scholl, **David. Sullivan, Jr.**
2) New angiogenesis inhibitors
   Inventors Jun Liu, Curtis Chong and **David Sullivan**
3) Malaria Diagnosis in Urine
   Inventors **David Sullivan**, Peter Scholl, Lirong Shi, Maria Rivarola
4) Tangible Property- Plasmids for Pf aldolase and Histidine-rich Protein II
5) Pyrvinium for *Cryptosporidium*
   Inventors David Sullivan Autumn Downey, Thaddeus Graczyck and Curtis Chong

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DAVID J. SULLIVAN JR. M.D.

PART II

TEACHING

Advisees

Undergraduate Students

Alexandra Surcel 2 years work study 1999-2001
Guadalupe Garbalena Howard Hughes Summer Res. Fellowship 1999
Noelle Briones Howard Hughes Summer Res. Fellowship 2000
Nina Washington Summer Scholar Leadership Alliance 2001
Justin Rafael pre medicial student summer and school break work 2002-2003
Adrian Wilson summer work 2003
Carly Wais Baltimore Ingenuity Project Polytechnic High School 2008
Victoire Ndong summer 2008
Sky Vanderburg Summer 2008

Rotation Students

Mark Dimena
Jessica Darmen
Rebecca Garten
Crystal Bennet
Jorge Maciel
Godfree Mlambo
Greg Noland
Davison Sangweme
Muneera Alghaferi
Nitya Nair
Ching Ng
Bjorn Kafsack
Kiwon Park
Anitha Moorthy
Sze-Wah (Eva) Tse
Kyle McLean
Adam Stroupe
Ronald Galiwango

Masters Students

Jayasree Iyer, Master of Science, MMI, May 1999 Thesis Title "The inhibition of *Plasmodium falciparum* heme polymerization by erythrocytic zinc protoporphyrin IX"
Mary Chen, Master of Science, MMI May 2000 “Comparative analysis of heme polymers and characterization of malarial histidine-rich protein 3D3H”
Shih-Jung Pan, Master of Science, MMI May 2000 (co-mentor with Brendan

Cormack-faculty outside of MMI “regualation of EPA1: a Candida glabrata adhesion”
Linda Hubbard MMI-MHS 2006

Doctoral Students

Oluwatosin Gisanrin graduated 5/26/2006 PhD
Curtis Chong MD/PhD SOM Pharmacology graduated 3/1/2006
John Pisciotta graduated May 2007
Thomas Jaenisch International Health

Postdoctoral Fellows And Professional Interns Trained And Supervised Former

Julie Gauthier PhD 1999-2001 Iron and the iron transporter gene in *P. falciparum* Assistant professor Nicholls State University LA.
Dominique Rasoloson PhD 2001-2005 Copper and Iron metabolism in *Plasmodium falciparum* Present position Lab manager for Geraldine Seydoux, Professor of Molecular Biology and Genetics JHU SOM
Leo Slater PhD Postdoctoral Malaria History candidate- for 2 years
Slater LB. Malarial birds: modeling infectious human disease in animals. Bull Hist Med. 2005 Summer;79(2):261-94.
Slater LB. Malaria chemotherapy and the "kaleidoscopic" organisation of biomedical research during world war II.Ambix. 2004 Jul;51(2):107-34.
Maria Rivarola-prenursing student-graduated nursing school in May 2005
Myaing Nyunt MD-supervised lab rotation and research project in Zambia
“Malaria drug resistant detection in pregnancy”

Present

Abhai Tripathi PhD 2003-2008- Cerebral malaria
Anya Bailis MD OB/GYN Fellow- Placental malaria

Participation In Preliminary Oral Examinations

BSPH

Susannah Brydges MMI PHD7/7/2000
Edward Luk Biochemistry and Molecular Biology PHD 12/15/2000
Rohit Arvind Chitale Epidemiology PHD 5/30/2002
John Matthew Pisciotta MMI PHD 9/25/2003
Thomas Jaenisch International Health PHD 3/17/2003
Oluwatosin Aderinsol Gisanrin MMI PHD 1/22/2003
Catherine Namugga Kibirige MMI PHD 8/27/2003
Janella Ulloa Environmental Health Sciences PHD 2/26/2004
Amornrat Naranuntarat Environmental Health Sciences PHD 12/2/2005
Maroya Spalding Biochemistry and Molecular Biology PHD 8/30/2005
Myaing Nyunt GTP Clinical Pharmacology PhD 2/24/2006
Sufia Dadabhai, Department of Epidemiology 5/17/2007

Jolyn Gisselberg, Biochemistry and Molecular Biology 12/4/2007

JHU

John Maxwell PhD Dept Chemistry 1999
Azin Nezami PhD Biology JHU 2000
Adam Rueben PhD Structural Biology 2003
Xinle Niu PhD Biomedical Engineering 2004
Shaaretha Pelly PHD Pathobiology JHU Med 2007
Lindsey Hess PHD Chemistry 2007

Participation In Final Oral Examinations

PhD

Xiu Fen Liu, PhD Env. Health Sci. JHSPH Jan. 12, 1999
Jong-Min Chen MMI 1999
Matthew E. Portnoy Biochemistry and Molecular Biology PhD 6/7/2001
Susannah Brydges MMI PhD 2/5/2004
Godfree Mlambo MMI PhD 9/1/2005
Jill Marie Harper MMI PhD 3/8/2005
Rohit Chitale Epi PhD 1/27/2006
Curtis Chong MD PhD 3/1/2006
Oluwatosin Aderinsol Gisanrin MMI PhD 5/26/2006
Xinle Niu PhD Biomedical Engineering 6/6/2006
Gregory Noland PhD MMI 2/20/2007
John Pisciotta, PhD MMI 3/1/2007
Thomas Jaenisch PhD International Health 1/17/2008
Myaing Nyunt PhD GTPCI 2/19/2008
Adam Rueben PhD, JHU Biology 2/27/2008
Autumn Girouard Downey PhD MMI 9/5/2008

SCM

Shihjung Pan MMI SCM 4/27/2001
Jayasree Iyer MMI SCM 1999
Mary Mei-Ying Chen MMI SCM 4/18/2000
Stacey Garland Biochemistry and Molecular Biology SCM 3/29/2000
Karen Elizabeth Rabenau MMI SCM 5/13/2002
Kimberly Ann Krummi, Epidemiology SCM 5/19/2003
Gloria Hoe-Jung Cha MMI SCM 5/10/2004

International thesis advisor/reader

Nokuhle Mtombeni - Master Science to University of Witwatersrand South Africa
Helped advise student and revise thesis-“The characterization of the Phosphatidyl-inositol-3-Kinase in *Plasmodium falciparum* and the effects of selective inhibitors of this enzyme on the parasite”. 2004
Kanyile K. Ncokazi “Interactions of Quinoline antimalarials with haematin and

their effect on beta-hematin formation" PHD Dept Chemistry University of Cape Town thesis committee and reader 2005

Maritza Jaramillo "Malaria Immunopathology:signaling and Cellular Mechanisms involved in hemozoin-inducible proinflammatory events". University of Laval, Quebec thesis committee and attended final thesis presentation in Quebec 2005

Uri McKakpo PhD student from Ghana who spent 2 months in laboratory project on malaria urine antigens Sept-Oct 2005

Moonga Hawela Masters Student to University of Zambia spent three months in my laboratory Sept-Dec 2006.

Classroom Instruction

Titles Of Courses For Which The Individual Has Had Primary Responsibility.

Online Malarology principal instructor and course creator- 6 of 15 lectures Started 3 quarter 2009.
Malariology 1998-2006 co primary faculty
Molecular Microbiology and Immunology (1999)
Biology of Parasitism (joint with Nirbhay Kumar and Clive Shiff and Thaddeus Grayzk)1999-2006
Public Helath Biology 2006 online course shared with Vernon Carruthers
Public Helath Biology 2007 and 2008- Course Director
Malariology, 2007and 2008-Course Director
OpenCourseWare- Malariology-directed faculty to convert lectures.

Harare, Zimbabwe May 2004 Malaria Resarch Training Program two week short course on "*P. falciparum* Drug Resistance Malaria Training Course" Supervised lectures and labs for two week course with 17 participants from Zimbabwe and Zambia. I gave 25% of lectures and supervised lab component

Ethiopia Distance EducationApril 2004- "Malaria"-organized short course transmitted by live internet video to Ethiopia. Participants were able to ask questions of instructors

Titles Of Courses In Which The Individual Has Participated In Teaching.

JHU Medical Students-cases in Infectious Diseases as part of Microbiology 2nd year students 1998-2002
Biology of Parasitism (260.634) 1998
Malariology (1-3 lectures and labs) 1998-2005
Summer Institute Tropical Diseases (Health and Medicine in the Tropics
Medical Parasitology(260.631)
Parasitology, University of Maryland School of Medicine 1 lecture and discussion session/yr 2000-2007
Introduction to Pathobiology
Issues in Public Health,undergraduate 2000
Parasitology to Pediatric and adult ID fellows 2000-2002

Medical Student Parasitology lectures- Developed three lectures covering all of clinical medical parasitology for 2nd year medical students 2001-2007
Ciders-Malaria in refugee populations 2002
Winter Institute- HIV Malaria and TB -2003-2008
Winter Institute Tropical Medicine- Malaria 2006 - 2008
Current Research Literature (120.852), JHU BSPH0 (1discussion session) 2003-2007
Wilderness medicine 2005 and 2006 JHU medical students "Malaria"
Bacteriology-Pneumonia and urinary tract infections lecture 2003-2008
School of Nursing Infectious diseases "Malaria" 2006, 2007 and 2008

RESEARCH GRANT PARTICIPATION

1. Grant title

R01AI045774-01 IRON METABOLISM IN PLASMODIUM, NIH NIAID TMP section 06/01/1999- 05/31/2004 Priority Score:154 Percentile: 5.4
R01AI045774-06A2 *PLASMODIUM FALCIPARUM* METAL METABOLISM NIH NIAID- Council selected for funding 09/26/2005 NGA pending 2005-2009

Principal Investigator and Funding Level (DJS salary only)

Myself 100 % complement to BWF grant below for 1999 - 2001, then 70% 2002-2004.2006-2009-40% total 5yr award $1,158,581

Main Grant Objective

R01AI045774-01 The long term objectives of this proposal are to improve targeted antimalarial chemotherapy by further definition of the vital sources of parasitic iron and by characterization of iron transport to essential compartments. Preliminary data implicate erythrocytic ferritin as a possible source of iron. Recent molecular cloning in my lab of the *P. falciparum* homologue to the mammalian iron transporter Natural Resistance Associated Macrophage Protein (*NRAMP*) will enable characterization of iron transport within the parasite. The specific aims are:1) to test erythrocytic iron as an iron source, 2) to localize the compartments in which *PfNRAMP* resides, 3) to assess the specificity of divalent metal cations transported by *PfNRAMP*, 4) to evaluate the kinetics and inhibition of this proton/cation symporter.and 5) to analyze its level of expression amongst quinoline-sensitive and resistant parasites.

R01AI045774-06A2 The broad long term objective is to further define the molecular process of heme crystal formation biology that the quinolines target and to develop *Plasmodium* metabolic profiling as a method of drug target validation, focused at first on metal related metabolism. Hypothesis 1 A unique combination of lipids and/ or proteins contributes to intracellular *Plasmodium* heme crystal formation. The specific aim directed to this hypothesis is: to compare heme crystal formation and inhibition initiated with subcellular parasite fractionations, in vitro lipid or protein formulations. Hypothesis 2 Iron and copper chelators inhibit *Plasmodium* via changes in oxidation-reduction pathways in contrast to chloroquine, that nonoxidatively disrupts heme chemistry or artemisinin that oxidizes PfATP6 to change calcium metabolism.
The specific aims directed to this hypothesis are: to identify common and unique metabolites of the uninfected erythrocyte compared to the infected erythrocyte that also responds to antimalarial drugs directed at metals, and to analyze the altered

Plasmodium metabolic profile in drug-resistant parasites. The overall goal is to investigate the vulnerable metal biology already targeted by existing quinoline antimalarials and to validate novel antimalarial metal-directed targets. This project will also advance *Plasmodium* biology into a metabolome analysis as part of the NIH "roadmap" to study metabolic components and networks in cells. *Plasmodium* parasitism provides a comparison of "simple" erythrocyte cell to more complex infected cell.

Principal Responsibilities Supervise and direct laboratory and students

2. Grant title

Burroughs Wellcome Career Award in the Biomedical Sciences "IRON METABOLISM IN *PLASMODIUM FALCIPARUM*" November 1997-October 2000

Burroughs Wellcome Fund (Sponsoring Agency)

Principal Investigator and Funding Level (DJS salary only)

Myself 71% total award $400,000

Main Grant Objective

My proposed plan is to gain further understanding of the mechanism of heme polymerization, to more precisely delineate the mechanism of quinoline inhibition of heme polymerization and to identify the source of iron used by the parasite for its metabolism. The specific goals are:1) To describe the structure of the histidine-rich proteins and regions that associate with heme to form hemozoin. 2) To isolate additional histidine-rich proteins involved in polymerizing heme. 3) To determine the binding affinity of the quinoline/heme complex to hemozoin. 4) To define the essential iron sources for *Plasmodium falciparum* and to understand iron metabolic pathways.

Principal Responsibilities Supervise and direct laboratory

3. Grant title

National Foundation of Infectious Diseases (NFID) New Investigator Matching Award 1999 "PLASMODIUM FALCIPARUM IRON TRANSPORT WITH THE NRAMP HOMOLOGUE"

Principal Investigator and Funding Level (DJS salary only)

Myself 1% $2,000 1 yr

Main Grant Objective

P. falciparum iron transport

Principal Responsibilities Supervisor

4. Grant title

Pew Scholars award in Biomedical Sciences "IRON METABOLISM IN *PLASMODIUM FALCIPARUM*" July 2000-June 2004 Pew Charitable Trust (Sponsoring Agency)

Principal Investigator and Funding Level (DJS salary only)

Myself 10% $240,000 over 4 years

Main Grant Objective

The laboratory research program is focused on delineating three aspects of the

vulnerable *P. falciparum* iron metabolism perturbed by antimalarial drugs. The specific goals are: 1)To elucidate the molecular mechanism of heme polymer formation by the *P. falciparum*-derived histidine-rich proteins, which is the target of the quinoline antimalarials. 2)To determine the role of erythrocytic zinc protoporphyrin IX (ZnPPIX) which caps heme polymer and protects from malaria. 3)To characterize the location and function of the *P. falciparum* iron transport homologue of the Natural Resistance Associated Macrophage Protein (NRAMP) recently cloned in our laboratory.

Principal Responsibilities Supervise and direct laboratory

5. Grant title

"DEVELOPMENT OF AN IMMUNO-CHEMICAL MASS SPECTROSCOPIC METHOD USING URINE FOR THE DIAGNOSIS OF HUMAN MALARIA INFECTION " January 2002-December 2003

JHU BSPH, Malaria Research Institute in collaboration with Peter Scholl at JHUAPL

Principal Investigator and Funding Level (DJS salary only)

Myself 0% $200,000 for two years

Main Grant Objective

The long term objectives of this joint APL-BSPH proposal are to develop a new urine assay that relies on the immunochemical capture of malaria antigens for their more sensitive and specific detection by a urine dipstick test or development for use by a prototype portable matrix assisted laser desorption-ionization mass spectrometry (MALDI-TOF-MS) for a urine or blood based test. The hypothesis is that common and species-specific malaria antigens in the urine of infected humans can be isolated immunochemically to diagnose malaria infections. The specific aims of this proposal are to identify urine malaria antigens via Western analysis, to identify urine malaria antigens by mass spectroscopy, to generate new antibody reagents and to apply the new reagents to a larger collection of malaria clinic urine samples and to develop an immunoaffinity protocol for both a urine dipstick detection and possibly the mass spectroscopic detection of malaria antigens in urine or blood.

Principal Responsibilities Supervise and direct laboratory work

6. Grant title

THE JOHNS HOPKINS CLINICAL COMPOUND SCREENING INITIATIVE

Jan 2003 to present JHU BSPH, Malaria Research Institute and SOM Pharmacology

Principal Investigator and Funding Level (DJS salary only)

CoPi with Jun Liu 5% total $200,000

Main Grant Objective

In this application, we propose to create a chemical library of available existing drugs that will be used to screen inhibition of parasite growth as well as new and classical *Plasmodium falciparum* targets. The specific aims are: To generate a chemical library of every available clinical drug in a 96-well plate format that is compatible with high-throughput screening. To identify promising candidates for treatment of malaria by performing *in vitro* inhibition of parasite growth assays and of new and classical *P. falciparum* targets, such as heme crystallization and the methionine aminopeptidase.

"Hits" identified in the target screens will be validated in parasite growth inhibition assays. To use existing knowledge of drug parameters (i.e. toxicity, pharmacokinetics) and potency data obtained from *in vitro* studies to form structure-activity relationships. In this regard, existing drugs can be used as templates for new, specific antimalarials with reduced toxicity. The long-term objectives are to provide researchers at Johns Hopkins with a library of existing drugs that can be screened against any target or disease, through collaboration. This project will also foster a closer relationship between the pharmacology department and the malaria research community.

Principal Responsibilities Supervise and direct laboratory

7. Grant title

THE JOHNS HOPKINS CLINICAL COMPOUND SCREENING INITIATIVE

Jan 2004-2005 JHU SOM Fund for Medical Discovery

Principal Investigator and Funding Level (DJS salary only)

CoPi with Jun Liu 5% $50,000

Main Grant Objective

The long-term objective is to provide researchers at Johns Hopkins with a library of existing FDA approved drugs that can be screened against any target or disease, through collaboration. The specific aims are: 1) To complete a chemical library of every available drug in clinical use in a 96-well plate format that is compatible with high-throughput screening. 2) To identify candidate drugs for inhibition of the malaria parasite and endothelial proliferation by performing in vitro inhibition growth assays. 3) To annotate the FDA approved library with pharmokinetic, toxicity and clinical use data

8. Grant title

"HIV AND MALARIA CO-INFECTION DURING PREGNANCY AND EFFECTS ON MOTHER-TO-CHILD TRANSMISSION OF HIV IN RAKAI, UGANDA"

Jan 2003 to present JHU BSPH and International Health with Ron Gray and Surgical Path with Dr. Fred Askins Funding sponsor-JHU BSPH MRI-2003-2004; JHUHIV CFAR

Principal Investigator and Funding Level (DJS salary only)

Co PI with Ron Gray, Heena Brahmnbhatt 10% total $180,000

Main Grant Objective

The two hypotheses are that 1) prevalence and severity of placental malaria are much higher in woman who are HIV+ compared to women who are HIV- and 2) both MTCT rates along with maternal HIV viral loads are higher in women who are co-infected with malaria and HIV, compared to women who are infected with HIV alone. Aim1: Advanced histopathological techniques will be used to improve the diagnosis and quantitation of malaria parasite and pigment and inflammatory changes in the placentas of HIV+ and HIV- mothers. Aim 2: Serological tests will be conducted to assess prevalence and titers of malaria serological markers in HIV+ and HIV- mothers. Aim 3: Analyses will be conducted to assess prevalence of placental malaria and titers of malaria serologic markers in HIV+ compared to HIV- mothers, and examine the association between placental malaria and serological markers of malaria and MTCT rates and among HIV+.

Principal Responsibilities Process and read placentas for malaria pathology and analyze data

9. Grant title

Methods for Malaria Detection by Laser Desorption Mass Spectrometry
Jan 2004-Jan 2006 JHU BSPH MRI-APL JHU Partnership Fund

Principal Investigator and Funding Level (DJS salary only)

Listed as PI-Co PI with Dr. Feldman and Demirev at APL and Kumar, Scholl here.
No salary support except for student in lab. 2 yr award $500,000

Main Grant Objective

The specific aims of the proposed studies are: 1) to further develop and optimize the LDMS-based assay for malaria detection and quantitation, and 2) to determine the performance characteristics (sensitivity/specificity) of the developed assay in sizeable human populations. These aims will be pursued by a combination of *in vitro* and *in vivo* experiments aimed at improving sample preparation methods (sensitivity/specificity of detection, logistical burden, cost of consumables per test), improving signal processing of LDMS spectra and heme detection algorithms, and optimizing MS instrument settings and data acquisition protocols. Underlying these developmental efforts will be fundamental scientific investigations aimed at understanding malaria-species-specific and test-protocol-specific limitations of LDMS detection of parasite hemozoin in infected blood.

Principal Responsibilities Supervise and direct laboratory, acquire human blood samples for analysis and analyze data

10. Grant title

HUMAN BRAIN ENDOTHELIAL CELL MODEL TO STUDY CEREBRAL MALARIA August 2003–August 2006 JHU BSPH MRI RO1 submitted fall 2005

Principal Investigator and Funding Level (DJS salary only)

Co PI Minique Stins 5% $200,000 over 3 years

Main Grant Objective

The endothelium of the blood brain barrier (BBB) forms the crucial interface between the brain vasculature and the parenchyma. Therefore, dissecting the interactions of Pf-IRBC with the human BBB endothelium may lead to the long term objective to prevent complications of cerebral malaria. To study the effects Pf-IRBC on the BBB, we developed an in-vitro model of the human BBB by isolating and characterizing human brain microvascular endothelial cells (HBMEC) and exposing these to Pf-IRBC. Our preliminary data show that Pf-IRBC decrease integrity of the BBB endothelium as measured by electrical resistance. We showed that this is multifactorial and involved both membrane associated components of Pf-IRBC and soluble factors released from Pf-IRBC. We partially isolated and characterized protein fractions released from Pf-IRBC. The functionality of these fractions and their effect on HBMEC resistance is currently under investigation and proposed as part of this grant submission. We hypothesize that *Plasmodium* factors released by Pf-IRBC specifically activate HBMEC, triggering signaling pathways leading to a perturbation of the BBB integrity. To further dissect the interaction of Pf-IRBC with the blood brain barrier

endothelium leading to a breach in barrier integrity, the following specific aims are proposed: Aim 1 To isolate and characterize parasite proteins that mediate decrease in HBMEC electrical resistance. Aim 2) Generate recombinant proteins and assess functionality, Aim 3) Characterize host brain endothelial signaling pathways involved in Pf-IRBC mediated decrease in resistance. We anticipate that the significant outcome of these investigations will lead to more insight into pathogenesis of cerebral malaria and possible intervention(s) to maintain BBB barrier integrity in cerebral malaria.

Principal Responsibilities Supervise and direct laboratory

11. Grant title

"DEVELOPMENT OF A MALARIA URINE DIAGNOSTIC ASSAY." Oct 2004-Oct 2005 Technology Transfer Seed Grant Program JHUBSPH

Principal Investigator and Funding Level (DJS salary only)

Myself 0% $10,000 over 1 year

Main Grant Objective

The goal is to bring a urine-based malaria diagnostic test to the homes of parents unable to travel with a sick child to get a malaria blood test. This will provide a true home based kit for the early detection of malaria to facilitate access to treatment. A partnership was formed with Binax corporation to pilot a true dipstick test for malaria diagnosis. The test detects malaria specific proteins in urine.

Principal Responsibilities Supervise and direct laboratory

12. Grant title

"EVALUATION OF THE NEW URINE MALARIA DIPSTICK TEST IN PEMBA" 2005-2006 JHU BSPH Faculty Research Initiative Fund

Principal Investigator and Funding Level (DJS salary only)

CoPI with Sunil Sazawal 0% $50,000 over 1 year

Main Grant Objective

The first ever urine-based malaria diagnosis test has been developed at JHUBSPH and initial feasibility tested in Macha, Zambia this past spring. At present increasing malaria drug resistance and use of the more expensive, less safe, artemisinin combination drugs increase the necessity of an accessible, accurate diagnosis of malaria. For multi-factorial reasons more than 80% of the 515 million people diagnosed with malaria each year lack a laboratory diagnosis and receive treatment on a clinical diagnosis alone. Numerous studies have also documented accuracy of clinical malaria diagnosis to be 50% or less. At present all malaria laboratory tests involve obtaining blood. The long-term objective is to increase the accessibility and availability of a simple nonblood test for malaria to the homes and rural clinics of malaria patients. The hypothesis is that urine diagnosis of malaria will be sensitive and specific. The specific aims are 1) to compare a more sensitive version of the malaria urine dipstick in blood film confirmed cases of both symptomatic and asymptomatic patients and 2) to compare the specificity in both symptomatic and asymptomatic malaria patients. The research design is a prospective observational malaria field substudy that will be nested within the large ongoing zinc supplementation trial on Pemba Island. The significance of development and validation of a urine-based

malaria diagnostic will be an increase accurate diagnosis and effective treatment of malaria, which will decrease malaria disease.

Principal Responsibilities Supervise and direct laboratory

13. Grant title

MICROSATELLITE DYNAMICS OF P. FALCIPARUM POPULATION DIVERSITY IN PEMBAN CHILDREN: IMPLICATIONS FOR ACQUIRED IMMUNITY. 2005-2006 JHU BSPH MRI

Principal Investigator and Funding Level (DJS salary only)

CoPI with Sunil Sazawal 10% $100,000 over 1 year

Main Grant Objective

This grant proposal will investigate by microsatellite analysis the dynamics of *P. falciparum* population diversity that result in severe malaria disease in children on Pemba Island, Tanzania-an area with holoendemic malaria. The study is nested within a large ongoing zinc supplementation trial enrolling 40,000 children with follow up for more than 3 years on Pemba Island. (PI Bob Black and Co-PI Sunil Sazawal, International Health). As part of this trial all clinical malaria information, hospitalizations and malaria slide counts on all children are available for all of this 3-year period. This proposal takes advantage of this investment to investigate the following:
Hypothesis 1 is that naturally acquired immunity as measured by malaria morbidity and mortality is a function of parasite genotype exposure, and/or the genetic distance between these genotypes over time. The specific aim is to analyze *P. falciparum* microsatellite data from blood samples collected a) in case control sets from the main study grouped by severe, mild and no disease and b) from individual children, age 3-12 months, in a prospective sequential bi-weekly fashion over one year in two cohorts of 6 months each. The research design is a prospective observational malaria field study combined with molecular laboratory microsatellite population genetics. Pemba Island with its high transmission intensity, relative geographic isolation, and a history of a recent bottleneck for *P. falciparum* population diversity create an optimal environment for this investigation. The significance of the project is not only to understand the biological correlates of malaria immunity, but also to establish a method for monitoring parasite population dynamics in the context of disease control interventions like vaccines, insect control or chemotherapy.

Principal Responsibilities Supervise and direct laboratory

14. Grant title

"MATRIX METALLOPROTEINASES IN CEREBRAL MALARIA" 2005-2006 BSPH MRI

Principal Investigator and Funding Level (DJS salary only)

PI Kathy Conant 5% $100,000 over 1 year

Main Grant Objective

In cerebral malaria, severe clinical disease has been associated with the sequestration of infected red blood cells (RBCs) in post-capillary venules. Other associated changes include activation and altered permeability of the blood brain barrier (BBB). Such changes may in turn affect proximal cells of the brain parenchyma through mechanisms that include the facilitated ingress of CNS derived toxins. Nonetheless, a

full understanding of the causes and consequences of malarial-induced changes in the brain vasculature is lacking. One class of proteins that might be upregulated by adhesive interactions, and might in turn play a role in disease pathogenesis, is the matrix metalloproteinases (MMPs). These enzymes can affect BBB permeability via their ability to degrade basement membrane proteins. MMPs might also activate endothelial cells via the recently described ability of at least one family member to act on a receptor for thrombin (proteinase activated receptor-1). Moreover, through their ability to degrade matrix proteins that support cell survival, as well as their ability to act on soluble molecules and cell surface receptors, MMPs can be significantly cytotoxic.

In the present proposal, we plan to test the hypothesis that interactions between infected RBCs (IRBCs) and bystander cells may stimulate the release of specific MMPs. In addition, we plan to test the hypothesis that such release follows from the engagement of select adhesion molecules and/or toll like receptors. More specifically, we will examine the ability of antagonists to ICAM-1, αvβ3, β1 integrins, and TLR-9 to block IRBC and hemozoin associated MMP release from leukocytes and endothelial cells. IRBCs may interact with both cell types, and when activated, both cell types can release MMPs. Moreover, T cells have been shown to play a pivotal role in the increased BBB permeability that occurs with murine malaria (*Plasmodium berghei* ANKA). In the present proposal we also plan to examine the possibility that MMPs play a role in the pathogenesis of cerebral malaria in a murine model. In planned experiments, MMP inhibitors will be tested for their ability to ameliorate CNS pathology.
Principal Responsibilities Supervise and direct laboratory

15. Grant title PI David Sullivan

Mapping Malaria Control for Clinical, Operation and Health Services Research NIH Fogarty Program Title: Planning Grants for International Malaria Clinical, Operational and Health Services Research Training Programs (D71) PAR-06-070 Mapping Malaria Control for Clinical, Operational and Health Services Research Training Grant in support of the Presidential Malaria Initiative in Zambia

Main Grant Objective

Our hypothesis is that a working dynamic geographic-based mapping and information system will enable the integration of malaria control efforts and epidemiological data to guide management of the disease and its impact at local and countrywide levels.

The specific aims are: 1) to improve technological gaps which affect accurate data acquisition; 2) to identify and demonstrate the use of mapping to acquire and analyse specific activities that constitute the various arms of malaria management and control, particularly involving community participation and health delivery systems.3) to use maps in order to assess effect and integrate malaria control activities where various agencies are involved; 4) to produce a cadre of trained personnel familiar with geographical spatial analysis, with the ability to integrate data collected from a variety of sources within the program areas that will be used for optimization of control and health management activities and effective planning of operations to sustain the programs; 5) to publicise the importance of these trained personnel and encourage governments to provide adequate career opportunities that will help ensure sustainability.

The planning grant will be used to organize a series of meetings in Zambia including principle partnerships already working in the country, to consult with WHO/AFRO personnel, WHO/INT and the MARA/Malaria Atlas Project in Africa to develop curricula that will meet these above objectives and to develop instructional instruments that will be used in the training programs.

Principal Responsibilities
Organize meeting and write training grant

16. Grant No. 48027(PI West) 01/01/09-12/31/09
Global Health Program of the Bill & Melinda Gates Foundation 12,043,426.00
Ancillary Benefits of Mass Treatment with Azithromycin in Trachoma endemic communities in Tanzania

Main Grant Objective

Evaluation of malaria, pneumonia, STD and diarrhea in communities treated with azithromycin for trachoma.

Principal Responsibilities
Onsite training in malariametric survey in Tanzania and laboratory supervision of PCR detection of *Plasmodium falciparum* with identification of drug resistant genes.

Training Grant Participation

1. 2000-2005 Malaria Research and Training Program in Zimbabwe NIH-Fogarty Center Nirbhay Kumar PI 2% funding

Main Grant Objective

The Malaria Research and Training Program in Zimbabwe (MRTPZ) linked the research and educational opportunities of the Molecular Microbiology and Immunology (MMI) Department of the Johns Hopkins School of Public Health with the internationally known Blair Research Institute (BRI) and the Biomedical Research and Training Institute (BRTI) for the purpose of invigorating the existing malaria prevention and control infrastructure of Zimbabwe. The long term objective will be to fortify and sustain a center of excellence in an African malaria endemic setting. The MRTPZ will knit comprehensive research training of two predoctoral and two masters level students at JHU MMI with home country education training in immunologic aspects of malaria transmission control, characterization of drug resistance patterns, vector control strategies, community involvement in malaria control and research methods training.

Principal Responsibilities

Train individuals here in laboratory research(PhD-Davison Sangweme and Godfree Mlambo-rotation students and thesis advisor and Nokuhle Mtombeni - Master Science to University of Witwatersrand South Africa) and travel to Zimbabwe to give 2-3 week course on “Malaria Chemotherapy and Resistance” June 2004

2. 1998- Training in the Molecular and Cellular Basis of Infectious Diseases(Diane Griffin, PI)
3. 1999- Infectious Diseases Training Program (Cynthia Sears, PI)
4. 2002- Pediatric Infectious Diseases Training Program (Kwan Sik Kim, PI)

5. "Malaria Training and Research Capacity Building in Southern Africa" in Zambia NIH-Fogarty Center Nirbhay Kumar PI 2% funding one year.

Main Grant Objective

The goal of this training grant is to create a center of excellence for malaria research in Southern Africa. It supports training workshops and the training of Master's and PhD students in the field of malaria in Zimbabwe and will extend the research and training to Zambia and neighboring Southern African countries.

Principal Responsibilities

Training in malaria drugs and online malaria course

ACADEMIC SERVICE

Division

MMI Dept.-Admissions Committee 1999-2003
MMI/ID Departmental seminar organizer for 2002/2003 and 2003/2004
MMI Dept Committee on Graduate Program
MMI Dept Committee on Appointments and Promotions
Mentor for Postdoctoral Malaria History candidate
Malaria Research Institute

Meeting regularly for the Malaria Research Institute planning
Member Steering Committee since before creation of Malaria Research Institute.
Facilitator of translation to malaria work of many Hopkins researchers.
Chairman of Molecular Biology of Malaria search committee while participating in seminars and hiring of other faculty candidates with weekly meetings for seminars and chalk talks on almost all prospective faculty candidates for over more than a year
Planning of annual yearly JHU BSPH International (3) and local (2) malaria meetings 2002-6.
Macha Malaria Human Clinical Studies Committee.
Planning committee of Research Advances in Malaria Cell Biology Meeting May 2009.

School

MMI Faculty Senate Appointment JHSPH 1999-2000
Academics Ethics Committee for BSPH 2001-2004
Fulbright Campus Committee review of MPH-BSPH applications 2007
Fulbright Campus Committee review of MPH-BSPH applications 2008
JHSPH Honors & Awards Committee 2008

University

Clinical Appointment in Division of Infectious Diseases
with part-time substitute on ID consult service approximately 1-2 weeks per year on average
Department liason to JHU Institute for Clinical and Translational Research (ICTR) 2007-2009
Biomedical Scholars program JHU internal review board-PEW, SEARLE, Burroughs Wellcome. 2008

PRESENTATIONS

Meetings

Molecular Parasitology Meeting, MBL, Woods Hole, MA 1998
"Characterization of the Plasmodium falciparum iron transporter NRAMP hommologue"

International Symposium-Munster, Germany- "Biochemical Principles And Mechanisms Of Biosynthesis And Biodegradation Of Polymers" Jun 3-6 1998.

Burroughs Wellcome Fund Career Awards Meeting July 22-24 1999 Coronado, CA

Molecular Parasitology Meeting, MBL, Woods Hole, MA Sept.1999
1)Talk Sullivan DJ, Shi L and Chen MJ "Comparison Of Malarial Pigment, Schistosomal Pigment And Beta-Hematin: Heme Polymers With Different Tertiary Structures."
2)Poster Iyer JK and Sullivan DJ "The Inhibition of *P. falciparum* Heme Polymerization By Erythrocytic Zinc Protoporphyrin IX"
3)Poster Gauthier JD, Shi L, Rivarola M and Sullivan DJ "Analysis Of The *P. falciparum* Iron Transporter NRAMP Homologue"

American Society Tropical Medicine and Hygiene, Washington DC 1999 Poster of abstract 1 and 2 above.

Molecular Parasitology Meeting, MBL, Woods Hole, MA 2000 "*P. falciparum* Histidine rich proteins"

Pew Scholars Annual Meeting Costa Rica March 2001 "Iron metabolism In Plasmodium falciparum"

Molecular Parasitology Meeting, MBL, Woods Hole, MA 2001 ***cancelled Sept 2001***
Abstract- The Disposition Of Iron By The P. falciparum Divalent Metal Transporter Homologue
Abstract- The Role Of A *P. falciparum* Copper ATPase Transporter Homologue In The Detoxification Of Oxygen Radical Production By Re-active Copper.

Pew Scholars Annual Meeting Peurto Vallarta March 2002 "The Structure of Heme Crystals"

Molecular Parasitology Meeting, MBL, Woods Hole, MA Sept 2002
Abstract- "A structural comparison of hemozoin crystals from *Plasmodium falciparum, P. vivax, P. ovale, P. malariae* to the mouse bird and Primate *Plasmodium"*
Abstract- "The biochemistry of reactive copper in *Plasmodium falciparum"*.
Abstract-"Rapid assay of hemozoin formation reveals reversible inhibition and identifies the cytochrome P450 inhibitor class".

Pew Scholars Annual Meeting Grand Bahama Island March 2003 “Malaria Metal Metabolomics”

International Bioiron 2003 May Washington DC Talk “The Unique Process Of Heme Crystallization Is A Method Or Iron Sequestration In Plasmodium That Is Vulnerable To Chemotherapy By The Quinolines” Poster “Reversible Inihibition Of Heme Crystallization By Antimalarials And Other Compounds: Implications For Drug Discovery.” And poster “The *P. Falciparum* Iron Pathway Characterized By The Divalent Metal Transporter Homologue.”

Pew Scholars Annual Meeting Peurto Rico March 2004 “Metal Metabolism In *Plasmodium falciparum”*

Molecular Parasitology Meeting, MBL, Woods Hole, MA 2004
1. “Metablomic analysis of uninfected and plasmodium falciparum infected erythrocytes in the absence and presence of antimalarials and metal chelators”
2. “Development of an in vitro human blood brain barrier model to study molecular changes during cerebral malaria”
3. “Chloroquine-resistant berghei forms and effluxes hemozoin”

Zambia-JHU Malaria meeting Jan 2005 Lusaka Zambia “Malaria Diagnosis”

Molecular Parasitology Meeting, MBL, Woods Hole, MA 2005
1.“Neutral Lipid Nanospheres in *Plasmodium falciparum* digestive vacuoles mediate heme crystallization”
2. “Soluble And Membrane Associated *P. falciaprum* Factors Induce ICAM-1 Expression On Human Brain Endothelium And Is NF Kappa B Dependent”
3. “Plasmodium infected erythrocytes affect BBB integrity: decreased electrical resistance in human brain microvascular endothelial cell monolayers”

American Society of Tropical Medicine and Hygiene Dec 2005 Washington DC
Invited CoChair two sessions-
88. American Committee of Molecular, Cellular and Immunoparasitology (ACMCIP) - Cellular Parasitology II and
100. Malaria - Diagnosis
Invited Talk
“Neutral lipid microspheres in *P. falciparum* digestive vacuoles mediate heme crystallization”
Invited Poster “Feasibility of urine diagnosis for *Plasmodium falciparum*”
CoPI for Talks from labwork
“*Plasmodium* infected erythrocytes activate human brain microvascular endothelial cells”
“Laser Desorption Mass Spectrometric Detection of Malaria Hemozoin in Human Clinical Samples”
“Elevated choline phosphate - a biomarker for in vivo malaria parasite detection by mass spectrometry”

"Soluble and Membrane Associated P. falciparum Factors Induce ICAM-1 Expression on Human Brain Endothelium through NFκb"
"Development of a rapid, accurate, low-cost malaria screening assay for epidemiologic and clinical applications"
CoPI poster "Genotyping of *Plasmodium falciparum* malaria by PCR on urine and saliva samples"

American Society of Tropical Medicine and Hygiene Nov 2006 Atlanta, GA
Symposium Organizer
11. Malaria Pigment: Biology, Antimalarial Inhibition and Malaria Immunopathogenesis
Speaker
Assays for In Vitro Heme Biocrystallization and New Antimalarial Drug Discovery
Poster Co PI
Activation of human blood brain barrier endothelium in Cerebral Malaria

Molecular Parasitology Meeting, MBL, Woods Hole, MA 2007
Poster Plasmodium falciparum Infected Erythrocytes Induces Hypoxia Like Global Gene Expression In Cerebral Endothelial Cells
Talk Changes In Global Metabolites Of Plasmodium Falciparum With Erythrocyte Development And Antimalarial Drugs

American Society of Tropical Medicine and Hygiene Nov 2007 Philadelphia, PA
Symposium Organizer
87. Cerebral Malaria: Parasite Signaling Across Blood Brain Barrier to Neuronal Dysfunction
Oral Presentation
(961) Efficacy of pyrvinium pamoate against Cryptosporidium parvum infection in vitro and in a neonatal mouse model

NYAS and JHMRI "Progress against Malaria: Developments on the Horizon" 2007
A Urine Dipstick for Malaria Diagnosis

Molecular Parasitology Meeting, MBL, Woods Hole, MA September **2008**

1. Causal anti-Plasmodium Activity of Isoniazid
2. Antimalarial action of Gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor.
3. Metabolic analysis of glycolysis, gluconeogenesis, and citric acid pathways for erythrocytes infected with ring and trophozoite stages of *Plasmodium falciparum*.

American Society of Tropical Medicine and Hygiene Dec **2008** New Orleans, LA
Antimalarial action of Gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor.

Invited Seminars

Brookhaven National Laboratory, Dept. of Biology. Departmental seminar "Heme Polymers" 1998

Laboratory of Parasitic Diseases, NIH, Bethesda, MD Departmental seminar "Inhibition of heme polymerization by the quinolines"1998

Munster, Germany The *Plasmodium* Heme Problem: Polymerization and inhibition by the quinolines within Symposium on "Biochemical Priniciples and Mechanisms of Biosynthesis and Biodegradation of Polymers" 1998

Georgetown University Biochemistry Dept seminar "Quinolines and hemozoin" 1999

Washington University Molecular Microbiology seminar "Metals and *Plasmodium*" 1999

Molecular Parasitology Meeting, MBL, Woods Hole, MA 1999"Comparison Of Malarial Pigment, Schistosomal Pigment And Beta-Hematin: Heme Polymers With Different Tertiary Structures."

Helminthological Society of Washington 'Hemozoin Crystals from Worms to Malaria'

University of Virginia Bioinformatics Institute, Blacksburg VA

University of Texas San Antonio- Microbiology department seminar series 2001

Medical Grand Rounds at Johns Hopkins- Clinical case presentation and update in malaria research. 2001

Tropical Medicine Dinner Club St. Louis-"Hemozoin" 2001

Costa Rica Pew Scholars Career Award annual meeting" Heme crystallization" 2001
Washington DC International BioIron "The Unique Process Heme Crystallization Is A Method Of Iron Sequestration In Plasmodium That Is Vulnerable To Chemotherapy By The Quinolines".

Harvard Institute of Proteomics *Plasmodium falciparum* Full Length Expression-Ready Gene (FLEXGENE) 2002

JHU Peds ID Microbiology Pathogenesis Interest Group MPIG

- 2003 "Malaria Metal Toxicity"
- 2004 "Placental Malaria And Mother To Child Transmission Of HIV In Rakai, Uganda"
- 2005 "Neutral Lipid Nanospheres Mediate Heme Crystallization"
- 2006 "Astemizole And Malaria Clinical Drug Library Screening"
- 2007-"Cerebral Malaria:Bedside to Bench"

Puerto Rico Pew Scholars Career Award annual meeting" Heme Crystallization" 2004

National Association of Black Journalists at WHO headquarters NY "Malaria" 2006

WRAIR Division Scientific meeting "Activity of FDA approved drugs against intraerythrocytic *Plasmodium falciparum*" 2006

Severe Malaria: Pathogenesis and Intervention Strategies, Nobel Forum, Karolinska Institutet and NYAS, Stockholm, Sweden- "Cerebral Malaria Changes Human Brain Endothelium Independent of Parasite Attachment" 2007

American Association of Pharmaceutical Scientists (AAPS) Annual Meeting San Diego, CA HOT TOPIC "Orphan Drug Discovery and Development"- 2007

Iron and Malaria- Interactions and Interventions: Where are we now and where do we go from here? Technical Working Group NICHD/NIH 24 April **2008** Rockville, Maryland "Plasmodium iron metabolism"

2nd World Conference on Magic Bullets (Ehrlich II) Nürnberg, Germany October 3-5, **2008** "Plasmodium Heme Crystallization: Methylene Blue and the Quinolines"

2nd Annual Collaborative Drug Discovery (CDD) - UCSF Community Meeting for Neglected Disease, Commercial and Orphan Drug Research San Francisco, CA October 7, **2008** "Repurposing Approved Clinical Drugs for Protozoan Diseases"

ADDITIONAL INFORMATION

Personal Statement Of Research

Malaria is a "stealer of dreams" for most of Africa, which bears the brunt of more than 80% morbidity and mortality from this protozoan disease. I treated my first malaria patient as an intern at Washington University in 1988 and have been focused on this pathogen since that time. My main research interest in malaria, has been the *molecular* biology of metals and how the quinolines interfere with heme iron sequestration into heme crystals called hemozoin. The laboratory is also investigating the *Plasmodium* biology of copper and zinc. Present and developing work includes new uses for existing drugs with creation of a library of more than 1,800 FDA approved drugs for which we have screened for antimalarial *cellular* activity. Two additional *organismal* areas include the pathogenesis of cerebral malaria with a coincubation of *P. falciparum* with a human brain endothelial model in order to study effects on endothelium and the pathogenesis of mother to child transmission of HIV in the setting of placental malaria. On the *population* level, the laboratory is investigating new malaria diagnostics based on detection of hemozoin in the blood by laser desorption mass spectrometry and also detection of malaria proteins and DNA in the urine. The population dynamics of acquisition of immunity followed by microsatellites in young children in malaria endemic areas is also being explored. My training in adult infectious diseases/internal medicine also has enabled other interactions within the department with HIV and TB researchers as well as teaching in tropical medicine and malaria schoolwide.

I consider my most important potential contributions to field are collaborating directly with fellow Johns Hopkins scientists to study malaria via the MRI: 1) Jun Liu (pharmacology) with FDA library construction and methione aminopeptidase inhibitors, 2) Peter Scholl (Envir. Health Sci.) and Phil Thuma (Macha, Zambia) with human malaria urine test, 3) Heena Brahmbhatt, Ron Gray (Pop. and Family Heath, IH) and Fred Askin (Surg Path) with interaction of HIV and placental malaria on MTCT, 4) Monique Stins (Ped Inf Dis) Human blood brain barrier model of cerebral malaria, 5) Andrew Feldman and Plamen Demirev (APL) on mass spectrometric malaria detection by hemozoin 6) Sunil Sazawal and Thomas Jaenisch (IH) with population dynamics of acquired malaria immunity in the malaria endemic island of Pemba, 7) Vladimir Shulaev (VBI) with metablomic characterization of the Plasmodium parasite with a present focus on lipids.

KEYWORDS

Malaria, *Plasmodium falciparum,* Quinoline anti malarials, Iron metabolism, Zinc, Histidine-rich proteins, Natural resistance associated macrophage protein - NRAMP, iron transport hemozoin, drugs, diagnosis, HIV, placental malaria.