Grant Application Package

GRANTS.GOV™

Opportunity Title:	Evolution of Infectious Diseases (R01)
Offering Agency:	National Institutes of Health
CFDA Number:	93.859
CFDA Description:	Biomedical Research and Research Training
Opportunity Number:	PA-07-130
Competition ID:	ADOBE-FORMS-A
Opportunity Open Date:	12/05/2008
Opportunity Close Date:	01/07/2011
Agency Contact:	Grants Info TTY 301-451-0088 E-mail: GrantsInfo@nih.gov Phone: 301-435-0714

This electronic grants application is intended to be used to apply for the specific Federal funding opportunity referenced here.

If the Federal funding opportunity listed is not the opportunity for which you want to apply, close this application package by clicking on the "Cancel" button at the top of this screen. You will then need to locate the correct Federal funding opportunity, download its application and then apply.

This opportunity is only open to organizations, applicants who are submitting grant applications on behalf of a company, state, local or tribal government, academia, or other type of organization.

*** Application Filing Name:** Hammer/Lansing/Karafet/Watkins R01

Mandatory Documents

Move Form to Complete

Move Form to Delete

Mandatory Documents for Submission

- SF424 (R & R)
- Research & Related Senior/Key Person Profile (E
- Research & Related Other Project Information
- Research & Related Project/Performance Site Loc
- PHS 398 Cover Page Supplement
- PHS 398 Research Plan
- PHS 398 Checklist

Optional Documents

- PHS 398 Modular Budget

Move Form to Submission List

Move Form to Delete

Optional Documents for Submission

- PHS 398 Cover Letter File
- Research & Related Budget
- R & R Subaward Budget Attachment(s) Form

Instructions

1 **Enter a name for the application in the Application Filing Name field.**

- This application can be completed in its entirety offline; however, you will need to login to the Grants.gov website during the submission process.
- You can save your application at any time by clicking the "Save" button at the top of your screen.
- The "Save & Submit" button will not be functional until all required data fields in the application are completed and you clicked on the "Check Package for Errors" button and confirmed all data required data fields are completed.

2 **Open and complete all of the documents listed in the "Mandatory Documents" box. Complete the SF-424 form first.**

- It is recommended that the SF-424 form be the first form completed for the application package. Data entered on the SF-424 will populate data fields in other mandatory and optional forms and the user cannot enter data in these fields.

- The forms listed in the "Mandatory Documents" box and "Optional Documents" may be predefined forms, such as SF-424, forms where a document needs to be attached, such as the Project Narrative or a combination of both. "Mandatory Documents" are required for this application. "Optional Documents" can be used to provide additional support for this application or may be required for specific types of grant activity. Reference the application package instructions for more information regarding "Optional Documents".

- To open and complete a form, simply click on the form's name to select the item and then click on the => button. This will move the document to the appropriate "Documents for Submission" box and the form will be automatically added to your application package. To view the form, scroll down the screen or select the form name and click on the "Open Form" button to begin completing the required data fields. To remove a form/document from the "Documents for Submission" box, click the document name to select it, and then click the <= button. This will return the form/document to the "Mandatory Documents" or "Optional Documents" box.

- All documents listed in the "Mandatory Documents" box must be moved to the "Mandatory Documents for Submission" box. When you open a required form, the fields which must be completed are highlighted in yellow with a red border. Optional fields and completed fields are displayed in white. If you enter invalid or incomplete information in a field, you will receive an error message.

3 **Click the "Save & Submit" button to submit your application to Grants.gov.**

- Once you have properly completed all required documents and attached any required or optional documentation, save the completed application by clicking on the "Save" button.
- Click on the "Check Package for Errors" button to ensure that you have completed all required data fields. Correct any errors or if none are found, save the application package.
- The "Save & Submit" button will become active; click on the "Save & Submit" button to begin the application submission process.
- You will be taken to the applicant login page to enter your Grants.gov username and password. Follow all onscreen instructions for submission.

APPLICATION FOR FEDERAL ASSISTANCE

SF 424 (R&R)

2. DATE SUBMITTED	Applicant Identifier
3. DATE RECEIVED BY STATE	**State Application Identifier**

1. * TYPE OF SUBMISSION

☐ Pre-application ☒ Application ☐ Changed/Corrected Application

4. Federal Identifier

5. APPLICANT INFORMATION

*** Organizational DUNS:** 806345617

* Legal Name: Arizona Board of Regents, University of Arizona

Department: Division:

* Street1: PO Box 3308

Street2:

* City: Tucson County:

* State: AZ: Arizona Province:

* Country: USA: UNITED STATES * ZIP / Postal Code: 85722-3308

Person to be contacted on matters involving this application

Prefix: * First Name: Sherry Middle Name:

* Last Name: Esham Suffix:

* Phone Number: (520) 626-6000 Fax Number:

Email: sponsor@u.arizona.edu

6. * EMPLOYER IDENTIFICATION *(EIN) or (TIN):* 74-2652689

7. * TYPE OF APPLICANT: H: Public/State Controlled Institution of Higher Education

Other (Specify):

Small Business Organization Type ☐ Women Owned ☐ Socially and Economically Disadvantaged

8. * TYPE OF APPLICATION:

☒ New ☐ Resubmission

☐ Renewal ☐ Continuation ☐ Revision

If Revision, mark appropriate box(es).

☐ A. Increase Award ☐ B. Decrease Award ☐ C. Increase Duration ☐ D. Decrease Duration

☐ E. Other (specify):

* Is this application being submitted to other agencies? Yes ☐ No ☒ What other Agencies?

9. * NAME OF FEDERAL AGENCY: National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER: 93.859

TITLE: Biomedical Research and Research Training

11. * DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:

Multi-Scale Coevolution of Infectious Diseases and Human Populations in the Indonesian Archipelago

12. * AREAS AFFECTED BY PROJECT *(cities, counties, states, etc.)*

N/A

13. PROPOSED PROJECT:

* Start Date: 04/01/2010 * Ending Date: 03/31/2013

14. CONGRESSIONAL DISTRICTS OF:

a. * Applicant: AZ-007 b. * Project: AZ-007

15. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: * First Name: John Middle Name: S

* Last Name: Lansing Suffix: Ph.D.

Position/Title: Professor

* Organization Name: Arizona Board of Regents, University of Arizona

Department: Anthropology Division:

* Street1: PO Box 210030

Street2:

* City: Tucson County:

* State: AZ: Arizona Province:

* Country: USA: UNITED STATES * ZIP / Postal Code: 85721

* Phone Number: (520) 626-2047 Fax Number:

* Email: jlansing@email.arizona.edu

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

16. ESTIMATED PROJECT FUNDING

a. * Total Estimated Project Funding	2,131,816.00
b. * Total Federal & Non-Federal Funds	2,131,816.00
c. * Estimated Program Income	0.00

17. * IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?

a. YES ☐ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ☒ PROGRAM IS NOT COVERED BY E.O. 12372; OR

☐ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

18. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

☒ * I agree

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

19. Authorized Representative

Prefix: | * First Name: Leslie | Middle Name:

* Last Name: Tolbert | Suffix: Ph.D.

* Position/Title: Vice President for Research

* Organization: Arizona Board of Regents, University of Arizona

Department: | Division:

* Street1: PO Box 3308

Street2:

* City: Tucson | County:

* State: AZ: Arizona | Province:

* Country: USA: UNITED STATES | * ZIP / Postal Code: 85722-3308

* Phone Number: (520) 626-6000 | Fax Number:

* Email: sponsor@u.arizona.edu

*** Signature of Authorized Representative**

Completed on submission to Grants.gov

*** Date Signed**

Completed on submission to Grants.gov

20. Pre-application | Add Attachment | Delete Attachment | View Attachment

21. Attach an additional list of Project Congressional Districts if needed.

Addtl Cong Dist.pdf | Add Attachment | Delete Attachment | View Attachment

OMB Number: 4040-0001
Expiration Date: 04/30/2008

NM-003, Santa Fe, NM
00-000, Jakarta, Indonesia

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: | * First Name: John | Middle Name: S

* Last Name: Lansing | Suffix: Ph.D.

Position/Title: Professor | Department: Anthropology

Organization Name: Arizona Board of Regents, University of Arizona | Division:

* Street1: PO Box 210030

Street2:

* City: Tucson | County:

* State: AZ: Arizona | Province:

* Country: USA: UNITED STATES | * Zip / Postal Code: 85721

* Phone Number: (520) 626-2047 | Fax Number:

* E-Mail: jlansing@email.arizona.edu

Credential, e.g., agency login: Lansing

*** Project Role:** PD/PI | **Other Project Role Category:**

***Attach Biographical Sketch** Lansing NIH biosketch.pdf | Add Attachment | Delete Attachment | View Attachment

Attach Current & Pending Support | Add Attachment | Delete Attachment | View Attachment

PROFILE - Senior/Key Person 1

Prefix: | * First Name: Michael | Middle Name:

* Last Name: Hammer | Suffix: PhD

Position/Title: Research Scientist | Department: Arizona Research Laboratories

Organization Name: Arizona Board of Regents, University of Arizona | Division: Biotechnology

* Street1: PO 210106

Street2:

* City: Tucon | County:

* State: AZ: Arizona | Province:

* Country: USA: UNITED STATES | * Zip / Postal Code: 85721

* Phone Number: (520) 621-9828 | Fax Number:

* E-Mail: mfh@email.arizona.edu

Credential, e.g., agency login: hammer

*** Project Role:** PD/PI | **Other Project Role Category:**

***Attach Biographical Sketch** Hammer_Biosketch.pdf | Add Attachment | Delete Attachment | View Attachment

Attach Current & Pending Support | Add Attachment | Delete Attachment | View Attachment

Delete Entry | Next Person

OMB Number: 4040-0001
Expiration Date: 04/30/2008

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Lansing, J. Stephen	Professor of Anthropology, University of Arizona Professor, Santa Fe Institute
eRA COMMONS USER NAME (credential, e.g., agency login)	
Lansing	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Wesleyan University, Middletown CT	B.A. (magna)	1972	Social Science
University of Michigan	M.A.	1974	Anthropology
University of Michigan	Ph.D.	1977	Anthropology

A. Positions and Honors. List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

1976 Doctoral Fellow, The Institute for Advanced Study, Princeton
1977 Assistant Professor of Anthropology, University of Southern California
1983 Associate Professor of Anthropology, University of Southern California
1986 Fulbright Senior Regional Research Fellow
1987-92 Chair, Department of Anthropology, University of Southern California
1990-6 Professor, University of Southern California
1995 J.I. Staley Book Prize ($7500) of the School of American Research
1995-8 Professor of Anthropology and Environment, University of Michigan
1997 University of Michigan Excellence in Research award
1998 Professor of Anthropology, University of Arizona
2000 Fellow, Center for Advanced Study in the Behavioral Sciences, Stanford
2002 Professor of Ecology & Evolutionary Biology, University of Arizona
2007 Julian Steward Book Prize for *Perfect Order*
2007 Winifred Jean Stubbs Fellow, Institute for Advanced Study, Durham University
2008- Senior Research Fellow, Stockholm Resilience Centre

B. Selected peer-reviewed publications (2000-2009)

Scarborough, Vernon L., John W. Schoenfelder and J. Stephen Lansing. 2000. "Early Statecraft on Bali: The Water Temple Complex and the Decentralization of the Political Economy". *Research in Economic Anthropology*, Vol. 20: 299-330.

Scarborough, Vernon L., John W. Schoenfelder, and J. Stephen Lansing Ancient Water Management and Landscape Transformation at Sebatu, Bali. 2000. *Bulletin of the Indo-Pacific Prehistory Association*_20: 79-92.

Lansing, J. Stephen, Vanda Gerhart, James N. Kremer , Patricia Kremer, Alit Arthawiguna, Suprapto, Ida Bagus Suryawan, I Gusti Arsana, Vernon L.Scarborough and Kimberly Mikita. 2001. "Volcanic Fertilization of Balinese Rice Paddies", *Ecological Economics* 38 (2001):383-390.

Lansing, J. Stephen. 2002. "'Artificial Societies' and the Social Sciences", Santa Fe Institute Working Papers and *Artificial Life* 8 (Oct. 2002): 279-292.

Lansing, J. Stephen. 2002. "Irrigation Societies", *International Encyclopedia of Social and Behavioral Sciences*, Elsevier Science Ltd., Oxford, 7910-7913

Lansing, J. Stephen. 2003. "Complex Adaptive Systems", *Annual Review of Anthropology* 32: 183-204.

Lansing, J. Stephen. 2003. "The Cognitive Machinery of Power: Reflections on Valeri's *Forest of Taboos*", *American Ethnologist,* August 2003

Lansing, J. Stephen 2004. "Blood is not the only social bond", *The Times Higher Education Supplement*, Dec. 3, 2004.

Lansing, J.S., A.J. Redd, T.M. Karafet, J. Watkins, I.W. Ardika, S.P.K. Surata, J.W. Schoenfelder, M. Campbell, A.M. Merriwether, and M.F. Hammer. An Indian Trader in Ancient Bali? Antiquity 78:300 (2004): 287-293.

Lansing, J. Stephen. 2005. On Irrigation and the Balinese State. *Current Anthropology* 46 (2):305-6.

Lansing, J. Stephen and John H. Miller. 2005. Cooperation Games and Ecological Feedback: Some Insights from Bali. *Current Anthropology* 46(2): 328-334.

Lansing, J. Stephen and Robert L. Axtell. *Afterword* to *Nonlinear Models for Archaeology and Anthropology: Continuing the Revolution*, edited by Christopher S. Beekman and William W. Baden. Ashgate Press, 2005: 139-146.

Karafet,T.M., J. S. Lansing, Alan J. Redd, Joseph Watkins, I. W. Ardika, S. P.K. Surata, Laura Mayer, Michael Bamshad, Lynn Jorde, Michael F. Hammer. A Balinese Y chromosome perspective on the peopling of Indonesia: Genetic contributions from pre-Neolithic hunter-gatherers, Austronesian farmers, and Indian traders. *Human Biology*, Feb. 2005, v. 77 no. 1, pp.93-114.

Lansing, J. Stephen, John Schoenfelder and Vernon Scarborough. Rappaport's Rose: Structure, Agency and Historical Contingency in Ecological Anthropology. In Biersack A. and Greenberg J.B., ed., Reimagining Political Ecology. Durham & London: Duke University Press, 2006: 325-358.

Lansing, J. Stephen, *Perfect Order: Recognizing Complexity in Bali.* Princeton University Press, 2006.

Lansing, J. Stephen, *Priests and Programmers: Technologies of Power in the Engineered Landscape of Bali.* Princeton University Press, 1991. Revised 2nd edition 2007.

Cox, Murray P., Alan J. Redd, Tatiana M. Karafet, Christine A. Ponder, J. Stephen Lansing, Herawati Sudoyo and Michael F. Hammer. 2007. A Polynesian motif on the Y chromosome: population structure in remote Oceania. Human Biology, October 2007, v. 79, no. 5, pp. 525–535.

Lansing, J. Stephen, Murray P. Cox, Sean S. Downey, Brandon M. Gabler, Brian Hallmark, Tatiana M. Karafet, Peter Norquest, John W. Schoenfelder, Herawati Sudoyo, Joseph C. Watkins, and Michael F. Hammer. 2007. Coevolution of languages and genes on the island of Sumba, eastern Indonesia. *Proc Natl Acad Sci USA* 104 (41): 16022-16026.

Sean S. Downey , Brian Hallmark, Murray P. Cox , Peter Norquest, and J. Stephen Lansing. Computational Feature-Sensitive Reconstruction of Language Relationships: Developing the ALINE Distance for Comparative Historical Linguistic Reconstruction. 2008. *Journal of Quantitative Linguistics;Volume* 15; Number 4; pp. 340–369

Lansing, J. Stephen, Tatiana M. Karafet, John Schoenfelder, and Michael F. Hammer. 2008. A DNA signature for the expansion of irrigation in Bali? In Sanchez-Mazas A, Blench R, Ross M, Peiros I, & Lin M (eds), Past Human Migrations in East Asia and Taiwan: matching archaeology, linguistics and genetics. London: Routledge, 376-394.

Lansing, J. Stephen, Sean S. Downey, Marco Jannsen, John Schoenfelder. A Robust Budding Model of Balinese Water Temple Networks. *World Archaeology* 2009,Vol. 41(1): 112–133.

C. Research Support.

SES-0725470 Lansing (PI) 09/15/07–08/31/10
National Science Foundation
HSD: Anthropological Modeling of Social Structure, Genetics, and Language Speciation in Indonesia
The goals of this project are to collect genetic, linguistic, demographic, environmental, medical and ethnographic data from villages in the Indonesian archipelago, to use non-coding genetic markers to study the emergence of patterns of relatedness among individuals within communities, and to investigate how community-scale historical processes produce patterns of human sociality, languages and disease prevalence.

SES-0432262 Lansing (PI) 09/2006 - 08/2007
National Science Foundation
Austronesian societies: reading social structure from the genome
The goals of this project were to use genetic markers to investigate the co-evolution of genes, languages and culture, to explore the history of settlement of Indonesia, and the robustness of social structure at the village scale, at first in Bali and later on several other Indonesian islands.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Hammer, Michael F.	Research Scientist, ARL Biotechnology, Dept. Ecology and Evolutionary Biology, Assoc. Professor, Anthropology Dept., University of Arizona
eRA COMMONS USER NAME Hammer	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Lake Forest College, IL	BA	1976	Biology
University of California, Berkeley, CA	PhD	1984	Genetics

A. Positions and Honors.

1978 to 1984 Graduate Student, Biochemistry Department, University of California, Berkeley, with Dr. Allan C. Wilson. Dissertation: "Of Mice and Lysozyme: Evolution and Regulatory Genetics" (1984)

1985 to 1988 Postdoctoral Fellow, Princeton University with Dr. Lee M. Silver
Origin and evolution of mouse *t* haplotypes.

1988 to 1991 Postdoctoral Fellow, Harvard University with Dr. Richard C. Lewontin
The Y chromosome and human evolution.

1991 to present Director of the Genomic Analysis and Technology Core (GATC),
Associate Research Scientist, ARL Division of Biotechnology, University of Arizona, Tucson, Arizona.
Joint appointment in the Department of Ecology and Evolutionary Biology, University of Arizona, Tucson, Arizona (1992)
Faculty member Graduate Interdisciplinary Program in Genetics (1997)
Member of Arizona Cancer Center (1997)
Associate Professor, Anthropology Department, University of Arizona, Tucson, Arizona (1999)
Full Research Scientist, ARL (2002)

1973-1975 Lake Forest College Dean's List
1976 Phi Beta Kappa
1976 Beta Beta Beta
1976 Society of Sigma Xi Commendations in Biology
1978-1983 National Institutes of Health Training Grant GM07127,
1985-1988 National Institutes of Health Postdoctoral Fellowship GM10728,
1988-1990 Alfred P. Sloan Postdoctoral Fellow,

B. Selected peer-reviewed publications (2006- Present).

Redd AJ, VA Contreras, VA Kearney, D Stover, T Karafet, and MF Hammer (2006) Genetic structure among 38 populations from the United States based on 11 U.S. core Y chromosome STRs. *J Foren Sci* **51**:580-585.

Hammer MF, VA Contreras, VA Kearney, D Stover, G Zhang, T Karafet, and Redd AJ (2006) Population structure of Y chromosome SNP haplogroups in the United States and forensic implications for constructing Y chromosome STR databases. *Foren Sci Internat* 164: 45-55.

Hammer MF, Karafet TM, Park H, Omoto K, Harihara S, Stoneking M, and Horai S (2006). Dual origins of the Japanese: common ground for hunter-gatherer and farmer Y chromosomes. *J. Hum. Genet.* **51**: 47-58.

Garrigan DW and MF Hammer. Reconstructing human origins in the genomic era (2006) *Nature Reviews Genetics* **7**, 669-680.

Wall JD, Hammer MF (2006) Archaic admixture in the human genome. *Curr Opin Genet Devel* **16**: 606-610.

Scheinfeldt L, Friedlaender F, Friedlaender J, Latham Krista, Koki G, Karafet T, Hammer MF, Lorenz J (2006) Unexpected NRY chromosome variation in Northern Island Melanesia. *Mol Biol Evol* **23**: 1628-1641.

Chaix R, Quintana-Murci L, Hegay T, Hammer MF, Mobasher Z, Austerlitz F, Heyer E (2007) From social to genetic structures in Central Asia. *Curr Biol* **17**: 43-48

Woerner A, Cox MP, Hammer MF (2007) Recombination-filtered genomic datasets by information maximization. *Bioinformatics* **23**: 1851-1853.

Lansing JS, Cox MP, Downey SS, Hallmark B, Karafet TM, Norquest P, Gabler BM, Schoenfelder JW Sudoyo H, Watkins JC, Hammer MF (2007) Coevolution of languages and genes on the island of Sumba, eastern Indonesia. *Proc Natl Acad Sci USA* **104**: 16022-16026

Cox MP, Redd A, Karafet TM, Ponder CA, Lansing JS, Sudoyo H, Hammer MF (2007) A 'Polynesian Motif' on the Y-Chromosome. *Hum Biol* **79**: 525-535.

Garrigan DW, Kingan SB, Pilkington MM, Wilder JA, Cox MP, Soodyall H, Strassmann BI, Destro-Bisol G, de Knijff P, Novelletto A, Friedlaender J, Hammer MF (2007) Inferring human population sizes, divergence times and rates of gene flow from mitochondrial, X and Y chromosome resequencing data. *Genetics* **177**: 2195-2207.

Pilkington MM, Angui T, Cox MP, Kingan S, Mobasher Z, Batini C, Destro-Bisol G, Soodyall H, Strassmann BI, Hammer MF (2008) Contrasting signatures of population growth for mitochondrial DNA and Y chromosomes among human populations in Africa. *Mol Biol Evol* **25**: 517-525

Cox MP, FL Mendez, TM Karafet MM Pilkington, SB Kingan, G Destro-Bisol, BI Strassmann, MF Hammer (2008) Testing for Archaic Hominin Admixture on the X-Chromosome: Model Likelihoods for the Modern Human *RRM2P4* Region from Summaries of Genealogical Topology under the Structured Coalescent. *Genetics* **178**: 427-437.

Walsh JB, AJ Redd, MF Hammer (2008) Joint match probabilities for Y chromosomal and autosomal markers. *For. Sci. Internat.* **174**: 234-238

Karafet TM, Mendez FL, Meilerman MB, Underhill PA, Zegura SL, Hammer MF (2008) New binary polymorphisms reshape and increase resolution of the human Y chromosomal haplogroup tree. *Genome Res* **18**:830-838

Garrigan D, Hammer MF (2008) Ancient lineages in the genome: a response to Fagundes et al. *Proc Natl Acad Sci U S A*, **105**:E3

Shlush LI, Behar DM, Yudkovsky G, Templeton A, Hadid Y, Basis F, Hammer MF, Itzkovitz S, Skorecki K (2008) The Druze: a population genetic refugium of the Near East. *PLoS ONE*, **3**:e2105-2114

Schlecht J, ME Kaplan, K Barnard, T Karafet, MF Hammer, NC Merchant (2008) Machine-learning approaches for classifying haplogroup from Y chromosome STR data. *PLoS Comp Biol* **4**: e1000093.

Wall JD, Cox MP, Mendez FL, Woerner A, Severson T, Hammer MF (2008) A novel DNA sequence database for analyzing human demographic history. *Genome Res* **18**: 1354-1361.

Hammer MF, Mendez FL, Cox MP, Woerner A, Wall JD (2008) Sex-biased evolutionary forces shape patterns of human diversity. *PLoS Genetics* **4**: e1000202.

Lansing JS, Watkins JC, Hallmark B, Cox MP, Karafet TM, Sudoyo H, Hammer MF (2008) Male dominance rarely skews the frequency distribution of Y chromosome haplotypes in human populations. *Proc Natl Acad Sci USA* **105**: 11645-11650

Cox MP, AE Woerner, JD Wall, MF Hammer (2008) Intergenic DNA sequences from the human X chromosome reveal high rates of global gene flow. *BMC Genetics* **9**: 76-87.

Malhi RS, A Gonzales-Oliver, K B Schroeder, BM Kemp, JA Greenberg, SZ Dobrowski, DG Smith, A Resendez, TM Karafet, MF Hammer, SL Zegura, T Brovko (2008) Distribution of Y chromosomes among Native North Americans: A study of Athapaskan Population History. *Am J Phys Anthropol* **137**: 412-424

Book Chapters (2006-Present)

Karafet TM, SL Zegura, and MF Hammer (2006) Historical peopling of new lands: an ancient link between Asia and Americas. Accepted in Vestnik VOGIS [in Russian].

Karafet TM, SL Zegura, and MF Hammer. Y Chromosome Variation (2006) In: Handbook of North American Indians, vol. 3, Environment, Origins, and Population. E Szathmary (ed.). Smithsonian Institute, Washington, pp 831-839.
Wilder JA, Hammer MF (2007) Extraordinary population structure among the Baining of New Britain. In: Genes, Language and Culture History in the Southwest Pacific, Friedlaender JS (ed) (2007). Oxford University Press, Oxford, pp 199-207.
Scheinfeldt L, Friedlaender F, Friedlaender J, Latham Krista, Koki G, Karafet T, Hammer MF, Lorenz J (2007) Y chromosome variation in Northern Island Melanesia. In: Genes, Language and Culture History in the Southwest Pacific, Friedlaender JS (ed) (2007). Oxford University Press, Oxford, pp 81-95.
Karafet TM, LP Osipova, and MF Hammer (2007) The effect of history and life-style on genetic structure of North Asian populations. In: Sagart L, R Blench, and A Sanchez-Mazas (eds). London and New York: Routledge Curzon=.
Lansing JS, TM Karafet, J Schoenfelder, and MF Hammer (2006) A DNA signature for the expansion of irrigation in Bali. In: Sagart L, R Blench, and A Sanchez-Mazas (eds). London and New York: Routledge Curzon.

C. Research Support.

Ongoing Research Support

BCS-0423123 Hammer (PI) 9/1/04–8/31/09
National Science Foundation (HOMINID)
A Novel Genetic Database for Testing Models of Human Origins
The goal of this project is to formulate and test several models of human evolution, focusing on the questions of ancient population structure, archaïc admixture, and human demography.
Role: Principal Investigator

SES-0725470 Lansing (PI) 09/15/07–08/31/10
National Science Foundation
HSD: Anthropological Modeling of Social Structure, Genetics, and Language Speciation in Indonesia
The goals of this project are to collect genetic, linguistic, demographic, environmental, medical and ethnographic data from villages in the Indonesian archipelago, to use non-coding genetic markers to study the emergence of patterns of relatedness among individuals within communities, and to investigate how community-scale historical processes produce patterns of human sociality, languages and disease prevalence..
Role: Co-Principal Investigator

Technical Support Working Group Hammer (PI) 06/27/06–12/31/09
Global DNA Database for Terrorism Related Identification
The purpose of this effort is to construct a database of Y chromosome and mitochondrial DNA haplotypes for 49 human populations originating between East Africa and Indonesia, and to develop machine learning approaches for predicting the ethnic origin or "genetic ancestry" of individual samples.
Role: Principal Investigator

Completed Research Support

BCS-0509019 Hammer (PI) 8/01/05–7/31/08
National Science Foundation
Collaborative Research on the Genetic Effects of Culture: Y Chromosome DNA, mtDNA, and Patrilineal Kinship in the Dogon of Mali
The goals of this project were to investigate the congruence between culturally recognized patrilineages and genetic patrilines as measured by Y-DNA haplotypes, to test the hypothesis that male members of a patrilineage cooperate with each other through reciprocity mediated kinship, and to explore the role played by menstrual taboos as a cultural practice for ensuring genetic patriliny.
Role: Principal Investigator

BCS 0432262 Lansing (PI) 9/1/04–8/31/07
National Science Foundation

Austronesian Societies: Reading Social Structure from the Genome
The goals of this project were to use genetic markers to investigate the co-evolution of genes, languages and culture, to explore the history of settlement of Indonesia, and the robustness of social structure at the village scale, at first in Bali and later on several other Indonesian islands.
Role: Co-Principal Investigator

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: | * First Name: John | Middle Name: S

* Last Name: Lansing | Suffix: Ph.D.

Position/Title: Professor | Department: Anthropology

Organization Name: Arizona Board of Regents, University of Arizona | Division:

* Street1: PO Box 210030

Street2:

* City: Tucson | County:

* State: AZ: Arizona | Province:

* Country: USA: UNITED STATES | * Zip / Postal Code: 85721

* Phone Number: (520) 626-2047 | Fax Number:

* E-Mail: jlansing@email.arizona.edu

Credential, e.g., agency login: Lansing

*** Project Role:** PD/PI | **Other Project Role Category:**

***Attach Biographical Sketch** Lansing NIH biosketch.pdf [Add Attachment] [Delete Attachment] [View Attachment]

Attach Current & Pending Support [Add Attachment] [Delete Attachment] [View Attachment]

PROFILE - Senior/Key Person 2

Prefix: | * First Name: Joseph | Middle Name: C

* Last Name: Watkins | Suffix:

Position/Title: Professor | Department: Mathematics

Organization Name: Arizona Board of Regents, University of Arizona | Division:

* Street1: PO 210089

Street2:

* City: Tuson | County:

* State: AZ: Arizona | Province:

* Country: USA: UNITED STATES | * Zip / Postal Code: 85721

* Phone Number: (520) 621-5245 | Fax Number:

* E-Mail: jwatkins@math.arizona.edu

Credential, e.g., agency login: JCWatkins

*** Project Role:** PD/PI | **Other Project Role Category:**

***Attach Biographical Sketch** biosketchwatkins.pdf [Add Attachment] [Delete Attachment] [View Attachment]

Attach Current & Pending Support [Add Attachment] [Delete Attachment] [View Attachment]

[Delete Entry] [Previous Person] [Next Person]

OMB Number: 4040-0001
Expiration Date: 04/30/2008

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Joseph Watkins	Professor of Mathematics
eRA COMMONS USER NAME	
JCWatkins	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Tennessee	BA	1971-1974	Mathematics
University of Tennessee	MA	1974-1976	Mathematics
University of Wisconsin	MS	1976-1978	Mathematics
University of Wisconsin	PhD	1978-1982	Mathematics

NOTE: The Biographical Sketch may not exceed four pages. Follow the formats and instructions on the attached sample.

A. Positions and Honors. List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

Positions and Employment

2006-	Professor, Mathematics, University of Arizona
1996-2006	Associate Professor, Mathematics, University of Arizona
1992-1996	Visiting Assistant Professor, Mathematics, University of Arizona
1986-1992	Assistant Professor, Mathematics, University of Southern California
1987	Senior Research Fellow, Northwestern University
1985	Postdoctoral Fellow, Institute for Mathematics and its Applications, University of Minnesota
1982-1985	Postdoctoral Fellow, University of British Columbia

Honors

2009	University of Arizona College of Science – Galileo Circle Fellow

B. Selected peer-reviewed publications (in chronological order). Do not include publications submitted or in preparation. For publicly available citations, URLs or PMC submission identification numbers may accompany the full reference. Note copies of these publications are no longer accepted as appendix material.

Watkins, Joseph C. (1984) A central limit problem in random evolutions. *Annals of Probability* **12**: 480-513.

Watkins, Joseph C. (1985) A stochastic integral representation for random evolutions. *Annals of Probability* **13** 531-557.

Watkins, Joseph C. (1985) Limit theorems for stationary random evolutions. *Stochastic Processes and their Applications* **19** 189-224.

Watkins, Joseph C. (1986) Limit theorems for products of random matrices: A comparison of two points of view. *Contemporary Mathematics* **50** 5-22.

Watkins, Joseph C. (1986) A companion to the Oseledec multiplicative ergodic theorem. *Proceedings of the American Mathematical Society* **99** 772-776.

Watkins, Joseph C. (1987) Central limit theorems and their associated large deviation principles for products of random matrices. Probability Theory and Related Fields **76** 133-166.

Watkins, Joseph C. (1989) Donsker's theorem for Lie groups. Annals of Probability **17** 1220-1242.

Watkins, Joseph C. (1990) A note on Kunita's decomposition theorem. *Stochastic Processes and their Applications* **35** 81-85.

Watkins, Joseph C. and Birgit Wossner (1991) Diffusion models for chemotaxis: A statistical analysis of noninteractive unicellular movement. *Mathematical Biosciences* **104** 271-303.

Heubach, Silvia P. and Joseph C. Watkins (1995) A stochastic model for the motion of a white blood cell. Advances in Applied Probability **27** 443-472.

Watkins, Joseph C. (1996) Review of *Lectures on Random Evolutions* by Mark A. Pinsky. *Annals of Probability* **24** 1647-1652.

Watkins, Joseph C. (1997) Mechanical models of cell movement-locomotion, translocation and migration. *Advances in Applied Probability* 34, 827-846.

Degrandi-Hoffman, Gloria, Joseph C. Watkins, Anita M. Collins, Gerald M. Loper, Joseph H. Martin, Maria C. Arias, and Walter S. Sheppard (1998) Queen development time as a factor in the Africanization of honey bee population. Annals of the Entomological Society of America **91**, 52-58.

Degrandi-Hoffman, Gloria, and Joseph C. Watkins (1998) Queen development time and the Africanization of European honey bee populations. *American Bee Journal* **26** 467-469.

Mendelson, Neil H., A. Bourque, K. Wilkening, Kevin R. Anderson, and Joseph C. Watkins. (1999) Organized cell swimming motions in *Bacillus subtilis* colonies: Patterns of short-lived whirls and jets. Journal of Bacteriology **181**, 600-609. \medskip

Velez, William Yslas, and Joseph C. Watkins (1999) The research mathematician as storyteller. *Contempory Issues in Mathematics Education* **36**, 45-56.

Degrandi-Hoffman, Gloria, and Joseph C. Watkins (1999) The foraging activity of honey bees (*Apis mellifora L.)* and non-*Apis* bees on hybrid sunflowers (*Helianthus annuus L.*) and its influence on cross-pollination and seed set. *Journal of Apicultural Research* **39**, 37-45.

Anderson, Kevin R., Neil H. Mendelson, and Joseph C. Watkins (2000) A new mathematical approach predicts individual cell growth behavior using bacterial population information. *Journal of Theoretical Biology* **202**, 87-94.

Watkins, Joseph C. (2000) Consistency and fluctuation theorems for discrete time structured sopulation models having demographic stochasticity, *Journal of Mathematical Biology*, 253-271.

Watkins, Joseph C. (2004) The role of marriage rules in the structure of genetic relatedness, *Theoretical Population Biology* **66**, 13-24.

Lansing, J. S., A. J. Redd, T. M. Karafet, J. Watkins, I. W. Ardika, S. P. K. Surata, J. S. Schoenfelder, M. Campbell, A. M. Merriwether, and M. F. Hammer (2004) An Indian trader in ancient Bali? *Antiquity* **78**, 287-293.

Karafet, Tatyana M., J. S. Lansing, Alan J. Redd, Joseph Watkins, I. W. Ardika, S. P. K. Surata, Laura Mayer, Michael Bamshad, Lynn Jorde, and Michael F. Hammer (2005) A Balinese Y chromosome perspective on the peopling of Indonesia: genetic contr ibutions from pre-neolithic hunter-gatherers, Austronesian farmers, and Indian traders, *Human Biology* **77**, 93-114.

Lansing, J. S., A. J. Redd, T. M. Karafet, J. Watkins, I. W. Ardika, S. P. K. Surata, J. W. Schoenfelder, M. Campbell, A. M. Merriwether, and M. F. Hammer (2006) Reply [to: Indian traders in ancient Bali: A reconsideration of the evidence. *Antiquity* 80: online at\\ http://www.antiquity.ac.uk/ProjGall/lansing/index.html\#response.

Watkins, Joseph C. (2007) Microsatellite evolution: Markov transition functions for a suite of models, *Theoretical Population Biology* **71**, 147-159.

Lansing, J. Stephen, Murray P. Cox, Sean S. Downey, Brandon M. Gabler, Brian Hallmark, Tatiana M. Karafet, Peter Norquest, John Schoenfelder, Herawati Sudoyo, Joseph C. Watkins, and Michael F. Hammer. Coevolution of languages and genes on the island of Sumba, eastern Indonesia. *Proceedings of the National Academy of Sciences USA* **104**,16022-16026.

J. Stephen Lansing, Joseph C. Watkins, Brian Hallmark, Murray P. Cox, Tatiana M. Karafet, Herawati Sudoyo, and Michael F. Hammer (2008) Male dominance rarely skews the frequency distribution of Y chromosome haplotypes in human populations. Proceedings of the National Academy of Sciences, USA **105**, 11645-11650.

Watkins, Joseph C. (2009) . Convergence time to the Ewens sampling formula in the infinite alleles Moran model. *Journal of Mathematical Biology* (in press)

Didelot, Xavier, Jesse E. Taylor, Joseph C. Watkins (2009) A duality identity between a model of bacterial recombination and the Wright-Fisher diffusion. *Markov Processes and Reated Topics: Festschrift in Honor of Thomas G. Kurtz. Institute of Mathematics and Statistics Collections* **4**, 315-324.

C. Research Support. List selected ongoing or completed (during the last three years) research projects (federal and non-federal support). Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and your role (e.g. PI, Co-Investigator, Consultant) in the research project. Do not list award amounts or percent effort in projects.

Ongoing Research Support

Anthropological Modeling of Social Structure, Genetics and Language Speciation in Indonesia, Human Social Dynamics, funding by the National Science Foundation 2007-2010 (Co-Investigator)

Completed Research Support

Collaborative to Advance Teaching, Technology and Science (CATTS)
Track 2 GK-12, funded by the National Science Foundation 2003-2008 (Co-Investigator)

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: | * First Name: John | Middle Name: S

* Last Name: Lansing | Suffix: Ph.D.

Position/Title: Professor | Department: Anthropology

Organization Name: Arizona Board of Regents, University of Arizona | Division:

* Street1: PO Box 210030

Street2:

* City: Tucson | County:

* State: AZ: Arizona | Province:

* Country: USA: UNITED STATES | * Zip / Postal Code: 85721

* Phone Number: (520) 626-2047 | Fax Number:

* E-Mail: jlansing@email.arizona.edu

Credential, e.g., agency login: Lansing

*** Project Role:** PD/PI | **Other Project Role Category:**

***Attach Biographical Sketch**	Lansing NIH biosketch.pdf	Add Attachment	Delete Attachment	View Attachment
Attach Current & Pending Support		Add Attachment	Delete Attachment	View Attachment

PROFILE - Senior/Key Person 3

Prefix: | * First Name: Tatiana | Middle Name:

* Last Name: Karafet | Suffix: PhD

Position/Title: Associate Research Scientist | Department: Arizona Research Laboratories

Organization Name: Board of Regents, University of Arizona | Division: Biotechnology

* Street1: PO 210088

Street2:

* City: Tucson | County:

* State: AZ: Arizona | Province:

* Country: USA: UNITED STATES | * Zip / Postal Code: 85721

* Phone Number: (520) 626-0404 | Fax Number:

* E-Mail: tkarafet@email.arizona.edu

Credential, e.g., agency login: Karafet

*** Project Role:** PD/PI | **Other Project Role Category:**

***Attach Biographical Sketch**	biosketch-Karafet.pdf	Add Attachment	Delete Attachment	View Attachment
Attach Current & Pending Support		Add Attachment	Delete Attachment	View Attachment

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OMB Number: 4040-0001
Expiration Date: 04/30/2008

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Karafet, Tatiana M.	Associate Research Scientist
eRA COMMONS USER NAME (credential, e.g., agency login) Karafet	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Institute of General Genetics, Moscow	PhD	1986	Genetics
Novosibirsk State University	M.S	1973	Cytology and Genetics

NOTE: The Biographical Sketch may not exceed four pages. Follow the formats and instructions on the attached sample.

A. Positions and Honors. List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

2009-present Associate Research Scientist, Genomic Analyses and Technology Core Laboratory, University of Arizona, Tucson, Arizona.
2007-present Independent expert and rewiewer, Institute of General Genetics, Moscow
1998-2008 Assistant Research Scientist, Genomic Analyses and Technology Core Laboratory, University of Arizona, Tucson, Arizona.
1994-1997 Research Associate, Genomic Analysis and Technology Core Facility, University of Arizona (Dr. Mike Hammer)
1989-1994 Senior Research Scientist, Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences, Novosibirsk, Russia.
1985-1989 Senior Research Scientist, Institute of Polar Medicine, Krasnoyarsk
1980-1985 Research Scientist, Institute of Polar Medicine, Krasnoyarsk
1974-1980 Research Scientist, Institute of Clinical and Experimental Medicine, Novosibirsk
1973-1974 Research Specialist, Institute of Clinical and Experimental Medicine, Novosibirsk

B. Selected peer-reviewed publications (in chronological order).
(Publications selected from 81 peer-reviewed publications

1978 Sukernik R.I., Karafet T.M., Osipova L.P. Distribution of blood groups serum markers and red cell enzymes in two human populations from northern Siberia. Hum. Hered. 28: 321-327.
1981 Karafet T.M., Sukernik R.I., Osipova L.P., and Simchenko Y.B. Blood groups, serum proteins and red cell enzymes in the Nganasans (Tavghi) - reindeer hunters from Taimir Peninsula. Amer. J. Phys. Anthropol. 56: 139-145.
1986 Sukernik R.I., Osipova L.P., Karafet T.M., Wiebe V.P., and Kirpichnikov G.A. Genetic and ecological studies of aboriginal inhabitants of North-Eastern Siberia. I. Gm-haplotypes and their frequencies in ten Chukchi populations. Genetic structure of Reindeer Chukchi. Genetika. 22: 2361-2368.
1990 Dubrova Yu.E., Karafet T.M., Sukernik R.I., Goltsova T.V. Heterozygosity and fertility relationship in the Forest Nentzi and Nganasans. Genetika. 26: 122-129.
1992 Karafet T.M. Some aspects of ecogenetic study of human populations in the North. In: A population and genetic study of the Northern aborigens. Novosibirsk: the Institute of Cytology & Genetics, Siberian Branch of the Russian Acad. Sci., Russia, P.7-18.
1994 Karafet T.M., Posukh O.L., Osipova L.P. Population-Genetic Studies of North Siberian Natives. Siberian Journal of Ecology, 2:105-118.

1996 J. McComb, M.H. Crawford, L.P. Osipova, T.M. Karafet, O.L. Posukh and M.S. Schanfield. DNA inter-populational variation in Siberian indigenous populations: the mountain Altai. Amer.J. of Hum.Biol, 8:599-607.

1997 Karafet T.M., Zegura S.L., Vuturo-Brady J., Posukh O.L., Osipova L.P., Wiebe V., Romero F., Long J.C., Harihara S., Jin F., Dashnyam B., Gerelasaikhan T., Omoto K., and M.F. Hammer. Y chromosome markers and Trans-Bering Strait Dispersals. Amer.J.Phys.Anthropol., 102:301-314.

1998 Karafet T.M., P. de Knijff, E.T. Wood, J. Ragland, A. Clarke, and M. H. Hammer. Different patterns of variation at the X- and Y- chromosome linked microsatellite loci *DXYS156X* and *DXYS156Y* in human populations. Human.Biology 70:979-992.

1998 Hammer, M.F. T.M. Karafet, A. Rasanayagam , E.T. Wood, T. K Altheide, T. Jenkins, R. C. Griffiths, A. R. Templeton, and S. L. Zegura. Out of Africa and back again: nested cladistic analysis of human Y chromosome variation. Mol.Biol.Evol. 15:427-441.

1999 Karafet T. M., Zegura S. L., Osipova L. P., Posukh O. L., Wiebe V. P., Klitz W., Bergen A., Long, J. Harihara S., de Knijff P., Griffiths R. C., Templeton A. R., and M. F. Hammer. Ancestral Asian source(s) Of New World Y chromosome founder haplotypes. Amer.J.Hum . Genet., 64:817-831.

1999 Karafet T. M., Osipova L. P., Posukh O. L., Wiebe V. P., and M. H. Hammer . Y chromosome microsatellite haplotypes and the history of Samoyed-speaking populations in Northwest Siberia. In: Goldstein D. B., Schlöttere , C. (eds.). Microsatellites: evolution and applications. Oxford University Press, Oxford. P. 249- 265.

2000 Hammer MF, Redd AJ, Wood ET, Bonner MR, Jarjanazi H, Karafet T, Santachiara-Benerecetti S, Oppenheim A, Jobling MA, Jenkins T, Ostrer H, Bonne-Tamir B.Jewish and middle eastern non-jewish populations share a common pool of Y-chromosome biallelic haplotypes. Proc. Natl. Acad. Sci. USA 97:6769-74.

2001 Karafet T.M., Xu L., Du R., Wang W., Feng S., Wells R.S., Redd A.J., Zegura S.L., Hammer M.F. Paternal population history of East Asia: sources, patterns, and microevolutionary processes. Am J Hum Genet., 69:615-28.

2001 M.F. Hammer, T.M. Karafet, A.J. Redd, H. Jarjanazi, Santachiara-Benerecetti, et al. Hierarchical patterns of global human Y-chromosome diversity. Mol.Biol.Evol. 18:1189-203.

2002 Karafet T.M., Osipova L. P., Gubina M. A., Posukh O. L., Zegura S.L and M. H. Hammer. High levels of Y-chromosome differentiation among native Siberian Populations and the genetic signature of a boreal hunter-gatherer way of life Human Biology 74:761-789.

2002 Redd AJ , Roberts-Thomson J, Karafet T, Bamshad M, Jorde LB, Naidu JM, Walsh B, and M. Hammer. Gene flow from the Indidan Subcontinent to Australia: Evidence from the Y chromosome. Current Biology, 12:673-677.

2004 Zegura S. L., Karafet T.M., Zhivotovsky L.A, and M.F. Hammer. High-resolution SNPs and microsatellite haplotypes point to a single, recent entry of Native American Y chromosomes into Americas. Mol.Biol.Evol. 21:164-175.

2004 Lansing, J.S , A.J Redd, T.M. Karafet, J.Watkins, I.W. Ardika, S.P.K. Surata, J.S. Schoenfelder, M. Campbell, A.M. Merriwether, and M.F. Hammer. A foreign trader in ancient Bali? Antiquity: 78, (.300):287-293.

2005 Karafet, T.M., J.S Lansing, A.J Redd, J. Watkins, S.P.K. Surata, W. A. Arthawiguna, L.Mayer, M. Bamshad, L. Jorde, and M. F. Hammer. A Balinese Y chromosome perspective on the peopling of Indonesia: Genetic contributions from pre-Neolithic hunter-gatherers, Austronesian farmers, and Indian traders Human Biology, 77(1):93-114.

2006 Redd AJ, Chamberlain VF, Kearney VF, Stover D, Karafet T, Calderon K, Walsh B, Hammer MF. Genetic structure among 38 populations from the United States based on 11 U.S. core Y chromosome STRs. J Forensic Sci. 51(3):580-5.

2006 Scheinfeldt L, Friedlaender F, Friedlaender J, Latham K, Koki G, Karafet T, Hammer M, Lorenz J. Unexpected NRY chromosome variation in Northern Island Melanesia. Mol Biol Evol.;23(8):1628-41.

2006 Karafet, T. M., S. L. Zegura and M. F. Hammer. Y Chromosomes. In: Handbook of North American Indians. Volume 3. Environment, Origins, and Populations. W.C. Sturtevant (ed). Smithsonian Institutution, Washington, pp. 831-839.

2006 Karafet T.M., Zegura S. L., and M.F. Hammer. Historical peopling of new lands: an ancient link between Asia and Americas, Vestnik VOGIS, 10:7-23.

2007 Lansing J.S., Cox M.P., Downey S.S., Hallmark B., Karafet T.M., Norquest P., Gabler B.M., Schoenfelder J.W. Sudoyo H., Watkins J.C., Hammer M.F. Language-gene co-evolution writ small: Contact induced language change on the eastern Indonesian island of Sumba. Proc. Natl. Acad. Sci. USA; 104(41):16022-6.

2008 Karafet, T.M., L.P. Osipova and M.F. Hammer. The effect of history and life-style on genetic structure of North Asian populations. In: *The Past Human Migrations in East Asia*, A. Sanchez-Mazas, R. Blench, M. Ross, I. Peiros, and M. Lin (eds), London and New York: Routledge,, pp.395-416.

2008 Cox M.P., Mendez F.L., Karafet T.M., Pilkington M. M., Kingan S. B., Destro-Bisol G., Strassmann B. I., and M. F. Hammer. Testing for archaic Hominin admixture on the X chromosome: model likelihoods for the modern human RRM2P4 region from summaries of genealogical topology under the structured coalescent. Genetics 178: 1–11.

2008 Malhi, R. S., A. Gonzalez-Oliver, K.B. Schroeder, B. M. Kemp, J. A. Greenberg, S. Z. Dobrowski, D. Glenn Smith, A. Resendez, T.Karafet, M.Hammer, S. Zegura, T. Brovko Distribution of Y chromosomes among native North Americans: A study of Athapaskan population history Amer.J.Phys.Anthropol.,137, 4, 412-424.

2008 Lansing J.S., Watkins J.C, Hallmark B., Cox M.P., Karafet T.M., Sudoyo H., Hammer M.F. Male dominance rarely skews the frequency distribution of Y chromosome haplotypes in human populations. Proc. Natl. Acad. Sci. USA; 105(33):11645-50.

2008 Karafet T.M, Mendez F.L., Meilerman M.B., Underhill P.L., Zegura S. L., and M. F. Hammer. New binary polymorphisms reshape and increase resolution of the human Y-chromosomal haplogroup tree. Genome Research, 18:830-838.

2009 Karafet T.M., Zegura S. L., and M. F. Hammer. Y-Chromosome Japanese roots. In: Ancient Human Migrations, Peter N. Peregrine, Ilia Peiros, and Marcus Feldman (eds), The University of UTAH Press, pp.137-148.

C. Research Support. List selected ongoing or completed (during the last three years) research projects (federal and non-federal support). Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and your role (e.g. PI, Co-Investigator, Consultant) in the research project. Do not list award amounts or percent effort in projects.

Ongoing Research Support

NSF/SES 0725470
HSD: **Anthropological Modeling of Social Structure, Genetics, and Language Speciation in Indonesia**
09/2007-08/2010
The overall goals: to analyze the patterns of social structure and language; to reconstruct the origins of the Indonesian people and the Austronesian expansion; to study genetic, demographic and linguistic processes in the recent (<5000 years) past.
Role: Co-PI

Salus Mundi Foundation
The Y chromosome: human evolution
2005-2010
The goal of this research proposal is to produce an updated tree showing the evolutionary relationships among modern Y chromosomes.
Role: PI

US Army Research Development and Engineering Command
Global DNA Database for Terrorism Related Indentification
01/2009-12/2009
The purpose of this project is to construct A database of Y chromosome genotypes, mitochondrial DNA, and nuclear SNP data to inferr the ethnic origin and ancestry of suspected terrorist samples.
Role: Co-PI

Completed Research Support

NSF/BCS 0742328
SGER: **Genetic, Linguistic Diversity of the Highland Populations of Daghestan**
09/2007-08/2008
The purpose of this project was to expand on preliminary studies of the indigenous Caucasus populations by collecting genetic and demographic data, as well as a Swadesh word list, from several key remote highland villages in the Northern Caucasus.
Role: PI

NSF/BCS 0432262
Austronesian societies: reading social structure from the genome
The aim was to gain a better understanding of the major variables that affect patterns of relatedness among human groups, including demography, migrations, language, kinship and economic adaptations.
09/2004-08/2007
Role: Co-PI

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: | * First Name: John | Middle Name: S

* Last Name: Lansing | Suffix: Ph.D.

Position/Title: Professor | Department: Anthropology

Organization Name: Arizona Board of Regents, University of Arizona | Division:

* Street1: PO Box 210030

Street2:

* City: Tucson | County:

* State: AZ: Arizona | Province:

* Country: USA: UNITED STATES | * Zip / Postal Code: 85721

* Phone Number: (520) 626-2047 | Fax Number:

* E-Mail: jlansing@email.arizona.edu

Credential, e.g., agency login: Lansing

*** Project Role:** PD/PI | **Other Project Role Category:**

***Attach Biographical Sketch**	Lansing NIH biosketch.pdf	Add Attachment	Delete Attachment	View Attachment
Attach Current & Pending Support		Add Attachment	Delete Attachment	View Attachment

PROFILE - Senior/Key Person 4

Prefix: | * First Name: Jonathan | Middle Name:

* Last Name: Wilkins | Suffix: PhD

Position/Title: Professor | Department:

Organization Name: Santa Fe Institute | Division:

* Street1: 1399 Hyde Park Rd

Street2:

* City: Santa Fe | County:

* State: NM: New Mexico | Province:

* Country: USA: UNITED STATES | * Zip / Postal Code: 87501

* Phone Number: (505) 946-2755 | Fax Number:

* E-Mail: wilkins@santafe.edu

Credential, e.g., agency login: wilkinsjo

*** Project Role:** PD/PI | **Other Project Role Category:**

***Attach Biographical Sketch**	Wilkins NIH Biosketch.pdf	Add Attachment	Delete Attachment	View Attachment
Attach Current & Pending Support		Add Attachment	Delete Attachment	View Attachment

Delete Entry | Previous Person | Next Person

OMB Number: 4040-0001
Expiration Date: 04/30/2008

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Jon F. Wilkins	Co-PI
eRA COMMONS USER NAME	
WILKINSJO	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and **include postdoctoral training.**)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Harvard College, Cambridge, MA	AB	1993	Physics
University of Wisconsin – Madison	MS	1998	Biochemistry
Harvard University, Cambridge, MA	PhD	2002	Biophysics

A. **Positions.**

Junior Fellow, Harvard Society of Fellows (2002-2005).

Professor, Santa Fe Institute (2005-present).

B. **Selected peer-reviewed publications (in reverse chronological order).**

Wilkins, J. F. & Godfrey-Smith, P. 2009 Adaptationism and the adaptive landscape. *Biology and Philosophy*. **24,** 199-214.

Jesus, F. F., Wilkins, J. F., Solferini, V. N & Wakeley, J. 2006 Expected coalescence times and segregating sites in a model of repeated glacial cycles. *Genet. Mol. Res.* **5,** 466-474.

Wilkins, J. F. 2006 Unraveling male and female histories from human genetic data. *Curr. Opin. Genet. Dev.* **16,** 611-617. [DOI: 10.1016/j.gde.2006.10.004]

Wilkins, J. F. & Marlowe, F. 2006 Sex-biased migration in humans: what should we expect from genetic data? *BioEssays* **28,** 290-300. [DOI: 10.1002/bies.20378]

Wilkins, J. F. 2006 Competitive signal discrimination, methylation reprogramming and genomic imprinting. *J. Theor. Biol.* **242,** 643-651. [DOI: 10.1016/j.jtbi.2006.04.015]

Wilkins, J. F. 2006 Tissue-specific reactivation of gene expression at an imprinted locus. *J. Theor. Biol.* **240,** 277-287. [DOI: 10.1016/j.jtbi.2005.09.007]

Wilkins, J. F. 2005 DNA methylation and imprinting: epigenetic canalization and conflict. *Trends Genet.* **21,** 356-365. [DOI: 10.1016/j.tig.2005.04.005]

Wilkins, J. F. 2004 Gene genealogies in a continuous habitat: a separation of timescales approach. *Genetics* **168**, 2227-2244. [DOI: 10.1534/genetics.103.022830]

Wilkins, J. F. & Haig, D. 2003 What good is genomic imprinting: The function of parent-specific gene expression. *Nat. Rev. Genet.* **4**, 359-368. [DOI: 10.1038/nrg1062]

Wilkins, J. F. & Haig, D. 2003 Inbreeding, maternal care and genomic imprinting. *J. Theor. Biol.* **221**, 559-564. [DOI: 10.1016/jtbi.2003.3206]

Wilkins, J. F. & Haig, D. 2002 Parental modifiers, antisense transcripts and loss of imprinting. *Proc. R. Soc. Lond. B* **269**, 1841-1846. [DOI: 10.1098/rspb.2002.2096]

Wilkins, J. F. & Wakeley, J. 2002 The coalescent in a continuous, finite, linear population. *Genetics* **161**, 873-888.

Wilkins, J. F. & Haig, D. 2001 Genomic imprinting at two antagonistic loci. *Proc. R. Soc. Lond. B* **268**, 1861-1867.

Book:

Wilkins, J. F., editor. 2008 *Genomic Imprinting*. Springer, New York and Landes Bioscience, Austin, TX. URL: http://www.landesbioscience.com/books/intelligence_unit/id/945

C. Research Support.

Ongoing Research Support

Grant/Project 0624351 PILastName (PI) Farmer Start – End Dates
Sponsor: NSF 9/15/06 – 8/31/09
Title of project: DHB: Financial Markets as an Empirical Laboratory to Study an Evolving Ecology of Human Decision Making
Major Goal: This project uses a new approach that synthesizes ideas from behavioral economics, agent-based modeling, evolutionary biology, ecology, and statistical physics. A convincing demonstration of the success of these methods could have a broad impact on agent modeling throughout social science. Other impacts of this project include educating and mentoring undergraduates, graduate students and postdoctoral researchers.
Role: co-PI

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: | * First Name: John | Middle Name: S

* Last Name: Lansing | Suffix: Ph.D.

Position/Title: Professor | Department: Anthropology

Organization Name: Arizona Board of Regents, University of Arizona | Division:

* Street1: PO Box 210030

Street2:

* City: Tucson | County:

* State: AZ: Arizona | Province:

* Country: USA: UNITED STATES | * Zip / Postal Code: 85721

* Phone Number: (520) 626-2047 | Fax Number:

* E-Mail: jlansing@email.arizona.edu

Credential, e.g., agency login: Lansing

*** Project Role:** PD/PI | **Other Project Role Category:**

***Attach Biographical Sketch**	Lansing NIH biosketch.pdf	Add Attachment	Delete Attachment	View Attachment
Attach Current & Pending Support		Add Attachment	Delete Attachment	View Attachment

PROFILE - Senior/Key Person 5

Prefix: | * First Name: Caroline | Middle Name:

* Last Name: Buckee | Suffix: PhD

Position/Title: Omidyar Fellow | Department:

Organization Name: Santa Fe Institute | Division:

* Street1: 1399 Hyde Park Rd

Street2:

* City: Santa Fe | County:

* State: NM: New Mexico | Province:

* Country: USA: UNITED STATES | * Zip / Postal Code: 87501

* Phone Number: (505) 946-3653 | Fax Number:

* E-Mail: cbuckee@santafe.edu

Credential, e.g., agency login: carolineb

*** Project Role:** PD/PI | **Other Project Role Category:**

***Attach Biographical Sketch**	BuckeeNIHBiosketch2009.pdf	Add Attachment	Delete Attachment	View Attachment
Attach Current & Pending Support		Add Attachment	Delete Attachment	View Attachment

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OMB Number: 4040-0001
Expiration Date: 04/30/2008

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Caroline O. Buckee	Co-PI
eRA COMMONS USER NAME	
CAROLINEB	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and **include postdoctoral training**.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Edinburgh University, UK	BSc (Hons)	2001	Biology (Hons Zoology)
York University, UK	MRes	2002	Bioinformatics
Oxford University, UK	PhD	2006	Infectious Disease Modeling

A. **Positions and Honors.**

Post-doctoral Research Fellow, Oxford University (2006-2007)
Sir Henry Wellcome Postdoctoral Research Fellow, Oxford University (2007-present)
Omidyar Fellow, Santa Fe Institute (2008-present)

Honors

Merton College Prize Scholarship for academic excellence, Oxford University (2005)
The Ashworth Prize for Zoology, University of Edinburgh (2001)
The John Muir Prize for Botany, University of Edinburgh (2000)

B. **Selected peer-reviewed publications (in reverse chronological order).**

Book chapters

Buckee CO, Gupta S. (2008) The effects of immune selection on bacterial population structure. In *Evolutionary Biology of Bacterial and Fungal Pathogens* Editors: Cassell, Gutierrez-Fuentes, Baquero, & Nombela. ASM Press.

Buckee CO, Gupta S (2009) Modelling malaria population structure and its implications for control. In *Modeling Parasite Transmission and Control.* Editors: Edwin & Spear. Landes Bioscience.

Buckee CO, Gupta S (in press) A network approach to understanding pathogen population structure: from host networks to antigen networks. In *Infectious Disease Informatics.* Editor: Sintchenko. Springer.

Journal articles

Boni MF, **Buckee CO**, White NJ. (2008) Mathematical models for a new era of malaria eradication. *PLoS Medicine* 25;5(11):e231.

Buckee CO, Bull PC, Gupta S (2009) Inferring malaria parasite population structure from serological networks. *Proc Biol Sci* 276(1656):477-85

Buckee CO, Jolley KA, Recker M, Penman B, Kriz P, Gupta S, Maiden MC. (2008) Immune selection and the evolution of lineages and virulence in bacterial pathogens. *PNAS* 105(39):15082-7.

Callaghan M, **Buckee CO**, McCarthy ND, Pavón AB, Brehony C, Faust S, Gray SJ, Kaczmarski EB, Levin M, Kroll JS, Maiden MCJ, Pollard AJ (2008) The Opa protein repertoires of disease-causing and carried meningococci: genetic diversity and association with clinical severity. *Journal Clin Micro* 46(9):3033-41.

Bull P, **Buckee CO**, Kyes S, Berriman M, Newbold C, Marsh K. (2008) Mapping of mosaic *Plasmodium falciparum var* genes onto a network of shared polymorphic blocks. *Mol Micro* 68(6):1519-34.

Buckee CO, Callaghan M, Jolley KA, Maiden MCM, Gupta S. (2008) The effects of immune selection on the structure of the meningococcal Opa protein repertoire. *PLoS Pathogens.* 14;4(3):e1000020

Recker M, Arinaminpathy N, **Buckee CO** (2008) The effects of *var* gene recombination and partitioning on the acquisition of clinical immunity against *Plasmodium falciparum* malaria. *Malaria Journal.* **7**:18.

Stone GN, Atkinson RJ, Rokas A, Aldrey J-LN, Melika G, Acs Z, Csoka G, Hayward A, Bailey R, **Buckee C**, McVean GAT. (2008) Evidence for widespread cryptic sexual generations in apparently asexual *Andricus* gallwasps. *Molecular Ecology.* **17(2)**: 652-665.

Buckee C, Danon L, Gupta S. (2007) Host community structure and the maintenance of pathogen diversity. *Proceedings of Biological Sciences B* **274(1619):** 1715-1721.

Bull P, Kyes S, Montgomery J, **Buckee C**, Kortok M, Newbold C, Marsh K. (2007) An approach to rapid classification of DBLα sequence tags sampled from *Plasmodium falciparum var* genes without prior alignment. *Molecular and Cellular Parasitology.* **154(1):** 98-102.

Imoukhuede EB, Andrews L, Milligan P, Berthoud T, Bojang K, Nwakanma D, Ismaili J, **Buckee C**, Njie F, Keita S, Sowe M, Lang T, Gilbert S, Greenwood B, Hill AVS. (2007) Low level malaria infections detected by a sensitive polymerase

chain reaction assay and use of this technique in the evaluation of malaria vaccines in an endemic area. *American Journal of Tropical Medicine and Hygiene.***76(3):** 486-493.

Buckee C, Koelle K, Mustard MJ, Gupta S. (2004) The effects of host contact network structure on pathogen diversity and strain structure. *PNAS* **101(29):** 10839-44.

Hall *et al.* (2002) Sequence of *Plasmodium falciparum* chromosomes 1, 3-9 and 13. *Nature* **419(6906):** 527-31.

C. Research Support.

Sir Henry Wellcome Postdoctoral Research Fellowship
Sponsor: Wellcome Trust
Title: The population structure and expression patterns of *Plasmodium falciparum var* gene repertoires
Duration: August 2007-July 2011

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: | * First Name: John | Middle Name: S

* Last Name: Lansing | Suffix: Ph.D.

Position/Title: Professor | Department: Anthropology

Organization Name: Arizona Board of Regents, University of Arizona | Division:

* Street1: PO Box 210030

Street2:

* City: Tucson | County:

* State: AZ: Arizona | Province:

* Country: USA: UNITED STATES | * Zip / Postal Code: 85721

* Phone Number: (520) 626-2047 | Fax Number:

* E-Mail: jlansing@email.arizona.edu

Credential, e.g., agency login: Lansing

*** Project Role:** PD/PI | **Other Project Role Category:**

***Attach Biographical Sketch** Lansing NIH biosketch.pdf | Add Attachment | Delete Attachment | View Attachment

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PROFILE - Senior/Key Person 6

Prefix: | * First Name: Herawati | Middle Name:

* Last Name: Sudoyo | Suffix: MD

Position/Title: Principal Research Fellow & Deputy Director | Department:

Organization Name: Eijkman Institute for Molecular Biology | Division:

* Street1: Diponegoro 69

Street2:

* City: Jakarta | County:

* State: | Province:

* Country: IDN: INDONESIA | * Zip / Postal Code: 10430

* Phone Number: 62-21-314-8694 | Fax Number:

* E-Mail: hera_sudoyo@yahoo.com

Credential, e.g., agency login:

*** Project Role:** Other (Specify) | **Other Project Role Category:** Co-Investigator

***Attach Biographical Sketch** Herawati Sudoyo Biosketch.pd | Add Attachment | Delete Attachment | View Attachment

Attach Current & Pending Support | Add Attachment | Delete Attachment | View Attachment

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OMB Number: 4040-0001
Expiration Date: 04/30/2008

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Sudoyo/ Herawati	Principal Research Fellow/Deputy Director
eRA COMMONS USER NAME (credential, e.g., agency login)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Monash University, Melbourne, Australia	PhD	1990	Biochemisty and Molecular Biology
School of Medicine, University of Indonesia, Jakarta, Indonesia	MD	1977	Medicine

NOTE: The Biographical Sketch may not exceed four pages. Follow the formats and instructions on the attached sample.

A. Positions and Honors. List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

1978 - now	Senior Lecturer, Department of Medical Biology, University of Indonesia.
1990	Research Scientist - Centre for Molecular Biology and Medicine, Monash University. Australia (Research Scientist, National Health and Medical Research Council).
1991	Research Scientist - Department of Biochemistry Monash University, Australia (Research Scientist, National Health and Medical Research Council).
1991 - now	Founding member of the Eijkman Institute for Molecular Biology; as Executive Manager responsible for the whole operation of the Institute.
1992 - 1995	Secretary - National Committee for the Development of Biotechnology, Ministry for Research and Technology (Indonesia).
1992 - now	Principal Investigator and Executive Manager, Eijkman Institute for Molecular Biology.
1992 - now	Principal scientist - Eijkman Institute for Molecular Biology; leader of the research groups on Mitochondrial Medicine and on Human Genome Diversity.
1996 - 1998	Member - Scientific Panel for Research Program on Mentoring Scheme on Medical Science and Technology (RISBIN IPTEKDOK) I, II dan III.
1996 - 2004	Member - Scientific Panel for Cooperative Research of Excellence Program Panel (a competitive research grant scheme - RUT), National Research Council (Indonesia).
2001	Temporary advisor - Joint WHO - Thai Health Research Forum Multi Regional Consultative Meeting (Bangkok).
2002 - now	Member - Scientific Panel for International Cooperative Research of Excellence Program (RUTI), Minister for Research and Technology.
2003	Delegate - APEC Centre for Technology Foresight, National Science and Technology Development Agency (Bangkok).
2003	Temporary advisor - WHO Meeting: Inter-Country Consultation on Identifying Regional Priorities in the Area of Human Genetics in SEAR (Bangkok).
2004 - now	Head of the Forensic Identification Unit, Eijkman Institute for Molecular Biology.
2005 - now	Lecturer, Indonesia: Police Science Universities

2005 - now Chairman - Scientific Panel for Research Program on Mentoring Scheme on Medical Science and Technology (RISBIN IPTEKDOK) (RISBIN IPTEKDOK).
2005 - now Member - National Jury for L'Oreal-Unesco for Women in Science.
2006 - now Lecturer, Post Graduate Study, Hasanuddin University (UNHAS – Makassar).

B. Selected peer-reviewed publications (in chronological order). Do not include publications submitted or in preparation. For publicly available citations, URLs or PMC submission identification numbers may accompany the full reference; copies of publicly available publications are not accepted as appendix material.

1988 Marzuki, S.,I.R Mackay, **Sudoyo H.**, A.S. Noer, The M2 autoantigens of *primary biliary cirrhosis are not sub units of the mitochondrial H^+-ATPase. Hepatology 8, 1180-1181*

1988 **Sudoyo H.**, S. Marzuki, I. Trounce and E. Byrne, Tissue specific expression of mitochondrial M2 autoantigens of primary biliary cirrhosis: correlation with capacity for aerobic metabolism. *Eur.Bionerg. Conf. Short Reports 5, 287.*

1989 Marzuki, S., A.S Noer, **Sudoyo H.**, S. Meltzer, H.B. Lukins and A. Linnane, Monoclonal antibodies as probes of assembly of the mitochondrial ATP synthases. *In Marzuki, S. (ed) Molecular Structure, Function and Assembly of ATP Synthases, Plenum, Publ. Co, New York, PP. 115-128.*

1989 **Sudoyo H.**, A.S.Noer., I.R Mackay, and S. Marzuki,. The association of the autoantigens of primary biliary cirrhosis with the mitochondrial H^+-ATPase- A reassessment. *Biochem. Internat. 18, 951-960.*

1989 **Sudoyo H.** and Marzuki, S.,. Antimitochondrial antibodies of primary biliary cirrhosis as a novel probe in the study of the biosynthetic regulation of the yeast 2-oxo acid dehydrogenase complexes. *Biochem. Biophys. Res. Commun. 158, 220-227.*

1989 Marzuki, S, Byrne E, Trounce I, **Sudoyo H.**, Noer AS and J.O'Day, Taperetinal degeneration in mitochondrial cytophaties, pp 74-82. *In proc. 5th Internat. Retinitis Pigmen-tosa Congress. Australian Retinitis Pigmentosa Foundation, Melbourne, Australia.*

1990 **Sudoyo H.**, Marzuki S, Trounce I and Byrne T.,. Antimitochondrial autoantibodies of primary biliary cirrhosis as a novel probe in the study of the 2-oxo acid dehydrogenasis in patients with mitochondrial myophaties. *J. Neurol. Sci. 98, 185-193.*

1991 Marzuki, A.S. Noer, P. Lertrit, P. Uthanaphol, D. Thyagarajan, R. Kapsa, **Sudoyo H.** and E. Byrne, Molecular pathology of mitochondrial respiratory disorders: normal variant of human mitochondrial genome and mtDNA lesion in MERRF encephalomyopathy. *In T. Sato (ed), Progress in Neuropathology, vol.7, Mitochondrial Encephalomyopathies, Raven Press, New York, pp.181-194.*

1991 Trounce, I., E. Byrne, S. Marzuki, X. Dennett, **Sudoyo H.**, F. Mastaglia, and S. Berkovic, Functional respiratory chain studies in subjects with chronic progressive external ophthalmoplegia and large heteroplasmic mitochondrial DNA deletions. *J. Neurol. Sci. 102, 92-99.*

1991 Noer, A.S., **Sudoyo H.**, P. Lertrit, D. Thyagarajan, P.Utthanaphol, R. Kapsa, E. Byrne and S, Marzuki, A $tRNA^{lys}$ in the mitochondrial DNA is the causal genetic lesion underlying myoclonic epilepsy and ragged red fibre (MERRF) syndrome. *Am. J. Hum. Genet. 49: 715-722.*

1991 Marzuki, S., A.S. Noer, **Sudoyo H.** and E. Byrne,. Mitochondrial DNA mutations in disease and ageing. *Aust. Physiol. Pharmacol. Soc. 22: 152-167.*

1991 Marzuki, S., **Sudoyo H.** and A.S Noer,. Polymorphism of the human mitochondrial DNA and forensic medicine. *J. Indon. Med. Assoc. 41: 737-740.*

1992 **Sudoyo H.**, S, Marzuki, F. Mastaglia and W. Caroll, Molecular genetics of *Leber's hereditary optic neuropathy*: study of a six-generation family from Western Australia. *J. Neurol. Sci. 108: 7-17.*

1992 S, Marzuki, P. Lertrit, A.S. Noer, R. Kapsa, **Sudoyo H.**, E. Byrne and D. Thyagarajan, The need for a joint effort in the construction of a reference data base for normal sequence variants of human mtDNA. *Am. J. Hum. Genet. 50: 1337-1340.*

1992 **Sudoyo H.**, S. Marzuki., E. Byrne, I. Trounce and F. Mastaglia,. Phenotypic expression of mtDNA heteroplasmy in the skeletal muscle of patients with oculomyophaty-defect in mitochondrial protein synthesis. *J. Neurol. Sci., 117: 83-91.*

1995 S. Marzuki, **Sudoyo H.** and P. Lertrit, Update in molecular genetics: mitochondrial energy transduction disorders. *SEA J. Trop. Med. 26 (Suppl 1): 155-161.*

1997 S, Marzuki, S.F. Berkovic, A.S. Noer, R.M.I. Kapsa, R.M. Kalnins, E. Byrne, Tedjo Sasmono and **Sudoyo H.**,. Developmental genetics of deleted mitochondrial oculomyopathy. *J. Neurol. Sci., 145: 155-162.*

1998 **Sudoyo H.**, M. Sitepu, S. Malik, H.D. Poesponegoro and S. Marzuki, *Leber's hereditary optic neuropathy* in Indonesia: two families with mtDNA 11778G>A and 14484T>C mutations. *J. Hum. Mutation (suppl. 1): 271-274.*

1998 H. Y. Handoko, P. J. Wirapati, **Sudoyo H.**, M. Sitepu and S. Marzuki. Meiotic breakpoint mapping of a proposed x-linked visual loss susceptibility locus in *Leber's hereditary optic neuropathy. J. Med. Genet., 35: 668-671.*

2000 S. Malik, **Sudoyo H.** and S. Marzuki, Microspectrometric analysis of NADH-tetrazolium reductase deficiency in fibroblasts of patients with *Leber's hereditary optic neuropathy. J. Inherit. Metab. Dis. 23: 730-744.*

2002 S. Malik, **Sudoyo H.**, H. Suryadi, P. Pramoonjago, H. Suryadi, T. Sukarna, M. Njunting, E. Sahiratmadja and S. Marzuki, Nuclear mitochondrial interplay in the modulation of the homopolymeric tract length heteroplasmy in the control (D-loop) region of the mitochondrial DNA. *J. Hum Genet. 110: 402-411.*

2002 Malik, S., **Sudoyo H.**, P. Pramoonjago, T. Sukarna, D. Darwis and S. Marzuki.. Evidence for de novo regeneration of the pattern of the length heteroplasmy associated with the T16189C variant in the control (D-LOOP) region of the mitochondrial DNA. *J. Hum. Genet.47:122-130.*

2002 S. Malik, **Sudoyo H.**, H. Suryadi, P. Pramoonjago, T. Sukarna, M. Njunting, E. Sahiratmadja and S. Marzuki, Nuclear mitochondrial interplay in the modulation of the homopolymeric tract length heteroplasmy in the control (d-loop) region of the mitochondrial DNA. *J. Hum Genet. 110: 402-411.*

2002 **Sudoyo H.**, H. Suryadi, P. Lertrit, P. Pramoonjago, D. Lyrawati and S. Marzuki, Asian specific mtDNA backgounds associated with the primary G11778A mutation of *Leber's hereditary optic neuropathy. J. Hum. Genet, 47:594-604.*

2003 **Sudoyo H.**, H. Suryadi, N. Sitorus, K. Tresnasari, D. Safari, S. Soegondo and A. Pranoto.. Mitochondrial genome and susceptibility to diabetes mellitus. *Adv Exp Med Biol. 153: 19-36.*

2003 S. Malik, **Sudoyo H.**, T. Sasmono, S. Winata, IY. Arhya, P. Pramoonjago, W. Sudana and S. Marzuki. Nonsyndromic sensorineural deafness in a Balinese family associated with the mutation in the mitochondrial small subunit ribosomal RNA. *J. Hum. Genet. 48: 119-124.*

2003 S. Marzuki, **Sudoyo H.**, H. Suryadi, I. Setianingsih and P. Pramoonjago. Human genome diversity and disease in the Island Southeast Asia. *Adv Exp Med Biol. 531: 3-18.*

2003 S. Malik, Pieter N, **Sudoyo H.**, A. Kadir and S, Marzuki. Prevalence of the mitochondrial DNA A1555G mutation in sensorineural deafness patients in island Southeast Asia. *J. Hum Genet, 48:480-483.*

2007 JS. Lansing. MP. Cox, SS. Downey, BM. Gabler, B. Hallmark, TM. Karafet, P. Norquest, JW. Schoenfelder, **H. Sudoyo**, JC. Watkins and MF. Hammer.. Coevolution of languages and genes on the island of Sumba, Eastern Indonesia. *PNAS, 104: 16022-16026.*

2007 S. Mona, M. Tommasseo-Ponzetta, S. Brauer, H. **Sudoyo**, S. Marzuki and M. Kayser. Patterns of Y-chromosome diversity intersect with the trans-new guinea hypothesis. *Mol. Biol. Evol.* 24(11*): 2546-2555.*

2007 Cox, Murray P., Alan J. Redd, Tatiana M. Karafet, Christine A. Ponder, J. Stephen Lansing, **Herawati Sudoyo** and Michael F. Hammer. A Polynesian motif on the Y chromosome: population structure in remote Oceania. *J. Hum.Biol., 79 (5): 525 (11).*

2007 Lansing, J. Stephen, Joseph C. Watkins, Brian Hallmark, Murray P. Cox, Tatiana M. Karafet, **Herawati Sudoyo** and Michael F. Hammer. Male dominance rarely skews the frequency distribution of Y chromosome haplotypes in human populations. *Proc. Natl. Acad. Sci USA 105 (33): 11645-11650.*

2008 **H. Sudoyo**, P.T. Widodo, H. Suryadi, Y.S. Lie, D. Safari, A. Widjajanto, D.A. Kadarmo, S. Hidayat and S. Marzuki,. DNA analysis in perpetrator identification on terrorism-related disaster: Suicide bombing of the Australian Embassy in Jakarta 2004. *Forensic Scie Internat 2/3: 231-237.*

2008 N. Nurainy, D.H. Muljono, **H. Sudoyo** and S. Marzuki,. Genetic diversity of hepatitis B virus in the ethnically diverse populations of indonesia: a new subgenotype of genotype b found in the Eastern Islands. *Arch Virol: DOI 10.1007/s00705-008-0092.*

2009 Jason A. Wilder, Jonathan A. Stone, Elisabeth G. Preston, Lauren E. Finn, Hannah L. Ratcliffe and **Herawati Sudoyo**. Molecular population genetics of SLC4A1 and Southeast Asian Ovalocytosis. *J. Hum. Genet: 1-6.*

2009 Nick Patterson, Desiree C. Petersen, Richard van der Ross, **Herawati Sudoyo**, Richard H. Glashoff, Sangkot Marzuki, David Reich and Vanessa M. Hayes. Genetic structure of a admixed population in South Africa. *In press, Hum. Molec. Genet.*

2009 S. Mona, K. Grunz, S. Brauer, L. Castrì, B. Pakendorf, **H. Sudoyo**, S. Marzuki, R.H. Barnes, J. Schmidtke, M. Stoneking and M. Kayser. Genetic admixture history of eastern Indonesian as revealed by Y-chromosome and mitochondrial DNA analysis. *In press, Mol. Biol.Evolution.*

C. Research Support. List selected ongoing or completed (during the last three years) research projects (federal and non-federal support). Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and your role (e.g. PI, Co-Investigator, Consultant) in the research project. Do not list award amounts or percent effort in projects.

Cooperative Research of Excellence Program (RUT): 1993-1996
The purpose of this project is study the Role of Mitochondrial DNA mutation in the ageing process.

Block grant from the Ministry Research and Technology of the Republic of Indonesia for Human Genome Diversity Project in relation to Disease Susceptibility.

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: | * First Name: John | Middle Name: S

* Last Name: Lansing | Suffix: Ph.D.

Position/Title: Professor | Department: Anthropology

Organization Name: Arizona Board of Regents, University of Arizona | Division:

* Street1: PO Box 210030

Street2:

* City: Tucson | County:

* State: AZ: Arizona | Province:

* Country: USA: UNITED STATES | * Zip / Postal Code: 85721

* Phone Number: (520) 626-2047 | Fax Number:

* E-Mail: jlansing@email.arizona.edu

Credential, e.g., agency login: Lansing

*** Project Role:** PD/PI | **Other Project Role Category:**

***Attach Biographical Sketch**	Lansing NIH biosketch.pdf	Add Attachment	Delete Attachment	View Attachment
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PROFILE - Senior/Key Person 7

Prefix: | * First Name: Murray | Middle Name: P

* Last Name: Cox | Suffix:

Position/Title: University Research Associate | Department: Arizona Research Laboratories

Organization Name: Arizona Board of Regents, University of Arizona | Division: Biotechnology

* Street1: PO 210077

Street2:

* City: Tucson | County:

* State: AZ: Arizona | Province:

* Country: USA: UNITED STATES | * Zip / Postal Code: 85721

* Phone Number: (520) 621-4064 | Fax Number:

* E-Mail: mpcox@u.arizona.edu

Credential, e.g., agency login:

*** Project Role:** Consultant | **Other Project Role Category:**

***Attach Biographical Sketch**	NIH_Bioskech_MPC_May09.pdf	Add Attachment	Delete Attachment	View Attachment
Attach Current & Pending Support		Add Attachment	Delete Attachment	View Attachment

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OMB Number: 4040-0001
Expiration Date: 04/30/2008

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Murray Cox, Ph.D.	Research Fellow Institute for Molecular BioSciences, *and* the Allan Wilson Centre for Molecular Ecology and Evolution, *and* the National Centre for Advanced BioProtection Technologies Massey University, Palmerston North, New Zealand
eRA COMMONS USER NAME COXMP1	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Otago, Dunedin, New Zealand	B.Sc. (Hons I)	1996-2000	Biochemistry
University of Otago, Dunedin, New Zealand	Ph.D.	2000-2003	Genetics
University of Olso, Oslo, Norway	Fellowship	2002-2003	Genetics
University of Cambridge, Cambridge, UK	Fellowship	2004-2005	Anthropology
Santa Fe Institute, Santa Fe, NM, USA	Fellowship	2007-2008	Complex Systems
University of Arizona, Tucson, AZ, USA	Fellowship	2005-2009	Genetics

A. Positions and Honors

2002-2003 **Visiting Research Scholar**
The Biology Institute, University of Oslo, Oslo, Norway

2003 **Lecturer in Molecular Biology**
School of Science and Veterinary Nursing, Otago Polytechnic, New Zealand

2004-2005 **Postdoctoral Fellow**
Leverhulme Centre for Human Evolutionary Studies, University of Cambridge, Cambridge, UK

2007-2008 **Adjunct Postdoctoral Associate**
Santa Fe Institute, Santa Fe, NM, USA

2005-2009 **Postdoctoral Associate**
Arizona Research Laboratories, University of Arizona, Tucson, AZ, USA

2009-present **Research Fellow**
Massey University, Palmerston North, New Zealand

- **Guest Researcher, Biology Institute, University of Oslo, Norway.** Partial funding from Dr Thor Heyerdahl, Kon-Tiki Museum, Oslo, Norway. 2002-2003
- **New Zealand Government Bright Futures Doctoral Scholarship.** Foundation for Research, Science and Technology, Wellington, New Zealand. 2000-2003
- **University of Auckland Postgraduate Scholarship.** University of Auckland, Auckland, New Zealand. 1999
- **University of Otago Postgraduate Scholarship.** University of Otago, Dunedin, New Zealand. 1999
- **Allan Wilkinson Summer Research Scholarship.** University of Otago Medical School, Dunedin, New Zealand. 1999-2000
- **Summer Research Scholarship.** Otago Medical Research Council, Dunedin, New Zealand. 1998-1999
- **Proudfoot Award in Experimental Science.** University of Otago, Dunedin, New Zealand. 1998
- **Shepherd Scholarship in Research Science.** Guardian Trust Estate Administrators, New Plymouth, New Zealand. 1996-1999

B. Selected Peer-Reviewed Publications

1. Lansing, J.S., **M.P. Cox**, S.S. Downey, M.A. Janssen and J.W. Schoenfelder. (2009) A Robust Budding Model of Balinese Water Temple Networks. *World Archaeology* **41**:112-133.
2. **Cox, M.P.**, F.L. Mendez, T.M. Karafet, M. Metni Pilkington, S.B. Kingan, G. Destro-Bisol, B.I. Strassmann and M.F. Hammer. (2008) Testing for Archaic Hominin Admixture on the X-Chromosome: Model Likelihoods for the Modern Human *RRM2P4* Region from Summaries of Genealogical Topology under the Structured Coalescent. *Genetics* **178**:427-437.
3. **Cox, M.P.**, A.E. Woerner, J.D. Wall and M.F. Hammer. (2008) Intergenic DNA Sequences from the Human X Chromosome Reveal High Rates of Global Gene Flow. *BMC Genetics* **9**:e76.
4. **Cox, M.P.** (2008) Accuracy of Molecular Dating with the Rho Statistic: Deviations from Coalescent Expectations under a Range of Demographic Models. *Human Biology* **80**:335-357.
5. **Cox, M.P.** (2008) The Genetic Environment of Melanesia: Clines, Clusters and Contact. In V.T. Koven (ed.), *Population Genetics Research Progress*, Chapter 2. Nova Science Publishers: New York, pp 45-83.
6. Downey, S.S., B. Hallmark, **M.P. Cox**, P. Norquest and J.S. Lansing. (2008) Computational Feature-Sensitive Reconstruction of Language Relationships : Developing the ALINE Distance for Comparative Historical Linguistic Reconstruction. *Journal of Quantitative Linguistics* **15**:340-369.
7. Hammer, M.F., F.L. Mendez, **M.P. Cox**, A.E. Woerner and J.D. Wall. (2008) Sex-Biased Evolutionary Forces Shape Genomic Patterns of Human Diversity. *PLoS Genetics* **4**:e1000202.
8. Hagelberg, E., **M.P. Cox**, W. Schiefenhövel and I. Frame. (2008). A Genetic Perspective on the Origins and Dispersal of the Austronesians: Mitochondrial DNA Variation from Madagascar to Easter Island. In A. Sanchez-Mazas, R. Blench, M.D. Ross, I. Peiros and M. Lin (eds.), *Past Human Migrations in East Asia: Matching Archaeology, Linguistics and Genetics*, Chapter 16. Routledge: London, pp 356- 375.
9. Lansing, J.S., J.C. Watkins, B. Hallmark, **M.P. Cox**, T.M. Karafet, H. Sudoyo and M.F. Hammer. (2008) Male Dominance Rarely Skews the Frequency Distribution of Y Chromosome Haplotypes in Human Populations. *Proceedings of the National Academy of Sciences U.S.A.* **105**:11645-11650.
10. Metni Pilkington, M., J.A. Wilder, F.L. Mendez, **M.P. Cox**, A. Woerner, T. Angui, S. Kingan, Z. Mobasher, C. Batini, G. Destro-Bisol, H. Soodyall, B.I. Strassmann and M.F. Hammer. (2008) Contrasting Signatures of Population Growth for Mitochondrial DNA and Y Chromosomes among Human Populations in Africa. *Molecular Biology and Evolution* **25**:517-525.
11. Russell, A.L., S.M. Goodman and **M.P. Cox**. (2008) Coalescent Analyses Support Multiple Mainland-to-Island Dispersals in the Evolution of Malagasy *Triaenops* Bats (Chiroptera: Hipposideridae). *Journal of Biogeography* **35**:995-1003.
12. Wall, J.D., **M.P. Cox**, F.L. Mendez, A. Woerner, T. Severson and M.F. Hammer. (2008) A Novel DNA Sequence Database for Analyzing Human Demographic History. *Genome Research* **18**:1354-1361.
13. **Cox, M.P.**, A.J. Redd, T.M. Karafet, C.A. Ponder, J.S. Lansing, H. Sudoyo and M.F. Hammer. (2007) A Polynesian Motif on the Y Chromosome: Population Structure in Remote Oceania. *Human Biology* **79**:525-535.
14. Garrigan, D., S.B. Kingan, M. Metni Pilkington, J.A. Wilder, **M.P. Cox**, H. Soodyall, B. Strassmann, G. Destro-Bisol, P. de Knijff, A. Novelletto, J. Friedlaender and M.F. Hammer. (2007) Inferring Human Population Sizes, Divergence Times and Rates of Gene Flow from Mitochondrial, X and Y Chromosome Resequencing Data. *Genetics* **177**:2195-2207.
15. Lansing, J.S., **M.P. Cox**, S.S. Downey, B.M. Gabler, B. Hallmark, T.M. Karafet, P. Norquest, J.W. Schoenfelder, H. Sudoyo, J.C. Watkins and M.F. Hammer. (2007) Coevolution of Languages and Genes on the Island of Sumba, Eastern Indonesia. *Proceedings of the National Academy of Sciences U.S.A.* **104**:16022-16026.
16. Woerner, A.E., **M.P. Cox** and M.F. Hammer. (2007) Recombination-Filtered Genomic Datasets by Information Maximization. *Bioinformatics* **23**:1851-1853.
17. **Cox, M.P.** (2006) Extreme Patterns of Variance in Small Populations: Placing Limits on Human Y-Chromosome Diversity through Time in the Vanuatu Archipelago. *Annals of Human Genetics* **71**:390-406.

18. **Cox, M.P.** (2006) Minimal Hierarchical Analysis of Global Human Y-Chromosome SNP Diversity by PCR-RFLP. *Anthropological Science* **114**:69-74.
19. **Cox, M.P.**, and M. Mirazón Lahr. (2006) Y-Chromosome Diversity Is Inversely Associated with Language Affiliation in Paired Austronesian- and Papuan-Speaking Communities from Solomon Islands. *American Journal of Human Biology* **18**:35-50.
20. **Cox, M.P.** (2005) Indonesian Mitochondrial DNA and Its Opposition to a Pleistocene Era Origin of Proto-Polynesians in Island Southeast Asia. *Human Biology* **77**:179-188.

C. RESEARCH SUPPORT

Ongoing Research Support
None

Pending Research Support
None

Completed Research Support
WGF 2006 Cox (PI) 2006
Wenner-Gren Foundation, New York, USA
Determining Prehistoric Interaction Spheres from Commensal Genetics: *Canarium indicum* in the Solomons Archipelago. The major goal was to determine whether human movement could be reconstructed from the genetics of commensal species.

RESEARCH & RELATED Other Project Information

1. * Are Human Subjects Involved? [X] Yes [ ] No

1.a If YES to Human Subjects

Is the IRB review Pending? [ ] Yes [X] No

IRB Approval Date: 10/16/2008

Exemption Number: [X] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6

Human Subject Assurance Number: 00004218

2. * Are Vertebrate Animals Used? [ ] Yes [X] No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? [ ] Yes [ ] No

IACUC Approval Date:

Animal Welfare Assurance Number

3. * Is proprietary/privileged information included in the application? [ ] Yes [X] No

4.a. * Does this project have an actual or potential impact on the environment? [ ] Yes [X] No

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? [ ] Yes [ ] No

4.d. If yes, please explain:

5.a. * Does this project involve activities outside the U.S. or partnership with International Collaborators? [X] Yes [ ] No

5.b. If yes, identify countries: Indonesia

5.c. Optional Explanation:

6. * Project Summary/Abstract Abstract.pdf Add Attachment | Delete Attachment | View Attachment

7. * Project Narrative Project Narrative.pdf Add Attachment | Delete Attachment | View Attachment

8. Bibliography & References Cited Bibliography.pdf Add Attachment | Delete Attachment | View Attachment

9. Facilities & Other Resources Facilities_Description_Combined.pdf Add Attachment | Delete Attachment | View Attachment

10. Equipment Eqpmt_Description.pdf Add Attachment | Delete Attachment | View Attachment

11. Other Attachments Add Attachments | Delete Attachments | View Attachments

OMB Number: 4040-0001
Expiration Date: 04/30/2008

The susceptibility of an individual to infectious disease is influenced by which genes they inherit and whether their ancestors underwent selection for resistant genotypes. The goal of this project is to elucidate the co-evolutionary history of humans and two infectious diseases, malaria and hepatitis B, in the Indonesian archipelago. We will first reconstruct the population history of village clusters across several Indonesian islands using neutral genetic markers, historical linguistics, and archaeology. Subsequently we will investigate the evolutionary history of disease resistance markers, which reflect strong natural selection by pathogen species. This will facilitate inferences about the causal mechanisms – such as ecological gradients, kinship practices, patterns of admixture, and demographic history – structuring variability at loci under selection in both hosts and pathogens. Because malaria and hepatitis differ in their patterns of transmission and response to environmental factors, studying both diseases in the same populations will help to clarify the diversity of host-parasite co-evolutionary dynamics.

The proposed research builds on an ongoing collaboration between researchers at the University of Arizona and the Eijkman Institute for Molecular Biology, which is responsible for the oversight of all genetic research in Indonesia. With prior support from three NSF grants, we gathered genetic, demographic, linguistic, ethnographic and environmental data from 2921 individuals in 69 villages on 13 Indonesian islands. Using these data we propose to investigate the evolutionary relationships between host genetics and infectious diseases; interactions between pathogens in endemic regions; the impact of different modes of transmission on disease ecology and evolution; and the evolution of drug resistance.

This project complements ongoing global whole-genome projects such as *1000 Genomes* and the *HapMap*. By focusing on finer geographic and temporal scales, we will attempt to resolve the environmental, demographic and co-evolutionary processes that generate the patterns observed in these global datasets. The Indonesian archipelago is especially well suited to this approach, exhibiting well-defined patterns of admixture reflecting successive Holocene migrations. Our team includes expertise in the epidemiology of tropical diseases, anthropology, demography and population genetics, modeling and inference, clinical medicine and public health in Indonesia.

Public Health Relevance

Understanding the co-evolution of human populations and pathogens is fundamental to controlling disease and devising effective public health programs. We will investigate the evolutionary relationships between host genetics and infectious diseases; interactions between pathogens in endemic regions; the impact of different modes of transmission on disease ecology and evolution; and the evolution of drug resistance. This project continues an ongoing collaboration with the Eijkman Institute for Molecular Biology in Jakarta, which has overall responsibility for genetic research in Indonesia, and works closely with the Indonesian Public Health Service. Anticipated benefits include insights into the evolution of these diseases and patterns of drug resistance in the archipelago; mapping and targeting of at-risk populations; development of predictive models for assessing the likely outcomes of different public health control programs; and strengthened international collaboration with Indonesian researchers.

8: Bibliography

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8. Cox MP. Indonesian mitochondrial DNA and its opposition to a Pleistocene era origin of proto-Polynesians in island southeast Asia. Hum Biol 2005;77:179-88
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UAGC RESOURCES AND ENVIRONMENT

The University of Arizona Genetics Core Facility is a multi-user, state subsidized, non-profit service core facility specializing in cutting edge genomics research. The University of Arizana Genetics Core Facility provides service to both in-state and out-of-state academics researchers as well as the private sector. The facility is run by Dr. Michael Hammer and operated by a full time staff of 10 technicians and specialists at FTE 1. The main focus of the University of Arizona Genetics Core Facility is to provide a range of molecular biology services, instruction in current molecular genetic methods, and an economical pay per service sequencing, genotyping, and informatics units. The research facility is comprised of two adjacent laboratories covering 3500 square feet of wet lab and equipment space as well as 1500 square feet of computing, office, and interactive space (see http://uagc.arl.arizona.edu).

DR MICHAEL HAMMER'S ENVIRONMENT

Dr. Hammer's lab space also occupies approximately 2,000 square feet on the University of Arizona Campus in a separate building from the work that will be done through the University of of Arizona Genetics Core .

Santa Fe Institute Facilities and Resources Statement

Facilities

The Institute's campus at 1399 Hyde Park Road currently provides 23,500 square feet of facilities, surrounded by 32 park-like acres. SFI has retained all but a fraction of the site in this natural state as part of its commitment to creating an environment conducive to scientific research. The building includes a large conference room seating up to 75, several small meeting rooms, administrative offices for a staff of 25, computer facilities, library space and shared office space for up to 50 scientists. The Institute's campus has no residential facilities. Its various Schools are held at residential colleges in the area, usually at St. John's College in Santa Fe.

Information Technology

The Institute has a fiber-optic network backbone connecting two hundred multi-function network ports around the facilities. Six megabits (Mbp/s) of Internet connectivity connect this network to the outside world for high-speed data transmission and to encourage real-time collaborations.

Scientific computing resources at SFI include 10 SMP (symmetric multi processor) workstations and servers, 20 64-bit Linux workstations, 15 additional Linux workstations, several Windows-based workstations, and approximately 30 Macintosh workstations, most of which are used by the staff. Administrative computing resources consist of around 20 servers for use in hosting SFI's website, email services, and other communication and network-based requirements for keep SFI "in touch" in today's technological world.

The institute has developed and deployed a scientific information management system, including a content management system (CMS), calendaring system and associated XML database, for storing, managing, searching and distributing the products of scholarship at the Institute. In addition, the Institute provides hosted community services to its extended research community, educational alumni, international fellows, and corporate collaborators. Online portals provide a platform and tools to support and foster the exchange of scientific information among these constituencies, and webcasting and podcasting capabilities extend the reach of the Institute's research programs to a broader audience.

Library

The current library collection includes about 12,000 volumes - a collection which represents the research profile of SFI science. Researchers and staff have access to a variety of tools on the World Wide Web (such as First Search, Web of Science, JSTOR, Inspec, and many others). In addition, First Search provides access to WorldCat, a database of over 50 million books in libraries worldwide. Library facilities are supplemented by subscriptions to hundreds of electronic journals as well as interlibrary loan arrangements nationwide. The Library is a member of AISTI, a science library consortium, giving SFI full access to member libraries, including Los Alamos National Laboratory and the University of New Mexico. Library staff provides complete support for researchers, including document delivery and research assistance.

Eijkman Institute facilities

The Eijkman Institute for Molecular Biology is a biomedical research institute under the auspices of and responsible directly to the Indonesian Minister for Research and Technology. It traces its origin to the Research Laboratory for Pathology and Bacteriology, founded in 1888 with Christiaan Eijkman as its first Director. The current Eijkman Institute, is a molecular cell biology research institute located in the historical building of the Eijkman Institute in central Jakarta. The 5,500 sq.m. complex includes extensive laboratories for molecular biology including a Biosafety Level 3 facility. It is staffed by about 75 scientists, working in six major research programs, five of which will be involved in this project:

Human Genome Diversity. Taking advantage of the huge human genetic resource of Indonesia, as reflected by its many ethnic populations, this fundamental research activity is strategic as the basis for disease genes discovery, with their medical and biotechnological applications.

Red Blood Cell Genetic Disorders. The definition of mutations underlying diseases such as the thalassemias in the ethnically diverse Indonesian populations, the biochemical and clinical manifestations of such mutations, and knowledge applications in prenatal diagnosis are important for the management of these most common genetic disorders.

Genetic Variants and Resistance to Malaria. The molecular mechanisms by which polymorphic variants of the red blood cells confer resistance towards malaria is not only of interest for its medical application but also of a fundamental biological importance.

The Molecular Basis of Malaria Infection. Includes studies on the molecular basis of resistance to antimalaria drugs and of cerebral malaria, and the development of new diagnostic methods and vaccines.

Hepatitis Viruses and their Genetic Diversity. The molecular characterization of hepatitis viruses and their variation, in particular of Hepatitis B and C, and the understanding of their pathogenic mechanism, is of strategic importance for diagnostic, vaccination and treatment strategies.

Selected Equipment housed in the UAGC:

(1) - Genome Sequencer FLX GS Roche
(3) - 3730XL - DNA Analyzer for sequencing
(1) - 3730 - DNA Analyzer for Fragment Analysis
(1) - Biomek NX Liquid handeling robot
(1) - Sequenom MassArray MALDI-TOF mass spectrometer
(1) - SNPstream high-throughput genotyping reader
(1) - Biomek FX liquic handeling robot
(1) - Matrix PlateMate - Automated Liquid Pipettor robot
(1) - RS1000 Nanodispenser robot
(1) - Abi 7900 realtime PCR engine
(2) - Abi 7300 realtime PCR engine
(1) - Bio-Rad iCycler Real time PCR engine
(1) - Tissue Lyser II
(1) - Z1 Coulter Particle Counter
(1) - Microarray Printer
(1) - Microarray Scanner
(1) - C02 Incubator ATP.Line C150
(1) - TBS-380 Fluorometer
(1) - Flx 800 Flourescent plate reader
(1) – Bioanalyzer (Agilent)
(2) - PCR Laminar flow hood
(1) - Isotemp Incubator
(1) - GeneChip Hybridization Oven
(4) - large rotor plate centrifuges
(2) - Mini centifuge
(3) – plate/tube speed vac
(4) - Applied Biosystems GeneAmp 9700 - 384well thermocyclers
(12) – MJ Reasearch Tetrad thermocyclers
(2) - ND-1000 Spectrophotometer
(1) - DU-64 spectrophotometer
(1) - ALPS 50V - plate sealer
(1) - UV stratalinker
(3) - freezer (-20 degree)
(2) – refrigerator (4 degree)
(2) - Polyacrylamide/agarose electrophoresis units

RESEARCH & RELATED Project/Performance Site Location(s)

Project/Performance Site Primary Location

Organization Name: Arizona Board of Regents, University of Arizona

* Street1: BioSciences West, Room 239

Street2: 1041 E. Lowell St.

* City: Tucson County:

* State: AZ: Arizona Province:

* Country: USA: UNITED STATES * ZIP / Postal Code: 85721

Project/Performance Site Location 1

Organization Name: Santa Fe Institute

* Street1: 1399 Hyde Park Rd

Street2:

* City: Santa Fe County:

* State: NM: New Mexico Province:

* Country: USA: UNITED STATES * ZIP / Postal Code: 87501

Additional Location(s) Add Attachment | Delete Attachment | View Attachment

OMB Number: 4040-0001
Expiration Date: 04/30/2008

RESEARCH & RELATED Project/Performance Site Location(s)

Project/Performance Site Primary Location

Organization Name: Arizona Board of Regents, University of Arizona

* Street1: BioSciences West, Room 239

Street2: 1041 E. Lowell St.

* City: Tucson County:

* State: AZ: Arizona Province:

* Country: USA: UNITED STATES * ZIP / Postal Code: 85721

Project/Performance Site Location 2

Organization Name: Eijkman Institute for Molecular Biology

* Street1: Jl Diponegoro 69

Street2:

* City: Jakarta County:

* State: Province:

* Country: IDN: INDONESIA * ZIP / Postal Code: 10430

Additional Location(s) Add Attachment Delete Attachment View Attachment

OMB Number: 4040-0001
Expiration Date: 04/30/2008

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix:
* First Name: John
Middle Name: S
* Last Name: Lansing
Suffix: Ph.D.

* New Investigator? ☐ No ☒ Yes

Degrees: PhD | MA | BA

2. Human Subjects

Clinical Trial? ☒ No ☐ Yes

* Agency-Defined Phase III Clinical Trial? ☐ No ☐ Yes

3. Applicant Organization Contact

Person to be contacted on matters involving this application

Prefix:
* First Name: Sherry
Middle Name:
* Last Name: Esham
Suffix:

* Phone Number: (520) 626-6000
Fax Number:
Email: sponsor@u.arizona.edu

* Title: Multi-Scale Coevolution of Infectious Disease

* Street1: BioSciences West, Room 239
Street2: 1041 E. Lowell St.
* City: Tucson
County:
* State: AZ: Arizona
Province:
* Country: USA: UNITED STATES
* Zip / Postal Code: 85721

PHS 398 Cover Page Supplement

4. Human Embryonic Stem Cells

* Does the proposed project involve human embryonic stem cells? ☒ No ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/registry/index.asp. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): ☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

OMB Number: 0925-0001

PHS 398 Research Plan

1. Application Type:

From SF 424 (R&R) Cover Page and PHS398 Checklist. The responses provided on these pages, regarding the type of application being submitted, are repeated for your reference, as you attach the appropriate sections of the research plan.

*Type of Application:

☒ New ☐ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

2. Research Plan Attachments:

Please attach applicable sections of the research plan, below.

1. Introduction to Application		Add Attachment	Delete Attachment	View Attachment
(for RESUBMISSION or REVISION only)				
2. Specific Aims	Specific aims.pdf	Add Attachment	Delete Attachment	View Attachment
3. Background and Significance	Background and Significance	Add Attachment	Delete Attachment	View Attachment
4. Preliminary Studies / Progress Report		Add Attachment	Delete Attachment	View Attachment
5. Research Design and Methods	Research Design.pdf	Add Attachment	Delete Attachment	View Attachment
6. Inclusion Enrollment Report		Add Attachment	Delete Attachment	View Attachment
7. Progress Report Publication List		Add Attachment	Delete Attachment	View Attachment

Human Subjects Sections

Attachments 8-11 apply only when you have answered "yes" to the question "are human subjects involved" on the R&R Other Project Information Form. In this case, attachments 8-11 may be required, and you are encouraged to consult the Application guide instructions and/or the specific Funding Opportunity Announcement to determine which sections must be submitted with this application.

8. Protection of Human Subjects	Human Subjects.pdf	Add Attachment	Delete Attachment	View Attachment
9. Inclusion of Women and Minorities		Add Attachment	Delete Attachment	View Attachment
10. Targeted/Planned Enrollment		Add Attachment	Delete Attachment	View Attachment
11. Inclusion of Children		Add Attachment	Delete Attachment	View Attachment

Other Research Plan Sections

12. Vertebrate Animals		Add Attachment	Delete Attachment	View Attachment
13. Select Agent Research		Add Attachment	Delete Attachment	View Attachment
14. Multiple PI Leadership Plan	Multiple PI Leadership plan	Add Attachment	Delete Attachment	View Attachment
15. Consortium/Contractual Arrangements	ConsortLtr_Santa Fe.pdf	Add Attachment	Delete Attachment	View Attachment
16. Letters of Support	Eikman letter.pdf	Add Attachment	Delete Attachment	View Attachment
17. Resource Sharing Plan(s)		Add Attachment	Delete Attachment	View Attachment

18. Appendix Add Attachments | Remove Attachments | View Attachments

2: Specific Aims

The goal of this project is elucidate the co-evolutionary history of humans and infectious diseases in the Indonesian archipelago, using two important diseases of the region as case studies: malaria and hepatitis B. The proposed research builds on an ongoing collaboration between researchers at the University of Arizona and the Eijkman Institute for Molecular Biology, which is responsible for the oversight of all genetic research in Indonesia. With support from three NSF grants, we gathered genetic, demographic, linguistic, ethnographic and environmental data from 2,921 individuals in 69 villages on 13 Indonesian islands. These samples represent the repository of DNA from which we will generate new data in this proposal. Based on these new data, we will investigate (1) the evolutionary relationships between host genetics and infectious diseases, (2) interactions between pathogens in endemic regions, (3) the impact of transmission mode on disease ecology and evolution, and (4) the evolution of drug resistance. To accomplish these goals we propose the following specific aims:

Aim 1: Reconstruct the history of human settlement within the study region using neutral genetic markers, language, ethnology and archaeology. Infer time of arrival, ancestral population sizes, migration patterns, and admixture rates, as well as the impact of kinship structures and post-marital residence.

Aim 2: Establish how patterns of genetic admixture vary across different spatial scales, from villages to islands and larger regions in the Indonesian archipelago. In our repository of > 2,900 samples:

- Genotype 40 highly informative SNPs (~20 autosomal and ~20 X-linked) that show high frequency differences between southern Chinese and highland Papua New Guinean populations.
- Genotype a panel of 16 highly polymorphic autosomal STRs from our human database.

Aim 3: Determine the extent of sex bias in migration patterns and admixture rates.

- Compare levels of diversity, migration rates, ancestral population sizes, and patterns of admixture based on X-linked and autosomal markers with those previously inferred from Y-chromosomal and mitochondrial markers from the same populations.

Aim 4: Investigate how the prevalence, population structure, and patterns of transmission of HBV relate to the cultural and demographic history of Indonesian populations.

- Estimate contributions of horizontal and vertical transmission to HBV population structure. Analyze antigenic structuring of the viral population; determine whether there is an interaction between HBV and malaria parasite infection; correlate prevalence with protective host alleles.

Aim 5: Determine how the prevalence and distribution of malaria-protective alleles have been shaped by (1) the admixture of Austronesian and Papuan populations, (2) selection by *Plasmodium* species, (3) epistatic and other interactions among protective variants, and (4) environmental factors.

- Compare introgression of loci under selection due to malaria in regions of varying transmission and prevalence to patterns of diversity among neutral genes.

Aim 6: Analyze the level and evolution of drug resistance within the malaria parasite populations in the region; infer selection pressure driving resistance among different regions.

- Develop predictive models for assessing the likely outcomes of public health control programs.

3: Background and significance

3.1: Innovative aspects of the project

The co-evolutionary arms race between host and pathogen is one of the most important selective processes driving the genetic structure of both species. Understanding how the evolutionary history of humans has been shaped by infectious disease is an important step towards identifying the genetic mechanisms determining susceptibility and resistance to pathogens, and the design of effective public health interventions. Although large-scale sequencing projects are rapidly generating genetic data from pathogen species, the size and complexity of the human genome have so far limited the power of clinical or genome-wide association studies to infer how human populations have responded to selection by pathogens.

Natural selection operates on different geographical scales, and selection for specific alleles varies in different parts of the world [1-3]. Moreover, the complex patterns of migration and admixture in human populations hamper our ability to distinguish the effects of selection from those of demographic history [4, 5]. Reconstructing the co-evolutionary history of humans and pathogens therefore requires an understanding of the underlying genetic structure of a particular human population on a micro-geographic scale before the effects of selection by pathogens can be explored.

We will analyze these dual aspects of host-pathogen co-evolution simultaneously. To establish the underlying genetic structure of our host population we will use detailed genetic, demographic, linguistic, and archaeological data from nearly 3000 individuals living in 69 villages on 13 Indonesian islands, which have already been collected as part of an ongoing collaboration involving Indonesian and American researchers, and the Indonesian Public Health Service. To understand how selection by pathogens has affected these communities, we will analyze a comprehensive set of human genetic loci known to be involved in immunity and protection against disease for the same individuals, as well as the population structure of the pathogen species they are carrying. In contrast to global, whole-genome analyses currently underway, therefore, our study will analyze these selective processes at a micro-geographic scale, providing unique insight into human-pathogen co-evolution within diverse human populations of known demographic history.

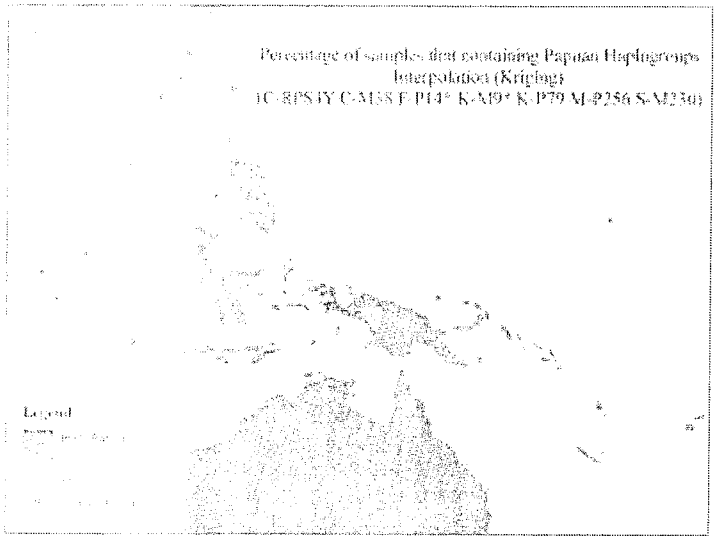
3.2: Relevant features of the demographic history of the Indonesian archipelago

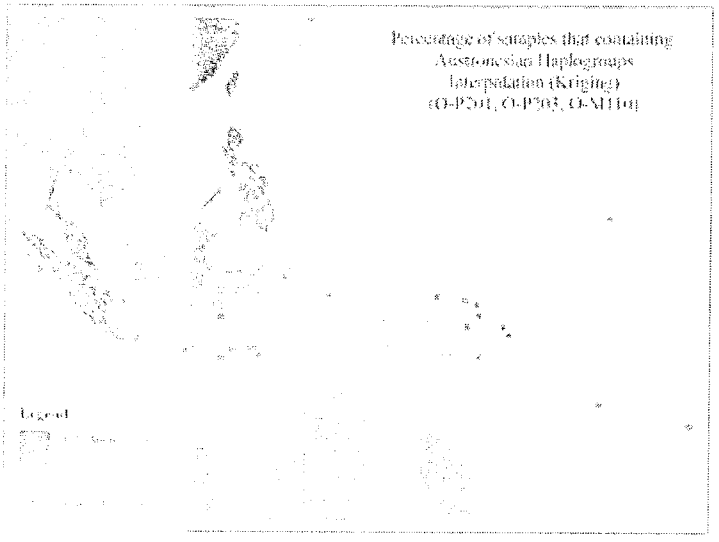
In the 1960's, geneticist Luca Cavalli-Sforza showed that a large-scale association exists between human genetic and language phylogenies. Ever since, researchers have observed varying statistical associations between genes, language families, and geography at continental or sub-continental scales. But all such patterns must originate from processes occurring at the community level. Since 2000, we have investigated variation in social structure, demography and language speciation in Indonesian villages. For example, we showed that it is possible to reconstruct the history of the arrival and expansion of prehistoric Austronesian-speaking farmers on the island of Sumba, about 4,000 years ago, because traces of their languages and genes persist in varying quantities in different parts of the island [6]. The combination of fine-grained linguistic and genetic information detected historical patterns of social interaction and language change on a scale of time and space that had not previously been observed.

Recently we have begun to investigate the co-evolution of hosts and pathogens in these villages. Our preliminary data from 12 villages shows significant variation at this scale in all of the relevant parameters, including levels of infection and frequencies of resistance markers. Two features of the late Holocene demographic history of these islands suggest that an expanded sample of islands and villages should lead to insights into the underlying mechanisms. The first feature is the long-term stability of these populations: on many islands, rates of migration are very low and communities have persisted for many generations. Hence there has been time for evolutionary changes in both hosts and pathogens to develop and persist, creating the diversity we see today. Second, there is a relatively clear pattern of

genetic variation between the older "Papuan" populations in Indonesia, which began to arrive approximately 50,000 years ago, and the most recent colonists from mainland Asia, the Austronesians, who began to arrive about 4,000 years ago. Ancestral populations of Papuans and Austronesians experienced very different environments in the Holocene. Figure 1 shows the distribution of Y-chromosome haplogroups or paragroups in 55 populations from Indonesia, Southeast Asia, and Oceania. There is substantial variation from eastern to western Indonesia, as shown in Figure 1, with Austronesian haplogroups dominating in the west and Papuan in the east. The four most prevalent haplogroups in eastern Indonesia (C-M38, K-M9*, M-P256, and S-M230), which account for 65% of eastern Indonesian Y chromosomes, are absent or only marginally present in western Indonesia.

Figure 1: Geographic distribution of 55 NRY haplogroups from Indonesia, Southeast Asia, and Oceania. Top: the older Papuan populations. Bottom: Austronesian haplogroups. Dots indicate sampled populations.





Along with Y-chromosome studies, a number of mitochondrial DNA and autosomal genetic studies have also attempted to investigate the Austronesian expansion, many focusing on peopling of Polynesia.

Some authors favor the rapid migration or "express train" [7] model out of Taiwan [8-13], while others prefer a major contribution to the Polynesian gene pool from eastern Indonesia and Melanesia [14-18]. A recent paper by Li et al. [19] proposed Daic populations as a source of paternal lineages for Taiwan aborigines and Indonesians. The definitive origins of Austronesians will not be unraveled until all disciplines characterize pre-Lapita populations in Wallacea and post-Lapita population movements in Remote Oceania [20]. Our preliminary analysis of Y-chromosome SNP and STR variation suggests that the settlement history was complex, with multiple waves of migration from different parts of Asia. In this proposal we plan to examine patterns of variation at diverse genetic markers in samples of populations from across the Indonesian archipelago (and source populations in Southeast Asia and Melanesia) to reconstruct the population history of the region.

3.3: Co-evolution of humans and pathogens

We have chosen two contrasting pathogens for our analysis of host-pathogen co-evolution in this unique study region, the malaria parasite (including four species of *Plasmodium*) and the Hepatitis B Virus (HBV). Both these pathogens are prevalent throughout the study area, cause significant levels of morbidity and mortality, and embody the two sides of host-pathogen co-evolution, selection by hosts on pathogens, and selection by pathogens on hosts. HBV is primarily transmitted vertically, and the genetic diversity of the virus appears to correlate well with the demographic structure of human populations, exhibiting particularly interesting population structure in Southeast Asia in general, and Indonesia in particular [21, 22]. By analyzing the population structure of HBV in our study region we will be able to infer how transmission patterns and immune selection, mediated by behavioral patterns within human populations, have structured viral diversity. In contrast, the malaria parasite has inflicted the strongest selective pressure on the human genome of any pathogen in our recent evolutionary history, and is transmitted by mosquito vectors on short spatial scales. We will analyze the impact of malaria on the human genome across different geographical scales within our study area, providing a detailed map of the effects of this selection against the background of the neutral genetic structure discussed above. In addition, for both pathogen species we will explore associations between current infection status and host genotype.

3.3.1: Selection on pathogens by humans – HBV population structure

Hepatitis B Virus (HBV) is endemic in Southeast Asia, chronically infecting five to ten percent of the population [23-25]. Transmitted vertically from mother to child during birth, or through contact with blood or other bodily fluids, HBV is highly contagious and represents a serious cause of morbidity and mortality through cancer and cirrhosis. Among the chronically infected, ~40% develop cancer and/or liver disease later in life (see, *e.g.,* [26, 27]). The HBV antigen exhibits substantial diversity at the population level; eight genotypes have been identified globally, some of which are classified further into several subgroups [28], and these are generally distributed according to geography and ethnicity [29]. It has been suggested that particular genotypes (B and C) are prevalent in highly endemic regions like Indonesia because HBV is primarily transmitted vertically in this setting. Conversely, genotypes A, D, E, and F may be more prevalent in areas where horizontal transmission accounts for most infections (reviewed in [30]). Causal relationships between modes of transmission and HBV genotypes are not well understood, however. Ethnic and cultural factors have also been shown to be important indicators of HBV prevalence and genotypic distribution [31], but these relationships have yet to be clarified. David Muljono's laboratory at the Eijkman Institute is presently screening for HBV in Indonesian populations.

This project will provide unique insights into human and HBV co-evolution from three perspectives. First, it will provide detailed inferences regarding sex-specific demographic patterns (see below) that will permit the comparison of HBV and human matrilineal population structures. Second, the substantial diversity of HBV genotypes in the region will also allow us to investigate the relationship between HBV genotype and mode of transmission. Specifically, a study in Papua identified three genotypes – B, C, and D – in the region, with diversity at the subgroup level [22], and in 2008, Eijkman Institute researchers reported a

novel subgenotype, HBV/B7, associated with regional populations in the Nusa Tenggara islands of eastern Indonesia [21]. Third, the unprecedented micro-geographical detail on cultural, ethnic, and genetic relationships among villages provided by this dataset will allow us to address the importance of these ethnic and cultural factors in determining HBV prevalence and genotype distribution for the first time. Since the emphasis of public health strategies for controlling HBV will depend on the horizontal/vertical transmission ratio and behavioral aspects of susceptibility, quantifying these factors will have significant implications for control program design. We will compare the genetic structure of the HBV population with that of human genetic markers to infer the relative importance of horizontal and vertical transmission, as well as ethnic and cultural factors that influence the rates and patterns of transmission.

3.3.2: Selection on humans by pathogens – the evolution of resistance to malaria

The human malaria parasite imposes one of the strongest selective forces on human populations of any pathogen, since it primarily kills young children, and has had a profound impact on the human genome during our recent evolutionary history [32]. This intense selection pressure probably began with the advent of slash and burn agriculture approximately 10,000 years ago, which facilitated the spread of the mosquito vector *Anopheles gambiae*, and allowed malaria parasite species to emerge *[33]*. Four protozoan species of the genus *Plasmodium* are responsible for causing human malaria: *Plasmodium falciparum, P. vivax, P. malariae*, and *P. ovale*. All four species of human malaria parasite are endemic in Indonesia, reaching extremely high rates of infection. Prevalence is highly variable, however, and little is known about how the species interact epidemiologically [34, 35].

The evolution of human populations in response to selection by malaria has resulted in a range of resistance markers affecting human red blood cells, which the parasites invade during infection, and various components of the immune system. For example, approximately 7% of the global population are carriers for hemoglobin disorders (http://www.who.int/en/), making them the most common genetic diseases of human populations. There is also increasing support for the theory that natural selection by pathogen species, particularly malaria parasites, is responsible for generating the extreme polymorphism of the human major histocompatibility complex (MHC) [36, 37]. These loci encode the human leukocyte antigens (HLA), whose function is to present particular peptide fragments from intracellular degradation on the surface of host cells and initiate an immune response. Since the wider the range of pathogen epitopes the HLA loci can present, the broader the protection offered by an individual's immune system, it has been suggested that co-evolution with pathogen species has led to the high levels of polymorphism observed in human populations. Particular HLA alleles have been associated with protection against severe malaria, and show extremely high frequencies in endemic areas [38-40].

Although the extent and mechanisms of protection have only been elucidated for a handful of these alleles, the geographical overlap between these polymorphisms and malaria endemicity is highly suggestive that they provide protection against severe disease [41]. The diversity of different types of resistance markers occurring in different geographical locations is quite remarkable, however. For example, the hemoglobinopathies can be roughly divided into two groups, those that generate structural variants of hemoglobin and those that affect the synthesis of α- and β-globin subunits; the thalassemias. Over 700 structural hemoglobin variants have been identified worldwide [42], and over 200 different mutations of the β-globin gene have been found in patients with β-thalassemia [43]. Apart from the general correlation with malaria prevalence, the distribution of some of these alleles, such as the mutation causing sickle hemoglobin, reflect the fact that they are balanced polymorphisms; heterozygotes are protected from severe malaria, but homozygotes for the resistance allele suffer from debilitating blood disorders [44]. Thus, they are strongly selected against in areas without malaria. Regional distribution may also be affected by interactions between resistance alleles, and it has recently been shown that the distribution of sickle hemoglobin and α-thalassemia reflects epistatic interactions between them, with inheritance of both mutations negating the protective effects of either one [45]. Other alleles may show non-overlapping distributions because they produce particularly severe blood disorders when they are inherited together, although these relationships have not been established for most

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mutations [43]. Currently we still have little understanding of how the distribution and combination of these alleles relates to natural selection by malaria parasites over the course of the last 10,000 years in different regions, although insights into these aspects of malaria resistance would provide invaluable targets for drug and vaccine design.

We will use an evolutionary approach to infer interactions between different malaria resistance alleles, leveraging detailed information about admixture between two distinct populations on a micro-geographic scale to assess selection for or against particular alleles in different transmission settings. Since both Papuan and Austronesian populations had previously been exposed to malaria, generating separate sets of resistance alleles, the mixing of these two populations led to a natural experiment in which different types of resistance markers were co-inherited to varying degrees. The study will not only provide unprecedented detail about the prevalence and combinations of various malaria-resistance markers in this region, it will also allow us to infer how selection has shaped combinations of alleles. Most studies try to assess the protective effects of these alleles by comparing clinical cases of varying severity or clinical versus asymptomatic cases. We take a different approach, looking for evidence of strong selection and asymmetries in the level of introgression of resistance markers compared to neutral loci among admixed populations. This control will give us an indication of long-term selection by malaria parasites, rather than depending on current prevalence and disease.

3.3.3: Drug resistance among malaria parasites in Southeast Asia

One of the most critical co-evolutionary processes occurring in the last century is the emergence of drug resistance among human pathogen species, particularly among malaria parasites. Drug resistance among malaria parasite populations in Southeast Asia is a global priority, since most of the global drug-resistance genes have originated in this region. Chloroquine resistance was first reported in Indonesian Papua in 1975, for example, and since then has been observed in all areas of the archipelago where studies have been conducted [46]. Chloroquine remains the first line treatment for malaria in Indonesia, despite the fact that day 28 failure rates of chloroquine in Eastern Indonesia exceed 65% for *P. vivax* and 52% for *P. falciparum* [47, 48]. The second line treatment in this region is a combination of sulfadoxine and pyremethamine (SP), however drug resistance to SP has also been widely observed across the country and throughout Southeast Asia [49]. A survey of drug resistance alleles in east Indonesia by Eijkman researchers uncovered considerable heterogeneity in the mutations causing drug resistance, including variants that are unique to this area, as well as African, South American, and Southeast Asian haplotypes [46, 50]. The evolution of these resistance genes is not fully understood, but represents an easily measurable aspect of host-pathogen co-evolution as well as a key public health priority. We will provide a detailed map of drug resistance alleles among malaria parasite populations in our study region. This will give insight into the evolution of drug resistance and the selection pressures on malaria parasites in the last several decades.

The establishment of a drug-resistance monitoring program in a local hospital in Sumba will allow us to analyze patterns of drug resistance over time. We hope to be able to provide insight into the best strategies and frontline therapies for this region, and detect the emergence of new types of drug resistance should new drugs, such as ACT, be introduced. We will develop a range of mathematical models to determine which public health strategies would be most effective in this area.

4: Prior results

This project is a further step in an ongoing collaboration between the Eijkman Institute in Indonesia and the University of Arizona that began in 2000. The Eijkman Institute collaborates with the Indonesian Public Health Service to map the genetic diversity of the archipelago, with the twin goals of identifying priorities for public health programs and developing more effective treatments. For example, recent publications by Eijkman researchers describe the discovery of a new biotype of HBV in eastern Nusa Tenggara, analyze the demographic breakdown of malaria infection by plasmodium species on the

island of Nias, report the public health status of malaria on the island of Sumba, and analyze the molecular epidemiology of *P. falciparum* resistance to antimalarial drugs in Indonesia [21, 46, 51, 52].

In 2000, Lansing (University of Arizona) began to work with Eijkman researchers to add an anthropological dimension to their research. With grant support from NSF, this collaboration eventually produced nearly 3000 genetic samples from 69 villages, collected with the assistance of the Indonesian Public Health Service, along with extensive demographic, environmental, ethnographic, linguistic and clinical information. This research was approved by the Institutional Review Boards of both the Eijkman Institute and the University of Arizona, and the Indonesian Ministry of Health. Following protocols agreed to by all of these parties, the goals of the research were carefully explained to subjects (usually by local Public Health clinical staff); those who agreed to participate gave written permission for their genetic materials, language samples and clinical and genealogical data to be used for medical research (see appendix: Subject Consent form). Genetic samples were shared by the Eijkman Institute and the Hammer lab at the University of Arizona.

The Eijkman team used their samples for medical research, while the Arizona researchers used theirs to reconstruct population genetic histories at the scale of individual villages and islands, and relate them to kinship patterns, environmental variation and language speciation. As the genetic and linguistic samples gradually accumulated, new analytical and computational tools were constructed for this purpose. They were needed because the anthropological questions go beyond the reconstruction of phylogenies and tests of statistical associations between genes, languages and geography. In essence, our goal was to understand the genesis and robustness of these patterns, by modeling processes that take place at the community scale. For example, how do marriage rules, migration histories or reproductive competition between descent groups affect the distribution of non-recombining Y-chromosome lineages in villages? This research has led to publications on models of microsatellite evolution to the co-evolution of languages and genes, the role of male dominance in 41 villages, Austronesian prehistory, historical linguistics, and the historical expansion of rice cultivation in Bali [6, 53-61].

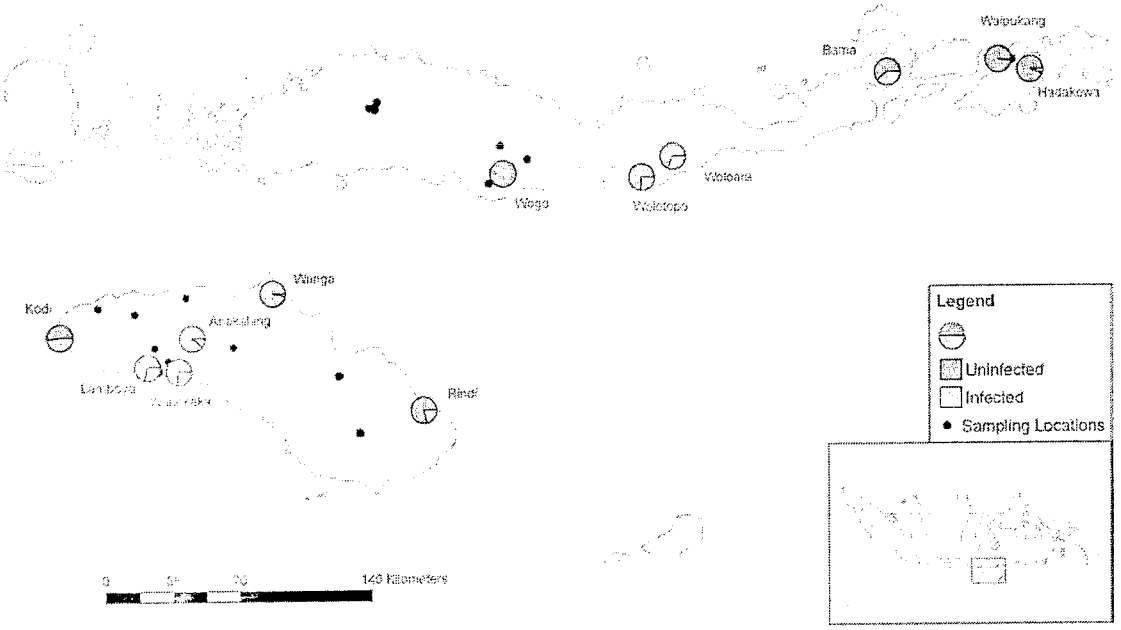
The new research proposed here is motivated by recent successful tests of the existing genetic samples for the presence of pathogens and host resistance markers. These preliminary tests show that we can sequence pathogen genetic material, and that there is intriguing variation in levels of infection, and in host and pathogen genetics between villages and islands, which can be analyzed in light of their demographic and environmental histories. For example, Table 1 and Figure 2 illustrate the prevalence of the four human malaria parasite species for 15 sampling locations on 5 islands within our study region.

Table 1: The prevalence of malaria infection for a subset of the study samples

		Single				Multiple							Total	
	Village	N	*f*	*m*	*o*	*v*	*fv*	*fm*	*fo*	*mv*	*mo*	*fvm*	Cases	%
FLORES		144	9	1	7	17	1		1	2			38	26.4
	Bajawa	49	5	1		10	1			2			19	38.8
	Waga	28											0	0
	Watetapa	28	1		2	5			1				10	26.3
	Watubara	39	3		5	1							9	31.0
LEMBATA		91	1			2							3	3.3
	Tanah Kedakewa	45	1			1							2	4.4
	Wagukung	46				1							1	2.2
SUMBA		256	9	3	1	28	8	5			3	1	2	60	23.4
	Anakalang	61				4	1							5	9.8
	Kodi	44	3	1		11		4			1		1	21	47.7
	Pindi	24	2	1		2								5	20.8
	Wunga	28	1											1	3.6
	Lambeya	49	2	1	1	4	4	1				1		14	28.6
	Wanokaka	52	1			2	3				2		1	14	26.9
NIAS		60												0	0
COASTAL NEW GUINEA		16	4											4	25
HIGHLAND NEW GUINEA		15												0	0
TOTAL		582	23	4	8	47	9	5	1	2	3	1	2	105	18
%			4.0	0.7	1.4	8.1	1.5	0.9	0.2	0.3	0.5	0.2	0.3		

f = *Plasmodium falciparum*
m = *Plasmodium malariae*
o = *Plasmodium ovale*
v = *Plasmodium vivax*

Figure 2: Prevalence of malaria in pilot data from 15 communities



Preliminary statistical analyses indicate that the variability in the level of infection observed both among and within islands is highly significant. Using Fisher's exact test, we have tested the null hypothesis that each village on a given island is subject to the same overall frequency of Plasmodium infection. The null hypothesis was rejected for Flores (4 villages, $p = 3.99 \times 10^{-4}$) and Sumba (6 villages, $p = 8.14 \times 10^{-6}$). The null hypothesis of equal frequency among islands was also strongly rejected (5 islands, $p = 3.34 \times 10^{-10}$) when the complete sample was considered. The null hypothesis was not rejected for comparison of only Sumba and Flores ($p = 0.54$). These results indicate substantial variation in pathogen prevalence at multiple scales in the study region, while at least two islands seem to have similar overall prevalence rates.

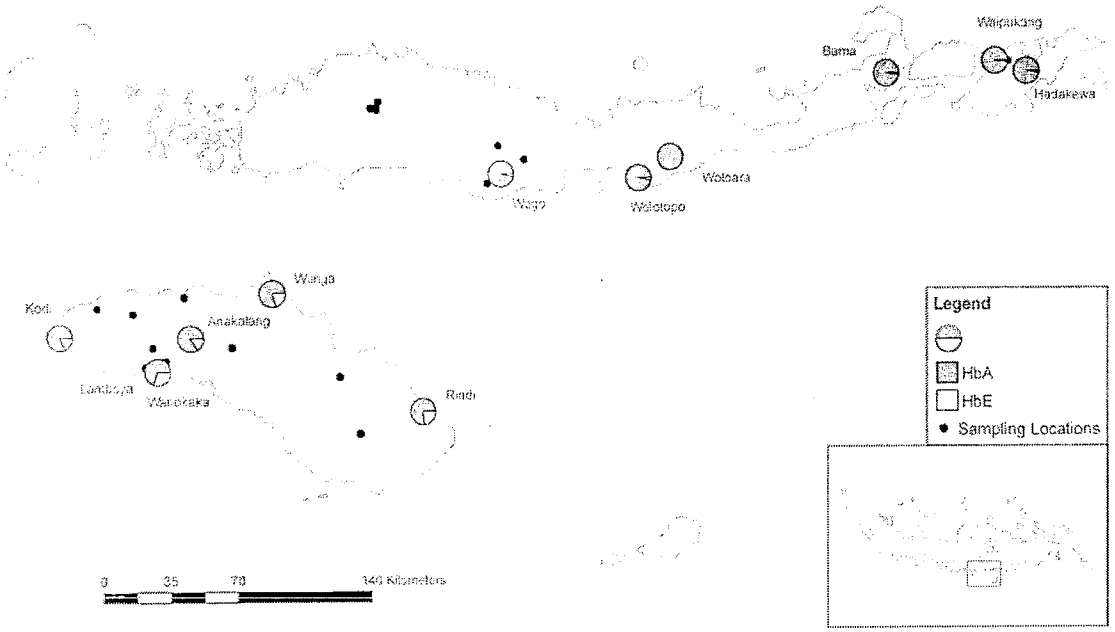
Table 2: The frequency of three resistance alleles among a subset of sampled individuals

	Hemoglobin E					CR1 (exon 22)					SLC4A1			
		Genotype			Freq		Genotype			Freq		Genotype		Freq
	N	(A,A)	(A,E)	(E,E)	E	N	(A,A)	(G,A)	(G,G)	G	N	(B,B)	(1,B)	(1,1)	1
FLORES	134	128	6		0.02	137	27	97	52	0.59	149	140	9		0.03
Bama	44	42	2		0.02	44	8	14	21	0.64	45	40	5		0.06
Wolowaru	28	28			0.00	26	4	8	15	0.70	29	29			0.00
Wolotopo	31	29	2		0.03	34	7	22	5	0.47	39	36	3		0.04
Wolga	31	29	2		0.03	31	8	12	11	0.55	36	35	1		0.01
LEMBATA	80	77	3		0.02	79	6	50	23	0.61	82	77	5		0.03
Desa Hadakewa	41	39	2		0.02	41	3	27	11	0.60	43	41	2		0.02
Waipukang	39	38	1		0.01	38	3	23	12	0.62	39	36	3		0.04
SUMBA	201	119	78	4	0.21	189	42	88	59	0.54	186	164	22		0.06
Anakalang	46	33	12	1	0.15	41	14	15	12	0.48	51	44	7		0.07
Kodi	43	28	15		0.17	41	5	22	14	0.61	43	38	5		0.06
Rindi	26	14	12		0.23	26	9	11	5	0.42	24	23	1		0.02
Wanokaka	51	23	25	3	0.39	51	9	29	13	0.54	39	35	4		0.05
Waingapu	35	21	14		0.20	31	5	11	15	0.66	29	24	5		0.09
NIAS	27	27			0					0.50					0
Gomo	21	21			0	28	7	14	7	0.50	22	22			0
Hilimbara	6	6			0	8	2	4	2	0.50	8	8			0
PNG	37	37			0	35	3	21	11	0.62	37	37			0
Madang	17	17			0	17	1	9	7	0.68	16	16			0
Highland	20	20			0	18	2	12	4	0.56	21	21			0
BALI	26	26			0	14	6	6	2	0.36	28	27	1		0.02

Table 2 shows the frequency of several resistance alleles in the same populations, and Figure 3 illustrates the geographic distribution of those allele frequencies. Preliminary analysis of the data shown in Table 2 suggests that the frequency of the HbE allele varies significantly (p = 2.2 X 10^{-16}) on different islands within the study region, with a frequency > 20% on Sumba, ~2% on Flores and Lembata, and no HbE in our samples from Nias, Bali, and PNG.

It has been suggested that HbE provides some protection against malaria virulence when heterozygous, but causes anemia when homozygous. In testing this allele for Hardy-Weinberg equilibrium, we found evidence for a surplus of heterozygotes on Sumba, consistent with this proposed protective effect (χ^2=5.26, p=0.022 based on village-by-village estimates of allele frequency; p=0.036 based on Fisher's exact tests, integrated over a binomial distribution on A/E and E/A genotypes).

Figure 3: Hemoglobin E levels in pilot data from 15 communities



The anemia associated with the HbE homozygotes is variable, but generally mild. However, double heterozygotes of HbE and β-thalassemia suffer severe anemia. The frequency of β-thalassemia in Indonesia is relatively high overall (~5-8%), and exhibits a high degree of regional variability within Indonesia, being virtually absent in parts of Sulawesi, and exceeding 10% in parts of Sumatra [43, 62, 63]. The selective pressures on HbE are likely to be highly variable in our study region, depending on the local frequency of β-thalassemia. The HbE allele dates back only 2,000-4,000 years [64] and the observed heterogeneity in the local frequency of HbE may reflect preexisting variation in the frequency of β-thalassemia at the time when this allele was first introduced.

One study has estimated that the selective advantage of the HbE heterozygote is approximately 8% [64]. Based on this estimate, it is possible to do a crude calculation to estimate this critical β-thalassemia level for HbE invasion. No estimates exist for the fitness cost of the HbE/β-thalassemia double heterozygote, so we simply assign this genotype a fitness value of $w_{\beta E}$ and assume that the frequency of β-thalassemia is small and equal to p_β. The fitness of an HbE allele when rare is then approximately

$$w_E = 1.08\left(1 - p_\beta\right) + p_\beta\, w_{\beta E}.$$

The allele will be able to invade when this mean fitness is greater than 1. This condition for invasion then becomes

$$p_\beta < \frac{0.08}{1.08 - w_{\beta E}}$$

Because the double heterozygote causes severe anemia, we expect the fitness consequences to be relatively large. If we assume a double heterozygote fitness of $w_{\beta E} = 0.5$, the critical frequency is 0.13. If the double heterozygote is lethal, the critical frequency for invasion drops to 0.07.

This simple analysis and the preliminary data presented in Table 2 (and Figure 3) suggest a prediction regarding frequency of β-thalassemia on different islands. Specifically, we expect to find significantly lower β-thalassemia levels on Sumba relative to other islands in the region. The extent of this reduction and other aspects of the distribution of alleles will allow us to estimate strengths of selection for both protective and deleterious genotypes.

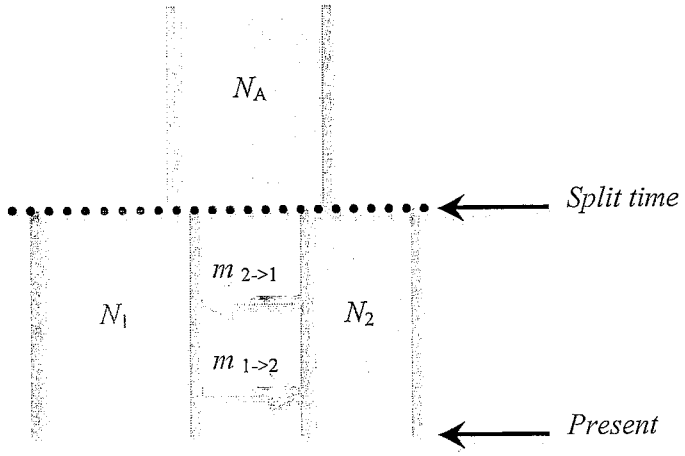
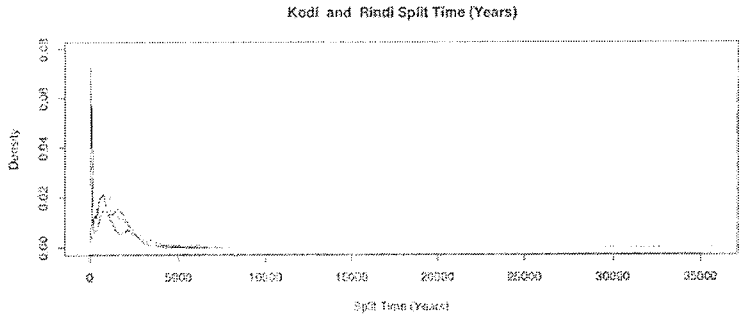


Figure 4: Schematic representation of the model implemented in IMa.

We have also carried out preliminary tests to confirm our ability to collect HBV sequence data from the existing samples, and have successfully collected 600-700 bp of DNA sequence from each of 11 samples from individuals on Sumba. We have also tested a small number of the Plasmodium-positive samples for the drug-resistance conferring *pfcrt* allele. So far, each of the Plasmodium samples has tested positive for this drug resistance marker.

Reconstruction of the demographic history of the communities represented in our sample will be approached using the coalescent inference software IMa [65-67]. The model implemented in IMa assumes the existence of an ancestral population that split into two descendant populations at some point in the past (see Figure 4). The program performs a Bayesian statistical analysis using Markov chain Monte Carlo to estimate the time of the population split, the effective population sizes of the ancestral and both descendant populations, and rates of migration between the two populations since the split. We have successfully used this method in the past to characterize the relationships among Indonesian islands and among villages on those islands [6]. For the current proposal, this method will help clarify demographic processes, a prerequisite for our host-pathogen modeling.

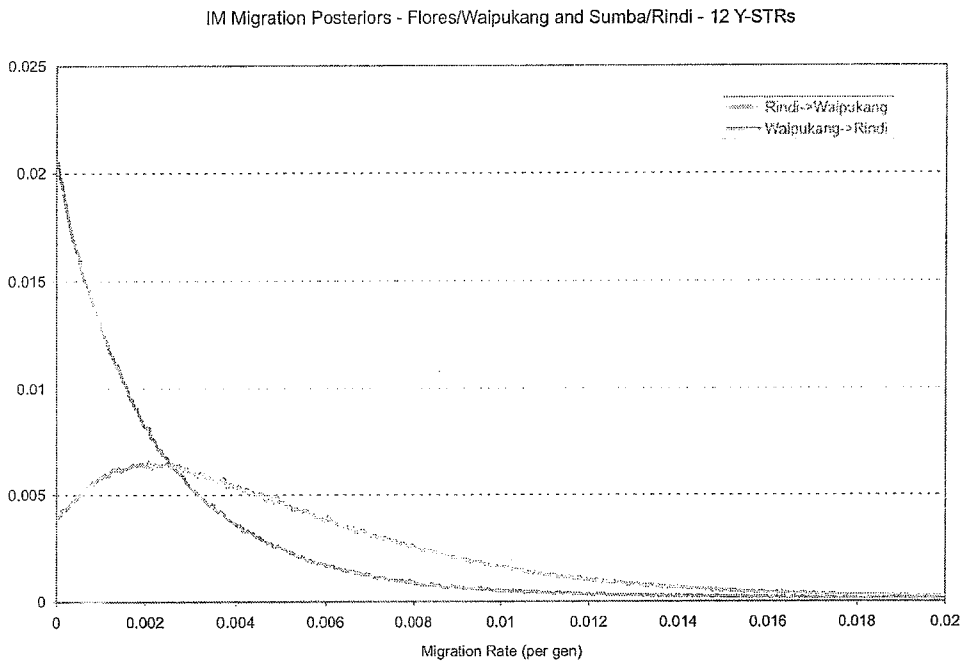
Figure 5: Posterior distribution of split times for Kodi and Rindi.



For example, we used IM to calculate the approximate date of divergence, effective population sizes, and subsequent migration rates for the villages of Kodi and Rindi on the island of Sumba, using completely linked Y-chromosome STRs (*N=14*). Our analysis assumes a single-step mutation model of microsatellite evolution with a mutation rate of 2.8×10^{-5} per locus per year[68].

Figure 5 shows the probability distribution over the split time for the two populations, estimated from these Y-chromosome STRs. Confidence bounds (95%) place the maximum divergence time between Kodi and Rindi at 4,875 years. These dates are not intended for direct comparison with, for instance, more precise archaeological radiocarbon dates, but they do set limits on the time depth inherent in the demographic processes examined here.

Figure 6: Posterior distribution of migration rates between Rindi and Waipukang.



We have also applied IMa to the same set of STRs for the village of Rindi on Sumba and the village of Waipukang on Flores. These two villages were chosen because they show significant differences in the frequency of the HbE allele, and in Plasmodium prevalence, yet had similar distributions of Y-chromosome haplotypes based on multi-dimensional scaling analysis (not shown). Figure 6 presents the posterior distribution over the two directional migration parameters. The estimated rate of migration from

Waipukang to Rindi has its peak at zero, suggesting complete isolation since the two populations diverged. The analysis suggests that the rate of migration from Rindi to Waipukang is non-zero, however, with mode at approximately $m = 0.002$ per generation.

We have also successfully integrated linguistic data with our genetic analyses to gain further insights into the history of interactions among villages on Sumba. The combined power of both datasets enhances our understanding of demographic patterns relevant to the spread of disease. The reconstructed phylogeny of Sumba's languages is consistent with a splitting model in which a common founding population gave rise to daughter populations that subsequently diverged and produced several language subgroups (Figure 7). We hypothesize that the ancestral Austronesian population settled in northern Sumba near Wunga and gradually expanded southward toward the center of the island. The first population split, which resulted in the divergence of group A from the rest of the populations, may have occurred before the Austronesians expanded south. By the time group B split and moved into the southwest, the main population must have expanded at least to the center of the island. This finding implies a later expansion to the east, with groups D and E splitting after the initial western expansion and probably after the main population (represented by group C) overtook the center of the island. Given the linguistic and genetic picture detailed previously, we hypothesize that this expansion must have involved a high degree of contact and intermarriage with the aboriginal population in successive stages, which would explain the generally low distribution of haplogroup O, its uneven distribution across the island, and the correlation with the percentage of retained Austronesian vocabulary in the subgroups. Further refinement of this reconstructed population history is anticipated thanks to the availability of more genetic and linguistic data. Prelminary analysis shows several of the same features on the island of Flores.

Figure 7: Integration of linguistic and genetic data on Sumba

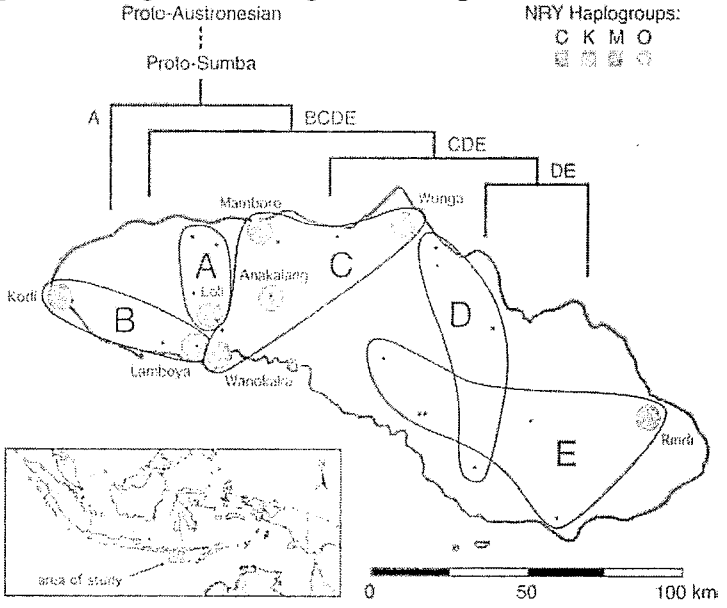


Figure 7 (reproduced from [6]) displays a phylogenetic tree of Sumbanese language groups (A–E) as well as a map of Sumba showing geographic distribution of these language groups and Y chromosome haplogroups (C, K, M, and O). Pie charts represent frequencies of four Y chromosome haplogroups at eight locations sampled for both DNA and languages. Small black dots indicate 20 additional language samples for which paired DNA samples were not available.

5: Research Design and Methods

5.1: Detailed aims

5.1.1-5.1.3: Aims 1–3. Infer the ancestral source populations for the people of the Indonesian archipelago, the extent to which admixture occurred during the settlement of the region, and whether there were sex biases in the process. Reconstruct this history of migration to the region and ascertain the structure of neutral variation in populations of the Indonesian archipelago. The impact of selection on a population can only be understood in light of a detailed understanding of its demographic history. The human population of Indonesia has been largely shaped by at least two great migratory events, which can be recognized today in the diversity of the extant Papuan and Austronesian-speaking populations. By genotyping a battery of SNPs exhibiting high F_{ST} (i.e., large frequency differences between putative source populations in Southeast Asia and Papua New Guinea), both on the X chromosome and autosomes, we will be in a position to infer the extent of admixture at varying geographic scales and whether the process was sex-biased. This will complement similar work on the Y chromosome and mitochondrial DNA, which showed that large frequency differences among lineages that are inferred to be of Austronesian and Papuan origin among villages and islands of the archipelago. One of the goals of this proposal is to determine whether malarial resistance markers were brought to the region after being positively selected in the source regions and/or whether selection took place after the arrival of Austronesian-speakers in Indonesia. Our database of neutral markers will allow us to investigate the relative roles of demographic processes like genetic drift and natural selection in influencing the frequencies of candidate SNPs for malarial and hepatitis B resistance. We will incorporate information gathered from language, ethnology, history, and archaeology to guide our investigation.

5.1.4: Aim 4. Investigate how the prevalence, population structure, and patterns of transmission of HBV relate to the cultural and demographic history of these populations. The mode of transmission of HBV is primarily vertical, with perinatal transmission from mother to child [69]. Therefore, we expect the population structure of the HBV viral genome to closely mirror the human matrilineal population structure. Deviations from this structure are expected to result from two sources. First, some additional intrafamilial transmission is expected [70], as well as some additional gene flow resulting from economic or social interactions among villages. One of the major aims of our study is to infer the sex-specific demographic history of populations in the region using a combination of neutral genetic markers described above. By comparing the patterns of diversity found in HBV sequences to the inferred matrilineal human demographic structure, we will produce estimates of the rates and patterns of horizontal transmission of HBV. The Eijkman Institute has already completed whole-genome sequencing of 54 HBV isolates from different ethnic groups across Indonesia [21], identifying extensive diversity and a new subgenotype. We anticipate collecting 50-100 additional whole-genome sequences, drawn from a fine-scale geographical sample. Importantly, we will have high-resolution cultural, linguistic, and genetic data sampled from the same set of individuals. This work will thus assemble a unique dataset for understanding the coevolution of HBV and human populations.

5.1.5: Aim 5. Determine how the prevalence and distribution of malaria-protective alleles have been shaped by: i) the admixture of Austronesian and Papuan populations, ii) selection by *Plasmodium* species, iii) epistatic interactions between protective variants, and iv) environmental factors. This dataset will offer one of the first opportunities to dissect the evolution of, and interactions between, different resistance alleles, hemoglobinopathies and HLA alleles. As a result of our analyses, we hope to identify the relative importance of these alleles for resistance, and potentially generate hypotheses about the molecular mechanisms behind clinical protection. Prior to admixture, both Austronesian and Papuan populations had been exposed to malaria and evolved a range of different resistance alleles. The migration of Austronesian populations into Indonesia would have caused these alleles to come into contact for the first time, creating a natural experiment in a range of malaria transmission zones. Since we will have detailed information on the genetic and demographic background of the individuals in our study area, we will be able to analyze how different combinations of hemoglobinopathies have interacted in variably admixed communities under different levels of selection due to malaria. This evolutionary approach overcomes problems of clinical studies, which are subject to the substantial stochasticity inherent to malaria prevalence and disease phenotypes.

5.1.6: Aim 6. Analyze the level and evolution of drug resistance within the malaria parasite populations in the region, infer selection pressure driving resistance among different regions. Drug resistance is one of the most important threats to global malaria control. In our study region, an extremely heterogeneous pattern of mutations account for the high failure rates of current first line therapies, chloroquine and SP [46]. We will create a detailed micro-geographic map of the patterns of drug resistance in our study region, and develop mathematical models to i) understand the evolution of these resistance genes, and ii) explore the efficacy of different malaria-control strategies on a local scale. By establishing a long-term monitoring program in the local hospital on Sumba island, we will be able to assess changes in drug-resistance over time and identify the emergence of new resistance alleles. We aim to provide practical advice about treatment strategies locally, as well as improve our general understanding of the evolution of drug resistance in regions endemic for both *P. falciparum* and *P. vivax*.

5.2: Experimental design

There will be two major aspects of the experimental work. The majority of our effort will focus on the analysis of DNA samples that have been previously collected, including typing of particular genetic markers and resequencing of specific loci of particular interest. These data will be subjected to a variety of analyses as described below. The second aspect of the proposed work will involve the collection of new samples in collaboration with the Eijkman Institute. These samples will be collected as part of an ongoing clinical study initiated by the Eijkman Institute at a small hospital on the island of Sumba. Additional genetic samples as well as demographic, clinical, environmental, and ethnographic data will be collected in villages within the catchment of this hospital, providing a baseline for drug-resistance studies.

In the following sections, we will describe the methods of analysis that will be employed in pursuit of each of the specific goals of the project. Following those sections, we provide an in-depth description of the laboratory techniques that will be employed.

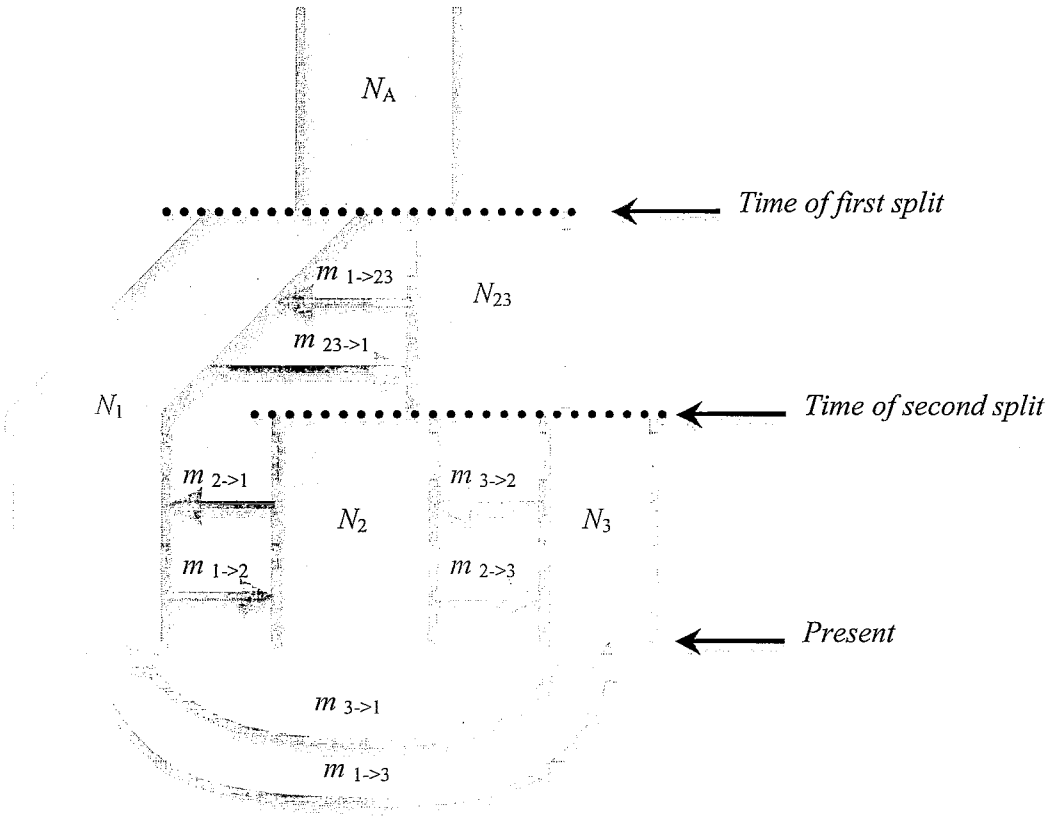
5.2.1: Aim 1. Reconstruction of the history of human populations

We begin our analysis using rapidly mutating genetic markers (paternally inherited Y-chromosome STRs, maternally inherited mtDNA control region sequences, and biparentally inherited autosomal STRs). These markers will be typed in DNA samples that have already been collected as a part of a previously funded NSF project. The high mutation rates at these loci (often exceeding 10^{-3} per generation) make them particularly valuable for inferring demographic events over very short timescales (see, for example, [6]). Demographic inference on this scale requires the application of advanced mathematical modeling and inferential techniques, employing both Bayesian and frequentist methodologies using both likelihood and summary statistic approaches.

Initially, we will determine the demographic history of these communities using the mixed Bayesian/likelihood method implemented in the coalescent inference software IMa, as described and illustrated above in Section 4. A disadvantage of the method of analysis implemented in IMa is that pairs of populations are considered in isolation from the rest of the population structure. The consequences of limiting analysis to pairs (e.g., the possibility of systematic biases in parameter estimation) have not been characterized. The most recent version of the program (IMa 2.0), estimates divergence times and migration rates for more than two populations simultaneously. We will apply this version of the program to our data in a hierarchical fashion. First, we will analyze each island separately, considering all of the villages for which we have data. Second, we will perform a regional analysis, treating each island as a population.

Because much of our inference is set to determine short time events, our ability to have accurate STR

mutation models is central to the reliability of inference. We will incorporate, wherever appropriate, the results in Watkins [61]. In addition to the use of IMa, we will develop a sequential importance sampler for STRs along the lines introduced by Stephens and Donnelly [71] and extended to symmetric single step mutation models by de Lorio and co-workers [72, 73]. For SNP data, we propose a strategy that uses the mutational information effectively so the distribution of population histories are chosen independent of the demographic parameters. The goal is to produce proposal distributions that are good approximation for parameter values close to those actually occurring in the population. This obviates the time-consuming step of constructing a separate proposal distribution for each set of parameter values [74].



Schematic representation of the multi-deme model implemented in IMa 2.0.

5.2.2: Aim 2. Assessment of admixture

We will genotype a minimum of 25 autosomal and X chromosome SNPs in >2,000 individuals from 62 populations in Indonesia and surrounding regions. SNPs have been chosen to exhibit high F_{ST} between Han Chinese and Papua New Guinea Highlanders (> 0.60 for X chromosome SNPs, and > 0.75 for autosomal SNPs). All SNPs are non-genic (i.e., not in exons, introns, UTRs, or immediate flanking regions), and are spaced >1 cM apart (i.e., they are unlinked genetic markers). Initially, we will estimate admixture rates using the non-parametric least-squares method described by Chakraborty et al. [75], modified to account for sampling error. We will implement a resampling method to calculate admixture rates and confidence intervals.

We will also use clustering procedures, which will provide a second method for characterizing the degree and pattern of admixture in the population. We will apply the program STRUCTURE [76] to our data, which will yield estimates of the proportion of Papuan and Austronesian ancestry at the level of

individuals. This will allow us to look for variation in admixture patterns among villages and among islands in our study region.

The algorithm implemented in STRUCTURE suffers from two major limitations. The first limitation is that the user must define the number of clusters to be used in the analysis. In our system, our initial choice of number of clusters (two) is less ad hoc compared with many applications of STRUCTURE. In this system, substantial prior work by our group and others in linguistics, anthropology, and genetics has established that the current population in the region is predominantly the product of admixture of two populations (Austronesian and Papuan), as described above.

The second limitation of STRUCTURE is that its assortment procedure assumes an underlying Gaussian probability distribution for the allele frequencies. While this assumption is reasonable in a variety of situations, it does not make full use of our knowledge of the distributions of allele frequencies that arise commonly from population-genetic processes.

In parallel with our analysis of the data, we will be working to develop an improved clustering algorithm that addresses both of these limitations. Specifically, we are developing a method based on a hierarchical Dirichlet process. The assumptions behind this approach are consistent with the stationary distribution of allele frequencies in an infinite alleles model of mutation with strength parameters α_H and α_k in the model based on mutation and migration rates, effective population sizes, and has the further advantage that the appropriate number of clusters emerges endogenously from the analysis of the data. An analogous approach has been developed and successfully implemented to cluster documents in a database [77, 78].

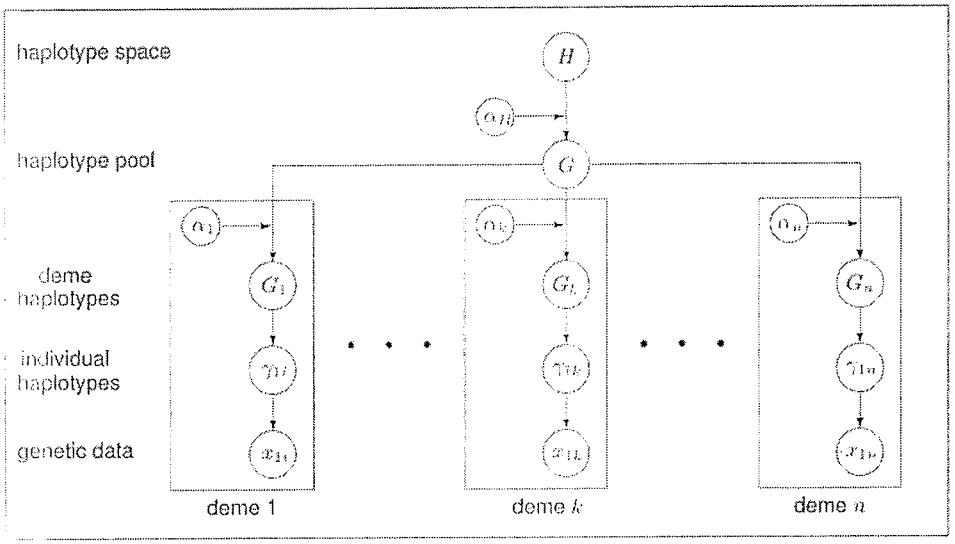


Figure Schematic of hierarchical Dirichlet processes.

5.2.3: Aim 3. Sex-biased demographic processes

The procedures described above will be used to infer admixture rates independently for autosomal SNPs and X chromosome SNPs, thus allowing us to estimate the degree to which admixture has been influenced by sex-specific demographic processes. This approach relies on the fact that the X chromosome is hemizygous in males and spends 2/3 of its time in females and 1/3 of its time in males. Therefore, differences between the patterns of variation on the X relative to those on the autosomes are indicative of sex-biased processes, such as post-marital residence practices, admixture rates, and mating strategy (e.g., polygyny).

Most attempts to characterize sex-biased demographic processes have focused on comparisons of the mtDNA and Y chromosome. These markers have the advantage of being inherited uniparentally; polymorphisms on these portions of the genome reflect the maternal and paternal lineage histories, respectively. However, because each of these loci is non-recombining (i.e., each is effectively a single locus), the statistical power of a Y-mtDNA comparison to infer sex-specific histories is limited by the intrinsic stochasticity of the genealogical process. The X-autosome comparison is more subtle, since each of these markers represents a weighted average of male and female histories. However, he availability of multi-locus data for the X-autosome comparison makes this approach potentially capable of greater statistical power in the inference of sex-biased processes [79].

5.2.4: Aim 4. Analysis of HBV population structure and transmission

In previous sections, we have described methods for using genetic data from these samples to infer the sex-specific demographic history in the study region. Approximately 1000 of the ~3000 DNA samples in our existing repository were originally collected as whole blood; each of these samples will also be tested for presence of HBV. For those samples containing the virus, we will sequence the entire ~3kb HBV genome. Based on the estimated 5-10% prevalence rates in the region, we anticipate being able to collect approximately 50-100 additional HBV whole-genome sequences. This dataset will allow us to address several specific questions related to both the patterns of HBV transmission and the effects of immune selection on the population structure of the virus.

i) What are the relative rates of vertical and horizontal HBV transmission?

If transmission of HBV were strictly limited to passage from mother to child, we should expect the population-genetic structure of the HBV genome to closely mirror that of the human matriline. Deviations from this structure will primarily be the result of horizontal transmission events. Minor deviations of the human matrilineal and HBV patterns of migration are also expected to arise from the fact that vertical transmission rates range from 10-90% depending on viral load of the mother (see, e.g., [80]). This viral load varies depending on host genetic background, HBV genotype, and co-infection with other pathogens. Therefore, we expect rates of vertical transmission to vary across the study region, depending on ecological factors, pathogen distributions, and local genetic composition of the host population. Our analysis will attempt to account for these confounding factors, and to identify likely genetic determinants of viral load and vertical transmission probability.

Estimates of the rates of horizontal transmission will be made by comparing the population genetic structure of HBV to the human female demographic history inferred by the methods described above. The precise scale at which we will be able to produce independent estimates of this transmission rate will depend on the exact number of and distribution of samples in our study set that test positive for the virus. We anticipate that, at a minimum, we will be able to produce separate estimates for each of the islands represented in our sample set. Depending on the precise distribution of HBV-positive samples and HBV genotypes in the region, we may also be able to estimate genotype-specific rates of horizontal transmission on individual islands.

That particular genotypes are correlated with modes of transmission is a hypothesis that has never been tested. Given that genotypes "associated" with both vertical and horizontal transmission are circulating in the wider region of the study site, we potentially have the opportunity to address this hypothesis. This dataset will also allow us to look for correlates of horizontal transmission rate, including host genetic composition, cultural practices, and patterns of social contact.

ii) How does HBV genotype and antigenic structure relate to host genetic background and patterns of population admixture?

Since transmission of HBV is primarily vertical, the genotype distribution of HBV is expected to have a strong correlation with many host genetic markers. Our data will provide insight into the detailed genetic relationships among individuals from different villages and from different islands, giving us an unprecedented opportunity for inferring co-evolutionary relationships between hosts and pathogens on multiple scales.

HBV generally causes chronic disease that kills only adults, and therefore does not impose a particularly strong fitness cost on its host in terms of reproductive success. Therefore, we do not anticipate finding signatures of selection in the human genome resulting from HBV exposure. However, host genetic factors are important in determining whether individuals clear an HBV infection or become persistent carriers. Thus, genetic factors present in the host population (*e.g.,* particular HLA phenotypes) may select for particular types of virus. In particular, HLA phenotype has been shown to affect the clearance of HBV in a number of studies, although results have been mixed[81-85]. A recent genome-wide association study focusing on Japanese and Thai populations identified both risk and protective haplotypes in a chromosomal region including HLA-DPA1 and HLA-DPB1 [86]. Evidence has also been presented for allelic variants of the class II cytokine receptor genes with effects on HBV persistence [87].

The demographic the study region provides a particularly attractive opportunity to examine the effects of immune selection on HBV. Based on patterns of Y-chromosome diversity and cultural practices, the islands in our study region appear to vary in their patterns of admixture. This suggests that separate islands or villages may present substantially different distributions of HLA phenotypes, thereby creating a variety of selective environments for HBV. We will be collecting HLA sequence data from all of the individuals in our sample, and will look for associations between the HLA phenotype and (1) HBV prevalence, (2) HBV genotype, and (3) inferred patterns of HBV horizontal transmission. Similar associations will also be investigated for the high-F_{ST} markers collected as a part of the demographic characterization of the human population. Comparison of the HBV population genetic structure with both of these patterns of variation in the human population will allow us to isolate the effects of immune selection from spurious correlations due to geographical structure and/or endogamy.

Selection, acting on various loci in the HBV genome, in *Plasmodium*, and in humans, is expected to be frequency dependent, subject to local patterns of disease prevalence and host genome composition. We propose extending models for selection beyond signatures of directional selection. Initially, we will rely on standard methods to uncover associations among various environmental and genetic factors. These include tests of departure from neutrality using site frequency spectrum based statistics. At later stages, however, we will want to make parametric inferences. These inferences will necessarily rely on simulation methods. We propose starting our parameter estimation strategy using both a parametric bootstrap and with hierarchical Dirichlet approaches [88].

Parameter estimation will also be performed using Approximate Bayesian Computation (ABC) [89, 90]. Loosely speaking, ABC involves the simulation of a large number of datasets. Parameter values for the simulations are drawn from a prior distribution. The simulations that produce data most similar to the empirically observed data are collected, and the parameter values associated with those simulations form the basis for constructing the posterior distribution over the parameter space and point estimates for individual parameters. The effectiveness of the ABC approach depends on the criteria used to determine which simulated datasets are "most similar" to the empirical data. Typically, similarity is defined using a vector of summary statistics. In our system, as in most population genetic systems, sufficient statistics are not available. We will use spanning summary statistics of the site frequency spectrum to determine which statistics yield the most power within a given range of demographic and selection histories.

When available, backward-in-time coalescent-based simulations are computationally more efficient than traditional, forward-in-time simulations. Simple forms of selection have been incorporated into the coalescent via the ancestral selection graph (ASG) [91-94]. In order to maximize the power of our ABC-based estimation procedures, we will work to develop extensions of the ASG that that permit the frequency-dependent and epistatic fitness effects relevant to our system.

The statistical estimates from these population genetic approaches will be used to parameterize a mathematical model exploring the effects of geographic and cultural separation of different villages within islands, as well as between different islands, on the population structure and evolution of a primarily vertically-transmitted viral pathogen like HBV. The separation of islands within our study region lends itself well to the development of a metapopulation model framework, in which individuals from the same island or interact more frequently than individuals from different islands. The classical metapopulation model devised by Levins [95] divides a habitat into isolated patches, which may or may not be occupied by a particular species over time, and provides insights into extinction and colonization dynamics. This metapopulation approach has been extensively developed by ecologists in order to understand the effects of immigration and emigration on population dynamics, and how metapopulation structure effects competition between species and the spread of infectious diseases such as measles [96-99]. These models have shown that reduced gene flow between geographically separate communities can lead to genetic differentiation between sub-populations, and an increase in overall genetic diversity as a result of local differences in allelic frequencies. The genetic differentiation of pathogenic species from different locations will therefore be dependent on its mode of transmission, as well as the mixing patterns of the host population within and between different communities.

Thus, we will have all of the modeling tools in place to study the effects of geographical separation of communities on the evolution of infectious diseases. Using the demographic history of the study region and the estimates of the ratio of vertical to horizontal transmission, these metapopulation models can be used to explore how the geographic and cultural separation has affected the population structure of the HBV virus, how genotype distribution has evolved in response to this metapopulation structure, and how immune selection has differentially affected antigenic loci and neutral HBV genes in the region. We anticipate that this framework will apply more generally
to other pathogen species and ecological frameworks.

5.2.5: Aim 5. Analysis of human-malaria parasite co-evolution

Each individual will be characterized with respect to a comprehensive set of genetic markers known to be associated with resistance to malaria, including Hemoglobin E, the thalassemias, ovalocytosis, complement receptor 1 (CR1) deficiency, ABO blood group, G6PD deficiency, TNFα polymorphisms, the Gerbich modification of glycophorin C, and the FY*A mutation of the Duffy blood group antigen. In addition, several HLA loci will be sequenced at polymorphic exons encoding extracellular domains known to be involved in antigen presentation (see in-depth methods for the exact SNPs and gene regions sequenced). Based on our preliminary analysis and previous studies in the region, we expect to find considerable diversity in these markers both within and between islands. By comparing the patterns of inheritance of these loci with those of neutral genes, we will be able to infer the extent to which different markers have been selected for, and in what combination, in the study populations. Statistical analyses and parameter estimation will be performed using the tools described in the preceding sections. Our analysis of the human-malaria co-evolutionary dynamics will focus on the following specific questions:

i) *How does the prevalence and co-infection of different malaria species relate to host genetic background?*

Given the limited sensitivity of light microscopy to assess parasitemia and co-infection, we will use a nested PCR technique to identify all four malaria parasite species in all individuals in the study, to create a detailed map of parasite prevalence. This is particularly important since the individuals for which we have samples are adults, who tend to have low parasitemias. It has been frequently suggested that interactions between different malaria parasite species leads to particular dependent patterns of co-infection [100-103]. We will test whether this is the case in our study area, and determine whether deviations from independence can be accounted for under these hypotheses, by host genetic background, by geographic factors, or by inter-island variability in transmission.

In addition to samples already collected, we will analyze an additional 200 samples each year from individuals from our study region with malaria admitted to Sumba hospital. As part of ongoing studies conducted at the Eijkman Institute, these samples will also be analyzed for all four *Plasmodium* species by nested PCR. This will considerably enlarge our dataset, and provide estimates of the effect of host genotype on malaria in childhood, which is a clinically important age group. Children have been shown to have a different species distribution from adults, with different species exhibiting different age profiles [104]. Some studies have suggested that the different age profiles of *P. vivax* and *P. falciparum* infections in children result from *P. vivax* acting as a natural "vaccine" against infection with *P. falciparum* [105]. We will test for these interactions using our clinical samples, to determine whether host genotype impacts these observations.

ii) How do the distribution of hemoglobinopathies and resistance alleles differ from neutral expectations based on Austronesian/Papuan admixture? What are the relative strengths of selection on different resistance alleles and hemoglobinopathies?

Despite decades of study, the vast majority of resistance alleles are not understood at the molecular level, and their evolutionary history is unknown [106]. Since our analysis of the neutral genes will give us detailed insight into the patterns of diversity in host genotypes generated by migration and inter-marriage between Austronesian and Papuan populations, we will be able to quantify the level of introgression of particular selected markers against this background. Our current understanding of the population history of the Indonesian archipelago suggests a relatively recent admixture of two previously separate populations. Papuan peoples are descendants of several earlier migrations, dating back possibly as far estimated to have begun ~50,000 years ago. When the populations came into contact, new alleles became available to each population that may have been more or less effective at protecting individuals against malaria than those previously circulating. Significant deviations among putative resistance alleles from neutral patterns of diversity, and asymmetries of introgression among resistance genes originating in Austronesian and Papuan populations, will therefore indicate the level of selection for or against them in different regions. Identifying the relative strengths of selection on different alleles will provide insights into their evolution over the last ten thousand years. For example, it appears as if Hemoglobin E has emerged in the last 2,000-4,000 years [64]. We will analyze the origins and evolutionary history of this and other polymorphisms in more detail against the background of human population structure, as discussed in the Prior Results section.

iii) How do different resistance alleles interact? Does the prevalence or absence of certain combinations suggest epistatic interactions?

Although epistatis is probably an important consideration among balanced polymorphisms affecting the same system (the red blood cells, for example), we have very little understanding of the interactions between the vast majority of resistance markers (with the exception of HbS and α-thalassemia, as discussed above [45]). By analyzing a large number of different resistance markers in the same population, we hope to be able to provide evidence for interactions between resistance markers in this area in areas of varying malaria transmission, and potentially generate hypotheses about the mechanisms underlying these interactions. The power of our approach lies in the ability to distinguish between linkage disequilibrium between alleles due to neutral population genetic effects, and linkage disequilibrium caused by selection. In addition, if we can determine whether particular resistance alleles originate in the Austronesian or the Papuan ancestral populations, we can reconstruct their evolutionary history and generate theoretical models to understand mechanisms leading to their distribution.

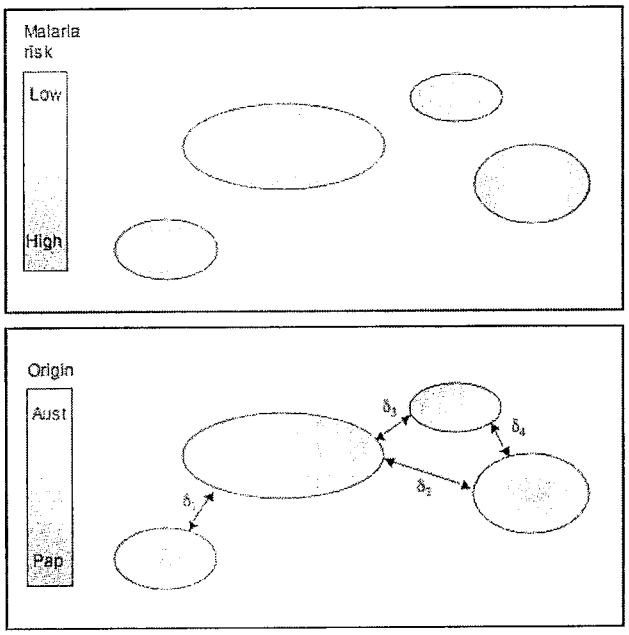


Figure 10: A schematic of a hypothetical metapopulation model formulation. Ovals represent islands, with different spectra of malaria transmission (and therefore selection) above in green, and the extent of Austronesian-Papuan admixture below in red. δ represents the different rates of gene flow between islands.

The theoretical framework to explore the evolution of the diversity of malaria resistance genes in the Indonesian archipelago will be developed by extending the metapopulation framework described above to explore how the introduction of Austronesian resistance alleles would have effected an equilibrium distribution of markers within the Papuan population. Here, we will need three levels in our hierarchy. At the top level, the individual islands will be modeled as 'patches', with variable rates of migration to and from each one over the course of the Austronesian expansion. At the second level are the villages on an island considered as a "linked-village" model [107] in which sexual reproduction occurs with a high frequency within communities, and a lower level between them, depending on inferred migration rates. The third level is the individual from whom we collect genetic data. This will allow us to explore the effects of population movements between villages within an island, as well as among different islands on a longer time scale. We expect that the variable level of admixture within these populations, ranging from primarily Papuan to primarily Austronesian, will have had an important effect on the exact alleles involved in this evolutionary process. Furthermore, climatic variation leading to differences in malaria prevalence will have changed the nature of selection pressures on different islands. We will model the expected effects of these two gradients on different islands on the distribution of different resistance alleles, and compare the outcomes with observed distributions. Figure 10 illustrates a hypothetical model. As discussed in the Prior Results section, the current distribution of resistance markers on different islands should depend on the phenotypic effect of co-inheritance of alleles, the historical frequency of particular alleles prior to admixture, and the level of selection by malaria since then. A theoretical framework will provide the basis for exploring how these processes may have led to the distribution we observe.

iv) Is there evidence for an interaction between HBV and malaria?

Interactions between infectious diseases are difficult to analyze, since they are often subtle and extremely complex. There is some evidence to suggest that malaria infection may provide protection against HBV, however [108, 109]. The fact that each of these pathogens is present at high frequency in our study region will permit us to explicitly test for evidence of interactions of this sort, particularly with the additional samples provided by Sumba hospital each year.

5.2.6: Aim 6. Analysis of drug-resistance evolution among malaria parasites

i) What are the patterns of drug-resistance in malaria parasites (both P. falciparum and P. vivax) in our study region?

Both theoretical models and empirical studies have failed to reach a general conclusion about the relationship between epidemiological parameters, such as malaria transmission intensity, and the evolution of drug resistance [110]. This implies that there is no one-size-fits-all solution to controlling the emergence of drug-resistance, or managing treatment once it has arisen. This is particularly true in Indonesia, where mutations causing resistance among malaria parasites are extremely diverse [46] and are found in both *P. falciparum* and *P. vivax*. The development of locally relevant, practical solutions to the pressing problem of drug resistance in our study region will therefore require a detailed understanding of the patterns of resistance on different islands. For each parasite-positive sample, we will analyze four genes involved in drug-resistance: dihydrofolate reductase (*dhfr*), dihydropteroate synthase (*dhps*), multidrug resistance 1 (*mdr1*), and chloroquine resistance transporter (*crt*).

As part of an extended malaria program at the Eijkman Insitute, we will also continually monitor drug resistance over the course of the grant at the hospital on the island of Sumba. We will assess any changes in the prevalence of drug resistance, and be able to determine the effects of changes in public health policy.

ii) What does this tell us about the evolution of drug resistance and the level of selection for resistance in this area?

Long-term strategies for controlling the emergence and spread of drug resistance among malaria parasites are desperately needed; few drugs are in the development pipeline, and there is now a suggestion that resistance has emerged in response to the use of ACT, the only drug treatment now effective in many parts of Asia [111]. Furthermore, there is increasing evidence that treatment with an ineffective drug may even exacerbate the severity of a malaria infection [112]. We still have very little understanding of the driving forces behind the evolution of drug resistance, however. The multiple scales of geographic detail afforded by our study, and the diverse mutations leading to drug resistance in the area, will provide insights into the evolution and emergence of different mutations, as well as patterns of resistance in *P. vivax*, which are under-studied in this regard.

We aim to develop mathematical models, both highly abstract and locally specific, to explore these processes following statistical analysis of our data. The complexity of the interactions between malaria parasites, mosquito vectors, and humans leads to nonlinear relationships between important epidemiological parameters, and the use of mathematical models can provide an important tool for understanding the transmission and evolution of malaria parasites [113, 114], and the emergence of drug resistance [115-118]. In the context of drug resistance, epidemiological models have shown the importance of factors such as the starting frequency of resistance, transmission rates, which affect the average number of clones per infection and therefore the probability of recombination between them, the number of genes contributing to resistance, the level of drug use in the region, and the duration of efficacy of a combination versus single therapy approach [119-121]. These factors combine in non-intuitive ways, which makes mathematical modeling an important tool for understanding drug resistance evolution. For example, drug resistance seems to evolve more rapidly in areas of either low or high transmission, with slower evolution occurring at intermediate transmission levels [122]. Generally these models are compartmental in nature following the basic model framework of Ross and McDonald [114]; the host population is divided into those that are susceptible, infected with a resistant parasite or a sensitive parasite (with or without treatment), and immune. The mosquito population is also modeled with respect to these parameters. We will modify this framework to include multiple levels of immunity and co-infection with multiple parasites of different species, and monitor the epidemiological outcomes of changes in drug policy. We will develop very specific models of potential public health strategies targeted

at controlling drug resistance in the region, producing predictions and recommendations for health policies on different islands. We believe this will be necessary because of the lack of generally applicable guidelines for drug resistance evolution and control, and very few theoretical studies have considered the implications of *P. vivax* in addition to *P. falciparum*.

5.3: In-depth methods

Field work and laboratory procedures

Additional collection of data

In 2007 Eijkman researchers conducted two point prevalence surveys of malaria in West Sumba [52]. Subsequently, the Eijkman Institute has formulated an agreement with a hospital in Sumba to collect additional clinical data and genetic samples. We will enhance this collaboration by collecting and analyzing approximately 200 new samples per year for the duration of the project, from villages in the catchment for the hospital (see letter from Dr. Sudoyo). The primary goals of this part of the project are i) to create a baseline for future monitoring of drug resistance following the introduction of new anti-malarial treatments in Sumba; ii) to collect additional data as a supplement to our existing DNA repository; iii) to obtain data on evolutionary and clinical patterns within families.

Using the same methods as in our previous research, we will gather sufficient genetic samples from each village to reconstruct its demographic history. Eijkman researchers and Lansing will also gather clinical, genealogical, ethnographic and environmental data, following the protocols approved by the Eijkman Institute IRB. DNA will be extracted at the Eijkman Institute in Jakarta, and tests will be performed to detect *Plasmodium* and drug resistance genes, as well as HBV genotyping and sequencing. Subsequently, genetic material will be shared with the American team to carry out the analyses described below.

Plasmodium detection

The parasites in the DNA samples will be detected using the nested PCR method. The species-specific nucleotide sequences of the 18S rRNA genes of *P.falciparum, P.vivax, P.ovale*, and *P.malariae* will be amplified as described previously [123], with minor modifications.

Resistance alleles

In the table below, we list the resistance markers we will include in our study on the left, with the specific alleles or gene sections that we will be analyzing in the middle, and the references we will use.

Loci	Alleles	Reference
Alpha globin (α2 and α1)	$-\alpha^{3.7}$, $-\alpha^{4.2}$, $-\alpha^{SEA}$, $-\alpha^{CS}$	[124, 125]
Beta globin	Sequence whole locus	[126, 127]
SLC4A1	27bp deletion	[128]
Gerbich blood group antigen	Exon 3 deletion, Glycophorin C	[129]
ABO blood group antigen	A1, A2, B, O1 and O2 alleles using the Sequenom® system	[130]
Duffy bloodgroup antigen	FY*A, FY*B	[131]
G6PD	Sequence all 13 exons	[132, 133]
TNFα	Sequence promoter region	[134]
CR1	L allele identified by HindIII RFLP; G3093T (exon 19), A3650G (exon 22); C5507G (exon 33)	[135]
HLA-A HLA-B	Exons 2 and 3 (extracellular domains)	[136, 137]

HLA-C HLA-DRB1 HLA-DPA1 HLA-DPA2 HLA-DQA1 HLA-DQA2		

HBV genome sequencing

For the full-length nucleotide sequences of HBV genomes five overlapping fragments will be amplified by PCR, employing sets of primers based on the most conserved regions [21]. If the full-length nucleotide sequences fail in some samples we will sequence the Pre-S2 and the S regions. Relevant fragments will be PCR amplified in a semi-nested manner [138]. Each PCR product will be purified and sequenced in the Genomic Analysis and Technology Core facility at the University of Arizona using ABI 3730 Automated Sequencers.

Drug resistant genes

Nested PCRs are performed for four genes: dihydrofolate reductase (*dhfr*), dihydropteroate synthase (*dhps*), *P. falciparum* multidrug resistance 1 (*pfmdr1*), and *P. falciparum* chloroquine resistance transporter (*pfcrt*). The PCR primers and conditions were as previously described for *dhfr, dhps*, and *pfmdr1* [139, Duraisingh, 1998 #75, 140], and *pfcrt* [141]. Secondary PCR products are resolved by electrophoresis on 2% agarose gels and visualized by staining with GelStar. For *pfmdr1* gene, the nested PCR product is digested with *Afl III* and *Apo I* restriction enzyme. For *dhfr*, the nested PCR products are digested with *Nla III, Tai I, Tsp 509I, Xmn I*, and *Dra I* to determine the polymorphisms at codons 16, 50, 51, 59, and 164, respectively. Three enzymes, *Alu I, Bsr I,* and *Scr FI,* are used to identify codon 108. For *dhps*, the PCR products are digested with *Msp A1I, Ava II*, and *Fok I* to determine the polymorphisms at codon 436, 437, and 540, respectively. In addition, restriction enzymes *Bst UI* and *Bsl I* are used to identify polymorphisms at codon 581, while *Mwo I, Bsa WI*, and *Age I* are used for codon 613. The *pfmdr1* PCR products are digested with *Afl III, Dde I, Ase I*, and *Eco RV* to determine the presence of polymorphisms at codons 86, 1034, 1042, and 1246, respectively [46].

Neutral markers

To investigate the paternal genetic relationships among Indonesian villages, we will genotype a set of 84 previously published binary Y chromosomal markers [142]. We will follow the hierarchical typing strategy [143], wherein additional genotyping of a sample will be restricted to markers on the appropriate branch of the haplogroup tree. In addition to binary polymorphisms, 14 Y-STRs (DYS19, DYD385a, DYS385b, DYS388, DYS389I, DYS389II, DYS390, DYS391, DYS392, DYS393, DYS426, DYS438, DYS439 and DYS457) will be typed in two multiplex PCR reactions. Primer sequences are published [144, 145], and PCR conditions are given by Redd et al. (2002). PCR products will be electrophoresced on a 3100 Genetic Analyzer (Applied Biosystems) using a 36 cm array and filter set D. The data will be analyzed with Genescan (v. 3.7, Applied Biosystems) and Genotyper (v. 1.1, Applied Biosystems).

To characterize maternally-inherited variation, mtDNA HVS1 will be amplified and sequenced and haplogroup will be inferred by specific sequence motifs [146]. Haplogroups will be confirmed by RFLP analysis or Sequenom® system. Sixteen autosomal STR's will be typed in two multiplex PCR reactions. To determine whether rates of Austronesian admixture varied across the Indo-Pacific region, particularly west to east across Melanesia we will perform SNP typing using TaqMan method and the Sequenom® system. This is an automated multiplexed system that can process 30-47 SNPs in each well of an arrayed 384-well plate. We will identify at least 35 unlinked autosomal and X-SNPs with FST > 0.5 between Han Chinese and Melanesians. These SNPs are good candidates to help determine admixture rates between Neolithic Austronesian migrants (ultimately from mainland Asia) and pre-existing population groups in Island Southeast Asia, Melanesia and Polynesia.

Human Subjects

The proposed research involves two types of data: data already collected by J. Stephen Lansing in collaboration with researchers from the Eijkman Institute for Molecular Biology, and new data to be collected from approximately 600 persons after the project begins.

The existing data were collected according to protocols reviewed and approved by the Institutional Review Boards of both the Eijkman Institute (under the auspices of the Ministry for Research and Technology of the Government of Indonesia), and the University of Arizona. A copy of the approval from the Eijkman Institute is attached. It lists Dr Lansing as a co-investigator for sub-program 1: Human genome variation, population structure and the peopling of Southeast Asia. In addition, copies of the Human Subjects consent forms approved by both institutions are attached, in the Indonesian language, with English translation. These consent forms state that the subjects give permission for their genetic materials, language samples and clinical and genealogical data to be used for medical research. A materials transfer agreement gives permission for the genetic samples to be used for research at the Hammer lab of the University of Arizona.

The new data that will be collected for this project will be of the same type as the previous data. We will request extensions of the existing permits from the two Institutional Review Boards for this project. At the request of the Eijkman Institute, only genetic material will be shared with the Arizona team; blood and tissue samples will not leave Indonesia.

Attachments:

1. Ethical Clearance from Eijkman Institute Research Ethics Commission
2. Ethical Clearance from University of Arizona Institutional Review Board
3. Copies of Human Subjects Consent Forms (Indonesian with English translation)

The proposed research project is a major program of the Eijkman Institute aimed at collecting data on the molecular genetic diversity of the populations of the (island) Southeast Asia, deriving information on the structure of the regional populations from such genetic diversity data, and examining their association to disease susceptibility and to the population distribution of common genetic and infectious diseases.

The proposed research project is basically the continuation of a research project entitled "Human and Malarial Parasite Co-evolution in Indonesian Archipelago", (EIREC ethical clearance Number 04, 2001), but has been extensively amended and extended to reflect the rapid progress that has occurred in the study of the human genome; the propose project now incorporates the latest state-of-the-arts tools of genomic analysis that have been made available recently, and will incorporate such new tools as they become available.

Populations examined include representatives of Indonesian, as well as neighbouring Southeast Asian populations. Diseases included in the program are thalassemia and other red blood cell abnormalities, malaria and complex polygenic diseases such as diabetes mellitus and obesity.

THE EIJKMAN INSTITUTE FOR MOLECULAR BIOLOGY

Project Number
(For Official Use Only)

EIJKMAN INSTITUTE RESEARCH ETHICS COMMISSION

ETHICAL CLEARANCE

The Eijkman Institute Research Ethics Commission has convened a meeting on 10th March 2005, to review the research proposal with the title "Human Genome Diversity and Disease" with Dr. Herawati Sudoyo, PhD as the coordinating principal investigator. After deliberations the Commission decided to grant ethical clearance.

Jakarta, 31st March 2005

Prof. Sangkot Marzuki, M.D., Ph.D., D.Sc.
Director of Eijkman Institute for Molecular Biology

A.A. Loedin
Chairman EIREC

1. **Research Project Title:** Human Genome Diversity and Disease

2. **Name(s), Title(s), Qualifications and Department/Location of Principal and Co-investigators.**

a. Dr. Herawati Sudoyo PhD (**Coordinating Principal investigator** Principal investigator of Sub-program 1, Coinvestigator sub-program 3) - Eijkman Institute, Jakarta

b. Dr. Iswari Setianingsih SpA PhD (Principal investigator - Sub-program 2) - Eijkman Institute, Jakarta

c. Dr. Safarina Malik PhD (Principal investigator - Sub-program 3) - Eijkman Institute, Jakarta

d. Dr. Din Syafruddin PhD (Principal investigator - Sub-program 4) - Eijkman Institute, Jakarta

e. Farah Coutrier SSi PhD (Principal investigator - Sub-program 5) - Eijkman Institute, Jakarta

f. Dr. Helena Suryadi MSc (Co-investigator – Sub-program 1) – Eijkman Institute, Jakarta

g. Dr. Sangkot Marzuki PhD DSc (Co-investigator – Sub-program 1 and 3) – Eijkman Institute, Jakarta

h. Mark Seilstadt PhD (Co-investigator – Sub-program 1) – Genome Institute of Singapore, Singapore

i. Mila Tomasseo PhD (Co-investigator – Sub-program 1) – Department of Anthropology University of Bari, Italy

j. Steven Lansing PhD (Co-investigator – Sub-program 1) – Department of Anthropology University of Arizona, USA

k. Dr. Alida Harahap SpPK PhD (Co-investigator – Sub-program 2) – Eijkman Institute, Jakarta

l. Dra. Ita Margaretha Nainggolan MSi (Co-investigator – Sub-program 2) – Eijkman Institute, Jakarta

m. Dr. Sidhartawan Soegondo SpPD KE DR (Co-investigator – Sub-program 3) – Eijkman Institute, Jakarta

n. Josephine Siregar SSi MSi (Co-investigator – Sub-program 4) – Eijkman Institute, Jakarta

o. Drg. Sekartuti MKes (Co-investigator – Sub-program 4) – National Institute of Health Research and Development, Jakarta

p. Dr. Irawan Yusuf PhD (Co-investigator – Sub-program 5) – Department of Physiology Hasanuddin University, Makassar

q. Ari Satyagraha BSc PGDiplMolBiol PhD (Co-investigator – Sub-program 5)

r. Ratna Agung SSi MSi (Co-investigator – Sub-program 5) – Eijkman Institute, Jakarta

s. Dr. David Mulyono PhD (Co-investigator – Sub-program 5) – Eijkman Institute, Jakarta

3. Have you **applied for external funding?**

No

(If No, go to Question 4)
(If Yes, indicate granting body)

(A copy of the relevant sections of the application appropriate to Question (4) and (5) must be attached. Answer to Questions (4) and (5) may then be omitted)

4. Give a succinct but comprehensive statement of the aims, hypotheses and potential significance of the research project

The general aim of the study is to obtain information on the human genome variation of the populations of the (island) Southeast Asia, and its association with the population structure, disease susceptibility, and disease distribution. The thesis that underlies the proposed study is that (a) the genetic diversity of the present human populations is the outcome of pattern of ancient human migration and subsequent adaptation to environment including pressure from infectious diseases, and (b) the population distribution of disease is determined by the human migration pattern and the success of particular populations to select for mutations of advantage against disease, i.e. disease susceptibility and resistance mutations.

As such, this major program has five semi-autonomous, yet very tightly linked, sub-programs: (a) Human genome variation, population structure and the peopling of Southeast Asia (Principal investigator - dr. Herawati Sudoyo PhD), (b) Molecular basis of hemoglobinopathies-thalassemia (Principal investigator - dr. Iswari Setianingsih PhD), (c) Human genome variation associated with susceptibility to complex diseases – diabetes mellitus and obesity **(Principal investigator** - dr. Herawati Sudoyo PhD), (d) Molecular epidemiology of human *Plasmodium* resistance to antimalarial drugs (Principal investigator - dr. Din Syafrudin PhD), and (e) Spectrum of mutations conferring resistance to malaria infection (Principal investigator: Farah Coutrier PhD).

The specific aims of the study are:

Sub-program 1. Human genome variation, population structure and the peopling of Southeast Asia

Aim:

To obtain molecular genetic evidence for the population structure and the dynamic of the peopling of the Southeast Asia; in particular the genetic relationship between the Austronesian and Papuan speaking populations and the contribution of the original Austroloid populations on the genetic make-up of the present mostly Austronesian speaking populations.

Significance:

The study of the genome variation may reveal valuable information on the population structure of Indonesia which is important for the development of diagnostic strategies, for gene hunting for disease-related mutation, and for pharmacogenomic basis of drug development. Information on the genome

variation in different populations is important also for our understanding of human history and identity. Such study would help us to understand the history of the peopling of the Indonesian archipelago, the dynamics of human migration in the region and the pattern of adaptation.

Sub-program 2. Molecular basis of hemoglobinopathies- thalassemias

Aim:
To define the molecular basis of haemoglobinopathies-thalassemias in different ethnic populations of Indonesia.

Significance:
The study on the frequency and the molecular basis of thalassaemia-hemoglobinopathies will provide essential data for designing a comprehensive and efficient control program of these diseases.

Sub-program 3. DNA polymorphims associated with susceptibility to complex diseases – diabetes mellitus and obesity

Aim:
To determine variations or polymorphisms in the nuclear and mitochondrial genomes that might be associated with susceptibility to complex polygenic diseases such as diabetes mellitus and obesity.

Significance:
The information on disease susceptibility genes will provide knowledge base for the development of prevention, treatment and management strategies

Sub-program 4. Molecular epidemiology of human *Plasmodium* resistance to antimalarial drugs

Aim:
To identify gene mutations in *P. falciparum* isolates from different malaria endemic areas associated with the malaria pathology and resistance to antimalarial drugs

Significance:
The information on the variation in the antimalarial drug resistance genes will contribute to the development of strategies for therapeutic intervention of malaria in Indonesia. Information on the genetic variation of malarial parasite genome is the basis for the study of variation in malaria.

Sub-program 5. Spectrum of mutations conferring resistance to malaria infection

Aim:
To define the molecular basis of known malaria related host genetic factors (Glucose-6-Phosphate Dehydrogenase/G6PD, ovalocytosis, Duffy blood group),

THE UNIVERSITY OF ARIZONA.

Human Subjects
Protection Program

1235 N. Mountain Ave.
P.O. Box 245137
Tucson, AZ 85724-5137
Tel: (520) 626-6721
http://www.irb.arizona.edu

16 October 2008

J.S. Lansing, PhD
Emil W Haury 122b
PO Box 210030

RE: **PROJECT NO. 07-0441-02** ANTHROPOLOGICAL MODELING OF SOCIAL STRUCTURE, GENETICS AND LANGUAGE SPECIATION IN INDONESIA

Dear Dr. Lansing:

We received your 14 October 2008 Request for Amendment Form and revised Informed Consent form [version: 09/30/08] for the above referenced project. The purpose of the amendment is to revise the wording in the Informed Consents so that they are identical to the Institutional Review Board of the Eijkman Institute having oversight in Indonesia for all genetic research. Approval for this change is granted effective 16 October 2008 and reflects the current expiration date of ***6 June 2009***.

The Institutional Review Board (IRB) of the University of Arizona has a current ***Federalwide Assurance*** of compliance, ***FWA00004218***, which is on file with Department of Health and Human Services and cover this activity.

Approval is granted with the understanding that no further changes or additions will be made either to the procedures followed or the consent form(s) used (copies of which we have on file) without the knowledge and approval of the Institutional Review Board. Any research related physical or psychological harm to any subject must also be reported to the appropriate committee.

A university policy requires that all signed subject consent forms be kept in a permanent file in an area designated for that purpose by the Department Head or comparable authority. This will assure their accessibility in the event that university officials require the information and the principal investigator is unavailable for some reason.

Sincerely,

Elaine Jones

Elaine G. Jones, PhD, RN, FNAP
Chair, Social and Behavioral Sciences Committee
UA Institutional Review Board

EGJ:daj

SURAT PERNYATAAN
PERSETUJUAN KEIKUTSERTAAN DALAM PENELITIAN KEANEKARAGAMAN GENOM MANUSIA DAN PENYAKIT

PENGESAHAN OLEH PENELITI

Bersama ini saya menyatakan telah memberi penjelasan tentang tujuan serta manfaat kegiatan penelitian "Keanekaragaman genom manusia dan penyakit", dan telah dimengerti oleh individu yang diteliti.

Tanda tangan : _____ Tanggal : _____
(Hari/Bulan/Tahun)

Nama peneliti : _____

PERSETUJUAN INDIVIDU YANG DITELITI

- ☐ Saya yang bertanda tangan di bawah ini telah diminta untuk ikut serta secara sukarela di dalam penelitian Keanekaragaman genom dan penyakit, yang bertujuan untuk mempelajari keanekaragaman genetik populasi Indonesia dalam kaitannya dengan ketahanan serta kepekaan terhadap penyakit infeksi seperti malaria.
- ☐ Saya tidak berkeberatan bila diambil data pribadi, data fisik, serta diambil sampel saya (darah/ rambut/ usap dinding pipi bagian dalam) dan dilakukan perekaman video pengucapan kata Swadesh untuk materi penelitian. Saya telah diberitahu bahwa dalam pengambilan sampel darah dan apusan mukosa pipi akan sedikit terasa sakit.
- ☑ Saya mengijinkan peneliti melakukan analisa golongan darah dan serum hepatitis B pada sampel yang saya berikan.
- ☐ Selain itu saya juga mengijinkan semua data tersebut dan sampel saya dipergunakan untuk penelitian terkait, sepanjang penelitian ini bermanfaat bagi peningkatan kesehatan dan kesejahteraan manusia.
- ☐ Saya tidak mengijinkan bila materi yang diambil dipergunakan untuk kepentingan komersil.
- ☐ Bila ada hasil yang mengindikasikan bahwa saya mengidap virus Hepatitis B, membawa gen thalassemia-β, hemoglobinopati, dan kelainan sel darah merah lainnya, maka saya bersedia/tidak bersedia* mendapatkan hasilnya.

Tanda tangan : _____ Tanggal : _____
(Hari/Bulan/Tahun)

Nama sukarelawan : _____

Disaksikan oleh:

Tanda tangan : _____ Tanggal : _____
(Hari/Bulan/Tahun)

Nama : _____

** coret yang tidak perlu*

INFORMED CONSENT STATEMENT
FOR PARTICIPATION IN HUMAN GENOMIC DIVERSITY AND DISEASE RESEARCH

RESEARCHER CERTIFICATION

I hereby certify that I have given the explanation about the purpose and benefit of the study on Human Genomic Diversity and Disease, and the explanation has been understood by the participants.

Signature: _____ Date : _____
(DD/MM/YY)

Researcher: _____

PARTICIPANT CERTIFICATION

- ☐ I agree to participate voluntarily in Human Genomic Diversity and Disease Research, a study on the diversity of Indonesian population genome and its relation with the resistance and sensitivity to infectious diseases such as malaria.
- ☐ I agree to give my personal data, physical data, and to allow my sample to be taken (blood/hair/cheek or buccal swab), and also to allow the video recording of Swadesh words pronounciation as the study materials. I have been told that the process to draw blood and swab the cheek epithelial cells will cause a little pain.
- ☐ I agree to allow researchers to do the blood group and hepatitis B serum analysis on the samples.
- ☐ I agree to allow all of my data mentioned above and my sample to be used for the related study, as long as the study could give benefit for the public health and welfare improvement.
- ☐ I do not allow the related materials in this study to be used for comercial purposes.
- ☐ If the test showed a positive result for Hepatitis B, thalassemia-β gene, hemoglobinopati, or any other red blood cell disorder, I would / would not * like the result to be informed to me.

Signature: _____ Date : _____
(DD/MM/YY)

Participant's Name: _____

Witnessed by:

Signature: _____ Date : _____
(DD/MM/YY)

Name : _____

* *cross over whichever does not apply*

Multiple PI Leadership Plan

Lansing will serve as the contact PI, and will be responsible for progress reports to NIH and all communication. Wilkins will serve as primary PI at the Santa Fe Institute. Sudoyo will serve as primary PI at the Eijkman Institute for Molecular Biology in Jakarta. All PIs will work together to define the overall research agenda. Lansing will be primarily responsible for integration of results with cultural, environmental and linguistic data, and for maintaining communication among the three participating institutions. Sudoyo will be responsible for the collection and analysis of the new samples on Sumba. Hammer and Karafet will be responsible for molecular and population genetic analysis of the DNA samples that have already been collected, experimental design, and demographic and phylogeographic inference. Watkins, Wilkins and Cox will be primarily responsible for statistical data analysis and development of novel analytical techniques. Cox will focus on inference in the context of Indo-Pacific population genetics and prehistory. Buckee will be responsible for coevolutionary and epidemiological modeling of the host-pathogen interactions.

The PIs will communicate weekly, either by phone, e-mail, or in person, to discuss experimental design, data analysis, and administrative responsibilities. All PIs will share their respective research results with other PIs, key personnel, and consultants. They will work together to discuss any changes in the direction of the research projects and the reprogramming of funds, if necessary. Publication authorship will be determined based on the relative scientific contributions of the PIs and key personnel.

Conflict Resolution

If a potential conflict develops, the PIs shall meet and attempt to resolve the dispute. If they fail to resolve the dispute, the disagreement shall be referred to an arbitration committee consisting of one impartial senior executive from each PI's institution and a third impartial senior executive mutually agreed upon by both PIs. No members of the arbitration committee will be directly involved in the research grant or disagreement.

Change in PI Location

If a PI moves to a new institution, attempts will be made to transfer the relevant portion of the grant to the new institution. In the event that a PI cannot carry out his/her duties, a new PI will be recruited as a replacement at one of the participating institutions.

SANTA FE INSTITUTE

May 27, 2009

Professor Steven Lansing
Dept of Anthropology
University of Arizona
Tucson, AZ 85721-0030

Dear Dr. Lansing:

The purpose of this letter is to inform you that the appropriate administrative and programmatic personnel at the Santa Fe Institute (SFI) involved in this grant application are aware of the NIH subaward policies and are prepared to establish the necessary consortium agreement consistent with those policies. The total amount we requesting for the subaward is $147,760 for the project entitled "Multi-scale coevolution of infectious diseases and human populations in the Indonesian archipelago " to be conducted at SFI under the direction of PI Jon Wilkins and Co-PI Caroline Buckee.

Please contact me at 505-946-2756 or via email to elisabeth@santafe.edu should you have any questions.

Sincerely,

Elisabeth V. Johnson
Director, Sponsored Research Planning and Administration

EIJKMAN INSTITUTE
for molecular biology

Our Ref: 72/LAB-EIJK/V/2009 26 May 2009

Prof. J. Stephen Lansing
Dept of Anthropology
University of Arizona
Tucson, AZ 85721-0030
USA

Dear Prof. Lansing,

I am delighted to join you as a co-principal investigator in your proposed research on "*Community genetic approach to host-resistance dynamics of malaria and HBV in Indonesia*". This project is very well suited to the mission of our Eijkman Institute for Molecular Biology, which aims to bring the benefits of molecular medicine to our people.

As we have discussed, my role as Co-PI on this project will have several components:

1. I will participate as a researcher and co-author on publications resulting from the grant.
2. My colleagues and I will gather clinical data and genetic samples from villagers on the island of Sumba who are patients of the Karitas Hospital, as part of our ongoing study of malaria & HBV. To the extent possible, we will attempt to gather this data from related individuals over several generations.
3. These genetic samples, estimated at 200 per year for three years, will be analyzed at the Eijkman Institute.

Our budget for the subaward to the Eijkman Institute is as follows:

• Clinical research and sampling in Sumba (3 years).....	$ 30,000
• DNA extraction of 600 samples	$ 4,200
• Plasmodium detection of 600 samples	$ 9,000
• Detection of drug resistance genes in ~200 samples.....	$ 16,800
• HBV genotyping and sequencing for 150 samples.....	$ 50,250
Total subaward to Eijkman Institute.....	**$ 110.250**

Yours sincerely,

Herawati Sudoyo, MD., Ph.D.
Principal Research Fellow/Deputy Director

PHS 398 Checklist

OMB Number: 0925-0001
Expiration Date: 9/30/2007

1. Application Type:

From SF 424 (R&R) Cover Page. The responses provided on the R&R cover page are repeated here for your reference, as you answer the questions that are specific to the PHS398.

* Type of Application:

☒ New ☐ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

Federal Identifier:

2. Change of Investigator / Change of Institution Questions

☐ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:
* First Name:
Middle Name:
* Last Name:
Suffix:

☐ Change of Grantee Institution

* Name of former institution:

3. Inventions and Patents (For renewal applications only)

* Inventions and Patents: Yes ☐ No ☐

If the answer is "Yes" then please answer the following:

* Previously Reported: Yes ☐ No ☐

4. * Program Income

Is program income anticipated during the periods for which the grant support is requested?

☐ Yes ☒ No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

5. Assurances/Certifications (see instructions)

In agreeing to the assurances/certification section 18 on the SF424 (R&R) form, the authorized organizational representative agrees to comply with the policies, assurances and/or certifications listed in the agency's application guide, when applicable. Descriptions of individual assurances/certifications are provided at: http://grants.nih.gov/grants/funding/424

If unable to certify compliance , where applicable, provide an explanation and attach below.

Explanation: Add Attachment | Delete Attachment | View Attachment

PHS 398 Cover Letter

OMB Number: 0925-0001

*Mandatory Cover Letter Filename: cover letter NIH.pdf

Add Cover Letter File | Delete Cover Letter File | View Cover Letter File

1. Application title:

   Multi-scale co-evolution of infectious diseases and human populations in the Indonesian archipelago

2. Funding opportunity announcement number: PA-07-130 (RO1)

3. Please assign this application to the following: Evolution of Infectious Diseases

4. List of individuals who should not review this application:

   1. Karen Day, professor of medicine, NYU

   2. Daniel Falush, University of Cork, Ireland

List of individuals who should review this application:

1. Daniel L. Hartl
Higgins Professor of Biology, Harvard
E-mail: dhartl@oeb.harvard.edu

2. James Beeson
Infection and Immunity Division
Walter and Eliza Hall Institute of Medical Research
Email: beeson@wehi.edu.au

3. David B. Goldstein
Institute for Genome Sciences and Policy, Duke University

4. Sarah Volkman
Dept of Immunology and Infectious Diseases, School of Public Health, Harvard
Email: svolkman@hsph.harvard.edu

5. Noah Rosenberg
Dept of Human Genetics, University of Michigan
Email: rnoah@umich.edu

6. Molly Przeworski
Dept of Genetics, University of Chicago
Email: mfp@uchicago.edu

7. Marc Feldman
Dept of Biology, Stanford University
email: marc@charles.stanford.edu

5. Disciplines involved, if multidisciplinary:

   Anthropology, population genetics, population biology of infectious diseases, computational biology, mathematics

6. N/A

7. N/A

8. N/A

9. N/A

Budget Justification, University of Arizona

Key Personnel

John S. Lansing, PhD, Principal Investigator (1 Calendar Month) Dr. Lansing will serve as the contact PI, and will be responsible for progress reports to NIH and all communication. He will jointly supervise all phases of the project with the other PIs. He will be primarily responsible for integration of results with cultural, environmental and linguistic data, and for maintaining communication among the three participating institutions.

Michael F. Hammer, PhD, Principal Investigator (1 Calendar Month) Dr. Hammer will be responsible for molecular analysis of the DNA samples, and will participate in developing the theoretical framework for the data collection, and writing publications.

Joseph C. Watkins PhD, Principal Investigator (2 Calendar Months) Dr. Watkins will coordinate modeling and inferential procedures, supervise the Computer Research Technician and a graduate student.

Tatiana M. Karafet PhD, Principal Investigator (12 Calendar Months). Dr Karafet will design experiments, supervise a PostDoc and a research specialist to ensure quality data, perform data analysis, and oversee DNA sequence alignment, retrieval and processing.

Murray P. Cox PhD, Consultant ($6,000). Dr Cox will consult in the interpretation of genetic and linguistic data in the context of Indo-Pacific prehistory.

Brian Hallmark MS (1/2 time for 12 Calendar Months) Mr. Hallmark will assist the research team in computer programming, software development, statistical analysis, and technical preparation of manuscripts for publication.

To Be Determined, PhD, Postdoc (12 Calendar Months). The postdoctoral fellow will assist with data collection in Indonesia; carry out PCR experiments and related laboratory procedures. She will assist with the integration of genetic analysis results with cultural, environmental and linguistic data; the modeling of co-evolutionary processes, and statistical analyses.

To Be Determined, Research Technician (12 Calendar Months). The research technician will perform laboratory analysis of genetic data under the supervision of Dr. Karafet and the post-doctoral fellow.

To Be Determined, graduate research fellow in the mathematical sciences. (1/2 time for 12 Calendar Months) Students will be drawn from one of the programs – biostatistics, public health, ecology and evolutionary biology, mathematics, applied mathematics, or statistics.

To Be Determined, undergraduate students from UBRP (Undergraduate Biology Research Program) (part time for the duration of the project) This program enables University of Arizona students to participate in research and receive mentoring from the research team.

Fringe benefits rates: Fringe benefit rates for University of Arizona employees are as follows:
7/1/08-6/30/09 for Staff 41.1%, 36.6% for Graduate Assistants, 2% for Undergraduate Students and Faculty 27.3% .
Future Rates Undetermined for Staff 41.1%, 36.6% for Graduate Assistants, 2% for Undergraduate Students and Faculty 27.3%.

Core Facility Costs
Service facility fees will consist of all data acquisition costs, specifically including charges for consumables involved with array capture enrichment, next-generation genome sequencing, Sanger sequencing, and initial rough data assembly and storage. Service facilities fees also involve prorated instrumentation running costs as well as annualized service and maintenance.

Consultant
We request $6,000 for a consultant, Dr Murray Cox, to assisting the interpretation of genetic and linguistic data in the context of Indo-Pacific prehistory.

Travel
Funds are requested for international travel to Indonesia by Dr. Lansing and the post-doc, to conduct fieldwork in Sumba and analysis at the Eijkman Institute in Jakarta Funds are also requested for all PI's for domestic travel between the University of Arizona and the Santa Fe Institute, and to attend scholarly conferences.

Materials and Supplies
We request funds for anthropological fieldwork in Indonesia, collecting genealogical, demographic, clinical, and environmental data.

Publication costs
We request $7,000 to help defray anticipated publication costs.

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 1

*** ORGANIZATIONAL DUNS:** 8063456170000

*** Budget Type:** [X] Project [ ] Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

*** Start Date:** 04/01/2010 *** End Date:** 03/31/2011 **Budget Period** 1

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		John	S	Lansing	Ph.D.	PD/PI	149,599.00			1.00	16,659.00	4,548.00	21,207.00
2.		Michael	F	Hammer	PhD	PD/PI	108,283.00			1.00	12,058.00	3,292.00	15,350.00
3.		Tatiana	M	Karafet	PhD	PD/PI	60,185.00	12.00			60,185.00	16,431.00	76,616.00
4.		Joseph	C	Watkins	PhD	PD/PI	83,250.00			2.00	18,541.00	5,063.00	23,604.00
5.													
6.													
7.													
8.													
9.	Total Funds requested for all Senior Key Persons in the attached file												

Total Senior/Key Person 136,777.00

Additional Senior Key Persons: Add Attachment | Delete Attachment | View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1	Post Doctoral Associates	12.00			41,796.00	11,410.00	53,206.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Technician	12.00			35,000.00	14,385.00	49,385.00
1	Research Specialist Senior	6.00			22,968.00	9,440.00	32,408.00
1	Undergratuate Student Assistant	6.00			10,000.00	200.00	10,200.00
1	Graduate Student Assistant	6.00			16,454.00	6,022.00	22,476.00
5	Total Number Other Personnel						

Total Other Personnel 167,675.00

Total Salary, Wages and Fringe Benefits (A+B) 304,452.00

Close Form

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1

* ORGANIZATIONAL DUNS: 8063456170000

* Budget Type: [X] Project [ ] Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Univ

* Start Date: 04/01/2010 * End Date: 03/31/2011 Budget Period 1

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	**Total funds requested for all equipment listed in the attached file**	
	Total Equipment	

Additional Equipment: Add Attachment | Delete Attachment | View Attachment

D. Travel

		Funds Requested ($)
1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	9,000.00
2.	Foreign Travel Costs	14,000.00
	Total Travel Cost	23,000.00

E. Participant/Trainee Support Costs

		Funds Requested ($)
1.	Tuition/Fees/Health Insurance	
2.	Stipends	
3.	Travel	
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees	**Total Participant/Trainee Support Costs**

Close Form

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 1

* ORGANIZATIONAL DUNS: 8063456170000

* Budget Type: [X] Project [ ] Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

* Start Date: 04/01/2010 * End Date: 03/31/2011 Budget Period 1

F. Other Direct Costs	Funds Requested ($)
1. Materials and Supplies	10,000.00
2. Publication Costs	1,000.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	58,749.00
6. Equipment or Facility Rental/User Fees	75,000.00
7. Alterations and Renovations	
8.	
9.	
10.	
Total Other Direct Costs	144,749.00

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	472,201.00

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1. MTDC	51.00	113,915.00	58,097.00
2. MTDC	51.50	341,745.00	175,999.00
3.			
4.			
Total Indirect Costs			234,096.00

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	706,297.00

J. Fee	Funds Requested ($)

K. * Budget Justification Justification Uof A.pdf Add Attachment Delete Attachment View Attachment

(Only attach one file.)

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 2

*** ORGANIZATIONAL DUNS:** 8063456170000

*** Budget Type:** [X] Project [ ] Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Univ

*** Start Date:** 04/01/2011 *** End Date:** 03/31/2012 **Budget Period** 2

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		John	S	Lansing	Ph.D.	PD/PI	154,087.00			1.00	17,159.00	4,684.00	21,843.00
2.		Michael	F	Hammer	PhD	PD/PI	111,531.00			1.00	12,420.00	3,391.00	15,811.00
3.		Tatiana	M	Karafet	PhD	PD/PI	61,991.00	12.00			61,991.00	16,923.00	78,914.00
4.		Joseph	C	Watkins	PhD	PD/PI	85,748.00			2.00	19,098.00	5,214.00	24,312.00
5.													
6.													
7.													
8.													
9.	Total Funds requested for all Senior Key Persons in the attached file												

Total Senior/Key Person 140,880.00

Additional Senior Key Persons: Add Attachment | Delete Attachment | View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1	Post Doctoral Associates	12.00			43,428.00	11,856.00	55,284.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Technician	12.00			36,050.00	14,817.00	50,867.00
1	Research Specialist Senior	6.00			23,657.00	9,723.00	33,380.00
1	Undergratuate Student Assistant	6.00			10,300.00	206.00	10,506.00
1	Graduate Student Assistant	6.00			16,948.00	6,202.00	23,150.00
5	**Total Number Other Personnel**					**Total Other Personnel**	173,187.00

Total Salary, Wages and Fringe Benefits (A+B) 314,067.00

Close Form

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2

* ORGANIZATIONAL DUNS: 8063456170000

* Budget Type: [X] Project [ ] Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

* Start Date: 04/01/2011 * End Date: 03/31/2012 Budget Period 2

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	**Total funds requested for all equipment listed in the attached file**	
	Total Equipment	

Additional Equipment: Add Attachment | Delete Attachment | View Attachment

D. Travel

		Funds Requested ($)
1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	5,000.00
2.	Foreign Travel Costs	18,000.00
	Total Travel Cost	23,000.00

E. Participant/Trainee Support Costs

		Funds Requested ($)
1.	Tuition/Fees/Health Insurance	
2.	Stipends	
3.	Travel	
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees	**Total Participant/Trainee Support Costs**

Close Form

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 2

* ORGANIZATIONAL DUNS: 8063456170000

* Budget Type: [X] Project [ ] Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

* Start Date: 04/01/2011 * End Date: 03/31/2012 Budget Period 2

F. Other Direct Costs	Funds Requested ($)
1. Materials and Supplies	10,000.00
2. Publication Costs	3,000.00
3. Consultant Services	3,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	72,449.00
6. Equipment or Facility Rental/User Fees	72,000.00
7. Alterations and Renovations	
8.	
9.	
10.	
Total Other Direct Costs	160,449.00

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	497,516.00

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1. MTDC	51.50	423,640.00	218,175.00
2.			
3.			
4.			
Total Indirect Costs			218,175.00

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	715,691.00

J. Fee	Funds Requested ($)

K. * Budget Justification: Justification Uof A.pdf (Only attach one file.)

Add Attachment | Delete Attachment | View Attachment

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 3

* ORGANIZATIONAL DUNS: 8063456170000

* Budget Type: [X] Project [ ] Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Univ

* Start Date: 04/01/2012 * End Date: 03/31/2013 Budget Period 3

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		John	S	Lansing	Ph.D.	PD/PI	158,710.00			1.00	17,674.00	4,825.00	22,499.00
2.		Michael	F	Hammer	PhD	PD/PI	114,877.00			1.00	12,793.00	3,492.00	16,285.00
3.		Tatiana	M	Karafet	PhD	PD/PI	63,850.00	12.00			63,850.00	17,431.00	81,281.00
4.		Joseph	C	Watkins	PhD	PD/PI	88,320.00			2.00	19,671.00	5,370.00	25,041.00
5.													
6.													
7.													
8.													
9.	Total Funds requested for all Senior Key Persons in the attached file												

Total Senior/Key Person 145,106.00

Additional Senior Key Persons: [ ] Add Attachment | Delete Attachment | View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1	Post Doctoral Associates	12.00			45,048.00	12,298.00	57,346.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Technician	12.00			37,132.00	15,261.00	52,393.00
1	Research Specialist Senior	6.00			24,367.00	10,015.00	34,382.00
1	Undergratuate Student Assistant	6.00			10,609.00	212.00	10,821.00
1	Graduate Student Assistant	6.00			17,456.00	6,388.00	23,844.00
5	Total Number Other Personnel					Total Other Personnel	178,786.00

Total Salary, Wages and Fringe Benefits (A+B) 323,892.00

Close Form

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3

* ORGANIZATIONAL DUNS: 8063456170000

* Budget Type: [X] Project [ ] Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Univ

* Start Date: 04/01/2012 * End Date: 03/31/2013 Budget Period 3

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	**Total funds requested for all equipment listed in the attached file**	
	Total Equipment	

Additional Equipment: Add Attachment | Delete Attachment | View Attachment

D. Travel

		Funds Requested ($)
1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	9,000.00
2.	Foreign Travel Costs	14,000.00
	Total Travel Cost	23,000.00

E. Participant/Trainee Support Costs

		Funds Requested ($)
1.	Tuition/Fees/Health Insurance	
2.	Stipends	
3.	Travel	
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees	**Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Close Form

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 3

* ORGANIZATIONAL DUNS: 8063456170000

* Budget Type: [X] Project [ ] Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

* Start Date: 04/01/2012 * End Date: 03/31/2013 Budget Period 3

F. Other Direct Costs

		Funds Requested ($)
1.	Materials and Supplies	
2.	Publication Costs	3,000.00
3.	Consultant Services	3,000.00
4.	ADP/Computer Services	
5.	Subawards/Consortium/Contractual Costs	86,210.00
6.	Equipment or Facility Rental/User Fees	60,000.00
7.	Alterations and Renovations	
8.		
9.		
10.		
	Total Other Direct Costs	152,210.00

G. Direct Costs

	Funds Requested ($)
Total Direct Costs (A thru F)	499,102.00

H. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.	MTDC	51.50	408,075.00	210,158.00
2.				
3.				
4.				
	Total Indirect Costs			210,158.00

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs

	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	709,260.00

J. Fee

	Funds Requested ($)

K. * Budget Justification Justification Uof A.pdf Add Attachment Delete Attachment View Attachment

(Only attach one file.)

RESEARCH & RELATED BUDGET - Cumulative Budget

		Totals ($)
Section A, Senior/Key Person		422,763.00
Section B, Other Personnel		519,648.00
Total Number Other Personnel	15	
Total Salary, Wages and Fringe Benefits (A+B)		942,411.00
Section C, Equipment		
Section D, Travel		69,000.00
1. Domestic	23,000.00	
2. Foreign	46,000.00	
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		457,408.00
1. Materials and Supplies	20,000.00	
2. Publication Costs	7,000.00	
3. Consultant Services	6,000.00	
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs	217,408.00	
6. Equipment or Facility Rental/User Fees	207,000.00	
7. Alterations and Renovations		
8. Other 1		
9. Other 2		
10. Other 3		
Section G, Direct Costs (A thru F)		1,468,819.00
Section H, Indirect Costs		662,429.00
Section I, Total Direct and Indirect Costs (G + H)		2,131,248.00
Section J, Fee		

OMB Number: 4040-0001
Expiration Date: 06/30/2011

R&R SUBAWARD BUDGET ATTACHMENT(S) FORM

Instructions: On this form, you will attach the R&R Subaward Budget files for your grant application. Complete the subawardee budget(s) in accordance with the R&R budget instructions. Please remember that any files you attach must be a PDF document.

Click here to extract the R&R Subaward Budget Attachment

Important: Please attach your subawardee budget file(s) with the file name of the subawardee organization. Each file name must be unique.

1) Please attach Attachment 1	RR_Budget_Sub_Santa Fe.pdf	Add Attachment	Delete Attachment	View Attachment
2) Please attach Attachment 2	RR_Budget_Sub_Eijkman.pdf	Add Attachment	Delete Attachment	View Attachment
3) Please attach Attachment 3		Add Attachment	Delete Attachment	View Attachment
4) Please attach Attachment 4		Add Attachment	Delete Attachment	View Attachment
5) Please attach Attachment 5		Add Attachment	Delete Attachment	View Attachment
6) Please attach Attachment 6		Add Attachment	Delete Attachment	View Attachment
7) Please attach Attachment 7		Add Attachment	Delete Attachment	View Attachment
8) Please attach Attachment 8		Add Attachment	Delete Attachment	View Attachment
9) Please attach Attachment 9		Add Attachment	Delete Attachment	View Attachment
10) Please attach Attachment 10		Add Attachment	Delete Attachment	View Attachment

SANTA FE INSTITUTE

BUDGET JUSTIFICATION

Personnel:

PI Jon Wilkins will be reimbursed for one calendar month per year. Wilkins will be responsible for population genetic analysis, developing statistical methods for inferring patterns of demographic history, and developing statistical methods for inferring the nature and strength of selection.

Co-PI Caroline Buckee will have her first year salary covered by a Wellcome Trust Fellowship. In year two we are requesting one summer month support for Buckee and in year three, two months. Buckee will be responsible for helping with the experimental design, especially analysis of host pathogen co-evolutionary dynamics. Her time devoted to the project will be higher in the third year to work on the collected human and pathogen data and to address the co-evolutionary questions.

Travel:

It will be critical for the investigators to meet frequently to confer on data analysis and to refine the experimental design. Therefore, we have budgeted trips each year for Wilkins and Buckee to travel to the University of Arizona from Santa Fe. In years two and three, Buckee will be traveling from Boston (Harvard), rather than from Santa Fe.

We have also budgeted costs for Wilkins and Buckee to attend one national confer ence per year to disseminate research results.

Travel costs are based on the following: domestic roundtrip airfare - $600; ground transportation - $140; lodging $150/night; and per diem .

Publication:

We have included page charge c osts for publication in Science and Nature, estimating two articles per year.

Indirect costs are calculated using SFI's indirect cost rate of 47.42% negotiated with the National Science Foundation, on August 23, 200 7.

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 1

* ORGANIZATIONAL DUNS: 1780449960000

* Budget Type: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: Santa Fe Institute

* Start Date: 04/01/2010 * End Date: 03/31/2011 Budget Period 1

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		Jonathan		Wilkins	PhD	PD/PI	97,524.00			1.00	8,127.00	1,626.00	9,753.00
2.		Caroline		Buckee	PhD	PD/PI	75,000.00				0.00	0.00	0.00
3.													
4.													
5.													
6.													
7.													
8.													
9.	Total Funds requested for all Senior Key Persons in the attached file												

Total Senior/Key Person 9,753.00

Additional Senior Key Persons: Add Attachment | Delete Attachment | View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
	Total Number Other Personnel						

Total Other Personnel

Total Salary, Wages and Fringe Benefits (A+B) 9,753.00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1

* ORGANIZATIONAL DUNS: 1780449960000

* Budget Type: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: Santa Fe Institute

* Start Date: 04/01/2010 * End Date: 03/31/2011 Budget Period 1

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	**Total funds requested for all equipment listed in the attached file**	
	Total Equipment	

Additional Equipment: Add Attachment | Delete Attachment | View Attachment

D. Travel

		Funds Requested ($)
1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	4,000.00
2.	Foreign Travel Costs	
	Total Travel Cost	4,000.00

E. Participant/Trainee Support Costs

		Funds Requested ($)
1.	Tuition/Fees/Health Insurance	
2.	Stipends	
3.	Travel	
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees	**Total Participant/Trainee Support Costs**

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 1

* ORGANIZATIONAL DUNS: 1780449960000

* Budget Type: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: Santa Fe Institute

* Start Date: 04/01/2010 * End Date: 03/31/2011 Budget Period 1

F. Other Direct Costs

		Funds Requested ($)
1.	Materials and Supplies	
2.	Publication Costs	1,000.00
3.	Consultant Services	
4.	ADP/Computer Services	
5.	Subawards/Consortium/Contractual Costs	
6.	Equipment or Facility Rental/User Fees	
7.	Alterations and Renovations	
8.		
9.		
10.		
	Total Other Direct Costs	1,000.00

G. Direct Costs

	Funds Requested ($)
Total Direct Costs (A thru F)	14,753.00

H. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.	MTDC	47.42	14,753.00	6,996.00
2.				
3.				
4.				
	Total Indirect Costs			6,996.00

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs

	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	21,749.00

J. Fee

	Funds Requested ($)

K. * Budget Justification Budget Just Santa Fe.pdf [Add Attachment] [Delete Attachment] [View Attachment]

(Only attach one file.)

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 2

* ORGANIZATIONAL DUNS: 1780449960000

* Budget Type: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: Santa Fe Institute

* Start Date: 04/01/2011 * End Date: 03/31/2012 Budget Period 2

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		Jonathan		Wilkins	PhD	PD/PI	100,450.00			1.00	8,371.00	1,675.00	10,046.00
2.		Caroline		Buckee	PhD	PD/PI	90,000.00			1.00	7,500.00	1,501.00	9,001.00
3.													
4.													
5.													
6.													
7.													
8.													
9.	Total Funds requested for all Senior Key Persons in the attached file												

Total Senior/Key Person 19,047.00

Additional Senior Key Persons: Add Attachment | Delete Attachment | View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
	Total Number Other Personnel					Total Other Personnel	

Total Salary, Wages and Fringe Benefits (A+B) 19,047.00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2

* ORGANIZATIONAL DUNS: 1780449960000

* Budget Type: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: Santa Fe Institute

* Start Date: 04/01/2011 * End Date: 03/31/2012 Budget Period 2

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	**Total funds requested for all equipment listed in the attached file**	
	Total Equipment	

Additional Equipment: Add Attachment | Delete Attachment | View Attachment

D. Travel

		Funds Requested ($)
1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	4,000.00
2.	Foreign Travel Costs	
	Total Travel Cost	4,000.00

E. Participant/Trainee Support Costs

		Funds Requested ($)
1.	Tuition/Fees/Health Insurance	
2.	Stipends	
3.	Travel	
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees	**Total Participant/Trainee Support Costs**

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 2

* ORGANIZATIONAL DUNS: 1780449960000

* Budget Type: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: Santa Fe Institute

* Start Date: 04/01/2011 * End Date: 03/31/2012 Budget Period 2

F. Other Direct Costs

		Funds Requested ($)
1.	Materials and Supplies	
2.	Publication Costs	1,000.00
3.	Consultant Services	
4.	ADP/Computer Services	
5.	Subawards/Consortium/Contractual Costs	
6.	Equipment or Facility Rental/User Fees	
7.	Alterations and Renovations	
8.		
9.		
10.		
	Total Other Direct Costs	1,000.00

G. Direct Costs

	Funds Requested ($)
Total Direct Costs (A thru F)	24,047.00

H. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.	MTDC	47.42	24,047.00	11,402.00
2.				
3.				
4.				
	Total Indirect Costs			11,402.00

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs

	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	35,449.00

J. Fee

	Funds Requested ($)

K. * Budget Justification Budget Just Santa Fe.pdf. Add Attachment Delete Attachment View Attachment

(Only attach one file.)

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 3

*** ORGANIZATIONAL DUNS:** 1780449960000

*** Budget Type:** ☐ Project ☒ Subaward/Consortium

Enter name of Organization: Santa Fe Institute

*** Start Date:** 04/01/2012 *** End Date:** 03/31/2013 **Budget Period** 3

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		Jonathan		Wilkins	PhD	PD/PI	103,463.00			1.00	8,622.00	1,725.00	10,347.00
2.		Caroline		Buckee	PhD	PD/PI	92,700.00			2.00	15,450.00	3,092.00	18,542.00
3.													
4.													
5.													
6.													
7.													
8.													

9. **Total Funds requested for all Senior Key Persons in the attached file**

Total Senior/Key Person 28,889.00

Additional Senior Key Persons: Add Attachment | Delete Attachment | View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
	Total Number Other Personnel					Total Other Personnel	

Total Salary, Wages and Fringe Benefits (A+B) 28,889.00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3

* ORGANIZATIONAL DUNS: 1780449960000

* Budget Type: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: Santa Fe Institute

* Start Date: 04/01/2012 * End Date: 03/31/2013 Budget Period 3

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	**Total funds requested for all equipment listed in the attached file**	
	Total Equipment	

Additional Equipment: Add Attachment | Delete Attachment | View Attachment

D. Travel

		Funds Requested ($)
1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	4,000.00
2.	Foreign Travel Costs	
	Total Travel Cost	4,000.00

E. Participant/Trainee Support Costs

		Funds Requested ($)
1.	Tuition/Fees/Health Insurance	
2.	Stipends	
3.	Travel	
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees	**Total Participant/Trainee Support Costs**

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 3

* ORGANIZATIONAL DUNS: 1780449960000

* Budget Type: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: Santa Fe Institute

* Start Date: 04/01/2012 * End Date: 03/31/2013 Budget Period 3

F. Other Direct Costs	Funds Requested ($)
1. Materials and Supplies	
2. Publication Costs	1,000.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8.	
9.	
10.	
Total Other Direct Costs	1,000.00

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	33,889.00

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1. MTDC	47.42	33,889.00	16,070.00
2.			
3.			
4.			
Total Indirect Costs			16,070.00

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	49,959.00

J. Fee	Funds Requested ($)

K. * Budget Justification Budget Just Santa Fe.pdf [Add Attachment] [Delete Attachment] [View Attachment]

(Only attach one file.)

RESEARCH & RELATED BUDGET - Cumulative Budget

		Totals ($)
Section A, Senior/Key Person		57,689.00
Section B, Other Personnel		
Total Number Other Personnel		
Total Salary, Wages and Fringe Benefits (A+B)		57,689.00
Section C, Equipment		
Section D, Travel		12,000.00
1. Domestic	12,000.00	
2. Foreign		
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		3,000.00
1. Materials and Supplies		
2. Publication Costs	3,000.00	
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1		
9. Other 2		
10. Other 3		
Section G, Direct Costs (A thru F)		72,689.00
Section H, Indirect Costs		34,468.00
Section I, Total Direct and Indirect Costs (G + H)		107,157.00
Section J, Fee		

OMB Number: 4040-0001
Expiration Date: 04/30/2008

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 1

* ORGANIZATIONAL DUNS: 7288627440000

* Budget Type: ☐ Project ☒ Subaward/Consortium

Enter name of Organization: Eijkman Institute For Molecul

* Start Date: 04/01/2010 * End Date: 03/31/2011 Budget Period 1

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		Herawati		Sudoyo	MD	PD/PI					0.00	0.00	0.00
2.													
3.													
4.													
5.													
6.													
7.													
8.													
9.	Total Funds requested for all Senior Key Persons in the attached file												

Total Senior/Key Person 0.00

Additional Senior Key Persons: Add Attachment | Delete Attachment | View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
	Total Number Other Personnel						

Total Other Personnel

Total Salary, Wages and Fringe Benefits (A+B) 0.00