

Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is “None”, please specify “None” as your response. “Not applicable” is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format.

1. **Grantee Institution:** The Pennsylvania State University
2. **Reporting Period (start and end date of grant award period):** 1/1/2010 - 12/31/2013
3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** John Anthony, MPA
4. **Grant Contact Person’s Telephone Number:** 814 935 1081
5. **Grant SAP Number:** 4100050904
6. **Project Number and Title of Research Project:** 51. Defining the Neonatal Septisome and Postinfectious Hydrocephalus
7. **Start and End Date of Research Project:** 12/12/2012 - 12/31/2013
8. **Name of Principal Investigator for the Research Project:** Steven J. Schiff, MD, PhD
9. **Research Project Expenses.**

9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

\$ 44,800 _____

9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Mu	Technician	50	9867.00
Nguyen	Undergraduate	10	1544.00
Riggio	Technician	50	4014.00

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Schiff	PI	10
Poss	Co-Investigator	10

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
BioRad T100 Thermal Cycler	Easily optimizes PCR assays in a single run	2995.00
Promega Fluorometer	Provides highly sensitive fluorescent detection when quantifying nucleic acids	1600.00

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes _____ No X _____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes X _____ No _____

If yes, please list the applications submitted (column A), the funding agency (National

Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert “not funded” in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
Defining the Neonatal Septisome and Postinfectious Hydrocephalus in East Africa	X NIH <input type="checkbox"/> Other federal (specify: _____) <input type="checkbox"/> Nonfederal source (specify: _)	06/2013	\$3,206,234	\$0
Control of the Neonatal Septisome and Hydrocephalus in sub-Saharan Africa	X NIH <input type="checkbox"/> Other federal (specify: _____) <input type="checkbox"/> Nonfederal source (specify: _)	10/2013	\$2,500,000	\$ pending – presently in finals for Pioneer Award

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes X No _____

If yes, please describe your plans:

If the pending Pioneer Award is not funded, I will continue to apply for funding until this project is on solid footing.

12. Future of Research Project. What are the future plans for this research project?

To define the neonatal septisome and the origins of postinfectious hydrocephalus.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes X No _____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male			1	
Female	2			
Unknown				
Total	2		1	

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic	2		1	
Unknown				
Total	2		1	

	Undergraduate	Masters	Pre-doc	Post-doc
White	1			
Black				
Asian	1		1	
Other				
Unknown				
Total	2		1	

14. Recruitment of Out-of-State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes _____ No X _____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes _____ No X _____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes _____ No X _____

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes _____ No X

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes _____ No X

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (β) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

This project seeks to test the hypothesis that: The pathogenic bacteria and viruses responsible for neonatal sepsis in sub-Saharan Africa have not been well characterized. A comprehensive evaluation of the responsible bacteria and viruses is the starting point to develop more rational methods of improving treatment and prevention to meaningfully reduce the morbidity and mortality from this syndrome.

Over 1 million neonates die each year from preventable and treatable infections in the neonatal period, and many of those that survive give rise to a cohort with substantial sequelae. The vast majority of these neonatal infections are in the developing world, about half in sub-Saharan Africa. Survivors of such infections also appear to constitute a substantial fraction of infant hydrocephalus. Nevertheless, we know little about the underlying bacterial and viral agents involved in neonatal sepsis in such settings, and have no rational basis to optimize treatment or prevention.

This project seeks to begin to characterize the neonatal septisome – the collection of invasive microorganisms that underlie neonatal sepsis. We further seek to characterize the particular agents associated with postinfectious hydrocephalus in survivors of neonatal sepsis. We will do this by a bacteriological and metagenomic evaluation of mother-infant pairs with neonatal sepsis, and a comprehensive metagenomic evaluation of postinfectious hydrocephalus.

The specific aims are:

1. Characterize the Neonatal Septisome from 80 mother-infant pairs with neonatal sepsis from the Mbarara Regional Hospital in Uganda using a metagenomic analysis of Bacterial 16S rRNA gene
2. Characterize an age matched cohort of postinfectious hydrocephalus infants (25) and non-postinfectious hydrocephalus patients (of known congenital cause and without a history of neonatal sepsis) using metagenomic analysis of Bacterial 16S rRNA gene from infant blood and cerebrospinal fluid (CSF)

We have made substantial progress towards these goals.

Aim 1:

We completed a comprehensive analysis of the bacteriology of the 80 mother-infant pairs with neonatal sepsis at Mbarara. We were able to recover the pathogenic organisms in 32.5% of these infants. The blood culture results were:

This spectra of pathogens from infants with sepsis is essentially the same as one published by Mugalu et al, from the National hospital at Kampala, and demonstrates that in nearly 2/3 of these cases, the putative causal organisms go unidentified.

In addition, we characterized the pathogens recovered from maternal vaginal specimens:

	n (of 53)	%
Klebsiella sp.	10	18.9
S. aureus	7	13.2
E. coli	6	9.4
C. albicans	2	3.8
Strep sp.	1	1.9
unidentified coliform	1	1.9

Yet stratification of pathogens from infants with positive blood cultures demonstrated no clear correspondence:

	<24 hr	24- 48 hr	Early-onset Overall n (of 19) 2-6 days	Late-onset		Totals			
				n (of 7)	%	n (of 80)	%		
S. aureus	6	2	5	13	68.4	3	42.9	16	20
E. coli	1	2	0	3	15.8	1	14.3	4	5
Klebsiella sp.	1	0	0	1	5.3	1	14.3	2	2.5
unidentified coliform	1	0	0	1	5.3	2	28.6	3	3.8
Group B Streptococcus	1	0	0	1	5.3	0	0	1	1.3
Total	10	4	5	19		7		26	32.5

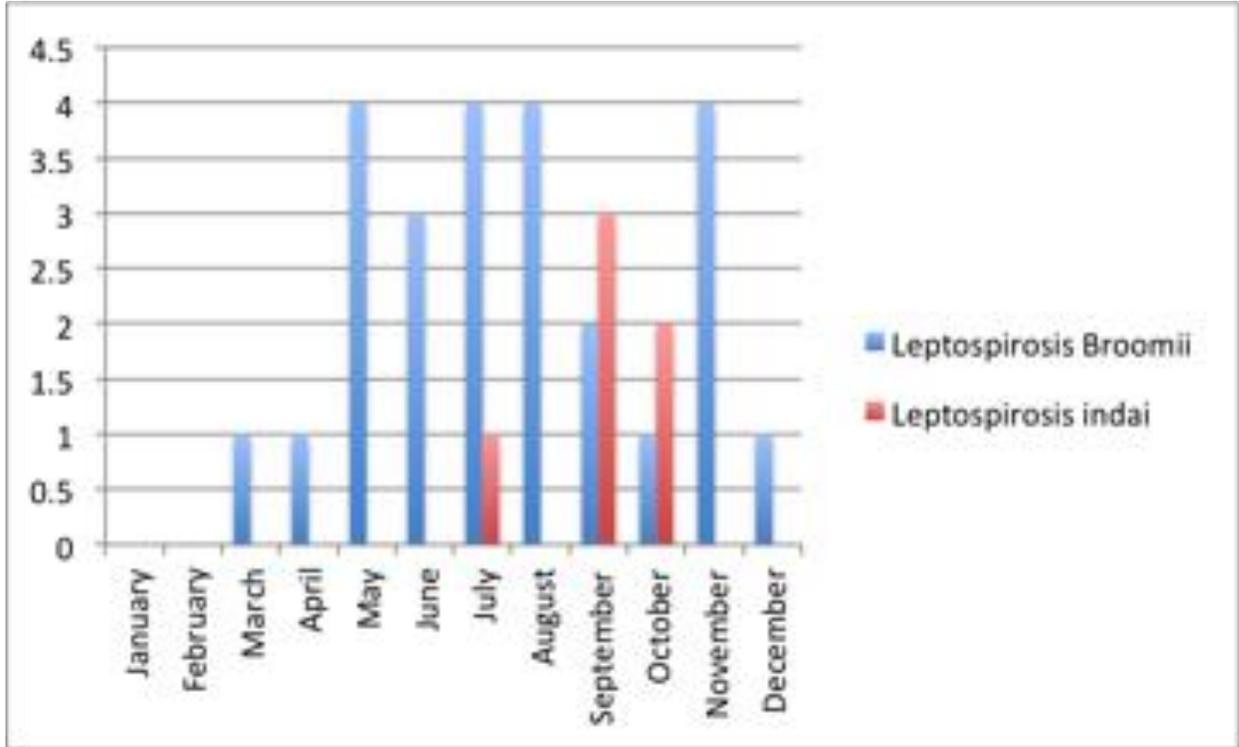
	Patient ID	Mother's vaginal swab culture	Infant's blood culture	Infant's CSF culture
1	NS008	E. coli	S. aureus	No growth
2	NS012	E. coli	S. aureus	No growth
3	NS019	Mixed growth - E. coli/S. aureus	Unidentified coliform	No growth
4	NS026	Klebsiella	S. aureus	No growth
5	NS035	Streptococcus sp.	S. aureus	No growth

Such findings are all supportive of the need for introducing molecular diagnostic techniques into such settings.

We have now processed the first 80 blood and CSF specimens for the ribosomal RNA 16S gene. We are still in the process of analyzing these data, and are using a no-cost continuation of an award for matching funds from Penn State and Penn State Hershey Medical Center, to complete this analysis by June 30, 2014.

We have discovered an association of pathogenic *Leptospira* species (Broomii and Indai) in 31/80 patients from blood specimens. We have confirmed species specificity using sequencing of reverse polymerase (rPO) gene for *Leptospira*. In 9 of these 31 patients there was a positive blood or CSF culture. Seven (7/9) were identified as *Staph aureus* by chemical analysis, but only 3 of these were confirmed by sequencing to be a *Staphylococcus* species.

Leptospirosis is one of the world's most common zoonoses, but is vastly underdiagnosed since it is extremely difficult to recover by bacteriological methods. It is harbored in the kidneys of mammals such as cow, dog, and rat, and spread through their urine. Such contamination is ubiquitous among the rural peoples whom we are studying who live in huts in close proximity to these mammalian species. It can infect the nervous system, and has a common association with rainfall. It can be vertically transmitted from mother to fetus, but previous reports are generally associated with death of the fetus. There are no previous reports of Leptospirosis as a cause of neonatal sepsis. We note several cases where sepsis was diagnosed in the first or second day after birth, suggesting strongly that we may see a mixture of both environmentally acquired (late onset in the weeks after birth) as well as evidence of maternal transmission. Since we have previous evidence that our cases of postinfectious hydrocephalus are rainfall sensitive, and rarely have a bacterial recovery on routine culture, *Leptospira* forms a potential pathogen of interest from such sequencing results. Our results suggest that our putative causal organisms may now be raised from 32.5 to over 60% given these new findings. The chart shows the number of cases of pathogenic *Leptospira* identified as a function of month of the year:



Also of interest is that there is increasing evidence for co-infections. Although no blood or CSF culture grew more than one organism, adding the Leptospira data suggest that up to 10% of these infants may have Leptospira present in addition to another pathogen.

We are at present sequencing the samples from the following year, in order to provide 2 full years of case data. We are simultaneously extracting satellite climate derived rainfall data for these same months, and correlating those rainfall amounts with the geographic districts from which these cases arose.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be “No.”

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

Yes
 No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

Yes
 No

If “Yes” to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both “No.”)

18(C) How many hospital and health care professionals were involved in the research project?

 3 Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

 80 Number of subjects originally targeted to be included in the study

 80 Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:

 Males

 Females

 80 Unknown

Ethnicity:

 Latinos or Hispanics

 80 Not Latinos or Hispanics

 Unknown

Race:

 American Indian or Alaska Native

 Asian

 80 Blacks or African American

 Native Hawaiian or Other Pacific Islander

 White

 Other, specify: _____

 Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

Uganda, United States

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?

Yes
 No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?

Yes
 No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

- Project 01 – Smith – Three cases of isolated
- Project 01 – Smith – Investigation of NEB1 deletions
- Project 03 – Zhang – Molecular profiling of aromatase
- Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. None				<input type="checkbox"/> Submitted <input type="checkbox"/> Accepted <input type="checkbox"/> Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes X No _____

If yes, please describe your plans:

Once we complete the project in June of 2014, we will submit the report that we plan for this project for publication.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project.

Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert “None”; do not use “Not applicable.” Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

This project involves a metagenomic analysis of 1) 80 mother-infant pairs with neonatal sepsis, and 2) an analysis of 50 patients age matched for postinfectious and non-postinfectious hydrocephalus. We have completed the metagenomic analysis of the infants with neonatal sepsis, and we are processing the hydrocephalus infants. We already have a major finding in terms of the first solid evidence for a role for Leptospirosis as a potential common pathogen in neonatal sepsis in Uganda. We will correlate these findings with our results of our metagenomic analysis of hydrocephalic infants, who by definition, were survivors of neonatal sepsis whose infections also involved the nervous system. Our findings are of potential substantial interest to neonatal sepsis worldwide, since Leptospirosis is so common a zoonotic infection.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment.

Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert “None”; do not use “Not applicable.” Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

We have discovered that Leptospirosis may have a substantial role in neonatal sepsis in Africa.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes _____ No X

If “Yes” to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is “No.”)

- a. Title of Invention:
- b. Name of Inventor(s):
- c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):
- d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes _____ No _____

If yes, indicate date patent was filed:

- e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes _____ No _____
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

- f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes _____ No _____

If yes, how many licenses were granted? _____

- g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes ___ No ___

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes _____ No X

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/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 Schiff, Steven J.	POSITION TITLE Director, Center for Neural Engineering Brush Chair Professor of Engineering		
eRA COMMONS USER NAME (credential, e.g., agency login) sschiff			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
M.I.T.	S.B.	1977	Biology
Duke University School of Medicine	M.D.	1980	Medicine
Duke University School of Medicine	Ph.D.	1985	Physiology

A. Personal Statement

I am Director of the Penn State Center for Neural Engineering, with appointments in the departments of Engineering Sciences and Mechanics, Neurosurgery, and Physics. I acquired considerable expertise in children's medicine, serving early in my career for 8 years as an attending pediatric neurosurgeon at the Children's National Medical Center where I was on the executive committee that designed and carried out the seminal randomized controlled clinical trial of hydrocephalus shunt valves. I also co-directed the epilepsy surgery program at the Children's Hospital, and for 5 years treated from the NIH Intramural program in epilepsy requiring surgery. Since leaving full time medical practice, I acquired considerable expertise in biological physics, and am likely the only person with Fellowship status in both the American College of Surgeons and the American Physical Society. In addition to actively publishing in physics, I have served for 13 consecutive years on the Editorial Boards of the journals of the American Physical Society: Physical Review E, Physical Review Letters (as Divisional Associate Editor), and now Physical Review X. At Penn State, I focused considerable effort on control engineering, culminating with the 2012 publication of a full-length textbook, Neural Control Engineering, published by The MIT Press. I simultaneously have put considerable effort into understanding the origin of much of the infant hydrocephalus in East Africa, which appears postinfectious with microbial origins in neonatal sepsis. I have focused my first efforts in Uganda, developing substantial collaborative infrastructure and maintaining medical licensure, and am PI (with Drs Warf and Kulkarni) on a new randomized clinical surgical trial at Mbale, Uganda, in a jointly sponsored Phase III clinical trial managed by NINDS and the Fogarty International Center. This present R01 project proposal represents an effort to comprehensively characterize the microbial underpinnings of neonatal sepsis in this sub-Saharan African country, and gain an understanding of the causes of postinfectious hydrocephalus as well. With the collaborative infrastructure I have built, I am now in an excellent position to coordinate and lead the proposed project with the goal of achieving this first characterization of what I call the *neonatal septisome*.

B. Positions and Honors

Positions and Employment

1981	Internship, General Surgery, Duke University School of Medicine
1982-1989	Neurosurgery Residency, Duke University School of Medicine
1989-1990	Fellowship, Pediatric Neurosurg, Children's Hosp of Philadelphia (Instructor, U Penn Med Sch)
1990-1994	Assistant Prof. Neurosurgery and Pediatrics, George Washington Univ. Sch. of Med. (GWUSM)
1993-1997	Co-Director, Epilepsy Surgery Program, Children's National Medical Center (CNMC)
1994-1998	Associate Prof. of Neurosurgery, Pediatrics, and Physiology, GWUSM,
1996-1998	Assoc Director, Ctr for Neurosci and Behavioral Medicine, Children's Res Inst, CNMC
1998-	Adjunct Professor of Pharmacology, GWUSM,
1998-2006	Chief, Laboratory of Neural Dynamics, Krasnow Institute, George Mason University (GMU),
1998-2006	Krasnow Professor of Neurobiology, Krasnow Institute, George Mason University,
1998-2006	Professor of Psychology, George Mason University (Tenured 1999)
2005-2006	Director, Center for Neural Dynamics, George Mason University
2006-	Brush Chair Professor of Engineering, Penn State University
2006 -	Professor of Neurosurgery, Engineering Sciences and Mechanics, and Physics (Courtesy Appt)
2007-	Director, Penn State Center for Neural Engineering

Other Experience and Professional Memberships

1992- Diplomat, American Board of Neurological Surgery; 1996- American Board of Pediatric Neurological Surgery certification; 1996- American Society for Pediatric Neurosurgery, (Elected to Membership 1996), 1995-1996 Biological Physics Prize Selection Committee, American Physical Society; 1998-4 NIH Study Section member, Integrative Functional Cognitive Neuroscience (IFCN)-8; 2000-2 Program Committee, Annual Computational Neuroscience Meeting; 2000-6 Editorial Board, Physical Review E; 2002-2 Translational Clinical Research Task Force, American Epilepsy Society; 2002-4 Chair, IFCN-8 Study Section (Now renamed Cognitive Study Section); 2005 Chair, Conte Center Study Section; 2005-8 Board of Directors, Annual Computational Neurosci Meeting; Journal of Computational Neuroscience, Action Editor, 2006-; Physical Review Letters, Divisional Associate Editor (Biological Physics), 2006-; Temporary Ugandan Med Lic 2008-
Honors: 1979-1984 James B. Duke Graduate Fellowship, Duke Univ; 1994- Fellow, American College of Surgeons; 2005- Fellow, American Physical Soc. Guide to America's Top Physicians (2005) /Surgeons (2006); 2012- Fellow, American Association for the Advancement of Science.

C. Publications Most Relevant to Hydrocephalus (selected from over 120 articles)

1. Drake, J. M., Kestle, J. R. W., Milner, R., Cinalli, G., Boop, F., Piatt, J., Haines, S., Schiff, S. J., Cochrane, D., Steinbok, T., MacNeil, N., and the collaborators, Randomized trial of cerebrospinal fluid shunt valve design in pediatric hydrocephalus, Neurosurgery, 1998 Aug;43(2):294-30. PMID: 9696082
2. Kestle J, Drake J, Milner R, Sainte-Rose C, Cinalli G, Boop F, Piatt J, Haines S, Schiff S, Cochrane D, Steinbok P, MacNeil N., Long-term follow-up data from the Shunt Design Trial, Pediatric Neurosurgery, 33: 230-236, 2000. PMID: 11155058
3. Mandell JG, Neuberger T, Drapaca CS, Webb AG, Schiff SJ. The dynamics of brain and cerebrospinal fluid growth in normal versus hydrocephalic mice. Journal of Neurosurgery: Pediatrics, 6:1-10, 2010 (Cover Article). PMID: 20593980
4. Li L, Padhi A, Ranjeva SL, Donaldson SC, Warf BC, Mugamba J, Johnson D, Opio Z, Jayarao B, Kapur V, Poss M, Schiff SJ, Association of Bacteria with Hydrocephalus in Ugandan Infants, Journal of Neurosurgery: Pediatrics, 7:73-87, 2011 (Cover Article). PMID: 21194290
5. Warf BC, Alkire BC, Bhai S, Hughes C, Schiff SJ, Vincent JR, Meara JG. The costs and benefits of neurosurgical intervention for infant hydrocephalus in sub-Saharan Africa. Journal Neurosurgery: Pediatrics, 8: 509-521, 2011. PMID: 22044378
6. Schiff SJ, Ranjeva S, Sauer T, and Warf BC. Rainfall Drives Hydrocephalus in East Africa. Journal of Neurosurgery: Pediatrics 10: 161-167, 2012 (Cover and lead article). PMID: 22768966
7. Kiwanuka J, Bazira J, Mwanga J, Tumusiime D, Nyesigire E, Lwanga N, Warf BC, Kapur V, Poss M, Schiff SJ. The Microbial Spectrum of Neonatal Sepsis in Uganda: Recovery of Culturable Bacteria in Mother-Infant Pairs. PLoS ONE 8(8): e72775, 2013. PMID: 24013829

Publications Most Relevant to Interdisciplinary Medical Science

8. Schiff, SJ. Neural Control Engineering. MIT Press, Cambridge, 384 pp, 2012.
9. Schiff SJ, Jerger K, Duong DH, Chang T, Spano ML, Ditto WL, Controlling Chaos in the Brain, Nature 370(1994) 615-20. PMID: 8065447
10. Schiff SJ. Forecasting brain storms. Nature Medicine 1998 Oct;4(10):1117-8. PMID: 9771736
11. Gluckman, B. J., Nguyen, H., Weinstein, S. L., and Schiff, S. J., Adaptive Electric Field Suppression of Epileptic Seizures, Journal of Neuroscience, 21: 590-600, 2001. PMID: 11160438
12. Schiff, S.J., Sauer, T., Kumar, R. Weinstein, S.L., Neuronal Spatiotemporal Pattern Discrimination: The Dynamical Evolution of Seizures. NeuroImage, 28: 1043-1055, 2005. PMID: 16198127
13. Schiff, SJ, Huang, X, Wu, JY, Dynamical Evolution of Spatiotemporal Patterns in Mammalian Middle Cortex, Physical Review Letters, 98, 178102, 2007. PMCID: PMC2039901
14. Schiff SJ, Sauer T, Kalman Filter Control of a Model of Spatiotemporal Cortical Dynamics, Journal of Neural Engineering 5: 1-8, 2008. PMCID: PMC2276637
15. Schiff SJ. Towards Model Based Control of Parkinson's Disease. Philosophical Transactions of the Royal Society A, 368:2269-2308, 2010. PMCID: PMC2944387

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME Poss, Mary	POSITION TITLE Professor		
eRA COMMONS USER NAME (credential, e.g., agency login)			
EDUCATION/TRAINING (<i>Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable</i>)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
Duke University, Durham, NC	BS	05/75	Zoology
University of New Hampshire, Durham, NH	MS	06/79	Biochemistry
Ohio State University, Columbus, OH	DVM	05/84	Veterinary Medicine
Colorado State University, Ft. Collins, CO	PhD	05/90	Exper. Pathology

A. Personal Statement. A goal of this research proposal is to investigate the microbial community associated with neonatal sepsis and postinfectious hydrocephalus in East Africa. As a veterinary pathologist and molecular biologist, I bring a general understanding of disease pathogenesis to this research team. Although my expertise is principally with viral infections, I have increasingly utilized high throughput sequencing approaches to identify novel microorganisms and microbial communities that are commensal or associated with disease. For example, we recently described a novel retrovirus and several new species of bacteria in the lymph nodes of healthy animal, which required that we detect rare microbial genomes against the dominant background of host sequences (Wittekindt et al 2010). I have collaborated with Dr. Schiff for several years on the neonatal sepsis and hydrocephalus projects and have provided the expertise to clone, sequence, and analyze the data that were the basis for the first description of the bacterial spectrum associated with one of the sequela of neonatal sepsis, hydrocephalus (Li et al 2011). In addition to our molecular proficiency, my lab has the expertise to assist in evolutionary and computational analysis of these metagenomic data. Thus, my experience complements those of this research team in providing the molecular tools needed to complete the objective of microbial detection and annotation in this proposal.

B. Positions and Honors

Positions and Employment

1984	Extern, Veterinary Clinic, Navajo Reservation, Tsaile, AZ. Mixed animal practice
1984-1985	Veterinarian, Rushford, NY. Mixed animal practice
1985-1987	Pathology Residency, Colorado State University, Ft. Collins, CO
1988-1991	National Research Service Award (F32 AI07814)
1990-1991	Post-doctoral fellow, Dr. W. M. Gallatin, Icos Corp, Bothell, WA
1991-1993	Senior Staff Scientist, Icos Corp, Bothell, WA
1994-1997	Clinical Investigator Award (K08 AI012190)
1995-1996	CFAR New Investigator Award
1994-1997	Senior Fellow, Dr Overbaugh, Dept of Microbiology, University of Washington, Seattle, WA
1998-2002	Assistant Professor, Division of Biological Sciences & Wildlife Biology, University of Montana, Missoula, MT
1999- 2007	Clinical Assistant Professor, Tufts University School of Veterinary Medicine, N Grafton, MA
2002-2006	Associate Professor, Division of Biological Sciences & Wildlife Biology, University of Montana, Missoula, MT
2007-	Professor of Biology and Veterinary and Biomedical Sciences. Penn State, University Park, PA
2007-2010	Director, Center for Infectious Disease Dynamics. Penn State, University Park, PA

C. Selected Peer-Reviewed Publications (Selected from 59 peer-reviewed publications)

Most Relevant to Current Application

1. Li L, A Padhi, S Ranjeva, S Donaldson, B Warf, J Mugamba, D Johnson, Z Opio, B Jayarao, V Kapur, M Poss, S Schiff. 2011. Association of Bacteria with Hydrocephalus in Ugandan Infants. *J Neurosurg Pediatrics* 7:73-87, 2011. PMID 21194290
2. Roy, S, J Lavine, F Chiaromonte, J Terwee, S VandeWoude, O Bjornstad, M Poss. 2009. Multivariate statistical analysis of host immunological response to simultaneous infection with a host adapted and a novel feline lentivirus. *PLoS ONE* 4(10):e7359. doi:10.1371/journal.pone.0007359. PMC2752991.
3. Wittekindt N, A Padhi, S Schuster, J Qi, F Zhao, L Tomsho, L Kasson, M Packard, P Cross, M Poss. 2010. Nodeomics: meta-transcriptomic exploration of a vertebrate lymph node microbiome. *PLoS One* 5(10): e13432. doi:10.1371/journal.pone.0013432. PMC2956653
4. Simeonov I, X Gong, O Kim, M Poss, F Chiaromonte, J Fricks. 2010. Exploratory Spatial Analysis of *in vitro* Respiratory Syncytial Virus Co-infections. *Viruses*, 2, 2782-2802; doi:10.3390/v2122782. (Special Edition on Virus Evolution and Dynamics)
5. Elleder, D, O Kim, A Padhi, J G Bankert, I Simeonov, S C Schuster, N E Wittekindt, S Motameny, M Poss. Polymorphic integrations of an endogenous gammaretrovirus in the mule deer genome. 2012. *J Virol*, 86(5):2787. PMID:21994640

Additional Relevant Publications

1. Poss M, J Gosink, E Thomas, JK Kreiss, JO Ndinya-Achola, K Mandaliya, J Bwayo and J Overbaugh. 1997. Phylogenetic evaluation of Kenyan HIV-1 isolates. *AIDS Res and Hum Retroviruses*. 13:493-499. PMID: 9100991.
2. Biek, R, A Drummond, M Poss. 2006. Virus reveals population structure and recent demographic history of its carnivore host. *Science*. 311:538-541. PMID 16439664
3. Pepin, Kim, Jia Wang, Colleen T. Webb, Gavin JD Smith, Mary Poss, Peter J Hudson, Wenshan Hong, Huachen Zhu, Steven Riley, Yi Guan. Multiannual patterns of influenza A transmission in a Chinese live-bird market system. 2012. *Influenza and Other Respiratory Viruses*. doi: 10.1111/j.1750-2659.2012.00354
4. Poss M, AG Rodrigo, J Gosink, GH Learn, D Panteleef, HL Martin, Jr, J Bwayo, JK Kreiss, and J Overbaugh. 1998. Evolution of envelope sequences from the genital tract and peripheral blood of women infected with clade A human immunodeficiency virus type 1. *J. Virol*. 72:8240-8251. PMC110179.
5. Poss M and J Overbaugh. 1999. Variants from the diverse virus population at seroconversion of a clade A human immunodeficiency virus type 1 infected woman have distinct biological properties. *J Virol*. 72:5255-5264. PMC112580.
6. Biek, R, AG Rodrigo, D Holley, A Drummond, C Anderson, M Poss. 2003. Epidemiology, genetic diversity, and molecular evolution of endemic FIV in a wild population of cougars *J. Virol*. 77:9578. PMC187433
7. Padhi, A and M Poss. 2009. Population dynamics and rates of molecular evolution of a recently emerged Paramyxovirus, the avian metapneumovirus subtype C. *J Virol*. 83:2015-2019. PMC2643776
8. Lavine, J, M Poss, B Grenfell. 2008. Directly transmitted viral diseases: modeling the dynamics of transmission. *Trends in Micro*. 16:165-172. PMID 18356058
9. Lloyd-Smith, J, M Poss, B Grenfell. 2008. HIV-1/parasite co-infection and the emergence of new parasite strains. *Parasitol*. 135:795-806. PMID 18371236
10. Thakar, J, M Poss, R Albert, G Long, R Zhang. 2010. Dynamic models of immune responses: what is the ideal level of detail? *Theoretical Biology and Medical Modeling* 7:35. PMC2933642