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PI: SAGOFF, MARK	Title: Ecological Concepts of Human Identity in Microbiome and Metagenomic Research	
Received: 02/18/2010	FOA: PA08-013	Council: 10/2010
Competition ID: ADOBE-FORMS-B	FOA Title: ELSI SMALL RESEARCH GRANT PROGRAM (R03)	
1 R03 HG006029-01	Dual:	Accession Number: 3270374
IPF: 819801	Organization: GEORGE MASON UNIVERSITY	
Former Number:	Department: inst for philosophy and public policy	
IRG/SRG: ELS (O1)	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 50,000 Year 2: 50,000	Animals: N Humans: N Clinical Trial: N Current HS Code: 10 HESC: N	New Investigator: N Early Stage Investigator: N
<i>Senior/Key Personnel:</i>		
<i>Organization:</i>		
<i>Role Category:</i>		
Mark Sagoff Ph.D.	University of Maryland	PD/PI

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The proposed research seeks to contribute to an emerging literature that assesses the philosophical implications of the ecological concepts, metaphors, and analogies that are beginning both to frame our understanding of the human microbiome and to challenge entrenched mechanistic concepts of the human body and the human being -- entrenched concepts that not only include the "blueprint" analogies of the Human Genome Project but stretch back at least to the discovery of the circulation of the blood. The proposed research will use philosophical analysis to explore and assess in the context of the Human Microbiome Project the application of ecological metaphors -- such as "community," "superorganism," "homeostasis" "ecosystem," "dynamics," "complexity," etc. -- to public and scientific understanding of such concepts as the "human body," the "human being" and the "human individual." The project acknowledges well-known problems in the ecological sciences that beset and may, indeed, defeat the application of concepts that attempt to unite organisms into natural systems and communities. The research proposed here will explore whether these kinds of problems also complicate the application of ecological concepts in the study of the human microbiome and metagenome. The proposed research will examine how normative concepts, such as "structure," "function," "interdependence," "community," and even "system" have moved back and forth between the medical and ecological sciences. It will discuss moral and conceptual implications of ecological images of the human individual -- for example, the picture of the individual as a composite of microbial and human cells, the representation of the human genome as a kind of landscape, and the idealization of the microbiome as a kind of mixmaster of human and microbial traits. The proposed project will produce published papers and conference presentations that will help scientists concerned with the microbiome and metagenome to understand the ecological framework in which they may set their research.

Public health research now presses on the frontiers of the human microbiome and metagenome but lacks a conceptual framework to integrate these microbial and genetic landscapes into recognizable images of the human being, the person, and the individual. By assessing through philosophical analysis emerging ecological concepts, metaphors, and analogies in terms of which scientists frame their research, the proposed project will help clarify the goals of the Human Microbiome Project (HMP) in its relation to conceptions of the patient and patient health the HMP seeks to serve.

The University of Maryland, College Park, is a major research university with adequate facilities for this project. The Principal Investigator, as director of one of the research institutes on campus, has access to the resources of the university. In addition he has collegial contacts with researchers at the Maryland Medical School and Maryland School of Law in Baltimore, at which major projects are underway with support from the Human Microbiome and ELSI programs.

In particular, the P.I. in earlier years has taught courses at the Maryland Law School and has often met with Diane Hoffman, the Associate Dean, who is P.I. on a recently funded ELSI microbiome project: "Federal Regulation of Probiotics: An Analysis of Existing Regulatory Frameworks." Sagoff has also met with and will continue to enjoy helpful advice from prominent experts at the University of Maryland Medical School, in particular, Dr. Claire Fraser-Liggett and Dr. Jacques Ravel (who has confirmed his willingness to join panels and otherwise guide the project). Both Fraser-Liggett and Ravel are engaged in major scientific microbiome projects.

The College Park campus has a strong Department of Cell Biology and Molecular Genetics with faculty, such as Associate Professor Najib M. El-Sayed, Ph.D., with whom the P.I. has consulted and who have been and will be helpful in discussing ELSI-related issues in the Human Microbiome Project. The immediate environment of the project – the Institute for Philosophy and Public Policy at the Maryland School of Public Policy – provides the collegial and intellectual context to assure the philosophical quality and policy relevance of the proposed research.

No special equipment is required.

PHS 398 Modular Budget, Periods 1 and 2

OMB Number: 0925-0001

Budget Period: 1				
Start Date: <input type="text" value="01/01/2011"/>		End Date: <input type="text" value="12/31/2011"/>		
A. Direct Costs			* Funds Requested (\$)	
* Direct Cost less Consortium F&A			<input type="text" value="50,000.00"/>	
Consortium F&A			<input type="text"/>	
* Total Direct Costs			<input type="text" value="50,000.00"/>	
B. Indirect Costs				
	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
1.	<input type="text" value="University Overhead for salaries, wages, benefits"/>	<input type="text" value="50"/>	<input type="text" value="50,000.00"/>	<input type="text" value="25,000.00"/>
2.	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
3.	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
4.	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Cognizant Agency (Agency Name, POC Name and Phone Number)		<input type="text"/>		
Indirect Cost Rate Agreement Date <input type="text"/>		Total Indirect Costs		<input type="text" value="25,000.00"/>
C. Total Direct and Indirect Costs (A + B)			Funds Requested (\$)	<input type="text" value="75,000.00"/>
Budget Period: 2				
Start Date: <input type="text" value="01/01/2012"/>		End Date: <input type="text" value="12/31/2012"/>		
A. Direct Costs			* Funds Requested (\$)	
* Direct Cost less Consortium F&A			<input type="text" value="50,000.00"/>	
Consortium F&A			<input type="text"/>	
* Total Direct Costs			<input type="text" value="50,000.00"/>	
B. Indirect Costs				
	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
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2.	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
3.	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
4.	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Cognizant Agency (Agency Name, POC Name and Phone Number)		<input type="text"/>		
Indirect Cost Rate Agreement Date <input type="text"/>		Total Indirect Costs		<input type="text" value="25,000.00"/>
C. Total Direct and Indirect Costs (A + B)			Funds Requested (\$)	<input type="text" value="75,000.00"/>

PHS 398 Modular Budget, Periods 3 and 4

Budget Period: 3				
Start Date: <input style="width: 100px;" type="text"/>		End Date: <input style="width: 100px;" type="text"/>		
A. Direct Costs				
* Direct Cost less Consortium F&A				* Funds Requested (\$)
Consortium F&A				<input style="width: 100px;" type="text"/>
* Total Direct Costs				<input style="width: 100px;" type="text"/>
B. Indirect Costs				
	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
1.	<input style="width: 95%;" type="text"/>	<input style="width: 40px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 60px;" type="text"/>
2.	<input style="width: 95%;" type="text"/>	<input style="width: 40px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 60px;" type="text"/>
3.	<input style="width: 95%;" type="text"/>	<input style="width: 40px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 60px;" type="text"/>
4.	<input style="width: 95%;" type="text"/>	<input style="width: 40px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 60px;" type="text"/>
Cognizant Agency (Agency Name, POC Name and Phone Number)		<input style="width: 95%;" type="text"/>		
Indirect Cost Rate Agreement Date <input style="width: 100px;" type="text"/>		Total Indirect Costs <input style="width: 100px;" type="text"/>		
C. Total Direct and Indirect Costs (A + B)				Funds Requested (\$) <input style="width: 100px;" type="text"/>
Budget Period: 4				
Start Date: <input style="width: 100px;" type="text"/>		End Date: <input style="width: 100px;" type="text"/>		
A. Direct Costs				
* Direct Cost less Consortium F&A				* Funds Requested (\$)
Consortium F&A				<input style="width: 100px;" type="text"/>
* Total Direct Costs				<input style="width: 100px;" type="text"/>
B. Indirect Costs				
	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
1.	<input style="width: 95%;" type="text"/>	<input style="width: 40px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 60px;" type="text"/>
2.	<input style="width: 95%;" type="text"/>	<input style="width: 40px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 60px;" type="text"/>
3.	<input style="width: 95%;" type="text"/>	<input style="width: 40px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 60px;" type="text"/>
4.	<input style="width: 95%;" type="text"/>	<input style="width: 40px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 60px;" type="text"/>
Cognizant Agency (Agency Name, POC Name and Phone Number)		<input style="width: 95%;" type="text"/>		
Indirect Cost Rate Agreement Date <input style="width: 100px;" type="text"/>		Total Indirect Costs <input style="width: 100px;" type="text"/>		
C. Total Direct and Indirect Costs (A + B)				Funds Requested (\$) <input style="width: 100px;" type="text"/>

PHS 398 Modular Budget, Periods 5 and Cumulative

Budget Period: 5	Start Date: <input style="width: 100%;" type="text"/>	End Date: <input style="width: 100%;" type="text"/>
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A. Direct Costs

* Direct Cost less Consortium F&A	* Funds Requested (\$)
Consortium F&A	
* Total Direct Costs	

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
1.	<input style="width: 95%;" type="text"/>	<input style="width: 50%;" type="text"/>	<input style="width: 50%;" type="text"/>	<input style="width: 50%;" type="text"/>
2.	<input style="width: 95%;" type="text"/>	<input style="width: 50%;" type="text"/>	<input style="width: 50%;" type="text"/>	<input style="width: 50%;" type="text"/>
3.	<input style="width: 95%;" type="text"/>	<input style="width: 50%;" type="text"/>	<input style="width: 50%;" type="text"/>	<input style="width: 50%;" type="text"/>
4.	<input style="width: 95%;" type="text"/>	<input style="width: 50%;" type="text"/>	<input style="width: 50%;" type="text"/>	<input style="width: 50%;" type="text"/>

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

Indirect Cost Rate Agreement Date Total Indirect Costs

C. Total Direct and Indirect Costs (A + B)

Funds Requested (\$)

Cumulative Budget Information

1. Total Costs, Entire Project Period

*Section A, Total Direct Cost less Consortium F&A for Entire Project Period	\$	<input style="width: 95%;" type="text" value="100,000.00"/>
Section A, Total Consortium F&A for Entire Project Period	\$	<input style="width: 95%;" type="text"/>
*Section A, Total Direct Costs for Entire Project Period	\$	<input style="width: 95%;" type="text" value="100,000.00"/>
*Section B, Total Indirect Costs for Entire Project Period	\$	<input style="width: 95%;" type="text" value="50,000.00"/>
*Section C, Total Direct and Indirect Costs (A+B) for Entire Project Period	\$	<input style="width: 95%;" type="text" value="150,000.00"/>

2. Budget Justifications

Personnel Justification	<input style="width: 95%;" type="text" value="1244-modbudget.justify.pdf"/>		Delete Attachment	View Attachment
Consortium Justification	<input style="width: 95%;" type="text"/>	Add Attachment		
Additional Narrative Justification	<input style="width: 95%;" type="text"/>	Add Attachment		

Principal Investigator/Program Director (Last, First, Middle): Sagoff, Mark

BUDGET JUSTIFICATION PAGE MODULAR RESEARCH GRANT APPLICATION				
Initial Budget Period	Second Year of Support	Third Year of Support	Fourth Year of Support	Fifth Year of Support
50,000	50,000			
Total Direct Costs Requested for Entire Project Period			\$	100,000

Personnel

The Principal Investigator, Mark Sagoff, Ph.D., will devote at least each year to the project over a two-year period, directing and co-ordinating the research, reviewing the literature, writing and co-authoring papers, helping to edit and revise the papers of other participants, and presenting the results of the project at conferences and meetings of relevant academic and scientific associations.

The project also calls for members of the advisory team to participate in panels at professional conferences and to make project-related presentations at professional and scientific conferences and meetings. The budget would be used as well to cover the customary and usual costs of traveling to and attending these meetings.

Consortium**Fee (SBIR/STTR Only)**

PHS 398 Research Plan

1. Application Type:

From SF 424 (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is 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 (for RESUBMISSION or REVISION only)	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
2. Specific Aims	1240-Specific_Aims.pdf	<input type="text"/>	Delete Attachment	View Attachment
3. *Research Strategy	1241-research_strategy.pdf	<input type="text"/>	Delete Attachment	View Attachment
4. Inclusion Enrollment Report	<input type="text"/>	Add Attachment	<input type="text"/>	<input type="text"/>
5. Progress Report Publication List	<input type="text"/>	Add Attachment	<input type="text"/>	<input type="text"/>

Human Subjects Sections

6. Protection of Human Subjects	<input type="text"/>	Add Attachment	<input type="text"/>	<input type="text"/>
7. Inclusion of Women and Minorities	<input type="text"/>	Add Attachment	<input type="text"/>	<input type="text"/>
8. Targeted/Planned Enrollment Table	<input type="text"/>	Add Attachment	<input type="text"/>	<input type="text"/>
9. Inclusion of Children	<input type="text"/>	Add Attachment	<input type="text"/>	<input type="text"/>

Other Research Plan Sections

10. Vertebrate Animals	<input type="text"/>	Add Attachment	<input type="text"/>	<input type="text"/>
11. Select Agent Research	<input type="text"/>	Add Attachment	<input type="text"/>	<input type="text"/>
12. Multiple PD/PI Leadership Plan	<input type="text"/>	Add Attachment	<input type="text"/>	<input type="text"/>
13. Consortium/Contractual Arrangements	<input type="text"/>	Add Attachment	<input type="text"/>	<input type="text"/>
14. Letters of Support	1245-Letters of Support.pdf	<input type="text"/>	Delete Attachment	View Attachment
15. Resource Sharing Plan(s)	<input type="text"/>	Add Attachment	<input type="text"/>	<input type="text"/>

16. Appendix Add Attachments | |

Specific Aims:

The Human Microbiome Project (HMP) has occasioned a shift from mechanistic to ecological concepts in the medical sciences. According to Lederberg and McCray (2001), Joshua Lederberg coined the term *microbiome* with an ecological analogy in mind -- "to signify the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space and have been all but ignored as determinants of health and disease." The proposed research seeks to contribute to an emerging literature that assesses the philosophical implications of the ecological terms that are beginning both to frame our understanding of the human microbiome and to challenge entrenched mechanistic concepts of the human body and the human being -- concepts that not only include "blueprint" analogies in the Human Genome Project but stretch back at least to the discovery of the circulation of the blood. Specifically:

1. The proposed research seeks to analyze and assess in the context of the HMP the application of ecological metaphors – such as "community," "superorganism," "homeostasis," "ecosystem," "dynamics," "complexity," etc. – to our philosophical understanding of such concepts as the "human body" and the "human being." The project described here seeks to examine whether well-known problems that arise in and may, indeed, defeat the application of these concepts in the ecological sciences may complicate their application in the medical sciences.
2. The proposed research will explore the concept of health and related concepts of integrity, homeostasis, resilience, etc., as these concepts have traveled from the medical to the ecological sciences and may now be working their way back again. It will more specifically examine the normative aspects of ecological concepts – a "community" may presuppose shared dependence, for example, and a "system" some kind of structure or function – to understand the extent to which ecological metaphors may inform (or mislead) the medical sciences and *vice-versa*.
3. The proposed research will discuss moral and conceptual implications of "ecological" images of the human individual – for example, the image of the human being as a "composite of microbial and human cells, the human genetic landscape as an aggregate of the genes in the human genome and the microbiome, and human metabolic features as a blend of human and microbial traits" (Turnbaugh et. al. 2007). The proposed research would build on a previous project in which the P.I. argued that the medical conception of the *patient* draws for particular purposes on – but should not be confused with -- various conceptions of the human individual. These include a) *homo sapiens*, a species concept; b) *person*, an ethical and legal concept; and c) *human being*, a cultural, aesthetic, and historical concept. By distinguishing the different kinds of concerns these kinds of concepts address, the project could suggest that the shift from mechanistic and interactionist to ecological metaphors in medicine is less philosophically consequential that it might at first appear.

Products: The project would produce a series of essays to be collected into a book, along with other articles and conference presentations, which will analyze and evaluate the philosophical implications of the HMP insofar as it replaces mechanistic and reductionist metaphors with ecological ones in the medical humanities and sciences.

Research Strategy

Biologists involved in the study of the human microbiome and metagenome often rely on ecological concepts, analogies, and metaphors to characterize the objects they study. The proposed research seeks to examine, analyze, and explore the ways biologists use ecological theory and ecological concepts to construct hypotheses and to interpret results as they pursue research related to the human microbiome and metagenome. The project also examines the relevance of ecological constructs on different conceptions of the human individual, e.g., as 1) a member of a biological species; 2) a person; and 3) a human being.

1. *Significance*

According to Turnbaugh et al. (2007), "If humans are thought of as a composite of microbial and human cells, the human genetic landscape as an aggregate of the genes in the human genome and the microbiome, and human metabolic features as a blend of human and microbial traits, then the picture that emerges is one of a human 'supra-organism'." Three biologists elaborate, "Humans and their collective microbiota are segmented into many local communities, each comprising an individual human with his or her symbionts. This ecological pattern, characterized by strong interactions within distinct local communities and limited interactions or migration between them, is described as a metacommunity" (Dethlefsen et al. 2007)

Ecological analogies are not always helpful; it is not clear, for example, how "local communities" each "comprise an individual human." In spite of their opacity – or perhaps because of it – ecological concepts and analogies dominate the discussion and interpretation of research in the microbiome and metagenome. Two geneticists speak in terms of a paradigm shift. "The superorganism concept is an important paradigm shift in understanding human biology" (Rajendhran and Gunasekaran 2009).

The project proposed here would in a preliminary way subject this putative "paradigm shift" to philosophical examination. It would allow the Principal Investigator (P.I.) 1) to write and publish philosophical analyses of ecological concepts that have entered the discussion of the metagenome and microbiome; and 2) to bring together at professional conferences biologists, philosophers, and other scholars better to understand ecological conceptions of the human individual or human being. This project would catalyze an interdisciplinary discussion -- and help constellate an interdisciplinary community of scholars -- to examine ecological concepts, metaphors, analogies, and principles used to characterize human beings in the context of the Human Microbiome Project (HMP) and metagenomics.

a. The interactionist credo

Philosophers and scientists who have engaged in "nature-nurture" controversies are familiar with what Philip Kitcher (2001) has dubbed the "interactionist credo," according to which one cannot attribute differences in complex traits, e.g., intelligence, memory, or irascibility, "primarily" to genetic or to environmental sources or to a mathematically determinate proportion of each. According to this credo, any attempt to explain complex phenotypic attributes must explore many gene-gene and gene-environment interactions – punctuated by "developmental," epigenetic, and contingent or even random factors (Carroll 2005).

The most familiar strategy used to conceptualize the interactionist credo envisions a "norm of reaction" -- a graph that represents the phenotypic value of a genotype across a range of environments (Sarkar 1999). Since the 1970s, biologists like R. C. Lewontin (1974) have

deployed this concept to debunk fallacies associated with genetic determinism and genetic essentialism. These scientists argued that the graph does not run smooth but can take quite different shapes with each individual; accordingly the correlation of genotypic inheritance with complex phenotypic traits will be highly contingent, conditional, and context-dependent.

The Human Microbiome Project (HMP) casts the interactionist credo in a new light. To explain the etiology of complex human attributes the HMP emphasizes the role of a vast number microbiota that inhabit, for example, the human gut, and are essential to human health and to many other traits, perhaps including psychological abilities or dispositions (Forsythe et al. 2010). These microbiota do not belong to the human genome; they have their own genetic material; besides, people are not born with many or most of them. These microbiota appear to be no more “environmental,” however, than is any cell that contributes to the functioning of an organism and is found in it. It is hard enough to understand if and how the genome and environment “interact” to form complex traits. It is a greater conceptual challenge to bring the microbiome and metagenome into account, or even to say what belongs to the “individual” and what to the “environment” in the interaction.

b. The metagenome

Writers both in the scientific and the popular press often remark on the finding that the human microbiome “contains 10 times more cells than the human body, and their collective genomes (the human microbiome) are estimated to contain 100 times more genes than the human genome itself” (Hsiao and Fraser-Liggett 2009). “The original human genome sequencing projects were, from this perspective, about only a tiny and unrepresentative complement of our genes” (Dupre´ and O’Malley 2007). According to a popular account, “Only about 10 percent of the trillions of cells that make up a person are truly human, researchers say. The other 90 percent are bacteria, viruses and other microbes swarming in your gut and on your skin” (Boyd 2009).

If 90 percent of the cells that are said to “make up a person” and may be involved in causing complex human traits neither replicate his or her genome (because they have their own genomes) nor belong to that person’s environment (because they “make up” the person), what should we conclude about the interactionist credo? The question becomes more perplexing in view of advances in epigenetics, the control of gene activity in development, and with it complex gene-gene, intrasomatic, as well as environmental-somatic interactions.

An initial response has been to lump the genomes of the microbiome together with the genome of the individual into a composite called the “metagenome” and to consider the metagenome to be what constitutes the “genetic” side of the “interaction.” A commentator states, concludes, “While humans differ by a minute fraction of their inherited nucleic acids, the additional genomes -- or rather metagenomes -- that they acquire a few months after birth carry major differences that distinguish each individual” (Aziz 2009).

The suggestion that the metagenome contributes to the identity of each individual introduces many conceptual puzzles. One obvious problem is that of identifying the “environment” with which a given metagenome interacts. It appears that each of the trillions of bacteria, viruses, and other microbes swarming in one’s gut and on one’s skin has its own environment, e.g., the surrounding microbes and other cells in its neighborhood. One might suppose that each of these trillions of biota has its own norm of reaction. Does the genome offer an environment for the microbiome, or vice-versa, perhaps in the same individual? None of many possibilities succeeds in weaving the human genome, microbiome, and metagenome into a coherent concept of a human individual or of a human being.

c. The ecological credo

Ecological concepts often appear as foundational terms in the agenda of metagenomic research. An ecological credo is displacing an interactionist credo. According to this perspective, “the human *body* should be understood as a ecosystem with multiple ecological niches and habitats in which a variety of cellular species collaborate and compete; and . . . human *beings* should be understood as ‘super-organisms’ that incorporate multiple symbiotic cell species into a single individual with very blurry boundaries, like a colony of blue-green algae on a massive scale of complexity” (Juengst 2010).

The National Research Council (NRC 2007) in a recent report, *The New Science of Metagenomics*, endorses this ecological perspective. The report announced, “All plants and animals, including humans, can be considered superorganisms composed of many species—animal, bacterial, archaeal, and viral.” The scientific literature represents the human individual as an ecosystem with a collective (or “meta”) genome. Two geneticists have written, “within each human body, intestinal and other microbiota along with the ‘host’ human cells, form a complex ecosystem that, as a whole, interactively performs various biological processes.” According to their view of individual identity, “we should regard ourselves as ‘superorganisms’ together with the indigenous microbes and that the composite genome should be referred to as the human ‘metagenome’” (Hattori and Taylor 2009).

The ecological credo (as Juengst suggests) confronts many difficulties. First, the NRC report urges metagenomic research to follow ecological research in identifying “unifying ecological principles that enable predictive modeling” of the behavior of biotic communities. Ecological science, however, has not succeeded in identifying unifying or governing principles that enable predictive modeling. Many ecologists argue that there are no laws in ecology or any clear criteria for distinguishing communities from mere collections of species that just happen to co-exist (Peters 1991; Lawton 1999; Lockwood 2008; O’Hara 2005). As Simberloff (2010) explains, the ecological literature is characterized by “the persistent controversy over the extent to which communities are coevolved, integrated complexes as opposed to simply those species found together in one place at one time.”

Ecologists have argued that any appearance of pattern or structure in an ecosystem “is a biological epiphenomenon, a statistical abstraction, a descriptive convention without true emergent properties but only collective ones, wholly referable in its properties to those of its constituent species, populations, and individuals” (Gilbert and Owen 1990). Ecosystems have not been shaped by evolution to perform functions (Levin 2001). Ecologists question whether ecosystems are *systems*. William Drury (1998) has written, “I feel that ecosystems are largely extemporaneous and that most species (in what we often call a community) are superfluous to the operation of those sets of species between which we can clearly identify important interactions Once seen, most of the interactions are simple and direct. Complexity seems to be a figment of our imaginations driven by taking the ‘holistic’ view.”

Second, concepts of the “community” and “ecosystem” are generally thought to exclude humans and human activity; indeed, humans are often considered to be disruptive forces. According to O’Neill (2001), “The ecosystem concept typically considers human activities as external disturbances . . . *Homo sapiens* is the only important species that is considered external from its ecosystem, deriving goods and services rather than participating in ecosystem dynamics.” Distinctions between the individual as biological species, as person, and as cultural agent will be needed to sort out ecological approaches to human identity.

Third, the NRC has proposed that the concept of *community* replace that of *organism* in view of current trends in microbiology. “Communities are dynamic assemblages governed by dependence and antagonisms among the members . . .” (NRC 2007). As the terms “governed,” “dependence,” and “antagonism” suggest, the concept of *community* is a normative one. The norms characteristic of an ecological or environmental ethic, however, may have little in common with those that guide a medical ethic. Indeed, normative concepts, such as those of health and disease, may *have* no function in ecological science. As Juengst (2009) has written, “If the human body is essentially an ecosystem, the notions of ‘purity,’ ‘integrity,’ and ‘wholeness,’ on one hand, and ‘infection,’ ‘contagion and ‘corruption’ on the other make little sense, since ecosystems are understood to have fluid boundaries and to support multiple species in [a] cycle of growth, predation, and decay. Moreover, there are no bad guys in ecosystems . . .”

The project proposed here would direct philosophical attention to ecological analogies and assumptions that now appear to frame metagenomic science. This study would help researchers understand differences between an ecological and a medical ethic that may challenge efforts to integrate them. A medical ethic may teach us to hope to overcome “natural” conditions or limits, an environmental ethic to accept them. The project proposed here is a small study, but it would encourage scientists engaged in microbiome research and who are attracted to ecological analogies and metaphors to look before they leap.

2. *Innovation*

The project proposed here promises to be innovative in at least three ways. First, since the HMP itself is only a few years old, there has been little philosophical discussion of its use of ecological concepts and analogies. (Examples of this sparse literature include Dupré and O'Malley 2009; Juengst 2009; and O'Malley and Dupré 2009.) To ask what ecological concepts, such as “community” and “superorganism,” could mean in the biomedical sciences, whether they can draw meaning from analogous terms in ecological science, and how well they have worked there is to propose an innovative inquiry. Ley et al. (2007) speak of “eliminating the biomedical/environmental dichotomy” in research on the microbiome. A declaration of this sort is by now familiar in the literature of microbiome research. What is innovative is an effort to sort out what if anything it says.

Second, the proposed project will bring philosophers of ecology together with bioethicists and scientists to discuss the ethical, legal, and social implications of ecological conceptions of human identity in the context of HMP-related research. The P.I. has assembled and will continue to build a network of scholars to discuss at professional conferences the normative and conceptual problems described in this proposal.

Third, the proposed project is innovative because it would try to understand historically as well as philosophically how concepts related to health migrated by analogy from the medical to the ecological sciences in the 1970s and 1980s only to return by the same route -- but as metaphors with ecological connotations -- to medical research related to the metagenome and microbiome today. In the 1970s and 1980s, environmental ethicists (including the P.I.; see, e.g., Sagoff 1988) sought to extend concepts of health, stability, resilience, and the like to the natural world, hoping to construct ecology as a clinical science needed to “restore” the natural environment to a “normal” condition. This project would make more available to medical researchers and ethicists controversies that confronted applications of normative concepts, such as “community,” “structure,” “function,” “integrity,” and “health,” in ecology, lest these analogies create ontological and normative confusion rather than understanding.

3. Approach

The method on which the proposed research relies is straight-forward philosophical analysis. This means that the P.I. will propose different ways to understand key concepts, draw out the logical and normative implications of these different assumptions, and offer counter-examples to test the consistency and credibility of opposing views. This project would result in a series of conference presentations and academic papers, aimed primarily at interdisciplinary audiences, each of which will address a subset of the issues raised here.

As an example of the approach the P.I. would take to this project, consider a statement, fairly typical of the current literature, that begins a recent article in *Chemical & Engineering News*. “You might as well accept the fact that you’re probably more microbe than human. ... Because human cells are much larger and bulkier than bacterial cells, we end up looking like people, but in reality, we are actually ‘multispecies superorganisms’” (Evert 2009, citing and quoting Jeffrey Gordon, a geneticist at Washington University in St. Louis).

To approach the idea that while we look like people “we are actually ‘multispecies superorganisms’” – which is the implication of a great deal of the commentary surrounding the HMP – the P.I. will draw on previous work which distinguished among different senses in which we might conceive of ourselves as individuals (Sagoff 2005 a, b). First, one may identify oneself as a member of the species *homo sapiens*. Research on the human metagenome and microbiome is unlikely to dislodge a biological conception of human identity that is basically historical and depends on phylogenetic descent. It may supplement and amplify this historical approach to human identity. Second, one may identify oneself as a person and therefore as having free will and capable of acting on rules one gives to oneself both personally and collectively. This concept relates to a moral and legal framework of rights and responsibilities – a framework to which no one has yet shown that research in the metagenome or microbiome is particularly relevant. Standard concepts of the person as a moral agent have not altered because of discoveries about the human genome, and they are unlikely to change as a result of metagenomic research.

Third, one may understand an individual to be a human being, i.e., as combining the animal faculties of pleasure and pain with freedom to make aesthetic and other normative judgments. Being *human* is a matter of the moral and aesthetic faculties, potentialities, and capacities associated with an animal of a particular species within the histories of various cultures. None of these conceptions of a human individual – as a member of a species, as a moral agent, or as an animal with that makes cultural and aesthetic (as well as moral) judgments may be affected very much by discoveries about the human microbiome or metagenome. One must ask, then, what concept of the individual human would have to change in view of the results of the HMP and metagenomic research.

The P.I. will write and publish scholarly papers addressing the problems described here. A group of advisors, some of whom are listed below, will engage with the P.I. in this research. The P.I. would draw on these advisors and other colleagues to organize panels and other presentations at professional meetings and conferences, such as the annual meetings of the American Society for Bioethics and the Humanities, the International Association of Bioethics, the American Society of Human Genetics, the National Society of Genetic Counselors, the American Association for the Advancement of Science, the Association for Politics and the Life Sciences. These presentations should serve not only to disseminate the results of the project and solicit helpful comments, but also to encourage deliberation about the conceptions of the human individual in microbiome and metagenomic research.

Members of the advisory panel who have indicated their willingness to participate include:

Celeste M. Condit (Ph.D. University of Iowa) is Professor, Department of Speech Communication University of Georgia. She studies and has published extensively on issues related to the social impact of genetics research and the ethical dimensions of public communication about genetics. Among her books is, *The Meanings of the Gene: Public Debates about Heredity* (University of Wisconsin Press, 1999).

Lindley Darden, Professor of Philosophy, University of Maryland, has a Ph.D. in the Conceptual Foundations of Science from the University of Chicago. In *Reasoning in Biological Discoveries Essays on Mechanisms, Interfield Relations, and Anomaly Resolution* (Cambridge), she collects some of her recent influential papers in the philosophy of biology.

Larry J. Forney is Professor of Biological Sciences and Bioinformatics and Computational Biology at the University of Idaho, where he also directs the Initiative for Bioinformatics and Evolutionary Studies (IBEST), which receives funding from the National Institutes of Health as a Center of Biomedical Research Excellence. He received his PhD in Microbiology and Public Health from Michigan State University.

John Huss, Assistant Professor, Department of Philosophy, University of Akron, received his PhD in the Conceptual Foundations of Science from The University of Chicago in 2004. He writes and teaches in the philosophy of science — particularly in paleobiology, ecology, and bioethics.

Amy L. McGuire, JD, PhD, is Associate Professor of Medicine and Medical Ethics and Associate Director of Research Center for Medical Ethics and Health Policy, Baylor College of Medicine. Her research focuses on legal and ethical issues in genetics and genomics, with a particular interest in genetic research and personalized genomic medicine.

Gregory Mikkelsen, Associate professor, School of Environment and Department of Philosophy, McGill University, received his Ph.D. in the Conceptual Foundations of Science, University of Chicago, and has published widely in the philosophy of ecology.

Gregg Mitman, Ph.D. is William Coleman Professor of History of Science at the University of Wisconsin-Madison, where he is also a professor in the Department of Medical History and directs the Nelson Institute for Environmental Studies, and the Robert F. and Jean E. Holtz Center for Science & Technology Studies. His teaching and writing interests span the history of ecology, nature, and health.

Jacques Ravel, Ph.D., Associate Professor, Department of Microbiology & Immunology, University of Maryland School of Medicine, Baltimore, focuses his research on the human microbiome, its ecology and metagenomics, to understand the effects of the endogenous microflora on human health. He co-directs a major 5-year NIAID-funded microbiome research project. (The P.I. developed this proposal after conversations with Dr. Ravel).

Sara Shostak, Assistant Professor of Sociology at Brandies University, holds a Ph.D. in Sociology from the University of California San Francisco. Her research and teaching interests include sociology of health and illness; science and technology studies; the sociology of the body; sociological perspectives on bioethics; environmental health and justice; genetics/genomics; and research methods

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The following letter of support was included as part of the original application and is provided with the permission of Dr. McGuire. An additional 8 letters were included in the original application but have been redacted to protect the privacy of individuals providing letters of support.

January 24, 2010

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Dear Mark:

Thank you for inviting me to participate by joining panels and exchanging ideas related to your proposed research on the use of ecological metaphors to describe the human microbiome. I would be pleased to help you in any way I can (by exchanging ideas, participating in panels, etc.). I believe this research can contribute significantly to our understanding of the ethical, legal, and social implications of the Human Microbiome Project (HMP).

The project will help us better understand legal and ethical issues in genetics and genomics related to personalized genomic medicine. Patient attitudes are likely to differ depending on the kinds of concepts or metaphors the medical sciences apply in conceptualizing the individual; these concepts and metaphors also influence the way that the individual understands him or herself. The idea of the genome as a “blueprint” for the human body has been sufficiently challenged, but the idea of a “metagenome” that organizes a “superorganism” or “ecosystem,” even if often invoked, is not well understood.

Since the HMP raises important issues regarding how we understand emergent qualities of the human body and the human being, I believe the analogies currently drawn with ecological metaphors should be more thoroughly explicated. I would like to help in developing relevant research strategies and in disseminating the results of these research findings to the many groups interested in medicine, bioethics, and the medical humanities.

Good luck with your proposal. I hope it succeeds.

Sincerely,



Amy L. McGuire, JD, PhD
Associate Professor of Medicine and Medical Ethics and Associate Director of Research
Center for Medical Ethics and Health Policy
Baylor College of Medicine

PHS 398 Checklist

OMB Number: 0925-0001

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)
<input type="text"/>	<input type="text"/>	<input type="text"/>
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5. * Disclosure Permission Statement

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

Yes No