UNIVERSITY OF LOUISVILLE PROGRAM IN METAGENOMICS AND HEALTH

A Proposal submitted to the School of Interdisciplinary and Graduate Studies and the Office of Research and Innovation in response to the internal RFP:

Academic and Research Excellence for the 21st Century University

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PROJECT BACKGROUND

a. Importance to Society.

US Health care costs are projected to rise at an average annual rate of 5.8% between 2014 and 2024 after averaging 4% between 2008 and 2013 (1). As a result, spending will grow from $3 trillion in 2013 to $5.4 trillion in 2024 amounting to 19.6% of the GDP, continuing to place a substantial burden on the economy (2). Therefore, development of new innovative strategies that can improve health outcomes and enhance the cost-effectiveness of patient care will be critical to long-term health care sustainability.

The recent establishment of a link between indigenous microbiota and health represents a major paradigm shift in biomedical research. Specifically, data from diverse studies suggest that microbial communities that colonize mucosal surfaces can modulate basic biological processes of the host, particularly those associated with immune homeostasis. Importantly, community transcriptome, proteome, metabolome and inflammatory signatures correlate with disease susceptibility and prognosis. These findings provide an opportunity for the development of a health initiative that would assess the potential utility of microbiomic signature as a biomarker of health in individuals as well as in different populations. Microbiome research was highlighted recently by the Obama administration in its latest science "moonshots" program (Science, May 13, 2016). This new national initiative is intended to create scientific tools, discoveries and training to advance microbiome research in the areas of human health and environmental science. To this end, the NIH, the NSF and the Gates Foundation have recently announced large (hundred million dollar) programs firmly placing microbiome research on the national agenda (http://www.nytimes.com/2016/05/13/us/politics/federal-microbiome-project-aims-to-solve-tiny-riddles-of-science.html?_r=0).

Separately, there is a growing understanding that physical health is substantially affected by specific, identifiable factors within the social environment. These factors or social determinants of health, encompass the circumstances in which people are born, grow up, live, work and age as well as the systems put in place to deal with life's needs and challenges. Importantly, research demonstrates that social determinants of health contribute significantly to observed health disparities (e.g., racial/ethnic; economic; gender) nationally and internationally. Social and economic disadvantage affects health throughout the lifespan (i.e., the social gradient of health). Disadvantage has many forms and tends to concentrate among the same people exerting a cumulative effect on health over time. Among the factors identified as having the most effect on health are: early life experiences (maternal health; prenatal care; birth weight; abuse/neglect); chronic stress; socioeconomic status, employment and job security, social support and cohesion, addiction (tobacco; alcohol; drugs), diet, food supply, and exercise. Many of these factors have been shown to affect host microbiota and the immune status (3). This raises the exciting possibility that a link exists between social determinants, microbiota and health, and that this axis may provide a tool for effective management of community health.

We propose to bring together the intellectual and technical resources of multiple Departments and Institutes at the University of Louisville to initiate such a project, i.e. the Program in Metagenomics and Health. The integration of biological data and social science data collection within the center represents a novel, cutting edge approach that is highly innovative. Studies that have an integrated approach would be able to solicit funds from multiple NIH institutes, the NSF and the Gates Foundation (see above). Similarly, the public health impact of studies that integrate the biological with the social aspects of health are highly significant.

b. Project Goals.

The overarching goal of the proposed project is to identify potential links between social determinants, microbiome and the prevalence/prognosis of select diseases, which in the long-term can be employed to manage community and individual health via personalized medicine (Fig. 1). Three specific aims are proposed.

Aim 1. To establish a core administrative structure that will oversee the organization and functioning of the Institute.

Aim 2. To develop databases on social determinants, health history and microbiota genome/metabolome/inflammatory signatures of patient populations.

Aim 3. To mine the databases and identify associations between social determinant profiles, microbiome signatures and disease

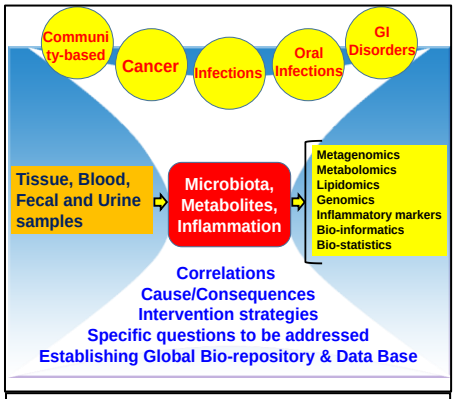

Figure 1: Overall goal of the Program in Metagenomics and Health.

susceptibility/prognosis.

Impact: We expect that successful completion of the above Aims will provide sufficient pilot data that will form the basis of a collaborative big data grant application to the NIH and will establish U of L as a global database Center for Community-based Metagenomics. This unique approach will allow us to involve the community in University research and bring interdisciplinary centers together to improve health.

PROJECT SCOPE AND APPROACH

The project is envisioned as an infrastructure endeavor that will allow the organization and the establishment of administrative, educational and scientific support structure leading to pilot preliminary data that will form the foundation of an external proposal. The specifics of the approach for each Aim and the expected outcomes are summarized below.

a. Processes and methods/roles and responsibilities.

Scientific Rationale: The primary hypothesis of this proposal is that inflammation is the central cause of most human diseases and that microbiota plays a critical role in mediating inflammation. Several factors including genetics, diet, environmental factors, life style, drug treatments and disease conditions influence dynamics of microbial communities and play a critical role in modulating both innate and adaptive immune systems (4-10). One of the major concerns in microbiota research is identification of beneficial commensals that can control microbial dysbiosis. Efforts are currently underway to define complex microbiota-host interactions (good *vs* bad; cause *vs* consequence) using animal models in germ-free conditions and antibiotic-induced microbiota depleted (AIMD) mice (8, 11-14). However, given the complexity of human gut microbiota, it is hard to predict which specific human bacterial pool is responsible for beneficial or pathogenic effects based solely on animal studies. Our goal in this RFP is to generate large data sets of patient samples obtained from various clinics at U of L such that investigators could generate testable hypotheses to determine the causal relationship between specific microbial profiles and disease via bioinformatics approaches (Figures 1 and 2). To establish the **Program in Metagenomics and Health at UofL,** we propose the following structure in three aims.

Aim 1. Administrative Core. Hire personnel to coordinate the administration of the collaborative research network, the clinical study and the database (see Figure 2). Additional activities of the core will include organization of a Symposia/seminar series, development of potential partnerships with concerns outside the University, assistance to participants in the preparation of manuscripts and ultimately the development of strategic plans for a large grant program. The core activities will be overseen by the co-PI's. The physical location of the core offices is yet to be determined but there is general agreement that the clinical study coordinator will initially be trained in the Division of Infectious Diseases Clinical and Translational Support Unit under the leadership of Dr. Julio Ramirez; whereas the database manager will be trained by Drs. Riten Mitra and Bert Little of the Department of Bioinformatics & Biostatistics and the Department of Health Management and Systems Sciences, respectively of the School of Public Health and Information Sciences. Ultimately, all administrative personnel will be placed in a central office. The Department of Microbiology and Immunology has sufficient office space on the 3rd floor of the A Tower on HSC that can accommodate the core.

Aim 2. Data Collection and analysis: Patient recruitment, collection of samples (blood, oral, respiratory, colonic and urine) and clinical history/follow-up data will be carried out by the clinical units. These units will initially include the Division of Infectious Diseases (Dr. Julio Ramirez), Brown Cancer Center (Dr. Jason Chesney), School of Dentistry (Dr. Richard Lamont), the Division of Gastrointestinal Diseases, Hepatology and Nutrition (Dr. Craig McClain) and the Department of Urology (Dr. Murali Ankem). We foresee expanding the number of participating clinical units going forward. Social determinant data will be collected in Kent School of Social Services under the leadership of Dr. Riaan Van Zyl. These activities will be coordinated by the Administrative and the Study Coordinators. All collected samples and the associated information will be housed in a central biorepository and database. The Department of Microbiology and Immunology has additional space to accommodate this facility on the 3rd floor of the A Tower.

Microbiota, metabolite and inflammatory signatures of collected samples will be analyzed by the genomics/metabolomics facilities under the leadership of Drs. Haribabu Bodduluri and Venkatakrishna Jala of the Department of Microbiology and Immunology. Drs. Bodduluri and Jala have extensive experience in the areas of microbiota and inflammation. They have established a Next-Gen sequencing facility exclusively to analyze microbiota and have partnered with Dr. Zhang Xiang in the Center for Regulatory and Environmental

Analytical Metabolomics (CREAM) for Metabolomics analysis. These studies led to several important collaborations on the host/microbiota interactions in a variety of settings including (i) race dependent microbiome analysis in colonoscopy subjects (15). (ii) Upper respiratory tract microbiome in severely patients from the infectious disease clinic (16). (iii) Influence of drug treatments in mouse models (17). (iv) microbiota of hypertension rats (18) (v) Microbiota in auto-immune lupus model (R01, PI: Dr. Kosiewicz, Bodduluri as co-I (5%) Jala as co-I (15%) (vi) Influence of IL17R on gut microbiota (vii) CCR2 modulating gut microbiota (R21 funded, PI:Jala). (viii) Effects of BLT1 in the on colon tumor dependent microbiota alterations (R01, PI: Dr. Bodduluri, Jala as co-I 25%). In summary, we already established methodologies to obtain large sets of data on microbiome, metabolites and inflammatory mediators that will enable rapid progress in the project. We propose the following sub-aims to achieve the goals.

Aim 2a: *Recruit healthy volunteers (YMCA, U of L athletic Dept) and patients from different clinics (lung, oral, urinary infections, GI and cancer) and establish a bio-repository for oral swabs, lung swabs (BAL fluids), cancer tissues, fecal, urine and blood samples.*
Aim 2b: *Determine microbial genome/metabolome and host inflammatory signatures.*
Aim 2c. *Collect social determinant data from patients.*

Aim 3. Bioinformatics. The databases will be mined to establish associations between select social determinants, microbiome signatures and health records. This process will be coordinated by the database manager with input from all participating units. Bioinformatics analyses will be overseen by Drs. Mitra and Little of the School of Public Health with assistance from the Database Manager. Administrative core will assist in the writing and submission of any publications that may emerge.

b. Relationship to the 21st Century University Strategic Mission and 2020 plan. This program is responsive to the 21st Century University Strategic Mission. It will empower undergraduate learning through special projects/summer internships; promote excellence in graduate and professional education by facilitating cross-disciplinary interactions and new thesis topics; is a multidisciplinary endeavor bridging social and biomedical sciences; and represents a novel emerging research area. It also is expected to enhance revenue via creation of opportunities for big data grant applications to federal and private sources. Similarly the program directly addresses at least 4 of 5 2020 plan priorities including educational excellence; research, scholarship and creative activity; community engagement; and creative and responsible stewardship.

c. Department and program commitments.
Kent School of Social Work. Personnel: Data collection. Financial: One new faculty position, $245,000 over 3 years. Contributing faculty: Riaan Van Zyl, Ph.D. Associate Dean for Research; Seana Golder, Ph.D, Associate Professor; Becky Antle, Ph.D., Associate Professor; Emma Sterrett, Ph.D., Assistant Professor.
School of Medicine, Division of Infectious Disease. Personnel: Clinical sample/data collection and database/repository expertise training. Financial: Seminar speakers/Symposia, $10,000. Contributing faculty: Julio Ramirez, M.D. FACP, Professor and Chairman.
J. G. Brown Cancer Center. Personnel: Clinical sample collection. Financial: Seminar speakers and Symposia, $10,000. Contributing faculty: Jason Chesney M.D., Ph.D., Deputy Director; Sucheta Telang, MBBS, Associate Professor, Pediatrics and Biochemistry, Rebecca Redman, M.D. Medical Oncology.
School of Medicine, Division of Gastroenterology, Hepatology and Nutrition. Personnel: Clinical sample collection and metabolomics. Financial: Seminar speakers and Symposia, $10,000. Contributing faculty: Craig McClain, M.D., Chief of Research Affairs, Associate Vice President for Health Affairs/Research and Translational Research; Shirish Barve, Ph.D. Professor, Pharmacology & Toxicology and Medicine. Zhang Xiang, Ph.D. Professor, Pharmacology & Toxicology and Chemistry.
School of Medicine, Department of Urology. Personnel: Clinical sample collection. Dr. Murali Krishna Ankem.
School of Dentistry, Department of Oral Immunology and Infectious disease. Personnel: Genomics expertise and clinical sample/data collection. Financial: Seminar speakers, $10,000. Contributing faculty: Richard Lamont, Ph.D. Co-PI, Professor and Chair; Don Demuth, Ph.D, Professor and Associate Dean for Research; David Scott, Ph.D., Professor, Huizhi Wang, Ph.D., Assistant Professor;.
School of Medicine, Department of Microbiology and Immunology. Personnel: Genomics/ metabolomics expertise. Financial: One new faculty hire with expertise in Microbiome (300,000 over 3 years + $ 250,000 in start-up funds); Seminar speakers and Symposia: $10,000. Contributing faculty: Nejat Egilmez, Professor and Chairman, Co-PI/PD; Haribabu Bodduluri, Professor; Krishna Jala, Assistant Professor.
School of Public Health and Information Sciences, Department of Bioinformatics & Biostatistics, and Department of Health Management & Systems Sciences. Personnel: Bioinformatics analysis. Contributing

faculty: Paul McKinney, Ph.D. Professor and Associate Dean for Research; Karunarathna Kulasekera Ph.D. Professor and Chairman, Bioinformatics & Biostatistics; Riten Mitra, Ph.D., Assistant Professor, Bioinformatics & Biostatistics; Bert Little, Ph.D. Professor, Health Management & Systems Sciences.

PROJECT MANAGEMENT, TIMELINE AND EXPECTED BENEFITS

a. Brief description of project management.

An overview of the primary elements of the proposed Program is depicted in Figure 2. This outline reflects the three primary aims of this proposal. The role of each of the proposed personnel will be as follows:

1) Administrative Coordinator – The primary role of this individual will be to facilitate and coordinate the University of Louisville Collaborative Research Network. This task will be facilitated by the creation of a Collaborative Research Network Database. University of Louisville investigators will access the database via a secure web interface with user accounts. The database will have the capability to store a network of connections and research interests among institute investigators and will allow for rapid, secure, search and visualization of research collaborations. This will assist in the connection of investigators who have similar interests or allow for connections between researchers who need each other's expertise. The ultimate goal of this Collaborative Research Network will be to generate new interdisciplinary grant proposals and manuscripts. The Administrative Coordinator will also facilitate Institute meetings and conferences.

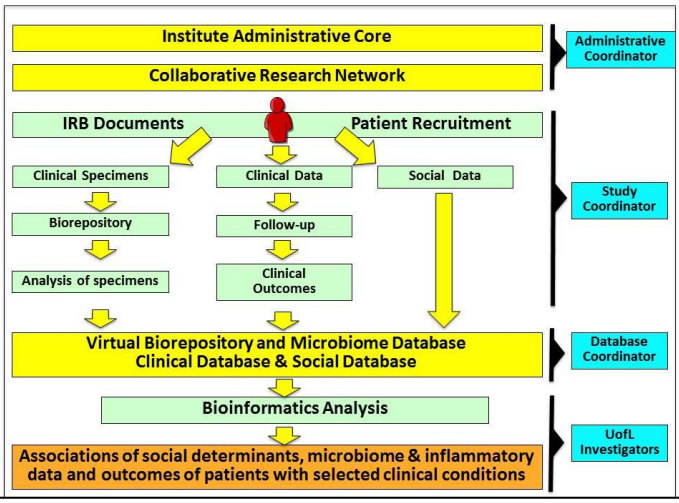

Figure 2. Proposed structure of the Program

2) Study Coordinator – Proposals initiated by the Collaborative Research Network within the proposed University of Louisville Program in Metagenomics and Health will be characterized as Clinical and Translational Research and will include recruitment of subjects. The Study Coordinator will be in charge of all regulatory elements of the research as well as collection of clinical data, patient follow-up, and laboratory specimens.
3) Database Coordinator – Patient specimens will be located in various laboratories across the University of Louisville campus. In order to coordinate specimen storage and retrieval, we will create a Virtual Biorepository Database. The clinical data and social data collected from each patient will be stored in a separate, central, secure, clinical database. The Biorepository and Clinical databases will be interfaced through unique identifiers. The development, maintenance, and management of these databases will be the responsibility of the Database Coordinator. The Collaborative Research Network database managed by the Administrative Coordinator will also be developed and maintained by the Database Coordinator. He/She will also assist the faculty in the Departments of Bioinformatics & Biostatistics and Health Management & Systems Sciences with the analysis of the bioinformatics data.

b. Timeline and Key Milestones.

1) Months 1-3: During the initial three months of the project, personnel will be hired.
2) Months 3-6: After hiring, new personnel will be trained by members of the Division of Infectious Diseases Clinical and Translational Support Unit (CTRSU, http://ctrsu.org). Members of the CTRSU have extensive experience on clinical trial coordination, database development and maintenance using REDCap, and statistical analysis of clinical and basic science data. The database Coordinator will undergo training by the Bioinformatics faculty in the School of Public Health and Information Sciences.
3) Months 4-9: During months four through nine, the Collaborative Research Network Database, Clinical Database, and Virtual Biorepository Databases will be developed and tested.
4) Months 6-12: Study Coordinator will begin enrolling patients, collecting clinical data and specimens, and will enter clinical, social, and specimen data into the databases.

5) Years 2-3: During the second and third year, patients will continue to be enrolled, data will be analyzed, manuscripts will be developed and submitted for publication, and new grant applications will be developed and submitted.

c. Expected Outcomes and Assessment Plan. The expected primary outcome of this proposal is the creation of federally-funded interdisciplinary research projects in the general area of big data approaches to biomedicine and public health. The Principal Investigators and primary collaborators will have monthly meetings. As part of these monthly meetings, an assessment will be performed to ensure the timeline and milestones are followed as planned or if any corrective actions and interventions are needed.

PROJECT IMPACT ON SOCIETY AND UNIVERSITY'S MISSION

a. Enhanced reputation of graduate programs. This project is expected to provide national visibility to multiple graduate programs including those of the Kent School of Public Health, the School of Medicine, the School of Public Health and the School of Dentistry via publication of high impact articles in top tier journals due to the interdisciplinary and complex nature of the project, an endeavor which cannot be carried out by highly-specialized individual units alone. The study has the potential to create a novel niche, which can help raise the national visibility of the University.
b. Increased research opportunities for graduate and undergraduate students. The broad nature of the project combining social, clinical and biological data with bioinformatics/systems approaches has the potential to create cross-disciplinary thesis projects for PhD candidates in multiple Departments. The wealth of information accumulated in the databases will provide a rich resource for future data-mining opportunities and thesis topics. The heavy emphasis on data collection and bioinformatics will create opportunities for high-achieving undergraduates to utilize this project for research papers as well as for summer internships supported by the University.
c. Increased research and scholarly productivity. Again, the cross-disciplinary systems approaches favored are expected to provide opportunities to experts in different fields to utilize the databases and the bioinformatics data. Going forward, we expect the Program to draw in researchers from across the University thus increasing overall scholarly productivity both at the undergraduate and graduate level.
d. Increased competitiveness for grants and philanthropic funding. The integrative and translational nature of the proposal along with its potential impact on health care is consistent with the priorities of the federal funding agencies. In addition, the broad applicability of the potential findings to many diseases is likely to be attractive to diverse private foundations that focus on different pathologies.

SUSTAINIBILITY PLAN

a. Engrained structure and plan to grow beyond this investment. A major focus of this application is to build a systems approach to health incorporating social and biological factors that affect community health. This strategy will be pursued from the unique perspective of social determinants of host microbiome and its role in health. The project will bring together researchers who are working in diverse fields including social sciences, public health and infectious/inflammatory diseases. The vertical and horizontal integration of social and biological data with big data bioinformatics and the collaboration engendered by the structure of the proposed program will facilitate interdisciplinary publications in higher ranked journals that would be not be possible with the study of single systems. This in turn will provide the preliminary metagenomic data that will drive collaborative cross-disciplinary grant applications that are favored by NIH.
b. Evidence of national funding program or philanthropic investment availability. The cross-cutting and translational aspects of the proposed studies are also in alignment with the stated goals of the NIH. Many private foundations support the research directions proposed here, including the American Heart Association, the Cystic Fibrosis Foundation and the Gates Foundation. Furthermore, several of the projects will form the basis of a COBRE P20 application on the microbiome in chronic inflammatory diseases that is planned for January 2017. Indeed, the administrative Core that will be put in place through this proposal will also serve in the same capacity for P20 application and will also provide support for a T32 training grant in inflammation planned for September 2016.

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