BU INTERDISCIPLINARY BIOMEDICAL RESEARCH OFFICE (BU IBRO)
EVANS CENTER FOR INTERDISCIPLINARY BIOMEDICAL RESEARCH (EVANS CENTER)

ARC/Thematic Project Title:

Preserving Child Health and Preventing Unhealthy Aging: the Pneumonia Affinity Research Collaborative (PneumoniARC)

Abstract (about 200 words):
Both young children and the elderly, especially those with co-morbidities such as chronic systemic disease, are highly susceptible to severe pneumonia. We propose a multidisciplinary team to attack this problem, integrating critical distinct perspectives into this complex disease process, including the basic biology disciplines of Lung Biology, Immunology, and Microbiology, combined with clinical research realms from those caring for children (Pediatrics) or older adults (Pulmonary & Critical Care Medicine). The PneumoniARC will coordinate the knowledge bases, research tools, and investigational activities of 9 principal investigators from 4 academic units across 6 different buildings, all of whom have studies that are complementary with others in the group and relevant to pneumonia. ARC meetings will focus on research of the different groups, on needs and opportunities that can be met with collaboration, and on mechanisms for generating extramural funding to support team science. Integrating these research programs into more unified and cohesive efforts at illuminating pneumonia biology will strengthen the research programs of each of these PIs. This ARC will lead to new avenues of investigation that foster more grant applications and importantly better grant applications, improved by being more collaborative, more multidisciplinary, more innovative, and more medically pressing.

A. Faculty

Names of ARC directors/members	Departmental and School Affiliation	Core Faculty ? (denote with *)
Joseph P. Mizgerd * (Director)	Pulmonary, BUSM	Yes, Core
Hans Dooms *	Rheumatology, BUSM	Yes, Core
W. Paul Duprex *	Microbiology, BUSM	Yes, Core
Rachel Fearns *	Microbiology, BUSM	Yes, Core
Yang Jin *	Pulmonary, BUSM	Yes, Core
Thomas B. Kepler *	Microbiology, BUSM; Mathematics, BUA&S	Yes, Core
Stephen I. Pelton *	Pediatrics, BUSM; Epidemiology, BUSPH	Yes, Core
Lee J. Quinton *	Pulmonary, BUSM	Yes, Core
Allan J. Walkey *	Pulmonary, BUSM	Yes, Core

B. New Applications

(1) Research Plans:

Rationale

Pneumonia is a microbial infection in the lung that destroys pulmonary function, occurring in diverse patient populations due to poorly understood immunological dysregulation (1). Pneumonia is a huge problem, being responsible for a greater global burden of disease than cancer, diabetes, dementia, malaria, HIV, tuberculosis, cerebrovascular diseases, COPD, asthma, or others (2, 3). It particularly afflicts the young and old. Pneumonia kills more children than any other disease on earth (4) and is the most common reason for children to be hospitalized in the US (5). Its impact on the other end of the age spectrum is even more striking, with close to 40 pneumonia cases per 1000 person-years and 12-25% mortality (1, 6, 7). US elderly are more likely to die during hospitalization for pneumonia than for any other cause (8). However, "older" is not very old; half of all adults hospitalized in the US for severe pneumonia are 57 or younger (9). Pneumonia requires hospitalization in 10-20% of cases (with >5 days typical), incurs 30-day re-admission rates of ~20%, and in the US alone costs more than 17 billion dollars annually (10-12). In addition to its direct impact, pneumonia accelerates unhealthy aging and worsens other lung diseases (13-16) as well as cardio/cerebrovascular diseases (17-19), cognitive decline (20, 21), functional disability (22), clinical depression (23), and more. For children (24) and adults (9) alike, the best and most current analyses indicate that respiratory viruses cause more US pneumonias than do any other agents. Despite its toll, pneumonia receives disproportionately little research attention compared to other diseases (25, 26).

Making advances against pneumonia will require the integration of diverse disciplines and approaches, but so far pneumonia research at BU and everywhere is addressed in a disjointed and discipline-specific fashion that is insufficient. BU has investigators and research programs with great skills and knowledge in pneumonia-related research, but these are piecemeal and disconnected from each other. Assembling BU pneumonia researchers into a cohesive multidisciplinary team will strengthen each of the individual PIs and research programs involved, will foster recognition of BU as a leader in this area of study, and will address very pressing unmet biomedical needs.

Specific Aims of Research

Aim 1. Build an organized community of pneumonia researchers at BU.
Aim 2. Generate tools, datasets, and infrastructure that support multi-investigator pneumonia research.
Aim 3. Obtain extramural funding for multidisciplinary and multi-investigator pneumonia-related research projects.

General Outline of Research Design

The 3 aims are mutually reinforcing. All 3 will begin immediately, but the ARC will transition through the 3-year duration, with activities in Aim 2 empowered by successes in Aim 1, and activities in Aim 3 empowered by successes in Aims 1 and 2. Forming a positive feedback loop, Aim 1 will be buttressed by the accomplishments in Aims 2 and 3.

The ARC will begin with an intensive meeting schedule, every 2 weeks for the first 3 months, to generate enthusiasm for the team effort, become better informed of each other's activities, identify and agree upon the most immediate needs and opportunities, discuss how best to address those needs as a group with ARC support, and establish plans and priorities for the 3-

year ARC and beyond. The 9 faculty members have each committed to this enterprise. For months 4-36, the ARC will meet monthly. Each meeting will be for an hour and include lunch. The first half-hour of discussion will be a led by a predetermined set of 2-3 related investigators who bring the group up to speed on their research efforts, strengths, limitations, and perspectives on opportunities and needs in pneumonia research. The second half hour will be a discussion of coordinated ARC activities. The first meetings will emphasize priorities and operating procedures for the ARC. Subsequently, the discussions will focus on topics to include progress in ongoing ARC-related activities, management of the program, new ARC activities, and extramural funding strategies. An additional component of community-building will be a seminar series in which visiting pneumonia specialists (3 per year, rotating amongst sites and units, freely open to all, and mandatory for the entirety of the ARC-associated faculty, trainees, and staff) are invited to BU to present their research, meet with faculty and research groups, and strengthen networking and connections for the trainees.

The tools, datasets, and infrastructure that will most substantially drive forward the multi-investigator pneumonia research of the group will be decided by group discussion, being a major focus of the first 6 meetings and 2-3 months especially. *Topics under consideration will include* but not be limited to: development of new models of pneumonia that would incorporate diverse expertises and be useful to multiple groups (e.g., naturally acquired heterotypic immunity against RSV in mice and cotton rats), clinical sample collection to complement basic science investigation (e.g., banking of serial blood and tracheal aspirates from ICU patients with pneumonia), mechanistic studies to inform the work of clinical researchers (e.g., using cell systems and animal models to test for causal relationships in associations observed by epidemiologists), developing datasets that would be useful to many (e.g., RNAseq profiles of experimentally generated or clinically collected samples of common interest), and piloting the collaborative pursuit of new directions (e.g., how acute lung infections intersect with chronic disease processes). Only activities spanning multiple groups and expanding well beyond currently funded projects will be considered, and those with greatest potential to profoundly improve collaborative research by multiple individuals within the ARC will be favored.

This interdisciplinary PneumoniARC will be unprecedented, a team that does not overlap with any other unit at BU or any university (based on searching the web and on seeing no such endeavor while visiting dozens of institutions to speak about pneumonia over the last 2+ decades). For example, the few Pulmonary Center investigators who study pneumonia pursue basic lung biology or do clinical research with aging adult patients, but have little expertise with microbiology, viral infections, childhood infections, adaptive immunity, etc. Similarly, the PIs from the other units have special expertises related to pneumonia, but they lack other aspects needed for integrated pneumonia research, elaborated upon further in the list and figure below. None of these 9 PIs are actively collaborating together yet in funded research, except for 3 of them with Mizgerd (see LJQ, HD, SIP biosketches) who assembled these 9 in order to create new and bigger and more multidisciplinary and more comprehensive and productive collaborations. *This ARC will build new collaborations that would not otherwise exist with out it*. And the discoveries that result from this ARC will have implications beyond pneumonia, to be brought back to the distinct academic units from which the PIs are based, thereby enriching the campus beyond the research of the 9 PIs and the pneumonia-related advances.

Funding opportunities and collaborative grant applications will be discussed at every meeting. As an example of planned new ARC collaborative endeavors, a first product of the PneumoniARC (originally suggested by Dr. Ravid) is underway even while the ARC is still in

nascent stages; in discussing how and why we could address questions together that none could address alone, Mizgerd, Kepler, and Fearns have established a new collaboration to respond to RFA HL-17-002: The Role of the Human Virome in Heart, Lung, and Blood Health and Resilience. Our proposed project will identify the virome exerting the most substantial immunological pressure on the lung, using Mizgerd's knowledge of lung-resident immunity, expertise in mouse models of lung infection, and access to live human lung samples; Kepler's knowledge of B cell biology, computational expertise, and IgG sequence variability analyses; and Fearns's abilities to collect, culture, characterize, and modify respiratory viruses. These 3 faculty have had multiple meetings already, are actively exchanging data and performing experiments, and will submit the R61/R33 application together as co-PIs in June 2016. The more frequent, focused, and informed discussions plus newly generated experimental models, clinical samples, datasets, etc. that are shared in this ARC will enable many more such new collaborative enterprises amongst the 9 researchers. Coordinated efforts, meetings, and investments under the leadership of the ARC program will greatly further the number and quality of collaborative applications from these groups, with a common theme of relevance to pneumonia.

References

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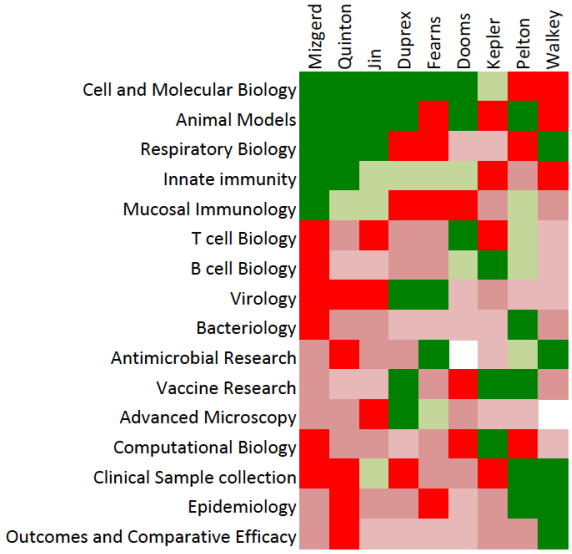
List the PIs who will be directly involved in each of the stated Aims of Research and their contribution to the interdisciplinary mission

The contributions of these PIs (what they will offer the group) can be appreciated in green in the matrix, matched with needs (areas that they wish to access or strengthen) shown in red, with color intensity indicating relative level:



Dooms – immunologist; CD4+ T cell biology; adaptive immunity, immunological memory, mouse models of immunological skewing and immunopathology, T cell cytokines.

Duprex – virologist; paramyxovirus host-pathogen interactions; reverse genetics, vaccine development, animal models of viral infection (mice, rats, non-human primates, and more), multimodal and live cell microscopic imaging

Fearns – virologist; fundamental biology of respiratory syncytial virus (RSV); viral replication and gene regulation, cell and molecular biology, intracellular antiviral innate immunity, novel antiviral drugs

Jin – lung biologist; mechanisms of lung injury; respiratory structure/function, cell and molecular biology, mouse models of acute and chronic lung diseases, membrane dynamics, exosomes, autophagy

Kepler – computational biologist *and* immunologist; mathematical approaches to immunology; B cell biology, germinal center reactions, antibody affinity maturation, immunoglobulin repertoire sequence analyses, vaccine development

Mizgerd – lung biologist; lung defense against infection; respiratory structure/function, cell and molecular biology, mouse models of pneumonia, innate immunity, lung-resident immunological memory, pneumococcal infections

Pelton – clinical researcher *and* bacteriologist; bacterial infections of the middle ear and respiratory tract of children; pediatrics, epidemiology, pneumococcus, chinchilla models of infection, effects of practice for vaccines and antibiotics

Quinton – lung biologist; integrative physiology during pneumonia and sepsis; respiratory structure/function, extrapulmonary responses to respiratory challenges, mouse models of sepsis and pneumonia, cell and molecular biology, innate immunity, Gram-negative bacterial infections

Walkey – clinical researcher; improving outcomes in intensive care; sepsis, pneumonia, ARDS, epidemiology, comparative effectiveness research

(2) ARC or pre-ARC Meetings and Workshops in preparation for ARC application- Dates, topics and names of presenters:

(3) Names and affiliation of trainees involved with pursuing the funded projects:

The following are current affiliated trainees:

pre- or post?	*Name*	*PI's Name*	*Program/Department*
Pre	Sila Ataca	Kepler	Microbiology PhD
Pre	Molly Braun	Fearns	Microbiology PhD
Post	David Chu, MD	Walkey	Pulmonary Med Fellowship
Pre	Fadie Coleman	Mizgerd	Microbiology PhD
Pre	Tessa Cressey	Fearns	Microbiology PhD
Pre	Stephanie D'Souza	Kepler	Combined MD/PhD
Post	Rachel Epstein, MD	Pelton	Pediatrics Fellowship
Pre	Michelle Fleury	Dooms	Immunology PhD
Pre	Yuri Kim	Quinton	Mol Transl Med PhD
Post	Rotem Lapidot, MD	Pelton	Pediatrics Fellowship
Post	Heedoo Lee, PhD	Jin	Pulmonary
Post	Barbara Ludeke, PhD	Fearns	Microbiology
Post	Anuj Mehta, MD	Walkey	Pulmonary Med Fellowship
Pre	Katherine Norwood	Kepler	Bionformatics PhD
Pre	Grace Olinger	Duprex	Microbiology PhD
Pre	Akshaya Ramesh	Kepler	Genetics & Genomics PhD
Pre	Kate Sawatzki	Kepler	Microbiology PhD
Post	Sabine Schnyder, MD	Pelton	Pediatrics Fellowship
Pre	Nicole Stauffer	Mizgerd	Immunology PhD
Post	James Streetley, PhD	Fearns	Visiting Scholar (U. Glasgow)
Post	Cristina Vazquez Mateo, PhD	Dooms	Rheumatology
Pre	Alicia Wooten	Mizgerd	Mol Transl Med PhD
Post	Duo Zhang, PhD	Jin	Pulmonary