Immune-Based Interventions Against Infectious Disease – Impact of a Phase I Center for Biomedical Research Excellence in Translational Infectious Diseases Immunology

ALAN L. ROTHMAN, MD; JENNIFER FRIEDMAN, MD; JONATHAN D. KURTIS, MD, PhD

ABSTRACT

In 2011, faculty from the University of Rhode Island (URI)'s Institute for Immunology and Informatics and Lifespan's Center for International Health Research collaborated to develop a successful application for a Phase I Center of Biomedical Research Excellence around the scientific theme of translational infectious diseases immunology. From 2013 to 2020, this COBRE supported significant discoveries in research on dengue, HIV, and malaria, among other diseases, and facilitated the career development of several independent Rhode Island (RI)-based early-stage investigators. Our experience illustrates both the potential and challenges for investigators with shared scientific interests to leverage the NIH COBRE program to enhance cross-institutional interactions.

KEYWORDS: immunology, infectious diseases, global health, translational research, host-pathogen interactions

INTRODUCTION

Research on infectious diseases is essential both in the U.S. and globally. Well-known infectious diseases continue to cause significant morbidity and mortality, and new and re-emerging infectious disease threats are being increasingly recognized, most recently exemplified by the COVID-19 pandemic.[1,2] The diversity of human pathogens requires a broad research strategy, including efforts to utilize or enhance innate and adaptive immune mechanisms for preventive strategies and as broad-spectrum therapeutics. There is also increasing attention to the need to modernize the structure and organization of scientific investigation.

The University of Rhode Island (URI), the state's primary public research university, lacks a medical school, and its infectious diseases research is divided among several colleges. In 2009, URI founded the Institute for Immunology and Informatics (iCubed) in the Biotechnology Center on the Providence campus, with a research mission in the immunology of human infectious diseases. Brown University has the state's only medical school. Its infectious disease and immunology research is spread across multiple departments and programs within the medical school and its affiliated teaching hospitals. In 2005, Rhode Island Hospital founded the Center for International Health Research (CIHR), an interdepartmental center with a research mission on immunity to malaria and schistosomiasis. These two centers were thus both actively conducting NIH-funded translational infectious diseases immunology research in downtown Providence. At the same time, both groups faced challenges associated with a small size and distinct mission, particularly limited resources to expand strategically into new research opportunities, provide career advancement for young scientists, and fund the purchase of advanced equipment.

The common scientific interests and philosophy and the proximity of iCubed and CIHR led us to institute a combined Journal Club/research-in-progress meeting and initiate discussions in 2011 regarding potential collaborative opportunities. The NIH Centers for Biomedical Research Excellence (COBRE) program provided an attractive solution. In contemplating a collaborative COBRE proposal, we defined two key priorities and objectives: a) achieving a "critical mass" of at least 8–10 full-time funded investigators with related scientific interests to make the groups competitive for institutional training grants and shared instrumentation grants; and b) creating a sustainable mechanism to promote career advancement of junior investigators and launch new research initiatives.

CONCEPT FOR THE PHASE I COBRE

In our COBRE Phase I application, "Immune-Based Interventions Against Infectious Diseases," we outlined a vision to build an entrepreneurial, multidisciplinary, and trans-institutional research team to address infectious diseases of global importance. The COBRE proposed to catalyze the

Figure 1. Logo for our COBRE focused on infectious diseases immunology. The logo highlights COBRE-supported research with images of dengue virus, a mosquito vector, *Plasmodium falciparum*-infected red blood cell, and human immunodeficiency virus (clockwise from upper left). The world map in the center highlights the focus on global health, and the subtitle highlights the multi-institutional collaboration.

partnership between the vital independent research programs in iCubed and CIHR around the unifying scientific theme of translational research in pathogen-host interactions (**Figure 1**).

This proposed COBRE's significance and innovation lay in its intent to pursue transformational advances in infectious disease immunology research, bypassing traditional paradigms of departmental growth to address high-priority research objectives. Distinctions from existing research programs in RI included: 1) applied research, 2) a global health focus, 3) interdisciplinary research including both MDs and PhDs, and 4) an emphasis on collaboration, shared governance of common resources, and recognition of faculty teamwork.

URI/iCubed served as the primary grantee for the COBRE, with a substantial component at RI Hospital/CIHR (**Figure 2**). Leadership was provided by a senior Program Director, a Steering Committee of established URI and Lifespan faculty, and an External Advisory Committee of 5 senior NIH-funded MD and PhD investigators. Support was solicited from the broader RI community of infectious disease and immunology researchers; affiliated faculty members were asked to participate in conferences and seminars, and in turn, would have priority access to COBRE core facilities.

Our Phase I COBRE proposed four Specific Aims:

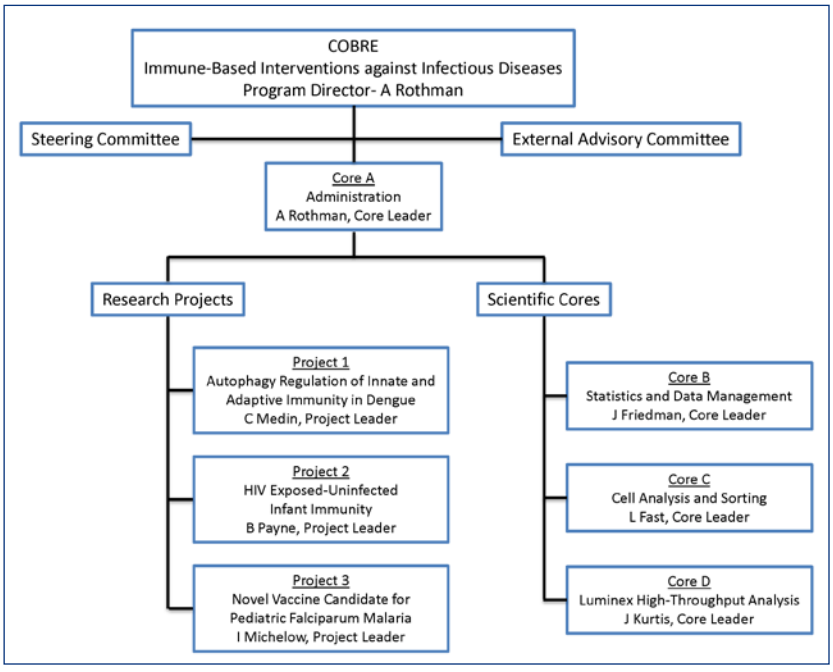
Aim 1 was to provide leadership to the RI research community in translational infectious diseases immunology. Visibility and identity for the COBRE would be established through support for conferences and pilot projects. These had already been accomplished on a smaller scale at iCubed, including through R13 and U19 grants. Support for conferences would include the established Vaccine Renaissance Conference, Journal Club, seminars, and an annual Research Retreat. The Pilot Projects program would support promising early-stage investigators and new interdisciplinary collaborations.

Aim 2 was to build infrastructure for immunology research. COBRE-supported scientific cores (**Figure 2**) were designed to provide CORBE investigators with the tools to generate and manage complex immunologic datasets. Our efforts focused on platforms with high-throughput capacity and multiparameter read-outs. The Cell Analysis and Sorting Core would provide immunoassay, flow cytometry, and cell sorting services focused on automation, throughput, and biosafety. The Core would leverage existing equipment (e.g., LSR II analyzer and AutoMACS) and would fund the purchase of a new Miltenyi MACSQuant Analyzer. The Core would focus on training and advising research staff and facilitating their use of the equipment. The Luminex High-Throughput Analysis Core would provide assays on an existing Luminex platform in a high-throughput mode. Under COBRE support, this equipment would be available for use by a more extensive cadre of researchers. Additional sample handling equipment would be acquired to increase assay capability. The Statistics and Data Management Core would support COBRE investigators in managing and analyzing these and other research data. The Core would assist COBRE investigators with managing complex datasets and performing sophisticated data analyses incorporating clinical predictors and outcomes collected in the field. The Core would also serve an educational role by providing both project-specific, tailored advice and broader education in epidemiology, data management, and biostatistics to facilitate communicating with collaborators, analyzing complex data, and writing grants.

Aim 3 was to recruit and mentor promising junior investigators. The strategic plan for the growth of the COBRE involved the direct investment in three junior investigators and new investigators' recruitment. Mentoring of these individuals was critical to this plan. We proposed a detailed mentoring plan, including the designation of a primary mentor and co-mentor for each of the junior investigators. Milestones and timelines were defined, with plans for regular meetings and evaluations, to be reviewed by the Steering Committee and External Advisory Committee.

Aim 4 was to support translational infectious diseases immunology research by junior investigators. Our COBRE proposal identified three junior investigator-led projects that would build on established iCubed and CIHR research

Figure 2. COBRE organizational chart at start of Phase I funding period. A fourth Research Project was added in Year 2.



programs but introduce novel study populations or models and new research techniques (**Figure 2**). "Autophagy Regulation of Innate and Adaptive Immunity in Dengue," led by Dr. Carey Medin, focused on host cell responses to dengue virus (DENV). This project proposed to analyze the induction of autophagy by DENV and its effects on innate immune signaling and activation of T lymphocytes by DENV-infected antigen-presenting cells. The significance of the project lay in the expanding global impact of dengue and the potential relevance of autophagy to dengue disease pathogenesis. Translational aspects of this project included the analysis of primary human cells and clinical isolates of DENV. "HIV Exposed-Uninfected Infant Immunity," led by Dr. Barbara Payne, focused on the impact of in utero exposure to HIV on development of the immune system. This project proposed to compare the repertoire of T lymphocytes in HIV-uninfected infants born to HIV-infected or uninfected mothers and define the maternal characteristics that affect the development of the infant immune system and the effects of a narrowed T cell repertoire on subsequent immune responses to infant vaccinations. The significance of the project lay in the increased risk for morbidity and mortality in infants of HIV-infected mothers despite preventing maternal-fetal transmission of HIV. Translational aspects of this project included the analysis of clinical specimens and clinically relevant outcomes. "Novel Vaccine Candidate for Pediatric Falciparum Malaria," led by Dr. Ian Michelow, focused on defining the mechanisms of protection by antibodies to a novel malaria antigen. This project proposed to analyze the expression of this antigen and its association with protection. The significance of the project lay in the need to identify protective malaria antigens for vaccine development. Translational aspects of this project included the focus on vaccine development and the use of clinical specimens.

EXECUTION AND OUTCOMES OF PHASE I COBRE ACTIVITIES

Through Phase I COBRE funding, iCubed and CIHR generated new and productive research collaborations, recruited additional investigators, and expanded the reach of these collaborations within RI.

Under Aim #1, iCubed and CIHR solidified the weekly joint research-in-progress/journal club meeting, which expanded to include several Pilot Project investigators and new hires. We also organized three local retreats/workshops bringing together RI-based academic and industry investigators in immunology, infectious diseases, and bioinformatics/big data, which served to catalyze several collaborative research and teaching initiatives. With an institutional contribution to the program from Lifespan, the COBRE Pilot Projects program supported a total of 14 projects over the phase I period (**Figure 3**). In addition to supporting junior investigators within iCubed and CIHR, pilot project funding

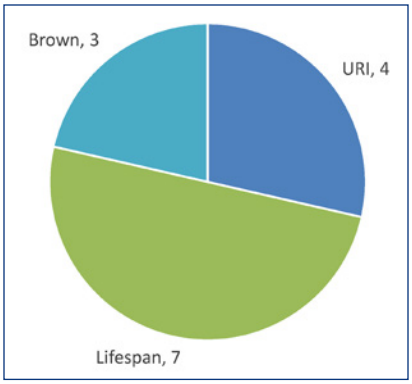


Figure 3. Distribution of funding from the COBRE Pilot Project program, by home institution (N = 14). Direct COBRE support for 10 pilot projects was supplemented by funding for 4 projects from Lifespan.

supported investigators in other units within URI (Pharmacy, Cell and Molecular Biology), Lifespan (Gastroenterology, Pediatrics, Oncology, Infectious Diseases), and Brown University (Molecular Microbiology and Immunology). Overall, these activities succeeded in raising the profile of infectious diseases immunology research within RI and encouraged new and interdisciplinary research collaborations. The COBRE triggered stronger interactions between URI and Brown University and its affiliated hospital systems that are an ongoing positive outcome of the COBRE.

Under Aim #2, COBRE funding expanded the laboratory infrastructure and made these resources available to the local scientific community through CoresRI.org and shared scheduling calendars. The Data Management and Statistics Core served as a model for other programs. Its personnel were recruited to participate in several other RI COBREs, and the Brown University Environmental influences on Child Health Outcomes (ECHO) program. Equipment added to the Cell Analysis and Sorting Core and the High-Throughput Luminex Immunoassay Core continues to support research at URI, Lifespan, and Brown University.

Under Aim #3, we recruited additional faculty members to iCubed and CIHR and paired younger investigators with senior mentors. During the phase I period, we recruited five new faculty investigators, two at iCubed and three at CIHR. One of these investigators was recruited using COBRE Research Project support, and three of the other investigators received COBRE pilot project funding. All of the Research Project Leaders and nearly all Pilot Project investigators submitted applications for external grant funding. Several Pilot Project investigators successfully transitioned to independent status, and others received smaller NIH or foundation grants as PI. Two Research Project leaders were promoted within their respective institutions.

Under Aim #4, we supported a total of four full Research Projects and 14 Pilot Projects during the Phase I period. All of the Research Project leaders had success at obtaining some external funding for their research; two achieved "independent" status as overall or local PI on an NIH R01 grant. Overall, 13 published manuscripts from Research Project leaders cited COBRE support. The Pilot Projects program

contributed to 4 R01s, 5 R21s, at least 15 smaller (e.g., foundation) grants, and 17 additional published manuscripts.

Major scientific outcomes from COBRE Research Projects included the following:

- COBRE research described a novel system for live-cell imaging of DENV-infected cells and demonstrated that DENV infection resulted in the suppression of mitochondrial fission through a reduction in intracellular levels of dynamin-related protein 1.[3,4] These findings identified a novel effect of DENV on cell function and provided insights into dengue pathogenesis.
- COBRE research demonstrated that maternal HIV infection was associated with elevated serum cytokine levels, elevated levels of cytokines in the cord blood of their HIV-exposed, uninfected (HEU) infants, and reduced T cell receptor beta chain gene diversity in a subset of these infants.[5,6] These findings demonstrated that maternal HIV infection affected in utero development of the immune system in HEU infants, potentially contributing to the higher risk of illness in these infants.
- COBRE research characterized a novel malaria parasite antigen expressed both on the parasite surface and on the surface of infected RBCs selectively recognized by cohort subjects at lower risk of illness. These findings identified a novel candidate for vaccines to prevent malarial disease.
- COBRE research identified malaria parasite antigens selectively recognized by individuals with low/undetectable gametocytaemia.[7] These findings point to a vaccination strategy to block parasite transmission.

CHALLENGES

Characteristics that made our Phase I COBRE unusual unfortunately also created challenges. Our COBRE aimed to catalyze a collaborative effort between groups at two different institutions that was at a very early stage. None of the senior or junior COBRE investigators held tenure-track faculty positions. The research projects targeted for support were at a very early phase, as COBRE support provided the resources to launch these independent research projects. While we envisioned the COBRE program as an excellent fit for our objectives, our model did not include more established (yet still early-stage) investigators and projects who could provide the "quick success" that some COBREs rely on and NIH study sections expect. The increasing time needed by young faculty to establish independent research funding is well documented[8] but not well aligned with the expected rate of transition of COBRE-supported investigators.

Notably, and in our minds regrettably, the challenges we faced have been amplified by changes to the COBRE application requirements. Per the current FOA, "Research Project Leaders must hold a tenure-track faculty appointment (or equivalent at research institutes) at the time the application is submitted." In practice, this can be fulfilled by written departmental confirmation of commitment of faculty-level salary, space and resources independent of the COBRE award. Nonetheless, appointment of non-tenure-track faculty as COBRE Project Leaders creates challenges at institutions like URI and others, which will further constrain the opportunities for such investigators. The period of COBRE support for individual Research Projects has been tightened, which further incentivizes "padding" of COBRE productivity by short-term appointments of investigators already poised to obtain R01 funding. Finally, current FOA requirements require that the lead institution keep most Research Projects and Scientific Cores in a COBRE and limit the total number of Projects and Cores an institution can hold as a subawardee. These changes make a truly balanced collaboration between institutions, such as in our COBRE, extremely difficult. Although these changes have rationale and seek to enhance the productivity and sustainability of COBREs, they may constrain the COBRE mechanism's ability to transform the research landscape.

CONCLUSION

In perhaps a stroke of irony, our Phase I COBRE focused on translational research in infectious diseases immunology closed in early 2020, just as the first wave of the COVID-19 pandemic was cresting in RI. Although we did not succeed in navigating the transition to Phase II, participation in the NIH COBRE program provided a significant direct and indirect financial impact to RI, a valuable learning and growth experience for the senior investigators involved, and incalculable career benefit to several of the young investigators supported.

References

1. Morens DM, Folkers GK, Fauci AS. The challenge of emerging and re-emerging infectious diseases. Nature 2004; 430:242-9.
2. Ehrenberg JP, Zhou XN, Fontes G, Rocha EMM, Tanner M, Utzinger J. Strategies supporting the prevention and control of neglected tropical diseases during and beyond the COVID-19 pandemic. Infect Dis Poverty 2020; 9:86.
3. Medin CL, Valois S, Patkar CG, Rothman AL. A plasmid-based reporter system for live cell imaging of dengue virus infected cells. JVirolMeth 2015; 211:55-62.
4. Barbier V, Lang D, Valois S, Rothman AL, Medin CL. Dengue virus induces mitochondrial elongation through impairment of Drp1-triggered mitochondrial fission. Virology 2017; 500: 149-60.
5. Lohman-Payne B, Gabriel B, Park S, et al. HIV-exposed uninfected infants: elevated cord blood Interleukin 8 (IL-8) is significantly associated with maternal HIV infection and systemic IL-8 in a Kenyan cohort. Clin Transl Med 2018; 7:26.

6. Gabriel B, Medin C, Alves J, et al. Analysis of the TCR Repertoire in HIV-Exposed but Uninfected Infants. Scientific reports 2019; 9:11954.
7. Nixon CP, Nixon CE, Michelow IC, et al. Antibodies to Pf-sEGXP, an Early Gametocyte-Enriched Phosphoprotein, Predict Decreased Plasmodium falciparum Gametocyte Density in Humans. The Journal of infectious diseases 2018; 218:1792-801.
8. Alberts B, Kirschner MW, Tilghman S, Varmus H. Rescuing US biomedical research from its systemic flaws. Proceedings of the National Academy of Sciences of the United States of America 2014; 111:5773-7.

Authors

Alan L. Rothman, MD, Institute for Immunology and Informatics and Department of Cell and Molecular Biology, University of Rhode Island.

Jennifer Friedman, MD, Center for International Health Research and Department of Pediatrics, Lifespan, Providence, RI.

Jonathan D. Kurtis, MD, PhD, Center for International Health Research, Lifespan, and Department of Pathology and Laboratory Medicine, Brown University, Providence, RI.

Correspondence

Alan L. Rothman, MD
alan_rothman@uri.edu