MEDICAL SCHOOL HOTLINE

Pacific Center for Emerging Infectious Diseases Research

Richard Yanagihara MD, MPH; Vivek R. Nerurkar PhD; George Hui PhD; and Gwen A. Jacobs PhD

The Medical School Hotline is a monthly column from the John A. Burns School of Medicine and is edited by Satoru Izutsu PhD and Kathleen Kihmm Connolly PhD; HJMPH Contributing Editors. Dr. Izutsu is the vice-dean of the University of Hawai'i John A. Burns School of Medicine and has been the Medical School Hotline editor since 1993.

Introduction

New, emerging, and re-emerging infectious diseases are among the most urgent public health threats and economic challenges facing global communities in the new millennium. Recent examples of outbreaks include the emergence and rapid spread of Ebola virus disease in Guinea, Liberia, and Sierra Leone;[1] Middle East respiratory syndrome in Saudia Arabia[2] and Korea;[3] avian influenza in Vietnam;[4] polio in Pakistan;[5] and the currently burgeoning epidemic of Zika virus (ZIKV) infection with associated microcephaly and other congenital neurological abnormalities in Brazil,[6] and elsewhere in South America, with autochthonous ZIKV transmission in Puerto Rico[7] and Florida,[8] and a recent travel-associated microcephaly case in Hawai'i.[9] Also, in the State of Hawai'i, on Hawai'i Island, the largest outbreak of dengue fever[10] was recorded since 1943, with 264 confirmed cases occurring between September 11, 2015 and March 30, 2016.

Thus, the past half-century has witnessed the emergence of previously unrecognized infectious diseases, such as HIV/AIDS, hantavirus pulmonary syndrome, severe acute respiratory syndrome and severe fever with thrombocytopenia syndrome, and the resurgence of once-conquered diseases, such as tuberculosis and poliomyelitis, so that today, infectious diseases have regained their prominent position as one of the leading causes of morbidity and mortality worldwide. Among the myriad factors responsible for the alarming worldwide resurgence of infectious diseases are the unprecedented population growth with uncontrolled urbanization, the rapid movements of people, animals (and their endo- and ecto-parasites), and commodities via jumbo jets and high-speed trains, the insidious breakdown of public health infrastructure, and the misplaced emphasis on curative rather than preventive medicine.[11]

Geographic Setting

Comprising 132 islands, reefs and shoals that extend for more than 2,400 km in the middle of the Pacific Ocean, the Hawaiian Archipelago lies 4,000 km from the US Mainland and nearly 8,000 km from mainland Asia. With its year-round, mild tropical weather, Hawai'i serves as a principal US gateway to and from Asia, and as a major tourist destination for people worldwide. It is also home to some of the Nation's most important Army, Navy, Air Force, and Marine Corps military bases. Thus, the heavy tourist traffic from Asia and elsewhere and the presence of military assets places Hawai'i at high risk for natural and deliberate introductions of infectious diseases. Moreover, by virtue of its geographic location and strong ties to academic institutions and ministries of health in the Asia-Pacific region, the University of Hawai'i at Manoa is strategically positioned as a sentinel post to monitor the emergence and spread of newly recognized and re-emerging infectious diseases.

Significance

Asia is generally considered the geographic birthplace of numerous newly recognized emerging infectious diseases, nearly all of which are either vector-borne or zoonotic. In recent years, these newly identified microbes have caused major outbreaks or epidemics, resulting in significant loss of human lives and devastating economic consequences worldwide. Accordingly, as originally conceived, the Pacific Center for Emerging Infectious Diseases Research (http://pceidr.jabsom.hawaii.edu/) was part of a larger vision to develop a regional translational science center of research excellence focusing on the development and deployment of rapid diagnostics, effective treatments, and affordable vaccines for newly recognized and neglected

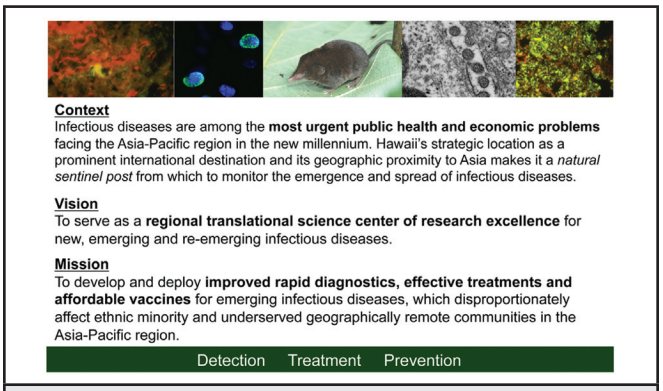

Figure 1. Context, Vision and Mission of the Pacific Center for Emerging Infectious Diseases Research

infectious diseases, which disproportionately affect ethnic minority and underserved geographically remote communities in the Asia-Pacific region (Figure 1). Funding for the development of technical cores in biocontainment, bioinformatics, and molecular and cellular immunology and the building of human capital, from the Centers of Biomedical Research Excellence (COBRE) initiative of the Institutional Development Award (IDeA) program, of the National Institute of General Medical Sciences of the National Institutes of Health (NIH), has been leveraged by broad support and investments from upper administration for faculty recruitment, resulting in heightened research productivity, as measured by peer-reviewed publications in high-impact journals and presentations at scientific conferences, as well as additional extramural funding in the form of investigator-initiated research project grants. Thus, the Pacific Center for Emerging Infectious Diseases Research has had a profound impact on creating the conditions that accelerate the pace of scientific discovery, heighten research productivity, and increase competitiveness for extramural funding.

Historical Overview

In 2003, the once-respected tropical medicine program at the University of Hawai'i at Manoa had lost much of its previous stature, primarily through faculty attrition, hiring freezes, and diminished institutional support. Changes began to occur in 1999 with the appointment of a new medical school dean, who declared that selected areas of research excellence would be developed, while maintaining the stellar problem-based learning curriculum and excellent community health training programs. Thus, in response to the regional resurgence of infectious diseases, and in response to needs of the University and the State to regain research excellence in tropical infectious diseases, highly productive, intramural NIH investigators were recruited to provide leadership in developing a nationally recognized research and training program in emerging infectious diseases.

The Pacific Center for Emerging Infectious Diseases Research was established during the initial phase of COBRE funding and considerably strengthened and transformed during the second phase. The construction of a fully State-funded BioSciences Building offered unparalleled laboratory space in which COBRE-funded investigators moved into in December 2005. The centralization of COBRE activities in state-of-the-art laboratories with adjoining spaces for core facilities, including the BSL-3/ABSL-3 Biocontainment Core, transformed the Center from a virtual concept into a brick-and-mortar entity for leading-edge biomedical sciences research. The centralization of the COBRE Center also brought COBRE faculty into physical proximity with other research faculty within selected high-priority research areas, resulting in heightened resource sharing and scientific exchange. Renewed funding for the COBRE for cardiovascular research and the COBRE on reproductive biology are direct consequences of this co-location of core facilities and human capital, as well as continued generous institutional commitment.

Not surprisingly, the investments in the Pacific Center for Emerging Infectious Diseases during the past 10 years have been leveraged into additional extramural grant support totaling more than $35 million. As importantly, the availability of cores have made possible an expanded critical mass of researchers engaged in emerging infectious diseases research. Thus, the Center is now well positioned to transition the core resources, developed during Phases I and II, into sustainable core facilities capable of supporting high-caliber basic, clinical, and translational research aimed at improving the diagnosis, treatment and prevention of new, emerging and re-emerging infectious diseases.

Organization and Governance

The overall organizational and governance structure of the Pacific Center for Emerging Infectious Diseases Research comprises visionary leadership; a dedicated and talented team of extramurally funded local mentors with study section experience; an External Advisory Committee, composed of NIH-funded senior scientists recognized for their seminal contributions in emerging infectious diseases research, who will serve as additional mentors; and a Steering Committee, composed of the COBRE Principal Investigator, Program Coordinator, Core Directors, representative core users, and COBRE Evaluator, which sets policies and monitors the overall operations of the Center. Finally, a collaborative Small Grants Program provides modest funding to faculty on a competitive basis to heighten research productivity and increase grants success, leading to further growth and competitiveness of the Center and its cores.

Building and Diversifying the Scientific Workforce

COBRE funding has supported the career development of faculty from across the University of Hawai'i at Manoa, including the John A. Burns School of Medicine (Sandra P. Chang, Guliz Erdem, Peter R. Hoffmann, Pakieli H. Kaufusi, James F. Kelley, Mukesh Kumar, Axel T. Lehrer, Apichai Tuanyok, Saguna Verma, Wei-Kung Wang), Cancer Center (Brenda Hernandez), Office of Public Health Studies (Allison Imrie), College of Natural Sciences (Hongwei Li, Tung T. Hoang), and Pacific Bioscience Research Center (Angel A. Yanagihara). Further, many more faculty and students, as well as scientists from the local biotech community, have benefited from the research and training services provided by the COBRE cores of biocontainment, bioinformatics, and molecular and cellular immunology. The profound impact of mentoring and project funding for each COBRE-supported investigator cannot be overstated. COBRE support has been transformative for their professional development, as evidenced by peer-reviewed scientific publications in high-impact journals and presentations at national and international scientific meetings, as well as successful research grants awarded by NIH and other funding agencies.

Moreover, the Center mentors have collectively been proactive in pursuing funding opportunities for expanding and diversifying the scientific workforce for emerging infectious diseases research. Building pipelines to diversify and expand the workforce for biomedical research cannot be confined to

Table 1. Training Grants to Strengthen and Diversify the Scientific Workforce				
Principal Investigator(s)	**Grant Number**	**Project Title**	**Project Period**	**Total Cost**
Hui GSN	R25DK078386* NIH/NIDDK	Pacific High Schools Step-Up to Biomedical Research	04/01/07-02/28/17	$2,719,597
Taylor DW	D43TW009074 NIH/FIC	Training of Cameroonian Scientists in Research on Malaria	08/01/11-07/30/16	$1,000,079
Nerurkar VR, Zunt JR, Kolars JC, John CC	R25TW009345* NIH/FIC	Northern/Pacific Universities Global Health Research Training Consortium	07/01/12-06/30/17	$5,745,660
Nerurkar VR, Taylor DW	T37MD008636 NIH/NIMHD	International Biomedical Research Training for Hawaiian & Pacific Island Students	12/01/13-11/30/18	$1,354,000

*Funding decisions to continue these grants until 2022 are pending.

college students but must start much earlier. As such, programs targeting high school students from underserved communities across the Pacific and initiatives aimed at providing international research experiences for undergraduate and graduate students and post-doctoral fellows have been developed to train future generations of biomedical and biobehavioral scientists, as well as to grow and diversify the user base for the COBRE cores. Examples of such training grants are listed in Table 1. COBRE mentors have also participated actively in other research infrastructure- and career-building programs, such as the IDeA Networks of Biomedical Research Excellence (INBRE) and the Minority Access to Research Careers (MARC). Moreover, COBRE mentors have assisted in the implementation of science education projects for school children on remote islands in Micronesia, funded by the Science Education Partnership Award (SEPA) program. Investments in building such pipelines of students and post-doctoral fellows will lead to long-term desirable outcomes of sustaining the Center.

COBRE Core Resources

Optimizing and streamlining core operations, growing and diversifying the core user base, and strengthening the core fiscal well-being are all part of the strategic plan for the sustainability of the COBRE cores. Just as the core values of institutions of higher learning are grounded in teaching, research and service, the triad of customized and collaborative service, research and development, and education and training guides each of the three technical cores (Figure 2) for biocontainment, bioinformatics and molecular and cellular immunology. In so doing, each core will expand and diversify the research workforce and create new revenue streams for sustainability.

Bioinformatics Core

Established with COBRE funds at a time when little attention was being paid to bioinformatics at University of Hawai'i at Manoa, the Bioinformatics Core is increasingly gaining the widespread demand and appreciation it deserves, particularly from faculty engaged in big-data, team-science research. A major thrust of the Bioinformatics Core is to provide customized services and education and training for data science, particularly as it relates to genomics, metagenomics, and epigenetics. Fortuitously, a

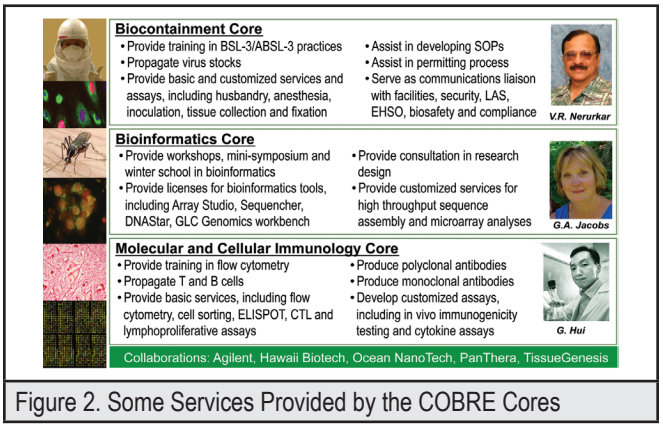

Figure 2. Some Services Provided by the COBRE Cores

six-story, 74,000-square-foot, energy-efficient, state-of-the-art Information Technology Center, dedicated in December 2013, supports essential statewide information services and protect critical information and communication resources for the entire University of Hawai'i System. Moreover, a new High-Performance Computing Cluster, with storage capacity to support "big data" applications, has been installed. University of Hawai'i President, Dr. David Lassner, a strong advocate of bioinformatics, has pledged that the infrastructure of the COBRE Bioinformatics Core will become fully supported within the next five years.

Biocontainment Core

The Biocontainment Core manages the ABSL-3/BSL-3 facility in the BioSciences Building in Kaka'ako, as well as provides services for research involving ABSL-2 and BSL-2 microbial agents. Core personnel develop pathogen-specific standard operating procedures, as well as develop and perform project-specific assays (such as production of virus stocks, virus titrations, plaque-reduction neutralization tests), animal inoculation, and collection of biological fluids and tissues. In addition, Core personnel assist in obtaining State and Federal permits for importing infectious agents and in shipping infectious agents to national and international collaborators; ensure the maintenance and recertification of the ABSL-3/BSL-3 facility; and develop training modules and improved methods for working with ABSL-3/BSL-3 and ABSL-2/BSL-2 agents.

Molecular and Cellular Immunology Core

Equipped with specialized instrumentation, including FACSAria, FACSCalibur, Attune NxT and Guava flow cytometers, ELISPOT reader and Luminex® technology, and staffed by a dedicated Core Manager with long-standing experience in optimizing specimen processing and data collection and analysis, the Molecular and Cellular Immunology Core provides hitherto unavailable capability and capacity to the research community within the University of Hawai'i System and beyond. In fact, prior to COBRE funding, services particularly for flow cytometry were either nonexistent or quite rudimentary. The Molecular and Cellular Immunology Core also provides training in flow cytometry and other immune-based assays, as well as develops new assay platforms, such as those based on Luminex® technology.

Future Research and Action Plan

Increased funding and resources are warranted for research into the factors that govern the emergence and epidemic spread of vector-borne and zoonotic infectious diseases, as well as whether newfound still-orphan viruses cause infection and disease in humans. By taking full advantage of the existing infectious disease research excellence and clinical expertise in Hawai'i and the Asia-Pacific region, and by networking the regional partners it will be feasible to develop and deploy broad suites of microbial antigens for point-of-care rapid diagnostics, broad-spectrum anti-pathogen countermeasures and effective treatments, including the repurposing of drugs for new applications, and off-the-shelf vaccine constructs to be better prepared to respond to the next infectious disease outbreak and to ensure the protection and health of the general public.

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Authors' Affiliations:
- Department of Pediatrics, John A. Burns School of Medicine, University of Hawai'i at Manoa, Honolulu, HI (RY)
- Department of Tropical Medicine, Medical Microbiology and Pharmacology, John A. Burns School of Medicine, University of Hawai'i at Manoa, Honolulu, HI (VRN, GH)
- Information Technology Services, University of Hawai'i at Manoa, Honolulu, HI (GAJ)

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