History

The influenza program at St. Jude has a long, distinguished history as a world-class leader in the study of the origins, evolution, and pathogenesis of influenza viruses. Based on this expertise, the program was designated a World Health Organization (WHO) Collaborating Center in 1975, a designation it still carries today.

The modern history of the program began in 1998, when, in collaboration with the University of Hong Kong (HKU), Dr. Robert Webster was awarded a National Institutes of Allergy and Infectious Diseases (NIAID) contract, “Pandemic Preparedness in Asia,” to elucidate the origins and impact of the H5N1 virus that had emerged the prior year in Hong Kong. The program made a number of seminal contributions to the influenza field and to public health.

The success of this program not only cemented the ties between St. Jude and HKU, but also laid the foundation for the 2007 NIAID Center of Excellence for Influenza Research and Surveillance (CEIRS) awards of which St Jude CEIRS (SJCEIRS) was an awardee. During the seven years of this award the SJCEIRS team made some important contributions that included:

- Development of infrastructure for influenza research in Egypt
- Development of a Centre of Influenza Research at HKU.
- Produced 8 World Health Organization H5N1 vaccine reference viruses.
- Detected the entry of clade 2.3.2.1 H5N1 viruses into Europe.
- Demonstrated that in commercial US pig populations influenza viruses circulate year round with an average incidence of around 4%.
- Determined that the inability to implement a successful poultry vaccination campaign in Egypt was related to interfering maternal antibodies.
- Rapidly determined the susceptibility of emerging H1N1 and H7N9 to available and developmental antivirals.
- Provided more than 12,000 shipments of reagents to the scientific and public health communities.
- Contributed to the realization that camels are a likely source of MERS coronavirus.
- Described the evolutionary events that led to the genesis of the H1N1/2009 pandemic influenza virus.
- Demonstrated that a higher dose of oseltamivir is needed for the treatment of more virulent viruses.
- Identified two monocyte populations in nasal washes of infected humans associated with pro and anti-inflammatory phenotypes. Overabundance of the former set appeared to associate with severe disease.
- Were the first to characterize the H7N9 virus causing human infection in China and detail the events that led to its emergence.

Current CEIRS Program

The SJCEIRS program builds upon many years of collaborative work by the primary investigators and proposes a comprehensive research program centering on the human-animal influenza interface. The program couples the skills of established and junior investigators and combines our historical program strengths in virology and immunology and our extensive and world-class facilities and resources, with novel and innovative study designs such as exploration of risk factors for human infection and mechanisms of virus transmission.

Importantly, the members of the SJCEIRS team provide NIAID with experts who are integrated into the influenza programs of key international agencies such as the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations, and the World Organization for Animal Health. These ties allow for the rapid assimilation of data to global public health in true “one-world, one-health” fashion.

The St Jude CEIRS (SJCEIRS) program will foster the integration of comprehensive global influenza virus surveillance with fundamental research that will provide insight into the mechanisms that foster pandemic influenza emergence at the human-animal interface. The Centers mission is being addressed through the implementation of research in four major areas, I) studies at the human-animal interface, II) mechanisms of transmission, III) influence of risk factors on influenza severity, and IV) host response to infection.

Studies at the Human-Animal Interface

Based on data generated from our ongoing and prior surveillance activities, our proposed surveillance-based research activities converge on four core geographic regions. Two of these, South Asia and North America have been historical strengths of the SJCEIRS investigators while two, South America (Colombia and Nicaragua) and Africa (Egypt) represent expansions of programs that were developed during the prior CEIRS award in response to the endemic nature of H5N1 and H9N2 viruses in Egypt and the paucity of data from Latin America. While each site has developed its sampling strategy based on local conditions and specific hypotheses, the Center design allows us to compare and contrast viral evolution in different countries and environmental conditions.

As stated by NIAID, the overall goal of the CEIRS program is to provide the Government with public health tools and strategies needed to control and lessen the impact of epidemic influenza and the increasing threat of pandemic influenza”. Central to this is the maintenance of laboratory capacity for the rapid analyses and distribution of influenza viruses. The provision of this capacity resides within the partners of SJCEIRS, namely St Jude, HKU, the Shantou University Medical College, Duke-National University of Singapore Medical School (Duke-NUS), Kansas State University, the National Research Center in Cairo, the University of Michigan, the University of Texas, the University of Wisconsin, and Jahangirnagar University, Bangladesh.

This laboratory capacity will be applied to understand the nature of influenza viruses in the following populations;

- wild birds in the Americas, Asia, and Africa.
- swine in the Americas, Asia, and South America.
- poultry in Africa, Asia, and South America.

Data from these surveillance activities will feed into surveillance-based research streams that will determine the evolutionary principles underpinning the emergence of novel viruses and also detail the mechanisms behind antiviral resistance generation. The viruses and data will also continue to serve the WHO and provide viruses and reagents for development of vaccine reference viruses.

While each site will initially focus on the animal side of the interface, each major site has the capacity and infrastructure to examine the nature, frequency, and risk factors associated with zoonotic transmission of influenza viruses.

Pathogenesis and Host Response Research.

Fully integrated into our surveillance base activities are three basic research programs utilizing the skills of investigators across the SJCEIRS sites. These projects are as follows;

Key sites in the active site of the influenza B neuraminidase
Identifying the immunological determinants of protective memory and clinical disease.

While murine genetic manipulation strategies allow us to dissect elements of the immune response involved in viral clearance, they at best model the key immune features that contribute to the disease burden in humans. The available data indicate that severe pathology in humans is a complex phenotype that is unlikely to reflect catastrophic gene deletions analogous to those in knockout animals. However, the published data are limited and the molecular correlates of severe disease are as yet of fairly low resolution. Indeed, the relative contribution of virus-driven morbidity and mortality versus illness resulting from a dysregulated immune response due to some other cause is not known. In this proposal, we will determine if disease burdens in diverse settings are influenced by the same immunological parameters. Our central hypothesis is that severe influenza disease can be understood as a dysregulation of the responding immune network and can be predicted based on immune profiles early in infection. The overall goal of this program is to determine the contribution of immune variation to the worldwide burden of human influenza disease.

Transmission of influenza viruses at the swine-human interface.

National and international agencies have highlighted transmission as a research priority. Transmission research has traditionally focused on virologic factors required for avian influenza viruses to acquire transmissibility in ferrets. The current paradigm based on avian influenza is that airborne transmissibility in ferrets requires a switch in receptor-binding specificity from α-2,3 to α-2,6-linked sialic acid. However, swine influenza viruses, which also pose a substantial pandemic threat, already possess α-2,6 receptor-binding specificity but many are not airborne transmissible in ferrets. Understanding what limits the transmission of swine viruses in ferrets is of particular relevance because of the extensive reassortments of pandemic H1N1 now taking place within swine globally, with evidence of zoonotic transmission. Integrated with our Surveillance activities, our proposed work will investigate how influenza virus transmission is determined by both (a) viral factors and (b) the generation and aerodynamics of virus-containing aerosols. We will also study the interspecies adaptation of avian H5N1 viruses and an avian precursor virus that has evolved into currently circulating Eurasian avian-like (EA)-lineage swine influenza viruses. Our overarching hypothesis is that "efficient human-to-human transmissibility, approximated by airborne transmission in ferrets, is conferred through specific viral and host factors that facilitate the generation, stability, and delivery of infectious airborne particles of a defined size range."

Influenza in high risk populations: impact on the virus and host.

During the 2009 influenza virus pandemic, obesity was shown epidemiologically for the first time to be a risk factor for increased influenza virus-induced morbidity and mortality. Using obese mouse models, we demonstrated that increased disease severity was associated with impaired lung wound repair and increased pulmonary edema. Further, our preliminary studies suggest that the obesigenic state impacts the evolution of the virus. The goals of these studies are to fill our gaps in knowledge and begin defining the mechanisms of acute lung injury (ALI) leading to acute respiratory distress syndrome (ARDS) in normal weight and obese animals and humans, and determine how the obese lung microenvironment can directly influence the virus itself. Finally, we’ll explore whether the evolutionary changes are unique to obesity or if they also occur during pregnancy; another population at high risk for developing severe influenza infection. These studies are responsive to the NIAID blue ribbon panel on influenza research report encouraging “increased understanding of influenza pathology and pathogenesis in humans” and to “expand understanding of influenza viruses in different human populations.” Our overall hypothesis is that obesity will affect the mechanisms of virus-induced ALI by directly impacting the host cellular responses as well as leading to specific changes within the virus itself.
Organizational Oversight for Research Areas

Scientific Advisory Board
- Stanley Perlman, University of Iowa
- Filip Claes, OIE
- Jackie Katz, CDC
- Jim Paulson, Scripps
- TBD WHO Member

Training & Mentoring Committee
- Peter Doherty
- Robert Webster

SJCEIRS Executive Committee
- R.J. Webby
- S. Schultz-Cherry
- P. McKenzie
- J. Osorio
- JSM Peiris
- Y. Guan
- M. Ali
- J. Richt
- G. Smith

Administrative Core
- P. McKenzie

Sentinel Activities
- Kansas State University
  - J. Richt
  - W. Ma
- Duke-National University of Singapore
  - G. Smith
  - V. Dhanasekaran
- National Research Center Cairo, Egypt
  - M.A. Ali
- HKU Collaborating Laboratories Southeast Asia
  - China
  - Vietnam
  - Sri Lanka
- Hong Kong University
  - J. S. M. Peiris
  - Y. Guan
- United States
  - Canada
  - Bangladesh

Pathogenesis & Host Response
- Human Immunology: P. Thomas, L. Poon, & V. Dhanasekaran
- Risk Factors for Flu: S. Schultz-Cherry, M. Peiris, M. Chan, J. Richt, & W. Ma
- Transmission: R.J. Webby, C. Russell, H. Yen, & M. Peiris
Perspectives

The past seven years of the CEIRS program has seen the Centers develop into an integrated, collaborative, and productive network. Continuing on this success, in this iteration we propose the integration of comprehensive global influenza virus surveillance with fundamental research that will provide insight into the mechanisms that foster pandemic influenza emergence at the human-animal interface. Central to our program is the training and support of young investigators who, along with the data generated through our activities, will ensure continued resources crucial to the pandemic preparedness activities of the U.S. Government.