Emory-UGA CEIRS

EMORY-UGA CENTER OF EXCELLENCE FOR INFLUENZA RESEARCH AND SURVEILLANCE

CEIRS
NIAID Centers of Excellence for Influenza Research and Surveillance

ATLANTA & ATHENS

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Our history: IPIRC

In 2007, Emory University and the University of Georgia (UGA) joined their broad expertise in infectious diseases and immunology to create the Emory/UGA Influenza Pathogenesis & Immunology Research Center (IPIRC). IPIRC was one of five Centers of Excellence for Influenza Research and Surveillance (CEIRS) designated by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). As a Center, our research projects were designed to lay the groundwork for new and improved control measures for influenza viruses and to interact cohesively with other centers to form the CEIRS collaborative network.

2014: Emory - UGA Center of Excellence for Influenza Research and Surveillance (CEIRS)

Our current structure presents strong programs in surveillance and basic influenza research projects, with expansion of the NIAID surveillance program both internationally and in the United States. The center encompasses researchers from a number of schools and centers at Emory and the University of Georgia, with access to a variety of laboratory and clinical resources. The pairing of the two institution's expertise in microbiology, immunology, vaccines, global health, emergency preparedness, and animal pathology creates a uniquely effective combination for studying animal viruses such as swine flu that can potentially infect humans. At Emory, researchers are located in the Department of Microbiology and Immunology, the Department of Biochemistry and the Division of Infectious Diseases in Emory University School of Medicine; the Emory Vaccine Center; the Winship Cancer Institute; the Departments of Global Health and Biostatistics and Bioinformatics in the Rollins School of Public Health, and the Children's Center for Immunology and Vaccines. Collaborations and expertise also reside in Emory Healthcare and its infectious diseases clinics. At the University of Georgia, researchers and resources in animal pathology are located in the Department of Infectious Diseases in the College of Veterinary Medicine. Our surveillance projects will provide the CEIRS network and relevant government agencies with the materials and information obtained through these studies to aid in the development and implementation of public health policies and preventive tools such as vaccines by providing virus isolates or viral genes for vaccine production, and other intervention strategies that are necessary for the control or prevention of influenza pandemics.

Surveillance, domestic

Multidisciplinary studies investigating the natural history of influenza in swine

Ralph Tripp, Mark Tompkins

This project will carry out surveillance in swine at the farms of the largest pork producer in the U.S., Smithfield/Murphy-Brown (S/M-B). The research program will focus on virologic, epidemiologic, and disease surveillance in swine with an emphasis on rapid identification and characterization of influenza viruses. This objective involves collection of samples through active and passive surveillance, cloning of important viral genes, and sequencing of virus isolates. In addition, we will provide characterized viruses of pandemic potential that are suitable for possible use in vaccine development, as well as accompanying data to the CEIRS network and research community. Aspects of this work will in partnership with SJCEIRS Director, Richard Webby. We will evaluate the dynamics of influenza infection at the virus-host interface and assess the host response to influenza virus infection, replication, and address innate host features in primary normal human or swine bronchoepithelial cells that restrict virus reassortment. We will measure cellular responses to infection to identify these determinants which will

provide new targets for interrupting transmission and reassortment, improving animal welfare and preventing zoonosis.

The overall objectives of this multidisciplinary approach are to investigate the natural history of influenza in swine and to provide the Federal government with information, public health tools, and strategies needed to control and lessen the impact of epidemic influenza and the increasing threat of zoonotic influenza. This will be accomplished by determining the prevalence of swine influenza virus (SIV) and reassorted influenza viruses in swine in close contact with humans, and understanding how these viruses evolve, reassort, adapt, transmit and cause disease. We will also assess the efficacy of existing and novel vaccine and anti-viral drug strategies against novel viruses. In doing so, we will determine the molecular, ecologic and host factors that influence the evolution, emergence, transmission and pathogenicity of influenza viruses allowing for the rational design and implementation of intervention strategies for agriculture and public health to block the emergence and spread of zoonotic influenza.

Surveillance, international

Animal influenza surveillance in Guangxi, China

Chinglai Yang, Hualan Chen

The focus of this project is to carry out influenza virus surveillance in farm animals including chickens, ducks and swine to test the hypothesis that the geographic conditions and farming practices in Guangxi may facilitate interspecies transmission of influenza viruses among domestic animal populations. The objectives of this study are to determine prevalence of different influenza viruses in these animal species, to determine antigenic, pathogenic, as well as transmissibility changes of these viruses over time, to investigate the frequency of influenza virus cross-species transmission, and to gain an in depth understanding of the effect of poultry influenza vaccination on virus evolution and inter- or intra-species spread. These results will enhance our knowledge of the epidemiology of animal influenza virus, and provide guidance for improving and better implementing public health and veterinary health policies for preventing or mitigating new influenza outbreaks and pandemics.

This animal influenza surveillance project will provide information on virus prevalence, subtype distribution, interspecies transmission, genotype mixing by reassortment between viruses of the same or different HA/NA subtype, viral antigenicity and pathogenicity changes, as well as potential for human infection and transmission. These studies are critical to achieve early detection of strains with pandemic potential, develop and implement new control measures, as well as facilitate vaccine and antiviral development. Through these studies, we will determine the prevalence of influenza virus infection in these animals, the frequency of genotype mixing by reassortment in different species, and the infectivity, transmissibility, as well as pathogenicity of these viruses for mammalian hosts. Analyses of results from these studies will reveal the impact of farming practices, local environmental conditions, endemic virus prevalence rates, and vaccination on inter-species transmission and evolution of influenza viruses.

Human Immunology

Human immune responses to influenza virus vaccination and infection

Rafi Ahmed, Bali Pulendran, Aneesh Mehta, Edmund Waller, Saad Omer

This study will encompass a comprehensive systems biological analysis of innate and adaptive immune responses to influenza virus vaccination and infection in humans. This will include a

comparative analysis of innate and adaptive signatures to: (i) influenza vaccination in pregnant versus non-pregnant women, and (ii) humans infected with influenza virus. We will also validate the importance of the gene expression network involving Calcium/calmodulin-dependent protein kinase IV (*CamkIV*) that we have shown to be correlated with HAI antibody titers after influenza vaccination. In later years of this aim we will do mechanistic experiments to functionally validate other signatures and networks identified in our pregnancy vaccination or infection studies. We will evaluate the longevity of humoral immunity to the influenza virus in humans. We will determine how long-term humoral immunity to influenza virus is generated and maintained. This will include: (i) tracking influenza vaccine-induced B cell responses, including broadly neutralizing HA stem reactive responses; (ii) comparative analysis of influenza-specific memory B cells, plasma cells in the blood, and plasma cells in the bone marrow; (iii) defining the antibody-intrinsic features that promote long-term persistence in the bone marrow plasma cells and memory B cells. (iv) Use proteomics-directed cloning to evaluate influenza specific clonotypes of the long-lived plasma cells.

Our project has two primary objectives: first, to understand the interplay between innate and adaptive immunity using a systems biological approach; and, second, to provide insight into the mechanisms that regulate the duration of humoral immunity to influenza virus. These studies will provide key information towards the development of a "universal influenza vaccine," a vaccine that could protect us not only from past and current influenza strains but perhaps also against any pandemic strains that may emerge in the future. In addition, the enhanced susceptibility of pregnant women to influenza with significant consequences to her developing fetus (i.e., low birth weight and prematurity) places a great premium on vaccinating this special population, and the CDC and WHO have highlighted vaccination of pregnant women as a major public health issue.

Pathogenesis and transmission

Influenza glycoprotein functions as determinants of host range, transmission, pathogenicity, and pandemic potential.

David Steinhauer, Richard Cummings, Jens Wrammert

The project involves relating how basic receptor binding and membrane fusion functions of the influenza hemagglutinin glycoprotein (HA) influence the biology of virus replication, host range, and potential for emergence in humans, as well as the mechanisms by which we might design broadly effective vaccines. Overall, the first task involves the identification of natural receptors for influenza viruses and their distribution in human tissues. The second task involves the characterization of the receptor destroying properties of the neuraminidase (NA) protein, and how this balances with HA binding activity. The third task involves defining the mechanism of action and range of specificity for the virus neutralization properties of anti-HA stem antibodies, which often display much broader specificity than HA head domain antibodies commonly induced by normal infection or standard vaccination.

The identification and characterization of natural endogenous receptors for influenza, and their distribution in human respiratory tissues, is of critical importance to the understanding of the emergence of pandemic viruses and their capacity to transmit efficiently. Similarly, the appreciation of the balance of HA binding and NA receptor destroying functions for such natural receptors will be critical to understanding drug resistance of NA inhibitors and the design of next generation anti-viral compounds. The task involving anti-HA stem antibodies will provide crucial insights on the potential to develop strategies for broadly effective or universal influenza vaccines that target more conserved regions of the HA.

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Host adaptation and reassortment

Interplay among host adaptation, reassortment and transmission of influenza viruses at the animal-human interface
John Steel, Anice Lowen

This study will evaluate reassortment of swine and human influenza viruses. More specifically, using a novel approach, we will determine how readily viruses of the North American swine TRIG lineage reassort with human 2009 pandemic strains. We will test the hypothesis that the efficiency of this reassortment is dependent on the species and type of host cell. Finally, we will characterize the infectivity and transmission of certain reassortant genotypes with particular focus on that comprising the pandemic 2009 M segment in the swine H3N2 subtype TRIG background. We will identify and characterize low fitness intermediates in the evolution of influenza viruses. Namely, we will test the hypothesis that different matrix genes derived from the Eurasian swine lineage over the period of 1979 to 2008 support differing levels of transmission efficiency and, in so doing, work to understand the mechanism by which the matrix protein impacts transmission. We will evaluate the impact of adaptation of avian influenza viruses to human cells on the potential for reassortment with human viruses and transmission among mammals. This aim will include evaluation of reassortment between novel H7N9 and human influenza viruses.

This project will elucidate the evolutionary processes that facilitate growth and transmission of animal influenza viruses in human hosts. Knowledge of the mechanisms by which influenza viruses at the animal-human interface overcome the human species barrier is critical to our ability to identify strains with zoonotic or pandemic potential and to understand the conditions under which such viruses are likely to emerge.

Pandemic response

IPIRC played a crucial role within the CEIRS network during the H1N1 pandemic in 2009, immediately redirecting focus to the H1N1 virus as part of a carefully planned overall CEIRS network response. CEIRS funding supported vital research and allowed a rapid response to the public health crisis. On June 11, 2009, the World Health Organization (WHO) declared swine-origin H1N1 the first level-six pandemic in 41 years, with the disease present in more than 70 countries. By midsummer, there were more than 37,000 cases in the United States, including 138 in Georgia. The first case at Emory University was announced on June 19, and Georgia became the state with the highest number of voluntarily reported swine flu cases in the nation. The Emory-UGA CEIRS is prepared to evaluate pandemic strains comprehensively once identified and redirect its research efforts to improving pandemic response.

Emerging Pathogens research

Our center participated in the CEIRS network response to the zoonotic H7N9 outbreak in China, including studies of the transmission and replication of the novel H7N9 virus in guinea pigs and ferrets, correlates of protection from infection following H7N9 vaccination, and host microRNA response to infection. To assess fundamental features of the virus, our scientists examined the structure of influenza virus, receptor binding and glycan binding, In addition to intertwined involvement of transmission and pathogenesis studies, the IPIRC team based at UGA developed surface enhanced Raman spectroscopic (SERS) hand held detection for H7N9, an important tool for rapid virus detection that can also be used with other influenza virus strains. Our scientists are evaluating the human type I and III IFN response in primary

normal human and swine bronchoepithelial cells infected with H7N9 and have produced purified H7 HA proteins from insect cells by using recombinant baculovirus which were used as an antigen to determine reactivity of AIV-positive samples, and also collaborated on a study of pre-existing human monoclonal antibodies that were shown to neutralize H7N9 with Mt. Sinai CEIRS. See CEIRS Network Projects.

An IPIRC researcher supported by our training program was able to initiate a cooperative research and development agreement with the Naval Medical Research Center (NMRC) to study hyperimmune humanized sera against H7N9 from transchromosomic cattle, which may provide a novel therapeutic approach for H7N9 as well as other infectious diseases.

Data Management

The data management team is critical and integral to the collection of research data generated by the center. The team has established systems to assist labs with laboratory specimen tracking and data management. The team is responsible for experimental laboratory and clinical data acquisition and storage; quality assurance; security, privacy, and confidentiality; and statistical approaches for visualization and analysis of high-dimensional flow cytometry. They are also exploring innovative methods for examining network data, important for the understanding of the role that complex biological systems and social networks play in influenza pathogenesis. They are responsible for data sharing and data release according to NIH policy.

Pilot Projects

The pilot program is designed to support innovative new directions for influenza research and obtain initial results that will be used as the basis for competitive grant applications. Two previous projects produced significant findings: a pilot project on the identification and validation of host genes required for influenza pathogenesis led to the discovery of novel influenza therapies by high-throughput RNA interference (RNAi) screens; and a pilot project on identification of social contacts in the emergency department provided valuable insights in developing a model for human influenza transmission which could help stem the spread of a pandemic virus. (Pending funding.)

Training

The Training/Career Development Program is intended to train advanced postdoctoral fellows or selected junior faculty candidates to become successful independent investigators in research on influenza viral immunology and/or pathogenesis. The training environment will offer multiple opportunities for productive research projects, exchange of ideas, multi-disciplinary collaboration, and career development. The training opportunities will focus on the central research themes of the Center: pathogenesis and immunobiology of influenza virus infection, and BSL-3 AG+ training at UGA. Training facilities will include the research laboratories of the participating investigators at Emory and UGA, including collaborating laboratories and core facilities. (Pending funding.)

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