Developments in NIAID Pandemic Influenza Research

The NIAID Pandemic Influenza Preparedness Program supports research in basic biology, surveillance and epidemiology, vaccine development and evaluation, and the development of antivirals against influenza.

Below is an overview of NIAID-supported research and global events dating back to 1997, when the word's first known cases of human infection with avian influenza viruses were documented.

YEAR	RESEARCH DEVELOPMENTS AND GLOBAL EVENTS
1997	In 1997, avian influenza (**H5N1**) infections occur in both poultry and humans in Hong Kong. This is the first time an avian influenza virus has ever been found to transmit directly from birds to humans. The virus kills six out of 18 people infected. All poultry in Hong Kong is culled. (**WHO**)
	Following the human infections with **H5N1** avian influenza, NIAID awards Protein Sciences (Meriden, CT) a contract to produce a single lot of recombinant H5N1 vaccine based on the Hong Kong virus for use in a small clinical trial enrolling laboratory personnel and public health officials deemed at high risk of infection.
	NIAID awards a grant to Baylor College of Medicine (PI, Pedro Piedra) to examine whether **vaccinating a large percentage of children** can protect a community from a possible influenza pandemic.
1998	NIAID awards a contract to Protein Sciences Corporation (PI, John Treanor) for the production of a recombinant **H5** hemagglutinin vaccine. Within three weeks, the company produces an investigational vaccine which is tested in NIAID-supported clinical trials. (**Related Article**)

Developments in NIAID Pandemic Influenza Research

1998		NIAID awards the **Influenza Pandemic Preparedness in Asia** contract to St. Jude Children's Research Hospital (**PI, Dr. Robert Webster**) to: • Establish an animal influenza surveillance center in Hong Kong • Determine the molecular basis of transmission of avian flu viruses • Provide characterized viruses suitable for vaccine development • Support training of new laboratory personnel • Produce reagents
		NIAID-supported scientists discover that human influenza A viruses employ the enzyme plasmin to help chop hemagglutinin in two. The discovery may explain what amplifies the disease-causing power of influenza A virus and makes the virus uncommonly deadly. (**Related Article**)
1999		NIAID awards a grant to the University of Wisconsin (PI, Dr. Yoshihiro Kawaoka) to investigate the molecular mechanisms of influenza pandemics. NIAID-supported researchers for the first time succeed in **engineering an influenza A virus entirely from cloned genes**, a breakthrough that could lead to improved influenza vaccines and new influenza-based gene delivery systems. (**Related Article**)
		NIAID-supported researchers at St. Jude Children's Research Hospital and the University of Wisconsin demonstrate that a new DNA-based vaccine protects mice from experimental challenge with the H5N1 virus. (**Related Article**)
		In March, **H9N2** infects two children in Hong Kong. Both children recover. (**WHO**) Meanwhile, in Italy, a two-year **H7N1** epidemic begins in the country's bird population. The H7N1 virus, originally of low pathogenicity, mutates in less than a year to a highly pathogenic form. More than 13 million birds die or are culled. (**WHO**)
2000		NIAID's **Vaccine and Treatment Evaluation Units** (VTEUs) **conduct a clinical trial** to compare the immune responses of healthy adults who receive either a full dose or a half dose of flu vaccine. (**Related Article**)
		NIAID awards the following **three challenge grants** to industry partners for vaccine development:
	 	• NIAID-supported researchers at St. Jude Children's Research Hospital and the University of Wisconsin demonstrate that a new DNA-based vaccine protects mice from experimental challenge with the **H5N1** virus. (**Related Article**)

Developments in NIAID Pandemic Influenza Research

2000		• NIAID awards a grant to Aventis Pasteur for the **DNA-based generation of avian influenza virus vaccines** (PI, Fred Vogel). The project goal is to use a DNA-based system to rapidly produce influenza vaccine candidates, including those against **H5** and/or **H7** pandemic influenza, which will be tested in clinical trials by NIAID.
		• NIAID awards a grant to Novavax (PI, Dr. Louis Potash) to produce several **non-egg-grown influenza vaccines**, with the goal being that the most promising will be prepared for use in clinical trials by NIAID.
		NIAID-supported researchers at St. Jude Children's Research Hospital streamline the use of reverse genetics down to eight plasmids - one for each gene in the virus genomes - making the process simpler and less expensive. (**Related Article**)
		NIAID-supported scientists take part in the **Options for the Control of Influenza IV Meeting**, held in Greece, September 23-28, 2000. The meeting objectives are to review the latest advances in molecular virology and pathogenesis of influenza viruses and relate them to the problems of surveillance, rapid diagnosis and improvement in strategies for the treatment and prevention of influenza.
2001		St. Jude scientists and University of Hong Kong (HKU) collaborators detect the re-emergence of **H5N1** in live bird markets in Hong Kong. More than one million birds are culled and "market rest day" is instituted. (**Related Article**). Researchers also identify quail as the mixing vessel for the spread of avian influenza viruses from aquatic birds to land-based poultry. Live quail is banned from live-bird markets the following year. (**Related Article**)
		NIAID-funded investigators at the University of Wisconsin use reverse genetics to discover that the PB2 gene is key to the virulence of the **H5N1** influenza strain. This discovery provides important information that may be useful in understanding the emergence of future viruses that may have pandemic potential. (**Related Article**)
		In July, NIAID sponsors the **Reverse Genetics Workshop** (**Executive Summary**), bringing together an international group of researchers in influenza viruses as well as scientists outside of the influenza field with research experience in other human

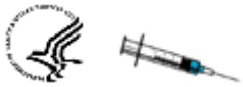
		viruses, biosafety, and public policy. The Workshop discussions are centered on using local biosafety committees to examine the research work that will be done at federally funded universities and to make risk assessments and safety recommendations.
2002		St. Jude scientists and HKU collaborators detect the second re-emergence of highly pathogenic **H5N1**. More than 20 farms are found to be infected and more than seven different **H5N1** genotypes are identified in wild aquatic birds. (**Related Article**)
		St. Jude scientists determine that the **H5N1** avian virus that killed six people in 1997 can bypass natural host defenses, which may explain the high lethality of avian strains. (**Related Article**)
		NIAID awards a grant to the American Registry of Pathology for the complete **characterization of the 1918 influenza virus** (PI, Dr. Jeffrey Taubenberger). (**Related Article**)
		Following an outbreak in May of **H7N2** among poultry in the Shenandoah Valley, Virginia, poultry production area, one person is found to have serologic evidence of infection with H7N2. (**CDC**)
2003		St. Jude scientists and HKU collaborators discover that **H9N2** viruses are endemic in land-based birds in China. (**Related Article**). It is also discovered that **gene segments of H9N2 flu viruses** found in ducks had undergone many changes, with some new combinations coding for antigens that could infect humans. (**Related Article**)
		In FY 2003, NIAID expands its **Pandemic Preparedness in Asia** contract. This expansion supports enhanced animal influenza surveillance sites in Asia, the generation of high-yielding pandemic vaccine candidates, and studies of a newly emerging influenza strain infecting swine in the United States. (**Related Article**)
		In September, NIAID convenes an international workshop on the **Development of a Clinical Trial Plan for Pandemic Influenza Vaccines** (**Meeting Summary**) to: • Review data from earlier trials of pandemic influenza vaccines • Identify manufacturing and regulatory hurdles • Prioritize pandemic influenza virus subtypes • Develop an agenda for the conduct of clinical trials • Initiate development of a U.S. Pandemic Influenza Vaccine Protocol

Developments in NIAID Pandemic Influenza Research

2003		NIAID awards a grant to Stanford University (PI, Dr. Ann Arvin) to study **vaccine-induced and naturally acquired influenza A immunity** as a model for in-depth analysis of the innate and adaptive immune response in children and adults.
		NIAID awards a grant to the University of Maryland to understand the **transmissibility of influenza A viruses** (PI, Dr. Daniel Perez). The project's objective is to study the interspecies transmission of avian influenza viruses.
		NIAID awards three grants to industry partners for influenza product development:
		• NIAID awards a grant to the Massachusetts Institute of Technology to investigate **RNA interference of influenza virus infection** (PI, Jianzhu Chen) as a new way of preventing and treating influenza infection. (**Related Article**)
		• NIAID awards a grant to Dynavax Technologies Corp. (PI, Gary Van Nest), to find a relatively stable component for use in a new kind of **more broadly protective influenza vaccine**. The vaccine candidate combines an internal flu protein that is less likely to be altered through mutation, NP, with a bioengineered molecule called an immunostimulatory DNA sequence, or ISS. (**Related Article**)
		• NIAID awards a grant to the University of Colorado at Boulder for the **development of a diagnostic microarray for influenza A** (PI, Kathy Rowlen), which may serve as a rapid diagnostic. The project's goal is to develop the "Flu Chip," that will provide information as to whether or not an individual is infected with influenza as well as provide both type and antigenic sub-type characterization of the virus.
		NIAID-supported researchers at the Vaccine and Treatment Evaluation Units at the University of Rochester and Baylor College of Medicine test an experimental vaccine to protect people against an **H9N2** bird flu. Clinical trials are completed and results are expected in early 2005.
		NIAID conducts a Phase II study to evaluate the **first trivalent baculovirus-based recombinant influenza virus vaccine**. The vaccine, produced by Protein Sciences, was evaluated in healthy elderly subjects and was shown

		to be safe and well tolerated. The vaccine may also provide a suitable cell culture system for the large-scale production of influenza virus vaccines as a viable alternative to the production of the vaccines in eggs.
2003		In February, two cases of avian influenza (**H5N1**) infection occur in a Hong Kong family that had traveled to southern China, resulting in one death. Less than two months later, a widespread outbreak of **H7N7** occurs on poultry farms in the Netherlands, killing a veterinarian. Cases of mild disease or conjunctivitis associated with **H7N7** are reported in more than 80 other individuals during this outbreak. (**WHO**) Later the same year in New York, a patient is admitted to a hospital in November with respiratory symptoms, recovers, and goes home after a few weeks. Subsequent confirmatory tests conducted in March 2004 show that the patient had been infected with an **H7N2** avian influenza virus. (**CDC**). In December, Korea reports an outbreak of avian influenza in chickens, verified to be **H5N1**, and more than one million chickens are infected. (**WHO**). That same month, a child in Hong Kong is infected with **H9N2** and recovers. (**WHO**)
2004		NIAID supports animal influenza training courses in Hong Kong and Japan.
		In 2004, NIAID awards **challenge grants** to six industry partners to develop new diagnostics, therapeutics, and vaccines against influenza virus:
		• Shire Biologics, Inc., for the **development of a tissue culture-derived influenza vaccine** (PI, Jonathan Seals).
		• Delsite Biotechnologies, Inc., for the **development of an inactivated intranasal influenza vaccine** (PI, Yawei Ni).
		• Biota Scientific Management, for the **development of a novel long-acting influenza antiviral drug (neuraminidase inhibitor)** (PI, Jane Ryan).
		• Columbia University/Griffin Analytical Technologies for the **development of new diagnostics** (PI, Walter Lipkin) to discriminate between several pathogens including influenza and SARS.
		• University of Texas at Austin/Radix BioSolutions for the **development of new diagnostics** (PI, Steven Kornguth) to discriminate between several pathogens including influenza and SARS.

Developments in NIAID Pandemic Influenza Research

2004		• BD Diagnostics (PI, Tobin Hellyer), for the development of new diagnostics to discriminate between several pathogens including influenza and SARS.
		**NIAID awards contracts to Aventis Pasteur and Chiron Corporation** to support the production of an investigational vaccine based on a strain of **H5N1** avian influenza. The vaccines will be tested for safety and immunogenicity in Phase I and Phase II clinical trials conducted by NIAID's Vaccine and Treatment Evaluation Units (VTEUs). Studies will test the vaccine in healthy adults first with subsequent studies planned in children and the elderly.
		NIAID awards a grant to Washington University for the **M2 Peptide Based Vaccines Against Influenza** project (PI, Andrew Pekosz). The project's goal is to generate an influenza vaccine with activity against a variety of virus strains using the M2 protein.
		NIAID **issues a task order** to Chiron Corporation for the production of an investigational **H9N2** vaccine. Chiron will produce up to 40,000 doses of vaccine with and without the MF59 adjuvant for clinical trials that will be conducted by NIAID, slated for 2005.
		NIAID awards a grant to Innoject, Inc. (PI, Richard Gillespie) for the development of an **auto-injector vaccine delivery system**. Not only could the device be easy to use, but it could be broadly distributed in the event of an influenza pandemic. The clinical trial of the new delivery system, led by Dr. William Barr of Virginia Commonwealth University, will be conducted during the 2005-2006 flu season.
		The Department of Health and Human Services (DHHS) issues the **National Pandemic Influenza Preparedness Plan**, designed to provide guidance to national, state, and local policy makers and health departments for public health preparation and response in the event of pandemic influenza outbreak.
		DHHS **issues a contract to Aventis Pasteur** to manufacture and store two million doses of avian influenza **H5N1** vaccine.
		DHHS **issues a contract to Sanofi Aventis Inc.,** to secure future egg supply for flu vaccines in the event of a pandemic flu outbreak or future vaccine shortages and to obtain initial investigational lots of pandemic influenza vaccines for clinical trials.

Developments in NIAID Pandemic Influenza Research

2004		NIAID awards a grant to Nexbio, Inc., to develop **novel therapeutics for pandemic and epidemic flu** (PI, Fang Fang). This novel class of fusion proteins may be capable of blocking infections by all strains of influenza viruses.
		NIAID awards a grant to the Mount Sinai School of Medicine of NYU (PI, Adolfo Garcia-Sastre) for the **molecular and biological characterization of the "Spanish Flu"** to examine the reason behind the high lethality of the 1918 influenza pandemic. (**Related Article**)
		NIAID awards a grant to the Wadsworth Center entitled **"Discovery of a Novel Promoter in Pathogenic Influenza"** (PI, David Wentworth) to further understand the molecular mechanisms of pathogenesis in avian influenza viruses.
		NIAID awards a grant to St. Jude Children's Research Hospital to study **combination chemotherapy for pandemic influenza** (PI, Robert Webster) and test the hypothesis that combination therapy with two classes of anti-influenza drugs offers clinical and strategic advantages in the event of an influenza pandemic.
		NIAID launches the **Influenza Genome Sequencing Project** that will put influenza sequence data rapidly in hands of scientists, enabling them to further study how influenza flu viruses evolve, spread, and cause disease and may ultimately lead to improved methods of detection, treatment, and prevention. This project is a collaborative effort among NIAID, NCBI/NLM, CDC, St. Jude Children's Research Hospital and others. (**Sequencing Information**)
		NIAID issues a **notice to the NIH Guide** highlighting its interest in receiving grant applications focused on influenza research.
		In January 2003, outbreaks of **H5N1** in Asia were reported by the Global Health Organization. The outbreaks continued ongoing among bird populations in a number of Asian countries and human cases are reported in Thailand and Vietnam throughout early 2004. (**WHO**). In Canada, **H7N3** infections in poultry workers in Canada are associated with an **H7N3** outbreak among poultry in February. The H7N3-associated illnesses consist of eye infections. (**CDC**). In Vietnam, a 16-year-old girl in Vietnam is infected with **H5N1** in December. The case coincides with several fresh poultry outbreaks reported in southern provinces. (**WHO**)
2005		In early 2005, NIAID expands its **Influenza Pandemic Preparedness in Asia contract** to include surveillance activities in Vietnam, Thailand and Indonesia.

Developments in NIAID Pandemic Influenza Research

	NIAID awards a challenge grant to AlphaVax Human Vaccines, Inc., (PI, Jeffrey Chulay) to support the **preclinical and clinical development of a vaccine** against pandemic influenza viruses. The vaccine will be developed using the company's new vaccine technology based on an RNA replicon vector system.
	NIAID awards a challenge grant to Corixa Corporation (PI, Witold Cieplak) for the **development of a rapid acting pandemic influenza vaccine**. Researchers at Corixa, in collaboration with Apovia, Inc., have developed a three-year development plan to identify a vaccine-adjuvant combination, conduct manufacturing, and perform clinical studies to assess the product's safety, immunogenicity and efficacy against influenza viruses.
	NIAID awards a challenge grant to Vaxin, Inc., (PI, Kent Van Kampen) to develop a new vaccine for **immunizing humans** against a virulent avian influenza virus by intranasal inoculation.
	NIAID awards a challenge grant to Vical, Inc., (PI, Lawrence Smith) to **design a vaccine** against avian influenza viruses that could be developed and manufactured quickly and safely, without handling the infectious virus.
	NIAID awards a grant to the University of Ghent (PI, Walter Fiers) to **develop a universal influenza A vaccine**. Researchers aim to base the vaccine on a more natural-like tetrameric M2-protein to enhance the efficacy and immunogenicity of the vaccine.
	NIAID awards a grant to Iomai Corporation (PI, Larry Ellingsworth) for the **development of an immune stimulant patch** to enhance biodefense vaccines and those vaccines that will be required to fight against new viral pathogens with pandemic potential, including influenza viruses. The patch is an adjuvant delivery system designed to improve the potency and efficacy of injected vaccines.
	NIAID awards a grant to Purdue University (PI, Suresh Mittal) to develop an **adenoviral vector-based pandemic influenza vaccine** to advance the molecular understanding towards the type of immunity required for long-lasting and effective protection against pandemic influenza viruses.
	NIAID awards a grant to Duke University (PI, You-Wen He) to examine whether the protein **Mindin can be used as molecular adjuvant** for bacterial and viral vaccines.
	NIAID awards a grant to Arizona State University (PI, Roy Curtiss) for the **development of a novel, rapidly modifiable, cost-effective oral vaccine delivery system**. The system will deliver DNA vaccines and protective

2005		antigents/epitopes to induce protective immunity in children and adults to prevent infection by influenza viruses.
		NIAID awards a grant to the Trudeau Institute (PI, Troy Randall) to examine the molecular **generation of effective memory CD8 T cells** to influenza. Researchers are exploring several new observations in T cell biology that could potentially have a significant impact on the ability of vaccines to generate long-lived highly-functional memory CDS cells, enhancing vaccine immunogenicity.
		NIAID awards a grant to the University of Wisconsin, Madison (PI, Christopher Olsen) to examine the **nature of human influenza virus infection** of swine cells and pigs.
		NIAID awards a grant to the University of Alabama at Birmingham (PI, Wayne Brouillette) to **identify new influenza A neuraminidase inhibitors** as antiviral drugs.
		NIAID awards a grant to Nexbio, Inc., (PI, Mang Yu) for the **preclinical and clinical development of Fludase™** , a therapeutic agent administered topically and locally to combat a variety of influenza viruses.
		NIAID awards a grant to Bowling Green State University (PI, Scott Rogers) for the **virological surveillance of influenza A in Asian lakes**.
		In March, NIAID **begins recruitment for a clinical trial** to investigate the safety of an **H5N1** avian influenza vaccine produced by sanofi-pasteur (formerly Aventis Pasteur). Clinical sites, part of the **NIAID VTEU network**, will test the vaccine's safety and ability to generate an immune response in 450 healthy adults, age 18-64. Preliminary data from a subset of the study subjects has shown that the vaccine was safe and that stronger doses of the vaccine resulted in higher immune responses.
		In July, NIAID initiates a trial to evaluate and compare the safety and immunogenicity of the **H5N1** vaccine produced by sanofi-pasteur given intramuscularly or intradermally in healthy adults. Enrollment of 100 individuals was completed by July 19th. Results are expected in March, 2006.
		In July, St. Jude researchers determine through mouse studies that the **antiviral drug oseltamivir** can suppress the **H5N1** avian influenza virus currently circulating in Asia. (**Related Article**)

Developments in NIAID Pandemic Influenza Research

2005		In August, NIAID awards a grant to support research by Hawaii Biotech, Inc., (PI, Carolyn Weeks-Levy) to **evaluate recombinant subunit proteins** of the avian influenza strain A/Hong Kong/156/97 (H5N1) as vaccine candidates for rapid production in Drosophila and Bombyx mori expression systems.
		In August, NIAID awards a grant (PI,Qing Ge) to develop **combinatorial siRNA strategies** aimed at the prevention and treatment of influenza. The program will include identification of target genes, and efficiency of target gene combinations, and appropriate delivery mechanisms.
		St. Jude researchers determine that wild waterfowl, including ducks, not only serve as reservoirs for circulating avian influenza strains, but also act to help the virus persist and evolve. Determining the key role of ducks in the viral lifecycle is important to understand how influenza is maintained in a wild reservoir, allowing new strains to spread and be introduced in a domestic setting. (**Related Article**)
		In September, HHS purchases vaccine **(developed by sanofi-pasteur) and antiviral medications (developed by GlaxoSmithKline)** that could be used in the event of a potential influenza pandemic. In October, **HHS purchases additional vaccine** through a contract with Chiron Corporation, which is to manufacture an avian influenza vaccine designed to protect against the **H5N1** influenza virus circulating in Asia.
		In October, NIAID issues a **Broad Agency Announcement** to establish the NIAID Centers of Excellence for Influenza Research and Surveillance. Through this initiative, NIAID will expand its animal influenza surveillance program, support studies to better understand the factors that influence pathogenesis, transmission, and evolution of influenza viruses, and further characterize the protective immune response to infection and vaccination.
		In October 2005, NIAID initiates a trial in healthy elderly subjects, age 65 years and older, to evaluate the safety and immunogenicity of the **H5N1** vaccine produced by sanofi-pasteur (For more information on the vaccine, see **original clinical trials in March 2005, for healthy adults**). Enrollment of 261 individuals was completed by December 7th. (For more information on this study, please see **ClinicalTrials.gov**).
2005		In October 2005, NIAID initiates a revaccination study to give booster doses of the **H5N1** vaccine to subjects who were vaccinated seven years ago with a recombinant **H5** hemaglutinin vaccine developed by Protein Sciences Corporation. (For background information, see original **1998 vaccine clinical trials**. For more information on the 2005 study, please see **ClinicalTrials.gov**).
		NIAID-supported researchers and collaborators, as part of the Influenza Genome Sequencing Project,

	demonstrate **that humans can act as a reservoir** to allow for reassortment of influenza viruses and help paint a more comprehensive picture of how influenza viruses evolve and are transmitted throughout human populations. (**Related Article**)
	By early October, NIAID-supported researchers and collaborators in the **Influenza Genome Sequencing Project** have determined the full genetic sequence of more than 500 distinct strains of human influenza virus. The information, being made available in a publicly accessible database, is expected to help scientists better understand how flu viruses evolve, spread and cause disease.
	NIAID-supported researchers characterize the avian influenza virus responsible for the 1918 pandemic and determine that the 1918 virus was not a reassortant virus (like those of the 1957 and 1968 pandemics), but more likely an entirely avian-like virus that adapted to humans. (**Related Article**)
	On November 2, HHS releases its updated **Pandemic Influenza Plan** to provide guidance on preparing the U.S. healthcare system for pandemic influenza.
	In November, NIAID-supported investigators present information at WHO on the status of H5 vaccine clinical trials.
	In November, under the **Collaborative Antiviral Study Group** contract, NIAID initiates a chart review in selected pediatric practices that used Oseltamivir in infants to gather safety data to help inform prospective use. Data have been collected and partially analyzed on 98 subjects to date. Data are expected to be collected and analyzed on 150-200 subjects by November, 2006.
	NIAID issues a **notice to the NIH Guide** highlighting its interest in receiving grant applications focused on influenza research.
	Throughout 2005, cases of **H5N1** avian influenza are confirmed in Cambodia, China, Indonesia, Thailand, and Vietnam. By December 30th, 74 of 142 confirmed cases have been fatal. (**WHO**)

Developments in NIAID Pandemic Influenza Research

2006

In January, NIAID initiates a **multicenter clinical trial** in healthy children to provide preliminary safety and immunogenicity data on sanofi's H5N1 A/Vietnam/1203/2004 inactivated influenza vaccine.

During early 2006, NIAID awards 8 grants under Project Bioshield, supporting research projects focused on the **development of rapid throughput assays** to identify novel influenza therapeutic candidates:

1) Integral Molecular, for development of a **high throughput ion channel assay** for identifying influenza therapeutics aimed at M2 activity. (PI, Benjamin Doranz)

2) University of Colorado at BC, for the **development of a high-throughput assay** for identifying influenza replicase/RNA polymerase inhibitors. (PI, Robert Kuchta)

3) University of Virginia, Charlottesville, for the development of genetically modified luciferase-encoded influenza viruses for screening antiviral compounds. (PI, Larisa Gubareva)

4) Viron Systems, Inc, for the **development of an accelerated viral inhibition assay**, for rapid easy identification of a broad spectrum of antiviral compounds. (PI, Maryna Eichelberger)

5) University of Virginia, Charlottesville, for the **development of yeast based growth assays** for anti-influenza drug discovery, and integration of these assays into a high throughput format.(PI, Daniel Engel)

6) Northwestern University, for the **development of high throughput assays** analyzing ion channel activities of influenza A and B viruses. (PI, Lawrence Pinto)

7) Southern Research Institute, for the **adaptation of established influenza inhibition assays**, to a high throughput screening format. (PI, James Noah)

8) University of Cambridge, for the **development of high throughput screening techniques** to identify inhibitors of influenza virus transcription complex assembly.(PI, Laurence Tiley)

Developments in NIAID Pandemic Influenza Research

		In February, NIAID holds an **internal summit** to review the Institute's influenza research portfolio and identify potential research gaps.
		In March, the **NIAID Influenza Genome Sequencing Project** surpasses 1000 full influenza virus genomes deposited in the publicly accessible GenBank database.
		In March, NIAID initiates **a multicenter clinical trial** in healthy adults to provide preliminary safety and immunogenicity data on Novartis's (formerly Chiron) H5N1 A/Vietnam/1203/2004 inactivated influenza vaccine formulated with or without aluminum hydroxide or MF59.
		In March, NIAID-supported investigators present information on a trial of intradermal vs. intramuscular delivery of H5N1 vaccine at the 8th International Respiratory Diseases Conference in Hawaii.
		In March, NIAID initiates a **multicenter clinical trial in healthy adults** to provide preliminary safety and immunogenicity data on sanofi's H5N1 A/Vietnam/1203/2004 inactivated influenza vaccine formulated with or without aluminum hydroxide.
		In March, NIAID initiates a **multicenter clinical trial in healthy elderly adults** to provide preliminary safety and immunogenicity data on sanofi's H5N1 A/Vietnam/1203/2004 inactivated influenza vaccine formulated with or without aluminum hydroxide.
		St. Jude researchers release data from the first large scale sequencing of avian influenza virus isolates. Preliminary analysis of the sequences reveal a potential marker of viral virulence. The new data doubles the amount of publicly available avian influenza virus sequencing information, which could lead to a better understanding of how the influenza virus evolves and which strains may be more virulent or more likely to transmit to humans. (**Related Article**)
		NIAID-supported researchers determine that the eight segments of RNA that make up the flu virus genome are organized in a distinct pattern. Although scientists have previous argued that the genes were arranged randomly, the team discovered that the segments invariably arrange into an ordered daisy-like pattern of seven rod-shaped structures spaced evenly around a central core. The finding could influence approaches to developing new drugs and vaccines to fight flu. (**Related Article**)
		Results from a clinical trial, conducted between March and July 2005 (see 2005 entry), demonstrate that high

			doses of the experimental **H5N1** avian influenza vaccine produced by sanofi pasteur can induce immune responses in healthy adults. For more information on the clinical trial results, please see the **NIAID News Release** and the **Related Article**.
			In May, **HHS awards** more than $1 billion to accelerate development and production of new technologies for influenza vaccines within the United States. The five contracts, awarded to GlaxoSmithKline, MedImmune, Novartis Vaccines & Diagnostics, DynPort Vaccine, and Solvay Pharmaceuticals, will support the advanced development of cell-based production technologies for influenza vaccines.
			In May, NIAID issues a **notice to the NIH Guide** highlighting its interest in receiving grant applications focused on influenza product development.
			In May, NIAID-supported investigators present information at the World Health Organization on the status of H5 vaccine clinical trials.
			In June, NIAID initiates a **multicenter Phase III pivotal safety and immunogenicity clinical trial** of CSL trivalent inactivated vaccine. The study is intended to support submission to U.S. Food and Drug Administration of a BLA for accelerated approval of the trivalent vaccine by CSL in early 2007.
			In July, NIAID awards a grant to Harvard University's Medical School to investigate the **structural basis of influenza amantadine-resistance**.(PI, James Chou)
			In July, NIAID, in collaboration with Hoffmann-LaRoche, Inc. (Roche), submits a pre-IND to the FDA with a protocol concept for a safety and pharmacokinetic/pharmacodynamic (PK/PD) prospective study of oseltamivir for the treatment of children under the age of two with documented influenza.
			Between October 2005 and July 2006, **NIAID's antiviral testing program** evaluated an additional 3000 compounds for *in vitro* activity against human or avian influenza viruses, and 24 compounds were tested for *in vivo* effect, with an emphasis on the preclinical evaluation of T-705, a novel influenza RNA polymerase inhibitor from the Toyama Chemical Company.
			In July, NIAID awards a grant to CSIRO Health Sciences and Nutrition in Australia, to investigate the **mechanisms of influenza neuraminidase drug resistance** observed between the various subtypes of influenza virus strains. (PI, Jennifer Mckimm-Breschkin)

Developments in NIAID Pandemic Influenza Research

In July, NIAID awards a grant to the University of Sheffield in England, to analyze the ability of **recombinant chimeric fusion proteins**, to enhance the immunogenicity of both DNA and protein based vaccines. (PI,Andrew Heath)

In July, NIAID awards a grant to Emory University to investigate the potential effectiveness of a **mixture of DNA and VLP vaccines** in eliciting protective immune responses against influenza virus infection. (PI, Chinglai Yang)

In July, NIAID awards a grant to St. Jude Childrens Research Hospital to develop **monoclonal antibodies to H5N1 influenza virus** as an effective, highly cross-reactive anti-influenza therapeutics for prevention and potentially for treatment of H5N1 infections. (PI, Richard Webby)

In September, NIAID convenes the "Influenza Blue Ribbon Panel" to evaluate the NIAID Influenza Research Program. The Panel is a follow-up to the NIAID **internal summit** held in February, 2006.

In September, NIAID-supported scientists at Baylor College of Medicine find that, when combined with an adjuvant, **low doses of an experimental vaccine** against **H9N2** avian influenza provoked a strong antibody response in human volunteers. (**NIAID News Release**)

In September, NIAID researchers determine that **experimental vaccines based on live, weakened versions** of different strains of the H5N1 avian influenza virus were well-tolerated and protected the animals from a deadly infection with naturally occurring H5N1 flu viruses. The findings demonstrate the ability to create a vaccine based on one particular strain of the H5N1 flu virus that could potentially protect against different emerging H5N1 flu strains. (**Related Article**)

In September, a clinical trial conducted at the NIAID-supported Viral Respiratory Pathogens Research Unit at Baylor College of Medicine found that **low doses of an experimental vaccine against H9N2** avian influenza, when combined with the adjuvant MF59, provoked a strong antibody response in human volunteers. (**Related Article**)

In September, NIAID-supported researchers at the University of Washington School of Medicine conducted the first comprehensive analysis of an animal's immune response to the **1918 influenza virus**. Scientists found that the 1918 virus triggered a hyperactive immune response that may contribute to the lethality of the virus. Results also suggest that it is the combination of all eight of the 1918 flu virus genes interacting synergistically that

		accounts for the exceptional virulence of this virus. (**Related Article**)
		Scientists at NIAID's Vaccine Research Center **develop a vaccine** that protects mice against the killer 1918 influenza virus and create a technique for identifying antibodies that neutralize the virus. The findings, published in October, could help contain future pandemic flu strains. (**Related Article**)
		Researchers at the Centers for Disease Control and Prevention and NIAID-supported scientists at the University of Colorado at Boulder collaborate to develop an inexpensive **"gene chip" test** that could allow scientists to quickly identify flu viruses, including avian influenza H5N1. The November findings indicate that the MChip could provide a significant advantage over available tests because it is based on a single gene segment that mutates less often than the flu genes typically used in diagnostic tests. As a result, the MChip may not need to be updated as frequently to keep up with the changing virus.
		In December, the pharmacokinetic/pharmacodynamic and safety evaluation of oseltamivir (Tamiflu) for the treatment of children under the age of two with documented influenza, opened for enrollment.
		In December, the **first human trial of a DNA vaccine** to prevent H5N1 avian influenza infection begins at NIH's Clinical Center in Bethesda, MD. The clinical trial of the vaccine, designed by scientists at NIAID's Vaccine Research Center, will enroll 45 volunteers between the ages of 18 and 60. (**More information**)
		By December 27, there have been 261 confirmed human cases of **H5N1** avian influenza since the beginning of 2003 in Azerbaijan, Cambodia, China, Djibouti, Egypt, Indonesia, Iraq, Thailand, Turkey, and Vietnam, 157 of which have been fatal. **(**WHO**)**
2007		In January, using a database established through the NIAID-supported Immune Epitope Database and Analysis Resources Program, researchers at the La Jolla Institute for Allergy and Immunology complete the **most comprehensive analysis** to date of published influenza A virus epitopes. The study should help scientists who are designing new vaccines, diagnostics and immune-based therapies against seasonal and pandemic influenza because it reveals in molecular detail exactly where the immune system focuses on the viruses. (**Related Article**)
		By January 12, there have been 265 confirmed cases of H5N1 avian influenza since the beginning of 2003, 159 of which have been fatal. **(**WHO**)**