Selected 35-Year Accomplishments

Acquired Immunodeficiency Syndrome Panels

- Major strides in the ability to clinically manage HIV-infected patients through the use of antiretroviral therapy. Many new drugs and drug regimens now are available for combination therapy. Significant advances have radically changed the approach to use of these drugs, including sensitive new technologies developed to monitor levels of HIV plasma RNA, immunologic parameters, and the development of drug resistance.

- Advances in understanding the role of mucosal immunity in vaccine development. Common mucosal immunity has been identified as being shared among nasal, oral, intestinal, and reproductive mucosal tissues in rodents, nonhuman primates, and humans. Recent studies in primate models demonstrate that simian immunodeficiency virus (SIV) enters the vaginal mucosa within 60 minutes of intravaginal exposure, infecting primarily intraepithelial dendritic cells. SIV-infected cells are found in draining lymph nodes within 18 hours. The rapidity of this spread indicates a serious challenge to development of a preventive HIV vaccine. In other studies, observation of SIV-specific immune responses induced in primates by nasal immunization suggested that an oral or nasal SIV/HIV vaccine may confer protection in the vaginal or rectal mucosa. Vaccine administration of an HIV DNA vaccine through the less invasive oral route could induce mucosal immunity.

- Progress in basic research on the development of vaccines, including the molecular epidemiology, genetic analysis, and immunologic classification of HIV. Findings demonstrate that immunologic classification does not correlate with genotypic classification and may be more relevant than genotypic classification for design of polyvalent vaccines.

- Use of human monoclonal antibodies to identify groups of HIV immunotypes for development of a polyvalent vaccine effective against all or most of the circulating strains and clades of HIV.

- Development of a simian/human immunodeficiency chimeric virus (C2/1) that is highly pathogenic in the cynomolgus monkey and extensive use of this virus to evaluate candidates for vaccine and therapeutic agents.

- Insight into the HIV epidemic in Asia through molecular epidemiology in Cambodia, Myanmar, Oceania, and Vietnam. Two env subtypes of HIV-1 strains B and E that are circulating in Southeast Asia have been identified by examination of the sequence of the glycoprotein 120 (gp120) V3 loop. A Sendai virus-based production system for subtype gp120 proteins enabled the serological survey of prevalence of HIV subtypes.

Acute Respiratory Infections Panels

- Identification and characterization of the outbreak of influenza A (H5N1; “chicken influenza” in Hong Kong, China, and assessment of the pandemic threat

- Description of the virus ecology and influenza A subtypes in domestic and migratory birds in Asia and North America

- Development and implementation of a public health policy in Japan for annual immunization of elderly adults with inactivated influenza virus vaccines

- Creation of a cooperative program for surveillance of human influenza in China by the World Health Organization influenza reference laboratories in the United States and Japan

- Identification of a new encephalopathy syndrome (other than Reye’s syndrome), which results in a high death rate in children in Japan

Cholera and Other Bacterial Enteric Infections Panels

- Purification of cholera toxin
- Recognition of the mechanism of action of cholera toxin
- The discovery that cholera toxin catalyzes the adenosine diphosphate ribosylation of the regulatory G protein of adenylate cyclase, thereby activating it
- Identification of ganglioside GM1 as the cholera toxin receptor
- Discovery of ToxR and transcriptional regulation of cholera toxin
- Discovery of the toxin co-regulated pilus (TCP) of *Vibrio cholerae* and the finding that the same mechanism regulates the expression of both TCP and cholera toxin
- Discovery that cholera toxin is encoded by a filamentous bacteriophage (CTX)
- Identification of the toxins of *Escherichia coli* that are similar to the Shiga toxin of *Shigella dysenteriae* type 1
- Development of killed oral vaccines
- Use of recombinant methods to construct vaccines containing attenuated, live bacteria

Environmental Genomics and Carcinogenesis Panels

- Generation of transgenic mouse models to compare development of normal and transgenic mice, for use in carcinogenicity assays
- Development of presentations of comparative data from in vitro assays for mutagenicity and carcinogenicity testing
- Presentation of each country's mode of preparation of cDNA (complementary DNA) chips for monitoring several thousand genes for effects of toxic chemicals in the United States and Japan
- Evaluation of comparative experimental and epidemiologic data on carcinogenicity of environmental toxicants, including chlorinated pesticides
- Collaborative studies in the genetics of cell-cycle regulation

Hepatitis Panels

- Identification, cloning, and sequencing of the entire genomes of five human hepatitis viruses and characterization of the cellular and molecular biology of these viruses
- Discovery of hepatitis B surface antigen (HBsAg) and antigens associated with hepatitis C virus (HCV), leading to the development of sensitive diagnostic tests for screening blood and blood products and thereby eliminating from the blood supply the predominant causative agents of transfusion-associated hepatitis, the hepatitis B and C viruses

- Development of first- and second-generation vaccines for hepatitis B virus (HBV), which have allowed universal immunization against hepatitis B and thereby decreased rates of hepatocellular carcinoma (HCC) related to hepatitis B in populations at risk

- Development of vaccines containing inactivated hepatitis A virus, which provide effective, active prophylaxis against the predominant causative agent of endemic infectious hepatitis

- Licensing and use of interferon α to treat chronic hepatitis B and C virus infections, and development and licensure of small-molecule antiviral agents that inhibit the replication of HBV

- Development of a first-generation vaccine for hepatitis E virus, now being evaluated in field trials in populations at risk for this endemic form of viral hepatitis

- Development and characterization of transgenic animal models of disease due to the primary causative agents of chronic viral hepatitis (HBV and HCV) and use of these models in studies that have better defined the pathogenesis of these diseases

- Identification and characterization of hepatitis G virus and TT viruses, which are potentially important, blood-borne, candidate hepatitis viruses that are transmitted by blood transfusion but have yet to be clearly associated with clinically significant liver injury

- Better understanding of the organization and function of the intrahepatic immune system, providing opportunities to intervene successfully in immunopathologic liver injury induced by infection with hepatitis virus

- Discovery that chronic infection with HBV or HCV is carcinogenic to humans, based on the following data:

    1. Investigations in the 1970s showing the slow, sequential progression from acute post-transfusion hepatitis C to chronic liver diseases and HCC

    2. Findings in the 1970s that the prevalence of HBsAg in patients with HCC was significantly higher than in healthy control subjects and those with other malignant conditions

    3. Later studies confirming this difference in prevalence of HBsAg in most of Africa, Asia, and Pacific countries

    4. A prospective study in 1980 demonstrating that chronic HBV infection precedes the development of HCC

    5. The conclusion, in 1993, by the International Agency for Research on Cancer and the World Health Organization that there is sufficient evidence in humans to confirm the carcinogenicity of chronic infection with HBV and HCV

Immunology Boards

- Major advances in understanding the molecular mechanisms of generating diversity in genes for antibodies and genes for T-cell antigen receptors, as well as the molecular mechanisms by which antibody genes switch their constant regions to maintain specificity while modifying their functions

- Identification of the fundamental principles of T-cell development in the thymus that lead to selection of an appropriate repertoire of T-cell specificities to fight infections while removing harmful self-reactive T cells

- Better understanding of immune recognition based on findings from the crystallization and structural analysis of the major histocompatibility complex (MHC) proteins at the atomic level

- Structural definition of MHC-antigen complexes and trimolecular complexes of T-cell antigen receptors combined with MHC-antigen complexes

- Elucidation of the Toll receptors that are important in innate immune responses and characterization of their functions in microbial recognition
- Identification of HIV co-receptors as members of the chemokine receptor family, thus opening new opportunities to develop therapeutic regimens

Nutrition and Metabolism Panels

- Identification, cloning and sequencing, and characterization of the human gene responsible for malabsorption of sodium glucose and galactose and accompanying perturbations that result in severe diarrhea and dehydration

- Identification, cloning and sequencing, characterization, and determination of tissue distribution of a divalent cation transporter responsible for mediation of iron absorption

- Identification and cloning of the human obesity gene (ob) and identification of its protein product (leptin)

- Demonstration that the human diabetes mutation (db) and fatty mutation (fa) are the results of mutations in the ob (leptin) receptor (obr)

- Identification of a missense mutation that is homozygous in patients with hereditary hemochromatosis related to MHC class I molecules involved in iron metabolism

Parasitic Diseases Panels

- Control of schistosomiasis and filariasis in Japan during the first 10 years of the U.S.-Japan Cooperative Medical Science Program

- Demonstration that paramyosin is a promising candidate for vaccine against *Schistosoma japonicum* and the start of vaccine trials in reservoir host animals

- Extensive study of genetic control of immune response to *S. japonicum* and of susceptibility to schistosomiasis in mice and humans

- Evidence of characteristic dimorphism and the presence of tight-linkage disequilibria in the gene for merozoite surface protein 1 (MSP-1), shown by genetic analyses of MSP-1 in *Plasmodium falciparum* (Study findings indicate that such evidence is the most reliable basis for strategies targeting the MSP-1 gene, which is one of the most promising approaches to development of vaccine against *P. falciparum*.)

- Clarification of the roles of heat-shock proteins (HSP) during host-parasite interactions in protozoan infections (HSP are new parameters of the virulence of malaria and some other hemoprotozoan infections.)

Tuberculosis and Leprosy Panels

- Development and proof of the efficacy of the rifamycins for treating tuberculosis and leprosy, by use of increasingly sophisticated clinical trial methods that may result in short-course treatment regimens for both diseases

- Complete genome sequencing of *Mycobacterium tuberculosis* and *Mycobacterium leprae*

- Elucidation of the structure and biochemistry of the mycobacterial cell wall, providing important information to enhance understanding of mechanisms of drug action and identification of potential new drug targets for treatment of tuberculosis and leprosy

- Identification of the mechanisms of action of antimycobacterial drugs and of the genetic determinants of drug resistance

- Creation of tools for molecular epidemiology of tuberculosis and their application to improved understanding of the dynamics of disease transmission

- Generation of animal models for tuberculosis and their use to screen dozens of potential vaccine candidates and to elucidate mechanisms of host immune response to *M. tuberculosis* infection

- Development of the mouse footpad method for propagating *M. leprae*

Viral Diseases Panels

- Achievement of a detailed understanding of the molecular biology of viral replication. This advance has made possible the other accomplishments of the Viral Disease Panels.

- Development of rapid means to identify the causative agents of epidemics of viral disease. Examples include rapid identification of (1) a previously unknown Hantavirus in the southwestern United States (sin nombre virus), as the causative agent of the epidemic Hantavirus pulmonary syndrome; (2) a previously unknown paramyxovirus (Nipah virus), as the causative agent of epidemic disease in Asia that was at first thought to be caused by Japanese encephalitis virus; and (3) West Nile virus, a virus previously known only from Africa and Eurasia, as the causative agent of an encephalitis epidemic in the New York City area.

- Development of vaccines against many viruses widespread in the Americas and Asia. Examples include vaccines that are either in development or in successful use against Japanese encephalitis virus, dengue virus, rotaviruses, and wildlife rabies.

- Achievement of an increased understanding of the interplay between the immune system and viral infection, leading to recovery from or exacerbation of viral disease. Examples include increasing understanding of the importance of T-cell immunity in control of (1) dengue infection, in which the more serious dengue hemorrhagic fever can develop, and (2) infection with measles virus, in which incomplete vaccination can result in the more serious atypical measles.

- Identification and characterization of numerous viruses, previously unknown, that cause human gastroenteritis. These include the human rotaviruses, astroviruses, and caliciviruses and calicivirus-like agents such as Norwalk- and Sapporo-ike viruses and Aichi virus.