

The J. David Gladstone Institutes

Robert W. Mahley, M.D., Ph.D., President

Affiliated with the University of California, San Francisco (UCSF), and located on the San Francisco General Hospital (SFGH) campus, the J. David Gladstone Institutes have become recognized worldwide for research into the causes and prevention of three critically important diseases of our time: cardiovascular disease, AIDS, and Alzheimer's disease.

The Institutes—Gladstone Institute of Cardiovascular Disease and Gladstone Institute of Virology and Immunology (Fig. 1)—are organized as a charitable trust created under the will of J. David Gladstone, a prominent southern California real estate developer. Mr. Gladstone bequeathed virtually his entire estate to establish scholarships for medical students and to fund medical research. Through inspired management, the Gladstone Trustees [Richard S. Brawerman, Albert A. Dorman, David Orgell (deceased), and Richard D. Jones] have increased the value of the bequest considerably—from ~\$8 million at the time of Mr. Gladstone's death in 1971 to ~\$147 million today—and made possible the realization of Mr. Gladstone's dream of benefiting humankind through medical research. From an initial complement of 25 employees in 1979, the Institutes have grown to a total staff of 225, including 18 faculty-level scientists, fellows, students, volunteers, and research and administrative support personnel. In 1997, the combined research budget for the Institutes was \$20.5 million.

The Gladstone Institute of Cardiovascular Disease, established in 1979 with Robert W. Mahley, M.D., Ph.D., as its Director, has focused on the causes, complications, and prevention of atherosclerosis. Since its inception, the Institute has relied on a distinguished Advisory Board whose members, including two Nobel laureates, scrutinize the direction and progress of research. The Institute occupies about 48,000 square feet of laboratory and office space and is organized

into six units: the Lipoprotein Metabolism and Biochemistry Unit, the Cell Biology Unit, the Molecular Biology Unit, the Vascular Biology Unit, Clinical Molecular Genetics Unit, and the new Molecular Neurobiology Program.

By applying a multidisciplinary approach to the study of lipid metabolism, integrating biochemistry, molecular biology, cell biology, physiology, and population genetics, the Institute has achieved an international reputation for its contributions to the field of cardiovascular research. Since 1979, more than 600 articles and book chapters from the Institute have been published, including seminal publications on two major factors involved in lipoprotein metabolism and atherogenesis, apolipoprotein (apo-) E and apo-B. Among their scientific accomplishments, Institute scientists have determined the structures of both of these proteins and their genes; localized the functional domains to specific receptor-, heparin-, and lipid-binding regions of the proteins; characterized mutations in human apo-E that cause type III hyperlipoproteinemia; and discovered and characterized a genetic lipoprotein disorder, termed familial defective apo-B100.

Gladstone researchers have been particularly successful in the production and study of transgenic mice and rabbits expressing a variety of genes important in cardiovascular disease, including those for apo-E, apo-B, acyl CoA:cholesterol acyltransferase, and α -tocopherol transfer protein. Other research focuses on the modification and study of G protein-coupled receptors, transfection of potentially therapeutic genes into vascular cells, the molecular mechanisms of cytokine receptors, and mechanisms of apo-B mRNA editing.

The Institute also engages in several significant outreach efforts. The Lipid Disorders Training Center educates physicians and other health care providers in the clinical management of plasma lipid disorders. The Gladstone Lipid Clinic is a patient-care teaching program involving UCSF medical school faculty, students, and patients. The ongoing Turkish Heart Study has produced fascinating data on a richly diverse and

Address correspondence and reprint requests to: Dr. Robert W. Mahley, The J. David Gladstone Institutes, Box 419100, San Francisco, CA 94141-9100, U.S.A. Phone: 415-826-7500; Fax: 415-285-5632; e-mail: robert_mahley@quickmail.ucsf.edu

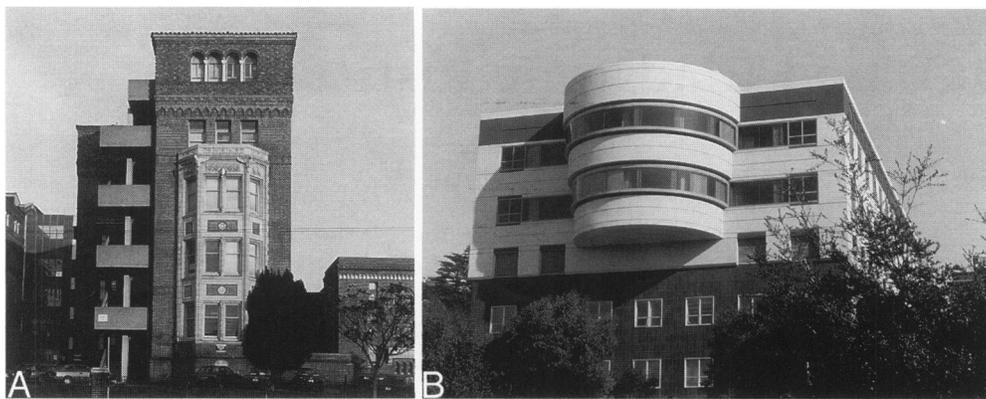


FIG. 1. (A) Gladstone Institute of Cardiovascular Disease and (B) Gladstone Institute of Virology and Immunology, San Francisco, California.

little studied population with unique lipid characteristics.

In recent years, the discovery of apo-E4 as a major risk factor for Alzheimer's disease (AD) prompted the Institute to expand its area of research into the neurosciences. The new Gladstone Molecular Neurobiology Program, which opened in 1996, pursues research into the molecular processes of AD, AIDS dementia complex, and other neurodegenerative diseases. Work has included studies of the role of apo-E isoforms in the pathogenesis of AD and the characterization of a transgenic rodent model that develops brain abnormalities similar to AD, including plaques containing β -amyloid, a hallmark of the disease. Other research concentrates on the role of inflammatory mediators (e.g., transforming growth factor β 1) and other injury-response factors in neurodegeneration.

The Gladstone Institute of Virology and Immunology opened in 1993, the culmination of a cooperative effort by the State of California, the City of San Francisco, UCSF, and the J. David Gladstone Institutes. The California state legislature proposed the development of a basic health science center dedicated to unraveling the mysteries of the AIDS virus and provided \$12 million in building funds. In partnership, the J. David Gladstone Institutes initially committed \$28 million and UCSF an additional \$4 million to the research program. At the time, this commitment constituted the largest contribution outside of the NIH to biomedical research on AIDS.

The Virology Institute, with 29,000 square feet of state-of-the-art laboratories and offices, is directed by Warner C. Greene, M.D., Ph.D., one of the country's leading molecular biologists. Its

advisory board is composed of internationally recognized scientists, including one Nobel laureate. The Institute is divided into five units: the Laboratory of Molecular Immunology, the Laboratory of Receptor and Viral Signal Transduction, the Laboratory of Viral Pathogenesis, the Laboratory of Interleukin-2 Receptor Signaling, and the Antiviral Drug Research Division.

Research at the Institute focuses on basic and clinical research into HIV and AIDS. Current research projects include a broad range of strategies in this effort. For example, experiments are in progress to utilize the recent discovery of chemokine receptors as obligatory co-receptors for viral cell entry to create small animal models of HIV infection. Other work focuses on the molecular functions of the various HIV gene products, mechanisms underlying the perinatal transmission of HIV and the pathogenesis of HIV in children and adults (particularly in the organs of blood formation), strategies to enhance immune function in HIV-infected patients (total lymph node irradiation), and the effects of chemokine and cytokine signaling events in HIV infection.

The presence of the Gladstone Institute of Virology and Immunology on the UCSF-affiliated SFGH campus contributes to a critical mass that promotes productive collaborations between AIDS researchers and the clinicians who direct patient care in the internationally recognized UCSF AIDS program at SFGH. Gladstone scientists are involved in several efforts to speed the development of new therapies from the bench to the bedside. Through an agreement with the NIH, the Institute's Antiviral Drug Research Division is using a mouse model of the human

immune system to evaluate compounds for potential use against HIV. The General Clinical Research Center, established by the NIH at SFGH, provides a means of further evaluating promising drug candidates in initial human trials.

The J. David Gladstone Institutes are major contributors to the basic and clinical research and training endeavors of UCSF and SFGH. Their presence on the SFGH campus acts as a cohesive

force, bringing together scientists from many disciplines to share in scientific discussions, seminars, and other collegial opportunities. The exciting scientific environment of the Institutes also fosters a comprehensive and well-rounded biomedical training experience for its postdoctoral fellows and graduate students. The future offers exciting challenges for the Institutes as new areas of research interest are added.