

Dedication*



On December 6, 2004, Gladstone celebrated its 25th anniversary by dedicating its new biomedical research building in Mission Bay. Capping a quarter century of scientific collaboration and discovery, the day's events proved memorable indeed.

"This striking building marks a true milestone in Gladstone's history," said Gladstone

President Robert W. Mahley. "With its enhanced technologies and with the many new opportunities that it provides for collaboration, it ensures that Gladstone will continue to contribute importantly to understanding the basic mechanisms -and ultimately the prevention -and treatment- of disorders such as cardiovascular disease, HIV/AIDS, and Alzheimer's disease."

Participating in the morning dedication ceremony were UCSF Chancellor J. Michael Bishop and former San Francisco Mayor Willie Brown. In a symbolic gesture to officially open the new laboratories Gladstone Trustees Richard D. Jones, Albert A. Dorman, and Andrew S. Garb unveiled a bust of the founder, J. David Gladstone.

A 12-minute video was debuted detailing the history of Gladstone and the development of the new building.

The standing-room-only crowd included members of the Gladstone Advisory Council and a broad spectrum of UCSF colleagues. Many more viewed the proceedings via live video feeds into adjoining conference rooms. After the program, all enjoyed a buffet held in a festive tent over the building's plaza area. With many past Gladstone employees on hand, current employees had a chance to mingle with old friends.

Although unable to attend, Dr. Joseph Martin, dean of Harvard Medical School and former UCSF sent his regards in a videotaped message, saying, "I congratulate the Trustees and for your great vision and leadership in putting into place this wonderful plan for the future of research in the areas for which the Gladstone Institutes is so well known."

The day-long celebration concluded with a dinner banquet, with a program of invited speakers including Dr. A. Eugene Washington, UCSF executive vice chancellor; Mauricio F. Cevallos, chairman of the Gladstone Advisory Council; Dr. Martin; Dr. Julius R. Krevans, UCSF chancellor emeritus; and Willie L. Brown, Jr., former mayor of San Francisco.

A highlight of the event was the inauguration of the Gladstone Trustee Awards. A surprise recipient was Dr. Mahley, honored for his contributions as founding director of the Gladstone Institute of Cardiovascular Disease and as president of the Institutes. The Trustees further honored him by declaring that the new 150-seat lecture hall would henceforth be known as the Robert W. Mahley Auditorium.

Other recipients of Trustee Awards were former UCSF Chancellors Martin and Krevans, who played crucial roles in the growth of the Gladstone Institutes, and Willie Brown. As mayor of San Francisco, Mr. Brown championed Gladstone's move to

Mission Bay, and earlier as speaker of the California State Assembly, he helped secure funding for Gladstone facilities in San Francisco General Hospital's Building 3.

"It was truly a day to remember for all of us," said Dr. Mahley. "Thanks to everyone at Gladstone who worked so hard to make this milestone in the history of the Gladstone so successful and so memorable."

Apolipoprotein E and HDL Levels

Robert W. Mahley

ApoE, a key mediator of lipid transport, has three major isoforms that differ at two positions. The functional consequences are profound. ApoE2 is associated with type III hyperlipoproteinemia, and apoE4 with increased risk of atherosclerosis and Alzheimer's disease. ApoE3 is considered the normal isoform. ApoE is the critical ligand in the clearance of atherogenic remnant lipoproteins by the liver. A key molecule in their initial capture or sequestration in the space of Disse is heparan sulfate proteoglycan (HSPG). Subsequent uptake by hepatocytes involves both low density lipoprotein (LDL) receptors and the HSPG/LDL receptor-related protein pathway.

This year, we continued to study heart disease risk factors as part of our Turkish Heart Study. Compared to western Europeans or Americans, Turks have greater (25–30%) hepatic lipase activity and lower (10–15 mg/dl) levels of high density lipoprotein cholesterol (HDL-C). This striking reduction in HDL-C occurs after puberty. The mean HDL-C levels in Turkish boys drop from ~58 to 37 mg/dl and remain at 36–37 mg/dl during adulthood. The HDL-C levels in Turkish girls decrease from ~55 to 43 mg/dl and remain at 40–43 mg/dl.

We are now looking for single nucleotide polymorphic sites in genes that may be associated with lipid abnormalities and coronary artery disease. For example, cholesterol ester transfer protein (CETP) is important in reverse cholesterol transport and HDL metabolism. More than 2000 random subjects from the Turkish Heart Study were screened for the CETP Taq IB polymorphism. The rare B2B2 genotype was associated with higher HDL-C and lower CETP activity. The B1B1 genotype was associated with 5–15% lower HDL-C than the B2B2 genotype in both sexes, with an additional 8–10% decrease in smokers.

We also assessed two sites in ABCA1, which participates in HDL-C formation. HDL-C was 8–10% higher in men (not women) with the rare -14T allele than in those with the C -14T promoter polymorphism. In combination with R219K, C -14T increased HDL-C in both sexes. The rare V771M polymorphism was associated with higher HDL-C in men and, in combination with I883M, with higher HDL-C in both sexes.

HDL-C levels in Turks may be modulated by an interaction between CETP polymorphisms and smoking and by ABCA1 polymorphisms.

Recent Publications

Bersot TP, Pépin GM, Mahley RW. (2003) Risk determination of dyslipidemia in populations characterized by low levels of high-density lipoprotein cholesterol. *Am. Heart J.* 146:1052–1060.

Hodoglugil U, Williamson DW, Huang Y, Mahley RW. An interaction between the Taq1 B polymorphism of cholesterol ester transfer protein and smoking is associated with changes in plasma high-density lipoprotein cholesterol levels in Turks. *Clin. Genet.* In press.

Mahley RW, Arslan P, Pekcan G, Pépin GM, Agaçdiken A, Karaagaoglu N, Rakicioglu N, Nursal B, Dayanikli P, Palaoglu KE, Bersot TP (2001) Plasma lipids in Turkish children: Impact of puberty, socioeconomic status, and nutrition on plasma cholesterol and HDL. *J. Lipid Res.* 42:1996–2006.

Mahley RW, Rall SC Jr. (2000) Apolipoprotein E: Far more than a lipid transport protein. *Annu. Rev. Genomics Hum. Genet.* 1: 507–537.

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