

DEPARTMENT OF  
HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE

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## GRANT APPLICATION

TYPE	PROGRAM 2 PO1	NUMBER GM20832-05
REVIEW GROUP	FORMERLY	
COUNCIL (Month, Year)	DATE RECEIVED	

TO BE COMPLETED BY PRINCIPAL INVESTIGATOR (Items 1 through 7 and 15A)

1. TITLE OF PROPOSAL (Do not exceed 53 typewriter spaces)

Genetics Research Project

## 2. PRINCIPAL INVESTIGATOR

2A. NAME (Last, First, Initial)

Cavalli-Sforza, Luigi L.

2B. TITLE OF POSITION

Professor of Genetics

2C. MAILING ADDRESS (Street, City, State, Zip Code)

Department of Genetics  
Stanford School of Medicine  
Stanford, California 94305

3. DATES OF ENTIRE PROPOSED PROJECT PERIOD (This application)

FROM 05-01-79 THROUGH 04-30-84

4. TOTAL DIRECT COSTS REQUESTED FOR PERIOD IN ITEM 3  
2,594,9475. DIRECT COSTS REQUESTED FOR FIRST 12-MONTH PERIOD  
487,687

2D. DEGREE

M.D.

2E. SOCIAL SECURITY NO.

2F. TELEPHONE AREA CODE TELEPHONE NUMBER AND EXTENSION  
415 497-5804

2G. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT (See Instructions)

Department of Genetics

2H. MAJOR SUBDIVISION (See Instructions)

School of Medicine

7. Research Involving Human Subjects (See Instructions)

A.  NO B.  YES Approved: \_\_\_\_\_ Date \_\_\_\_\_  
C.  YES - Pending Review

8. Inventions (Renewal Applicants Only - See Instructions)

A.  NO B.  YES - Not previously reported  
C.  YES - Previously reported

TO BE COMPLETED BY RESPONSIBLE ADMINISTRATIVE AUTHORITY (Items 8 through 13 and 15B)

9. APPLICANT ORGANIZATION(S) (See Instructions)

Stanford University  
Stanford, California 94305

IRS No. 94-1156365

Congressional District No. 12

11. TYPE OF ORGANIZATION (Check applicable item)

 FEDERAL  STATE  LOCAL  OTHER (Specify)  
Non-Profit University

12. NAME, TITLE, ADDRESS, AND TELEPHONE NUMBER OF OFFICIAL IN BUSINESS OFFICE WHO SHOULD ALSO BE NOTIFIED IF AN AWARD IS MADE

K.D. Creighton  
Associate Vice President - Controller  
Stanford University  
Stanford, California 94305

Telephone Number 415) 497-2251

10. NAME, TITLE, AND TELEPHONE NUMBER OF OFFICIAL(S) SIGNING FOR APPLICANT ORGANIZATION(S)

D'Ann B. Downey  
Sponsored Projects Officer  
Sponsored Projects Office

Telephone Number (s) (415) 497 2883

13. IDENTIFY ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR INSTITUTIONAL GRANT PURPOSES (See Instructions)

School of Medicine - 01

14. ENTITY NUMBER (Formerly PHS Account Number)  
IRS No. 94-1156365

15. CERTIFICATION AND ACCEPTANCE. We, the undersigned, certify that the statements herein are true and complete to the best of our knowledge and accept, as to any grant awarded, the obligation to comply with Public Health Service terms and conditions in effect at the time of the award.

SIGNATURES (Signatures required on original copy only. Use ink. "Per" signatures not acceptable)	A. SIGNATURE OF PERSON NAMED IN ITEM 2A	DATE 2/1/78
	B. SIGNATURE(S) OF PERSON(S) NAMED IN ITEM 10	DATE

## GENETICS RESEARCH PROJECT

## PROGRAM SUMMARY AND MANAGEMENT

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The program project outlined here is a request for the extension and renewal of an ongoing effort that was initiated 15 May 1974. The principal investigator up to the present date was Professor Joshua Lederberg. Dr. Lederberg has been called to the presidency of Rockefeller University, in New York City, effective July 1, 1978 -- an event that was not clearly settled and announced until a few days before the present writing. In anticipation of that possibility, the present material has been aggregated in close collaboration with Professor L. L. Cavalli-Sforza, who will also assume the responsibilities of the role of Principal Investigator, effective July 1, both for the continuation of the present term of the grant, and for the renewal, as noted by the inscription of his name on the front sheet. The appropriate forms for requesting this succession will be furnished for the continuation applications. Dr. Cavalli-Sforza is well known for his work on human genetic variation, which constitutes the central theme of this project. Dr. Lederberg will continue his longstanding interest in the substantive research which he has helped to coordinate here, but will do this in an informal way without appearing on any of the budgets.

The renewal program includes several new projects, and a substantial evolution of the ones currently under way, as indicated in the following table:

## OLD PROJECTS

1. Screening for Inborn Errors of Metabolism  
Dr. Joshua Lederberg  
Department of Genetics
2. Fetal Cells in Maternal Circulation  
Dr. Leonard A. Herzenberg  
Department of Genetics
3. Polymorphic Genetic Markers  
Dr. Howard M. Cann  
Departments of Pediatrics and Genetics
4. Polymorphisms of Specific Binding Proteins  
Dr. Luigi L. Cavalli-Sforza  
Department of Genetics
5. Impact of Genetic Counseling Practices  
Dr. Clifford Barnett  
Department of Pediatrics

## NEW PROJECTS

- Terminated
6. The Maternal Bloodstream - Another Source of Fetal Tissue for Prenatal Diagnosis of Genetic Disorders
  2. Linkage Relationships of Gene Loci In Man
  3. Genetic Polymorphisms and Disease Etiology
  - Will seek other avenue of funding
  1. Hereditary Resistance to Oral Anticoagulant Drugs  
Dr. Terrence F. Blaschke  
Department of Medicine, Division of Clinical Pharmacology
  4. Isolation and Characterization of Male-Specific Chromosomal DNA by Molecular Cloning Methods  
Dr. Stanley N. Cohen  
Department of Medicine, Division of Clinical Pharmacology and Department of Genetics
  5. Chromosome Mediated Transformation in Human Cells  
Dr. A. T. Ganesan  
Department of Genetics
  7. Interchange of fetal and maternal erythrocytes bearing genetically determined polymorphic markers  
Dr. Leonard A. Herzenberg, Department of Genetics  
Dr. Paul A. Hensleigh, Department of Gynecology and Obstetrics
  8. Genetic Heterogeneity of Hyperuricemia  
Dr. Elizabeth M. Short  
Department of Medicine
  9. Human Mitochondrial Diseases  
Dr. Douglas C. Wallace  
Department of Genetics

Although this program is centered within the Genetics Department at Stanford University Medical School, it has been developed so as to maximize its ramifications for other, especially clinical disciplines. We have spent substantial effort during the past six months in seeking out such opportunities, and in developing the scientific rationale for the proposed efforts. That very process has opened up many opportunities that were not previously evident to us, already a highly rewarding justification for the program-project style of funding. At Stanford, the Genetics Department does not have clinical responsibilities; a program of this kind is then especially important in providing the means and the resources to override departmental boundaries in the prosecution of research of the greatest human importance. The development of the utility of monoclonal antibody reagents for several projects, resulting from the work in Dr. Herzenberg's laboratory, illustrates the cross-fertilization of technical thinking at a more basic level.

The present roster of projects is manifestly more closely integrated than was its predecessor - again testimony to the intellectual interchange and experimental cooperation fostered by this kind of program support.

The underlying theme that unifies the range of specific studies outlined below is genetic variation in man. The physician views this as the source of genetic disease; the basic scientist as an expression of gene mutation and evolutionary pressures. These are roles shared within as well as among individual investigators. To these challenges are brought a combination of clinical insights, experience with several aspects of basic genetics, and new analytical technologies -- the application of instruments and reagents like the computer, the cell sorter, monoclonal antibodies, radiolabelled ligands.

Although several departments are represented in this project, we have found that an informal organization, based primarily on intellectual kinship, is quite effective. All of the participants, whatever their department, recognize Genetics as the common focus, and respect the leadership of Dr. Cavalli-Sforza as a well-known leader of research in both the demographic and physiological aspects of polymorphisms.

As Principal Investigator, Dr. Cavalli-Sforza will have executive responsibility for the program, including the formulation and budget allocations of extended and new projects, with the advice of the group of participants. He will confer periodically with the project leaders and staff, which is no more than his intellectual responsibility for the relevant themes, and seek out other avenues of cooperation and coordination within the institution. He will be responsible for the critical drafting, internal discussion, and submission of periodic progress reports to NIGMS. However, these functions are so deeply embedded in the natural professorial relationships, that we have not felt it essential to segregate a separate budget category for these responsibilities. This is in keeping with the existing decentralization of academic and administrative authority at a mature research organization.

Dr. Howard Cann, who shares a joint appointment between the Genetics and Pediatrics departments will have particular responsibility for the integrity of clinical liaisons, and for the exercise of legal and ethical responsibilities where human subjects are involved.

At this time, a committee of the medical school is engaged in the designation of a successor to Dr. Lederberg as chairman of the department of Genetics. Its recommendations will almost surely be available before the review of this proposal is completed. In the current climate of the school, the appointment will almost certainly be made from amongst the present faculty and his positive involvement in this project is therefore essentially assured.

## CLINICAL FACILITIES

The faculty of the School are organized into seven basic science and ten clinical departments. They are based mainly at the Stanford University Medical Center, a complex of ten interconnecting buildings that include the Stanford University Hospital, the University Clinics, the Lane Medical Library, the Fleischman Laboratories and Learning Center, and the teaching and research facilities of the School. The most recent additions, completed in 1976, are the expansion of the Hospital and the Sherman Fairchild Center, which provides space for several basic science departments and an auditorium.

**Stanford University Hospital:** Located within the Stanford University Medical Center complex, the 643-bed Stanford University Hospital is the major clinical facility of the School of Medicine. The Hospital includes two large pavilions for patients joined by a central core containing service facilities, diagnostic and therapeutic radiology, pediatrics, emergency medicine, operating and delivery suites, and clinical laboratories. Beds for dermatology, gynecology and obstetrics, internal medicine, neurology, pediatrics, psychiatry, and surgery are located in the patient pavilions.

**Stanford University Clinics:** Immediately adjoining the central core of the Stanford University Hospital is a building containing Stanford University Clinics, outpatient areas for internal medicine and its divisions, surgery and the surgical specialties, pediatrics, and gynecology and obstetrics. Psychiatry (including child psychiatry) is located adjacent to the Clinics building. Since Stanford serves as a center of consultation, patients are drawn not only from northern California but also from several neighboring states. The Clinics have a capacity of more than 135,000 patient visits yearly.

**Children's Hospital at Stanford:** Located on Stanford lands near the School of Medicine, the Children's Hospital has 65 beds for infants, children, and adolescents. An independent, charitable institution affiliated with the School of Medicine and Medical Center, the Children's Hospital specializes in acute and chronic care for children with major and sometimes catastrophic illness, offering both inpatient and outpatient services. The Hospital has been completely rebuilt in the last few years and now provides the finest in pediatric facilities. The program emphasizes child and family centered care, utilizing the full complement of professional disciplines for

comprehensive planning. Under an affiliation agreement, all physicians on the staff of the Children's Hospital are members of the voluntary or full-time School of Medicine faculty. Residents from the Department of Pediatrics and Surgery (Orthopedics) rotate through the Children's Hospital and participate in the care of patients. Laboratories for investigations related to selected disease states are situated at the Children's Hospital.

**Santa Clara Valley Medical Center:** Operated by the County of Santa Clara and located approximately 22 miles southeast of the campus, the Santa Clara Valley Medical Center has 378 beds, including 60 acute rehabilitation beds. The outpatient department has 120,000 visits annually. Certain affiliated residency training programs are undertaken at the Santa Clara Valley Medical Center.

**Palo Alto Veterans Administration Hospital:** Located on Stanford lands, approximately four miles southeast of the School of Medicine, the Veterans Administration Hospital has 803 beds, including 296 for general medical and surgical patients and 507 for psychiatry including geriatrics. A Dean's Committee of the Medical School supervises the educational and research activities of the Veterans Administration Hospital. Residency training, student teaching, and research are integrated with similar programs at the Stanford University Medical Center.

#### RESEARCH FACILITIES:

**Department of Genetics:** The department is located in the Clinical Research Building of the Stanford Medical Center, with modern, well-equipped laboratories and instrumentation provided for research in molecular, microbial, cell and human genetics, as well as in population studies. Included are advanced instrumentation for chemical and biophysical analysis with sophisticated computer support, in connection with advanced computer research and an interdisciplinary research program in human genetic polymorphisms.

Additional detail is discussed within each projects description.

The undersigned agrees to accept responsibility for the scientific and technical conduct of the project and for the provision of required progress reports if a grant is awarded as the result of this application.

Jan 29, 1978  
Date

Luigi L. Cavalli-Sforza  
Program Director  
Luigi L. Cavalli-Sforza