

Research Proposal submitted to the National Science Foundation
Continuation of Grant GF 41150

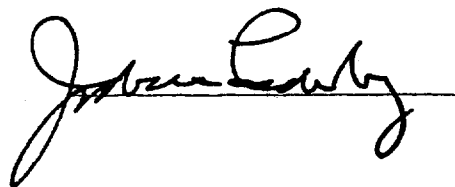
Proposed Amount : \$29,012
Proposed Effective Date: 1 March 1977
Proposed Duration : 12 months
Title : STANFORD-PAVIA SCIENCE EXCHANGE IN GENETICS
An exchange program in Genetics between Research
scientists from the Department of Genetics
University of Pavia
Pavia, Italy
and
Department of Genetics
Stanford University School of Medicine
Stanford, California 94305

Principal Investigator : Joshua Lederberg
Chairman
Department of Genetics
Stanford School of Medicine

Make Grant to : Department of Genetics
Stanford School of Medicine
Stanford, California 94305

Endorsements:	Principal Investigator	Institution Official
Name	Joshua Lederberg	
Title	Chairman	
Date	17 January 1977	

Signature



STANFORD-PAVIA SCIENCE EXCHANGE IN GENETICS

INTRODUCTION

Since 1965, a number of research projects going on at the Stanford Genetics Department have been carried out in collaboration with the Istituto di Genetica of Pavia University. This exchange activity started having the support of the NSF and of the Italian CNR about ten years ago and has been almost uninterruptedly continued on both sides. A number of Italian research workers have been active in the Stanford department over this period, and vice versa, under a variety of research interests which are represented both at Stanford and Pavia. Most of the Italian people have spent periods at Stanford varying from one month to four years. The average stay has been of the order of two years, believed to be an adequate period both from the point of view of receiving satisfactory training and of carrying to a reasonable end a good research project.

Our request for further funding, is, as earlier, directed towards offering the continuation of exchange and collaboration with the Italian University. Salaries for long term appointments will in general be requested under the specific research contracts mentioned. The grant requested of the NSF is aimed basically at supplying salaries in the U.S. for short term visits by Italian scientist who come here, for writing joint papers, learning techniques, etc.; also, for paying traveling expenses for scientists based in the U.S. who travel to Pavia for short courses, consulting on research, etc. Funds for foreign travel are difficult to obtain today from other sources while it seems entirely appropriate to request them for exchange programs such as the present one. The Italian grant, which is now active, provides funds in a strictly complementary way, i.e. pays travel to Italian based scientists coming to Stanford and salary or living expenses for visiting Stanford scientists.

A description of the ongoing U.S. grants which involve the collaboration of Italian scientists and trainees follows in Part I. In Part II, we describe a new research project on Endogenous Reservoirs of Metabolites in Human Plasma - GC/MS Studies on Substances Bound to Plasma Albumin, which is expected to be carried out collaboratively with Pavia scientists.

STANFORD-PAVIA SCIENCE EXCHANGE IN GENETICS

PART I

1. NIH GM 20467-04 Human Population Genetics

Principal Investigator: L. L. Cavalli-Sforza

6/1/76 - 7/31/81

We are engaged in improving the description and explanation of genetic variation in Man employing a combination of theoretical and experimental work. We are developing: a data bank, to be used for analyzing geographic patterns of genetic variation; new models of population structure; new types of gene frequency maps. We are also collecting historical and paleoanthropological information that is useful for interpreting the present picture of human variation. We have started experimental work of human population genetics aimed at the study of genetic polymorphisms by a technique of electrophoresis and after radioactive ligands have been added to blood. The introduction of this procedure has led to the detection of several new polymorphisms which require further investigation.

Italian trainees:

In the past: Rosalba Matessi, Laura Sgaramella-Zonta, Alberto Piazza.

At present: Paolo Menozzi

2. Center Research Grant

NIH 1 P01 GM 20832-02 Polymorphisms of Specific Binding Proteins

Principal Investigator: L. L. Cavalli-Sforza

5/1/76 - 4/30/77

In this research we are looking for new genetic polymorphisms by adding radioactive ligands to blood or other biological fluids, then carrying electrophoresis by autoradiography for detecting proteins which specifically bind these ligands. We have thus detected three new polymorphisms: one for vitamin B₁₂, one for thyroxine and a third putative one for testosterone. While these new polymorphisms are being further analyzed by testing segregations, linkage and ethnic variation with NIH grant 20467, in the present contract we propose the research of new polymorphisms with new ligands and variation of this binding.

Italian trainees: the technique here used was developed in an earlier NIH grant by trainee P.F. Pignatti, and at present is used also by Dr. G. Romeo, a distinguished Italian Medical Geneticist (whose salary is presently paid in part on this grant).

3. NIH GM 10452-13 Stochastic Models in Medicine and Biology

Principal Investigator: Samuel Karlin
Co-Principal Investigator: L. Cavalli-Sforza

8/1/75 - 7/31/78

Major interest remains with the analysis of a variety of population genetic models and some related data analysis especially the interpretation of observed data in human and other populations. The emphasis is both on a more penetrating and complete solution of some of the important classical models and on making progress on the more complex models (employing a combination of mathematical and computing methodology) with the objective to interpret observed data and gain insight into general population genetic structure and mechanisms.

The complexity of the models often precludes any complete analytical treatment and requires the development of appropriate approximation procedures and, in some cases, systematic numerical surveys of the models using computer techniques and simulation. It is expected that many of the models will be tested on actual field data.

The interplay between theoretical analysis and an awareness of the biological problems has been a key factor in our program. The collaborative efforts between the Genetics Department (Prof. L. Cavalli-Sforza since 1971), the Biology Department (Prof. M. Feldman), and the Mathematics Department (Professors S. Karlin and J. McGregor) has provided an ideal set up in achieving several of the research objectives of the grant. It will be our special aim to maintain and strengthen the unique collaboration we have developed between the Departments of Mathematics, Genetics and Biology. Prof. W. Bodmer of Oxford who is closely associated with our group will continue as a regular consultant.

Our interdisciplinary collaboration encourages the study of problems as they arise in continuing research activities.

This grant has paid part of salary of Italian trainee Carlo Matessi.

At present it supports Alberto Piazza.

4. ERDA AT(04)326 PA #33 Mutational Rates and Mutational Loads in Man

Principal Investigator: L. Cavalli-Sforza

10/1/75 - 9/30/76

Objective: Analysis of mutation drift and selection in human evolution.

A study of overall fitness and analysis of its components due to survival and fertility in a human population has been made possible by record linking of parish books. The correlation between relatives for survival is small, but significant. That for fertility is under study.

Social phenomena can largely affect biological evolution. Examples are being considered and analyzed. The evolution of social structures may have deeply affected, for instance, the relative role of drift. Demographic trends may have had deep effects on gene frequencies. Thus, there are important

interactions between cultural and biological evolution and analyses of populations of which the historical and prehistorical record is known or can be investigated which may be especially instructive for understanding the spread of mutations, also deleterious ones.

At present this pays for part of salary of Giovanni Romeo.

5. NSF BNS76-15095 Neolithic Economies and Settlement in Calabria (Italy)
National Science Foundation

Principal Investigator: L. Cavalli-Sforza

Co-Principal Investigator: A. Ammerman

6/1/76 - 12/31/77

The project will investigate the subsistence economies and settlement patterns of early food-producing (Neolithic) communities in Calabria, a region of southern Italy where recent survey work has led to the identification of dense Neolithic site distributions. The study will involve archaeological excavations (directed by A. Ammerman) at two early Neolithic settlements and will include both studies concerned with obsidian procurement and exchange systems and specialist studies of faunal remains, seeds, charcoal fragments, pollen and soils. Attention will be paid to the examination of settlement patterns on several different levels of organization and also the question of the role of growth in the development of settlement systems. Emphasis will be placed on trying to study the interactions that occur between local ecology, subsistence, settlement and exchange systems.

Italian trainees: this research grant involves part time work in Italy. It is the only one that carries foreign travel and only for one round trip for Dr. A. Ammerman. Dr. Paolo Menozzi presently in Stanford has worked on this research and will again have a part in it in the future on his return to Italy.

STANFORD-PAVIA SCIENCE EXCHANGE IN GENETICS

PART II

ENDOGENOUS RESERVOIRES OF METABOLITES IN HUMAN PLASMA. GC/MS STUDIES ON SUBSTANCES BOUND TO PLASMA ALBUMIN.

Albumin accounts for approximately one half of the total plasma protein. Due to its high affinity for ions, especially anions, and its capacity to bind also nonionic substances, albumin serves an important function as a transport and a storage protein. Many data are available dealing with specific metabolites or groups of them that may be isolated bound to plasma protein, both under normal and pathological conditions. Furthermore, studies have been performed on the capacity of isolated plasma protein to bind specific metabolites, dyes, drugs and other chemicals as well as on the binding interactions between different compounds. However, to our knowledge no systematic study has been conducted to ascertain both qualitatively and quantitatively and under carefully defined experimental conditions the pattern distribution of a large spectrum of the metabolites that are characteristically bound to albumin. The aim of the proposed research is to establish the qualitative and quantitative composition of different groups of physiologically significant metabolites non-covalently bound to plasma albumin. Once a normal pattern has been established, it will be possible to ascertain the existence of deviations from such a normal pattern. Such a study may provide a convenient analytical tool to evaluate such phenomena as:

1. variation in the pattern of bound metabolites at different stages of development;
2. variation in the primary protein pattern or in the metabolites spectrum as evidenced by variations in the composition of bound metabolites in relation to (a) genetic diseases and (b) environmental factors;
3. interactive effects between normal metabolites and drugs and other environmental influences;
4. identification in vitro of possible defects in the storage and/or transport of important metabolites, hormones, drugs, etc.

The proposed research relies on the utilization of gas chromatography to mass spectrometry as a system for the rapid separation, identification and quantitation of a large number of different metabolites. At the moment the analyses will be performed on the following groups of compounds for which the relevant prior extractions and techniques have been already developed:

- 1.. acidic compounds (including fatty acids, phenols, etc.);
2. neutral compounds (including carbohydrates, alcohols, etc.);

3. amino acids and amines.

Concurrent studies will be conducted to ascertain the optimal conditions for the separation of serum albumin under conditions that minimize the loss of bound metabolites while ensuring the elimination of unbound metabolites (immuno-precipitation, gel filtration, density gradient centrifugation). In addition, experiments will be performed to establish the experimental conditions for the isolation of the bound metabolites (acid or solvent precipitation of the protein, ion-exchange chromatography, dialysis under denaturing conditions). In the first year the above reported experiments will be performed on commercial preparations of pooled human plasma albumin and from individual specimens of normal plasma.

STANFORD-PAVIA SCIENCE EXCHANGE IN GENETICS

PROPOSED BUDGET

1 March 1977 to 28 February 1978

PERSONNEL

J. Lederberg	Chairman	-----
L.L. Cavalli-Sforza	Professor	-----
O. Ciferri	2 months as Visiting Professor	\$ 5,800.00
A. Piazza	2 months as Visiting Professor	\$ 5,800.00
Staff Benefits	9/1/76 - 8/31/77 @19%	
	9/1/77 - 8/31/78 @20%	<u>\$ 2,262.00</u>
Total Personnel		\$13,862.00

TRAVEL

Stanford scientists to Italy	4 trips @ \$1,000 each	\$ 4,000.00
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COMMUNICATIONS

Postage, telegrams telephones		<u>\$ 500.00</u>
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TOTAL DIRECT COSTS		\$18,362.00
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INDIRECT COSTS	@ 58%	<u>\$10,650.00</u>
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TOTAL BUDGET REQUESTED		\$29,012.00
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