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AMERICAN CANCER SOCIETY

CALIFORNIA DIVISION

APPLICATION FOR SPECIAL GRANT*

Date March 1, 1955

American Cancer Society, California Division
3333 Parrell Street
Berkeley, California 94702

Application is hereby made for a special grant in the amount of \$6,850.00

Period from July 1, 1955 to June 30, 1956 inclusive (not to exceed one year)
(Grant period ends 30 June)

The purpose of conducting the following project:
(Chief Descriptive Title)

Chemical Studies on Human Plasma Proteins in Malignant Disease

Name and Title of Person Conducting Project Samuel H. Bassett, M.D., Ch. Research Serv. Vet. Admin. Center, Los Angeles; Clin. Prof. of Med., UCLA Medical Center, L.A., Responsible Investigator (Cont'd Page 1a)	Mailing Address of Person Conducting Project Samuel H. Bassett, M.D. Clinical Professor of Medicine Univ. of California Medical Center School of Medicine Department of Medicine Los Angeles 24, California
Signature of Person Conducting Project /s/ Samuel H. Bassett, M.D. Samuel H. Bassett, M.D.	
Name of Institution and Department University of California Medical Center School of Medicine Department of Medicine	Mailing Address of Institution 405 Hilgard Avenue Los Angeles 24, California
Signature of Department Head /s/ John S. Lawrence, M.D. John S. Lawrence, M.D.	
Name and Title of Official Authorized to Sign for Institution Robert G. Sproul, President Signature of Official /s/ Robert G. Sproul Robert G. Sproul, President	Mailing Address of Official Robert G. Sproul, President University of California Berkeley, California
Indicate to Whom Check Should be Made Payable Paul C. Hannum, Business Manager The Regents of the University of California	Mailing Address to Which Check Should be Sent Paul C. Hannum, Business Manager University of California Administration Building 405 Hilgard Avenue Los Angeles 24, California

* Please read carefully "Policies and Procedures" governing special grants and instructions on each page of this form before completing this application.

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Name and Title of Person Conducting Project (continued)

A. Dubbs, Ph.D., Chief Biochemist, Research Service, Admin. Center, Los Angeles, Principal Investigator

William S. Adams, M.D., Assoc. Prof. of medicine, UCLA Medical Center, Los Angeles; Attending Physician, Metabolic Section, Admin. Center, Los Angeles, Associate Investigator

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The specific aim, the plan of attack and significance of work in sufficient detail for the Committee and Board of Directors to be able to judge the adequacy of methods and of facilities and the probable scientific value. This outline must be in sufficient detail for other scientists to determine the feasibility of the program to attain its objectives. A complete outline must be submitted, even though the application is for renewal of a project previously approved. Remember that in your application you are selling your project to your fellow scientists on a committee. (Use continuation sheets of plain white paper, if necessary.)

It is proposed to study several chemical properties of human plasma proteins in multiple myeloma disease, particularly multiple myeloma in which unusually high concentrations of these proteins may occur.

Previous investigators have conclusively demonstrated the great heterogeneity among myeloma proteins isolated from the plasma of one or many patients. Relatively little information, however, is available on similarities. For example, chemical properties that different myeloma proteins may share in common, yet properties which may set them apart as a group from any protein found in significant amounts in normal plasma require investigation. It would be these common properties which would truly reflect disease processes that are typical of all myeloma patients. It is hoped to find such similarities by emphasizing the following specific features in this work:

- (a) Isolation of relatively pure, undenatured protein subfractions by use of new and more effective techniques, not previously applied to this problem.
- (b) Preliminary physicochemical characterization of the subfractions, followed by determination of amino acid compositions (fundamental information that, with techniques available today, should be obtained early in the study of any newly isolated protein material).
- (c) A special study of ion-binding properties which, because of selective affinities between certain ions and complementary structural groups within the protein molecule, should provide a tool of great value in detecting biologically significant identities among different proteins. Special attention will be given to calcium binding, which others have indicated, is increased for myeloma proteins.
- (d) Selected parallel fractionations and studies on normal plasma where needed to evaluate the identity or non-identity of corresponding normal and myeloma subfractions.

Plan of Attack

It is proposed to isolate relatively pure and undenatured protein subfractions. Satisfactory and conclusive information cannot be obtained merely by determining the average properties of gross fractions in which significant subfractions may often remain masked by bulk protein. This objection applies to several previous studies, for which the newer and superior techniques were not available or were not used.

Multiple myeloma and other plasma characterized by profound protein abnormalities are amply available to the investigators. The plasma (or serum) will be fractionated by the ~~isoelectric focusing~~ electrophoresis-convection procedure (1). Early runs can provide perhaps four gross fractions (albumin, alpha, beta,

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and gamma globulins) for preliminary study, followed by more thorough subfractionation as later indicated. Others (1) have demonstrated that at least eight distinct subfractions of bovine gamma globulins can be prepared by electrophoresis-convection, and have also given evidence that production of artifacts is minimized in the process.

Fortunately, the design of the electrophoresis-convection apparatus is such that two different plasmas, contained in separate cellophane channels, can be placed in intimate contact with each other in the same apparatus and be fractionated simultaneously under essentially identical conditions. This feature facilitates the preparation of electrophoretically-analogous subfractions from normal and myeloma plasma, and should prove advantageous in establishing the identity, similarity, or non-identity of these subfractions.

Selected subfractions will receive preliminary physicochemical characterization by standard electrophoretic procedures (for electrophoretic homogeneity, mobility and isoelectric point). Other workers, especially Putnam and associates (2,3) and Rundles and associates (4), have obtained extensive data of this type on myeloma plasma and urinary proteins. The purpose of the present study, however, is to obtain just enough such data for proper orientation of these subfractions (with a secondary possibility of correlating some of these data with later chemical data).

Amino acid compositions will be determined by chromatography (qualitative analysis by small-scale paper chromatography; quantitative analysis by the Moore and Stein elution ion-exchange column (5)).

Special attention will be focused on ion-binding properties in order possibly to detect and single out significant protein components or groups within the protein that are entirely missed by the previous work above.

Paper electrophoresis provides a rapid screening method for this purpose (6). Thus a given inorganic or organic ion may be added to a protein fraction, to the original plasma, possibly after partial ion depletion with ion-exchange resin treatment. After electrophoresis on paper, the location of the ion in a particular protein fraction or subfraction may be determined by an appropriate color reagent.

For more quantitative work, measuring bond strengths and binding capacities (especially for calcium), equilibrium dialysis (7,8) will be used and/or potentiometric measurements with ion-exchange membrane electrodes (9).

It would also be interesting to develop an ion-exchange resin equilibrium method (after Schubert (10)) for measuring the protein-bound calcium of whole plasma. A good clinical method for this purpose would be useful in studying the bone decalcification process that occurs in myeloma.

Significance

A question of current interest is whether or not myeloma proteins are abnormal products. If this should be true, unique metabolic processes, possibly localized in "malignant" plasma cells (11), must occur in myeloma. Conversely, if myeloma proteins are only normal proteins produced in excess, the basic processes of protein synthesis must be normal, except certain of these processes are abnormally accelerated.

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The procedure outlined herein offers a new approach to this problem. A myeloma subfraction and appropriate normal subfractions will be compared, not only for simple electrochemical properties and amino acid composition, but for selective ion-binding properties: (a) two subfractions may show markedly different affinities for one or more ions tested. (Consider the unique affinity of beta₂-microglobulin, specifically transferrin, for ferric ion). (b) If qualitatively similar, the two fractions may show quantitative differences (9). The difference may be traced to either or both (a) bond strength (type of bond) or (b) binding capacity (number of binding sites per molecule); and if no significant difference is apparent at one pH, it may appear at another pH. If one cannot find quantitative differences after testing the proteins with several ions under varying pH conditions, the evidence for chemical identity of the proteins becomes quite convincing.

Whether or not a given myeloma protein can be identified with a normal protein, its increased concentration can be expected to imbue myeloma plasma with certain chemical properties distinct from those of normal plasma. When each such property is detected, it may also be sought in other myeloma proteins from the same plasma, or from other plasmas. In this way the extent to which the property is a general characteristic of all myeloma proteins would be evaluated.

It is probable that such ion-binding similarities between different myeloma proteins would reside in relatively few though biologically potent, groups within the large molecules. Such groups would never be found by physico-chemical methods that evaluate size, shape, charge density, etc., of whole molecules. Nor is it likely that immunological methods would detect these groups, whose contributions to the total immunological properties of an antibody would be insignificant against the contributions of far more extensive, but biologically non-specific, portions of the molecules (Reference may be made to Porter (12) who, in his review of the relationships of chemical structure to biological activity of proteins, has recommended the study of small molecule-protein interactions as a most profitable approach to this general problem).

Another question concerns the possible secondary effect of excess myeloma proteins in the blood. If they bind essential metabolites, they may well function as "poisons". The increased binding of calcium may be an example, but perhaps there are many more such metabolites, presently unsuspected. From the standpoint of therapy, it is conceivable that the myeloma patient would be able to tolerate a defective protein synthesis much better if any deleterious effects of the proteins produced were recognized and counteracted. The proposed work may give valuable information on this question.

Additional potential advantages of the proposed work can be summarized:

(a) Many workers (8) are presently studying the chemical structures that are responsible for the binding of given ions by large molecules. As their body of information is extended and confirmed valuable inferences as to the groups in any unknown protein molecule may be provided by a simple knowledge of ion-binding properties.

(b) Ion-binding measurements should assist in evaluating the homogeneity of a protein fraction. If a given fraction is further separated into two

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apparent subfractions (as by cutting an electrophoretic zone into halves), both of which still show the same quantitative ion-binding properties, homogeneity is evidenced.

These same measurements can be used as a quantitative check on denaturation. If, after any suspected treatment, the binding of a given ion has decreased by a certain amount, denaturation has proceeded by the same amount, insofar as the groups responsible for binding the given ion are concerned.

Estimate time required for this project. The full work outlined herein could obviously extend over an indefinite period. The opportunity provided by this grant should permit the investigators to obtain significant experimental results, enough to invite continuing support from any of several sources.

(The California Division does not commit itself to support beyond one year)

Has any work been done previously on this project by the person conducting it (person named on Page 1)? Yes x No _____.

If yes, give below the significant results and publications to date. If possible, enclose ten (10) copies of pertinent reprints and if this is a continuing project, include ten (10) copies of the progress report.

During the past several years, numerous routine electrophoretic patterns on the plasma and urine of multiple myeloma and other patients have been obtained by the investigators. More pertinent is current preliminary electrophoresis-convection work (using a loaned apparatus); for example, marked purification of an "abnormal" gamma globulin fraction from the other components of a myeloma plasma has been achieved by a single 22 hour run at 4° C (Fig. 1) (15 hours were probably sufficient.) The Moore and Stein elution chromatography has also been emphasized; however, the economy fraction collector used has not satisfactorily met the performance specifications of Moore and Stein for quantitative work.

4. What pertinent results bearing on this project have been obtained by other investigators? The answer should be complete enough to reveal the investigator's knowledge of the literature. Do not expect the Committee members to take time to look up the literature but list the important publications of other investigators.

Bence-Jones protein, commonly occurring in the urine of myeloma patients, was first detected over 100 years ago by its unique thermal behavior; precipitating at 45° to 55°, dissolving at 100°, and reprecipitating upon cooling. Of low molecular weight, 24,000 to 90,000 (4), it can be readily filtered through the kidney. While primarily accumulating in the urine, its presence in plasma has been assumed. Although proposed as a degradation product of the higher molecular weight non-filterable proteins, Putnam discounts this view on the basis of isotope experiments (13), demonstrating a much more rapid turnover of Bence-Jones urinary protein than for myeloma plasma protein. However, this evidence does not preclude a labile complex in the serum between more long-lived protein and Bence-Jones protein that may be readily split off and replaced by other freshly-synthesized Bence-Jones Protein. The presence of such complexes has been postulated by others to explain certain observations (14,15).

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Bence-Jones protein is not a single protein individual. A given ^{patient} ~~protein~~ may
 form several varieties, while different patients will each form additional
 varieties. This wide diversity has been demonstrated in many properties;
 physicochemical: sedimentation constant, electrophoretic mobility, isoelectric
 point, molecular weight; immunological; and chemical, especially variation in
 terminal groups.

While the overall picture is one of great diversity, similarities have been
 found among all Bence-Jones proteins studied. Most notable is the absence or
 very low content of methionine, and an elevated serine and threonine content.
 Many workers have confirmed this information, but the most comprehensive work
 is by Dent and Rose (16) who also suggest, because of these chemical similar-
 ities to known virus proteins, that Bence-Jones is the protein-portion of a
 virus causing multiple myeloma.

The previous work on myeloma plasma proteins will be summarized according to
 the experimental approach:

Physicochemical Methods: After the initial demonstration by Longworth,
 Shedlovsky and MacInnes (17) that myeloma plasmas can give very bizarre electro-
 phoretic patterns, many other workers have pursued this approach, the most
 comprehensive collection of patterns being that of Adams, Alling, and Lawrence
 (15). These patterns reveal a variety of myeloma proteins, migrating anywhere
 in the beta to gamma region. This physical diversity among these proteins
 has been further shown by every physical property studied: mobility, isoelec-
 tric point and mobility-pH curves by electrophoresis; sedimentation constants
 by ultracentrifugation, and diffusion constants. Molecular weights vary
 between 120,000 to 200,000 (4). In general, however, the myeloma plasma pro-
 tein of any one patient appears more nearly homogenous than normal gamma
 globulin, suggesting the presence of fewer major constituents therein. This is
 one basis for the proposal of many that a given myeloma protein is really a
 normal protein produced in unusual excess by the patient.

Immunological Methods: The most thorough work, just published by Slater, Ward
 and Kunkel (18), has shown that every one of the ten myeloma plasma proteins
 studied was immunologically different. Of particular interest to the present
 proposed work is their finding that all gamma-type myeloma proteins were
 related to each other, all beta-type myeloma proteins were similarly related,
 and some gamma-types were related to some beta-types. (These relationships or
 similarities presumably confirm the existence of certain common groups within
 these molecules; such groups are what one would attempt to find by ion-binding.)
 These workers felt that myeloma proteins are most likely abnormal.

End Group Determinations: Putnam (19), using Sanger's methods, has recently
 found that, whereas aspartic acid and glutamic acid are the major N-terminal
 groups of normal human gamma globulin, aspartic acid alone or neither acid is
 an end group in myeloma gamma globulin (5 specimens). If confirmed, the absence
 of glutamic acid end groups could be an abnormal property characteristic of
 myeloma proteins. (McFadden and Smith (20), however, found both aspartic and
 glutamic acid end groups in a single cryoglobulin from myeloma).

Amino Acid Determination: The only publication on amino acid analysis of
 myeloma plasma proteins is by Grisolia and Cohen (21) who, using salt frac-
 tionated proteins from eight patients and microbiological assays, find

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variations in composition for 16 amino acids. They find an overall similarity to normal gamma globulin. No striking features, as in the case of Bence-Jones proteins, were found.

Ion-Binding Work: The only ion-binding study is that of Rawson and Sunderman (22) who found for six myeloma proteins a variable, but usually greater, calcium-binding capacity (mg. Ca per gm. protein) than for normal proteins. They state that the results obtained in this study are based upon the assumption that globulin does not lose its bound calcium as a result of precipitation (by methanol) of the protein. To our knowledge, no evidence bearing upon this assumption is available. This work needs confirmation and extension by more reliable methods available today.

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5. Provide a brief biographical sketch for all professional personnel selected who are to be actively engaged in this project.

Samuel Hopkins Bassett

Born Coleman Station, N.Y. - December 7, 1897 - U.S. Citizen
Married 1927 to Louise K. Weber - 2 children

Education:

Cornell University, Ithaca, N.Y. - Premed. A.B. June 1920
Cornell University, Med. College, N.Y. - M.D. June 1924

Employment:

1926-21 Cornell University Medical College, Ithaca - Assistant in Anatomy
1924-25 Reconstruction Hospital, New York, N.Y. - Interne
1925-26 New York Hospital, New York, N.Y. - Jr. Asst. Physician
Ambulance Surgeon; Sr. Asst. Physician; House Physician
1927 Lane Hospital, San Francisco, Cal. - Asst. Res. Physician
1927-28 Strong Memorial Hospital, Rochester, N.Y. - Resident Physician
and Instructor in Medicine
1928-30 University of Rochester, School of Medicine and Dentistry,
Rochester, N.Y. - Instructor in Medicine
1930-41 University of Rochester, School of Medicine and Dentistry,
Rochester, N.Y. - Assistant Professor of Medicine
1941-48 University of Rochester, School of Medicine and Dentistry,
Rochester, N.Y. - Associate Professor of Medicine
1945-48 University of Rochester, Atomic Energy Project - Head of Section
on Human Metabolism
1948 Veterans Administration Center, Los Angeles 25, California
Chief, Research Service
1948 School of Medicine, University of California at Los Angeles -
Clinical Professor of Medicine

Membership in Scholarly Societies:

American Medical Association
Medical Society of State of New York
Rochester Academy of Medicine
American Society for Clinical Investigation
New York Academy of Sciences
Certified American Board of Internal Medicine
Rochester Chapter of Sigma Xi
Alpha Omega Alpha
Society for Experimental Biology and Medicine,
Southern California Section
Western Society for Clinical Research
Member of the Josiah Macy Jr. Foundation Conference Group on
Metabolic Interrelations, 1948 to 1953.
American Society for the Advancement of Science

(continued on Page 4a)

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Clyde A. Dubbs

Born:

Educational:

B.S. Chemistry, California Inst. of Technology, 1943
Ph.D. Bio-Organic Chemistry, Plant Physiology, California Institute of Technology, 1946

Positions:

1946 Research Assistant in Biology (Biochemistry) California Institute of Technology
1947-48 Research Assoc. in Bacteriology & Parasitology (Biochemistry), University of Southern California, Medical School.
1948- Biochemist, Research Service, V.A. Center

Societies:

American Chemical Society
American Association for the Advancement of Science
American Association of Clinical Chemists
Botanical Society of America
"Certified Clinical Chemist" American Board of Clinical Chemists (1952)

William Sprague Adams

Born - - U.S. Citizen
Married to - 3 children

Education:

Cornell University, Ithaca, N.Y. - A.B. Chemistry, 1939
University of Rochester, School of Medicine - M.D., 1943

Employment:

1941-42 University of Rochester, School of Medicine and Dentistry, Rochester, N.Y. - Student Fellow in Medicine
1944 University of Rochester, School of Medicine and Dentistry, and Strong Memorial Hospital, Rochester, N.Y. - Interne in Medicine
1944-45 University of Rochester, School of Medicine and Dentistry, Rochester, N.Y. - Assistant Resident in Medicine.
1945-46 Active Duty with the Medical Corps of the United States Navy, Dublin, Georgia.
1946-47 University of Rochester, School of Medicine and Dentistry, Rochester, N.Y. - Research Fellow in Medicine
1947-48 University of Rochester, School of Medicine and Dentistry, Rochester, N.Y. - Instructor in Medicine
1950- Wadsworth General Hospital, Veterans Administration, Los Angeles, Calif. - Attending Physician Internal Medicine
1949- Harbor General Hospital, Torrance, Calif. - Senior Attending Physician
1948-49 University of California at Los Angeles, School of Medicine, Los Angeles, Calif. - Assistant Clinical Professor of Medicine
1948-50 Veterans Administration Center Hospital, Los Angeles, Calif. - Physician Full-Grade. (continued on Page 4b)

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(Continuation sheets may be used, if necessary, to provide further information on any of these questions)

1. (a) What financial support has been received for this or related projects by the person conducting the project, or his associates, in years previous to current year?

Source	Title of Project	Amount	What Period
Cancer Research Coordinating Com. Univ. of Calif.	"Study of Plasma Proteins in Malignant Diseases Using the Tiselius Electrophoresis Apparatus"	\$5,750.000	July 1, 1951 to June 30, 1952
ibid	ibid	ibid	7-1-52 to 6-30-53
ibid	ibid	ibid	7-1-53 to 6-30-54

(b) What support, if any, is being received during the current year? (Year during which application is filed)

Source	Title of Project	Amount	What Period
The Veterans Administration has and will continue to contribute substantial assistance in certain categories:			
1. Ample clinical material (from the Metabolic Ward and through the V.A. Center.			
2. Use of the General laboratory space and facilities of the Metabolic Unit, including a cold room (approximately 2000 square feet of laboratory area providing the basic chemical needs of this project).			
3. Salary of the principal investigator			
(continued on Page 5a)			

(c) What support, if any, are you expecting to run concurrently to that requested herewith, i.e. have you applied to another agency for support of this project for the same or overlapping period as you are now applying to the American Cancer Society, California Division? Yes No See 1.(e)

If yes, which agency, how much, what period?

If no, why have you not applied to a national agency?

(d) What requests for financial assistance on this or related projects are now pending or are contemplated with other agencies, public or private?

Title of Project	Agency	Amount	What Period
Same as present	U.S. Public Health Service	Not yet established	7-1-56 for 3 to 5 years

(e) If you have been refused funds for this project, what agency refused and why?

Our original application on this project dated 8-1-54, to the American Cancer Society was regrettably refused by the Committee on Growth (by letter of 1-10-55 from Dr. Ray, Executive Secretary), with the information that "funds (continued on Page 5a)

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BUDGET 1.(b) continued

4. Special equipment already available for use: Tiselius Electrophoresis Apparatus, Research Model, American Instrument Co.; associated conductivity and photographic equipment; miscellaneous chromatographic equipment and microware; automatic pipetting machines.

5. Other equipment already available for use if required includes: Beckman DU Spectrophotometer, with photomultiplier, ultra-violet and flame attachments, Coleman universal spectrophotometer, pH meters, microscopes and micro to macro centrifuges.

6. Consultation, and perhaps some special work, if needed, from other specialists at this Center.

Because the V.A. is now operating on a very tight budget, it can provide this project with very little money from current or future funds, perhaps \$300 to \$400 for new equipment, supplies and special services during the next year.

During the past year, this work has received some part time assistance from two technicians. Since, however, their other duties have had priority, this assistance has been on a variable and unreliable basis. The present grant will provide needed full-time assistance on the specific work described herein.

BUDGET 1.(e) continued.

available represented less than 70% of the funds requested"; and the expressed hope that we shall be able to obtain the support we need from other sources.

The present application has been modified slightly in the light of subsequent work and our further thoughts have been outlined in greater detail.

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BUDGET - (Cont.)

BUDGET FOR PROPOSED PROJECT

NOTE: Under "other" indicate funds expected to be available from other sources, including your own institution.

PERSONNEL (Itemize all positions by indicating type and names of personnel if selected)

Flyde A. Dubbs, Ph.D.
Principal Investigator

Junior Biochemist

~~Retirement or other security benefits (Total)~~
~~9% S.E.R.S.~~

	BUDGET	
	Requested from the American Cancer Society	Other
None	None	\$7,040.00
\$4,000.00	\$4,000.00	None
360.00	360.00	
CATEGORY TOTAL	\$4,000.00	\$7,040.00
Permanent Equipment (Itemize)		
Fraction Collector, drop counting Technicon or equivalent	\$1,500.00	
Electrophoresis-convection apparatus (E-C Appar. Co., No. EC25 or equivalent) (to replace present apparatus on loan)	350.00	
Refrigerated bath for above (E-C Appar. Co., No. EC-6 or equivalent)	490.00	
Paper Electrophoresis Apparatus, with power supply. (E-C Appar. Co., No. EC-305 or equivalent)	400.00	
Attachment for quantitative evaluation of paper strips (use with Beckman Spectrophotometer)	50.00	
CATEGORY TOTAL	\$2,790.00	None
Consumable Supplies (Itemize)		
Ion-exchange resins, amino acids, reagents, glassware	\$ 100.00	\$ 200.00
CATEGORY TOTAL	\$ 100.00	\$ 200.00
Other Expense (Itemize) (Travel and overhead not allowed)		
Services: Glassblowing, Machine Shop Work		\$ 200.00
CATEGORY TOTAL	None	\$ 200.00
GRAND TOTAL	\$6,890.00	\$7,440.00