JUDITH GRAHAM POOL

Postdoctoral Research

Fellowships in Bleeding Disorders

PREVIOUSLY FUNDED FELLOWSHIPS

1972-2004

NATIONAL HEMOPHILIA FOUNDATION
116 West 32nd Street, 11th Floor
New York, NY 10001-3212

Phone (800) 42-HANDI or (212) 328-3700 • Fax (212) 328-3788

In 1965, Dr. Judith Graham Pool discovered a simple method of extracting the clotting factor from human plasma. This opened the door to a series of rapid developments which have revolutionized the treatment of hemophilia. Replacement therapy (infusion of the missing clotting factor to prevent or stop bleeding) has made it possible for persons with hemophilia to live relatively normal and productive lives and to avoid, in large measure, the potentially crippling effects of the disease. But the battle against bleeding disorders is far from over.

The National Hemophilia Foundation's Judith Graham Pool (JGP) postdoctoral research fellowships are competitively awarded to promote bleeding disorders-related research. The JGP fellowships support research of high scientific merit and relevance to bleeding disorders. The JGP postdoctoral fellowship program aims to foster a life-long commitment to bleeding disorders research.

Since the program's inception in 1972, 63 scientists (including 40 renewals) have been funded for one- or two-year studies which have produced vital insights into the mystery of hemophilia and other bleeding disorders. JGP fellows have played a role in the development of better concentrate, more accurate hemophilia carrier testing, and more detailed understanding of the genetics of hemophilia.

The attached list profiles Judith Graham Pool fellows and their research projects.

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Funds for Judith Graham Pool postdoctoral research fellowships are contributed by individuals, hemophilia organizations, and chapters of the National Hemophilia Foundation.

All donations designated for research are used solely for that purpose.

JUDITH GRAHAM POOL
POSTDOCTORAL RESEARCH FELLOWS

1972 – 2004

2003-2004

Ting-Chang Hsu, Ph.D.
Puget Sound Blood Center
Seattle, WA

Project Title: Structure of Factor VIII's C Domains and Their Epitopes

Description: Will identify surface binding sites and epitopes onfactor VIII's C domains. The first aim will be to address structural issues by expressing, isolating, and characterizing C1C2. The second will be to identify domain-specific antibody fractions reacting to clusters of epitopes isolated by immunoaffinity chromatography. Results will significantly influence treatment strategies for acute bleeding episodes and elucidate rationales for specific immune tolerance induction for or prevention of alloimmune responses in hemophilia and/or immunosuppression of autoantibodies to factor VIII.

Sponsor: *Arthur R. Thompson, M.D. Ph.D.*
Puget Sound Blood Center
Seattle, WA

2003-2004

Christine L. Kempton, M.D.
University of North Carolina
Chapel Hill, NC

Project Title: Platelet Mechanism Regulating Thrombin Generation Project

Description: Will attempt to begin to understand the mechanisms that control thrombin generation and account for difference between individuals. The objective of this study is to determine what changes occur on the platelet surface in response to specific platelet agonists and antagonists that up-regulate thrombin generation. Results will make it possible to look for abnormalities in thrombin generation in patients with unexplained bleeding disorders and module the response in patients with known bleeding disorders.

Sponsor: *Harold R. Roberts, M.D.*
University of North Carolina
Chapel Hill, NC

2003-2004
2002-2003

Julie Fradette, Ph.D.
University of Pittsburgh
Pittsburgh, PA

Project Title: Development of a Novel Gene Transfer Approach for the Treatment of Hemophilia Based on Transduction of Adipose Tissue Using Replication-Defective HSV-1 Genomic Vectors

Description: Will test the use of HSV-based replication-deficient viral vectors to provide solutions encountered with other vector systems, building on recent progress made in the engineering, production, and purification of HSV-based vectors. The studies proposed will directly test the hypothesis that the delivery of FVIII and FIX with a recombinant HSV-based vector by transduction of adipose tissue can be used to effectively treat mouse models of hemophilia A or hemophilia B.

Sponsor: *Joseph C. Glorioso, Ph.D.*
Department of Molecular Genetics and Biochemistry
School of Medicine, University of Pittsburgh
Pittsburgh, PA

2003-2004
2002-2003

Andrey Garunovich Sarafanov, Ph.D.
American Red Cross Holland Laboratory
Rockville, MD

Project Title: Identification of Complement-Type Repeats of LRP Responsible for Interaction with A2 Domain of Factor VIII

Description: Will build on the finding of a pathway in which factor VIII is cleared from plasma from its complex with von Willebrand factor. The clearance of FVIII involves a low-density lipoprotein receptor-related protein (LRP). The present study will attempt to identify the site of LRP. Better understanding of the mechanisms of FVIII clearance from plasma may lead to prolongation of FVIII lifetime in circulation.

Sponsor: *Evgueni Saenko, Ph.D.*
American Red Cross Biochemistry Department
Rockville, MD

2003-2004
2002-2003

Hongmin Sun, Ph.D.
University of Michigan Medical School
Ann Arbor, MI

Project Title: Function of Coagulation Factor V in Plasma and Platelet Pools

Description: Will study the relative contributions of different factor V pools to blood clotting using genetically modified mice as a model. The studies will lead to a better understanding of the roles of factor V in normal blood coagulation as well as in bleeding and clotting disease. Insights gained could lead to significant advances in the treatment of hemophilia and related blood clotting disease.

Sponsor: *David Ginsburg, M.D., Ph.D.*
University of Michigan Medical School
Ann Arbor, MI

2003-2004
2002-2003

Lisa S. Webb, Ph.D.
The Jackson Laboratory
Bar Habor, ME

Project Title: Exploiting Mouse Models to Elucidate the Cellular and Molecular Mechanisms Involved in the Pathogenesis of Platelet Storage Pool Deficiencies

Description: Will use mouse models of storage pool deficiencies to identify genes involved in the pathways affected in these diseases. Understanding these biochemical pathways is an important step toward designing effective treatments for these diseases and eventually finding a cure.

Sponsor: *Luanne L. Peters, Ph.D.*
The Jackson Laboratory
Bar Harbor, ME

2002 – 2003
2001 – 2002

Anja Ehrhardt, Ph.D.
Stanford University
Stanford, CA

Project Title: Development of Improved Adenoviral Vectors Lacking All Adenoviral Coding Sequences for Hemophilia Gene Therapy

Description: Will study two new approaches for developing adenoviral vectors devoid of all adenoviral genes for *in vivo* hemophilia gene therapy. The first will be to design a system that allows the small amounts of helper-virus contaminants from viral stock that contaminate all current vector preparations to be further reduced or eliminated from the final product. The second will be to produce a deleted adenovirus capable of integration into chromosomal DNA, as current deleted adenoviruses are not believed to persist life-long.

Sponsor: *Mark A. Kay, M.D., Ph.D.*
Program in Gene Therapy
Stanford University
Stanford, CA

2002 – 2003
2001 – 2002

Peter Vincent Jenkins, Ph.D.
University of Rochester Medical School
Rochester, NY

Project Title: Study of Interactive Sites of Factor VIIIa with Factor IXa

Description: Will study mutations in the amino acid sequence on a region of the A2 domain of factor VIIIa that interacts with factor IX. These mutations will be examined to determine their effect on the ability of factor VIIIa to increase the efficiency of factor IXa and how they affect the stability of the factor VIIa-factor IXa interaction. The aim is to show that a surface region of the factor VIII A2 domain is key in the action of factor VIIIa on factor IXa.

Sponsor: *Philip J. Fay, Ph.D.*
University of Rochester Medical School
Rochester, NY

2002 – 2003
2001 – 2002

Bin Zhang, Ph.D.
University of Michigan Medical School
Ann Arbor, MI

Project Title: Molecular Mechanisms of Combined Factors V and VIII Deficiency

Description: Will attempt to locate and determine the function of one of two genes believed responsible for combined factors V and VIII deficiency that is likely involved in the export of factors V and VIII from the cells. The results should improve diagnosis and potential novel approaches to treatment. Further, better understanding of how factor VIII is made in the cells may lead to improved recombinant factor VIII production, better gene therapy strategies for hemophilia, and new approaches to boosting factor VIII production in patients with mild to moderate hemophilia A.

Sponsor: *David Ginsburg, M.D.*
University of Michigan Medical School
Ann Arbor, MI

2001 – 2002
2000 – 2001

Cathryn Sanghae Mah, Ph.D.
University of Florida
Gainesville, FL

Project Title: Treatment of a Mouse Model of Hemophilia Using AAV Vectors Expressing Murine Factor VIII

Description: Will use two adeno-associated viruses (AAV) to package the heavy and light chain genes of murine factor VIII separately for the treatment of a mouse model of hemophilia A. After entry into the host cell, AAV genomes have been found in repeat, end-to-end arrangements. This phenomenon, in conjunction with the inclusion of genetic splice elements, could mimic the structure of the normal full-length factor VIII gene, resulting in greater expression of a more functionally stable product as compared to the separate expression of both halves alone. A further aim of the project is to develop AAV vectors for liver-targeted gene therapy, achieving a greater therapeutic effect than approaches using muscle as targets.

Sponsor: *Barry J. Byrne, M.D., Ph.D.*
University of Florida
Gainesville, FL

2001-2002
2000-2001

Lingfei Xu, M.D., Ph.D.
Washington University School of Medicine
St. Louis, MO

Project Title: Retroviral Vector-Mediated Gene Therapy for Canine Hemophilia B

Description: Will test the use of two retroviral vectors in hemophilic mice before attempting to correct bleeding manifestations of hemophilia B in newborn dogs from the canine hemophilia colony at the University of North Carolina. The dogs will be injected via a peripheral vein and monitored for toxicity of the procedure, correction of bleeding tendency, blood levels of factor IX, and the development of antibodies against factor IX. These studies may lead to the development of similar vectors for use in human patients.

Sponsor: *Katherine Ponder, M.D.*
Division of Hematology
Washington University School of Medicine
St. Louis, MO

2001 – 2002
2000 – 2001

Yubin Kang, M.D.
University of Iowa College of Medicine
Iowa City, IA

Project Title: Correction of Factor VIII Deficiency by Nonprimate Lentivirus-Based Gene Therapy

Description: Hypothesizes that factor VIII bone marrow gene therapy will lead to long-term factor VIII expression, the induction of tolerance to factor VIII, and the elimination of inhibitory anti-factor VIII antibody production. A feline immunodeficiency virus (FIV) vector encoding a reporter gene will be used to optimize the transduction conditions in hematopoietic stem cells. Then FIV vectors will deliver B-domain deleted murine factor VIII into bone marrow stem cells from hemophilic mice; the cells will in turn be injected into factor VIII-deficient mice, who later are assessed for factor VIII expression and phenotypic correction. Finally, the recombinant FIV/FVIII virus particles will be applied intravenously for *in vivo* gene therapy, an important step toward future clinical trials in humans.

Sponsor: *Paul B. McCray, Jr., M.D.*
Department of Pediatrics
University of Iowa
Iowa City, IA

2000 – 2001
1999 – 2000

Frank Park, Ph.D.
Stanford University
Stanford, CA

Project Title: Mechanisms Involved in Transduction of Human Lentivirus in Liver: A Strategy for Hemophilia Gene Therapy

Description: Will study a gene therapy vector system based on a lentivirus, the human immunodeficiency virus (HIV). The study will address the mechanisms that may be required for efficient gene transfer of therapeutic genes into the liver. One of the main advantages of using an attenuated HIV vector system is its ability to integrate into the DNA of the host cell (e.g., liver). However, many important biological and safety parameters need to be addressed before these vectors are used in patients. The investigation will study the biological processes involved in vector insertion into the cells as well as different methods of liver-directed gene transfer required to achieve safe, optimal gene delivery and therapeutic concentrations of clotting factors in animal models of hemophilia.

Sponsor: *Mark A. Kay, M.D., Ph.D.*
Stanford University
Stanford, CA

2000 – 2001
1999 – 2000

Jo Chao Tsai, Ph.D.
Beth Israel Deaconess Medical Center/East
Boston, MA

Project Title: Vascular Bed-Specific Regulation of the vWF Gene

Description: Will define the environmentally responsive promoter elements that mediate vWF expression in specific vascular beds. Previous work has shown that in transgenic mice, discrete regions of the vWF promoter contain information for selective expression in a subset of endothelial cells within the blood vessels of the heart, skeletal muscle, and brain, and that heart-specific expression is mediated by a platelet-derived growth factor signaling pathway. A combination of transient and stable transfections will be employed to study the effect of cellular environments on vWF promoter function *in vitro*. More importantly, the findings from transfection experiments in transgenic mice will be confirmed. These studies will not only uncover the mechanisms by which the vWF gene is regulated in the intact vascular tree, but also provide a framework for understanding how this gene may be differentially modulated in both physiological and pathophysiological states.

Sponsor: *William C. Aird, MD*
Beth Israel Deaconess Medical Center/East
Boston, MA

1999 – 2000

Bing-guan Chen, M.D., Ph.D.
University of Michigan
Ann Arbor, MI

Project Title: Induction of Immune Tolerance to Factor IX

Description: Will overcome the immune problem in either factor IX gene transfer or protein replacement for hemophilia B. This proposed investigation seeks to demonstrate the feasibility of inducing long-term immune tolerance to human FIX in naïve mice. Also, the presence of anti-factor IX antibody in the circulation will be overcome by inducing specific T and B-cell immunity to anti-factor IX antibodies in a factor IX knockout mouse model. This strategy will permit a cure of hemophilia B patients without or with factor IX inhibitor. Results of this study could be interpreted to apply to hemophilia A or other autoimmune diseases.

Sponsor: *Kotoku Korachi, Ph.D.*
University of Michigan
Ann Arbor, MI

2000 – 2001
1999 – 2000

You-Kyung Hwang, Ph.D.
Emory University
Atlanta, GA

Project Title: New Therapeutics for Hepatitis C

Description: Will use the hepatitis C viral polymerase as a target for developing new therapeutic strategies. The approach to be taken will produce the HCV protein (NS5B polymerase) that synthesizes the viral genome using common bacterial and genetic engineering techniques. In addition, an animal cell system will be developed to study the HCV NS5B polymerase. The essential factors for the viral RNA replication will be identified. The system to be used will identify small molecules that inhibit synthesis of HCV RNA. The knowledge gained from these studies can eventually pave the way to new treatments for chronic hepatitis C.

Sponsor: *Curt H. Hagedorn, M.D.*
Emory University
Atlanta, GA

2000 – 2001
1999 – 2000

Mark Thomas Reding, M.D.
University of Minnesota
Minneapolis, MN

Project Title: T Cell Epitopes on Factor VIII

Description: Will examine the T cell epitopes on factor VIII that are recognized by CD4+ cells in hemophilia A patients with factor VIII inhibitors in order to advance understanding of immune tolerance. Through challenges with proliferation assays, comparisons will be made of hemophilia patients with FVIII inhibitors, those who do not have inhibitors but have anti-FVIII antibody, those with autoimmune hemophilia, and healthy subjects. The ultimate goal is to lay the groundwork for the design of a treatment for hemophilia A patients with inhibitors based on nasal tolerization of the anti-FVIII CD4+ cells.

Sponsors: *Bianca M. Conti-Fine, M.D./Nigel Key, M.D.*
University of Minnesota
Minneapolis, MN

1999 – 2000
1998 – 1999

Paul Edward Monahan, M.D.
University of North Carolina
Chapel Hill, NC

Project Title: AAV Hemophilia Gene Therapy Vectors

Description: Will better define and improve muscle as a target organ to support gene therapy for hemophilia B. Multiple studies have documented delayed gene expression from recombinant adeno-associated virus (rAAV) vectors, with expression rising over the first month following intramuscular injection. The proposed investigations seek to define the molecular events leading to this pattern of expression. Using injected mouse muscle, a molecular model for the events leading to factor IX expression will be established that will allow critical predictions regarding timing, persistence, and efficiency of rAAV-factor IX vector transduction. Also, a mouse model will be used to examine the capacity of skeletal muscle to integrate rAAV vectors.

Sponsor: *Richard Jude Samulski, Ph.D.*
University of North Carolina
Chapel Hill, NC

1999 – 2000
1998 – 1999

Jonathan Bernard Rosenberg, Ph.D.
Blood Center of SE Wisconsin
Milwaukee, WI

Project Title: Impact of vWF on Factor VIII Gene Targeting

Description: Will study the role that von Willebrand factor plays in the storage and secretion of factor VIII. The hypothesis to be tested is that endothelial cells in reticuloendothelial tissues (liver, spleen, lymph nodes, and bone marrow) possess the regulatory mechanisms necessary to create an intracellular storage pool of vWF/FVIII, and that vWF functions as the critical delineator of regulated FVIII intracellular storage. The study will investigate the cellular biology of co-expressing vWF/FVIII storage cells, explore the mechanisms behind release of the storage pool, and identify and characterize the normal FVIII/vWF storage pool through *ex vivo* laboratory methods. Results of this study could yield information relevant to gene therapy for mild hemophilia A and von Willebrand disease.

Sponsor: *Robert M. Montgomery, M.D.*
Blood Center of SE Wisconsin
Milwaukee, WI

1998 – 1999
1997 – 1998

Beth A. Bouchard, Ph.D.
New England Medical Center
Boston, MA

Project Title: Vitamin K-Dependent Carboxylase

Description: Determine the relationship between the protein structure of the enzyme vitamin K-dependent carboxylase. This enzyme is responsible for an essential modification of vitamin K-dependent blood coagulation proteins, including factor IX. Using recombinant enzyme, biochemical studies will be performed to gain insight into the role of specific amino acid residue, cysteine in enzyme function and structure. Other studies are designed to begin to elucidate the orientation of the enzyme within the cell. Understanding the structure and function of the vitamin K-dependent carboxylase will be useful in the development of therapies for disorders of blood coagulation, including hemophilia B.

Sponsor: *Barbara C. Furie, Ph.D.*
New England Medical Center
Boston, MA

1998 – 1999
1997 – 1998

Steven Shahin Fakharzadeh, M.D., Ph.D.
University of Pennsylvania
Philadelphia, PA

Project Title: Factor VIII Delivery via Skin

Description: Will determine the feasibility of using the epidermis of the skin as a target tissue for expressing factor VIII to correct factor VIII deficiency in a murine model for hemophilia A. *In vitro* experiments will entail transfecting the factor VIII gene into epidermis-derived keratinocytes and assaying for expression of functional factor VIII protein. *In vivo* studies will involve generating transgenic mouse lines that direct human factor VIII expression to the skin. Experiments to evaluate localization of expression and levels of circulating factor VIII will be done. Transgenic mice will be mated with factor VIII-deficient mice that have been created through targeted gene disruption to generate mice that express factor VIII in the skin but not at sites where it is normally expressed. Analysis of these mice will determine whether factor VIII expression in the skin can overcome the factor VIII deficiency phenotype.

Sponsor: *Haig Kazazian, M.D.*
University of Pennsylvania
Philadelphia, PA

1997 – 1998
1996 – 1997

Dewey G. McCafferty, Ph.D.
Harvard Medical School
Boston, MA

Project Title: Vitamin K-Dependent Carboxylase

Description: Determine the mechanisms of vitamin K-dependent carboxylase, an enzyme responsible for the post-translational modification of key proteins in the blood coagulation cascade such as prothrombin and factor IX. Improper modification of these coagulation proteins results in downstream coagulation disorders such as hemophilia B. Peptide substrates will be synthesized chemically and recombinantly and used to determine enzyme processivity, directionality, and substrate recognition. In addition, photoaffinity labels will be developed for covalent modification and identification of the vitamin K binding site.

Sponsor: *Christopher T. Walsh, Ph.D.*
Hamilton Kuhn Professor
Harvard Medical School
Boston, MA

1997 – 1998
1996 – 1997

Degang Zhong, Ph.D.
Holland Laboratories
American Red Cross
Rockville, MD

Project Title: Interaction of Factor VIII with Factor IXa

Description: Determine the precise site of factor VIII that interacts with factor IX by replacing several regions of factor VIII with homologous regions of factor V. In addition, factor VIII inhibitors from hemophilia patients will be investigated for their effects on the binding between factor VIII and factor IX. These studies will enhance our understanding of hemophilia and factor VIII inhibitors.

Sponsors: *Dorothea Scandella, Ph.D.*
Scientist II
Holland Laboratory
American Red Cross
Rockville, MD

1996 – 1997
1995 – 1996

David Bruce Schowalter, M.D., Ph.D.
University of Washington
Seattle, WA

Project Title: Persistent Expression of Factor IX

Description: Will evaluate technologies that will allow hepatic cells transfected with adenovirus factor IX gene to produce adequate quantities of the coagulation protein for a prolonged period of time. Modification of the immune response after adenovirus gene transfer will attempt to block the cellular and humoral immunity that limit the expression and ultimate usefulness of this gene vector system *in vivo*.

Sponsor: *Mark Kay, M.D., Ph.D.*
Assistant Professor
Medical Genetics
University of Washington
Seattle, WA

1995 – 1996
1994 – 1995

Scott A. Tenenbaum, Ph.D.
Tulane University School of Medicine
New Orleans, LA

Project Title: HIV Resistance in Hemophiliacs

Description: Demonstrate via enzyme-linked immunoassay and Western blot analysis the presence of anti-HIV antibodies in banked sera from HIV-exposed/HIV-seronegative hemophiliacs that correspond to years of exposure to HIV-contaminated clotting factor concentrates. Additionally, studies will be performed to determine the direct (cell to cell) and indirect (lymphokine) immunological characteristics that may afford protection against permanent HIV infection in HIV-exposed/HIV seronegative hemophiliacs and long-term survival in HIV-seropositive hemophiliacs.

Sponsors: *Cindy A. Leissinger, M.D.*
Director, Louisiana Comprehensive Hemophilia Care Center
Assistant Professor
Department of Medicine, Hematology/Oncology Section
Tulane University School of Medicine
New Orleans, LA

1994 – 1995

Qicheng Yang, Ph.D.
The Salk Institute
San Diego, CA

Project Title: Gene Therapy for Hemophilia B

Description: Examine the use of non-pathogenic adeno-associated virus (AAV) vectors for *in vivo* gene transfer into intact liver using the hemophilia B dog as a model system. New methods will be developed to produce high titres of recombinant AAVs, which will be used for *in vivo* delivery of human factor IX gene to the liver of mice and hemophilia dogs by either infusion into portal veins, or injection into tail veins or liver lobes. The integration of AAV vectors and the persistent expression of factor IX protein will be investigated in both *in vivo* and *in vitro* studies.

Sponsor: *Inder M. Verma, Ph.D.*
Professor, Molecular Biology and Virology Laboratory
The Salk Institute
San Diego, CA

1994 – 1995
1993 – 1994

Dwight D. Koeberl, M.D., Ph.D.
University of Washington
Seattle, WA

Project Title: Factor VIII Gene Therapy Vectors

Description: Design gene therapy vectors which produce long-term, high yields of active factor VIII *in vivo*. Inhibitory sequence within the promoter is hypothesized as the cause of low factor VIII expression, suggesting that the cDNA sequence might be manipulated to allow high expression from gene therapy vectors. The project will include the demonstration of a localized RNA inhibitory sequence, followed by separation of factor VIII domains to eliminate any interaction causing inhibition, and subsequent delineation of the sequence element responsible for the inhibitory effect.

Sponsor: *A. Dusty Miller, Ph.D.*
Associate Member, Fred Hutchinson Cancer Research Center
Affiliate Associate Professor, Department of Pathology
University of Washington
Seattle, WA

1993 – 1994
1992 – 1993

Sylvia T. Singer, M.D.
Children's Hospital Oakland
Oakland, CA

Project Title: Factor VIII - Specific T Lymphocytes

Description: Study the *in vitro* proliferative response to factor VIII in larger number of patients with and without hemophilia, using both unfractionated and T cell-enriched peripheral blood leukocytes (PBL) populations, and to establish stable factor VIII specific T lymphocyte lines *in vitro*. Long-term goals are to determine the role of factor VIII-specific T cells in the initiation and maintenance of the factor VIII inhibitor antibody response.

Sponsors: *Joseph E. Addiego, Jr., M.D.*
Director, Hematology/Oncology Department and Hemophilia Treatment Center
Alexander H. Lucas, Ph.D.
Research Immunologist
Children's Hospital Oakland
Oakland, CA

1992 – 1993
1991 – 1992

Frederick K. Askari, M.D., Ph.D.
University of Michigan Medical Center
Ann Arbor, MI

Project Title: Gene Therapy of Hemophilia B

Description: Develop an *in vivo* hepatocyte directed gene therapy for hemophilia B by: 1) constructing human factor IX expression vectors with different promoter and enhancer elements; 2) constructing asialoorosomucoid (ASOR)-polylysine conjugates; 3) constructing DNA/protein complexes and test their transient activity *in vivo* in rats to determine optimal transcriptional regulatory units; and 4) studying stable expression.

Sponsor: *James M. Wilson, M.D., Ph.D.*
Assistant Professor of Internal Medicine and Biological Chemistry
University of Michigan Medical Center
Ann Arbor, MI

1992 – 1993
1991 – 1992

Athan Kuliopulos, M.D., Ph.D.
Harvard Medical School
Boston, MA

Project Title: Vitamin K-Dependent Carboxylase

Description: Determine the mechanisms of vitamin K-dependent carboxylase/monooxygenase and to answer the fundamental question of how the enzyme recognizes specific glutamate residues of proteins involved in the blood clotting cascade. Affinity labels will be developed for covalent modification and identification of both the enzyme and active-site/propetide recognition-site peptides since the carboxylase has not been purified.

Sponsor: *Christopher Walsh, Ph.D.*
Professor and Chair
Harvard Medical School
Boston, MA

1992 – 1993
1991 – 1992

William C. Nichols, Ph.D.
University of Michigan Medical Center
Ann Arbor, MI

Project Title: Genetics of Type I/III von Willebrand Disease

Description: Determine if defects at the level of von Willebrand factor (vWF) mRNA expression could account for some of the cases of type I/III von Willebrand disease (vWD). A polymerase chain reaction analysis of peripheral blood platelet RNA using exonic vWF locus polymorphisms will be developed. Further studies will be initiated to map the locus responsible for this disease to eventually identify a potential second vWD gene. In addition to identifying molecular mechanisms responsible for type I/III vWD, these studies may facilitate precise DNA-based diagnosis and clarification of vWD.

Sponsor: *David Ginsburg, M.D.*
Associate Professor of Medicine and Human Genetics
University of Michigan Medical Center
Ann Arbor, MI

1991 – 1992

Theo Palmer, Ph.D.
Fred Hutchinson Cancer Research Center
Seattle, WA

Project Title: Gene Therapy for Hemophilia A and B

Description: Therapeutic amounts of factor IX can be produced in laboratory rodents by transplanting fibroblasts that express a clotting factor IX transgene. Unfortunately, retrovirally transferred genes are gradually inactivated over a period of several weeks. This project examines the use of alternate enhancer/promoter elements or elimination of negative regulatory elements from retroviral gene transfer vectors as an approach to prolonging clotting factor production via transplanted fibroblasts. Since transgene inactivation may be specific to rodent tissues or to fibroblasts in general, cells from other species (dogs) or other tissue types (skeletal muscle) will also be tested with the existing vectors.

Sponsor: *A. Dusty Miller, Ph.D.*
Member
Fred Hutchinson Cancer Research Center
Seattle, WA

1990 – 1991

Jay Nelson Lozier, M.D., Ph.D.
University of North Carolina at Chapel Hill
Chapel Hill, NC

Project Title: Replacement of the Factor IX Gene in a Canine Hemophilia B Model

Description: Utilize a retroviral vector containing canine factor IX cDNA to transfer the gene for factor IX into fibroblasts from a dog with hemophilia B. Cells cultured from canines with hemophilia B will be infected by canine factor IX-containing retroviruses. Infected cells expressing normal canine factor IX utilizing the selectable neomycin resistant marker will be propagated and their production of factor IX characterized. Modified cells will be re-implanted autologuosly to correct or modify the canine hemophilia B and to assess the practicality of this technique *in vivo*.

Sponsor: *Katherine A. High, M.D.*
Assistant Professor of Medicine and Pathology
University of North Carolina at Chapel Hill
Chapel Hill, NC

1990 – 1991
1989 – 1990

Josephine A. Carew, Ph.D.
Dana-Farber Cancer Institute
Boston, MA

Project Title: Carbohydrate and Carbohydrate Sulfation in the Structure and Function of von Willebrand Factor

Description: Characterize the sulfated N-linked glycans and O-linked glycans of human von Willebrand factor (vWF), and alter the amino acids modified by individual glycans in order to determine their contributions to the structure and function of vWF. Determine whether certain phenotypic abnormalities, characteristic of plasma vWF patients with type II von Willebrand disease, might arise from specific defects either in carbohydrate sulfation or in glycosylation.

Sponsor: *Dennis C. Lynch, M.D., Ph.D.*
Assistant Professor of Medicine
Harvard Medical School
Boston, MA

1989 – 1990

Jack C. Rayner, D.V.M.
The Blood Center of Southeastern Wisconsin
Milwaukee, WI

Project Title: Molecular and Cell Biology of von Willebrand Factor Variants

Sponsor: *Robert R. Montgomery, M.D.*
Director of Research
The Blood Center of Southeastern Wisconsin
Milwaukee, WI

1988 – 1989

Monica D. Traystman, Ph.D.
John Hopkins University School of Medicine
Baltimore, MD

Project Title: Characterization of Gene Defects in Hemophilia A

Sponsor: *Haig H. Kazazian, Jr., M.D.*
Professor of Pediatrics
The Johns Hopkins Hospital
Baltimore, MD

1988 – 1989

James P. Evans, M.D.
University of North Carolina
Chapel Hill, NC

Project Title: The Molecular Biology of Canine Hemophilia B

Sponsor: *Harold Roberts, M.D.*
Chairman, Division of Hematology
Department of Internal Medicine
University of North Carolina
Chapel Hill, NC

1987 – 1988

Wadie Bahou, M.D.
University of Michigan
Ann Arbor, MI

Project Title: Von Willebrand's Disease: Molecular Studies in the Porcine Model

Sponsor: *David Ginsburg, M.D.*
Assistant Professor
Hematology and Human Genetics
University of Michigan
Ann Arbor, MI

1987 – 1988
1986 – 1987

Nancy Collins O'Brien, M.D.
University of Texas System Cancer Center
Houston, TX

Project Titles: The Role of Hepatitis B and Hepatitis Delta Virus as Cofactors in the Acquired Immunodeficiency Syndrome in a Hemophilia Population (1987 - 1988)

The Role of Other Blood-Borne Infectious Agents as Cofactors in the Acquired Immunodeficiency Syndrome in a Hemophilia Population (1986 - 1987)

Sponsor: *W. Keith Hoots, M.D.*
Associate Professor of Pediatrics
Department of Pediatrics
University of Texas System Cancer Center
Houston, TX

1987 – 1988
1986 – 1987

Paula Silverman, M.D.
University Hospitals of Cleveland
Cleveland, OH

Project Titles: Studies in Fibrinolysis: Human Endothelial Cells in Culture and *In Vivo* Studies in Hemophilia (1987 - 1988)

Modulation of Plasminogen Activator and Plasminogen Activator from Human Endothelial Cells (1986 - 1987)

Sponsor: *George H. Goldsmith, M.D.*
Associate Professor of Medicine
Case Western Reserve University
Cleveland, OH

1986 – 1987

Michael Katzman, M.D.
Case Western Reserve University
Cleveland, OH

Project Title: Mechanisms of Retroviral Integration Recombination

Sponsor: *Jonathan P. Leis, Ph.D.*
Professor of Biochemistry
Department of Biochemistry
Case Western Reserve University
Cleveland, OH

1986 – 1987
1985 – 1986

Barbara G. Schach, M.D.
University of Washington
Seattle, WA

Project Title: DNA Analysis of the Factor IX Gene and the Role of B-Hydroxyaspartic Acid in the Vitamin K-Dependent Coagulation Factor (1986 - 1987)

Sponsor: *Earl W. Davie, M.D.*
Professor Biochemistry
Department of Biochemistry
University of Washington
Seattle, WA

Project Title: DNA Analysis of the Factor IX Gene from a Patient with Hemophilia B (1985 - 1986)

Sponsor: *Kotoku Kurachi, Ph.D.*
Research Associate Professor
Department of Biochemistry
University of Washington
Seattle, WA

1985 – 1986

Bruce Harold Odegaard, Ph.D.
University of Vermont College of Medicine
Burlington, VT

Project Title: Characterization of Intermediates and Products of the Factor Xa-Catalyzed Activation of Factor V

Sponsor: *Kenneth G. Mann, Ph.D.*
Professor and Chairman
Department of Biochemistry
University of Vermont College of Medicine
Burlington, VT

1984 – 1985

Gordon Lewis Bray, M.D.
Children's Orthopedic Hospital and Medical Center
Seattle, WA

Project Title: Functional Characterization of the Carboxy-Terminal Domain of Human Factor IX

Sponsor: *Arthur R. Thompson, M.D., Ph.D.*
Associate Professor of Medicine
Chief, Department of Hematology
Pacific Medical Center
Seattle, WA

1984 – 1985
1983 – 1984

Peggy Weintrub, M.D.
University of California at San Francisco
San Francisco, CA

Project Title: Immunologic Abnormalities in Patients with Hemophilia A

Sponsor: *Arthur J. Ammann, M.D.*
Director, Pediatric Clinical Research Center
Chairman, Department of Pediatric Immunology
University of California at San Francisco
San Francisco, CA

1983 – 1984

Carolyn Beach Daul, Ph.D., M.D.
Tulane University School of Medicine
New Orleans, LA

Project Title: Studies in Factor VIII: Effects of Commercial Preparations of Antihemophilic Factor in Immunocompetent Cell Populations

Sponsor: *W. Abe Andes, M.D.*
Associate Professor
Department of Medicine, Hematology/Oncology Section
Tulane Medical School
New Orleans, LA

1983 – 1984
1982 – 1983

James B. Bussell, M.D.
Cornell University Medical College
New York, NY

Project Title: Immune Complexes and Immune Function in Hemophilia

Sponsor: *Margaret W. Hilgartner, M.D.*
Professor of Pediatrics
Director of Pediatric Hematology/Oncology
New York Hospital
New York, NY

1982 – 1983

Karen S. Kolba, M.D.
University of Arizona Health Sciences Center
Tucson, AZ

Project Title: A Pharmacologic Approach to the Treatment of Hemophilic Arthropathy

Sponsor: *Eric P. Gall, M.D., Associate Professor*
James J. Corrigan, M.D., Professor
Department of Internal Medicine
University of Arizona Health Sciences Center
Tucson, AZ

1979 – 1980

Michael W. Chopek, M.D.
University of Washington
Seattle, WA

Project Title: Studies on Factor VIII: Immunological and Biochemical Characterization of Procoagulant Activity and Subunit Interactions

Sponsor: *Earl W. Davie, M.D.*
Chairman, Department of Biochemistry
University of Washington
Seattle, WA

1979 – 1980

Frederick A. Ernst, Ph.D.
Wright State University
Kettering, OH

Project Title: Biofeedback-Assisted Progressive Relaxation to Attenuate Complications of Hemophilia

Sponsor: *Paul Kezdi, M.D.*
Director, Cox Heart Institute
Wright State University School of Medicine

Kettering, OH

1979 – 1980

David R. McCarroll, Ph.D.
University of Tennessee
Knoxville, TN

Project Title: Molecular Pathology of von Willebrand's Disease

Sponsor: *James P. Chen, Ph.D.*
Associate Professor of Medical Biology
University of Tennessee Memorial Research
Knoxville, TN

1978 – 1979
1977 – 1978

Jonathan C. Goldsmith, M.D.
University of North Carolina
Chapel Hill, NC

Project Title: Mutant Molecular Forms of Factor IX

Sponsor: *H.R. Roberts, M.D.*
Chief, Division of Hematology
University of North Carolina School of Medicine
Chapel Hill, NC

1978 – 1979
1977 – 1978

Gordon A. Vehar, Ph.D.
University of Washington
Seattle, WA

Project Title: Structure and Function of Factor VIII

Sponsor: *Earl W. Davie, M.D.*
Chairman, Department of Biochemistry
University of Washington
Seattle, WA

1977 – 1978

Mary Ellen Switzer, M.D.
Duke University
Durham, NC

Project Title: Further Studies of the Molecular Structure-Function Relationships of the Human Antihemophilic/von Willebrand Proteins

Sponsor: *Patrick A. McKee, M.D.*
Professor of Cardiology
Department of Medicine
Duke University Medical Center
Durham, NC

1977 – 1978

Annita Weidenbach, Ph.D.
Oklahoma Medical Research Foundation
Oklahoma City, OK

Project Title: Study of Cellular Interactions with Plasminogen Activator in Hemophilia and von Willebrand's Disease

Sponsor: *James H. Hampton, M.D.*
Head, Hematology Research Laboratory
Oklahoma Medical Research Foundation
Oklahoma City, OK

1976 – 1977

Myatt S. Lipscomb, Jr., Ph.D.
Temple University
Philadelphia, PA

Project Title: Interaction Between Coagulation Factors and Platelets

Sponsor: *P.N. Walsh, M.D, Ph.D.*
Associate Professor of Medicine
Thrombosis Research Center
Temple University Health Sciences Center
Philadelphia, PA

1976 – 1977
1975 – 1976

James E. Brown, Ph.D.
University of California
San Diego, CA

Project Title: Studies on Bovine Factor VIII and the Relationship to the Human Platelet Aggregating Factor (PAF)

Sponsor: *Cecil Hougie, Ph.D.*
Professor of Pathology
University of California
San Diego, CA

1976 – 1977
1975 – 1976

John Lazarchick, M.D.
University of Connecticut Health Center
Farmington, CT

Project Title: Properties of Human Antibodies to Antihemophilic Factor

Sponsor: *Leon W. Hoyer, M.D.*
Chief, Hematology Division
University of Connecticut Health Center
Farmington, CT

1975 – 1976
1974 – 1975

Eric Jaffee, M.D.
Cornell Medical School
New York City, NY

Project Title: Synthesis of AHF Antigen by Cultured Endothelial Cells

Sponsor: *Ralph L. Nachman, M.D.*
Chief, Division of Hematology
Cornell University Medical College
New York, NY

1975 – 1976
1974 – 1975

Charles Heldebrant, Ph.D.
University of Washington
Seattle, WA

Project Title: Isolation and Characterization of Abnormal Factor VIII Present in von Willebrand's Disease

Sponsor: *Earl W. Davie, M.D.*
Chairman, Department of Biochemistry
University of Washington
Seattle, WA

1974 – 1975
1973 – 1974

Margaret E. Rick, M.D.
University of Connecticut
Farmington, CT

Project Title: Molecular Forms of Factor VIII

Sponsor: *Leon W. Hoyer, M.D.*
Chief, Hematology Section
Department of Medicine
University of Connecticut Health Center
Farmington, CT

1973 – 1974
1972 – 1973

Judith C. Anderson, M.D.
Duke University School of Medicine
Durham, NC

Project Title: Biochemical Characterization of Human Factor VIII

Sponsor: *Patrick McKee, M.D.*
Professor, Cardiology
Department of Medicine
Duke University
Durham, NC

1972 – 1973

Andrew E. Weiss, M.D.
University of North Carolina
Chapel Hill, NC

Project Title: Development of Immuno-Assay for Circulating Inhibitors to Factor VIII

Sponsor: *H.R. Roberts, M.D.*
Chief, Division of Hematology
University of North Carolina School of Medicine
Chapel Hill, NC