CAREER DEVELOPMENT AWARD

In Bleeding Disorders Research

PREVIOUSLY FUNDED AWARDS

2000-2004

NATIONAL HEMOPHILIA FOUNDATION
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In 1998, the National Hemophilia Foundation (NHF) launched a capital campaign entitled It's Time for a Cure to raise millions of dollars for research specifically into cures for bleeding disorders. The money raised by this campaign bolsters NHF's research program by creating new levels of multiyear study and support for scientists working in the field of inherited bleeding disorders. Grants awarded under this program complement NHF's existing Judith Graham Pool Postdoctoral Research Fellowships in Bleeding Disorders.

The overall objectives of the three-year NHF Career Development Award are to advance bleeding disorders research by promoting development of novel and innovative studies by established investigators. The emphasis of this initiative is to promote basic, pre-clinical, and clinical research approaches aimed ultimately at a cure. Multiple experimental strategies may be undertaken to cure the hemophilias. While gene therapy is the most promising approach, no one method has been demonstrated to be superior, and considerably more effort will be required to make this a reality for the estimated 300,000-400,000 persons affected by severe bleeding disorders worldwide.

Career Development Award recipients must hold an MD, PhD, or equivalent degree and be an assistant professor (or equivalent) with up to six years of experience since completion of training. The Award is intended to provide support for scientists who have demonstrated a commitment to bleeding disorders research.

The attached list profiles Career Development Award recipients and their research projects.

CAREER DEVELOPMENT AWARDS IN BLEEDING DISORDERS RESEARCH

2000 - 2004

2003 – 2004

Andrew John Gale, PhD.
The Scripps Research Insitiute
La Jolla, California

Project Title: Structure and Function of Stabilized Engineered Coagulation Factor VIIIa

Description: Will study previously created, recombinant factor VIII variants with increased stability to determine their in vitro characteristics relating directly to their potential as therapeutic agents. Further, the investigation will make use of these variants to characterize interactions of activated fVIII with activated protein C. The proposed studies will increase the understanding of molecular mechanisms for the function and inactivation of fVIIIa and perhaps provide improved therapeutic agents for treatment of hemophilia. Also, a variant of fVIII with increased stability might be a valuable tool for correction of hemophilia A through gene therapy.

2003 – 2004

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

Project Title: Double-stranded Adeno-associated Virus (dsAAV) Vectors to Improve Efficacy and to Evaluate Safety of Factor IX Gene Therapy

Description: Will extend previous work on the potential for increased factor IX expression using novel AAV vectors (dsAAV) that deliver therapeutic genes in a double-stranded form, resulting in more immediate onset of expression and achieving higher expression levels at a given vector dose. The overall goal of the project is to employ dsAAV to overcome limitations to factor IX expression occurring after receptor binding so as to achieve improved efficacy, and as tools to examine the safe application of AAV gene therapy for hemophilia.

2003 – 2004

Hiroyuki Nakai, M.D., Ph.D.
Stanford University School of Medicine
Stanford, California

Project Title: Esablishing the Factors Responsible for Hepatcoyte Permissiveness to AAV Vectors

Description: Will attempt to better understand restricted hepatocyte transduction with recombinant adeno-associated virus (rAAV) based on serotype 2 and other-serotyped vectors, develop methodologies for single-cell functional genomics using microarray techniques to understand hepatocyte biology with respect to rAAV vector transduction, and apply single-cell global gene expression analyses for identification of cellular factors that determine rAAV permissiveness. The bioinformatics information that will be obtained will build a better understanding of rAAV vector trandsductions in the liver and develop a new area of research on vector toxicology. Further, the results will lead to the development of improved rAAV-vector mediated hepatic gene therapy for hemophilia with greater safety.

2003 – 2004
2002 – 2003

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

Project Title: Non-primate Lentiviral Vector-Based Gene Therapy for Hemophilia A

Description: Will build on results obtained in investigating the efficacy of intravenous delivery of a feline immunodeficiency virus-based lentiviral vector in correcting factor VIII deficiency in an animal model of hemophilia A. To improve gene transfer efficiency in a effort to achieve optimal FVIII expression levels, three areas will be studied. The vector construct technology will be optimized to increase FVIII production and improve safety. The viral envelope protein will be optimized to increase hepatocyte transduction efficiency and improve FVIII production. Finally, the FVIII expression level and duration will be evaluated in an immuno-compromised hemophilia A mouse model.

2003 – 2004
2002 – 2003

Carol H. Miao, Ph.D.
University of Washington
Seattle, Washington

Project Title: Nonviral Gene Delivery for Hemophilia

Description: Will build on the previous development of liver-specific expression cassettes that can produce therapeutic level and persistent factor IX gene in mouse livers after naked DNA transfer. Different nonviral delivery pathways will be explored to efficiently transfer factor IX as well as factor VIII gene expression cassettes into the liver. These nonviral gene transfers strategies will then be tested for the efficacy and duration of correction of the phenotype in hemophilia B and A mouse models.

2003 – 2004
2002 – 2003

Frank Park, Ph.D.
Louisiana State University
New Orleans, LA

Project Title: Gene Transfer of Factor VIII to the Liver in Vivo

Description: Will address whether a newly developed lentiviral vector system can be useful as a therapeutic vehicle for hemophilia A. To determine its utility, different “enhancing” genetic sequences will be inserted into the vector to increase its ability to integrate into the host genome and also increase the ability factor VIII transgene to be expressed in the circulatory system. Also, to potentially minimize the immune response against the factor VIII protein, different liver-specific promoters will be incorporated into the vector to limit the gene expression to a site of optimal synthesis.

2003 - 2004
2002 - 2003
2001 – 2002

Hengjun Chao, M.D.
University of North Carolina
Chapel Hill, North Carolina

Project Title: Gene Therapy for Hemophilia B by Direct Intramuscular Injections of Recombinant Adeno-Associated Virus Serotype Vectors

Description: Will attempt to improve results obtained from direct intramuscular injection of recombinant adeno-associated virus, which has failed to obtain levels of factor IX expression sufficient to prevent spontaneous bleeding in the large hemophilia B animal models. Previous studies conducted at UNC have demonstrated that the five AAV serotypes other than type 2 produce more factor IX than type 2, the most studied and used experimentally. The different AAV serotypes will be tested in hemophilic mice and dogs. The results of the proposed work will serve as the platform studies required by the NIH and FDA regulatory agencies before testing can occur in patients.

2002 – 2003
2001 – 2002
2000 – 2001

Steven Wesley Pipe, M.D.
University of Michigan
Ann Arbor, Michigan

Project Title: Development and Characterization of Novel Genetically Engineered Factor VIII Molecules with Increased Activity and Stability

Description: Will study hemophilia A patient mutations that provide insight into factor VIII structure and function. An attempt will be made to reengineer novel forms of factor VIII with increased activity and stability and characterize these molecules in animal models. The goal is to derive essential information relative to the molecules' efficiency and safety as alternative replacement products and potential for use in gene therapy applications.

2002 – 2003
2001 – 2002
2000 – 2001

Roland W. Herzog, Ph.D.
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Project Title: Immunology of Liver-Derived Expression of Factor IX from AAV Vectors

Description: Will strive to identify the mechanism of inhibitor formation in liver-directed gene therapy using an adeno-associated viral vector that includes a factor IX gene. The results should help improve safety in the design of clinical trials and may lead to a protocol that confers tolerance to factor IX in the patient so that subsequent treatment by gene therapy can be performed with a greatly reduced risk of an inhibitor response.

2002 – 2003
2001 – 2002
2000 – 2001

Tal Kafri, M.D., Ph.D.
University of North Carolina
Chapel Hill, North Carolina

Project Title: Correction of Hemophilia with Lentiviral Vectors

Description: Will attempt to advance the lentivirus vector system for gene therapy to a point where it will be considered suitable for human clinical trials. To achieve this outcome, improvements in vector production and in transgene expression will be undertaken and tested in hemophilic mice and dogs. These experiments may also enable a better understanding of the development of inhibitory antibodies to newly expressed factor IX.