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Abstract

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Grant Number: 5P01DK055820-020004
PI Name: HORWITZ, MARSHALL
PI Email:
PI Title:
Project Title: STEM CELL GENES IN LEUKEMIA PATHOGENESIS

Abstract: Leukemia is a leading cause of cancer death and requires a significant expenditure of the national healthcare budget to treat. There is substantial evidence that hereditary factors contribute to leukemia predisposition and the frequently observed familial clustering and racial variations in risk. In many families, affected individuals have developed leukemias of differing type and subtype, suggesting a defect in a gene responsible for hematopoietic stem cell differentiation. A unusual of familial leukemia is that it is inherited with "anticipation" in the form of a declining age of onset with each passing generation, and we hypothesize that a defect in a mitotic clock might be responsible for this phenomenon. A locus for familial AML in association with inherited platelet defects has been mapped to chromosome 21q. Preliminary evidence suggests a second locus for familial AML on chromosome 16q in families that do not have a platelet defect. The specific aims are the following: 1) Clone the locus for familial leukemia on chromosome 21: A. Collect new individuals with the familial platelet disorder/AML syndrome, B. Narrow the critical region on chromosome 21q by studying Down syndrome patients, C. Positionally clone the chromosome 21q locus from leukemia families by mutational analysis of candidate genes from the critical region; 2) Confirm and clone a locus for familial AML on chromosome 16q: A. Use leukemia families to narrow the critical region, B. Use sporadic cases of AML and myelodysplasia to refine the critical region, C. Positionally clone the chromosome 16q AML gene; and c) Characterize the role of familial leukemia genes in hematopoietic stem cell differentiation and leukemia pathogenesis: A. Functionally characterize the genes for familial leukemia, B. Develop animal models, C. Search for common but low penetrance alleles among sporadic leukemia cases.

Thesaurus Terms:
acute myelogenous leukemia, family genetics, gene mutation, hematopoietic stem cell, molecular cloning, pathologic process
Downs syndrome, allele, cell differentiation, cellular pathology, chromosome 21, disease /disorder model, dyserythropoietic anemia, genetic disorder, model design /development, platelet disorder
gene targeting, laboratory mouse, transgenic animal

Institution:	UNIVERSITY OF WASHINGTON 3935 UNIVERSITY WAY NE SEATTLE, WA 98195
Fiscal Year:	2001
Department:	
Project Start:	
Project End:	
ICD:	NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
IRG:	ZDK1

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Grant Number:	5P01DK055820-029001
PI Name:	HORWITZ, MARSHALL S.
PI Email:	
PI Title:	
Project Title:	CORE--CLINICAL SAMPLE COLLECTION AND GENOTYPE ANALYSIS

Abstract: This is a core facility designed to (1) establish cell lines and extract nucleic acids from clinical material and (2) perform molecular genotype analysis. The core will support Project 3 (Mapping of the Cyclic Hematopoiesis Gene) and Project 4(Mapping of the Familial Leukemia Gene). For Project 3, this unit will process venous blood and bone marrow specimens and will be responsible for additional genotype analysis of the region first identified in family 619. For Project 4, this core facility will prepare immortalized lymphoblastoid cell lines from members of leukemia families and store aliquots of frozen bone marrow. DNA will be extracted and used in genotype analysis. RNA will also be prepared when needed for mutational analysis.

Thesaurus Terms:
biomedical facility, genotype, tissue /cell preparation
DNA, RNA, artificial chromosome, bone marrow, cell line, cell transformation, hematopoietic stem cell, linkage mapping, lymphoblast

Institution:	UNIVERSITY OF WASHINGTON 3935 UNIVERSITY WAY NE SEATTLE, WA 98195
Fiscal Year:	2001
Department:	
Project Start:	
Project End:	
ICD:	NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
IRG:	ZDK1

Version 2.0

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Grant Number:	5R01DK058161-02
PI Name:	HORWITZ, MARSHALL S.
PI Email:	horwitz@aecom.yu.edu
PI Title:	ASSOCIATE PROFESSOR
Project Title:	MOLECULAR GENETIC BASIS OF CYCLIC HEMATOPOIESIS

Abstract: Human cyclic hematopoiesis (also known as cyclic neutropenia, MIM #162800) is an autosomal dominant disease in which circulating blood cell counts oscillate with an invariant 21 day period resulting from periodic fluctuations in the production of cells by the bone marrow. The cycling of blood counts is most pronounced for neutrophils, causing opportunistic infections to arise during the neutropenic nadir, and monocytes, which cycle in a phase opposite to that of neutrophils. In preliminary studies genetic linkage analysis has been used to map the locus for cyclic hematopoiesis to chromosome 19p13.3 (maximum 2-point LOD score of 13.1 at theta = 0) and with a positional cloning strategy 7 different single base substitutions have been identified in the gene encoding neutrophil elastase, a chymotryptic serine protease of neutrophil and monocyte granules, in 13 of 13 families as well as a new mutation in one sporadic case. Neutrophil elastase is the target for protease inhibition by alpha-1-antitrypsin, and its unopposed release is involved in tissue damage at sites of inflammation. The mutations responsible for cyclic hematopoiesis cluster in regions of the molecule implicated in substrate specificity and interaction with alpha-1- antitrypsin. We hypothesize that a perturbed interaction between neutrophil elastase and its inhibitors or other biochemical abnormality may interrupt a feedback circuit and thereby lead to hematopoietic cycling. We propose Specific Aims to investigate the molecular genetic effects of the observed mutations and plan to link the biochemical deficit to the biological observation of hematopoietic cycling through a transgenic mouse model containing various human constructs crossed into genetic backgrounds which modify neutrophil elastase and alpha-1-antitrypsin interactions. The broad, long-term objective is to understand the 21 day biological clock of the bone marrow, whose cycle is made evident in this disease.

Thesaurus Terms:
biological clock, bone marrow, cell cycle, circadian rhythm, gene mutation, hematopoiesis, molecular pathology
alpha 1 antitrypsin, autosomal dominant trait, blood disorder, cell differentiation, cytogenetics, elastase, elastase inhibitor, enzyme activity, gene expression, neutrophil bioassay, bone marrow transplantation, immunoprecipitation, laboratory mouse, transgenic animal, yeast two hybrid system

Institution:	UNIVERSITY OF WASHINGTON 3935 UNIVERSITY WAY NE SEATTLE, WA 98195
Fiscal Year:	2001
Department:	MEDICINE
Project Start:	15-AUG-2000
Project End:	31-JUL-2005
ICD:	NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
IRG:	MGN