Civin Curt

FORM APPROVED
O.M.B. NO. 68-R0249

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

GRANT APPLICATION

FOLLOW INSTRUCTIONS CAREFULLY

LEAVE BLANK		
TYPE	ACTIVITY	NUMBER
REVIEW GROUP		FORMERLY
COUNCIL/BOARD (Month, year)		DATE RECEIVED

1. TITLE OF APPLICATION (Do not exceed 56 typewriter spaces)

Antigenic Analysis of Hematopoiesis

2. RESPONSE TO SPECIFIC PROGRAM ANNOUNCEMENT [X] NO [ ] YES (If "YES," state RFA number and announcement title)

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR

3a. NAME (Last, first, middle)
Civin, Curt I.

3b. SOCIAL SECURITY NUMBER
057-38-0564

3c. MAILING ADDRESS (Street, city, state, zip code)
Oncolgy 3-120
Johns Hopkins Oncology Center
600 North Wolfe Street
Baltimore, Maryland 21205

3d. POSITION TITLE
Assistant Professor, Oncology & Pediatrics
Johns Hopkins University School of Medicine

3e. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT
Oncology

3f. TELEPHONE (Area code, number and extension)
301/955-8816

3g. MAJOR SUBDIVISION
School of Medicine

4. HUMAN SUBJECTS, DERIVED MATERIALS OR DATA INVOLVED
[ ] NO [X] YES (If "YES," Form HEW 596 required)

5. RECOMBINANT DNA RESEARCH SUBJECT TO NIH GUIDELINES
[X] NO [ ] YES

6. DATES OF ENTIRE PROPOSED PROJECT PERIOD (This application)
From: April 1, 1982 Through: March 30,1987

7. TOTAL DIRECT COSTS REQUESTED FOR PROJECT PERIOD (from page 5)
$503,873

8. DIRECT COSTS REQUESTED FOR FIRST 12-MONTH BUDGET PERIOD (from page 4)
$78,449

9. PERFORMANCE SITES (Organizations and addresses)

Oncology 3-120
Johns Hopkins Oncology Center
600 North Wolfe Street
Baltimore, Maryland 21205

10. INVENTIONS (Competing continuation application only) N/A
Were any inventions conceived or reduced to practice during the course of the project?
[ ] NO [ ] YES - Previously reported
[ ] YES - Not previously reported

11. APPLICANT ORGANIZATION (Name, address, and congressional district)

Johns Hopkins University
School of Medicine
720 Rutland Avenue
Baltimore, Maryland 21205
7th Congressional District

DEFENDANT EXHIBIT 117

12. ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR INSTITUTIONAL GRANT (See instructions)

Code 011 Description:
School of Medicine

13. ENTITY IDENTIFICATION NUMBER
152059511OA5

14. TYPE OF ORGANIZATION (See instructions)
[X] Private Nonprofit
[ ] Public (Specify Federal, State, Local):

15. OFFICIAL IN BUSINESS OFFICE TO BE NOTIFIED IF AN AWARD IS MADE (Name, title, address and telephone number)
Mr. Kenneth Hoffmeyer, Director
Office of Accounting Services
The Johns Hopkins University
Charles & 34th Streets
Balto., Md. 21218 (301)338-8157

16. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION (Name, title, address and telephone number)

David A. Blake, Ph.D
Assistant Dean for Research Programs
School of Medicine Administration
720 Rutland Avenue
Baltimore, MD 21205 (301) 955-3061

17. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.
Curt I. Civin, MD

SIGNATURE OF PERSON NAMED IN 3a (In addition, "Per" signature not acceptable)
Curt I. Civin, MD

DATE
6-19-81

18. CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true and complete to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as the result of this application. A willfully false certification is a criminal offense. (U.S. Code, Title 18, Section 1001.)

SIGNATURE OF PERSON NAMED IN 16 (In addition, "Per" signature not acceptable)
David A. Blake

DATE
6/25/81

PHS-398
Rev. 10/79

JH052174

CIVIN, Curt I. 057-38-0564

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PROTECTION OF HUMAN SUBJECTS ASSURANCE/CERTIFICATION/DECLARATION

☒ ORIGINAL ☐ FOLLOWUP ☐ REVISION

☒ GRANT ☐ CONTRACT ☐ FELLOW ☐ OTHER

☒ NEW ☐ RENEWAL ☐ CONTINUATION

APPLICATION IDENTIFICATION NUMBER (If known)

STATEMENT OF POLICY: Safeguarding the rights and welfare of subjects at risk in activities supported under grants and contracts from DHHS is primarily the responsibility of the institution which receives or is accountable to DHHS for the funds awarded for the support of the activity. In order to provide for the adequate discharge of this institutional responsibility, it is the policy of DHHS that no activity involving human subjects to be supported by DHHS grants or contracts shall be undertaken unless the Institutional Review Board has reviewed and approved such activity, and the institution has submitted to DHHS a certification of such review and approval, in accordance with the requirements of Public Law 93-348, as implemented by Part 46 of Title 45 of the Code of Federal Regulations, as amended, (45 CFR 46). Administration of the DHHS policy and regulation is the responsibility of the Office for Protection from Research Risks, National Institutes of Health, Bethesda, MD 20205.

1. TITLE OF PROPOSAL OR ACTIVITY

Antigenic Analysis of Hematopoiesis

2. PRINCIPAL INVESTIGATOR/ACTIVITY DIRECTOR/FELLOW

Curt I. Civin, M.D.

3. DECLARATION THAT HUMAN SUBJECTS EITHER WOULD OR WOULD NOT BE INVOLVED

☐ A. NO INDIVIDUALS WHO MIGHT BE CONSIDERED HUMAN SUBJECTS, INCLUDING THOSE FROM WHOM ORGANS, TISSUES, FLUIDS, OR OTHER MATERIALS WOULD BE DERIVED, OR WHO COULD BE IDENTIFIED BY PERSONAL DATA, WOULD BE INVOLVED IN THE PROPOSED ACTIVITY. (IF NO HUMAN SUBJECTS WOULD BE INVOLVED, CHECK THIS BOX AND PROCEED TO ITEM 7. PROPOSALS DETERMINED BY THE AGENCY TO INVOLVE HUMAN SUBJECTS WILL BE RETURNED.)

☒ B. HUMAN SUBJECTS WOULD BE INVOLVED IN THE PROPOSED ACTIVITY AS EITHER: ☐ NONE OF THE FOLLOWING, OR INCLUDING: ☒ MINORS, ☐ FETUSES, ☐ ABORTUSES, ☐ PREGNANT WOMEN, ☐ PRISONERS, ☐ MENTALLY RETARDED, ☐ MENTALLY DISABLED. UNDER SECTION 6, COOPERATING INSTITUTIONS, ON REVERSE OF THIS FORM, GIVE NAME OF INSTITUTION AND NAME AND ADDRESS OF OFFICIAL(S) AUTHORIZING ACCESS TO ANY SUBJECTS IN FACILITIES NOT UNDER DIRECT CONTROL OF THE APPLICANT OR OFFERING INSTITUTION.

4. DECLARATION OF ASSURANCE STATUS/CERTIFICATION OF REVIEW

☐ A. THIS INSTITUTION HAS NOT PREVIOUSLY FILED AN ASSURANCE AND ASSURANCE IMPLEMENTING PROCEDURES FOR THE PROTECTION OF HUMAN SUBJECTS WITH THE DHHS THAT APPLIES TO THIS APPLICATION OR ACTIVITY. ASSURANCE IS HEREBY GIVEN THAT THIS INSTITUTION WILL COMPLY WITH REQUIREMENTS OF *DHHS Regulation 45 CFR 46*, THAT IT HAS ESTABLISHED AN INSTITUTIONAL REVIEW BOARD FOR THE PROTECTION OF HUMAN SUBJECTS AND, WHEN REQUESTED, WILL SUBMIT TO DHHS DOCUMENTATION AND CERTIFICATION OF SUCH REVIEWS AND PROCEDURES AS MAY BE REQUIRED FOR IMPLEMENTATION OF THIS ASSURANCE FOR THE PROPOSED PROJECT OR ACTIVITY

☒ B. THIS INSTITUTION HAS AN APPROVED GENERAL ASSURANCE (DHHS ASSURANCE NUMBER G0174) OR AN ACTIVE SPECIAL ASSURANCE FOR THIS ONGOING ACTIVITY, ON FILE WITH DHHS. THE SIGNER CERTIFIES THAT ALL ACTIVITIES IN THIS APPLICATION PROPOSING TO INVOLVE HUMAN SUBJECTS HAVE BEEN REVIEWED AND APPROVED BY THIS INSTITUTION'S INSTITUTIONAL REVIEW BOARD IN A CONVENED MEETING ON THE DATE OF [illegible]80 IN ACCORDANCE WITH THE REQUIREMENTS OF THE *Code of Federal Regulations on Protection of Human Subjects (45 CFR 46)*. THIS CERTIFICATION INCLUDES, WHEN APPLICABLE, REQUIREMENTS FOR CERTIFYING FDA STATUS FOR EACH INVESTIGATIONAL NEW DRUG TO BE USED (SEE REVERSE SIDE OF THIS FORM).

THE INSTITUTIONAL REVIEW BOARD HAS DETERMINED, AND THE INSTITUTIONAL OFFICIAL SIGNING BELOW CONCURS THAT

EITHER ☐ HUMAN SUBJECTS WILL NOT BE AT RISK; OR ☒ HUMAN SUBJECTS WILL BE AT RISK.

5. AND 6. SEE REVERSE SIDE

7. NAME AND ADDRESS OF INSTITUTION

The Johns Hopkins University School of Medicine
720 Rutland Avenue
Baltimore, Maryland 21205

8. TITLE OF INSTITUTIONAL OFFICIAL

David A. Blake, Ph.D
Assistant Dean for Research Programs

TELEPHONE NUMBER

301/955-[illegible]

SIGNATURE OF INSTITUTIONAL OFFICIAL

DATE

HHS-596 (Rev. 5-80)

ENCLOSE THIS FORM WITH THE PROPOSAL OR RETURN IT TO REQUESTING AGENCY.

JHOT2175

5. INVESTIGATIONAL NEW DRUGS - ADDITIONAL CERTIFICATION REQUIREMENT

SECTION 46.17 OF TITLE 45 OF THE Code of Federal Regulations states, "Where an certification is required to be made or to submit a certification . . . and the proposed involves an investigational new drug within the meaning of *The Food, Drug, and Cosmetic Act*, the drug shall be identified in the certification together with a statement that the 30-day delay required by *21 CFR 130.3(a)(2)* has elapsed and the Food and Drug Administration has not, prior to expiration of such 30-day interval, requested that the sponsor continue to withhold or to restrict use of the drug in human subjects or that the Food and Drug Administration has waived the 30-day delay requirement: provided, however, that in those cases in which the 30-day delay interval has neither elapsed nor been waived, a statement shall be forwarded to DHHS upon such expiration or upon receipt of a waiver. No certification shall be considered acceptable until such statement has been received."

INVESTIGATIONAL NEW DRUG CERTIFICATION

TO CERTIFY COMPLIANCE WITH FDA REQUIREMENTS FOR PROPOSED USE OF INVESTIGATIONAL NEW DRUGS IN ADDITION TO CERTIFICATION OF INSTITUTIONAL REVIEW BOARD APPROVAL, THE FOLLOWING REPORT FORMAT SHOULD BE USED FOR EACH IND: (ATTACH ADDITIONAL IND CERTIFICATIONS AS NECESSARY).

- IND FORMS FILED: ☐ FDA 1571, ☐ FDA 1572, ☐ FDA 1573
- NAME OF IND AND SPONSOR _____
- DATE OF 30-DAY EXPIRATION OR FDA WAIVER
  (FUTURE DATE REQUIRES FOLLOWUP REPORT TO AGENCY) _____
- FDA RESTRICTION _____
- SIGNATURE OF INVESTIGATOR _____ DATE _____

6. COOPERATING INSTITUTIONS - ADDITIONAL REPORTING REQUIREMENT

SECTION 46.16 OF TITLE 45 OF THE *Code of Federal Regulations* IMPOSES SPECIAL REQUIREMENTS ON THE CONDUCT OF STUDIES OR ACTIVITIES IN WHICH THE GRANTEE OR PRIME CONTRACTOR OBTAINS ACCESS TO ALL OR SOME OF THE SUBJECTS THROUGH COOPERATING INSTITUTIONS NOT UNDER ITS CONTROL. IN ORDER THAT THE DHHS BE FULLY INFORMED, THE FOLLOWING REPORT IS REQUESTED WHEN APPLICABLE.

USE FOLLOWING REPORT FORMAT FOR EACH INSTITUTION OTHER THAN GRANTEE OR CONTRACTING INSTITUTION WITH RESPONSIBILITY FOR HUMAN SUBJECTS PARTICIPATING IN THIS ACTIVITY: (ATTACH ADDITIONAL REPORT SHEETS AS NECESSARY).

INSTITUTIONAL AUTHORIZATION FOR ACCESS TO SUBJECTS

- SUBJECTS: STATUS (WARDS, RESIDENTS, EMPLOYEES, PATIENTS, ETC.) _____
  NUMBER _____ AGE RANGE _____
  NAME OF OFFICIAL (PLEASE PRINT) _____
  TITLE _____ TELEPHONE _____
  NAME AND ADDRESS OF COOPERATING INSTITUTION _____
- OFFICIAL SIGNATURE _____

NOTES: *(e.g., report of modification in proposal as submitted to agency affecting human subjects involvement)*

JH052176

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: Curt I. Civin, M.D.

CHECKLIST

This is the required last page of the application.

Check the appropriate boxes and provide the information requested.

TYPE OF APPLICATION:

[X] NEW application (*This application is being submitted to the PHS for the first time.*)

[ ] COMPETING CONTINUATION of grant number: _____
(*This application is to extend a grant beyond its original project period.*)

[ ] SUPPLEMENT to grant number: _____
(*This application is for additional funds during a funded project period.*)

[ ] REVISION of application number: _____
(*This application replaces a prior version of a new, competing continuation or supplemental application.*)

[ ] Change of Principal Investigator/Program Director.
Name of former Principal Investigator/Program Director: _____

ASSURANCES IN CONNECTION WITH:

Civil Rights	Handicapped Individuals	Sex Discrimination	Human Subjects General Assurance (If applicable)	Laboratory Animals (If applicable)
[X] Filed	[X] Filed	[X] Filed	[X] Filed	[X] Filed
[ ] Not filed	[ ] Not filed	[ ] Not filed	[ ] Not filed	[ ] Not filed

INDIRECT COSTS:

Indicate the applicant organization's most recent indirect cost rate established with the appropriate DHEW Regional Office. If the applicant organization is in the process of initially developing or renegotiating a rate, or has established a rate with another Federal agency, it should, immediately upon notification that an award will be made, develop a tentative indirect cost rate proposal based on its most recently completed fiscal year in accordance with the principles set forth in the pertinent *DHEW Guide for Establishing Indirect Cost Rates*, and submit it to the appropriate DHEW Regional Office. Indirect costs will not be paid on foreign grants, construction grants, and grants to individuals, and usually not on grants in support of conferences.

[X] DHEW Agreement Dated: May 7, 1981.

_____ % Salary and Wages or 50 % Total Direct Costs.

Is this an offsite or other special rate, or is more than one rate involved? [ ] YES [ ] NO
Explanation: On-campus rate

[ ] DHEW Agreement being negotiated with _____ Regional Office.

[ ] No DHEW Agreement, but rate established with _____. Date _____.

[ ] No Indirect Costs Requested.

JH052177

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR: Curt I. Civin, M.D.

DETACH AND CLIP TO THE SIGNED FACE PAGE OF THE APPLICATION

PERSONAL DATA ON

PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR

The Public Health Service has a continuing commitment to monitoring the operation of its review and award processes to detect—and deal appropriately with—any instances of real or apparent inequities with respect to age, sex, race, or ethnicity of the proposed principal investigator/program director.

To provide the PHS with the information it needs for this important task, the principal investigator/program director is requested to complete the form below and attach a single copy to the signed face page of the application.

Upon receipt and assignment of the application by the PHS, this form will be detached from the application. It will NOT be duplicated and will NOT be a part of the review process. Data will be confidential, and will be maintained in Privacy Act record system 09-25-0036, "Grants: IMPAC (Grant Contract Information)." All analyses conducted on the data will report aggregate statistical findings only and will not identify individuals.

If you decline to provide this information, it will in no way affect consideration of your application.

Your cooperation will be appreciated.

Date of Birth: 5/29/49 (Month/Day/Year)

Sex: ☐ Female ☒ Male

Race and/or Ethnic Origin:

Check one:

- ☐ American Indian or Alaskan Native
- ☐ Asian or Pacific Islander
- ☐ Black, not of Hispanic origin
- ☐ Hispanic
- ☒ White, not of Hispanic origin

NOTE: The category that most closely reflects the individual's recognition in the community should be used for purposes of reporting mixed racial and/or ethnic origins. Definitions are on the back of form.

JH052178

PHS-398
Rev. 10/79

057-38-0564 Curt I. Civin, MD

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

LEAVE BLANK

PROJECT NUMBER

ABSTRACT OF RESEARCH PLAN

NAME AND ADDRESS OF APPLICANT ORGANIZATION (Same as item 11, page 1)
Johns Hopkins University School of Medicine
720 Rutland Avenue, Baltimore, Maryland 21205

TITLE OF APPLICATION (Same as item 1, page 1)

Antigenic Analysis of Hematopoiesis

Name, Title and Department of all professional personnel engaged on project, beginning with Principal Investigator/Program Director

Curt I. Civin, M.D. (principal investigator), Assistant Professor of Oncology & Pediatric
Lyle L. Sensenbrenner, M.D. (co-investigator), Associate Professor of Oncology & Medicine
Lewis C. Strauss, M.D., Fellow in Oncology

ABSTRACT OF RESEARCH PLAN: Concisely describe the application's research aims, methodology and long-term objectives, making reference to the scientific disciplines involved and the multidisciplinariness of the project. The abstract should be self-explanatory so that it can serve as a succinct and accurate description of the application when separated from it. DO NOT EXCEED THE SPACE PROVIDED.

Many of the mechanisms of self-renewal & differentiation of hematopoietic precursor cells, including the regulation of these processes, remain to be elucidated. In many respects, further detailed experimental analysis of hematopoiesis depends on the identification, isolation, and molecular characterization of pluripotent and committed hematopoietic precursor cells. Immunologic identification and study of subsets of cells has led to dramatic progress in understanding other differentiating organ systems; and initial studies (including our own) reveal impressive heterogeneity of myeloid cell surfaces that should allow manipulation by immunologic probes. We propose further development and use of murine and human monoclonal antibodies, specifically directed against small subsets of myeloid cells, to approach the identification and isolation of human hematopoietic precursor cells. Several collectively unique approaches to antibody development and characterization will be employed. Resulting antibodies will be used to isolate precursor cells, and to study hematopoiesis in model systems. This work might have eventual broad application for the understanding, diagnosis and treatment of leukemia and aplastic anemia in man.

LABORATORY ANIMALS INVOLVED. Identify by common names. If none, state "none"

Mice

JH052179

TABLE OF CONTENTS

Number pages consecutively at the bottom throughout the application. Do not use suffixes such as 5a, 5b. Type the name of the Principal Investigator/Program Director at the top of each printed page and each continuation page.

SECTION 3. Appendix (*Six sets*) (*No page numbering necessary for Appendix*)

Number of publications: 8 Number of manuscripts: 0

~~CHECKLIST~~ LIST:

1. Civin et al, 1981
2. Mirro et al, 1981 (preprint)
3. Marie et al, 1981a (preprint)
4. Marie et al, 1981b (preprint)
5. Sieber et al, 1981 (galley proof)
6. Tatsumi et al, 1981 (abstract)
7. Civin et al, 1976
8. Garver and Sensenbrenner, 1980 (abstract)

Application Receipt Record, form PHS 3830

Form HEW 596 if Item 4, page 1, is checked "YES"

JH052180

SECTION I

DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

APPLICATION
FOR CONTINUATION GRANT

FORM APPROVED OMB No. 68-40249

REVIEW GROUP	TYPE	PROGRAM	GRANT NUMBER (IN SHORT)
	5	R01	CA32518-02

TOTAL PROJECT PERIOD
FROM: 05/01/82 THROUGH: 04/30/85

REQUESTED BUDGET PERIOD
FROM: 05/01/83 THROUGH: 04/30/84

TO BE VERIFIED BY APPLICANT (CHECK INFORMATION IN ITEMS 1 THROUGH 6 IF INCORRECT, FURNISH CORRECT INFORMATION IN ITEM 13)

1. TITLE

ANTIGENIC ANALYSIS OF HEMATOPOIESIS

2A. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (Name and Address, Street, City, State, Zip Code)

CIVIN, CURT I
JOHNS HOPKINS ONCOLOGY CENTER
600 NORTH WOLFE STREET
BALTIMORE, MD 21205

4. APPLICANT ORGANIZATION (Name and Address, Street, City, State, Zip Code)

JOHNS HOPKINS UNIVERSITY
SCHOOL OF MEDICINE
720 RUTLAND AVENUE
BALTIMORE, MD 21205

2B. DEGREE: M.D.

2C. SOCIAL SECURITY NO.: 057-38-0564

5. PHS ACCOUNT NUMBER: 1520595110A5

2D. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT

ONCOLOGY CENTER

2E. MAJOR SUBDIVISION

SCHOOL OF MEDICINE

6. TITLE AND ADDRESS OF OFFICIAL IN BUSINESS OFFICE OF APPLICANT ORGANIZATION

DIRECTOR
OFFICE OF ACCOUNTING SERVICES
JOHNS HOPKINS UNIVERSITY
CHARLES & 34TH STREETS
BALTIMORE, MD 21218

3. ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR INSTITUTIONAL GRANT PURPOSES

01 SCHOOL OF MEDICINE

COMPLETE THE FOLLOWING (See INSTRUCTIONS)

7. RESEARCH INVOLVING HUMAN SUBJECTS (See Instructions)
☐ NO ☒ YES APPROVED: 12/14/82 (DATE)

8. INVENTION CERTIFICATION (See Instructions)
☒ NO ☐ YES-NOT PREVIOUSLY REPORTED ☐ YES-PREVIOUSLY REPORTED

9. PERFORMANCE SITE (S)

Oncology 3-120
Johns Hopkins Oncology Center
600 North Wolfe Street
Baltimore, MD 21205

TELEPHONE INFORMATION

	AREA CODE	TELE. NO. & EXT
11A. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (ITEM 2A)	301	955-8816 -8142
11B. NAME OF BUSINESS OFFICIAL (ITEM 6) Kenneth Hoffmeyer	301	338-8157
11C. NAME AND TITLE OF ADMINISTRATIVE OFFICIAL (ITEM 10B) S. William Appelbaum Director of Financial Affairs	301	955-3061

10. DIRECT COSTS REQUESTED FOR BUDGET PERIOD: $74,885

12A. CONGRESSIONAL DISTRICT OF APPLICANT ORGANIZATION SHOWN IN ITEM 4: 4th

12B. COUNTY OF APPLICANT ORGANIZATION SHOWN IN ITEM 4: Baltimore City

13. USE THIS SPACE FOR CORRECTIONS TO ITEMS 1 THROUGH 6. INDICATE THE NUMBERED WHERE ANSWERS APPLY

JH052247

14. CERTIFICATION AND ACCEPTANCE. WE, THE UNDERSIGNED, CERTIFY THAT THE STATEMENTS HEREIN ARE TRUE AND COMPLETE TO THE BEST OF OUR KNOWLEDGE AND ACCEPT, AS TO ANY GRANT AWARDED, THE OBLIGATION TO COMPLY WITH PUBLIC HEALTH SERVICE TERMS AND CONDITIONS IN EFFECT AT THE TIME OF THE AWARD.

SIGNATURES (Signatures required on original copy only. Use ink. "Per" signatures not acceptable.)		DATE
	14A. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR: Curt I. Civin	2-15-83
	14B. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION: S. William Appelbaum	2/25/83

PHS 2590-1 OPTIONAL REV. 6-68

RETURN COMPLETED APPLICATION TO PHS AS SOON AS POSSIBLE:

OMB No. 0925-04

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PROTECTION OF HUMAN SUBJECTS ASSURANCE/CERTIFICATION/DECLARATION

☒ ORIGINAL ☐ FOLLOWUP ☐ EXEMPTION (previously undesignated)

☒ GRANT ☐ CONTRACT ☐ FELLOW ☐ OTHER

☐ New ☐ Competing continuation ☒ Noncompeting continuation ☐ Supplemental

APPLICATION IDENTIFICATION NO. (if known)

CA 32318-02

POLICY: A research activity involving human subjects that is not exempt from HHS regulations may not be funded unless an institutional Review Board (IRB) has reviewed and approved the activity in accordance with Section 474 of the Public Health Service Act implemented by Title 45, Part 46 of the Code of Federal Regulations (45 CFR 46—as revised). The applicant institution must submit certification of IRB approval to HHS unless the applicant institution has designated a specific exemption under Section 46.101(b) which applies to the proposed research activity. Institutions with an assurance of compliance on file with HHS which covers the proposed activity should submit certification of IRB review and approval with each application. (In exceptional cases, certification may be accepted up to 60 days after the receipt date for which the application is submitted.) In the case of institutions which do not have an assurance of compliance on file with HHS covering the proposed activity, certification of IRB review and approval must be submitted within 30 days of the receipt of a written request from HHS for certification.

1. TITLE OF APPLICATION OR ACTIVITY

ANTIGENIC ANALYSIS OF HEMATOPOIESIS

2. PRINCIPAL INVESTIGATOR, PROGRAM DIRECTOR, OR FELLOW

Curt I. Civin, M.D.

3. FOOD AND DRUG ADMINISTRATION REQUIRED INFORMATION *(see reverse side)*

4. HHS ASSURANCE STATUS

☒ This institution has an approved assurance of compliance on file with HHS which covers this activity.

M1011 Assurance identification number 01 IRB identification number

☐ No assurance of compliance which applies to this activity has been established with HHS, but the applicant institution will provide written assurance of compliance and certification of IRB review and approval in accordance with 45 CFR 46 upon request.

5. CERTIFICATION OF IRB REVIEW OR DECLARATION OF EXEMPTION

☒ This activity has been reviewed and approved by an IRB in accordance with the requirements of 45 CFR 46, including its relevant Subparts. This certification fulfills, when applicable, requirements for certifying FDA status for each investigational new drug or device. *(See reverse side of this form.)*

12/14/82 Date of IRB review and approval. *(If approval is pending, write "pending." Followup certification is required.)*
(month/day/year)

☒ Full Board Review ☐ Expedited Review

☐ This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by 45 CFR 46 will be reviewed and approved before they are initiated and that appropriate further certification *(Form HHS 596)* will be submitted.

☐ Human subjects are involved, but this activity qualifies for exemption under 46.101(b) in accordance with paragraph _____ *(insert paragraph number of exemption in 46.101(b), 1 through 6)*. But the institution did not designate that exemption on the application.

6. Each official signing below certifies that the information provided on this form is correct and that each institution assumes responsibility for assuring required future reviews, approvals, and submissions of certification.

APPLICANT INSTITUTION	COOPERATING INSTITUTION
NAME, ADDRESS, AND TELEPHONE NO. Johns Hopkins University School of Medicine 720 Rutland Avenue Baltimore, Maryland 21205 (301) 955-3061	NAME, ADDRESS, AND TELEPHONE NO.
NAME AND TITLE OF OFFICIAL *(print or type)* S. William Appelbaum Director of Financial Affairs	NAME AND TITLE OF OFFICIAL *(print or type)*
SIGNATURE OF OFFICIAL LISTED ABOVE *(and date)* S William Appelbaum 12/14/82	SIGNATURE OF OFFICIAL LISTED ABOVE *(and date)* JHOJ22Yf

HHS 596 (Rev. 1/82)

If additional space is needed, please use ...

3. FOOD AND DRUG ADMINISTRATION REQUIRED INFORMATION *(From front page)*

According to 45 CFR 46.121, if an application is made to HHS requiring certification and involving use of an investigational new drug or device additional information is required. In addition, according to 21 CFR 312.1(a)(2), 30 days must elapse between date of receipt by FDA of Form FD-1571 and use of the drug, unless the 30 day delay period is waived by FDA.

3a. INVESTIGATIONAL NEW DRUG EXEMPTION *(If more than one is involved, list others below under NOTES):*

SPONSOR NAME

Not applicable

DRUG NAME

DATE OF END OF 30-DAY EXPIRATION OR WAIVER	NUMBER ISSUED

3b. INVESTIGATIONAL DEVICE EXEMPTION:

SPONSOR NAME

Not applicable

DEVICE NAME

Unless notified otherwise by FDA, under 21 CFR 812.2(b) (ii) a sponsor is deemed to have an approved IDE if: (1) the IRB has agreed with the sponsor that the device is a nonsignificant risk device; and (2) the IRB has approved the study. *(Check applicable box.)*

☐ The IRB agrees with the sponsor that this device is a nonsignificant risk device.

OR

☐ The IDE application was submitted to FDA on *(date)* _____. Number issued _____.

NOTES.

J H05 2249

SECTION I (continued)
SUMMARY OF PROPOSED WORK

GRANT NUMBER
CA 32318-02

KEY PROFESSIONAL PERSONNEL ENGAGED ON PROJECT

NAME	POSITION TITLE	DEPARTMENT AND ORGANIZATION
Curt I. Civin, M.D.	PI - Asst. Prof., Oncol. and Pediatr.	Johns Hopkins Oncology Ce Johns Hopkins University School of Medicine
Lyle L. Sensenbrenner, M.D.	Co I - Assoc. Prof., Oncol. and Med.	"
Lewis C. Strauss, M.D.	Instructor Oncol. and Pediatr.	"

Give a brief summary of plans for the next year of support, including the objectives and specific aims as well as the methodology to be used to achieve these aims. DO NOT EXCEED THE SPACE PROVIDED.

Our general goal is to use specific anti-progenitor cell monoclonal antibodies to dissect human hematopoietic differentiation. In Year 2 of this grant, we will continue to derive increasingly specific murine anti-human progenitor cell monoclonal antibodies, using mice immunized with (1) myeloid leukemia cell lines or (2) progenitor cell-enriched fractions of normal human marrow cells. We will test these monoclonal antibodies for binding to an array of (in vitro) colony-forming cells. Using immune adherence techniques with the antibodies exhibiting the highest degree of specificity for early myeloid cell surface differentiation antigens (such as anti-My-10, an antibody we have already developed), we will isolate small, progenitor-rich human marrow cell populations. We will study the morphology, cytochemistry, antigenic phenotype, and cell cycle phase of these cells. Finally, we will examine the changes in these cells after stimulation by exposure to soluble factors and other (possible regulatory) cell types.

J1405-2250

VERTEBRATE ANIMALS INVOLVED ☐ NO ☒ YES If "YES," identify by common names and scientific synonyms. Mice. We will also make very limited use of marrow cells from a few other species (including various primates, if possible) that are being sacrificed by other investigators for other purpose We will notify NIH if this use becomes substantial.

5. Tatsumi, E., Sugimoto, T., Minato, K. Sagawa, K., Civin, C.I., Early, A., Preisler, H., Henderson, E., and Minowada, J. Heterogeneity of AML and CML Blasts as Determined by Multiple Monoclonal Antibodies. Proc. Am. Soc. Clin. Oncol. 1: 137, 1982.

6. Civin, C.I., Strauss, L.C., Brovall, C. and Shaper, J.H. Characterization of Four Monoclonal Antibodies Reactive with Human Marrow Subsets. Blood 50(5): 95a, 1982.

7. Vaughan, W.P., Strauss, L.C., Burke, P.J., Skubitz, K.M., Schwartz, J.F., Karp, J.E., and Civin, C.I. Surface Marker Phenotype (SMP) Predicts Response to Therapy in Acute Non-Lymphocytic Leukemia (ANLL). Amer. Soc. Clin. Oncol., In press, 1983.

8. Strauss, L.C., Vaughan, W.P., Schwartz, J.F., Burke, P.J., Karp, J.E., and Civin, C.I. Surface Marker Phenotype (SMP) and Blast Morphology in Acute Non-Lymphocytic Leukemia (ANLL). Amer. Fed. Clin. Res., In press, 1983.

9. Strauss, L.C., Stuart, R.K., and Civin, C.I. Antigenic Analysis of Hematopoiesis. Amer. Assoc. Cancer Res. 23: 266, 1982.

10. Civin, C.I., Brovall, C., Strauss, L.C., Schwartz, J.F., and Shaper, J.H. Cell Surface Antigens Defined by Four Monoclonal Antibodies Raised Against KG-1a Cells. Hybridoma 2: 125a, 1983.

Report:

1. General Scientific Goals

Unchanged from original grant proposal.

2. Concise Description of Year 1 Results

(Keyed to Experimental Design and Specific Aims Sections of Initial Grant)

(1) Development of monoclonal antibodies (McAb) directed against immature human myeloid cells.

(1a) Murine McAb raised to human myeloid leukemia cell lines and mature granulocytes:

We showed that anti-My-1, the first anti-human granulocytic cell-specific McAb (which reacted specifically with neutrophils and all morphologically-defined neutrophilic precursor cells) did not bind to granulocyte/macrophage colony-forming cells (CFC-GM), though it recognized leukemic cell lines and blast cells from patients (Strauss et. al., 1983). Thus, My-1 does not appear to be a hematopoietic progenitor cell antigen. A number of McAb with similar specificity have been reported (Perussia et. al., 1982; Knapp, 1982; Skubitz et. al, 1983). We showed that of 17 additional IgM anti-neutrophil McAb that we obtained, all recognized an oligosaccharide epitope contained specifically in Lacto-N-fucopentaose III (Huang et. al, 1983). Surprisingly, this immunodominant antigen is also expressed in normal and

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malignant human lung and intestinal tissue and is the stage-specific embryonic antigen, SSEA-1 (Huang et. al, 1983).

The anti-neutrophil McAb, AHN-1-3, 7 and 8, were studied in similar fashion (Strauss et. al., 1983). AHN-1-3 recognize the My-1 epitope, but on glycoproteins as well as glycolipids (Skubitz et. al., 1983). The AHN-7 IgG_1 McAb recognizes all granular leukocytes (neutrophils, basophils, eosinophils, and monocytes) and binds to about 75% of CFC-GM (revealing previously undescribed heterogenity of CFC-GM). The AHN-8 IgG_1 McAb is unique in its specificity for neutrophils beyond the metamyelocyte stage of maturation.

We have raised other McAb against myeloid cell lines, and characterization of these is progressing. Anti-My-10-13, 4 anti-KG-1a McAb selected for binding to the KG-1a (undifferentiated leukemia) cell line, but not to mature granulocytes, appear particularly interesting (Civin et. al., 1983) as candidate anti-progenitor cell McAb. Of these 4 monoclonal antibodies, anti-My-10 has the most narrow cellular specificity. It binds to KG-1a and KG-1 cells, but not to other lymphoid or myeloid cell lines or to normal human blood cells. Only approximately 3% of normal human marrow cells bind this antibody. This My-10-positive marrow cell population includes morphologically immature blast forms of many lineages. Our data using immune adherence ("panning") techniques indicate that My-10 is expressed on all CFC-GM. In addition, the My-10-positive marrow cell population is highly enriched in terminal deoxynucleotidyl transferase-positive cells. Early results suggest that erythroid burst-forming units (BFU-E) are also My-10-positive, but definitive experiments with erythroid and multipotent (CFU-GEMM) progenitors are in progress. Work in progress will fully characterize the cellular distribution of the My-10 antigen, but it is already clear that My-10 is unique in its expression on cell surfaces of hematopoietic progenitors, but not on mature myeloid cells of any lineage. Using vectorial cell surface labelling with ^{125}I and immunoprecipitation or Western blotting, we have established that the My-10 antigen is a cell membrane protein of approximately 115 kD. Our preliminary data also indicate that CFU-GM express My-11 and My-13, but not My-12. My-11 has an apparent Mr of approximately 230 kD.

(1b) <u>Murine McAb raised to progenitor-enriched marrow cell populations</u>:

We have hyper-immunized mice with My-1-negative normal human marrow cells (which are 2-5-fold enriched for CFC-GM), obtained by treatment of plastic-nonadherent marrow cells with anti-My-1 and complement then recovery of residual whole viable cells by density gradient centrifugation. In one fusion, we identified an IgG_{2a} McAb that, by indirect immunofluorescence, binds to 1-10% of normal marrow cells, but not to mature neutrophils, lymphocytes, monocytes, or red cells.

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We have recently hyperimmunized mice with My-10-positive normal human marrow cells (obtained by panning; 5-30-fold enriched for CFC-GM) and are preparing to derive McAb from these mice. We will screen the hybridomas for binding to subsets of My-10-positive cells.

(1c) Development of human anti-progenitor McAb:

This work has been postponed until techniques for production of human McAb are perfected.

(2) McAb binding to colony-forming cells:

As described above, candidate anti-progenitor cell McAb, such as anti-My-10-13, are being tested for binding to defined colony-forming units. Interesting preliminary experiments suggest that the "pre-CFC-GM" (as defined in "continuous" human marrow culture) expresses My-10.

(3) Isolation and study of hematopoietic progenitor cells:

Using complement-mediated cytotoxicity, combined with density gradient centrifugation, panning, and fluorescence-activated cell sorting with the appropriate McAb, we can greatly enrich for CFC-GM and other morphologic blast cells. We have begun to study these immature cell populations. For example, preliminary experiments using propidium iodide staining of nuclei indicate a difference in DNA content between My-10-positive and -negative marrow cell populations.

References:

1. Strauss, L.C., Stuart, R.K., and Civin, C.I. Antigenic Analysis of Hematopoiesis: I. Expression of the My-1 Granulocyte Surface Antigen on Human Marrow Cells and Leukemic Cell Lines. Blood, In press, 1983.

2. Perussia, B., Trinchieri, G., Lehman, D., Jankiewicz, J., Lang, B., and Rovera, G. Monoclonal Antibodies that Detect Differentiation Surface Antigens on Human Myelomonocytic Cells. Blood 59: 382, 1982.

3. Knapp, W. Monoclonal Antibodies Against Differentiation Antigens of Myelopoiesis. Blut 45: 301, 1982.

4. Stuhlitz, K.M., Zhen, T., and August, J.T. A Human Granulocyte-Specific Antigen Characterized by Use of Monoclonal Antibodies. Blood 61: 19, 1983.

5. Huang, L.C., Civin, C.I., Magnani, J.L., Shaper, J.H., and Ginsburg, V. My-1, the Myeloid-specific Antigen Detected by Mouse Monoclonal Antibodies, Is a Sugar Sequence Found in Lacto-N-fucopentaose III. Blood, In press, 1983.

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6. Strauss, L.C., Skubitz, K.M., August, J.T., and Civin, C.I. Antigenic Analysis of Hematopoiesis: III. Expression of Human Neutrophil Antigens on Normal and Leukemic Marrow Cells. Submitted, 1983.

7. Civin, C.I., Brovall, C., Strauss, L.C., Schwartz, J.F., and Shaper, J.H. Antigenic Analysis of Hematopoiesis II. Cell Surface Antigens Defined by Four Monoclonal Antibodies Raised Against KG-1a Cells. Submitted, 1983.

3. Specific Objectives for the Coming Year (Year 2)

(1) Continued McAb development:

(1a) Murine McAb raised to human myeloid leukemia cell lines and mature granulocytes:

We have raised new murine McAb against the K-562 cell line and against mature granulocytes and red cells (the latter two sets of McAb as parts of other projects). We will test the most novel of these for marrow cell reactivity, giving priority to McAb which detect protein antigens. We have hyperimmunized fresh mice with the KG-1a, K-562, and HEL cell lines, respectively, and we will develop McAb from these mice, using screening strategies designed to select IgG McAb directed against immature hematopoietic cells. In separate, but related projects, we will characterize the antigens recognized by these antigens, using biochemical methods.

(1b) Murine McAb raised to progenitor-enriched marrow cell populations:

We will study the cellular specificity of the IgG_{2a} McAb raised to My-1-negative normal human marrow cells (see Section 2 (1b) above). We will probably not, however, use the mice immunized with My-1-negative marrow cells, since we now have available mice hyperimmunized with immature normal myeloid cells in more pure form (i.e., My-10-positive cells, which are more enriched for CFC-GM). From these latter mice, we will develop and select McAb which specifically bind to subsets of My-10-positive marrow cells. We have developed a method to test for binding to the small numbers of available My-10-positive marrow cells, using cytocentrifuged, gently-fixed (0.5% paraformaldehyde) cells obtained by panning as targets; IgG-secreting hybridomas will be tested for binding to My-10-positive normal marrow cells using a biotinylated protein-A/FITC- or enzyme-labelled avidin system for sensitive detection (anti-My-10 McAb [an IgG_1] bound to the cells will not be detected by protein A at pH 7.4). In addition, we can screen by flow cytometry and select McAb that react with <10% of whole marrow and no My-10-negative cells. For the immediate future, we will ignore progenitors that may be My-10-negative and concentrate on subdividing the My-10-positive progenitor-rich cells. We feel that this scheme of immunizing and screening using normal marrow progenitors has sufficient potential for obtaining extremely progenitor-specific McAb to justify the much

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greater effort required, compared to the above approach using cell lines. However, both approaches will be attempted concurrently, since the approach of using cell lines has already yielded valuable McAb (see above).

(1c) Development of human anti-progenitor McAb:

Since major contributions can be made to the study of hematopoiesis by development of appropriately specific murine McAb, a process which is now routine in our hands, we will continue to exploit murine McAb. We will await technical improvements in methodology for production of human McAb.

(2) McAb binding to colony-forming cells:

Candidate anti-progenitor cell McAb will be tested for binding to as many types of measurable colony-forming cells as possible. Since these are murine anti-human McAb, human colony-forming cells have highest priority. Until recently, we tested McAb only for binding to human CFC-GM, using a soft agar/human placenta conditioned medium system. In addition, we are now (i) testing human CFC-GM using methylcellulose cultures and other sources of colony-stimulating factor, (ii) testing human BFU-E, CFU-E, and CFU-GEMM using several methods, (iii) testing "pre-CFU-GM" in "continuous" human marrow cultures, and (iv) exploring assays for other progenitors and in other species (where reconstitution experiments could be done).

We are especially interested in the multilineage colonies described by Dr. M. Ogawa (Exp. Hematol. 10 (Suppl): 166, 1982; Dr. Ogawa has kindly offered to teach us his methodology, and in several weeks, Dr. L. Strauss will spend a sufficient amount time in Dr. Ogawa's laboratory to learn these methods). In essence, Dr. Ogawa's cultures contain colonies of all the myeloid lineages and large numbers of "mixed" colonies; our routine use of these cultures might supplant the use of several cultures to test each committed CFC separately, and would at the same time allow testing of the presumed earlier progenitor cells that give rise to mixed colonies. Thus, in Year 2, we will expand the repertoire of CFC tested for McAb binding.

(3) Isolation and study of hematopoietic progenitor cells:

In isolating antigen-positive versus -negative marrow cells, we have found that the panning technique fits our needs very well. We will continue to use this method, along with complement-mediated cytotoxicity (where possible), to screen initially for marrow cell binding by our McAb. Flow cytometry and fluorescence-activated cell sorting will be used to ask questions related to quantitative antigen expression.

McAb isolated, progenitor-rich cells (e.g., My-10-positive marrow cells) will be evaluated for:

(a) cytomorphology and cytochemistry,
(b) terminal deoxynucleotidyl transferase content,

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(c) expression of other antigens (defined by other McAb).
(d) DNA content by flow cytometry (cell cycle phase)

We will place the progenitor-rich cells into liquid culure, and evaluate them over time by the above parameters, with and without the addition of various factors or cell types, e.g.

(a) colony-stimulating factor
(b) erythropoietin
(c) burst-promoting factor
(d) helper T-cells
(e) cytotoxic/suppressor T-cells
(f) granulocytes
(g) lactoferrin
(h) endotoxin
(i) drugs which affect adenyl cyclase activity
(j) McAb and purified antigens

4. Human Subjects

Unchanged from original grant proposal.

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SECTION I

Form Approved OMB No. 0925-0001

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

APPLICATION FOR CONTINUATION GRANT

REVIEW GROUP	TYPE	ACTIVITY	GRANT NUMBER (Insert on all pages)
BBB	5	R01	CA32318-03

TOTAL PROJECT PERIOD
From 05/01/82 Through 04/30/85

REQUESTED BUDGET PERIOD
From 05/01/84 Through 04/30/85

To Be Verified By Applicant. Check information in Items 1 Through 6. If Incorrect, Furnish Correct Information in Item 13.

1. TITLE
ANTIGENIC ANALYSIS OF HEMATOPOIESIS

2a. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (Name and address, street, city, state, zip code)
CIVIN, CURT I
JOHNS HOPKINS ONCOLOGY CENTER
600 NORTH WOLFE STREET
BALTIMORE, MD 21205

4. APPLICANT ORGANIZATION (Name and address, street, city, state, zip code)
JOHNS HOPKINS UNIVERSITY
SCHOOL OF MEDICINE
720 RUTLAND AVENUE
BALTIMORE, MD 21205

5. ENTITY IDENTIFICATION NUMBER
152059511085

2b. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT
ONCOLOGY CENTER

2c. MAJOR SUBDIVISION
SCHOOL OF MEDICINE

3. ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR BIOMEDICAL RESEARCH SUPPORT GRANT (See instructions)
01 SCHOOL OF MEDICINE

6. TITLE AND ADDRESS OF OFFICIAL IN BUSINESS OFFICE OF APPLICANT ORGANIZATION
DIRECTOR
OFFICE OF ACCOUNTING SERVICES
JOHNS HOPKINS UNIVERSITY
CHARLES & 34TH STREETS
BALTIMORE, MD 21218

COMPLETE THE FOLLOWING (See instructions)

7. HUMAN SUBJECTS
☐ NO ☒ YES
OR ☐ Exemption # _____
OR ☒ Form HHS 596 enclosed

8. RECOMBINANT DNA
☒ NO ☐ YES

11. INVENTIONS (See instructions)
☐ NO ☒ YES
OR ☐ Previously reported
OR ☒ Not previously reported

9. PERFORMANCE SITE(S) (Organizations and addresses)
Oncology 3-121
Johns Hopkins Oncology Center
600 North Wolfe Street
Baltimore, Maryland 21205

TELEPHONE INFORMATION

	AREA CODE	TELEPHONE NO. AND EXTENSION
12a. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (Item 2a)	301	955-8816 -8142
12b. NAME OF BUSINESS OFFICIAL (Item 6) Lawrence E. Johnston	301	338-8137
12c. NAME AND TITLE OF OFFICIAL SIGNING FOR APPLICANT ORGANIZATION (Item 15) David A. Blake, Ph.D. Associate Dean for Research	301	955-3061

10. DIRECT COSTS REQUESTED FOR BUDGET PERIOD
$77,734

13. USE THIS SPACE FOR CORRECTIONS TO ITEMS 1 THROUGH 6. INDICATE THE NUMBER(S) WHERE ANSWER(S) APPLY

JH052260

14. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application. Willful provision of false information is a criminal offense (U.S. Code, Title 18, Section 1001)	SIGNATURE OF PERSON NAMED IN 2a. (In ink. "For" signature not acceptable) Curt I. Civin, MD	DATE 2/7/84
15. CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true and complete to the best of my knowledge and accept the obligation to comply with the Public Health Service terms and conditions if a grant is awarded as the result of this application. A willfully false certification is a criminal offense (U.S. Code, Title 18, Section 1001)	SIGNATURE OF PERSON NAMED IN 12c. (In ink. "For" signature not acceptable) David A. Blake	DATE 2/7/84

RETURN COMPLETED APPLICATION TO PHS AS SOON AS POSSIBLE:
NO LATER THAN 1 MARCH 1984

INVENTION

Title: Human Stem Cells and Monoclonal Antibodies

Inventor: Curt I. Civin, M.D.

Patent applied for: February 6, 1984

JH052261