

CLINICAL INVESTIGATION STUDY PROPOSAL

- I. Activity: Nuclear Medicine Branch, Radiology Department, Naval Hospital, NMCNCR, Bethesda, Maryland 20814.
- II. Title: Phase III study of Indium - 111 labeled granulocytes for detection of inflammatory processes in humans.
- III. Investigators:
- A. Principal:  
Naval Hospital, NMCNCR, Bethesda, MD  
LCDR Eugene D. Silverman, MC, USN, Head, Nuclear Medicine Branch,  
Radiology Department  
Telephone: 295-4982
- 5% of time required for study  
Projected rotation date: July 1985
- B. Associates:  
Naval Hospital, NMCNCR, Bethesda, MD  
LT Walter E. Drane, MC, USNR  
Nuclear Medicine Staff Physician  
Radiology Department  
Telephone: 295-4983
- 5% of time required for study  
Projected rotation date: August 1986
- C. Naval Hospital, NMCNCR, Bethesda, MD  
LCDR Kastytis Karvelis, MC, USNR  
Resident in Nuclear Medicine  
Telephone: 295-4976
- 5% of time required for study  
Projected rotation date: August 1985
- D. Estimated Duration of Study: 2 years
- IV. Identification of Drugs and Devices to be used in the study:  
Indium - 111 Oxine labeled granulocytes for the detection of inflammatory processes in humans (no trade name)
- V. Manufacturing Information:
- A. Source of drug: Amersham Corporation 2636 South Clearbrook Dr.,  
Arlington Heights, IL 60005
- B. Dosage form: Indium - 111 labeled granulocytes, intravenous injection
- C. FDA forms - FD1571, 1572, 1573: See enclosed forms..

D. Cost to CIP for drugs and devices:

Outside of incidental lab supplies such as needles and syringes, the only item requiring special purchase will be the In-111 oxine. The cost is approximately \$50.00 per vial, and this will provide enough material to scan two patients. The cost of enough Ga-67 to scan two patients is also \$50.00. Thus, we see no need to request additional funds in order to undertake this study.

VI. Preclinical information and pharmacology: See enclosed manufacturers brochure.

VII. Clinical Information:

A. Objectives:

- 1) To evaluate inflammatory processes with In-111 oxine labeled granulocytes.

B. Background:

1) Despite increasing success of new antibiotic therapy, a significant number of our patients continue to experience serious morbidity and mortality as a result of infectious complications of their disease and of the therapy administered. This is particularly true in patients who develop bone marrow suppression and resulting neutropenia. In spite of multiple diagnostic procedures, including both radiographic examinations and laboratory tests, we are frequently unable to define the site of the infectious process.

Within the past few years, use of radionuclide imaging has become valuable imaging modality to define abscess sites. The major tracer employed for this purpose is Gallium-67 as the citrate (1). Attempts at further specificity have included tagging patient white blood cells with this radiotracer, thereby hopefully better defining sites of infection (2). Although the results of this technique are somewhat variable, the concept of radiolabeling white cells carries major clinical implications.

Indium-111 is a radionuclide which has been clinically employed for bone marrow imaging (3,4). The physical characteristics which include a half life of 67 hours and excellent gamma ray energies suitable for camera imaging (173 and 247 keV) have lead to the use of this tracer for tagging human platelets, polymorphonuclear leukocytes, and lymphocytes (5-7).

The labeling of white blood cells using Indium-111 complex, when dissolved in ethanol, diffuses passively through the white cell membrane, allowing the In-111 to bind to intracellular components (6). Between 75 and 80% of the radionuclide can be tagged to the white cells and following the in vivo administration, the radiolabeled cells remained stable for approximately 24 hours. Clearance of the tracerlabeled cells from the circulating blood occurs with a half time of approximately 8-9 hours and produces accumulation in the normal liver and spleen, as well as sites of infection.

When compared to abscess detection using Gallium-67 citrate, the In-111 labeled white cells produced abscess-to-blood radiation ratios of between 35/1 and 117/1 vs. a maximum 8/1 ratio seen with Ga-67 imaging (3).

2) Investigational Drugs:

Many clinical trials have been reported utilizing In-111 oxine labeling of a variety of blood components (8-10). With respect to platelet tagging, labeling efficiencies of 65% have been achieved, and the In-111 stays bound to the platelets with little tracer seen in the plasma and none in the urine or feces; blood disappearance curves are similar to those manifested when Chromium-51 is used as the platelet label (10). Results of these studies indicate that the technique is not only safe (6, 11, 12) but the data, in the form of image formation, has significant clinical relevance for detecting abscesses and sites of venous thrombosis.

3) Protocol Design:

Due to the large number of patients which have already been evaluated using Indium-111 leukocytes, and the apparent efficacy and safety that the product has demonstrated, we wish to commence with Phase III investigation.

- 1) A total of 150 patients will be studied.
- 2) Patients will be 18 years or older and non-pregnant.
- 3) Patient will be admitted to the study after referral to Nuclear Medicine by a primary physician.
- 4) All patients should have elevated temperature, white blood cell count and other pertinent diagnostic data leading to the suspicion of abscess.

White blood cells will be procured from the patient being imaged. Fifty ccs of blood will be processed to remove red cell and plasma fractions. The remaining white blood cells (approximately  $1 \times 10^8$  cells) will be used for the scan.

The In-111 oxine preparation will be supplied by Amersham Corporation, Arlington Heights, Illinois. The labeling will be performed under the direction of Richard Adams, radiochemist, of the Nuclear Medicine Branch, Radiology Department, Naval Hospital, NMCNCR, Bethesda, Maryland.

All radiolabeled blood components will be quantitated and calibrated in the Nuclear Pharmacy prior to injection. An aliquot of the labeled blood component will be chromatographed to determine labeling efficiency, and an aliquot will be saved for sterility and pyrogen testing.

Patients entered in the study will be imaged in the Department of Nuclear Medicine. Imaging will be performed between 18-24 hours after administration of the labeled granulocytes. If the clinical situation warrants, images may be obtained as early as four hours post infusion.

The patient's clinical presentation will determine the anatomic region of the body selected for scanning (ie. whole body vs. limited views).

## POSSIBLE TOXICITIES

1) Pulmonary reaction: It is known that with the transfusion of large numbers of granulocytes, pulmonary leukoagglutination with complement activation can occur. The concentration of granulocytes to be delivered under this protocol is not large enough to cause significant pulmonary reactions. Also, only autologous granulocytes will be used for labeling and injection.

Published data indicate that the usual injected dose is between 200 and 500 microcuries of In-111 (8, 10, 12). For comparative purposes, the usual injected dose of In-111 chloride bone marrow imaging is 2.0 mCi. We will be administering approximately 300 uCi doses.

Estimates of radiation dose following In-111 oxine labeled lymphocytes have been published.

### PUBLISHED DOSIMETRY DATA FOR INDIUM-111 OXINE

#### LABELED BLOOD COMPONENTS

#### Rads for 500 microcuries injected dose

<u>Target</u>	<u>Neutrophils</u> (8)	<u>Platelets</u> (10)	<u>Lymphocytes</u> (12)
Whole Body	.3	.2	.3
Liver	2.4	.3	.8
Spleen	10.2	12.3	10.0

The initial phase of the study will be terminated after 150 patients have been studied. At this time, a review of the protocol will be undertaken in order to determine whether an extension of the study would be clinically warranted.

VIII. Informed Consent: See enclosed Informed Consent Form.

IX. Qualifications of Investigators: See enclosed curriculum vitae.

X. Other Supporting Data:

The use of In-111 labeled blood products has become a widely accepted clinical tool in nuclear medicine. Attached, please find a bibliography as well as additional references which detail the widespread use of this diagnostic agent. In addition, the recently approved 'orphan drug act', will make it possible for several drug companies to obtain FDA approval for this agent in the near future, thus eliminating the need to sponsor our own IND.