CITY OF HOPE NATIONAL MEDICAL CENTER
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DEPARTMENT OF RADIATION ONCOLOGY

TITLE: Pilot Study: Detection of Carcinomas Using ^{64}Cu-Labeled M5A Antibody to Carcinoembryonic Antigen (CEA)

CITY OF HOPE PROTOCOL NUMBER/VERSION: IRB # 14238 **Protocol Version date: 05/03/2018**

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Amendment 06	Protocol Dated 08/11/16	Version: 06
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Amendment 08	Title Page Dated 01/24/17	Version: 08
Amendment 09	Title Page Dated 03/01/17	Version: 09
Amendment 10	Protocol Dated 09/27/17	Version: 10
Amendment 11	Title Page Dated 10/25/17	Version: 11
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Amendment 13	Title Page/Protocol 05/03/18	Version: 13
Amendment 14	Title Page Dated 07/03/18	Version: 14
Amendment 15 at Continuation	Title Page Dated 06/03/19	Version: 15
Amendment 16 at Continuation	Title Page Dated 5/18/20	Version: 16
Amendment 17 at Continuation	Protocol Dated 05/03/2018 (tp)	Packet: 17
Amendment 18 at Continuation	Protocol Dated 05/03/2018 (tp)	Packet: 18
Amendment 19 at Continuation	Protocol Dated 05/03/2018 (tp)	Packet: 19

SITE: CEA-Producing Malignancies
STAGE (If applicable): Any
MODALITY: Radioimmunoimaging IV
TYPE: Pilot

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Protocol Synopsis

Protocol Title:
Pilot Study: Detection of Carcinomas Using ^{64}Cu-Labeled M5A Antibody to Carcinoembryonic Antigen (CEA)
Brief Protocol Title for the Lay Public (if applicable):
Pilot Study: Detection of Carcinomas Using ^{64}Cu-Labeled M5A Antibody to Carcinoembryonic Antigen (CEA)
Study Phase:
Pilot
Participating Sites:
City of Hope
Rationale for this Study:
CEA expression in normal tissues is largely restricted to the intestinal epithelium but is also seen in other sites, such as the testes. This very limited normal tissue distribution combined with the widespread occurrence of CEA in tumors, has led CEA to be a prominent target for experimental monoclonal antibody based radioisotopic imaging (radioimmunoscintigraphy).
Objectives:
The primary objective of this pilot study is to determine the ability of ^{64}Cu labeled M5A antibody to localize to CEA positive cancers (such as GI, lung, medullary thyroid and breast cancers), as determined by PET imaging. Secondary objectives are: 1. To characterize the frequency and titer of the human anti-human antibody (HAHA) response to ^{64}Cu labeled M5A antibody. 2. To determine the safety of administration of ^{64}Cu labeled M5A antibody.
Study Design:
This is a three-year open-labeled pilot study that will enroll **20** patients with CEA-producing malignancies at the City of Hope National Medical Center.
Endpoints:
The primary aim of this pilot study is to evaluate the tumor targeting, pharmacokinetic, and immunogenicity properties of ^{64}Cu labeled M5A antibody. The results of this pilot study will be used to determine if the antibody should be studied in a larger imaging trial. The data for the 20 patients imaged will be used to summarize the scan results.
Sample Size:
20 patients

Estimated Duration of the Study

3 years

Summary of Subject Eligibility Criteria:

Inclusion Criteria:

Inclusion Criteria

- ❖ Disease Status
    - Patients must have histologically confirmed primary or metastatic cancer. If biopsies were performed at an outside facility, the histology must be reviewed and confirmed by the Department of Pathology at the City of Hope.
    - Patients must have tumors that produce CEA as documented by a current or past history of an elevated serum CEA above the institutional limit of normal, or by immunohistochemical methods. NOTE: Patients with colorectal cancer are exempt from this requirement since >95% are CEA positive.
- ❖ Age Criteria, Performance Status and Life Expectancy
    - Patients must be 18 years of age or older.
- ❖ Child Bearing Potential

The effects of ^{64}Cu-M5A on the developing fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control or abstinence) prior to study entry and for six months following duration of study participation. Should a woman become pregnant or suspect that she is pregnant while participating on the trial, she should inform her treating physician immediately.

- ❖ Protocol-Specific Criteria
    - Patients must have a known site of disease. Please note, for patients undergoing neoadjuvant therapy, this requirement must be met retrospectively prior to the start of neoadjuvant therapy. Patients who are in radiological/clinical remission after neoadjuvant therapy, prior to infusion of radiolabeled antibody, are still eligible.
    - Although not mandated by the protocol, the results of the CT scans and labs (CBC, CMP) that are performed as part of the standard work up should be available and should have been done within 2 months prior to study entry.
- ❖ Informed Consent/Assent

All subjects must have the ability to understand and the willingness to sign a written informed consent.

- ❖ Prior Therapy
    - Prior therapy (chemotherapy, immunotherapy, radiotherapy) must be completed at least 2 weeks prior to infusion of radiolabeled antibody
    -

Exclusion Criteria:

- Patients should not have any uncontrolled illness including ongoing or active infection.
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to ^{64}Cu-M5A.
- Patients must not have received prior chemotherapy or radiation for ≥ 2 weeks before study enrollment.
- Pregnant women are excluded from this study because ^{64}Cu-M5A is an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ^{64}Cu-M5A, breastfeeding should be discontinued if the mother is treated with ^{64}Cu-M5A.

❖ Study-Specific Exclusions

- Any patient who has had exposure to mouse or chimeric (human/mouse) immunoglobulin and has antibody to the M5A.

❖ Non-Compliance

Subjects, who in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study.

Investigational Product Dosage and Administration:

15 mCi/5 mg ^{64}Cu-labeled M5A antibody, IV

Clinical Observations and Tests to be Performed:

See study calendar, section 10.

Statistical Considerations:

The data will be summarized using two methods. Both methods will examine the efficacy of each modality in locating cancer in each of four regions: primary, hepatic, extra-hepatic abdominal, and extra-abdominal. For the first method, referred to as a lesion analysis, the efficacy of each modality will be evaluated where a successful outcome will be defined as the ability of at least one known tumor identified by conventional imaging modalities to be imaged using the M5A antibody. For the second method, referred to as a region analysis, a successful outcome will be defined as the identification of suspicious tissue within a region.

Sponsor/Licensee:

City of Hope

Table of Contents

Abbreviations

Abbreviation	Meaning
AE	Adverse Event
CEA	Carcinoembryonic Antigen
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLT	Dose Limiting Toxicity
DSMC	Data Safety Monitoring Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IDS	Investigational Drug Services
IND	Investigational New Drug
IRB	Institutional Review Board
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
PD	Progressive Disease
PI	Principal Investigator
PMT	Protocol Monitoring Team
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease

1 Goals and Objectives (Scientific Aims)

The primary objective of this pilot study is to determine the ability of ^{64}Cu labeled M5A antibody to localize to CEA positive cancers (such as GI, lung, medullary thyroid and breast cancers), as determined by PET imaging.

Secondary objectives are:

- To characterize the frequency and titer of the human anti-human antibody (HAHA) response to ^{64}Cu labeled M5A antibody.
- To determine the safety of administration of ^{64}Cu labeled M5A antibody.

2 Background

2.1 Introduction/Rationale for Development

Carcinoembryonic antigen (CEA) is a 180 kD glycoprotein that was among the first tumor markers to be identified (1). This antigen is well characterized with respect to both its molecular nature and its tissue distribution in man (2-4). CEA expression in normal tissues is largely restricted to the intestinal epithelium but is also seen in other sites, such as the testes (5). This very limited normal tissue distribution combined with the widespread occurrence of CEA in tumors, has led CEA to be a prominent target for experimental monoclonal antibody based radioisotopic imaging (radioimmunoscintigraphy) (6-8).

Early work with polyclonal anti-CEA antibodies and ^{131}iodine label (6-8) was sufficiently encouraging to prompt further trials using murine monoclonal anti-CEA antibodies labeled with the metallic radionuclide ^{111}indium (^{111}In) (9-11). ^{111}In labeled anti-CEA antibody radioimmunoscintigraphy clinical trials were initiated by Drs. Beatty and Shively at the City of Hope first using the murine anti-CEA monoclonal antibody, designated T84.66 (BB-IND 2014), an IgG1 with very high affinity for CEA (K=2.6 x 10^{10} M-1) and with no cross-reactivity to normal tissues (12, 13). Initial trials used relatively low doses (2 mCi ^{111}In activity/200 µg T84.66 antibody) to minimize patient anti-antibody response. With this agent approximately 67% (18/27) of primary colorectal carcinomas and 75% (3/4) of extra-abdominal colorectal metastases were visualized as hot spots (10, 14-16). No significant adverse effects were noted. This trial also provided correlation of radioimmunoscintigraphy findings with surgical and pathologic findings at the time of laparotomy. This allowed histologic confirmation of tumor in the areas of increased antibody uptake and correlation of tumor images with tumor ^{111}In activity, tumor CEA content, and tumor histologic characteristics. Tumors that were imaged had higher uptake of ^{111}In (10.7 + 3.5 %ID/kg vs. 3.6 + 1.5 %ID/kg), were larger (38.1 + 17.8 cm^3 vs. 6.0 + 1.7 cm^3), were more fungating than ulcerative, suggesting better vascularity, had higher CEA content (12.9 + 3.6 µg/gm vs. 3.3 + 1.7 µg/gm), and, by immunohistology, had CEA staining at the apical regions of the cells or the intraluminal regions of tumor. Overall, these results suggested that the best imaging results were in tumors that were large, well-vascularized, and had large amounts of CEA that was accessible to the antibody. Although approximately 40% of hepatic metastases were detected, almost all were visualized as cold spots due to the relatively high non-specific uptake of ^{111}In labeled T84.66 antibody by surrounding normal liver.

Murine antibodies have the disadvantage of being recognized as foreign by the patient's immune system, which can lead to the formation of human anti-mouse antibodies (HAMA) in 30-50% of patients (17-20). The formation of HAMA can hasten blood clearance and therefore compromise the imaging or therapeutic efficacy of subsequently administered antibody (19, 21). Investigators have recently evaluated human/mouse chimeric and humanized antibodies, which have demonstrated decreased immunogenicity (22-26). Chimeric T84.66 (cT84.66) is a human/murine chimeric IgG1 monoclonal antibody developed at the City of Hope with high affinity (KA = 1.16 x 10^{11} M-1) and specificity to CEA (27). Chimeric T84.66 was initially evaluated at this institution, conjugated to isothiocyanatobenzyl DTPA and radiolabeled with ^{111}In, in a pilot biodistribution trial which entered patients with metastatic CEA-producing malignancies of various histologies (28). ^{111}In-DTPA-cT84.66 was further evaluated in an antibody protein dose escalation trial in 15 patients with colorectal cancer (29). Results from these two studies demonstrated targeting to CEA-producing metastatic sites, imaging sensitivity comparable to other intact anti-CEA monoclonals, no allergic reactions, decreased immunogenicity compared to murine monoclonals, and no significant changes in biodistribution or tumor localization with escalation of antibody protein doses from 5 mg to 105 mg. In addition, antibody uptake determined from biopsy samples demonstrated that cT84.66, if labeled with ^{90}yttrium (^{90}Y), could potentially deliver therapeutic radiation doses to tumor and regional lymph nodes in a subset of patients.

M5A is the humanized version of cT84.66 engineered to further reduce the immunogenicity compared to cT84.66. Recently a phase I therapy trial of ^{111}In/^{90}Y labeled M5A was completed. Tumor targeting was demonstrated. Eighteen patients received the initial ^{111}In-M5A imaging dose of the antibody, with 17 of 18 targeting known sites of disease. Sixteen patients received the therapy dose of ^{90}Y radiolabeled M5A of which only two patients demonstrated an anti-antibody response suggesting further decrease in immunogenicity compared to chimeric T84.66. No allergic reactions were seen. (Wong et al, unpublished results; manuscript in preparation)

Given the experience with M5A to date, M5A may also be a potential imaging agent of CEA+ cancers, especially when labeled with a positron emitters such a Cu-64 for PET imaging. PET imaging is rapidly becoming an important imaging modality for an increasing number of malignancies for its ability to detect and differentiate metabolic and phenotypic differences between tumor and normal tissues. The use of positron emitting radionuclides provides advantages in imaging quality over traditional imaging using gamma-emitting radionuclides.

Cu-64 is a promising PET radionuclide with a half-life of 12.7 hours. It is currently being evaluated in clinic trials, which including ^{64}Cu-ATSM, which targets tumor hypoxia, and ^{64}Cu-trastuzumab, which targets Her2+ cancers. Images with ^{64}Cu-trastuzmab compare favorably to those seen on an earlier COH trial using ^{111}In-trastuzumab in patients with Her2+ breast cancer.

2.2 Overview of Proposed Study

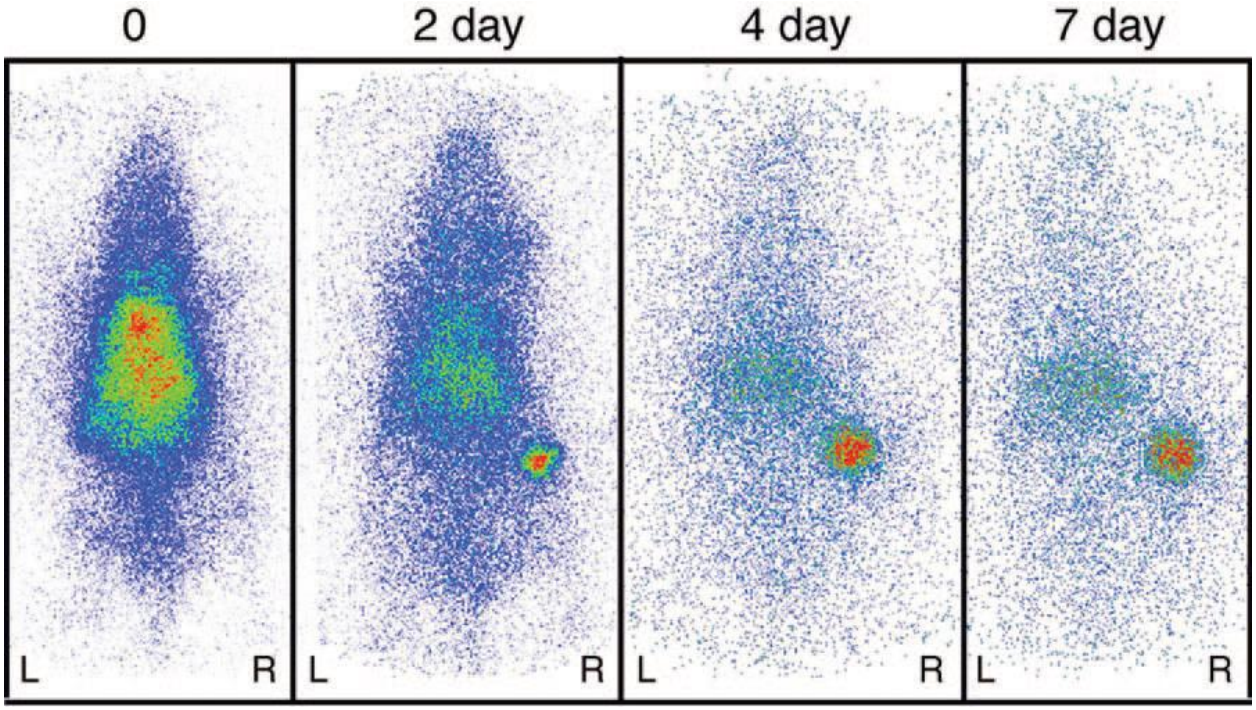
This is a three-year open-labeled pilot study that will enroll **20** patients with CEA-producing malignancies at the City of Hope National Medical Center.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

2.3 Preclinical Studies

In-111-DOTA M5A Anti-CEA Antibody

The pre-clinical characterization of M5A has been published (30). Tumor uptake at 48 hours was 32.65 %injected dose/gram in LS174T human colon cancer xenograft tumor bearing mice. Murine imaging studies with In-111-DOTA M5A are shown below with clearly seen tumor targeting.



Tumor imaging by PET and targeting is also seen with ^{64}Cu-DOTA-M5A in the same tumor bearing mouse model. (Image at 23 hours in mouse with right and left SQ tumors; see Fig. 3)

The preclinical evaluation of Cu-64 labeled M5A is summarized below:

Radiolabeling of hT84.66-M5A/NHS-DOTA

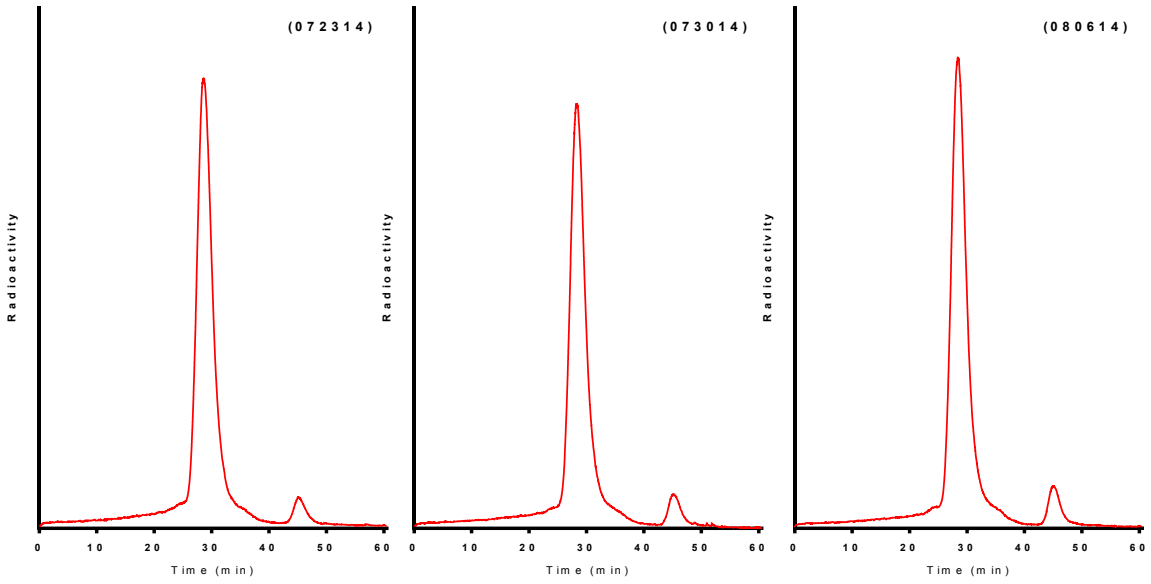
Radiolabeling with Copper-64

The hT84.66-M5A/NHS-DOTA Final Vialed Product (FVP) was radiolabeled with Copper-64 (^{64}Cu) obtained from Washington University (St. Louis) in a manner similar to that planned for clinical studies. The radiolabelings was performed on July 23, 2014 to August 6, 2104 according to **RIT SOP 0311** "Radiolabeling of hT84.66-M5A/NHS-DOTA with Cu-64 for Clinical Use"

and purified by Size Exclusion Chromatography according to **RIT SOP-0322** "HPLC Purification of Radiolabeled Antibodies for Clinical Use". The ^{64}Cu-labeled hT84.66-M5A/NHS-DOTA was purified using Superdex 200. The radioactive trace (red) and the UV (A280) trace (blue) from these 3 runs are presented in **Error! Reference source not found.** and showed a single peak with no evidence of aggregates or unincorporated ^{64}Cu. The peak was collected and pooled. Reference is made to **Section 11.4.8** and **11.4.10** for a copy of the noted SOPs.

The ^{64}Cu to be used in the clinical trial proposed under this IND will be purchased from the Mallinckrodt Institute of Radiology at the Washington University School of Medicine. Radiolabeling will be carried out in the City of Hope Radiopharmacy. The process entails incubating conjugated antibody with the ^{64}Cu for 45 minutes at 43°C, followed by a chase with DTPA and subsequent purification on a size exclusion preparative grade Superdex 200 column. Appropriate fractions will be pooled and filtered to make up the patient dose, which will be formulated with human serum albumin (HSA) and dispensed through the radiopharmacy at City of Hope.

Figure 1: Purification of ^{64}Cu-hT84.66-M5A/NHS-DOTA by High Performance Liquid Chromatography using Size Exclusion (Superdex 200 GL)



Purity of Radiolabeled Product

Samples of the purified radiolabeled hT84.66-M5A/NHS-DOTA were taken for analysis of radiochemical purity and immunoreactivity as well as endotoxin level and sterility.

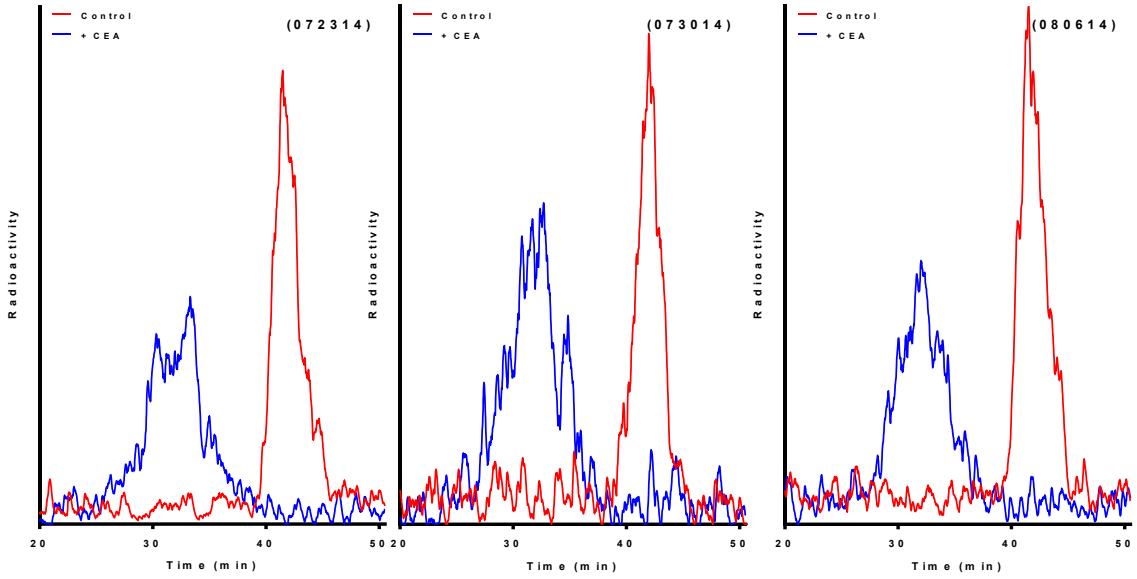
Size Exclusion Chromatography

The purity of the pooled peak preparation was analyzed on an analytical HPLC Size Exclusion Chromatograph using Superose-6. The purified radiolabeled ^{64}Cu-labeled hT84.66-M5A/NHS-

DOTA exhibited a single peak at a size consistent with IgG (**Error! Reference source not found.** [red]).

The immunoreactivity of the ^{64}Cu-labeled hT84.66-M5A/NHS-DOTA post-labeling was tested using human CEA protein in an HPLC SEC shift assay. The immunoreactivity was expressed as a percentage of the CEA -bound ^{64}Cu-labeled hT84.66-M5A/NHS-DOTA vs. unbound ^{64}Cu-labeled hT84.66-M5A/NHS-DOTA as determined by radioactive monitoring of size exclusion HPLC. The immunoreactivity of this ^{64}Cu-labeled hT84.66-M5A/NHS-DOTA preparation was found to be 100% as evidenced by the shift of the radiolabeled product (**Error! Reference source not found.** [blue]). The final product was of exceptional purity and immunoreactivity as demonstrated by SEC-HPLCs of the purified products.

Figure 2: Immunoreactivity of ^{64}Cu-hT84.66-M5A/NHS-DOTA to Carcinoembryonic Antigen Analyzed by Size Exclusion Chromatography (Superose 6 GL)



Limulus Amoebocyte Lysate (LAL)

The endotoxin content of the products post-labeling will be determined using the Charles River's Endosafe™-PTS system which is a rapid, point-of-use test system that utilizes FDA-licensed LAL formulations loaded into a test cartridge along with a handheld spectrophotometer. The endotoxin concentration is routinely determined to be < 0.05 endotoxin units/mL. The amount of final product administered is 25 mL. Therefore the administered dose will normally have <1.25 EU. No product will be administered with > 2 EU/mL. Results from the three lots labeled between July 23, 2014 to August 6, 2104 had <0.05 EU/mL.

Sterility

Sterility of the radiolabeled products will be tested according to USP 27, Chapter 71 under **RIT SOP 0501** "Sterility Test". This is a 14 day test and the ^{64}Cu has a half-life of approximately

12.7 hours. Therefore, the results of the sterility test will not be obtained until after the drug has been administered. Test labelings of ^{64}Cu-labeled hT84.66-M5A/NHS-DOTA, including those of July 23, 2014 to August 6, 2014, has always been shown to be sterile.

Stability of hT84.66-M5A/NHS-DOTA

Stability Monitoring Program

A stability monitoring program has been established for the vialed product for radiolabeling. The stability of antibody constructs that are radiolabeled prior to patient administration will be monitored on a regular basis.

We will evaluate the purity, sterility and immunoreactivity of the antibody constructs after radiolabeling on a schedule to ensure that no more than 6 months has elapsed between stability testing and administration to a patient. The following tests will be performed.

Assay	**Specifications**
Sterility	Sterile
Pyrogen Level	<50 EU per patient dose
Immunoreactivity	>80% immunoreactivity
Size Exclusion Chromatography	IgG Single peak ≥. 95.0% Aggregates ≤ 5.0%

The testing will be performed using the following SOPs. The data will be reviewed by the Director of the Radiopharmacy.

RIT SOP 0501	Sterility Testing (USP)
RIT SOP 0503	Pyrogenicity Testing using Endosafe PTS System
RIT SOP 0504	Immunoreactivity by Liquid Phase HPLC Assay*

* This SOP is based on the use of purified antigen and a shift in the elution of the radiolabeled material to a higher molecular weight.

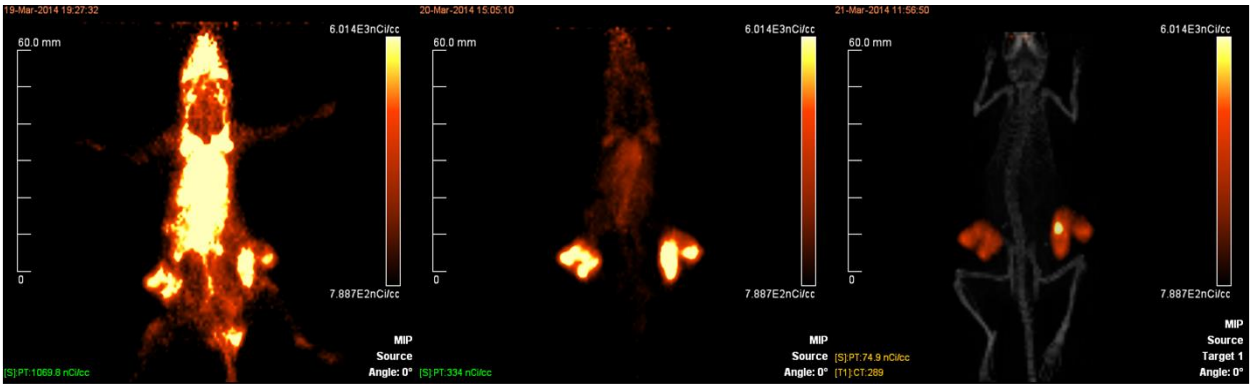
***In Vivo* Studies using ^{64}Cu-labeled hT84.66-M5A/NHS-DOTA.**

Following purification on the TosoHaas G2000SW column, ^{64}Cu–labeled hT84.66– M5A/NHS-DOTA IgG pooled peak material (≈ 100μCi/mouse) was injected into athymic mice bearing the

human xenotransplanted colon carcinoma, LS–174T (≈ 1 × 10^6 cells s.c. bilaterally). Tumor imaging and biodistribution studies were conducted.

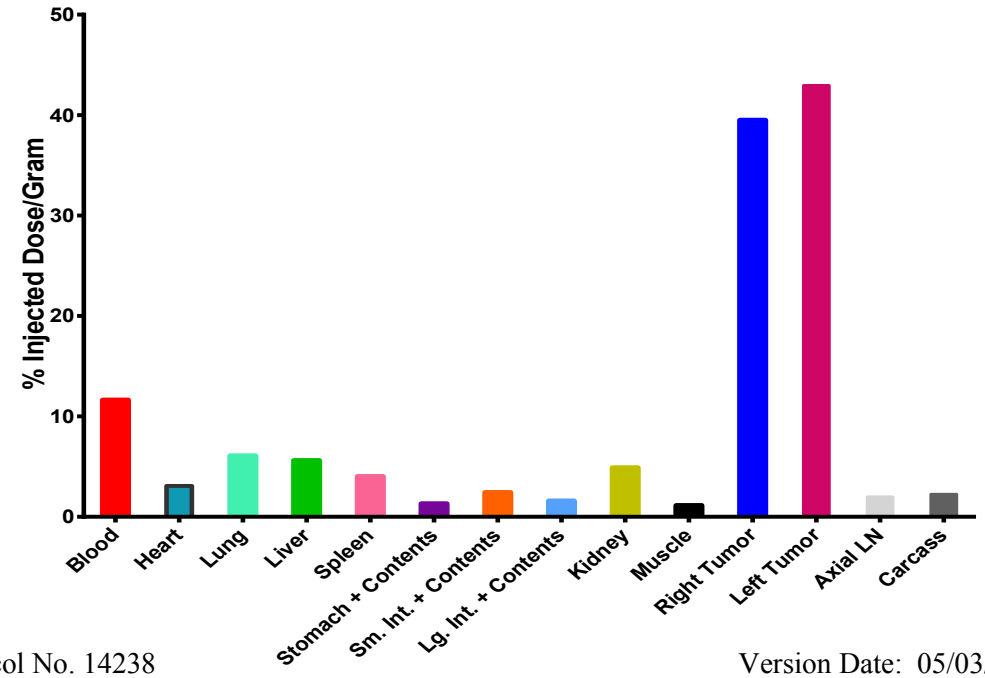
PET images were taken at 4hrs and at 1 and 2 days (**Figure 3)**. The blood pool can be seen in the early image which clears over time. The bilateral tumors are detected by 4 hrs and show increased uptake at 1 day.

Figure 3: PET Imaging of ^{64}Cu-hT84.66-M5A/NHS-DOTA in Mice Bearing Bilateral Human Colorectal Cancer Xenografts



The animals were euthanized after the 2 day images and the tissues were weighed and counted. The tumors retained approximately 40% of the injected dose per gram (**Figure 4**). The blood has approximately 11%ID/gm while the other major organs retained 3-5%ID/gm.

Figure 4: Biodistribution of ^{64}Cu-hT84.66-M5A/NHS-DOTA in Mice Bearing Bilateral Human Colorectal Cancer Xenografts



2.4 Human Studies

Yttrium-90 labeled Humanized Anti-CEA M5A Antibody

Initial studies evaluated the antibody as a therapy agent labeled with Y-90. They are summarized below and are currently closed to accrual.

IRB 05198 A Phase I Study of Yttrium-90 labeled Humanized Anti-CEA M5A Antibody in Patients with CEA Producing Advanced Malignancies: Recently a phase I therapy trial of 111In/90Y labeled M5A was completed.

Originally the study combined Y-90 M5A and Gemcitabine. Three patients were enrolled at the first dose level (12 mCi/m^2 Y-90) with Gemcitabine. Two received 2 cycles and had stable disease. One received 1 cycle and had progressive disease. One patient was enrolled at the next dose level with Gemcitabine and she had stable disease. The toxicities seen with Y-90 and Gemcitabine were more severe, sooner and longer in duration than our previous study; therefore we amended the protocol to omit Gemcitabine .

Since then 6 patients have been treated on the first dose level (12 mCi/m^2 Y-90) without Gemcitabine. The 1st and 6th patient had dose limiting toxicities (DLT) (toxicities did not return to grade 1 by 10 weeks post RIT), therefore we amended the protocol to state that we would enroll 6 patients at a lower dose level (10 mCi/m^2 Y-90) without Gemcitabine, and then close the trial (Serial No. 0003, submitted August 19, 2008).

Of the 6 patients who received the 12 mCi/m^2 Y-90 without Gem, 2 had SD and 4 had PD. One had a positive anti-antibody result. None received a 2nd cycle.

Six patients have been treated on the reduced dose (10 mCi/m^2 Y-90) without Gemcitabine. Four of the 6 received a second cycle. Best responses for these 6 patients include 5 with stable disease, 1 with progressive disease. One patient had an antibody response. None of these 6 patients experienced a DLT.

IRB 09053 : A Phase II Trial of Radioimmunotherapy (Y-90 M5A) Following Hepatic Resection and FOLFOX Chemotherapy (±Bevacizumab) for Metastatic Colorectal Carcinoma to the Liver

We have consented five patients on this trial. Three eventually decided not to participate on the trial; another was too ill and has since passed away. The remaining patient was treated on the study but progressed 5 months post antibody treatment. We are currently following her for survival.

IRB 10038: A Phase I Trial of Radioimmunotherapy (Y-90 M5A) in Combination with FOLFIRI and Bevacizumab Chemotherapy for Metastatic Colorectal Carcinoma

Three patients were enrolled on this study. Two had DLTs: one was low ANC requiring neupogen support; and the other was grade 4 PLT count with prolonged platelet recovery. All patients received only one cycle. Since two out of the first three patients experienced a DLT on the first dose level, we closed the study. Best responses were 1 partial response (PRu), 2 stable

disease (SD). The patient with PRu has now progressed (8 mo post study therapy) and one patient with SD has progressed (4.6 mo post study therapy). The third patient underwent debulking surgery. As of this time, all three patients have expired due to disease progression.

In our previous imaging studies, no significant adverse events have been seen. However, an emergency cart will be available near the patient at all times of injection. Anticipated events and management would be: fever and chills, which will be treated with acetaminophen; hypotension or frank anaphylactic shock, which will be treated with intravenous fluids, pressors, and corticosteroids; bronchospasm and respiratory distress, which will be treated with bronchodilators. The patients will also be observed for other possible toxicities, including pulmonary toxicity, renal toxicity, skin rash, and serum sickness. Appropriate therapy will be instituted if any one or more of these develop. Adverse reaction form (see Case Report Form) will be completed in all patients suffering any potential adverse reaction. The toxicity will be graded using the NCI common toxicity scale CTCAE v4.03. Any patient developing any chest pain, respiratory distress, fever or hypotension with a fall of more than 25mm in systolic blood pressure will not be given further injection of antibody.

3 Patient Eligibility

3.1 Inclusion Criteria

3.1.1 Disease Status

- Patients must have histologically confirmed primary or metastatic cancer. If biopsies were performed at an outside facility, the histology must be reviewed and confirmed by the Department of Pathology at the City of Hope.
- Patients must have tumors that produce CEA as documented by a current or past history of an elevated serum CEA above the institutional limit of normal, or by immunohistochemical methods. NOTE: Patients with colorectal cancer are exempt from this requirement since >95% are CEA positive.

3.1.2 Age Criteria, Performance Status and Life Expectancy

- Patients must be 18 years of age or older.

3.1.3 Child Bearing Potential

The effects of ^{64}Cu-M5A on the developing fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control or abstinence) prior to study entry and for six months following duration of study participation. Should a woman become pregnant or suspect that she is pregnant while participating on the trial, she should inform her treating physician immediately.

3.1.4 Protocol-Specific Criteria

- Patients must have a known site of disease. Please note, for patients undergoing neoadjuvant therapy, this requirement must be met retrospectively prior to the start of neoadjuvant therapy. Patients who are in radiological/clinical remission after neoadjuvant therapy, prior to infusion of radiolabeled antibody, are still eligible.
- Although not mandated by the protocol, the results of the CT scans and labs (CBC, CMP) that are performed as part of the standard work up should be available and should have been done within 2 months prior to study entry.

3.1.5 Informed Consent/Assent

All subjects must have the ability to understand and the willingness to sign a written informed consent.

3.1.6 Prior Therapy

- Prior therapy (chemotherapy, immunotherapy, radiotherapy) must be completed at least 2 weeks prior to infusion of radiolabeled antibody

3.2 Exclusion Criteria

- Patients should not have any uncontrolled illness including ongoing or active infection.
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to ^{64}Cu-M5A.
- Patients must not have received prior chemotherapy or radiation for ≥ 2 weeks before study enrollment.
- Pregnant women are excluded from this study because ^{64}Cu-M5A is an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ^{64}Cu-M5A, breastfeeding should be discontinued if the mother is treated with ^{64}Cu-M5A.

3.2.1 Study-Specific Exclusions

- Any patient who has had exposure to mouse or chimeric (human/mouse) immunoglobulin and has antibody to the M5A.

3.2.2 Non-Compliance

Subjects, who in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study.

3.3 Inclusion of Women and Minorities

The study is open anyone regardless of gender or ethnicity. Efforts will be made to extend the accrual to a representative population, but in a trial which will accrue approximately 10 subjects, a balance must be struck between subject safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

4 Screening and Registration Procedures

4.1 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial will be done only after obtaining written informed consent. Studies or procedures that were for clinical indications (not exclusively to determine study eligibility) may be used for baseline values, even if the studies were done before informed consent was obtained. Reference is made to Section 10.0 – Study Calendar.

4.2 Informed Consent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the subject and a signed informed consent will be obtained. Documentation of informed consent for screening will be maintained in the subject's research chart and medical record.

4.3 Registration Requirements/Process

Subjects will be registered by the assigned Clinical Research Nurse and Clinical Research Coordinator.

4.4 Randomization and/or Dose Level Assignment

All patients will receive 15 mCi/5 mg ^{64}Cu-labeled M5A Antibody

5 Treatment Program

5.1 Treatment Overview

Ten patients will be enrolled in this pilot study. The patients will receive 15 mCi/5 mg ^{64}Cu labeled M5A antibody.

All study treatment will be outpatient.

5.1.1 Schedule

For a tabular view of the treatment, monitoring, and follow-up schedule, see study calendar in Section 10.

The infusion of the ^{64}Cu-labeled M5A Antibody will be given on "Day 0", and there will be scans on days 1 and 2, and blood draws for PK analysis on Day 0, Day 1 and Day 2. See study calendar in Section 10.

ANTIBODY ADMINISTRATION

As in the case of any radioactive material, care will be taken to minimize radiation exposure to the patient, consistent with proper patient management, and to ensure minimum radiation exposure to the occupational worker. There will be strict adherence to aseptic technique throughout.

M5A antibody will be labeled with ^{64}Cu. Activity, volume, date and time of the radiopharmaceutical preparation will be recorded on the radiopharmacy CRF. Fifteen mCi/5 mg of the labeled M5A antibody (^{64}Cu labeled M5A antibody) will be brought up to approximately 25 mL of saline with 1% human serum albumin (HSA) and mixed prior to infusion. Antibody dose will be given by slow IV push.

After the injection is completed, the patients are then observed per routine. In addition to routine observation, vital signs including pulse, respirations, blood pressure and temperature will be taken prior to study drug administration, every 15 minutes for up to one hour following administration, and at approximately the 3-4 hour post start of infusion blood draw. The use of ^{64}Cu labeled M5A antibody will be recorded in the drug accountability form.

IMAGING STUDIES

1. PET images will be performed in 3D mode (septa retracted) and corrected for tissue attenuation based on co-registered CT acquired during the same examination. PET images will be reconstructed with spatial resolution of approximately 9 mm full-width-at-half maximum (FWHM) using an iterative algorithm (OSEM).

2. ^{64}Cu -DOTA-M5A. Patients will be injected via a peripheral or central vein with 15 mCi of ^{64}Cu-DOTA-M5A. Scans will be performed the following day (Day 1) and Day 2. Because of the limited amount of activity to be injected and the fact that only 20% of ^{64}Cu decays produce a positron, the count rates will be low. To compensate, time per bed position will be

relatively long and the axial field of view relatively short. (Day 1: 2-3 bed positions encompassing known tumors; 30 min per bed position if 2 bed positions, 20 min per bed position if 3 bed positions; Day 2: 1 bed position, 60 min). Based on prior phantom studies, we expect the scanning protocol defined above to yield adequate tumor visualization as well as measurements of tumor uptake and tumor: adjacent background activity concentration ratios ("tumor:bdg contrast") for tumors of at least 2 cm in diameter and average SUV (= tumor activity concentration/injected activity per unit body weight) of at least 3 in body regions for which tumor:bdg contrast is at least 4. The precision (coefficient of variation) of tumor SUV and tumor:bgd contrast measurements is expected to be about 10% and 15%, respectively.

3. Image Analysis: The Cu-64 SUVs will be evaluated in tumors, adjacent non-tumor tissue and selected non-tumor organs and tissues (heart, extracardiac mediastinum, liver, skeletal muscle). Tumor sizes (product of maximum mutually perpendicular transaxial diameters as well as maximum axial diameter) will be estimated from coregistered CT. Tumor uptake of ^{64}Cu-DOTA-M5A will be parameterized in terms of single-voxel maximum values SUVmax and whole-tumor volumes of interest (SUVwhtum) as defined from the coregistered CT images. Ratios of tumor to non- tumor activity concentration will also be calculated for adjacent tissue, extracardiac mediastinum, liver, and skeletal muscle. Receiver-operator curve (ROC) analysis will be performed to estimate optimal cutoff values of SUVmax, SUVwhtum, tumor:background and tumor:organ ratios for classifying tumors as “CEA positive” or “CEA negative.” Note: the image analysis will be done prior to completion of the study (not in real time).

5.2 Planned Duration of Therapy

Study duration is 3 months. See study calendar in section 10. Each patient will be considered to have completed the study three months following antibody infusion with the completion of the HAHA sample and provided that all case report forms have been completed to the principal investigator's satisfaction.

5.3 Criteria for Removal from Treatment

Patients may withdraw from the study for personal reasons at any time. A patient may also be dropped from the study by the investigator for other reasons including medical concerns or failure to comply with the protocol.

5.4 Subject Follow-Up

See study calendar.

5.5 Supportive Care, Other Concomitant Therapy, Prohibited Medications

Not applicable.

5.6 Additional Studies

Not applicable.

5.6.1 Laboratory Studies

See study calendar section 10.

6 Dose Delays/Modifications for Adverse Events

In our previous imaging studies, no significant adverse events have been seen. Anticipated events and management would be: fever and chills, which will be treated with acetaminophen; hypotension or frank anaphylactic shock, which will be treated with intravenous fluids, pressors, and corticosteroids; bronchospasm and respiratory distress, which will be treated with bronchodilators. The patients will also be observed for other possible toxicities, including pulmonary toxicity, renal toxicity, skin rash, and serum sickness. Appropriate therapy will be instituted if any one or more of these develop. Adverse reaction form (see Case Report Form) will be completed in all patients suffering any potential adverse reaction. The toxicity will be graded using the NCI common toxicity scale CTCAE v4.03. Any patient developing any chest pain, respiratory distress, fever or hypotension with a fall of more than 25mm in systolic blood pressure will not be given further injection of antibody.

7 Data and Safety Monitoring Plan

Definition of Risk Level

This is a Risk Level 4 study, as defined in the City of Hope Institutional Data and Safety Monitoring Plan [policy dated 07/09/2014]. This determination was made because the study involves COH as IND holder and radioimmunoimaging with ^{64}Cu-labeled M5A antibody.

Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) is responsible for monitoring the data and safety of this study. The PMT consists of the Principal Investigator (PI), Collaborating Investigator(s), Biostatistician, Research Protocol Nurse and Clinical Research Coordinator.

The PMT is required to submit periodic status reports (i.e., the PMT Report) according to the frequency prescribed in the City of Hope Institutional Data and Safety Monitoring Plan [policy dated 07/09/2014]. Important decisions made during PMT meetings (i.e., dose escalation, de-escalation, etc.) only need to be noted in the PMT Report submitted to the Data and Safety Monitoring Committee (DSMC).

Adverse Events and Serious Adverse Events

The PI will be responsible for determining the event name, assessing the severity (i.e., grade), expectedness, and attribution of all adverse events.

Adverse Event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Reporting Non-serious Adverse Events – Adverse events will be collected after the patient is given the study treatment or any study related procedures. Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the PMT Report.

Serious Adverse Event (SAE) [Modified from the definition of unexpected adverse drug experience in 21 CFR 312.32] - defined as *any expected* or *unexpected adverse event*s that result in any of the following outcomes:

- Death
- Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary malignancy
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Reporting Serious Adverse Events - begins after study treatment or any study related procedures. All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to the approved City of Hope's Institutional policy [policy effective date: 05/14/14]. Serious Adverse Events that require expedited reporting will be submitted electronically using iRIS.

Adverse Event Name and Severity

The PI will determine the adverse event name and severity (grade) by using the CTCAE version 4.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event, OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Unexpected Adverse Event [21 CFR 312.32 (a)] – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Adverse Event Attribution

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

Definite - The AE is clearly related to the investigational agent or study procedure and unrelated to any other cause.

Probable - The AE is likely related to the investigational agent or study procedure and unlikely related to other cause(s).

Possible -The AE may be related to the investigational agent or study procedure and may be related to another cause(s).

Unlikely -The AE is doubtfully related to the investigational agent or study procedure and likely related to another cause(s).

Unrelated -The AE is clearly not related to the investigational agent or study procedure and is attributable to another cause(s).

COH Held IND

Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

The criteria that require reporting using the Medwatch 3500A are:

- Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]
- Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]
- Any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

The PI or designee will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the approved City of Hope's Institutional policy [policy effective date: 05/14/14].

Deviations and Unanticipated Problems

Deviation - A deviation is a divergence from a specific element of a protocol that occurred without prior IRB approval. Investigators may deviate from the protocol to eliminate immediate hazard(s) for the protection, safety, and well-being of the study subjects without prior IRB approval. For any such deviation, the PI will notify the COH DSMC and IRB within 5 calendar days of its occurrence via iRIS in accordance with the Clinical Research Protocol Deviation policy [policy effective date: 11/07/11].

Single Subject Exception (SSE)

An SSE is a planned deviation, meaning that it involves circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient. It is a deviation that is anticipated and receives prior approval by the PI and the IRB. The SSE must be submitted as a "Single Subject Exception Amendment Request" via iRIS in accordance with IRB guidelines and the Clinical Research Protocol Deviation policy [policy effective date: 11/07/11]. An IRB approved SSE does not need to be submitted as a deviation to the DSMC.

Unanticipated Problem (UP) – Any incident, experience, or outcome that **meets all three** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research

protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

Any UP that occurs during study conduct will be reported to the DSMC and IRB in accordance with the City of Hope's Institutional policy [policy effective date: 05/14/14] using iRIS.

COH Held IND

The Office of IND Development and Regulatory Affairs (OIDRA) will assist the PI in reporting the event to the Food and Drug Administration (FDA).

8 Agent Information and Risks

8.1 DOTA-M5A humanized anti-CEA antibody

8.1.1 Description

Chemistry/Mechanism of Action: M5A is a humanized IgG monoclonal antibody developed at the City of Hope National Medical Center. It recognizes the A3 domain of the CEA molecule and has little cross reactivity with other members of the CEA family. It binds CEA with a high affinity (approximately 2 x 10^{10} /M) and is able to bring a bound radioisotope into close proximity. It is labeled with Cu-64 to form the imaging agent. This will be under COH IND #125855.

8.1.2 Toxicology

A possible complication of treatment is also the development of human anti-human antibody antibodies (HAHA).

8.1.3 Pharmacology – Handling, Storage, Dispensing and Disposal

Formulation: Cu-64-DOTA-M5A anti-CEA antibody is produced and labeled at the City of Hope by the Department of Immunology. See below for details.

Administration: See below for details regarding administration and radiation safety.

Supplier: M5A anti-CEA antibody is an investigational agent produced and labeled at the City of Hope by the Department of Immunology.

Test Preparations: The DOTA-M5A antibody will be provided as a sterile, apyrogenic solution. All test preparations will be packaged in identical 2 mL CZ plastic vials. Each vial containing 1 ml of M5A antibody at a concentration of 6.78 mg/ml.

Radiolabeling of the ^{64}Cu labeled M5A antibody will be performed by the Radioimmunotherapy section. The ^{64}Cu will be purchased from the Mallinckrodt Institute of Radiology at the Washington University School of Medicine, which is preparing the radiolabel for clinical use. Labeling will be accomplished by incubating conjugated antibody with the ^{64}Cu for 45 minutes at 43^{o} C, followed by a chase with DTPA and subsequent purification on a size exclusion preparative grade Superdex-200 column. Appropriate fractions will be pooled and filtered to make up the patient dose, which will be formulated with human serum albumin. All preparations will be purified by HPLC. Each administered dose of antibody is also tested for endotoxin, sterility, and immunoreactivity.

Labeling and Drug Identification

The drug label is permanently attached to the drug container. The label contains the name, list, lot number of the drug and the words ***Caution: New Drug—Limited by Federal (U.S.A.) law to investigational use.*** All used and unused containers will be accounted for on the Drug Accountability Log.

Storage and Disposition of Supplies

The M5A anti-CEA antibody is stored at 4ºC in the Center for Biomedicine and Genetics (CBG) or Investigational Pharmacy. All drug supplies are kept at 4ºC in a refrigerator that is connected to the central alarm system. The investigator will maintain a current running inventory of drug supplies on the form provided (OMB No. 0925-0240).

8.1.4 Risks

In our previous imaging studies, no significant adverse events have been seen. Anticipated events and management would be: fever and chills, which will be treated with acetaminophen; hypotension or frank anaphylactic shock, which will be treated with intravenous fluids, pressors, and corticosteroids; bronchospasm and respiratory distress, which will be treated with bronchodilators. The patients will also be observed for other possible toxicities, including pulmonary toxicity, renal toxicity, skin rash, and serum sickness.

9 Correlative/Special Studies

HAHA (anti-antibody assay): Approximately 5 ml (1 teaspoon) of blood in a red top tube will be drawn for this test at 3 time points (see study calendar, section 10). It will be delivered at ambient temperature to Dr. Colcher's laboratory for analysis of immunogenicity.

Blood pharmacokinetics: Approximately 5 cc (1 teaspoon) of blood will be collected for blood analysis of radioactivity (approx. 2.5 ml in a red top tube and approx. 2.5 ml in a EDTA tube). These will be drawn at 7 time points (see study calendar, section 10). These will be delivered at ambient temperature to Dr. Colcher's laboratory for analysis.

10 Study Calendar

	Pre-Study	Day 0	Day 1	Day 2	1 mo post study drug (+/- 7 days)	3 mo post study drug (+/- 14 days)
STANDARD OF CARE						
Medical history	S					
Physical exam	S					
Vital signs (pulse, BP, resp rate, temp)	S					
Weight	S					
RESEARCH						
Informed consent	R					
Urine pregnancy test (if applicable)	R^					
HAHA (Anti-antibody assay)[#]	R^				R	R
^{64}Cu-M5A infusion		R				
Vital signs (pulse, BP, resp rate, temp)		R*				
Radioactivity						
Pharmacokinetics		R**	R	R		
Imaging (per section 5)			R	R		

* approx every 15 min post start of infusion for 1 hr, then again at approx 3-4 hours.

** 1 EDTA tube and 1 red top tube drawn at pre-infusion, and at approx 30 min, 1 h, 2 h and 3-4 h post start of infusion

^ To be completed within 4 weeks prior to antibody infusion

[#] 1 red top tube to Dr. Colcher's lab.

STUDY CALENDAR NOTES:

"R" represents tests that are done purely for research purposes

"S" indicates tests that are done for standard of care. If these tests are done for standard of care purposes, the data from these tests will be collected, however they are not required for research purposes. If they are not done, it will not exclude the patient from participation on the trial, and will not constitute a protocol deviation.

11 Endpoint Evaluation Criteria/Measurement of Effect

11.1 Response Criteria

Not applicable.

12 Data Reporting/Protocol Deviations

12.1 Data Reporting

12.1.1 Confidentiality and Storage of Records

The protocol will uses Electronic Data Collection (EDC) and the data will be stored in encrypted, password protected, secure computers that meet all HIPAA requirements. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed. Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. They will be made available for review, as required by the FDA, HHS, or other authorized users such as the NCI, under the guidelines established by the Federal Privacy Act and rules for the protection of human subjects.

12.1.2 Subject Consent Form

At the time of registration, the original signed and dated Informed Consent form, HIPAA research authorization form, and the California Experimental Subject's Bill of Rights (for the medical record) and three copies (for the subject, the research record, and the Coordinating Center) must be available. All Institutional, NCI, Federal, and State of California requirements will be fulfilled.

12.1.3 Data Collection Forms and Submission Schedule

All data will be collected within approximately 30 days post antibody administration using EDC. Data will be sent to the location identified in Section 12.1.1 and stored in a secure location.

12.1.3.1 Eligibility Checklist

The Eligibility Checklist must be completed by a protocol nurse or clinical research associate and signed by an authorized investigator prior to registering the subject. See Section 4.3 for the registration procedure.

12.1.3.2 Prior Therapy Forms and On-Study Forms

Within 2 weeks of registration, the clinical research associate will submit baseline data forms within the EDC.

13 Statistical Considerations

13.1 Study Design

The primary aim of this pilot study is to evaluate the tumor targeting, pharmacokinetic, and immunogenicity properties of ^{64}Cu labeled M5A antibody. The results of this pilot study will be used to determine if the antibody should be studied in a larger imaging trial. The data for the 20 patients imaged will be used to summarize the scan results.

13.2 Sample Size Accrual Rate

This is a three-year open-labeled pilot study that will enroll **20** patients with CEA-producing malignancies at the City of Hope National Medical Center.

13.3 Statistical Analysis Plan

The data will be summarized using two methods. Both methods will examine the efficacy of each modality in locating cancer in each of four regions: primary, hepatic, extra-hepatic abdominal, and extra-abdominal. For the first method, referred to as a lesion analysis, the efficacy of each modality will be evaluated where a successful outcome will be defined as the ability of at least one known tumor identified by conventional imaging modalities to be imaged using the M5A antibody. For the second method, referred to as a region analysis, a successful outcome will be defined as the identification of suspicious tissue within a region.

For both methods, using the standard statistical formulas, the number of true positives (TP), false positives (FP), true negatives (TN), false negatives (FN), as well as the sensitivity and corresponding 95% confidence interval will be estimated using the method of Lee and Dubin (31) or Rao and Scott (32), which accounts for the correlation between lesions within the same subject.

General clinical findings and serum concentration data will be tabulated and descriptive statistics computed. Safety data will be displayed and abnormal laboratory values flagged. The frequency of adverse events will be tabulated by body system.

14 Human Subject Issues

14.1 Institutional Review Board

In accordance with City of Hope policies, an Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol and the informed consent form prior to initiation of the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

14.2 Recruitment of Subjects

Subjects will be recruited by the PI, Co-PI and participating clinicians in their respective clinics.

14.3 Advertisements

Advertisements to include print, media (radio, television, billboards), telephone scripts, lay summary to be posted on City of Hope's public Clinical Trials On-Line^{SM} website, etc., will be reviewed and approved by the IRB prior to their use to recruit potential study subjects.

14.4 Study location and Performance Sites

This study will be performed at COH.

14.5 Confidentiality

This research will be conducted in compliance with federal and state of California requirements relating to protected health information (PHI). The study will record individual demographics, cancer history, tumor targeting and any side effects, and this will be linked to the subject's identity using a coded study number. The principal investigator, co-investigators, clinical research nurses and clinical research coordinators will have access to this information, but all information will be treated confidentially. No identifiers will be used in any subsequent publication of these results.

14.6 Financial Obligations and Compensation

The investigational drug, ^{64}Cu-M5A, will be provided free of charge by COH.

The research participant will not be paid for taking part in this study.

14.7 Informed Consent Processes

The Principal Investigator or IRB approved named designate will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Research subjects will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with City of Hope. Research subjects will be afforded sufficient time to consider whether or not to participate in the research.

Should sufficient doubt be raised regarding the adequacy of comprehension, further clarifications will be made and the questionnaire repeated until a satisfactory result is obtained. Prospective research subjects who cannot adequately comprehend the fundamental aspects of the research study with a reasonable amount of discussion, education and proctoring will be ineligible for enrollment. For those subjects who do comprehend the fundamental aspects of the study, consent will be obtained and documented, followed by eligibility testing. The research team will review the results of eligibility testing and determine if the subject is a candidate for study enrollment.

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