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TITLE: Development of a PET Prostate-Specific Membrane Antigen Imaging Agent: Preclinical Translation for Future Clinical Application

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14. ABSTRACT

The overall objective of this research project is to collect chemistry and preclinical data on two promising new small-molecule peptidomimetic imaging agents labeled with positron emitting fluorine-18. These data will enable the filing of an exploratory IND (expIND; phase 0) application to the FDA by the end of the funding period. The small molecule imaging agents under study home to prostate specific membrane antigen (PSMA) that is prevalent on a majority of prostate cancers. The availability of these imaging agents will support diagnosis and staging of prostate cancer without the need for a biopsy as well as provide valuable information to guide therapeutic intervention and monitor the treatment outcome.

15. SUBJECT TERMS
Prostate Cancer, Prostate Specific Membrane Antigen (PSMA), Fluorine-18, Molecular Imaging, Radiotracer, Automated Synthesis, Phosphoramidate, Inhibitor, Peptide Mimic, Peptidomimetic

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1. INTRODUCTION:

The overall objective of this research project is to collect chemistry and preclinical data on two promising new small-molecule peptidomimetic imaging agents labeled with positron emitting fluorine-18. These data will enable the filing of an exploratory IND (expIND; phase 0) application to the FDA by the end of the funding period. The small molecule imaging agents under study home to prostate specific membrane antigen (PSMA) that is prevalent on a majority of prostate cancers. The availability of these imaging agents will support diagnosis and staging of prostate cancer without the need for a biopsy as well as provide valuable information to guide therapeutic intervention and monitor the treatment outcome.

2. KEYWORDS:

Prostate Cancer, Prostate Specific Membrane Antigen (PSMA), Fluorine-18, Molecular Imaging, Radiotracer, Automated Synthesis, Phosphoramidate, Inhibitor, Peptide Mimic, Peptidomimetic

3. ACCOMPLISHMENTS:

What were the major goals and objectives of the project?

Aim 1: Prepare non-radioactive precursor phosphoramidate PSMA targeting molecules and their corresponding fluorobenzamide analogs. Perform radiochemistry to form [^{18}F]fluorobenzamide – phosphoramidate peptidomimetics. Optimize the synthesis of the [^{18}F]fluorobenzamide coupling.

- Task 1.1: Prepare the non-radioactive phosphoramidate labeling precursors
- Task 1.2: Prepare the non-radioactive fluorobenzamido-phosphoramidate standard compounds
- Task 1.3: Radiolabel the precursor phosphoramidates with [^{18}F]succinimidyl fluorobenzoate.
- Task 1.4: Optimize [^{18}F]succinimidyl fluorobenzoate labeling of the phosphoramidates.
- Task 1.5: Explore solid phase extraction for purification (SPE) of the fluorobenzamido-phosphoramidates

Aim 2: Determine pharmacokinetic and toxicologic properties of the fluorobenzamidophosphoramidates

- Task 2.1: Obtain DoD animal approval for the imaging and metabolism studies
- Task 2.2: Biodistribution studies of the two [^{18}F]fluorobenzamido-phosphoramidates
- Task 2.3: Obtain DoD approval for the toxicology studies
- Task 2.4: Radiotracer Stability studies
- Task 2.5: Radiotracer *in vivo* metabolism studies
- Task 2.6: Radiotracer Dosimetry studies
- Task 2.7: Toxicity evaluation

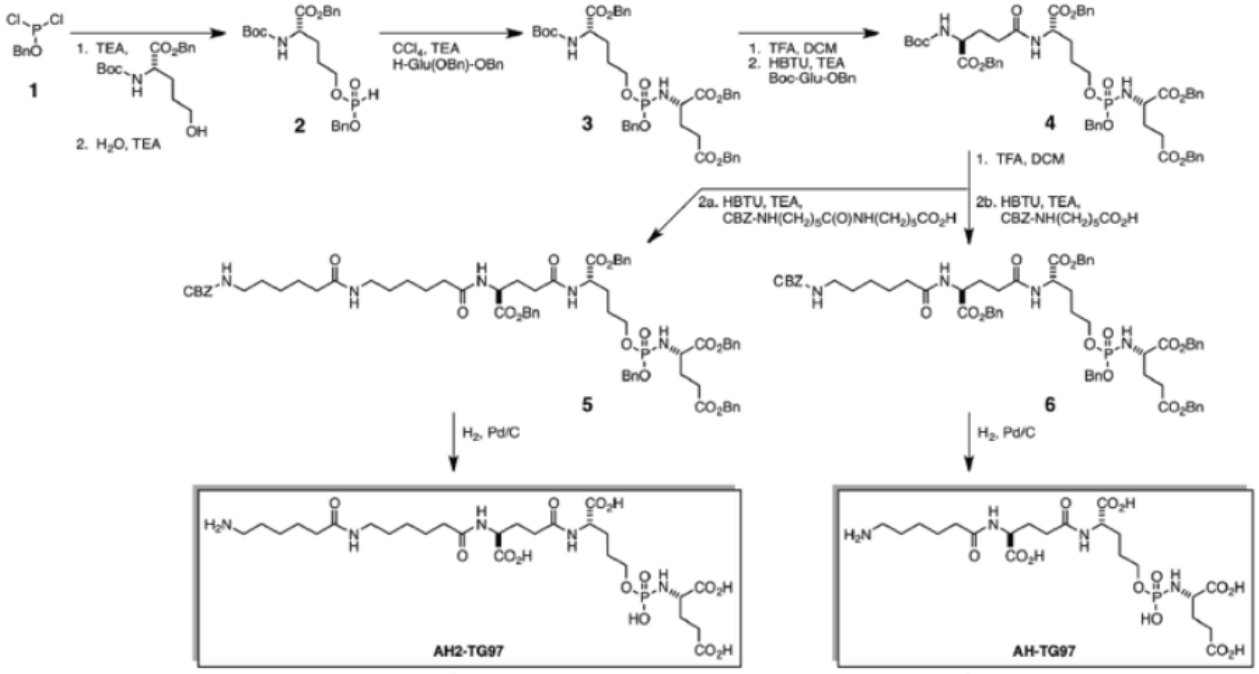
Aim 3: Collect final data for the submission of the exploratory IND to the FDA

- Task 3.1: Automate the [^{18}F]fluorobenzamido-phosphroramidate synthesis on the Neptis® synthesis unit.
- Task 3.2: Prepare SOPs and batch record Documents for the radiosynthesis
- Task 3.3: Human Studies Protocol for submission to UCSF IRBs
- Task 3.4: Final radiosynthesis validation runs with full Quality Control analysis
- Task 3.5: Complete the exploratory IND for FDA submission
- Task 3.6: Submit IND to FDA, Respond to FDA Questions
- Task 3.7: DoD Final Report

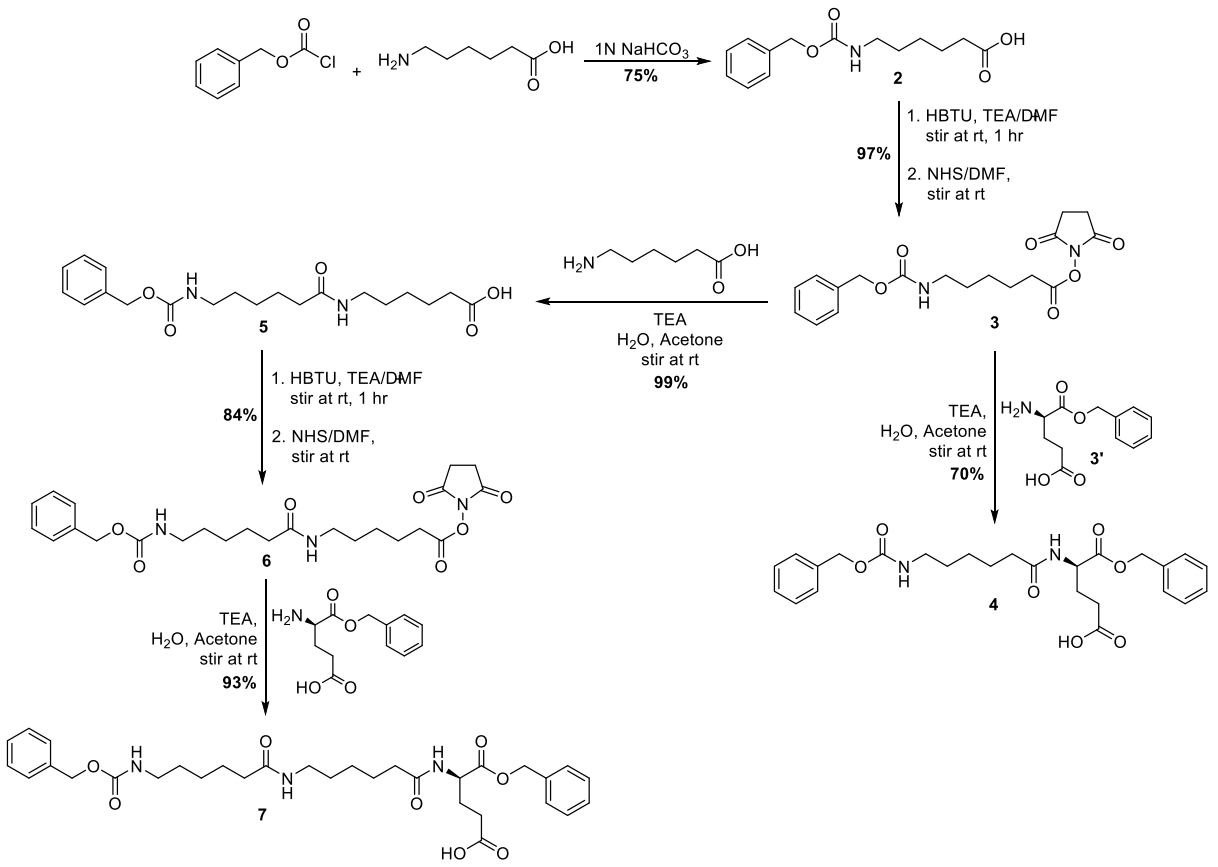
What was accomplished under these goals?

Task 1.1: Prepare the non-radioactive phosphoramidate labeling precursors.

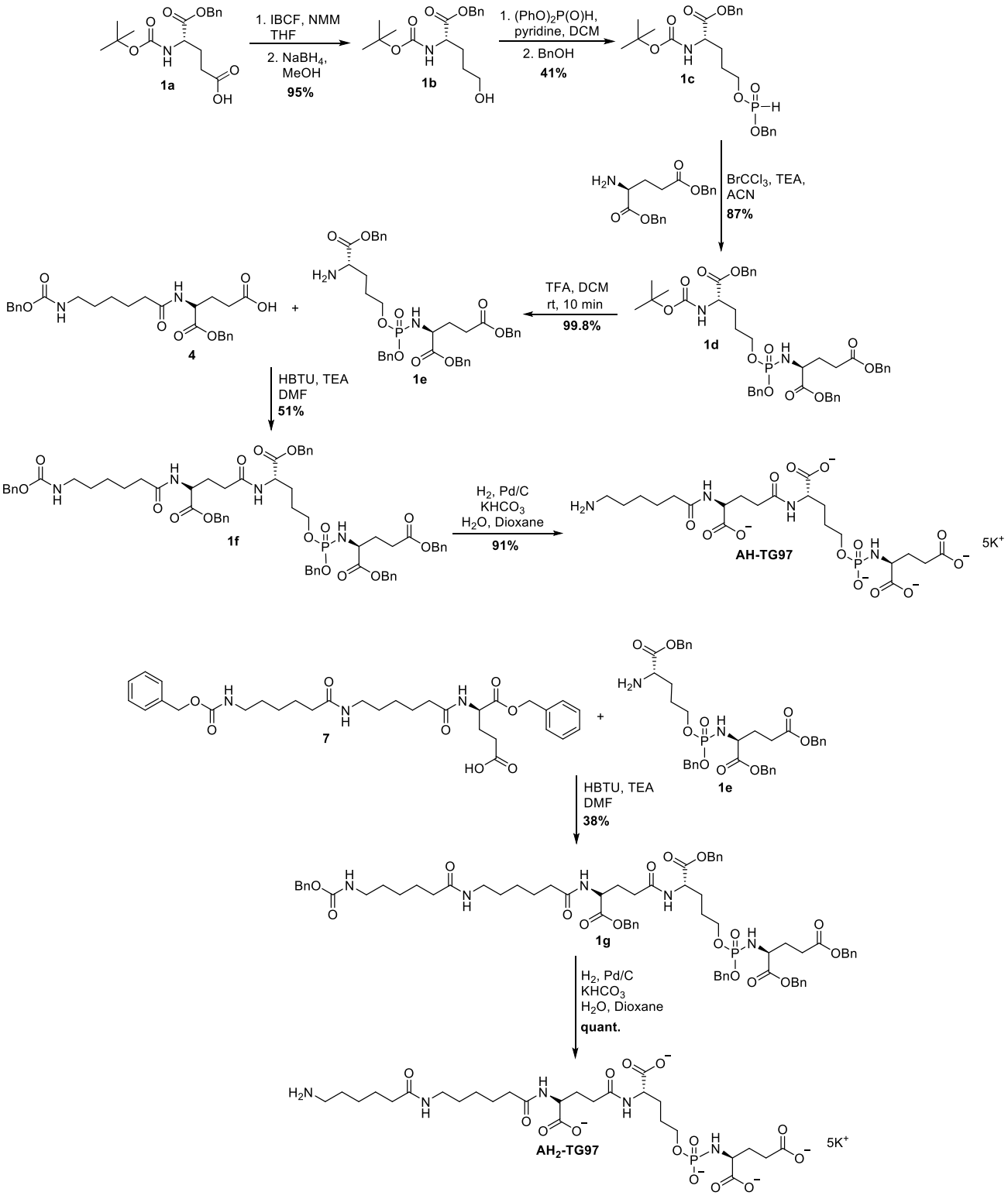
Non-radioactive standards of AH-TG97 and AH2-TG97 were prepared as proposed. The initial route to AH-TG97 and AH2-TG97 is outlined in Scheme 1. In preparation for scale-up and manufacturing, the synthesis of these radiolabeling precursors was optimized to minimize the number of steps and preparation of reagents, decrease chromatographic demands, and increase yields. The current optimized synthesis of the radiolabeling precursors AH-TG97 and AH2-TG97 is outlined in Scheme 2.



Scheme 1. Original Synthesis of the radiolabeling precursors AH-TG97 and AH2-TG97.



Scheme 2. Modified synthesis of the radiolabeling precursors AH-TG97 and AH2-TG97.



Scheme 2 (cont'd). Modified synthesis of the radiolabeling precursors AH-TG97 and AH2-TG97.

Both radiolabeling precursors were characterized by ^{1}H and ^{31}P NMR. Spectra for both AH-TG97 and AH2-TG97 are shown below in Figure 1 and 2. They were also characterized by mass spectral analysis.

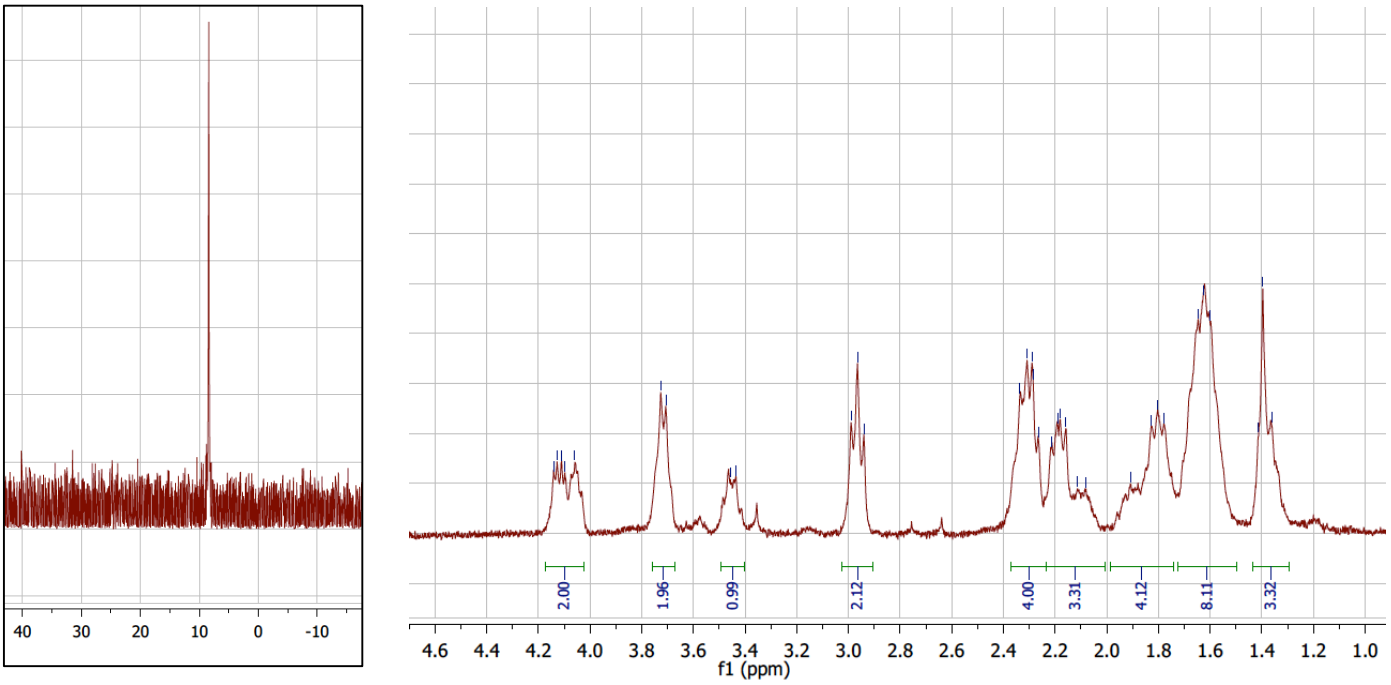


Figure 1. ^{1}H and ^{31}P NMR of AH-TG97

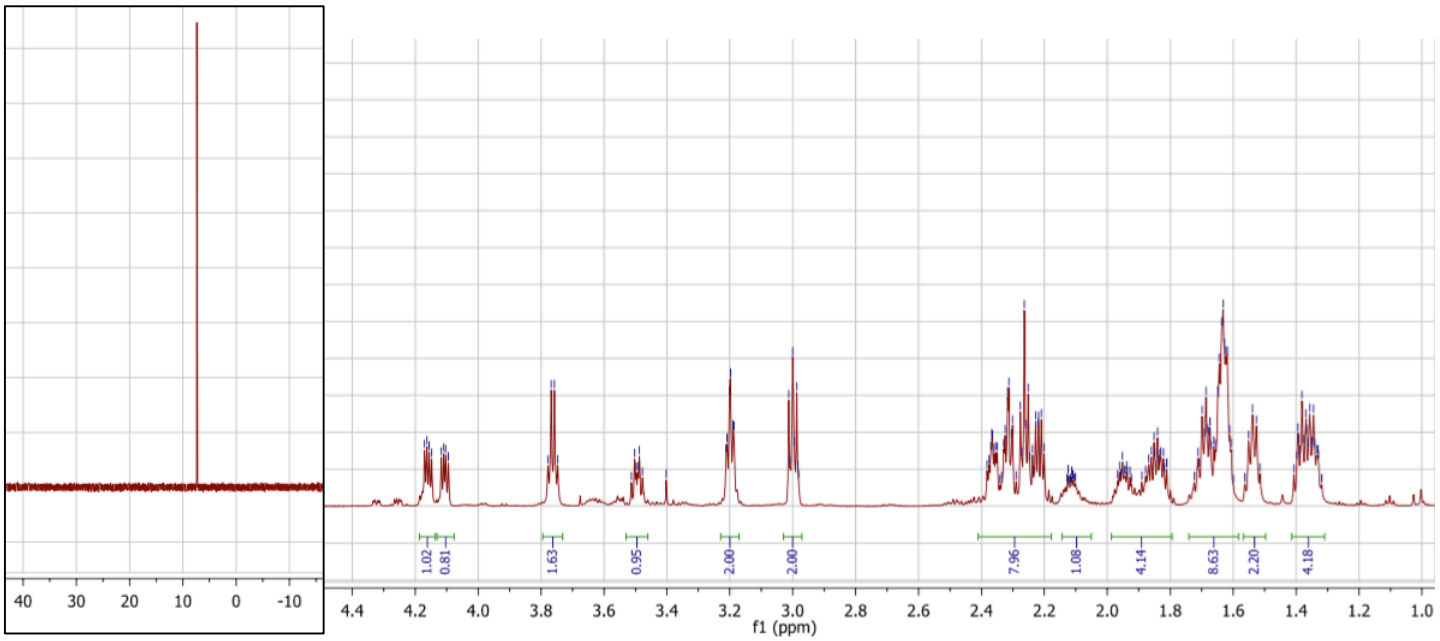
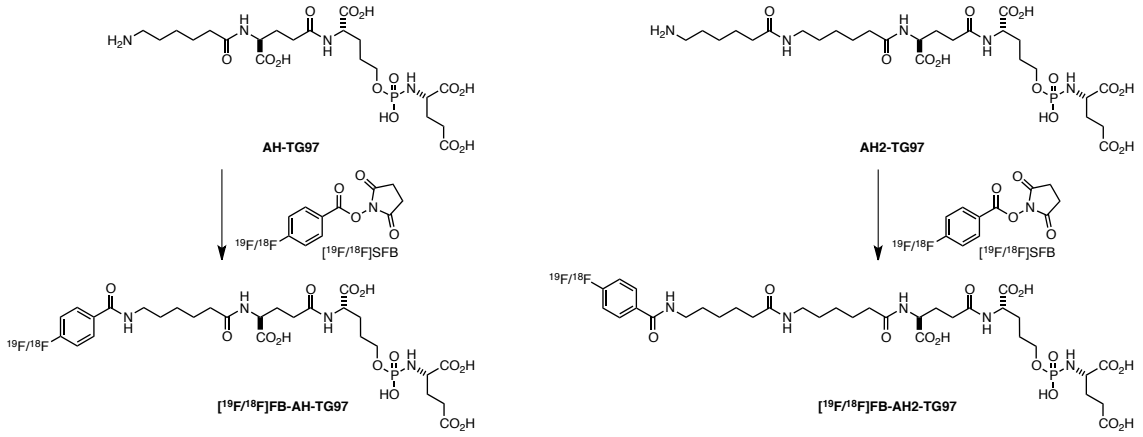


Figure 2. ^{1}H and ^{31}P NMR of AH2-TG97

Task 1.2: Prepare the non-radioactive fluorobenzamido-phosphoramidate standard compounds.

Non-radioactive standards of FB-AH-TG97 and FB-AH_2-TG97 were prepared as proposed. The corresponding non-radioactive ^{19}F-fluorobenzyl-AH-TG97 (FB-AHTG97) was prepared as shown in Scheme 3.



Scheme 3. Coupling step from radiolabeling precursors (AH-TG97 and AH2-TG97) to the radioactive and non-radioactive final products $^{18/19}$FB-AH-TG97 and $^{18/19}$FB-AH2-TG97.

Task 1.3: Radiolabel the precursor phosphoramidates with [^{18}F]succinimidyl fluorobenzoate.

Completed in Year 1

Task 1.4: Optimize [^{18}F]succinimidyl fluorobenzoate labeling of the phosphoramidates.

Completed in Year 1

Task 1.5: Explore solid phase extraction for purification (SPE) of the fluorobenzamido-phosphoramidates

Completed in Year 1

Task 2.1: Obtain DoD animal approval for the imaging and metabolism studies

In progress

Task 2.2: Biodistribution studies of the two [^{18}F]fluorobenzamido-phosphoramidates

To be completed upon animal approval (Task 2.1)

Task 2.3: Obtain DoD approval for the toxicology studies

In progress

Task 2.4: Radiotracer Stability studies

During the qualification runs the stability of ^{18}FB-AH-TG97 was monitored over 5 hours. The full quality control battery (Table 1 below) of tests were performed on 3 production batches of the radiotracer immediately after production and at 5 hours post production to establish the expiration time for the radiolabeled ^{18}FB-AH-TG97. There was no observable degradation in product quality over the 5 hour period. The current expiration of the batch has been established at 5 hours post manufacturing.

Task 2.5: Radiotracer *in vivo* metabolism studies

To be completed upon animal approval (Task 2.1)

Task 2.6: Radiotracer Dosimetry studies

To be completed upon animal approval (Task 2.1)

Task 2.7: Toxicity evaluation

To be completed upon animal approval (Task 2.3)

Task 3.1: Automate the [^{18}F]fluorobenzamido-phosphroramidate synthesis on the Neptis® synthesis unit.

We translated the synthesis of ^{18}FB-AH-TG97 with SPE purification to the NEPTIS® automated synthesis unit in the UCSF Radiopharmaceutical facility. The schematic diagram of the reagent setup and a photograph of the actual unit with the cassettes and reagents in place are shown in Figures 3 and 4, respectively. The automated unit was used to prepare the validation/qualification runs for quality testing of the ^{18}FB-AH-TG97.

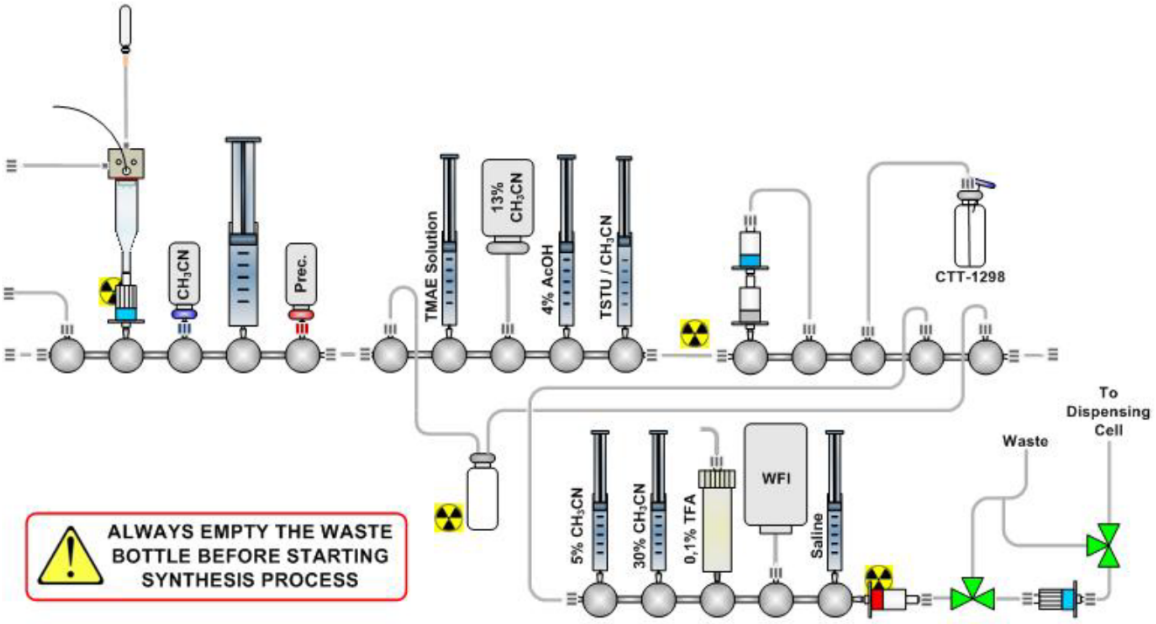


Figure 3. Schematic diagram showing the placement of reagents in the cassettes on the face of the NEPTIS® automated synthesis unit.

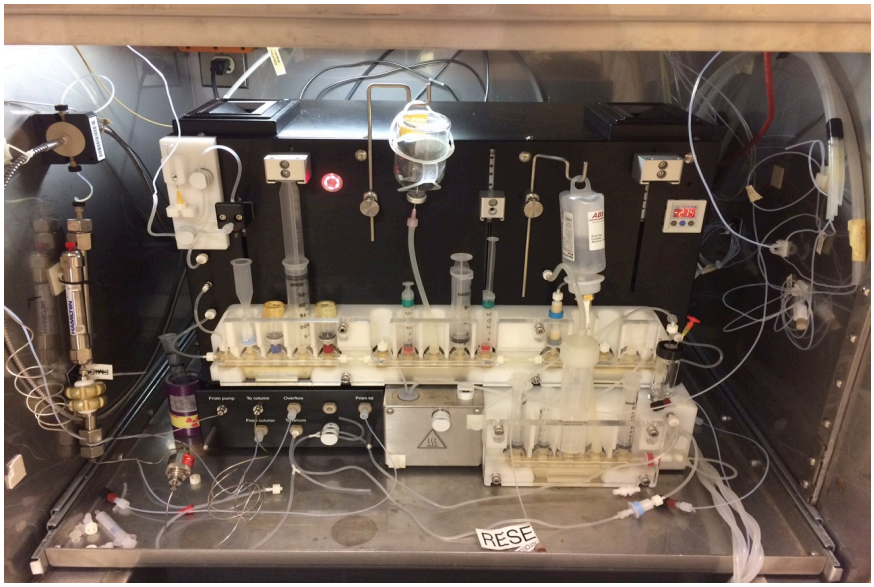


Figure 4. Photo showing the setup of the NEPTIS® automated synthesis unit for preparation of ^{18}FB-AH-TG97.

Task 3.2: Prepare SOPs and batch record documents for the radiosynthesis

We developed a Batch Record that serves as the overarching standard operating procedure for the entire production of ^{18}FB-AH-TG97 (CTT1057). This batch record outlines all of the steps from pre-production through the quality control and analysis of the final product. Ultimately release of the final product for human imaging studies (not covered under this funding) will be predicated on meeting all of the quality control specifications (Table 1, Task 3.4 below). Within the Batch Record, SOPs for various tasks are called out. All of these SOPs have been developed and validated for the laboratory operations associated with this and other radiotracers prepared in our facility.

Task 3.3: Human Studies Protocol for submission to UCSF IRBs

Dr. Spencer Behr and Dr. Rahul Aggarwal (no effort on this project) finalized the protocols for the first patient populations to be evaluated using the ^{18}F-AH-TG97 (clinical research is not funded under this grant). This protocol was approved by the UCSF Helen Diller Family Comprehensive Cancer Center Protocol Review Committee (PRC). The UCSF human use application was submitted for review by the IRB and the Radiation Safety Committee. The protocol was added to the IND.

Task 3.4: Final radiosynthesis validation runs with full Quality Control analysis

The specifications for the quality assessment of the ^{18}F-AH-TG97 are given in Table 1. These specifications must be met before the compound may be released for patient injection with the exception of the sterility test, which is a 14 day test. Before submission of the IND three full ^{18}F-AH-TG97 syntheses were completed and the quality tests were applied. The data from the 3 runs is shown in Table 2. These data were submitted in the IND for review by the FDA.

TABLE 1 Quality Control Test and Specifications of ^{18}FB-AHTG97

Test	Specification	Notes
Appearance	Colorless/free from particles l	Visual test for particulates and color in the final solution
Filter integrity	Agree with manufacturer specs.	Final sterilizing filter must be intact after the solution has passed through it. A pressure test is used to demonstrate that it has not been compromised
Radiochemical purity	≥ 90 %	Radiochemical purity will be determined by HPLC – the peak area should be >90% of the total radioactivity injected.
Radiochemical identity	RRT = 1.00 ± 0.05 as standard	Retention time by HPLC for the radiotracer will be determined
Radionuclidic purity	511 KeV peak must be present	A gamma spectrum will be obtained for the final product
Radionuclidic identity	107 m < half-life < 112.4 m ^{18}F half-life (109.7 minutes)	A well counter will be used to follow the radioactive decay of the sample. Half-life must be within ±2.5% of ^{18}F half-life (109.7 min).
Specific Activity	≥ 500 Ci/mmol (18.5 TBq/mmol)	The mass in the sample will be determined by HPLC and a standard curve. The mass associated with a given sample of radioactivity will be determined.
pH	4.8 - 5.6	Measured with a pH strip
Chemical purity	Residual solvents < accepted limits	Measure by GC for residual solvents from reaction and purification process.
Pyrogen test	≤ 7.5 EU/mL	The chip-based Limulus Ameboctye Lysate coagulation assay (horseshoe crab) using the Associates of Cape Cod Endosafe® reader will be employed. Endosafe® will determine the level of pyrogens.
Sterility test (at release)	Test initiated	An aliquot from each batch solution will be sent to Quest Laboratories (or suitable microbiological laboratory) for culture and identification.

Table 2: Qualification run results.

Quality Control Test and Specifications of CTT1057 3 Qualification Batches				
Test	**Specification**	**151104CTT**	**151105CTT**	**151106CTT**
Appearance	Colorless/free from particles	Colorless/free from particles	Colorless/free from particles	Colorless/free from particles
Filter Integrity	>50 psi (manufacturer spec)	64 psi	64 psi	66 psi
Radiochemical purity	≥ 85 %	89%	89%	91%
Radiochemical identity	RRT = 1.00 ± 0.05 as standard	0.96	0.96	0.96
Radionuclidic purity	511 KeV peak must be present	511KeV present	511KeV present	511KeV present
Radionuclidic identity	107 m < half-life < 112.4 m ^{18}F half-life (109.7 minutes)	108.9 min	109.3 min	109.3 min
Specific Activity	≥ 500 Ci/mmol (18.5 TBq/mmol) (NLT 0.7 mCi/µg)	6,354 Ci/mmol (9 mCi/µg)	4,240 Ci/mmol (6 mCi/ µg)	3,533 Ci/mmol (5 mCi/ µg)
pH	4.5 – 7.5	5.5	5.5	5.5
Chemical purity	Residual solvents Acetonitrile < 0.04% ≤ 3 µg of non-carrier mass per single administered dose	0.007%	0.006%	0.017%
Bacterial endotoxins (LAL)	≤ 7.5 EU/mL	<5 EU/ml	<5 EU/ml	<5 EU/ml
Sterility test (at release)	Pass/ Fail	Pass	Pass	Pass

Task 3.5: Complete the exploratory IND for FDA submission

The Chemistry Manufacturing and Control (CMC) section of the IND was prepared with the collected synthesis data and the quality control data. The completed CMC was provided to the IND sponsor to complete that submission package.

Task 3.6: Submit IND to FDA, Respond to FDA Questions

A manufacturer sponsored IND #124021 was submitted to the FDA. The IND was reviewed by the FDA during the first quarter of 2016. There were several rounds of questions related to the purity and stability of the precursor (beyond the scope of this application) between the FDA and the sponsor. The questions were addressed to the satisfaction of the FDA and the IND was removed from clinical hold on August 5, 2016. See FDA letter in appendix.

What opportunities for training and professional development has the project provided?

The UCSF postdoctoral fellow on this project, Dr. Kiel Neumann, has gained significant practical knowledge about the preparation of radiopharmaceuticals and their translation for human use. The process of taking a labeled product from the laboratory to the clinic offer many opportunities to learn about the manufacturing and regulatory aspects of the process. He was instrumental in preparation of the Chemistry, Manufacturing and Control section of the FDA IND application and assisted in responding to the FDA questions.

Two senior undergraduate students (Sophia Beyer and Matthew Galliher) and two 1st-year graduate students (Bradley Roberts and Feyisola Olatunji) were given research experience in Dr. Berkman's laboratory to assist Dr. Cindy Choy in the preparation of the radiolabeling precursors AH-TG97 and AH2-TG97. All students participated in group meetings and presented updates on their experiments related to the preparation of AH-TG97 and AH2-TG97. In addition to their practical laboratory training, the students were also involved in discussions related to the translation of our laboratory "bench" research to the clinical "bedside" setting. The two undergraduate students are now 1st-year graduate students in Chemistry programs at the University of Michigan and the University of Texas-Austin.

How were the results disseminated to the communities of interest?

A manuscript entitled "Automated Syntheses Towards Clinical Production of the PSMA Imaging Agent [^{18}F]CTT1057" is in preparation.

An abstract entitled "Fully automated preparation of [^{18}F]CTT1057, a new prostate cancer imaging agent, prepared using the ORA Neptis Perform Synthesizer®" has been submitted to the International Symposium on Radiopharmaceutical Sciences for presentation in May 2017.

What do you plan to do during the next reporting period to accomplish the goals?

Over the next reporting we will finish the validation runs ^{18}FB-AH2-TG97 and collect the qualification data for the Chemistry Manufacturing and Control section of the IND. We will complete the collection of the preclinical data in Task 2 for both radiotracers.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

It is anticipated that the radiotracers being advanced to clinical trials will replace the current clinically available radiotracer Prostascint for PSMA imaging in prostate cancer. Prostascint is a mouse antibody that homes to a binding site on the PSMA that is inside of the cancer cells. The antibody is a large molecule (~300 times the weight) compared to the current compounds being developed in this proposal. Prostascint has a difficult time crossing the intact cell membrane to bind to its target. The molecules in this proposal bind to a site on the PSMA protein on the outside of the cancer cell making the interaction more feasible. Successful application of the new tracers will have a fill a significant unmet need for a PSMA imaging agent and provide a means of staging disease and monitoring treatment.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

The new diagnostic imaging agents will benefit those suffering from prostate cancer by offering important information that will inform therapy and monitor disease progression and remission.

5. Changes/Problems:

Changes in approach and reasons for change

Nothing to report

Actual or anticipated problems or delays and action or plans to resolve them

Nothing to Report

Changes that had a significant impact on expenditures

Nothing to Report

Significant changes in use of care of human subjects, vertebrate animals, biohazards and/or select agents

Nothing to Report

6. PRODUCTS:

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name: Project Role: Nearest person month worked: Contribution to Project: Funding support:	Henry VanBrocklin PI 4 Dr. VanBrocklin oversaw and directed the research studies under this project. He coordinated efforts with Dr. Cliff Berkman at Washington State University (subcontract). He worked with Salma Jivan to prepare the Chemistry Manufacturing and Control section of the IND. He worked with Dr. Spencer Behr and Rahul Aggarwal on the final protocol for the IND submission. He reviewed and analyzed all of the data and prepared the annual report. FDA U01, NIH U01, 2 NIH R21s, 2 NIH R01s, 2 NIH SBIRs, 1 NIH UM1
Name: Project Role: Nearest person month worked: Contribution to Project: Funding support:	Joseph Blecha Research Associate 2 Mr. Blecha performed radiosynthesis and purification of PSMA agents NIH R01, NIH U01, FDA U01
Name: Project Role: Nearest person month worked: Contribution to Project: Funding support:	Kiel Neumann Postdoctoral Fellow 6 Dr. Neumann developed the assay for the precursor in the final product solution. He optimized the radiochemistry for translation to the NEPTIS® unit. He developed the SPE purification. He developed the HPLC methods for purification and analysis of the tracer NIH U01
Name: Project Role: Nearest person month worked: Contribution to Project: Funding support:	Spencer Behr Co-Investigator 0.3 Dr. Behr contributed to the development of the protocol for the first-in-human imaging study submitted to the IRB NIH SBIR, Clinical Support

Name: Project Role: Nearest person month worked: Contribution to Project: Funding support:	Salma Jivan Research Associate 3 Translated the radiotracer synthesis to the Neptic Automated Synthesis Unit. She developed the Batch Record and SOPs for the synthesis and quality control. She performed the synthesis of the 3 qualification batches and collected the data for the CMC section of the IND. Departmental and Clinical Support

Name: Project Role: Nearest person month worked: Contribution to Project: Funding support:	Clifford Berkman Washington State Univ Subcontract PI 2 Dr. Berkman has overseen the synthesis and analytical work on the radiolabeling precursors and authentic standards, as well as transferring non-radioactive methods to the Dr. VanBrocklin's lab. He has also facilitated the transfer of precursor material to Dr. VanBrocklin's lab for the laboratory and automation preparation of the tracers. He worked with Dr. VanBrocklin on the data analysis and preparation of this report. NIH R21 and DoD
Name: Project Role: Nearest person month worked: Contribution to Project: Funding support:	Cindy Choy Research Assistant Professor 2 Dr. Choi conducted synthesis and analytical work on the radiolabeling precursors and authentic standards. She also oversaw the training of 2 undergraduate students and 2 graduate students. DoD

8. SPECIAL REPORTING REQUIREMMENTS: None

9. APPENDICES:

A. QUAD CHART

B. IND Letter

Development of a PET Prostate-Specific Membrane Antigen Imaging Agent: Preclinical Translation for Future Clinical Application

W81XWH-14-1-0603

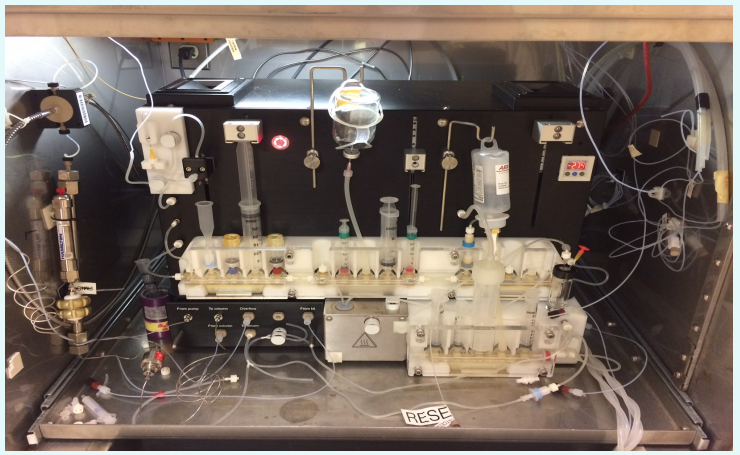
PI: Henry F. VanBrocklin, Ph.D. **Org:** University of California San Francisco **Award Amount:** $1,421,999

Study/Product Aim(s)

- **Aim 1:** Prepare non-radioactive precursor phosphoramidate PSMA targeting molecules and their corresponding fluorobenzamide analogs.
- **Aim 2:** Determine pharmacokinetic and toxicologic properties of the fluorobenzamidophosphoramidates
- **Aim 3:** Collect final data for the submission of the exploratory IND to the FDA

Approach

The overall objective of this research project is to collect chemistry and preclinical data on two promising new small-molecule peptidomimetic imaging agents labeled with positron emitting fluorine-18 for diagnosis and monitoring of prostate cancer. These data will enable the filing of an exploratory IND (expIND; phase 0) application to the FDA by the end of the funding period.



Full automation (unit shown here) and purification of ^{18}FB-AH-TG97 has been completed. A final batch record and quality control SOPs and specifications have been written.

Timeline and Cost

Activities FY	15	16	17
Aim 1 Synthesis			
Aim 2 Preclinical Assessment			
Aim 3 Automate Prep/ IND CMC Data			
Estimated Budget ($K)	**$735**	**$667**	**NCE**

Updated: 12/10/16

Key Research Accomplishments

- Optimized radiolabeling and analysis of ^{18}FB-AH-TG97 and ^{18}FB-AH2-TG97
- Fully automated the synthesis of ^{18}FB-AH-TG97 with solid phase extraction purification
- Finalized SOPs, Batch Record, quality specifications, quality tests
- Performed qualification runs and stability test for CMC data
- Submitted IND for ^{18}FB-AH-TG97 to FDA, responded to questions, received FDA approval to initiate clinical trials under separate funding.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 124021

REMOVE FULL CLINICAL HOLD

Cancer Targeted Technology
Attention: Dr. Liz Whalley, Ph.D.
14241 N.E. Woodinville-Duvall Rd #143
Woodinville, WA 98072

Dear Dr. Whalley:

Please refer to your Investigational New Drug Application (IND) 124021, submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for [F-18] CTT1057.

We also refer to your amendment dated July 12, 2016, which provides a complete response to our Continue Full Clinical Hold letter of May 6, 2016, which cited the chemistry reasons for placing this IND on full clinical hold and the information needed to resolve the chemistry full hold issues.

We have completed the review of your submission and have concluded that the clinical trial may be initiated.

However, regarding your study protocol, please find below the **FDA Chemistry Comments:**

As advised previously, to ensure that clinical investigations will yield reliable and interpretable data, address the following CMC issues prior to initiating the Phase 2 studies:

1. Develop suitable analytical method(s) to assure identity and purity of the precursor, drug substance reference standard and drug product for release as well as stability. As development progresses, establish correlations between early and current analytical methods.

2. Improve purity of the precursor, drug substance reference standard and drug product to >90%.

3. Maintain a reliable drug substance reference standard, including retest results.

4. Assess mass balance.

We also refer you to the FDA Guidance *"INDs for Phase 2 and Phase 3 Studies Chemistry, Manufacturing, and Controls Information"* at:
http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070567.pdf

ADDITIONAL IND RESPONSIBILITIES

As Sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm.

Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

  If the IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information above.

  If the IND is not in eCTD format:

  - You should submit 7-day reports by a rapid means of communication by email. You should address each submission to the Regulatory Project Manager (Ms. Thuy M. Nguyen: Thuy.Nguyen@fda.hhs.gov) and to the Chief, Project Management Staff (Dr. Kyong Kang: Kyong.Kang@fda.hhs.gov);

  - If you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);

  - Also, submit to the FDA, as a formal official submission, in triplicate hard copies along with an electronic copy on CD-Rom (PDF) of these reports to this IND, and the submission should have the same date as your email submission and be clearly marked as "Duplicate."

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If the IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If the IND is not in eCTD format, you may submit 15-day reports in triplicate paper format along with an electronic copy on CD-Rom; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND became active (the date clinical studies were permitted to begin) [21 CFR 312.33].

NOTE: All amended / revised protocol, consent form and any other revised document should be submitted as an annotated version (with red-lined, track-changes) along with a clean revised version and a summary of changes.

SUBMISSION REQUIREMENTS

Submit all formal official submissions to the U.S. FDA CDER – Division of Medical Imaging Products, with a cover letter, Forms FDA 1571, 1572, 3674, or 356h (as applicable) in *triplicate* hard copies along with an electronic copy on CD-Rom (PDF), as follows:

Courier/Overnight/Postal Service
Libero Marzella, M.D., Ph.D., Division Director
Division of Medical Imaging Products
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration (FDA)
Attention: FDA Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Solely electronic submissions to the FDA via Gateway / Global Submit Review (GSR) – See the following links for information:

http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If the IND is in eCTD format, you should obtain an ESG account. For additional information, refer to: http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/.

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** or **Exploratory IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

Note: Secure email between CDER and Sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to: SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs or Exploratory INDs not in eCTD format).

If you have any questions regarding this IND, please contact Ms. Thuy M. Nguyen, M.P.H., Senior Regulatory Health Project Manager at: Thuy.Nguyen@fda.hhs.gov or (301) 796-1427.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Division Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
U.S. Food and Drug Administration