Award Number: W81XWH-14-1-0603

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

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San Francisco, CA 94103

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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

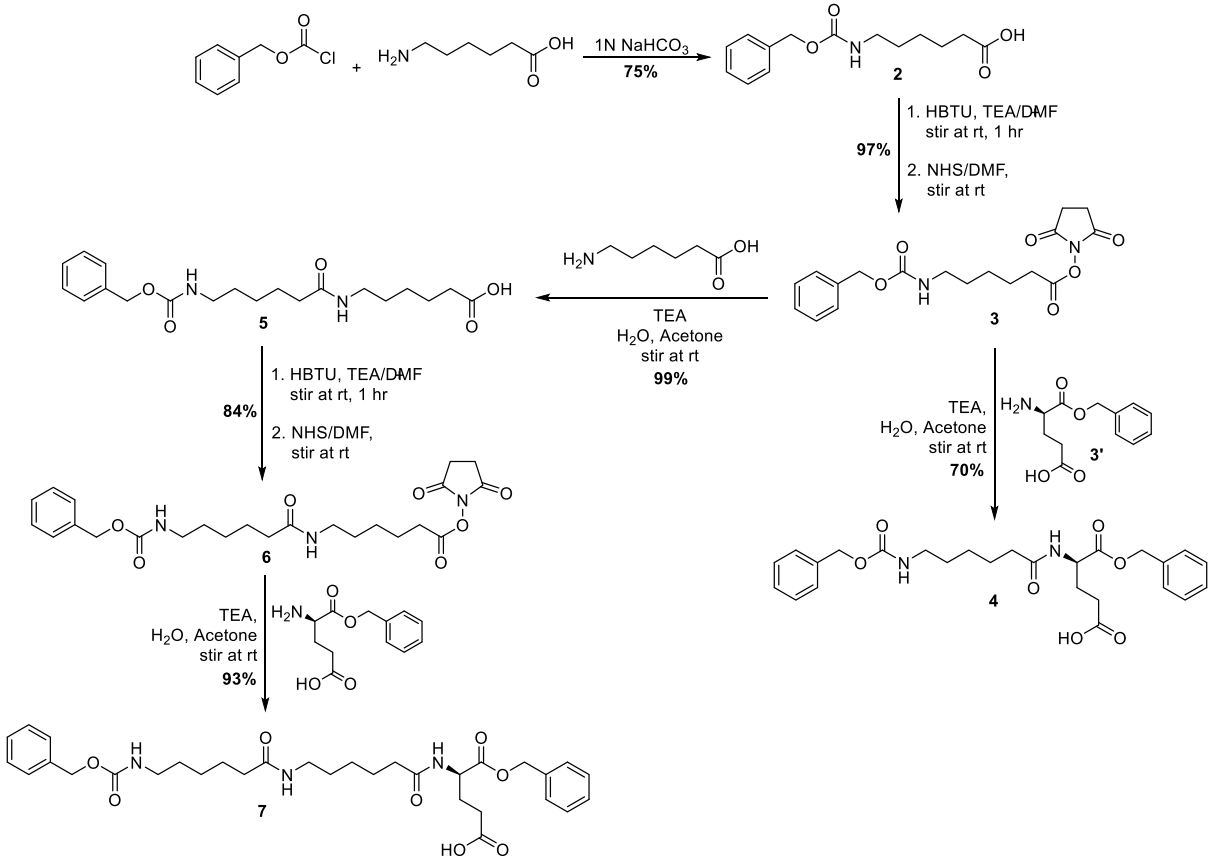
Aim 3: Collect final data for the submission of the exploratory IND to the FDA

- 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

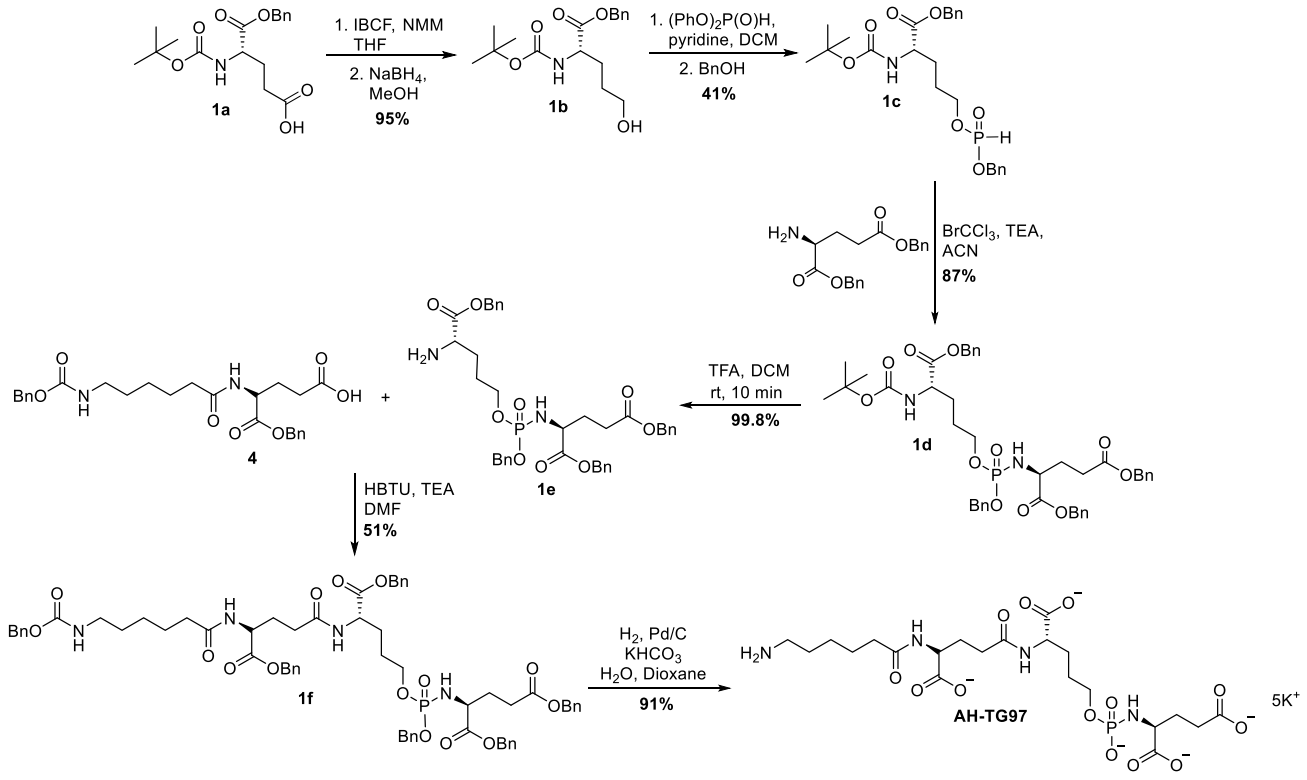
What was accomplished under these goals?

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

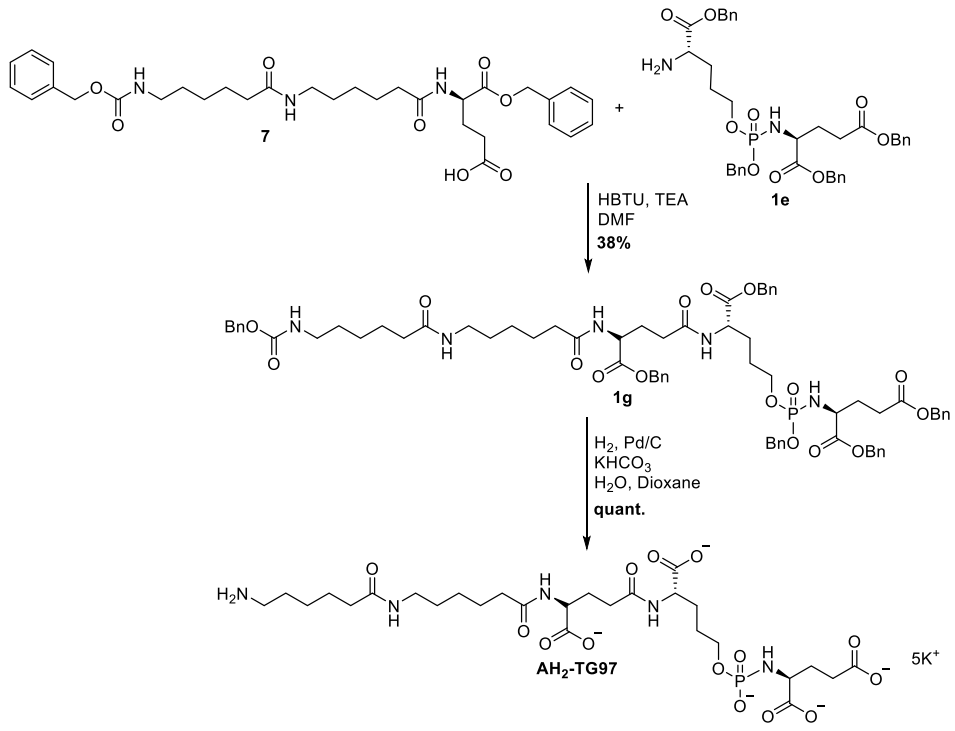
A focus was made on the synthesis of larger quantities of AH2-TG97 (as well as AH-TG97) in preparation for scale-up for toxicity studies. Methods have been optimized to improve yields as shown in the **Schemes 1** and **2** below.



Scheme 1. Optimized synthesis of the radiolabeling precursors AH-TG97 and AH2-TG97.



Scheme 2a. Optimized synthesis of the radiolabeling precursors AH-TG97



Scheme 2b. Optimized synthesis of the radiolabeling precursors 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 in Scheme 3. The method to prepare and purify ^{19}F-fluorobenzyl-AH-TG97 (FB-AH-TG97) was slightly modified to improve the coupling yield. Specifically, the coupling step with SFB and AH-TG97 was performed in potassium phosphate buffer (0.5 M, pH 7.5). The product was purified using G-10 size-exclusion chromatography resulting in 94.5% purity (254 nm); HPLC trace shown below (Figure 1).

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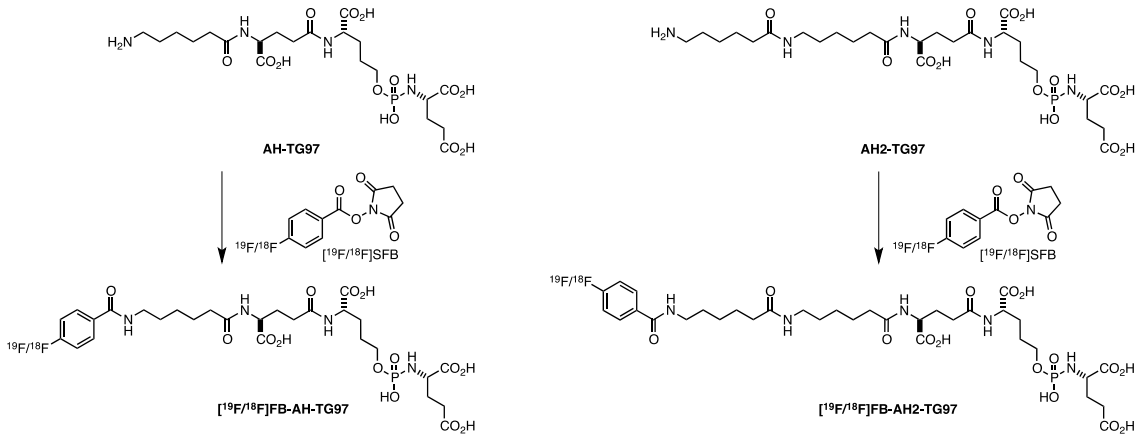

Scheme 3. Coupling step from radiolabeling precursors (AH-TG97 and AH2-TG97) to the radioactive and non-radioactive final products $^{18/19}$FB-AH-TG97 and $^{18/19}$FB-AH2-TG97.

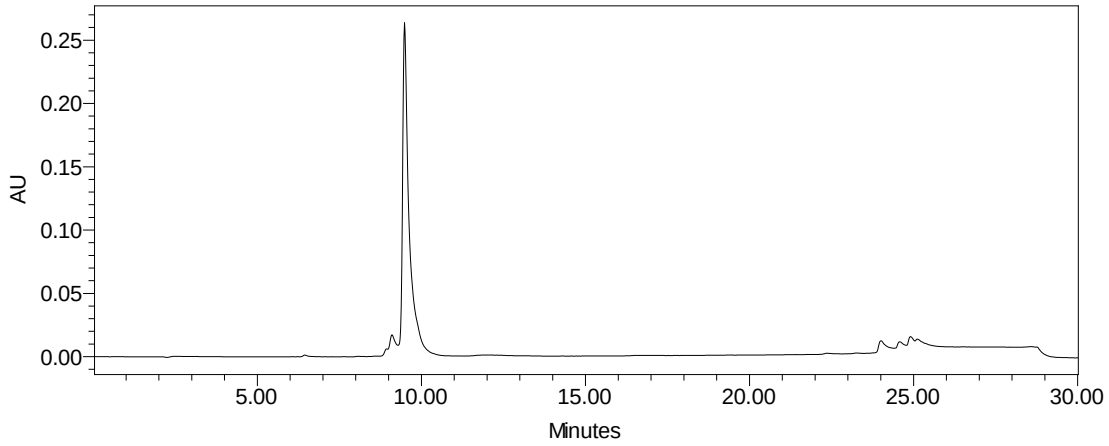

Figure 1. HPLC trace of the final product.

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.

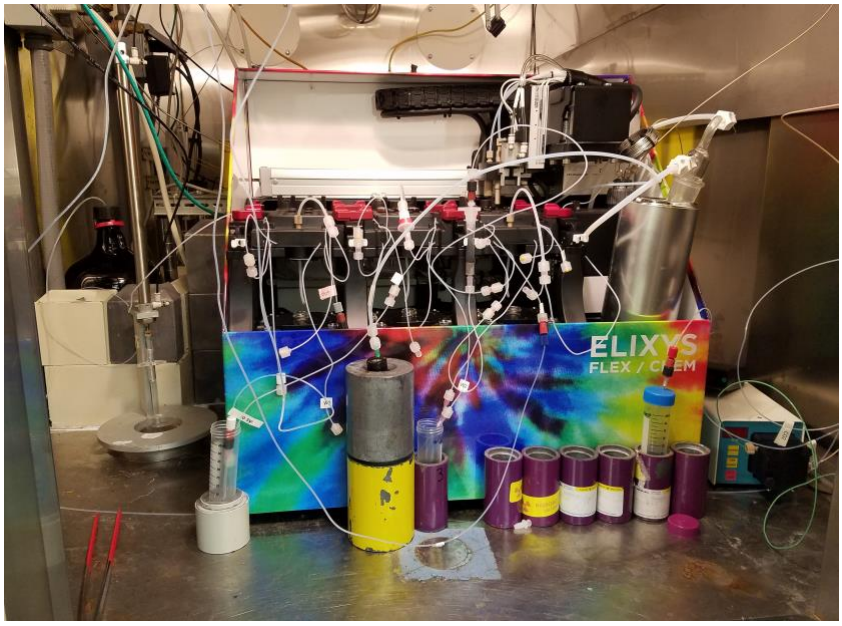

Figure 2. Elixys synthesis unit that has been programmed to prepare SFB and label the AH-TG97 precursors.

^{18}FB-AH-TG97 optimization was completed in Year 1 and labeling parameters for the reproducible preparation of the ^{18}FB- AH-TG97 on the NEPTIS automated synthesis unit were determined (Task 3.1). We revisited the optimization of the ^{18}FB-AH-TG97 and ^{18}FB-AH2-TG97 in an attempt to increase the overall yield of the final product. We programmed the Sofie Biosciences Elixys synthesis unit, pictured in Figure 2, to prepare [^{18}F]succinimidyl fluorobenzoate (SFB) for coupling with AH-TG97 and AH2-TG97. Modifications to the synthesis of SFB including potassium carbonate/ kryptofix for the 1^{8}F-fluoride ion incorporation and added TSTU for the formation of the imidazole did not significantly improve yield. Optimization of the SFB coupling to the TG97 precursors including adjusting solvent volumes, concentration, reaction times, buffer and pH are ongoing. Initial studies revealed that solvent volume and ratio of acetonitrile to water impact the SFB coupling yields to give the final products.

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

phosphoramidates

Solid phase extraction (SPE) for ^{18}FB-AH-TG97 was completed in Year 1. We revisited the SPE for AH_2-TG97 during year 3. We evaluated changing solvent strengths for the purification steps to separate the precursor AH2-TG97 from ^{18}FB-AH2-TG97. To date the separation remains incomplete.

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

Final approval of the ACURO for preclinical imaging and metabolism was obtained.

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

Male nude mice were implanted with PC3 PSMA+ and PC3 PSMA- tumor cells. When the tumors reached ~105 mm^3 we injected the mice (5 per cohort group) with ~50 µCi of ^{18}F-AH-TG97 or ^{18}F-AH2-TG97. Cohorts were euthanized at 0.5, 1, 2 and 4h post injection. One cohort was pretreated 1 hour before radiotracer injection to block PSMA binding. This cohort was euthanized 1h post radiotracer injection. Blood, organ and tissue samples were collected, weighed and counted. The data is currently being analyzed.

Task 2.3: Obtain DoD approval for the toxicology studies

Final approval of the ACURO for toxicological studies was obtained. Contract with Charles Rivers/MPI the CRO that will conduct the toxicology studies was completed.

Task 2.4: Radiotracer Stability studies

During requalification of the ^{18}FB-AH-TG97 the stability was evaluated at 8 hours post preparation. The stability data is shown in Table 1. The current expiration of the batch has been established at 8 hours post manufacturing.

Table 1: Eight-hour stability data for ^{18}FB-AH-TG97

Quality Control Test and Specifications of ^{18}FB-AH-TG97 Stability – 8 Hours		
Test	Specification	170201FCTT
Appearance	Colorless/free from particles	Colorless/free from particles
Radiochemical purity	>85%	92%
Radiochemical Identity	RRT = 100 ± 0.05 as standard	0.96
Radionuclidic purity	511 keV peak must be present	511 keV present
Radionuclidic Identity	107 m < half life < 112.4 m ^{18}F half-life (109.7minutes)	108 min
Specific Activity	≥ 500Ci/mmol (18.5 TBq/umol) (NLT 07 mCi/µg)	680 Ci/mmol (0.96 mCi/µg)
pH	4.5 – 7.5	5.5

Stability of ^{18}FB-AH2-TG97 was evaluated in saline solution at room temperature for 6 hours. Serial HPLC injections were performed over the 6 hours. No change in the chromatograms was noted over the 6 hour time period.

A solution of non-radioactive FB-AH2-TG97 was dissolved at 0.4 mg/mL in saline. HPLC chromatograms were taken in triplicate and the sample was split into 2 sealed vials, one stored at room temperature and the other at -20 °C. Samples were retested by HPLC at 1, 4, 7, 14, 21, 29, and 35 days. Area under the chromatogram peak was used to determine the stability of solutions. The stability is shown graphically in Figure 3.

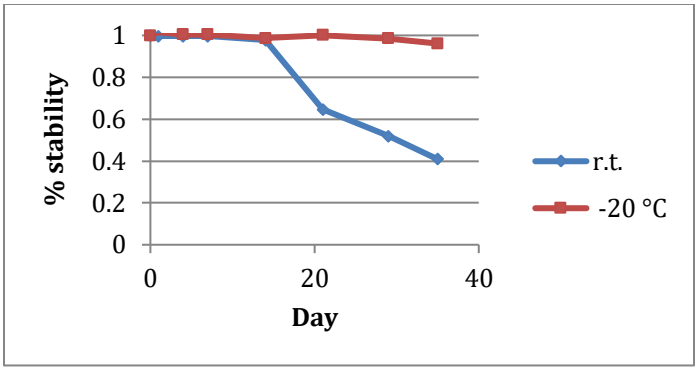

Figure 3. Stability of non-radioactive FB-AH$_2$-TG97 in saline at room temperature and -20˚C.

Task 2.5: Radiotracer *in vivo* metabolism studies

Four normal Sprague Dawley male rats were injected with ~0.5 mCi of ^{18}F-AH2-TG97 in saline while anesthetized. Rats were kept under anesthesia for the entirety of the study. Vials containing micropipet tubes were weighed prior to the experiment. At 15, 30, 60, 90, 120, 180 and 240 mins a rear paw of the rat was poked with a needle and the drop of blood was collected in the micropipet. This was then counted and compared against a on a gamma counter system. The percent injected dose in the blood was determined (Figure 4). The clearance of activity from the blood was rapid. The initial amount of activity in the blood at 15 minutes was very low.

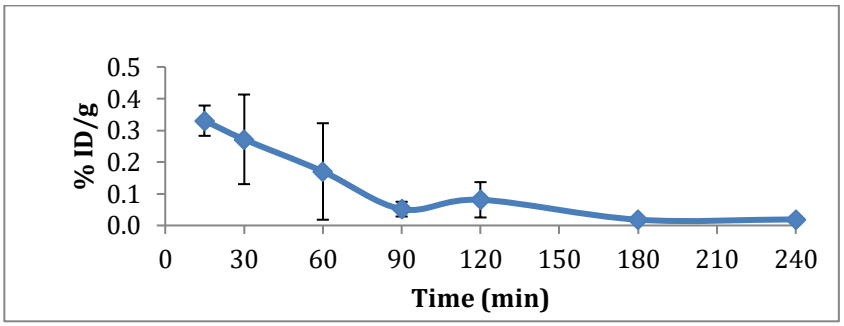

Figure 4. Percent injected dose of ^{18}F-AH2-TG97 per gram of rat blood.

Injected ~0.5 mCi of ^{18}F-AH2-TG97 into Sprague Dawley male rat. The rat was euthanized at 1h post injection and blood and urine were harvested. There was less than 1 µCi of activity in 100-200 µL of blood. This was insufficient to extract and perform the metabolite studies.

^{18}F-AH2-TG97 was added to commercially available rat whole blood, 20-30 µCi in 200 µL blood per tube at 37 ˚C. Tubes were processed at 1, 2 3 4, 5 and 6h after activity addition. The blood samples were centrifuged, the serum was removed and precipitated with 200 µL of acetonitrile. These were centrifuged to remove the precipitated proteins and the resulting supernatant was injected onto an analytical reversed phase gradient HPLC. ^{18}F-AH2-TG97 was added to saline at 37 ˚C as a control. There was one peak in the saline chromatograms with a retention time of ~7.5-8 min over the 6 hours. The blood chromatograms showed 2-4 peaks with a retention time that overlapped the saline peak. The majority of the peak appears to be the unchanged parent radiotracer peak.

Task 2.6: Radiotracer Dosimetry studies

The radiation dosimetry studies for ^{18}FB-AH-TG97 and ^{18}FB-AH2-TG97 were initiated. Tracer was prepared and injected into Sprague Dawley male rats. The time course of distribution was followed by imaging using the Siemens InVeon microPET/CT. The tracer concentration in each organ was calculated from time activity curves generated from the images. The area under the curves will be entered into OLINDA (radiation dosimetry software) and the whole body and organ dosimetry will be determined. As seen in Figure 5, the distribution in male rats shown the uptake and clearance from the kidney through the bladder. This activity clears from the body over the 6h study. There appears to be some intestinal uptake that also rapidly clears over the course of the study.

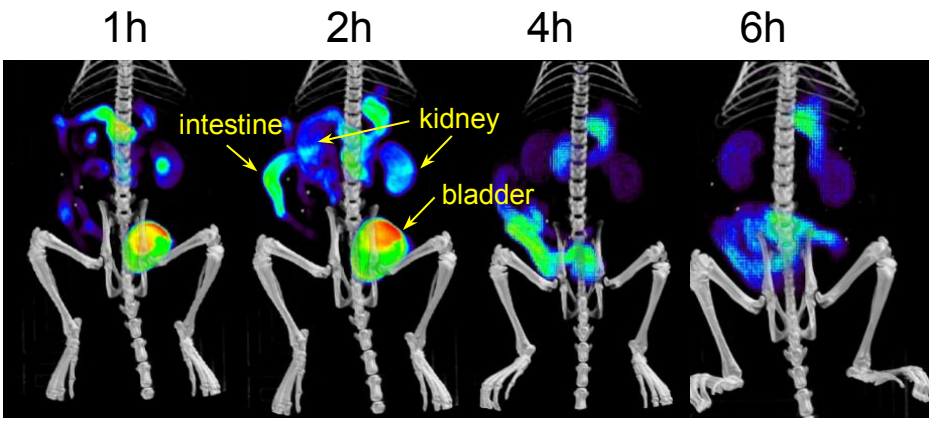

Figure 5. Temporal distribution of radiotracer in normal Sprague-Dawley rats.

Task 2.7: Toxicity evaluation

The contract with Charles River/ MPI, the CRO that is conducting the toxicology studies, was completed. (Task 2.3) The study summary is shown below. Final data analysis will be reported in the final report.

Go Beyond with MPI Research

Proposal for The Regents of the University of California

Expanded Acute Intravenous Toxicity Study in Rats

Proposal Number 17-053987

REGULATORY COMPLIANCE: GLP

OBJECTIVE: The objective of this GLP study is to further characterize the toxicity of the test article in order to provide the information needed to establish a safe starting dose for human clinical trials.

STUDY DESIGN:

	Males [a]
Vehicle Control	15
High Dose	15

[a] *10/group euthanized on Day 2 and five/group euthanized on Day 15*

ANIMALS: Naïve CD® rats, Charles River Laboratories

HOUSING: Socially housed, solid bottom caging

TEST ARTICLE: Small molecule

DOSE ROUTE/FREQUENCY: Intravenous, bolus (up to 2 minutes)/Once on Day 1

DOSE PREPARATION: Once

CAGESIDE OBSERVATIONS: Twice daily (mortality/moribundity)

DETAILED CLINICAL OBSERVATIONS: Pretest and on Days 1, 2, 3, 7, 10, and 14

BODY WEIGHTS: Pretest and on Days 1, 2, 3, 7, 10, and 14

FOOD CONSUMPTION: Pretest and on Days 1, 2, 3, 7, 10, and 14

OPHTHALMOLOGY: All animals pretest and prior to each necropsy

CLINICAL PATHOLOGY: Hematology, coagulation, clinical chemistry, and urinalysis evaluations on all animals (ten/group on Day 2 and five/group on Day 15)

NECROPSY: All animals (ten/group on Day 2 and five/group on Day 15)

ORGAN WEIGHTS: Adrenal glands, brain, epididymides, heart, kidneys, liver, pituitary gland, prostate gland, spleen, testes, thymus, thyroid gland (with parathyroid)

SLIDE PREPARATION/MICROSCOPIC PATHOLOGY: All animals on Day 2 and all found dead animals: full tissue list; target organs from all animals on Day 15 (to be determined, additional cost); gross lesions from all animals

STATISTICAL ANALYSIS: Standard

FORMULATION ANALYSIS: Sample analysis for one batch included (homogeneity and concentration); validation will be conducted under a separate study number (additional cost).

REPORTING: Audited draft report approximately ten weeks after final necropsy*

SEND DATA: Will include SEND v3.0 data sets.

STUDY PRICE: $97,600

*If there are a significant number of target organs, the timing of the audited report could be impacted

MPI RESEARCH

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

We previously translated the synthesis of ^{18}FB-AH-TG97/ AH2-TG97 with SPE purification to the NEPTIS® automated synthesis unit in the UCSF Radiopharmaceutical facility. The schematic diagram of the reagent setup with the cassettes and reagents in place is shown in Figure 6. The inset is the original SPE purification pathway where all of the materials and solvents went through the environmental C18. The new approach, shown in the full cassette, has a 3-way valve before and after the environmental C18 cartridge (red). This allows us to load the C18 column and then rinse it to waste before eluting the product onto the quaternary ammonium (QMA) cartridge (light blue). Then the C18 is bypassed and the final product is eluted with saline from the QMA without going through the C18 cartridge as was previously done. This process is more efficient and eliminates cleaning the C18 cartridge completely before eluting the tracer from the QMA. It also reduces residual solvent issues and eliminates small byproducts in the final preparation.

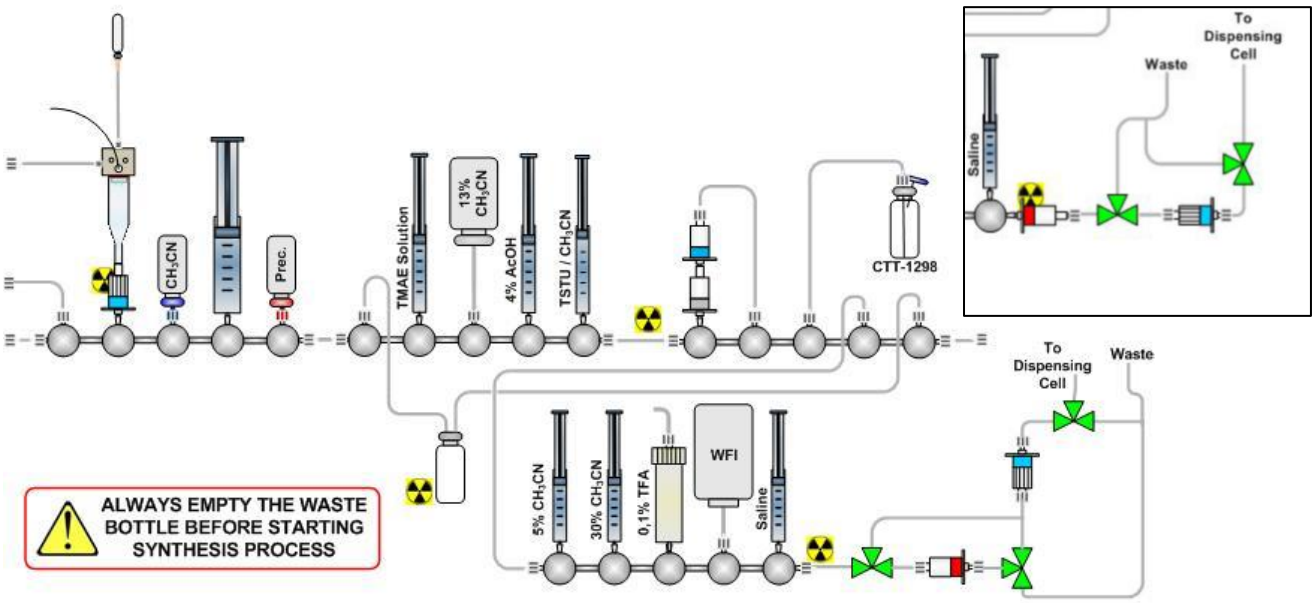


Figure 6. Schematic diagram showing the placement of reagents in the cassettes on the face of the Neptis synthesis unit.

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

Completed in year 2.

Task 3.3: Human Studies Protocol for submission to UCSF IRBs

Completed in year 2

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

Completed in year 2

Task 3.5: Complete the exploratory IND for FDA submission

Completed in year 2

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

Complete for ^{18}FB-AH-TG97 in year 2.

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

The UCSF postdoctoral fellow on this project, Dr. Thomas Hayes, 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 had not performed tracer development with short-lived positron emitting radioisotopes before joining UCSF. He has been a quick study and automated the tracer synthesis on the Elixys so that he could begin to further improve the tracer production while preparing doses for the preclinical studies.

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.

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

Over this final funding/ reporting period we will complete all of the remaining tasks in this project. Major tasks include final analysis/evaluation of the preclinical data. The toxicologic evaluation in rats will be completed with Charles Rivers/ MPI research. A final report summariazing all activities will be written.

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. Additionally, other solid tumors including renal cell carcinoma and hepatocellular carcinoma express PSMA. The agents developed herein may also be used to visualize tumor and metastatic tissue.

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 1 Dr. VanBrocklin oversaw and directed the research studies under this project. He coordinated efforts with Dr. Cliff Berkman at Washington State University (subcontract). He completed the ACURO for the toxicology studies. He coordinated the activities of the postdoctoral fellow, Dr. Hayes. 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:	Thomas Hayes Postdoctoral Fellow 1 Dr. Hayes automated the radiotracer synthesis in the Elixys synthesis unit. He prepared tracers for preclinical studies. NIH U01
Name: Project Role: Nearest person month worked: Contribution to Project: Funding support:	Youngho Seo Co-investigator 1 Dr. Seo assisted with the analysis of the preclinical studies. NIH U01

Name: Project Role: Nearest person month worked: Contribution to Project: Funding support:	Clifford Berkman Washington State Univ Subcontract PI 1 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 1 Dr. Choi conducted synthesis and analytical work on the radiolabeling precursors and authentic standards DoD

8. SPECIAL REPORTING REQUIREMMENTS: None

9. APPENDICES:

A. QUAD CHART

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

W81XWH-14-1-0603 (PC130431)

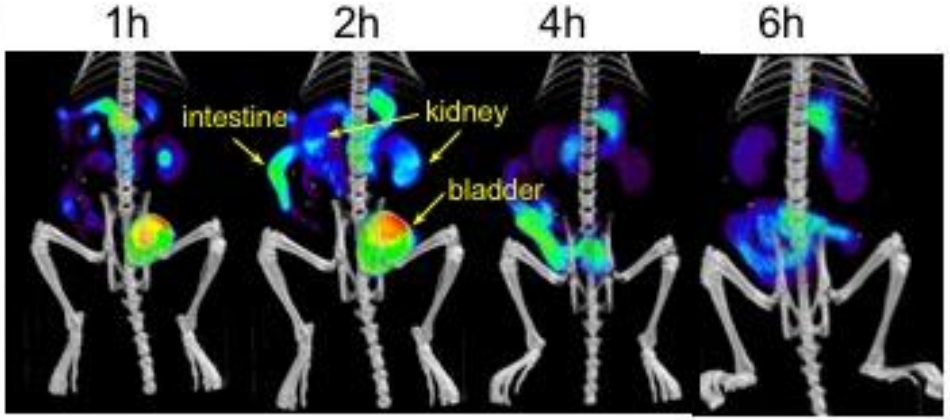
PI: Henry F. VanBrocklin, Ph.D. **Org:** University of California San Francisco **Award Amount:** $1,421,999

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.



Pharmacokinetic evaluation of ^{18}FB-AH2-TG97 in normal male Sprague-Dawley rats. Normal distribution and clearance of the imaging agent is seen. The tracer clears mainly through the kidneys and bladder. Some gut uptake is noted. Images from InVeon microPET/CT.

Timeline and Cost

Activities FY	15	16	17	18
Aim 1 Synthesis				
Aim 2 Preclinical Assessment				
Aim 3 Automate Prep/ IND CMC Data				
Estimated Budget ($K)	**$735**	**$667**	**NCE**	**NCE**

Updated: 10/30/18

Key Research Accomplishments

- Prepared FB-AH$_2$-TG97 (non-radioactive) for toxicology studies
- Prepared ^{18}F-AH-TG97 and ^{18}F-AH$_2$-TG97
- Evaluated distribution of FB-AH-TG97 and FB-AH$_2$-TG97 in mice with PSMA+ and PSMA- tumors
- Contracted for toxicology studies
- Completed imaging studies for dosimetry calculation.
- Completed metabolism studies in rats.