AWARD NUMBER: W81XWH-16-1-0604

TITLE: 68Ga Bombesin PET/MRI in Patients with Biochemically Recurrent Prostate Cancer and Noncontributory Conventional Imaging

PRINCIPAL INVESTIGATOR: Andrei Iagaru, MD

CONTRACTING ORGANIZATION: The Leland Stanford Junior University
Stanford, CA 94305

REPORT DATE: October 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2017	Annual	30 Sep 2016 - 29 Sep 2017

4. TITLE AND SUBTITLE

68Ga Bombesin PET/MRI in Patients with Biochemically Recurrent Prostate Cancer and Noncontributory Conventional Imaging

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-16-1-0604

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Andrei Iagaru

E-Mail: aiagaru@stanford.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

THE LELAND STANFORD JUNIOR UNIVERSITY
450 SERRA MALL
STANFORD CA 94305-2004

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Purpose: ^{68}Ga-labeled DOTA-4-amino-1-carboxymethyl-piperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH2 (^{68}Ga-RM2) is a synthetic bombesin receptor antagonist that targets gastrin-releasing peptide receptors (GRPr). GRPr proteins are highly overexpressed in several human tumors, including prostate cancer (PCa).

Methods: We enrolled 15 men with biochemically recurrent PCa from May to Sep 2017, 63-79 year-old (mean±standard deviation (SD): 70.3±4.3). Imaging started at 41-89 minutes (mean±SD: 53.6±14.1) after injection of 127.5-146.5 MBq (mean±SD: 141.0±4.7) of ^{68}Ga-RM2 using a time-of-flight (TOF)-enabled simultaneous positron emission tomography (PET) / magnetic resonance imaging (MRI) scanner. T1-weighted (T1w), T2-weighted (T2w) and diffusion-weighted images (DWI) were acquired.

Results: All patients had rising prostate specific antigen (PSA) (range: 0.2-12.5 ng/mL; mean±SD: 4.2±4.4) and negative CI (CT or MRI, and ^{99m}Tc MDP bone scan) prior to enrollment. The observed ^{68}Ga-RM2 PET detection rate was 73.3%. ^{68}Ga-RM2 PET identified recurrent PCa in 11 of the 15 participants.

Conclusions: ^{68}Ga-RM2 PET can be used for assessment of GRPr expression in patients with biochemically recurrent PCa. High uptake in multiple areas compatible with cancer lesions suggests that ^{68}Ga-RM2 is a promising PET radiopharmaceutical for localization of disease in participants with biochemically recurrent PCa and negative conventional imaging.

15. SUBJECT TERMS

Prostate cancer, Bombesin, PET, PET/MRI, clinical research, receptors

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	9	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

Page

INTRODUCTION

Prostate cancer (PCa) is the most common malignancy in elderly men (1) and the second leading cause of cancer death after lung and bronchus tumors (2). Up to 40% of prostate cancer patients develop biochemical recurrence within 10 years after radical treatments (3) and morphological imaging methods exhibit considerable limitations in detecting relapsed disease early (4). Gastrin releasing peptide receptors (GRPr), part of the bombesin (BBN) family, are overexpressed in several human tumors including prostate cancer.

Combined positron emission tomography (PET) and magnetic resonance imaging (MRI) targeting the GRPr with a ^{68}Ga-labelled bombesin analog receptor antagonist (RM2) is used as a promising diagnostic method for patients with suspicion of PCa recurrence. Here, we evaluate the role of ^{68}Ga-RM2 PET/MRI in patients with biochemical recurrence of PCa and negative conventional imaging.

The main goal of our study is to evaluate if ^{68}Ga-RM2 PET/MRI can improve the diagnostic accuracy of recurrent prostate cancer earlier, when PSA level is still low and no disease is seen by conventional imaging. This would lead to timely and more accurate treatments with impact on overall survival and quality of life.

References:

1. Attard G, Parker C, Eeles RA, et al. (2016) Prostate cancer. Lancet 387:70-82.
2. Siegel RL, Miller KD, Jemal A (2016) Cancer statistics, 2016. CA Cancer J Clin 66:7-30.
3. Isbarn H, Wanner M, Salomon G, et al. (2010) Long-term data on the survival of patietns with prostate cancer treated with radical prostatectomy in the prostate-specific antigen era. BJU International 106(1):37-43.
4. Bott SRJ. Management od recurrent disease after radical prostatectomy (2004). Prostate Cancer & Prostatic Disease. 7930:211-216.

KEYWORDS

Prostate cancer, bombesin, ^{68}Ga, RM2, PET, PET/MRI, clinical research, receptors

ACCOMPLISHMENTS

Major goals of the project

Specific Aim 1 (specified in Project Narrative)	Original Timeline	Progress	Date Completed
To compare the diagnostic performance of ^{68}Ga-RM2 PET/MRI to that of conventional imaging (CI) for detecting recurrent prostate cancer.	Months		
Time needed to get protocol approved by HRPO	1-5	100%	03/20/17
Prepare to start enrollment of participants	1-2	100%	05/01/17
Enroll participants	Ongoing	15%	Ongoing

Accomplishments under goals

1) *Major activities:* enrolling eligible patients and reviewing ^{68}Ga-RM2 PET/MRI images to investigate its role as stated in #2.

   We enrolled 15 participants in the Jun-Sep 2017 time frame. June is effectively the start date for enrollment since we needed time for HRPO approval and to run validation runs locally afterwards. At this accrual rate (>4 enrolled each month) we are on target for complete and timely accrual.

2) *Specific objectives:* The specific objectives of the goals included: obtaining study approvals from the Stanford Institutional Review Board and the DOD CDMRP HRPO, designing the clinical database, enrolling eligible patients, performing ^{68}Ga PET/MRI of the eligible patients, review images.

   All of the above have been completed or are in progress, as detailed in #1.

3) *Significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative)*:

   ^{68}Ga-RM2 PET/MRI was able to detect findings compatible with prostate cancer recurrence in 11 of the 15 participants enrolled to date. There were no failures in ^{68}Ga-RM2 synthesis, scanner operation or otherwise.

4) *Stated goals not met:*

   None

Opportunities for training and professional development

We hired a research fellow as specified in the submission. In addition, in the Division of Nuclear Medicine and Molecular Imaging are assisting with the enrollment of eligible participants and collecting and analyzing data, respectively. This is an excellent opportunity for them to learn about clinical research.

Results disseminated to communities of interest

^{68}Ga-RM2 PET/MRI is promising for improving the diagnostic accuracy in patients with biochemical recurrence of prostate cancer and negative conventional imaging. We presented the results at local and regional meetings, including at a patient outreach event organized by Stanford HealthCare. We plan to continue to present results at local, national and international meeting in order to disseminate results to communities of interest.

Plans for next reporting period to accomplish goals

We plan to closely monitor study enrollment, with the goal of enrolling 2-3 patients a month in order to meet the study recruitment goal of 100 participants overall. If the study recruitment goals are met early, we will make every attempt to complete the project in a timely manner and expedite efforts where we can.

IMPACT

Impact on the development of the principal discipline(s) of the project

Nothing to report

Impact on other disciplines

Nothing to report

Impact on technology transfer

Nothing to report

Impact on society beyond science and technology

Nothing to report

CHANGES/PROBLEMS

Changes in approach and reasons for change

Nothing to report

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

Nothing to report

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards, and/or select agents

Nothing to report

PRODUCTS

Journal publications

Nothing to report

Books or other non-periodical, one-time publications

Nothing to report

Other publications, conference papers, and presentations

Nothing to report

Website(s) or other Internet site(s)

Nothing to report

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

Nothing to report

Other products

Nothing to report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Individuals who have worked on the project

Name:	Iagaru, Andrei Horia
Project Role:	Principal Investigator
Nearest person month worked:	1
Contribution to project:	Dr. Iagaru has worked with all personnel to oversee the project (no change)

Name:	Brooks, James Duane
Project Role:	Co-Investigator
Nearest person month worked:	<1
Contribution to project:	Dr. Brooks has assisted with participants referrals

Name:	Loening, Andreas Markus
Project Role:	Co-Investigator
Nearest person month worked:	<1
Contribution to project:	Dr. Loening has assisted with analysis of MRI data

Name:	Mittra, Erik S
Project Role:	Co-Investigator
Nearest person month worked:	<1
Contribution to project:	Dr. Mittra has assisted with analysis of PET data

Name:	Srinivas, Sandhya
Project Role:	Co-Investigator
Nearest person month worked:	<1
Contribution to project:	Dr. Srinivas has assisted with coordinating the clinical study

Name:	Vasanawala, Shreyas Shreenivas
Project Role:	Co-Investigator
Nearest person month worked:	<1
Contribution to project:	Dr. Vasanawala has assisted with analysis of MRI data

Name:	Baratto, Lucia
Project Role:	Clinical Postdoctoral Fellow
Nearest person month worked:	10
Contribution to project:	Dr. Baratto has assisted with patient enrollment and consenting, data collection and analysis.

Name:	Rosenberg, Jarrett
Project Role:	Statistician
Nearest person month worked:	<1
Contribution to project:	Dr. Rosenberg has assisted with data analysis.

Name:	Jordan Cisneros
Project Role:	Research Coordinator
Nearest person month worked:	2
Contribution to project:	Jordan Cisneros has assisted with patient recruitment and scheduling.

Changes in active other support of the PD/PI(s) or senior/key personnel since the last reporting period

Nothing to declare

Other organizations involved as partners

Nothing to report

Location of organization:

Partners contribution to the project:

SPECIAL REPORTING REQUIREMENTS

Nothing to report

APPENDICES

Nothing to report