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TITLE: Characterizing the Aggressiveness of Prostate Cancer with Multi-Modality Imaging

PRINCIPAL INVESTIGATOR: Prof. Timothy J. Scholl

CONTRACTING ORGANIZATION: University of Western Ontario

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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> The goal of this research project is to demonstrate the ability of multimodality imaging to improve detection of prostate tumors and accurately determine their aggressiveness by comparing non-invasive molecular imaging to pathological examination. This project will study a total of 45 men with biopsy-proven prostate cancer. Prior to prostatectomy, they will undergo molecular imaging. After prostatectomy, sections of their prostates will be examined under a microscope by a pathologist. This examination is the gold-standard for characterizing tumors and will be used to establish how accurately the pre-surgical multimodality imaging assay was able to find tumors and predict their aggressiveness.					
<b>15. SUBJECT TERMS</b> prostate cancer, multi-modality imaging, MRI, PET, tissue sodium concentration, prostate specific membrane antigen, prostatectomy biopsy, tumour aggressiveness, Gleason grade					
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## TABLE OF CONTENTS

	<u>Page</u>
1. INTRODUCTION	4
2. KEYWORDS	5
3. ACCOMPLISHMENTS	6
4. IMPACT	8
5. CHANGES/PROBLEMS	9
6. PRODUCTS	10
7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS	11
8. SPECIAL REPORTING REQUIREMENTS	13
9. APPENDICES	14

## 1) INTRODUCTION

The title of this research project is “Characterizing the Aggressiveness of Prostate Cancer with Multi-Modality Imaging”. Its goal is to demonstrate the ability of multimodality imaging to improve detection of prostate tumors and accurately determine their aggressiveness by comparing non-invasive molecular imaging to pathological examination. This project will study a total of 45 men with biopsy-proven prostate cancer. Prior to prostatectomy, they will undergo molecular imaging. After surgery, sections of their prostates will be examined under a microscope by a pathologist. This examination is the gold-standard for characterizing tumors and will be used to establish how accurately the pre-surgical multimodality imaging assay was able to find tumors and predict their aggressiveness.

## 2) KEYWORDS

prostate cancer  
multi-modality imaging  
magnetic resonance imaging  
positron emission tomography  
tissue sodium concentration  
prostate specific membrane antigen  
prostatectomy  
biopsy  
histopathology  
tumour aggressiveness  
Gleason grade

### 3) ACCOMPLISHMENTS

- **Major goals for Year 1**
  - Filing paperwork with Human Review Ethics Board.
  - Submission of HRPO documents.
  - Subtask 1: Evaluation of RF hardware.  
Evaluation of Sodium MRI pulse sequences.  
Manuscript preparation.
  - Graduate student recruitment.
  - Pathology Assistant recruitment.
  - Subtask 2: Recruitment of first study patients.  
Human imaging acquisition
- **What was accomplished under these goals?**
  - HREB paperwork submitted and approval received.
  - HRPO completed for submission October 2020.
  - Subtask 1: Evaluation of sodium RF hardware  
Experiments to assess imaging performance were undertaken by comparing sodium signal acquired at St. Joseph's hybrid PET/MRI (Biograph mMR, Siemens) to Robarts 3T MRI (Discovery MR750 3T, GE Healthcare). Free-induction decay measurements were acquired using a phantom containing 100 mM sodium and identical RF coils at both sites. Signal-to-noise ratios (SNR) were identical across sites for the same acquisition parameters. This validates that the sodium MR imaging performance demonstrated in our preliminary study at the Robarts Research Institute (Broeke NC, *et al.*, *Characterization of clinical human prostate cancer lesions using 3.0-T sodium MRI registered to Gleason-graded whole-mount histopathology*. *Journal of Magnetic Resonance Imaging*, 2019. **49**(5): p. 1409-1419.) has been achieved for the first time at the combined PET/MRI hybrid system.
  - Subtask 1: Pulse sequence development  
A pulse sequence known as “density-adapted 3D projection reconstruction” was acquired via site-to-site transfer from our collaborator, Armin Nagel (MRI Physics Group University Hospital, Erlangen, Germany). Professor Nagel is an expert in sodium MRI and has developed this pulse sequence for efficient *in vivo* 3D sodium imaging (Nagel AM, *et al.*, *Sodium MRI using a density-adapted 3D radial acquisition technique*. *Magnetic Resonance in Medicine*, 2009. **62**(6): p. 1565-1573). This pulse sequence is a series of instructions for the MRI to collect an image. They were compiled for the Biograph mMR hybrid PET/MRI scanner. Imaging SNR was compared with a similar radial sequence separately developed by Alireza Akbari for the GE Discovery MR750 3T using a phantom and identical acquisition parameters. This validates the pulse sequence implementation. Preliminary MR imaging data for a healthy prostate is shown in Figure 1 of the Appendix.

- Subtask 1: Manuscript preparation.  
The RF hardware, which was developed for this project is being described in a manuscript for submission in NMR in Biomedicine. This manuscript is being written by Mr. Adam Farag, the PhD student working on this project as part of his thesis. This manuscript will include exemplary PET and MRI (proton and sodium) images. This will be acquired with the first human volunteer later this fall.
- PhD student (Josephine Tam) was recruited but could not join project in Year 1 due to COVID-19 pandemic. This graduate student will join project in 2021. A second PhD student (Adam Farag) is currently training in this project.
- Dr. Mena Gaed is a pathologist with significant experience in preparation of whole-mount prostate sections and prostate lesion grading. He has been salaried for the duration of this project and will process tissue specimens, grade lesions and co-register *in vivo/ex vivo* imaging data.
- Subtask 2: Recruitment of first study patients.  
Patient recruitment for this study was not possible due to suspension of all medical research at Ontario hospitals due to Provincial guidelines. Recruitment will begin Fall 2020.
- Subtask 2: Human imaging acquisition.  
Unanticipated delays have been encountered which have prevented us from acquiring human imaging data. These include a change of radio-labeled PET tracer, which required a new application to Health Canada; moratorium on hospital and university research by the Province of Ontario; final submission of the HRPO documentation. The moratorium on research and delays in submission of the HRPO documentation were related to the COVID-19 pandemic, which prevented us from recruiting patients and completion of our paperwork.
- **Opportunities for training and professional development.**
  - Mr. Adam Farag is currently working on this research project as part of his PhD thesis in Medical Biophysics at Western University.
- **How were the results disseminated to communities of interest?**
  - No human imaging has been undertaken due to COVID-19 delays. A manuscript describing the novel RF hardware is being written and will be submitted to a journal for publication after peer review.
- **What do you plan to do during the next reporting period to accomplish the goals?**
  - We expect that the first human subjects will be recruited for imaging experiments in the Fall of 2020.

#### 4) IMPACT

- **What was the impact on the development of the principal discipline(s) of the project?**  
Nothing significant to report at this juncture.
- **What was the impact on other disciplines?**  
Nothing significant to report at this juncture.
- **What was the impact on technology transfer?**  
Nothing significant to report at this juncture.
- **What was the impact on society beyond science and technology?**  
Nothing significant to report at this juncture.

## 5) CHANGES/PROBLEMS

- **Changes in approach and reasons for change**
  - We have changed the original radio-labeled PET tracer from [<sup>18</sup>F]DCFPyL to PSMA-1007. Licencing for production of [<sup>18</sup>F]DCFPyL from the Centre for Probe Development and Commercialization (CPDC) in Hamilton, ON will cease in 2021 and we determined that it was preferable to complete the entire study using the newer PET tracer, PSMA-1007, which is reported to have more specificity than <sup>18</sup>F]DCFPyL. This PET tracer will ultimately be produced at the St. Joseph's cyclotron in London under licence from the CPDC. This technical change to our study has already been submitted to Health Canada and approval has been received to use PSMA-1007. This has caused a short delay in our research timeline. Cost and availability for the new tracer remain unchanged.
- **Actual or anticipated problems or delays and actions or plans to resolve them**
  - The Province of Ontario temporarily ceased all research at Ontario hospitals and university due to the COVID-19 pandemic. This effectively halted our research efforts from 03/2020 to 09/2020. The prostate imaging team continued Zoom meetings during this hiatus but no hands-on work with the imaging equipment has been possible for most of 2020. We now have access to the hospital hybrid PET/MRI and have been refining our hardware and pulse sequences. It should be noted, that while our research has resumed, we must work within Provincial guidelines, which limit the occupancy of our research facilities at the hospital and university (currently 40% of normal occupancy). This number is periodically revised by the Province of Ontario under response to changes in the infection rates. Currently, this province has been experiencing a second wave of infections and the province is considering further curbs on social interactions, which could further impact our research over the next reporting period. Never-the-less, we plan to continue our efforts under the current guidelines, making as much progress as possible.
- **Changes that had a significant impact on expenditures**
  - None.
- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
  - None.
- **Significant changes in use or care of human subjects**
  - None.
- **Significant changes in use or care of vertebrate animals**
  - None.
- **Significant changes in use of biohazards and/or select agents**
  - See earlier discussion of use of a new PET tracer, PSMA-1007 to replace [<sup>18</sup>F]DCFPyL.

## 6. PRODUCTS

- 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 licences
  - Nothing to report.
- Other Products
  - Nothing to report.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- What individuals have worked on the project?

The following individuals have worked on this project in Year 1. (This list will expand to include other individuals named in the project who have yet to participate until patients are recruited.)

<b>Name:</b>	Timothy Scholl, PhD
<b>Project Role:</b>	Nominated Principal Investigator
<b>Researcher Identifier:</b>	I-6178-2012 (Publons)
<b>Nearest person month worked:</b>	3 months
<b>Contribution to Project:</b>	Project oversight and administration
<b>Funding Support:</b>	University faculty
<b>Name:</b>	Jonathan Thiessen, PhD
<b>Project Role:</b>	Principal Investigator
<b>Researcher Identifier:</b>	B-3514-2015 (Publons)
<b>Nearest person month worked:</b>	3 months
<b>Contribution to Project:</b>	Hybrid PET/MRI
<b>Funding Support:</b>	Hospital scientist and university faculty
<b>Name:</b>	Glenn Bauman, MD
<b>Project Role:</b>	Principal Investigator
<b>Researcher Identifier:</b>	D-5986-2011 (Publons)
<b>Nearest person month worked:</b>	1 month
<b>Contribution to Project:</b>	Clinical oversight of study
<b>Funding Support:</b>	Hospital physician and university faculty
<b>Name:</b>	Matthew Fox, PhD
<b>Project Role:</b>	Research Assistant
<b>Researcher Identifier:</b>	
<b>Nearest person month worked:</b>	2 months
<b>Contribution to Project:</b>	Evaluation of PET/MRI imaging hardware
<b>Funding Support:</b>	This project (25%)
<b>Name:</b>	Alireza Akbari, PhD
<b>Project Role:</b>	Research Assistant
<b>Researcher Identifier:</b>	
<b>Nearest person month worked:</b>	2 months
<b>Contribution to Project:</b>	Sodium MRI pulse sequence and hardware
<b>Funding Support:</b>	Other, outside this project
<b>Name:</b>	Adam Farag, MSc
<b>Project Role:</b>	Graduate student

<b>Researcher Identifier:</b>	
<b>Nearest person month worked:</b>	2 months
<b>Contribution to Project:</b>	Thesis project, preparation of manuscript
<b>Funding Support:</b>	This project (25%)
<b>Name:</b>	Mena Gaed
<b>Project Role:</b>	Pathologist
<b>Researcher Identifier:</b>	
<b>Nearest person month worked:</b>	2 months
<b>Contribution to Project:</b>	Pathology and lesion grading
<b>Funding Support:</b>	This project (100%)
<b>Name:</b>	Catherine Hildebrand
<b>Project Role:</b>	Research Coordinator
<b>Researcher Identifier:</b>	
<b>Nearest person month worked:</b>	2 months
<b>Contribution to Project:</b>	Ethics paperwork etc.
<b>Funding Support:</b>	This project

- **Has there been a change in the active other support of the PD/PIs or senior/ley personnel since the last reporting period?**
  - No.
- **What other organizations were involved as partners?**
  - None.
- **Locations of organization**
  - Not applicable.
- **Partners contribution to the project**
  - Not applicable.

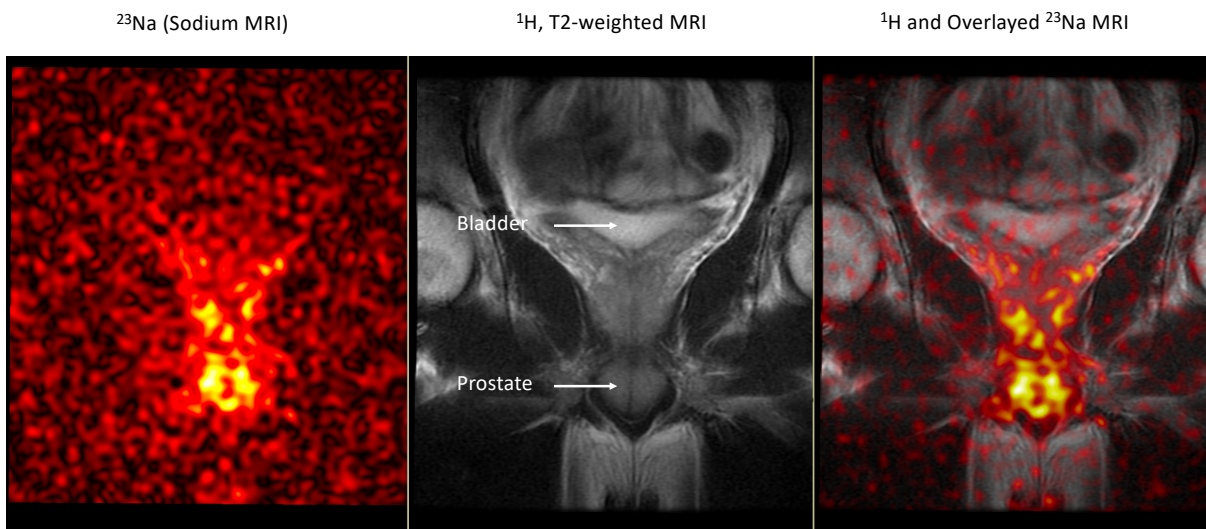
## 8. SPECIAL REPORTING REQUIREMENTS

- Collaborative Awards
  - None.
- Quad Charts
  - None.

## 9) APPENDICES

Figure 1: Exemplary MR imaging data for a prostate from a healthy volunteer.

### Coronal View of Healthy Prostate



In-plane resolution 3x3 mm<sup>2</sup>, FOV 18 x 18 cm<sup>2</sup>, slice thickness 30mm, TE/TR 1.2/100 ms