

AWARD NUMBER: W81XWH-19-1-0721

TITLE: Characterizing the Aggressiveness of Prostate Cancer with Multimodality Imaging

PRINCIPAL INVESTIGATOR: Prof. Timothy J. Scholl, PhD

CONTRACTING ORGANIZATION: The University of Western Ontario

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TYPE OF REPORT: ANNUAL

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

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14. ABSTRACT 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.						
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1. INTRODUCTION: *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

The purpose of this research 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.

2. KEYWORDS: *Provide a brief list of keywords (limit to 20 words).*

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

3. ACCOMPLISHMENTS: *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

- 1) Evaluation of dual frequency proton/sodium MRI RF hardware for prostate imaging (completed, 12/2020)
- 2) Evaluation of non-Cartesian pulse sequence for sodium MRI (completed, 12/2020)
- 3) Redesigned external RF hardware for sodium-MRI (completed 06/2022)
- 4) Manuscript preparation dissemination results of 1), 2) and 3) (in preparation, 09/2022)
- 5) Recruitment of patients for imaging study (Recruitment is underway, but delayed due to restrictions on research at Canadian hospitals during COVID-19. To date, 5 of 45 men have been recruited.)
- 6) Multivariate analysis (awaiting completion of recruitment)
- 7) Dissemination of study results (to be completed at end of study)

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Patient recruitment has been hampered by the COVID-19 pandemic (see discussion below). We have recruited the first 5 men into our research study, and they have been imaged with multi-parametric MRI, sodium-MRI and PET using the latest prostate cancer tracer, PSMA-1007, which is now being manufactured at our own cyclotron. Histology has been completed for four of these cases. Histological examination of one prostate sample was not possible due to the very poor condition of the excised prostate. To improve our imaging assessment of tissue sodium concentration, we constructed an external transmit/receive butterfly RF coil, which eliminates the insertion of an endorectal receive RF coil for sodium-MRI. The new RF hardware produces uniform signal assessment throughout the entire prostate, and it is much better tolerated than the endorectal coil. Development of the non-invasive RF coil for sodium-MRI will decrease the concerns of discomfort for men considering participating in this study. Further, over the next 12 months, the availability of PSMA-1007 from our local facility will give us better flexibility on scheduling of our patient imaging prior to prostatectomy. These two developments will be key to imaging increasing our patient accrual.

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

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

This project is providing training for:

- 1) Ms. Josephine Tan, a Doctoral student currently supervised by Prof. J. Thiessen and T. Scholl. This student presented this research at three international conferences (see below).
- 2) Dr. Alireza Akbari, a Research Scientist currently supervised by T. Scholl. This individual has received mentorship and attended conference workshops focused on sodium magnetic resonance imaging.

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Ms. Tan presented her research at London Imaging Discovery Day, London, ON. (June 2022) and at the Department of Oncology Research & Education Day, London, ON. (June 2021). These events are open to the public and present biomedical research from clinical and basic science.

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

If this is the final report, state “Nothing to Report.”

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We are doubling our efforts to increase patient uptake for our study this includes recruitment from the surgical practice of three urological surgeons. We have developed and implemented a non-invasive RF coil for measurement of tissue sodium concentration throughout the entire prostate. We expect that replacing the endorectal RF coil with this new external RF coil will improve uptake of patients who were concerned with possible discomfort of the internal coil during an hour-long imaging session.

4. **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

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

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

We have demonstrated the ability to non-invasively measure tissue sodium concentration (TSC) throughout the entire prostate. We have acquired TSC data and multiparametric proton MR imaging data simultaneously with positron emission tomography using PSMA-1007 (a tracer that binds to prostate specific membrane antigen, which is over-expressed in prostate cancer. Biomarkers from these data have been extracted for comparison with cancer aggressiveness determined from histological examination after prostatectomy.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report.

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report.

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report.

- 5. CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

We have changed the original radio-labeled PET tracer from [18F]DCFPyL to PSMA-1007, which is now being manufactured locally at our own cyclotron under license from the Centre for Probe Development and Commercialization (CPDC) in Hamilton, ON. Local production of this agent improves the access to this agent so that it is available to us on a weekly schedule to assist with patient recruitment schedule conflicts. As mentioned above, we are now using an external RF coil for sodium-MRI to reduce patient anxiety with possible discomfort of the placement of an endorectal RF coil.

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

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Compared with the experience in the United States, the impact of COVID-19 has been more significant on the socialized healthcare system in Canada, causing millions of cancelled surgeries, diagnostic exams, screenings, and other medical procedures. Exact numbers are not known, but these cancellations include prostatectomies, and as a result, many men have been placed on hormone therapy in lieu of immediate treatment. As a result, recruitment has been hampered by limited surgical availability, patient hesitancy to participate in this study during COVID and the backlog of patients who were placed on hormone therapy, now being triaged for surgical intervention. While hormone therapy is obviously helpful for the patient, it makes accurate Gleason grading of the disease after prostatectomy impossible. As a result, these men are not eligible for our study as we require whole-mount histopathology as our gold-standard for comparison with MRI and PET imaging data. The province has provided additional funding to reduce surgical wait times and reduce the backlog of men awaiting treatment. Hesitancy regarding masking and social distancing has subsided in Canada and men are becoming more amenable to participating in our study. Finally, we have developed an external RF coil system to replace the endorectal RF coil mitigating any discomfort, which was a concern for men who were considering participation in our study. A further benefit of our new RF coil is that it now provides uniform detection of sodium concentration throughout the entire prostate, while previously, our imaging sensitivity was limited to the peripheral zone of the prostate where 80% of all lesions are typically found.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

None.

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

None.

Significant changes in use or care of vertebrate animals

None. No animals were involved in this study.

Significant changes in use of biohazards and/or select agents

None.

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”*

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Peer-Reviewed Journal Publication (In preparation)

Tan, JL, Thiessen JD, Scholl TJ, and Akbari A; **Development of an external butterfly coil for sodium MRI of human prostate cancer**; NMR in Biomedicine (other); acknowledgement of federal support (yes).

International Conference Presentations

Tan JL. **Comparison of external butterfly and endorectal coils for sodium MRI of human prostate cancer.** *Accepted for poster presentation.* World Molecular Imaging Congress (WMIC), Miami, FL. Sep 2022.

Tan, JL. **Multiparametric MRI, sodium MRI and PSMA PET of prostate cancer with histological validation of Gleason grade.** *Poster presentation.* International Society for Magnetic Resonance in Medicine Conference, London, United Kingdom. May 2022.

Tan, JL. **Characterization of Human Prostate Cancer using Non-Invasive Molecular Imaging.** *Poster Presentation,* World Molecular Imaging Congress. Virtual. Oct 2021.

Books or other non-periodical, one-time publications. Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

None.

Other publications, conference papers and presentations. Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

Tan JL. **Multiparametric MRI, sodium MRI and PSMA PET of prostate cancer with histological validation of Gleason grade.** Oral presentation. London Imaging Discovery Day, London, ON. Jun 2022.

Tan, JL. **Characterization of Human Prostate Cancer using Non-Invasive Molecular Imaging.** Poster Presentation, Department of Oncology Research & Education Day, Virtual Jun 2021.

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

We have developed two different RF systems for sodium-MRI of the prostate.

- 1) transmit-only volume birdcage RF coil integrated with a receive-only endorectal RF coil
- 2) transmit/receive external butterfly surface RF coil.

We have found that the non-invasive external butterfly RF coil is better tolerated by the patients.

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

None.

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

None.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change”.

Example:

Name: Mary Smith
Project Role: Graduate Student
Researcher Identifier (e.g. ORCID ID): 1234567
Nearest person month worked: 5

Contribution to Project: Ms. Smith has performed work in the area of combined error-control and constrained coding.
Funding Support: The Ford Foundation (Complete only if the funding support is provided from other than this award.)

Name:	Timothy Scholl, PhD (no change)
Name:	Jonathan Thiessen, PhD (no change)
Name:	Glenn Bauman, MD (no change)
Name:	Aaron Ward, PhD (no change)
Name:	Joseph Chin, MD (no change)
Name:	Alireza Akbari, PhD (no change)
Name:	Josephine Tan, MSc (no change)
Name:	Catherine Hildebrand, PhD (no change)
Name:	Mena Gaed, MD
Project Role:	Pathology (2019-present) and <i>Patient Recruitment (2021-present)</i>
Researcher Identifier:	
Nearest person month worked:	12
Contribution to Project:	Patient recruitment, pathology, and lesion grading

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report.

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner’s contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner’s facilities for project activities);*
- *Collaboration (e.g., partner’s staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner’s staff use each other’s facilities, work at each other’s site); and*
- *Other.*

Organization Name: Ontario Institute for Cancer Research

Location of Organization: Toronto, Ontario, Canada, M5G 0A3

Partner's Contribution to the Project: Prof. Scholl is an Investigator with OICR and receives salary support from this organization.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ebrap.org/eBRAP/public/index.htm> for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on <https://www.usamraa.army.mil/Pages/Resources.aspx>) should be updated and submitted with attachments.*

9. **APPENDICES:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*