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TITLE: Firing Up the Tumor Microenvironment in Metastatic Prostate Cancer with Synergistic PSMA-Targeting Radioligands and STING Agonist Nanotherapies

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CONTRACTING ORGANIZATION: Massachusetts General Hospital

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14. ABSTRACT

Outcomes for patients with metastatic prostate cancer remain poor. There is thus an unmet clinical need to develop new therapy approaches to manage this disease. Given poor results to date of immunotherapy treatment for prostate cancer, likely due to the immunosuppressive nature of the tumor microenvironment, new ways to augment the localized anti-tumor inflammatory response are needed.

This proposal aims to explore the synergy of two highly promising types of treatment for prostate cancer for this purpose. The systemically targeted radionuclide therapy ^{177}Lu-PSMA-617 has shown high potential to reduce patient disseminated disease burden and is poised to be FDA-approved in the near future. Radiation therapy is known to modulate the tumor immune environment and may potentially augment the effects of other promising immunotherapies. However, how ^{177}Lu-PSMA-617 impacts the tumor microenvironment is underexplored to date. In concert, nanotherapies have been shown to improved localized delivery of drugs, including immune- modulating molecules to tumor sites, while reducing systemically toxicity of these drugs. Importantly, we and others have previously demonstrated that radiation effects on tumor immune cell infiltration can be harnessed to increase tumor nanotherapy delivery. Building upon these previous observations, here we propose to understand the evolution of the tumor immune environment during ^{177}Lu-PSMA-617, and how this may synergize with a promising class of immunotherapy that activates the STING pathway via nanoparticle delivery.

15. SUBJECT TERMS
Prostate Cancer, nanotherapy, immunotherapy, PSMA-617

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INTRODUCTION:

Survival outcomes for patients with disseminated metastatic prostate cancer remain poor, with 5-year survival ~30%. Immunotherapeutic approaches for managing this disease are being extensively explored, but success in this endeavor has been limited. Recent and prior work in preclinical and clinical settings have identified key interactions between radiation therapy and the immune system, which can have detrimental and positive responses against the tumor. Understanding these interactions is especially vital at this juncture, given the recent clinical adoption of systemically delivered radiation therapy in prostate cancer (^{177}Lu-PSMA-617, Pluvicto). Taking advantage of this advance, the overarching goal of this study is to develop and assess a synergistic approach combining systemic radiation therapy treatment with nano-immunotherapy approaches to treat metastatic prostate cancer. The scope of this research encompasses understanding the immune response to ^{177}Lu-PSMA-617 therapy and developing synergistic nano therapy-based approaches to complement radiation treatment.

KEYWORDS:

Prostate cancer, nanotherapy, MSA-2, STING, PSMA-617, flow cytometry, CyTOF, immunotherapy, targeted radionuclide therapy

ACCOMPLISHMENTS:

1. **What were the major goals of the project?**

Specific Aim 1: Understand the impact of ^{177}Lu-PSMA-617 on the evolution of the tumor microenvironment in metastatic prostate cancer.

Major Task 1: Spatial and cytometric immunophenotyping of tumor response to TRT

Specific Aim 2: Assess the efficacy of combination STING-agonist nanotherapy and ^{177}Lu-PSMA-617 to elicit an efficacious immune response in metastatic prostate cancer.

Major Task 2: Optimize the timing of nanotherapy delivery during TRT treatment.

Major Task 3: Assess the efficacy of combination TRT and STING- agonist treatment.

2. **What was accomplished under these goals?**

Specific Aim 1: Understand the impact of ^{177}Lu-PSMA-617 on the evolution of the tumor microenvironment in metastatic prostate cancer

Major Task 1: Spatial and cytometric immunophenotyping of tumor response to TRT

Subtask 1: Acquire IACUC/Radiation safety approvals for proposed studies.

We have obtained the IACUC and Radiation safety approvals for the proposed studies. Given the high user volume of our institution's radiochemistry and radiation-approved spaces, we have added additional spaces to our protocols to allow for redundancy. These spaces have been approved on our protocol and will allow for added flexibility for subsequent studies.

Subtask 2: Establish labeling workflow for ^{177}Lu-PSMA-617

We have established a robust radiolabeling workflow for PSMA-617. This was first tested with stable isotopes of lanthanide metals with properties similar to ^{177}Lu. >99% chelation of the metal on PSMA-617 was confirmed by LC/MS (Figure 1). The labeling method was achieved within 1 hour and without significant purification required.

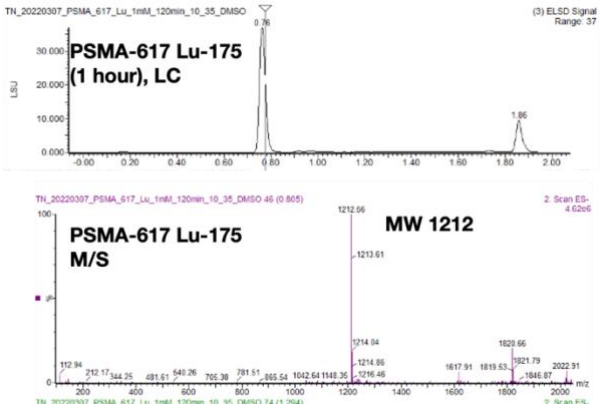

Figure 1: LCMS of PSMA-617 labeling

Based on this we verified established radiolabeling methods with shorter-lived radioisotopes to confirm the translation feasibility of our methods. Both ^{68}Ga and ^{64}Cu were stably labeled onto PSMA-617 in our hands with previously established methodology. Radio-TLC was used to ascertain purity (Figure 2).

Finally, confirming this protocol with radioisotopes enabled us to pursue this with ^{177}Lu. Again, we successfully labeled PSMA-617 with this isotope within an hour and with >99% completion and purity. This was verified with radio-HPLC. Furthermore, the stability of this labeled compound was confirmed up to 1 week post the labeling procedure (Figure 3).

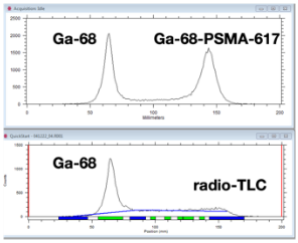

Figure 2: Radio-TLC of PSMA-617 labeling

In conclusion, we have established a functional workflow for the robust synthesis of ^{177}Lu-PSMA-617

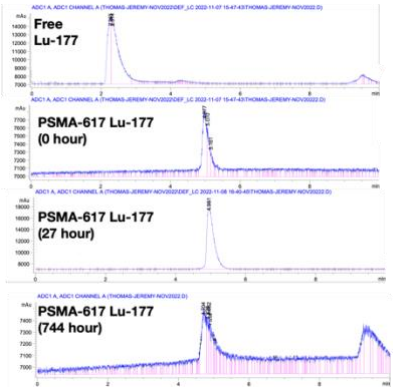

Figure 3: radio-HPLC of PSMA-617 labeling

Subtask 3: Establish workflow for imaging cytometry and RNA-seq

Preparation for imaging cytometry and transcriptomic analysis was initially pursued with non-radioactive samples. The primary goal and hurdles here lie in establishing a workflow compatible with radioisotopes and the requirements for sufficient decay before using samples on non-radiation-approved facilities and equipment. To this end, we have developed a workflow whereby samples are rapidly frozen in portable cryo-compatible containers, based on dry ice. Samples are then cryopreserved in radiation-compatible -80C freezers or a portable liquid nitrogen tank. Samples were stored in these conditions for periods commensurate with the expected decay time of radioisotopes within the tissue and cell samples, about 2-4 weeks.

Samples were collected from RM1.PGLS tumors, other tissue organs as well as cell lines to test the stability of sample preparation. Flow cytometry readouts were used to compare fresh and frozen cytometry samples, showing relative stability of readout after cryopreservation (Figure 4). Mass cytometry processing of these samples with the injection of stable isotope labeled PSMA-617 could discern labeled cells with Lu-PSMA-617 localization (Figure 5). Imaging cytometry from the same tumor samples was processed with flash-frozen tissue embedded in OCT and paraffin-embedded samples fixed in 4% paraformaldehyde. Multiplexed labels of these tissues were overall stable across multiple cell populations, although Lu and PSMA staining signals were weak. We are currently investigating how to improve the robustness of these staining with multiple PSMA antibodies and potentially using an anti-DOTA antibody fragment construct to stain for PSMA-617[1], opening opportunities for fluorescent imaging.

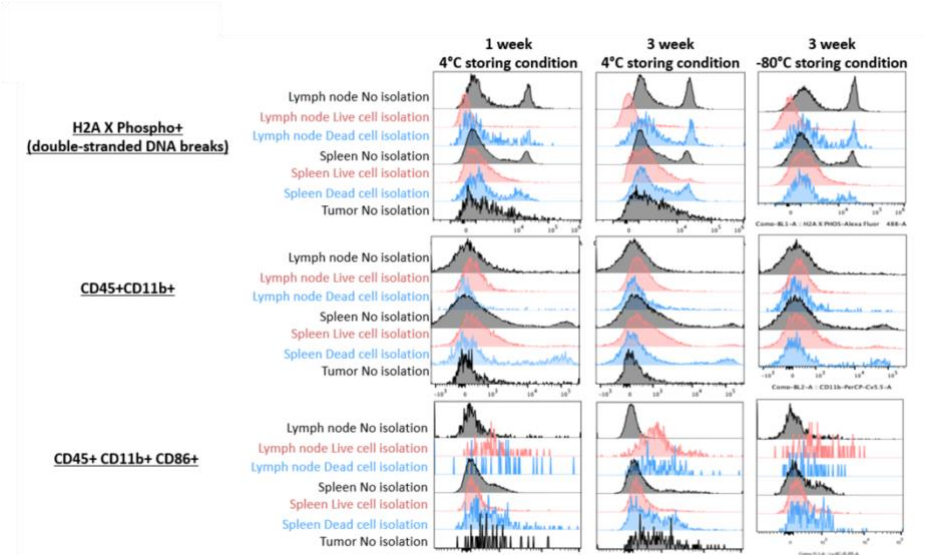

Figure 4: Stability of cytometry with cryopreservation across tissues. This was performed with and without dead cell removal, in anticipation of RNA-seq processing

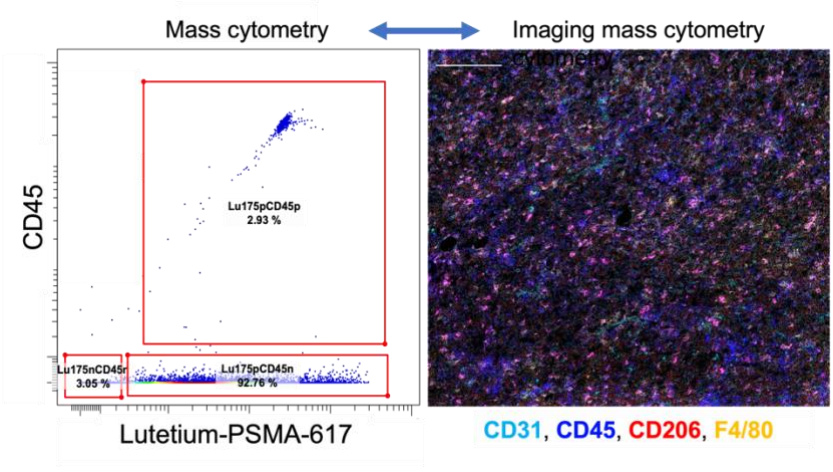

Figure 5: Multiplexed CyTOF and imaging CyTOF of RM1.PGLS tumor enables visualization of multiple cellular markers. Work ongoing to confirm robustness of Lu-PSMA-617 detection.

Currently, we have a setup that enables the analysis of tissues after cryopreservation. Work is ongoing to optimize the staining of tissues for imaging cytometry.

Cytometry and transcriptomics

Subtask 4-9: Establish models of metastatic prostate cancer in immunocompetent C57BL/6 mice

We proposed to examine cellular changes in metastatic RM1.PGLS models, guided by previous reports that these models were able to be established with intra-cardiac injection[2]. Flow cytometry analysis shows

both high and low PSMA-expressing populations in RM1.PGLS prior to tumor inoculation, ably propagated by a PSMA-targeted magnetic bead sorting method (Figure 6).

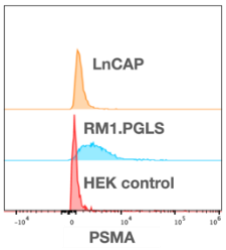

Figure 6: PSMA-expression of prostate tumor cell lines

Multiple attempts with intra-cardiac tumor inoculation were performed. Although tumors were able to be established, including metastases to the lungs and liver, a protocol that allows a robust number of mice to be inoculated at any one time prior to succumbing to extensive tumor burden have been challenging, given the aggressive growth kinetics of this cell line. This remained challenging despite lowering the injection cell number down to 5000-10000 cells.

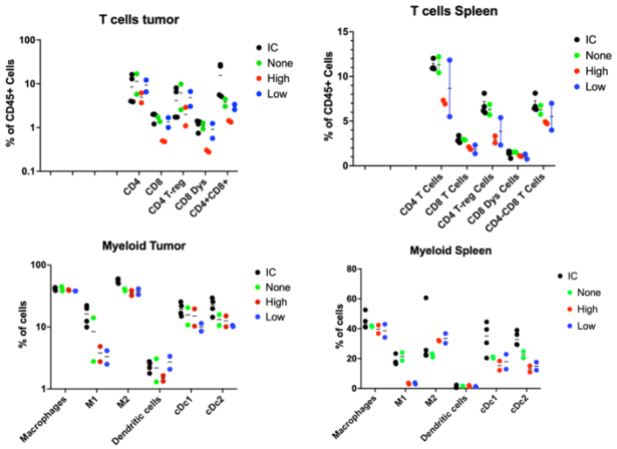

Figure 7: Comparison of flow cytometry profiles between intra-cardiac generated lesions (IC) vs. subcutaneous lesions with and without 177Lu-PSMA-617

Thus, we adopted the approach that pursuing a subcutaneous model for major studies in this task would be viable and would lay the platform for possible subsequent metastatic modeling. To confirm whether significant differences in cell populations were noted between subcutaneous and metastases, we compared the flow cytometry profiles between subcutaneous tumors and thoracic metastatic lesions. Flow cytometry profiles showed no dramatic differences between the two sites (Figure 7). Based on these results we decided to pursue follow-up studies based on the subcutaneous models.

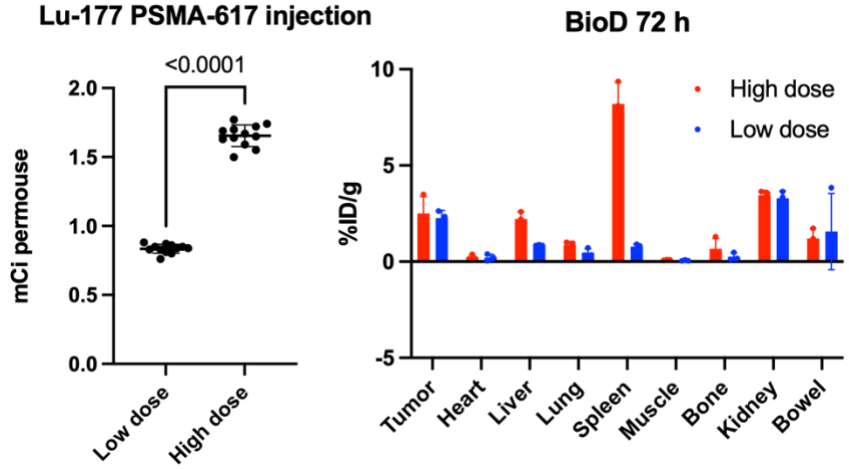

Figure 8 Injection of activity (left), Biodistribution of PSMA-617 as measured by gamma counting

Animal studies with high and low-dose ^{177}Lu-PSMA-617 treated RM1.PGLS tumors have been performed. Tumor samples were acquired at early (4 days) and late (7, 11 days) time points post-radiation injection. As measured by gamma-counting tissue biodistribution, the injected dose of PSMA-617 reaching the tumor was commensurate with prior studies (Figure 8). Interestingly, splenic uptake of the tracer was especially high in our cohort, which was not necessarily observed previously.

Initial analysis shows trends towards increased T-cell and macrophage infiltration across both low and high-dose radiation, with the majority of macrophages M2- polarized (Figure 9). Dendritic cell populations were similar across the treatment cohorts. Elevated PDL-1 expression was noted in immune subsets regardless of treatment over time (Figure 10), and also in non-CD45+ cells, with a slight trend of increase in the low-dose administration. As expected, PSMA+GFP+cells decreased with the treatment of PSMA-617. Unexpectedly, PSMA expression also decreased over 7 days in control animals. This was not observed in prior studies in our hands, nor previously reported. We are currently checking whether this is artifactual or potentially related to the natural evolution of this model.

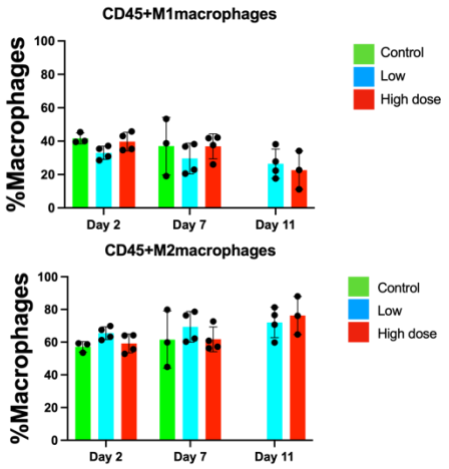

Figure 9: Macrophage polarity across PSMA-617 treatment

We are currently processing tissues and cellular samples for further imaging and transcriptomics analysis, and pursuing follow up examinations. Follow-up studies in humanized mice are planned, once an understanding of C57Bl/6 mice results are clarified.

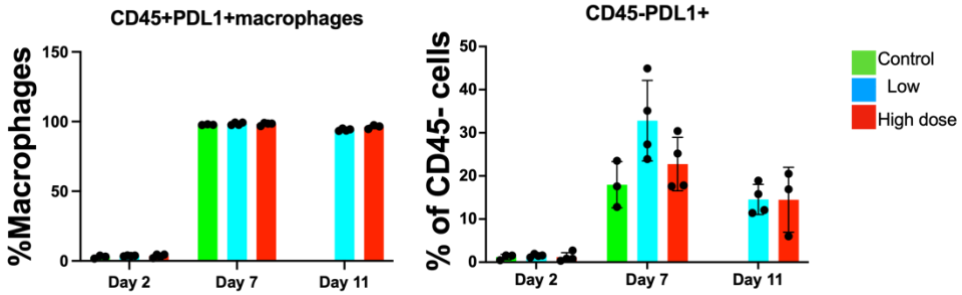

Figure 10 PDL1 expression in macrophages and non-tumor cells with PSMA-617 treatment

<u>Specific Aim 2: Assess the efficacy of combination STING-agonist nanotherapy and ^{177}Lu-PSMA-617 to elicit an efficacious immune response in metastatic prostate cancer</u>

Major Task 2: Optimize the timing of nanotherapy delivery during TRT treatment

Subtask 1: Synthesize labeled model nano therapy for imaging

Model nanotherapies developed include lipid nanoparticles (LNP) and albumin-labeled macromolecules. We adopted these nanotherapies given the recent interest of LNPs in the broader context of medicine (e.g. vaccines) and recent interest in our lab. We have successfully labeled LNP-TMR and Albumin-Alexa Fluor 647 to allow for both imaging and flow cytometry analysis purposes.

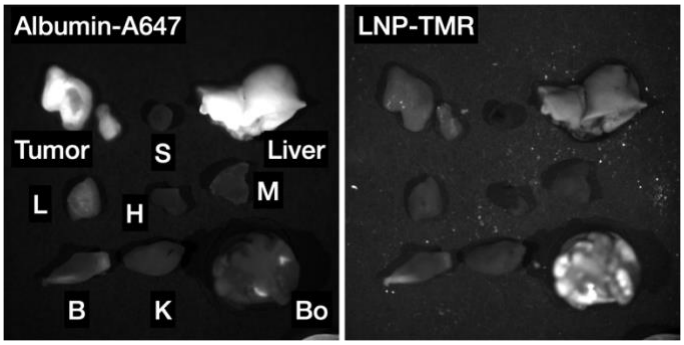

Figure 11: Optical fluoresence imaging of albumin-A647 and LNP-TMR in PSMA-617 treatment animals (S: spleen, M: muscle, L: lung, H: heart, B: bone, K: kidney, Bo:Bowel

Using these probes, we performed uptake experiments in relation to low-dose and high-dose radiation as encountered in Specific Aim 1. Timepoints were extended to 2,7- and 11-days post-treatment to keep with prior studies. Labeled nanoprobes were injected intravenously approximately 24 hours before sacrifice. Tissue samples were dissected and immediately frozen for cryopreservation. Optical fluorescent microscopy of thawed intact tissue organs was performed after the appropriate time for decay. A piece of the tumor was used for flow cytometry. Overall, higher albumin uptake into the tumor was observed across the board compared to LNP-TMR (Figure 11). No significant changes in uptake were noted with the administration of high or low-dose radiation in bulk. Flow cytometry analysis confirmed this - although a trend towards higher LNP infiltration was noted with the high radiation dose, this was offset with the much higher albumin tumor uptake by comparison. Both nanotherapy partitioned to non-immune and immune subsets. Of particular interest for our application, albumin was uptaken dramatically within antigen-presenting cells (macrophages and dendritic cells, Figure 12).

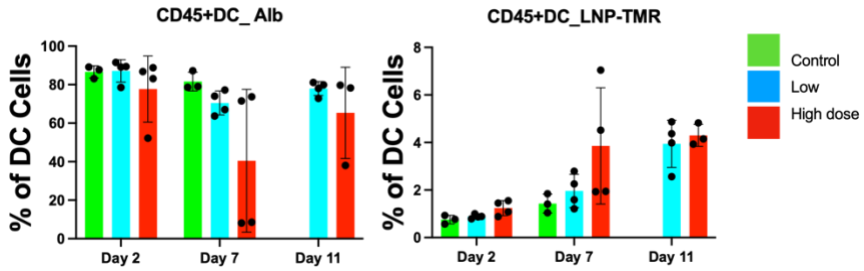

Figure 12: Nanotherapy uptake in dentritic cells with PSMA-617 therapy

Contrary to our hypothesis, systemically administered radiation does not appear to confer an added advantage to nanotherapy uptake. However, regardless, a high level of nanotherapy tumor uptake, in particular, albumin, was noted for uptake in this prostate cancer model, especially so for antigen-presenting cells. This suggests that loading these nanotherapies with STING, or other immunostimulatory agents may be a viable model going forward. Additionally, the elevated overall tumor uptake of albumin nanotherapy in particular also paves the way for the delivery of radiosensitizers which may augment the efficacy of systemic radiation. Results also suggest no significant temporal dependence on nanotherapy tumor uptake is noted.

Major Task 3: Assess the efficacy of combination TRT and STING- agonist treatment.

The over-arching goal of this proposal is to develop a synergistic nano therapy combined with radiation for the treatment of aggressive prostate cancer. Based on Task 2 results, we are pursuing the efficacy of STING agonist loading onto both albumin and LNP (size 78±5nm, zeta potential ~0mV) platforms in conjunction with radiation. Both albumin and LNP agents were stably labeled with STING agonists (and alternate immunotherapies) at a high and stable level (Figure 13) over a week.

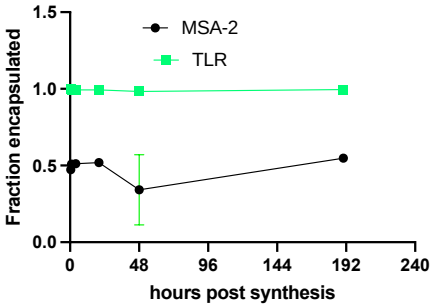

Figure 13: Stability of STING (MSA-2) and TLR agonist in LNPs over time

Given the intricacies associated with systemic radiation, including the high radiation dose per shipment and the desire to maximize the utility of each run, it made sense to perform treatment optimization in between runs. Therefore, as a test bed surrogate for ^{177}Lu-PSMA-617 to facilitate STING and nanoSTING dosing optimization, we adopted external beam radiation with doses guided by dosimetry calculated from ^{177}Lu-PSMA-617 biodistribution studies described in Task 1 and Task 2. Combination RT+nanoSTING treatments were given to the RM1.PGLS tumor models, and compared to control, (2-8Gy) RT, small molecule STING and nanoSTING cohorts.

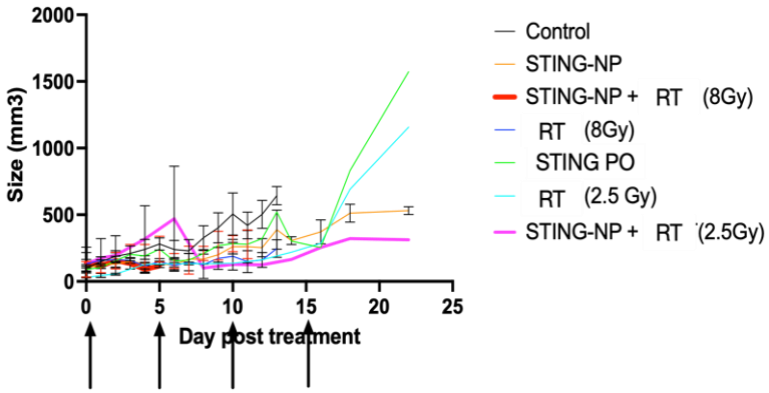

Figure 14: nanoSTING compared to STING and RT in RM1.PGLS. Arrow indicates treatment

As shown in preliminary studies (Figure 14), both RT and STING have antitumor effects, but this was less efficacious compared to nanoSTING and especially when added to RT. Both low and high-dose radiation combined with STING showed treatment response, albeit requiring multiple dosing. Given the higher uptake of albumin into the tumor, albumin-STING was also tested, with early results suggested improved efficacy in combination with radiation compared LNP. This efficacy is seen for both tumor size changes and survival (Figure 15). Current experiments are ongoing to optimize the dosing of this combination before testing further with systemic radiation. Given the elevated PDL1 expression seen in the above results, it is likely incorporation of immune checkpoint blockade is necessary for robust efficacy, as proposed. Current efforts are focused on identifying candidate nanoSTING for testing with combined immune checkpoint and system radiation delivery.

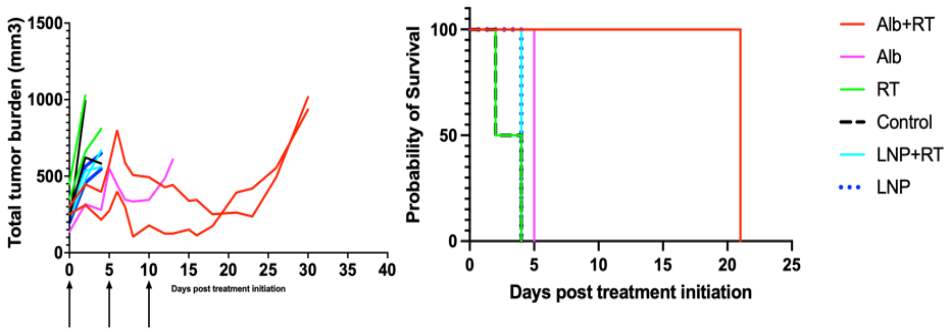

Figure 15: Albumin-STING compared to LNP-STING in RM1.PGLS, arrow indicates treatment

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

This project has provided ample training and professional development opportunities for the principal investigator and others contributing to the project. As outlined in my research development plan, I have participated in several didactic series locally, including attending GU Oncology, Nuclear Medicine, and Radiation Oncology seminars at MGH and DF/HCC. I have also garnered knowledge of the field nationally.

In particular, I have attended the Society of Nuclear Medicine, Annual Meeting with plans to attend the upcoming High Country Nuclear Medicine meeting; both meetings have a significant component of exploring the basic science and clinical aspects of systemic radionuclide therapy, in particular in the prostate cancer domain.

To gain a functional understanding of the clinical context in which immune profiling of prostate cancer plays vital roles in its management, I was invited to join the GU oncology committee in the NRG Oncology Cancer Cooperative Group and am poised to gain experience in the design of studies incorporating immunotherapies and radionuclide therapies in clinical trials, complementing the knowledge I am gaining working on this project. Attendance to local and national courses for cancer immunotherapy is planned for this coming year.

Extensive training in the project's scientific aspects has been developed through my interactions with mentors at MGH, especially at the Center for Systems Biology. Regular meetings with my mentors, especially Dr. Miles Miller, have aided the project's progress, fine-tuned my research and management acumen, and developing approaches to overcome the inevitable hurdles that any research project provides. Drs. Pai and Garris at CSB have provided consultation on the immunological aspects of this work, especially on the technical aspects of RNAseq sample preparation, cytometric analysis, and experimental design. Consultation with Core facility technical support has aided in understanding the technical aspects of CyTOF design and guidance in preparing samples for downstream processing. I have participated in online tutorials on cytometry software analysis design, including using R and FlowJo for these purposes, and have worked through the Stanford *Immune Monitoring Virtual Course*. Additional advice on dosimetry and radiochemistry has been sought and provided by senior facultyand staff across DF/HCC, CSB, the MGH Martinos Center for Biomedical Imaging and the Department for Radiation Safety at MGH.

As proposed, I completed the MGH *Leadership Development Program for Researchers*. I have enrolled in the Harvard Catalyst multi-year *Grant Review and Support Program for Career Development Awardees,* currently participating in the longitudinal activities and networking provided by the program. Working on this awarded project has also allowed me to mentor trainees, manage technical staff, foster collaborations to execute the experiments successfully, and explore ideas built upon this project for future grant applications. All the above opportunities contribute to my development into an independent translational researcher in this field.

1. **How were the results disseminated to communities of interest?**

A significant part of my clinical practice this year has been the administration of ^{177}Lu-PSMA-617 to patients with metastatic prostate cancer. This treatment modality has an especially heightened interest given its recent FDA approval and the lack of alternative therapies for eligible patients. A key part of my consultations with these patients is to discuss the context of PSMA-617 therapy within other types of therapies available and associated research into these opportunities. I have had the opportunity to discuss results and plans from the results to date with these patients, offering them hope and understanding of the promise and considerations needed when contemplating PSMA-617 treatment.

I also had the pleasure of meeting patient advocates for GU oncology at recent Annual Meetings, some of whom also participate in Department of Defense programs. I have taken this opportunity to discuss my work with them.

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

I will continue to discuss my work with patients and patient advocates to increase awareness of research advances in this field. I have increased my interactions with my GU colleagues in oncology and radiation oncology, and plan to develop collaborations and knowledge with them as I develop my research expertise.

Additionally, an essential part of my work is to mentor the next generation, spanning the range of high school and undergraduate students, medical/graduate school graduates, and imaging residents. I will use these opportunities to model and discuss the results and possibilities of the project with these populations and hopefully inspire them to go into this field.

The results and experiments achieved during the past year have provided the basis for continued progress on the project. This year will focus on building on identifying the optimal treatment combination to test, and to apply the immunologic analysis on control and treatment cohorts. In particular, working with Core facilities and focusing on developing my expertise in cytometric analysis and experiment design will emphasize my goals this year to accomplish the project aims. Once a more clear understanding of the optimal treatment regimen on immunocompetent murine models are identified, we will begin to expand our explorations to humanized models – discussions with the local humanized mouse Core facility about this have been undertaken.

I will continue to develop my knowledge base in cytometry and transcriptomics analysis, with plans to attend workshops in this topic area. In addition, one focus raised during reviews was the need to gain statistics expertise – this will be facilitated by attendance at the Harvard Catalyst Biostatistics course offered later in the year.

In addition, I will begin to prepare grant proposals based on my work at CSB and on this project to be competitive for federal grants by the latter part of the award period. This will significantly be facilitated by my mentors and participation in the GRASP program.

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:*

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

Combination nanoSTING therapy with radiation shows synergy for prostate cancer in preliminary studies. We are consolidating this finding, hopefully allowing our strategy to translate to clinical trials.

We are pioneering the analysis of multiplexed cytometry for the analysis of systemic radiation treatment. We hope to extend this technique for further use in this field.

    2. **What was the impact on other disciplines?**

Nothing to Report

    3. **What was the impact on technology transfer?**

Nothing to report.

    4. **What was the impact on society beyond science and technology?**

Nothing to report.

5. **CHANGES/PROBLEMS:**

1. **Changes in approach and reasons for change**

There was a period where a Lutetium 177 production delay was experienced during parts of the prior year. Additionally, the minimum dose per shipment is relatively high, warranting the need to maximize use of each batch per study. To work around these considerations and to make progress on treatment optimization promptly, we adopted external radiation as a test bed with dosages guided by ^{177}Lu-PSMA-617 dosimetry to advance the exploration of nano-STING/RT optimization and exploration.

Similarly, changes in staffing in the mass cytometry Core Facility necessitated the pursuit of flow cytometry approaches – which were enabled with access to a new multiplexed flow cytometer now available in our lab. Current results thus far suggest that both flow and mass cytometry approaches can be pursued in subsequent studies, and will correlate with imaging cytometry.

2. **Actual or anticipated problems or delays and actions or plans to resolve them**

I developed a medical condition during the prior year which required workup for diagnosis and management. This required me to take sporadic medical leave which may have impacted my experiment approach. With my colleagues' and trainees' help, we have continued to make progress. We anticipate that, if needed, additional experiments will be performed to complete the project during the no-cost extension period.

3. **Changes that had a significant impact on expenditures**

Turnover in lab staffing the past year has altered staff support allocations. This has been rectified with recent hiring.

The more costly proposed techniques and experiments, including transcriptomics, in depth cytometry, and expansive animal models have shifted to be performed in the upcoming and subsequent years – anticipating shift to increase expenditure for this period.

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

   None

5. **Significant changes in use or care of human subjects**

   N/A

6. **Significant changes in use or care of vertebrate animals.**

   None

7. **Significant changes in use of biohazards and/or select agents**

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."*

    1. **Publications, conference papers, and presentations**
    Nothing to report

    2. **Website(s) or other Internet site(s)**
    Nothing to report

    3. **Technologies or techniques**
    Nothing to report

    4. **Inventions, patent applications, and/or licenses**
    Nothing to report

    5. **Other Products**
    Nothing to report

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	Sheung Chee Thomas Ng
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-3676-1800*
Nearest person month worked:	5
Contribution to Project:	*Dr. Ng is the principal investigator of this study and participated in all aspects of the planning and execution of the project*
Funding Support:	

Name:	Dylan Matvey
Project Role:	*Research Technician*
Researcher Identifier (e.g. ORCID ID):	*0000-0003-3825-2345*
Nearest person month worked:	1
Contribution to Project:	*Dylan aided with development and performance of cellular and in vitro assays, including nanoparticle assessment and cytometry.*
Funding Support:	National Institutes of Health, this current project

Name:	Jeremy Quintana
Project Role:	*Radiochemist*
Researcher Identifier (e.g. ORCID ID):	*0000-0001-9820-1297*
Nearest person month worked:	1
Contribution to Project:	*Dr. Quintana aided in the radiolabeling and radiation aspects of the work*
Funding Support:	National Institutes of Health

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

No

What other organizations were involved as partners?

None

References

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