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14. ABSTRACT

The aim of this project was to develop a new MRI approach to characterize aggressive prostate cancers and differentiate them from low grade tumors based on genetic/proteomic induced metabolic differences and perfusion abnormalities. The project was designed to then apply this new approach in preclinical transgenic prostate cancer models to obtain the required preliminary data for future clinical trials. This project has gone extremely well accomplishing the technical milestones described in the original approved Statement of Work (SOW) and performing the unprecedented prostate cancer model studies demonstrating the ability of these new methods to measure significantly different metabolic and perfusion parameters in aggressive high grade cancers compared to low grade. The results of this project demonstrate feasibility and strongly support the hypothesis that this new approach can distinguish aggressive from indolent prostate cancer. This project has resulted in new technical advances and the strong preclinical data that will serve as the basis for justifying and designing future clinical trials investigating their value in patients with prostate cancer.

15. SUBJECT TERMS

Magnetic Resonance Imaging, Prostate Cancer, Aggressiveness, Cancer Characterization, Metabolism, Perfusion, Non-Invasive, Hyperpolarized Carbon-13, Mutation Detection, Quantitative Imaging, Pre-clinical.

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Table of Contents

	Page
1. Introduction……	4
2. Keywords……	4
3. Overall Project Summary…….	4
4. Key Research Accomplishments……..	10
5. Conclusion……..	10
6. Publications, Abstracts, and Presentations……..……	11
7. Inventions, Patents and Licenses……..	11
8. Reportable Outcomes..……	11
9. Other Achievements……	11
10. References……	11
11. Appendices……	N/A

1. INTRODUCTION:

A pressing need facing the clinical management of prostate cancer is an accurate method for distinguishing aggressive prostate cancer from indolent disease (a PCRP Overarching Challenge). The American Cancer Society estimates that 241,740 men will be diagnosed with prostate cancer in the United States in 2012, which is a higher incidence figure than any other non-cutaneous human malignancy [1]. There is currently no cure for metastatic prostate cancer and an estimated 28,710 men will die of the disease in the United States in 2012, a figure surpassed only by lung cancer [1]. The decision on how to manage prostate cancer poses a great dilemma for patients and their physicians because prostate cancers demonstrate a tremendous range in biologic diversity and are treated with a broad spectrum of approaches from "active surveillance" to aggressive surgical, radiation and other focal therapies [2]. Such therapies have tradeoffs since treatment is frequently associated with changes in health-related quality of life [3] [4]. Moreover, many prostate tumors follow such an indolent course that they might never threaten the duration or quality of lives of affected men if left untreated. Unfortunately, differentiation of aggressive prostate cancers from indolent disease cannot be confidently predicted in individual patients using current prognostic markers [5] [6]. This project is developing a new MRI approach to characterize aggressive cancers based on their genetic/proteomic and perfusion abnormalities and apply this method in preclinical models to obtain the required preliminary data for FDA approval for future clinical trials. Hyperpolarized (HP) carbon-13 MRI is a powerful new molecular imaging method which uses specialized instrumentation to provide signal enhancements of over 5-orders of magnitude for carbon-13 enriched, safe, endogenous, non-radioactive compounds as described in a recent NIH-supported "White Paper" [7]. The first human Phase 1 clinical trial has demonstrated the safety and feasibility of HP ^{13}C-pyruvate MRI approach in prostate cancer patients [8]. This project aims, for the first time, to develop and test a new dual-agent HP MRI approach for simultaneous dynamic metabolic + perfusion imaging using HP-pyruvate and also HP urea to detect altered vascular perfusion in aggressive prostate cancers in a preclinical transgenic model. HP urea is not metabolized and can provide an excellent internal-standard measure of perfusion to detect altered blood flow parameters in cancer.

2. KEYWORDS:

Magnetic Resonance Imaging, Prostate Cancer, Aggressiveness, Cancer Characterization, Metabolism, Perfusion, Non-Invasive, Hyperpolarized Carbon-13, Mutation Detection, Quantitative Imaging, Pre-clinical.

3. OVERALL PROJECT SUMMARY:

The final year of this DOD project went extremely well accomplishing the milestones described in the original approved Statement of Work (SOW). No changes in the SOW were needed (or done). In this last year, the technical developments were refined and the transgenic mouse model studies were performed to investigate the ability of this technology to differentiate aggressive prostate cancer from indolent disease. Below we list each original specific aim from the SOW and describe the progress on each. Figures of the technical developments and data acquired are included. This work was presented at the International Society of Magnetic Resonance in Medicine in June of this year. One manuscript on the technical developments and one on the results of the preclinical studies are in preparation for Magnetic Resonance in Medicine and Cancer Research respectively.
Note: In this revised progress report we have added the requested additional data (text & Figures 5 -7) from the studies for Specific Aim 3 for assessing the utility of these techniques in prostate cancer metastasis models.

Specific Aim 1. *ACQUISITION DEVELOPMENT FOR RAPID 3D HYPERPOLARIZED PERFUSION & METABOLIC MRI*

1a. Development of New Three-Resonance Excitation Pulses (months 1 – 2)
1b. Development of 3D volumetric Carbon-13 MRI sequence (months 1 – 6)

- Create and simulate response of new multi-band RF pulse designs for simultaneous ^{13}C-pyruvate, ^{13}C-lactate and ^{13}C-urea excitation
- Implement 3D volumetric echo planar sampling
- Test new acquisition method with in vitro solutions of ^{13}C-pyruvate, ^{13}C-lactate and ^{13}C-urea
- Optimize methods for highest spatial resolution, temporal resolution and SNR

Progress: The 3D dynamic MRSI sequence designed in year 1 to acquire the metabolic and perfusion data was further refined and applied in the animal studies as shown in Figure 1.

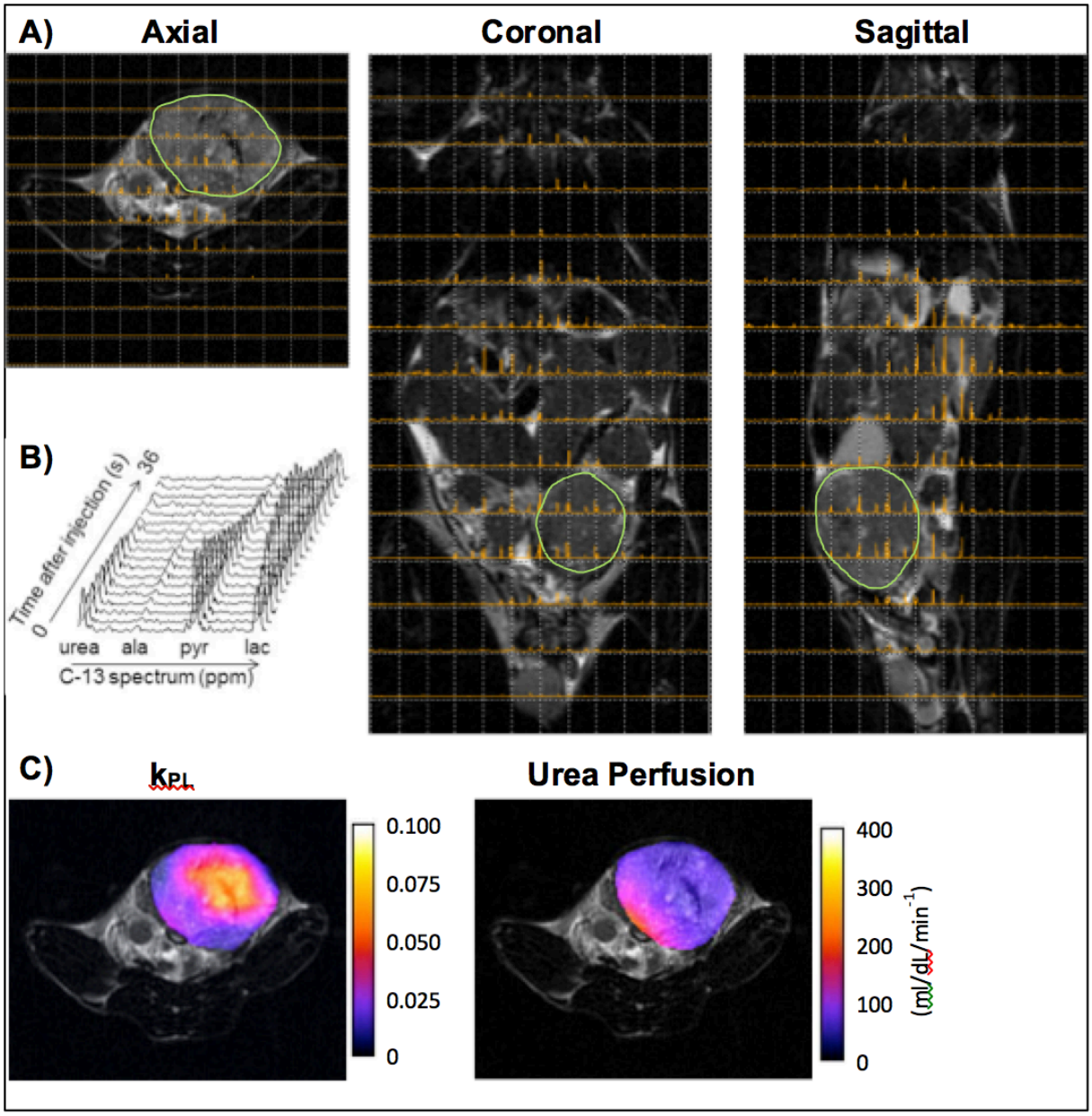

Figure 1. A) In vivo 3D EPSI images of co-polarized HP ^{13}C-pyruvate and ^{13}C-urea using the 3D dynamic acquisition in the axial, coronal, and sagittal direction overlaid on T_2-weighted anatomical references. This imaging protocol boasts a spatial resolution of 3.3mm in-plane and 5.4mm axial. The spectroscopic images offer view not only of high lactate production in the tumor, but the concentration of each HP-^{13}C tracers in different regions within the tumor mass. B) A temporal HP-^{13}C spectrum was extracted from a 0.059(cm^3) voxel. The chemical shift spectrum is designed to efficiently use bandwidth and allows for sparsity in spectral direction. Note that aliasing were introduced to urea and lactate peaks. The time direction provides 2(s) temporal resolution and optimal SNR at each time point for quantitative modeling of metabolism and perfusion/ permeability. C) Overlay of pyruvate-to-lactate conversion rate k_{PL} and perfusion area under curve on T_2-FSE anatomical references, respectively.

Metabolic and Perfusion Modeling: In this project we developed specialized analysis methods to calculate quantitative measures from the dynamic hyperpolarized ^{13}C-pyruvate and ^{13}C-urea data. Conversion between pyruvate and lactate was modeled as:

$$\frac{dC_{lac}(t)}{dt} = k_{pl}C_{pyr}(t) - k_{lp}C_{lac}(t)$$

Tumor microcirculation can be characterized by the perfusion and permeability between blood and tissue [9]. The perfusion dynamics can be described as [10]:

$$\frac{dC_{tissue}(t)}{dt} = k_{trans}C_{blood}(t) - k_{ep}C_{tissue}(t)$$

Nonlinear fitting was applied to data for both models, where a correction was incorporated to account for the multiband excitation and variable flip angles. T_1 relaxation was assumed to be equal for all ^{13}C tracers. These methods are depicted in Figure 2.

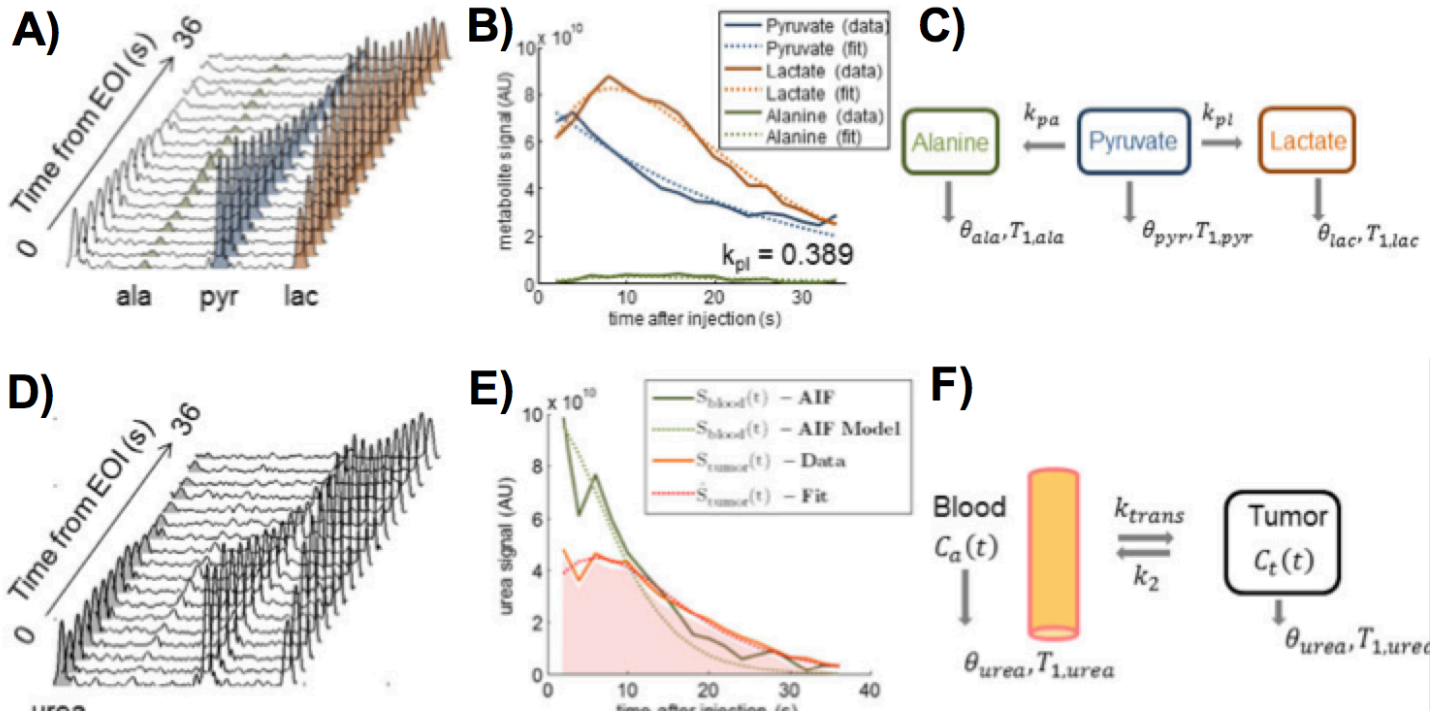

Figure 2. Quantitative measurement of tumor metabolism and perfusion can be done by applying kinetic modeling on the temporal data. For modeling of metabolism, **A)** Spectroscopic signals of HP-^{13}C pyruvate, lactate and alanine were extracted from the temporal spectrum. **B)** A typical *in-vivo* dynamics of high-grade tumor, where the lactate was being rapidly produced from pyruvate. Lactate signal increased and reached maximum around 10-15 seconds after the end of injection. Acquired data (solid line) was compared to fit (dashed line) **C)** A compartmental model of pyruvate-to-lactate exchange, with the rate constant k_{PL}. The multiband excitation, the variable flips, also T_1 relaxation were taken into account for the signal loss. For perfusion modeling **D)** Signal of HP-^{13}C urea was extracted from both tumor and arterial input function **E)** Applying dynamic models on urea perfusion curve **F)** Two-compartment model gives rate constant k_{trans}.

Specific Aim 2. *HP METABOLIC & PERFUSION IMAGING IN A TRANSGENIC MODEL OF PROSTATE CANCER WITH TISSUE ASSAY CORRELATIONS*

2a. Perform Perfusion & Metabolic Molecular Imaging with HP ^{13}C-pyruvate and HP ^{13}C-urea in 20 Early Stage Cancers (months 6 – 20)

2b. Perform Perfusion & Metabolic Molecular Imaging with HP ^{13}C-pyruvate and HP ^{13}C-urea in 20 Late Stage Cancers (months 6 – 20)

2c. Tissue assay determinations of cancer aggressiveness including histologic analysis, Ki-67 proliferative assays, lactate dehydrogenase (LDH) activity, *LDH-A* expression, cellularity, and micro-vessel density and hypoxia measurements (months 6 – 20)

- Imaging exams including the HP metabolic and perfusion MR techniques developed in Specific Aim 1.

- Subsequent pathologic, immunohistochemical analysis, and molecular assays. H&E staining as well as immunohistochemical markers for proliferation (KI-67) and micro-vessel density (CD31), hypoxia (pimonidazole, PIM) will be evaluated microscopically, mRNA will be isolated for RT-PCR analysis of LDH-A expression and LDH activity assays will be performed.
- Perform correlations of HP MR molecular imaging parameters with tissue analyses of cancer aggressiveness in 20 transgenic mice with low-grade early stage prostate cancers and 20 transgenic mice with high-grade cancers.

Progress: Following the technical development phase, we preformed the preclinical studies in the transgenic model of prostate cancer studying both Early Stage and Late Stage cancers. The results of these hyperpolarized MR molecular imaging studies were extremely encouraging with significantly higher pyruvate to lactate conversion rates (k_{PL}) observed in the high grade tumors compared to low grade with no overlap as shown in figure 3. Also the perfusion measurements calculated from these dynamic imaging studies showed a significant reduction in the high grade tumors and also an increase in k_{trans} indicating increased leaky-ness (Figure 4).

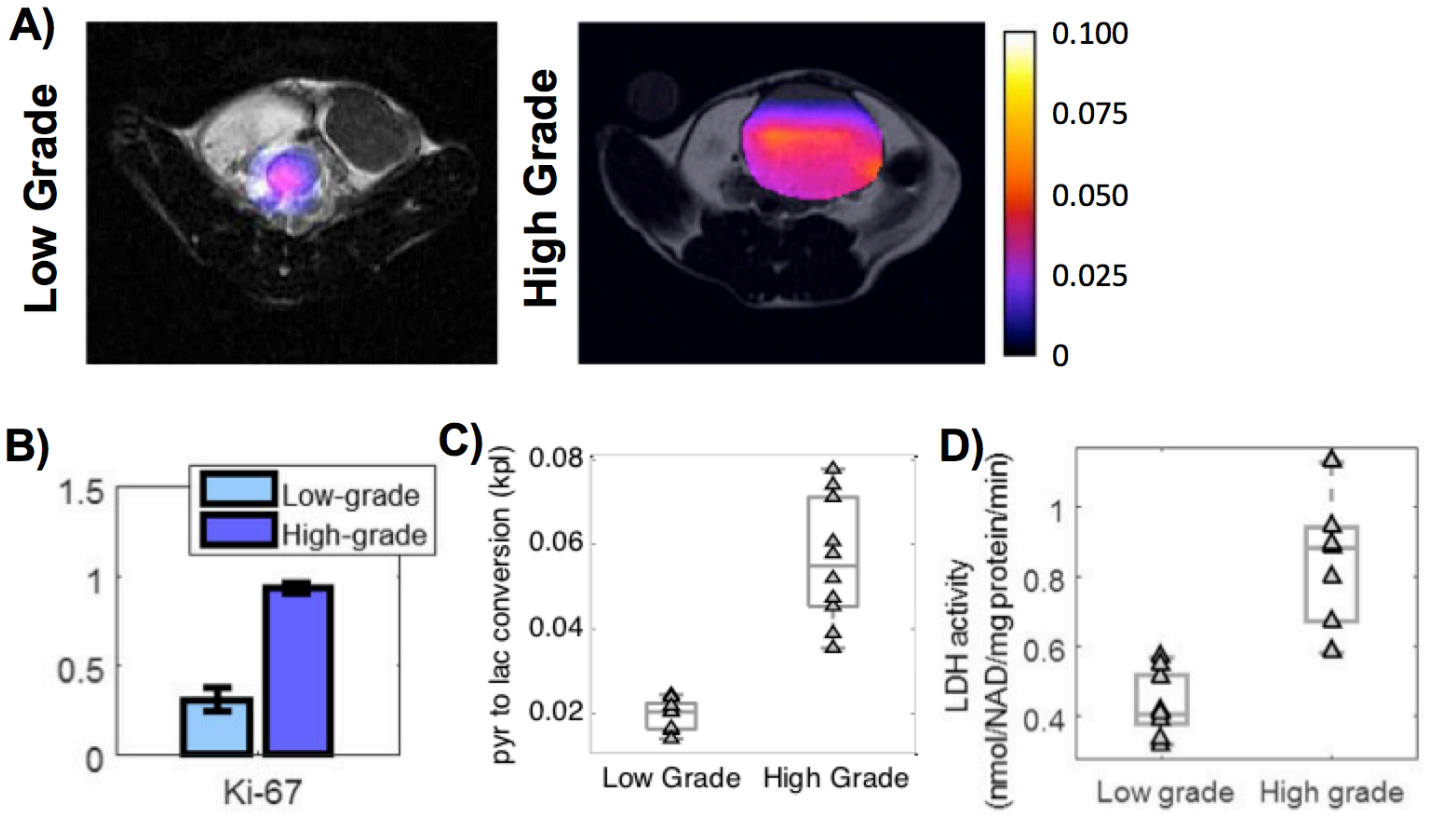

Figure 3. Quantitative measurement of metabolism in low- high-grade tumor in TRAMP tumors (N=19, 9 low- vs. 10 high-grades). A) Map reflects the estimate of pyruvate-to-lactate conversion rate k_{PL} overlaid on T_2-FSE anatomical references B) The bar plot shows Ki-67 immunostaining area in low- and high-grade tumors. C) The calculated pyruvate-to-lactate conversion k_{PL} were found to be significantly ($P<0.00001$) increased in high- versus low-grade tumor. D) This correlated with tissue LDH enzymatic activity assays that were also measured to be significantly increased in high grade tumor.

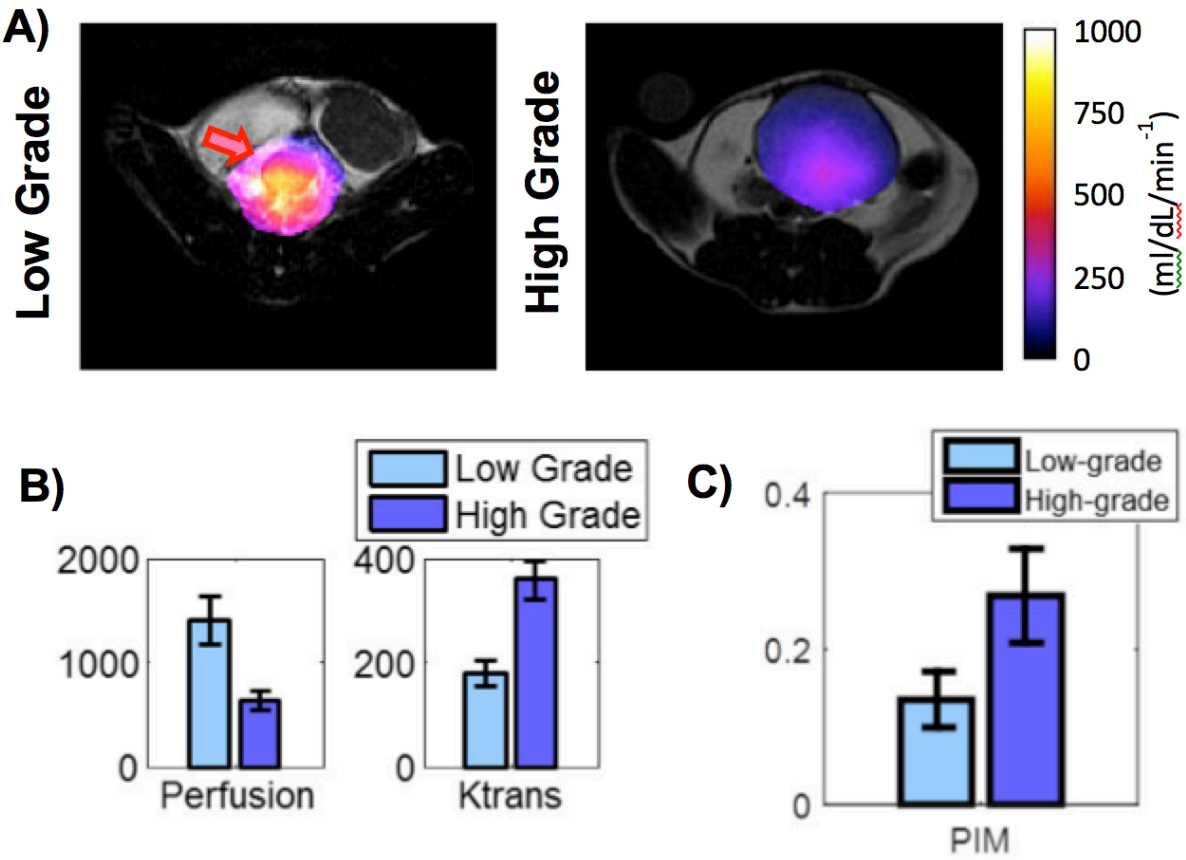

Figure 4. Quantitative measurement of perfusion in low- high-grade tumor in TRAMP tumors (N=19, 9 low- vs. 10 high-grades). **A)** Map reflects the estimate of perfusion area under curve (AUC) overlaid on T_2-FSE anatomical references. **B)** Estimated perfusion AUC significantly (P<0.004) declined in high- versus low-grade tumor, but k_{trans} significantly increased (P<0.002). **C)** The bar plot shows PIM immunostaining area in low- and high-grade tumors.

The results of this study strongly supports our hypotheses that aggressive prostate cancer would show higher metabolic flux through LDH to lactate and that adaptive changes in perfusion of the tumor microenvironment and increased cellularity would result in decreased perfusion in high-grade prostate cancers. This demonstrates a clear potential for this new technology to address the unmet clinical need of differentiating aggressive prostate cancers from indolent disease.

Specific Aim 3. *PERFORM HP METABOLIC/PERFUSION MRI EXPERIMENTS TO INVESTIGATE METASTATIC PROSTATE CANCER*

- **2a**. Perform Perfusion & Metabolic Molecular Imaging with HP ^{13}C-pyruvate and HP ^{13}C-urea in 20 Transgenic Mice with Metastatic Prostate Cancers (months 12 – 24)
- **2a**. Perform Tissue Sample Collection from both metastases and primary tumors following MR exam. (months 12 – 24)
- **2c**. Tissue assay determinations of cancer aggressiveness including histologic analysis, Ki-67 proliferative assays, lactate dehydrogenase (LDH) activity, *LDH-A* expression, cellularity, and micro-vessel density and hypoxia measurements (months 12 – 24)

Progress: In addition to the animal model studies described in Specific Aim 2, we also applied these novel MR metabolic imaging techniques to the study of transgenic TRAMP mice with metastatic cancers. The studies on metastatic cancers demonstrated the same increases in hyperpolarized [1-^{13}C]pyruvate to [1-^{13}C]lactate conversion as detected for the primary high grade cancers. As shown in Figure 5, the lymph node metastasis demonstrated high, up-regulated conversion of HP ^{13}C-pyruvate to lactate through lactate dehydrogenase (LDH), just like in the primary late-stage prostate cancer. As shown in Figure 6, we observed no significant differences between the metastatic and primary tumors in k_{PL} conversion rates (primary tumor k_{PL} =0.057±0.011, metastasis

k_{PL} =0.059±0.026 sec^{-1}, p>0.8). Figure 7 shows the findings that perfusion values also were found to be similar between the late-stage primary tumors and the lymph node metastases with no statistically significant difference. (primary =679.4 ± 254.2; metastasis 909.1 ± 520.2 , p>0.4) The results of these experiments in this mouse model of prostate cancer indicate that this molecular imaging approach may be valuable for assessing abnormal metabolism & perfusion in lymph node metastases of prostate cancer with values similar to high grade primary cancers.

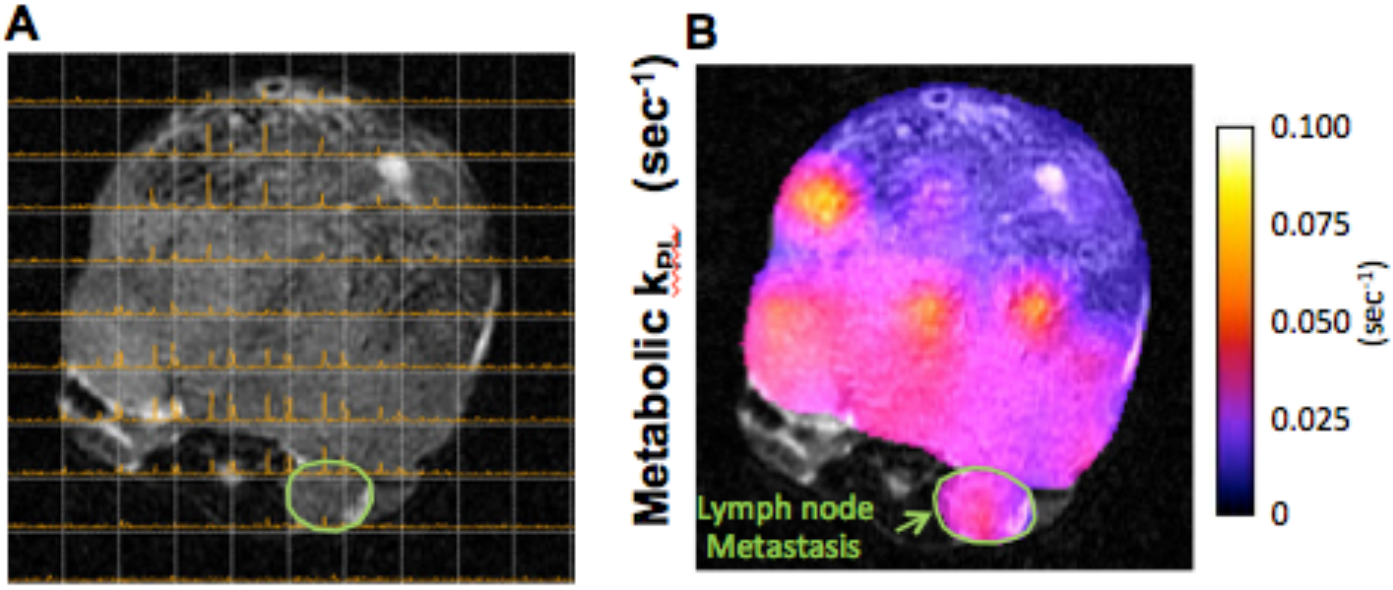

Figure 5. Representative Hyperpolarized Carbon-13 MR data in a high-grade tumor with a lymph-node metastasis. The 3D dynamic ^{13}C-MR data (A) were acquired using the novel acquisition methods developed in Specific Aim 1 with a spatial resolution of 3.3mm in-plane and 5.4mm axial (0.059cm^3 voxel) encompassing the primary tumor. The overlaid spectra acquired using the 3D dynamic MR sequence with compressed sensing showed high conversion of ^{13}C-pyruvate to ^{13}C-lactate both in the aggressive primary tumor and also in the metastasis. The calculated metabolic conversion rate of ^{13}C-pyruvate to ^{13}C-lactate (k_{PL}) map (B) demonstrated high values in the lymph node metastasis and throughout the majority of this late-stage primary tumor.

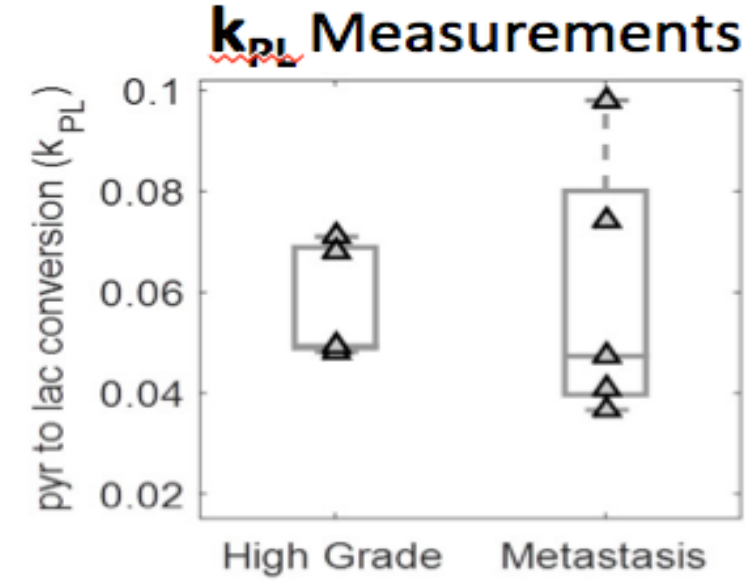

Figure 6. Quantitative measurement of metabolic HP ^{13}C-pyruvate to ^{13}C-lactate conversion rates (k_{PL}) in high-grade TRAMP tumors and lymph-mode metastasis. This data showed similar, high conversion rates for the metastases as compared to the primary tumors with no significant difference in k_{PL} observed between high-grade primary and metastasis values. (Primary tumor k_{PL} = 0.057±0.011, metastasis 0.059±0.026 sec^{-1}, p>0.8)

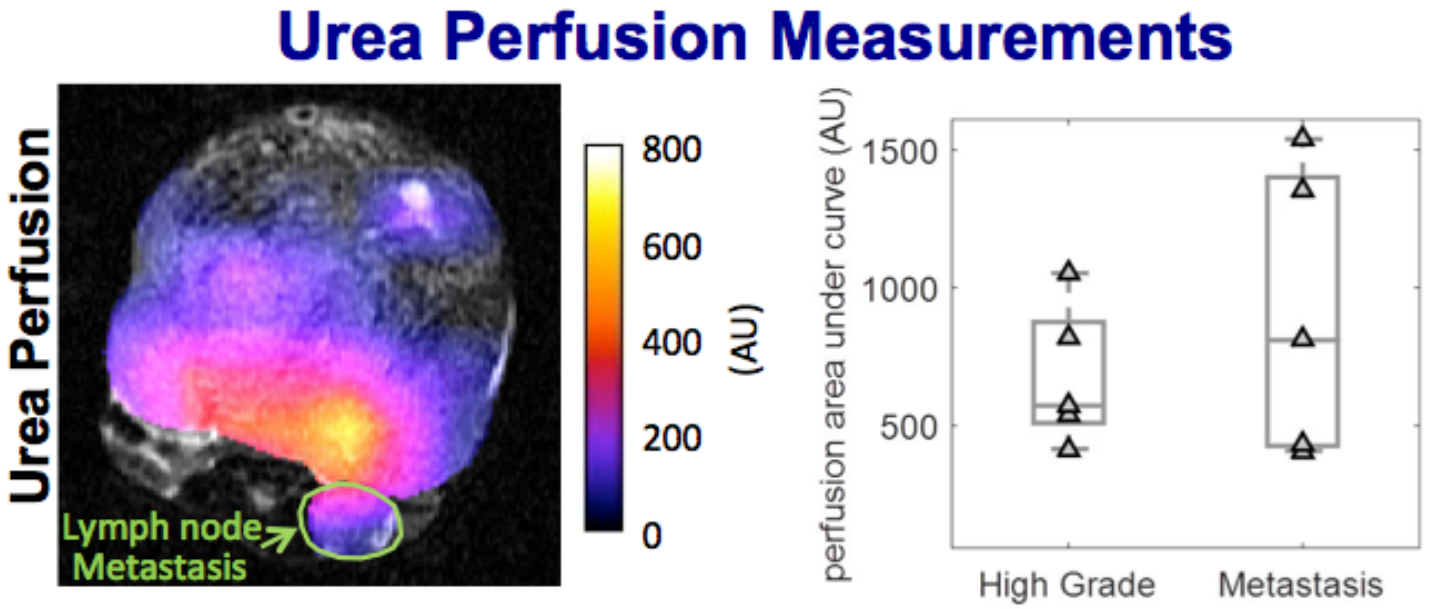

Figure 7. Left: The HP ^{13}C-Urea perfusion "area under curve" (AUC) map is shown for the same case as in Figure 5. On the right is the graph of perfusion values for high-grade tumor and metastases. The values were similar with no significant difference between the primary tumor and metastasis (primary =679.4 ± 254.2; metastasis 909.1 ± 520.2, $p>0.4$). The increased individual variation in the metastasis values may reflect variability in cell density and in the partial volume inclusion of adjacent tissues and/or vasculature differences.

4. KEY RESEARCH ACCOMPLISHMENTS:

- Developed new multiband RF pulses to simultaneously excite hyperpolarized ^{13}C-pyruvate, ^{13}C-lactate and ^{13}C-urea.
- Developed a novel volumetric acquisition sequence for obtaining hyperpolarized MR metabolic and perfusion images simultaneously.
- Created and tested specialized modeling techniques to provide quantitative measures of dynamic metabolic and perfusion data.
- Applied these new methods for the first time in preclinical models of Early-Stage and Late-Stage prostate cancers and observed significantly higher pyruvate-to-lactate conversion rates (k_{PL}) in the high grade tumors compared to low grade. Also the perfusion measurements calculated from these dynamic imaging studies showed a significant reduction in the high grade tumor.
- HP carbon-13 MR studies in metastatic tumors showed similar metabolic and perfusion rates as the high-grade primary tumor indicating that this technology may be valuable for assessing metastatic prostate cancer as well as organ-confined disease.

5. CONCLUSION:

This project was designed to address the PCRP Overarching Challenges especially to "Distinguish aggressive from indolent disease". In this project, we developed a new approach for simultaneous MR metabolic and perfusion imaging to distinguish aggressive prostate cancers from indolent disease based on up-regulated lactate-dehydrogenase (LDH) conversion of HP-pyruvate to lactate and altered vascular perfusion measured using HP-urea. We are obtaining the preclinical performance and safety experience needed for future FDA IND approval that is required before patient clinical trials utilizing these new techniques. These transgenic animal model studies with correlations to pathologic and histochemical tissue assays of cancer aggressiveness provide preclinical accuracy data for the IND to justify the potential of this method to be effective (as well as safe) for future human studies. Also this method could ultimately provide new accurate assessments for monitoring patients on active surveillance, guiding biopsies to the sites of most abnormal perfusion/metabolism correlating with the most aggressive cancers, treatment selection and to monitor therapeutic response. Thus this new imaging approach could also have a role in addressing the other overarching challenge through the evaluation and iterative development of effective treatments for prostate cancer.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

1. Lay Press:

2. Peer-Reviewed Scientific Journals:

3. Invited Articles:

4. Abstracts:

1. Chen HY, Larson PEZ, Bok R, von Morze C, Delos Santos R, Sriram R, Delos Santos J, Kurhanewicz J, Vigneron DB. Assessment of Prostate Cancer Aggressiveness with Hyperpolarized Dual-Agent 3D Dynamic Imaging of Metabolism and Perfusion. ISMRM Twenty-Third Scientific Meeting, Toronto, Canada, May 2015, p 3955.

7. INVENTIONS, PATENTS AND LICENSES: Nothing to Report.

8. REPORTABLE OUTCOMES: Nothing to Report.

9. OTHER ACHIEVEMENTS: Nothing to Report.

10. REFERENCES:

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11. APPENDICES:
None.

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1. Chen HY, Larson PEZ, Bok R, von Morze C, Delos Santos R, Sriram R, Delos Santos J, Kurhanewicz J, Vigneron DB. Assessment of Prostate Cancer Aggressiveness with Hyperpolarized Dual-Agent 3D Dynamic Imaging of Metabolism and Perfusion. ISMRM Twenty-Third Scientific Meeting, Toronto, Canada, May 2015, p 3955.

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