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TITLE: Dynamic Tissue Culture System from Prostate Biopsy Specimens as a Model for Predicting Tumor Radio-sensitivity to Ionizing Radiation Treatment

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14. ABSTRACT The underlying hypothesis driving this project is the notion that all prostate carcinomas are not the same (even if they have the same clinical stage, Gleason score, and pretreatment PSA). By studying individual tumor specimens from patient's prostate carcinomas prior to treatment, it will be possible to obtain information that will make it possible to understand the pathologic factors and molecular regulators that are involved in determining radiation induced apoptosis and intrinsic radio-sensitivity. Our long term goal, for which this proposal will be the first stop, is to develop a system to better individualize each patient's treatment based on various clinical, pathological and molecular biological parameters, thereby maximizing the treatment potential benefit to the patient, while also minimizing the potential treatment toxicity to the patient.					
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Table of Contents

- **Cover.....1**
- **SF 298.....2**
- **Introduction.....4**
- **Body.....4**
- **Key Research Accomplishments.....5**
- **Reportable Outcomes.....5**
- **Conclusions.....5**
- **References.....5**
- **Appendices.....5**

Introduction

The underlying hypothesis driving this project is the notion that all prostate carcinomas are not the same (even if they have the same clinical stage, Gleason score, and pretreatment PSA). By studying individual tumor specimens from patient's prostate carcinomas prior to treatment, it will be possible to obtain information that will make it possible to understand the pathologic factors and molecular regulators that are involved in determining radiation induced apoptosis and intrinsic radio-sensitivity. Our long term goal, for which this proposal will be the first step, is to develop a system to better individualize each patient's treatment based on various clinical, pathological and molecular biological parameters, thereby maximizing the treatment potential benefit to the patient, while also minimizing the potential treatment toxicity to the patient

Body

Study Design: Specific Aim 1 will utilize tissue culture techniques and molecular biology knowledge to develop and optimize a dynamic tissue culture system to obtain and maintain human prostate carcinoma biopsy specimens *in vitro* for up to 72 hours. Specific Aim 2 will utilize molecular biology, immunohistochemistry and radiobiology approaches to evaluate the impact of various molecular regulators of apoptosis on intrinsic radio-sensitivity and tumor response to treatment with prostate brachytherapy.

Specific Aims: 1) Establish a dynamic tissue culture system for prostate biopsy specimens

Specific Aim 1 has been addressed in prior annual reports and thus I will not address this now.

2) Assess the role of p53, bcl-2, and NFκB in determining radiation induced apoptosis, and intrinsic radio-sensitivity the biopsy specimens maintained in a dynamic tissue culture system, as well as the clinical tumor response that is achieved in patients undergoing a curative course of radiation treatments.

- A) Assess the intracellular levels of various molecular regulators of apoptosis and cell death in biopsy specimens obtained from patients with prostate carcinoma
- B) Determine the association between p53, bcl-2, and NFκB and established clinical and pathologic prognostic factors.
- C) Assess the role of p53, bcl-2, and NFκB in determining the extent of radiation induced apoptosis and the intrinsic radio-sensitivity of the biopsy specimens.
- D) Determine the impact of modulating the intracellular levels of p53 and NFκB, on the radio-sensitivity of the biopsy specimens.
- E) Determine the impact of the above studies on the clinical tumor response that is achieved in patients undergoing radiation treatments.

Unfortunately the current PI (Walker) is the third PI on this project and little if any has been completed on this task since the last annual report. Important tasks since the last report are 1) extraction this project regulatory purgatory associated with the sudden loss of the prior PI, and thus the lack of a PI. Formally establishing Walker as the current PI, currently we are approved to collect tissue samples and all IRB regulatory documentation has been updated and completed. 2) Establishing the groundwork for the completion of the final specific aim. This includes a steady stream of patients that should allow for obtaining prostatic biopsies on weekly bases. Thus we would expect to have the procured number of specimens (30) within 6 months of active accrual. I have the support of the critical personal involved with the initiation of this grant still committed to it completion. Our current plans are to collect and process each sample and then create a tissue array for each patient. This will allow for rapid uniform staining of each sample. We also have access to an automatic slide processor that will allow for rapid immuno- staining once all the samples have been processed again ensuring uniformity across each unique antibody.

Given the lapses in the PI we are currently asking for a no cost extension. The first change of PI resulted in at least a year delaying this project as has the second change in PI thus we are asking to extended this project to April 30 2007 to allow us an opportunity to complete this project. If this request is not granted by the Army COR this will be our final report. If a request for extension is granted an addendum to this final report will be provided upon the completion of the project.

Key Research Accomplishments

No active research has been conducted given the regulatory hold placed by the IRB on this project.

Reportable Outcomes

We have no reportable outcomes.

Conclusions

Despite a failure to progress since the last annual report we are poised ready to address the second specific aim and hope to be finished by April 2007. All regulatory requirements have been completed and we are awaiting approval of a no cost extension to address the uncompleted work on this project.

References

None at this time.

Appendices

None at this time.