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Award Number: W81XWH-05-1-0187

TITLE: Molecular Targeting of the P13K/Akt Pathway to Prevent the Development
Hormone Resistant Prostate Cancer

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REPORT DATE: February 2007

TYPE OF REPORT: Annual

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

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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE (DD-MM-YYYY) 01-02-2007		2. REPORT TYPE Annual		3. DATES COVERED (From - To) 15 JAN 2006 - 14 JAN 2007	
4. TITLE AND SUBTITLE Molecular Targeting of the P13K/Akt Pathway to Prevent the Development Hormone Resistant Prostate Cancer				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-05-1-0187	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Jonathan Walker, M.D. E-Mail: walkerj1@email.arizona.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Arizona Tucson, AZ 85733-4390				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Recently the PI3K/Akt pathway has been found to be a significant factor in the development and progression of prostate cancer. It is our belief that the PI3K/Akt pathway is the critical pathway that is maintaining survival by blocking apoptosis in the absence of hormonal stimulation. We will use molecular targeting to inhibit the phosphorylation of Akt. Celecoxib is a FDA approved COX-2 inhibitor, however unique to celecoxib is its ability to inhibit the phosphorylation of Akt. This effectively turns off the PI3k/Akt pathway leading to apoptosis. Celecoxib has been shown to induce apoptosis in a number of different malignancies. Unfortunately the IC50 of celecoxib is less than usually clinically obtainable. Therefore, in an attempt to improve upon the Akt activity and decrease the IC50 concentration to clinically obtainable levels, Chin et al. synthesized multiple 2nd and 3 rd generation compounds. These newer compounds have significantly lower IC50 and thus therapeutic levels can be obtained clinically. We will use celecoxib and these newer compounds to evaluate the effects of combined PI3K/Akt inhibition and androgen ablation.					
15. SUBJECT TERMS No subject terms were provided.					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	5	19b. TELEPHONE NUMBER (include area code)

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Introduction

Our principle hypothesis for the proposal is that combined inhibition of the PI3K/Akt pathway and the androgen pathway will result in a synergistic effect to include: increased apoptosis, decreased proliferation, and a decreased tumor growth.

The rational for our proposal is that hormone refractory prostate cancer has over expression of the PI3K/Akt pathway both at the genomic and protein level implying a significant role in prostate cancer proliferation. Akt has multiple downstream effectors all of which promote growth and survival. There is a direct connection between Akt and the AR that allows Akt to directly activate the AR, and thus activating the androgen pathway. We believe selectively inhibiting both the PI3K/Akt and androgen pathway will cause a synergistic effect. Thus, with combined inhibition, apoptosis will be increased with a corresponding decrease in proliferation ultimately leading to the purpose of our study; a prolongation in patient's survival with metastatic prostate cancer.

Body

Specific Aim 1: Assess the Effectiveness of Combined Hormonal Ablation and PI3K/Akt Pathway Inhibition *In vitro* using a Human Prostate Tissue-Based Organ Culture Model System.

Task 1: Determine the Utility of Using Precision Cut Thin Tissue Sections from Non Radical Prostatectomy Specimens

o Experimental Design and Methodology

Currently, we are procuring tissue to determine tissue viability. Our greatest non-project related issue involves the dramatic shift in surgical technique of radical prostatectomies. There has been a pronounced shift in the operative technique related to laparoscopic and robot techniques. The primary disadvantage of this technique is that by the time prostate can be procured and available for slicing, the tissue is no longer viable for culture. We are currently improving our time to improve our ability to obtain viable prostates. We are also pursuing alternatives for obtaining prostatic specimens as well.

In regards to evaluating slicing non-whole prostatic specimens, we have been able to cut the transurethral specimens. We are working on optimization of the growth medium. The determination of the appropriate medium has been quite difficult given the non-viable prostatectomy specimens we have been using. Our initial plan was to optimize for whole prostatectomy cancers and then extrapolate to TUR specimens; however, we have been forced to pursue each independently.

In the last year we have continued to have the similar issues with prostate procurement related to viable specimens. As we were trying to expand our organ culture program my tech left secondary to fear over funding related issues. Currently we are looking to replace the tech so we can continue to expand our organ culture so we can optimize our organ growth

conditions. Currently with the viable specimens we are working on optimizing the serum concentration DHT and other hormone concentrations optimal for growth during our incubation time period.

Task 2: Determine the Optimal Timing for Evaluation the Effects of a Combined Inhibition.

We are still currently delayed in this second task by the marked reduction in viable prostate specimens that were expected to be used in Task 1.

Task 3: Assessing the Effectiveness of Combined Hormonal Ablation and PI3K/Akt Pathway Inhibition *In vitro* using a Thin Tissues Sections

Currently this task as well has been delay by the marked reduction in viable prostate specimens that were expected to be used in Task 1.

Key Research Accomplishments:

Currently, we are still working to develop the optimal medium for prostate cancer growth. As previously stated the non-viable prostates have significantly hindered our ability to move forward with the whole prostate specimens as well as the TUR specimens. We are currently expanding our options for prostate procurement hopefully we will have greater success in the next year.

Reportable Outcomes

We have no reportable outcomes at this time.

Conclusions

The primary hurdle we currently have is obtaining viable prostates from robotic laparoscopic prostatectomies. Patients when given the options are almost routinely choosing a robotic approach. Therefore given that this approach will only become more popular, we have to change how we perform the surgery to overcome this problem. We anticipate that once we have a steady stream of viable prostates, we can complete Task 1 and quickly move forward.

References – None at this time.

Appendices – None at this time.