Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-231-2825.

1. **Grantee Institution:** American College of Radiology

2. **Reporting Period (start and end date of grant award period):** 1/1/2011 – 12/31/2014

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Stephen M. Marcus, M.S.

4. **Grant Contact Person's Telephone Number:** 267-940-9403

5. **Grant SAP Number:** 4100054841

6. **Project Number and Title of Research Project:** 6: Leveraging the Androgen Receptor Axis to Improve Treatment of Locally Advanced Prostate Cancer

7. **Start and End Date of Research Project:** 7/1/2012 – 12/31/2014

8. **Name of Principal Investigator for the Research Project:** Karen Knudsen, PhD

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 100,000

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Knudsen, Karen	Professor (PI)	5% all years	$64,102.54

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
None		

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None Purchased		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No___X_____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes___X_____ No_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds awarded:
Philadelphia Prostate Cancer SPORE	☑NIH ☐ Other federal (specify:__) ☐ Nonfederal source (specify:)	May 2014	$11.5 M	$0

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes___X_____ No_____

If yes, please describe your plans:

This research will be submitted as a part of a larger NIH R01

12. Future of Research Project. What are the future plans for this research project?

This research will be integrated into an R01 submission that is currently being formulated.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes_____ No__X_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc

Hispanic				
Non-Hispanic				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian				
Other				
Unknown				
Total				

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No____X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes_____ No____X____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes___X_____ No_____

If yes, please describe the collaborations:

Collaborations were developed with Felix Feng, MD, a Radiation Oncologist at the University of Michigan. Dr. Feng's work focuses on non-coded RNA, and was invaluable to the completion of this project. Dr. Feng will be a part of the new to-be-submitted R01.

16(B) Did the research project result in commercial development of any research products?

Yes_____ No___X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No___X_____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Specific Aim 1: Determine the in vivo efficacy of mTOR inhibitors as a means to combinatorially suppress Androgen Receptor (AR) function in prostate cancer cells and sensitize them to radiation therapy:

Due to delays in subcontracting for this project, the project components for Aim 1 were initiated, completed, and published using start-up funds provided to Dr. Knudsen. As a result, no grant funds were used for work on Aim 1 but we were able to advance what we had initially planned in terms of the timeline for Aim 2, which is a natural extension of the Aim 1 outcomes. Notably, these have significant translational potential.

Specific Aim 2: Determine the influence of new AR-directed therapeutics on the radiotherapy response of prostate cancer cells:

We made substantial progress in the first year. For these studies, we built on our recent publication identifying AR as a major mediator of double-strand DNA break repair as mediated by the ability of AR to regulate the expression and activity of the DNAPK enzyme. The catalytic subunit of the DNA-dependent protein kinase (DNAPKcs) plays a major role in the non-homologous end joining (NHEJ) double strand break repair pathway and was demonstrated to be critical in the AR-mediated response to damage. Surprisingly, DNAPKcs also interacts with AR in a damage-independent fashion serving as a coactivator of AR transcriptional activity and forming a positive feedback circuit linking hormone action to the DNA damage response. This feedback circuit suggests that DNAPK may significantly impact global transcription in the absence of DNA damage.

New findings in year one demonstrated that DNAPKcs expression is positively correlated with decreased freedom from metastases in prostatic adenocarcinoma (PCa) patients (Figure 4) suggesting that DNAPKcs may drive disease progression and metastatic phenotypes. We have also made substantial progress on this aim in the final 6 months, and have submitted a publication which is currently in review for a major journal. Major findings are summarized below:

DNA-PK interacts with AR and is recruited to sites of AR action

The ability of AR to alter response to radiation is controlled by DNAPK. Our observation that DNA-PK is induced by AR activity and functions as an AR coactivator in advanced PCas that are progressing despite anti-androgen therapy (castration-resistant prostate cancer, CRPC) provided a strong impetus for further interrogation of DNA-PK-mediated transcriptional regulation and utilization of CRPC as a platform for discovery related to DNA-PK function. PCas are dependent on AR activity for growth and progression, and therapeutics intended to suppress AR activity through ligand deprivation (ie pharmacologic castration through feedback inhibition) are the first line of therapeutic intervention for metastatic disease. While effective, tumors ultimately recur, almost invariably through restoration of AR activity. Thus, discerning the impact of DNA-PK on AR function in advanced disease is of obvious translational relevance. Consistent with identification of *PRKDC* as an androgen-regulated gene in CRPC, hormone deprivation decreased DNA-PK activity and levels in CRPC (Fig. 1A). As such, experiments to assess the function of DNA-PK as a transcriptional regulator were performed in hormone-proficient conditions. As expected, chromatin immunoprecipitation (ChIP) analysis revealed AR occupancy at two well-characterized AR regulatory loci, the *KLK3/*PSA and *TMPRSS2* enhancers (Fig. 1B, left), wherein DNA-PK was also detected (Fig. 1B, right), demonstrating

that DNA-PK is present at multiple AR regulatory loci, and similar to observations in hormone therapy (HT)-sensitive cells. In response to DHT, AR was recruited to each site within 30 minutes, with maximum occupancy observed at 16 hrs post-treatment (Fig. 1C, left). In contrast, DNA-PK occupancy was delayed until 6 hrs post-treatment, with maximum occupancy observed at 16 hrs (Fig. 1C, right). Combined, these findings suggest that DNA-PK is recruited to sites of AR function in response to AR occupancy. The impact of DNA-PK recruitment was determined by monitoring *KLK3/*PSA and *TMPRSS2* transcript levels in parallel studies. While significant induction of both *KLK3/*PSA and *TMPRSS2* was observed by 3 hrs post-DHT (Fig. 1D), maximum induction was not observed until after peak recruitment of AR and DNA-PK to regulatory sites, suggesting that DNA-PK occupancy is likely required for robust AR activity. Co-immunoprecipitation analyses further revealed that AR and DNA-PK are found in complex, and that the interaction is not further enriched by exogenous DHT (Fig. 1E). The AR-DNA-PK interaction is not dependent on DNA binding, as pre-addition of ethidium bromide did not disrupt the complex (Fig. 1F). Further, DNA-PK activity is not required for this interaction, as shown by treatment with the specific DNA-PK inhibitor NU7441. By contrast, NU7441 decreased DHT-stimulated AR target gene expression, further supporting a coactivator role for DNA-PK in AR-mediated transcription. In sum, these findings reveal that DNA-PK binds AR and impacts transcriptional activation at sites of AR action.

DNA-PK is a selective effector of transcriptional networks

Though AR is a known oncogenic factor in PCa, influence of many other transcriptional drivers made it imperative to discern the overall global impact of DNA-PK in regulation of transcriptional networks and cellular outcomes. Gene expression analyses were performed in CRPC cells either depleted of DNA-PK or treated with a specific DNA-PK inhibitor (Fig. 2A, left); as shown, the si*PRKDC* pool suppressed DNA-PK expression, whereas the DNA-PK inhibitor had no effect on DNA-PK levels (Fig. 2A, right). Genes identified as up- or downregulated by more than 1.5 fold were selected for further analysis (Fig. 2B). For both manipulations, the number of genes downregulated far exceeded those that were upregulated, suggesting that DNA-PK primarily positively regulates transcriptional events but can also function as a negative regulator of gene expression. Comparison between the groups demonstrated that DNA-PK depletion results in overlapping but distinct effects as compared to enzymatic inhibition. To minimize any potential off-target effects of NU7441, subsequent analyses were primarily focused on transcriptional alterations induced by DNA-PK knockdown. Gene Set Enrichment Analysis (GSEA) and associated motif analysis revealed significant enrichment of genes regulated by MAZ, MYC and the known DNA-PK-interacting partner Sp1, validating the concept that DNA-PK modulates a select subset of transcriptional networks (Fig. 2C). Additionally, GSEA gene ontology (GO) analysis demonstrated that genes sensitive to DNA-PK are associated with distinct biological processes including transcription, DNA-dependent transcription, and regulation of gene expression, further supporting a role for DNA-PK in gene regulation (Fig. 2D). Combined, these findings begin to define the cellular consequence of DNA-PK mediated transcriptional regulation, and demonstrate that DNA-PK selectively governs transcriptional networks.

DNA-PK and AR cooperate to suppress UGT enzyme expression in CRPC

Numerous pathways associated with metabolic and hormone pathways of potential clinical impact in PCa were identified as upregulated by DNA-PK depletion (Fig. 3A), including

steroid hormone biosynthesis, wherein marked upregulation of UGT glycosyltransferases was observed (Fig. 3B). UGT enzymes catalyze the transfer of glucuronic acid to small hydrophobic molecules (including androgens), facilitating metabolism and excretion. In the prostate, local inactivation of androgens occurs when DHT is directly modified by glucuronidation or is metabolized to 5α-androstane-3α-diol (3α-diol) and androsterone, which are then glucuronidated by UGT2B15 and UGT2B17, both of which were upregulated by DNA-PK depletion (Fig. 3B). Consistent with previous reports suggesting that these genes are also AR regulated, AR was occupied the proximal promoters of both *UGT2B15* and *2B17*, and residence increased in cells upon DNA-PK depletion (Fig. 3C). Parallel analyses revealed DNA-PK co-occupancy (Fig. 3D), suggesting that negative regulation of *UGT2B15* and *2B17* expression by DNA-PK is direct. DNA-PK depletion resulted in increased *UGT2B15* and *2B17* expression in two independent CRPC models, underscoring the impact of DNA-PK on this pathway (Fig. 3E). This finding is of strong translational relevance, as UGT2B15 and 2B17 are being developed as prognostic markers and pharmacologic targets for PCa management, and the mechanisms of regulation are not well understood. Notably, UGT2B15 and 2B17 protein accumulation was also enhanced upon DNA-PK depletion (Fig. 3F); as such, the impact of DNA-PK depletion on free and glucuronidated-DHT (G-DHT) levels was quantified by high-performance liquid chromatography (HPLC). While cells depleted of DNA-PK showed a trend towards decreased overall levels of free DHT (Fig. 3G), this did not reach statistical significance, suggesting that elevated UGT2B15 and 2B17 is not sufficient to independently alter hormone metabolism. GSEA KEGG analysis in response to the DNA-PK inhibitor further confirmed the selective function of DNA-PK as a negative regulator of transcription. On balance, these findings are the first to identify gene networks that are negatively regulated by DNA-PK, and identify DNA-PK as a key modulator of the UGT enzyme cancer-associated pathway.

Figures

Figure 1

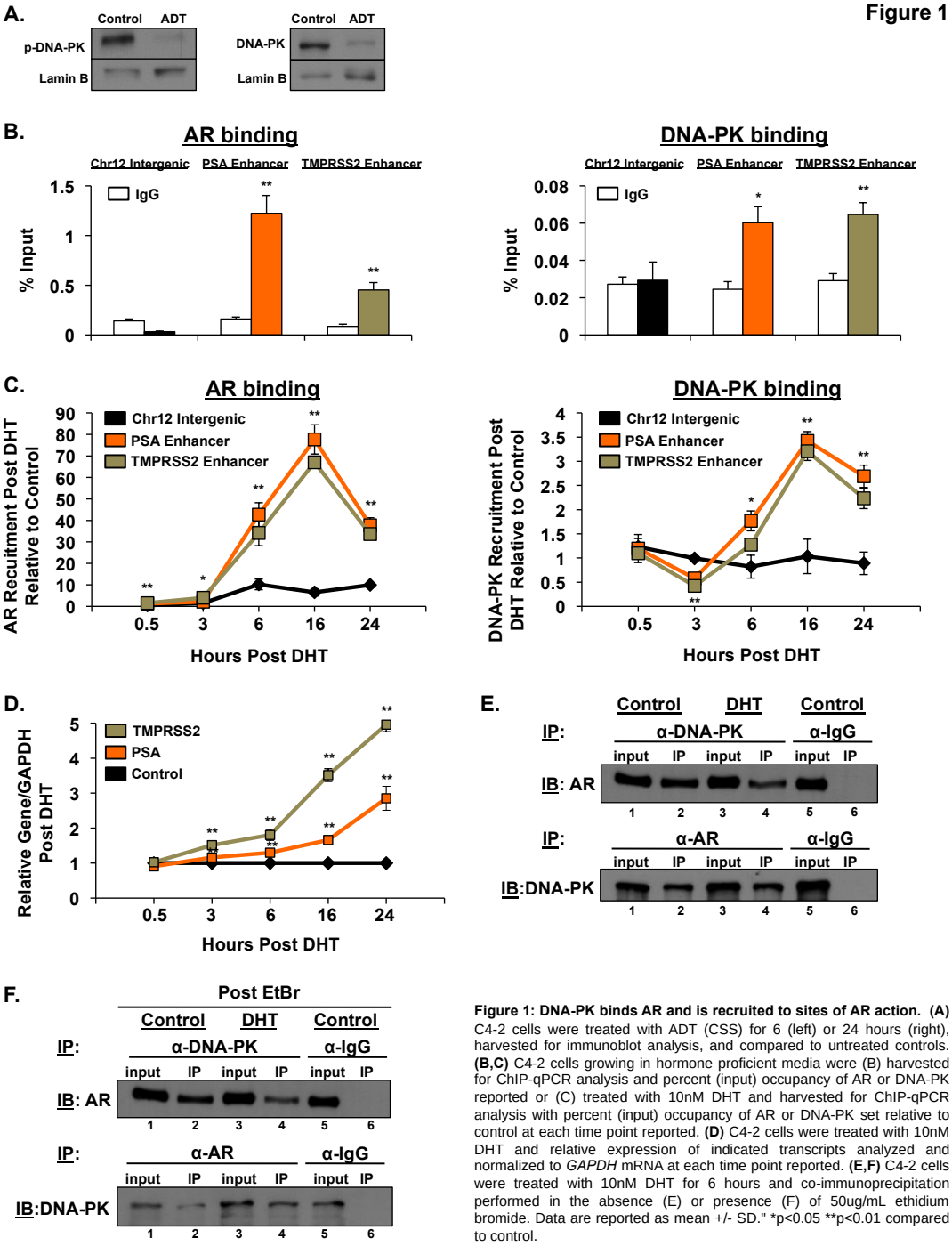

Figure 1: DNA-PK binds AR and is recruited to sites of AR action. (A) C4-2 cells were treated with ADT (CSS) for 6 (left) or 24 hours (right), harvested for immunoblot analysis, and compared to untreated controls. **(B,C)** C4-2 cells growing in hormone proficient media were (B) harvested for ChIP-qPCR analysis and percent (input) occupancy of AR or DNA-PK reported or (C) treated with 10nM DHT and harvested for ChIP-qPCR analysis with percent (input) occupancy of AR or DNA-PK set relative to control at each time point reported. **(D)** C4-2 cells were treated with 10nM DHT and relative expression of indicated transcripts analyzed and normalized to *GAPDH* mRNA at each time point reported. **(E,F)** C4-2 cells were treated with 10nM DHT for 6 hours and co-immunoprecipitation performed in the absence (E) or presence (F) of 50ug/mL ethidium bromide. Data are reported as mean +/- SD." *p<0.05 **p<0.01 compared to control.

Figure 2

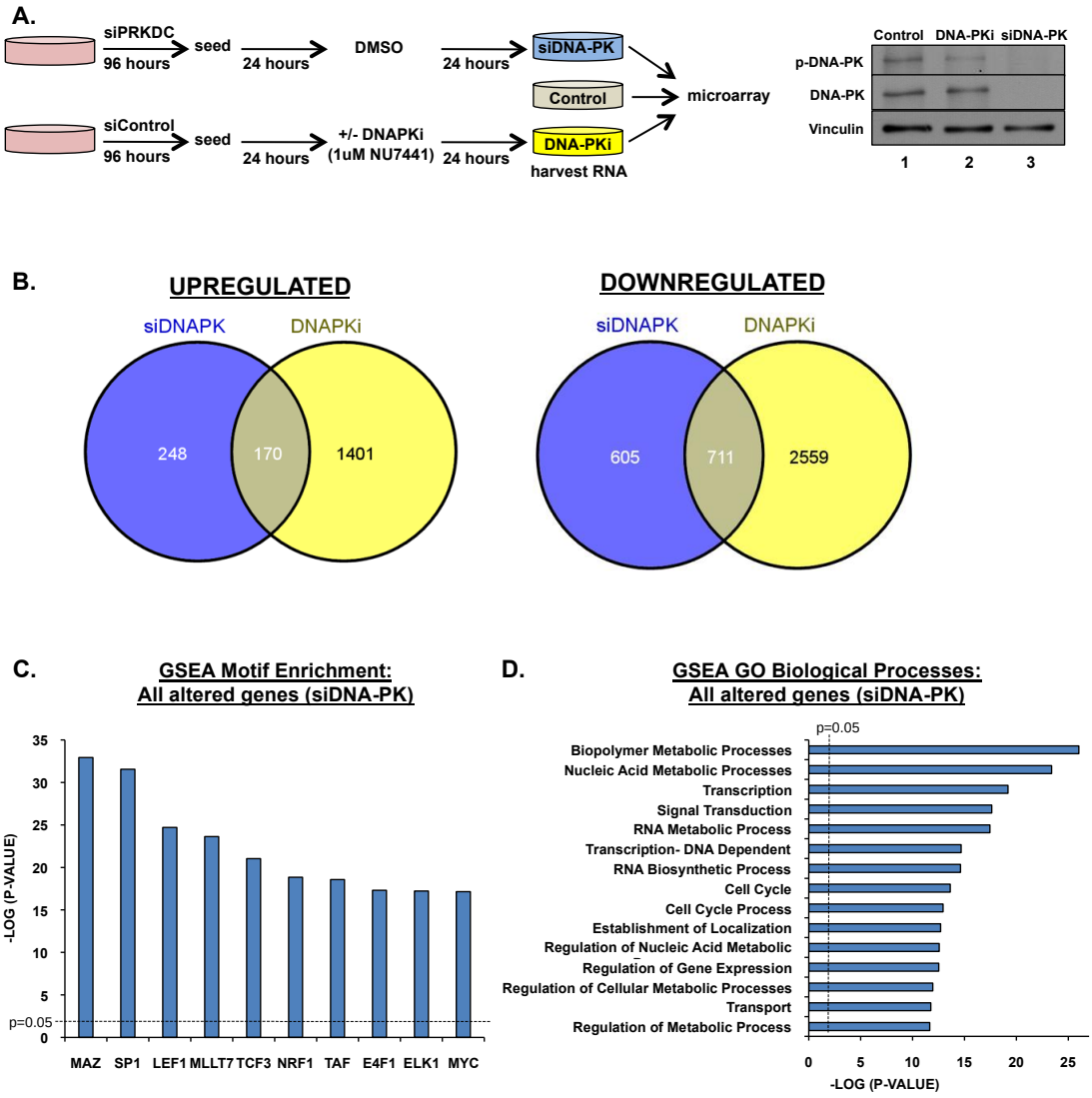

Figure 2: DNA-PK impacts global gene expression in CRPC. **(A)** RNA harvested from C4-2 cells depleted of DNA-PK or treated with 1uM NU7441 for 24 hours was analyzed by microarray analysis. **(B)** Genes identified by 1.5 fold cut off compared to untreated control. **(C,D)** GSEA analyses of all genes identified to be significantly altered after DNA-PK knockdown.

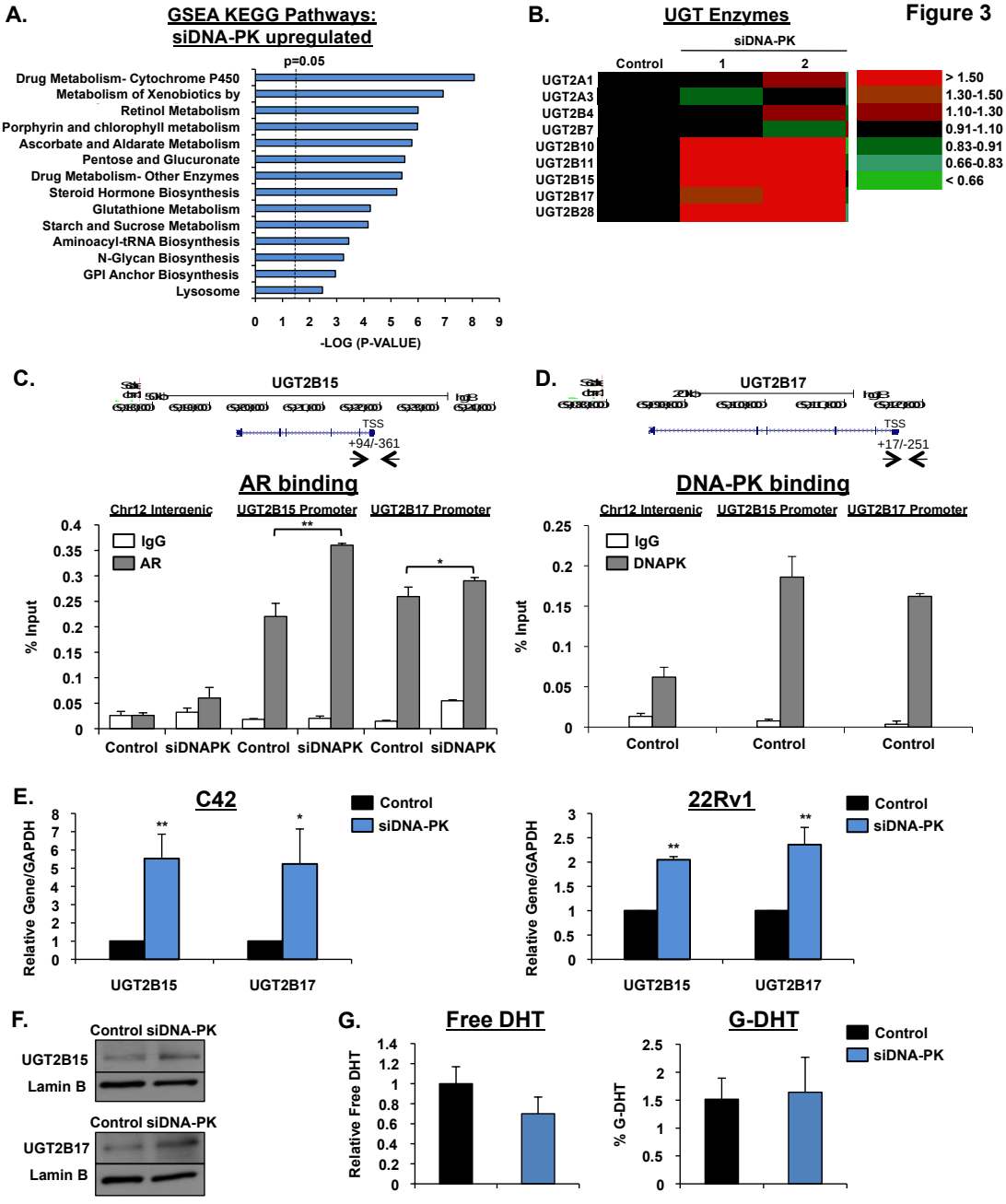

Figure 3: DNA-PK and AR cooperate to suppress UGT enzyme expression in CRPC. (A) GSEA KEGG pathway analysis of genes identified to be upregulated by at least 1.5 fold compared to control after DNA-PK knockdown. **(B)** Heat map of transcript change of UGT enzymes in the DNA-PK knockdown groups. **(C,D)** C4-2 cells depleted of DNA-PK were harvested for ChIP-qPCR analysis and percent (input) occupancy of AR or DNA-PK reported. **(E,F)** CRPC cells depleted of DNA-PK were subject to either qPCR (transcript, E) or immunoblot (protein, F) analysis. **(G)** Free and G-DHT levels in C4-2 cells depleted of DNA-PK were determined by HPLC . Data are reported as mean +/- SD. *p<0.05 **p<0.01

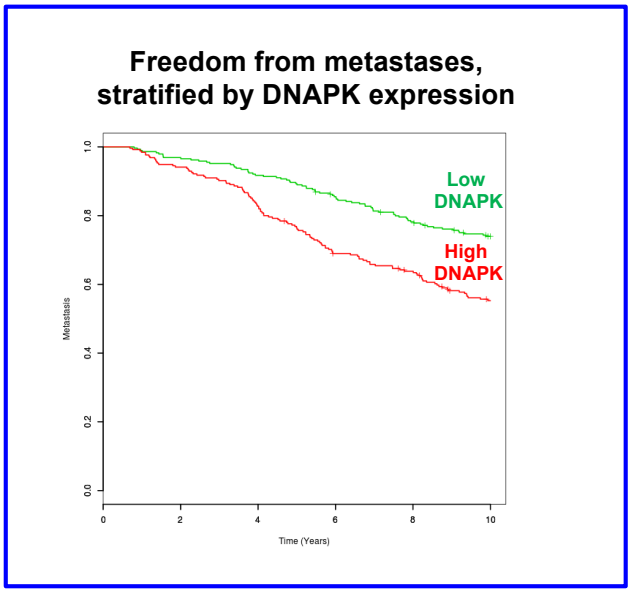

Figure 4. High DNAPK expression predicts for metastases in a cohort of PCa patients

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X___No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X___No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
__X___ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. Models of neuroendocrine prostate cancer	Berman-Booty, LD, Knudsen, KE	Endocrine Related Cancer	October 2014	☐Submitted ☐Accepted ☑Published
2. Consequence of the tumor-associated conversion to CyclinD1b	Augello MA, Berman-Booty LD, Carr R, Yoshida A, Dean JL, Schiewer MJ, Feng FY, Tomlins, SA, Gao E, Woch WJ, Benovic JL, Diehl JA, Knudsen KE	EMBO Molecular Medicine	December 2014	☐Submitted ☑Accepted ☐Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes_____ No__X_____

If yes, please describe your plans:

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?

Yes_____ No___

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No___
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No___

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No___

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No___X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages.

BIOGRAPHICAL SKETCH

NAME Karen E. Knudsen	POSITION TITLE Professor of Cancer Biology, Urology, and Radiation Oncology Thomas Jefferson University
eRA COMMONS USER NAME KKNUDSEN	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education,*

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
The George Washington University	B.S.	1990	Biology
University of California San Diego, La Jolla CA	Ph.D.	1996	Molecular Biology
Ludwig Institute for Cancer Research	Post-doc	1997-99	AR & cell cycle

A. Personal Statement

My lab is dedicated to delineating the molecular mechanisms that govern these events. We currently have four main projects in the lab: regulation of AR dependent gene expression and cellular proliferation by cell cycle crosstalk in prostate cancer; impact of SWI/SNF chromatin remodeling factors on AR function and prostate tumorigenesis; impact of cell cycle deregulation on therapeutic efficacy; role of endocrine disrupting compounds in circumventing the androgen requirement.

B. Positions and Honors *(limited to current due to page constraints):*

Positions:

2007-present Member, Kimmel Cancer Center
2007-present Director, Greater Philadelphia Prostate Cancer Working Group
2010-present **Professor**, Departments of Cancer Biology (primary), Urology, and Radiation Oncology, Thomas Jefferson University (TJU
2014-present **Professor** and **Director of Research**, Medical Oncology, TJU
2014 Vice Provost of Research, TJU (*on hiatus*)
2015-present **Interim Director**, Sidney Kimmel Cancer Center
2015-present **Interim Chair**, Cancer Biology

Honors:

Current Editorial Positions:

2006-present **Editorial Board**, *Molecular Cancer Therapeutics*
2007-present **Associate Editor**, *Endocrine Related Cancer*
2008-present **Editorial Board**, *The Prostate*
2008-present **Editorial Board**, *American Journal of Pathology*
2009-present **Editorial Board**, *Environmental Health Perspectives*
2010-present **Editorial Board**, *Molecular Endocrinology*
2010-present **Editorial Board**, *Oncogene*
2013-present **Editor-in-Chief,** *Molecular Cancer Research*

Current Grant Review and Scientific Advisory Boards:

2012-present NIH Molecular and Cellular Endocrinology (**MCE**) Study Section, Ad Hoc

Recent Awards:

2009 Endocrine Society Laureate (Richard E. Weitzman Memorial) Award
2011 Ron Ross Award, Pacific Rim Breast & Prostate Cancer Foundation
2012 Jefferson College of Graduate Studies Distinguished Mentor Award

2015 SBUR/SWIU Award for Excellence in Urologic Research

Current National Society Positions:

2008-present American Association for Cancer Research Annual Meeting Exhibits Committee,
2009-present Society for Basic Urologic Research Membership Committee

Invited International Conference Lectures and Leadership (selected from 2012-present)

2012 Oslo Prostate Cancer Symposium (Norway)
2012 AACR Annual Meeting
2012 Endocrine Society, Annual Meeting
2013 Endocrine Society, Annual Meeting
2013 Gordon Conference on Hormone Action (***Chair**)
2013 4th SOGUG Scientific Meeting (Spain)
2014 AACR Annual Meeting
2014 ASTRO Annual Meeting
2014 Prostate Cancer Foundation Annual Meeting

C. Peer-Reviewed Publications: *(from>77 papers; H index 26; 1,981 citations)*

1. Burd, C.J., Petre, C.E., Morey, L.M., Wang, Y, Revelo, M.P., Haiman, C.A., Lu, S., Fenoglio-Preiser, C.M,, Li, J., Knudsen, E.S., Wong, J., and **Knudsen, K.E.** (2006) The cyclin D1b variant influences prostate cancer growth through aberrant AR regulation. *Proc. Natl. Acad. Sci.*, 103(7): 2190-5.
2. Sharma, A., Berrera, J., Knudsen, E.S., Morey, L.M., Hess-Wilson, J.K., and **Knudsen, K.E.** (2007) RB status is a critical determinant of therapeutic response in prostate cancer. *Cancer Research*, 67(13):6192-203.
3. Olshavsky, N., Groh, E., Burd, CJ, Morey, L., Comstock, CE, Wang, Y, Revelo, MP, and **Knudsen, KE** (2008) Cyclin D3 impact on androgen signaling and prostate cancer, *Oncogene*.27(22):3111-21.
4. Shen, H., Powers, N, Saini, N, Comstock, CES, Sharma, A, Weaver, K, Revelo, MP, Gerald, W, Williams, E, Jessen, WJ, Aronow, BJ, Rosson, G, Weissman, B, Yaniv, M, Muchardt, C, and **Knudsen, KE** (2008) The SWI/SNF ATPase Brm is a gatekeeper of proliferative control in prostate cancer, *Cancer Research*, Dec 15;68(24):10154-62. (*selected for cover/Highl. section).
5. Comstock, CES, Augello, MA, PeBenito, R, Karch, J, Tran TH, Utama, FE, Tindall, EA, Wang, Y, Burd, CJ, Groh, EM, Hoang, HN, Giles, GG, Severi, G, Hayes, VM, Henderson, BE, Le Marchand, L, Kolonel, LN, Haiman, CA, Baffa, R., Gomella, LG., Knudsen, ES, Rui, H, Henshall, SM, Sutherland, RL and **Knudsen, KE** (2009) Cyclin D1 splice variants: polymorphism, risk, and isoform specific regulation in prostate cancer. *Clinical Cancer Research* 15(17): 5338-49. (* selected as the featured cover article)
6. Augello MA, Hickey TE, and **Knudsen KE.** (2011) FOXA1: master of steroid receptor function in cancer. *EMBO J.* Sep 20. doi: 10.1038/emboj.2011.340. PMID: 21934649
7. Schiewer MJ, Goodwin JF, Han S, Brenner JC, Augello MA, Dean JL, Liu F, Planck JL, Ravindranathan P, Chinnaiyan AM, McCue P, Gomella LG, Raj GV, Dicker AP, Brody JR, Pascal JM, Centenera MM, Butler LM, Tilley WD, Feng FY, **Knudsen KE**. (2012) Dual roles of PARP-1 promote cancer growth and progression. *Cancer Discov*. 2012 Dec;2(12):1134-1149.
8. Goodwin JF, Schiewer MJ, Dean JL, Schrecengost RS, de Leeuw R, Han S, Ma T, Den RB, Dicker AP, Feng FY, **Knudsen KE**. (2013) A hormone-DNA repair circuit governs the response to genotoxic insult. *Cancer Discov* 2013 Sept 11 [epub ahead of print].
9. Goodwin JF, **Knudsen KE**. (2014) Beyond DNA Repair: DNA-PK Function in Cancer. *Cancer Discov* 2014 Oct;4(10):1126-1139