TITLE: Small Molecule Inhibitors of ERG and ETV1 in Prostate Cancer

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The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.
The research involves laboratory studies utilizing xenograft models to test the hypothesis that targeting a member of the ETS transcription factor family with small molecules such as YK-4-279 may effectively treat prostate cancer. In year three, Dr. Morrissey was to evaluate the anti-tumor effect of the S-enantiomer of YK-4-279 on 4 human prostate xenograft lines subcutaneously and 2 lines intra-tibial. Dr. Uren supplied Dr. Morrissey with the required compound. The S-enantiomer of YK-4-279 had no significant effect on tumor growth on the first and second ERG+ xenograft lines. It had an effect on the third ERG+ xenograft line, and no effect on the control xenograft line. A gene expression analysis of the first study suggested a change in the expression of epithelial-mesenchymal transition associated genes in ERG treated tumors. However, immunohistochemical analyses of these proteins in the tumors of treated and untreated animals suggested the change in expression only occurred in a subset of cells within the tumors. Dr. Uren has met with and Skyped with Dr. Morrissey to ensure continued collaboration. We are currently completing a study on the effect of the S-enantiomer of YK-4-279 on intra-tibial tumors and have requested a no cost extension to complete the intra-tibial animal studies.
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Introduction

A group of chromosomal translocations were recently discovered in prostate cancer that fuses the 5’ region of TMPRSS2 (a serine protease) gene to the 3’ region of ETS transcription factor genes (1). TMPRSS2 is an androgen responsive gene and contributes only its promoter region and usually a very short exon-1 (2, 3). This causes aberrant expression of an ETS transcription factor in response to androgen. The most common ETS member involved in prostate cancer chromosomal translocations is ERG but other members such as ETV1, ETV4 and ETV5 have been also observed (4, 5). The more aggressive prostate cancers often contain these translocations, thus potentially increasing their utility as both diagnostic and prognostic marker (6-8). Cell culture and transgenic animal models suggest that increased expression of ETS members, as a result of the chromosomal translocations, increase cell invasion without affecting the proliferative potential (9-11). However, in some xenograft models reducing expression of TMPRSS2-ERG protein slows down prostate cancer growth (12, 13). Therefore, ETS proteins emerge as potential novel targets for treatment of primary and/or metastatic disease in prostate cancer.

We developed small molecule inhibitors that target protein products of chromosomal translocations containing ETS transcription factors (14). We further established that our lead compound, YK-4-279, directly binds to both ERG and ETV1 proteins (15). YK-4-279 inhibits ERG and ETV1 mediated transcriptional activity and subsequent cellular invasive phenotype of prostate cancer cell lines. These effects were only observed in prostate cancer cell lines containing ETS chromosomal translocations such as VCaP and LNCaP and absent in the PC3 prostate cancer cell line that does not contain any ETS chromosomal translocations. Expression of ERG in PC3 cells from an expression vector sensitized them to YK-4-279 and inhibiting ERG expression in VCaP resulted in resistance to YK-4-279 effect (15). Therefore, we hypothesized that targeting ETS family of transcription factors by small molecules will inhibit malignant phenotypes of human prostate cancer cells.

Keywords

Prostate Cancer, TMPRSS2-ERG, ERG, patient derived xenografts, YK-4-279, Tumor growth, Proliferation, ERG Inhibitor, and treatment resistance.

Accomplishments

**Major goals:**

This research project involved laboratory studies utilizing xenograft models to test the hypothesis that ERG is a target for castration resistant prostate cancer and that targeting a member of the ETS transcription factor family with small molecules such as YK-4-279 may effectively treat prostate cancer. Our role within the project was defined in Task 3. Evaluate anti-ETS compounds in xenograft models. (Months 13-36). Our specific role was:

3c. Evaluate anti-tumor effect of YK-4-279 and/or the most effective two derivatives on 4 primary human prostate xenograft lines (3 fusion-positive and one fusion-negative) (Months 10-26) (Morrissey Lab)

3d. Evaluate effect of the most potent compound on 3 fusion positive primary human prostate xenograft lines in the bone microenvironment (Months 25-36) (Morrissey Lab)

3e. Evaluate molecular signature in anti-ETS treated tumors. (Months 18-36) (Morrissey Lab)
Accomplishments:

In year 1 Dr. Uren screened ETS transcription factors to test in animal models of prostate cancer at the University of Washington. Dr. Morrissey obtained all approvals to start the animal studies in year 2 and consistently met and Skyped with Dr. Uren to discuss the fine details of the animal studies. Dr. Uren screened a panel of derivatives and determined that none of the derivatives were more effective at inhibiting ERG than YK-4-279. Therefore we moved ahead with testing YK-4-279 in the xenograft models as proposed. Dr. Morrissey has tested YK-4-279 in 4 patient derived xenograft lines as proposed (Figure 1). One of the ERG positive xenograft lines LuCaP 23.1 responded to treatment (Figure 2), LuCaP 86.2 had a limited response (Figure 3), and LuCaP 35 did not respond to treatment (Figure 4). The ERG negative line LuCaP 96 as expected did not respond to treatment (Figure 5). For all tissue acquired from the animals, half paraffin embedded and the remainder was flash frozen in OCT. The paraffin embedded tumors were sectioned and stained by hematoxylin and eosin. Then a tissue microarray was constructed. All xenografts were stained for ERG to ensure ERG positivity and to determine if the levels of ERG are altered in response to therapy (Figure 6). No significant differences in ERG expression were observed in the YK-4-279 treated animals. In addition we did a western analysis to determine if any changes in ERG expression could be observed, but there were no changes between YK-4-279 treated and untreated tumors (data not shown). This TMA was stained for Ki67 to assess proliferation (Figure 7). A significant decrease in Ki67 positivity was observed in YK-4-279 treated animals for LuCaP 86.2 and LuCaP 96, but not for LuCaP 23.1 and LuCaP 35 (Figure 8). One explanation why LuCaP 23.1 treated animals did not show a decrease in proliferation relative to controls could be due to the fact that the tissues were all end of study treatment resistant tissues that were no longer suppressed by ERG inhibition.

To determine if a set of genes are expressed in ERG positive prostate cancer metastases and the xenografts we did an independent study of primary prostate cancer, prostate cancer metastases and the LuCaP xenografts by gene expression analysis. We determined that the overlap between primary prostate cancer, metastases and the LuCaP xenografts was limited (Figure 9). Therefore we could not rely on the literature to look at markers of response. To identify ERG regulated genes that were suppressed by YK-4-279 we did molecular profiling by RNAseq of tissues treated with the YK-4-279 compound (Figure 10). We determined that epithelial-mesenchymal transition (EMT) associated proteins RASAL2, VIM, NREP, and BCL11A were decreased among others. ERG has been associated with EMT in the past. To verify these changes at the protein level we analyzed additional EMT associated proteins to determine if we could identify changes in protein expression in the xenografts. A tissue microarray that was constructed from the study tissues was stained for CD34, Caspase 3, vimentin, CTGF, as well as ZEB1, SOX4, Twist examples of staining shown in Figure 11. For CD34 staining we did not observe any significant difference in microvessel density between the YK-4-279 treated and untreated tumors (data not shown). For Caspase 3 staining (apoptosis) we did not observe any increase in YK-4-279 treated tumors (data not shown). For the EMT associated genes we did not see significant differences in EMT-associated expression, but did observe high Twist expression in cells with elongated nuclei in the tumors, suggesting the EMT-associated proteins were being expressed in a subset of cells in the tumors that may be undergoing EMT. We have recently published a similar observation in metastasis specimens from patients with castration resistant prostate cancer (CRPC) (16).

There was limited toxicity due to weight loss in the animals in response to YK-4-279 treatment. This impacted the tumor volumes, serum PSA and survival outcomes for all xenograft lines. Further, after discussion and review of previously obtained and new data Dr. Uren determined that the R-enantiomer of YK-4-279 had no effect on ERG activity and it had associated toxicity in vitro and in vivo (Figure 12; Table 1 and 2). Therefore we used the S-enantiomer as the second derivative. We tested the S-enantiomer of YK-4-279 in the same 4 patient derived xenograft lines as proposed. For all tissue acquired from the animals, half paraffin embedded and the remainder was flash frozen in OCT. Unfortunately the ERG positive xenograft lines LuCaP 23.1 (Figure 13) and 35 did not respond to treatment (Figure 14), however, the LuCaP 86.2 treated tumors were significantly different in tumor volume to the untreated tumors (p=0.0009) (Figure 15). The ERG negative line LuCaP 96 as expected did not respond to treatment (Figure 16).
To determine if the YK-4-279 S-enantiomer would impact tumor growth in bone we injected intra-tibial tumors (LuCaP 96 (control) and LuCaP 86.2) into animals. The LuCaP 96 control tumors took in the tibia. No significant change in serum PSA was observed and body weights did not change (Figure 17). Unfortunately tumors took in only eight animals in the LuCaP 86.2 cohort. This was not sufficient to provide a statistically significant number of animals in the group for analysis so no further analysis was done on the tibiae from these animals.

To determine if a set of genes are expressed in prostate cancer metastases and the xenografts we did an independent study of primary prostate cancer, prostate cancer metastases and the LuCaP xenografts by gene expression analysis. Using gene expression analysis on primary prostate and metastases specimens we determined that ERG was expressed in fewer patients with metastases than patients with primary prostate cancer (Figure 18). IHC revealed that 43% of primary prostate cancers were ERG+, 35% of the LuCaP xenografts were ERG+, and 18% of the CRPC metastases were ERG+, representing 12 of 48 patients (25%) with at least 1 ERG+ metastasis (Figure 19). Additionally we identified a protein DCLK1 that was associated with ERG expression. DCLK1 was upregulated at the protein level in both ERG+ primary prostate cancer and CRPC metastases (p=0.0013 and p<0.0001, respectively) (Figure 20). In primary prostate cancer, ERG status or expression of targeted proteins was not associated with BCR-free survival. However, ERG+DCLK1+ patients exhibited shorter time to BCR (p=0.06) compared to ERG+DCLK1- patients (Figure 21). However, we saw no association of DCLK1 with ERG inhibition in the LuCaP xenografts. This could be for a number of reasons, as DCLK1 has been described as a putative stem cell marker and may not reside in sufficient numbers of cells for us to identify the change in DCLK1 in the xenograft models.

Opportunities for Professional Development:
Nothing to report.

Dissemination of Results:
The results were presented in national meetings in a poster format and lecture format, one article was published and one is in preparation – All are listed under products.
Figure 1. Response of individual animals bearing the ERG positive (A) LuCaP 23.1, (B) LuCaP 86.2, (C) LuCaP 35 and (D) LuCaP 96 xenograft to YK-4-279.
Figure 2. Response of animals bearing the ERG positive LuCaP 23.1 xenograft to YK-4-279. (A) Tumor volume, (B) Serum PSA, (C) Body weight, and (D) Survival. The ERG positive LuCaP 23.1 xenograft responded to ERG inhibition both at the tumor volume and serum PSA level. A significant change in body weight was observed in the animals treated with YK-4-279. No significant difference in survival was observed between the YK-4-279 and vehicle treated animals.
Figure 3. Response of animals bearing the ERG positive LuCaP 86.2 xenograft to YK-4-279. (A) Tumor volume, (B) Serum PSA, (C) Body weight, and (D) Survival. The ERG positive LuCaP 86.2 xenograft responded to ERG inhibition, (but was short of significance) both at the tumor volume and serum PSA level. No significant change in body weight was observed in the animals treated with YK-4-279. No significant difference in survival was observed between the YK-4-279 and vehicle treated animals.
Figure 4. Response of animals bearing the ERG positive LuCaP 35 xenograft to YK-4-279. (A) Tumor volume, (B) Serum PSA, (C) Body weight, and (D) Survival. The ERG positive LuCaP 35 xenograft did not respond to ERG inhibition, both at the tumor volume and serum PSA level. No significant change in body weight was observed in the animals treated with YK-4-279. No significant difference in survival was observed between the YK-4-279 and vehicle treated animals.
Figure 5. Response of animals bearing the ERG positive LuCaP 96 xenograft to YK-4-279. (A) Tumor volume, (B) Serum PSA, (C) Body weight, and (D) Survival. The ERG negative LuCaP 96 xenograft did not respond to ERG inhibition, both at the tumor volume and serum PSA level. No significant change in body weight was observed in the animals treated with YK-4-279. A significant difference in survival was observed between the YK-4-279 and vehicle treated animals.
Figure 6. (A) ERG staining of representative samples of the LuCaP xenografts treated with vehicle. LuCaP 23.1, 86.2, and 35 are all ERG positive, LuCaP 96 is ERG negative. Note in LuCaP 96 there are still ERG positive endothelial cells. (B) ERG expression in YK-4-279 treated and untreated LuCaP xenografts. No significant changes in ERG expression were observed between groups.
Figure 7. Ki67 staining of representative samples of the LuCaP xenografts treated with YK-4-279. LuCaP 23.1, 86.2, and 35 are all ERG positive, LuCaP 96 is ERG negative.
Figure 8. Ki67 staining of the LuCaP xenografts treated with YK-4-279. LuCaP 23.1, 86.2, and 35 are all ERG positive. LuCaP 96 is ERG negative. There was a significant decrease in LuCaP 86.2 and LuCaP 96 Ki67 positivity in YK-4-279 treated relative to control treated animals.
Figure 9. Gene expression array of Primary prostate cancer, LuCaP xenografts, and CRPC metastases. The top 25 genes found on expression analysis in 11 primary prostate cancers (5 ERG-, 6 ERG+), 20 LuCaP xenografts (13 ERG-, 7 ERG+), and 45 CRPC metastases (30 ERG-, 15 ERG+) specimens relative to ERG positivity based on IHC are shown. Genes highlighted in yellow have been previously found to correlate with ERG activity in the literature. Note the limited number of genes differentially expressed in the LuCaP xenografts.
**Figure 10.** Genes decreased in expression after YK-4-279 treatment in ERG positive LuCaP 23.1, 35 and 86.2 xenografts. RNAsSeq was performed to identify genes that were suppressed by YK-4-279. Epithelial-mesenchymal transition associated proteins were downregulated in the expression arrays. Note that differences in expression are significantly different between lines. U= Untreated; T = Treated.
Figure 11. SOX4, Twist, and ZEB1 expression in LuCaP 23.1, 35, 86.2, and 96. While no difference was observed in staining between YK-4-279 treated and untreated xenografts, differences in the presence of cells with elongated nuclei that stained for SOX4, Twist and ZEB1 were observed. Arrows highlight nuclear staining of epithelial cells with elongated nuclei.
Table 1. *In vitro* response of cells to the S and R enantiomer of YK-4-279 taken from a previous publication by Dr. Uren: Oncotarget 2012; 3: 172-182. The racemic compound has 8.7 fold (8.88 uM/1.02 uM) therapeutic window (comparing IC50 of Ewing cells to non-Ewing Cells). The S enantiomer has 20.2 fold (6.86 uM / 0.34 uM) therapeutic window. This suggests the S enantiomer may be less toxic *in vivo*.

<table>
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<th>Cell Line</th>
<th>Histology</th>
<th>µM IC50 at 3 days (+/- SEM)</th>
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<tr>
<td></td>
<td></td>
<td>YK-4-279</td>
</tr>
<tr>
<td>TC32</td>
<td>ESFT (Type 1)</td>
<td>0.94 (0.14)</td>
</tr>
<tr>
<td>TC71</td>
<td>ESFT (Type 1)</td>
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<tr>
<td>RDES</td>
<td>ESFT (Type 2)</td>
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</tr>
<tr>
<td>SKES</td>
<td>ESFT (Type 2)</td>
<td>0.33 (0.03)</td>
</tr>
<tr>
<td>MMH-ES-1</td>
<td>ESFT (Type 2)</td>
<td>0.94 (0.13)</td>
</tr>
<tr>
<td>STA-ET 7.2</td>
<td>ESFT (Type 2)</td>
<td>0.60 (0.04)</td>
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<tr>
<td>A4573</td>
<td>ESFT (Type 3)</td>
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<tr>
<td>PC3</td>
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<tr>
<td>MCF7</td>
<td>breast</td>
<td>22.82 (7.19)</td>
</tr>
<tr>
<td>MDA-MB-231</td>
<td>breast</td>
<td>0.82 (0.02)</td>
</tr>
<tr>
<td>PANC1</td>
<td>pancreatic</td>
<td>1.514 (0.6503)</td>
</tr>
<tr>
<td>ASPC1</td>
<td>pancreatic</td>
<td>14.28 (3.50)</td>
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Figure 12. In the original grant Dr. Uren identified that the YK-4-279 effect is enantiomer specific. (A) Racemic YK-4-279 was separated to its two enantiomers by HPLC. (B) Recombinant ERG protein was immobilized on a Biacore CM5 sensorchip. Racemic YK-4-279 and its S and R enantiomers were injected over the protein surface to measure direct binding. (C) Cos-7 cells were transfected with ERG responsive luciferase reporter and an ERG expressing vector. S enantiomer that showed direct binding in Biacore also inhibited luciferase assay.
<table>
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<th></th>
<th>Number of animals</th>
<th>Number of deaths</th>
<th>Mortality Rate</th>
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<tr>
<td>400 mg/kg YK-4-279</td>
<td>5</td>
<td>4</td>
<td>80 %</td>
</tr>
<tr>
<td>400 mg/kg (S)-YK-4-279</td>
<td>7</td>
<td>2</td>
<td>26 %</td>
</tr>
<tr>
<td>400 mg/kg (R)-YK-4-279</td>
<td>4</td>
<td>2</td>
<td>50 %</td>
</tr>
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</table>

Table 2. Two week survival data from healthy mice (5-6 week old C57BL/6J). Animals received 400 mg/kg 5 days a week for 2 weeks.
Figure 13. Response of animals bearing the ERG positive LuCaP 23.1 xenograft to the S-enantiomer of YK-4-279. (A) Tumor volume, (B) Serum PSA, (C) Body weight, and (D) Survival. The ERG positive LuCaP 23.1 xenograft did not respond to ERG inhibition using the S-enantiomer of YK-4-279.
Figure 14. Response of animals bearing the ERG positive LuCaP 86.2 xenograft to the S-enantiomer of YK-4-279. (A) Tumor volume, (B) Serum PSA, (C) Body weight, and (D) Survival. Surprisingly, the ERG positive LuCaP 86.2 xenograft responded significantly to ERG inhibition.
Figure 15. Response of animals bearing the ERG positive LuCaP 35 xenograft to the S-enantiomer of YK-4-279. (A) Tumor volume, (B) Serum PSA, (C) Body weight, and (D) Survival. The ERG positive LuCaP 35 xenograft did not respond to ERG inhibition.
Figure 16. Response of animals bearing the ERG negative LuCaP 96 xenograft to the S-enantiomer of YK-4-279. (A) Tumor volume, (B) Serum PSA, (C) Body weight, and (D) Survival. The ERG negative LuCaP 96 xenograft did not respond to ERG inhibition.
Figure 17. Response of animals bearing the intra-tibial ERG negative LuCaP 96 xenograft to the S-enantiomer of YK-4-279. (A) Body Weight, (B) Serum PSA, and (C) X-ray of S-enantiomer YK-4-279 untreated and treated (100 mg/kg) animals. As expected, the ERG negative LuCaP 96 xenograft did not respond to ERG inhibition.
Figure 18: ERG gene expression in primary prostate cancer and CRPC metastases. Agilent gene expression array Log₂ signal intensities of LNCaP (ERG-) and VCaP (ERG+) cells, primary prostate cancer, and CRPC metastases. Based on ERG microarray expression Cy3 values primary prostate cancer specimens were divided into those with low (<2750), medium (>2750 <20,000) and high (>20,000) levels of ERG expression. Of note, the CRPC metastases group contains a large cohort of medium ERG expressors.
Figure 19: ERG IHC in primary prostate cancer and CRPC metastases. ERG+ staining was observed in 43% of primary prostate cancer patients (bar graph, left). 18% of CRPC metastases expressed ERG+ with the majority showing high intensity staining. **IHC images:** A: ERG+ primary prostate cancer with tumor cell nuclei in brown; B: ERG- prostate cancer specimen (note ERG+ endothelial cells); C: Diffusely ERG+ visceral metastasis; D: Diffusely ERG+ bony metastasis.
Figure 20. DCLK1 protein expression in ERG+ and ERG- primary prostate cancer and CRPC. A. DCLK1+ was found in 51% of ERG+ primary prostate cancer revealing significant correlation with ERG+ ($r=0.290$, $p=0.001$). Representative IHC images of DCLK1+ in ERG+ (a) and ERG- (b) primary prostate cancer are shown. B. DCLK1 was present in 62% of ERG+ CRPC specimens revealing significant correlation with ERG+ ($r=0.391$, $p<0.0001$). Representative IHC images of DCLK1+ cells in ERG+ (a) and ERG- (b) CRPC specimens are shown.
Figure 21. Primary prostate cancer BCR-free survival and proliferation relative to DCLK1 status. A. Kaplan-Meier analysis of DCLK1+ vs. DCLK1- status did not correlate with BCR-free survival overall (p=0.11). There was a positive correlation with Ki-67 proliferation relative to DCLK1 status (r=0.194, p=0.0350). B. In ERG+ samples, DCLK1+ vs. DCLK1- status revealed a trend towards worsened BCR-free survival (p=0.06). DCLK1 did not correlate significantly with Ki-67 proliferation in this grouping (r=0.110, p=0.4419).
Impact

Project and Extended Products:

1. The ERG inhibitor has an impact on tumor volume in patient derived xenograft models of prostate cancer.
2. Not all ERG positive tumors respond to therapy.
3. The effects of the ERG inhibitors are not non-specific as no effect was observed in an ERG negative xenograft line.
4. The S-enantiomer of YK-4-279 has limited impact on tumor volume in patient derived xenograft models of prostate cancer.
5. The S-enantiomer of YK-4-279 is the active component but is no less toxic than the racemic mixture in vivo.
6. ERG regulated genes in prostate cancer metastases may be different to ERG regulated genes in primary prostate cancer.
7. We uncovered DCLK1 is a novel protein that may be downstream of ERG in prostate cancer.

Impact on Other Disciplines:
Nothing to report.

Impact on Technology Transfer:
Nothing to report.

Changes/Problems

To identify ERG regulated genes in ERG positive prostate cancer metastases and the xenografts we did an independent study of primary prostate cancer, prostate cancer metastases and the LuCaP xenografts by gene expression analysis. We determined that the overlap between primary prostate cancer, metastases and the LuCaP xenografts was limited. Therefore we could not rely on the literature to look at markers of response. Additionally, our final xenograft study was to determine if the YK-4-279 S-enantiomer would impact tumor growth in bone we injected intra-tibial tumors (LuCaP 96 (control) and LuCaP 86.2) into animals. The LuCaP 96 control tumors took in the tibia. Unfortunately tumors took in only eight animals in the LuCaP 86.2 cohort. This was not sufficient to provide a statistically significant number of animals in the group for analysis so no further analysis was done on the tibiae from these animals.
**Products**

The data suggests ERG inhibitors can impact tumor volume in some but not all ERG positive prostate cancer tumors. It also reveals that the YK-4-279 racemic mixture has some toxicity which limits its efficacy in these studies. We determined the S-enantiomer does not have significantly less toxicity then the racemic mixture. Additionally, we determined that the decrease in tumor volume and serum PSA was not only due to a decrease in proliferation. We determined that fewer patients with prostate cancer metastases are ERG positive than patients with primary prostate cancer. Furthermore, we used RNASeq data and immunohistochemistry to identify ERG regulated genes impacted by ERG inhibition and identified a novel ERG regulated protein DCLK1 in prostate cancer. We did not identify mechanisms of resistance to ERG inhibition.

Papers:

*Papers in preparation:*

Abstracts:


Presentations:
Pacific Northwest SPORE Presentation - Identifying Common Molecular Features of ERG Positive Tumors in Primary and Castration Resistant Prostate Cancer, October 2013.

**Participants & Other Collaborating Organizations**

This grant was a Partnering PI grant with Dr. Aykut Uren at Georgetown. The PI at the University of Washington was Dr. Colm Morrissey and Co-I Dr. Eva Corey. There was no change in support during the project.
Appendices


