AWARD NUMBER: W81XWH-18-1-0200

TITLE: Mutational Landscape of the Y Chromosome and Prostate Cancer

PRINCIPAL INVESTIGATORS: Nikolaus D. Schultz, PhD

CONTRACTING ORGANIZATION: Sloan Kettering Institute for Cancer Research

REPORT DATE: July 2020

TYPE OF REPORT: Annual Report

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
JULY 2020	Annual	15 June 2019 – 14 June 2020

4. TITLE AND SUBTITLE
Mutational Landscape of the Y Chromosome and Prostate Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-18-1-0200

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Philip Kantoff
Nikolaus Schultz

E-Mail: kantoffp@mskcc.org; schultzn@mskcc.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Sloan Kettering Institute for Cancer Research
1275 York Avenue
New York, NY 10065

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development 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
Mortality from prostate cancer (PC), an estimated 33,330 deaths in 2020, is associated with development of aggressive and treatment-insensitive metastatic castration-resistant prostate cancer (mCRPC). We will investigate the status and role of Y chromosome (ChrY) genes in regulating drug sensitivity and mCRPC development and progression. Though ChrY loss in men is associated with increased risk of disease and mortality, the role of ChrY genes in regulating PC progression is poorly understood. To investigate the clinical impact of ChrY gene expression, we developed new methodology to analyze mutational variants of ChrY genes in PC patient cohorts, previously unsuccessful due to the high number of repetitive sequences and paralog families. Using a custom reference for each paralog family, our method increased ChrY read depth coverage to be on par with whole-exome sequencing allowing for normal/tumor variant calling. We also generated the first CRISPR/Cas9 library targeting human ChrY to further understand the role of individual ChrY genes in regulating antiandrogen treatment sensitivity and mCRPC development in PC models in vitro and in vivo. This multifaceted approach will potentially identify predictive markers for treatment sensitivity based on ChrY. These markers will allow for development of tailored therapies and serve as targets for drug development.

15. SUBJECT TERMS
Metastatic castration-resistant prostate cancer, Y chromosome, antiandrogen therapy, epigenetics, biomarkers, tumor suppressor, mutations, CRISPR/Cas9 library screening

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
Unclassified	Unclassified	Unclassified	Unclassified	29	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

MUTATIONAL LANDSCAPE OF THE Y CHROMOSOME AND PROSTATE CANCER

1. INTRODUCTION

Prostate cancer (PC) is the second most common cancer and second leading cause of cancer death among men in the United States with an estimated 33,330 deaths in 2020. PC associated mortality is attributed to the development of metastatic castration-resistant prostate cancer (mCRPC) which is characterized by its aggressiveness and poor response to treatment. Though loss of the Y chromosome (ChrY) in men has been associated with increased risk of disease and mortality, the role of ChrY genes in disease progression is poorly understood (Dumanski et al., 2016; Forsberg, 2017; Noveski et al., 2016). Our team presented the first report of a ChrY gene, *KDM5D*, which regulates tumor growth and docetaxel sensitivity through epigenetic modification of key cell cycle regulators and androgen receptor signaling (Komura et al., 2016; Komura et al., 2018). The study also reported the loss of *KDM5D* to be associated with increased mortality and aggressive disease in patient cohorts suggesting its role as a potential biomarker for mCRPC. Together, these studies highlight the urgency to further explore the role of ChrY genes in PC progression and further determine its mutational landscape to develop therapeutic targets as well as biomarkers and gene expression signatures which will allow physicians to predict drug response in patients and thereby prescribe effective treatment regiments. This multidisciplinary approach will help determine the clinical impact of ChrY genes on PC progression and treatment resistance.

2. KEYWORDS:

Prostate cancer, metastatic castration-resistant prostate cancer, Y chromosome, antiandrogen therapy, drug insensitivity, docetaxel, epigenetics, biomarkers, tumor suppressor, precision medicine, mutations, CRISPR/Cas9 library screening

3. ACCOMPLISHMENTS

What were the major goals of the project?

The major goals of the project as outlined in the SOW are:

SPECIFIC AIM 1: To determine the mutational landscape of the Y chromosome (ChrY) in men with prostate cancer in the SU2C/PCF, TCGA, and other cohorts

Major Task 1: Structural analysis of the Y chromosome (ChrY). This goal is 50% complete, in accordance with the SOW (1–36 months, responsible PIs and sites: Schultz, MSK; Van Allen, DFCI).

Major Task 1, Subtask 1: Identify the samples with ChrY loss. This goal is 50% complete, in accordance with the SOW (1–36 months, responsible PIs and sites: Schultz, MSK; Van Allen, DFCI).

Major Task 1, Subtask 2: Quantify the focality of ChrY loss. This goal is 50% complete, in accordance with the SOW (1–36 months, responsible PI and site: Schultz, MSK).

Major Task 1, Subtask 3: Assess mutual exclusivity of ChrY loss with genomic lesions in prostate cancer pathways. This goal is 25% complete, in accordance with the SOW (1–36 months, responsible PI and site: Schultz, MSK).

Major Task 1, Milestones: Define the extent of ChrY loss in metastatic prostate cancer and evaluate the association with clinically actionable signaling pathways This goal is 50% complete, in accordance with the SOW (At 36 months).

Major Task 2: Determine functional features associated with ChrY mutations. This goal is 50% complete, in accordance with the SOW (1–36 months, responsible PI and site: Schultz, MSK).

Major Task 2, Subtask 1: Identify the putative tumor suppressors that are inactivated on ChrY. This goal is 70% complete, in accordance with the SOW (1–36 months, responsible PI and site: Schultz, MSK).

Major Task 2, Subtask 2: Assess differential AR activity between samples that show ChrY loss and samples without alterations on ChrY. This goal is 50% complete, in accordance with the SOW (1–36 months, responsible PI and site: Schultz, MSK).

Major Task 2, Subtask 3: Correlation of ChrY loss with Gleason score and sample type. This goal is 50% complete, in accordance with the SOW (1–36 months, responsible PI and site: Schultz, MSK).

Major Task 2, Milestones: Define the mutational landscape of ChrY and determine if the LOY is significantly associated with disease risk. This goal is 50% complete, in accordance with the SOW (At 36 months).

SPECIFIC AIM 2: To perform genetic screening by CRISPR to identify ChrY genes that are of importance in the development of castration-resistant prostate cancer (CRPC) or resistance to androgen receptor (AR)–targeted therapies.

Major Task 3: Forward genetic screening of ChrY genes. This goal is 50% complete, in accordance with the SOW (1–12 months, responsible PIs and sites: Kantoff and Schultz, MSK).

Major Task 3, Subtask 1: Establish barcoded cell line model systems. Cell lines used: LNCaP, VCaP, LAPC4, LNCaP-Abl, and RWPE-1 (Kantoff Lab). This goal is 50%

complete, in accordance with the SOW (1–12 months, responsible PI and site: Kantoff, MSK).

Major Task 3, Subtask 2: Construct and optimize ChrY CRISPR/Cas9 library. This goal is 100% complete, in accordance with the SOW (1–12 months, responsible PI and site: Kantoff, MSK).

Major Task 3, Subtask 3: Screening of ChrY CRISPR/Cas9 library. Cell lines used: LNCaP, VCaP, LAPC4, LNCaP-Abl, and RWPE-1 (Kantoff Lab). This goal is 50% complete, in accordance with the SOW (1–24 months, responsible PI and site: Kantoff, MSK).

Major Task 3, Subtask 4: Sequencing analysis of sgRNAs and barcodes to identify target genes. This goal is 50% complete, in accordance with the SOW (1–24 months, responsible PIs and sites: Kantoff and Schultz, MSK).

Major Task 3, Milestones: Identify ChrY candidate genes that are of importance for development of CRPC and drug resistance and generate hypothetical models for further functional validations. This goal is 50% complete, in accordance with the SOW (At 24 months).

SPECIFIC AIM 3: To characterize the functional significance of genes involved in resistance in cell culture and animal models. We will confirm the functional importance of *KDM5D* and *UTY* in progression to CRPC. The clinical significance of these genes will be corroborated with an evaluation of the ChrY landscape in prostate cancer specimens.

Major Task 4: Perform functional validation of candidate genes including *KDM5D* and *UTY* in cell line models. This goal is 0% complete, in accordance with the SOW (1–36 months, responsible PIs and sites: Kantoff and Schultz, MSK; Gerke, MCC).

Major Task 4, Subtask 1: Apply specific gene silencing and/or over-expression (as relevant) in a broader panel of prostate cancer cell lines to assess the impact of the expression of a specific candidate gene on cell growth, invasiveness, and drug sensitivities with or without androgen treatment. This goal is 0% complete, in accordance with the SOW (1–36 months, responsible PI and site: Kantoff, MSK).

Major Task 4, Subtask 2: To identify the pathways/mechanisms that a specific gene involved in leading to the observed phenotypes by RNA-seq, ChIP-seq, or phospo-kinase screening. This goal is 0% complete, in accordance with the SOW (1–36 months, responsible PIs and sites: Kantoff and Schultz, MSK).

Major Task 4, Milestones: Determine molecular mechanisms/pathways underpinning the involvement of ChrY genes in prostate cancer progression This goal is 0% complete, in accordance with the SOW (At 36 months).

Major Task 5: Perform functional validation of candidate genes in mouse xenograft model. This goal is 0% complete, in accordance with the SOW (1–36 months, responsible PI and site: Kantoff, MSK).

Major Task 5, Subtask 1: Generate mouse xenografts using stable cell lines with inducible knockdown or overexpression of candidate genes. This goal is 0% complete, in accordance with the SOW (1–36 months, responsible PI and site: Kantoff, MSK).

Major Task 5, Subtask 2: Treat mouse xenografts with drug or vehicle and measure tumors. 10 NOD/SCID IL-2 gamma null mice will be used in each experimental or control arm [10 mice per group X 2 groups = 20 mice per experiment]; the number of experiments will be determined by the number of candidate genes identified in Specific Aim 2. This goal is 0% complete, in accordance with the SOW (1–36 months, responsible PI and site: Kantoff, MSK).

Major Task 5, Milestones: Determine the impact of gain and loss of a specific candidate gene on tumor growth in the absence of androgen or in response to a specific drug treatment in vivo. This goal is 0% complete, in accordance with the SOW (At 36 months).

Major Task 6: Clinical validation of the role of target genes on PC progression within PC cohorts. This goal is 5% complete, in accordance with the SOW (12–36 months, responsible PIs and sites: Kantoff and Schultz, MSK; Gerke, MCC).

Major Task 6, Subtask 1: Assess the clinical impact of *KDM5D* and *UTY* expression on prostate cancer outcomes in four different cohorts. This goal is 70% complete, in accordance with the SOW (12–24 months, responsible PIs and sites: Kantoff and Schultz, MSK; Gerke, MCC).

Major Task 6, Subtask 2: Validate the clinical impact of newly identified target genes on prostate cancer outcomes in four different cohorts. This goal is 20% complete, in accordance with the SOW (24–36 months, responsible PIs and sites: Kantoff and Schultz, MSK; Gerke, MCC).

Major Task 6, Milestones: Characterization of ChrY-associated genes that impact prostate cancer clinical outcome in the context of treatment with androgen deprivation therapy or AR-targeted drugs. This goal is 5% complete, in accordance with the SOW (At 36 months).

What was accomplished under these goals?

Major progress has been made towards the aims outlined in the original application, following the timeline indicated in the SOW.

SPECIFIC AIM 1: To determine the mutational landscape of the Y chromosome (ChrY) in men with prostate cancer in the SU2C/PCF, TCGA, and other cohorts

Major Activities

The analysis of the landscape of somatic copy-number alterations and somatic mutations of the ChrY in PC were supervised by the Schultz/Van Allen groups at MSK and DFCI. To circumvent the problem of numerous paralogs on ChrY, we previously developed a new method to specifically call mutations in paralogous genes, allowing us to map the landscape of mutations on the ChrY. We switched our focus from mutation calling to determining copy-number alterations; this is another challenge on the ChrY due to the fact that there is only a single copy, and all existing copy-number methods were written for chromosomes that exist in two copies.

Specific Objectives

The specific objectives proposed in the SOW were to 1) identify the samples with ChrY loss 2) quantify the focality of ChrY loss, 3) assess mutual exclusivity of ChrY loss with genomic lesions in prostate cancer pathways, 4) identify the putative tumor suppressors that are inactivated on ChrY, 5) assess differential AR activity between samples that show ChrY loss and samples without alterations on ChrY, 6) correlate ChrY alterations with Gleason score and sample type, and 7) define the mutational landscape of ChrY and determine if loss of the Y chromosome is significantly associated with disease risk.

Significant Results or Key Outcomes

While initially focusing on calling mutations in genes on ChrY, as reported in last year's report, we have now expanded our analysis to include copy-number alterations as well. In this analysis, we sought to identify tumor samples that had a ChrY loss in PC, as well as determine the clinical relevance of ChrY loss and the association with clinicopathological features using the PCF/SU2C metastatic prostate cancer cohort. In addition, we are now beginning to survey the frequency of ChrY loss across different cancer types in MSK-IMPACT, our internal targeted sequencing cohort, as well as The Cancer Genome Atlas (TCGA) cohort, using a modified FACETS algorithm and correlating results with clinical outcomes, sample type and cancer type. FACETS is an allele-specific copy number analysis tool which provides accurate ploidy and purity corrected integer copy-number calls from the sequencing data. The current version of the algorithm excludes the analysis of the ChrY. We modified the algorithm to include the allele specific calls from Y chromosome (https://github.com/BastienNguyen/facetsY). The integer copy-number calls were used to determine the presence of complete chromosome loss. We defined a sample to have complete chromosome loss if a chromosome had greater than 50% of total copy number (TCN) to be equal to zero.

The PCF/SU2C cohort comprises 444 patients with mCRPC. This dataset consists of mutation and copy-number (CNA) data, as inferred from whole exome sequencing (WES), clinicopathologic features and outcome data, as well as RNA-sequencing data from two different capture methods (Poly-A capture and SureSelect capture).

To identify samples with ChrY loss in this cohort, the segmented copy-number data, as derived from WES, were processed using the R package CNtools (v1.4). The mean segment data was calculated for each sample. The thresholds were set to log2 copy ratios <-0.2 as ChrY loss and >=-0.2 as no loss. Based on this, we identified 26% of the samples (117/443) with ChrY loss (**Figure 1**).

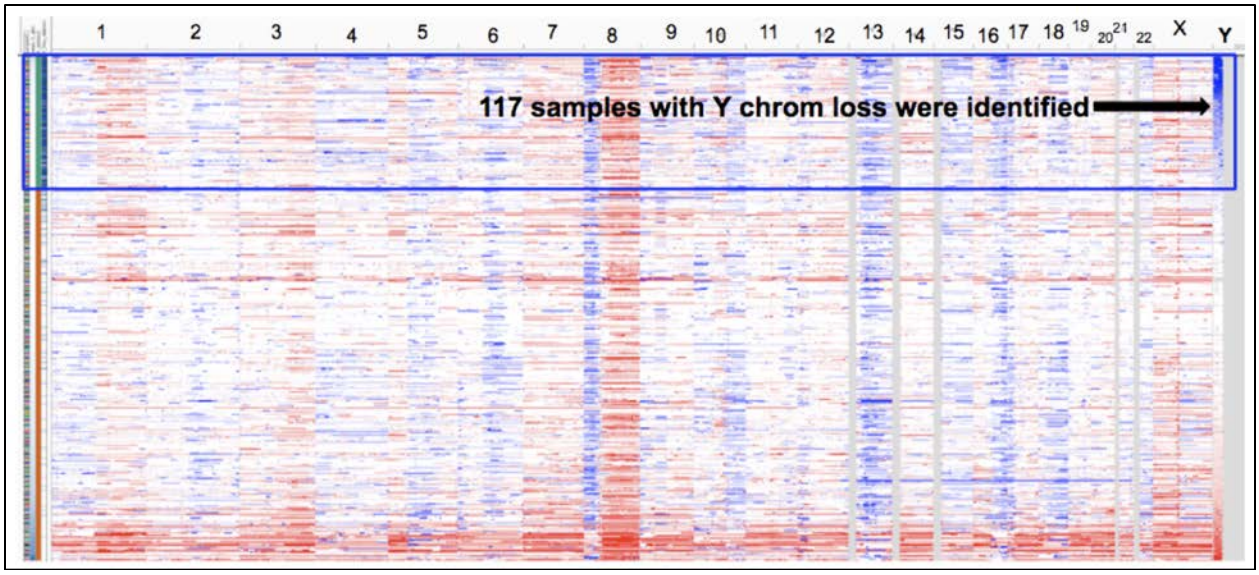

Figure 1. ChrY loss in the PCF/SU2C cohort.Samples are shown from top to bottom, chromosomes from left to right (1-22, x, y). Copy-number changes are shown by different colors: diploid regions are white, gains are red, losses/deletions are blue.

To assess the correlation of clinicopathological features according to ChrY loss, we evaluated features such as age, Gleason grade, prostate-specific antigen (PSA), abiraterone/enzalutamide exposure, pathological classification, etc. (**Table 1**). ChrY loss was associated with neuroendocrine (NE) and small cell histology ($p = 0.046$), and a higher frequency of ChrY loss samples were exposed to first-line next-generation androgen receptor signaling inhibitor ($p = 0.09$) (ARSI; abiraterone or enzalutamide). We did not observe an association with survival.

Table 1. Clinical and pathologic associations with chromosome Y loss.

Features		No loss	Y loss	P value
Total (n)		**326**	**117**	
Age at diagnosis	<=61Y.	148 (50.7%)	49 (49%)	
	> 61y.	144 (49.3%)	51 (51%)	0.861
Gleason Score	UNK	62 (19%)	23 (19.7%)	
	6	24 (7.4%)	5 (4.3%)	
	7	82 (25.2%)	25 (21.4%)	
	8+	158 (48.5%)	64 (54.7%)	0.484
PSA	<14	128 (48.5%)	53 (55.8%)	
	>14	136 (51.5%)	42 (44.2%)	0.271
Pathological Classification	Adenocarcinoma	247 (79.4%)	79 (73.1%)	
	Adenocarcinoma with NE features	8 (2.6%)	6 (5.6%)	
	Inadequate for diagnosis	41 (13.2%)	11 (10.2%)	
	Small Cell	15 (4.8%)	12 (11.1%)	0.046
OS Status	Deceased	69 (63.3%)	15 (55.6%)	
	Living	40 (36.7%)	12 (44.4%)	0.603
Abi/Enza exposure	Exposed	139 (42.6%)	64 (54.7%)	
	Naïve	168 (51.5%)	42 (35.9%)	
	On treatment	11 (3.4%)	8 (6.8%)	
	Unknown	8 (2.5%)	3 (2.6%)	0.009
Tissue site	Adrenal	0 (0%)	2 (1.7%)	
	Bone	119 (36.5%)	40 (34.2%)	
	Brain	0 (0%)	1 (0.9%)	
	Liver	46 (14.1%)	18 (15.4%)	
	Lymph Node	129 (39.6%)	38 (32.5%)	
	Other soft tissue	21 (6.4%)	8 (6.8%)	
	Prostate	7 (2.1%)	5 (4.3%)	
	Lung	3 (0.9%)	4 (3.4%)	
	Unknown	1 (0.3%)	1 (0.9%)	0.044
Center	Cornell	50 (15.5%)	23 (20.2%)	
	DFCI	56 (17.4%)	20 (17.5%)	
	Karmanos	4 (1.2%)	3 (2.6%)	
	Michigan	60 (18.6%)	14 (14%)	
	MSK	52 (16.1%)	25 (21.9%)	
	RoyalMarsden	32 (9.9%)	14 (12.3%)	
	Washington	68 (21.2%)	13 (11.4%)	0.114

A total of 269 patients had RNA-Seq data using the Poly-A capture method, and 211 patients had RNA-Seq data from SureSelect capture, out of which 26% of patients (n=71) in the Poly-A capture cohort and 23% of patients (n=49) in the SureSelect cohort had ChrY loss. Differential expression analysis was performed separately in both data sets, and the Wilcoxon test was used to detect significant expression differences between the two groups. In the samples with PolyA capture, only 13 out of 13870 (0.09%) genes were significantly differentially expressed between the two groups. Out of these, 11 genes were encoded on the ChrY (**Figure 2A**), validating the copy-number detection method. Among the SureSelect samples, 11 out of 18509 (0.06%) genes were differentially expressed in the ChrY loss group (**Figure 2A**). Previously published reports (Komura et al., J Clin Invest. 2018, and Komura et al., PNAS 2016) have shown that the expression of KDM5D, a histone demethylase located on ChrY, is associated with a more aggressive phenotype and poorer prognosis. We noticed that *KDM5D* expression was significantly lower in the ChrY loss group compared to the no loss group, in both methods (p<0.001) (**Figure 2B**). We assessed the correlation of expression levels with copy-number using both methods for *KDM5D* (one tailed dosage effect) (**Figure 2C**). We also performed a gene set enrichment analysis (GSEA) with the GSEA tool, using the GSEA-C2 curated dataset. Several cell cycle and DNA replication pathways were upregulated, suggesting chromosome instability, and several histone and chromatin remodelling pathways were downregulated in the ChrY loss group.

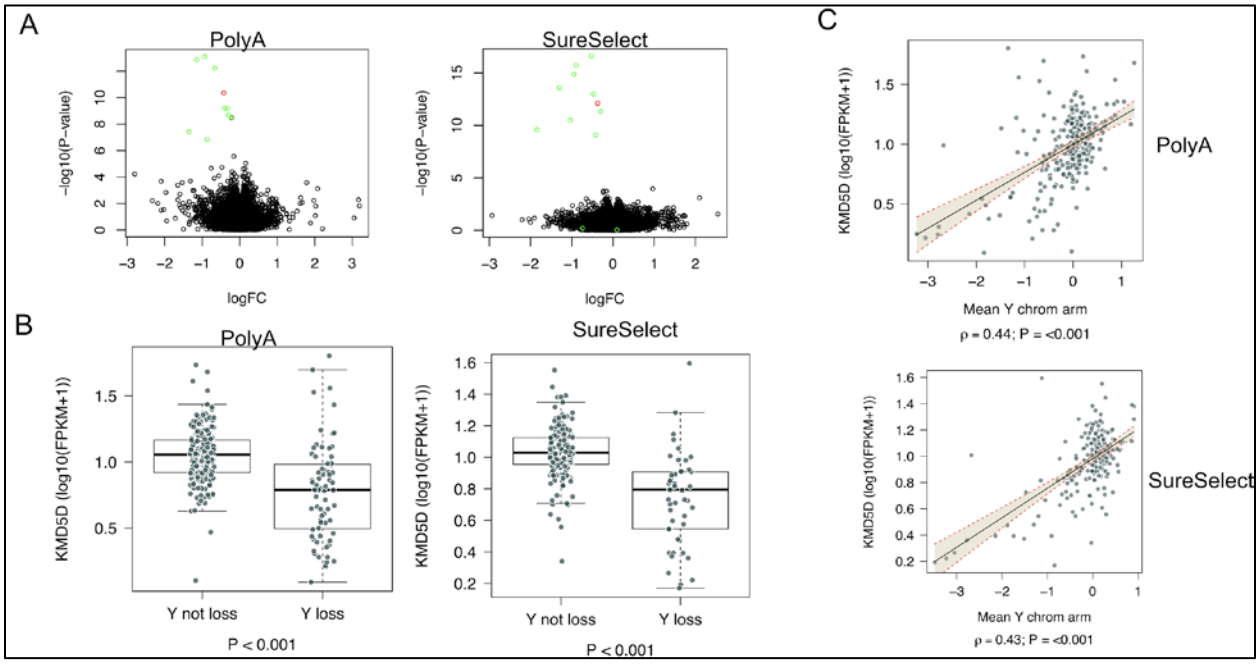

Figure 2. RNA-Seq analysis of Poly A and SureSelect Capture methods from the PCF/SU2C cohort. A) Differential expression analysis of ChrY loss vs no loss by Wilcoxon test using log10(FPKM+1). Green dots indicate differential expressed genes with FDR <0.05. B) KDM5D expression levels (log10(FPKM+1)) between ChrY loss vs no loss group. C) Correlation of expression level (log10(FPKM+1)) vs mean copy number of ChrY (Spearman correlation).

In addition, we performed a genomic analysis to compare the ChrY loss and no loss groups. ChrY loss was associated with a higher fraction of genome alteration ($p<0.001$); however, it was not associated with differences in tumor mutation burden (Figure 3A). We also investigated the difference in the prevalence of specific genomic alterations by ChrY loss status. Strikingly, we found that AR mutation was less frequently observed in samples with ChrY loss. Only 2/117 (1.7%) samples had an AR mutation whereas 45/326 (13.8%) samples in the no loss group had an AR mutation ($p=0.00007$) (**Figure 3B**). Furthermore, we analyzed the prevalence of ten oncogenic signaling pathways (Sanchez-Vega et al., Cell 2018): cell cycle, Myc, Hippo, Notch, PI3K, TGF-Beta, WNT, p53, Nrf2, and RTK-RAS. We did not observe any significant difference based on pathway level alterations between the two groups (**Figure 3C**).

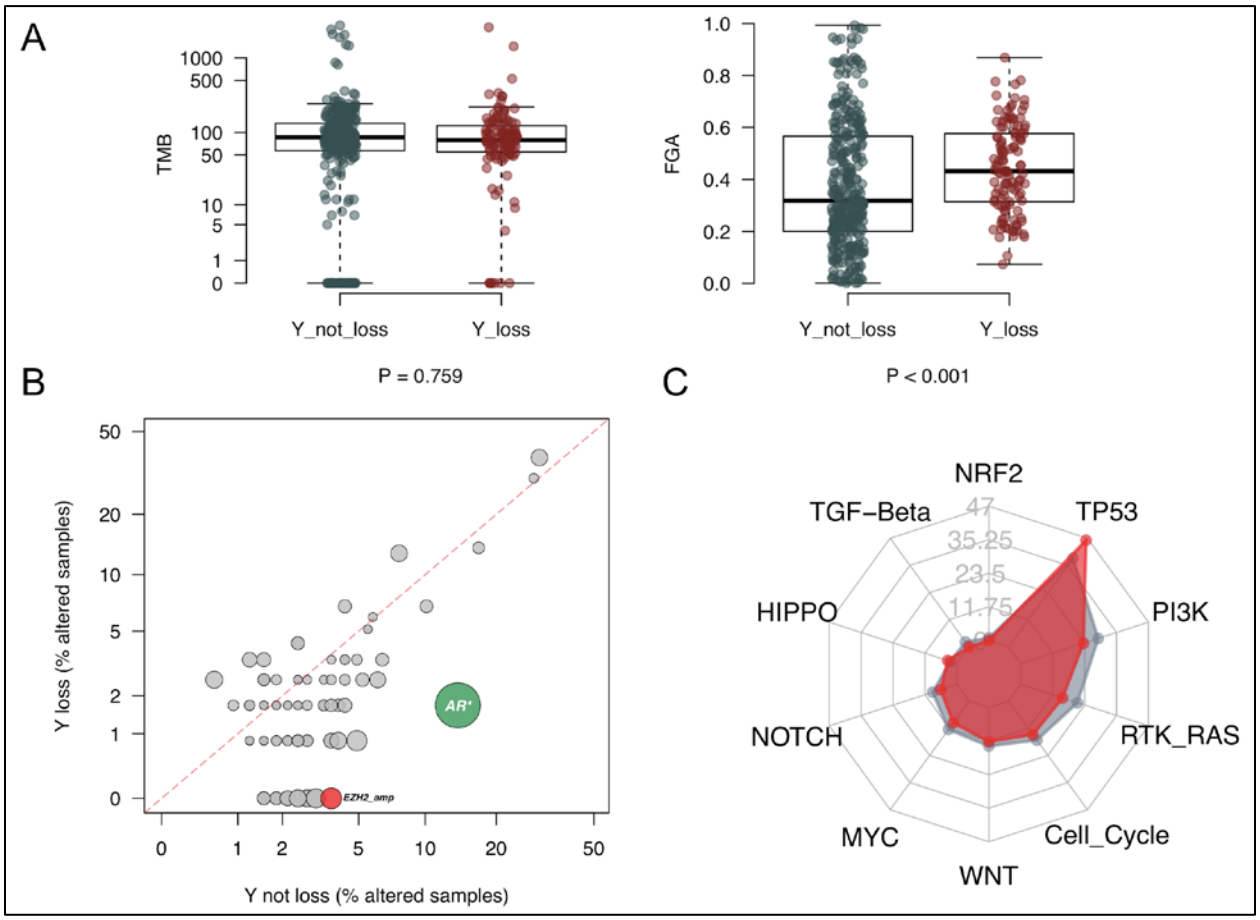

Figure 3. Genomic analysis of ChrY loss samples in SU2C cohort. A) tumor mutation burden and fraction of genome alteration in the ChrY loss vs no loss groups. B) Gene enrichment analysis between ChrY loss vs no loss groups. AR mutations were significantly less frequently observed in samples with ChrY loss. C) Oncogenic pathway level alteration comparison between ChrY loss vs no loss groups using curated pathways templates.

Other Achievements
Nothing to report

SPECIFIC AIM 2: To perform genetic screening by CRISPR to identify ChrY genes that are of importance in the development of castration-resistant prostate cancer (CRPC) or resistance to androgen receptor (AR)–targeted therapies.

Major Activities
Genetic screening by CRISPR will be conducted in the Kantoff group at MSK. As proposed in the SOW, we have completed generation of ChrY targeting CRISPR/Cas9 virus library. We are in the process of generating and screening cell lines expressing the library.

Specific Objectives
The objectives proposed in the SOW were to: 1) establish barcoded cell line model systems; 2) design and construct ChrY CRISPR/Cas9 library; 3) optimize the CRISPR/Cas9 library in target cell lines; and 4) conduct positive selection screens with the ChrY CRISPR/Cas9 library to identify genes responsible for mCRPC development and antiandrogen resistance.

Significant Results or Key Outcomes
We have successfully generated a ChrY CRISPR/Cas9 virus library. The pooled library is constructed to be used in a lentiviral system allowing high transduction efficiency. Positive genetic screens for anti-androgen resistance have been concluded for LNCAP and RWPE1 cells expressing this ChrY CRISPR/Cas9 library. These samples have been submitted for sequencing. Sequencing results were delayed due to sequencing core-facility shutdown following COVID-19 related personnel reorganization.

Other Achievements
In addition to spectral karyotyping in target cell lines, we also conducted XY FISH on patient-derived PC organoids (Gao et al., 2014). We assayed ChrY gene expression using qPCR and immunoblotting to gain an understanding of the ChrY expression landscape in patient-derived PC models. As shown in **Figure 4** all patient derived organoids had a Chr Y. This validates the patient-derived organoids as a potential model to conduct further positive-selection screens using out CRISPR/Cas9 library to identify regulators of anti-androgen sensitivity. It is important to consider that XY FISH is not a measure of function and presence of Chr Y in these organoids does not equal expression of ChrY genes.

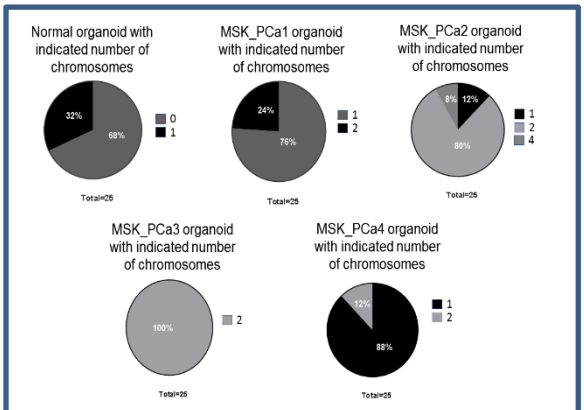

Figure 4. XY paint analysis or patient-derived prostate cancer organoids

REFERENCES

1. Dumanski JP, Lambert JC, Rasi C, Giedraitis V, Davies H, Grenier-Boley B, Lindgren CM, Campion D, Dufouil C, European Alzheimer's Disease Initiative I, Pasquier F, Amouyel P, Lannfelt L, Ingelsson M, Kilander L, Lind L, Forsberg LA. Mosaic Loss of Chromosome Y in Blood Is Associated with Alzheimer Disease. Am J Hum Genet 2016;98:1208-19. PMCID: PMC4908225
2. Forsberg LA. Loss of chromosome Y (LOY) in blood cells is associated with increased risk for disease and mortality in aging men. Human Genetics 2017;136:657-63.
3. Gao D, Vela I, Sboner A, Iaquinta PJ, Karthaus WR, Gopalan A, Dowling C, Wanjala JN, Undvall EA, Arora VK, Wongvipat J, Kossai M, Ramazanoglu S, Barboza LP, Di W, Cao Z, Zhang QF, Sirota I, Ran L, MacDonald TY, Beltran H, Mosquera JM, Touijer KA, Scardino PT, Laudone VP, Curtis KR, Rathkopf DE, Morris MJ, Danila DC, Slovin SF, Solomon SB, Eastham JA, Chi P, Carver B, Rubin MA, Scher HI, Clevers H, Sawyers CL, Chen Y. Organoid cultures derived from patients with advanced prostate cancer. Cell 2014;159:176-187. PMCID: PMC4237931
4. Komura K, Jeong SH, Hinohara K, Qu F, Wang X, Hiraki M, Azuma H, Lee GS, Kantoff PW, Sweeney CJ. Resistance to docetaxel in prostate cancer is associated with androgen receptor activation and loss of KDM5D expression. Proc Natl Acad Sci U S A 2016;113:6259-64. PMCID: PMC4896695
5. Komura K, Yoshikawa Y, Shimamura T, Chakraborty G, Gerke TA, Hinohara K, Chadalavada K, Jeong SH, Armenia J, Du SY, Mazzu YZ, Taniguchi K, Ibuki N, Meyer CA, Nanjangud GJ, Inamoto T, Lee GM, Mucci LA, Azuma H, Sweeney CJ, Kantoff PW. ATR inhibition controls aggressive prostate tumors deficient in Y-linked histone demethylase KDM5D. J Clin Invest 2018;128:2979-95. PMCID: PMC6025984
6. Noveski P, Madjunkova S, Sukarova Stefanovska E, Matevska Geshkovska N, Kuzmanovska M, Dimovski A, Plaseska-Karanfilska D. Loss of Y Chromosome in Peripheral Blood of Colorectal and Prostate Cancer Patients. PLoS One 2016;11:e0146264. PMCID: PMC4706411

SPECIFIC AIM 3: To characterize the functional significance of genes involved in resistance in cell culture and animal models. We will confirm the functional importance of *KDM5D* and *UTY* in progression to CRPC. The clinical significance of these genes will be corroborated with an evaluation of the ChrY landscape in prostate cancer specimens.

Major Activities

As per the timeline in the SOW, work on Specific aim 3 will begin in month 24 following identification of candidate genes from Specific aim 2.

Specific Objectives

The specific objectives described in the SOW were to: 1) Perform functional validation of candidate genes including KDM5D and UTY in cell lines models; 2) identify pathways/mechanisms that a specific gene is involved in leading to the observed phenotype

by RNA-seq, CHIP-seq, or phosphor-kinase screening; 3) generate mouse xenografts using stable cell lines with inducible knockdown or overexpression of candidate genes and treat them with drug or vehicle to measure tumors followed by molecular characterization, and 4) assess the clinical impact of KDM5D, UTY, and candidate gene expression on PC outcomes in clinical datasets from the following patient cohorts: SUC2/PCF cohort, TCGA cohort, Harvard Prostate Tumor cohorts (Health Professionals Follow-Up and Physician's Health

Significant Results or Key Outcomes

Nothing to report.

Other Achievements

Nothing to report.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

The project is currently underway in accordance with the timeline outlined in the SOW.

The ChrY CRISPR/Cas9 library has been generated. Positive genetic screens for LNCaP and RWPE-1 cells expressing this CRISPR/Cas9 library have been completed and samples have been submitted for next-generation sequencing. We will continue genetic screens to identify regulators of anti-androgen resistance in LAPC4 and LNCaP-Abl cell line models.

As outlined in Specific Aim 3, functional validation of candidate genes and xenograft studies will be conducted in the Kantoff and Schultz groups at MSK. Clinical validation of candidate genes in patient cohorts will be conducted by the Kantoff and Schultz groups at MSK and the Gerke group at Moffit Cancer Center.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS

a. **Changes in approach and reasons for change**

The initial narrative proposed RWPE-1, LNCaP, LAPC4, LNCaP-Abl and VCaP as cell line systems. Our efforts to optimize lentiviral transduction protocols in VCaP cells have resulted in sub-optimal selection. The low transfection efficiency of these cells results in them being unsuitable to conduct shRNA and CRISPR screens. We have therefore excluded VCaP cells from our analysis. This will not affect the power of our analysis as cell lines–RWPE-1, LNCaP, LAPC4 and LNCaP-Abl are sufficient and present enough ChrY heterogeneity for our purposes.

b. **Actual or anticipated problems or delays and actions or plans to resolve them**

We experienced a delay of 3 months because of a mandated shutdown of facilities because of the COVID-19 pandemic. This has not significantly affected our timeline and our current accelerated pace is quickly compensating for past delays.

c. **Changes that had a significant impact on expenditures**

Nothing to report.

d. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to report.

e. **Significant changes in use or care of human subjects**

Nothing to report.

f. **Significant changes in use or care of vertebrate animals.**

Nothing to report.

g. **Significant changes in use of biohazards and/or select agents**

Nothing to report.

6. PRODUCTS

a. **Publications, conference papers, and presentations**

Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers, and presentations.

Nothing to report.

b. **Website(s) or other Internet site(s)**

Nothing to report.

c. **Technologies or techniques**

Nothing to report.

d. **Inventions, patent applications, and/or licenses**

Nothing to report.

e. **Other Products**.

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. **What individuals have worked on the project?**

Philip Kantoff, Initiating Principal Investigator; no change

Nikolaus Schultz, Collaborating Principal Investigator; no change

Bastien Nguyen, Research Fellow, no change

Subhiksha Nandakumar, Bioinformatic Engineer, no change

Eliezer Van Allen, Principal Investigator; no change

Eric Kofman, Computational Biologist; no change

Rahim Hirani, Research Technician; no change

Name:	Sai Harisha Rajanala
Project Role:	Research Fellow
Researcher Identifier (e.g. ORCID ID):	0000-0002-7096-3756
Nearest person month worked:	11 **[last reporting period was 5]**
Contribution to Project:	Dr. Rajanala has replaced Yuki Yoshikawa, MD. She will conduct genetics screens to identify regulators of antiandrogen therapy sensitivity using generated CRISPR/Cas9 screens. Dr. Rajanala will also conduct functional validation of candidate genes following positive genetic screens.
Funding Support:	Institutional

Name:	Travis Gerke
Project Role:	Site Principal Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-9500-8907
Nearest person month worked:	1
Contribution to Project:	Dr. Gerke will be responsible for the analysis of gene expression data from the

	Health Professionals Follow-up Study (HPFS) and the Physicians' Health Study (PHS). Additionally, he will broadly assist with the epidemiologic and statistical interpretation of findings and manuscript writing
Funding Support:	H. Lee Moffitt Cancer Center and Research Institute, Inc.

b. **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

KANTOFF, PHILIP
New Grants Since Last Submission
Title: P01 CA228696 The Impact of DNA Damage Repair Abnormalities in Prostate Cancer
Role: Principal Investigator
Sponsoring Agency: NIH/NCI **Effort:** 0.6 cal (Admin Core); 0.6 cal (Project 1)
Level of Funding: $374,642 **Dates:** 9/1/2019–8/31/2024
Agency Contact: Kelly Filipsky
Agency Contact Information: (Email) kelly.filipski@nih.gov
Goals/Aims: The overarching goal of "The Impact of DNA Damage Repair Abnormalities in Prostate Cancer" is to increase our understanding of DNA repair pathways and the abnormalities therein in high risk localized and oligometastatic PC. We aim to optimize the therapeutic approach to patients who have functional DDR aberrations, to detect and treat potentially lethal disease early, and to improve outcomes for patients and their relatives who carry DDR aberrations.
Specific Aim1. To determine the association between long-term clinical outcome and pathogenic germline and somatic variants in DDR genes across different ethnic groups
Specific Aim 2. To develop treatment strategies for patients with high-risk localized and oligometastatic PC with germline or somatic alterations in DDR pathways
Specific Aim 3. To evaluate the functional and clinical significance of specific alterations in DDR genes in the context of other alterations present
Overlap: No overlap

Title: PC180533 Identification and Characterization of Novel Targetable Mechanisms Associated with Homologous Recombination Repair Defects in mCRPC Patients
Role: Principal Investigator
Sponsoring Agency: CDMRP **Effort:** 0.6 calendar
Level of Funding: $196,549 **Dates:** 8/1/2019–7/31/2022
Goals/Aims: Aim 1: To investigate WNK1 kinase as a potential therapeutic target for mCRPC that harbors BRCA2-RB1 codeletion. Aim 2: To investigate the combined effect of Src and PARP inhibition in model systems of mCRPC with HRR defects. Aim 3: To use integrative genetic screening to identify and validate kinases with potential to overcome resistance to PARPi-based therapy.

Overlap: No overlap

Grants Terminated Since Last Submission
Title: GC232671 Prostate Cancer Outcomes: An International Registry to Improve Outcomes in Men with Advanced Prostate Cancer (IRONMAN Registry)
Role: Principal Investigator
Sponsoring Agency: Movember Canada **Effort:** 0.60 calendar
Level of Funding: $43,076 **Dates:** 11/30/2016–11/29/2019
Agency Contact: Paul Villanti
Agency Contact Information: (Email) info.us@movember.com
Prostate Cancer Outcomes: An International Registry to Improve Outcomes in Men with Advanced Prostate Cancer (IRONMAN Registry)
Goals/Aims: The overarching mission of the Prostate Cancer Outcomes: An International Registry to improve outcomes in men with advanced prostate cancer is to provide an evidence basis for improving the patient management, experiences, and outcomes among men with advanced prostate cancer internationally.
Overlap: No overlap

Title: W81XWH1810330 Cholesterol Synthesis and Statin Therapy in Prostate Cancer
Role: Mentor
Sponsoring Agency: CDMRP **Effort:** 0.60 calendar
Level of Funding: $107,564 **Dates:** 7/1/2018–6/30/2020
Agency Contact: Jennifer Shankle
Agency Contact Information: (Email) Jennifer.e.shankle.civ@mail.mil
Goals/Aims: To assess cholesterol biosynthesis as a prognostic biomarker in metastatic prostate cancer and as a predictive biomarker for statin therapy.
Aim 1: To validate intratumoral cholesterol biosynthesis as a prognostic factor for lethality among patients with localized prostate cancer.
a) To validate IHC for HMGCR protein expression in archival prostate cancer tissue. We will generate HMGCR quantification cut-offs and compare with SQLE mRNA measured in a subset of patients.
b) To define the risk of lethal prostate cancer associated with HMGCR protein expression in tumor tissue at cancer diagnosis. We will quantify the risk of metastasis and cancer death after prostatectomy (HPFS, PHS cohorts) and in a watchful waiting setting (SWWS cohort) to establish HMGCR as a protein biomarker.
Aim 2: To assess cholesterol biosynthesis as a predictive biomarker for ADT resistance.
a) To quantify the risk of development of CRPC on ADT associated with HMGCR protein expression. We will test whether HMGCR expression at cancer diagnosis predicts duration of response to ADT (SWWS). Aim 3: To assess cholesterol biosynthesis as a prognostic biomarker in metastatic prostate cancer and as a predictive biomarker for statin therapy.
a) To assess the prognostic value of SQLE mRNA expression in metastatic CRPC. We hypothesize that high SQLE mRNA expression is associated with poor overall survival in mCRPC (SU2C/PCF cohort).
b) To assess the predictive value of SQLE mRNA for the association of statin therapy and overall survival in metastatic CRPC (SU2C/PCF cohort).

Overlap Statement: No overlap

SCHULTZ, NIKOLAUS

New Grants Since Last Submission

Title: P01 CA225639, The Impact of DNA Damage Repair Abnormalities in Prostate Cancer (Sequencing Core)
Role: Co-Investigator
Sponsoring Agency: NIH/NCI **Effort:** 0.6 calendar
Level of Funding: $392,154 **Dates:** 9/1/2019–8/31/2024
Agency Contact: Shane Woodward
Agency Contact Information: (Email): woodwars@mail.nih.gov
Goals/Aims: Alterations in genes that help repair damaged DNA are seen in 20 25% of men with metastatic castration-resistant prostate cancer, the lethal form of prostate cancer. We have assembled a multidisciplinary team to increase our understanding of the role these alterations play in prostate cancer, to evaluate the usefulness of testing for these alterations, to develop new strategies to treat the potentially lethal form of the disease early, and to improve outcomes for patients and their relatives who carry inherited alterations in these genes.
Project Goals/Specific Aims: The overarching objectives of the Sequencing Core are 1) to perform prospective and retrospective molecular analysis of prostate tumors and normal DNA to facilitate the aims of the P01 research program and 2) to facilitate sharing of genomic data and linked clinical annotation among the P01 investigators and with the broader scientific community. Specific Aim 1. To conduct deep sequencing of known DDR pathways and whole exome sequencing of prostate tumors and paired germline DNA from clinically annotated cohorts of men diagnosed with localized high-risk or metastatic prostate cancer treated with standard of care and/or the PARP inhibitor niraparib. Specific Aim 2: To explore mechanisms of treatment resistance by analyzing tumors and cell-free DNA before and after treatment with niraparib. Specific Aim 3: To facilitate data sharing and scientific collaboration within the P01, with the broader research community, and with NCI.
Overlap: None

Title: W81XWH-19-1-0449, Clinical-grade tumor and longitudinal cell-free DNA/RNA molecular profiling to optimize treatment in lethal non-castrate prostate cancer
Role: Co-Investigator
Sponsoring Agency: CDMRP **Effort:** 0.24 calendar
Level of Funding: $249,078 **Dates:** 8/1/2019–7/31/2022
Agency Contact: Nrusingha Mishra
Agency Contact Information: (Email): Nrusingha.Mishra.civ@mail.mil
Goals/Aims: Develop a cell-free RNA profiling assay to study tumor-derived fusions and transcriptome in blood plasma.
Overlap: None

Title: Phase II maintenance trial of nivolumab for newly diagnosed primary CNS lymphoma patients with persistent circulating tumor DNA in the cerebrospinal fluid after completion of methotrexate-based first-line chemotherapy
Role: Bioinformatician
Sponsoring Agency: Cycle for Survival **Effort:** 0.6 calendar
Level of Funding: $195,000 **Dates:** 9/1/2019–8/31/2021
Agency Contact: Kathleen Bourke
Agency Contact Information: (Email): bourkek@mskcc.org
Goals/Aims: We will assess clinical efficacy of immune checkpoint inhibition as maintenance strategy in primary central nervous system lymphoma (PCNSL) with persistent circulating-tumor DNA (ctDNA) in the cerebral spinal fluid (CSF) after successful completion of first-line chemotherapy. We will establish ctDNA in the CSF as a diagnostic tool for PCNSLs, identify minimal residual disease in PCNSL by genomic profiling of CSF and prevent early relapse by checkpoint inhibitor maintenance therapy
Overlap: None

Title: Retrieval of clinical data elements for the identification of genomic predictors of outcome and treatment response in cancer
Role: Principal Investigator
Sponsoring Agency: MSK MIND **Effort:** 1.20 calendar
Level of Funding: $200,000 **Dates:** 1/1/2020–12/31/2022
Agency Contact: Christie Park
Agency Contact Information: (Email): ParkC1@mskcc.org
Goals/Aims: We propose to develop new methods to retrieve specific clinical data elements from the electronic medical records at MSK and make them available in a structured format. We will focus on the data elements most relevant to treatment, response and disease progression. We will employ a variety of methods, ranging from simple pattern matching and natural language processing to state-of-the-art machine learning methods.
Overlap: None

VAN ALLEN, ELIEZER

New Grants Since Last Submission
Title: P01 CA228696 The Impact of DNA Damage Repair Abnormalities in Prostate Cancer – Administrative Core
Role: Core Leader
Sponsoring Agency: NIH/NCI **Effort:** 0.6 calendar
Level of Funding: $334,555 **Dates:** 9/1/2019–8/31/2024
Agency Contact: Kelly Filipsky
Agency Contact Information: (Email) kelly.filipski@nih.gov
Goals/Aims: The overarching goal of "The Impact of DNA Damage Repair Abnormalities in Prostate Cancer" is to increase our understanding of DNA repair pathways and the abnormalities therein in high risk localized and oligometastatic PC. We aim to optimize the therapeutic approach to patients who have functional DDR

aberrations, to detect and treat potentially lethal disease early, and to improve outcomes for patients and their relatives who carry DDR aberrations.
Specific Aim1. To determine the association between long-term clinical outcome and pathogenic germline and somatic variants in DDR genes across different ethnic groups
Specific Aim 2. To develop treatment strategies for patients with high-risk localized and oligometastatic PC with germline or somatic alterations in DDR pathways
Specific Aim 3. To evaluate the functional and clinical significance of specific alterations in DDR genes in the context of other alterations present
Overlap Statement: No overlap

Title: R37 CA222574, Molecular origins and evolution to chemoresistance in germ cell tumors
Role: Principal Investigator
Sponsoring Agency: NIH/NCI **Effort:** 2.28 calendar
Level of Funding: $2,035,875 **Dates:** 2/1/2018–1/31/2023
Agency Contact: Ian M. Fingerman
Agency Contact Information: (Email): fingerma@mail.nih.gov
Goals/Aims: Aim 1: To define the genetic defects associated with reciprocal loss of heterozygosity in primary germ cell tumors. Aim 2: To identify the molecular features of tumor evolution leading to chemoresistant germ cell tumors. Aim 3: To assess the clinical utility of pluripotency markers as prognostic for GCT outcomes**.**
Overlap: None

Title: U24 CA224316, Cancer Immunologic Data Commons (CIDC)
Role: Co-Investigator
Sponsoring Agency: NIH/NCI **Effort:** 0.24 calendar
Level of Funding: $130,000 **Dates:** 9/30/2017–6/30/2022
Agency Contact: Magdelena Thurin
Agency Contact Information: (Email): thurinm@mail.nih.gov
Goals/Aims: The goals of this project are to 1) coordinate with the CIMAC and Laboratory Coordinating Committee (LCC) to harmonize assay protocols and data format standards, 2) develop a centralized data repository and management system, and coordinate CIMAC data submission to the CIDC, 3) Develop uniform bioinformatics processing pipelines and computing infrastructure for computation intensive analyses for the CIMACs and the larger research community, 4) Provide bioinformatics algorithms to enable integrative and correlative analysis of CIMAC as well as integrate other accessible databases and resources for biomarker discovery, 5) Develop centralized role-based data access functions with advanced programming interface to enable sharing of IMAC data, 6) Develop interactive web visualization functions to enable investigators and the immunology communities to examine the CIMAC data, and 7) Coordinate within the CIMACs-CIDC Network logistic and scientific activities for biomarker discovery and validation.
Overlap: None

Title: R21 CA242861, A statistical framework to systematically characterize cancer driver mutations in noncoding genomic regions
Role: Principal Investigator
Sponsoring Agency: NIH/NCI **Effort:** 0.24 calendar
Level of Funding: $425,867 **Dates:** 7/1/2019–6/30/2021
Agency Contact: David J. Miller
Agency Contact Information: (Email): david.miller3@nih.gov
Goals/Aims: Overall, this proposal will enable a systematic interrogation of the landscape of noncoding driver mutations and assess the impact of different mutational processes on the clinical response to immune checkpoint therapies. Aim 1: To define the landscape of noncoding cancer driver mutations using nucleotide context. Aim 2: To determine the impact of passenger mutation distribution patterns on neoantigen development and response to cancer immunotherapy.
Overlap: None

Title: Analysis of Cryptic Variants in Cancer Genomes using Long Read Sequencing - Johns Hopkins University Sub
Role: Co-Investigator
Sponsoring Agency: Mark Foundation **Effort:** 0.18 calendar
Level of Funding: $49,996 **Dates:** 10/1/2019–9/30/2020
Goals/Aims: We will share DNA specimens from our outlier cancer families project with the Schatz Lab to perform long read genome sequencing. We will then collaborate to identify structural variants that may contribute to the familial inheritance phenotypes.
Overlap: None

Title: PCF Challenge Award - A genomics-guided clinical interpretation and translational discovery engine for prostate cancer
Role: Principal Investigator
Sponsoring Agency: Prostate Cancer Foundation **Effort:** 0.36 calendar
Level of Funding: $1,000,000 **Dates:** 9/1/2019–8/31/2021
Goals/Aims: The specific aims of this proposal are: 1) To develop deep learning algorithms for molecular discovery in large harmonized cohorts of primary and metastatic prostate cancer; 2) To predict clinical outcomes for MPC patients using natural language processing and deep learning models applied to both clinical text and molecular data; and 3) To develop a prostate cancer clinical trial decision support framework and determine the feasibility of delivering molecular data for MPC patients at the point of care.
Overlap: None

Title: Characterization of non-coding driver mutations based on the 3D cancer genome structure - Carnegie Mellon University Sub
Role: Co-Investigator
Sponsoring Agency: Mark Foundation **Effort:** 0.18 calendar
Level of Funding: $125,000 **Dates:** 10/1/19–9/30/2020

Goals/Aims: We will develop computational methodology for identification of noncoding mutations in cancer genomes. We will collaborate with the Ma Lab to map these candidates to 3D structures using multi-modal data sets from experimental systems.
Overlap: None

Title: Emerging Leader Award, Convergence of machine learning and translational genomics for prostate cancer precision medicine
Role: Principal Investigator
Sponsoring Agency: Mark Foundation **Effort:** 0.12 calendar
Level of Funding: $750,000 **Dates:** 1/1/2020–12/31/2022
Goals/Aims: The specific aims of this proposal are: 1) To develop deep learning algorithms for molecular discovery in large harmonized cohorts of primary and metastatic prostate cancer; 2) To predict clinical outcomes for MPC patients using natural language processing and deep learning models applied to both clinical text and molecular data; and 3) To develop a prostate cancer clinical trial decision support framework and determine the feasibility of delivering molecular data for MPC patients at the point of care.
Overlap: None

Title: W81XWH2010057, Molecular and genetic determinants of response to carboplatin with or without an ATR inhibitor (M6620) in mCRPC
Role: Co-Investigator
Sponsoring Agency: DoD **Effort:** 0.12 calendar
Level of Funding: $26,287 **Dates:** 2/15/2020-2/14/2023
Goals/Aims: Aims: 1) to correlate genetic and molecular features from pre-treatment tumor biopsy and cfDNA with clinical outcomes for M6620+carboplatin and docetaxel+carboplatin; 2) to discover genetic correlates of resistance to therapy from end-of-study cfDNA specimens and optional tumor biopsies; 3) to functionally characterize novel genetic alterations identified in pre- and post-treatment specimens using pre-clinical model systems.
Overlap: None

Grants Terminated Since Last Submission
Title: Deep learning models to accelerate translational cancer genomics
Role: Principal Investigator
Supporting Agency: Brown Performance Group **Effort**: 0.18 calendar months
Level of Funding: $200,000 **Dates:** 6/4/2018–6/3/2020
Agency Contact: Audrey Cook
Agency Contact Information: acook@brownperformance.com
Goals/Aims: Aim 1. To develop a biologically informed machine learning model for outcome prediction and hypothesis generation using cancer genomics. Aim2. To apply P-net to translational and clinical cancer genomics challenges and identify novel predictive markers.
Overlap Statement: No overlap

Title: Phase II: Broad Institute Cancer Model and Development Center
Role: Investigator
Supporting Agency: Broad Institute/NCI Effort: 0.60 calendar
Level of Funding: $12,134 Dates: 12/1/2018–5/31/2020
Agency Contact: David Hoffman (Broad Institute)
Agency Contact Information: hoffmann@broadinstitute.org
Goals/Aims: The Broad CMDC has three goals: 1) Achieve industry scale: Produce 100 patient-derived models per year with a focus on cancer types currently lacking precision therapies Gastroesophageal, Pancreas, Glioblastoma and Pediatric Solid Tumors); 2) Innovate to maximize efficiency: Iteratively optimize and refine workflows to improve success rates, maximize efficiencies and reduce costs; 3) Succeed for rare cancers: Demonstrate proof-of-concept for how to overcome key bottlenecks in rare and underrepresented cancers.
Overlap Statement: No overlap

GERKE, TRAVIS

New Grants Since Last Submission
Title: R21 CA234787, Predicting patient-specific responses to personalize androgen deprivation therapy for prostate cancer
Role: Co-Investigator
Sponsoring Agency: NIH/NCI **Effort:** 0.6 calendar
Level of Funding: $152,399 **Dates:** 12/1/2018–11/30/2020
Agency Contact: Miguel Ossandom
Agency Contact Information: (Email): ossandom@mail.nih.gov
Goals/Aims: We will investigate PCaSC dynamics as resistance mechanisms and integrate these into quantitative models that predict and optimize responses to IADT for individual patients with a specific goal of identifying clinically actionable cues for pausing and resuming IADT cycles.
Overlap: None

Title: T2017-017, Genomic predictors of aggressive and lethal prostate cancer in African American men
Role: Co-Investigator
Sponsoring Agency: V Foundation for Cancer Research **Effort:** 0.6 calendar
Level of Funding: $181,818 **Dates:** 12/19/2017–11/1/2020
Goals/Aims: To identify epigenetic and genomic predictors of aggressive and lethal PCa in AAM. We hypothesize that aggressive and lethal PCa in AAM is characterized by distinct epigenetic and gene signature profiles that predispose this population to less durable responses to conventional treatments.
Overlap: None

Title: R21 CA241647, Curated prostate cancer data for novel and reproducible prognostic modeling
Role: Site Principal Investigator
Sponsoring Agency: NIH/NCI **Effort:** 1.2 calendar
Level of Funding: $49,937 **Dates:** 4/1/2020–3/31/2022

Agency Contact: Lisa Gallicchio
Agency Contact Information: (Email): lisa.gallicchio@nih.gov
Goals/Aims: A necessary condition for successful discovery and development of reproducible omic-based prognostic tools is model training and extensive validation in multiple cohorts. We propose to generate such a dataset in PCa, and then use this dataset to estimate immune infiltration, tumor purity and stromal contribution.
Overlap: None

Title: 09-33661-20-03, Differences in prostate cancer molecular features by HIV status
Role: Co-Investigator
Sponsoring Agency: Miles for Moffitt **Effort:** 0.6 calendar
Level of Funding: **Dates:** 2/1/2020–1/31/2021
Goals/Aims: To evaluate the hypothesis that prostate cancers in HIV-infected men harbor distinct molecular features, we will leverage existing prostate tumor specimens from both the AIDS Cancer Specimen Resource (ACSR) and Moffitt.
Overlap: None

Title: W81XWH1910435, Characterize the immune-oncologic profile of lethal prostate cancer in African American men and develop new therapeutic avenues of therapy for this patient population
Role: Co-Investigator
Sponsoring Agency: DoD **Effort:** 0.6 calendar
Level of Funding: $331,678 **Dates:** 8/1/2019–7/31/2022
Goals/Aims: The goal of this project is to characterize immune regulators of lethal PCa in AAM as compared with EAM and to identify novel immune targets for treatment.
Overlap: None

Title: P30 CA076292, Cancer Center Support Grant: Years 17-23
Role: Co-Investigator
Sponsoring Agency: NIH/NCI **Effort:** 1.20 calendar
Level of Funding: $1,738,934 **Dates:** 2/1/2017–1/31/2022
Agency Contact: Krzysztof Ptak
Agency Contact Information: (Email): krzysztofptak@ninds.nih.gov
Goals/Aims: To support infrastructure for transdisciplinary cancer-relevant research and to foster studies that would not occur without the climate, facilities, and research resources that a cancer center can uniquely provide.
Overlap: None

Title: 02-25999-19-48, DV3: A customer-driven framework for data spoke creation, access and governance
Role: Co-Principal Investigator
Sponsoring Agency: DPR Construction **Effort:** 0.36 calendar
Level of Funding: $50,000 **Dates:** 5/1/2019–8/31/2020
Goals/Aims: Through a collaborative effort that spans CSDC, BBSR, IT, and research faculty, this project seeks to redefine the spoke data delivery pipeline through data virtualization, a data deliverable viewer, and data versioning (DV3).

Overlap: None

c. **What other organizations were involved as partners?**

1. **Organization Name: Dana-Farber Cancer Institute**
2. **Location of Organization:** Boston, MA
3. **Partner's contribution to the projec**t
    a. **Financial support:** None
    b. **In-kind support**: None
    c. **Facilities**: MSK and MCC staff will use the facilities resources at their respective institutions for this project. Dr. Van Allen and his team will use the facilities and resources available to them at DFCI.
    d. **Collaboration**: Dr. Van Allen oversees all efforts related to this proposal in close collaboration with Dr. Schultz. Personnel from both the Schultz and Van Allen groups will collaborate on sequencing analysis for the project.
    e. **Personnel exchanges***:* None
    f. **Other: None**

1. **Organization Name:** Moffit Cancer Center
2. **Location of Organization:** Tampa, FL
3. **Partner's contribution to the projec**t
    a. **Financial support:** None
    b. **In-kind support:** None
    c. **Facilities:** MSK and DFCI staff will use the facilities resources at their respective institutions for this project. Dr. Gerke will use the facilities and resources available to him at MCC.
    d. **Collaboration:** Dr. Gerke will work with the MSK study team to integrate findings from the Health Professionals Follow-up Study (HPFS) and Physicians' Health Study (PHS) into the broader scope of the project. Dr. Gerke will also assist in the epidemiologic and statistical interpretation of findings from the study.
    e. **Personnel exchanges:** None
    f. **Other:** None

8. SPECIAL REPORTING REQUIREMENTS

a. COLLABORATIVE AWARDS:

Drs. Kantoff and Schultz are submitting duplicative reports with tasks clearly marked with the responsible PI and research site.

b. QUAD CHARTS:

Not applicable.