

AD_____

Award Number: W81XWH-12-1-0160

TITLE: Investigating Genomic Mechanisms of Treatment Resistance in
Castration Resistant Prostate Cancer

PRINCIPAL INVESTIGATOR: Terence W. Friedlander, MD

CONTRACTING ORGANIZATION: University of California, San Francisco
San Francisco, CA 94118

REPORT DATE: May 2015

TYPE OF REPORT: Annual Summary Report

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

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

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.

REPORT DOCUMENTATION PAGE		<i>Form Approved</i> <i>OMB No. 0704-0188</i>	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.			
1. REPORT DATE May 2015		2. REPORT TYPE Annual Summary	
4. TITLE AND SUBTITLE Investigating Genomic Mechanisms of Treatment Resistance in Castration Resistant Prostate Cancer		3. DATES COVERED 1May2014 - 30Apr2015	
		5a. CONTRACT NUMBER W81XWH-12-1-0160	
		5b. GRANT NUMBER PC110126	
6. AUTHOR(S) Terence W. Friedlander, MD E-Mail: terence.friedlander@ucsf.edu		5c. PROGRAM ELEMENT NUMBER	
		5d. PROJECT NUMBER	
		5e. TASK NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of California, San Francisco San Francisco, California 94143		5f. WORK UNIT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012		8. PERFORMING ORGANIZATION REPORT NUMBER	
		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

Purpose and Scope: The purpose of this work is to better understand the mechanisms of resistance to androgen biosynthesis inhibitors in men with castration resistant prostate cancer, and to investigate clinical methods of overcoming resistance.

Key Accomplishments and Findings to date:

- Primary endpoint of Phase II study of Dose-Increased Abiraterone Acetate in Men with mCRPC (PI: Friedlander) met, showing that increase in dose of abiraterone at the time of clinical resistance does not result in second PSA declines. This data was presented at the 2015 ASCO Genitourinary Symposium (Orlando, FL). Manuscript currently in process.
- CTCs collected in 38 men with abiraterone-naïve mCRPC at baseline on the aforementioned study. Cells have been enumerated for CTCs, CTC clusters, CTCs expressing stem-like and epithelial markers. A trend towards higher CTC counts was observed in patients who were primarily refractory to abiraterone acetate. Patients with more CTC clusters were more likely to have longer responses to abiraterone acetate ($p=0.085$). CD44 expression on CTCs was not correlated with response to abiraterone.
- Array comparative genomic hybridization (aCGH) of CTC data has been performed in CTCs however the genomic data has been of an inconsistent nature due to multiple reasons discussed in the body of this report. Exploration of the immunocytochemistry, analysis of CTCs isolated on the Epic platform, and experiments to derive genomic data from these cells are underway.
- Phase I study of Abiraterone Acetate plus ARN-509 in men with mCRPC (UCSF PI: Friedlander) fully accrued, initial results showing PSA declines in men with treated with prior abiraterone and prior chemotherapy observed, indicating activity of this combination. Results presented at 2015 ASCO Annual Meeting and 2015 AACR annual meeting.
- Integration of both clinical trials with SU2C "West Coast Dream Team" castration-resistant prostate cancer biopsy protocol. Analysis of genomic data (RNAseq, whole exome sequencing) underway.

15. SUBJECT TERMS

Prostate cancer, castration-resistant prostate cancer, abiraterone, androgens, circulating tumor cells, treatment resistance

16. SECURITY CLASSIFICATION OF:

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE	UU	32	USAMRMC
U	U	U			19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
Introduction.....	5
Keywords	5
Overall Project Summary.....	5
Key Research Accomplishments.....	14
Conclusion	15
Publications, Abstracts, and Presentations	15
Inventions, Patents and Licenses.....	16
Reportable Outcomes	16
Other Achievements.....	17
References	18
Appendices	19

INTRODUCTION

Although androgen biosynthesis inhibitors (ABIs) including ketoconazole and abiraterone improve clinical outcomes and prolong survival in men with castration resistant prostate cancer (CRPC), none are curative, and all patients eventually develop resistance followed by disease progression and death. Resistance is hypothesized to result from either increased systemic or tumor androgen production, mutations in the androgen receptor (AR) signaling pathway leading to ligand-independent AR activity, or through AR-independent pathways. The work being carried out under this grant aims to better understand how this therapeutic resistance develops through genomic analysis (gene copy number and gene methylation status) of tumor biopsies and circulating tumor cells (CTCs) taken from men with CRPC. Further, the work here explores whether clinically targeting proposed mechanisms of resistance can improve outcomes in these patients.

KEYWORDS

Prostate cancer, castration resistant prostate cancer, secondary hormonal therapy, circulating tumor cells, treatment resistance.

OVERALL PROJECT SUMMARY

Statement of Work Aim A: Determine whether resistance to androgen biosynthesis inhibitors (ABIs) is mediated by genomic upregulation of androgen synthesis or by autonomous AR function.

To evaluate whether increased androgen synthesis is implicated in androgen biosynthesis inhibitor resistance work has focused on analyzing biospecimens (circulating tumor cells and metastatic biopsies) derived from CC12551, a Phase II study of dose-increased abiraterone acetate, performed as part of this grant. In this study patients take standard-dose abiraterone acetate (1000mg daily), and at the time of PSA or clinical progression patients increase the dose of abiraterone (1000mg twice daily). Clinical results of this clinical trial are discussed in Aim B.

Forty-one patients have been accrued to this study and baseline circulating tumor cells have been collected on 38 patients (93%) starting initial abiraterone therapy. Additionally 13 men underwent a matched baseline metastatic tumor biopsy. CTCs were recovered in 20 patients progressing on standard-dose abiraterone. As the elevated dose of abiraterone did not result in any PSA declines in the first 14 patients who progressed and took the increased abiraterone dose (to be discussed more in Aim B below) CTC analysis has been restricted to the baseline CTCs and CTCs at the time of initial progression on standard-dose abiraterone.

CTC enrichment has occurred using the VitaCap assay (Vitatex), which enriches circulating cancer cells able to invade into a fluorescently-labeled collagenous matrix. Cells recovered are then enumerated using FACS. Flow-sorted CTCs then undergo lysis and DNA extraction, followed by batched gene copy number profiling using array comparative genomic hybridization (aCGH). For the metastatic biopsies, tumors are obtained as part of the SU2C-PCF West Coast Dream Team metastatic biopsy acquisition

protocol, and tumor is microdissected from surrounding tissue using laser capture microdissection. DNA and RNA are then isolated for analysis per a formalized protocol. For the purposes of this grant this biopsy data is made available to me for analysis, however the patients undergoing biopsy are consented under a separate IRB-approved protocol and funding for the biopsy analysis is separate from this research training grant.

While initial data derived from CTCs showed clear overlap of aCGH profiles derived from CTCs and matched metastatic biopsy (Figure 1), multiple other aCGH profiles of CTCs did not reveal copy aberrations despite findings of multiple copy aberrations in metastatic tumors. This discordance has unfortunately created a significant challenge in terms of the analysis of work originally planned in this Aim. Reasons for this discrepancy and strategies to overcome these are discussed below.

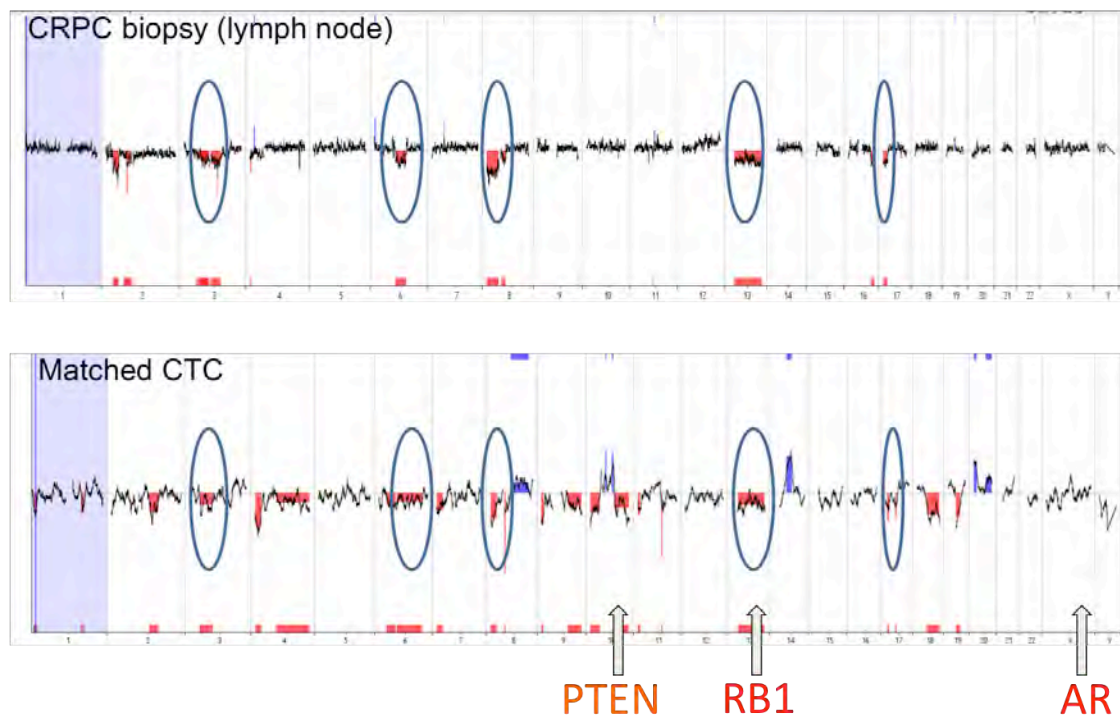


Figure 1: Successful array CGH of CTC and matched metastatic biopsy. Ovals show overlap in multiple segments of chromosomal copy loss. PTEN and RB1 are deleted in both samples. Androgen receptor is copy-normal (wild-type) in both samples.

While the discordance in genomic results between CTCs and metastatic biopsy may reflect heterogeneity in the CTC pool (i.e. metastases from less copy-aberrant primary intact tumors versus from more evolved/copy aberrant metastases) another more likely explanation is an insufficient purity of CTC DNA. This may be due to the fact that the Vitatex assay enriches for CTCs based on the ability of cells to invade into a collagenous matrix, but does not exclude invasive leukocytes. In our hands we have been able to show that coupling this assay with FACS as described yields high-purity CTCs (in excess of 90%, Table 1). Despite this high purity there are nonetheless contaminating leukocytes.

As we have shown that DNA isolation works best when performed from 10-cell aliquots (data not shown) it may be that these contaminating “normal” cells have significantly impaired our ability to derive actionable genomic information from CTCs enriched on the Vitatex platform.

Purity % (iCTC/WBC)		
	Pre-FACS	Post-FACS
PC3 spike-in	0.02%	92%
CRPC	0.01%	47%
CRPC	0.35%	96.7%
CRPC	1.43%	93.3%

Table 1: CTCs isolated on the Vitatex platform were defined as nucleated (DAPI+), leukocyte-antigen negative (CD45/14-), and showed evidence of uptake of fluorescently-label collagen adhesion matrix (CAM) fragments (CAM+). Cells after initial FACS were re-run to assess purity. Results indicate that flow sorting significantly enriches for leukocyte-antigen negative cells, suggesting high-purity CTCs.

This absence of clear copy aberrations in most samples has created a significant challenge in our ability to dissect genomic mechanisms of resistance using the CTC pool. To address this problem we have taken a number of approaches. Firstly we have begun a genomic analysis of the metastatic biopsies obtained in 13 patients starting on therapy, using RNASeq to explore the transcript levels of androgen synthesis enzymes at baseline as well as by DNA sequencing. DNA sequencing is being pursued over aCGH (as originally described in the PCRP-PRTA grant) due to the increased ability to detect point mutations, indels, as well as genomic translocations, in addition to individual gene copy number. More data describing the expression level and copy number of androgen synthesis enzymes from baseline biopsies is expected to be available at the time of the next update.

To address the challenge of insufficient genomic data from CTCs from this study we have begun using a second, enrichment-free CTC platform working in conjunction with Epic Biosciences. In this platform blood from patients enrolled on this study is placed on a glass slide without any prior enrichment, and fluorescent antibodies are used to distinguish CTCs from surrounding leukocytes. CTCs are defined as nucleated (DAPI+), cytokeratin positive (CK+), and CD45-; a fourth channel is available for characterization of individual proteins of interest. Thus far we have been able to identify the androgen receptor using a fluorescently labeled antibody directed against the AR protein. We have thus far acquired images for 3 patients from this study who have progressed on standard-dose abiraterone and observed that the AR is expressed in all 3 subjects (Figure 2), suggesting that downregulation of AR protein is unlikely to be a major mechanism by which abiraterone resistance develops. As AR splice-variantion, in which alternative

splicing of AR mRNA leads to a constitutively-active, androgen-independent AR protein, has recently been shown to have predictive value in understanding abiraterone and enzalutamide resistance¹ work is currently underway to stain cells isolated on the Epic platform with an AR N-terminal domain antibody to evaluate for the presence of truncated AR protein suggestive of AR splice variants.

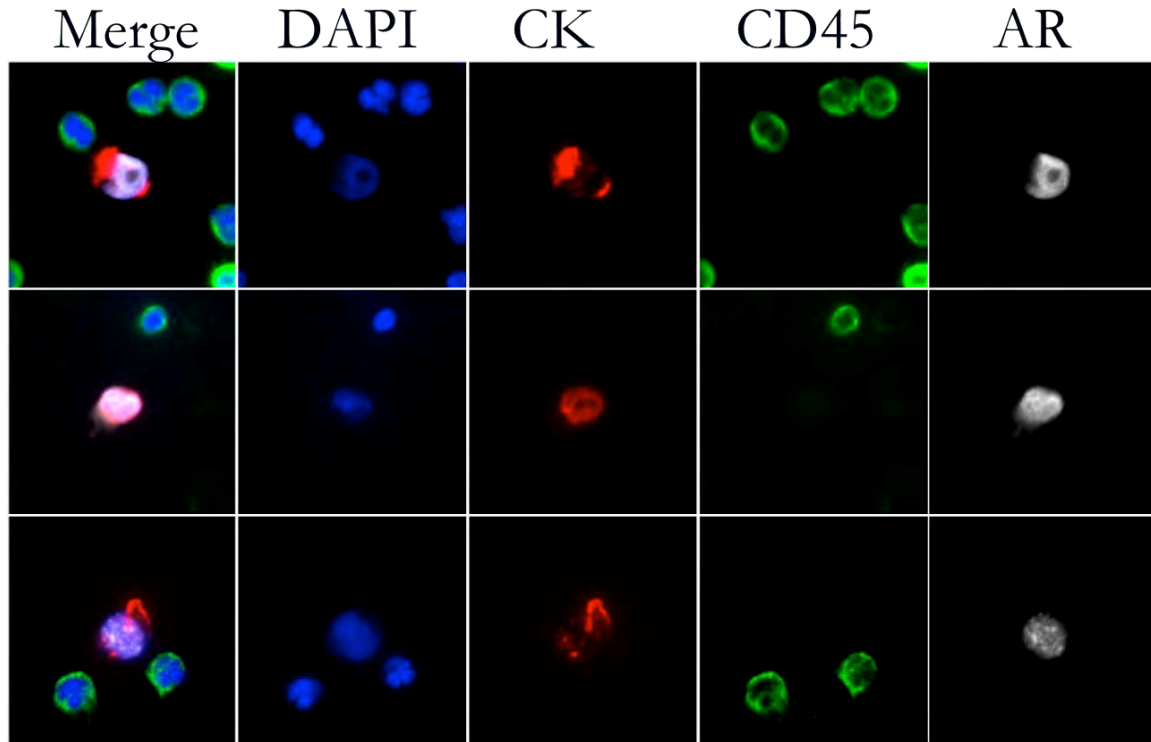


Figure 2: CTCs taken from patients progressing on standard-dose abiraterone acetate isolated using the Epic platform. Each row represents one patient. CTCs are defined as DAPI+/CK+/CD45-. All CTCs continue to express AR protein at the time of abiraterone resistance as evinced by strong cytoplasmic staining.

Similarly, we have initiated a series of studies in which CTCs identified on the Epic platform are individual picked from the slide using an automated cell recovery device, recovered, and genomically profiled. Figure 3 shows data from a series of cell-line experiments showing that PC3 prostate cancer cells are recoverable and informative genomic information is obtainable using aCGH. Further work will explore the ability to recover interpretable genomic data from CTCs obtained in patients resistant to abiraterone as assessed using the Epic CTC technology coupled with genomic analysis at UCSF.

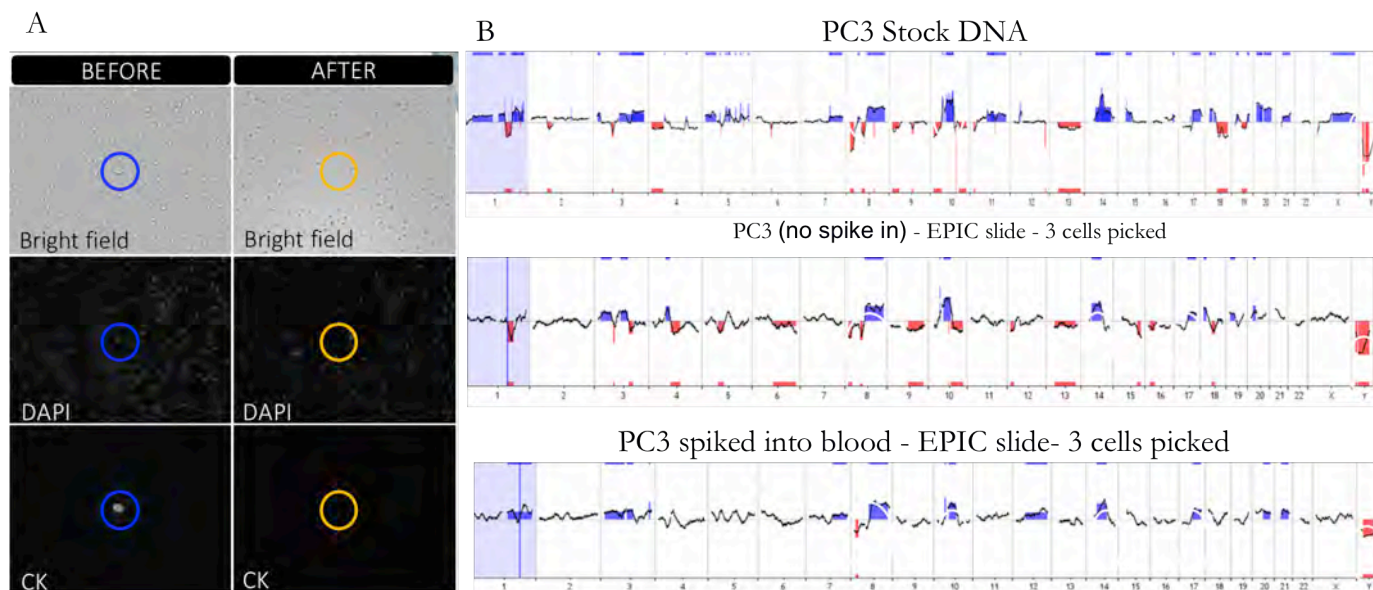


Figure 3. A. Automated cell picking allows for identification, picking, and recovery of single cells. Left column: CK+/DAPI+ CTC prior to cell picking. Right column: CTC removed without disturbing surrounding lymphocytes. B. Genomic analysis of individually recovered CTCs. Top row: aCGH of PC3 stock DNA shows copy gains and losses across the entire genome, with clear deletion of chromosome 8p and amplification of 8q. Middle row: aCGH of PC3 cells (n=3) plated onto Epic slide, then recovered using automated single-cell picking technology. Bottom row: aCGH of PC3 cells (n=3) spiked into healthy donor blood, identified on the Epic platform, then recovered using cell-picking technology. Results show high concordance of copy aberrations across all three experiments.

Given the challenges in assessing the genomics of CTCs from this study a third strategy has been undertaken to evaluate whether baseline CTC subpopulations, as identified immunocytochemically using the original Vitatex platform, can be used as biomarkers to help understand which patients are likely to have primary resistance or quickly develop acquired resistance to abiraterone. Here we hypothesized that higher CTC counts would predict for either primary resistance or shorter responses to abiraterone, that the expression of CD44, a putative marker of cancer stem cells, would be associated with more aggressive disease and treatment resistance, and that CTC clusters, defined as 2 or more co-localized CTCs on microscopy, would be a marker of epithelial differentiation (in contrast to solitary CTCs which may represent a more mesenchymal phenotype) and be associated with a higher likelihood of response to AR-targeted therapy.

We observed a non-significant association of higher CTC counts with the lack of PSA response to abiraterone (median count = 44 CTCs/ml in 6 patients primary refractory to abiraterone, compared to a median of 20 CTCs/ml in 25 patients who responded to abiraterone for >6 months). While not statistically significant this may be due to inadequate power to detect in a different given the relatively small sample size.

In looking at stem-like CTCs we observed a wide variation in CD44 expression in CTCs (Figure 4), however did not observe a clear trend with identification of CD44+ CTCs with subsequent response to abiraterone. A trend however was observed with higher CTC cluster numbers observed in patients who subsequently responded to abiraterone for 6 months or more, compared to patients who never responded or responded for <6 months. (Figure 5). While the sample size here is small, the results are nonetheless intriguing and merit further follow up in subsequent studies. Components of this data described in Aim A has been presented in poster format at the 2014 ASCO Annual Meeting (Chicago, IL; selected for poster discussion), the 2014 and 2015 ASCO Genitourinary Symposiums (San Francisco, CA and Orlando, FL), and at UCSF and the PCF Scientific Retreats.

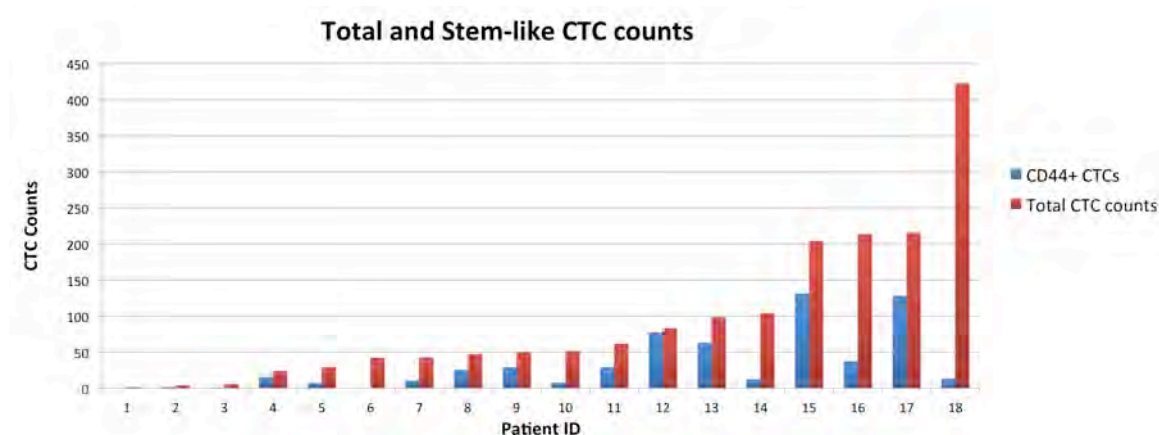


Figure 4: Heterogeneous expression of CD44 in patients starting standard dose abiraterone. No significant correlation was observed between the initial CD44 count and the likelihood of PSA response to abiraterone.

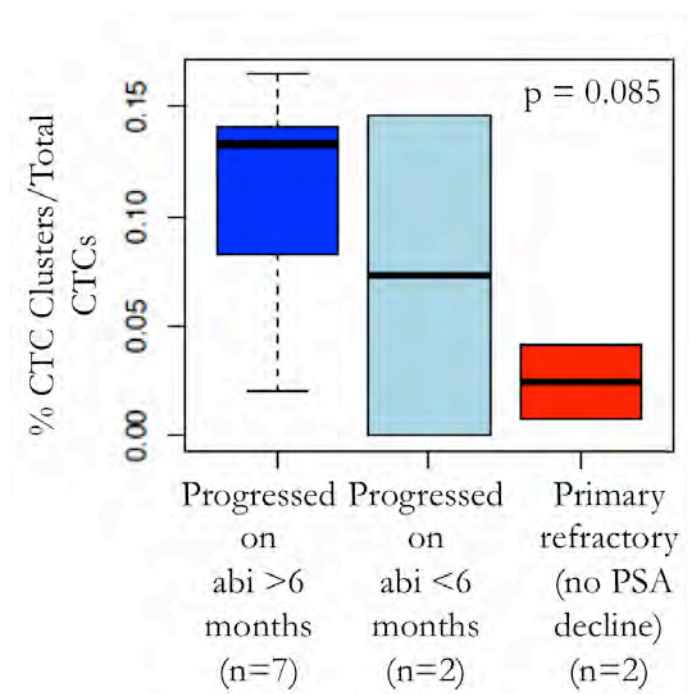


Figure 5: More CTC clusters at baseline associated with a trend towards longer responses to standard-dose abiraterone.

Statement of Work Aim B: Determine whether resistance to ABIs can be overcome by increased inhibition of androgen synthesis.

To understand whether increased androgen synthesis inhibition can overcome ABI resistance we carried out a Phase II study of Dose-Increased Abiraterone Acetate in Men with mCRPC (PI: Friedlander) in conjunction with investigators at Oregon Health Sciences University and the Knight Cancer Center. The study fully accrued the required 41 patients and late last year and an analysis for the early stopping rule for lack of efficacy was undertaken after a preplanned 14 patients had taken standard dose abiraterone, progressed by PSA or radiographically, and took the elevated dose for at least 12 weeks. While the 1000mg BID dose of abiraterone was well tolerated, and resulted in PSA declines at 12 weeks in 34/41 (83%) of subjects, in this analysis we did not observe any sustained PSA responses to the elevated dose of abiraterone in the first 14 evaluable patients who took this dose. (Figure 6) Because of this, and in discussion with the industry sponsor, the elevated-dose arm was closed for lack of efficacy, and it was concluded that escalating the dose of abiraterone at the time of clinical resistance. Patients remaining on the standard dose arm have continued to remain on study and are continuing therapy. Currently there are 3 patients on the standard-dose arm.

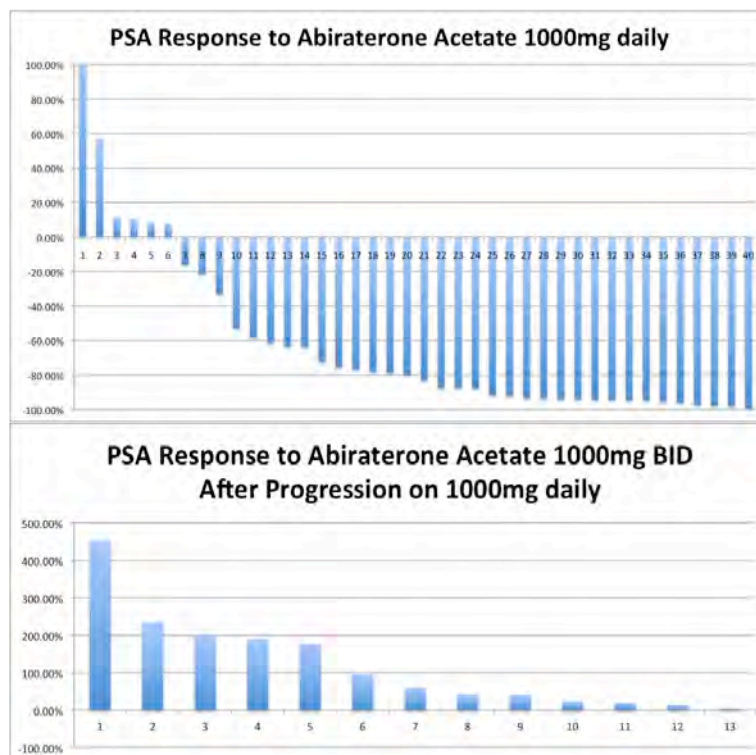


Figure 6: PSA Waterfall plots. Most patients responded to standard dose abiraterone acetate, however no responses were observed after dose-increase in men who progressed on standard dose abiraterone,

Abiraterone pharmacokinetics have been collected and are under analysis at the present time. Initial pK analysis has shown that patients who were primary refractory to abiraterone (ie no PSA decline after 12 weeks of therapy) have lower median pK after one month of standard dose therapy compared to patients who had PSA declines. (Table 2) This data is currently preliminary and requires statistician review, which is pending. This suggests that primary resistance to abiraterone may be in part mediated by differential metabolism of the drug. Initial pK analysis interestingly shows that median abiraterone levels are *higher* at the time of resistance after initial response. While this is somewhat unexpected as it was hypothesized that progression may be due to increased metabolism of abiraterone leading to lower levels, it may in part explain why increasing the dose of abiraterone at this time of initial disease progression was not effective in reducing PSA or slowing disease progression.

	After 1 month of Standard dose (1000mg daily)	At PSA Progression	After 1 month of Escalated-Dose (1000mg BID)
Responders	7.38 (n=16)	19 (n=20)	29.9 (n=7)
Non Responders	3.69 (n=7)	5.97 (n=15)	-

Table 2: Abiraterone pK. Patients who did not respond to standard dose abiraterone (defined as no PSA decline from baseline after 12 weeks of therapy) had lower abiraterone levels after one month of therapy. Abiraterone levels at the time of PSA progression after response were higher than after one month, and median levels after dose-escalated therapy were also higher as expected.

A recent report² has shown that a metabolite of abiraterone termed D4A has high AR binding affinity and may be a major mechanism by which abiraterone functions in decreasing AR signaling. In collaboration with the lead author of this report Dr. Sharifi at the Cleveland Clinic, the next steps include assay of D4A levels at baseline and at progression in banked serum samples taken from patients enrolled in this study to evaluate whether D4A levels, in addition to parent drug levels, are predictive of response or resistance to abiraterone.

In this Phase II study circulating androgen levels have been collected to see if baseline androgen levels correspond with likelihood of response to abiraterone, and to see if circulating androgen levels rise at the time of resistance, as a possible mechanism of acquired resistance. Analysis thus far indicates that higher baseline ACTH levels are associated with a longer duration of response to abiraterone. Specifically median baseline ACTH levels in patients (n=8) responding for more than 6 months was 57 pg/ml, compared to 10 pg/ml for patients (n=9) who responded less than 6 months, p=0.048.

Analysis of other hormonal levels in banked serum samples and their predictive or prognostic capability is underway.

This data was presented in poster format in part at the 2015 ASCO Genitourinary Symposium (Orlando, FL), as well as intramurally as part of an oral presentation at the 2015 UCSF Prostate Cancer Program Retreat. A manuscript describing the clinical data is currently in process.

Statement of Work Aim C: Determine whether resistance to ABIs can be overcome by AR-targeted therapy.

The clinical trial as described in this grant proposal aims to investigate the value of AR targeted therapy as a way to overcome resistance to androgen biosynthesis inhibitors. A Phase II study of the combination of Abiraterone/prednisone monotherapy, with ARN-509 (a novel AR antagonist) added at the time of resistance in men with abiraterone and chemotherapy naïve metastatic CRPC was developed by Dr Friedlander at UCSF after an agreement was established with Aragon Pharmaceuticals. After the acquisition of Aragon by Janssen the plan for this clinical trial was modified to become a Phase I, open-label, single-arm multicenter study of the combination of abiraterone acetate plus prednisone plus ARN-509 in men with mCRPC (including patients with prior abiraterone and/or prior chemotherapy) with a focus on the pharmacokinetics and drug-drug interaction of these agents. CTC collection from this study has been limited due to the multiple protocol changes as well as the multi-site nature of this study.

This combination study opened at UCSF in late 2014 (UCSF PI: Friedlander). To date twenty-nine patients started treatment on study at all sites, of whom 14 had previous docetaxel, 12 had previous abiraterone, and 12 had previous enzalutamide. Forty-one percent of patients have had a confirmed PSA decline of >50% including in 3 patients who progressed despite prior abiraterone and enzalutamide. Overall the combination has been well tolerated. pK analyses suggest that ARN-509 may lower the pK of abiraterone, while pK of ARN-509 was unaffected compared to historical controls of ARN-509 monotherapy, therefore a second cohort of patients currently being accrued to further explore these findings. The clinical results were presented at the 2015 ASCO Annual Meeting, and have served as the basis for a larger Phase III study currently in planning with industry support. The pK data was presented separately at the 2015 AACR meeting.

Statement of Work: Training Plan

The major focus of my training thus far has been in the design and conduct of prospective clinical trials. To that end I have met weekly with my primary mentor Dr. Charles Ryan and co-mentor Dr. Eric Small, to review progress in the development of the clinical protocols described in the Statement of Work and in the execution and analysis of the clinical data. I have continued meeting twice weekly with my primary scientific advisor Dr. Pamela Paris, who has been integral in helping to think through the laboratory experiments (circulating tumor cell capture and analysis) and to help troubleshoot

problems encountered. Unfortunately both Drs. Phillip Febbo and Carlo Maley left UCSF to pursue academic and industry interests shortly after this grant was awarded. I nonetheless maintain contact with Dr. Febbo through email and through discussions and in person at PCF and ASCO meetings. To make up for their departure and the loss of their input regarding the genomic studies I have sought out advice from collaborators in bioinformatics at the University of California, Santa Cruz, including Dr. Robert Baertsch, whom which our group has developed a close working relationship related to the Stand Up to Cancer metastatic biopsy study described in Aim A. The analysis of tissue biopsies described will proceed with his assistance.

With the initial focus on protocol development, patient accrual, and work related to CTC and biopsy collection I have deferred the coursework until the second-half of the grant period. I am enrolled in the UCSF Biomedical Sciences Graduate Program class BMS 255: Genetics: Basic Genetics and Genomics. This class is set to start in January 2016. Given a large number of clinical, teaching, and research duties I will plan to enroll in BMS 270a: Epigenetics of Reprogramming and Disease, BMS 270b Practical Bioinformatics with Programming, and IB249 Seminar in Evolutionary Genomics once I complete BMS 255.

KEY RESEARCH ACCOMPLISHMENTS

- Primary endpoint of Phase II study of Dose-Increased Abiraterone Acetate in Men with mCRPC (PI: Friedlander) met, showing that increase in dose of abiraterone at the time of clinical resistance does not result in second PSA declines. This data was presented at the 2015 ASCO Genitourinary Symposium (Orlando, FL). Manuscript currently in process.
- CTCs collected in 38 men with abiraterone-naïve mCRPC at baseline on the aforementioned study. Cells have been enumerated for CTCs, CTC clusters, CTCs expressing stem-like and epithelial markers. A trend towards higher CTC counts was observed in patients who were primarily refractory to abiraterone acetate. Patients with more CTC clusters were more likely to have longer responses to abiraterone acetate ($p=0.085$). CD44 expression on CTCs was not correlated with response to abiraterone.
- Array comparative genomic hybridization (aCGH) of CTC data has been performed in CTCs however the genomic data has been of an inconsistent nature due to multiple reasons discussed in the body of this report. Exploration of the immunocytochemistry, analysis of CTCs isolated on the Epic platform, and experiments to derive genomic data from these cells are underway.
- Phase I study of Abiraterone Acetate plus ARN-509 in men with mCRPC (UCSF PI: Friedlander) fully accrued, initial results showing PSA declines in men with treated with prior abiraterone and prior chemotherapy observed, indicating activity of this combination. Results presented at 2015 ASCO Annual Meeting and 2015 AACR annual meeting.

- Integration of both clinical trials with SU2C “West Coast Dream Team” castration-resistant prostate cancer biopsy protocol. Analysis of genomic data (RNAseq, whole exome sequencing) underway.

CONCLUSION

Continued progress has been made in terms of achieving goals set forth in the statement of work for this project. We have met the primary endpoint of the dose-escalated abiraterone study and have found that increasing the dose of abiraterone at the time of resistance to standard dose therapy does not result in significant clinical activity. Continued investigation of the genomic basis for this, as described above, along with exploration of alternative CTC enrichment platforms and correlation with genomic data from paired biopsies is underway. The combination of abiraterone with ARN-509 appears to be well tolerated, and further work is underway to better elucidate the pharmacokinetics of this combination and to better test its clinical efficacy.

PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS

1. Anantharaman A, Friedlander TW. A Stepping Stone Toward Personalized Oncology: Genomic Analysis of Circulating Tumor Cells to Guide Management of Metastatic Castration-resistant Prostate Cancer. *Eur Urol*. 2015 Aug 13. pii: S0302-2838(15)00712-5. doi: 10.1016/j.eururo.2015.07.053. [Epub ahead of print] PubMed PMID: 26278804.
2. Terence W. Friedlander, MD, Julie Graff, MD, Li Zhang, PhD, Gayatri Premasekharan, PhD, Archana Dilip, MS, Rosa Paz BA, Rahul Aggarwal, MD, Won Kim, MD, Amy M. Lin, MD, Lawrence Fong, MD, Eric J. Small, MD, Pamela L. Paris, PhD, and Charles J. Ryan, MD. A Phase II Study of Increased-Dose Abiraterone Acetate in Patients with Castration Resistant Prostate Cancer (CRPC): Circulating Tumor Cell Correlatives. Oral abstract presented at 2015 UCSF Prostate Cancer Program Retreat; September 2015; San Francisco, CA.
3. Edwin M. Posadas, Kim N. Chi, Ronald De Wit, Maja J. De Jonge, Gerhardt Attard, Terence W. Friedlander, Margaret K. Yu, Peter Hellemans, Caly Chien, Charlene Connelly Abrams, Martha Gonzalez, GERALYN Carol Trudel, Vijay Chauhan, Juhui James Jiao, Fred Saad. Phase 1b study of ARN-509 with abiraterone acetate (AA) and prednisone (P) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). Poster presented at: 2015 ASCO Annual Meeting; June 2015; Chicago, IL. *J Clin Oncol* 33, 2015 (suppl; abstr 5028)
4. Edwin M. Posadas, Kim N. Chi, Ronald de Wit, Maja JA de Jonge, Gerhardt Attard, Terence Friedlander, Margaret Yu, Peter Hellemans, Caly Chien, Charlene Abrams, Martha Gonzalez, G  ralyn C. Trudel, Vijay Chauhan, Fred Saad. Pharmacokinetics (PK) and safety of ARN-509 with abiraterone acetate (AA) and prednisone (P) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). [abstract]. In: Proceedings of the 106th Annual Meeting of the American Association for Cancer Research; 2015 Apr 18-22; Philadelphia, PA. Philadelphia (PA): AACR; Cancer Res 2015;75(15 Suppl):Abstract nr CT302. doi:10.1158/1538-7445.AM2015-CT302

5. Terence W. Friedlander, Julie Nicole Graff, Li Zhang, Rosa Paz, Gayatri Premasekharan, Archana Dilip, Andrew Caleb Hsieh, Rahul Raj Aggarwal, Won Kim, Amy M. Lin, Lawrence Fong, Eric Jay Small, Pamela Paris, Charles J. Ryan. Initial results from a phase II study of increased-dose abiraterone acetate in patients with castration resistant prostate cancer (CRPC). Poster presented at: 2015 Genitourinary Cancers Symposium; February 2015; Orlando, FL. J Clin Oncol 33, 2015 (suppl 7; abstr 188)
6. Friedlander TW, Fong L. The end of the beginning: circulating tumor cells as a biomarker in castration-resistant prostate cancer. J Clin Oncol. 2014 Apr 10;32(11):1104-6. doi: 10.1200/JCO.2013.54.7307. Epub 2014 Mar 10. Erratum in: J Clin Oncol. 2014 Jun 10;32(17):1863. PubMed PMID: 24616311.
7. Terence W. Friedlander, MD Julie Graff, MD, Li Zhang, PhD, Rosa Paz, Evelyn Hang, Andrew Hsieh, MD, Rahul Aggarwal, MD, Won Kim, MD, Amy M. Lin, MD, Lawrence Fong, MD, Eric J. Small, MD, Pamela L. Paris, PhD, and Charles J. Ryan, MD. Initial Results from a Phase II Study of Increased-Dose Abiraterone Acetate in Patients with Castration Resistant Prostate Cancer (CRPC). Poster presented at the 21st Annual Prostate Cancer Foundation Scientific Retreat; October 2014; Carlsbad, CA.
8. Terence W. Friedlander, Gayatri Premasekharan, Vy Ngo, Evelyn Hang, Julie Nicole Graff, Charles J. Ryan, Pamela Paris. Molecular and genomic characterization of invasive circulating tumor cells (iCTCs) from men with metastatic castration-resistant prostate cancer (mCRPC). 2014 ASCO Annual Meeting; June 2014; Chicago, IL. Selected for poster discussion. J Clin Oncol 32:5s, 2014 (suppl; abstr 11013)
9. Terence W. Friedlander, Gayatri Premasekharan, Vy Ngo, Shaun Doty, Anna Harris, Michael Winter, Elizabeth Gilbert, Charles Craik, Pamela Paris. Molecular and genomic characterization of invasive circulating tumor cells (iCTCs) from men with metastatic castration-resistant prostate cancer (mCRPC). Poster presented at: 2014 Genitourinary Cancers Symposium; February 2014; San Francisco, CA. J Clin Oncol 32, 2014 (suppl 4; abstr 120)

INVENTIONS, PATENTS, AND LICENCES

None

REPORTABLE OUTCOMES

Two clinical protocols and a laboratory protocol for the work have been developed for this grant. Since the last Update clinical data from CC12551 (Dose escalated study of abiraterone acetate in men with mCRPC) has been presented as an oral abstract at the 2015 UCSF Prostate Cancer Program Retreat, and in poster format at the the ASCO 2015 Genitourinary Cancers Symposium, the 21st Annual PCF Scientific Retreat, and the ASCO 2014 Annual Meeting. A clinical manuscript is underway. The initial results of the Phase I study of ARN-509 plus Abiraterone Acetate and prednisone were presented at the ASCO 2015 Annual Meeting and at the 2015 AACR annual meeting, both in poster

formats. I have authored an editorial about CTCs in prostate cancer in the Journal of Clinical Oncology as well as a perspective (about findings related to this scope of work) of the clinical importance of AR-V7 in CTCs published in HemOnc Today³. Additionally I authored an invited editorial on the same topic published in European Urology.

OTHER ACHIEVEMENTS

The CTC development work supported by this grant led to a separate study of circulating tumor cells in bladder cancer, which was recently published in the Journal of Urology.

See: Alva A, Friedlander T, Clark M, Huebner T, Daignault S, Hussain M, Lee C, Hafez K, Hollenbeck B, Weizer A, Premasekharan G, Tran T, Fu C, Ionescu-Zanetti C, Schwartz M, Fan A, Paris P. Circulating Tumor Cells as Potential Biomarkers in Bladder Cancer. J Urol. 2015 Sep;194(3):790-8. doi: 10.1016/j.juro.2015.02.2951.Epub 2015 Apr 23. PubMed PMID: 25912492.)

I similarly received a \$25,000 grant to explore the potential for CTC isolation, genomic profiling, and treatment with personalized therapy for patients with metastatic bladder cancer, through the Cancer League.

REFERENCES

1. Antonarakis ES, Lu C, Wang H, Lubner B, Nakazawa M, Roeser JC, Chen Y, Mohammad TA, Chen Y, Fedor HL, Lotan TL, Zheng Q, De Marzo AM, Isaacs JT, Isaacs WB, Nadal R, Paller CJ, Denmeade SR, Carducci MA, Eisenberger MA, Luo J. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med. 2014 Sep 11;371(11):1028-38. doi: 10.1056/NEJMoa1315815. Epub 2014 Sep 3. PubMed PMID: 25184630; PubMed Central PMCID: PMC4201502.
2. Li Z, Bishop AC, Alyamani M, Garcia JA, Dreicer R, Bunch D, Liu J, Upadhyay SK, Auchus RJ, Sharifi N. Conversion of abiraterone to D4A drives anti-tumour activity in prostate cancer. Nature. 2015 Jul 16;523(7560):347-51. doi: 10.1038/nature14406. Epub 2015 Jun 1. PubMed PMID: 26030522; PubMed Central PMCID: PMC4506215.
3. HemOnc Today Men with AR-V7 variant may benefit from taxanes for advanced prostate cancer. July 6th, 2015. Available at <http://www.healio.com/hematology-oncology/prostate-cancer/news/online/%7Bca85417b-9e66-4b4d-ad80-9f0db95a598f%7D/men-with-ar-v7-variant-may-benefit-from-taxanes-for-advanced-prostate-cancer>

APPENDIX/SUPPORTING DATA

1. UCSF Cancer Center (laboratory) protocol 125511: CC#125511: Determination of Gene Copy Changes Associated with Resistance to Androgen Biosynthesis Inhibitors in Men with Metastatic Castration Resistant Prostate Cancer. IRB approval letter.
2. Curriculum Vitae



**Human Research Protection Program
Committee on Human Research**

Notification of Expedited Review Approval

Principal Investigator
Terence W Friedlander

Co-Principal Investigator

Type of Submission: Continuing Review Submission Form
Study Title: CC#125511: Determination of Gene Copy Changes associated with Resistance to Androgen Biosynthesis Inhibitors in Men with Metastatic Castration Resistant Prostate Cancer

IRB #: 12-08760

Reference #: 138186

Committee of Record: Mount Zion Panel

Study Risk Assignment: Minimal

Approval Date: 06/26/2015

Expiration Date: 07/19/2016

Regulatory Determinations Pertaining to this Approval (if applicable):

The requirement for individual Research HIPAA Authorization is waived for all subjects. The use or disclosure of the requested information does not adversely affect the rights and welfare of the individuals and involves no more than a minimal risk to their privacy based on, at least, the presence of the following elements: (1) an adequate plan to protect the identifiers from improper use and disclosure; (2) an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or if such retention is otherwise required by law; (3) adequate written assurances that the requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the Privacy Rule; (4) the research could not practicably be conducted without the waiver; and (5) the research could not practicably be conducted without access to and use of the requested information.

A waiver or alteration of informed consent is acceptable because, as detailed in the application: (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation. The waiver or alteration of informed consent applies to all subjects.

All changes to a study must receive CHR approval before they are implemented. Follow the [modification request](#) instructions. The only exception to the requirement for prior CHR review and approval is when the changes are necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.103.b.4, 21 CFR 56.108.a). In such cases, report the actions taken by following these [instructions](#).

Expiration Notice: The iRIS system will generate an email notification eight weeks prior to the expiration of this study's approval. However, it is your responsibility to ensure that an application for [continuing review](#) approval has been submitted by the required time. In addition, you are required to submit a [study closeout report](#) at the

completion of the project.

Approved Documents: To obtain a list of documents that were approved with this submission, follow these steps: Go to My Studies and open the study – Click on Submissions History – Go to Completed Submissions – Locate this submission and click on the Details button to view a list of submitted documents and their outcomes.

For a list of all currently approved documents, follow these steps: Go to My Studies and open the study – Click on Informed Consent to obtain a list of approved consent documents and Other Study Documents for a list of other approved documents.

San Francisco Veterans Affairs Medical Center (SFVAMC): If the SFVAMC is engaged in this research, you must secure approval of the VA Research & Development Committee in addition to CHR approval and follow all applicable VA and other federal requirements. The CHR [website](#) has more information.

University of California, San Francisco
CURRICULUM VITAE

Name: Terence W. Friedlander, MD
Position: HS Assistant Clinical Professor, Step 2
Medicine
School of Medicine

Address: University of California, San
Francisco San Francisco, CA 94143

EDUCATION

1995 - 1999	Brown University, Providence RI	BA	Biology
1999 - 2003	New York University Medical School	MD	Medicine
2003 - 2004	University of California, San Francisco	Internal Medicine Internship	Medicine
2004 - 2006	University of California, San Francisco	Internal Medicine Residency	Medicine
2006 - 2007	Utrecht University, Netherlands	MA	Medical Ethics
2007 - 2010	University of California, San Francisco	Fellowship	Hematology/Oncology
2009 - 2010	University of California, San Francisco	Chief Fellow	Hematology/Oncology
2010 - 2011	University of California, San Francisco	Fellowship	Urologic Oncology

LICENSES, CERTIFICATION

2004	Medical Licensure, California (Licence number A88888)
2006	American Board of Internal Medicine, Internal Medicine Certification
2010	American Board of Internal Medicine, Medical Oncology Certification

PRINCIPAL POSITIONS HELD

2011 -	University of California, San Francisco	Assistant Clinical Professor of Medicine
--------	---	--

HONORS AND AWARDS

2000	Herman Goldman Scholarship	NYU Medical School
2003	Spiegel Award for Academic Excellence	NYU Medical School
2003	Alpha Omega Alpha	National Medical Honors Society
2003	Medical Degree with Honors	NYU Medical School
2006	Fulbright Scholarship in Medical Ethics	Netherlands-America Foundation
2010	Young Investigator Award	American Society of Clinical Oncology
2012	Young Investigator Award	Prostate Cancer Foundation
2012	Physician Research Training Award	United States Department of Defense
2012	Travel Award	Advances in Circulating Tumor Cells Conference Foundation
2013	Poster Award	UCSF Annual Prostate Cancer Retreat

KEYWORDS/AREAS OF INTEREST

Prostate Cancer, Bladder Cancer, genomics, microarrays, pharmacogenetics, circulating tumor cells, androgen biosynthesis inhibitors, hormonal therapy, immunotherapy, clinical trials

PROFESSIONAL ACTIVITIES

CLINICAL

Attending Physician, Genitourinary Medical Oncology, UCSF: Since 2010 I have seen patients and served as an attending physician in the Mt Zion Genitourinary Medical Oncology clinic weekly, seeing patients and supervising rotating fellows, residents and medical students.

Attending Physician, San Francisco General Hospital and SFGH Oncology Clinic: Since July 2011 I have been personally seeing patients in the SFGH general oncology clinic one day per week and have attended on the inpatient Oncology Consult service at San Francisco General Hospital 8 weeks out of the year, supervising fellows, residents and medical students.

Fellow, Hematology/Oncology, UCSF Medical Center: During the clinical phase of my training from 2007-2009 I worked on the inpatient Hematology/Oncology consult services at UCSF, SFGH, and the VAMC as well as in the twice weekly at either the VAMC, SFGH, or Mt. Zion oncology clinics. During the research phase from 2009-2010 I worked twice weekly in the Mt Zion Genitourinary Oncology clinic.

SUMMARY OF CLINICAL ACTIVITIES

Attending, Genitourinary Medical Oncology, UCSF: Since 2010 I have seen patients and served as an attending physician in the Mt Zion Genitourinary Medical Oncology clinic weekly, seeing patients and supervising rotating fellows, residents and medical students.

Attending, San Francisco General Hospital and SFGH Oncology Clinic: Since July 2011 I have been personally seeing patients in the SFGH general oncology clinic one day per week and have attended on the inpatient Oncology Consult service at San Francisco General Hospital 8 weeks out of the year, supervising fellows, residents and medical students.

PROFESSIONAL ORGANIZATIONS

Memberships

2008 - American Society of Clinical Oncology
2010 - American Association of Cancer Researchers

Service to Professional Organizations

2014 -	American Society of Clinical Oncology, Prostate Cancer Program Committee	Committee Member
2015 -	National Comprehensive Cancer Network Bladder/Penile Cancers Panel	Committee Member
2012 -	American Society of Clinical Oncology, General Meeting	Prostate Cancer Poster Discussant

SERVICE TO PROFESSIONAL PUBLICATIONS

2011 - Ad hoc referee for the following journals: Journal of Clinical Oncology, Cancer, Clinical Genitourinary Cancer, Urology, European Urology, Molecular Cancer Therapeutics, Growth Hormone and IGF Research, Human Mutation, and The Protein Journal

INVITED PRESENTATIONS**INTERNATIONAL**

2015	European Association of Urology, Annual Meeting, Madrid, Spain	Oral presentation
2015	Global Congress on Prostate Cancer, Rome, Italy	Oral presentation
2013	9th Annual International Symposium on Minimal Residual Disease, Paris, France	Oral Presentation
2012	Advances in Circulating Tumor Cell Conference Committee, Athens, Greece	Oral presentation

NATIONAL

2015	American Society of Clinical Oncology Genitourinary Symposium	Poster Presentation
2015	American Society of Clinical Oncology, Best of ASCO Review Meeting	Oral Presentation
2014	American Society of Clinical Oncology Annual Meeting	Poster Discussion
2014	Prostate Cancer Foundation Annual Scientific Retreat	Poster Presentation
2014	Southwest Oncology Group (SWOG) Spring Meeting	Oral Abstract
2013	Prostate Cancer Foundation Annual Research Symposium	Poster Presentation
2014	American Society of Clinical Oncology Genitourinary Symposium	Poster Presentation
2013	American Society of Clinical Oncology Annual Meeting	Poster Presentation
2012	American Society of Clinical Oncology Genitourinary Symposium	Poster Presentation
2011	American Society of Clinical Oncology Genitourinary Symposium	Oral Plenary Abstract
2010	American Society of Clinical Oncology, Annual Meeting	Poster Presentation
2010	American Society of Clinical Oncology, Genitourinary Symposium	Poster Presentation

REGIONAL AND OTHER INVITED PRESENTATIONS

2015	UCSF Molecular Tumor Board	Oral Presentation : Applied Prostate Cancer Genomics
2015	UCSF Prostate Cancer Program Retreat	Oral Presentation
2015	UCSF Hematology and Oncology Research Retreat	Poster Presentation
2014	SFGH Cancer Awareness Resources and Education	Oral Presentation
2014	UCSF Prostate Cancer Spore Planning Meeting	Oral Presentation

2013	UCSF Prostate Cancer Retreat	Oral Presentation
2013	UCSF Bladder Cancer Support Group	Oral Presentation
2013	UCSF Hematology Oncology Research Retreat	Poster Presentation
2012	UCSF Prostate Cancer Research Retreat	Oral Presentation
2012	UCSF Radiation Oncology Department Grand Rounds	Oral Presentation
2012	SFGH Cancer Awareness Resources and Education	Oral Presentation
2011	UCSF Hematology Oncology Research Retreat	Oral Presentation
2011	UCSF Hematology Oncology Research in Progress Seminar	Oral Presentation
2011	UCSF Bladder Cancer Research Retreat	Oral Presentations
2011	SFGH Cancer Awareness Resources and Education	Oral Presentation
2011	UCSF Prostate Cancer Research Retreat	Poster Presentation
2010	Pfizer Inc. Research Conference	Oral Presentation
2010	UCSF Urologic Oncology Seminar Series	Oral Presentation
2010	UCSF Hematology Oncology Research Retreat	Oral Presentation
2009	SFGH Cancer Awareness Resources and Education	Oral Presentation
2009	Stanford University 11th Annual Multidisciplinary Management of Cancer	Discussant
2009	Cancer and Lymphoma Group B (CALGB) Early Career Investigators Meeting	Oral Presentation

CONTINUING EDUCATION COURSES ATTENDED

2007	UCSF Hematology/Oncology weekly Journal Club
2007	UCSF Hematology/Oncology weekly Clinical Case Conference

UNIVERSITY AND PUBLIC SERVICE

UNIVERSITY SERVICE

UCSF CAMPUS-WIDE

2015 -	Helen Diller Family Comprehensive Cancer Center, Reviewer Clinical Trials Protocol Review Committee (PRC)
--------	--

SCHOOL OF MEDICINE

2014 -	Urology Oncology Fellowship Program (Dept of Urology)	Interviewer for prospective fellows
2014 -	Hematology and Oncology Fellowship Program	Interviewer for prospective fellows

2014 -	UCSF Mini-Medical School for the Public	Lecturer
2013 -	Longitudinal Clinical Experience (LCE)	Preceptor
2012 -	Hematology and Oncology Fellowship Program	Didactic Lecturer
2009 -	M3 Oncology	Small Group Leader

SCHOOL OF PHARMACY

2015 - 2015	PC152 Drug Discovery and Development	Lecturer
-------------	--------------------------------------	----------

DEPARTMENTAL SERVICE

2010 - 2011	UCSF Division of Hematology Oncology	Chief Fellow
-------------	--------------------------------------	--------------

PUBLIC SERVICE

2009 - 2014	SFGH Cancer Awareness Resources Education (CARE)	Speaker
-------------	--	---------

SUMMARY OF SERVICE ACTIVITIES

As an LCE preceptor I personally precept and mentor a visiting 3rd year medical student for one afternoon per week for >20 weeks in the GU Medical Oncology clinic at the Cancer Center.

As a lecturer for the UCSF MiniMedical School I have given talks on the management of GU malignancies for a general public audience. These have been video and audio recorded and are available on social media sites including YouTube.

I have served as a small group leader multiple times for the M3 module for second year medical students reviewing case histories as part of the module.

Working with the CARE program at SFGH, giving talks 2-3 times per year I help discuss new trends in oncology management and strategies for survivorship in a Spanish-language community outreach and support program.

As Chief Fellow I organized and planned fellowship recruitment and orientation, designed fellows' schedules, implemented year-long performance-improvement projects, served as liaison to program director and division faculty, and mentored junior fellows.

TEACHING AND MENTORING

TEACHING

FORMAL SCHEDULED CLASSES FOR UCSF STUDENTS

Qtr	Academic Yr	Course Number and Title	Teaching Contribution	Units	Class Size
F	2009 - 2014	M3: Mechanisms, Molecules, and Malignancies	Discussion Group Leader; 2 two hour sessions		12
S	2015 - 2015	PC 152 Drug Discovery and Development	Lecturer		20

POSTGRADUATE AND OTHER COURSES

2013 - 2015	Longitudinal Clinical Experience Preceptorship	Weekly clinical mentoring with a 3rd year UCSF Medical Student
2011 - 2014	Hematology Oncology Fellowship Didactic Lectures	Introduction to Bladder cancer
2013 - 2014	Hematology Oncology Fellowship Didactic Lectures	Introduction to Testicular Cancer
2013 - 2015	UCSF GU Medical Oncology Program Research Training	Testis, Kidney, Bladder Cancer didactics.
2013 - 2014	SFGH Family Practice Residency Didactic Lectures	Prostate Cancer Review
2011 - 2013	Internal Medicine Residency Noon Lectures	Updates in Prostate Cancer

INFORMAL TEACHING

2010 - 2015	Genitourinary Clinic Attending (weekly with fellow, resident, or medical student)
2011 - 2015	SFGH Oncology Consult Service (8 weeks, with fellows, residents, and/or medical students)

TEACHING NARRATIVE

My teaching activities consist of a combination of formal sessions with medical students as a discussion group leader, didactic sessions with the first and second year oncology fellows and medical residents, weekly on-the-go teaching with my LCE medical student during clinic hours, periodic didactics with the SFGH primary care residents and with UCSF Radiation Oncology residents, didactics with research coordinators in the GU Medical Oncology Program, and informal teaching with fellows, residents, and students in the oncology clinics and on the wards.

MENTORING

PREDOCTORAL STUDENTS SUPERVISED OR MENTORED

Dates	Name	Program or School	Role	Current Position
-------	------	-------------------	------	------------------

Dates	Name	Program or School	Role	Current Position
2014 - 2015	Jonathan Ostrem	UCSF Medical School	LCE Preceptor and Mentor	Medical Student
2013 - 2014	Max Jan	UCSF Medical School	LCE preceptor and Mentor	Medical Student

POSTDOCTORAL FELLOWS AND RESIDENTS DIRECTLY SUPERVISED OR MENTORED

Dates	Name	Fellow	Faculty Role	Current Position
2015 -	Archana Anantharaman		Mentor in GU Medical Oncology	Hematology Oncology Fellow
2013 - 2014	Gayatri Premasekharan			Post-doctoral fellow

OTHER VISITING FACULTY SUPERVISED

2014 - 2014 Curro Zambrana, MD Hospital Infanta Sofia, Madrid, Spain

MENTORING NARRATIVE

Working as an LCE preceptor and mentor I meet weekly with a 3rd year UCSF Medical Student, in the GU Medical Oncology clinic to see patients, discuss clinical findings, and help them to develop critical clinical problem solving skills. We also discuss career choices and I provide mentoring in this regard.

I have recently begun mentoring Dr. Anantharaman, a first year hematology-oncology fellow, now working with the GU Medical Oncology group. Together we are designing a plan for her research in the 2nd and 3rd years of her fellowship.

Dr. Curro Zambrana was a visiting MD in early 2014, and we worked together weekly in clinic and on a research projects reviewing the UCSF experience with autologous stem cell transplant for advanced germ cell tumors.

Working at Mission Bay I have helped supervise and mentor Gayatri Premasekharan, PhD, a post-doctoral fellow in the Paris lab, focusing on the clinical and translation role for circulating tumor cells in prostate cancer.

TEACHING AND MENTORING AIDS

UCSF Mini-Medical school videotaped lectures: Kidney Cancer and Testicular Cancer, available online.

Prostate Cancer Treatment and Research Handout for patients in GU Medical Oncology clinic, describing how prostate cancer is treated and describing current UCSF research

SUMMARY OF TEACHING AND MENTORING HOURS

2010 - 2011	130 total hours of teaching (including preparation) Formal class or course teaching hours: 20 hours Informal class or course teaching hours: 110 hours Mentoring hours: 0 hours Other hours:
2011 - 2012	240 total hours of teaching (including preparation) Formal class or course teaching hours: 20 hours Informal class or course teaching hours: 220 hours Mentoring hours: 0 hours Other hours:
2012 - 2013	240 total hours of teaching (including preparation) Formal class or course teaching hours: 20 hours Informal class or course teaching hours: 220 hours Mentoring hours: 0 hours Other hours:
2013 - 2014	240 total hours of teaching (including preparation) Formal class or course teaching hours: 20 hours Informal class or course teaching hours: 220 hours Mentoring hours: hours Other hours:
2014 - 2015	Total anticipated hours of teaching: 240 hours

RESEARCH AND CREATIVE ACTIVITIES

RESEARCH AWARDS

CURRENT

A119352 (PI)	03/01/2012 - 02/28/2016
Prostate Cancer Foundation	
Investigation of Genomic Mechanisms of Androgen Biosynthesis Inhibitor Resistance in Castration Resistant Prostate Cancer	
P0043122 (PI)	05/01/2012 - 04/30/2017
Department of Defense	

Investigation of Genomic Mechanisms of Androgen
Biosynthesis Inhibitor Resistance in Castration Resistant
Prostate Cancer

PAST

A114463 (PI)

07/01/2010 - 06/30/2011

American Society of Clinical Oncology, Young Investigator
Award

Determination of Genotypic Markers of Docetaxel
Resistance in Castration Resistant Prostate Cancer.

PEER REVIEWED PUBLICATIONS

1. Alva A, Friedlander T, Clark M, Huebner T, Daignault-Newton S, Hussain M, Lee C, Hafez K, Hollenbeck B, Premasekharan G, Ionescu-Zanetti C, Schwartz M, Paris P. "Circulating Tumor Cells as Potential Biomarkers in Bladder Cancer" J Urol. 2015 Apr 22. pii: S0022-5347(15)03852-5.
2. Kim W, Zhang L, Wilton JH, Fetterly G, Mohler JL, Weinberg V, Morse A, Szmulewitz RZ, Friedlander TW, Fong L, Lin AM, Harzstark AL, Molina A, Small EJ, Ryan CJ. "Sequential Use of the Androgen Synthesis Inhibitors Ketoconazole and Abiraterone Acetate in Castration-Resistant Prostate Cancer and the Predictive Value of Circulating Androgens" Clin Cancer Res. 2014 Oct 21. [Epub ahead of print]
3. Friedlander TW, Ngo VT, Dong H, et al: Detection and characterization of invasive circulating tumor cells (ictcs) derived from men with metastatic castration resistant prostate cancer (mCRPC). Int J Cancer. 2014 May 15;134(10):2284-93. doi: 10.1002/ijc.28561. Epub 2014 Jan 2.
4. Friedlander TW, Roy R, Tomlins SA, Ngo VT, Kobayashi Y, Azameera A, Rubin MA, Pienta KJ, Chinnaiyan A, Ittmann MM, Ryan, CJ, Paris PL, "Common Structural and Epigenetic and Changes in the Genome of Castration Resistant Prostate Cancer" Cancer Res. 2012 Feb 1;72(3):616-25.
5. Friedlander TW, Weinberg VK, Huang Y, Mi JT, Formaker CG, Small EJ, Harzstark AL, Lin AM, Fong L, Ryan CJ. "A Phase II Study of Insulin-like Growth Factor Receptor Inhibition with Nordihydroguaiaretic Acid in Men with Non-Metastatic Hormone Sensitive Prostate Cancer". Oncol. Rep. 2012 Jan;27(1):3-9.
6. Friedlander TW, Weinberg VK, Small EJ, Sharib J, Harzstark AL, Lin AM, Fong L, Ryan CJ. Effect of the Somatostatin Analog Octreotide Acetate on Circulating Insulin-Like Growth Factor-1 and Related Peptides in Patients with Castration-Resistant Prostate Cancer (CRPC): Results of a Phase II Study. Urol Oncol. 2010; Sep 28. Epub ahead of print.

Review Articles

1. Friedlander TW, Premasekharan G, Paris PL (2014). Looking Back, to The Future of Circulating Tumor Cells". Pharmacol Ther; 142(3): 271-280
2. Friedlander TW, Ryan CJ. "Targeting the Androgen Receptor" Urol Clin N Am 2012 Nov

(39): 453-464

3. Friedlander TW, Ryan CJ. Novel hormonal approaches in prostate cancer. *Curr Oncol Rep* 2009; 11:227-234

Books and Chapters

1. Friedlander TW, Ryan CJ, Small EJ, Torti F "Testicular Cancer" in Niederhuber, Armitage, Doroshow, Kastan, Tepper (Eds) *Abeloff's Clinical Oncology, 5th Edition*. Elsevier (Churchill Livingstone)

2.

Friedlander, T.W. Ryan, C.J. (2010). "Adrenal Androgen Synthesis Inhibitor Therapies in Castration Resistant Prostate Cancer." In W. Figg, E. Small, C. Chau (Eds.), *Drug Management of Prostate Cancer*. (pp 91-100). Totowa: Humana Press.

Other Publications

1. Anantharaman A, Friedlander T "The Double Edged Sword of Androgen Deprivation Therapy: Emerging Evidence of Cardiovascular, Pulmonary, and Renal Risks (Editorial). *Oncology*. 2015 Jan;29(1):67-8

2. Anantharaman A, Friedlander TW. A Stepping Stone Toward Personalized Oncology: Genomic Analysis of Circulating Tumor Cells to Guide Management of Metastatic Castration-resistant Prostate Cancer. *Eur Urol*. 2015 Aug 13. pii: S0302-2838(15)00712-5.

3. Friedlander TW, Fong L. (2014). The End of the Beginning: Circulating Tumor Cells as Prognostic Biomarkers in Castration Resistant Prostate Cancer. (Editorial) *J Clin Oncol*;32(11):1104-6

4. Friedlander TW. (2013) Whole Exome Sequencing to Map the Genomic Evolution of Metastatic Prostate Cancer. (Editorial) *Hum Mutat* 34:1231-1241

Friedlander TW, Ryan CJ. (2010) Editorial Comment on Adrenocorticotrophic hormone (ACTH) regulates androgen synthesis in men receiving androgen deprivation therapy for localized prostate cancer. *J Urol*;184(5):1976

6. Friedlander, TW; Ryan CJ. "Beyond the Abstract – Functional phenotyping and genotyping of circulating tumor cells from patients with castration resistant prostate cancer." *UroToday* 7 Aug. 2009. Available from:
http://www.urotoday.com/3341/browse_categories/beyond_the_abstract/beyond_the_abstract_functional_phenotyping_and_genotyping_of_circulating_tumor_cells_from_patients_with_castration_resistant_prostate_cancer08072009.html

ABSTRACTS

1. Results of a multicenter phase I/II trial of abiraterone acetate plus BEZ235 in metastatic, castration-resistant prostate cancer. ASCO Annual Meeting
2. Molecular and genomic characterization of invasive circulating tumor cells (iCTCs) from men with metastatic castration resistant prostate cancer. ASCO Annual Meeting
3. Phase I study of pazopanib (PAZ) in combination with abexinostat (ABX) in patients with metastatic solid tumors. ASCO Annual Meeting
- 4.

Terence W. Friedlander, Vivian K. Weinberg, Alex Yeung, James Burke, Donald L. Lamm, James M. McKiernan, John J. Nemunaitis, Joe Stephenson Jr., Eric Jay Small, Lawrence Fong, Maxwell V. Meng; **Activity of intravesical CG0070 in rb-inactive superficial bladder cancer after BCG failure: Updated results of a phase I/II trial.**

Presented at ASCO Genitourinary Symposium and ASCO Annual Meeting 2012

RESEARCH PROGRAM

My research is focused on understanding the biology of advanced prostate and bladder cancers and developing novel therapeutics to treat these diseases. Specifically I am interested in understanding the genomics of advanced prostate cancer through the acquisition of castration-resistant biopsies and circulating tumor cells, then using array based techniques to identify pathways and mechanisms of treatment resistance. Similarly I am interested in developing novel chemotherapeutic and immunotherapeutic strategies to treat both localized and advanced bladder cancer. I also collaborate with basic scientists at UCSF to use circulating tumor cells both as biomarkers of response and resistance to therapy in prostate and bladder cancer, and also as a tool to investigate the basic biology of these tumors.

SIGNIFICANT PUBLICATIONS

See "Peer Reviewed Publications" above

ADDITIONAL RELEVANT INFORMATION:

Fluent in Spanish, conversant in French and Italian