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TITLE: Pharmacologic Dose Testosterone to Treat Castration-Resistant Prostate Cancer: Mechanisms of Action and Drivers of Response

PRINCIPAL INVESTIGATOR: Michael Schweizer

CONTRACTING ORGANIZATION:
University of Washington

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14. ABSTRACT

Purpose: Single-arm studies have demonstrated preliminary signs of efficacy for intermittent pharmacologic dose testosterone (i.e. Bipolar Androgen Therapy; BAT) in treating advanced prostate cancer. In this project, we will conduct detailed molecular assessments on biospecimens (i.e. blood, metastatic tissue) from men receiving BAT to determine somatic and germline factors that predict for response/resistance. We will also evaluate additional PDT-based regimens (e.g. combinatorial treatments) in preclinical models.
Scope: This annual technical progress report details progress made during the first year of funding for this project (30 Sep 2018 – 1 Oct 2019).
Major Findings: During Year 3 we have continued to collect biospecimens from men enrolled to studies testing BAT. We have published correlative research showing responses to BAT are enriched in patients with mutations in DNA damage repair (DDR) genes. Preclinical studies have supported the hypothesis that DDR abnormalities predict for response to BAT and have also shown that responses are enhanced when BAT is given in combination with PARP inhibition.

15. SUBJECT TERMS
Castration-resistant prostate cancer, testosterone, bipolar androgen therapy, supraphysiologic testosterone, biomarker, mechanism of action

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TABLE OF CONTENTS

1. INTRODUCTION:

The androgen receptor (AR) is frequently upregulated as prostate cancer (PC) adapts to a low androgen environment – likely driving resistance to AR-signaling inhibition. Interestingly, some adapted PC cell lines display blunted growth when exposed to high androgen levels, potentially due to the induction of dsDNA breaks and errors in DNA relicensing. We hypothesized that the adaptive autoregulation of AR may serve as a therapeutic liability; sensitizing PC cells to supraphysiologic testosterone (SPT) induced cell death. To explore this concept further, we designed a mode of SPT therapy termed Bipolar Androgen Therapy (BAT), whereby men with castration-resistant prostate cancer (CRPC) are treated intermittently with very high Pharmacologic Dose Testosterone (PDT). In a proof of concept study, we showed that BAT resulted in PSA and radiographic responses in ~50% of men. However, this study did not incorporate biospecimen acquisition that would have allowed us to determine the molecular events driving these clinical responses. Recently, a large randomized trial testing BAT *vs.* enzalutamide in men with CRPC was launched. As part of our participation in this study, we will obtain blood and metastatic biopsies from men receiving BAT in order to identify biomarkers that predict for response/resistance to BAT and understand the mechanisms of action underlying these responses.

2. KEYWORDS:

Castration-resistant prostate cancer, testosterone, bipolar androgen therapy, supraphysiologic testosterone, biomarker, mechanism of action

3. ACCOMPLISHMENTS:

Major goals of the project:
Major goals of the project as indicated in the Statement of Work. Milestones/target dates for important subtasks, with completion dates or percentage of completion. Note: months are from the start of the funding period (9/30/2016).

Training-Specific Tasks:

Major Task: Training and educational development in prostate cancer research	**Months**	**Percent completed (date of completion)**
Subtask 1: Audit select courses	24-48	50%
Subtask 2: Attend UW training seminars	1-18	100%
Subtask 3: Attend UW conferences/tumor boards	1-48	75%
Subtask 4: Attend National Conferences/Committees	1-48	75%
Major Task: Training and educational development in prostate cancer research	**Months**	**Percent completed (date of completion)**
Subtask 5: Present research at least once per year at Pacific Northwest Prostate Cancer SPORE research conferences	1-48	75%
Subtask 6: Provide direct care for patients with prostate cancer in my clinic. Supervise and educate medical residents and interns and medical oncology fellows	1-48	75%
Subtask 7: Prepare a grant submission to test a novel targeted therapy in the context of precision oncology trials	36-48	0%

Research-Specific Tasks:

Specific Aim 1: Identify somatic alterations in castration-resistant prostate cancers that associate with response and resistance to PDT and determine their causal roles in mediating treatment effects.		
Major Task 1: Biospecimen Acquisition	**Months**	**Percent completed (date of completion)**
Subtask 1: Enroll ≥20 patients onto Phase II BAT *vs.* Enzalutamide Trial*	1-24	90%
Subtask 2: Perform metastatic biopsies and collect blood samples from men receiving BAT*	1-24	90%
Subtask 3: Isolate CTCs*	1-24	90%
Subtask 4: Process plasma from ctDNA*	1-24	90%
**Note:* 17 patients were enrolled and this study has now finished accrual. We continue to enroll to a separate Phase II study testing BAT plus olaparib; including ongoing biospecimen collection.		
Major Task 2: Conduct Targeted Assays to Determine Somatic Features that Associate with Response to BAT		
Subtask 1: Conduct studies to assess for the presence of biallelic loss of DNA damage repair genes	24-40	50%
Subtask 2: Conduct studies to assess for alterations in AR at the genomic, transcript and protein levels	24-40	50%
Subtask 3: Conduct immunohistochemistry and immunofluorescence studies to assess for evidence of DNA damage and decreased cellular proliferation	24-40	50%
Subtask 4: Analyze results to determine if biallelic loss of DNA damage repair genes or alterations in AR associate with response to BAT	40-43	50%
Major Task 3: Conduct Molecular Profiling Studies to Determine Somatic Features that Associate with Response to BAT		
Subtask 1: Conduct transcriptome profiling (RNA-seq) studies on CTCs and metastatic tumors	24-40	50%
Subtask 2: Analyze transcriptome profiling results to assess for predictors of response to BAT	40-43	0%

Specific Aim 2: Evaluate the association of germ-line variations in genes contributing to AR activity and androgen metabolism with response and resistance to PDT.		
Major Task: Evaluate the impact of germ-line variations in androgen transport genes on response and resistance to BAT		
Subtask 1: Evaluate for the presence of germline *SLCO* polymorphisms using qRT-PCR	24-40	50%
Subtask 2: Perform liquid chromatography-mass spectrometry (LC/MS) assays on metastatic biopsy specimens to determine: intratumoral androgen (i.e. testosterone, DHT) and hormonal substrate (i.e. DHEA-S) levels	24-40	0%

Specific Aim 3: Conduct preclinical studies designed to augment the effectiveness of PDT including dosing schedules, testosterone concentrations, and drug combinations.		
Major Task: Conduct preclinical studies to evaluate different PDT schedules, testosterone concentrations and drug combinations		
Subtask 1: Establish LNCaP95 xenografts in castrated SCID-17B mice	12-18	100%
Subtask 2: Evaluate the effect of different PDT schedules, testosterone concentrations and drug combinations on LNCaP95 xenograft growth	18-30	50%
Subtask 2: Perform immunohistochemical studies to evaluate the effects of PDT on AR-FL, AR-SV and γ-H2AX.	18-30	0%

Year 3 Research Accomplishments:

The project entails conducting detailed molecular assessments on biospecimens obtained from men enrolled to a Phase II study testing bipolar androgen therapy (BAT) *vs.* enzalutamide. As outlined in the Statement of Work, Year 3 has focused on ongoing biospecimen acquisition, molecular analyses on samples collected and preclinical studies. Accomplishments from this funding period are provided below.

- Year 3 Objectives: Begin downstream cell-free circulating tumor DNA (ctDNA), circulating tumor cell (CTC) and tumor tissue analyses. Conduct pre-clinical studies to evaluate the mechanisms driving responses to supraphysiologic testosterone (SPT)

- Major Activities: We have enrolled 17 out of a projected 20 subjects to the Phase II BAT *vs.* enzalutamide study. This study has now completed accrual and we do not anticipate enrolling any additional patients to this trial. I have recently initiated a separate Phase II study testing BAT in combination with the PARP inhibitor olaparib. Biospecimens are being obtained from this clinical trial and may be used to complete some of the described correlative work (e.g. measuring intratumoral androgens, etc).

  Thirteen patients enrolled to the randomized BAT *vs.* enzalutamide study have received BAT to date. Three individuals enrolled to this randomized study have had metastatic biopsies performed (one patient underwent baseline and Day 8 biopsy). We have also received 67 plasma samples for ctDNA studies from our collaborators at Johns Hopkins. We have optimized UW-OncoPlex (a targeted next-generation DNA sequencing panel) for use on plasma samples (i.e. cell-free circulating tumor DNA; ctDNA) samples and have sequenced these samples (plasma and tumor tissue). We found that the PSA response rate in patients with mutation in DNA damage repair (DDR) genes was significantly higher than those with intact DDR genes. In collaboration with Johns Hopkins, we have also analyzed CTC-based transcript profiling results; however, there was no association noted between full length androgen receptor (AR-FL) or androgen receptor splice variant (AR-Vs) expression and response/resistance to BAT.

  Preclinical studies as described in Specific Aim 3 have been partially completed, with additional studies underway. Initial *in vitro* work has been published showing that: i) SPT effects are enhanced in prostate BRCA2-null prostate cancer models, and ii) combining SPT with olaparib (PARP inhibition) augments the clinical effects of SPT. These results have been published. Additional *in vivo* studies are ongoing.

- Results and Outcomes: We have published a paper detailing our finding that DDR mutations predict for response to BAT along with additional preclinical studies supporting a mechanistic basis for this finding. We have also shown that combining PAPR inhibition with SPT has enhanced anti-tumor effects, further supporting our ongoing Phase II study testing BAT plus olaparib. As part of this Phase II trial, additional blood and metastatic tissue collection is ongoing. Molecular assessments on these samples are planned in Years 4 of the project.

- Goals not Met: Given that few patients agreed to metastatic biopsy as part of the randomized BAT vs. enzalutamide study, we are planning to utilize tissue from patients enrolled to our BAT + olaparib study to complete the molecular assessments described in the Statement of Work. We continue to collect metastatic tissue and blood for CTC studies from men enrolled to this trial and we are on track to complete molecular assessments in Year 4. This includes, completion of transcript profiling studies, evaluation of germline androgen transport gene polymorphisms and measuring intratumoral hormone levels.

Year 3 Training and Professional Development:
This Training Award includes a multi-dimensional plan designed to endow me with the skills and practical knowledge that will allow me to recognize, develop and effectively exploit new approaches for treating prostate cancer. This training plan involves both didactic and 'hands-on' professional development experiences. Experiences from Year 3 are outlined below.

- Seminars and Conferences: As outlined in the Statement of Work, participation in a number of seminars is ongoing through the end of this Training Award. I continue to attend and present at the weekly Pacific Northwest Prostate Cancer SPORE conference series, as well as attend the weekly Oncology Center grand rounds. I regularly attend the Prostate Cancer Precision Tumor Board and GU Tumor Board, and actively participate in our Localized and Advanced GU Oncology Clinical Trials Conferences. In addition, I have attended seminars and workshops as outlined in the SOW.
- National Conferences and Committees: This past year I have attended the ASCO GU meeting and the Prostate Cancer Foundation annual retreat.
- Clinical Development: I see and manage men with localized and advanced prostate cancer on an outpatient basis 1.5 days per week. I also attend on the inpatient unit ~2-4 weeks per year. I receive clinical management advice from Dr. Nelson, Dr. Yu and other senior faculty. In my clinic I actively enroll patients onto clinical trials, including studies testing BAT-based regimens.
- Mentoring/Training: I interact regularly with medical residents, oncology fellows and medical students. I am also mentoring a second-year oncology fellow. We have published a few case reports/review articles and are in the process of completing a retrospective review project. We have also developed a prospective clinical trial that we anticipate will open in late-2019. Finally, I have been working with three medicals students on a retrospective analysis and hope to have this submitted for publication in late 2019.
- Lectures: I have delivered several lectures over the past year. These include speaking locally at Grand Rounds, our SPORE Seminar Series, the Seattle Cancer Care Alliance Comprehensive Hematology and Oncology Review Course and at residency/fellowship educational conferences. I have also given invited lectures at the Gordon's Research Conference: Hormone Dependent Cancers meeting and at the annual Cancer Immunotherapy Trial Network meeting.

- Peer Review Activities: Over the past year, I have reviewed a number of articles for peer-reviewed journals. I also served on a grant review committee for the DoD PCRP, Prostate Cancer Foundation Australia and our SPORE Pilot Grant.

Results Dissemination:

- *Chatterjee, P., †**Schweizer, M.T.**, Lucas, J.M., Coleman, I., Nyquist, M.D., Frank, S.B., Tharakan, R., Mostaghel, E., Luo, J., Pritchard, C.C., Lam, H.M., Corey, E., Antonarakis, E.S., Denmeade, S.R. & Nelson, P.S. Supraphysiological androgens suppress prostate cancer growth through androgen receptor-mediated DNA damage. The Journal of clinical investigation 130(2019).
  †Co-first author

- **Schweizer MT**, Antonarakis ES, Eisenberger MA, Nelson PS, Luo J, Pritchard C, Denmeade SR. Genomic determinants of sensitivity to bipolar androgen therapy (BAT) in castrate-resistant prostate cancer (CRPC). Poster presetend at: 2019 Genitourinary Cancers Symposium, San Francisco, CA

Funding Year 4 Plans:

Over the next reporting period, I will continue to collect biospecimen as outlined in the Statement of Work, with a focus on metastatic tissue acquisition. I will also complete the molecular assessments described in Specific Aims 1 and 2, with a focus on completing tumor tissue analyses on metastatic biopsy specimens. Preclinical studies (Specific Aim 3) to assess combinatorial PDT-based regimens in LNCaP95 xenografts have been completed and we plan to conduct mechanistic studies on treated xenograft tissue as described in Aim 3.

4. IMPACT:

We have initiated a Phase II clinical trial testing BAT plus olaparib (PARP inhibitor). This combinatorial approach is supported by our findings that: i) responses to BAT are enriched in patients with mutations in DNA repair genes, and ii) co-treatment with PAPR inhibitors can augment responses to BAT.

5. CHANGES/PROBLEMS:

We had difficulty convincing patients to agree to on-treatment biopsies as part of the randomized BAT *vs.* enzalutamide trial. Since that study is now completed, we are obtaining metastatic biopsies as part of our BAT plus olaparib trial to use toward completing the work described in Specific Aims 1 and 2.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

1. Graham, L.S., Schade, G. & **Schweizer, M.T.** Multimodality Treatment of Bilateral Wilms Tumor in a Pregnant Female. Urology (2019).

2. Labrecque, M.P., Coleman, I.M., Brown, L.G., True, L.D., Kollath, L., Lakely, B., Nguyen, H.M., Yang, Y.C., Gil da Costa, R.M., Kaipainen, A., Coleman, R., Higano, C.S., Yu, E.Y., Cheng, H.H., Mostaghel, E.A., Montgomery, B., **Schweizer, M.T.**, Hsieh, A.C., Lin, D.W., Corey, E., Nelson, P.S. & Morrissey, C. Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer. The Journal of clinical investigation 130(2019).

3. Chatterjee, P., †**Schweizer, M.T.**, Lucas, J.M., Coleman, I., Nyquist, M.D., Frank, S.B., Tharakan, R., Mostaghel, E., Luo, J., Pritchard, C.C., Lam, H.M., Corey, E., Antonarakis, E.S., Denmeade, S.R. & Nelson, P.S. Supraphysiological androgens suppress prostate cancer growth through androgen receptor-mediated DNA damage. The Journal of clinical investigation 130(2019).
   †Co-first author

4. Lam, H.M., Nguyen, H.M., Labrecque, M.P., Brown, L.G., Coleman, I.M., Gulati, R., Lakely, B., Sondheim, D., Chatterjee, P., Marck, B.T., Matsumoto, A.M., Mostaghel, E.A., **Schweizer, M.T.**, Nelson, P.S. & Corey, E. Durable Response of Enzalutamide-resistant Prostate Cancer to Supraphysiological Testosterone Is Associated with a Multifaceted Growth Suppression and Impaired DNA Damage Response Transcriptomic Program in Patient-derived Xenografts. European urology (2019).

5. Winters, B.R., De Sarkar, N., Arora, S., Bolouri, H., Jana, S., Vakar-Lopez, F., Cheng, H.H., **Schweizer, M.T.**, Yu, E.Y., Grivas, P., Lee, J.K., Kollath, L., Holt, S.K., McFerrin, L., Ha, G., Nelson, P.S., Montgomery, R.B., Wright, J.L., Lam, H.M. & Hsieh, A.C. Genomic distinctions between metastatic lower and upper tract urothelial carcinoma revealed through rapid autopsy. JCI insight 5(2019).

6. **Schweizer MT**, Antonarakis ES, Bismar TA, Guedes LB, Cheng HH, Tretiakova MS, Vakar-Lopez F, Klemfuss N, Konnick EQ, Mostaghel EA, Hsieh AC, Nelson PS, Yu EY, Montgomery RB, True LD, Epstein JI, Lotan TL, Pritchard CC. Genomic characterization of prostatic ductal adenocarcinoma identifies a high prevalence of DNA repair gene mutations. JCO Precision Oncology (2019).

7. Brennen, W.N., **Schweizer, M.T.**, Wang, H., Bivalacqua, T.J., Partin, A.W., Lim, S.J., Chapman, C., Abdallah, R., Levy, O., Bhowmick, N.A., Karp, J.M., De Marzo, A., Isaacs, J.T. & Denmeade, S.R. In Reply to the Letter to the Editor from Raj et al.: Clinical Evidence Indicates Allogeneic Mesenchymal Stem Cells Do Not Pose a Significant Risk for Cancer Progression in the Context of Cell-Based Drug Delivery. Stem cells translational medicine (2019).

8. **Schweizer, M.T.**, Gulati, R., Beightol, M., Konnick, E.Q., Cheng, H.H., Klemfuss, N., De Sarkar, N., Yu, E.Y., Montgomery, R.B., Nelson, P.S. & Pritchard, C.C. Clinical determinants for successful circulating tumor DNA analysis in prostate cancer. The Prostate (2019).

9. Marshall, C.H., Sokolova, A.O., McNatty, A.L., Cheng, H.H., Eisenberger, M.A., Bryce, A.H., **Schweizer, M.T.** & Antonarakis, E.S. Differential Response to Olaparib Treatment Among Men with Metastatic Castration-resistant Prostate Cancer Harboring BRCA1 or BRCA2 Versus ATM Mutations. European urology (2019).

10. **Schweizer, M.T.**, Wang, H., Bivalacqua, T.J., Partin, A.W., Lim, S.J., Chapman, C., Abdallah, R., Levy, O., Bhowmick, N.A., Karp, J.M., De Marzo, A., Isaacs, J.T., Brennen, W.N. & Denmeade, S.R. A Phase I Study to Assess the Safety and Cancer-Homing Ability of Allogeneic Bone Marrow-Derived Mesenchymal Stem Cells in Men with Localized Prostate Cancer. Stem cells translational medicine (2019).

11. Nava Rodrigues, D., Rescigno, P., Liu, D., Yuan, W., Carreira, S., Lambros, M.B., Seed, G., Mateo, J., Riisnaes, R., Mullane, S., Margolis, C., Miao, D., Miranda, S., Dolling, D., Clarke, M., Bertan, C., Crespo, M., Boysen, G., Ferreira, A., Sharp, A., Figueiredo, I., Keliher, D., Aldubayan, S., Burke, K.P., Sumanasuriya, S., Fontes, M.S., Bianchini, D., Zafeiriou, Z., Teixeira Mendes, L.S., Mouw, K., **Schweizer, M.T.**, Pritchard, C.C., Salipante, S., Taplin, M.E., Beltran, H., Rubin, M.A., Cieslik, M., Robinson, D., Heath, E., Schultz, N., Armenia, J., Abida, W., Scher, H., Lord, C., D'Andrea, A., Sawyers, C.L., Chinnaiyan, A.M., Alimonti, A., Nelson, P.S., Drake, C.G., Van Allen, E.M. & de Bono, J.S. Immunogenomic analyses associate immunological alterations with mismatch repair defects in prostate cancer. The Journal of clinical investigation 128, 4441-4453 (2018).

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

Nothing to report.

Other publications, conference papers and presentations.

- **Schweizer MT**, Antonarakis ES, Eisenberger MA, Nelson PS, Luo J, Pritchard C, Denmeade SR. Genomic determinants of sensitivity to bipolar androgen therapy (BAT) in castrate-resistant prostate cancer (CRPC). Poster presented at: 2019 Genitourinary Cancers Symposium, San Francisco, CA

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name:	*Michael Schweizer*
Project Role:	*PI*

eRA Commons User Name: *mschwei9*
Nearest person month worked: *6*
Contribution to Project: *Coordinates all aspects of the research in this project, including: planning, data gathering and analysis.*
Funding Support: *DoD PCRP PRTA (W81XWH-16-1-0484)*

Name: *Peter Nelson*
Project Role: *Mentor*
eRA Commons User Name: *pnelson*
Nearest person month worked: *1*
Contribution to Project: *Provides advice and resources to ensure this project is carried our as described.*
Funding Support: *PNW Prostate Cancer Spore (P50 CA097186-12)*

Change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period:

Updated Support Document for the PI (Dr. Schweizer) is attached as an appendix.

Other organizations involved as partners:

Organization Name: Johns Hopkins School of Medicine
Location of Organization: Baltimore, MD
Partner's contribution to the project

- *Provided biospecimens from men receiving bipolar androgen therapy (BAT).*

8. APPENDICES:

SUPPORT
SCHWEIZER, MICHAEL T.

CURRENT

Title: A Randomized Phase II Study Comparing Bipolar Androgen Therapy vs. Enzalutamide in Asymptomatic Men with Castration Resistant Metastatic Prostate Cancer: The TRANSFORMER Trial
Effort: 0.60 CM
Funding Agency: DoD (W81XWH-14-2-0189)
Contracting Officer: Ting Wang (Johns Hopkins); twang2@jhmi.edu
Performance Period: 09/01/15 – 03/29/20
Funding Level: $156,016
Goal: To determine if treatment with supraphysiologic testosterone will improve radiographic progression free survival compared to enzalutamide in men with metastatic castrate-resistant prostate cancer post-treatment with abiraterone.

Title: Cancer Center Support Grant New Investigator Support
Effort: 0 CM
Funding Agency: NCI/NIH (P30 CA015704)
Grants Officer: Heidi Tham; hharbach@fredhutch.org
Performance Period: 12/15/15 – 12/31/19
Funding Level: $75,000
Goal: Use next generation sequencing to determine the prevalence of genomic hypermutation within the general population of prostate cancer patients and determine if mismatch repair deficiency underlies this phenotype.
Specific Aims: 1) Use mSINGS to estimate the frequency of hypermutated prostate cancer within the general population of prostate cancer patients. 2) Use UW-OncoPlex to confirm hypermutation status and to evaluate for alterations in mismatch repair genes that may associate with this phenotype.

Title: A Phase III, Open-Label, Multicenter, Randomized Study of Atezolizumab (Anti-PD-L1 Antibody) Vs. Observation as Adjuvant Therapy in Patients with High-Risk Muscle-Invasive Urothelial Carcinoma After Surgical Resection
Effort: 0.60 CM
Funding Agency: F. Hoffmann-LaRoche / Genentech
Grants Officer: Jonathan Kursar; kursar.jonathan@gene.com
Performance Period: 10/14/16 – 06/30/20
Funding Level: $181,055
Goal: To evaluate the efficacy of adjuvant atezolizumab treatment in patients with muscle- invasive urothelial carcinoma (UC), as measured by disease-free survival.
Specific Aims: 1) To evaluate the efficacy of adjuvant atezolizumab treatment, as measured by overall survival. 2) To evaluate the efficacy of adjuvant atezolizumab treatment, as measured by disease-specific survival.

Title: A Phase 2 Study of ARN-509 in Active Surveillance Patients
Effort: 0.60 CM
Funding Agency: Janssen Scientific Affairs, LLC
Grants Officer: Afrouz Bazmi; (724) 935-2140
Performance Period: 04/12/17 – 04/30/20
Funding Level: $202,187
Goal: The main goal is to determine if a 90-day course of ARN-509 will lead to a negative repeat prostate biopsy in active surveillance patients.
Specific Aims: Determine the negative repeat biopsy rate by site directed and systematic prostate biopsy after 90-days of ARN-509.

Title: Pharmacologic Dose Testosterone to Treat Castration-Resistant Prostate Cancer: Mechanisms of Action and Drivers of Response

Effort: 4.8 CM
Funding Agency: Department of Defense
Grant Specialist: Mirlene Desir; (301) 619-7733; mirlene.desir.civ@mail.mil
Performance Period: 09/30/16 – 09/29/20
Funding Level: $630,457
Goal: This is a Physician Research Training Award. The goal of the program is to assist young investigators in their first years of research, and this project will focus on developing new therapeutic strategies that reduce the morbidity and mortality attributable to prostate cancer.
Specific Aims: Establish an intensive didactic training program, design and conduct early phase translational trials, and exploit findings from these trials to discover new pathways, targets, and strategies capable of improving prostate cancer outcomes.

Title: A Phase I Study of a DNA Vaccine Encoding Androgen Receptor Ligand-Binding Domain (AR LBD), With or Without Granulocyte Macrophage Colony-Stimulating Factor Adjuvant, in Patients with Metastatic Prostate Cancer
Effort: 0.36 CM
Funding Agency: Madison Vaccine Inc.
Grants Officer: Richard Lesniewski; rick@madisonvaccines.com
Performance Period: 01/30/17 – 01/29/21
Funding Level: $392,305
Goal: The major goal of this study is to determine if a vaccine called pTVG-AR can enhance patients' immune response against prostate cancer.

Title: Bipolar Androgen Therapy Plus Olaparib in Patient with Castration-Resistant Prostate Cancer
Effort: 0.60 CM
Funding Agency: AstraZeneca
Grants Officer: Gayle Ewing, gayle.ewing@astrazeneca.com
Performance Period: 08/01/19-03/31/23
Funding Level: $430,010
Goal: The major goal of this study is to determine the PSA50 response rate (i.e., percent of patients with a PSA decline of at least 50% below baseline) following 12-weeks of treatment with bipolar androgen therapy (BAT) plus olaparib in men with asymptomatic metastatic castration-resistant prostate cancer (mCRPC) who have progressed on abiraterone and/or enzalutamide.
Specific Aims: 1) Determine the percent of mCRPC patients achieving a radiographic response per RECIST 1.1 criteria following treatment with BAT plus olaparib. 2) Determine the radiographic progression free survival (PFS) in mCRPC patients treated with BAT plus olaparib using RECIST 1.1 criteria for soft tissue metastases and Prostate Cancer Working Group 3 (PCWG3) criteria for bone metastases.

Title: A Phase 1 Safety and Tolerability Study of ZEN003694 in Combination with Enzalutamide in Patients with Metastatic Castration-Resistant Prostate Cancer
Effort: 0.60 CM
Funding Agency: Zenith Epigenetics, Ltd
Grant Specialist: Drew Davis, PCCTC, LLC.; davisa1@mskcc.org
Performance Period: 07/27/18 – 04/30/23
Funding Level: $344,738
Goal: The major goal of this study is to determine the appropriate dosage of ZEN003694 in combination with enzalutamide in patients with mCRPC.
Specific Aims: 1) To determine the safety, tolerability and maximum tolerated dose of ZEN003694 in combination with enzalutamide in patients with mCRPC who have progressed during prior treatment with enzalutamide or with abiraterone. 2) To confirm the safety and tolerability and MTD and recommended Phase 2 dose of ZEN003694.

Title: A Phase 1, First-in-Human, Dose Escalation Study of JNJ-63898081 in Subjects with Advanced Stage Solid Tumors

Effort: 0.60 CM
Funding Agency: Janssen Research & Development
Contracting Officer: Tammy Norton; TNorton2@its.jnj.com
Performance Period: 3/19/19 – 05/01/2024
Funding Level: $1,351,000
Goal: The major goal of this study is to determine whether JNJ-63898081 will direct the body's immune cells to kill the malignant cells overexpressing prostate-specific membrane antigen (PSMA).
Specific Aims: Part 1 (Dose Escalation): Determine the recommended Phase 2 dose (RP2D) regimen and the maximum tolerated dose; Part 2 (Expansion): Determine the safety of JNJ-63898081 at the RP2D regimen.

Title: A Phase 1, First-in-Human, Dose Escalation Study of JNJ-63898081 in Subjects with Advanced Stage Solid Tumors
Effort: 0.60 CM
Funding Agency: Janssen Research & Development
Contracting Officer: Tammy Norton; TNorton2@its.jnj.com
Performance Period: 11/17/2015 – 11/16/2020
Funding Level: $1,351,000
Goal: The major goal of this study is to determine whether JNJ-63898081 will direct the body's immune cells to kill the malignant cells overexpressing prostate-specific membrane antigen (PSMA).
Specific Aims: Part 1 (Dose Escalation): Determine the recommended Phase 2 dose (RP2D) regimen and the maximum tolerated dose; Part 2 (Expansion): Determine the safety of JNJ-63898081 at the RP2D regimen.

Title: A Phase 1 Dose Escalation and Expanded Cohort Study of PF-06821497 in the Treatment of Adult Patients with Relapsed/Refractory Small Cell Lung Cancer (SCLC), Castration Resistant Prostate Cancer (CRPC) and Follicular Lymphoma (FL).
Effort: 0.60 CM
Funding Agency: Pfizer, Inc. (C2321001)
Contracting Officer: María José San Emeterio; MariaJose.SanEmeterio@PAREXEL.com
Performance Period: 06/28/2018 – 02/28/2023
Funding Level: $410,665
Goal: To conduct a Phase I/II study testing an EZH2 inhibitor (PF-06821497) in patients with advanced cancers, including metastatic castration-resistant prostate cancer (CRPC).
Specific Aims: Part 1 (Doose Escalation) Determine the recommended Phase II dose (RP2D) for PF-06821497 in combination with standard cancer therapeutics; Part 2 (Expansion): evaluate the efficacy of PF-06821497 at the RP2D in combination with standard cancer therapeutics.

COMPLETED

Title: Minimally Invasive Assessments of Tumor Molecular Composition for Precision Diagnostics and Monitoring Treatment Response
Effort: 0.36 CM
Funding Agency: NCI/NIH (P30 CA015704)
Grants Officer: Heidi Tham; hharbach@fredhutch.org
Performance Period: 07/01/15 – 06/30/16
Funding Level: $100,000
Goal: The goal of this project is to develop technology that will allow for the molecular assessment of circulating tumor cells. The assays developed will be utilized in a prospective biomarker trial to evaluate for determinates of response and resistance to prostate cancer therapies.
Specific Aims: Aim 1) Determine the molecular identity and genomic diversity between image-guided core tumor biopsies and parallel assessments of CTCs and ctDNA from the same patients. Aim 2) Determine if molecular assessments of AR-SVs and somatic alterations in DNA repair mechanisms (e.g. BRCA2 loss/mutation) from ctDNA or CTCs associate with clinical responses to: (i) agents targeting the AR pathway; or (ii) genotoxic therapeutics (e.g. carboplatin), respectively. Aim 3) Determine if quantitative

measures of AR-SVs (for therapeutics targeting the AR pathway) or DNA repair gene defects (for genotoxic therapeutics) in CTCs or ctDNA can serve as dynamic measurements of responses and early indicators of treatment failures when measured over time during a course of treatment.

Title: Targeted Niche Therapy (TNT) to Cure Metastatic Prostate Cancer
Effort: 0.60 CM
Funding Agency: Prostate Cancer Foundation
Grants Officer: Howard Soule, PhD; (310) 570-4596
Performance Period: 08/01/14 – 08/17/17
Funding Level: $19,000
Goal: The goal of this project is to determine the kinetics of prostate cancer cell mobilization from the bone marrow in response to CXCR4 inhibition as well as to explore the effect that docetaxel has on prostate cancer cells that have been mobilized. Molecular profiling studies have also been built into this project to further characterize prostate cancer cells both within the protective bone marrow niche and those that have been mobilized.
Specific Aims: Aim 1) Perform a Phase 0 trial to determine the kinetics of prostate cancer cell mobilization from the bone marrow in response to the CXCR4 inhibitor AMD3100. Aim 2) Define the phenotype of PCa cells that are mobilized from the HSC niche.

Title: A Phase I Study of Niclosamide in Men with AR-V Positive CRPC
Effort: 0.36 CM
Funding Agency: NCI/NIH (P30 CA015704)
Grants Officer: Jennifer Jacyszyn; (206) 667-6250
Performance Period: 01/01/15 – 12/30/17
Funding Level: $49,239
Goal: The goal of this project is to determine the safety and tolerability of high-dose niclosamide when given in combination with enzalutamide. As a secondary objective, I will assess the effects of this therapy on androgen receptor splice variants (AR-Vs) pre- and post-treatment using a qRT-PCR assay.
Specific Aims: Aim 1) Conduct a Phase I study to assess the safety and pharmacokinetics of oral niclosamide in men with AR-V positive castration-resistant prostate cancer. Aim 2) Assess the impact of oral niclosamide on AR-V transcript levels.

Title: A Phase I Study of Niclosamide in Men with AR-V Positive CRPC: Molecular Correlates
Effort: 0.24 CM
Funding Agency: NCI/NIH (P50 CA097186)
Grants Officer: Samantha Farrell, farrellsa@mail.nih.gov
Performance Period: 04/01/15 – 08/31/17
Funding Level: $29,300
Goal: The goal of this project is to determine the effects of high-dose niclosamide on the transcriptional program of androgen receptor splice variant (AR-V) positive prostate cancer cells.
Specific Aims: Aim 1) Determine the effect of oral niclosamide plus enzalutamide on the transcriptional program of circulating tumor cells (CTCs) through RNA-seq.

Title: A Neoadjuvant Clinical Trial to Assess the Effectiveness of Intense Combinatorial Targeting of AR-Signaling to Eradicate Prostate Carcinoma
Effort: 0.36 CM
Funding Agency: NCI/NIH (P30 CA015704)
Grants Officer: Heidi Tham; hharbach@fredhutch.org
Performance Period: 01/01/17 – 12/31/18
Funding Level: $35,000
Goal: We will test a neoadjuvant AR-signaling ablative regimen that includes the AKR1C3 inhibitor indomethacin. Our primary objective will be to determine the pathologic complete response rate following 3-months of therapy in men with high-risk prostate cancer.

Specific Aims: Aim 1) Determine if high intensity short course combinatorial suppression of AR signaling with abiraterone, ARN-509, degarelix and indomethacin will eradicate prostate cancer cells within the prostate microenvironment and tumor cells that have disseminated to lymph nodes. Aim 2) Identify molecular features of prostate cancer cells and their microenvironments that associate with response and resistance to combinatorial AR pathway targeting.

Title: Bipolar Androgen Therapy (BAT): Molecular Drivers of Response and Resistance
Effort: 0.60 CM
Funding Agency: Prostate Cancer Foundation
Grants Officer: Howard Soule, PhD; (310) 570-4596
Performance Period: 10/12/15 – 10/12/18
Funding Level: $250,000
Goal: We will determine the drivers of response/resistance to supraphysiologic testosterone in men with castration-resistant prostate cancer. This will be accomplished by conducting molecular assessments on circulating tumor cells and metastatic biopsies obtained from men enrolled to a Phase II trial testing this therapy.
Specific Aims: Aim 1) Biospecimen acquisition from patients receiving BAT. Aim 2) Identify somatic features that associate with tumor response and resistance to BAT. Aim 3) Evaluate germ-line/host factors that may impact response and resistance to BAT

PENDING

Title: Erdafitinib plus Abiraterone Acetate or Enzalutamide in Double Negative Prostate Cancer (DNCP)
Effort: 0.60 CM
Funding Agency: Janssen Research & Development
Contracting Officer: Susan Meisenbach, smeisenb@its.jnj.com
Performance Period: 06/01/19 – 05/31/24
Funding Level: $250,000
Goal: The major goal of this study is to determine the objective tumor response rate in subjects with measurable lesions as defined by RECIST v1.1 criteria in metastatic castrate resistant prostate cancer (mCRPC) patients with a DNPC molecular phenotype receiving either enzalutamide or abiraterone acetate.
Specific Aims: 1) Determine the radiographic progression-free survival (PFS) in patients using RECIST 1.1 criteria for soft tissue metastases and Prostate Cancer Working Group 3 (PCWG3) criteria for bone metastases. 2) Determine the time to response using RECIST 1.1 criteria.

Title: A dose escalation and expansion study of TRX518 in Combination with Cyclophoshamide Plus Avelumab in Advanced Solid Tumors
Effort: 0.60 CM
Funding Agency: Leap Therapeutics Inc.
Contracting Officer: Keitia Brooks; kfbrooks@cei3inc.com
Goal: The major goal of this study is to evaluate treatment with TRX518 in combination with CTX plus avelumab for any evidence of anti-tumor activity

OVERLAP

None