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TITLE: "Development of Molecular Chaperone Inhibitors for (Re) Sensitization of CRPC to Enzalutamide and Abiraterone and to Synergize with Metabolic Inhibitors"

PRINCIPAL INVESTIGATOR: Dr. Leonard Neckers

CONTRACTING ORGANIZATION: The Geneva Foundation, Tacoma, WA

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14. ABSTRACT

Objective: (1) Improve the solubility and pharmacodynamic properties of previously identified Hsp40 & Hsp70 inhibitors in preparation for Phase I clinical evaluation in CRPC patients. (2) Determine whether these chaperone inhibitors sensitize resistant CRPC to Enz and/or Abi and, if so, by what mechanism(s). (3) Increase our understanding of the role of these chaperones in regulating CRPC metabolic deregulation, with the goal of identifying novel synergistic combinatorial approaches to target CRPC.

Impact: By identifying a chaperone-based approach to inhibit or reverse CRPC resistance to Enz and/or Abi, the current research proposal addresses the dual 2018 PCRP Overarching Challenges of (1) developing treatments that improve the outcomes for men with lethal prostate cancer and (2) better defining the biology of lethal prostate cancer to reduce death. Further, consistent with the mandate of the PCRP Impact Award, a key goal of our research strategy is to position the program for first-in-human clinical evaluation of one or more of these chaperone inhibitors within 5 years after completion of this Award.

15. SUBJECT TERMS
Cancer, Prostate Cancer, Oncology

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Table of Contents

1 . INTRODUCTION: Androgen receptor (AR) signaling remains important in CRPC. Accordingly, two potent second line anti-androgen agents, abiraterone and enzalutamide, were developed. Abiraterone is a CYP17A1 inhibitor (blocking both 17-alpha-hydroxylase and 17,20 desmolase enzymatic activities) which causes a marked reduction of androgen in serum and in CRPC osseous metastases. Enzalutamide is a competitive antagonist of AR, which binds the ligand binding domain (LBD), preventing nuclear translocation and AR-dependent gene transcription. Unfortunately, most patients that initially respond to these drugs develop resistance, concomitant with reactivated AR signaling. The emergence of ADT-resistant CRPC is frequently associated with expression of a number of AR splice variants (ARv), including but not limited to ARv7, which lack a carboxy-terminal LBD. Consequently, these ARv are insensitive to anti-androgens or androgen ablation and are constitutively active. Notably, ARv7 expression has been associated with poor prognosis, shorter overall survival and resistance to standard of care treatments in CRPC patients. In addition to ARv expression, another key mechanism underlying resistance to enzalutamide is metabolic dysregulation through enhanced dependence on glucose metabolism. PCa is characterized by dependence on glycolysis and altered fatty acid and glutamine metabolism, and this metabolic reprogramming is regulated, in part, by the transcriptional activity of full-length AR. Expression of ARv (in particular, ARv7) has been shown to further increase dependence of CRPC on glutaminolysis and reductive carboxylation. Thus, alternative approaches to disrupt the AR and ARv7 signaling axis and its effects on metabolic disrregulation and ADT resistance in CRPC are of great clinical importance and remain a critical unmet need. Such a strategy would be expected to provide efficacy in CRPC and may also (re-)sensitize ADT-resistant CRPC to LBD targeted therapy (e.g., enzalutamide and/or abiraterone). The research plan described in the current proposal builds on the current team's multi-year ongoing and successful collaboration, funded by the 2015 PCRP Idea Development Award, that identified Hsp40 and Hsp70 inhibitors as novel therapeutic agents with *in vitro* and *in vivo* activity toward enzalutamide- and abiraterone-resistant CRPC expressing AR splice variants, including ARv7. The current research proposal addresses the dual 2018 PCRP Overarching Challenges of (1) developing treatments that improve the outcomes for men with lethal prostate cancer and (2) defining the biology of lethal prostate cancer to reduce death. Further, consistent with the mandate of the PCRP Impact Award, a key goal of our research strategy is to position the program for first-in-human clinical evaluation of one or more of these chaperone inhibitors within 5 years after completion of this Award.

2 . KEYWORDS: castration-resistant prostate cancer, androgen, androgen receptor, ARv7, chaperone inhibitors, Hsp70, Hsp40, metabolism, glycolysis, oxidative phosphorylation

3 . ACCOMPLISHMENTS:

What were the major goals of the project?

SA1/Major Task 1: Synthesis and characterization of sufficient amounts of C86, JG-98, JG-231 and other analogs.

Milestones	target dates	actual dates	%completion
n/a	1-36 months	12-24 months	60%

SA1/Major Task 2: Lead optimization of JG-231 analogs. From this Task, we will produce 1-2 optimized candidates for testing in efficacy models.

Milestones	target dates	actual dates	%completion
n/a	1-18 months	12-24 months	45%

SA1/Major Task 3: Hit-to-lead optimization of C86 and analogs. From this Task, we will identify the binding site of C86 and understand whether this site can accommodate drug-like molecules.

Milestones	target dates	actual dates	%completion
n/a	12-36 months	12-24 months	0%

SA2/Major Task 4: Assess combinatorial activity of chaperone inhibitors in 3 resistant CRPC models (22Rv1, VCaP, C4-2).

Milestones	target dates	actual dates	%completion
Validation of ability of Hsp40/Hsp70 inhibitors to sensitize resistant CRPC cells and tumors to enzalutamide and/or abiraterone	1-18 months	12-24 months	50%

SA2/Major Task 5: Determine mechanistic basis of combinatorial activity underlying chaperone inhibitor-mediated sensitization to enzalutamide and/or abiraterone.

Milestones	target dates	actual dates	%completion
Identification of one or more mechanisms by which Hsp40 and/or Hsp70 inhibitors sensitize resistant CRPC cells to enzalutamide and/or abiraterone.	6-18 months	12-24 months	60%

SA3/Major Task 6: Assess combinatorial activity of Hsp40 and Hsp70 inhibitors with inhibitors of glycolysis, pentose phosphate pathway, glutaminolysis and fatty acid synthesis.

Milestones	target dates	actual dates	%completion
Identification of synergy between chaperone inhibitors and selected metabolic inhibitors; identification of metabolic pathways, whose inhibition (alone or combined with chaperone inhibition) sensitizes resistant CRPC to enzalutamide and/or abiraterone; validation of non-invasive MRSI to predict treatment efficacy *in vivo*.	12-36 months	12-24 months	50%

Specific Aims:

1. Initiate a pre-clinical development program to improve solubility and pharmacokinetic properties of Hsp40 & Hsp70 inhibitors to maximize in vivo safety, efficacy and bioavailability.

2. Examine whether current Hsp40 and/or Hsp70 inhibitors sensitize CRPC to Enz and/or Abi in vitro and in vivo, and by what mechanism(s).
3. Determine whether additive/synergistic activity is observed in CRPC when Hsp40/Hsp70 inhibition is combined with inhibitors of distinct metabolic pathways deregulated in CRPC.

What was accomplished under these goals?

Specific Aim 1: The goal of Specific Aim 1 is to advance the development of clinical candidates targeting Hsp70 and Hsp40. In the 2019 funding cycle, we focused on the critical issues of target validation and compound selectivity. Recent hit-to-lead work had produced a set of chemical probes, such as JG-98, JG-194, JG-231 and JG-294, that interrupt Hsp70 function by binding to an allosteric site (Shao et al. 2018 J. Med. Chem.) and we had shown that some of these molecules have promising anti-proliferative activity in cellular and animal models of CRPC (Moses et al. 2018 Cancer Res). However, it is critical to support a pre-clinical program with strong evidence of target engagement. Accordingly, we pursued two innovative approaches: (i) whole genome CRISPRi screens and (ii) genetic validation with a tryptophan mutant. In the CRISPR screens, we treated K562 cells stably expressing dCas9 with a series of Hsp70 inhibitors and then transduced with sgRNA in lentiviral vectors (Fig 1A). We are still validating these screening results, but the initial findings suggest that the probes are selective for Hsp70s. However, we also uncovered an unexpected difference in the types of Hsp70s that are bound. For example, JG-98 and JG-194 primarily relied on Hsp70s of the cytoplasm and mitochondria (HSPA1A, HSPA8 and HSPA9) for their phenotypic effects (Fig 1B), while JG-294 required the ER-resident Hsp70 (termed BiP or HSPA5). Moreover, these results showed that a series of SLC transporters are required in all cases, suggesting that the compounds are actively transported. We will continue to explore this dataset in the next cycle.

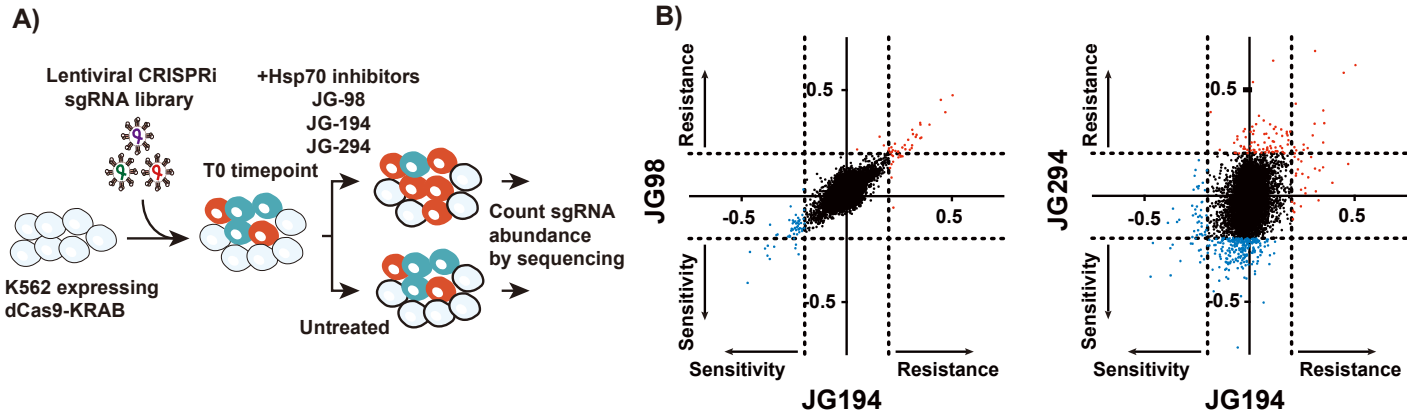


Fig 1. Hsp70 inhibitors have preference for distinct members of the family. (A) Workflow for the whole genome CRISPRi screens. Hsp70 inhibitors were used at their EC50 values (approx. 1,000 to 300 nM). Samples were deep sequenced at the initial and final time point to quantify sgRNA counts. (B) Comparison of CRISPRi screenin results of JG-98 with JG-194 and JG-294, respectively. JG98 and JG194 have very similar CRISPRi profiles, while JG-294 is different. The top hits in the JG-98 and JG-194 experiments were cytoplasmic and mitochondrial Hsp70s, plus a series of SLC transporters, while the top hits in the JG-294 treated samples were ER-resident Hsp70s and SLC transporters.

In the second approach, we developed a new way to explore the selectivity of allosteric inhibitors. Briefly, alanine scanning is a traditional method for creating loss-of-function mutants in enzymes. Then, these mutants can be introduced into cells to determine whether the resulting phenotypes match those collected using small molecules. If the compound treatment and genetic mutants give the same phenotype, then the compound is likely acting by an on-target mechanism. However, this strategy does not work well for allosteric inhibitors, because one cannot simply create alanine mutants of key residues to phenocopy inhibitor binding. Accordingly, we developed a new approach, in which tryptophan (rather than alanine) is introduced in the allosteric site, mimicking the small molecule. This structure-guided approach created an Hsp70 mutant Y149W that appears 100% compound-bound, based on structural and functional studies. This work was published (Taylor et al. 2020 Chem Sci. 11:1892), so we will not include the figures here.

Publications:

Taylor, I. R.*, Assimon, V. A.*, Kuo, S. Y.*, Rinaldi, S., Li, X., Young, Z. T., Morra, G., Green, K., Nguyen, D., Shao, H., Garneau-Tsodikova, S., Columbo, G., Gestwicki, J. E. "Tryptophan scanning mutagenesis as a way to mimic the compound-bound state and probe the selectivity of allosteric inhibitors in cells" 2020 Chem. Sci. 11:1892-1904. *these authors contributed equally.

Specific Aim 2: The goal of Specific Aim 2 (and a Major Task under this aim) is to determine whether Hsp40 and/or Hsp70 inhibitors sensitize resistant CRPC to enzalutamide and/or abiraterone. In a previous publication (Moses MA, et al. Cancer Res. 2018 Jul 15;78(14):4022-4035) we demonstrated that the Hsp40 inhibitor C86 and the Hsp70 inhibitor JG-98 each had single agent activity toward 22Rv1 CRPC cells in vitro and in vivo. In the previous report, we provided preliminary data demonstrating single agent activity ofHsp40 inhibitor the Hsp70 inhibitor JG98 and the Hsp40 inhibitor C86. We also provided preliminary data demonstrating that both agents resensitize 22Rv1 CRPC cells to the anti-androgen enzalutamide and the androgen synthesis inhibitor abiraterone. In the current cycle, we confirmed and expanded on these fiindings using the Incucyte instrument which allows multi-concentration 6-day analysis of cell growth which can be monitored in real time (see Fig. 2 below) Unfortunately, we have not yet been able to initiate in vivo experiments to corroborate the in vitro data, as the ongoing Covid-19 pandemic has delayed recruitment of needed personnel. Necessary personnel are now on board (arrived 9/21) and we hope to rapidly make up ground so that we can make significant inroads to completion of these experiments in year 3 of this award.

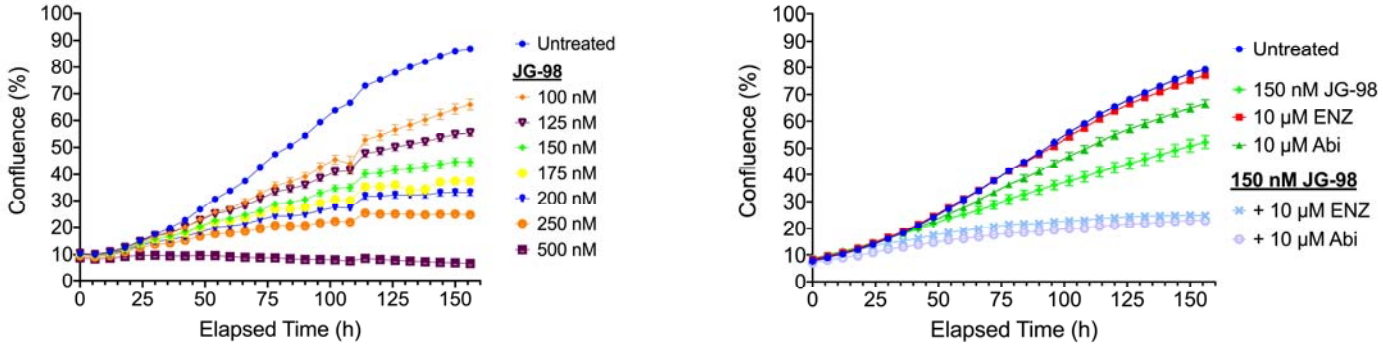
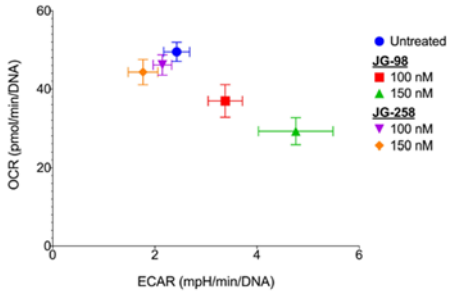


Fig. 2. Inhibition of Hsp70 by JG-98, while causing complete single agent growth inhibition of 22Rv1 cells over 6

days at 500 nM concentration, a lower concentration of JG-98 with minimal to moderate single agent activity (150 nM) resensitizes these CRPC cells to enzalutamide and abiraterone (which have essentially no single agent activity in this model). A. Six day continuous Incucyte growth analysis of 22Rv1 CRPC cells in the presence of JG-98 alone. B. Incucyte growth analysis of 22Rv1 CRPC cells in the presence of 150 nM JG-98 +/- 10 µM Enzalutamide or Abiraterone.

Specific Aim 2 also includes the Major Task of determining the mechanistic basis of the combinatorial activity underlying chaperone inhibitor-mediated sensitization to enzalutamide and/or abiraterone. During the current cycle, we have continued to make inroads in addressing this question (see energy map in Fig. 3 below). This progress involves demonstrating that JG98 promotes a reduction in mitochondrial Oxidative Phosphorylation (OxPhos), the preferred energy pathway of CRPC cells, while increasing a shift to glycolysis, the preferred energy pathway of normal prostatic epithelium. Under these altered metabolic conditions, resensitization to androgen deprivation therapy occurs.

Fig. 3. An energy map demonstrating that JG-98 at concentrations that are synergistic with enzalutamide and abiraterone reduce the Oxygen Consumption Rate (OCR, indicator of mitochondrial activity), while increasing a shift to aerobic glycolysis (ECAR, Extracellular Acidification Rate). JG-258 is used as an inactive control for JG-98.



In exploring the mechanistic basis of this activity, we used mass spectrometry to make the preliminary observation that brief treatment with JG-98 impedes delivery of mitochondrial ribosomal subunits and assembly proteins from cytosol into mitochondria (see Fig. 4 below). This shouls have deleterious effects on activity of the various protein complexes that make up the mitochondrial electron transport chain (ETC), an essential component of ATP production in mitochondria. We are further exploring the impact of this observation on ETC function.

A

Mitochondrial Large Ribosome Subunits	
Gene Symbol	log2 Ratio (JG/Untrt)
MRPL2	-0.405042953
MRPL9	-0.697134451
MRPL10	-0.399551538
MRPL11	-0.646625848
MRPL13	-0.651545304
MRPL16	-0.859020912
MRPL17	-0.318596638
MRPL18	-0.333843501
MRPL19	-0.370500535
MRPL20	-0.367509989
MRPL22	-0.335064231
MRPL24	-0.542686138
MRPL27	-0.486279741
MRPL28	-0.722202587
MRPL30	-0.581765726
MRPL33	-0.918649498
MRPL33	-0.519081023
MRPL34	-0.712707855
MRPL37	-0.465220221
MRPL41	-0.533282235
MRPL42	-0.672082914
MRPL45	-0.48880048
MRPL47	-0.63325838
MRPL48	-0.426007467
MRPL51	-0.505207477
MRPL54	-0.357989293
MRPL55	-0.455067635
MRPL57	-0.612511418
MRPS18A (18-3)	-0.491703416

Mitochondrial Small Ribosome Subunits	
Gene Symbol	log2 Ratio (JG/Untrt)
MRPS2	-0.417257274
MRPS5	-0.803594605
MRPS7	-0.575995015
MRPS9	-0.627165294
MRPS10	-0.524673184
MRPS11	-0.499890632
MRPS12	-0.991745451
MRPS14	-0.685781414
MRPS15	-0.57251233
MRPS16	-0.407826656
MRPS18B (18-2)	-0.451951935
MRPS21	-1.305966729
MRPS26	-0.449641992
MRPS27	-0.446177774
MRPS28	-0.40397971
MRPS30	-0.33763968
MRPS31	-0.453633492
MRPS33	-0.44605328
MRPS34	-0.424559931
MRPS35	-0.563987438

Mitochondrial Ribosome Assembly	
Gene Symbol	log2 Ratio (JG/Untrt)
DDX28	-0.511275439
DHX30	-0.382361793
mTERF3	-0.331316179
mTERF4	-0.313591434
FASTKD2	-0.383186108
ERAL1	-0.81185354
GRSF1	-0.50176218

B.

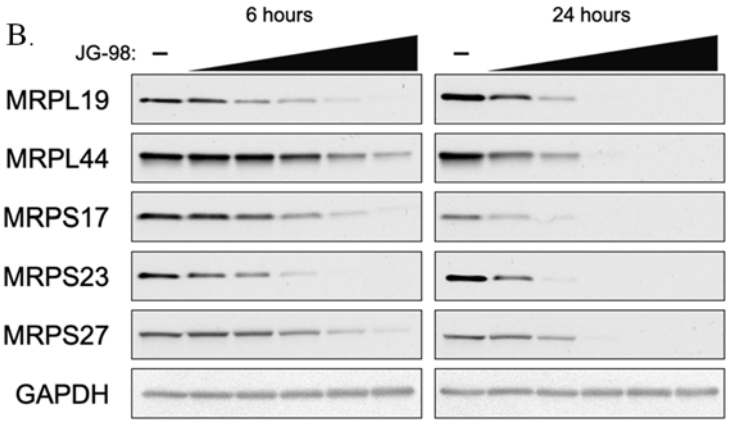


Fig. 4. Inhibition of Hsp70 by JG-98 selectively decreases protein levels of mitochondrial ribosomal subunits. A. Table of mitochondrial ribosomal subunits and assembly factors down-regulated due to 4h JG-98 treatment. B. Western blot validation of mass spec data in 22Rv1 whole cell extract after 6h or 24h treatment with JG98.

Specific Aim 3: The goal of Specific Aim 3 is to determine whether combinatorial activity can be demonstrated between Hsp40/Hsp70 inhibitors and specifically targeted metabolic inhibitors. Further, the ability of certain metabolic inhibitors to synergize with or restore sensitivity to enzalutamide and/or abiraterone is a sub-task of SA3. In the last cycle, we obtained preliminary in vitro evidence that certain metabolic inhibitors have significant growth inhibitory activity in 22Rv1 cells that are constitutively resistant to enzalutamide and abiraterone. Further, we obtained preliminary evidence of reversal of resistance. IACS-010759 (IACS) is a synthetically derived inhibitor of mitochondrial complex I. Complex I oxidizes NADH supplied by glycolysis and the TCA cycle to help establish a proton gradient across the inner mitochondrial membrane while generating electrons which pass along the mitochondrial ETC, resulting in oxidative phosphorylation and ATP synthesis. **In the current cycle, we have used the Incucyte instrument to confirm that** 22Rv1 CRPC cells are growth inhibited by low concentrations of IACS. (see Fig**. 5** below**).** Further, we found that complex I inhibition is able to resensitize these cells to enzalutamide.

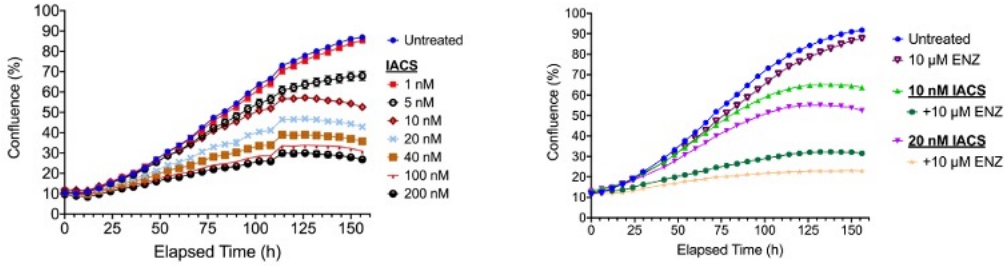


Fig. 5. Electron Transport Chain inhibition sensitizes CRPC cells to ADT drugs. The ETC complex I inhibitor IACS inhibits 22Rv1 cell growth in vitro (left panel) and resensitizes these CRPC cells to enzalutamide (right panel).

The mitochondrial ETC is comprised of four multi-subunit complexes. Like the complex I inhibitor IACS, the complex II inhibitor, MitoVES, displays dose-dependent, single-agent growth inhibition of 22Rv1 cells as visualized by Incucyte assay. However, single agent MitoVES causes 22Rv1 cell death at concecntrations of 1 µM and above (see Fig. 6 below). In addition, we have confirmed preliminary data showing that MitoVES partially resensitize 22Rv1 cells to enzalutamide and abiraterone in vitro (The complex II inhibitor demonstrates greater resensitization to enzalutamide. These data make clear that sensitivity of CRPC cells in vitro to both enzalutamide and abiraterone can be restored by targeting mitochondrial function.

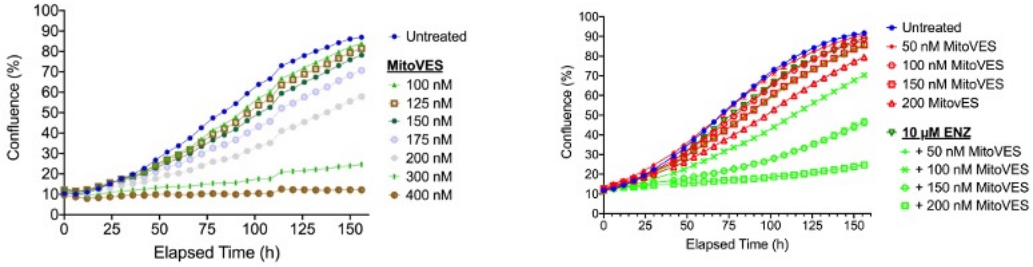


Fig. 6. Electron Transport Chain inhibition sensitizes CRPC cells to ADT drugs. Incucyte growth analysis of single agent complex II inhibitor MitoVES (left). Incucyte growth analysis of MitoVES resensitization to enzalutamide (50, 100, 150, or 200 nM MitoVES +/- 10 µM Enzalutamide (right).

Another Major Task under Specific Aim 3 is to determine whether Hsp40 or Hsp70 inhibitors can synergize with metabolic inhibitors in inhibiting the growth of CRPC cells in vitro and in vivo. In this cycle, we have confirmed the in vitro combinatorial impact of including JG-98 with both complex I and complex II inhibition (see Fig. 7 below). In the next cycle, we hope in to validate these combinations in vivo.

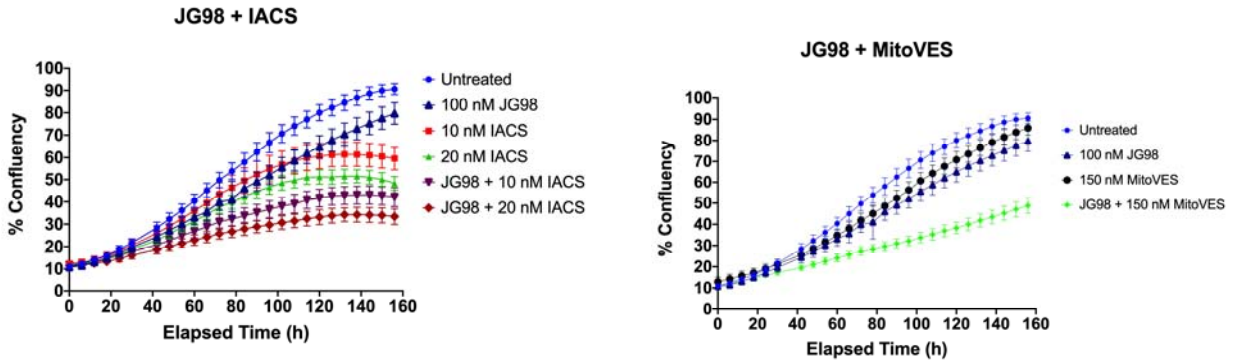


Fig. 7. Addition of low dose JG-98 (100 nM) to either the complex I inhibitor IACS (10 & 20 nM, left) or the complex II inhibitor MitoVES (150 nM, right) is synergistic in vitro.

In the next cycle, additional metabolic inhibitors, described in SA3/Major Task 6 will be similarly evaluated.

What opportunities for training and professional development did the project provide?
How were the results disseminated to communities of interest? Krista Reynolds joined the project as a new Post-Bac Fellow in the Neckers lab. Her previous experience in college was in animal science, where she obtained proficiency in several useful molecular and cellular biology techniques. In the current project, she is being mentored by a Senior Research Fellow, Frank Echtenkamp, to develop further skills related to the studies described in the SOW, Specific Aims 2 and 3. She is also able to take relevant courses at the FAES Graduate School, which are offered to her at no cost. She will be able to attend seminars, workshops and conferences related to her work. As a participant in this award, Krista will obtain increased knowledge and skills relating to translational biology of CRPC. Genesis Rivera-Marquez has become a Geneva Foundation employee and works on the same project as a collaborator. She also is able to attend virtual seminars, journal clubs, workshops and conferences and to take relevant courses at the FAES graduate school at no cost to her.

How were the results disseminated to communities of interest?
Publication and virtual seminars

What do you plan to do during the next reporting period to accomplish the goals and objectives?
Work on Specific Aim 1 was and continues to be severely impacted by the Covid-19 pandemic in California. In year 3, Dr. Gestwicki will make every effort to complete the sub-tasks in SA1 in as timely a manner as possible. We will continue working on uncompleted sub-tasks in SA2 and SA3, with a particular effort put forth to begin animal studies, which were delayed due to the impact of Covid-19. Conditions permitting, we hope to be on track with in vivo experiments by beginning in the next cycle. In vitro experiments will continue as planned.

4) IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
We identified a unique metabolic sensitivity of CRPC cells to mitochondrial inhibitors and we showed synergy with the Hsp70 inhibitor JG98. We also uncovered a potential impact of JG98 on Hsp70-mediated transport of nuclear encoded mitochondrial subunit and assembly proteins from cytosol into mitochondria. This is likely to have a major impact on mitochondrial function.
What was the impact on other disciplines?
Nothing to Report

What was the impact on technology transfer?
Nothing to Report

What was the impact on society beyond science and technology?
Nothing to Report

5) CHANGES/PROBLEMS:

Changes in approach and reasons for change: Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them: Work on SA1 and in vivo studies in SA2 and SA3 were significantly impacted by Covid-19 in the current cycle. We hope to get back on schedule during the next cycle, but this will depend on the status of the pandemic in California and Maryland.

Changes that had a significant impact on expenditures
Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents: Animal studies were delayed because of impact of Covid-19 on recruiting personnel. Within the last month, this has been rectified.

Significant changes in use or care of human subjects: Nothing to Report

Significant changes in use or care of vertebrate animals: Animal experiments have been delayed due to the Covid-19 pandemic, but these should resume during the upcoming cycle, conditions permitting.

Significant changes in use of biohazards and/or select agents: Nothing to Report

6) PRODUCTS:

Publications, conference papers, and presentations

Journal publications: Taylor, I. R.*, Assimon, V. A.*, Kuo, S. Y.*, Rinaldi, S., Li, X., Young, Z. T., Morra, G., Green, K., Nguyen, D., Shao, H., Garneau-Tsodikova, S., Columbo, G., Gestwicki, J. E. "Tryptophan scanning mutagenesis as a way to mimic the compound-bound state and probe the selectivity of allosteric inhibitors in cells" 2020 Chem. Sci. 11:1892-1904. *these authors contributed equally.

Books or other non-periodical, one-time publications:
Nothing to Report

Other publications, conference papers, and presentations: **Presentation: (1)** Neckers L. Targeting Castration-resistant prostate cancer with inhibitors of molecular chaperones Hsp40 and Hsp70. [to be presented on 11/18/2020 as part of the Proteostasis Consortium Weekly Seminar Series (virtual). **(2)** Sensitivity of castration-resistant prostate cancer to mitochondrial electron transport chain inhibitors, synergy with JG98 and resensitization to enzalutamide.

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:	Jason Gestwicki
Project Role:	Collaborator
Researcher Identifier (e.g. ORCID ID):	0000-0002-6125-3154
Nearest person month worked:	1
Contribution to Project:	Responsible for Specific Aim 1
Funding Support:	(direct costs, year 1)

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? Nothing to Report

What other organizations were involved as partners? Nothing to Report

8) SPECIAL REPORTING REQUIREMENTS:

QUAD CHARTS:

9) APPENDICES: